Ambulatory blood pressure is better associated with target organ damage than clinic blood pressure in patients with primary glomerular disease

CURRENT STATUS: UNDER REVIEW

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DOI:
10.21203/rs.2.20536/v1

SUBJECT AREAS
Urology & Nephrology

KEYWORDS
Ambulatory blood pressure, Clinic blood pressure, Target organ damage, Primary glomerular disease
Abstract

Background: Blood pressure is an important and modifiable cardiovascular risk factor. Ambulatory blood pressure monitoring (ABPM) provides valuable prognostic information in patients with chronic kidney disease (CKD), yet little is known about the association of various types of BP measurements with target organ damage (TOD) in patients with primary glomerular disease. The goal of this study was to investigate whether ambulatory blood pressure is better associated with TOD than clinic blood pressure in patients with primary glomerular disease.

Methods: 1178 patients with primary glomerular disease were recruited in this cross-sectional study. TOD were assessed by the following 4 parameters: left ventricular mass index (LVMI or LVH, left ventricular hypertrophy), estimated glomerular filtration rate (eGFR<60ml/min/1.73m^2), albumin-to-creatinine ratio (ACR≥30mg/g) and carotid intima-media thickness (cIMT) or plaque. Receiver operating characteristic (ROC) curve and multivariate logistic regression analyses were used to evaluate the relationship between ambulatory or clinic systolic blood pressure (SBP) indexes and TOD.

Results: Among 1178 patients (mean age, 39 years, 54% men), 116, 458, 1031 and 251 patients had LVH, eGFR < 60 ml/min/1.73m^2, ACR≥30mg/g and cIMT≥0.9mm or plaque respectively. Area under ROC curves for TOD in ambulatory SBP, especially nighttime SBP, was greater than that in clinic SBP ( P <0.05). Multivariate logistic regression analyses showed that 24h SBP, daytime SBP and nighttime SBP were significantly associated with LVH, eGFR<60 ml/min/1.73m^2 and ACR≥30mg/g after adjustment for clinic SBP, while the association of clinic SBP was attenuated after further adjustment for nighttime SBP.

Conclusions: Ambulatory blood pressure, especially nighttime blood pressure, is superior to clinic blood pressure in estimating TOD in patients with primary glomerular disease.

Key Words: Ambulatory blood pressure, Clinic blood pressure, Target organ damage,
Primary glomerular disease

Background

Chronic kidney disease (CKD) is a worldwide public health problem. In these patients, hypertension is prevalent and considered the leading risk factor for death, which contributes to 45% of male deaths and 46% of female deaths. Hypertension is also among the most important modifiable risk factors for end-stage renal disease (ESRD). Therefore, appropriate evaluation and management of hypertension to achieve blood pressure (BP) goals in CKD patients is necessary and valuable.

Ambulatory blood pressure monitoring (ABPM) could provide detailed information on BP over a 24 h period, and it is unanimously recommended by guidelines for BP management. Previously, we have reported the high prevalence and prognostic value of nighttime hypertension in CKD patients compared with clinic blood pressure. Recent evidence from large-scale cohort study also suggests that higher 24-hour and nighttime blood pressure measurements were significantly associated with greater risks of death and cardiovascular disease, even after adjusting for other office-based or ambulatory blood pressure measurements. All these data suggested ABPM was better than clinic blood pressure when assessing target organ damage (TOD) and prognosis in CKD patients.

However, CKD patients with different etiologies, like primary glomerular disease and diabetic kidney disease, were enrolled in prior studies at the same time. Primary glomerular disease and diabetic kidney disease were two main causes of CKD in many countries, but show different BP characteristics and prognosis. Patients with diabetic kidney disease seems to have a worse outcome. The percentage of patients with diabetic kidney disease or diabetes mellitus at enrollment was 11–65%. Once in the period of massive albuminuria, the progression rate of diabetic kidney disease to ESRD is about 14
times that of other renal diseases, indicating patients with diabetic kidney disease would have more severe subclinical TOD, so it might be a big difference on the priority of ABPM between patients with and without diabetic kidney disease. It is very important to evaluate various types of BP measurements, especially ABPM, and assess the strength of their associations with TOD, focusing on patients with primary glomerular disease considering primary glomerular disease continues to be the very common in our country. Accordingly, the objective of this study is to investigate whether ambulatory blood pressure is better associated with TOD than clinic blood pressure in patients with primary glomerular disease.

Methods

Study population

The study protocol was approved by the ethics committee of the Fifth Hospital of Sun Yat-Sen University (Guangdong, China) and adhered to the Declaration of Helsinki. Informed consent was obtained from each participant. Consecutive patients were recruited from the Fifth Affiliated Hospital of Sun Yat-Sen University (Guangdong, China) between July of 2017 and Nov of 2019. Patients (14–75 years) with primary glomerular disease proved by renal biopsy or clinic findings after exclusion of secondary renal damage factors, were included. Patients were excluded from the study in case of: 1) diabetes mellitus; 2) acute changes in the eGFR > 30% in the previous three months; 3) maintenance dialysis or history of kidney transplantation; 4) cardiovascular disorders (unstable angina pectoris, heart failure, life-threatening arrhythmia, atrial fibrillation, stroke and grade III–IV retinopathy); 5) pregnancy; 6) night work or shift-work employment; 6) intolerance to ABPM or invalid ABPM data; 7) inability to communicate and comply with all of the study requirements; Finally, a total of 1178 patients were enrolled in this study (Fig. 1).

Ambulatory and clinic blood pressure monitoring
Patients underwent 24-hour ABPM using a Mobil-O-Graph Monitor (I.E.M. GmbH, Stolberg, Germany). Appropriate cuff size was chosen based on the arm circumference and directly placed on the non-dominant arm. The monitor was programmed to measure every 15 minutes during the day (7:00 am to 10:00 pm), and every 30 minutes during the night (10:00 pm to 7:00 am). Monitoring was performed on a working day. Patients were instructed to maintain their usual but not strenuous level of activity, and to keep motionless at the time of measurement. ABPM data were invalid in cases of: 1) > 30% of measurements were lacking; 2) > 3 hours data were missing; 3) sleep time at night was < 6 or > 12 hours during monitoring.

Clinic BP was measured at the physician’s office with a standard mercury sphygmomanometer after a 5-minute rest in a sitting position. For all patients, sphygmomanometric measurements were recorded by the same physician, who was not aware of the results of ABP recordings. Reported values of clinic BP were the mean of 2 or 3 measurements at 1–2 min intervals, recorded during the 2 days in which the ABPM device was installed and removed.

Cardiac, renal and carotid assessment

Cardiac structure and function were assessed by 2 investigators trained for this purpose before starting the study. Linear measurements of interventricular septal wall thickness (IVSd), end-diastolic left ventricular internal dimension (LVIDd), and posterior wall thickness (PWTd) were obtained from M-mode tracings, using 2-dimensional echocardiography. LVM was calculated using the Duverex method. The left ventricular mass index (LVMI) was obtained by calculating the ratio of LVM to body surface area.

Concentrations of serum creatinine (Scr) were measured by an enzymatic method traceable to isotope dilution mass spectrometry. The estimated Glomerular Filtration Rate (eGFR) was calculated using 2009 Chronic Kidney Disease Epidemiology Collaboration
(CKD-EPI) creatinine equation. Awaking(7:00 am to 10:00 pm), bedtime(10:00 pm to 7:00 am) and 24-hour urine samples were collected to detect excretion levels of urinary albumin, protein, and creatinine. Patients were asked to void their bladders at 7:00 am and 10:00 pm to ensure valid results.

Carotid intima-media thickness (cIMT) was determined by averaging 3 measurements taken on each carotid artery (in anterior, lateral and posterior directions), measuring the distance between the leading edge of the lumen-intima interface, and the leading edge of the collagenous upper layer of the adventitia using high-resolution B mode ultrasonography. Measurements were taken in areas free of obvious atherosclerotic plaques around the level of the carotid bifurcation.

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ultrasonography. Measurements were taken in areas free of obvious atherosclerotic
plaques around the level of the carotid bifurcation.

Collection of other data

Information including age, sex, height, weight, smoking and alcohol consumption status,
antihypertensive medication were obtained at the time of the BP measurement.
Laboratory data (hemoglobin, albumin, calcium, phosphorus, intact parathyroid hormone,
triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density
lipoprotein cholesterol, uric acid and blood urea nitrogen) were obtained at the initial
study visit. Blood samples were taken in the morning and analyzed using a 7180
Biochemistry Autoanalyzer (Hitachi, Tokyo, Japan) with reagents from Roche Diagnostics
(Mannheim, Germany).

Definitions

CKD was divided into 5 stages and defined as the presence of kidney damage or
decreased renal function (eGFR < 60 mL/min per 1.73 m2) for ≥ 3 months according to the
Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline.
Clinic hypertension was defined as clinic blood pressure (BP) ≥ 140/90 mmHg and
ambulatory blood pressure (ABP) was defined as 24-hour BP ≥ 130/80 mmHg. Masked
hypertension was defined as a normal clinic BP (≤ 140/90 mm Hg) and an elevated ABP (> 130/80 mm Hg). White coat hypertension was regarded as increased clinic BP (> 140/90 mm Hg) and normal ABP (≤ 130/80 mmHg). Normotension was defined as both
clinic BP < 140/90 mm Hg and ABP < 130/80 mmHg; Sustained hypertension was regarded
as clinic BP ≥ 140/90 mm Hg and ABP ≥ 130/80 mmHg. Nighttime hypertension was defined
as nighttime systolic BP (SBP) ≥ 120 mm Hg or/and diastolic BP (DBP) ≥ 70 mmHg. Isolated
nighttime hypertension was defined as daytime BP < 135/85 mm Hg and nighttime BP ≥ 120/70 mmHg. Participants with a reduction in SBP of ≥ 10% at night-time compared with daytime were considered to have a “dipper” pattern, and an “extreme dipper pattern” referred to a > 20% reduction at nighttime. A “non-dipper” pattern referred to a < 10% reduction at nighttime and a “reversed dipper pattern” referred to higher SBP at nighttime compared with daytime. Target organ damage (TOD) was defined if it met any of four conditions: 1) left ventricular hypertrophy (LVH), namely LVMI ≥ 125 g/m2 (man) or ≥ 120 g/ m2 (woman); 2) eGFR < 60 mL/ min per 1.73 m^2; 3) Urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g; 4) cIMT ≥ 0.9 mm or existence of carotid plaque in ultrasonography.

Statistical analysis

Statistical analysis was performed with SPSS 25.0 (IBM Corp., Armonk, NY) and Medcalc 18.9(Broekstraat, Mariakerke, Belgium). Descriptive statistics were mean ± SD for continuous variables or median (25-75th interquartile range) for non-normality variables. Frequency and percentage were used for categorical variables. To analyze the sensitivity and specificity of different BP indexes in relationship to TOD:LVH,eGFR < 60 ml/min per 1.73 m^2,ACR ≥ 30 mg/g,cIMT ≥ 0.9 mm or carotid plaque, we generated and compared receiver operating characteristic (ROC) curves, including area under the curve (AUC) and their 95% CIs. Considering each TOD may be affected by other important factors, and clinic and ambulatory SBP may have different prognostic value, we established 12 multivariate adjusted logistic regression models in all. Model 1-3, 4-6, 7-9 and 10-12 corresponded with LVH,eGFR < 60 ml/min per 1.73 m^2,ACR ≥ 30 mg/g,cIMT ≥ 0.9 mm or carotid plaque, respectively. Model 1 included adjustment for age, sex, BMI, smoking, alcohol consumption status, hemoglobin, albumin, eGFR and ACEI/ARB use. Model 4 included adjustment for age, sex, BMI, smoking, alcohol consumption status, hemoglobin.
albumin, ACR, iPTH, uric acid, calcium* phosphate product and ACEI/ARB use. Model 7 included adjustment for age, sex, BMI, smoking, alcohol consumption status, hemoglobin, albumin and uric acid. Model 7 included adjustment for age, sex, BMI, smoking, alcohol consumption status, eGFR, LDL-C and statin use. Model 2, 5, 8, 11 included adjustment for the variables in Model 1, 4, 7, 10 respectively and additional adjustment for clinic SBP when examining 24 h/daytime/nighttime SBP as the independent variable. Model 3, 6, 9, 12 included adjustment for the variables in Model 1, 4, 7, 10 respectively and additional adjustment for nighttime SBP when examining clinic SBP as the independent variable. Probability values were 2-tailed and P < 0.05 was considered statistically significant for all comparisons.

Results

Demographic and clinical characteristics of the study population

Mean age of the study population was 38.8 years, and 53.7% was male. A total of 752 patients (63.8%) had renal biopsy reports. The number of patients with IgA nephropathy, mesangial proliferative glomerulonephritis (MsPGN), minimal change disease (MCD), membranous nephropathy (MN); focal segmental glomerulosclerosis (FSGS) and membranoproliferative glomerulonephritis (MPGN) was 354, 17, 38, 162, 36 and 9, respectively; 18.5% of patients were current smokers, and 101 patients (8.6%) consumed alcohol. The prevalence of LVH, eGFR < 60 ml/min/1.73 m², ACR ≥ 30 mg/g, cIMT ≥ 0.9 mm or plaque was 9.8%, 38.9%, 87.5%, 21.3%, respectively (Table 1).

Table 1

| Parameters               | Value          |
|--------------------------|----------------|
| No. of Patients          | 1178           |
| Age(years)               | 38.8 ± 14.0    |
| Male[n(%)]               | 633(53.7)      |
| BMI(kg.m⁻²)              | 22.9 ± 3.5     |
| Smoker[n(%)]             | 218(18.5)      |
| Drinker[n(%)]            | 101(8.6)       |
| Primary Glomerular Diseases |            |
| IgA[n(%)]                | 354(30.1)      |
| Disease                | n(%)       |
|-----------------------|------------|
| MsPGN                 | 17(1.4)    |
| MCD                   | 38(3.2)    |
| MN                    | 162(13.8)  |
| FSGS                  | 36(3.1)    |
| MPGN                  | 9(0.8)     |
| Others                | 562(47.7)  |

Medication

| Medication          | n(%)       |
|---------------------|------------|
| ACEI or ARB         | 576(48.9)  |
| β-blocker           | 179(15.2)  |
| CCB                 | 362(30.6)  |
| α-blocker           | 71(6.0)    |
| Statin              | 200(17.0)  |

Antihypertensive medication use

| Use                  | n(%)       |
|----------------------|------------|
| 0                    | 347(29.5)  |
| 1                    | 570(48.4)  |
| 2                    | 172(14.6)  |
| 3                    | 78(6.6)    |
| 4                    | 11(0.9)    |

Laboratories

| Parameter          | Value       |
|--------------------|-------------|
| Hemoglobin [g/L]   | 124.8 ± 27.6|
| Albumin [g/L]      | 34.5 ± 9.0  |
| Total cholesterol [mmol/L] | 5.3(4.3,6.9) |
| LDL cholesterol [mmol/L] | 3.2(2.4,4.4) |
| HDL cholesterol [mmol/L] | 1.2(1.0,1.5) |
| Triglycerides [mmol/L] | 1.5(1.0,2.3) |
| Calcium [mg/dL]    | 8.8 ± 0.8   |
| Phosphate [mg/dL]  | 3.7 ± 0.4   |
| Calcium*            | 35.3 ± 9.9  |
| Phosphate [mg^2/dL^2] | 4.9(3.4,8.5) |
| iPTH [pmol/L]       | 4.9(3.4,8.5) |
| Uric acid [µmol/L]  | 442.8 ± 132.7 |
| Creatinine [µmol/L] | 97.0(68.3,200.0) |

CKD Stages

| Stage | n(%)       |
|-------|------------|
| 1     | 489(42.4)  |
| 2     | 231(19.6)  |
| 3     | 165(14.0)  |
| 4     | 96(8.1)    |
| 5     | 197(16.7)  |

eGFR-EPI [ml/min/1.73 m^2] | 78.0(30.0,108.0) |

eGFR < 60 ml/min/1.73 m^2 [n(%)] | 458(38.9) |
| ACR [mg/g]           | 302.4(85.6,851.2) |
| ACR ≥ 30 mg/g [n(%)] | 1031(87.5) |
| cIMT-left [mm]       | 0.7 ± 0.2 |
| cIMT-right [mm]      | 0.7 ± 0.2 |
| cIMT ≥ 0.9 mm or plaque [n(%)] | 251(21.3) |
| Left ventricular mass index [g/m^2] | 92.1 ± 24.4 |
| Left ventricular hypertrophy [n(%)] | 116(9.8) |

Numbers are mean ± SD, median (25-75th interquartile range) or number (percentage). MsPGN, mesangial proliferative glomerulonephritis; MCD, minimal change disease; MN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; LDL, low-density lipoprotein; HDL, high-density lipoprotein; iPTH, intact parathyroid hormone. ACR, albumin-to-creatinine ratio; cIMT, carotid intima-media thickness.

Characteristics of ABPM in the study population

The prevalence of nighttime hypertension in these patients was 62.2%, while 272 patients (23.1%) had isolated nighttime hypertension. A total of 609 (51.7%) patients had non dipper pattern and 197 (16.7%) patients had reversed dipper pattern, while only 341 (28.9%) patients had a dipper pattern.
129 (10.9%) of patients had white-coat hypertension and 175 (14.9%) had masked hypertension.

(Table 2)

| Parameters                        | Value      |
|-----------------------------------|------------|
| Clinic SBP (mmHg)                | 135.9 ± 23.1 |
| Clinic DBP (mmHg)                | 85.8 ± 14.4 |
| 24 h SBP (mmHg)                  | 126.3 ± 16.7 |
| 24 h DBP (mmHg)                  | 78.9 ± 11.3  |
| Daytime SBP (mmHg)               | 127.8 ± 16.7 |
| Daytime DBP (mmHg)               | 80.3 ± 11.4  |
| Nighttime SBP (mmHg)             | 119.6 ± 18.4 |
| Nighttime DBP (mmHg)             | 73.7 ± 12.7  |
| Nighttime hypertension [n(%)]    | 733 (62.2)  |
| Isolated nighttime hypertension [n(%)] | 272 (23.1) |
| Circadian patterns               |            |
| Riser [n(%)]                     | 197 (16.7)  |
| Non dipper [n(%)]                | 609 (51.7)  |
| Dipper [n(%)]                    | 341 (28.9)  |
| Extreme dipper [n(%)]            | 31 (2.6)    |
| Clinic-ambulatory BP status      |            |
| Normotension [n(%)]              | 446 (37.9)  |
| White-coat HBP [n(%)]            | 129 (10.9)  |
| Masked HBP [n(%)]                | 175 (14.9)  |
| Sustained HBP [n(%)]             | 428 (36.3)  |

Receiver-Operating Curve Analysis for Prediction of target organ damages

In receiver-operating curve analysis, all SBPs were significant predictors of LVH. Areas under the curve (AUC) were 0.779, 0.770, 0.760, 0.721 for nighttime SBP, 24 h SBP, daytime SBP and clinic SBP respectively. What’s more, nighttime and 24 h SBP ROC curves had greater AUC compared with clinic SBP in detecting LVH (P < 0.05).

When prediction of eGFR < 60 ml/min/1.73 m², AUC were 0.756, 0.762, 0.756, 0.725 for nighttime SBP, 24 h SBP, daytime SBP and clinic SBP respectively, and statistical analysis showed daytime, nighttime and 24 h SBP had great AUC compared with clinic SBP in detecting eGFR < 60 ml/min/1.73 m² (P < 0.05).

When considering ACR ≥ 30 mg/g, AUC were 0.671, 0.654, 0.647, 0.629 for nighttime SBP, 24 h SBP, daytime SBP and clinic SBP respectively, and only nighttime SBP had great AUC compared with clinic SBP in detecting ACR ≥ 30 mg/g by statistical analysis (P < 0.05).

Finally, when prediction of cIMT ≥ 0.9 mm or plaque, AUC were 0.680, 0.681, 0.676, 0.694 for
nighttime SBP, 24 h SBP, daytime SBP and clinic SBP respectively, and statistical analysis did not show any difference between ambulatory SBP and clinic SBP in detecting cIMT ≥ 0.9 mm or plaque. (Fig. 2 and Table 3).

Table 3
Diagnostic performance of different BP indexes for TOD

| TOD assessments | LVH  | eGFR<60 ml/min/1.73 | ACR ≥ 30 mg/g | cIMT ≥ 0.9 mm or plaque |
|-----------------|------|---------------------|--------------|------------------------|
| AUC (95%CI)     |      |                     |              |                        |
| Clinic SBP      | 0.721(0.667, 0.774) | 0.725(0.695, 0.755) | 0.629(0.586, 0.671) | 0.694(0.645, 0.743)   |
| 24 h SBP        | 0.770(0.722, 0.819) | 0.762(0.734, 0.790) | 0.654(0.610, 0.698) | 0.681(0.632, 0.729)   |
| Daytime SBP     | 0.760(0.711, 0.810) | 0.756(0.728, 0.784) | 0.647(0.603, 0.691) | 0.676(0.627, 0.725)   |
| Nighttime SBP   | 0.779(0.733, 0.824) | 0.756(0.728, 0.784) | 0.671(0.627, 0.715) | 0.680(0.632, 0.728)   |
| P value, Z value|      |                     |              |                        |
| 24 h vs. Clinic SBP | 0.048, 1.977 | 0.007, 2.686 | 0.204, 1.272 | 0.570, 0.568   |
| Daytime vs. Clinic SBP | 0.115, 1.578 | 0.026, 2.221 | 0.368, 0.900 | 0.441, 0.771   |
| Nighttime vs. Clinic SBP | 0.028, 2.197 | 0.037, 2.083 | 0.045, 2.008 | 0.587, 0.543   |

Factors associated with target-organ damage by multivariate logistic regression analyses

Multivariate logistic regression analyses were carried out to clarify factors associated with target-organ damage. Higher clinic and ambulatory BPs were significantly associated with higher prevalence of LVH, eGFR < 60 ml/min/1.73 m², and ACR ≥ 30 mg/g (P < 0.05). 24 h SBP, daytime SBP and nighttime SBP were still significantly associated with LVH, eGFR < 60 ml/min/1.73 m² and ACR ≥ 30 mg/g (P < 0.05) after adjustment by clinic SBP. However, the association of clinic SBP with LVH, eGFR < 60 ml/min/1.73 m² and ACR ≥ 30 mg/g (P < 0.05) was attenuated after further adjustment for nighttime SBP (P = 0.133, P = 0.055, P = 0.054, respectively). With respect to cIMT ≥ 0.9 mm or plaque, ambulatory SBP or clinic SBP was not significant in multivariate adjusted models with clinic and 24 h/daytime/nighttime SBP included. (Table 4)
|                | Odds ratio (95% CI), P value |
|----------------|-----------------------------|
|                | Clinic SBP | 24 h SBP | Daytime SBP | Nighttime SBP |
| LVH            |            |          |            |              |
| Unadjusted     | 1.033(1.025, 1.041), <0.001 | 1.063(1.050, 1.076), <0.001 | 1.061(1.046, 1.074), <0.001 | 1.056(1.045, 1.067), <0.001 |
| Model 1(M1)    | 1.016(1.006, 1.025), 0.001 | 1.033(1.018, 1.048), <0.001 | 1.031(1.016, 1.046), <0.001 | 1.030(1.017, 1.043), <0.001 |
| Model 2 (M1 + Clinic SBP) | — | 1.028(1.011, 1.045), 0.001 | 1.025(1.008, 1.042), 0.003 | 1.025(1.011, 1.040), <0.001 |
| Model 3 (M1 + Nighttime SBP) | 1.008(0.998, 1.019), 0.133 | — | — | — |
| eGFR < 60 ml/min per 1.73 m² |            |          |            |              |
| Unadjusted     | 1.041(1.035, 1.048), <0.001 | 1.068(1.058, 1.078), <0.001 | 1.066(1.056, 1.076), <0.001 | 1.059(1.050, 1.068), <0.001 |
| Model 4(M4)    | 1.018(1.008, 1.028), <0.001 | 1.031(1.017, 1.045), <0.001 | 1.030(1.016, 1.044), <0.001 | 1.028(1.015, 1.040), <0.001 |
| Model 5 (M4 + Clinic SBP) | — | 1.024(1.008, 1.041), 0.004 | 1.022(1.006, 1.039), 0.008 | 1.022(1.008, 1.036), 0.001 |
| Model 6 (M4 + Nighttime SBP) | 1.010(1.000, 1.021), 0.055 | — | — | — |
| ACR ≥ 30 mg/g  |            |          |            |              |
| Unadjusted     | 1.023(1.014, 1.032), <0.001 | 1.036(1.024, 1.049), <0.001 | 1.034(1.022, 1.047), <0.001 | 1.038(1.026, 1.050), <0.001 |
| Model 7(M7)    | 1.021(1.010, 1.032), <0.001 | 1.031(1.016, 1.046), <0.001 | 1.029(1.014, 1.044), <0.001 | 1.035(1.020, 1.049), <0.001 |
| Model 8(M7 + Clinic SBP) | — | 1.021(1.004, 1.039), 0.017 | 1.019(1.001, 1.036), 0.035 | 1.028(1.012, 1.044), <0.001 |
| Model 9(M7 + Nighttime SBP) | 1.012(1.000, 1.024), 0.054 | — | — | — |
| cIMT ≥ 0.9 mm or plaque |            |          |            |              |
| Unadjusted     | 1.030(1.021, 1.039), <0.001 | 1.038(1.026, 1.050), <0.001 | 1.038(1.026, 1.050), <0.001 | 1.030(1.020, 1.041), <0.001 |
| Model 10(M10)  | 1.013(1.002, 1.024), 0.017 | 1.015(0.999, 1.031), 0.060 | 1.016(1.000, 1.032), 0.051 | 1.009(0.996, 1.023), 0.165 |
| Model 11 (M10 + Clinic SBP) | — | 1.006(0.987, 1.025), 0.527 | 1.007(0.988, 1.026), 0.463 | 1.002(0.986, 1.017), 0.839 |
| Model 12(M10 + Nighttime SBP) | 1.013(1.000, 1.025), 0.050 | — | — | — |

M1, M4, M7, M10 were short for Model 1, Model 4, Model 7 and Model 10, respectively. Model 1 included adjustment for age, sex, BMI, smoking, alcohol consumption status, hemoglobin, albumin, eGFR and ACEI/ARB use. Model 4 included adjustment for age, sex, BMI, smoking, alcohol consumption status, hemoglobin, albumin, eGFR, ACR, iPTH, uric acid, calcium*phosphate product and ACEI/ARB use. Model 7 included adjustment for age, sex, BMI, smoking, alcohol consumption status, hemoglobin, albumin and uric acid. Model 10 included adjustment for age, sex, BMI, smoking, alcohol consumption status, eGFR, LDL-C and statin use. Model 2, 5, 8, 11 included adjustment for the variables in Model 1, 4, 7, 10 respectively and additional adjustment for clinic SBP when examining 24 h/daytime/nighttime SBP as the independent variable. Model 3, 6, 9, 12 included adjustment for the variables in Model 1, 4, 7, 10 respectively and additional adjustment for nighttime SBP when examining clinic SBP as the independent variable.

Discussion

In this cross section study, we explore and compare associations of different BP indexes with TOD in CKD patients with primary glomerular disease. We found that ambulatory SBP, especially nighttime SBP, performed better than clinic SBP when detecting TOD. What’s more, higher 24 h, daytime and nighttime SBP were significantly associated with TOD in these patients even adjusted clinic SBP in multivariate logistic regression analyses. All these data suggested that ABPM is superior to clinic
blood pressure in estimating TOD in patients with primary glomerular disease, and we should pay
special attention to the use of ABPM in these patients in clinical practice.

Over the past years, ABPM developed into the recommended technique for BP measurement, risk
stratification and classification of hypertension. Compared with clinic BP, ABPM increased the ability
to identify circadian variations in BP and identify daytime and nighttime BP. Prior studies have
consistently demonstrated significant and superior association of ambulatory SBP with TOD in
hypertensive patients, as well as in CKD patients. However, all these data were from CKD patients
with different causes. CKD patients mixed with different etiologies like primary glomerular disease
and diabetic kidney disease, were all included in these studies. Many factors such as glucose,
inflammatory, salt intake would affect blood pressure status, so studies enrolled more diabetic
patients would draw different conclusion compared with studies enrolled fewer diabetic patients. In
previous studies, percentage of patients with diabetic kidney disease or diabetes mellitus at
enrollment is up to 65%.\textsuperscript{12−16} As the high glucose influences the microenvironment of target organ,
including heart, kidney and arteries, patients with diabetic kidney disease showed a more severe
TOD, and progressed to ESRD more quickly than other renal disease, once in the period of massive
albuminuria. It reminds us of different meanings about ABPM in CKD patients with different
etiologies. So we cannot directly extend these conclusions from patients with diabetic and non-
diabetic kidney disease to patients with primary glomerular disease.

Primary glomerular disease is a class of relative consistent etiologies in CKD patients, and still
predominant in hospitalized rural patients in China. Data of ABPM in patients with primary
glomerular disease was very limited and mostly compared with secondary or diabetic kidney disease
in a small sample size.\textsuperscript{7} Patients with primary glomerular disease seems to have a better control of
BP and lower prevalence of abnormal circadian rhythm, which may lead to a big difference on the
priority of ABPM between patients with and without secondary glomerular disease, especially
diabetic kidney disease. Moreover, associations of ABPM with TOD were poorly declared in past studies. Thus, after recruiting a large sample of these population, we evaluate various types of BP measurements—especially ABPM, and assess the strength of their associations with TOD.

The current study strengthened the notion that ABPM, especially nighttime BP carries valuable prognostic information in patients with primary kidney disease. These data confirmed the importance and superiority of ABPM in these patients. Future studies are required to ascertain whether individuals could benefit from BP-lowering interventions targeting the ambulatory monitory results and ultimately reduce cardiovascular events.

Some limitations of our study deserve mention. Firstly, the size of the study population was large but was from a single center. Secondly, all enrolled CKD patients underwent only one ABPM and we could not rule out subsequent changes in ABPM. Thirdly, some patients with non-severe proteinuria or renal damage might have been excluded, leading to bias. Finally, we cannot infer a cause-effect relationship based on our cross-sectional data.

Conclusion

In conclusion, we have provided the first evidence that higher 24 h, daytime, nighttime SBP, better than clinic SBP, were significantly associated with greater prevalence of TOD in CKD patients with primary glomerular disease, after adjustment for demographics and clinical characteristics. Thus, ABPM should be considered optimal and preferred measurement for estimating cardiovascular risk in these patients.

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the Ethics Committee of the Fifth Hospital of Sun Yat-Sen University (Guangdong, China). Participants were required to provide written consent to participate. Written informed consent for participation in the study was obtained where participants are children (under
16 years old) from their parent or guardian.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare no conflict of interests. The results presented in this paper have not been published previously in whole or part, except in abstract format.

**Funding**

There is no funding to declare.

**Authors’ contributions**

Study concept and design: RWW, XQC CW. Acquisition, analysis, and interpretation of data: RWW, XQC, YZ, JT K, YD. Drafting of the manuscript: RWW, XQC. Critical revision of the manuscript for important intellectual content: RWW, XQC. Statistical analysis: RWW, XQC. All authors read and approved the final manuscript.

**Acknowledgements**

We would like to thank all patients and their families for participating in this study.

**Abbreviations**

BP, Blood pressure; ABPM, Ambulatory blood pressure monitoring; TOD, Target organ damage; CKD: Chronic kidney disease; CKD-EPI: CKD Epidemiology Collaboration; ESRD: End stage renal disease; LVMI, Left ventricular mass index; LVH, Left ventricular hypertrophy; eGFR, Estimated glomerular filtration rate; ACR, Albumin-to-creatinine ratio; cIMT, Carotid intima-media thickness; ROC, Receiver operating characteristic.
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Figures
Figure 1

Shows the flowchart of included patients.
Figure 2

Shows receiver operating characteristic (ROC) curves of different BP indexes for TOD in four conditions: (A) left ventricular hypertrophy (LVH): LVMI $\geq 125$ g/m$^2$ (man) or $\geq 120$ g/ m$^2$ (woman), (B) eGFR $< 60$ ml/min per 1.73 m$^2$, (C) ACR $\geq 30$ mg/g, (D) cIMT $\geq 0.9$ mm or carotid plaque. Value in the bracket is the area under the curve of each line.