RESEARCH ARTICLE

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Diastolic hypertension is associated with proteinuria in pediatric patients

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Abstract

Background and Aims: Blood pressure lability has been observed in certain cohorts of pediatric patients with variable degrees of proteinuria; however, the impact of proteinuria on blood pressure is not fully elucidated. The objective of our study was to analyze blood pressure and heart rate in pediatric patients with proteinuria.

Methods: We performed a retrospective chart review of patients (age 1-18) diagnosed with idiopathic nephrotic syndrome, with varying degrees of proteinuria. Blood pressure and heart rate data were analyzed in relation to anthropometric and biochemical parameters. A total of 72 urine sample analyses, along with associated blood pressure measurements, were obtained from the charts of 33 children (males = 25).

Results: Diastolic blood pressure Z-scores were significantly higher in proteinuric patients (urine protein/creatinine >0.02 g/mmol) compared to non-proteinuric patients ($P = .006$; Cohen-d 0.97 [0.41; 1.53]). Systolic blood pressure was also significantly higher in proteinuric patients ($P = .04$), but with a less significant effect size (Cohen-d 0.54 [−0.002; 1.08]). Proteinuria (>0.02 g/mmol) was the most significant predictor of diastolic ($\beta = .79$, $P = .04$), but not systolic blood pressure elevation on multivariate analysis.

Conclusions: We observed a disproportionate increase in diastolic blood pressure vs systolic blood pressure in patients with proteinuria.

KEYWORDS
diastolic hypertension, pediatrics, proteinuria

1 | INTRODUCTION

Proteinuria in children is defined as a urinary protein to creatinine ratio (UPrCr) > 0.02 g of protein/mmol.[1] Proteinuria can reflect glomerular inflammation or injury and is transient, or progressive. One of the most common causes of proteinuria in children is nephrotic syndrome (NS), which has been shown to be associated with hypertension.[2]

Traditionally, it is believed that arterial hypertension leads to proteinuria; however, in most instances, children with NS do not suffer from primary hypertension. Yet, they may develop increased arterial blood pressure (BP) throughout the course of NS.[2-4] Blood pressure lability has been observed in these cohorts of pediatric patients with variable degrees of proteinuria; however, the impact of proteinuria on BP is not fully elucidated.[2-4] Clarifying this further may impact therapeutic approaches for hypertension in patients with proteinuria, even if it is only transient.

Thus, the objective of our study was to analyze BP in proteinuric patients to determine the propensity for isolated systolic, diastolic, or

combined arterial hypertension and to assess whether systolic blood pressure (SBP) or diastolic blood pressure (DBP) elevations are associated with the degree of proteinuria.

2 | METHODS

Data for this study were collected retrospectively from all patients who had been consecutively enrolled in an ongoing prospective, observational study on NS at The Children's Hospital of Eastern Ontario (CHEO), in Ottawa, Ontario, Canada, between September 2019 and March 2020. We enrolled children aged 1 to 18 with incident or prevalent idiopathic NS, diagnosed based on proteinuria (UPrCr >0.2 g/mmol), hypoalbuminemia (serum albumin <25 g/L), and edema. Children with NS secondary to glomerulonephritis, infection or medications were excluded. A research ethics board application (*CHEO REB: 18/168X*) was approved and all patients consented or assented to enrollment in the ongoing prospective, observational trial. If the patients were too young to consent or assent, their parents or guardians consented to their enrollment. This retrospective study is an ancillary analysis of the ongoing, prospective study on NS.

Demographic data, biochemical data, BP, and heart rate (HR) measurements were obtained from the chart of enrolled patients. Body mass index (BMI) was calculated from the weight in kilograms divided by the height in meters (kg/m^2). The BP/HR measurement and biochemical data were associated with the urine sample analysis contributed at the same clinic visit. Because of this, individual patients could have one (or more) urine samples analyzed as proteinuric and one (or more) as non-proteinuric, depending on the degree of proteinuria at the time of the provided urine sample (ie, Patient 1 can be proteinuric when giving urine sample 1 and 2, but once in remission, can be non-proteinuric for urine sample 3).

Because this was a minimal risk study, blood work obtained for routine clinical practice was evaluated when available, but patients did not provide blood samples for the purpose of the study. The following biochemical results were analyzed: urea, creatinine, Cystatin-C eGFR (GFR), serum sodium, cholesterol, serum albumin, and hemoglobin. Urine protein was analyzed using a Roche C401 analyzer. Other information obtained from the charts were: Prednisone exposure (yes/no; 33 samples obtained from patients on varying doses of prednisone) and Prednisone dose (mg/m^2/day or other day). None of our patients were being treated with antihypertensive agents, but some were on maintenance Tacrolimus (25 samples obtained from patients on tacrolimus, while only 4 were on both Tacrolimus and Prednisone at any one time when a sample was obtained).

2.1 | Classification of patients/events

All samples came from 33 patients (25 males) with idiopathic NS (1 with query focal segmental glomerulosclerosis (FSGS) on biopsy, 21 with biopsy-proven minimal change disease, and 11 with presumed minimal change disease).

We evaluated BP and biochemical parameters in relation to proteinuria based on each random urine sample obtained. Sixteen patients contributed multiple urine samples (range 2-8), while 17 patients contributed a single urine sample. As the median time between repeated samples was 20 days (14;32) and the clinical status of an NS patient may change very quickly within days, we considered each urine sample as independent (even though some samples were obtained from the same patient) and analyzed for proteinuria in concert with other anthropometric, biochemical and HR/BP data associated with that urine sample (i.e., a patient contributes a urine sample, blood work, a BP, and an HR measurement at a single clinic visit).

For the primary analysis, samples were divided based on presence or absence of proteinuria: PROT (UPrCr >0.02 g/mmol (>0.2 mg/mg) vs NOPROT (UPrCr ≤0.02 g/mmol [≤0.2 mg/mg]). For the secondary analysis, samples were divided based on the presence of nephrotic range proteinuria: NEPH (UPrCr >0.2 g/mmol [>2 mg/mg]) vs NONEPH (UPrCr ≤0.2 g/mmol [≤2 mg/mg]) to observe for the effect of heavy proteinuria on BP. SBP and DBP Z-scores were then analyzed in relation to UPrCr to assess for influence of the degree of proteinuria on BP.

2.2 | BP and HR measurement

BP and HR measurements were obtained in the clinic by the same two experienced nurses using an automatic BP device (Dinamap, GE Healthcare). BP was measured 1 to 3 times within 5 minutes in a quiet position on the non-dominant arm. An average of multiple BP measures obtained during the clinic visit was taken into analysis, unless the patient had a single measurement (only two patients). Although not optimal, we accepted the contribution of a single BP measurement as it is in keeping with published, normative data for BP in children.[5]

All BP values (mmHg) and HR values (beats per minute) per a given sample were then converted into Z-scores using age, height, and sex normative data found in the literature.[5,6] Specifically, Z-scores were calculated as follows: (patient actual BP value subtracted by the mean BP value for a given age and height) divided by BP SD for a given age and height. Elevated BP and HR values were defined as Z-scores >1.65. Pulse pressure (PP) was calculated according to the standard formula (SBP-DBP) and expressed in mmHg.

2.3 | Statistical analyses

Continuous variables were expressed as mean ± standard deviation (*SD*) or median (interquartile range, IQR) for non-normal distributions; the normal/non-normal distribution of variables was analyzed with the Shapiro-Wilk test. Group differences between SBP and DBP Z-scores in PROT vs NOPROT and NEPH vs NONEPH events were assessed using Student's *t*-test for normally distributed variables or the Wilcoxon rank-sum test for non-normally distributed variables. Effect size of the difference between variables was assessed using Cohen-*d*. The relationship between SBP and DBP Z-scores was analyzed using linear regression. We also performed univariate and

multivariate linear regression analysis to analyze predictors of SBP and DBP Z-score elevations. We included presumed clinically relevant parameters in our univariate analysis (proteinuria, BMI, prednisone as a categorical variable, and various prednisone doses), and if a significant relationship was identified on univariate analysis, these variables were used in our multivariate analysis. Lastly, we evaluated a receiver operating characteristic (ROC) curve for categorical outcome variables DBP hypertension (DBP Z-score > 1.65), and SBP hypertension (SBP Z-score > 1.65), using proteinuria as a classifier of these binary outcomes. Areas under the curve (AUC) for DBP and SBP were compared using a bootstrap method with 2000 resamples (pROC package in R). A P-value of <.05 was considered statistically significant. All tests were performed using R and Python, and associated packages.[7]

3 | RESULTS

A total of 72 urine sample results with associated BP measurements were analyzed. BP and biochemical data associated with the time of urine sample collection are summarized in Table 1.

There was no significant difference between age, height, weight, and BMI at the time of urine sample collection in the NOPROT versus PROT groups. Renal function assessed by urea, creatinine, and GFR was not significantly different between the NOPROT and PROT groups (Table 1). There was also no difference in serum sodium or hemoglobin levels.

The mean ± SD SBP, and DBP Z-score associated with all samples for the entire cohort of patients was 0.33 ± 0.98 and 0.65 ± 1.0, respectively. In the NOPROT urine sample group, the mean ± SD SBP Z-score was 0.19 ± 0.98 while the PROT urine sample group had a mean ± SD SBP Z-score of 0.72 ± 0.89 (P = .042, Cohen-d 0.54 (−0.002; 1.08). The DBP Z-score difference between NOPROT and PROT group samples was even higher with a mean ± SD DBP Z-score of 0.41 ± 0.79 vs 1.33 ± 1.25, (P = .006; Cohen-d 0.97 [0.41; 1.53]; Figure 1). In addition, we restricted our analysis to only the first urine sample obtained from each patient (33 samples, 1 per patient), and reanalyzed for differences in DBP between NOPROT and PROT patients. We reaffirmed our findings that PROT patients had higher DBP than NOPROT patients (P = .03).

In the PROT group, SBP was elevated (>1.65 Z score) in 3/19 (15%) samples, whereas DBP was elevated in 8/19 (42%) samples. Of these 19 PROT group samples, 7 (37%) were associated with only DBP hypertensive values, 1 (5%) was associated with combined SBP and DBP hypertensive values, and 1 (5%) was associated with isolated SBP hypertensive values.

To further analyze the relationship between SBP and DBP Z-scores, we plotted the SBP Z-scores against the DBP Z-scores with a line of identity for reference (Figure 2). The regression analysis showed a significant correlation between DBP and SBP Z-scores (R = 0.44, P < .01), but also a significant skew toward a greater change in DBP Z-scores in relation to the change in SBP Z-scores. Lastly, we

TABLE 1 Biochemical and clinical characteristics of the patient cohort analyzed in this study

Clinical information	Overall	NOPROT	PROT	P val.	Cohen-d (CI)
Age (years)	9.0 (5;12)	9.0 (6;13)	9.0 (3;10)	.131	0.42 (−0.12;0.95)
Height (cm)	135 ± 27	138 ± 25	126 ± 28	.100	0.48 (−0.05;1.02)
Weight (kg)	31 (21;53)	32 (22;53)	27 (21;51)	.557	0.19 (−0.35;0.72)
BMI (kg/m^2)	17.6 (16;21)	17 (15;20)	19 (16;22)	.100	−0.39 (−0.94;0.14)
CysC-eGFR (ml/min/1.73 m^2)	94 ± 16	91 ± 13	108 ± 22	.218	−1.15 (−1.72;−0.58)
Creatinine (μmol/L)	48 (37;54)	48 (41;54)	39 (32;48)	.316	0.49 (−0.05;1.03)
Urea (mmol/L)	4.8 ± 1.2	4.8 ± 1.0	4.9 ± 1.9	.916	−0.07 (−0.61;0.46)
Na (mmol/L)	140 ± 2.2	140 ± 1.6	139 ± 3.7	.445	0.59 (0.05;1.13)
Cholesterol (mmol/L)	3.8 (3.6;4.5)	3.8 (3.6;4.4)	3.7 (3.5;12.8)	.976	−1.52 (−2.11;−0.93)
Serum albumin (g/L)	42 (40;44)	42 (40;44)	36 (13;44)	.344	1.41 (0.83;1.99)
Hgb (g/L)	131 ± 12	129 ± 12	138 ± 8.4	.153	−0.74 (−1.29;-0.19)
SBP (mmHg)	102 (96;107)	102 (96;107)	103 (96;108)	.758	−0.17 (−0.71;0.36)
SBP Z score	**0.33 ± 0.98**	**0.19 ± 0.98**	**0.72 ± 0.89**	**.042***	**0.54 (−0.002;1.08)**
DBP (mmHg)	**64 ± 7.9**	**63 ± 7.6**	**68 ± 7.9**	**.010***	**0.67 (0.13;1.22)**
DBP Z score	**0.65 ± 1.0**	**0.41 ± 0.79**	**1.33 ± 1.25**	**.006****	**0.97 (0.41;1.53)**
HR (bpm)	**97 ± 19**	**94 ± 17**	**107 ± 22**	**.020***	**0.75 (0.20;1.30)**
HR Z score	0.99 ± 1.35	0.83 ± 1.27	1.44 ± 1.49	.135	0.45 (−0.08;0.99)
PP (mmHg)	41 (31;44)	41 (34;44)	36 (31;44)	.454	0.26 (−0.27;0.80)

Note: Data shown are mean ± SD for normally distributed variables, median (IQR) for non-normally distributed variables. Comparisons are made with unpaired t-tests (normally distributed variables) or Mann-Whitney U-test (non-normally distributed variables). Cohen d expressed as mean effect size with 95%ile confidence intervals in brackets. P val. <.05 considered significant.

Abbreviations: BMI, body mass index; CysC-eGFR, Cystatin C estimated glomerular filtration rate; DBP, diastolic blood pressure; Hgb, hemoglobin; HR, heart rate; Na, sodium; NOPROT, UPrCr ≤0.02 g/mmol of Cr; PP, pulse pressure; PROT, UPrCr >0.02 g/mmol of Cr; SBP, systolic blood pressure.

*P val. < 0.05; **P val. < 0.01.
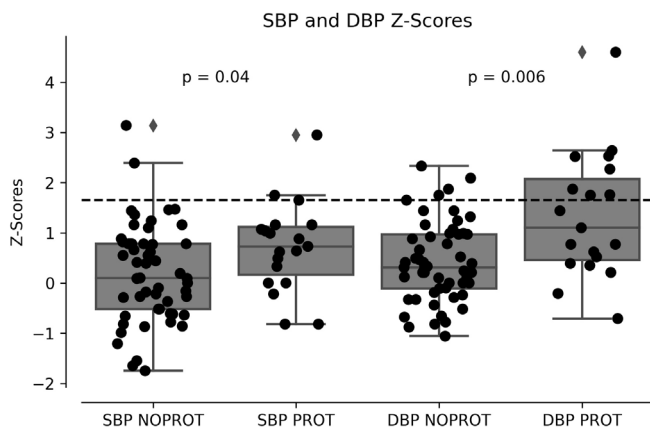
SBP and DBP Z-Scores

FIGURE 1 SBP and DBP Z-scores in patients with NOPROT vs PROT. SBP (left) and DBP (right) Z-scores between patients with NOPROT and PROT. Dotted line indicates Z-score of 1.65. PROT refers to a UPrCr >0.02 g/mmol
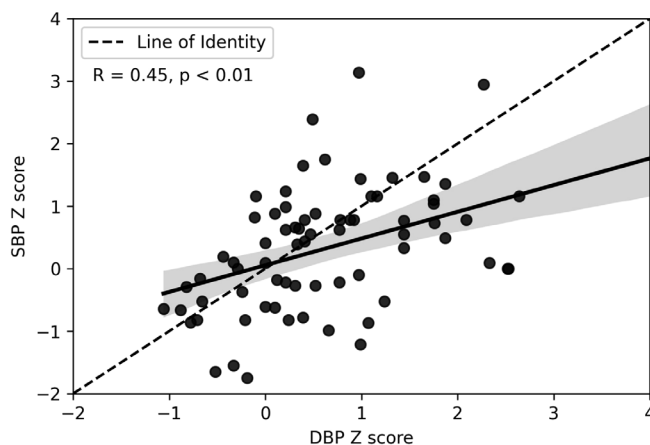

FIGURE 2 SBP Z-scores vs DBP Z-scores in comparison with the line of identity as reference. Shaded area is the 95th percent confidence interval
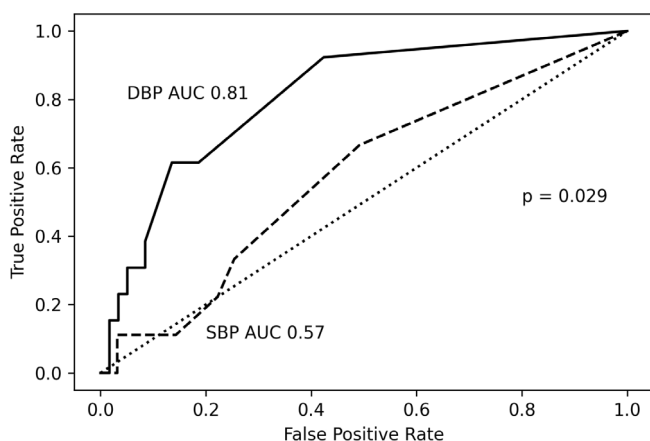

FIGURE 3 Receiver operating characteristic analysis for categorical outcome DBP hypertension, or SBP hypertension, with urinary protein to creatinine ratio as a classifier. Hypertension defined as Z-score >1.65. AUC, area under the curve; DBP, diastolic blood pressure; SBP, systolic blood pressure

used ROC analysis to determine the AUC for proteinuria as a classifier of the binary outcomes, SBP hypertension, or DBP hypertension. We noted excellent discriminatory ability between the continuous variable proteinuria, and DBP hypertension (AUC = 0.81), where the association between proteinuria and SBP hypertension was non-discriminatory (AUC = 0.57), the difference between AUCs was significant at $P = .029$ (Figure 3).

In addition, we analyzed the data with nephrotic range proteinuria cut-offs (NEPH and NONEPH). The creatinine, GFR, and urea were not significantly different; whereas cholesterol was higher, and serum albumin and serum sodium were lower (data not shown). The NON-EPH median (IQR) DBP Z-score was 0.40 (−0.1,1.0) while the NEPH median (IQR) DBP Z-score was 1.6 (0.94,1.84, $P = .03$). For SBP, the median (IQR) NONEPH Z-score was 0.40 (−0.5,0.9) and the median (IQR) NEPH Z-score was 0.57 (0.37;0.71, $P = .49$).

To better delineate the effect of the degree of proteinuria on BP, we assessed the changes in both SBP and DBP Z-scores vs UPrCr. On linear regression, there was no statistically significant association between the degree of proteinuria and SBP ($P = .28$), but there was a significant association with DBP and UPrCr ($P = .03$). We evaluated other clinically relevant parameters in univariate analyses with outcomes of SBP Z-score or DBP Z-score, as outlined in Table 2. Briefly, we noted no significant relationship between the independent variable prednisone exposure, or varying doses of prednisone on the SBP Z-score but did note a borderline significant association with BMI ($P = .05$). Not surprisingly, on multivariate analysis with similar independent variables, there was no signal ($P > .05$). On univariate analysis with the dependent variable DBP Z-score, we noted a significant relationship with proteinuria ($P = .03$) and 60 mg/m^2 prednisone daily ($P = .009$). There was a borderline significant association with prednisone (yes/no) ($P = .05$). When taking these three independent variables into multivariate regression analysis, the only significant association was between proteinuria and DBP Z-score ($P = .04$), with high-dose prednisone being borderline significant ($P = .06$). We analyzed the effect of Tacrolimus on BP in univariate analysis and found a negative association with SBP Z-score ($\beta = -.48$, $P = .04$), and DBP Z-score ($\beta = -.59$, $P = .01$).

We observed a significant difference in absolute HR values ($P = .02$) but only a trend in HR Z-score differences ($P > .05$) between PROT and NOPROT samples (Table 1). Heart rate Z-score did not correlate with SBP Z-score but correlated well with DBP Z-scores ($P = .0003$).

In considering the impact of body mass on BP in our cohort, we examined the SBP and DBP Z-scores, with cut-offs for BMI above or below 25 kg/m^2. Of importance, there were no statistically significant differences in the SBP Z-scores between those with a BMI > 25 kg/m^2, and those with a BMI < 25 kg/m^2. When analyzing this for DBP, there was also no significant difference ($P = .55$). Taken further, we examined this in NOPROT and PROT groups, and similarly found no significant difference ($P > .05$) in either SBP or DBP Z-scores between those patients who had BMI above or below 25 kg/m^2. Similar non-significant results were obtained at a threshold BMI above, or below, 20 kg/m^2. Because of the known association with weight and BP, we

TABLE 2   Linear regression analysis

Variable	Estimate	Standard error	T	P value
A. Univariate analysis: Outcome SBP Z-score				
Proteinuria	0.43	0.38	1.09	.28
Prednisone	−0.32	0.23	−1.38	.17
BMI	0.05	0.03	1.95	.05
Prednisone 1	0.17	0.30	−0.54	.58
Prednisone 2	0.04	0.32	0.13	.90
Prednisone 3	−0.55	0.34	−1.59	.12
B. Univariate analysis: Outcome DBP Z-score				
Proteinuria	**0.89**	**0.39**	**2.27**	**.03***
Prednisone	0.46	0.24	1.98	.05
BMI	−0.03	0.03	−0.98	.33
Prednisone 1	**0.80**	**0.30**	**2.68**	**.009****
Prednisone 2	0.02	0.33	0.05	.96
Prednisone 3	−0.04	0.36	−0.12	.90
C. Multivariate analysis: Outcome DBP Z-score				
Proteinuria	**0.79**	**0.38**	**2.07**	**.04***
Prednisone	0.14	0.26	0.52	.60
Prednisone 1	0.66	0.34	1.95	.06

Note: Data shown are from the univariate and multivariate regression analysis with estimate, standard error, T-value and P-value included. The outcome measure is either SBP Z-score or DBP Z-score, as labeled. (A) Univariate analysis with several clinically relevant variables, with an outcome measure of SBP Z-score. (B) Univariate analysis with several clinically relevant variables, with an outcome measure of DBP Z-score. (C) Multivariate analysis, including the significant univariate variables, and the borderline significant variable Prednisone. Significant results bolded, $P < .05$. Prednisone = yes/no variable. Prednisone 1 = 60 mg/m^2/day. Prednisone 2 = 40 mg/m^2/other day. Prednisone 3 = less than 40 mg/m^2/day. Proteinuria = UPrCr >0.02 g/mmol.
Abbreviation: BMI, body mass index.
*P val. < 0.05; **P val. < 0.01.

analyzed the standard deviation (*SD*) between weights for children who contributed more than one sample, as well as the coefficient of variation (*CV = SD*/mean). There was no significant correlation between *SD*, or *CV*, and the SBP and DBP Z-scores.

4 | DISCUSSION

The main finding of our study is that children in our cohort had significantly elevated BPs at the time of proteinuria, and the DBP elevation is disproportionately higher than the SBP elevation.

Previous studies have identified, and attempted to characterize, hypertension in both pediatric and adult patients with NS.[2-4,8,9] Cameron et al. noted significantly elevated BP measurements in 31% of patients older than 15 years of age in their study of minimal change disease,[10] and this seemed to coincide with the proteinuric state. In addition, between 10% and 30% of pediatric patients with steroid-resistant NS, or genetic forms of NS, were hypertensive on presentation on analysis of the PodoNet registry data.[9] Shatat et al, also highlighted the prevalence of hypertension in a cohort of patients with FSGS.[11] These studies did not highlight specific differences between systolic and diastolic hypertension and did not comment whether there was a propensity for disproportionate DBP elevations.

When focusing on DBP elevations, an analysis on the report of the International Study of Kidney Disease in Children (ISKDC) revealed diastolic hypertension, defined as >98th percentile, in 26.2% of patients with heavy proteinuria (12.8% of children with minimal change disease and in 13.4% of those with FSGS).[12] Diastolic hypertension was further described by Flynn[13] on analysis of the Chronic Kidney Disease in Children Study (CKiD) where they noted hypertension in 28% of patients with nephrotic range proteinuria (14% diastolic, 14% systolic). The association between proteinuria and diastolic hypertension was confirmed in our study where the degree of BP elevation was significantly skewed toward DBP elevations (Figure 2). DBP Z-scores were disproportionately higher than the SBP Z-scores in the PROT group, suggesting proteinuria has a greater impact on DBP. In addition, we noted a high number of PROT patient samples had isolated DBP elevations (37%), whereas isolated SBP elevation was associated with only 1 (5%) PROT patient sample. In contrast to the aforementioned studies (ISKDC, CKiD), where some patients had renal insufficiency, or were treated for hypertension, all our patients had normal renal function, and none were treated for hypertension at the time of urine sampling, nor were known to be hypertensive prior to entering the study.

The etiology of hypertension in patients with NS is probably multifactorial. It has been suggested that hypertension in proteinuric patients is related to acute issues (fluid shifting), but also may be related to chronic changes, such as renal injury secondary to progression of underlying renal disease.[14] We explored the possible impact of weight (fluid) on BP in our cohort. Those patients who contributed more than one sample, also contributed more than one weight. We analyzed the difference in weight, relative to the difference in BP, using absolute weight values, CV and SD, and found no significant correlation with BP.

Taken further, patients with NS have significant co-morbid conditions and medication exposures, which may have an impact on BP dynamics. Using univariate regression analysis, we noted a significant relationship between proteinuria ($P = .03$) and elevations in DBP Z-score, but no impact from steroid exposure as a categorical variable ($P = .05$). We did, however, note a significant association between high-dose prednisone and DBP Z-score elevation on univariate analysis (Table 2). The apparent negative association with Tacrolimus and SBP and DBP Z-score is likely explained by the fact that most patients on Tacrolimus did not have proteinuria. The multivariate analysis for SBP Z-score elevations (Table 2) revealed no impact from proteinuria, BMI or prednisone exposure ($P > .05$). However, the multivariate analysis for the dependent variable DBP Z-score (Table 2), revealed that proteinuria ($P = .04$) was the only significant variable in the model, with a trend toward an association with high dose prednisone. Taken further, we identified proteinuria as an excellent discriminator for the binary outcome DBP hypertension, whereas it was non-discriminatory for SBP hypertension. This fits with our existing hypothesis that the

effect of proteinuria on BP is skewed toward a more significant impact on DBP.

It is tempting to hypothesize that the disproportionately elevated DBP Z-score and absolute HR elevations may be related to endothelial dysregulation and vasoconstriction; however, we were unable to analyze for direct markers of endothelial injury or vasoconstriction. When examining the HR of patients with proteinuria, we did note a significant difference in absolute HR between patients with proteinuria and those without, with a significant effect size (Cohen-d = 0.75). When converted to HR Z-scores, the p-value was insignificant, but the effect size was still of medium significance (Cohen-d = 0.45, Table 1). We also noted a significant correlation between HR Z-scores and DBP Z-scores (P = .0003), but no correlation between SBP Z-scores and HR Z-scores.

Our study is limited due to the retrospective nature of data collection, and the relatively small number of patients. In addition, we analyzed proteinuric and non-proteinuric patients with a background of NS only. Whether this applies to other groups of patients with proteinuria remains to be determined. Strengths of our study include a detailed SBP, DBP, PP, and HR analysis using classic point estimate assessments and comparison of effect sizes using Cohen-d.

In summary, we observed a disproportionate increase in diastolic versus systolic BP in NS patients with varying degrees of proteinuria.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Conceptualization: Robert Myette, Dylan Burger, Pavel Geier, Janusz Feber

Formal Analysis: Robert Myette, Janusz Feber

Funding Acquisition: Not applicable

Writing—Original Draft Preparation: Robert Myette, Dylan Burger, Pavel Geier, Janusz Feber

Writing—Review & Editing: Robert Myette, Dylan Burger, Pavel Geier, Janusz Feber

All authors have read and approved the final version of the manuscript.

Janusz Feber and Robert Myette had full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

Robert Myette affirms that this manuscript is an honest, accurate, and transparent account of the study being reported that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant) have been explained.

DATA AVAILABILITY STATEMENT

The authors confirm that the data are available upon request.

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