When prognosis precedes diagnosis: putting the cart before the horse

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Each year in the United States, some 6 million people present to emergency departments with chest pain.[1] Although only 15%–20% of these patients are ultimately diagnosed with an acute coronary syndrome (ACS),[2] about half are admitted for evaluation. Conversely, 2% of patients with ACS are mistakenly discharged.[2] As patients with ACS have a relatively high risk of major adverse cardiovascular events in the short term, there is a clear need for accurate, objective tools by which to identify them.

Biomarkers can be used to aid in diagnosis and prognosis. Traditionally, diagnostic tests are used to determine whether a patient has a particular disease. In contrast, prognostic tests are used to determine the probability of a specific clinical outcome in a patient known to have the disease. Inevitably there is overlap, typically because a positive result for a diagnostic test will identify a patient as having a disease that carries a poor prognosis. The measurement of troponin concentrations in serum, for example, serves as the current "gold standard" for the diagnosis of myocardial infarction;[3] because it accurately identifies the presence of myocyte necrosis, the test is also used to define ACS patients at increased risk of death and ischemic complications.[4–6] Nonetheless, when evaluating a potential new biomarker, it is important to consider carefully the role it may best serve and hence how it should best be judged.

One such test involves the albumin–cobalt binding assay. In the presence of ischemia, the amino-terminal end of albumin undergoes structural changes that appear to involve modifications to an aspartate–alanine–histidine–lysine sequence by acidosis, low oxygen tension and free radicals.[7] These changes decrease the binding capacity for cobalt, which serves as the basis for measuring ischemia-modified albumin (IMA). Elevated levels of IMA have been documented in patients experiencing myocardial ischemia in the setting of percutaneous coronary intervention.[8–10] More recently, the utility of IMA measurement for the diagnosis of ACS has been tested in patients with chest pain.[11–13] Using boundaries of either 85 U/mL (the 95th percentile in healthy volunteers and the assay manufacturer's recommended upper limit of the normal range) or 90 U/mL, these investigators found that IMA levels were elevated in more than 70% of patients presenting to an emergency department with chest pain, and that the test had good sensitivity (in the area of 80%–90%) but poor specificity (around 30%–50%).

Worster and colleagues[14] examined the utility of IMA using a different approach, as reported in this issue. They enrolled 189 patients who presented to the emergency department within 6 hours of the onset of potential ACS symptoms, for whom the treating physician ordered a troponin test, who had no serious cardiovascular outcome and for whom no decision to admit to hospital was made before the results of the first troponin test became available. Enrolled patients were followed for 72 hours for the occurrence of a serious cardiovascular outcome, defined as cardiovascular death, myocardial infarction, congestive heart failure, a serious arrhythmia, or refractory ischemic pain. Thus, it was the prognostic rather than the diagnostic capacity of IMA measurement that was investigated.

The results in this study were disappointing. Nearly 13% of the cohort had a serious cardiovascular outcome during the next 72 hours. When patients were stratified by baseline IMA and a cut-off value of 80 U/mL was applied, event rates were about 12% in those with high IMA levels and higher (just under 16%) in those with low IMA concentrations. The authors calculated the positive likelihood ratio to be 0.92 (95% confidence interval [CI] 0.69–1.22) and the negative likelihood ratio as 1.25 (95% CI 0.63–2.46). As these are prognostic data, the authors might have chosen to calculate the relative risk of an adverse outcome after a positive test result, which, based on the data, was 0.77 (95% CI 0.34–1.74). Regardless of the metric, the message is qualitatively the same: IMA measurements do not appear to provide any useful prognostic data in this setting.

However, these results are not surprising and may be explained by taking into account the characteristics of the IMA test. Before this publication, it was already clear that IMA elevation is nonspecific and hence generates many false-positive results. The false positives will represent patients with non-ischemic chest pain, who tend to have a good prognosis and hence attenuate any statistical association between IMA elevation and serious cardiovascular outcomes. Therefore, using a nonspecific biomarker such as IMA for prognosis before first establishing diagnosis is a bit like putting the cart before the horse.

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Compounding this problem is the fact that Worster and colleagues[14] opted to use 80 U/mL as the cut-off value for IMA elevation, which is lower than the manufacturer's recommendation of 85 U/mL. At the ≥ 80-U/mL threshold, IMA levels were considered to be elevated in 75% of patients at presentation and in 94% at any time during the first 6 hours. Understandably, then, it would be hard for those with elevated IMA levels to be at increased risk compared to the rest of the group, when those with IMA elevations constitute almost the entire group. The authors note that when they looked into using the assay manufacturer's recommended cut-off point of 85 U/mL, their study results were not appreciably different. It would have been useful to have seen not only those data but also a receiver-operating-characteristic curve analysis.

In conclusion, the study by Worster and colleagues reinforces the fact that IMA elevation is relatively nonspecific and is thus unlikely to help identify a subgroup of patients at high risk for serious adverse cardiovascular events. However, IMA levels may still prove useful to clinicians in 2 situations. First, in terms of diagnosis, the high sensitivity of the IMA test has excellent negative predictive value; IMA measurements could thus be used to help rule out ischemia in patients with chest pain. However, since more than 70% of patients who present to the emergency department have an IMA level above the manufacturer's suggested cut-off value, the application of current thresholds would aid in the exclusion of ischemia in only a minority of patients. Higher thresholds would remedy this problem, but may erode the test's negative predictive value and thus will require further investigation. Second, measuring serum IMA levels may provide important prognostic information in patients diagnosed with unstable angina, who (by definition) have normal troponin measurements.

A reliable marker of myocardial ischemia remains an important unmet need in cardiology.[15] Whether the measurement of IMA will fill this need, only time, and additional large, well-designed studies, will tell.

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