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Association of pulse pressure, pulse pressure index and ambulatory arterial stiffness index with kidney function in a cross sectional pediatric chronic kidney disease cohort from the CKiD study

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Keywords: pulse pressure, AASI, pulse pressure index, inflammation, chronic kidney disease

Abstract

The morbidity and mortality of adult and pediatric chronic kidney disease (CKD) and end-stage renal disease (ESRD) populations are mainly driven by cardiovascular disease (CVD). Improving CVD outcomes focuses on risk assessment of factors including diastolic blood pressure (DBP), systolic blood pressure (SBP), left ventricular mass index (LVMI), pulse pressure (PP), and pulse pressure index (PPi), which is calculated as PP/SBP. These markers are also proven predictors of CKD progression; however, their role in children has not been established. This study aims to evaluate the relationship between PP, PPi, ambulatory arterial stiffness index (AASI), and proteinuria with kidney function in pediatric CKD patients; it is a retrospective analysis of 620 patients (1-16 years) from the NIDDK Chronic Kidney Disease in Children (CKiD) registry. We analyzed data for three separate cohorts: an overall CKD as well as immunological versus non-immunological cause for CKD groups. An inverse relationship was found between SBP, DBP, and PP with iGFR and LVMI in the overall CKD group. Our immunological CKD subgroup showed significantly higher serum creatinine, SBP, DBP, and PP values with significantly lower serum albumin levels compared to the non-immunological group. There were no significant differences with iohexol-based glomerular filtration rate (iGFR), LVMI, PPi or high-sensitivity C-reactive protein (hs-CRP) between the two groups. A subgroup analysis demonstrated that SBP, DBP, and PP all correlated significantly with LVMI in the immunological

CKD patients but not the non-immunological sub-group. Additionally, AASI data in the overall CKD population was significantly correlated with PP, PPi, and DBP. This study is one of the first to correlate noninvasive measurements of vascular compliance including PP, PPi, and AASI with iGFR and LVMI in a pediatric CKD cohort. Improving our understanding of surrogate markers for early CVD is integral to improving the care of pediatric CKD population as these patients have yet to develop the hard endpoints of ESRD, heart failure, myocardial infarction or stroke.

Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are a significant burden for patients due to their high morbidity and associated mortality; furthermore, CKD and ESRD care is complex and requires a significant portion of our health care resources [1]. The morbidity and mortality of adult and pediatric CKD/ESRD populations are mainly driven by cardiovascular disease (CVD) [2]. Hypertension (HTN) has long been identified as a paramount independent risk factor for CVD development as well as CKD progression; improving CVD outcomes has focused on risk assessment including analysis of systolic blood pressure (SBP) and diastolic blood pressure (DBP) [3]. However, as medical management of HTN has improved, the onus of care has shifted to prevention including early detection of evolving vascular pathology prior to changes in blood pressure and recently the emphasis has shifted to noninvasive arterial elasticity measurements.

The strong prognostic value of arterial stiffness measurements has been firmly established over the last two decades in the adult CKD and ESRD populations [2]. Furthermore, we know that arterial stiffness measurements offer additive predictive value to traditional risk factors with respect to cardiovascular outcomes [2]. However, measurements of arterial stiffness have not been well evaluated in the pediatric CKD populations. While well-established markers such as pulse wave velocity (PWV) and the augmentation index have excellent prognostic value in adults, they are cumbersome due to the need for specialized equipment and remain mostly utilized in research [4,5]. Thus, clinicians need arterial stiffness parameters that are accessible for routine practice; two such potential parameters include pulse pressure (PP) and ambulatory arterial stiffness index (AASI). PP is well established and easily calculated as the difference between maximal systolic blood pressure (SBP) and minimal diastolic blood pressure (DBP), and increased PP is associated with poor CKD outcomes in adults [6]. AASI is a newer method and is mathematically derived from 24-hour ambulatory blood pressure monitoring (ABPM) [7]. The utility of PP has its limitations, however, including its propensity to increase or decrease in an individual while not

reflecting absolute blood pressure levels [8]. To account for this, Peng-Lin and Yue-Chun proposed a new parameter: pulse pressure index (PPi) (calculated as (SBP – DBP)/SBP), as a more accurate indirect measure of vascular compliance [6]. Its structure is similar to the fluid–flow analog presented by Ohm's law (pressure gradient = volume flow rate x resistance) [8]. Thus, PPi accounts for absolute blood pressure changes and is superior to PP alone as an indication of vascular compliance and may potentially be a better predictor of CV outcomes[8].

Persistent low-grade inflammation is a hallmark of CKD and increased inflammation is a risk factor for CKD morbidity and mortality in adults [9-12]. Various immunological biomarkers, including interleukin-1 (IL-1), IL-1 receptor antagonist (IL-1RA), interleukin-6 (IL-6), tumor necrosis factor–alpha (TNF-α), tumor necrosis factor-beta (TNF-β), high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and serum albumin, have been implicated in CKD progression [12-14]. However, their role in CKD in children has not been established.

The value of establishing non-invasive prognostic markers for CVD morbidity/mortality as well as loss of kidney function is integral to improving the care of pediatric CKD population as these patients have yet to develop the hard endpoints of ESRD, heart failure, myocardial infarction or stroke. Children are thus a population with the greatest potential for preventative care and improvement in long-term outcomes and are deserving of increased research. This study aims to investigate the relationship of PP, PPi, AASI, and proteinuria with kidney function using the Chronic Kidney Disease in Children (CKiD) database from the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) registry.

Material and Methods

Study design: This is a retrospective and a cross-sectional study of 620 pediatric CKD patients (age 1-16 years) from the CKiD database of the NIDDK registry. The correlation analysis of multiple variables present in CKD was retrospectively assessed while the correlation analysis of AASI was cross-sectional. Data in this manuscript was collected by the Chronic Kidney Disease in Children (CKiD) study with clinical coordinating centers (Principal Investigators) at Children's Mercy Hospital at the University of Missouri - Kansas City (Bradley Warady, MD), Children's Hospital of Philadelphia (Susan Furth, MD, PhD), Central Biochemistry Laboratory (George Schwartz, MD) at the University of Rochester Medical Center, and the Data Coordinating Center (Alvaro Muñoz, PhD and Derek Ng, PhD) at Johns Hopkins' Bloomberg School of Public Health. This data includes renal function, measurements of CV risk factors, co-morbidities, neurocognitive functions, and clinical events related to End Stage Renal Disease (ESRD) and death. Children < 1-year-old were excluded from the registry as glomerular filtration rate (GFR) increases during the first year of life, even in the presence of renal insufficiency.

Study population: Only patients aged 1-16 years with iohexol-based glomerular filtration rate (iGFR) < 60 ml/min/1.73 m^2 (n = 620) were selected for pulse pressure and AASI correlation analysis.

Data collection: Data regarding demographics (age, sex, race), etiology of CKD, estimated GFR (eGFR) (Schwartz formula), and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) were recorded. Laboratory markers including serum creatinine (SCr), urine protein levels, and immunological markers (high-sensitive C-reactive protein (hs-CRP) and serum albumin) data were also collected.

Blood pressure was measured via auscultation using an aneroid sphygmomanometer (Mabis MedicKit 5, Mabis Halthcare, Waukegan , IL), with the average of three auscultatory BP measurements utilized for analysis; the averaged HR from these three BP measurements was also used. PP was calculated by subtracting DBP from SBP and PPi was calculated by using the formula PP/SBP. The 24-hour ambulatory blood pressure monitoring (ABPM) was completed utilizing a Spacelabs 90217 monitor (SpaceLabs Healthcare, Issaquah, WA); BP was measured every 20 minutes during the day and night. After completion of the monitoring period, the monitors were processed and analyzed at the ABPM center (University of Texas Health Science Center at Houston). Requirements for analysis included that the monitor was worn for ≥21 hours and ≥18 hours with ≥1 successful BP measurement per hour [15]. The AASI was calculated from unedited recordings as follows: the regression of diastolic on systolic BP was estimated for each participant (not forcing the regression line through 0), and AASI = (1–regression slope) [4]. Echocardiograms by M-mode and Doppler were performed at individual participating centers, with the official read and analyses performed by the Cardiovascular Core Imaging Research Laboratory at Cincinnati Children's Hospital Medical Center, to measure left ventricular mass (LVM) [16]. Left ventricular mass index (LVMI) was then calculated by indexing the LVM to the height of the participant [17]. ABPM, AASI and LVMI measurements were analyzed with BP and laboratory data from the most proximate clinic visit. Correlation analysis was also performed for proteinuria with SBP and DBP. For analysis, significant proteinuria was defined as a calculated urine protein to creatinine ratio (Up/c) of 0.2 < 2, while nephrotic range proteinuria was defined as a calculated Up/c ≥ 2.0 [18].

Statistical Analysis: Descriptive statistics (mean, standard deviation & percentage) were used to describe study population demographics, measures of renal function, blood pressure variables, and etiology of CKD. The correlation of multiple variables within the overall CKD group as well as between the immunological and non-immunological CKD groups were evaluated utilizing the Pearson's correlation and backward logistic regression analysis to adjust for any potential risk factors. T-tests were utilized to check for significant differences in renal function measures, blood pressure variables, immunological biomarkers, and use of ACEi/ARB between immunological and

non-immunological CKD groups. Specifically, for proteinuria analysis, linear regression was performed and compared to the normal range Up/c (<0.2). For AASI calculations, the Fisher exact test was used to test differences between proportions while the T-tests were performed to compare the continuous data across the various CKD groups. Any variables of interest with a highly skewed distribution were log-transformed before analysis. Additionally, univariate logistic regression analysis was used to calculate the significance F-factors while the independently associated variables with each stiffness parameter were evaluated by multiple linear regression using an ordinary least squares model.

Results

Patient demographics and baseline characteristics are shown in Table 1. On average (mean ± standard deviation), patients were 9.63 ± 4.34 years old and weighed 40.4 ± 22.5 kg. The majority of patients were male and Caucasian (59.7% and 69.03%, respectively). Other characteristics of the studied population are shown in Table 1. The most common causes of CKD were obstructive uropathies followed by aplastic/hypoplastic/dysplastic kidneys and reflux nephropathy (Table 2).

Among all patients (n= 620), 16% (99/620) had CKD due to immunological causes while 64% (521/620) had CKD due to non-immunological causes (Table 2). In comparison to the non-immunological group, patients with immunological CKD had significantly higher SCr levels, SBP, DBP and PP (Table 3). Serum albumin was significantly lower in the immunological than the non-immunological CKD group (Table 3). In contrast, there were no significant differences in iGFR, LVMI, PPi or hs-CRP between the two groups. However, there was increased usage of ACEi/ARBs noted in the immunological CKD group compared to the non-immunological CKD group (Table 3).

The correlation of multiple variables was investigated for the overall CKD group (Table 4 and Figure 1). There was a significant correlation between SBP and iGFR ($R^2 = 0.033$; $p< 0.001$), SBP and SCr ($R^2= 0.136$; $p<0.001$), and SBP and LVMI ($R^2 = 0.013$; $p<0.001$). Similarly, DBP and iGFR ($R^2 = 0.013$; $p < 0.001$), DBP and SCr ($R^2= 0.061$; $p<0.001$), and DBP and LVMI ($R^2 = 0.005$; $p=0.035$) were significant. In addition, PP and SCr ($R^2 = 0.039$; $p < 0.001$), PP and LVMI ($R^2 = 0.005$; $p=0.029$), and PP and iGFR ($R^2 = 0.017$; $p = 0.011$) were significant. Finally, PPi and SCr ($R^2 = 0.0005$; $p=0.265$) were significant but not PPi and LVMI ($R^2 = 0.001$; $p=0.437$) nor PPi and iGFR ($R^2 = 0.001$; $p=0.309$). There was no significant correlation between proteinuria and SBP (p=0.11), nor proteinuria and DBP (p=0.38) (Table 5). Nephrotic-range proteinuria was also not significantly correlated with SBP (p=0.06). However, a significant correlation was found between nephrotic-range proteinuria and DBP (p=0.03).

Correlations were investigated for the immunological CKD group (Table 4 and Figure 2). Significant correlations were seen between SBP and iGFR ($R^2 = 0.058$; $p< 0.001$), SBP and SCr

(R^2 = 0.150; p<0.001), and SBP and LVMI (R^2 = 0.104; p<0.001). Similarly, DBP and iGFR (R^2 = 0.070; p<0.001), DBP and SCr (R^2 = 0.103; p<0.001), and DBP and LVMI (R^2 = 0.04; p=0.006) showed significance. In addition, PP and SCr (R^2 = 0.021; p=0.001), and PP and LVMI (R^2 = 0.031; p=0.016) showed significance. However, there was no correlation between PP and iGFR (R^2 = 0.0003; p=0.755). Lastly, PPi and SCr (R^2= 0.009; p=0.033) and PPi and iGFR (R^2 = 0.021; p=0.011) showed significance. However, there was no correlation between PPi and LVMI (R^2 = 0.003; p=0.492). To adjust for potential risk factors, a backward logistic regression analysis was conducted with LVMI as the dependent variable, and DBP, PP, and serum albumin as independent variables (Table 6). DBP, PP and serum albumin were all significantly associated with LVMI with an Odd's ratio (95% Confidence Interval; p value) of 0.16 (0.05, 0.28; p=0.005), 0.20 (0.07, 0.32; p=0.002), and -4.84 (-7.89, -1.78; p= 0.002), respectively. Logistic regression analysis with iGFR as the dependent variable, and DBP, PP, and serum albumin as independent variables was also performed. DBP was the only statistically significant factor associated with iGFR with an OR of -0.27 (-0.38, -0.16; p<0.001). Logistic regression analysis with SCr as the dependent variable, and DBP, PP, and serum albumin as independent variables was done. For SCr, both DBP and PP were statistically significant with an OR of 0.03 (0.03, 0.04; p<0.001), and 0.02 (0.01, 0.03; p<0.001), respectively.

Correlations were also investigated for the non-immunological CKD group (Table 4 and Figure 3). There were again significant correlations between SBP and iGFR (R^2 = 0.026; p< 0.001), and SBP and SCr (R^2 = 0.130; p<0.001). However, SBP and LVMI (R^2 = 0.003; p=0.156) was not significant. Similarly, DBP and iGFR (R^2 = 0.004; p = 0.03) and DBP and SCr (R^2= 0.049; p<0.001) showed significance. However, DBP and LVMI (R^2 = 0.001; p=0.512) was not. In addition, PP and SCr (R^2 = 0.044; p<0.001) and PP and iGFR (R^2= 0.017; p<0.001) were significant. However, PP and LVMI (R^2 = 0.001; p=0.302) was not. Finally, PPi and SCr (R^2 = 0.002; p=0.065) and PPi and iGFR (R^2 = 0.005; p=0.018) showed significance. However, PPi and LVMI (R^2 = 0.001; p=0.442) was not significant. To adjust for potential risk factors, a backward logistic regression analysis was conducted with LVMI as the dependent variables and DBP, PP, and serum albumin as independent variables (Table 6). Serum albumin was the only statistically significant factor associated with LVMI with an OR of -2.63 (-4.41, -0.86; p=0.004). Logistic regression analysis with iGFR as the dependent variable, and DBP, PP, and serum albumin as independent variables showed that DBP, PP, and serum albumin were all significantly associated with an OR of -0.10 (-0.16, -0.04; p=0.002), -0.17 (-0.24, -0.11; p<0.001) and 3.95 (2.16, 5.74; p<0.001), respectively. Lastly, logistic regression analysis with SCr as the dependent variable, and DBP, PP, and serum albumin as independent variables was performed. DBP, PP and serum albumin were all significantly associated with an OR of 0.03 (0.02, 0.03; p<0.001), 0.03 (0.03, 0.04; p<0.001) and -0.25 (-0.38, -0.12; p<0.001), respectively.

AASI data was evaluated for correlations with SBP, DBP, PP, PPi, iGFR, and LVMI. The data is only presented for the overall CKD population as there was no statistically significant difference between the immunological and non-immunological group (Table 4). When analyzing the correlation for all six variables with AASI, only DBP (R^2=0.001; $p < 0.001$), PP (R^2=0.024; $p < 0.001$), and PPi (R^2=0.021; $p < 0.001$) showed significant correlation with AASI. AASI did not correlate with iGFR (R^2=0.004; $p < 0.001$), SBP (R^2=0.001; $p < 0.001$), or LVMI (R^2=0.002; $p < 0.001$).

Discussion

Assessment of vascular compliance and function in pediatric CKD populations is integral to the identification and stratification of CVD risk factors necessary for further development of treatment and preventative care strategies aimed at ameliorating long-term morbidity and mortality. Currently, arterial assessments can utilize multiple modalities including Doppler ultrasound, applanation tonometry, oscillometer, and magnetic resonance imaging. However, these modalities are often difficult to incorporate in clinical practice due to the need for specialized equipment [19,20]. Furthermore, interval references for each of these measurements by sex and/or body size have not been well defined in the pediatric population. This is the first study to provide analysis of markers of arterial compliance, including PP, PPi, and AASI, in a pediatric CKD cohort. We identified an inverse relationship between increased SBP, DBP, and PP with GFR and LVMI, similar to adult CKD cohorts. The study also evaluates these factors based on CKD etiology as immunological vs non- immunological. Investigations to clarify which modality or markers are best for CVD risk stratification may perhaps be best carried out in a cohort of CKD children who have developed "hard outcomes," such as ESRD; thus, our findings are hypothesis-generating and can serve as an informative preliminary arbiter of risk discrimination.

Pulse pressure is mainly determined by the direct force of ventricular ejection and the viscoelasticity of large arteries, and indirectly by wave reflections [21]. Wave reflection are formed when forward-moving blood is partially reflected back from areas with transition in arterial impedance; for example, arterial bifurcations, stenoses, and peripheral beds. Increased arterial stiffness causes the vessel's wave reflection to become larger and arrive earlier in systole thus, greatly increasing PP [3]. Endothelial stress and arteriosclerosis increase PP as loss of vascular compliance increases SBP while simultaneously decreasing DBP [3]. Arteriosclerosis in CKD and ESRD patients increases arterial stiffness driving hypertension and increases PP. Elevated PP has previously been associated with adverse cardiovascular outcomes, death and dialysis in adult patients with CKD stages 4 and 5 [22]. Our study is the first to investigate this

relationship in a pediatric population and demonstrate a significant correlation between increased PP and decreased kidney function in all three groups of pediatric CKD patients (Figure 1).

Pulse pressure index is significantly associated with atherosclerosis, CV morbidity and CKD in adults; these are likely due to PPi's negative correlation with vascular compliance [20,23,24]. PPi is also associated with increased left ventricular filling pressure and left ventricular diastolic dysfunction, which are common in adult CKD patients, especially those in pre-dialysis [7]. In our overall pediatric CKD group, we found that PP had significant associations with iGFR, SCr and LVMI; however, PPi was not significantly associated with any of the variables. Among the immunological CKD group, SCr significantly associated with both PP and PPi, iGFR correlated with PPi, and LVMI correlated only with PP. Among the non-immunological group, PP and PPi were significantly correlated with both iGFR and SCr but not LVMI. Additionally, AASI only significantly associated with PP, PPi, and DBP. The mechanism behind the variability of these associations is unclear; however, the finding that SBP and DBP always correlate with iGFR and SCr while PP and PPi do so only occasionally may be indicative of the overall vascular compliance of our young population. The loss of vascular compliance is a common endpoint of CKD and ESRD; however, the amount of time a patient has suffered from advanced CKD, as well as the presence of inflammation due to their disease, may be an important prognostic indicator for loss of vascular compliance in children. Additionally, proteinuria is also strongly associated with CKD progression and cardiovascular outcomes in adults. In our study, nephrotic range proteinuria with Up/c ≥ 2 was significantly associated with hypertensive range DBP. In regard to SBP, there was a trend toward an association with proteinuria, though it was non-significant. In general, proteinuria has been shown to accompany various types of hypertensive renal diseases in pediatric patients, such as glomerulonephritis.

AASI has been established as an effective predictor of arterial stiffness in the general adult population as well as CKD patients; however, AASI has not been evaluated in a pediatric CKD population. Among adult hemodialysis patients, those with increased arterial stiffness have significantly increased risk of all-cause and cardiovascular mortality, and increased AASI also associates with early signs of renal damage in adults with primary hypertension [25]. In a retrospective analysis of 418 untreated hypertensive patients PP was identified as a crucial parameter for arterial stiffness and strong independent predictor of increasing AASI [26]. We found a significant association of AASI with three of our six variables of interest including PP, PPi and DBP. The association of AASI with established markers of vascular compliance such as PP was not unexpected. However, we found that AASI correlated with DBP but not SBP. This is consistent with findings by Franklin et al. that predictors of CVD gradually shift from DBP to SBP and then to PP with increasing age; specifically, in patients <50 years of age, DBP was the strongest predictor of CVD [21]. This gradual age-based change is the result of how cardiac

afterload is affected by arterial stiffening. Peak SBP in the ascending aorta is affected by peripheral SBP distortion secondary to wave reflection in older individuals. In young hypertensives patients, reduced peripheral amplification of SBP due to altered wave reflection leads a greater peripheral increase in DBP than in SBP while there is a parallel rise in both central SBP and DBP. Thus, in young individuals, elevated peripheral DBP is superior in predicting CVD [21,27]. However, this finding will need to be replicated in a prospectively analyzed pediatric CKD population, and more observations are necessary in order to truly elucidate AASI's associations with CVD and long-term cardiovascular morbidity in our specific population.

LVH is the strongest risk factor for CVD in hypertensive populations. LVH is common among adult CKD patients and also occurs in 17% - 49% of children with CKD [28,29]. Reduction of LVM correlates with decreased CV events and mortality in adult hypertensive patients as well as in CKD stage 5 patients on renal replacement therapy [28,29]. Common risk factors for LVH in CKD include anemia, fluid overload and hypertension [28]. In our cohort, SBP and DBP significantly correlated with LVMI in the overall CKD group and immunological CKD group. However, LVMI did not correlate with SBP nor DBP in the non- immunological group. This finding is consistent with adult CKD data that immunological markers such as CRP, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) are LVH risk factors [30]. Furthermore, inflammation is also highly prevalent in pre-dialysis CKD patients and immunological markers are associated with increased LVMI in adult CKD patients [31,32].

Studies have established the association of low-grade chronic inflammation and immunological markers with progression of CKD and all-cause mortality [9,12]. The underlying mechanisms of chronic low-grade inflammation in CKD include increased production and reduced clearance of pro-immunomodulatory cytokines, oxidative stress, acidosis, chronic or recurrent infections, altered metabolism of adipose tissue and intestinal dysbiosis [10,33]. Various immunological biomarkers, including IL-1, IL-6, TNF-alpha, TNF-beta, hs-CRP, fibrinogen and serum albumin, have been implicated in the progression of CKD [12]. Furthermore, increased levels of immunological markers (fibrinogen and TNF-alpha) and reduced levels of serum albumin are associated with rapid loss of renal functions in pediatric CKD patients [12]. However, the exact mechanism by which inflammation contributes to CKD progression is unknown [10]. While our study did include the immunological marker hs-CRP, we did not find a significant difference in hs-CRP levels between patients with immunological and non-immunological CKD. However, we did demonstrate that serum albumin was significantly lower in the immunological than the non-immunological CKD group. Unfortunately, the relationship between hs-CRP, serum albumin, and iGFR could not be established due to variation in data collection time points.

Inflammation has been linked to elevated blood pressure and cardiovascular morbidity and mortality [34,35]. Approximately 50% of CKD patients have increased mortality due to CV

complications, such as advanced calcific arterial and valvular disease, which has been linked to chronic inflammation [36]. Probable underlying pathogenesis includes an imbalance between vasoconstrictors and vasodilators, increased thrombogenesis, platelet activation, and the direct effect of immunological mediators [35]. Increased levels of CRP, IL-6 and leukocyte adhesion molecules were shown to predict the risk of CV events [13]. Our study showed significant elevations in SBP, DBP and PP in the immunological CKD group (Figure 2) compared to the non-immunological group (Figure 3). In addition, both PP and DBP were significantly associated with LVMI on regression analysis for the immunological CKD group but not the non-immunological group. ACEi/ARBs were significantly higher among the immunological CKD group implying higher blood pressures among these patients (Table 3). In the future, prospective studies should be conducted in order to further corroborate the results shown.

Conclusion

This study is one of the first to assess a pediatric CKD cohort using non-invasive surrogate markers of arterial stiffness. We have demonstrated an inverse relationship between SBP, DBP, and PP with decreased GFR and elevated LVMI in children, similar to adults. In addition, we have demonstrated differences in these relationships by CKD etiology as immunological or non-immunological, which is unique and hypothesis-generating. Our immunological CKD subgroup children showed significantly higher SCr, SBP, DBP, PP and significantly lower serum albumin levels. Subgroup analysis of CKD patients demonstrated that SBP, DBP, and PP were all significantly correlated with LVMI in immunological CKD patients but not non-immunological. These findings suggest that effective blood pressure control is of paramount importance in children with CKD due to immunological causes to decrease their long-term CV morbidity.

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Figure Legends

Figure 1: Significant correlations within the overall CKD group. SBP association with iGFR (a), SCr (b), and LVMI (c). DBP association with iGFR (d), SCr (e), and LVMI (f). PP correlation with iGFR (g), SCr (h), and LVMI (h). PPi correlation with SCr (i). iGFR, iohexol glomerular filtration rate; LMVI, left ventricular mass index; SBP, systolic blood pressure.

Figure 2: Significant correlation within the immunological CKD group. SBP association with iGFR (a), SCr (b), and LVMI (c). DBP association with iGFR (d), SCr (e), and LVMI (f). PP correlation with SCr (g), and LVMI (h). PPi correlation with iGFR(i) and SCr (j). iGFR, iohexol glomerular filtration rate; LMVI, left ventricular mass index; SBP, systolic blood pressure.

Figure 3: Significant correlation within the non-immunological CKD group. SBP association with iGFR (a) and SCr (b). DBP association with iGFR (c) and SCr (d). PP correlation with iGFR (e) and SCr (f). PPi correlation with iGFR(g) and SCr (h). iGFR, iohexol glomerular filtration rate; LMVI, left ventricular mass index; SBP, systolic blood pressure.

Table 1: Demographics and clinical characteristics at baseline.

Characteristics	**Mean +/- SD (n = 620)**
Age (years)	9.63 ± 4.34
Sex (male (%))	59.7
Weight (kg)	40.4 ± 22.5
Serum creatinine (μmol/L)	50 ± 31
iGFR (ml/min/1.73 m²)	37.9 ± 12.1
LVMI	30.9 ± 9.3
SBP (mmHg)	107.9 ± 13.5
DBP (mmHg)	66.3 ± 11.4
PP (mmHg)	41.7 ± 10.8
PPi	0.38 ± 0.8
ACEi/ARB (%)	50.5 (n = 313)
Race	
Caucasian	69.03% (n = 428)
African American (AA)	15.16% (n = 94)
Asian	2.26% (n = 14)
American Indian	1.13% (n = 7)
Native Hawaiian	0.48% (n = 3)
Other	4.03% (n = 25)
More than one race (excluding AA)	4.52% (n = 28)
More than one race (including AA)	3.39% (n = 21)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; iGFR, iohexol-based GFR; LVMI, left ventricular mass index; PP, pulse pressure; PPi, pulse pressure index; SBP, systolic blood pressure.

Table 2: Causes of chronic kidney disease.

Immunological diseases	**% of patients (n = 99)**
Hemolytic uremic syndrome	5% (n = 31)
Systemic immunological disease (including SLE)	2.74% (n = 17)
Pyelonephritis/interstitial nephritis	1.94% (n = 12)
Chronic glomerulonephritis	1.61% (n = 10)
IgA nephropathy (Berger's)	1.29% (n = 8)
Membranoproliferative glomerulonephritis type I	0.81% (n = 5)
Idiopathic crescentic glomerulonephritis	0.65% (n = 4)
Membranous nephropathy	0.48% (n = 3)
Henoch Schoenlein nephritis	0.48% (n = 3)
Membranoproliferative glomerulonephritis type II	0.32% (n = 2)
Other glomerular diagnosis	0.65% (n = 4)
Non-immunological diseases	**% of patients (n = 521)**
Obstructive uropathy	17.74% (n = 110)
Aplastic/hypoplastic/dysplastic kidneys	17.74% (n = 110)
Reflux nephropathy	13.71% (n = 85)

Focal segmental glomerulosclerosis	8.39% (n = 52)
Polycystic kidney disease (Autosomal recessive)	3.55% (n = 22)
Renal infarct	3.06% (n = 19)
Cystinosis	1.77% (n = 11)
Syndrome of agenesis of abdominal musculature	1.77% (n = 11)
Medullary cystic disease/juvenile nephronophthisis	1.61% (n = 10)
Familial nephritis (Alport's)	1.45% (n = 9)
Methylmalonic acidemia	0.97% (n = 6)
Congenital urologic disease (bilateral hydronephrosis)	0.81% (n = 5)
Perinatal asphyxia	0.65% (n = 4)
Congenital nephrotic syndrome	0.48% (n = 3)
Wilms' tumor	0.48% (n = 3)
Polycystic kidney disease (Autosomal dominant)	0.48% (n = 3)
Sickle cell nephropathy	0.16% (n = 1)
Oxalosis	0.16% (n = 1)
Branchio-oto-renal disease/syndrome	0.16% (n = 1)
Other non-glomerular diagnosis	8.87% (n = 55)

I, immunological; IgA, immunoglobin A; N, non-immunological.

Table 3: Comparison of clinical parameters between patients of CKD due to immunological and non-immunological diseases.

Baseline parameters	CKD due to immunological diseases (n=99)	CKD due to non-immunological diseases (n = 521)	P
Serum creatinine (mg/dL)	1.60 ± 0.70	1.40 ± 0.67	0.0069
iGFR (ml/min/1.73 m²)	39.65 ± 11.09	40.76 ± 10.98	0.3561
LVMI	31.59 ± 9.59 (n = 51)	32.91 ± 9.65 (n = 317)	0.3648
SBP (mmHg)	112.97 ± 12.73	105.30 ± 12.85	<0.0001
DBP (mmHg)	68.9 ± 11.71	65.15 ± 11.25	0.0026
PP (mmHg)	44.07 ± 10.88	40.12 ± 10.55	0.0007
PPi	0.39 ± 0.8	0.38 ± 0.8	0.9046
ACEi/ARB (%)	73.5	43.1	<0.0001
Serum albumin (g/dL)	3.82 ± 0.78	4.27 ± 0.96	<0.0001
hs-CRP (mg/L)	4.82 ± 21.42 (n=70)	2.64 ± 6.82 (n=311)	0.1359

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; hs-CRP, high sensitive C-reactive protein; iGFR, iohexol-based glomerular filtration rate; LVMI, left ventricular mass index; PP, pulse pressure; PPi, pulse pressure index; SBP, systolic blood pressure.

Table 4: Pearson's correlation analysis.

All Patients						
	iGFR		**SCr**		**LVMI**	
	R^2	**P**	**R^2**	**P**	**R^2**	**P**
SBP	0.033	<0.001	0.136	<0.001	0.013	<0.001
DBP	0.013	<0.001	0.061	<0.001	0.005	<0.035
PP	0.017	0.011	0.005	0.029	0.017	0.011
PPi	0.001	0.309	0.001	0.265	0.001	0.437
AASI	0.004	<0.001	-	-	0.002	<0.001
Immunological CKD						
	iGFR		**SCr**		**LVMI**	
	R^2	**P**	**R^2**	**P**	**R^2**	**P**
SBP	0.058	<0.001	0.150	<0.001	0.104	<0.001
DBP	0.070	<0.001	0.103	<0.001	0.040	0.006
PP	0.000	0.755	0.021	0.001	0.031	0.016

PPi	0.021	0.011	0.009	0.033	0.003	0.492
Non-Immunological CKD						
	iGFR		**SCr**		**LVMI**	
	R^2	**P**	**R^2**	**P**	**R^2**	**P**
SBP	0.026	<0.001	0.130	<0.001	0.003	0.156
DBP	0.004	0.030	0.049	<0.001	0.001	0.512
PP	0.017	<0.001	0.044	<0.001	0.001	0.302
PPi	0.005	0.018	0.002	0.065	0.001	0.442

DBP, diastolic blood pressure; iGFR, iohexol-based glomerular filtration rate; LVMI, left ventricular mass index; PP, pulse pressure; PPi, pulse pressure index; SBP, systolic blood pressure; SCr, serum creatinine.

Table 5: Proteinuria analysis vs. blood pressure variables.

	Proteinuria vs SBP			
	< 90th percentile	90th to 95th percentile	>95th percentile	P-value
Significant (Up/c 0.2-2)	60%	67%	60%	0.11

Nephrotic (Up/c > 2)	13%	17%	17%	0.06
	Proteinuria vs DBP			
	< 90th percentile	90th to 95th percentile	>95th percentile	P-value
Significant (Up/c 0.2-2)	62%	67%	54%	0.38
Nephrotic (Up/c > 2)	2%	13%	23%	0.03

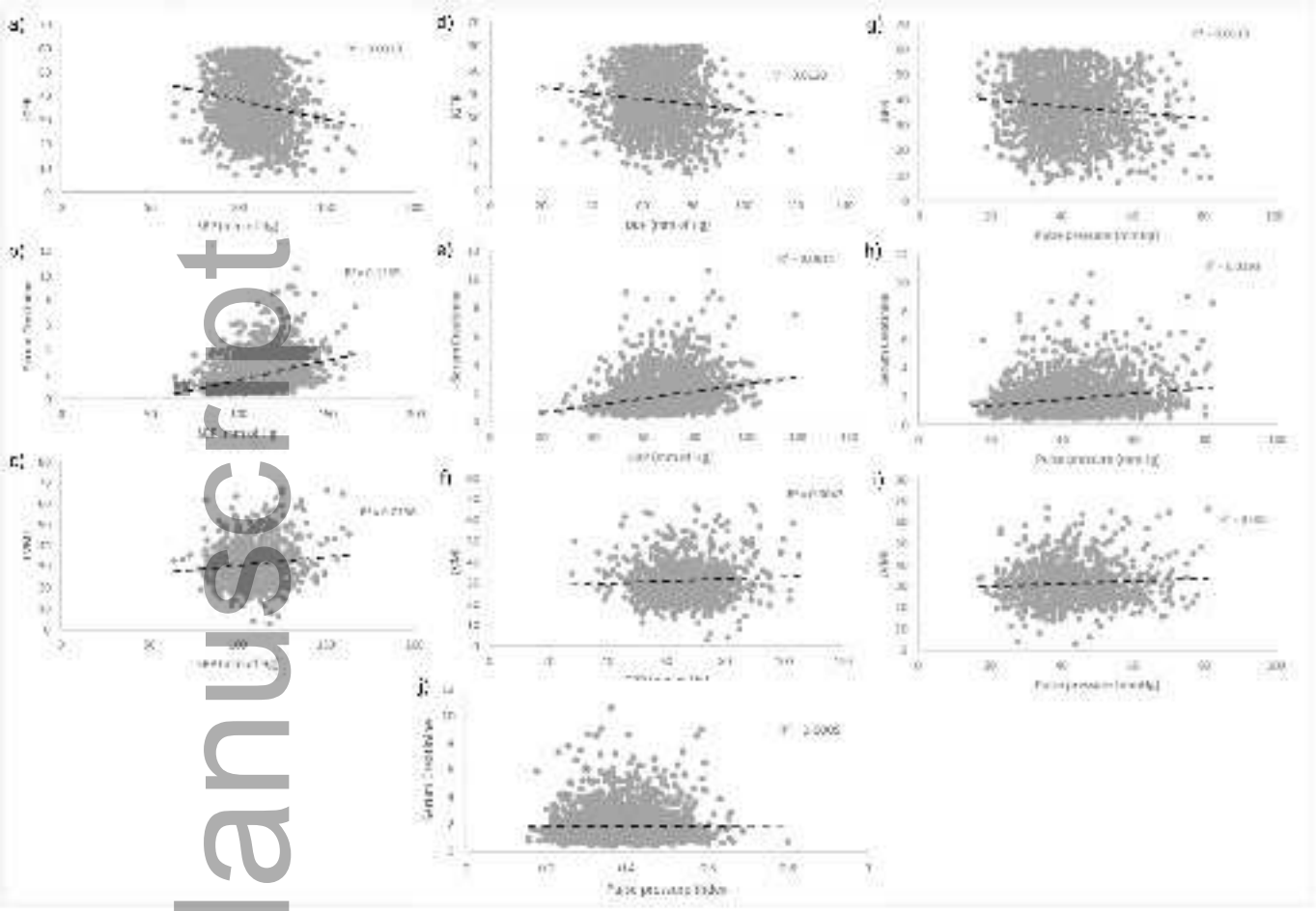
DBP, diastolic blood pressure; SBP, systolic blood pressure; Up/c, urine protein to creatinine ratio. The P value evaluated the linear trends across the three blood pressure levels and were compared to the normal Up/c range of < 0.2.

Table 6: Backward Logistic Regression Analysis for Immunological vs. Non-Immunological CKD.

Immunological CKD				
	LVMI			
	Odd's Ratio	95% CI High	95% CI Low	P value
DBP	0.16	0.28	0.05	0.005
PP	0.20	0.32	0.07	0.002
Serum albumin	-4.84	-1.78	-7.89	0.002
	iGFR			
	Odd's Ratio	95% CI High	95% CI Low	P value
DBP	0.27	-0.16	-0.38	<0.001
	SCr			

	Odd's Ratio	95% CI High	95% CI Low	P value
DBP	0.03	0.04	0.03	<0.001
PP	0.02	0.03	0.01	<0.001
Non-Immunological CKD				
	LVMI			
	Odd's Ratio	95% CI High	95% CI Low	P value
SBP	-2.63	-0.86	-4.41	0.004
	iGFR			
	Odd's Ratio	95% CI High	95% CI Low	P value
DBP	-0.10	-0.04	-0.16	0.002
PP	-0.17	-0.11	-0.24	<0.001
Serum albumin	3.95	5.74	2.16	<0.001
	SCr			
	Odd's Ratio	95% CI High	95% CI Low	P value
DBP	0.03	0.03	0.02	<0.001
PP	0.03	0.04	0.03	<0.001
Serum albumin	-0.25	-0.12	-0.38	<0.001

DBP, diastolic blood pressure; iGFR, iohexol-based glomerular filtration rate; LVMI, left ventricular mass index; PP, pulse pressure; SCr, serum creatinine.



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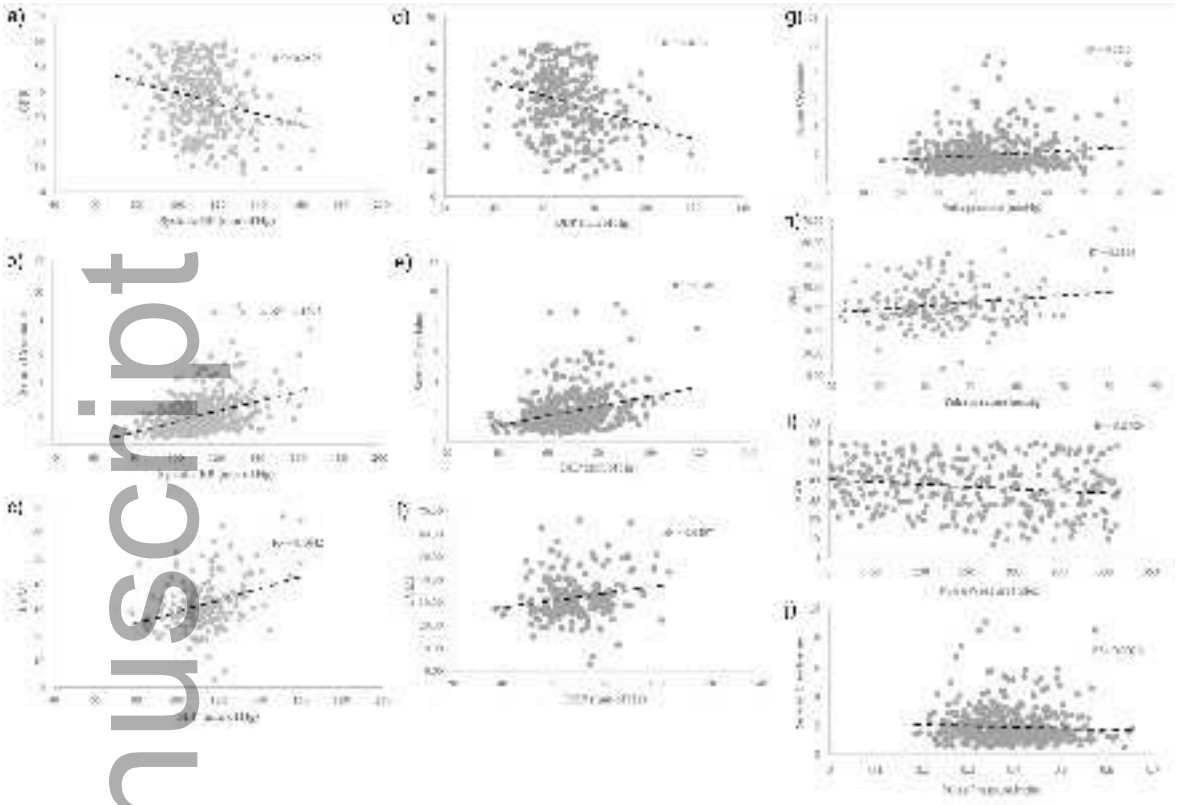

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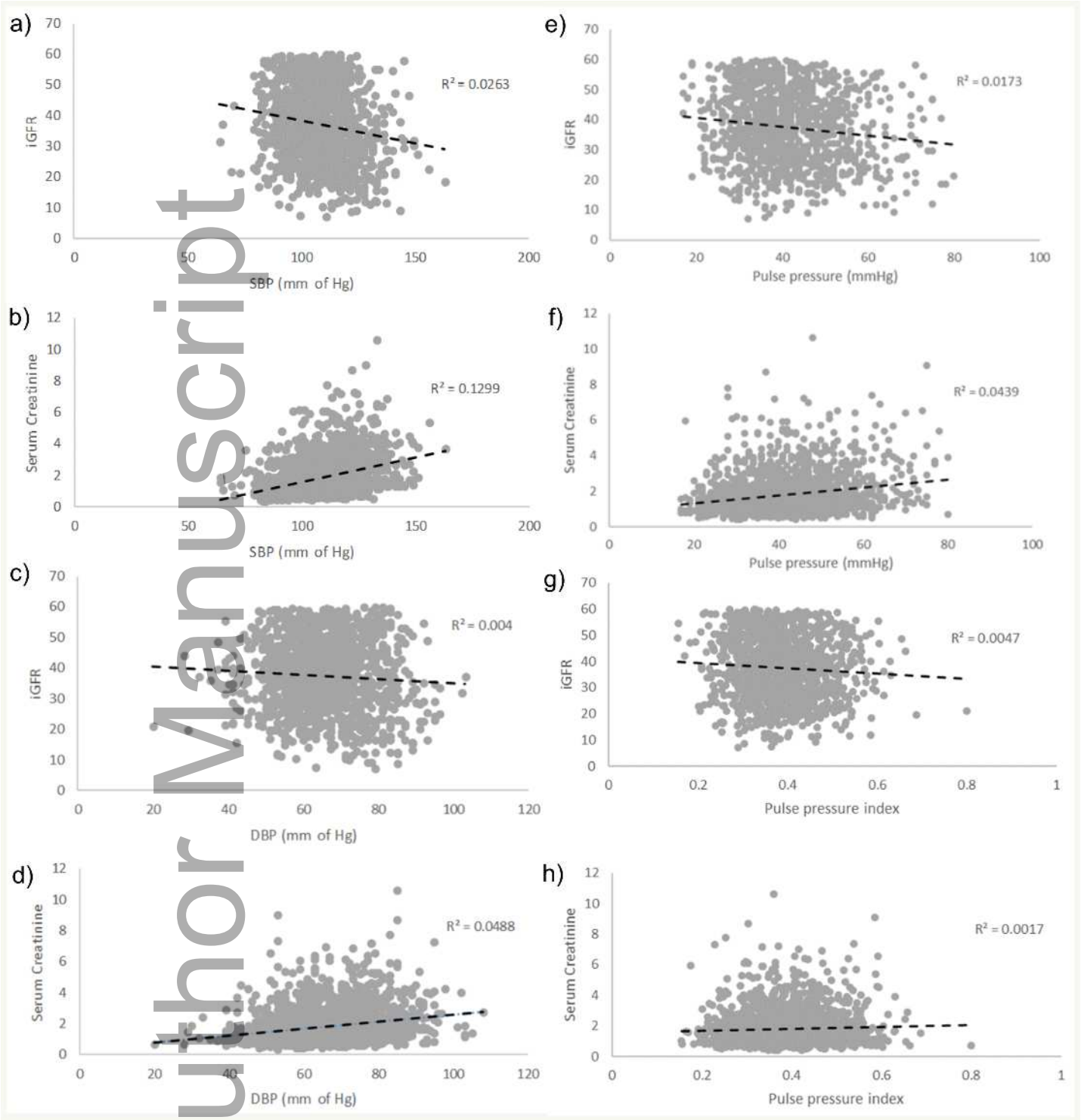

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