Prognostic value of tissue inhibitor of metalloproteinase-matrix metalloproteinase biomarkers at 30 days in patients with acute myocardial infarction without reperfusion therapy

Hui-Fang Pang, Yan Gao, Jia-Min Liu, Jia-Peng Lu, Yan-Ping Wang, Si-Ming Wang, Li-Bo Hou, Ao-Xi Tian, Yan Gao

National Clinical Research Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center for Cardiovascular Diseases, Beijing 100037, China.

To the Editor: Ischemic coronary artery disease is the leading cause of heart failure (HF) which is a major public health burden worldwide. Over the past decades, development of new pharmacological therapies and implementation of early reperfusion strategies have contributed to a significant reduction in mortality associated with acute myocardial infarction (AMI). However, improved survival in acute cardiac ischemic event has expanded the pool of patients prone to cardiac remodeling and adverse cardiovascular (CV) outcomes.

Extracellular matrix proteolysis and turnover is a pivotal mechanism for post-acute AMI cardiac remodeling. Some markers in the tissue inhibitor of metalloproteinase-matrix metalloproteinase (TIMP-MMP) axis were observed to be associated with cardiac structural and functional changes. The present study aimed to systematically analyze the association between post-AMI CV outcomes at 30 days and TIMP-MMP family biomarkers and assess their potential prognostic value.

This study included 1105 AMI patients from the China Patient-centered Evaluative Assessment of Cardiac Events prospective AMI study based on the following criteria: (1) having no prior AMI, (2) receiving no reperfusion treatment (thrombolysis, percutaneous coronary intervention, or coronary artery bypass grafting) during the index AMI hospitalization, and (3) having blood samples collected within 72 h of symptom onset. The study was approved by the Institution’s Ethics Committee at Fuwai Hospital (No. 2012-377), and registered at www.clinicaltrials.gov (Registration No. NCT01624909).

Clinical outcomes included hospitalized HF and CV-related events. Hospitalized HF was defined as an event where the patient was admitted to hospital for new or worsening symptoms of HF. CV-related event was a composite of CV events, including non-fatal CV-related events (AMI, revascularization, angina pectoris, ischemic stroke, HF) and CV death. The events of elective revascularization were excluded.

Blood samples were obtained from all patients during the first 24 h of hospital admission. N-terminal pro b-type natriuretic peptide (NT-proBNP) from ethylene diamine tetraacetic acid plasma was measured by a Cobas e601 analyzer (Roche, Japan, Germany). For heparin plasma, TIMP3 was tested by the Abnova TIMP3 enzyme-linked immunosorbent assay kit (Abnova Ltd., Taipei, Taiwan, China); MMP2, MMP8, MMP9, TIMP1, TIMP2, and TIMP4 were assessed by the Bio-Plex Pro Human MMP panel kit and the Bio-Plex Pro Human TIMP panel kit (Bio-Rad Ltd, Berkeley, CA, USA).

In this study, 20 (1.80%) patients developed HF and 64 (5.79%) patients developed CV-related events within 30 days follow-up. In the Kaplan-Meier plots, cut-off points of biomarkers’ concentration were determined based on the highest differentiation in the receiver operating characteristic curve analysis, and used to dichotomize patient groups. For HF events, patients with NT-proBNP (\(P < 0.0001\)), TIMP1 (\(P < 0.0001\)), or TIMP4 concentration (\(P = 0.0003\)) above the indicated cut-off point (2724 pg/mL for NT-proBNP, 213 ng/mL for TIMP1, 2.75 ng/mL for TIMP4) had higher event rates than those below the cut-off point. For CV-related events, patients with NT-proBNP (\(P < 0.0001\)), TIMP1 (\(P = 0.0002\)), TIMP2 (\(P = 0.0006\)), or TIMP4 concentration (\(P = 0.0003\)) above the indicated cut-off point (1953 pg/mL for NT-proBNP, 192 ng/mL for TIMP1, 118 ng/mL for TIMP2, and 2.83 ng/mL for TIMP4) had higher event rates than those below the cut-off point.

Correspondence to: Dr. Yan Gao, National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China
E-Mail: yan.gao@fwoxford.org

Copyright © 2021 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2021;134(4)
Received: 14-05-2020 Edited by: Ning-Ning Wang
Figure 1: Hazard ratios for association of biomarker concentrations (log scale) with heart failure (A) and cardiovascular event (B). For NT-proBNP, hazard ratio (HR) was calculated based on per 1000 ng/mL (1 unit) increase in NT-proBNP concentration. For TIMP1, MMP2, and MMP2/TIMP4, HR was calculated based on per 10 ng/mL (1 unit) increase in concentration or per ten-fold increase in the ratio. ∗Cox regression model adjusted for age and sex. CI: Confidence interval; HR: Hazard ratio; MMP: Matrix metalloproteinase; NT-proBNP: N-terminal pro b-type natriuretic peptide; TIMP: Tissue inhibitor of metalloproteinase.
In the Cox regression models after adjustment for age and sex, NT-proBNP, TIMP1, and MMP2/TIMP1 ratio at baseline were significantly associated with both HF and CV-related events during 30 days follow-up; while MMP8/TIMP1 ratio was only associated with CV-related events [Figure 1].

The prognostic value of the biomarkers was further evaluated by c-statistics. In the models for HF events, compared with NT-proBNP (C = 0.776) alone, the c-statistics values were improved when combining NT-proBNP with TIMP4 (C = 0.828), MMP2/TIMP1 (C = 0.819), TIMP1 (C = 0.804), and MMP2/TIMP4 (C = 0.799), respectively. In the models for CV events, none of the c-statistics values reached 0.7 when combining NT-proBNP with any of the TIMP-MMP biomarkers, compared with NT-proBNP (C = 0.619) alone.

Our study found that TIMP1 level at baseline was associated with HF and CV-related events after AMI, which could be supported by the previous studies. A large population-based study found that elevated TIMP1 level was associated significantly with increased risk of all study endpoints in a 13-year follow-up, including CV event, coronary artery disease, AMI, stroke, and all-cause death.[12] Another study reported that elevated levels of TIMP1 were associated with a higher chance of major adverse cardiovascular events in patients with AMI.[13] In addition, the prognostic value of TIMP1 for HF was further demonstrated by c-statistics in our model combining TIMP1 with the established NT-proBNP, which indicated that TIMP1 had clinical implications as a biomarker in HF outcome in AMI patients without reperfusion treatment.

Clinical studies have already demonstrated that elevated levels of MMP2 were associated with clinical outcomes, such as infarct size and left ventricular dysfunction, in patients with myocardial infarction (MI).[4] In this study, however, we found no association of baseline MMP2 level with risk of future HF or CV-related events within 30 days after AMI in patients without reperfusion treatment. The difference in the findings may be due to the different outcomes selected for observation. For the hard endpoints in this study, the predictive effects of MMP2 may take longer to observe. Nevertheless, we observed that elevated MMP2/TIMP1 ratio showed predictive value for a decreased risk of HF and CV-related events. This may indicate that the homeostasis balance of MMP2 and TIMP1 was disturbed after AMI, and the severity in the imbalance status could predict the occurrence of HF and CV-related events.

A previous study has reported that elevated MMP-8 level and MMP8/TIMP1 ratio were both associated with the risk for MI during 13-year follow-up in the general population.[4] In this study, we observed that MMP8/TIMP1 ratio rather than MMP8 level showed the prediction ability for CV-related events independently of age and sex. Given that MMP8 protein expression was observed to be increasing at the 2nd week post-ligation and persisting through 16 weeks post-MI, which suggested that MMP8 was actively participating in the late remodeling events,[5] the 30 days follow-up in this study may be too short to present the relationship between MMP8 and CV-related outcome.

In conclusion, this study showed that MMPs and TIMPs at acute stage could predict the occurrence of HF or CV-related events within 30 days follow-up in AMI patients without reperfusion therapy. Specifically, TIMP1 levels and MMP2/TIMP1 ratio in plasma could predict risk of HF and CV-related events. MMP8/TIMP1 ratio showed predictive value for risk of CV-related events. Moreover, combining the biomarker (TIMP4, MMP2/TIMP1, or TIMP1) with NT-proBNP provided incremental prognostic value in c-statistics model. Further studies are warranted to evaluate whether these biomarkers could be effectively used for prognosis and early intervention in AMI patients.

Declaration of patient consent

All participants provided their written informed consent before participating in the study. In the form, the patient provided consent for their clinical information to be reported in the journal. The patient understands that their name and initials will not be published and that due efforts will be made to conceal their identity but that anonymity cannot be guaranteed.

Funding

This work was supported by the grants from the CAMS Innovation Fund for Medical Sciences (CIFMS; No. 2017-12M-2-002) and the National Natural Science Foundation of China (No. 81903399).

Conflicts of interest

None.

References

1. Kumar D, Li J, Li X, Lin Z, Harlan MK, Jiang L, et al. The China patient-centered evaluative assessment of cardiac events (China PEACE) retrospective study of acute myocardial infarction: study design. Circ Cardiovasc Qual Outcomes 2013;6:732–740. doi: 10.1161/CIRCOUTCOMES.113.000441.
2. Kormi I, Nieminen MT, Havulinna AS, Zeller T, Blankenberg S, Tervahartiala T, et al. Matrix metalloproteinase-8 and tissue inhibitor of matrix metalloproteinase-1 predict incident cardiovascular disease events and all-cause mortality in a population-based cohort. Eur J Prev Cardiol 2017;24:1136–1144. doi: 10.1177/2047487317706585.
3. Kelly D, Squire IB, Khan SQ, Dhillon O, Narayan H, Ng KH, et al. Usefulness of plasma tissue inhibitors of metalloproteinases as markers of prognosis after acute myocardial infarction. Am J Cardiol 2010;106:477–482. doi: 10.1016/j.amjcard.2010.03.060.
4. Nilsson L, Hallen J, Atar D, Jonsson L, Swahn E. Early measurements of plasma matrix metalloproteinase-2 predict infarct size and ventricular dysfunction in ST-elevation myocardial infarction. Heart 2012;98:31–36. doi: 10.1136/heartjnl-2011-30079.
5. Peterson JT, Li H, Dillon L, Bryant JW. Evolution of matrix metalloproteinase and tissue inhibitor expression during heart failure progression in the infarcted rat. Cardiovasc Res 2000;46:307–315. doi: 10.1016/s0008-6363(00)00029-8.

How to cite this article: Pang HF, Gao Y, Liu JM, Lu JP, Wang YP, Wang SM, Hou LH, Tian AX, Gao Y. Prognostic value of tissue inhibitor of metalloproteinase-matrix metalloproteinase biomarkers at 30 days in patients with acute myocardial infarction without reperfusion therapy. Chin Med J 2021;134:481–483. doi: 10.1097/CM9.000000000001144.