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Optimal cut-off value of high-sensitivity troponin I in diagnosing myocardial infarction in patients with end-stage renal disease

Eunsoo Lim, MD[a], Min-Jeong Lee, MD[b,*]

Abstract

End-stage renal disease (ESRD) is a major risk factor for cardiovascular disease and the prognosis after myocardial infarction (MI) is dismal. Although cardiac troponin is a key diagnostic test, troponin levels are often elevated in ESRD patients without evidence of MI. Thus, this study attempted to determine the optimal diagnostic value of high-sensitivity troponin I (hsTnI) by dialysis modality in ESRD patients.

Medical records of adult dialysis patients who visited tertiary emergency department (ED) were collected retrospectively. Diagnosis of MI was made according to the fourth universal definition of MI. The cut-off values were calculated using a receiver operating characteristic (ROC) curve.

Medical records of 1144 patients were analyzed and MI was diagnosed in 82 patients (75 on hemodialysis and 7 on peritoneal dialysis). The optimal cut-off value of hsTnI in hemodialysis patients was 75 ng/L, with 93.33% sensitivity and 60.76% specificity. Area under the curve (AUC) was .870 (95% confidence interval (CI) .833–.906). The optimal cut-off value of hsTnI in peritoneal dialysis patients was 144 ng/L, with 100.00% sensitivity and 83.10% specificity. AUC was .943 (95% CI .893–.992).

The dialysis modality should also be considered when diagnosing MI using hsTnI in ESRD patients.

Abbreviations: AUC = area under the curve, CI = confidence interval, CKD = chronic kidney disease, CK-MB = creatine kinase – MB, ECG = electrocardiogram, ED = emergency department, ESC = European Society of Cardiology, ESRD = end-stage renal disease, hsTnI = high-sensitivity troponin I, IQR = interquartile range, MI = myocardial infarction, NSTEMI = non-ST-elevation myocardial infarction, ROC = receiver operating characteristic, STEMI = ST-elevation myocardial infarction, URL = upper reference limit.

Keywords: chronic hemodialysis, chronic renal failure, myocardial infarction, peritoneal dialysis, troponin

1. Introduction

As glomerular filtration rate declines, major adverse cardiac events and all-cause mortality increase.[1] Patients receiving dialysis are not an exception, and they have a higher risk of acute coronary syndrome and worse prognosis after MI.[2–5] Han reported that the 2-year post MI mortality rates are as high as 74% in patients with ESRD.[6]

Nevertheless, diagnosis of acute MI in patients with ESRD is challenging in the ED. Many ESRD patients have comorbidities such as diabetes that cause their symptoms to be vague and atypical. Dyspnea due to volume overload irrelevant to acute coronary syndrome is also frequent. Cardiac troponin levels are raised in up to 71% of patients with chronic kidney disease (CKD),[3,5,7–11] and these elevation of troponin levels are thought be due to subtle chronic myocardial damage rather than acute MI.

In diagnosing MI, fourth universal definition of MI proposed by European Society of Cardiology (ESC) is most widely used. And type 1 MI, which is a type of MI caused by coronary artery disease, is consisted of two major components. One is the elevated cardiac troponin values with at least one value above the 99th percentile upper reference limit (URL), and the other is one of the following: symptoms of acute myocardial ischemia, new ischemic electrocardiogram (ECG) changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.[12]

ESC suggests that the criteria for diagnosing MI in patients with CKD should not be different from that of general population.[12] However, cardiac troponin levels are frequently increased in patients with ESRD without evidence of ongoing

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This study has been approved by the institutional review board of Ajou University Hospital (AJIRB-MED-MDB-18). As this study was a retrospective review, informed consent has been waivered by the institutional review board.

The authors report no conflicts of interest.

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[a] Department of Emergency Medicine, [b] Department of Nephrology, Ajou University School of Medicine, Yeongtong-gu, Suwon, Gyeonggi-do, Republic of Korea.

[*] Correspondence: Min-Jeong Lee, Department of Nephrology, Ajou University School of Medicine, 164 World Cup Road, Yeongtong-gu, Suwon, Gyeonggi-do, Republic of Korea (e-mail: km3136@hanmail.net).

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acute MI.[3,5,7–11] Studies of hsTnI in diagnosing acute MI in ESRD patients with consideration of characteristics of dialysis is limited.[2,13] Thus, this study attempted to determine the optimal rule-out value of hsTnI for diagnosis of acute MI in ESRD patients by dialysis modality that visited our ED.

2. Materials and methods

2.1. Study patients and data collection

Adult patients who visited ED at Ajou University Medical Center, a major tertiary hospital which covers more than a million people around the Kyeonggi province, from January 2010 to May 2018 were retrospectively assessed for eligibility. Among patients who visited ED, patients who have tested hsTnI because of their ischemic symptoms and who have medical records of hemodialysis or peritoneal dialysis during index visit were selected for eligibility (n = 1260). Ischemic symptoms were defined as substernal chest pain, chest tightness or pressure associated with shortness of breath, sweating, and anxiety. After excluding patients with insufficient medical records, patients were divided into ESRD+MI group (n = 117) and ESRD group (n = 1138) according to their final diagnosis at hospital discharge. Patients who have an elevated hsTnI and indeterminate ECG but neither echocardiography nor coronary angiography were performed were categorized as insufficient medical records and excluded from the study. Finally, patients with impending ESRD who started their renal replacement therapy at the time of their ED visit were excluded from both groups. All patients who met the eligibility criteria and who did not met the exclusion criteria were enrolled. As a result, total of 82 patients were included in ESRD +MI group and 1062 patients were included in ESRD group.

Clinical characteristics, laboratory test values and dialysis records of the eligible patients were collected from the electronic medical record database. Age, sex, dialysis modality, time from symptom onset to emergency room door, underlying diseases, previous history of ischemic heart disease, ischemic stroke or peripheral artery obstructive disease, smoking, family history of ischemic heart disease, hsTnI level at presentation and creatine kinase-MB (CK-MB) level at presentation were obtained. The following data were also reviewed on patients in the MI group: whether MI occurred within 24 hours of dialysis, whether the ST segment was elevated, low density lipoprotein level, high density lipoprotein level, coronary angiographic results, whether the patients had undergone coronary artery bypass graft surgery and mortality at time of hospital discharge. The time of ischemic symptom onset was set to be the time of MI onset.

ECGs were taken along with blood sampling at the time of ED visits. As stated in the hospital policy, blood samples were filled up into serum-separating tube and immediately sent to laboratory for analysis at room temperature. All hsTnI and CK-MB were analyzed using Centaur XPT (Siemens, Berlin, Germany). According to the manufacturer, the detection limit of the hsTnI assay is 2.21 ng/L, and the 99th percentile of the URL is 47.34 ng/L. the detection limit of the CK-MB assay is 2.21ng/L and the 99th percentile of the URL is 4.4 ng/mL.

Diagnosis of MI was further adjudicated by the first author and attending cardiologists reviewing all available medical records: patient history, physical examination, laboratory tests, ECG, echocardiography, coronary angiography according to the fourth universal definition of type 1 MI.[12] Specifically, diagnosis of ST-elevation MI (STEMI) was made only by ECG at the ED without laboratory results. Therefore, in STEMI patients, the attending cardiologists were unaware of the hsTnI results at the time of diagnosis, because the hsTnI results were unavailable at the moment. In non-ST-elevation MI (NSTEMI) patients, all patients had an elevated value above the 99th percentile URL and had one of the followings: newly developed wall motion abnormalities consistent with myocardial ischemia, and/or significant coronary artery stenosis or obstruction which warranted angiographic interventions. And in patients whose diagnosis were presumed to be NSTEMI, either echocardiography or coronary angiography or both were performed as soon as feasible, within a few hours.

This study was carried out according to the principles of the *Declaration of Helsinki* and approved by the institutional review board. (AJIRB-MED-MDB-18) Also, informed consent has been waivered by the institutional review board.

2.2. Statistical analyses

Sample size was determined with 90% power and type I error of .05. The hypothesized area under the ROC curve was set to .95. As a result, the minimal number of patients in ESRD + MI group was 4 and the minimal number of patients in ESRD was 40. All variables went through normality testing. Categorical variables with skewed distribution were reported as percentages and analyzed using Chi-square test. Non-categorical variables with skewed distribution were reported as median and IQR and analyzed using the Mann-Whitney test. The cut-off values were calculated by ROC curve. Optimal cut-off values were determined using the Youden index. The discriminative performance of the test was measured by the AUC. As sensitivities were lower than 80% in previous studies, the authors set the minimum sensitivity to 80% in each group.[2,13,14] To determine the best value to rule out MI, the authors applied the net benefit approach to various cut-off values including the one provided by the manufacturer.[15] P values less than .05 were considered significant. Sample size was determined using MedCalc (MedCalc Software, Ostend, Belgium). All other statistical analyses were performed with Stata 12 (StataCorp, TX).

3. Results

A flowchart describing patient selection is shown in Figure 1. Medical records of 1144 patients were analyzed and baseline characteristics of these patients are shown in Table 1. MI was diagnosed in 82 patients. The median age was older in the ESRD +MI group (66 years) than in ESRD group (61 years), and the difference was statistically significant ($P = .04$). In the ESRD+MI group, 75 patients were on maintenance hemodialysis and 7 patients were on peritoneal dialysis. Additional baseline characteristics of MI patients are shown in Table 2. The median symptom onset-to-door time was 5 hours, and one-third of the patients arrived at the hospital within 2 hours of ischemic symptom onset. Among 75 patients who were on hemodialysis, MI occurred within 24 hours following dialysis in 32 patients (42.7%) and before dialysis (i.e., all other times except the 24 hours immediately following dialysis) in 43 patients (57.3%). Among the 32 patients, 16 patients started to have symptoms during or right after the hemodialysis so they visited hospital in 4 hours from their symptom onset. Seventeen patients were diagnosed as STEMI, and the other 65 patients were diagnosed as NSTEMI. In NSTEMI patients, echocardiography or coronary angiography were performed within median 6 hours (interquar-

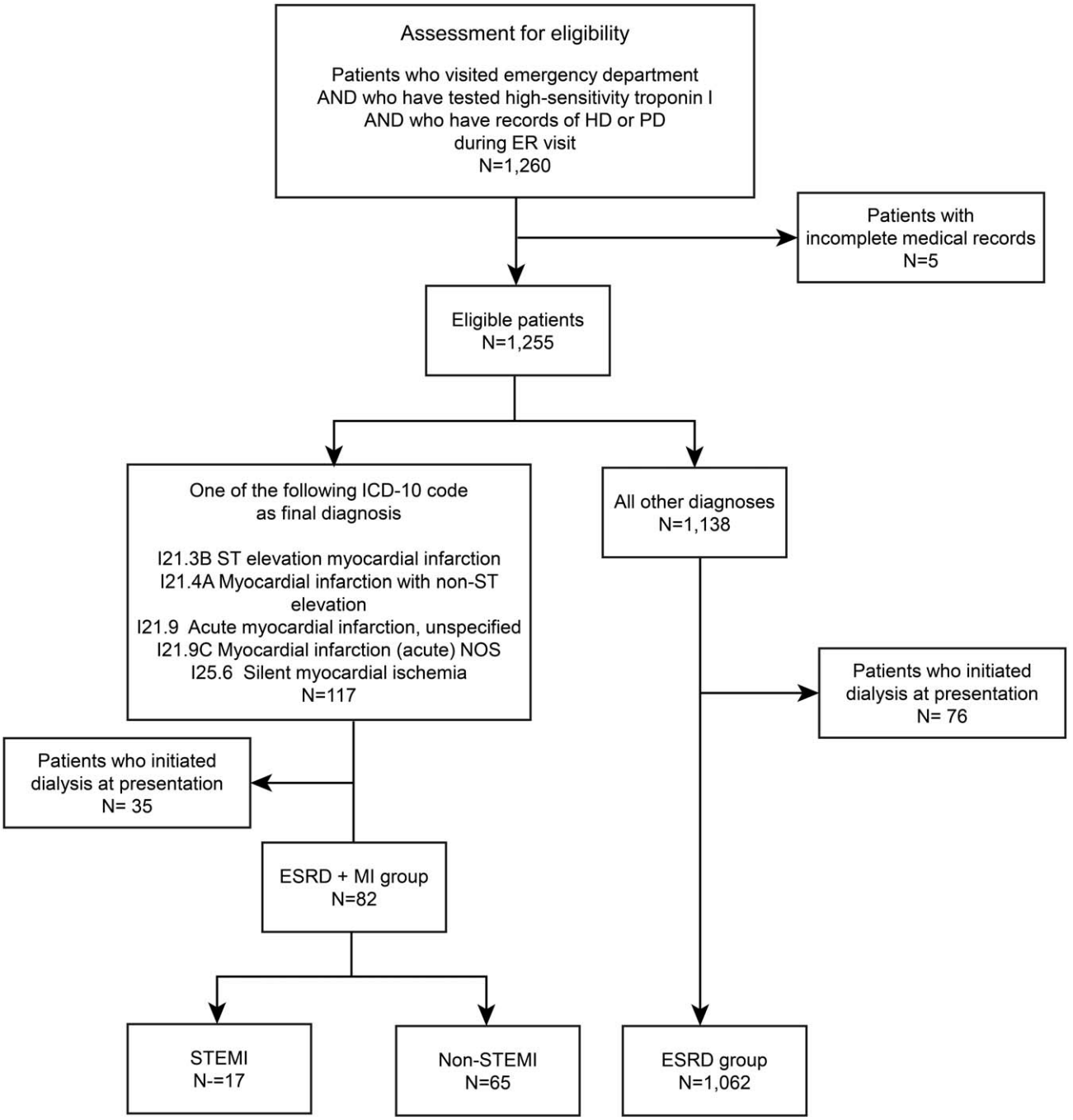

Figure 1. Flowchart describing patient enrolment.

tile range (IQR) 2–14.5 hours)) to establish the final diagnosis. In ESRD group, presumptive cause of their symptoms concluded by ED physicians were as follows: pulmonary edema due to volume overload in 481 (45.3%), unstable/stable angina in 174 (16.4%) patients, systemic infections including pneumonia in 166 (15.6%) patients, pulmonary embolism in 9 (.8%) patients, aortic dissection in 2 (.1%) patients and non-specific pain from musculoskeletal origin in 230 (21.7%) patients. Eleven patients (13.4%) died at the time of hospital discharge. Cardiogenic shock or fatal arrhythmias were cause of death in all 11 cases. There were no major adverse events regarding coronary angiography procedure.

HsTnI and CK-MB levels at presentation according to classification of MI were as follows: Although hsTnI levels of the ESRD+STEMI group (2687ng/L; IQR 202–8299 ng/L)) seemed to be higher than in the ESRD+NSTEMI group (815ng/L; IQR 168–11415ng/L)), it was not statistically significant ($P = .97$). There was no significant difference in CK-MB levels between the two groups. When categorized by the time patients visited the ED because of their ischemic symptoms, hsTnI levels of patients who were diagnosed with MI before their hemodialysis was 660 ng/L (150–11415 ng/L as IQR) and hsTnI levels of patient who were diagnosed with MI after their hemodialysis (i.e.,

Table 1

Baseline characteristics.

	Total (n = 1144)	ESRD+MI (n = 82)	ESRD (n = 1062)	*P* value
Sex (male/female)	667/477 (58.3/41.7)	51/31 (62.2/37.8)	616/446 (58.0/42.0)	.45
Age (years)	61 (52–72)	66 (56–74)	61 (52–72)	.05
Dialysis method				.21
Hemodialysis	995 (87.0)	75 (91.5)	920 (86.6)	
Peritoneal dialysis	149 (13.0)	7 (8.5)	142 (13.4)	
Underlying disease				
Diabetes mellitus	703 (61.5)	53 (64.6)	650 (61.2)	.54
Hypertension	1026 (89.7)	70 (85.4)	956 (90.0)	.18
Coronary artery obstructive disease	230 (20.1)	35 (42.7)	195 (18.4)	.00
Cerebrovascular disease/Peripheral artery obstructive disease	172 (15.0)	27 (33.0)	145 (13.7)	.00
Smoking				.01
Non-smoker	932 (81.5)	61 (74.4)	871 (82.0)	
Current smoker	89 (7.8)	4 (4.9)	85 (8.0)	
Ex-smoker	123 (10.7)	17 (20.7)	106 (10.0)	
Family history of ischemic heart disease	11 (1.0)	3 (3.7)	8 (.8)	.01
High-sensitivity troponin I level at presentation (ng/L)	54.5 (20.0–163.5)	899.5 (168.0–9889.0)	46.0 (18.0–129.0)	.00
Creatine kinase-MB level at presentation (μg/L)	2.2 (1.1–4.25)	6.85 (3.7–21.3)	2.1 (1.0–3.8)	.00

ESRD = end-stage renal disease, MI = myocardial infarction.

in 24 hours after hemodialysis) was 2658 ng/L (193–9944 ng/L as IQR). There was no significant difference in hsTnI levels according to the timing of MI ($P = .53$). HsTnI and CK-MB levels at presentation are shown in Table 3, according to the type of dialysis. The hsTnI level at presentation were higher in HD+MI patients, but it was not statistically significant ($P = .94$).

The optimal cut-off value of hsTnI in hemodialysis patients was 75 ng/L, with 93.33% sensitivity and 60.76% specificity. AUC was .870 (95% CI .833–.906). The optimal cut-off value of hsTnI in peritoneal dialysis patients was 144ng/L, with 100.00% sensitivity and 83.10% specificity. AUC was .943 (95% CI .893-.992). The results are summarized in Table 4 and ROC curves of each dialysis group are shown in Figure 2A and B. Sensitivities and specificities were much higher in hsTnI compared with CK-MB according to dialysis method.

Table 2

Baseline characteristics of myocardial infarction patients.

	ESRD+MI (n = 82)
From symptom onset to door time (hours)	5 (2–15)
Before/After dialysis	
Before hemodialysis	43
After hemodialysis	32
Not applicable (Peritoneal dialysis)	7
Classification of MI	
STEMI	17
NSTEMI	65
Low density lipoprotein (mg/dL)	31.5 (14–44)
High density lipoprotein (mg/dL)	20 (11–30)
Coronary angiographic results	
3 vessel disease	32 (39.0)
2 vessel disease	23 (28.1)
1 vessel disease	16 (19.5)
Not done	11 (13.4)
Coronary artery bypass graft	8 (9.8)
Mortality	11 (13.4)

ESRD = end-stage renal disease, MI = myocardial infarction, NSTEMI = non-ST-elevation myocardial infarction, STEMI = ST-elevation myocardial infarction.

To settle down the optimal rule-out value, the net benefits of various values were calculated and compared: 47 ng/L from 99th percentile of URL provided by manufacturer, 75 ng/L from the optimal value of hemodialysis patients and 144 ng/L from the optimal value of peritoneal dialysis patients. When threshold probability was set to 20%, 15%, and 10%, the net benefits were consistently higher when calculated separately according to dialysis method than when cut-off value was set to 99th percentile of URL. The results of calculated net benefit are shown in Supplement 1, http://links.lww.com/MD/D552.

Lastly, cross tabulations of hemodialysis patients and peritoneal dialysis patients according to the optimal cut-off values of each group are shown in Table 5. Positive predictive values were 16.2% in HD patients and 23.3% in PD patients. However, negative predictive value in each group reached 99.11% and 100%, respectively.

4. Discussion

To our knowledge, this is the first study to investigate the optimal cut-off values of hsTnI for MI diagnosis in patients receiving renal replacement therapy and also the first such study to enroll peritoneal dialysis patients. The optimal cut-off values of hsTnI according to dialysis method were significantly different compared with that of patients with normal kidney function. The optimal cut-off value of hsTnI in hemodialysis patients was 75 ng/L, and the optimal cut-off value of hsTnI in peritoneal dialysis patients was 144 ng/L. Sensitivities were as high as 93.33% and 100.00%, respectively. And specificities were also

Table 3

High-sensitivity Troponin I and Creatine Kinase-MB level according to type of Dialysis.

	HD+MI (n = 75)	PD+MI (n = 7)	*P* value
HsTnI (ng/L)	961 (153–10000)	602 (246–6953)	.94
CK-MB (μg/L)	6.7 (3.5–21.3)	7.0 (4.9–30.5)	.78

CK-MB = creatine kinase-MB, HD = hemodialysis, HsTnI = high-sensitivity troponin I, MI = myocardial infarction, PD = peritoneal dialysis.

Table 4

High-sensitivity Troponin I levels according to specific conditions.

	Cut-off value (ng/L)	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC (95% CI)
99th percentile of URL	47	97.56%	50.28%	1.9623	0.0485	
Optimal cut-off value in HD patients	75	93.33%	60.76%	2.3786	0.1097	.870 (.833– .906)
Optimal cut-off value in PD patients	144	100.00%	83.10%	5.9160	0.0000	.943 (.893-.992)

AUC = area under the curve, CI = confidence interval, HD = hemodialysis, LR = likelihood ratio, PD = peritoneal dialysis, URL = upper reference limit.

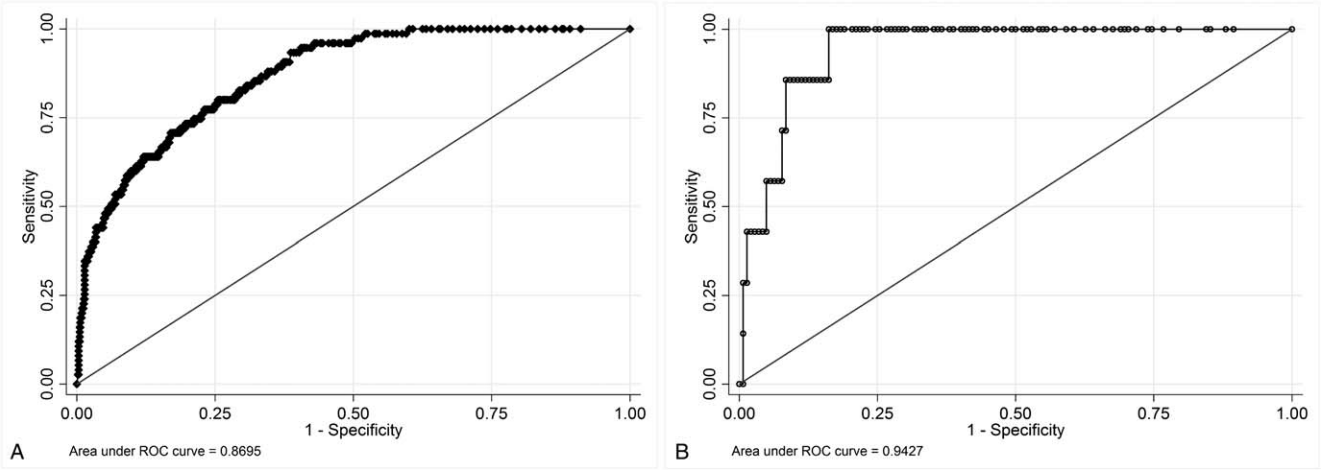

Figure 2. Receiver operating curve of hsTnI according to dialysis modality. A: Hemodialysis patients, B: peritoneal dialysis patients.

higher than that of 99th percentile of URL. This study is worthwhile in that the results of this study can help physicians make decisions even before follow-up test results are available hours after.

Few previous studies have investigated how to increase the diagnostic accuracy of MI in patients with CKD. However, patients on maintenance dialysis were excluded in one study[13] and patients with STEMI were excluded in another study.[14] Yang et al reported that CKD stage-specific cut-off values should be considered in diagnosing MI, but they used the cardiac troponin T assay.[2] Procopio et al recently proposed a mathematical model which enables calculating the individualized biphasic curve and the peak level of troponin in STEMI patients.[16,17] Although this model is not specifically designed for CKD patients, modulating and applying this model to ESRD patients can be another

Table 5

Cross tabulation of patients according to myocardial infarction diagnosis and the optimal cut-off value of the study.

	Cut-off value of ESRD patients		
	99th percentile of URL		
All patients	HsTnI ≥47ng/L	HsTnI <47ng/L	Total
ESRD+MI	80	2	82
ESRD	523	539	1062
Total	603	541	1144
	Cut-off value of HD patients		
	HsTnI ≥75ng/L	HsTnI <75ng/L	Total
HD+MI	70	5	75
HD	361	559	920
Total	431	564	995
	Cut-off value of PD patients		
	HsTnI ≥144ng/L	HsTnI <144ng/L	Total
PD+MI	7	0	7
PD	23	119	142
Total	30	119	149

ESRD = end-stage renal disease, HD = hemodialysis, HsTnI = high-sensitivity troponin I, MI = myocardial infarction, PD = peritoneal dialysis, URL = upper reference limit.

plausible option in interpreting cardiac troponin results in the future.

Cardiac troponin assays are grossly divided into cardiac troponin I assays and cardiac troponin T assays. Compared to high-sensitivity troponin T, many previous studies have shown that the diagnostic performance of hsTnI is superior in patients with CKD.[7,11,13] Although there are conflicting data regarding how many cardiac troponin I molecules and troponin T molecules adhere to the dialyzer membrane,[18,19] a recent study by Badiou et al insisted that up to 48% of the troponin T is removed by hemodiafiltration.[20] In addition, despite the fact that troponin T is cardiac specific, cross-reaction between cardiac troponin T and skeletal troponin T is still exists.[8] Therefore, we choose to analyze hsTnI instead of high-sensitivity troponin T assays in this study.

The reason why the optimal cut-off value of hsTnI in peritoneal dialysis group is almost twice as high as in hemodialysis group is yet to be determined, however, hsTnI removal by the dialyzer probably contributes to the substantial difference between the two groups. HsTnI molecules are known to be removed from blood to some extent by adhering to the dialyzer membrane in hemodialysis patients.[18,19,21] On the other hand, to date, excretion of hsTnI in patients with peritoneal dialysis is unknown.

There were no differences in hsTnI or CK-MB levels between the STEMI and NSTEMI groups. Given the fact that the degree of elevation of cardiac biomarker reflects the degree of myocardial damage, NSTEMI causes serious myocardial damage just as STEMI does. Thus, as the authors have already emphasized, considering elevated cardiac biomarker as a non-specific feature of ESRD can be misleading.

Of note, among 75 patients in the ESRD+MI group, MI occurred before dialysis in 43 patients (57.3%) and in 24 hours after dialysis in 32 patients (42.7%). Because considerable negative hemodynamic changes on myocardial perfusion occur due to the hemodialysis procedure itself,[10] we assumed that MI would take place after hemodialysis more often than before hemodialysis. However, more patients were diagnosed with MI before hemodialysis than after hemodialysis, and hsTnI and CK-MB levels at presentation were not statistically different. The authors could not find any proper explanation for this phenomenon.

There are several limitations of our study. First, this is a retrospective study which was conducted in one university hospital. Second, as we only enrolled Asian patients, especially Korean, the results of this study are hard to generalize across all racial groups. Third, only one troponin I assay test was used, even though there are several commercial troponin I assays available. Although hsTnI is superior over cardiac troponin T in patients with ESRD, hsTnI is relatively unstable and susceptible to proteolysis.[18] Thus, standardization of hsTnI assays is lacking. Fourth, we did not include serially measured cardiac biomarkers in our study because many patients underwent coronary angiography before serial measurement. Fifth, the study has the possibility of incorporation bias in diagnosing NSTEMI although we only included patients with clear evidences of MI in echocardiography or coronary angiography. Sixth, the possibility of partial verification bias is also present. The results of hsTnI might have influenced the physician's decision to perform further tests in NSTEMI patients. Finally, the number of peritoneal dialysis patients was relatively small to elicit a conclusion compared with hemodialysis group. Despite the small number of peritoneal dialysis patients, the authors still believe that the result being valuable because this is the first study to enroll peritoneal dialysis patients in this subject to date.

In conclusion, the optimal values of hsTnI in diagnosing MI in hemodialysis patients and peritoneal dialysis patients were 75 ng/L and 144 ng/L, which is much higher than in patients with normal kidney function. By considering dialysis method and applying different cut-off values, interpretation of elevated hsTnI in ESRD patients in ED is going to be more accurate and diagnosing MI in ESRD patients will be more precise and faster. However, with its limitations, the results presented in this study are not conclusive and should be further validated in an independent cohort before they could be applied to real clinical practice. Further researches including large number of patients with more diverse high-sensitivity troponin I assays are warranted in the future.

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Author contributions

Conceptualization: Eunsoo Lim.
Data curation: Eunsoo Lim.
Formal analysis: Eunsoo Lim.
Investigation: Eunsoo Lim.
Methodology: Eunsoo Lim.
Supervision: Min-Jeong Lee.
Visualization: Min-Jeong Lee.
Writing – original draft: Eunsoo Lim, Min-Jeong Lee.
Writing – review & editing: Eunsoo Lim, Min-Jeong Lee.
Min-Jeong Lee orcid: 0000-0002-2611-7333.

References

[1] Miller-Hodges E, Anand A, Shah ASV, et al. High-sensitivity cardiac troponin and the risk stratification of patients with renal impairment presenting with suspected acute coronary syndrome. Circulation 2018;137:425–35.
[2] Yang H, Liu J, Luo H, et al. Improving the diagnostic accuracy of acute myocardial infarction with the use of high-sensitive cardiac troponin T in different chronic kidney disease stages. Sci Rep 2017;7:41350.
[3] Stacy SR, Suarez-Cuervo C, Berger Z, et al. Role of troponin in patients with chronic kidney disease and suspected acute coronary syndrome: a systematic review. Ann Intern Med 2014;161:502–12.
[4] Iliou MC, Fumeron C, Benoit MO, et al. Factors associated with increased serum levels of cardiac troponins T and I in chronic haemodialysis patients: chronic haemodialysis and new cardiac markers evaluation (CHANCE) study. Nephrol Dial Transplant 2001;16:1452–8.
[5] Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. N Engl J Med 1998;339:799–805.
[6] Han JH. Interpretation of cardiac troponins in patients with chronic kidney disease and suspected acute coronary syndrome in the emergency setting. Emerg Med Card Res Educ Group 2005;3:1–0.
[7] Kraus D, von Jeinsen B, Tzikas S, et al. Cardiac troponins for the diagnosis of acute myocardial infarction in chronic kidney disease. J Am Heart Assoc 2018;7:e008032.
[8] Chen S, Huang C, Wu B, et al. Cardiac troponin I in non-acute coronary syndrome patients with chronic kidney disease. PLoS One 2013;8:e82752.
[9] Huang HL, Zhu S, Wang WQ, et al. Diagnosis of acute myocardial infarction in hemodialysis patients with high-sensitivity cardiac troponin T assay. Arch Pathol Lab Med 2016;140:75–80.

[10] Castini D, Persampieri S, Floreani R, et al. Troponin I levels in asymptomatic hemodialysis patients. Blood Purif 2017;44:236–43.
[11] Pfortmueller CA, Funk GC, Marti G, et al. Diagnostic performance of high-sensitive troponin T in patients with renal insufficiency. Am J Cardiol 2013;112:1968–72.
[12] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40: 237–69.
[13] Twerenbold R, Wildi K, Jaeger C, et al. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. Circulation 2015;131: 2041–50.
[14] Gunsolus I, Sandoval Y, Smith SW, et al. Renal dysfunction influences the diagnostic and prognostic performance of high-sensitivity cardiac troponin I. J Am Soc Nephrol 2018;29:636–43.
[15] Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ 2016;352:i6.
[16] Procopio A, De Rosa S, García MR, et al. Experimental modeling and identification of cardiac biomarkers release in acute myocardial infarction. *IEEE Trans Control Syst Technol.* In press.
[17] Procopio A, De Rosa S, Covello C, et al. A model of cardiac troponin T release in patient with acute myocardial infarction. Melbourne: IEEE 56th Annual Conference on Decision and Control; 2017.
[18] Jain N, Hedayati SS. How should clinicians interpret cardiac troponin values in patients with ESRD? Semin Dial 2011;24:398–400.
[19] Gaze DC, Collinson PO. Cardiac troponin I but not cardiac troponin T adheres to polysulfone dialyser membranes in an in vitro haemodialysis model: explanation for lower serum cTnI concentrations following dialysis. Open Heart 2014;1:e000108.
[20] Badiou S, Boudet A, Leray-Moragues H, et al. Monthly reference change value of cardiac troponin in hemodialysis patients as a useful tool for long-term cardiovascular management. Clin Biochem 2016;49:1195–8.
[21] Svagusa T, Golub A, Pikivaca T, et al. High sensitive troponin concentration stability in dialysate of anuric patients on hemodialysis. Signa Vitae 2018;14(Suppl 1):35–8.