Visit-to-visit variability in blood pressure and kidney disease progression in IgA nephropathy
Chen Tang1,2,3,∗, Xiao-Yan Zhang4,∗, Ji-Cheng Lv1,2,3, Su-Fang Shi1,2,3, Xu-Jie Zhou1,2,3, Li-Jun Liu1,2,3 and Hong Zhang1,2,3

1Renal Division, Peking University First Hospital, Peking University Institute of Nephrology, Beijing, China, 2Key Laboratory of Renal Disease, Ministry of Health of China, Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing, China, 3Research Units of Diagnosis and Treatment of Immune-Mediated Kidney Diseases, Chinese Academy of Medical Sciences, Beijing, China and 4Renal Division, Beijing Yanqing Hospital of Traditional Chinese Medicine, Beijing, China

∗C.T. and X.Y.Z. contributed equally to this work
Correspondence to: Li-Jun Liu; E-mail: lijun.liu@aliyun.com.

ABSTRACT
Background. The visit-to-visit variability (VVV) in blood pressure (BP) is an important risk factor for stroke and coronary heart disease and may also be associated with kidney damage and the development of chronic kidney disease (CKD). Data on the association between VVV in BP and the risk of CKD progression among patients with immunoglobulin A nephropathy (IgAN) are limited. We aimed to evaluate the relationships of variability in BP with the progression of IgAN.

Methods. We assessed 1376 patients with IgAN at Peking University First Hospital. The main VVV in BP was expressed as the standard deviation (SD), coefficient of variation (CV) and average real variability (ARV). The associations of variability in BP with composite kidney disease progression events, defined as a 50% decline in estimated glomerular filtration rate (eGFR) and kidney failure, were examined using Cox models.

Results. During a median follow-up of 44.1 months (interquartile range 23.0–76.7), 247 (18.0%) patients experienced composite kidney disease progression events. With a higher SD in systolic BP (SBP) values, the risk of kidney disease progression events increased [hazard ratio [HR] 1.07 [95% confidence interval (CI) 1.03–1.11]; P < .001] after maximal adjustment, including baseline SBP and mean SBP during the first 12-month period. Using the first quartile of SD SBP values as the reference, the risk of composite kidney disease progression events was higher among patients with higher SD SBP values; the HR was 2.12 (95% CI 1.31–3.44) in the highest quartile (P for trend < .001). A similar trend could be observed when analysing the SD of diastolic BP, but the risk was not significantly increased. The associations were similar when analysed with the CV and ARV.

Conclusion. SBP variability was significantly associated with kidney disease progression in IgAN.
INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and the major cause of chronic kidney disease (CKD) and renal failure [1]. Of note, hypertension remains the most prevalent clinical manifestation of IgAN and the prevalence rate is 63.3% [2]. Hypertension, proteinuria and decreased estimated glomerular filtration rate (eGFR) are well-known clinical predictors of renal outcome in IgAN. Although the best therapeutic strategy to be applied to all patients with IgAN has not yet been identified, antihypertensive treatment, especially renin–angiotensin–aldosterone system inhibitors (RAASi) treatment is paramount to reduce the loss of renal function [3]. Blood pressure variability is important in the diagnostic and therapeutic management of hypertension [4]. There is growing evidence that visit-to-visit variability (VVV) in blood pressure (BP), defined as the variation in BP, is an important risk factor for stroke, coronary heart disease and mortality [5]. In terms of renal outcomes, previous studies have also suggested that increased VVV in BP may be associated with kidney damage and the development of CKD [6]. However, relatively little is known about VVV in BP in patients with IgAN, because most previous studies have focused on mean BP or short-term variability in BP [2, 7, 8].

Our aim was to conduct a retrospective study of VVV in BP in a large cohort of patients with IgAN. We hypothesized that greater variability in systolic BP (SBP) or diastolic BP (DBP) would be associated with a greater risk of CKD progression among IgAN patients.

MATERIALS AND METHODS

Study population

Our study is a retrospective analysis of a single-centre cohort. We reviewed the medical records from our IgAN registration database at Peking University First Hospital from 2003 to 2021. The main inclusion criteria were patients with IgAN confirmed by renal biopsy with CKD stage 1–4. The diagnosis of IgAN was based on the dominant deposition of IgA in the mesangial area, as observed with immunofluorescence. The main exclusion criteria included patients with crescentic IgAN (defined by crescents in >50% of the glomeruli); patients with secondary IgAN, such as IgA vasculitis, systemic lupus erythematosus and rheumatic disease; and patients without baseline or follow-up data. Patients with <18 months of follow-up were also excluded. All patients were followed up regularly every 3–12 months.

This study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Peking University First Hospital Clinical Research Ethics Committee.
BP and VVV

At each visit, the patients’ BP was measured by trained clinic staff using an automated device (OMRON 750 CP; Otsuka Medical, Tokyo, Japan), with repeat measurements after at least 5 min of quiet rest.

All available BP readings taken during any office visits within the Peking University Health System and recorded in patients’ electronic medical records were extracted. Variability was assessed using three metrics: intra-individual standard deviation (SD) of BP (SBP and DBP) across visits, the coefficient of variation (CV) calculated as SD/mean [9] and the average real variability (ARV) across the visits. The ARV is the average absolute difference between successive BP measurements, and in contrast with SD and CV, it takes the order of the BP measurements into account [10].

We analysed BP measurements during a 12-month period after the initial outpatient measurement to characterize the VVV of BP. Fig. 1 shows the timeline for the measurement of BP and outcome ascertainment of this study. To increase the accuracy of the estimates, patients with fewer than four visit records during the first 12 months of follow-up were excluded from this study.

**Covariates**

Clinical data, including age, sex, diabetes, body mass index (BMI), 24-hour urine protein excretion, SBP, DBP and serum creatinine (SCr) levels at the time of kidney biopsy and at each visit were collected. In order to assess the VVV of BP, the ‘baseline’ was defined as 12 months after patients were first included in our follow-up cohort. The mean SBP and DBP and time-averaged (TA) proteinuria were calculated during the assessment period. The mean SBP and DBP were defined as the average of all available SBP and DBP records. TA proteinuria was calculated as the average of all available values, if any [11]. The use of other medications that might affect BP, including corticosteroids (CSs), other immunosuppressive (IS) agents and antihypertensives, was also recorded. The eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula using SCr [12]. Histopathologic elements were evaluated according to the Oxford classification. All assays were performed in the Department of Clinical Laboratory of Peking First Hospital using standard methods.

For analysis of the associations between VVV and the composite kidney disease progression outcome, patients were divided into four groups according to the quartiles of intra-individual SD of BP, CV of BP and ARV of BP.

**Outcomes and follow-up**

The main analysis evaluated the association between VVV in BP and kidney disease progression during the study. For each outcome, visits after the event occurrence were excluded from evaluation. The outcome was defined as a 50% decrease in eGFR from baseline or end-stage kidney disease (ESKD). ESKD was defined as an eGFR <15 ml/min/1.73 m² or the need for kidney replacement therapy (KRT), including haemodialysis, peritoneal dialysis or kidney transplantation.

Each patient was followed until the date of incidence of an outcome event, death or the last follow-up visit, whichever occurred first.

**Statistical analyses**

Quantitative variables are presented as means ± standard deviations (SDs) and were compared using a t-test for normally distributed data. Non-normally distributed data are summarized as medians and interquartile ranges (IQRs) and were compared using the Mann–Whitney test. Categorical data are expressed as percentages or frequencies and were assessed with the chi-squared test.

For analysis of the associations between VVV and the composite kidney disease progression outcome, patients were divided into four groups according to the quartiles of intra-individual SD of BP, CV of BP and ARV of BP. Cox proportional hazards models were used to generate hazard ratios (HRs) and associated 95% confidence intervals (CIs) for outcomes. Each variability metric was assessed as a continuous variable and quartiles, using the lowest quartile as a reference group. Three models of adjustments were performed: model 1, which was adjusted for age, sex, diabetes, BMI, baseline proteinuria, eGFR and SBP or DBP; model 2, which was adjusted for all variables in model 1 as well as TA proteinuria, Oxford classification (MEST-C scores) and the use of RAASi, other antihypertensive medications (β-blockers, α-blockers, calcium channel blockers, diuretics), CSs or ISs during the follow-up period; and model 3, which was adjusted for the variables in model 2 with additional adjustment for the mean SBP during the first 12-month period when evaluating the variability in SBP or the mean DBP when evaluating DBP variability. Because SBP is generally considered to be a stronger risk factor for outcomes than DBP [13], exploratory analyses assessing possible modifications of the association between SD SBP and kidney disease progression were also performed for the following variables: age (<35 versus ≥35 years), sex, BMI (<24 versus ≥24 kg/m²), baseline proteinuria (<1 versus ≥1 g/day), TA proteinuria (<1 versus ≥1 g/day), baseline SBP (<120 versus ≥120 mmHg), mean SBP during the first 12-month period (<120 versus ≥120 mmHg) and use of CSs or ISs (yes versus no).

A two-tailed P-value <.05 was considered statistically significant in all analyses. All analyses were performed using SPSS Statistics version 22.0 (IBM, Armonk, NY, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).
RESULTS

Characteristics of study participants

A total of 1376 patients with IgAN satisfied the inclusion and exclusion criteria. The general characteristics of the study participants are presented in Table 1. There were 712 (51.7%) men and the mean age was 37.1 ± 13.3 years. The baseline proteinuria level was 0.62 g/day (IQR 0.29–1.31) and the mean eGFR was 72.16 ± 26.21 ml/min/1.73 m².

The SD SBP, CV SBP and ARV SBP were 9.1 ± 3.7 mmHg, 7.5 ± 2.9% and 10.4 ± 4.7 mmHg, respectively. The corresponding DBP parameters were 6.5 ± 2.5 mmHg, 8.5 ± 3.2% and 7.5 ± 3.2 mmHg, respectively. Patients were divided into four groups according to the quartiles of SD SBP values (Table 1). All BP parameters increased with the increase in SD SBP from quartile 1 (Q1) to Q4. Moreover, participants in the top quartile of SD SBP were older, had a lower eGFR and had a higher BMI at baseline. During the follow-up period, these participants had a higher TA proteinuria level, required more concomitant antihypertensive medication use and had a higher rate of CS use.

Participants in the highest quartile of DBP variability were more likely to have a lower eGFR and higher proteinuria level at baseline. They also had a higher TA proteinuria value during follow-up (Supplementary Table 1).

After a median follow-up of 44.1 months (IQR 23.0–76.7), 43 (3.1%) patients were lost to follow-up and 247 (18.0%) patients reached composite kidney outcomes, namely, there were 237 (17.2%) patients with a 50% decline in eGFR and 83 (6.0%) with kidney failure.

Variability in SBP and outcomes

The adjusted HRs by intra-individual SD of SBP are displayed in Table 2. In the Cox proportional hazards model, there was a significant positive relationship of SD of SBP with the risk of composite kidney disease progression [HR 1.07 (95% CI 1.03–1.11), \( P = .001 \)] after maximal adjustment including baseline SBP and...
the mean BP. Using the first quartile of SD SBP levels as the reference, the risk of composite kidney disease progression events was higher among patients with higher SD SBP levels: the HRs were 1.62 (95% CI 0.99–2.66) in the second quartile, 1.95 (95% CI 1.21–3.14) in the third quartile and 2.12 (95% CI 1.31–3.44) in the fourth quartile (P for trend = .019) (Table 2 and Fig. 2). The association was similar for CV SBP (Supplementary Table 2) and ARV SBP (Supplementary Table 4). The association of VVV of SBP was qualitatively similar when we used CV or ARV, although the trend was not significantly obvious as for ARV (P = .071).

**Variability in DBP and outcomes**

Table 3 displays the associations of long-term variability in DBP (assessed as intra-individual SD) and clinical outcomes. In the Cox regression model, SD DBP level was first analysed as a continuous variable, and we found a trend that a higher SD DBP was also associated with kidney disease progression [HR 1.07 (95% CI 1.01–1.13), P = .027]. However, compared with the patients in the first quartile, patients in the highest quartile did not have a significantly increased risk of composite kidney disease progression in fully adjusted models [HR 1.49 (95% CI 0.96–2.30), P = .074] (Table 3). The analysis with CV DBP and ARV DBP showed similar results (Supplementary Tables 3 and 5).

**Exploratory subgroup analyses**

We further performed exploratory subgroup analyses to assess the effect of SD SBP on the primary outcome in various subgroups. Variables, including age, sex, BMI, baseline SBP, mean SBP during the first 12-month period and the use of CSs or ISs, did not obviously modify the association between SD SBP and primary outcome (P for interactions > .05). However, the association between variability in SBP and risk of kidney disease progression was significantly stronger among patients with less proteinuria (<1 g/day) during the assessment period (P for interaction = .021; Figure 3).

**DISCUSSION**

Our study demonstrated that higher SD SBP was significantly associated with kidney disease progression among patients with IgAN. The association persisted after multivariable adjustment for important confounders such as baseline eGFR, proteinuria and mean BP. Similar associations also tended to be present for CV and ARV. These results suggest the potential need for consistent BP control in non-dialysis-dependent IgAN patients.

Recently, long-term BP variability has been shown to be significantly associated with all-cause and cardiovascular disease (CVD) mortality, CVD events, stroke and myocardial infarction, independent of mean BP [14]. In fact, VVV can provide valuable prognostic information even when derived from ‘non-standardized’ BP values from routine office visits [15]. The effects of BP variability on renal function have also been explored in several studies. Viauzzi et al. [16] showed that increased long-term BP variability could predict CKD in patients with type 2 diabetes. The post hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial also suggested that patients with the highest SD SBP had a 2.05-fold (95% CI 1.25–3.36) higher risk for incident ESKD or a 50% decline in eGFR, but more than 40% of them had a history of diabetes, myocardial infarction, stroke or other atherosclerotic CVD [17]. For people without diabetes and CVD, BP variability still has significant prognostic value for renal function decline, but the main population was patients with hypertension and no underlying history of CKD [18]. In China, IgAN represents the most common form of primary glomerulonephritis, while hypertension remains the most prevalent clinical manifestation of IgAN [19]. Our study showed a significantly greater risk of kidney disease progression among patients within the top quartile of VVV in SBP, and the proportion of diabetic patients in our cohort was relatively small. To the best of our knowledge, this is the first report on a relationship between VVV in BP and the development of IgAN in a sizable cohort. Notably, this association was not attenuated by adjustment for baseline or mean BP or for proteinuria or other commonly accepted predictors of poor outcomes in IgAN.

The potential biological mechanisms underlying the association of long-term BP variability and renal impairment may be related to the pathological manifestations of IgAN. Intrarenal arterial and arteriolar lesions, including thickening of the intimal wall and hyaline, can commonly be observed in IgAN patients with hypertension [20]. Increasing numbers of normotensive IgAN patients are also presenting with ischaemic renal injury [21]. Long-term poor BP control causes haemodynamic changes in the renal microcirculation, which may aggravate ischaemic renal injury and lead to poor renal prognosis [22]. Moreover, IgAN is often associated with increased arterial stiffness and renin–angiotensin system activity [23]. Fluctuations in BP can definitely exacerbate arteriolosclerosis and activate the renin–angiotensin system activity [23].
angiotensin system [24]. Thus long-term BP variability may play an important role in IgAN.

Of interest, patients with proteinuria <1 g/day were more likely to be adversely affected by SBP variability in the subgroup analysis. The possible reason may be that these patients were more likely to show fewer risk factors and comorbidities and were therefore more vulnerable to SBP variability. In addition, persistent proteinuria in patients with IgAN, typically >1 g/day, is strongly associated with poorer kidney outcomes [25, 26], which may overshadow the impact of SBP variability. Furthermore, we cannot ignore the involvement of therapeutic factors. During outpatient follow-up, patients with higher proteinuria often receive intensive BP-lowering therapy, and the prognostic impact of VVV may be reduced among patients with well-controlled BP through timely intervention with medication. Clinicians should pay additional attention to fluctuations if the BP of patients increases over time.

In addition, recent studies have also shown that dietary sodium and potassium can jointly modulate short-term BP variability [27]. Unfortunately, not all patients in our cohort had regular monitoring of urinary sodium levels.

On the other hand, although the relationship between patients in the highest quartile of SD DBP and primary outcome was not statistically significant, the increase in SD DBP, as a continuous variable, was still a risk factor for kidney disease progression. One explanation was that we had a relatively small number of people included in this study, which may have made the results less obvious. In addition, the fluctuation in variability in DBP was also relatively small in our cohort, which may have led us to underestimate its impact on the primary outcome.

Our study has several limitations. First, as this is a single-centre retrospective study, the size of our cohort and the number of people included were relatively small compared with other studies. Other factors that may affect BP variability, such as...
Table 3: Incidence and HR of CKD progression outcomes by SD of DBP.

| Quartiles of SD of DBP, mmHg | Outcome | Q1 (<4.8) | Q2 (4.8–6.3) | Q3 (6.3–8.1) | Q4 (≥8.1) | P for trend | Per SD |
|-----------------------------|---------|-----------|--------------|--------------|------------|------------|--------|
| CKD progression | Events/at risk, n | 38/344 | 44/344 | 71/344 | 94/344 |          |        |
| Crude model | Reference | 1.21 (0.78–1.88) | 1.86 (1.25–2.76)** | 2.24 (1.53–3.28)*** | <.001 | 1.15 (1.10–1.21)*** |        |
| Model 1 | Reference | 0.96 (0.63–1.56) | 1.32 (0.87–1.99) | 1.45 (0.97–2.16) | .021 | 1.06 (1.00–1.11)* |        |
| Model 2 | Reference | 0.90 (0.56–1.45) | 1.38 (0.90–2.13) | 1.45 (0.96–2.19) | .018 | 1.06 (1.01–1.21)* |        |
| Model 3 | Reference | 0.91 (0.56–1.46) | 1.39 (0.90–2.16) | 1.49 (0.96–2.30) | .019 | 1.07 (1.01–1.13)* |        |

CKD progression events were a 50% decrease in the eGFR or kidney failure.

Model 1 was adjusted for age, sex, diabetes, BMI, baseline proteinuria, eGFR and DBP.

Model 2 was adjusted for all variables in model 1 plus log-transformed TA proteinuria, which was a time-varying covariate, Oxford classification (MEST-C scores) and the use of RAASis, other antihypertensive medications (α-blockers, β-blockers, calcium channel blockers, diuretics), CSs or ISs during the first 12-month period.

Model 3 was adjusted for covariates in model 2 plus the mean DBP during the first 12-month period.

"P < .05, **P < .01, ***P < .001.

Figure 3: Stratified analyses of the effect of each 1-SD increase in SD SBP on the renal composite outcome.

smoking status, blood lipid levels and a history of other cardiovascular diseases, could not be considered. In addition, the combination of antihypertensive treatment during the follow-up may have caused some bias in the analysis. Therefore this study was hypothesis generating, and we cannot estimate a predictive value. We believe that validation of external cohorts and other multicentre clinical studies with larger populations are needed to confirm these findings.

CONCLUSION

Our study suggests that VVV in SBP is significantly associated with the risk of kidney disease progression among patients with IgAN. Beyond that, in addition to monitoring BP targets, clinicians should remain cautious about visit-to-visit fluctuations in BP. Therefore, if our results are further confirmed by future studies, identification and control of VVV in addition to BP management should be an important strategy to slow the loss of kidney function in patients with IgAN.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

L.J.L. was responsible for the research idea and study design. C.T. and X.Y.Z. were responsible for data acquisition. C.T. was responsible for data analysis/interpretation and statistical analysis. J.C.L., S.F.S., X.J.Z., L.J.L. and H.Z. were responsible for supervision and mentorship. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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