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【 ORIGINAL ARTICLE 】

Impact of Aging on High-sensitivity Cardiac Troponin T in Patients Suspected of Acute Myocardial Infarction

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Abstract:

Objective High-sensitivity cardiac troponin T (hs-cTnT) is widely used for the diagnosis of acute myocardial infarction (AMI). The current cut-off value of 0.014 ng/mL was determined based on the 99th percentile of a normal reference population; however, little data exist regarding the appropriate cut-off value in the elderly (≥75 years). Accordingly, we aimed to investigate the accuracy of the current cut-off value in an elderly population.

Methods We assessed 355 consecutive patients (mean age =66.7±16.1 years, male =210) whose hs-cTnT levels were measured at Kanazawa University Hospital from January 2014 to July 2015. Twenty-six patients were eventually diagnosed with AMI. Hs-cTnT was measured during a visit to the emergency or outpatient department. Receiver operating characteristic (ROC) curves were assessed to determine the appropriate cut-off levels, yielding the maximum sensitivity and specificity while dividing the subjects into two groups according to ages (≥75 or ≤74 years).

Results The appropriate overall cut-off value was 0.038, the sensitivity and specificity of which were 85% and 89%, respectively, with an area under the ROC curve (AUC) of 0.945 overall. The conventional cut-off value (99th percentile: 0.014 ng/mL) provided low specificity, particularly in the elderly or those with renal dysfunction. In contrast, a calculated appropriate cut-off provided higher sensitivity with significantly larger c-statistics in the elderly (0.940 vs. 0.629, p<0.001).

Conclusion When measuring hs-cTnT, careful assessments are needed in elderly subjects.

Key words: high-sensitivity cardiac troponin T, acute myocardial infarction, elderly

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Introduction

Acute myocardial infarction (AMI) is caused by acute ischemia to the myocardium, resulting from numerous factors, with one example being coronary artery stenosis. AMI is an acute disease with a high mortality rate, causing death and disability worldwide (1). A timely diagnosis of AMI is crucial as the initiation of early, effective, evidence-based medical management, including early revascularization, is essential for the best outcome (2, 3). Recently, more sensitive cardiac troponin (cTn) assays have been developed with a limit of detection below the 99th percentile of healthy reference populations, thus improving precision in clinical practice (4-6). However, their clinical utility in the elderly has been questioned (7), which is also the case for renal dysfunction with elevated baseline cTnT levels (8). According to the universal definition of AMI, the 99th percentile could be an acceptable reference value for diagnosis (9); however, in practice, reference values required for optimal clinical decision making at presentation may differ. We therefore aimed to examine the diagnostic performance of high-sensitivity cTnT (hs-cTnT) assays and to identify the appropriate cut-off levels for the early diagnosis of AMI in the elderly.

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Materials and Methods

Study population

We investigated patients referred to the emergency and outpatient departments at Kanazawa University Hospital from January 2014 to July 2015. We assessed 355 consecutive patients who were measured their hs-cTnT levels for any reasons. Patients who suffered out-of-hospital cardiac arrest were excluded. The elderly were defined as those over 75 years of age.

Clinical assessments

The diagnosis of AMI was based on the criteria from the following organizations: Joint European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and World Heart Federation Task Force definition (10). AMI was indicated in the presence of at least one of the following features, including: symptoms of ischemia, new ST-T changes or development of pathologic Q waves in electrocardiography (ECG), evidence of further loss of viable myocardium, or regional wall motion abnormalities in imaging findings. AMI was defined as clinical evidence of ischemia with an increase or decrease in the troponin levels.

Biochemical analysis

The hs-cTnT analyses were performed using the Elecsys 2010 system (Roche Diagnostics) with a limit of detection of 2 ng/L, a 99th-percentile cut-off point of 14 ng/L, and a coefficient of variation of less than 10 at 13 ng/L (11). We used the hs-cTnT levels measured at the earliest timing after the onset, and none of the patients were assessed earlier than one hour after the onset.

Clinical evaluations

Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medication. Diabetes was defined using the guidelines of the Japan Diabetes Society (12), or in the case of patient use of diabetes medication. The plasma levels of low-density lipoprotein (LDL) cholesterol ≥160 mg/dL, plasma triglycerides <200 mg/dL, or the use of lipid-lowering agents indicated hypercholesterolemia. Stage 3 chronic kidney disease (CKD) or greater denoted impaired kidney function. Coronary artery disease (CAD) was defined by the presence of angina pectoris, myocardial infarction, or severe stenotic region(s) in the coronary artery, identified either by an angiogram or by computed tomography.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD); categorical variables are presented as numbers and percentages. Continuous and categorical variables were compared using the Mann-Whitney test and the Pearson χ^2 test, respectively. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of cTn measurements and to compare their ability to diagnose AMI. Logistic regression was used to combine the cTn levels at presentation with early changes in the cTn levels. A comparison of the areas under the ROC curves (AUC) was performed as recommended by DeLong et al. (13). The appropriate cut-off values were determined by the point furthest from the bisector of the ROC curve. All hypothesis testing was two-tailed, and p values of 0.05 were considered to be statistically significant. All statistical analyses were performed with R statistical software program.

Results

Characteristics of study subjects

The hs-cTnT levels of 355 consecutively enrolled patients were measured at presentation; 128 (36%) were over 75 years old. The elderly differed from those under 75 years of age in several baseline characteristics (see Table 1). Among the total subjects, 26 patients fulfilled the criteria of AMI, of whom, 8 were over 75 years old. As expected, the prevalence of hypertension (85% vs. 53%, p<0.001), diabetes (36% vs. 21%, p<0.001), prior coronary artery disease (29% vs. 13%, p<0.001), prior coronary artery bypass grafting (CABG) (9% vs. 2%, p<0.001), impaired kidney function (27% vs. 10%, p<0.001), previous stroke (20% vs. 8%, p<0.001), and estimated glomerular filtration (eGFR) <60 (54% vs. 24%, p<0.001) were significantly larger in the elderly than those under 75 years of age. Furthermore, the eGFR levels in the elderly were lower than those under 75 years old (58.89 mL/min/1.73 m^2 vs. 78.94 mL/min/1.73 m^2, p<0.001).

Optimal cut-off for cardiac troponin in the early diagnosis of AMI determined by ROC curve

The appropriate cut-off values were determined based on the ROC curve for diagnosis of AMI (Fig. 1-3, Table 2). Based on the ROC curve analysis, the optimal cut-off value of hs-cTnT was 0.038 ng/mL, and sensitivity and specificity were 85% and 89%, respectively, with an overall AUC of 0.945 (Fig. 1). When we divided the subjects into two groups based on age, the optimal cut-off value of hs-cTnT for the AMI diagnosis in the elderly was 0.07 ng/mL, the sensitivity and specificity of which were 84% and 88%, respectively, with an AUC of 0.94; whereas, the optimal cut-off value of hs-cTnT in patients under 75 years was 0.02 ng/mL, the sensitivity and specificity of which were 76% and 100%, respectively, with an AUC of 0.95 (Fig. 2). When we compared the AUCs between the conventional cut-off value (0.014 ng/mL) and the values determined for each age group by ROC curve, the AUC in the elderly group was significantly larger than that of the conventional cut-off value (0.94 vs.0.629, p<0.001, Table 2). On the contrary, the

Table 1. Baseline Characteristics of Subjects.

Variable	All	≥75years	<75years	p value
	n=355	n=128	n=227	
AMI	26	8	18	0.673
Male gender	210 (59%)	70 (55%)	140 (62%)	0.217
Age (years)	66.7±16.1	81.6±5.0	58.3±14.0	<0.001
Hypertension	229 (65%)	109 (85%)	120 (53%)	<0.001
Hypercholesterolemia	111 (31%)	44 (34%)	67 (30%)	0.343
Diabetes mellitus	95 (27%)	46 (36%)	49 (22%)	<0.001
Current smoking	47 (13%)	9 (7%)	38 (17%)	0.0326
Prior coronary artery disease	66 (19%)	37 (29%)	29 (13%)	<0.001
Prior myocardial infarction	34 (10%)	17 (13%)	17 (7%)	0.0909
Prior PCI	46 (13%)	22 (17%)	24 (11%)	0.0674
Prior CABG	16 (5%)	11 (9%)	5 (2%)	<0.001
Impaired kidney function	57 (16%)	34 (27%)	23 (10%)	<0.001
Previous stroke	44 (12%)	25 (20%)	19 (8%)	<0.001
Peripheral artery disease	12 (3%)	9 (7%)	3 (1%)	<0.001
eGFR<60mL/min/1.73m^2	124 (35%)	69 (54%)	55 (24%)	<0.001
Creatinine, mg/dL	1.13 ± 1.64	1.15 ± 1.01	1.11 ± 1.88	0.829
eGFR, mL/min/1.73m^2	71.71 ± 31.2	58.89 ± 26.6	78.94 ± 31.2	<0.001
CK, IU/L	235 ± 644	308 ± 919	194 ± 410	0.111
CKMB, IU/L	21 ± 45	26 ± 64	19 ± 26	0.186
BS, mg/dL	146 ± 65	152 ± 64	142 ± 65	0.194
HbA1c, %	6.18 ± 1.15	6.34 ± 0.95	6.08 ± 1.23	0.112
LDL-C, mg/dL	103 ± 38	77 ± 29	112 ± 41	0.0206

Data are given as n (%) or mean ± SD. AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, eGFR: estimated glomerular filtration rate, BS: blood suger, LDL-C: low-density lipoprotein cholesterol

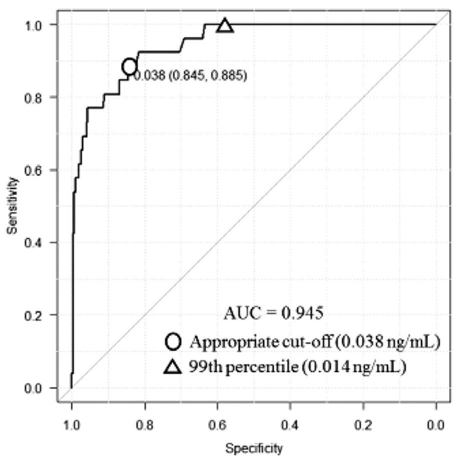

Figure 1. ROC curve determining the overall appropriate cut-off levels. A circle indicates the appropriate cut-off value determined by ROC curve. A triangle indicates the conventional cut-off value.

difference in AUCs between ROC curve and conventional cut-off values in patients under 75 years was much smaller, although statistically significant (0.95 vs. 0.849, p<0.001, Table 2).

Similar trends were observed for the renal function; the optimal cut-off value of hs-cTnT for AMI diagnosis in the group with eGFR <60 mL/min/1.73 m^2 was 0.239 ng/mL, the sensitivity and specificity of which were 95% and 80%, respectively, with an AUC of 0.899; whereas, the optimal cut-off value of hs-cTnT was 0.07 ng/mL in patients with a normal renal function, the sensitivity and specificity of which were 98% and 81%, respectively, with an AUC of 0.959 (Fig. 3). When we compared the AUCs between the conventional cut-off value (0.014 ng/mL) and the values determined for each renal function group by the ROC curve, the AUC in the group with eGFR <60 mL/min/1.73 m^2 was significantly larger than that of the conventional cut-off value (0.899 vs. 0.615, p<0.001, Table 2). Conversely, the difference in AUCs determined by the ROC curve and those of conventional cut-off values was much smaller, although they were statistically significant (0.959 vs. 0.845, p<0.001, Table 2).

Discussion

In this retrospective study, we investigated the diagnostic performance of hs-cTnT for the early diagnosis of AMI in the elderly. We found that the conventional cut-off value (99th percentile: 0.014 ng/mL) provided low specificity, particularly in the elderly or those with renal dysfunction.

The hs-cTnT assay is currently widely used in the global clinical setting for the diagnosis of AMI. In addition to its usage for making a diagnosis, there are a number of studies showing the prognostic value of the hs-cTnT levels, in addi-

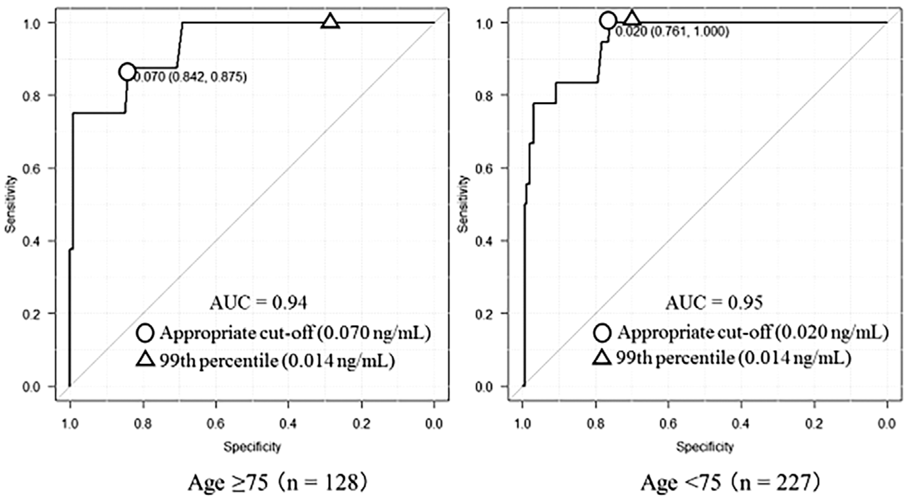

Figure 2. ROC curve determining the appropriate cut-off levels divided by age. Circles indicate the appropriate cut-off values determined by ROC curves. Triangles indicate the conventional cut-off values.

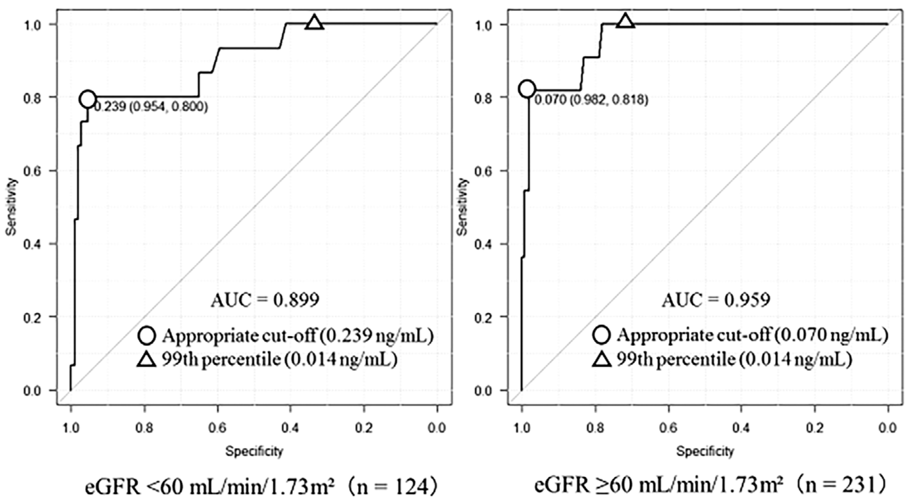

Figure 3. ROC curve determining the appropriate cut-off levels divided by renal function. Circles indicate the appropriate cut-off values determined by ROC curves. Triangles indicate the conventional cut-off values.

Table 2. Comparisons between the AUC of Conventional Cut-off and That of Appropriate Cut-off Divided by Age and Renal Function.

	conventional cut-off					appropriate cut-off					p value
	Value (ng/mL)	AUC	Sensitivity (%)	Specificity (%)	NPV (%)	Value (ng/mL)	AUC	Sensitivity (%)	Specificity (%)	NPV (%)	
All patients (n=355)		0.769	100	53	100	0.038	0.945	89	85	99	<0.001
Age											
≥75 (n=128)		0.629	100	26	100	0.07	0.94	88	84	99	<0.001
<75 (n=227)	0.014	0.849	100	71	100	0.02	0.95	100	76	100	<0.001
eGFR (mL/min/1.73m^2)											
<60 (n=124)		0.615	100	23	100	0.239	0.899	80	95	97	<0.001
≥60 (n=231)		0.845	100	69	100	0.07	0.959	81	98	99	<0.001

AUC: area under curve, NPV: negative predictive value

Table 3. Concurrent Diseases in the Patients with False Positive.

False positive	n=151
Cardiac disease	
Heart failure	19
Supraventricular arrhythmia	6
After cardiopulmonary resuscitation	5
Ventricular arrhythmia	4
Aortic dissection	4
Takotsubo cardiomyopathy	2
Pericarditis	2
Myocarditis	1
Aortic rupture	1
Non cardiac disease	
Stroke	8
Respiratory disease	5
Gastrointestinal disease	12
Hypoglycemia	3
Unknown	79

tion to significant associations with other established biomarkers in different types of cardiac diseases (14-18). Determining the cut-off values is vitally important for any disease. In the case of hs-cTnT, the currently accepted cut-off value (0.014 ng/mL) was determined according to the 99th percentile of a healthy reference population. However, recent clinical studies have suggested that this value might not be appropriate in some specific individuals, such as in patients with renal dysfunction. In addition, a separate study demonstrated that the optimal cut-off value may also be different in the elderly. Determining the optimal cut-off values for these two groups is therefore quite important because both situations are apparent risk factors of AMI. In the current study, we demonstrate that the optimal cut-off values for renal patients and the elderly should be different from the conventional one in the Japanese population.

Another aspect we observed in this study was the complexity when the patient suffers from heart failure. The most frequent cause of false positive of hs-cTnT was heart failure (Table 3). It is not surprising that pressure and/or volume overload could lead to a mild elevation of the hs-cTnT as reported elsewhere (19). Accordingly, careful attention should be paid in such a situation.

Study limitations

The limitations associated with this study include its retrospective nature and observational analysis at a single center. However, it uses one of the largest sample sizes to investigate the diagnostic value of hs-cTnT in the Japanese population. In addition, our findings were consistent with previous studies. A further limitation of this study was lack of any data regarding the timing of measurements which could affect the values. However, at least one hour had passed since the onset in all of the patients in this study, thus, a significant elevation should be observed if the patients truly suffered AMI at that point. In addition, we assessed the initial hs-cTnT value, not the peak hs-cTnT values, which potentially undervalues the power of hs-cTnT. However, the initial assessment is the most important, since the judgement at that point should directly affect the prognosis of the patient. Related to this point, we also acknowledged the fact that sensitivity using conventional cut-off value was 100%, suggesting that the timing after the onset of all of our patients with MI might have been sufficient. A further study investigating the patients with a very acute phase (within oue hour after the onset) would be needed. In addition, most of the patients with AMI (nineteen out of twenty-six) were ST-elevation MI (STEMI), where the information for hs-cTnT is not necessarily needed for the diagnosis of AMI. Accordingly, a further study investigating a sufficient number of patients with non-STEMI could more fully elucidate the clinical usefulness of hs-cTnT. Finally, we could not evaluate whether or not an older age is an independent predictor of the elevated hs-cTnT. Further studies are therefore needed to elucidate this point using a sufficient number of study samples.

Conclusion

In summary, these data suggest that the conventional cut-off value (99th percentile: 0.014 ng/mL) provides low specificity in the elderly in addition to those with renal dysfunction. When measuring hs-cTnT, careful assessments are therefore needed in the elderly.

The authors state that they have no Conflict of Interest (COI).

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References

1. Mozaffarian D, Benjamin EJ, Go AS, et al; Writing Group Members. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation **133**: e38-e360, 2016.
2. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J **28**: 1598-1660, 2007.
3. Kushner FG, Hand M, Smith SC Jr, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol **54**: 2205-2241, 2009.
4. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH; National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. Circulation **115**: e352-e355, 2007.
5. Apple FS, Smith SW, Pearce LA, Ler R, Murakami MM. Use of

the Centaur TnI-Ultra Assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. Clin Chem **54**: 723-728, 2008.

6. Melanson SE, Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin I assay with improved sensitivity. Am J Clin Pathol **128**: 282-286, 2007.

7. Reiter M, Twerenbold R, Reichlin T, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J **32**: 1379-1389, 2011.

8. 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 **131**: 2041-2050, 2015.

9. Jaffe AS, Apple FS, Morrow DA, Lindahl B, Katus HA. Being rational about (im)precision: a statement from the Biochemistry Subcommittee of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the definition of myocardial infarction. Clin Chem **56**: 941-943, 2010.

10. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation **116**: 2634-2653, 2007.

11. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem **56**: 254-261, 2010.

12. Seino Y, Nanjo K, Tajima N, et al; Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig **1**: 212-228, 2010.

13. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics **44**: 837-845, 1988.

14. Kimura K, Tomiyama H, Matsumoto C, et al. Correlations of arterial stiffness/central hemodynamics with serum cardiac troponin T and natriuretic peptide levels in a middle-aged male worksite cohort. J Cardiol **66**: 135-142, 2015.

15. Shionimya H, Koyama S, Tanada Y, et al. Left ventricular end-diastolic pressure and ejection fraction correlate independently with high-sensitivity cardiac troponin-T concentrations in stable heart failure. J Cardiol **65**: 526-530, 2015.

16. Saito T, Hojo Y, Hirose M, Ikemoto T, Katsuki T, Kario K. High-sensitivity troponin T is a prognostic marker for patients with aortic stenosis after valve replacement surgery. J Cardiol **61**: 342-347, 2013.

17. Kusumoto A, Miyata M, Kubozono T, et al. Highly sensitive cardiac troponin T in heart failure: comparison with echocardiographic parameters and natriuretic peptides. J Cardiol **59**: 202-208, 2012.

18. Sato Y, Yamamoto E, Sawa T, et al. High-sensitivity cardiac troponin T in essential hypertension. J Cardiol **58**: 226-231, 2011.

19. Jungbauer CG, Riedlinger J, Buchner S, et al. High-sensitive troponin T in chronic heart failure correlates with severity of symptoms, left ventricular dysfunction and prognosis independently from N-terminal pro-b-type natriuretic peptide. Clin Chem Lab Med **49**: 1899-1906, 2011.

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