Opinion Paper

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Opinion paper on utility of point-of-care biomarkers in the emergency department pathways decision making

Abstract: Overcrowding of the emergency department (ED) is rapidly becoming a global challenge and a major source of concern for emergency physicians. The evaluation of cardiac biomarkers is critical for confirming diagnoses and expediting treatment decisions to reduce overcrowding, however, physicians currently face the dilemma of choosing between slow and accurate central-based laboratory tests, or faster but imprecise assays. With improvements in technology, point-of-care testing (POCT) systems facilitate the efficient and high-throughput evaluation of biomarkers, such as troponin (cTn), brain natriuretic peptide (BNP) and neutrophil gelatinase-associated lipocalin (NGAL). In this context, POCT may help ED physicians to confirm a diagnosis of conditions, such as acute coronary syndrome, heart failure or kidney damage. Compared with classic laboratory methods, the use of cTn, BNP, and NGAL POCT has shown comparable sensitivity, specificity and failure rate, but with the potential to provide prompt and accurate diagnosis, shorten hospital stay, and alleviate the burden on the ED. Despite this potential, the full advantages of rapid delivery results will only be reached if POCT is implemented within hospital standardized procedures and ED staff receive appropriate training.

Keywords: brain natriuretic peptide (BNP); neutrophil gelatinase-associated lipocalin (NGAL); point-of-care testing (POCT); troponin.

DOI 10.1515/cclm-2014-0267
Received March 11, 2014; accepted April 4, 2014; previously published online May 24, 2014

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Introduction

Historically, emergency physicians have been caught between the proverbial rock and a hard place when evaluating patients admitted with chest pains. Our choices were limited to using rapid but analytically imprecise assays or more accurate but significantly slower laboratory platforms. Since it is currently agreed that the time delay of the slower tests is "just an hour or so difference" [1], the risk of patient morbidity and mortality increases with more time spent in the emergency department (ED) [2]. A Canadian study, which examined the association between waiting times and short-term mortality and hospital admission after departure from ED of more than 13 million ED patients, showed as a secondary result, that the odds of acute death increased dramatically (OR=1.79) when the ED length of stay (LOS) exceeded 6 h compared with >1 h [3]. Furthermore, increased LOS contributes to overcrowding of the ED, which is rapidly becoming a global challenge and a major source of concern for emergency physicians.

Considering that patients requiring cardiac marker testing represent up to 25% of the ED workload [4], there is a need for an increase in efficiency and throughput in the evaluation of patient cardiac biomarkers so that emergency physicians can reduce their therapeutic turnaround

time and ultimately shorten the ED LOS. However, diagnostic accuracy is also essential to prevent misdiagnosis. A retrospective study of 8000 patients showed that there was an increase in mortality of nearly 250% in patients who received pre-hospital medication for an erroneous diagnosis of heart failure compared with those who were diagnosed correctly [5]. Ultimately, fast and wrong is no better than slow and right.

The evolution of point-of-care testing (POCT) systems has provided the opportunity to reach the standard of "fast and right" for the evaluation of cardiac biomarkers, such as troponin (cTn), brain natriuretic peptide (BNP) and neutrophil gelatinase-associated lipocalin (NGAL). A US study has shown that adopting POCT to evaluate cTn and CK-MB provided a sensitivity of 96.9% and a negative predictive value (NPV) of 99.6% for the diagnosis of MI within 90 min, thereby dismissing acute MI and reducing the median turnaround time from the blood sampling withdrawal to the laboratory result to 24 min, compared with 71 min for central laboratory testing [6]. Furthermore, Storrow et al. showed that a turnaround time of 20–40 min results in the treatment of more patients, shorter LOS and therefore reduced ED overcrowding [7]. The CRUSADE registry study also demonstrated that hospitals with a high troponin POCT usage had a reduced ED LOS and were less likely to administer aspirin, β-blockers, and heparin during the first 24 h of care [8].

However, to unlock the full potential of POCT a reduction in turnaround time alone is insufficient to improve the ED LOS and the outcome of patients. In fact the "therapeutic turnaround time" has to be reduced, which means a reduction of the time between ordering a test and an interpretation of its results and making a decision; e.g., Koehler et al. showed that turnaround "door-to troponin results" time significantly decreased from 105 to 51 min ($p<0.000$) following troponin POCT implementation, however, this was not accompanied by a significant shortening in LOS (290–255 min, $p=0.082$) [9]. The average reduction of the turnaround times shown in the different studies through the use of POCT ranges from 47 to 65 min [1, 7, 9].

The evaluation of cTn, BNP, NGAL with POCT in the ED could be of great utility in facilitating prompt and appropriate decision making to improve patient management, providing it is implemented in ED standard operating procedures and staff receive the necessary training. For example, the utility of POCT was demonstrated in a triage system; the results were reported to be helpful in 56% of patients, the triage level changed in 15% of patients following testing, and 6% of patients were brought back for rapid physician evaluation [10]. Furthermore, ownership of the POCT results among nurses has shown to improve communication among ED staff members [9], thereby facilitating physicians to confirm a diagnosis, reduce their therapeutic turnaround time and expedite patient discharge. If implemented correctly, POCT has the potential to reduce the burden on ED, both in terms of resources and treatment costs [11].

Troponin point-of-care testing

Increases in blood cTn are indicative of myocardial injury and essential to confirm a diagnosis of acute MI [12, 13]. A change in blood concentration of cTn, with at least one value above the 99th percentile limit of distribution of a reference population can be used to confirm a diagnosis of acute MI when accompanied by other signs of ischemia [14]. Thresholds for cTn are assay-dependent but can be defined for each individual assay [15]. The evaluation of cTn is usually processed by a central laboratory assay and limited by the time required by the specific assay used, however, POCT of cTn has been shown to reduce the waiting time to obtain these results [1].

Despite the rapid turnover in results, early POCT had a poor sensitivity for detecting low cTn levels, resulting in fewer patients that could benefit from an accelerated test time in the clinic. In fact, the landmark ASPECT study, which used an accelerated POCT protocol in 3582 suspected acute coronary syndrome (ACS) patients, reported that only 9.8% could be safely discharged 2 h after presentation [16]. In contrast, the ADAPT/APACE studies, which investigated the utility of a slower central laboratory assay albeit with a higher sensitivity to troponin in 2044 patients, showed that this platform resulted in 41.5% of patients being discharged from the ED early [17]. Therefore, there is a need for improved sensitivity with POCT assays.

Identifying candidates for early and safe discharge is the key to reducing ED overcrowding. As tested by Cullen et al. in their validation study, a possible solution of this problem could be to perform a rapid POCT and a higher sensitivity but slower central laboratory cTn assay simultaneously. A positive cTn result from the rapid POCT leads to immediate hospitalization, whereas an undetectable reading (as occurs in nearly 90% of patients [17]), results in the patient being admitted to the chest pain unit (CPU) for higher sensitivity central laboratory cTn testing. This approach allows a rapid diagnosis in the acute MI patient, and facilitates prompt referral for follow-up analysis when the POCT assay is inconclusive. For many institutions, it is difficult to justify simultaneous testing platforms, particularly as this approach may result in a higher rate of patient

referral to the CPU, therefore EDs have been left with the impossible dilemma between speed and accuracy.

However, the situation may change with the introduction of high-sensitivity POCT as high-sensitive troponin tests have been shown to effectively rule out acute MI in as little as 2 h [16, 17], meaning that more than 40% of patients reporting chest pain can be immediately discharged from the ED. Moreover, for patients at high risk of ACS a myocardial perfusion evaluation should be performed on the same day rather than waiting for the 6 h of serial marker evaluation [17].

Data from our group demonstrated the advantage of POC testing with the next generation high-sensitivity troponin I by Alere Triage® compared to traditional troponin I platform utilized in the central laboratory (Beckman Coulter cTnI Assay System). In this study, 90 patients presenting at the ED with chest pain were evaluated for cTn on admission and 4–6 h post-admission. Evaluation at admission with POCT Alere Triage® showed 100% sensitivity, 91.5% specificity, a positive predictive value (PPV) of 75% and a NPV of 100% in identifying patients with MI (Figure 1). Of the 90 patients enrolled, 19 patients were diagnosed with MI following a positive cTn measurement using the POCT. Moreover, POCT and central laboratory cTn measured at admission showed an AUC of 0.97 and 0.90, respectively, for diagnosis of MI (Figure 2). Finally, there was an acceptable Cohen K factor agreement of 0.769 (95% CI 0.620–0.918) between Alere Triage® Troponin I and the Beckman Coulter cTnI Assay System.

Similar results were found in the MIDAS study, which compared the analysis of blood samples from patients presenting with suspected ACS at ED arrival, and 90, 180, and

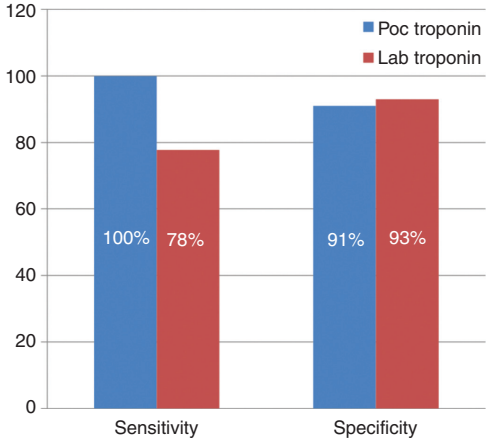

Figure 1 Clinical utility of POCT troponin I by Alere Triage® compared with central laboratory testing using Beckman Coulter cTnI Assay System.

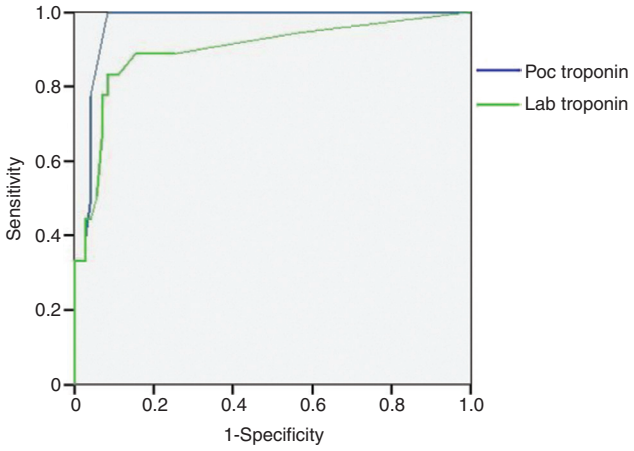

Figure 2 ROC curve of POC test (AUC 0.97) and central laboratory troponin (AUC 0.90) [Beckman Coulter cTnI Assay System] for diagnosis of myocardial infarction.

540 min post-admission using the next generation high-sensitivity troponin I by Alere Triage® and the Beckman UniCel Dxl AccuTnI analyzer. The study concluded that the high-sensitivity POCT produced a good diagnostic accuracy compared to central laboratory assays; at 3 h the POCT showed 84.7% sensitivity, 93.4% specificity, 60.4% PPV, 98.1% NPV, and an AUC of 0.95 to diagnose acute MI in a subpopulation diagnosed with ACS. Furthermore, serial testing beyond 3 h did not improve assay performance for ACS [18].

Considering the high NPV and the time to evaluate cTn levels in the central laboratory (1 h compared to 15 min with POCT Alere Triage®), the next generation POCT could assume an important role in the ED decision-making process to facilitate early discharge and reduce overcrowding. Furthermore, POCT has the potential to improve the management of patients reporting to the ED with chest pains by overcoming the delays in transporting blood samples and the lack of 24-h availability of central laboratory assays.

BNP point-of-care testing

Many biomarkers have been studied to improve the diagnosis of heart failure, such as C-reactive protein, cytokines (e.g., interleukin-1 and -6) and neurohormones (big endothelin-1, noradrenaline), troponins, and natriuretic peptides, in particular BNP [19, 20].

BNP is synthesized by myocytes as a preprohormone, before it is cleaved into the prohormone BNP [21]. Once BNP is released into the circulation upon increases in

ventricular pressure or heart volume, it promotes diuresis, natriuresis and arterial vasodilation, and activates the reninangiotensin-aldosterone system and sympathetic nervous system, all of which play an important role in the pathogenesis of heart failure [19, 22].

BNP is a valuable biomarker in the ED for the diagnosis of heart failure. Current cardiology guidelines cite BNP values above 400 pg/mL as correlated with a diagnosis of heart failure, while values below 100 pg/mL exclude a diagnosis of acute onset heart failure [23, 24]. The clinical utility of this cut-off was first demonstrated using the Alere Triage POCT in the 'Breathing Not Properly' Study, which confirmed that this was the ideal threshold in terms of cost-effectiveness for diagnosing heart failure in patients presenting to the ED with a chief complaint of dyspnea [25]. A total of 1586 patients were investigated in this study, with 744 confirmed with a final diagnosis of heart failure. The BNP cut-off level of 100 pg/mL demonstrated 90% sensitivity, 76% specificity, 79% PPV and 83% accuracy. This cut-off has since been applied to all central laboratory-based BNP assays.

Rapid diagnosis of acute heart failure and prompt initiation of effective treatments, such as intravenous vasodilators, is associated with improved patient outcome [26, 27]. This requirement was highlighted in the ADHERE registry study, which showed that a delay in the treatment of heart failure was associated with a 250% increase in acute mortality, and >150% increase in both hospital and ICU LOS [28]. Evaluating BNP can enhance diagnostic accuracy in patients with acute dyspnea and allow treatment to be initiated sooner; McCullough et al. demonstrated that clinical indecision concerning a diagnosis of heart failure was reduced by 74% following BNP measurements [29].

Several studies have demonstrated the effectiveness, speed and reliability of BNP POCT in comparison to standard laboratory tests. The clinical utility of BNP POCT was demonstrated in the BASEL study, which showed that the addition of BNP testing in clinical evaluations reduced the time of onset for correct treatment (63 vs. 90 min), shortened LOS (8 vs. 11 days), and reduced total costs by 26% [30].

BNP is also a useful prognostic marker to assess severity of heart failure before discharge. Data from our group showed that a reduction in BNP >46% compared to the admission levels, coupled with an absolute BNP value <300 pg/mL was a very powerful NPV for future cardiovascular outcomes in patients hospitalized with acute decompensated heart failure (Figure 3) [31]. Furthermore, analysis of a large Medicare database has shown that discharge BNP measurements are the most important

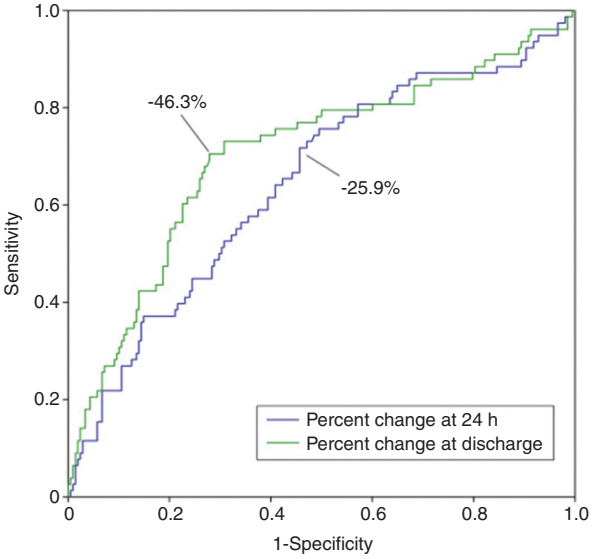

Figure 3 Utility of serial assessment of BNP with POCT testing during hospitalization.

characteristic for predicting 1-year mortality (HR 1.34, 95% CI 1.28–1.40) and 1-year death or rehospitalization (HR 1.15, 95% CI 1.12–1.18) among older patients hospitalized with heart failure [32].

Data from the recent literature have shown that the BNP POCT is comparable to laboratory standards in terms of efficiency and sensitivity in diagnosing heart failure and serving as a prognostic factor for discharge, and can therefore differentiate between other causes of dyspnea. Moreover, BNP POCT may aid in ruling out heart failure in patients with preserved ejection fraction, as ultrasound is not suitable for these patients. Heart failure is often not recognized in patients with exacerbations of COPD due to the imprecise symptoms, therefore BNP POCT can help to avoid a misdiagnosis of acute heart failure. Furthermore, BNP measurements can yield valuable information concerning myocardial tissue. Testing is now firmly established to augment risk assessment for patients with ACS, and has a significant impact on patient care and outcome in high-risk groups and patients with suspected ACS.

NGAL point-of-care testing

NGAL, a member of the lipocalin family of proteins, is secreted in low amounts by kidney tubule cells but increases dramatically after ischemic, septic, or nephrotoxic renal injury [33–35]. As there are no tests to detect acute kidney injury (AKI) at the time of onset, the diagnosis of worsening renal function (WRF) is achieved by

serial creatinine measurements [36]. However, creatinine is a non-sensitive and late marker for AKI [37], and identifying AKI earlier may allow interventions to prevent WRF, therefore the use of NGAL to detect early AKI may be of considerable clinical importance.

Increased NGAL occurs within 2 h after renal injury, precedes increases in creatinine by 12–24 h [38], and is highly predictive of the subsequent development of AKI. Although sometimes reversible, AKI is associated with increased morbidity, prolonged hospital stay, the need for dialysis, and potential mortality. A recent review of 203 clinical trials revealed that 56 studies had identified NGAL as an early AKI biomarker [39].

The use of NGAL as a marker of AKI has been specifically evaluated in the ED; in one prospective consecutive enrolment study of 635 patients, NGAL accurately differentiated AKI from pre-renal azotemia, chronic kidney disease, and those with normal renal function, compared with creatinine and other renal injury markers [40]. The use of NGAL rather than creatinine to differentiate renal risk in the ED could allow renal protection strategies to be initiated earlier [40]. In a second study using a NGAL ED POCT in potentially septic patients, NGAL was considerably more sensitive than serial creatinine for the identification of subsequent renal failure or death [36].

Other studies support the measurement of NGAL measurement at ED presentation to identify patients at risk of AKI. Bagshaw et al. measured NGAL at 0, 12, 24, and 48 h after admission in 83 septic patients, finding significantly higher NGAL levels at enrolment in patients with septic AKI [41].

Our group showed that NGAL is not only highly sensitive in evaluating the risk of AKI development in the ED, it can also be measured in conjunction with creatinine to strengthen clinical judgment. We tested the ability of BNP and NGAL POCT to predict the worsening renal function in patients admitted to the ED; the measurement of BNP and NGAL in patients with acute heart failure at the point of ED admission showed a 20.4% development of AKI. In this study, serial NGAL and creatinine were measured during the first 72 h, and the ED physicians indicated their initial assessment of the probability of AKI. AKI was confirmed in 7% of patients on the basis of expert nephrologists' adjudication of cases defined by RIFLE AKI criteria, which was in contrast to the ED physicians' initial assessments that it was present in 33% of patients. While the ED physicians' initial judgment lacked sensitivity and specificity, overpredicting the diagnosis of AKI in 27% of the cohort while missing 20% of those with AKI as a final diagnosis, NGAL testing was more precise. The AUC for NGAL predicting AKI at presentation was 0.80 at admission (T0), which increased to 0.90 when added to the ED physician's initial clinical judgment. This was significantly greater compared to the AUC of the T0 estimated glomerular filtration rate obtained either by modification of diet in renal disease equation (0.78) or Cockroft-Gault formula (0.78) (p=0.022 and p=0.020, respectively) [42].

The high AKI-related mortality as a result of multiple organ failure [43], the frequent overcrowding of EDs [44], and the limited utility of the RIFLE criteria in an emergency setting due to a non-relevant increase in baseline creatinine levels suggest that specific biomarkers for early identification of AKI are absolutely necessary in emergency medicine.

There is considerable evidence indicating that NGAL is a sensitive early marker of injury that is highly suited to AKI risk evaluation (Figure 4). These data strongly suggest that future investigations should integrate NGAL with existing clinical markers in order to refine the assessment of risk and target individual patient therapies in the ED.

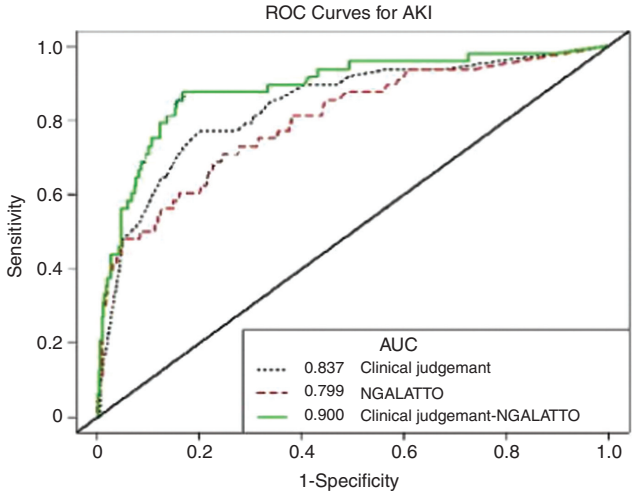

Figure 4 ROC curve for NGAL predicting AKI.

Conclusions

The evaluation of biomarkers in the ED is critical to improve diagnostic accuracy, perform risk assessments and monitor treatment response in patients with acute disease. Compared with central laboratory assay platforms, efficient and high throughput POCT has the potential to expedite physicians' treatment decisions and reduce therapeutic turnaround time, resulting in a shorter hospital LOS and less ED overcrowding. However, to realize the full benefit of POCT it should be implemented within standardized procedures in the ED to take advantage of the fast delivery of results.

The recent literature has shown that the use of more sensitive cTn, BNP and NGAL with Alere Triage® has facilitated prompt and accurate diagnosis of ACS, acute heart failure and AKI in patients admitted to the ED.

Nevertheless, POCT devices should get connected and all test results being transmitted to the Laboratory Information System. Periodically performed control measurements should be under the supervision of the central laboratory.

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

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