Estimated Creatinine Clearance and Cognitive Impairment in Thai Older Adults: A Pilot Study from the Dementia and Disability Project in Thailand

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Background: *Chronic kidney disease and dementia are the two common conditions in the older adults. The recent study from the US older adult populations has shown that the lower levels of kidney function are associated with increased prevalence of cognitive impairment.*
Objective: *Exploring the relationship between levels of kidney function and cognitive function in Thai community base older adults and finding the threshold of kidney function for which general practitioner should screen for cognitive impairment.*
Material and Method: *Bangkok community dwelling older adults were recruited during 2004-2006. Serum creatinine and cognitive function were measured. Kidney function was represented in estimated creatinine clearance (eCrCl), calculated by Cockcroft-Gault formula. Cognitive function assessment was evaluated by Mini Mental State Exam Thai version (TMSE). The participants were divided into 4 groups, Model 1, those stratified by level of eCrCl; ≥ 90, 60-89, 30-59 and < 30 mL/min respectively. Unfortunately, after the authors categorized eCrCl as a Model 1, the number of participants are largely unequally distributed among the 4 groups. Therefore, the authors developed Model 2. In Model 2, eCrCl was divided, by tertile, into 3 groups; eCrCl > 65, 48-65 and < 48 mL/min respectively. Participants with TMSE < 24 were considered to have cognitive impairment. The association between kidney function and cognitive impairment was determined by univariable and multivariable logistic regression models.*
Results: *317 participants were enrolled, 65.71% (n = 207) were women. The mean age was 71.13 years (SD = 7.99). In Model 1, the authors found a trend which indicated that eCrCl < 30 mL/min increased the prevalence of cognitive impairment when compared with eCrCl ≥ 90 mL/min (adjusted odds ratio 3.82; 95% CI 0.90-16.19, p-value = 0.07). In Model 2, the authors also found that populations of eCrCl < 48 mL/min had a trend to increase the prevalence of cognitive impairment when compared with eCrCl > 65 mL/min (adjusted odds ratio 1.76; 95% CI 0.99-3.12, p-value = 0.052).*
Conclusion: *In the present study, the authors could not demonstrate any statistical significant of an association between the lower eCrCl and cognitive impairment. However, the authors found that eCrCl < 48 mL/min may have a trend to associate with cognitive impairment. Therefore, the authors may use this eCrCl level for screening prevalence of cognitive impairment in the older adult population.*

Keywords: *Creatinine clearance (CrCl), Chronic kidney disease (CKD), Cockcroft-Gault formula, Cognitive impairment and Mini Mental State Exam Thai version (TMSE)*

J Med Assoc Thai 2013; 96 (Suppl. 2): S47-S53
Full text. e-Journal: *http://jmat.mat.or.th*

Chronic kidney disease (CKD) and dementia are the two common conditions in the older adults, who are becoming a large proportion of the population in many countries in the world. Unfortunately, the mechanism explaining cognitive impairment in kidney dysfunction has been unclear. However, the mechanism was proposed in the pattern of conceptual diagram, shown in Fig. 1[1]. CKD is associated with traditional

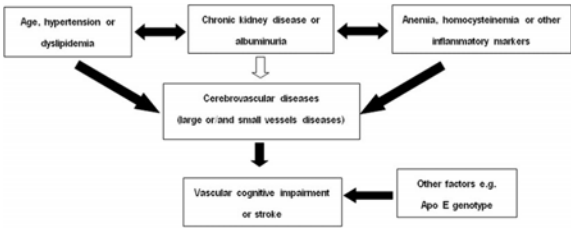

Fig. 1 Conceptual diagram demonstrating relationship between vascular risk factors, chronic kidney disease and cognitive impairment (Modified from Daniel E. Weiner[1])

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cardiovascular risk factors[2,3] (e.g. hypertension, diabetes and dyslipidemia). Several studies showed association between nontraditional cardiovascular disease risk factors, such as hyperhomocysteinemia, anemia and other inflammatory markers, with subsequent cognitive decline. Therefore, these findings are less consistent than seen form traditional risk factors and studies did not design for detecting the relationship between kidney disease and the risk factors[4,5]. CKD may have a potential to produce cerebrovascular diseases. The cerebrovascular pathology that occurs at the level of large or small vessels can cause a cognitive impairment. Thus, the hypothesis is made that CKD have a potential to produce a cognitive impairment.

With this hypothesis, many studies particularly which were performed in the past decade, revealed the association between both cognitive impairment or dementia and moderated or severe CKD populations in both men and women[6,7,9,10]. A recent cross-sectional study with 30,000 participants (US adults community base populations) age ≥ 45 years old, was conducted by Kurella-Tamura et al. That showed the same result as the previous study[11].

As most studies were published from Western countries, so the authors objectives are a pilot study in Thailand that explore an association between kidney function and cognitive performance in Thai community-based older adults and attempt to discover the threshold of kidney function that should screen for cognitive impairment.

Material and Method

Study design and participants

The present study, a pilot study, is provided the data from The Dementia and Disability Project (DDP) that is a cross-sectional community-based health survey study in older adults aged ≥ 60 years old who live in the vicinity of Siriraj Hospital. DDP is supported by Forgathy International Research Collaboration Award, Thailand Research Foundation and Mahidol University Research Foundation. The data was obtained from both an in-home interview and physical and laboratory examination by the physician. The authors collected history about cardiovascular risk factors (e.g. age, history of hypertension, smoking and diabetes), history of coronary heart disease and cerebrovascular diseases. The authors performed physical examinations which included blood pressure measurement, anthropometric measurements, a general physical examination and cognitive function assessment. The authors collected the blood samples for measurement of level of serum creatinine.

Evaluation of kidney function

In the present study, the kidney function was estimated by Cockcroft-Gault formular[6] and reported in term of estimated creatinine clearance (eCrCl); eCrCl = [(140-age) x Body weight (Kg)/(serum creatinine x 72)] x 0.85 (if female). In the model 1 eCrCl was divided into 4 groups; group 1: eCrCl ≥ 90 mL/min, group 2: eCrCl 60-89 mL/min, group 3: eCrCl 30-59 mL/min and group 4: eCrCl < 30 mL/min. Unfortunately, after the authors divided eCrCl as a model 1, the number of participants were largely unequally distributed among the 4 groups. Therefore, the model 2 was developed in order to correct this problem. The authors divided eCrCl, by tertile fashion, into 3 groups; group 1: eCrCl > 65 mL/min, group 2: eCrCl 48-65 mL/min, and group 3: eCrCl < 48 mL/min.

Cognitive function assessment

Mini Mental State Exam Thai version[7] (TMSE) was used for assessing the cognitive function. Scores range from 0 to 30 points, with higher scores denoting better cognitive function. The cognitive function was divided to 2 groups similar both model 1 and model 2; cognitive impairment group was defined by a TMSE score of less than 24 points and the normal cognitive function group was defined by TMSE scores of 24 points or greatest.

Statistical analysis

The authors used standard descriptive statistics to assess baseline characteristics and to test differences in characteristics among the eCrCl group and with or without cognitive impairment. The association between kidney function and cognitive impairment was determined by univariable and multivariable logistic regression models (expressed as an odds ratio (OR), 95% confidence interval (95% CI) and p-value).

Covariates

The odds ratio was adjusted by factors include history of hypertension (HTN), diabetes (DM), smoking, coronary heart disease (CHD) and cerebrovascular disease (CVD). Hypertension was defined as a systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of antihypertensive medications. Diabetes was defined by a fasting glucose of ≥ 126 mg/dl[8] or use of insulin or hypoglycemic medications. CHD was defined as the presence of one or more of the following

conditions: myocardial infarction, angina pectoris, coronary angioplasty, or coronary artery bypass surgery. CVD was defined as the presence of one or more of the following: brain infarction, transient ischemic attack (TIA), or intra parenchymal hemorrhage.

Results

Of 331 participants between January 1, 2004 and December 31, 2006, 14 participants were excluded due to incomplete data (lack of serum creatinine level or/and TMSE), the remaining 317 participants were included.

A mean age was 71.13 years (SD = 7.99) years, 65.7% were women, 33.28% had TMSE < 24 points. The characteristics of Model 1 and 2 are shown in Table 1. The authors found that the poorer kidney function group had trend to be older and low body weight with a higher prevalence of CVD and high serum creatinine level compared with better kidney function group.

In an unadjusted analyses of the Model 1 in Table 2, the authors compared group 4; eCrCl < 30 mL/min, group 3; eCrCl 30-59 mL/min, or group 2; eCrCl 60-89 mL/min with group 1; eCrCl ≥ 90 mL/min (reference group). When compared group 4 with group 1; OR 2.17; 95% CI 0.69-10.47; p-value 0.15, group 3 with group 1; OR 0.83; 95% CI 0.35-1.97); p-value 0.68, group 2 with group 1; OR 0.52; 95% CI 0.21-1.28; p-value 0.16. The group 4 had a trend of increased prevalence of cognitive impairment, but didn't show a statistical significant. After adjusted OR with covariate factors, the outcome still exhibited no statistical significant as an indicator of increased prevalence of cognitive impairment.

After analysis of the Model 1, the authors found the greater difference of the population numbers among 4 groups. The unequal population numbers are the leading cause of inaccurate statistical analysis so the authors developed the Model 2 to correct this problem. The characteristics of Model 2 are showed in Table 1 (right panel). The authors found that the poorer kidney function group tended to be older, with low body weight and high serum creatinine level compared with the better kidney function group.

In an unadjusted analyses of the Model 2 in Table 2, the authors compared it with group 3; eCrCl < 48 mL/min, or group 2; eCrCl 48-65 mL/min, with group 1; eCrCl > 65 mL/min (reference group). When the authors compared group 3 with group 1; OR 1.62; 95% CI 0.92-2.84; p-value 0.09, group 2 with group 1; OR 0.72; 95% CI 0.39-1.32; p-value 0.29. The group 3 had a tendency to increased prevalence of cognitive impairment but it doesn't have statistical significant. After adjusted OR with covariate factors, when the authors compared group 3 with group 1, this was the result; OR 1.76; 95% CI 0.99-3.12; p-value 0.052. The authors did not find a statistical significant of increased prevalence of the cognitive impairment in eCrCl group 3 but we found that the lower eCrCl, eCrCl < 48 mL/min, may have a tendency to associate with cognitive impairment.

Discussion

This is the first study, which describes the association between lower level of kidney function and cognitive impairment in Thailand. The results of the present study show that participants with eCrCl < 48 mL/min have a trend to exhibit increased prevalence of cognitive impairment. Furthermore, this tendency is independent of the residual effects of HTN, DM, smoking, history of CHD and CVD, for these are known to confound the association between CKD and cognitive function.

Many previous studies of kidney dysfunction and cognitive impairment reported similar results. The severity of kidney dysfunction that associates with cognitive impairment ranges from moderate kidney dysfunction to advanced chronic kidney disease that requires the dialysis and both in men and women. Most study used the Modification of Diet in Renal Disease (MDRD) formula[9,12-14] to estimate kidney function, while some studies used inverse of serum creatinine[10] (1/SCr) but the authors used the Cockcroft Gault formula to estimate kidney function based on the evidence that the Cockcroft Gault formula was more accurate in the advanced chronic kidney disease conditions and in older adults[15,16]. In the Health, Aging and Body Composition Study, was conducted by Kurella et al[9] and they found that the participants with CKD had a 1.3 to 2.4 fold higher risk of cognitive decline. The Health Aging and Body Composition Study used the Cockcroft Gault formula as a part to estimate the kidney function same as the present study. Also similar to findings reported here, Seliger et al[10], found moderate kidney insufficiency, defined as an elevated serum creatinine, to be associated with a 37% increased risk for dementia among community dwelling participants who were 65 years and older and participating in the Cardiovascular Health Cognition Study. Hailpern et al[12] reported that moderate CKD, defined as an estimated GFR of 30-59 ml/min/1.73 m^2, was associated with poorer concentration and attention among 20-59 year old in the third national health and nutrition examination survey (NHANES III) partici-

Table 1. Characteristics of Model 1 and Model 2

	Baseline Creatinine Clearance (mL/min)								
	Model 1					Model 2			
	< 30 (n = 14)	30-59 (n = 158)	60-89 (n = 120)	≥ 90 (n = 25)	p-value	< 48 (n = 105)	48-65 (n = 105)	> 65 (n = 107)	p-value
Age (yr)	76.86 ± 7.44	73.62 ± 6.47	67.94 ± 5.80	66.64 ± 4.41	< 0.001	75.23 ± 6.80	70.65 ± 6.01	67.37 ± 5.32	< 0.001
Female (%)	9 (64.30)	98 (62.00)	82 (68.30)	19 (76.00)	0.48	67 (63.80)	67 (63.80)	74 (69.20)	0.64
Body weight (kg)	44.57 ± 6.77	53.10 ± 9.87	61.09 ± 10.70	65.76 ± 8.33	< 0.001	51.04 ± 9.77	55.75 ± 10.46	63.60 ± 9.68	< 0.001
Hypertension (%)	9 (64.30)	67 (42.40)	57 (47.50)	12 (48.00)	0.42	50 (47.60)	47 (44.80)	48 (44.90)	0.89
Diabetes mellitus (%)	4 (28.60)	24 (15.20)	12 (10.00)	2 (8.00)	0.17	21 (20.00)	10 (9.50)	11 (10.30)	0.04
History of previous CVD (%)	3 (21.40)	7 (4.50)	2 (1.70)	0 (0)	0.002	6 (5.80)	5 (4.80)	1 (0.90)	0.15
History of previous CHD (%)	1 (7.10)	27 (17.20)	12 (10.00)	2 (8.00)	0.23	17 (16.30)	13 (12.40)	12 (11.20)	0.52
History of Smoking (%)	7 (50.00)	51 (32.30)	33 (27.50)	8 (32.00)	0.37	33 (30.80)	37 (31.40)	29 (31.50)	0.99
Serum creatinine (mg/dL)	1.49 ± 0.41	0.99 ± 0.26	0.78 ± 0.16	0.56 ± 0.14	< 0.001	1.12 ± 0.32	0.86 ± 0.20	0.71 ± 0.16	< 0.001

CVD = Cerebrovascular diseases, CHD = Coronary heart disease

Table 2. Association between Estimated Creatinine Clearance (eCrCl) and Odds of Cognitive Impairment, Model 1 and Model 2

	eCrCl (mL/min)[+]						
	Model 1				Model 2		
Cognitive Impairment	< 30 (n = 14)	30-59 (n = 158)	60-89 (n = 120)	≥ 90 (n = 25)	< 48 (n = 105)	48-65 (n = 105)	> 65 (n = 107)
	Odds Ratio (95% Confidence Interval, p-value[++])				Odds Ratio (95% Confidence Interval, p-value[++])		
Crude (n = 317)	2.70 (0.69-10.47, 0.15)	0.83 (0.35-1.97, 0.68)	0.52 (0.21-1.28, 0.16)	1.00 (reference)	1.61 (0.92-2.82,0.09)	0.75 (0.41-1.37,0.35)	1.00 (reference)
Risk factors adjusted[+++] (n = 317)	3.82 (0.90-16.19, 0.07)	0.89 (0.37-2.13, 0.79)	0.52 (0.21-1.29, 0.16)	1.00 (reference)	1.76 (0.99-3.12, 0.052)	0.76 (0.42-1.38, 0.37)	1.00 (reference)

* Defined as TMSE < 24, eCrCl = estimated creatinine clearance
[+] eCrCl as calculated according to the Cockcroft-Gault formula
[++] Statistical significance defined as p-value < 0.05
[+++] adjusted for hypertension, diabetes mellitus, smoking, cerebrovascular diseases and coronary heart diseases

pants. In a study of CKD and hemodialysis patients by Kurella et al[17], among 80 hemodialysis patients (mean age 61.2 years), 38 percent had severe impairment in executive function and 33 percent severe memory impairment.

Many various studies used various methods to assess the cognitive function. Reasons for geographic and racial differences in stroke study (REGARDS) study, conducted by Kurella et al[14], used 6-items screener, the health aging and body composition study[9] used modified mini-mental state exam (3MS), third national health and nutrition examination survey (NHANES III)[12] used simple reaction time test (SRTT), symbol digit substitution test (SDST) and serial digit learning test (SDLT) to assess cognitive function. In the present study, the authors used TMSE to assess the cognitive function. In Thailand, TMSE is wildly and commonly used in the outpatient clinics and in epidemiological community studies. Its sensitivity and validity in Thai is well documented[7].

Age and body weight are the primary confounding factors. They are components of both MDRD and Cockcroft-Gault formulas. Therefore, if the authors used the estimated glomerular filtration rate and eCrCl that were calculated by MDRD and Cockcroft-Gault formula, respectively, to analyze the association between kidney function and cognitive impairment, interpretation of the result should be conducted with caution because the authors could not clearly exclude the age and body weight from the equation. In future studies, the direct measurement kidney function should be done to avoid the other confounding factors.

From this result, the authors could not conclude anything significant about the threshold of eCrCl level for screening cognitive impairment of older adult populations. However, the present study found that eCrCl < 48 mL/min has a trend to be associate with cognitive impairment. The limitation of the present study is that the sample size is small and only cross-sectional data was obtained. The strength of this study is that participants are recruited and the data are from a community base cohort and that is the first exploratory study about relationship between kidney function and cognitive impairment in Thai elders.

Conclusion

In our pilot study, the authors could not demonstrate the statistical significant of the association between the lower eCrCl and cognitive impairment. However, the authors found that the lower eCrCl, eCrCl < 48 mL/min, may have a tendency to associate with cognitive impairment. Because of the eCrCl and TMSE are easily obtained in outpatient setting, if future research can recruit more number of participants, the result may potentially show the significant association between lower eCrCl and cognitive impairment. Although, the authors may use the result of this association for screening prevalence of cognitive impairment in older adult population with lower kidney function and the authors should also more extensive analyze about the association of non traditional risk factors, kidney dysfunction, brain imaging finding and cognitive impairment. Using direct of kidney function measurement and neuropsychological battery test will almost certainly provide more accurate result of the future study.

Acknowledgement

The Dementia and Disability Project (DDP) is granted by Thailand Research Fund (TRF), Mahidol University 2004-2007 fiscal years and Fogathy International Research Collaborative Award (FIRCA). Professor Jeffrey L Cummings from Lou Ruvo Center for Brain Health, Cleveland Clinic, 888 W Bonneville Ave, Las Vegas, NV 89106, USA.

Potential conflicts of interest

None.

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Estimated Creatinine Clearance และภาวะความผิดปกติของ *Cognition* ในผู้สูงอายุ: การศึกษาเบื้องต้นจากข้อมูลของโครงการโรคสมองเสื่อมและภาวะทุพลภาพในประเทศไทย

ปรัชญา ศรีวานิชภูมิ, วรพรรณ เสนาณรงค์

ภูมิหลัง: *ภาวะไตวายเรื้อรังและสมองเสื่อมเป็นภาวะที่พบบ่อยในผู้สูงอายุ การศึกษาที่ผ่านมาจากประเทศสหรัฐอเมริกาพบว่ากลุ่มประชากรสูงอายุที่มีค่าการทำงานของไตน้อยกว่าปกติเป็นกลุ่มที่มีความชุกของภาวะความผิดปกติของ cognition เพิ่มขึ้น*

วัตถุประสงค์: *เพื่อแสดงถึงความเกี่ยวพันระหว่างค่าการทำงานของไตที่ลดลงกับความผิดปกติของ cognition ในประชากรผู้สูงอายุที่อยู่ในชุมชนของประเทศไทยและเพื่อหาค่าการทำงานของไตที่เหมาะสมเพื่อตรวจคัดกรองภาวะความผิดปกติของ cognition*

วัสดุและวิธีการ: *การศึกษานี้ได้คัดเลือกผู้เข้าร่วมเป็นผู้สูงอายุจากชุมชนในกรุงเทพมหานครระหว่างปีพ.ศ. 2547 ถึง พ.ศ. 2549 ผู้เข้าร่วมจะได้รับการตรวจวัดระดับค่าครีอะตินินในเลือดและได้รับการประเมิน cognition โดยการประเมินการทำงานของไตนั้นจะคำนวณด้วยสูตร Cockcroft-Gault ซึ่งผลที่ได้จะออกมาในรูปของค่า estimated creatinine clearance (eCrCl) ส่วนการทดสอบเกี่ยวกับ cognition นั้นผู้เข้าร่วมจะได้รับการทดสอบด้วยแบบทดสอบ Mini Mental State Exam ฉบับภาษาไทย (TMSE) ซึ่งในการวิจัยรูปแบบที่ 1 ผู้เข้าร่วมจะถูกแบ่งออกเป็น 4 กลุ่มโดยใช้ค่า eCrCl ซึ่งสามารถแบ่งได้เป็นกลุ่มที่มีค่า eCrCl มากกว่าหรือเท่ากับ 90, 60-89, 30-59 และน้อยกว่า 30 มิลลิลิตรต่อนาที ตามลำดับ แต่เนื่องจากการศึกษารูปแบบที่ 1 มีความแตกต่างของจำนวนผู้เข้าร่วมในแต่ละกลุ่มมาก ทางผู้วิจัยจึงได้พัฒนารูปแบบการศึกษาที่ 2 ขึ้นโดยแบ่งกลุ่มผู้เข้าร่วมเป็น 3 กลุ่มโดยใช้ค่า eCrCl ที่มากกว่า 65, 48-65 และน้อยกว่า 48 มิลลิลิตรต่อนาทีเป็นเกณฑ์ซึ่งทำให้ได้จำนวนผู้เข้าร่วมในแต่ละกลุ่มใกล้เคียงกัน ส่วนผู้เข้าร่วมที่มีค่าการทดสอบ TMSE น้อยกว่า 24 จะถูกพิจารณาว่าเป็นผู้ที่มีความผิดปกติของ cognition โดยข้อมูลการศึกษาความเกี่ยวพันระหว่างค่าการทำงานของไตและภาวะความผิดปกติของ cognition นั้นจะได้รับการวิเคราะห์ทางสถิติด้วยวิธีการวิเคราะห์ความแปรปรวนทั้งแบบตัวแปรตามเดี่ยวและตัวแปรตามหลายตัว*

ผลการศึกษา: *ผู้เข้าร่วมการศึกษาทั้งหมด 317 คน เป็นผู้หญิง 207 คน คิดเป็นร้อยละ 65.71 ค่าอายุเฉลี่ย 71.13 ปี ค่าเบี่ยงเบนมาตรฐานเท่ากับ 7.99 ซึ่งรูปแบบการศึกษาที่ 1 ผู้วิจัยพบว่าผู้เข้าร่วมที่อยู่ในกลุ่มที่ eCrCl น้อยกว่า 30 มิลลิลิตรต่อนาทีนั้นมีแนวโน้มที่จะมีภาวะความผิดปกติของ cognition มากกว่าเมื่อเทียบกับกลุ่มที่ eCrCl มากกว่าเท่ากับ 90 มิลลิลิตรต่อนาที โดยค่า odds ratio เท่ากับ 3.82 ค่า 95%CI อยู่ในช่วงตั้งแต่ 0.90 ถึง 16.19 และค่า p เท่ากับ 0.07 และเมื่อพิจารณารูปแบบการศึกษาที่ 2 พบว่าผู้เข้าร่วมการศึกษาที่อยู่ในกลุ่มที่ eCrCl น้อยกว่า 48 มิลลิลิตรต่อนาทีนั้นมีแนวโน้มที่จะมีภาวะความผิดปกติของ cognition มากกว่าเมื่อเทียบกับกลุ่มที่ eCrCl มากกว่า 65 โดยค่า odds ratio เท่ากับ 1.76 ค่า 95%CI อยู่ในช่วงตั้งแต่ 0.99 ถึง 3.12 และค่า p เท่ากับ 0.52*

สรุป: *การศึกษาในเบื้องต้นนี้ไม่สามารถแสดงถึงความเกี่ยวพันระหว่างค่าการทำงานของไตที่ลดลงกับภาวะความผิดปกติของ cognition ได้อย่างมีนัยยะสำคัญทางสถิติ แต่อย่างไรก็ตามการที่ผู้สูงอายุมีค่าการทำงานของไตที่น้อยกว่า 48 มิลลิลิตรต่อนาทีนั้นมีแนวโน้มที่จะพบภาวะความผิดปกติของ cognition ได้ ดังนั้นการตรวจคัดกรองภาวะความผิดปกติของ cognition อาจพิจารณาทำในกรณีที่ผู้สูงอายุมีค่าการทำงานของไตน้อยกว่า 48 มิลลิลิตรต่อนาที*