Research Article

Initial Concentrations of miR-1 MicroRNA Precursor and High-Sensitivity Troponin in the Diagnosis of Non-ST Myocardial Infarction among Patients with and Those without Chronic Kidney Disease

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Keywords

miR-1 microRNA precursor · High-sensitivity troponin · Non-ST-segment elevation myocardial infarction · Chronic kidney disease

Abstract

Background: The early diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI) in patients with chronic kidney disease (CKD) remains a challenge. **Methods:** The study consecutively enrolled patients who had suffered from chest pain within 3 h whose electrocardiogram had no elevation in the ST segment. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², and the diagnostic criteria for NSTEMI were defined according to the recommended guideline. Circulating microRNA-1 was collected and determined by quantitative real-time reverse transcription polymerase chain reaction. **Results:** A total of 456 patients with suspected NSTEMI were included. There were 115 patients in the CKD group, including 67 with NSTEMI, 20 with stable angina, 7 with unstable angina, 18 with heart failure, and 3 with other disorders. Compared with the NSTEMI group, the non-NSTEMI group just had significant differences in microRNA-1 and high-sensitivity cardiac troponin I (hs-cTnI) (both $p < 0.05$). The relative expression of microRNA-1 was significantly increased in the NSTEMI group as compared with that in the other disease groups (all $p < 0.05$). A receiver op-

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erating characteristic (ROC) curve analysis suggested that microRNA-1 and hs-cTnI had advantages in the early diagnosis of NSTEMI with CKD (AUC [area under the ROC curve] 0.879 and 0.812, respectively, both $p < 0.05$). Compared with that in the non-CKD group, the accuracy of microRNA-1 was almost as good in the CKD group (84.3 vs. 89.4%, $p > 0.05$). However, the diagnostic accuracy of hs-cTnI was significantly decreased (79.1 vs. 91.5%, $p < 0.05$), as was its specificity (75.0 vs. 95.5%, $p < 0.05$). There was no significant difference in the correlation between microRNA-1 and eGFR ($p > 0.05$), but a statistically significantly negative correlation between hs-cTnI and eGFR ($p < 0.05$). **Conclusion:** Circulating microRNA-1 is capable of early diagnosis of NSTEMI in patients with CKD suffering from chest pain. © 2019 S. Karger AG, Basel

Introduction

Acute myocardial infarction (AMI), leading to high mortality and poor prognosis, is one of the most common cardiovascular diseases; timely revascularization within 3 h can repair the ischemic myocardium, ultimately reducing the mortality rate and improving prognosis [1]. In current clinical practice, AMI is classified into ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) based on electrocardiogram (ECG) performance. Studies have suggested that the prognosis for NSTEMI patients is worse than that for STEMI patients, which may be due to the following reasons: (1) patients with NSTEMI are older and have a greater burden of cardiovascular comorbidities; (2) underutilization of effective cardiac medications and primary percutaneous coronary intervention and greater delays in the time to receipt of primary percutaneous coronary intervention occur among patients with NSTEMI, which may also contribute to the differences in post-discharge death rates observed for these patients; and (3) STEMI patients have a more typical ECG performance, which is helpful for an early diagnosis and thus early reperfusion treatment [2].

The clinical manifestations of early NSTEMI are often not typical, because there are no obvious changes in ECG and biomarkers. Unfortunately, if there is a contraindication to coronary angiography or refusal of invasive treatment at this time, a dilemma will be caused [3, 4]. In particular, the high incidence of NSTEMI [5, 6], its atypical symptoms [7, 8], and the more severe treatment-related adverse events in patients with chronic kidney disease (CKD) deserve more attention [9, 10]. CKD would cause an increase in high-sensitivity cardiac troponin (hs-cTn) to interfere with diagnosis, and there is a large relative decrease in utilization of coronary angiography among patients with CKD [11]. The rapid and accurate diagnosis or exclusion of AMI in such patients can help the emergency department speed up the identification and treatment of the actual cause of illness, reduce the anxiety of patients, and save medical resources [12]. The European Society of Cardiology (ESC) recommends the 0/1-h algorithm to solve the issue [13]. However, in patients with CKD, the ESC 0/1-h algorithm is safe, but the specificity of rule-in and overall efficacy are decreased. Modifications of the rule-in and rule-out thresholds did not improve the safety or overall efficacy of the 0/1-h algorithm [14].

Circulating microRNAs (miRNAs, miRs) are highly conserved, noncoding, short-chain RNAs (21–24 nt) that regulate gene expression and participate in the regulation of multiple signaling pathways [15]. Being stable in peripheral blood and having significant differences in expression profiles between healthy and diseased individuals, miRNAs have the potential to become biomarkers [16]. miRNA-1 (miR-1) is the first biomarker found to be associated with cardiovascular development. Previous studies have found that miRNA-1 can be used as a biomarker for early diagnosis of AMI [17, 18], but there is no clear report on the relationship between miRNA-1 and CKD. Therefore, our study aimed to elucidate the value of early detection of circulating miRNA-1 in suspected NSTEMI patients with CKD.

Subjects and Methods

Study Population

Through a prospective cohort study, consecutive patients with a suspected NSTEMI onset <3 h were enrolled and divided into a CKD and a non-CKD (NCKD) group based on the presence or absence of renal insufficiency. The mean time from the onset of chest pain to the time of sampling for the first miRNA-1 microRNA precursor and hs-cTnI was 2.4 h. Renal function was quantified by estimated glomerular filtration rate (eGFR) with the CKD epidemiology collaboration formula depending on age, sex, ethnicity, and the plasma creatinine level obtained at presentation to the emergency department, and CKD was defined as an eGFR <60 mL/min/1.73 m² [19].

Excluded were patients with onset times >3 h, regular dialysis patients and cancer patients, AMI patients within 4 weeks, patients with STEMI, patients with uncertain diagnoses even if they had a trend towards AMI, and patients with a lack of creatinine data.

Adjudicated Final Diagnosis

The diagnostic criteria for NSTEMI and hs-cTn levels were defined as recommended in the current guidelines [13, 20]. In short, a patient has ischemic symptoms associated with elevated troponin levels. The dynamic variation in troponin is measured many times during the whole diagnosis and treatment process. NSTEMI may be diagnosed if the value of troponin is consistent with the AMI time window. In our study, if there were situations of disagreement between the two cardiologists, cases were reviewed and adjudicated in collaboration with a third cardiologist.

Study Design

The basic clinical characteristics of the CKD group and the NCKD group, and of the NSTEMI and non-NSTEMI subgroups within the CKD group, were compared. The concentrations of miRNA-1 in patients with NSTEMI and those with no NSTEMI were compared between the CKD group and the NCKD group; they were used to assess the diagnostic potential of miRNA-1. A receiver operating characteristic (ROC) curve was constructed to evaluate the diagnostic efficacy of circulating miRNA-1 in the early diagnosis of NSTEMI in the CKD group and the NCKD group. The correlation between miRNA-1 and eGFR in the CKD group was analyzed with the Spearman's rank correlation method.

Specimen Collection and Processing

Five-milliliter samples of venous blood were collected from patients with suspected NSTEMI in tubes containing ethylenediaminetetraacetic acid (EDTA-K2), and plasma was extracted by centrifugation at 3,000 rpm for 3 min after collection and stored at –80 °C for testing.

Determination of Circulating miRNA-1

Total RNA was extracted from the plasma samples with the mirVana PARIS kit (Applied Biosystems, USA). Reverse transcription of miRNAs was done using the miScript reverse transcription kit (Applied Biosystems). As described previously, miRNA-1 was quantitated by using the TaqMan miRNA quantitative reverse transcriptase polymerase chain reaction assay [21], and U6 RNA was used as an internal miRNA control. All assays were performed in triplicate. According to well-established methods [22], the data were analyzed with an automatic setting for assigning the baseline. The threshold cycle (Ct) was defined as the fractional cycle number at which the fluorescence exceeded the given threshold. The plasma levels of miRNA were assessed and analyzed independently by two investigators blinded to the clinical characteristics of the patients. Relative miRNA expression was calculated using the 2^{–ΔΔCt} method.

Investigational hs-cTnI Measurements

Measurement of serum hs-cTnI levels was performed with a BECKMAN DXI800 system and followed the manufacturer's instructions. The upper limit of reference was 0.01 µg/L. We used the first test result for statistics.

Statistical Analysis

Categorical variables are presented as numbers and percentages, and continuous variables are expressed as median (quartiles) (M [QL, QU]). Continuous variables were compared between the two groups with the Mann-Whitney U test. For categorical variables, the Pearson χ^2 test or Fisher's exact test was used, as appro-

Table 1. Baseline characteristics of the patients in each group

Group	CKD (n = 115)	NCKD (n = 341)	p value	CKD		p value
				NSTEMI (n = 67)	non-NSTEMI (n = 48)	
Age, years	70 (61.77)	67 (59.75)	0.068	70 (62.77)	71 (61.76)	0.644
Male gender, n (%)	75 (65)	249 (73)	0.111	39 (58)	36 (75)	0.096
Current smokers, n (%)	65 (57)	112 (33)	0.000	39 (58)	26 (54)	0.810
Hypertension, n (%)	86 (75)	229 (67)	0.157	48 (72)	38 (79)	0.485
Diabetes mellitus, n (%)	39 (34)	100 (29)	0.420	27 (40)	12 (25)	0.131
TC, mmol/L	4.07 (3.45, 4.69)	4.15 (3.61, 4.83)	0.074	4.21 (3.48, 4.72)	3.75 (3.36, 4.64)	0.285
TG, mmol/L	1.55 (1.07, 2.09)	1.37 (0.89, 2.10)	0.156	1.57 (1.07, 2.11)	1.49 (1.00, 1.97)	0.570
History of CVD, n (%)	7 (6)	13 (4)	0.443	2 (3)	5 (10)	0.127
Heart rate, bpm	81 (72, 101)	75 (65.86)	0.000	84 (72, 106)	78 (69.91)	0.100
Body mass index, kg/m ²	23.44 (19.16, 27.94)	23.31 (20.42, 26.03)	0.380	23.05 (19.16, 27.14)	23.95 (19.20, 23.95)	0.396
Creatinine, μmol/L	128.2 (106.9, 128.2)	71.2 (65.6, 88.2)	0.000	128.2 (99.0, 157.5)	129.9 (113.5, 210.9)	0.124
eGFR, mL/min/1.73 m ²	45.41 (32.00, 54.92)	89.09 (77.70, 96.53)	0.000	45.30 (32.96, 53.47)	45.45 (30.09, 55.53)	0.816
Creatine kinase MB, U/L	21.90 (14.20, 51.00)	15.50 (12.30, 20.40)	0.000	25.20 (14.60, 56.30)	17.35 (13.30, 44.75)	0.227
hs-cTnI, μg/L	0.83 (0.21, 8.24)	0.13 (0.02, 0.39)	0.000	3.23 (0.40, 25.51)	0.38 (0.18, 1.19)	0.000
β-Blocker, n (%)	13 (11)	26 (8)	0.222	8 (12)	5 (10)	0.799
CCB, n (%)	40 (35)	106 (31)	0.462	27 (40)	13 (27)	0.142
ARB, n (%)	22 (19)	113 (33)	0.004	13 (19)	9 (19)	0.930
ACEI, n (%)	16 (14)	42 (12)	0.657	9 (13)	7 (15)	0.860
Statins, n (%)	50 (44)	100 (29)	0.005	33 (49)	17 (35)	0.140
Hypoglycemia, n (%)	24 (21)	66 (19)	0.724	15 (22)	9 (19)	0.636
miR-1, 2 ^{-ΔΔCt}	3.55 (1.99, 5.54)	1.85 (1.07, 2.91)	0.000	5.02 (3.14, 7.16)	1.10 (0.67, 2.06)	0.010

Continuous variables are expressed as median (quartiles). TC, total cholesterol; TG, triglyceride; CVD, cardiovascular disease; NSTEMI, non-ST-segment elevation myocardial infarction; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease, which was diagnosed if the eGFR was <60 mL/min/1.73 m²; NCKD, non-chronic kidney disease; hs-cTnI, high-sensitivity cardiac troponin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium antagonist.

Fig. 1. Concentration of miRNA-1 in each group. miR-1, microRNA-1; SA, stable angina; UA, unstable angina; AHF, acute heart failure; NSTEMI, non-ST-segment elevation myocardial infarction; CKD, chronic kidney disease; NCKD, non-chronic kidney disease.

priate. The correlation between continuous variables was analyzed with Spearman's rank correlation method. A ROC curve was constructed to assess the diagnostic efficacy of circulating miRNA-1. The AUC (area under the ROC curve) was calculated, with an AUC <0.5 meaning no diagnostic value. miRNA-1 and hs-cTnI were assessed for both diagnostic and prognostic purposes. They were compared as recommended by DeLong et al. [23]. The McNemar test and the MedCalc 15.2.2 software program (MedCalc, Ostend, Belgium) were used for comparison of multiple diagnostic tests. Statistical analyses were performed with the SPSS 19.0 (SPSS Inc., an IBM company, USA) statistical package [24]. All hypothesis testing was two-tailed. A p value <0.05 was statistically significant.

Results

Characteristics of the Patients

The baseline characteristics of all groups are shown in Table 1. A total of 456 patients with suspected NSTEMI were included. There were 115 patients in the CKD group, including 67 cases of NSTEMI, 20 cases of stable angina, 7 cases of unstable angina, 18 cases of heart failure, and 3 others. The other 341 patients were in the NCKD group, including 75 cases of NSTEMI, 106 cases of stable angina, 91 cases of unstable angina, 51 cases of heart failure, and 18 others. Compared with the NCKD group, there were no significant differences in age, gender, hypertension, diabetes, cholesterol, triglycerides, history of coronary heart disease, and body mass index in the CKD group (all $p > 0.05$). In the CKD group, compared with NSTEMI patients, non-NSTEMI patients only had a significant difference in hs-cTnI levels ($p < 0.05$).

Levels of miRNA-1 according to the Final Diagnosis

The circulating miRNA-1 concentrations in NSTEMI patients were markedly higher than those in non-NSTEMI patients both within the CKD group and the NCKD group. Furthermore, levels of miRNA-1 in NSTEMI patients were also significantly higher than those in non-NSTEMI patients both within the CKD group and the NCKD group (all $p = 0.000$; Fig. 1).

Early Diagnosis of NSTEMI with miRNA-1 in the CKD and the NCKD Group

ROC curve analysis showed that miRNA-1 and hs-cTnI were both able to potentially diagnose NSTEMI early in the CKD and the NCKD group (Fig. 2; Table 2). Compared with the NCKD group, the accuracy of miRNA-1 was almost as good in the CKD group (84.3 vs. 89.4%, $p > 0.05$), and the sensitivity was even significantly improved (86.6 vs. 77.3%, $p < 0.05$). However, the diagnostic accuracy of hs-cTnI was significantly decreased (79.1 vs. 91.5%, $p < 0.05$), as was its specificity (75.0 vs. 95.5%, $p < 0.05$).

Fig. 2. Receiver operating characteristic curves analyzing the diagnostic accuracy of circulating miRNA-1 (<3 h) in comparison with hs-cTnI in early non-ST-segment elevation myocardial infarction patients in both the CKD group (a) and the NCKD group (b). miR-1, microRNA-1; hs-cTnI, high-sensitivity cardiac troponin I; CKD, chronic kidney disease; NCKD, non-chronic kidney disease.

Table 2. Diagnostic value of miRNA-1 and hs-cTnI in the CKD and the NCKD group

Biomarker	AUC (95% CI)	p value	Cutoff	Sens.	Spec.	Acc.	PPV	NPV	LR+	LR–
<i>Diagnostic performance for NSTEMI in the CKD group</i>										
miRNA-1	0.879 (0.814–0.944)	0.000	2.205	86.6%	81.2%	84.3%	0.866	0.813	4.617	0.165
hs-cTnI	0.812 (0.733–0.891)	0.000	0.460	82.1%	75.0%	79.1%	0.821	0.75	3.284	0.239
<i>Diagnostic performance for NSTEMI in the NCKD group</i>										
miRNA-1	0.893 (0.849–0.937)	0.000	3.180	77.3%	92.9%	89.4%	0.753	0.936	10.827	0.244
hs-cTnI	0.908 (0.859–0.956)	0.000	0.580	77.3%	95.5%	91.5%	0.829	0.937	17.142	0.237

miRNA-1, microRNA-1; hs-cTnI, high-sensitivity cardiac troponin I; CKD, chronic kidney disease; NCKD, non-chronic kidney disease; AUC, area under the receiver operating characteristic curve; CI, confidence interval; Sens., sensitivity; Spec., specificity; Acc., accuracy; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR–, negative likelihood ratio.

Relationship of miRNA-1 and hs-cTnI to eGFR in the CKD Group

There was no significant correlation between miRNA-1 and eGFR ($p > 0.05$), but a statistically significantly negative correlation between hs-cTnI and eGFR ($p < 0.05$) in the CKD group (Fig. 3).

Discussion

In this prospective cohort study, we evaluated the value of miRNA-1 in the early diagnosis of NSTEMI in patients with chest pain and renal insufficiency. The results suggest that miRNA-1 and hs-cTnI were comparable in the early diagnosis of NSTEMI in the NCKD group,

Fig. 3. Correlation of both hs-cTnI and miRNA-1 with eGFR in the CKD group. miR-1, microRNA-1; hs-cTnI, high-sensitivity cardiac troponin I; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; *n*, number of cases; *r*, correlation coefficient.

and both had a good diagnostic value and could be used as markers. For patients with CKD, the diagnostic efficacy of miRNA-1 was better than that of hs-cTnI, with obvious specific advantages. Further analyzing the correlation of miRNA-1 and hs-cTnI with eGFR revealed that hs-cTnI was significantly negatively correlated with eGFR and the prevalence of NSTEMI was markedly higher in the CKD group than in the NCKD group, which is consistent with the results of a previous study [25].

We considered that the performance of miRNA-1 was better than that of hs-cTnI in patients suspected of having NSTEMI with CKD mainly because miRNA-1 was not affected by CKD, which was one of the causes of the decline in hs-cTnI specificity. The reason why we selected hs-cTnI and not hs-cTnT was that we took a previous study into account which suggested that renal function had less of an effect on hs-cTnI than hs-cTnT [26]. Actually, the current consensus is that both of them provide similar diagnostic and prognostic information in all patients, and their accuracy is not affected by molecular biological characteristics [14]. Many studies have confirmed that miRNA-1 and miRNA-499 are useful as biomarkers for early diagnosis of AMI [27–29]; especially their time windows are more conducive than those of cTn. In this regard, studies have concluded that when myocardial infarction occurs, cTn is released into the blood, and the release of circulating miRNA is affected by cellular stress such as hypoxia, lactic acidosis, or cell edema, which occur earlier than AMI [30]. Of note, increased concentrations of miRNA-499 and hs-cTn were identified in patients with end-stage renal disease even without any evidence of cardiac injury [31]. For these reasons, the diagnostic specificity of miRNA-1 for AMI needs to be tested, especially in NSTEMI patients with CKD.

In addition, there are several points that need to be clarified in this study. Firstly, the failure to use scaled troponin values is a shortcoming of this study, because previous work had demonstrated that using scaled troponin values instead of absolute values helps to better detect NSTEMI [32]. Secondly, the hs-cTnI test results were not blinded for the clinicians, making them susceptible to clinicians' subjective opinions, whereas the miRNA-1 results were blinded, which made the results more objective. Thirdly, the adjudication of AMI put cTn in a

decisive position, which unavoidably caused a reference test bias. As a result, it was difficult to consider new biomarkers except cTn. Fourthly, there have been many reports about a miRNA-1 relation to tumors; thus, our study excluded cancer patients to avoid this bias [33]. Fifthly, no conclusions could be made about patients with regular hemodialysis, as these patients were excluded from the study. Sixthly, relevant studies have suggested that renal insufficiency is an independent risk factor for painless myocardial infarction [34, 35], but the patients we selected all had symptomatic myocardial infarctions; therefore, we did not have enough data on these patients. Seventhly, the absence of data regarding albuminuria is also a limitation, for it is a powerful predictor of cardiovascular disease as well as of kidney outcomes.

At present, studies of miRNAs for the early diagnosis of AMI vary. Because the diagnostic value of different miRNAs is dissimilar, it takes 2 or 3 miRNA combinations to be superior to the current gold standard cTn, resulting in corresponding increases in cost. Detection of circulating miR-1 takes longer than that of hs-cTnI. Highly efficient miR-1 detection methods have always been the focus of research. Detection methods such as the enzyme-linked immunosorbent assay are being studied for the detection of miR-1. It is believed that researchers will be able to solve such technical problems in the near future.

Clinical application of miRNAs still requires large-scale, multicenter studies to further clarify which is the most diagnostically valuable miRNA while accelerating findings regarding their stability, transmembrane conductance, specificity, safety, and drug-making. Also, how to establish a test to meet clinical demands needs a methodology and further study.

Conclusion

Circulating microRNA-1 is capable of early diagnosis of NSTEMI in chest pain patients with CKD.

Statement of Ethics

This study complies with the Declaration of Helsinki, and The Third Affiliated Hospital of Soochow University Research Ethics Committee approved the research protocol. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

The authors declare no potential conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Author Contributions

X.L. and C.Y. conceived and designed the study. T.S., X.S., and Z.H. take responsibility for the integrity of the data and the accuracy of the data analysis. X.Z. is responsible for the data analysis and interpretation. T.S. and X.Z. are responsible for drafting of the manuscript. X.L. and X.Z. supervised the study.

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