ORIGINAL RESEARCH

Differential Association Between Significant Coronary Stenosis and Cardiac Troponin T Serial Algorithms in Chronic Kidney Disease Patients Diagnosed with Non-ST-Segment Elevation Acute Coronary Syndromes

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Background: High-sensitivity cardiac troponin T (hs-cTnT) is recommended for diagnosing non-ST segment elevation acute coronary syndromes (NSTE-ACS). While the guidelines recommend using the 0,1-hour (hr) and 0,3-hr hs-cTnT algorithms, their efficacy has not been clearly established in chronic kidney disease (CKD) patients. We aimed to assess the differential associations between the two algorithms mentioned above with significant coronary stenosis in CKD patients.

Methods: This was a retrospective cohort study. Patients aged ≥18 years who were diagnosed with NSTE-ACS and had undergone coronary angiogram were recruited. The differential association between significant coronary stenosis and being ruled in based on the 0,1-hr and 0,3-hr hs-cTnT algorithm was analyzed and reported.

Results: There were 158 and 160 patients in the CKD and normal renal function groups. Among CKD patients, determinants of significant coronary stenosis were hypertension (OR = 2.68; 95% CI 1.10–6.50) and being ruled in by the 0,3-hr algorithm (OR = 3.65; 95% CI 1.27–10.52). In the normal renal function group, age (OR = 1.04; 95% CI 1.01–1.06), male sex (OR = 2.15; 95% CI 1.09–4.22), and being ruled in by the 0,1-hr algorithm (OR = 3.12; 95% CI 1.20–8.10) were associated with significant coronary stenosis.

Conclusion: Being ruled in according to the 0,3-hr algorithm was significantly associated with coronary stenosis in CKD patients, making this a likely algorithm of choice in these patients.

Keywords: renal dysfunction, cardiac biomarkers, troponin, acute coronary syndromes, Asian

Introduction

Coronary artery disease (CAD) is a leading cause of death worldwide.[1] There are several known atherosclerotic risk factors for CAD, both reversible and irreversible.[2] One significant risk factor is renal dysfunction.[3,4] Patients who have an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 or chronic kidney disease (CKD)[5] are at risk of cardiovascular disease, partly due to preexisting cardiovascular risk factors (eg, hypertension and dyslipidemia).[3,6–8] Other novel cardiovascular risk factors in CKD patients are chronic inflammation, calcium–phosphate metabolism disturbances, oxidative stress, malnutrition, anemia, fluid overload, fluctuation in systemic fluid volume, disturbances in the coagulation system, accumulation of metabolic products, and numerous undefined toxic agents associated with atherosclerosis.[9–11] Unfortunately, the diagnosis of CAD in CKD patients often requires thorough history taking and physical examination as well as a high level of suspicion due to their atypical presentations.[12]

Generally, an electrocardiogram (ECG) is performed in patients who present at the emergency department (ED) with symptoms compatible with acute coronary syndromes (ACS). If the ECG does not show ST-segment elevation

myocardial infarction (STEMI), high-sensitivity cardiac troponin (hs-cTn) is recommended as a cardiac biomarker for evaluating whether patients have non-ST segment elevation acute coronary syndromes (NSTE-ACS).[13]

CKD is one of the determinants of cardiac troponin (cTn) level.[14] There is evidence of chronic cTn elevation in CKD patients, even in the absence of significant coronary artery stenosis.[15] There have also been studies aimed at determining the cTn cut-off level for diagnosing myocardial infarction in CKD patients.[16–18] However, serial testing has yielded the best results in the screening for and diagnosing of NSTE-ACS in both CKD patients and those with normal renal function.[19–23]

Previous treatment guidelines recommended using a 0,3-hour algorithm in the serial testing of cTn, and this method has since been adopted worldwide.[24] However, due to the development of hs-cTn assays, the latest European Society of Cardiology (ESC) guidelines for the management of ACS in patients presenting without persistent ST-segment elevation recommend the use of a 0,1-hour algorithm regardless of renal function to rule in and rule out NSTE-ACS at the ED rapidly.[13] Many studies, however, have shown the efficacy of the 0,1-hour algorithm to be lower than that of the 0,3-hour algorithm in CKD patients.[19,23] Furthermore, in current real-world practice, it is not uncommon for ED physicians to use the 0,3-hour algorithm to test for NSTE-ACS regardless of the recommendations.[22,23]

We, therefore, aimed to assess the differential association between these two algorithms and significant coronary stenosis in CKD patients.

Materials and Methods
Study Design and Population
This was a retrospective cohort study conducted in the ED of Srinagarind hospital, a 1000-bed tertiary care university hospital in northeast Thailand, from December 2014 to December 2018.

Patients aged 18 years (yr) or over who presented with chest pain were initially diagnosed with NSTE-ACS and underwent coronary angiogram (CAG) during the same admission were recruited. Patients who presented with cardiac arrest or had incomplete data regarding serum creatinine levels, CAG, or hs-cTnT were excluded from the study.

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Khon Kaen University Ethics Committee for Human Research approved the study and waived the written individual informed consent as the research is no more than minimal risk. To protect confidentiality, all identifiers were eliminated from the obtained data (HE621312).

Operating Definitions
NSTE-ACS
NSTE-ACS, including unstable angina and non-ST-elevation myocardial infarction (NSTEMI), was diagnosed by an intervention cardiologist on duty according to the 4th universal definition of myocardial infarction criteria (details are provided in the Online Supplementary Materials).[25]

CKD
CKD was defined as an eGFR of less than 60 mL/min/1.73 m^2 computed according to the KDICO formula (details are provided in the Online Supplementary Materials).[26]

0,1-hr Algorithm
NSTE-ACS was ruled in according to the 0,1-hr algorithm if hs-cTnT was ≥52 ng/l at presentation or if the difference between hs-cTnT at presentation and after 1 hour was ≥5 ng/l (Figure 1) in accordance with the latest ESC guidelines.[13]

0,3-hr Algorithm
NSTE-ACS was ruled in according to the 0,3-hr algorithm if hs-cTnT was ≥70 ng/l at presentation, if there was a >20% difference in hs-cTnT at presentation and after 3 hours, if hs-cTnT at presentation was ≥14 ng/l, or if there was a >7 ng/l change in hs-cTnT after 3 hours, if hs-cTnT at presentation was <14 ng/l (Figure 2), according to the 2015 ESC guidelines.[24]
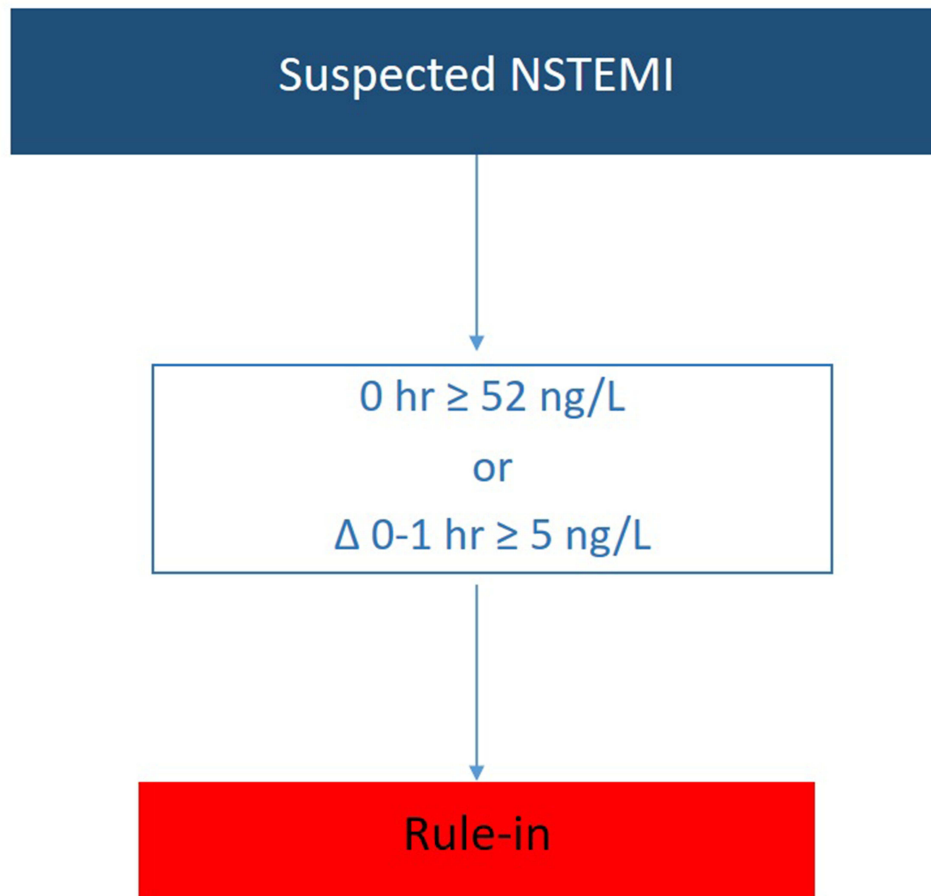
Figure 1 0,1-hr rule-in algorithms using hs-cTnT assays (Elecsys®) in patients presenting with suspected non-ST-elevation acute coronary syndromes.
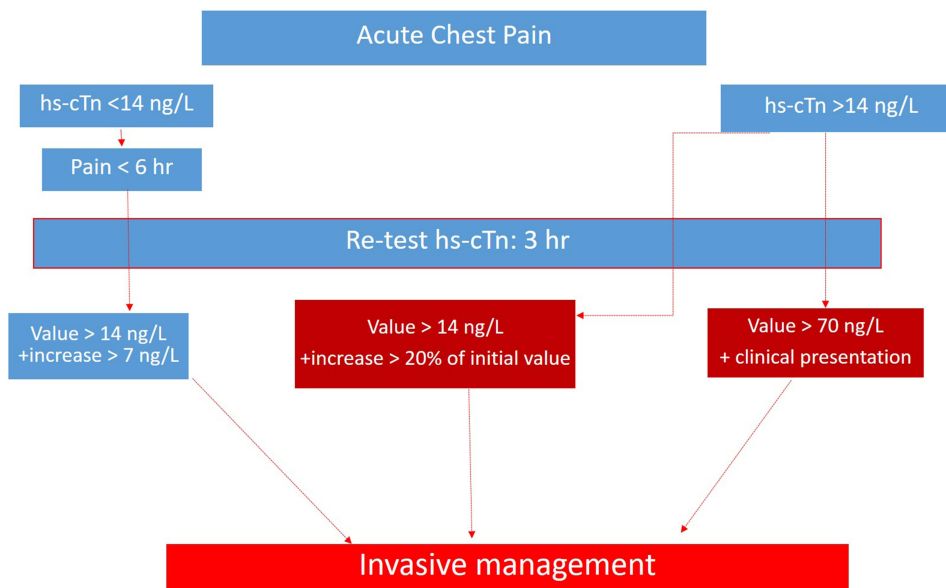

Figure 2 0,3-hr rule-in algorithm of non-ST-elevation acute coronary syndromes using high-sensitivity cardiac troponin assays (Elecsys®).

Positive CAG

Positive CAG was defined as >50% stenosis of the left main coronary artery or >70% stenosis of right coronary artery (RCA), left circumflex coronary artery (LCx), or left anterior descending (LAD) coronary artery.[27]

Primary Outcome and Statistical Analysis

The primary outcome was the association between significant coronary stenosis and NSTE-ACS being ruled in based on the two hs-cTnT algorithms (0,1-hr and 0,3-hr) in both CKD patients and those with normal renal function. The secondary outcomes were other determinants of significant coronary stenosis.

The patient's baseline characteristics and clinical measurements were reported as mean ± standard deviation (SD) for continuous variables and number and percentage for categorical variables. For comparison between the CKD and the normal renal function groups, an independent sample *t*-test was used for continuous variables and Pearson's chi-square test for proportions for categorical variables.

We used the cross tables derived from the official ESC assay-specific cut-off criteria for rule-in to determine the rule-in group.[13,24] The association between significant coronary stenosis and rule-in status as a categorical variable (1 = ruled in, 0 = not ruled in) together with other conventional cardiovascular risk factors were subjected to binary logistic regression analysis and presented as unadjusted odd ratios (OR). Considering clinical importance and using $P < 0.20$ as a criterion, age, sex (male), and hypertension (HT) were included in the regression analysis, with the rule-in group from the 0,1-hr algorithm in model 1 and the 0,3-hr algorithm in model 2. The adjusted ORs were also reported.

All hypothesis testing was 2-tailed, and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics for MAC, version 23.0 (SPSS Inc).

Results

Patient Characteristics

We enrolled 318 patients in this study, 158 in the CKD group and 160 in the normal renal function group. Baseline characteristics of patients with CKD differed from those with normal renal function in multiple respects, including older age (70 yr vs 62 yr, $P < 0.001$) and higher prevalence of HT and diabetes mellitus (DM; 83.0% vs 54.7% and 63.3% vs 26.7%, respectively; $P < 0001$). More patients in the CKD group were ruled in by both the 0,1-hr and the 0,3-hr algorithm (Table 1).

There was a higher prevalence of significant coronary stenosis in the CKD group than in the normal renal function group (70.4% vs 57.8%, $P = 0.028$). Furthermore, length of stay (LOS) was longer in the former group than in the latter (16 days vs 11 days, $P = 0.007$; Table 1).

Determinants of a Significant Coronary Stenosis

Factors associated with significant coronary stenosis in the total study population were an older age (OR = 1.04; 95% CI 1.02–1.06), male sex (OR = 1.82; 95% CI 1.12–2.95), HT (OR = 1.93; 95% CI 1.16–3.22), and NSTE-ACS being ruled in by the 0,1-hr algorithm (OR = 3.53; 95% CI 1.61–7.73) or 0,3-hr algorithm (OR 2.24; 95% CI = 1.16–4.34, Table 2).

Among CKD patients, factors associated with significant coronary stenosis were HT (OR = 2.68; 95% CI 1.10–6.50), and NSTE-ACS being ruled in based on the 0,3-hr algorithm (OR = 3.65; 95% CI 1.27–10.52; Table 2). In the normal renal function group, factors associated with significant coronary stenosis were older age (OR = 1.04; 95% CI 1.01–1.06), male sex (OR = 2.15; 95% CI 1.09–4.22), and NSTE-ACS being ruled in by the 0,1-hr algorithm (OR = 3.12; 95% CI 1.20–8.10).

After adjusting for age, male sex, and HT, patients in the total population ruled in by either the 0,1-hr algorithm or 0,3-hr algorithm were significantly more likely to have significant coronary stenosis (OR = 3.09; 95% CI 1.37–6.94 and OR = 2.60; 95% CI 1.27–5.34, respectively; Table 3). However, NSTE-ACS being ruled in by the 0,3-hr algorithm was the only independent determinant of significant coronary stenosis in the CKD patients. In patients with normal renal function, older age, male sex, and NSTE-ACS being ruled in by the 0,1-hr algorithm were significantly associated with significant coronary stenosis, but being ruled in by the 0,3-hr algorithm was not (Table 3).

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Table 1 Baseline Characteristics of the NSTE-ACS Patients, Categorized by Kidney Function

	All Patients (N=318)	Patients with CKD (n=158)	Patients without CKD (n=160)	P
Age, years	66.3±13.1	70.3±10.4	62.4±14.2	<0.001
Male, n (%)	182 (57.2)	85 (53.8)	97 (60.6)	0.257
Chest pain onset, hr	455±1084	569±1310	343.5±791	0.074
Duration of chest pain, hr	3.68±15.17	3.52±18.51	3.84±11.02	0.858
Initial vital signs:				
SBP, mmHg	136±31	139±32	133±29	0.089
DBP, mmHg	72±17	71±16	74±19	0.097
PR, bpm	83±20	82±19	84±21	0.316
O_2 sat, %	95±13	96±6	94±17	0.116
Laboratory results:				
eGFR	58.3±35.1	28.3±19.2	88.0±17.8	<0.001
NT-proBNP, pg/mL	1750.0±8057.6	2730.5±11,054.9	781.9±2621.1	0.031
Initial hs-cTnT, ng/dL	413.92±1277.80	376.69±830.26	450.68±1603.70	0.606
1-hr, ng/dL	371.79±1131.12	238.59±304.51	479.04±1490.85	0.214
3-hr, ng/dL	479.61±1318.15	560.02±1359.32	387.00±1271.37	0.395
1-hr algorithm, n (%)	200 (85.1)	124 (93.9)	76 (73.8)	<0.001
3-hr algorithm	191 (78)	115 (85.8)	76 (68.5)	0.002
Hypertension, n (%)	204 (68.7)	122 (83.0)	82 (54.7)	<0.001
Diabetes mellitus, n (%)	133 (44.8)	93 (63.3)	40 (26.7)	<0.001
Ejection fraction, %	37.9±24.9	39.9±23.5	35.9±26.2	0.162
LV mass index	132.6±53.5	130.9±52.3	133.9±55.6	0.865
Positive CAG results, n (%)	185 (64)	100 (70.4)	85 (57.8)	0.028
- SVD, n (%)	69 (23.9)	31 (21.8)	38 (25.9)	0.491
- DVD, n (%)	45 (15.6)	25 (17.6)	20 (13.6)	0.418
- TVD, n (%)	68 (23.5)	42 (29.6)	26 (17.7)	0.019
- LM disease, n (%)	32 (11.1)	21 (14.8)	11 (7.5)	0.060
PCI/CABG performed, n (%)	154 (53.1)	82 (57.3)	72 (49)	0.160
LOS, day	13±16	16±17	11±16	0.007
Dead, n (%)	17 (6.3)	11 (8)	6 (4.5)	0.317

Abbreviations: NSTE-ACS, non-ST segment elevation acute coronary syndromes; hr, hour; SBP, systolic blood pressure; DBP, diastolic blood pressure; mmHg, millimeter of mercury; PR, pulse rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; CAG, Coronary Angiogram; SVD, single vessel disease; DVD, double vessel disease; TVD, tripple vessel disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LOS, length of stay.

Table 2 Unadjusted Odd Ratio (OR) of a Significant Coronary Stenosis by Using Regression Analysis in the Total Population and After Categorized by Kidney Function

Covariates	Total Population (N=318)		CKD (n=158)		Non-CKD (n=160)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age, per 1 year	1.04 (1.02–1.06)	<0.001	1.03 (1.00–1.07)	0.080	1.04 (1.01–1.06)	0.008
Sex, (Men=1, Women =0)	1.82 (1.12–2.95)	0.016	1.67 (0.81–3.46)	0.165	2.15 (1.09–4.22)	0.027
Creatinine, per 1 mg/dL	1.08 (0.98–1.19)	0.103	1.03 (0.93–1.15)	0.550	1.76 (0.36–8.51)	0.485
Hypertension, (1=Yes, 0=No)	1.93 (1.16–3.22)	0.012	2.68 (1.10–6.50)	0.030	1.34 (0.69–2.59)	0.385
Ejection fraction, per 1%	1.01 (1.00–1.02)	0.276	1.01 (1.00–1.03)	0.163	1.00 (0.99–1.01)	0.919
Rule in 0,1 hr	3.53 (1.61–7.73)	0.002	3.72 (0.79–17.65)	0.098	3.12 (1.20–8.10)	0.020
Rule in 0,3 hr	2.24 (1.16–4.34)	0.017	3.65 (1.27–10.52)	0.016	1.34 (0.56–3.18)	0.510

Abbreviation: hr, hour.

Table 3 Adjusted Odd Ratio (OR) of a Significant Coronary Stenosis by Using Regression Analysis

Covariates	Total Population (N=318)		CKD (n=158)		Non-CKD (n=160)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Model 1						
Age, per 1 year	1.03 (1.01–1.06)	0.025	1.02 (0.98–1.06)	0.428	1.04 (1.01–1.08)	0.034
Sex, (Men=1, Women =0)	2.34 (1.24–4.43)	0.009	1.34 (0.57–3.15)	0.496	4.80 (1.74–13.27)	0.003
Hypertension, (1=Yes, 0=No)	1.59 (0.80–3.16)	0.185	1.55 (0.52–4.64)	0.431	1.94 (0.70–5.42)	0.205
Rule in 0,1 hr	3.09 (1.37–6.94)	0.006	3.00 (0.60–15.00)	0.181	3.69 (1.29–10.56)	0.015
Model 2						
Age, per 1 year	1.04 (1.02–1.07)	0.001	1.02 (0.98–1.06)	0.453	1.06 (1.02–1.10)	0.001
Sex, (Men=1, Women =0)	3.27 (1.73–6.18)	<0.001	1.85 (0.77–4.40)	0.165	6.25 (2.28–17.14)	<0.001
Hypertension, (1=Yes, 0=No)	1.38 (0.71–2.71)	0.345	1.97 (0.64–6.01)	0.236	0.95 (0.38–2.37)	0.917
Rule in 0,3 hr	2.60 (1.27–5.34)	0.009	3.17 (1.06–9.52)	0.040	2.39 (0.87–6.60)	0.092

Abbreviation: hr, hour.

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Discussion

This study showed that being ruled in by either the 0,1-hr algorithm or the 0,3-hr algorithm was significantly associated with significant coronary stenosis in patients with suspected NSTE-ACS. However, there was a differential association between the rule-in group determined by each algorithm in CKD patients. CKD patients ruled in based on the 0,3-hr algorithm but not the 0,1-hr algorithm were more likely to have significant coronary stenosis.

In a 2018 study by Twerenbold et al,[19] the 0,1-hr algorithm yielded a lower specificity and overall efficacy in CKD patients than those with normal renal function (96.5% vs 88.7% and 81% vs 51%, respectively). Furthermore, Chesnaye et al found that CKD patients had chronically elevated cTn.[15] In addition, Sittichanbuncha et al, Chenevier-Gobeaux et al, and Van Lente et al found a higher cTn cut-off point to be more effective in CKD patients.[16–18]

Studies by Eggers et al and Chesnaye et al found that cTn was elevated in conditions other than type 1 myocardial infarction (MI) such as tachycardia, heart failure, and hypertensive crisis.[14,15] The two algorithms' differential association with significant coronary stenosis in this study may be explained by the false or chronic elevation of hs-cTnT in CKD patients. The initial hs-cTnT cut-off level for the 0,1-hr algorithm is 52 ng/L, much lower than that of the 0,3-hr algorithm (70 ng/L). The lower cut-off level of the 0,1-hr algorithm might result in patients being recruited whose hs-cTnT elevation is caused by diseases or conditions other than type 1 MI.

Our study showed that the determinants of significant coronary stenosis patients with normal renal function were older age and male sex, generally considered conventional risk factors for CAD.[2] Another factor significantly associated with significant coronary stenosis was NSTE-ACS being ruled in based on the 0,1-hr algorithm, which has proven its efficacy and is recommended for use in the latest ESC guidelines.[13] However, we found that being ruled in based on the 0,3-hr algorithm was not associated with significant coronary stenosis. A possible explanation might be that a 3-hour interval for serial hs-cTnT measurement allows for its elevation by conditions associated with cardiac myocyte injury other than acute type 1 MI. This hypothesis is supported by some previous studies, which have attributed cTn release to tachycardia, pericarditis, congestive heart failure, myocarditis, Takotsubo syndrome, pulmonary embolus, hypertrophic cardiomyopathy, and severe aortic stenosis.[28,29] Furthermore, we explored the final diagnoses in patients with a normal renal function whose coronary angiograms did not reveal significant lesions. These patients were diagnosed with vasospasm (17%), arrhythmias (13%), myocarditis (13%), heart failure (13%), sepsis (13%), hypertrophic cardiomyopathy (6%), stroke (6%), Takotsubo syndrome (6%), and endocarditis (3%).

To the best of our knowledge, this was the first study to examine the association between significant coronary stenosis and the hs-cTnT algorithm used. All coronary angiograms were performed in the same tertiary care center. The same hs-cTnT assay (Elecsys®) was used for both the 0,1-hr and 0,3-hr algorithm, which allowed for clear data, unbiased comparison. However, there were some potential limitations to this study. First, due to the retrospective nature of the data collection, some laboratory data and some risk factors that might influence the results were missing. Second, although interventional cardiologists determined coronary angiogram results, we did not collect the data regarding any additional angiogram methods used such as intravascular ultrasound (IVUS) or fractional flow reserve (FFR). Third, this was a single-center study conducted at a university hospital in rural Thailand, apart from the relatively small sample size which may have some effect on the power of the study, our study population may differ from others in terms of biological, genetic, and cultural factors. Care should thus be taken when extrapolating the results.

Conclusions

Patients ruled in using the 0,3-hr algorithm were significantly more likely to have significant coronary stenosis, making this algorithm a possible algorithm of choice in CKD patients. However, a randomized clinical trial might be needed to determine the clinical efficacy of this algorithm in predicting coronary angiogram results in CKD patients.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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