**TITLE PAGE**

**Title: Association between long-term pulse pressure trajectories and risk of end-stage renal diseases in incident malignant hypertensive nephropathy: a cohort study**

**RUNNING TITLE: trajectory of PP predicting ESRD in MHN**

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**Conflict of interests and source of funding**: None declared.

Word count: Abstract 250 Main text 2,455 Reference 23 Table 3 Figure 3

**ABSTRACT**

**OBJECTIVE**

The trajectories of pulse pressure (PP) might affect the prognosis of malignant hypertensive nephropathy (MHN). We aimed to describe the association between PP trajectories and the future risk of end-stage renal disease and to identify and compare associated patient characteristics of any distinct trajectory patterns in MHN patients.

**METHODS**

Patients with newly diagnosed biopsy-proven MHN 2010-2015 were included. Latent class growth analysis was applied to the PP measured over 3 years prior to biopsy to identify distinct trajectories. Concurrent systolic blood pressure, diastolic blood pressure, plasma creatinine, and 24-hour urine protein measurements for each trajectory group were modelled using generalised estimating equations. Risk of end-stage renal disease (with kidney replacement therapy as a proxy) were estimated using Logistic regression.

**RESULTS**

203 patients were included (median-age 34 years, and 19.7% female). A two-group cubic model was optimal, with trajectories distinguished by rate of PP and absolute level at final measurement. Trajectory Group-1 (n=84) was characterised by ‘first-increased-then-decreased’ PP and trajectory Group-2 (n=119) was characterised by ‘first-decreased-then-increased’ PP over 3 years prior to biopsy. Systolic and diastolic blood pressure, plasma creatinine, and 24-hour urine protein differed by trajectory group. Baseline characteristics differed substantially between trajectory groups. Compared with Group-1, Group-2 had a 66% greater risk of developing into end-stage renal disease in the subsequent 3 years.

**CONCLUSIONS**

Two distinct 3-year trajectories for PP exist with MHN. Early introduction of intensive antihypertensive treatment might delay development of end-stage renal disease among patients with malignant hypertension.

**Keywords:** Malignant hypertension; Pulse pressure; Trajectory

**INTRODUCTION**

Hypertension is the dominant risk factor for cardiovascular diseases (1). Malignant hypertension, is a subtype of hypertension, and is characterised by extreme high systolic blood pressure and out of range of office diastolic blood pressure (above 120 mmHg at the time of diagnosis), in combination with ischemic retinal changes consistent with grade III or IV hypertensive retinopathy (2, 3). Malignant hypertension is rare in the general population with an annual incidence of 2-7/100,000 (4). It often has a poor prognosis including 80% mortality within 2 years in the absence of treatment (5). In recent years, with the advent of antihypertensive therapy, the general survival of malignant hypertension has considerably improved, however, the associated end-stage renal disease remains a dominant driver of morbidity and mortality for patients with malignant hypertension (6). Indeed, end-stage renal disease develops in 20-40% patients with malignant hypertension within 5 years (7). It has been estimated in the Dutch population that the attributable risk of kidney replacement therapy due to malignant hypertension has increased by 40% over the past 20 years (8).

While systolic and diastolic blood pressure are the usual measures recorded in clinical practice, the derived pulse pressure has been utilised as a prognostic factor for renal function as pulse pressure indicates adequacy of cardiac function and arterial elasticity, and cardiac function and arterial elasticity have significant impacts on the renal function (9).

Pulse pressure levels at different time points prior to the incident diagnosis of biopsy-proven malignant hypertensive nephropathy represent the malignant hypertension status at a particular time point (10). The rate of increase in pulse pressure in a specific prior-biopsy time window reflects the velocity of blood pressure change (11). A steeper change in slope of pulse pressure at a particular time point is indicative of the potential for reperfusion injuries at a later stage of life (12). We hypothesised that a changing pulse pressure slope during the period prior to biopsy-proven malignant hypertensive nephropathy would be predictive of kidney replacement therapy (end-stage renal disease), and that this would be independent of the absolute pulse pressure value at the same time point. To test our hypothesis, using data from a longitudinal dataset, we built up (1) a retrospective cohort to describe the trajectories of pulse pressure prior to biopsy-proven malignant hypertensive nephropathy and (2) a prospective cohort to investigate the association between the identified trajectories and the risk of end-stage renal disease (proxied by kidney replacement therapy).

**PATIENTS AND METHODS**

**Study design**

This present study utilised longitudinal data from the malignant hypertensive nephropathy registry dataset (MHNRD) at the First Affiliated Hospital, Zhengzhou University. All patients with newly diagnosed, biopsy-proven, malignant hypertensive nephropathy in 2010-2015 were included in this study. All available medical records from patients attending either the First Affiliated hospital or external hospitals prior to the renal biopsy were collected and independently reviewed by three nephrologists. Records agreed by ≥2 nephrologists were used in this study. Ethics approval was granted by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Reference NO: 2019-KY-361). Written informed consent was obtained from all participants before inclusion.

**Data collection and outcomes of interest**

Renal puncture biopsy was then conducted using a 16G ejection needle with the aid of B ultrasound. Renal biopsy specimens were exam­ined under a light microscope with the following methods: haematoxylin and eosin (H&E), periodic Schiff-methenamine silver (PASM) and Masson's staining; immunofluorescence for IgG; as well as IgA, IgM, C3, C4 and C1q examination. Blood pressure, creatine and urine protein was measured and recorded during the clinical visits in outpatient or inpatient settings prior the biopsy. Blood pressure was measured three times by standard method BP after at least 5 minutes of rest in the sitting position. Other clinical measurements and information on antihypertensive treatments were collected by the date of the kidney biopsy. The laboratory tests were measured by automated analyser (Olympus AU600 autoanalyser, Olympus Optical, Tokyo, Japan). All patients were followed up in October 2018. The follow-up period for each participant was > 3 years. The outcome of this study was defined as the initialisation of kidney replacement therapy.

**Statistical analysis**

Latent class growth analysis was used to model individual pulse pressure trajectories over time. A one-group quadratic model was initially fitted to the data as it was hypothesised that the trajectories in our data set would be non-linear. A search for the optimal quadratic model was conducted by sequentially increasing the number of groups by one until model fit no longer improved. We also explored whether the same optimum model would have been concluded if a cubic model had been assumed, and if any group-specific cubic terms were statistically significant (p<0.05). Model fit statistics included Akaike Information Criteria (AIC), the Bayesian Information Criteria (BIC) and the sample-size adjusted BIC (ABIC), with lower absolute values of statistics indicating better model fit. Entropy (value 0-1) was used to indicate how well the model predicted class membership with values > 0.8 desirable [(13)]. We also considered that for a model to be optimal, all class sizes should be >1% of the total sample (to minimise the potential for the specific class not to be replicated in another dataset) and that class-specific average posterior probabilities were >0.7 (14). To check whether a global solution had been reached in the estimation algorithm, models were re-run using 5,000 different starting values to examine whether the same model likelihood was attained irrespective of starting values. If the highest log likelihood was repeated in more than two final stage solutions, a global solution was then concluded (15). All models were fitted using maximum likelihood estimation and missing data were assumed to be missing at random (15).

In each group defined by the latent class growth analysis, the marginal estimation of systolic blood pressure with diastolic blood pressure, creatinine and urine protein at each time point were analysed using General Linear Models, Time-specific fixed-effect estimates were presented with 95% confidence intervals, calculated using robust standard errors if the outcome was not normally distributed (16).

Demographic, clinical characteristics and the antihypertensive treatments at the kidney-biopsy date were examined descriptively by trajectory group as continuous variables were tested by analysis of covariance and categorical variables were tested by Logistic regression. Data management and analysis were performed using Stata MP Software V15.1 (StataCorp, College Station, TX, USA).

**RESULTS**

*Study population*

A total of 203 malignant hypertension patients had a renal-biopsy and were diagnosed as malignant hypertensive nephropathy in 2010 and 2015 (median (Inter Quartile Range) age: 34.00 (28.50 to 41.00) years, 19.70% female). The clinical measurements, comorbidities and antihypertensive treatment are presented in **Table-1**.

*Trajectories of recovery*

The cubic two-group model was deemed the optimal solution on low AIC, BIC and ABIC, high entropy and average posterior probabilities ≥0.78. By comparison, the three-group model had reduced entropy and lower posterior probabilities. The group sizes were (**Table-1**). The two groups n=84 (Group-1, n=84 and Group-2, n=119) were differentiated mainly on the pulse pressure 2 years before the biopsy-proven malignant hypertensive nephropathy. Group-1 and Group 2 showed a similar pulse pressure 3 years before the biopsy-proven malignant hypertensive nephropathy. However, 2 years before the biopsy, Group 2 had a significant increase, while Group 1 experienced a decrease in pulse pressure. After this time. The pulse pressure in Group 2 decreased, while that in Group 1 increased such that by the time of biopsy, Group-2 showed a higher level of pulse pressure comparing Group-1 (**Figure-1**).

When comparing systolic and diastolic pressure for each of the two trajectory groups, there were distinctively differences in trajectory trends for systolic and diastolic blood pressure (Figure-2). For Group-1, systolic blood pressure increased from 3-year to 2-year and remained plateau between 2-year to 1-year prior to biopsy and then declined in the following 12 months before biopsy; diastolic blood pressure presented the linear decrease between 3-year to 1-year prior to biopsy and remained stable in the following 12 months. For Group-2, systolic blood pressure gradually increased over 3 years prior to biopsy and diastolic blood pressure remained stable unchanged high level.

There were no notable differences in trajectory trend for creatinine or 24-hour urine protein (Figure-3), with gradually increasing over the 3 years prior to biopsy slightly higher level of creatinine and 24-hour urine protein was observed in Group-2 at each time-point comparing with Group-1.

*Participant characteristics*

The overall sample characteristic observed by the biopsy showed distinctively difference patterns of re-distribution following trajectory-group assignment (**Table-1**). Comparing with Group-2, Group-1 had higher proportion of male gender, and farmer occupation; lower proportion of cardiovascular diseases, diabetes, and hypertensive retinopathy grade II or IV; higher level of eGFR, 24 hour urine volume, high density lipoprotein cholesterol, carbon dioxide combination power, total bilirubin, direct bilirubin, red blood cell count, and haemoglobin; lower level of body mass index, systolic and diastolic blood pressure, creatinine, HbA1c, triglyceride, total cholesterol, low density lipoprotein cholesterol, urine protein, urea, and urine acid. Despite people in each group taking at least one type of antihypertensive prescription, the proportion of each antihypertensive prescription was higher in Group-1 and the proportion of taking ≥ 3 types of antihypertensive drugs was also higher in Group-1, suggesting that patients in Group-1 were more likely to take multiple antihypertensive prescriptions.

*Risk of end-stage renal disease*

**Table-2** shows the incidence of end-stage renal disease by group. After adjustment for age, gender, comorbidities and measurements by biopsy-date, Group-2 had 1.66 (1.51 to 1.84) higher risk of end-stage renal diease than those in Group 1.

**DISCUSSION**

*Main findings*

To our knowledge, this is the first study to use group-based modelling to examine prognostic trajectories of pulse pressure prior to diagnosis of biopsy-proven malignant hypertensive nephropathy. We were able to group more than 40% of patients into a better prognostic trajectory. Our study provided a clearly differentiated prior blood pressure and creatinine characteristic across each prognostic trajectory. Of the patient characteristic collected by the biopsy-date, many provided clear differentiated patient characteristics between two prognostic trajectories. Moreover, the two trajectories discriminated the future risk of end-stage renal disease, that suggest the trajectories would help to identify patients at high-risk of end-stage renal disease.

*Explanations / mechanisms of trajectories*

In previous study, pulse pressure change over 10 years was found to be significant risk factor for mortality in elder patients with hypertension(17). Blood pressure measurements were taken from existing reliable medical records, and our findings may provide some insights into their nature. In general the pattern (Group-1) we observed involved an increased pulse pressure between 2 and 3-years prior to biopsy, with subsequent decline over the following 24 months as would be predicted for better prognosis for malignant hypertensive nephropathy. This pattern represents patients with ‘first-increased –then-declined’ systolic blood pressure and continuously decreased diastolic blood pressure. The mechanism for this pattern might be implicated. It is possible that patients in this group might be tailored several intensive antihypertensive treatments (e.g. polypharmacy) at 3-year prior to biopsy with some adjustments in the following 12 months then fully engage with the most effective treatment. The unsuccessful blood pressure control in the adjustment period (between 2 and 3-years prior to biopsy) would explain the sharp increase in systolic blood pressure in this period (18). In contrast, the other group with decreased pulse pressure between 2 and 3-years prior to biopsy that increased over the following 24 months as would be predicted for poorer prognosis for malignant hypertensive nephropathy (19). This pattern represents patients with ‘slowly-growing’ systolic blood pressure and slightly decreased yet still high diastolic blood pressure, which might reflect the natural development of malignant hypertension (20). The mechanism might be patients without full engagement of intensive antihypertensive treatment or with under-prescription from medical settings as diastolic blood pressure constantly remained above 125 mmHg. Although the combined prescription of antihypertensive drugs for patients were not fully recorded over the 3 years prior to biopsy, the prescriptions pattern was less like to be dynamically changed for most patients over time. This study could still suggest which multi-antihypertensive prescriptions would be better, as higher proportion of multiple antihypertensive prescription in Group-1 comparing with Group-2.

Another explanation of the two differentiated trajectory groups might be the differences in comorbidities. As diabetes and cardiovascular diseases were more common to be observed in Group-2. Moreover, the clinical measurements like lipid profiles, HbA1c were higher in Group-2, which might suggest we observed a group of patients with poor conditions which were more likely to have poor prognosis (21). It would also be possible that these comorbidities and poor clinical measurements were newly developed over prior 3 years, which partly due to the unsuccessful blood pressure control over the period.

A further possible biological mechanism to explain the two trajectories, could be differences in renin activity among patients with malignant hypertension. Increased activation of renin-angiotensin-aldosterone system is evident among patients with malignant hypertension. It has been observed that plasma renin activity and an angiotensin 2-dependant aldosterone secretion does vary in patients with malignant hypertension (22, 23). Therefore, the distinctive patterns of pulse pressure observed in our study might reflect patterns of plasma renin activity and aldosterone among patients with malignant hypertension. However, neither plasma renin activity nor aldosterone were measured in this study.

*Renal function by trajectory*

Although most patients involved in this study entered the cohort with severely reduced kidney function and similar patterns of creatinine and urine protein, the magnitude of mean creatinine and urine protein was lower in Group-1 than those in Group-2 at each year over 3 years. Group 2 had a 66% greater risk of developing end-stage renal disease. The mechanism behind the differences in renal function by trajectory could be reperfusion injuries caused by the deteriorated blood pressure over the period (7, 23).

*Clinical implications of trajectories*

This study might have some clinical implications. First, the two distinctive prognostic trajectory groups suggest that more intensive antihypertensive therapy at least 3 years before the diagnosis of malignant hypertensive nephropathy would result in a better prognosis in the following 6 years (24). Second, the trajectory of pulse pressure identified in this study could be used as a tool to screen patients at high risk of developing the end-stage renal disease, which means at biopsy time, clinicians based on the recorded past 3 years’ pulse pressure to identify patients with high risk of development to end-stage renal disease. Patients could be then advised of their greater risk to maximise their adherence to home blood pressure monitoring, intensive treatment and their visits to clinic.

*Limitation of this study*

The study has a number of limitations. Firstly, the antihypertensive treatment information over 3 years prior to diagnosis of malignant hypertensive nephropathy was not available although the dynamic change of prescription patterns were less likely to observe. Therefore the modification effect of antihypertensive treatments on the formation of trajectory could not be evaluated in this study and need to be further investigated in future studies. Secondly, 3 years of study in the retrospective cohort was short, and future studies with a longer retrospective period could more accurately establish the time-to-malignant-hypertensive-nephropathy. In the current study, many patients had already developed reduced renal function 3 years prior to their biopsy. Thirdly, the sample size in our study is relatively small although biopsy-proven malignant hypertensive nephropathy is a rare condition in the general population. Future studies with a larger sample size are warranted. Fourthly, proportion of drug resistant hypertension could be different between two trajectory groups. The information of drug resistant hypertension was not available in this study. Therefore, future validation studies with this information are warranted. Finally, although male gender is more likely be affected by malignant hypertension, there might be potential distinctive trajectories of pulse pressure in female. Restricted by the sample size of female participants, gender specific trajectory analysis was not implemented in this study. Future studies in female gender are warranted.

Two distinct trajectories for pulse pressure over 3 years prior to biopsy for malignant hypertensive nephropathy. These findings suggest that progression to end-stage renal disease may be delayed or prevented in this group of patients with more intensive antihypertensive treatment, commencing as early as possible, with more frequent increments in therapy.

**ACKNOWLEDGEMENT**

**Funding**

None.

**CONFLICT OF INTEREST**

The authors have declared that no conflict of interest exists.

**REFERENCES**

Bovet P, Chiolero A: Prevalence and control of hypertension Lancet. 2018; 392:1305-1306.

Keith NM, Wagener HP, Barker NW: Some different types of essential hypertension: their course and prognosis Am J Med Sci. 1974; 268:336-345.

Ahmed ME, Walker JM, Beevers DG, Beevers M: Lack of difference between malignant and accelerated hypertension Br Med J (Clin Res Ed). 1986; 292:235-237.

van den Born BJ, Koopmans RP, Groeneveld JO, van Montfrans GA: Ethnic disparities in the incidence, presentation and complications of malignant hypertension J Hypertens. 2006; 24:2299-2304.

Gosse P, Coulon P, Papaioannou G, Litalien J, Lemetayer P: Impact of malignant arterial hypertension on the heart J Hypertens. 2011; 29:798-802.

Shavit L, Reinus C, Slotki I: Severe renal failure and microangiopathic hemolysis induced by malignant hypertension--case series and review of literature Clin Nephrol. 2010; 73:147-152.

Lip GY, Beevers M, Beevers DG: Does renal function improve after diagnosis of malignant phase hypertension? J Hypertens. 1997; 15:1309-1315.

Amraoui F, Bos S, Vogt L, van den Born BJ: Long-term renal outcome in patients with malignant hypertension: a retrospective cohort study BMC Nephrol. 2012; 13:71-2369-13-71.

Mackenzie IS, Wilkinson IB, Cockcroft JR: Assessment of arterial stiffness in clinical practice QJM. 2002; 95:67-74.

Fernandez-Fresnedo G, Rodrigo E, de Francisco AL, de Castro SS, Castaneda O, Arias M: Role of pulse pressure on cardiovascular risk in chronic kidney disease patients J Am Soc Nephrol. 2006; 17:S246-9.

Greenwald SE: Pulse pressure and arterial elasticity QJM. 2002; 95:107-112.

Kronas N, Kubitz JC, Forkl S, Kemming GI, Goetz AE, Reuter DA: Functional hemodynamic parameters do not reflect volume responsiveness in the immediate phase after acute myocardial ischemia and reperfusion J Cardiothorac Vasc Anesth. 2011; 25:780-783.

Trindade IA, Ferreira C, Pinto-Gouveia J: The longitudinal effects of emotion regulation on physical and psychological health: A latent growth analysis exploring the role of cognitive fusion in inflammatory bowel disease Br J Health Psychol. 2018; 23:171-185.

Coertjens L, Donche V, De Maeyer S, Vanthournout G, Van Petegem P: Modeling change in learning strategies throughout higher education: a multi-indicator latent growth perspective PLoS One. 2013; 8:e67854.

Yu D, Cai Y, Qin R, Tian X, Xiao J, Zhao Z: Dialysate Creatinine Response Patterns During Peritoneal Equilibration Test and the Association Between Cardiovascular Mortality: Findings from a Prospective Cohort Study Kidney Blood Press Res. 2018; 43:162-169.

Nicholls E, Thomas E, van der Windt DA, Croft PR, Peat G: Pain trajectory groups in persons with, or at high risk of, knee osteoarthritis: findings from the Knee Clinical Assessment Study and the Osteoarthritis Initiative Osteoarthritis Cartilage. 2014; 22:2041-2050.

Balietti P, Spannella F, Giulietti F, Rosettani G, Bernardi B, Cocci G et al.: Ten-year changes in ambulatory blood pressure: The prognostic value of ambulatory pulse pressure J Clin Hypertens (Greenwich). 2018; 20:1230-1237.

Shantsila A, Lip GYH: Malignant Hypertension Revisited-Does This Still Exist? Am J Hypertens. 2017; 30:543-549.

van den Bogaard B, Immink RV, Westerhof BE, van Montfrans GA, van Lieshout JJ, van den Born BJ: Central versus peripheral blood pressure in malignant hypertension; effects of antihypertensive treatment Am J Hypertens. 2013; 26:574-579.

Paris B, Bobrie G, Rossignol P, Le Coz S, Chedid A, Plouin PF: Blood pressure and renal outcomes in patients with kidney infarction and hypertension J Hypertens. 2006; 24:1649-1654.

Januszewicz A, Guzik T, Prejbisz A, Mikolajczyk T, Osmenda G, Januszewicz W: Malignant hypertension: new aspects of an old clinical entity Pol Arch Med Wewn. 2016; 126:86-93.

Kato T, Mizuguchi N, Ito A: Characteristics of podocyte injury in malignant hypertensive nephropathy of rats (MSHRSP/Kpo strain) Biomed Res. 2015; 36:313-321.

Ortiz RM, Graciano ML, Mullins JJ, Mitchell KD: Aldosterone receptor antagonism alleviates proteinuria, but not malignant hypertension, in Cyp1a1-Ren2 transgenic rats Am J Physiol Renal Physiol. 2007; 293:F1584-91.

Klein JD, Murrell BP, Tucker S, Kim YH, Sands JM: Urea transporter UT-A1 and aquaporin-2 proteins decrease in response to angiotensin II or norepinephrine-induced acute hypertension Am J Physiol Renal Physiol. 2006; 291:F952-9.

**Table-1**. Patients’ baseline characteristics and clinical measurements overall and by trajectory group

***Median with interquartile rage was presented for continuous variables.***

***P-value indicates the statistical difference between Group-1 and Group-2.***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Measurements by renal-biopsy** | **Group=1 (N=84)** | **Group=2 (N=119)** | ***P-value*** |
| Age, years | 34.00 (28.50 to 41.00) | 33.00 (28.50 to 40.00) | 34.00 (28.75 to 42.00) | 0.067 |
| Female gender, n (%) | 40 (19.70) | 15 (17.86) | 25 (21.01) | 0.004 |
| Marital status: Married, n (%) | 161 (79.31) | 62 (84.13) | 99 (83.58) | 0.056 |
| Farmers, n (%) | 84 (41.38) | 38 (45.45) | 46 (39.01) | 0.005 |
| Current smoking, n (%) | 83 (40.89) | 35 (41.67) | 48 (40.47) | 0.047 |
| Current drinking, n (%) | 85 (41.87) | 38 (45.30) | 47 (39.55) | 0.003 |
| Known cardiovascular disease, n (%) | 50 (24.63) | 19 (22.62) | 31 (26.05) | 0.001 |
| Diabetes, n (%) | 26 (12.81) | 5 (6.07) | 21 (17.39) | <0.001 |
| Hypertensive retinopathy grading III or IV, n (%) | 25 (12.31) | 10 (11.90) | 15 (12.60) | 0.059 |
| Body mass, index, kg/m2 | 28.25 (23.56 to 32.56) | 28.26 (22.32 to 31.63) | 29.12 (23.66 to 33.06) | 0.052 |
| Systolic blood pressure, mmHg | 200.19 (168.73 to 215.66) | 188.88 (167.51 to 190.25) | 203.95 (190.64 to 214.96) | <0.0001 |
| Diastolic blood pressure, mmHg | 125.62 (115.43 to 135.97) | 121.06 (119.99 to 122.18) | 126.80 (118.35 to 137.25) | <0.001 |
| Heart rates, times/min | 84.00 (77.80 to 90.50) | 84.00 (77.80 to 88.82) | 84.00 (77.80 to 90.50) | 0.052 |
| Breath rates, times/min | 20.00 (18.00 to 21.00) | 19.75 (17.67 to 21.00) | 20.00 (18.00 to 21.00) | 0.078 |
| Triglyceride, mmol/L | 1.74 (1.24 to 2.42) | 1.71 (1.25 to 2.39) | 1.90 (1.19 to 2.51) | 0.049 |
| Total cholesterol, mmol/L | 4.52 (3.84 to 5.41) | 4.47 (3.79 to 5.22) | 4.52 (3.87 to 5.45) | 0.047 |
| Low density lipoprotein, mmol/L | 2.79 (2.30 to 3.56) | 2.73 (2.26 to 3.28) | 2.85 (2.31 to 3.51) | 0.039 |
| High density lipoprotein, mmol/L | 1.02 (0.85 to 1.20) | 1.07 (0.84 to 1.31) | 1.00 (0.85 to 1.19) | 0.036 |
| 24 hours urine volume, L | 2.13 (1.77 to 2.55) | 2.20 (1.85 to 2.42) | 2.13 (1.74 to 2.60) | 0.093 |
| Carbon dioxide-combining power, mmol/L | 22.12 (20.50 to 23.90) | 22.45 (21.05 to 23.67) | 22.12 (20.35 to 23.90) | 0.046 |
| Urine total protein, mg/24 h | 1.13 (0.88 to 3.67) | 1.06 (0.56 to 4.91) | 1.15 (0.90 to 3.42) | 0.041 |
| Urea, mmol/L | 13.86 (9.42 to 19.66) | 12.96 (8.85 to 18.84) | 14.61 (10.10 to 19.93) | <0.001 |
| Urine acid, µmol/L | 433.45 (372.60 to 498.33) | 417.27 (372.60 to 498.33) | 434.50 (369.67 to 498.33) | <0.001 |
| Mean corpuscular haemoglobin concentration, g/L | 331.50 (325.00 to 3366.50) | 331.33 (325.00 to 336.50) | 331.50 (323.00 to 336.50) | 0.021 |
| Total bilirubin, µmol/L | 6.24 (4.83 to 8.90) | 6.40 (5.00 to 9.00) | 6.24 (4.83 to 8.65) | 0.016 |
| total protein, g/L | 64.65 (59.69 to 69.80) | 67.15 (61.10 to 70.60) | 63.90 (59.40 to 68.80) | <0.001 |
| Albumin, g/L | 40.90 (37.30 to 44.35) | 42.61 (38.10 to 44.85) | 40.30 (37.23 to 43.76) | <0.001 |
| Direct bilirubin, mg/dL | 2.73 (2.13 to 3.40) | 2.85 (2.26 to 3.38) | 2.70 (2.10 to 3.40) | 0.035 |
| Alkaline phosphatase, IU/L | 69.50 (60.50 to 86.50) | 67.74 (58.69 to 80.40) | 70.00 (61.25 to 86.50) | <0.001 |
| Phosphorus, mmol/L | 1.39 (1.23 to 1.60) | 1.36 (1.23 to 1.61) | 1.40 (1.23 to 1.60) | 0.042 |
| Red blood cell, 1012/L | 4.10 (3.47 to 4.68) | 4.12 (3.36 to 4.68) | 4.09 (3.47 to 4.72) | 0.037 |
| Red blood cell distribution width, % | 13.87 (13.25 to 14.40) | 13.87 (13.30 to 14.40) | 13.85 (13.23 to 14.39) | 0.073 |
| Haematocrit, % | 0.41 (0.35 to 9.44) | 0.41 (0.35 to 3.82) | 0.42 (0.35 to 10.79) | 0.048 |
| Creatinine, μmoI/L | 347.87 (196.00 to 561.15) | 264.40 (171.00 to 551.90) | 365.27 (204.00 to 581.13) | <0.001 |
| estimated glomerular filtration rate, mL/min/1.73m2 | 23.88 (13.38 to 42.79) | 27.31 (15.42 to 48.25) | 20.50 (12.18 to 41.23) | <0.001 |
| HbA1c, % | 5.34 (5.06 to 5.50) | 5.33 (5.00 to 5.50) | 5.50 (5.13 to 5.95) | 0.001 |
| platelet distribution width, % | 16.95 (16.50 to 17.33) | 16.95 (16.40 to 17.41) | 16.95 (16.53 to 16.95) | 0.078 |
| Platelet hematocrit, % | 0.17 (0.13 to 0.21) | 0.17 (0.13 to 0.21) | 0.17 (0.13 to 0.21) | 0.083 |
| Haemoglobin, g/L | 117.00 (100.00 to 131.71) | 120.75 (101.56 to 131.71) | 116.00 (99.50 to 131.71) | <0.001 |
| Taking angiotensin converting enzyme inhibitors, n (%) | 15 (7.33) | 7 (7.83) | 8 (6.97) | 0.026 |
| Taking angiotensin receptor blockers, n (%) | 54 (26.73) | 25 (30.24) | 29 (24.25) | <0.001 |
| Taking beta-blocker, n (%) | 87 (42.78) | 38 (45.69) | 48 (40.72) | <0.001 |
| Taking calcium channel blockers, n (%) | 127 (62.73) | 56 (66.74) | 71 (59.9) | <0.001 |
| Taking diuretics, n (%) | 27 (13.07) | 14 (16.34) | 13 (10.76) | <0.001 |
| Taking alpha blockers, n (%) | 72 (35.43) | 34 (40.25) | 38 (32.03) | <0.001 |
| Taking central action of antihypertensive drugs, n (%) | 10 (4.87) | 4 (4.76) | 6 (4.95) | 0.021 |
| Taking ≥ 3 types of antihypertensive drugs, n (%) | 83 (40.89) | 39 (46.43) | 44 (36.97) | <0.001 |

**Table-2**. Absolute risk and adjusted incidence rates ratio of end-stage renal disease (proxied by kidney replacement therapy) by trajectory membership

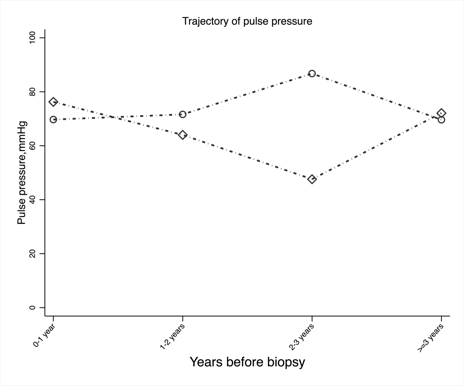
*Age, gender, comorbidities (cardiovascular diseases and diabetes), systolic and diastolic blood pressure, eGFR, urine protein, low density lipoprotein, and HbA1c were adjusted.*

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No. of KRT** | **Incidence, %** | **Adjusted Incidence rates ratio** |
| Group -1 (N=84) | 13 | 15.5 (8.24 to 26.5) | reference |
| Group -2 (N=119) | 27 | 22.7 (15.0 to 33.0 | 1.66 (1.51 to 1.84) |

**Figure Legends**

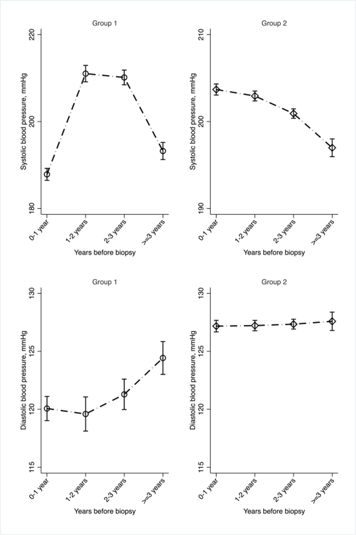
**Figure-1**. Pulse pressure by group-based trajectory membership.

***Circle line indicates Group-1 trajectory; Diamond line indicates Group-2 trajectory.***



**Figure-2**. Comparison of systolic and diastolic blood pressure over time, by group-based trajectory membership.

***Circle line indicates Group-1 trajectory; Diamond line indicates Group-2 trajectory.***



**Figure-3**. Comparison of creatinine and urine protein over time, by group-based trajectory membership.

***Circle line indicates Group-1 trajectory; Diamond line indicates Group-2 trajectory.***

