To the Editor:
I read with great interest the article by Kobayashi et al which again highlighted the potential utility of matrix metalloproteinase-9 (MMP9) as a biomarker in acute coronary syndrome (ACS).1 Authors measured the levels of MMP9 and high-sensitivity troponin T (hs-TnT) in 266 patients with ACS and compared them with levels measured in 40 stable angina pectoris (SAP) patients who served as controls. Of the patients who presented early (both ST elevation ACS [STEACS] and non-STEACS [NSTEACS]), plasma levels of MMP9 were significantly higher than in the late presenters. Median MMP9 in both STEACS and NSTEACS were higher than in the SAP control group. Further, the authors showed that similar diagnostic values for MMP9 were as good as, if not better than, hs-TnT in the early stages of ACS according to receiver operating curve analysis.2

The concept that MMP9 can be a biomarker in ACS makes sense. In addition to their latest contribution, Kobayashi et al also quoted several key studies supporting the potential role of MMP9 as a biomarker for atherosclerotic plaque rupture: MMP9 has been directly identified in the shoulder region of vulnerable plaques;2 patients with features of ruptured plaques on intravascular imaging also had higher plasma levels of MMP9;3 higher levels of MMP9 are observed in patients presenting with ACS compared to SAP (the plaque rupture event has already occurs in ACS patients);4 and plasma MMP9 returns to a lower level days after the presentation with ACS and approaches the same as that observed in SAP.4 All the evidence supports a feasible role of MMP9 for the diagnosis of vulnerable plaque, particularly in the setting of acute vascular syndromes.

There have also been many reports, however, showing inconsistent results despite these convincing rationales and experimental data. For example, a prospective study by Jefferis et al in an older age group of patients did not find a significant association between serum MMP9 levels and the risk of incident myocardial infarction and stroke;5 Tayebjee et al reported a lack of correlation between MMP9 and severity of coronary artery disease demonstrated on coronary angiography;6 and Jonsson et al reported an increased level of MMP9 expression by neutrophils in SAP patients compared to healthy controls but failed to demonstrate any difference in the plasma levels of MMP9 between the two groups.7

One possible explanation for the disparity of findings in clinical studies of MMP9 in coronary artery disease lies in the pre-analytical issues known to affect measurement of MMP9 and blood samples. The level of MMP9 is typically higher in serum compared to plasma.8 This is not surprising given that MMP9 can be secreted by blood components such as neutrophils7 and platelets,9 both of which are activated during the coagulation process. The measured levels of MMP9 also vary depending on the type of anticoagulants used to prepare the plasma samples. EDTA plasma contains a higher level of MMP9 compared to paired plasma prepared with lithium heparin or citrate as anticoagulant.10 Furthermore, delay in centrifugation would also lead to variable levels of MMP9 measured in plasma.11

There may be no clear answer on what should be the most appropriate sample matrix for the study of MMP9. It could also be difficult to set an agreed standard sample matrix to be used for its measurement, especially when most of the studies investigating this biomarker rely on existing samples that have already been collected. It would therefore be extremely valuable for every research report, such as the one reported by Kobayashi et al, to document the sample preparation protocol, including the type of anticoagulant used and the centrifugation settings, to allow for comparison between studies. This would be a further step in consolidating the utility of MMP9 as a biomarker in acute vascular syndromes.

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References