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Original Article

ORIGINAL ARTICLE

Kidney function–specific cut-off values of high-sensitivity cardiac troponin T for the diagnosis of acute myocardial infarction

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ABSTRACT

Background. The diagnosis of acute myocardial infarction (AMI) using high-sensitivity cardiac troponin T (hs-cTnT) remains challenging in patients with kidney dysfunction.

Methods. In this large, multicenter cohort study, a total of 20 912 adults who underwent coronary angiography were included. Kidney function–specific cut-off values of hs-cTnT were determined to improve the specificity without sacrificing sensitivity, as compared with that using traditional cut-off value (14 ng/L) in the normal kidney function group. The diagnostic accuracy of the novel cut-off values was validated in an independent validation cohort.

Results. In the derivation cohort ($n = 12\,900$), 3247 patients had an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Even in the absence of AMI, 50.2% of participants with eGFR <60 mL/min/1.73 m^2 had a hs-cTnT concentration ≥ 14 ng/L. Using 14 ng/L as the threshold of hs-cTnT for diagnosing AMI led to a significantly reduced specificity and positive predictive value in patients with kidney dysfunction, as compared with that in patients with normal kidney function. The kidney function–specific cut-off values were determined as 14, 18 and 48 ng/L for patients with eGFR >60, 60–30 and <30 mL/min/1.73 m^2, respectively. Using the novel cut-off values, the specificities for diagnosing AMI in participants with different levels of kidney dysfunction were remarkably improved (from 9.1%–52.7% to 52.8–63.0%), without compromising sensitivity (96.6%–97.9%). Similar improvement of diagnostic accuracy was observed in the validation cohort ($n = 8012$).

Conclusions. The kidney function–specific cut-off values of hs-cTnT may help clinicians to accurately diagnose AMI in patients with kidney dysfunction and avoid the potential overtreatment in practice.

Keywords: acute myocardial infarction, high-sensitivity troponin T, renal dysfunction

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KEY LEARNING POINTS

What was known:

- Acute myocardial infarction (AMI) is prevalent in patients with kidney dysfunction.
- In patients with kidney dysfunction, using the traditional cut-off value of high-sensitivity cardiac troponin T (hs-cTnT) reduced the specificity for diagnosing AMI.

This study adds:

- The kidney function–specific cut-off values of hs-cTnT determined in patients with varying level of an estimated glomerular filtration rate by a principle without sacrificing sensitivity, were developed, and validated the improved specificity in the validation cohort.
- Using the kidney function–specific cut-off values, the performances of hs-cTnT for diagnosing AMI were improved.

Potential impact:

- The kidney function–specific cut-off values of hs-cTnT may help clinicians to accurately diagnose AMI in patients with kidney dysfunction and avoid the potential overtreatment in practice.

INTRODUCTION

Acute myocardial infarction (AMI) is the leading cause of death worldwide [1]. Early screening and accurate diagnosis of AMI are critical in the clinical practice. High-sensitivity cardiac troponin T (hs-cTnT) is a sensitive biomarker and is recommended to screen for AMI. Current guidelines recommend a cut-off of 14 ng/L of hs-cTnT, the 99th percentile upper reference limit drawn from healthy population, for the diagnosis of AMI [2, 3].

However, previous studies reported that 32%–74% of patients with chronic kidney disease (CKD) exhibit an increase in the level of hs-cTnT, exceeding 14 ng/L, even in patients without AMI [4–7]. Sub-analyses of prospective cohort studies have shown a reduced diagnostic performance of high-sensitivity cardiac troponin in patients with impaired kidney function [7–10]. The specificity and positive predictive value of hs-cTnT for AMI, using the cut-off value of 14 ng/L, are significantly lower in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 than in those with preserved kidney function [7–12]. Diagnosing AMI in patients with CKD remains challenging [13–16], particularly due to the absence of a specific cut-off value of hs-cTnT to optimize the diagnostic accuracy of AMI in patients with kidney dysfunction.

We therefore conducted a multicenter, observational cohort study including 20 912 hospitalized patients who received percutaneous coronary angiography (CAG). The diagnostic accuracy of hs-cTnT for AMI in patients stratified by eGFR levels was examined. Furthermore, kidney function–specific cut-off values of hs-cTnT were determined in patients with different levels of kidney dysfunction and were validated in an independent validation cohort. Given that AMI is a common and life-threatening complication in patients with CKD, this study may help clinicians accurately diagnose AMI in the clinical practice.

MATERIALS AND METHODS

Study population and data source

The study population was selected from hospitalized patients in six tertiary hospitals around China from 1 January 2016, to 31 December 2019. The electronic health records were relied on data from the China Renal Data System (CRDS) database (http://www.crds-network.org.cn/#/database). The recorded data comprised the patients' demographic characteristics, physical measurements, diagnosis data based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), prescription information, surgical details, laboratory test results and medical notes, and other relevant data. To ensure data quality, the database underwent a process of anonymization, cleaning, standardization and pooling at the CRDS data center located at the National Clinical Research Center of Kidney Disease in Guangzhou. The accuracy and completeness of this database have been verified in our previous research [17, 18].

The study initially included 142 818 patients aged >18 years old who received at least one hs-cTnT test (Roche, reference range from 3 ng/L to 14 ng/L) during hospitalization. Patients who did not undergo CAG were excluded. Considering that the atypical characteristics of patients with eGFR higher than 120 mL/min/1.73 m^2 and the strong correlation between hs-cTnT levels and dialysis process time, we further excluded the following participants: (i) lack of available demographic information, (ii) no serum creatinine (Scr) test, (iii) eGFR $\geq$120 mL/min/1.73 m^2, (iv) received dialysis during hospitalization, and (v) diagnosed with acute kidney injury (AKI) before CAG, based on the diagnosis code, or the detection algorithm established by Xu *et al.* [19].

Participants were divided into the derivation cohort (hospital 1–5) and validation cohort (hospital 6). The derivation cohort was used to determine the kidney function–specific thresholds of hs-cTnT and the validation cohort was used to evaluate the diagnostic performance of eGFR-adjusted cut-off values of hs-cTnT, respectively. Figure 1 shows the flowchart of this study.

The investigation was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University (NFEC-2019-213) and the China Office of Human Genetic Resources for Data Preservation Application (2021-BC0037). The study waived the requirement for patient informed consent because of the retrospective nature. This study was conducted in accordance with the Declaration of Helsinki and according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. This study meets all five of the CODE-EHR minimum framework standards for the use of structured healthcare data in clinical research.

Kidney function and other covariates

For each hs-cTnT test, the patient's kidney function was calculated by the Chronic Kidney Disease Epidemiology Collaboration 2009 formula [20] using the closest Scr measurement obtained within 48 h. Kidney dysfunction was defined as eGFR <60 mL/min/1.73 m^2 at baseline.

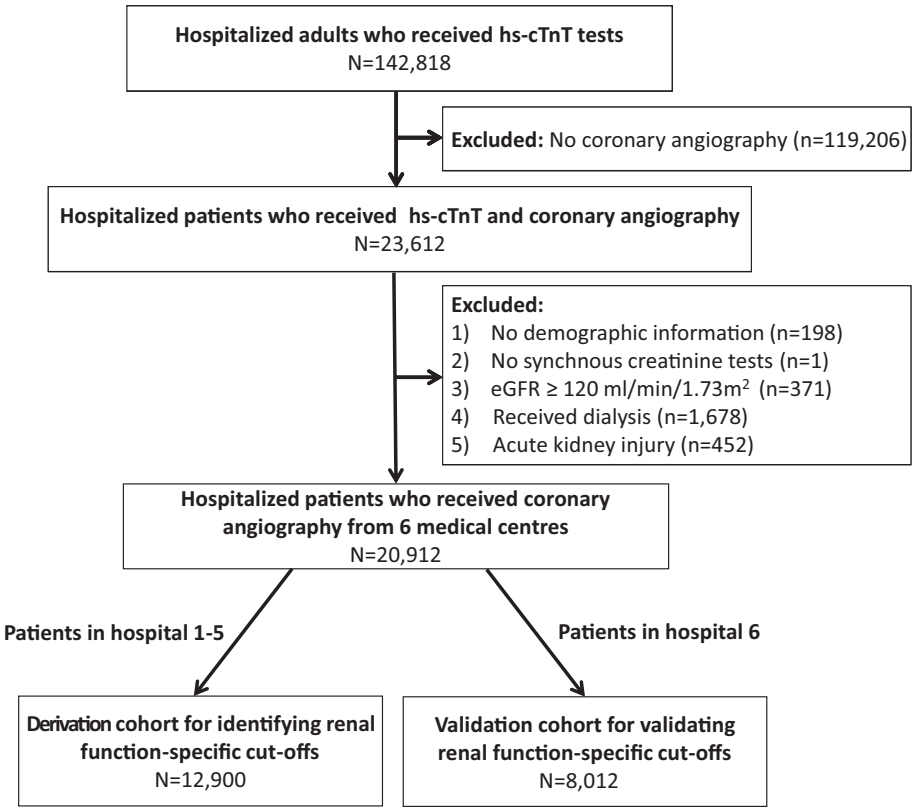


Figure 1: Flowchart of the study population.

All medications were coded according to the Anatomical Therapeutic Chemical classification system, including blood pressure–lowering drugs [angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blocker, β-blocker and α-blocker], lipid-lowering drugs, diuretics and antiplatelet drugs. Co-medications were defined based on prescriptions issued within a 3-day window before or after the troponin test. All available diagnostic codes in the ICD-10-CM before and at discharge were used to define comorbidities, which included diabetes, hypertension, hyperlipidemia, malignancy, heart failure, chronic obstructive pulmonary disease, atrial fibrillation and supraventricular tachycardia.

Exposure

The study only included hs-cTnT test measured by Roche, with reference range from 3 ng/L to 14 ng/L. The cut-off value of Roche hs-cTnT test is 14 ng/L. For simulating real-world clinical scenarios, such as elective surgery for non-ST segment elevation myocardial infarction, the highest value of hs-cTnT before CAG within 3 days was utilized for evaluating the performance of each hs-cTnT cut-off value.

Outcomes

The study outcome was the diagnosis of AMI, which was determined by the ICD-10-CM code (I21). It is worth mentioning that the diagnosis data were made by the charge clinicians with all available medical records, including the chief complaint, the laboratory data, the hospitalization notes and CAG records. AMI without significant coronary obstruction (myocardial infarction with nonobstructive coronary arteries) was also captured in the study. In the analysis, the diagnosis records were also reviewed and verified by two experienced clinicians. To ensure the accuracy of outcome, only the diagnostic information at discharge were used for defining AMI.

Statistical analysis

Baseline was defined as the time of CAG. For patients who received multiple CAGs over one or more visits, only the first CAG was included in the analysis. Baseline characteristics were presented as the mean (standard deviation) or median (interquartile range) for normally or nonnormally distributed continuous variables, respectively, and as the frequency (percentage) for categorical variables.

The highest hs-cTnT concentration measured before CAG was used for the analysis. To evaluate the screening performance of hs-cTnT using a particular cut-off value for the diagnosis of AMI, specificity, sensitivity, negative predictive value (NPV) and positive predictive value (PPV) were calculated. The NPV was calculated as the number of patients without an AMI diagnosis (true negative) divided by the total number of people with a hs-cTnT concentration lower than the cut-off value (test negative). The PPV and NPV were calculated according to Equations (1) and (2), respectively:

$$NPV = \frac{true\ negative}{true\ negative + false\ negative} \quad (1)$$

$$PPV = \frac{true\ positive}{true\ positive + false\ positive} \quad (2)$$

Table 1: Baseline characteristics of the derivation population.[a]

Patients' clinical characteristics	No AMI		AMI	
	eGFR ≥60 (N = 8741)	eGFR <60 (N = 2957)	eGFR ≥60 (N = 912)	eGFR <60 (N = 290)
Male, *n* (%)	5226 (59.8)	1625 (55.0)	745 (81.7)	190 (65.5)
Age, years	63 (55, 69)	72 (65, 78)	61 (53, 69)	74 (65, 80)
hs-cTnT, ng/L	8 (5, 14)	14 (8, 29)	1063 (272, 3501)	994 (258, 3857)
Patients with hs-cTnT ≥14 ng/L, *n* (%)	2182 (25.0)	1485 (50.2)	879 (96.4)	297 (99.0)
eGFR, mL/min/1.73 m^2	79 (70, 89)	51 (43, 56)	86 (73, 97)	46 (36, 54)
Hemoglobin, g/L	136 (126, 146)	128 (116, 139)	137 (126, 147)	120 (107, 134)
Albumin, g/L	40 (37, 43)	38 (35, 41)	40 (36, 43)	37 (34, 40)
CRP high, *n* (%)[b]	2036 (23.3)	1019 (34.5)	416 (45.6)	166 (57.2)
Comorbidities, *n* (%)				
Diabetes	1713 (19.6)	757 (25.6)	245 (26.9)	127 (43.8)
Hypertension	4165 (47.6)	1760 (59.5)	440 (48.2)	205 (70.7)
Hyperlipidemia	2180 (24.9)	684 (23.1)	300 (32.9)	97 (33.4)
Malignancy	376 (4.3)	172 (5.8)	38 (4.2)	17 (5.9)
Heart failure	1290 (14.8)	627 (21.2)	444 (48.7)	172 (59.3)
COPD	352 (4.0)	176 (6.0)	43 (4.7)	25 (8.6)
Arrhythmia[c]	666 (7.6)	284 (9.6)	38 (4.2)	27 (9.3)
Co-medications, *n* (%)[d]				
ACEI/ARB	4582 (52.4)	2097 (70.9)	624 (68.4)	218 (75.2)
Other BP-lowering drugs	6621 (75.7)	2559 (86.5)	777 (85.2)	254 (87.6)
Lipid-lowering drugs	7840 (89.7)	2704 (91.4)	897 (98.4)	286 (98.6)
Diuretics	763 (8.7)	551 (18.6)	83 (9.1)	72 (24.8)
Antiplatelet drugs	7418 (84.9)	2642 (89.3)	899 (98.6)	287 (99.0)

[a]Continuous variables are presented as median (25th percentile, 75th percentile).
[b]The high CRP was defined as a CRP level >10 mg/L or a high-sensitivity CRP level >3 mg/L.
[c]Arrhythmia included atrial fibrillation and supraventricular tachycardia.
[d]BP-lowering drugs included ACEI/ARBs, β-blockers, calcium channel blockers and α-blockers. The lipid-lowering drugs included all agents in the class C10 based on Anatomical Therapeutic Chemical code and their combinations, such as statins, fibrates and ezetimibe.
BP, blood pressure; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease.

To determine the kidney function–specific cut-off values, we exhaustively tested the sensitivity and specificity of different cutoffs, which started at 14 ng/L and increased by 1 ng/L (15 ng/L, 16 ng/L, 17 ng/L, etc.). The primary objective of establishing kidney function–specific hs-cTnT levels is to avoid individuals without AMI from being misdiagnosed as AMI based on traditional cut-off value. In patients with different levels of kidney dysfunction, we expected the new cut-off values to achieve a sensitivity equal to or higher than that using 14 ng/L as the cut-off in the normal kidney function group, and with a specificity as high as possible. The performance in terms of sensitivity, specificity, NPV and PPV for kidney function–specific thresholds were further evaluated in the independent validation cohort.

Subgroup analyses were conducted to compare the performance of using a cut-off value of 14 ng/L for diagnosing AMI with the performance of using kidney function–specific cut-off values for AMI diagnosis within sex, age and diabetes subgroups.

All the statistical analyses were performed with a significance level of 0.05 (two-sided) using R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of the derivation cohort

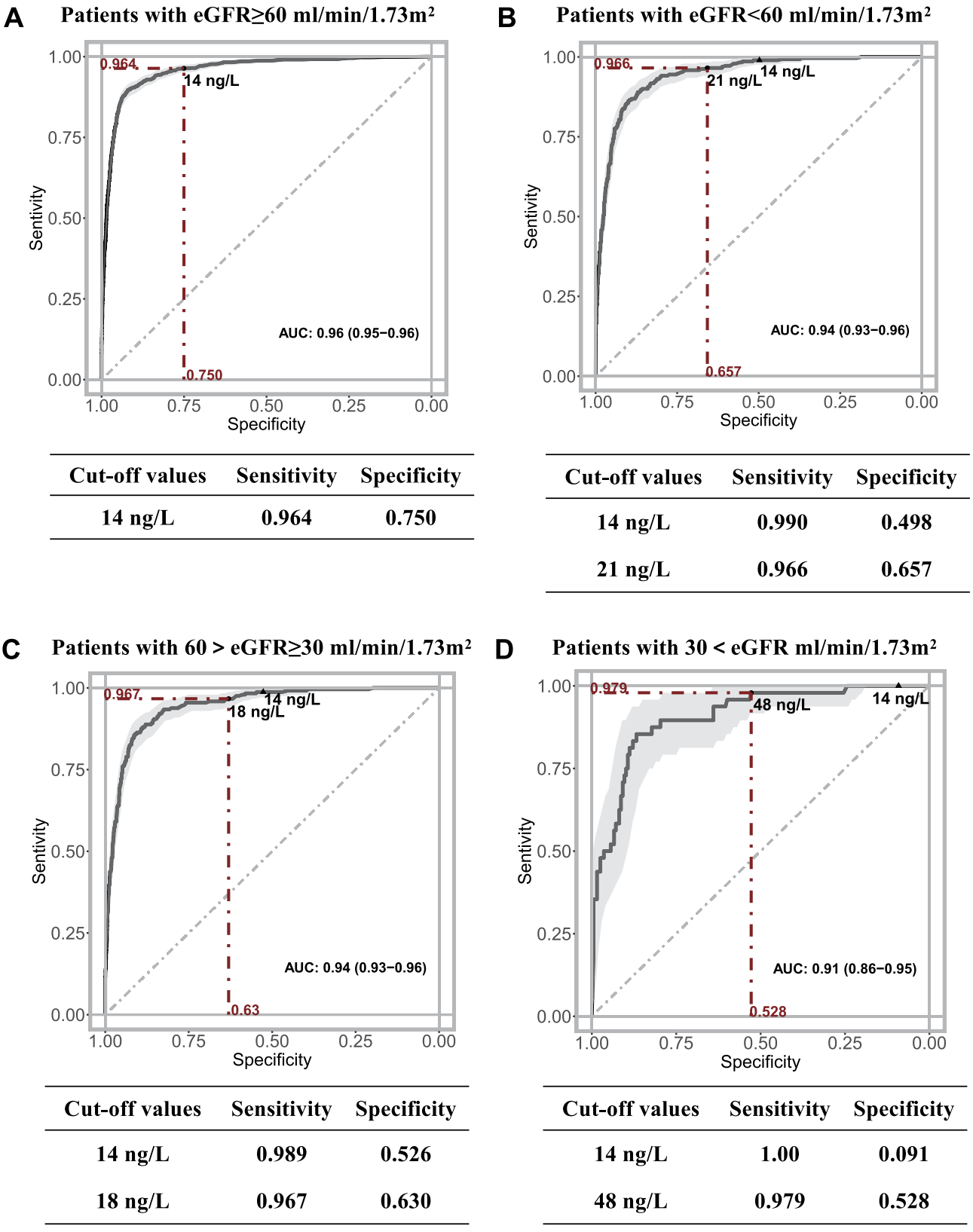
Of 12 900 patients included in the derivation cohort, 3247 (25.2%) patients had kidney dysfunction at baseline and 1202 (9.3%) were diagnosed with AMI after CAG. Compared with those without AMI, the AMI group had a higher proportion of males, diabetes and hypertension, and were more likely to have been administered anti-hypertension and lipid-lowering drugs. The median eGFR in AMI patients and non-AMI patients was 78 (61, 94) and 73 (60, 85) mL/min/1.73 m^2, respectively. The baseline characteristics of the study population are summarized in Table 1.

Kidney function and concentration of hs-cTnT

The median hs-cTnT concentration was 10 (6, 25) ng/L with the concentration of hs-cTnT elevated (>14 ng/mL) in 4843 (37.5%) patients. The density plot demonstrated that the hs-cTnT distribution was shifted to the right (higher concentrations) for patients with lower eGFRs in both the AMI and non-AMI group (Supplementary data, Fig. S1). Among non-AMI patients with kidney dysfunction, nearly 50% had a concentration of hs-cTnT ≥14 ng/L, which was 2-fold higher than that in non-AMI patients with normal kidney function (50.2% versus 25.0%, respectively) ($P < .001$). Among those without AMI diagnosis after CAG, hs-cTnT concentrations were significantly correlated with eGFR (Spearman correlation coefficient, $r = -0.11$, $P < .001$).

Diagnostic performance of hs-cTnT using 14 ng/L as a cut-off value

The diagnostic accuracy, evaluated by the area under curve beneath the receiver operating characteristic curve, was high (0.91–0.96) for all eGFR subgroups (Fig. 2). Table 2 shows the diagnostic performance of hs-cTnT using 14 ng/L as cut-off value in patients with different eGFR levels. When using 14 ng/L as cut-off value, a significant decrease in the specificity and PPV, combined with a slight increase in the sensitivity and NPV,



Cut-off values	Sensitivity	Specificity
14 ng/L	0.964	0.750

Cut-off values	Sensitivity	Specificity
14 ng/L	0.990	0.498
21 ng/L	0.966	0.657

Cut-off values	Sensitivity	Specificity
14 ng/L	0.989	0.526
18 ng/L	0.967	0.630

Cut-off values	Sensitivity	Specificity
14 ng/L	1.00	0.091
48 ng/L	0.979	0.528

Figure 2: The receiver operating characteristic curves of hs-cTnT for diagnosing AMI in the derivation cohort stratified by the eGFR level. (**A**) In patients with eGFR ≥60 mL/min/1.73 m^2; (**B**) in patients with eGFR <60 mL/min/1.73 m^2; (**C**) in patients with 60 > eGFR ≥ 30 mL/min/1.73 m^2; (**D**) in patients with eGFR <30 mL/min/1.73 m^2.

Table 2: The performance of hs-cTnT for diagnosing AMI using 14 ng/L as the cut-off value in the derivation cohort stratified by eGFR.[a]

eGFR (mL/min/1.73 m^2)	No. AMI/total	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)
eGFR ≥60	**912/9653**	96.4 (95.1, 97.5)	75.0 (74.1, 75.9)	99.5 (99.3, 99.7)	28.7 (27.9, 29.5)
60 > eGFR ≥ 30	**242/3002**	98.8 (97.1, 100)	52.7 (51, 54.5)	99.8 (99.5, 100)	15.5 (15, 16)
eGFR <30	**48/245**	100 (100, 100)	9.1 (5.1, 13.7)	100 (100, 100)	21.1 (20.4, 22)

[a]N = 12 900.

Table 3: The sensitivity and specificity of hs-cTnT for diagnosing AMI based on the cut-off values obtained in the derivation cohort stratified by eGFR.[a,b]

hs-cTnT	eGFR ≥60 mL/min/1.73 m^2				60 > eGFR ≥ 30 mL/min/1.73 m^2				eGFR <30 mL/min/1.73 m^2			
cut-off, ng/L	SE	SP	NPV	PPV	SE	SP	NPV	PPV	SE	SP	NPV	PPV
13	96.5	72.7	99.5	27.0	98.8	49.3	99.8	14.6	100.0	8.6	100.0	21.1
14	**96.4**	**75.0**	**99.5**	**28.7**	98.8	52.7	99.8	15.5	100.0	9.1	100.0	21.1
15	96.3	76.8	99.5	30.2	98.3	56.1	99.7	16.4	100.0	10.7	100.0	21.4
17	95.4	79.6	99.4	32.8	97.5	60.8	99.6	17.9	100.0	14.2	100.0	22.1
18	95.0	80.7	99.4	33.9	**96.7**	**63.0**	**99.5**	**18.7**	100.0	16.8	100.0	22.6
19	94.7	81.6	99.3	35.0	95.9	65.3	99.4	19.5	100.0	18.3	100.0	23.0
47	90.1	91.1	98.9	51.3	89.3	85.9	98.9	35.6	97.9	50.8	99.0	32.6
48	90.1	91.2	98.9	51.7	89.3	86.2	98.9	36.1	**97.9**	**52.8**	**99.0**	**33.6**
49	90.1	91.3	98.9	52.0	88.8	86.3	98.9	36.3	95.8	53.3	98.1	33.3

[a]N = 12 900.
[b]Bold values indicate the kidney function–specific cut-off values of hs-cTnT for diagnosing AMI in patients with different level of baseline eGFR.
SP, specificity; SE, sensitivity.

were observed with kidney function worsening. The specificity (49.8%) of hs-cTnT for diagnosing AMI using 14 ng/L as cut-off value in patients with kidney dysfunction was significantly lower than that in patients with normal kidney function (75.0%); the specificity was especially low (9.1%) in patients with an eGFR <30 mL/min/1.73 m^2. This specificity indicates that if clinicians used 14 ng/L as a cut-off value in patients with severe CKD, nearly 90% of patients without AMI would test positive before CAG.

Kidney function–specific cut-off values of hs-cTnT

To ensure a sensitivity not lower than 96.4% (the sensitivity in patients with normal kidney function using 14 ng/L as the cut-off), the kidney function–specific cut-off level in patients with an eGFR <60 mL/min/1.73 m^2 was 21 ng/L, with a specificity of 65.7% (Fig. 2). More specifically, we determined the kidney function–specific cut-off values in patients with 60 > eGFR ≥ 30 mL/min/1.73 m^2 and eGFR <30 mL/min/1.73 m^2 as 18 ng/L and 48 ng/L, respectively. After applying the eGFR-adjusted cut-off values, the specificity of hs-cTnT increased in patients with different levels of kidney dysfunction compared with the specificity using 14 ng/L as cut-off (Fig. 2, Table 3, Supplementary data, Table S2). The specificity in patients with 60 > eGFR ≥ 30 mL/min/1.73 m^2 and eGFR <30 mL/min/1.73 m^2 rose from 52.6% to 63.0% and 9.1% to 52.8%, respectively. Therefore, the results suggest that 21.3% (10/47) and 47.8% (43/90) patients without an AMI diagnosis but tested positive when using 14 ng/L as the cut-off would test negative, as expected, after applying the kidney function–specific cut-off values. The kidney function–specific cut-off values constructed by Youden index were 57 ng/L, 95 ng/L, 90 ng/L and 309 ng/L for patients with eGFR ≥60 mL/min/1.73 m^2, eGFR <60 mL/min/1.73 m^2, 60 > eGFR ≥ 30 mL/min/1.73 m^2 and eGFR <30 mL/min/1.73 m^2, respectively. The specificity, sensitivity, NPV and PPV of diagnosing AMI when using Youden index–optimized kidney function–specific cut-off values are also shown in Supplementary data, Fig. S2. The specificities ranged from 86.8% to 90.0% while the sensitivities were damaged to the range 85.4% to 86.2% (Supplementary data, Fig. S2).

Validation of the kidney function–specific cut-off values

The kidney function–specific cut-off values of hs-cTnT for the early diagnosis of AMI were further validated in the independent validation cohort. Of the 8012 participants, 4.1% (329) were with eGFR <60 mL/min/1.73 m^2, and 26.1% (n = 2094) were diagnosed as AMI (Supplementary data, Table S1). The performance of hs-cTnT at 14 ng/L for diagnosing AMI in this cohort was presented in Table 4. Similar decreases in specificity and PPV among patients with kidney dysfunction were observed in the validation cohort. After applying the kidney function–specific cut-off levels derived from the derivation cohort, the specificity and PPV were significantly improved in each eGFR subgroup (Table 4).

Subgroup analyses

The performance of hs-cTnT for diagnosing AMI using 14 ng/L and the kidney function–specific cut-off values were also examined in the sex, age and diabetes subgroups of the derivation cohorts (Supplementary data, Table S3). The observations showed that using the eGFR-adjusted cut-off values improved the specificity of hs-cTnT for diagnosing AMI with a relevantly

Table 4: The performance of hs-cTnT for diagnosing AMI using the traditional (14 ng/L) or kidney function–specific cut-off values in the validation cohort stratified by eGFR.[a]

eGFR (mL/min/1.73 m^2)	No. AMI/total	hs-cTnT cut-off	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)
eGFR ≥60	1955/7683	14 ng/L	91.8 (90.6, 92.9)	71.5 (70.3, 72.7)	96.2 (95.7, 96.8)	52.4 (51.2, 53.5)
60 > eGFR ≥ 30	132/314	14 ng/L	97.7 (94.7, 100)	22.5 (16.5, 28.6)	93.6 (85, 100)	47.8 (45.9, 50)
		18 ng/L	97 (93.9, 99.2)	35.2 (28, 42.3)	94.2 (88.3, 98.6)	52 (49.4, 55)
eGFR <30	7/15	14 ng/L	100 (100, 100)	0	0	46.7 (46.7, 46.7)
		48 ng/L	100 (100, 100)	50 (12.5, 87.5)	100 (100, 100)	63.6 (50, 87.5)

[a]N = 8012.

high sensitivity (>92%, except in the female group with eGFR <30 mL/min/1.73 m^2).

DISCUSSION

In this nationwide cohort of hospitalized adults who received CAG, we found that the diagnostic specificity was significantly decreased when using the currently recommended cut-off value of hs-cTnT (14 ng/L) for diagnosing AMI in patients with impaired kidney function. We determined the eGFR-adjusted cut-off values of hs-cTnT that improved the specificity without sacrificing sensitivity in patients with different levels of kidney dysfunction. We validated the diagnostic accuracy of the novel cut-off values in an independent validation cohort.

Consistent with previous reports, we found that hs-cTnT concentrations were markedly increased in patients with kidney dysfunction even in the absence of AMI [4–7]. Previous studies supported that smaller degraded cTnT products could be filtered through kidney and could accumulate in the setting of kidney dysfunction [14, 21]. However, decreased kidney clearance could not account entirely for the increase of hs-cTnT in patients with kidney dysfunction [22]. An alternative explanation is that subclinical myocardial injury associated with kidney dysfunction may contribute to elevated hs-cTnT levels [23]. Although the pathophysiology of the phenomenon has not been fully elucidated, there has been an enormous amount of experimental and epidemiological evidence published supporting the association between eGFR and hs-cTnT concentration [5, 24–29]. In our study, 90% of patients with eGFR <30 mL/min/1.73 m^2 showed a level of hs-cTnT over 14 ng/L in the absence of AMI. Thus, it is of paramount importance to determine the appropriate cut-off values of hs-cTnT in patients with different degrees of kidney dysfunction to accurately diagnose AMI.

Optimized cut-off values of hs-cTnT in patients with kidney dysfunction has aroused increasing interest. Previous studies used the Youden index to optimize the hs-cTnT cut-off values, which balanced the specificity and sensitivity [7, 8, 30–32]. In a multicenter cohort study, the sensitivity of hs-cTnT for diagnosing AMI was 88% when using 14 ng/L as the cut-off value in patients with preserved kidney function ($n = 2366$) [7]. However, in those with kidney dysfunction ($n = 447$), the sensitivity of hs-cTnT was much lower (84%) when using the cut-off value driven from Youden index [7]. Similarly, a reduced diagnostic sensitivity using Youden index–based cut-off (86.2%) was also found in our study. Considering the high prevalence and poor prognosis of AMI in patients with kidney dysfunction, a cut-off value sacrificing the sensitivity may be unsafe in clinical practice. Our principle of determining the new cut-off values of hs-cTnT by increasing specificity without sacrificing sensitivity would be more acceptable for clinical practice.

To the best of our knowledge, this is the largest study to determine the kidney function–specific cut-off value of hs-cTnT for the diagnosis of AMI. A major strength of our study is the large sample size encompassing both secondary and tertiary care hospitals and a wide range of clinical settings. In addition, considering the varying degrees of eGFR reduction, an "one-size-fits-all" cut-off value of hs-cTnT in previous studies may not be appropriate for all patients with kidney dysfunction [14]. The adequate sample size of present study enables us to determine kidney function–specific cut-off values for each degree of kidney impairment. Furthermore, we validated the diagnostic accuracy of the novel cut-off values in an independent cohort. Thus, we believed that our findings are representative and generalizable.

Rapid and accurate diagnosis of AMI in patients with kidney dysfunction merits particular attention. Patients presenting with kidney dysfunction have a high prevalence of AMI and are at a substantially higher risk of mortality than patients with normal kidney function [12, 33]. Furthermore, patients with kidney dysfunction are more prone to adverse events related to cardiovascular medication and interventions, such as contrast-induced AKI [2, 34]. Physicians, especially nephrologists and cardiologists, call for kidney function–specific cut-off values to ensure diagnostic accuracy in patients with kidney dysfunction. Our results confirmed the importance of applying the specific cut-off values of hs-cTnT in patients with decreased kidney function for the early diagnosis of AMI. This improvement has the potential to avoid overtreatment and its related side effects in patients with reduced kidney function in clinical practice.

Limitations

We noted several limitations in our study. First, the study was unable to distinguish type 1 myocardial infarction and type 2 myocardial infarction based on ICD codes, since the diagnoses were not widely used in the hospital information system around China. Second, although we adopted methods such as using diagnosis made at discharge, to enhance the accuracy of diagnosis, the possibility of missing diagnosis of AMI remains present. However, with patients all undergoing CAG, clinicians have more evidence to differentiate the etiology of the myocardial injury during the operation, which can offer a panoramic image of the coronary. Thus, in this population, it was probably less likely to have a missing diagnosis at discharge. Third, classification of kidney function is mainly based on the measurements during hospitalization. Although we excluded the patients with diagnosed AKI, patients without enough Scr testing may not have been excluded. Whether an acute decline of renal clearance could affect the diagnostic accuracy of hs-cTnT is still unknown.

Fourth, patients who had undergone dialysis were excluded due to evidence that hs-cTnT levels change in the process of dialysis [35]. The results may not generalize to dialysis patients. Fifth, although 0/1-h algorithm was reported to improve the diagnostic efficacy of hs-cTnT, our study was unable to compare the accuracy of our method with the 0/1-h algorithm due to the small number of patients with serial hs-cTnT measurements. Sixth, the study was conducted in two cohorts of Chinese patients, which allowed for a more representative assessment of this specific population. However, this focus potentially limits the generalizability of the findings to other ethnic or geographic groups. Therefore, further validation using populations from diverse regions around the world is warranted. Additionally, the representation of patients with kidney dysfunction in the validation cohort differs from that in the derivation cohort, underscoring the need for external validation in studies with larger proportions of patients with kidney dysfunction.

CONCLUSIONS

In conclusion, our study found that using 14 ng/L as the threshold of hs-cTnT for diagnosing AMI significantly reduced the specificity in patients with kidney dysfunction. We determined and validated the kidney function–specific cut-off values to improve the diagnosis accuracy of hs-cTnT for AMI. The novel cutoff values of hs-cTnT might help physicians to avoid the potential overtreatment in patients with kidney dysfunction and suspected AMI.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

F.F.H., S.N., X.X. and R.C. conceptualized the study; R.C., M.P., H.Y., L.S., Y.L., X.Z., F.L., R.X. and Q.G. were responsible for the data curation; S.N. and R.C. were responsible for the formal analysis; F.F.H., S.N. and X.X. were responsible for the funding acquisition; S.Z. and D.G. were responsible for the investigation; F.F.H., X.X., S.N. and R.C. were responsible for the methodology; F.F.H., S.N. and X.X. provided supervision; R.C., L.S. and Y.L. were responsible for the visualization; S.N. and R.C. wrote the original draft; and F.F.H. and X.X. reviewed and edited the manuscript.

DATA AVAILABILITY STATEMENT

The original clinical data can be requested from the corresponding author on reasonable request of collaboration to the China Renal Data System (CRDS, http://www.crds-network.org.cn/#/database). In consideration of the security, privacy and data protection issues, the data used for research were limited to the collaborators of the CRDS database. Researchers who possess the requisite resources, expertise or infrastructure to effectively utilize the data are warmly welcomed to CRDS. The summary statistics and code used in the analyses are available by contacting chenrx114@163.com.

CONFLICT OF INTEREST STATEMENT

None declared.

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