INCIDENCE AND RISK FACTORS FOR RAPID DECLINE OF PRESERVED ESTIMATED GLOMERULAR FILTRATION RATE AMONG PATIENTS WITH HYPERTENSION IN A COMMUNITY HOSPITAL

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Abstract

Background: Hypertension is the second most common leading cause of chronic kidney disease. Related studies explored the causes of the rapid decline of kidney function in advanced kidney disease. However, the causes of the rapid decline of kidney function in the early stage or preserved function of hypertension-related kidney disease are less evident.

Objectives: The study aimed to identify the incidence and associated risk factors for the decline of the glomerular filtration rate (GFR) among patients with hypertension with preserved kidney function, estimated GFR (eGFR) above 60/mL/min/1.73m^2, at a community hospital.

Methods: A retrospective cohort study was conducted among patients with hypertension with 2 eGFR measures at least 1 year apart and were identified from all cases attending at the Outpatient Department, Sanam Chai Khet Hospital, Chachoengsao Province. The incidence of the estimated rate of eGFR decline greater than 5 mL/min/1.73m^2 yearly (ERGFR5/yr) was determined. In addition, potential risk and protective factors were identified using Poisson Regression.

Results: Of 1,328 patients with hypertension, 53.05% were females. The mean age was 59.68 ± 11.58 years. The mean GFR measure at the 1st visit was 88.71± 14.73 mL/min/1.73m^2. The incidence of ERGFR5/yr was 11.1 (95% CI: 10.1-12.3)) per 100-person year. Risk factors were being 60 years or older with an incidence rate ratio (IRR) of 1.4 (95% CI: 1.11-1.77), having diabetes mellitus with an IRR of 1.67 (95% CI: 1.37-2.04) and uncontrolled hypertension with an IRR of 1.15 (95% CI: 1.10-1.20).

Conclusion: The incidence of ERGFR5/yr among renal preserved patients with hypertension was relatively low compared with other studies. Aggressive intervention among patients with comorbidity could reduce the incidence of rapid decline in eGFR.

Keywords: Hypertension, Rapid decline kidney function, Incidence, Risk factors

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Introduction

Hypertension is one of the most problematic noncommunicable diseases affecting millions of people around the world.[1] Moreover, hypertension leads to premature morbidity and mortality. It has been forecasted that by 2025, the prevalence of hypertension will rise to 1.56 trillion people worldwide. In developing countries, the prevalence may be as high as 80%.[1, 2] Hypertension also predisposes the patient to develop other chronic diseases such as cerebrovascular disease, heart failure, cardiovascular diseases, peripheral arterial disease and chronic kidney diseases; thus, leading to premature morbidity and mortality.[1,2] In 2014, data from the National Health Examination Survey V suggested that hypertension affects nearly one in five individuals. Unfortunately, the overall prevalence of hypertension among Thai individuals older than 15 years had increased from 17% in 1992 to 24.7% in 2014.[3] Furthermore, another study found that the prevalence of uncontrolled hypertension in Thailand was around 25%.[4] In 2009, the National Health Examination Survey IV reported that 25.4% of Thai individuals were hypertensive. [5, 6]

Chronic kidney disease (CKD) is another common noncommunicable chronic disease in Thailand with a prevalence of around 20%. [7, 8] CKD management incurs a high healthcare cost, especially in end-stage kidney disease when dialysis or kidney transplantation is needed.[9] Combined eGFR, albuminuria and other factors may affect the progression of CKD but no guiding bases have been established within therapeutic guidelines. (10)

The glomerular filtration rate (GFR) is the universal concept for assessing kidney function. The GFR is usually estimated with creatinine values because creatinine values remain constant in the case of constant food intact and muscle mass.[11, 12] A rapid decline in estimated GFR (eGFR) means having an eGFR that decreases more than 5mL/min/1.73² yearly may predict the progression of worsening kidney function among patients with CKD. (11, 13, 14) Later on, the terminology of rapid decline in eGFR is used to describe the nature of eGFR decline in a patient already receiving a diagnosis of CKD to predict a poor prognosis. [15]

Diabetes and hypertension are the leading etiologies of CKD.[9] To determine what factors led to decreased kidney function among patients with hypertension, this study aimed to identify risk factors for eGFR decline among patients with hypertension using a cutoff point of >5mL/min/1.73² yearly, like those with CKD. The incidence and risk factors associated with the eGFR declining greater than 5 mL/min/1.73m^2 yearly (ERGFR5/yr) among patients with hypertension who had started eGFR above 60/mL/min/1.73m^2 were studied. Factors investigated were comorbidities i.e., diabetes mellitus, dyslipidemia, cerebrovascular diseases, cardiovascular disease and arthritis including gout. Occupation, history of smoking and alcohol consumption were also recorded. Results could be used to prevent further decline in kidney function among patients with hypertension having preserved kidney function. [14, 19, 20]

Methods

Study population

A retrospective cohort study was conducted at a community hospital, Sanam Chai Khet Hospital, Chachoengsao Province. The Institutional Review Board of the Royal Thai Army approved the study with the identification code M030h/64. The eligibility criteria for patients were 18 years and older who were hypertensive with at least two creatinine levels taken more than one year apart from 2011 to 2021. Moreover, the baseline eGFR was more than 60 mL/min/1.73m². Patients who were pregnant or meeting the criteria for acute kidney injury (AKI) using Kidney Disease Improving Global Outcomes (KDIGO) were excluded from the study.

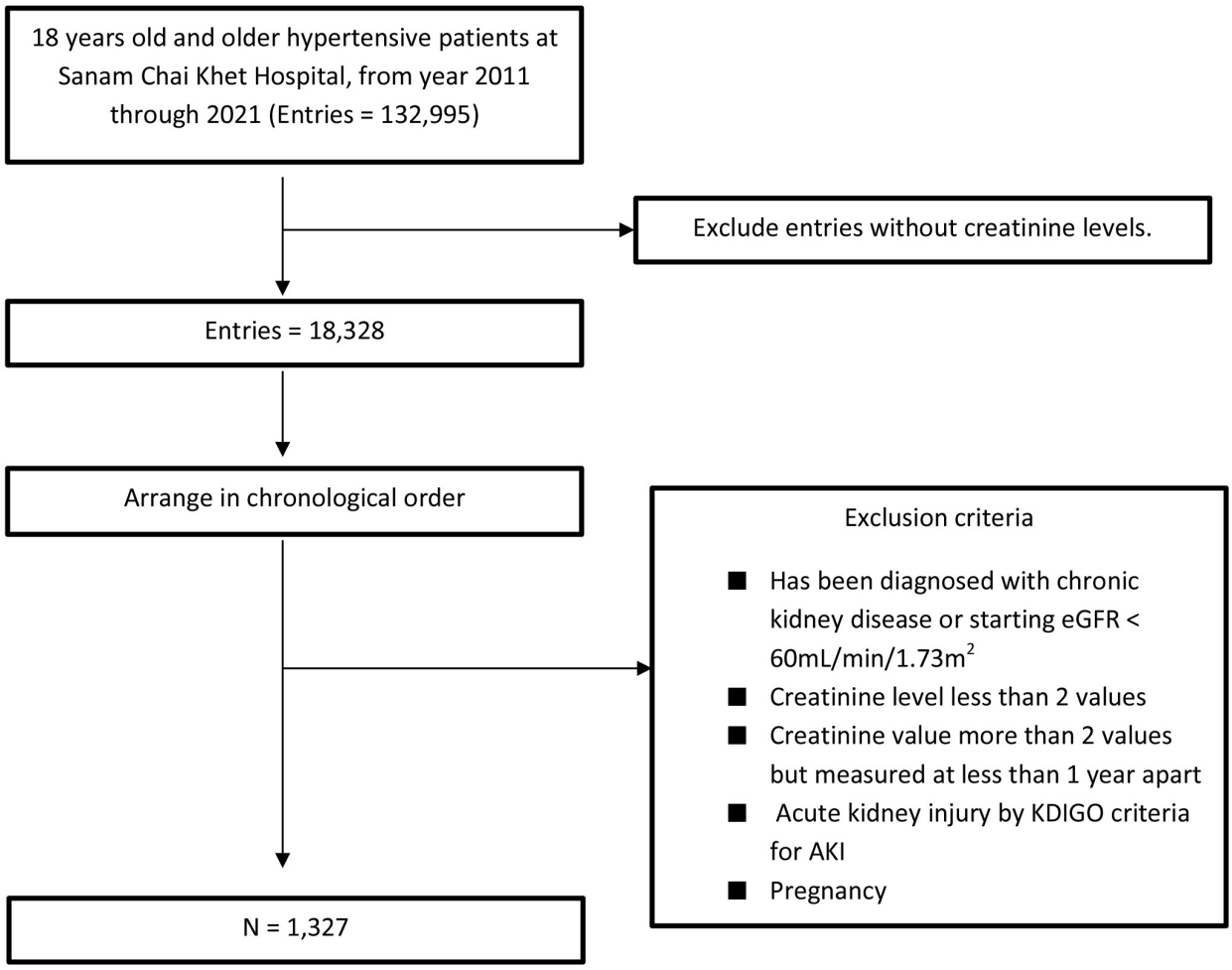

Figure 1. Flowchart for selection of patients in the study

Data collection

From 2011 to 2021, data were collected from patient's medical records at Sanam Chai Khet Hospital. According to ICD-10, cases with hypertension (I10) were extracted from the database along with demographic characteristics, comorbidity, body weight and height and baseline systolic and diastolic blood pressure. Patients were screenednusing inclusion and exclusion criteria as described in **Figure 1**. Of 132,997 OPD visits, thosewithout creatinine levels were excluded, down to 18,330 OPD visits. Then we excluded patients presenting creatinine levels <60 mL/min/1.73m², those with creatinine levels less than one year apart and those with acute kidney injury using KDIGO criteria and pregnancy using ICD10 (Z34), respectively.

Other covariates were extracted; cardiovascular disease included ischemic heart disease (I25-). Cerebrovascular diseases included I63-, I67-, I68- and I69-. Arthritis included gouty arthritis and osteoarthritis that might be exposed to the use of NSAID (M10- and M06-). Furthermore, atrial fibrillation included those that received a diagnosis of ICD10 (I48-).[16] In this study, creatinine levels were determined using the enzymatic method. The CKD-EPI formula from "The Nephrology Society of Thailand" in 2018 was used to calculate. A rapid decline in eGFR was defined as greater than 5 ml/min/1.73m² yearly using the KDIGO criteria.[17] The rate equation used to calculate the estimated decline rate of eGFR is shown below.

Sex	Creatinine level mg/dL	Equation
Female	≤0.7	$GFR = 141 \times \left(\frac{SCr}{0.7}\right)^{-0.329} \times 0.993^{Age}$
	>0.7	$GFR = 141 \times \left(\frac{SCr}{0.7}\right)^{-1.209} \times 0.993^{Age}$
Male	≤0.9	$GFR = 141 \times \left(\frac{SCr}{0.9}\right)^{-0.329} \times 0.993^{Age}$
	>0.9	$GFR = 141 \times \left(\frac{SCr}{0.9}\right)^{-0.329} \times 0.993^{Age}$

$$\frac{eGFR_{creatinine\ visit\ 2} - eGFR_{creatinine\ visit\ 1}}{days\ between\ visit\ 1\ and\ 2 \Big/ 365}$$

Statistical analysis

STATA14 was used to determine descriptive statistics of the baseline characteristics and demographic data.[18] Continuous data were classified into ordinal scales such as age, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI) and baseline eGFR. Likewise, the categorical data such as occupation, smoking and alcohol consumption was presented as a percentage.

Using multiple Poisson regression, adjusted relative risks, 95% Confidence Interval (CI), and p-values were determined. Each potential risk factor was adjusted for sex, age group, occupation, smoking status, alcohol status, BMI, diabetes, dyslipidemia, cardiovascular disease, atrial fibrillation, gout, osteoarthritis, cerebrovascular disease, baseline eGFR groups, and SBP and DBP groups. The risk factors were identified using IRR and 95% CI. For survival analysis, the study time was from October 2011 to October 2021. Right censoring was performed when the patient did not achieve the rate of rapid decline eGFR <5 mL/min/1.73m^2 until the end of the follow-up. The person-time calculated comprised the observation time until the event occurred, presumably the end time at which the mean eGFR was >5 mL/min/1.73m^2.

RESULTS

Clinical characteristics

A total of 1,326 patients with hypertension and serial eGFR values at least one year apart were included in the analysis. For the baseline characteristics, 53.1% were female and the mean age was 59.7 ± 11.5 years **(Table 1).** Of these, 21.2% smoked and 23.4% consumed alcohol. For BMI, 10.3% were underweight (BMI<18 kg/m²), 24.2% presented normal BMI (18 to 22.9 kg/m²) and 65.5% were obese (BMI >23 kg/m²). Among all patients with hypertension and preserved kidney function, 29.2% had diabetes mellitus. Other comorbidities comprised 49.0% dyslipidemia, 4.2% cardiovascular disease, 3.2% arthritis, 1.6% atrial fibrillation and 4.8% cerebrovascular diseases.

Incidence of ERGFR5/yr and hypertension

The incidence of ERGFR5/yr among renal preserved patients with hypertension was 11.1 person per 100 person-year (95% CI: 10.1-12.3) with a mean follow-up time of 1.7 years **(Table 1).** The rate of decline in eGFR yearly was 0.65 units yearly (95% CI: 0.34-0.96).

Risk factors for developing ERGFR5/yr

The study showed that age 60 years or older was associated with ERGFR5/yr with an adjusted IRR of 1.40 (95% CI: 1.11 to 1.77). Moreover,

having diabetes mellitus was associated with a rapid decline in eGFR with an adjusted IRR of 1.67 (95% CI: 1.37 to 2.04). On the other hand, having uncontrolled hypertension or blood pressure ≥140/90 mmHg was associated with developing ERGFR5/yr with an IRR of 1.15 (95% CI: 1.10 to 1.20).

DISCUSSION

The incidence of ERGFR5/yr was 11.1 person per 100 person-year among patients with hypertension and GFR above 60 mL/min/1.73m^2, with a mean follow-up time of 1.7 years. This constituted the first study investigating the incidence and risk factors of ERGFR5/yr among patients in this community hospital. We identified modifiable and nonmodifiable risk factors for eGFR decline. Our study reported that the risk factor of ERGFR5/yr was uncontrolled hypertension greater than 140/90 mmHg similar to the study by Bai et al.; the rapid decline of eGFR was associated with systolic hypertension.[12] Other related studies found that diabetes was associated with a rapid decline in kidney function.[19, 20] Similarly, in our study, those with diabetes and hypertension were more likely to develop ERGFR5/yr. However, dyslipidemia and atrial fibrillation did not show any association with ERGFR5/yr. In contrast to related studies, dyslipidemia was associated with a rapid decline in kidney function.[21] Other related studies showed that among patients already receiving a diagnosis of CKD; the incidence was lower than among those in China where a 23.9% cumulative incidence of rapid decline eGFR among elderly patients with hypertension was reported.[11, 22]

Table 1. General characteristics of patients with hypertension with preserved kidney function and incidence of rapid decline eGFR

Characteristic	
N	1326
Sex	
Female	704 (53.1)
Male	622 (46.9)
Age (y)	59.7±11.5
≤60	693 (52.3)
>60	633 (47.7)
Smoking	
No	1045 (78.8)
Yes	281 (21.2)
Alcohol Cption	
No	1015 (76.6)
Yes	311 (23.4)
Body Mass Index	
<18	136 (10.3)
18-22.9	321 (24.2)
≥23	869 (65.5)
Diabetes	
No	939 (70.8)
Yes	387 (29.2)
Dyslipidemia	
No	676 (51.0)
Yes	650 (49.0)

Table 1. General characteristics of patients with hypertension with preserved kidney function and incidence of rapid decline eGFR (Cont.)

Characteristic	
Cardiovascular disease	
No	1271 (95.9)
Yes	55 (4.2)
Atrial Fibrillation	
No	1305 (98.4)
Yes	21 (1.6)
Arthritis	
No	1283 (96.8)
Yes	43 (3.2)
Cerebrovascular disease	
No	1262 (95.2)
Yes	64 (4.8)
Baseline eGFR	
≥90	634 (47.8)
60-89.9	692 (52.2)
BP ≥ 140/90 mmHg	
No	381 (28.7)
Yes	945 (71.3)
FBS >180mg/dL	
No	1172 (88.4)
Yes	154 (11.6)
TG≥150 mg/dL	
No	629 (63.4)
Yes	363 (36.6)
LDL≥100mg/dL	
No	265 (29.1)
Yes	645 (70.9)
Median follow-up time, years (IQR)	1.7 (1.1-2.2)
Outcomes	
Person-years of exposure	3403
Number of events	379
Incidence rate /100 person-years (95%CI)	11.1 (10.1-12.3)
Rate decline eGFR per year (ml/min/1.73m^2/year)	0.65 (0.34-0.96)

The related study found that chronic kidney progression was associated with higher levels of nonHDL cholesterol in the blood.[23] In contrast to this study, our patients had received lipid-lowering agents. In addition, long term medication to treat noncommunicable diseases ultimately played an important role in kidney function. On the other hand, among patients with atrial fibrillation, studies compared the effects of nonvitamin K antagonist oral anticoagulant (NOAC) and warfarin; NOAC provided more reno-protective effects than warfarin.[24-26] Therefore, further investigation regarding drug use is crucial for establishing a solid conclusion.

Table 2. Multiple Poisson Regression analysis of incidence and risk factors of rapid renal progression among patients with hypertension

	Person-years of exposure	Number of events	Incidence rate /100 person-years (95%CI)	Crude IRR (95%CI)	*p*-value	Adjusted IRR (95%CI)	*p*-value
Sex							
Female	1579	201	12.7 (11.1-14.6)	1		1	
Male	1824	178	9.8 (8.4-11.3)	0.99 (0.65-1.52)	0.965	1.10 (0.67-1.81)	0.716
Age (years)							
≤60	1829	169	9.2 (7.9-10.7)	1		1	
>60	1574	210	13.3 (11.7-15.3)	1.39 (1.30-1.49)	<0.001	1.40 (1.11-1.77)	0.004
Smoking							
No	2705	297	11.0 (9.8-12.3)	1		1	
Yes	698	82	11.8 (9.5-14.6)	1.03 (0.95-1.11)	0.473	1.05 (0.63-1.74)	0.850
Alcohol Consumption							
No	2614	287	11.0 (9.8-12.3)	1		1	
Yes	789	92	11.7 (9.5-14.3)	1.02 (0.95-1.10)	0.599	0.94 (0.39-2.23)	0.881
Body Mass Index							
<18	387	40	10.3 (7.6-14.1)	1		1	
18-22.9	796	102	12.8 (10.6-15.6)	1.08 (0.73-1.58)	0.701	1.19 (1.15-1.23)	<0.001
≥23	2221	237	10.7 (9.4-12.1)	0.94 (0.74-1.19)	0.604	1.25 (1.07-1.45)	0.005
Diabetes Mellitus							
No	2436	227	9.3 (8.2-10.6)	1		1	
Yes	967	152	15.7 (13.4-18.4)	1.73 (1.27-2.36)	<0.001	1.67 (1.37-2.04)	<0.001
Dyslipidemia							
No	1727	173	10.0 (8.6-11.6)	1		1	
Yes	1676	206	12.3 (10.7-14.1)	1.33 (0.95-1.86)	0.092	0.92 (0.62-1.35)	0.666
Cardiovascular disease							
No	3278	365	11.1 (10.1-12.3)	1		1	
Yes	126	14	11.1 (6.6-18.8)	0.97 (0.40-2.35)	0.955	1.27 (0.28-5.77)	0.754
Atrial Fibrillation							
No	3345	375	11.2 (10.1-12.4)	1		1	

able 2. Multiple Poisson Regression analysis of incidence and risk factors of rapid renal progression among patients with hypertension (Cont.)

	Person-years of exposure	Number of events	Incidence rate /100 person-years (95%CI)	Crude IRR (95%CI)	*p*-value	Adjusted IRR (95%CI)	*p*-value
Yes	58	4	6.8 (2.6-18.2)	0.60 (0.46-0.77)	<0.001	0.35 (0.08-1.55)	0.165
Arthritis							
No	3268	368	11.3 (10.2-12.5)	1		1	
Yes	135	11	8.2 (4.5-14.7)	0.80 (0.66-0.98)	0.030	1.04 (0.88-1.24)	0.621
Cerebrovascular disease							
No	3239	358	11.1 (10.0-12.3)	1		1	
Yes	164	21	12.8 (8.3-19.6)	1.14 (0.83-1.57)	0.414	1.52 (1.06-2.19)	0.023
Baseline eGFR							
≥90	1589	176	11.1 (9.6-12.8)	1		1	
60-89.9	1815	203	11.2 (9.7-12.8)	1.10 (0.94-1.28)	0.225	1.22 (0.88-1.70)	0.228
BP ≥ 140/90 mmHg							
No	943	117	12.4 (10.4-14.9)	1		1	
Yes	2460	262	10.6 (9.4-12.0)	0.92 (0.91-0.93)	<0.001	1.15 (1.10-1.20)	<0.001
FBS >180mg/dL							
No	3013	308	10.2 (9.1-11.4)	1		1	
Yes	391	71	18.2 (14.4-22.9)	1.71 (1.43-2.03)	<0.001	1.18 (0.91-1.52)	0.220
TG≥150 mg/dL							
No	1607	171	10.6 (9.2-12.4)	1		1	
Yes	982	108	11.0 (9.1-13.3)	1.05 (0.86-1.28)	0.616	1.06 (0.75-1.48)	0.747
LDL≥100mg/dL							
No	581	82	14.1 (11.4-17.5)	1		1	
Yes	1535	177	11.5 (9.9-13.4)	0.85 (0.83-0.87)	<0.001	0.95 (0.82-1.10)	0.479

ICD 10 for diabetes: E10-E14- , ICD 10 for dyslipidemia: E78- , ICD 10 for cardiovascular disease (ischemic heart disease): I25- , ICD 10 for atrial fibrillation: I48- , ICD 10 for arthritis M10-, M06- and ICD 10 for cerebrovascular disease included I63-, I67-, I68-, I69-

The results of this study agreed with that of Chamnanmont et al.[26] investigating the prevalence and associated factors for the decline of eGFR among patients attending a community hospital and reported the incidence of eGFR<60 mL/min/1.73m^2 was 20.3%; risk factors included age, NSAIDs use and presenting high blood pressure.

In this study, the patients with hypertension exhibited good or mild impaired renal function or a baseline eGFR >60 mL/min/1.73m^2. Early intervention could be used in this particular group as shown that the rate of eGFR was lower compared with other studies that included patients with established CKD. Morbidity and mortality could possibly be reduced long term if we focused on blood pressure control among patients receiving an early diagnosis of hypertension.[26]

This study encountered limitations. Proteinuria data was not included as one of the variables; proteinuria could be a mediator or extraneous variable and used as the main predictor for poor prognosis and increasing rate of kidney function decline. [17, 27] Additionally, proteinuria was also a major biomarker for the diagnosis of early stages of kidney disease.[17] Therefore, the study population included patients with hypertension alone and those with hypertension and CKD I or II. Thus, further investigation is required for a conclusive result.

In this study, certain ICD 10 were excluded, i.e., being pregnant and those with the criteria of AKI by KDIGO definition. However, more substile events that could be lower such as the history of infection or hospital admission between the two OPD visits had not been explored. Of 130,000 patients with hypertension, 1,326 patients had the criteria of having two creatinine levels one year apart and having a baseline eGFR >60%. The study did not eliminate the degree of natural variation of serum creatinine levels which tended to be higher than those with normal creatinine levels. Thus, further study with a larger data pool is required to establish a strong association. This study only determined a rate of decreased eGFR among patients with hypertension and preserved kidney function. However, patients with hypertension and eGFR <60 were not studied in the same setting. Additionally, this study did not include the potential effects of medication in developing rapid decline in kidney function.

CONCLUSION

The incidence of ERGFR5/yr among renal preserved patients with hypertension was 11.1 person per 100 person-year with a mean follow-up time of 1.7 years. Factors positively linked to the ERGFR5/yr included age >60 years, BP >140/90 mmHg and diabetes mellitus. Early intervention for adequate hypertension control and optimal control for diabetes could prevent the decline of eGFR among patients with hypertension and preserve renal function.

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