

A Rapid Point-of-Care Cardiac Marker Testing Strategy Facilitates the Rapid Diagnosis and Management of Chest Pain Patients in the Emergency Department

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Abstract

We compared a rapid, point-of-care multimarker protocol with a single and serial troponin I (TnI)-only protocol in 5,244 patients admitted to the emergency department with chest pain. The diagnosis of acute myocardial infarction (AMI) was based on a doubling myoglobin level accompanied by at least a 50% increase in the creatine kinase (CK)-MB level with no detectable TnI; a doubling of myoglobin level together with any detectable TnI; or a TnI level of 0.4 ng/mL (0.4 µg/L) or more, irrespective of myoglobin or CK-MB results. By using these new criteria, 145 of 148 cases were positive for AMI (positive predictive value [PPV], 92.4%) and 3 were negative, which were also negative by the core laboratory TnI assay. Twelve confirmed non-AMI cases were positive by the new protocol, with 10 of 12 confirmed by the core laboratory as positive for TnI. The negative predictive value (NPV) was 99.9%; the overall diagnostic accuracy was 99.7%. The TnI-only protocol had a sensitivity of 68.2% with an NPV of 99.1%. With lower TnI-only cutoffs, 4 patients had false-negative results, and a PPV of 36.4% was observed. Our rapid multimarker protocol seems superior to a TnI-only approach for rapidly triaging patients with chest pain or AMI.

According to American Heart Association statistics, cardiovascular disease accounted for more than one third of all deaths in 2004 in the United States,¹ with death and disability from acute myocardial infarctions (AMI), or heart attack, continuing to be major health concerns. Indeed, it is estimated that in the United States, nearly 1.1 million AMIs occur each year, with approximately 515,000 associated deaths.² Because approximately half of these deaths occur within hours of onset of symptoms (usually outside the hospital setting), we believe that for patients admitted to the emergency department (ED), rapid diagnosis and early treatment of AMI are essential for reducing associated morbidity and mortality.

Nearly 8 million patients with chest pain are evaluated each year by EDs in the United States, with approximately 50% admitted to the hospital for further observation and evaluation. Surprisingly, only about 30% of the hospitalized patients end up with a cardiac-related diagnosis.^{3,4} In addition, current literature suggests that although the use of patient history, physical examination findings, electrocardiogram (ECG) findings, and other test results significantly improves the accuracy of diagnosis of acute coronary syndrome (ACS), these tools still miss a significant portion of patients with AMI,⁵ especially patients with non-ST segment elevation MI (STEMI). We conclude that false-positive (FP) AMI screening results in the ED drive unnecessary hospital admissions, and false-negative (FN) AMI screening findings can result in a missed diagnosis, which is unacceptable. Clearly, given the need to make more accurate evidence-based diagnostic and triage decisions, the use of a more rapid screening protocol in the ED with biochemical cardiac markers designed for patients admitted with early, middle, and late chest pain is required.

The cardiac markers routinely used to diagnose and risk stratify patients with chest pain include myoglobin, creatine kinase (CK)-MB, and cardiac troponins T (cTnT) and I (cTnI). These cardiac markers are released into the blood following irreversible myocardial necrosis and are known to have the following unique release characteristics and kinetics⁶: (1) The myoglobin level elevates in 1 to 2 hours after the onset of symptoms; measurement is useful in patients who come to the ED soon after the onset of chest pain (early chest pain). (2) Cardiac troponins can be detected within 3 to 4 hours after symptom onset; measurement is useful in patients who come to the ED a longer time after symptom onset (middle and late chest pain). (3) The CK-MB level is elevated within 5 to 6 hours after onset of symptoms; measurement is useful in patients who come to the ED several hours after the onset of chest pain (late chest pain).^{7,8} However, these markers must be ordered as a panel in the ED because no single marker meets all criteria for an ideal marker of AMI diagnosis for all patients who arrive at the ED at various times after the onset of the symptoms.

As reviewed by Karras and Kane,⁹ CK-MB levels seem to be normal in one fourth to one half of patients with AMI at the time of ED admission; however, the CK-MB level has an excellent diagnostic value at 6 or more hours after the onset of symptoms. Like CK-MB, cardiac troponin is really best regarded as a late marker for AMI because values are generally elevated between 6 and 24 hours after an AMI.^{8,9} Although myoglobin seems to be highly sensitive for patients with early chest pain, it is of marginal use in patients with middle to late chest pain.

Because an AMI is a biochemical event involving irreversible damage to a cluster of myocytes in the heart, a timed protocol for testing is required to detect clinically significant changes in the blood levels of the aforementioned cardiac markers. Hence, because of variation the time of admission to the ED of patients with chest pain and the narrow windows of the 3 aforementioned cardiac markers, it is no surprise that a timed multisample, multimarker screening strategy has been shown to be extremely useful in rapid diagnosis of AMI in a number of studies.^{7,10}

With these considerations in mind, current American College of Cardiology/American Heart Association guidelines emphasize a rapid turnaround time in the diagnosis of possible AMI and require or recommend that the results be available within 60 minutes, preferably within 30 minutes. Clearly, the turnaround time required for cardiac testing must coincide with the chest pain protocol ED physicians decide to use. These guidelines further state that point-of-care (POC) systems, if implemented at the bedside, have the advantage of reducing delays due to transportation and processing in a central laboratory and can eliminate delays due to lack of 24-hour availability of central laboratory assays. Consequently, we

present an evaluation of a multiple marker approach combined with obtaining serial specimens and POC testing that provides results in approximately 15 minutes. Our study is unique because we applied this multimarker algorithm with cases positive for AMI based on a TnI level of 0.4 ng/mL (0.4 µg/L) or more in any sample or a doubling of the myoglobin level between sequential specimens with detectable TnI or with an increase of 50% or more in CK-MB level without detectable TnI in any specimen.

Materials and Methods

Study Design and Population

This study was conducted at 3 medical centers in Texas: Medical City Dallas (Dallas), Plaza Medical Center (Fort Worth), and Medical Center of Arlington (Arlington) to evaluate the Biosite Triage Cardiac Panel (Biosite, San Diego, CA) using a rapid serial specimen multimarker algorithm in the ED. Before commencement of testing of patient samples, all 3 sites verified manufacturer's claims for precision, accuracy, and reportable range. The coefficient of variation (CV) of the TnI assay at the 0.4 ng/mL (0.4 µg/L) cutoff was approximately 12.5%, whereas at 0.05 ng/mL (0.05 µg/L), the CV was approximately 25%. Specific cutoffs were not used for CK-MB or myoglobin levels in our study (see "Data Analysis"). However, the CV of CK-MB at 4.3 ng/mL (4.3 µg/L) was 10.5%; for myoglobin at 107 µg/L (6.1 nmol/L; 95th percentile), the CV was 10.4%.

The Triage Cardiac Panel assays for TnI, CK-MB, and myoglobin were compared with the Dade Behring assays on the Dimension RxL (Dade Behring, Deerfield, IL). The study population was a convenience sample of patients admitted to the ED with chest pain during the study period, February 9 through May 31, 2004.

Study Protocol

EDTA anticoagulated whole blood was drawn for POC testing using the Triage Cardiac Panel and performed by ED nurses. Heparin-anticoagulated whole blood was drawn and processed to plasma if tests were ordered for the Dimension RxL. Dimension RxL testing was conducted by hospital laboratory personnel. The Triage system and the Dimension RxL were interfaced to the laboratory information systems.

The first blood specimen was obtained shortly after admission. A second specimen was ordered between 1 and 3 hours after the initial specimen was drawn in patients whose chest pain could not be ruled in for AMI based on history, physical examination, and ECG findings and/or cardiac marker concentrations (especially elevated levels of TnI) obtained from the first specimen. Additional specimens were ordered

on patients for whom the ED physician had a high degree of suspicion of AMI but whose cardiac marker results were inconclusive in prior specimens. In most, but not all cases, a heparin-anticoagulated specimen was also obtained for testing in the central laboratory. If the patient was admitted, subsequent tests were performed by the hospital laboratory using heparinized plasma.

Data Analysis

The hospitals' information systems were queried for the *International Classification of Diseases, Ninth Revision (ICD-9)* and diagnosis-related group (DRG) codes for all patients in the study. Patients with *ICD-9* codes 410.xx and/or DRG codes 121, 122, 123, 516, and 526 were considered to have had an AMI. Patients with a TnI concentration of 0.4 ng/mL (0.4 µg/L) or more in any specimen, patients with a doubling of myoglobin concentrations between 2 sequential specimens with any detectable TnI at least by the second of the 2 specimens, and patients with myoglobin (doubling) and CK-MB concentrations increasing by 50% or more in 2 or 3 specimens were considered to be positive for an AMI according to the POC multimarker algorithm. All discrepancies between the diagnosis based on *ICD-9* or DRG coding and cardiac biomarker results were adjudicated by a chart review by trained medical personnel. Laboratory cardiac biomarker test results were checked for all remaining discrepancies.

This evaluation of our multimarker approach was a retrospective analysis whereby the final diagnoses were based on TnI levels from the central laboratory, clinical observations, and/or cardiac catheter findings (when the latter procedure was performed). The TnI test performed in the central laboratory was available to clinicians as part of existing protocols. We described the patient population by age and sex. Because time from onset of chest pain is a subjective measure, we decided to not consider this factor as a critical component of the analysis.

In addition to the POC multimarker algorithm analysis, the data were analyzed using the TnI results alone. This analysis included the determination of the sensitivity, specificity, accuracy, and predictive values for the first specimen only and for the serial specimens. The analysis was performed using a TnI concentration of 0.4 ng/mL (0.4 µg/L) or more as a positive result and any detectable TnI (approximately the 99th percentile of the reference range) as a positive result.

A preliminary evaluation was conducted of the clinical and operational outcomes for patients admitted to the ED with chest pain from all 3 centers who had cardiac markers done. Data indicating ED admission and discharge times and total hospital length of stay (LOS) were obtained from February 2004, when the protocol was initiated, through May 2004. Hospital LOS data were also obtained from a baseline period of January to April 2003, for 2 of the hospitals, approximately

1 year before the implementation of POC cardiac markers and their integration into the patient care pathway.

Statistical Analysis

Data for patients with STEMI with a TnI level of less than 0.4 ng/mL (0.4 µg/L) in a single specimen were excluded from analysis because more than 1 specimen was necessary for analysis using the POC multimarker algorithm if the TnI result was negative with the first specimen. Data from the *ICD-9* and DRG codes and POC multimarker algorithm analysis are expressed as true-positive (TP), FP, true-negative (TN), and FN. The sensitivity and specificity were computed by using the standard formula to describe the accuracy of the POC multimarker algorithm to detect AMI in patients admitted to the ED with chest pain. To understand the true prevalence of AMI using the POC multimarker algorithm, positive predictive and negative predictive values (PPV and NPV, respectively) were calculated by using the following formulas:

$$\text{PPV} = \text{TP}/(\text{TP} + \text{FP}) \times 100 \text{ and}$$

$$\text{NPV} = \text{TN}/(\text{FN} + \text{TN}) \times 100$$

Data for PPV and NPV are expressed using the mean as a measure of central tendency with SD as a measure of spread.

Results

A total of 5,241 patients with chest pain admitted to the ED were initially included in the study. Data for 40 patients who had negative POC cardiac biomarker results but were diagnosed with an AMI based on ECG and/or patient history and physical examination findings before the prescribed time for a second specimen were removed from the analysis because the serial specimen protocol was not completed. The mean \pm SD age of the study population for all 3 centers was 58.4 ± 18.2 years and for patients diagnosed with AMI in the study population, 65.6 ± 15.7 years. Additional demographic data on the study population based on the individual medical centers are provided in **Table 1**.

The distribution of data for AMI diagnosis using the POC multimarker algorithm results vs the *ICD-9* codes for each of the 3 centers is shown in **Figure 1**. Of the 2,263 patients admitted to Medical City Dallas, 2,224 had non-AMI *ICD-9* or DRG codes, and 39 had an *ICD-9* or a DRG code with AMI indication. Of 2,224 patients, 17 had elevated POC marker levels (myoglobin, TnI, and CK-MB), and results for 13 of these agreed with the laboratory results. Further chart review revealed that 12 of these patients had conditions or procedures consistent with ACS, 4 had no cardiac follow-up, and 1 had normal results of a catheter examination. Of 39 patients with an AMI indication, 26 had POC marker patterns consistent with rule-in AMI; 11 cases were ruled in based on

Table 1
Demographic Data for Patient Populations From Three Centers in Texas

	Medical City Dallas		Plaza Medical Center, Fort Worth		Medical Center of Arlington		Combined Data	
	Male	Female	Male	Female	Male	Female	Male	Female
Patient distribution (%)	40.8	59.2	41.9	58.1	40.4	59.6	40.9	59.1
Mean ± SD age (y)	57.9 ± 18.1	59.9 ± 18.9	60.4 ± 16.1	64.1 ± 16.5	52.8 ± 17.2	56.5 ± 18.3	56.7 ± 17.6	59.5 ± 18.4
AMI confirmed (%)	60.5	39.5	69.2	30.8	43.7	56.3	54.7	45.3
Mean ± SD age (y)	62.0 ± 13.8	69.5 ± 16.0	58.4 ± 13.8	75.5 ± 13.4	62.3 ± 15.6	70.3 ± 15.7	61.0 ± 14.5	71.0 ± 15.3

AMI, acute myocardial infarction.

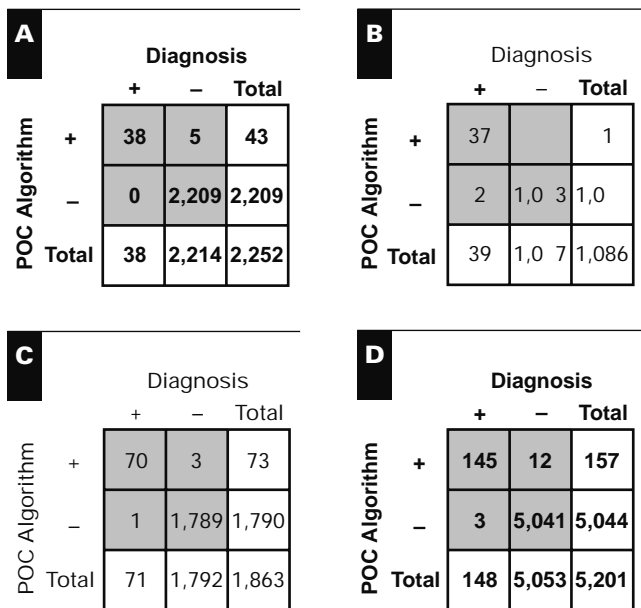


Figure 1 Comparison of patient distribution for acute myocardial infarction diagnosis using *International Classification of Diseases, Ninth Revision* codes and chart review (shown as Diagnosis) vs point-of-care (POC) multimarker algorithm approach (POC algorithm) from 3 urban centers in Texas: Medical City Dallas, Dallas (**A**); Plaza Medical Center, Fort Worth (**B**); and Medical Center of Arlington, Arlington (**C**). **D**, Combined data from all 3 centers.

ECG or clinical judgment after a single specimen; 1 patient did not have an AMI at the time of admission but had an AMI a day after leaving the ED; and 1 patient did not have an AMI according to chart review.

Data from Plaza Medical center showed that 8 of 1,051 patients with non-AMI *ICD-9* or DRG codes had elevated POC marker levels. Four of these patients had conditions or procedures consistent with ACS; 2 had renal insufficiency with mildly elevated marker levels by POC and laboratory testing; 2 had mildly elevated marker levels by POC and laboratory testing without any discernible reason. Of 51 patients with an AMI indication, 35 had a POC marker pattern consistent

with rule-in AMI; 13 cases were ruled in based on ECG findings; 2 cases did not have rule-in markers but POC results agreed with laboratory marker values; and 1 had an AMI after leaving the ED.

The study population at Medical Center of Arlington comprised 1,800 patients with non-AMI *ICD-9* or DRG codes and 81 with an AMI indication. Of the 1,800 patients with non-AMI coding, 11 had elevated POC marker levels, with 7 with conditions consistent with ACS, 1 with renal failure, 1 with normal catheterization results, 1 with no chart (data removed from analysis), and 1 with elevated markers by POC and laboratory testing. Of the 81 patients with an AMI indication, 63 had POC markers consistent with rule-in AMI; 16 were ruled in based on ECG findings; 1 did not have rule-in markers but POC results agreed with laboratory marker values; and 1 had no mention of AMI on the chart.

The sensitivity, specificity, accuracy, PPV, and NPV for the data from each of the 3 centers are provided in **Table 2**. The overall PPV for AMI diagnosis using the multimarker algorithm (for all 3 markers) was 92.4% with an overall diagnostic accuracy of 99.7%. Plasma samples from the 3 AMI patients (Figure 1) that the algorithm missed were analyzed in the laboratory, and the results indicated that all 3 were negative for TnI and CK-MB. Samples from 11 of 12 apparent FP cases were tested using the laboratory method; 10 of the 11 apparent FP cases (Figure 1) had elevated levels of TnI on the Dimension RxL. The most frequent algorithm-positive result was a troponin level of more than 0.4 ng/mL (0.4 µg/L; 101/145). The next was doubling of the myoglobin level with any detectable TnI (43/145), and last was 1 case of a doubling of the myoglobin level with a 50% increase in the CK-MB level and TnI remained undetectable.

Data from the initial specimen vs serial specimens for TnI levels only as a single POC marker were evaluated in all 5,201 patients. The comparison charts for the first POC specimen with a TnI concentration of 0.4 ng/mL (0.4 µg/L) or more vs the diagnosis at each of the 3 centers are shown in **Figure 2**, and the performance characteristics are shown in **Table 3**. As shown in Figure 2, 2 cutoff values, 0.05 ng/mL (0.05 µg/L) and 0.4 ng/mL (0.4 µg/L) were used to analyze the data. The use of TnI at a 0.4 ng/mL (0.4 µg/L)

Table 2
Statistical Analysis of Point-of-Care Testing in Three Texas Hospitals for Diagnosis of Acute Myocardial Infarction Using the Multimarker Algorithm*

	Medical City Dallas	Plaza Medical Center, Fort Worth	Medical Center of Arlington	Combined Data
Sensitivity (%)	100 (100-100)	94.9 (87.9-101.8)	98.6 (95.9-101.3)	98.0 (95.7-100.2)
Specificity (%)	99.8 (95.6-100.0)	99.6 (99.2-100)	99.8 (99.6-100)	99.8 (99.6-99.9)
Accuracy (%)	99.8 (99.6-100.0)	99.0 (99.0-99.9)	99.8 (99.6-100)	99.7 (99.6-99.9)
Positive predictive value (%)	88.4 (78.8-98.0)	90.2 (81.2-99.3)	95.9 (91.3-100.4)	92.4 (88.2-96.5)
Negative predictive value (%)	100 (100-100)	99.8 (99.5-100.1)	99.9 (99.8-100.1)	99.9 (99.9-100.0)

* Data are expressed as the mean (95% confidence interval).

cutoff resulted in an unacceptable number of missed AMIs, irrespective of the number of specimens used in the analysis. If any detectable TnI (≥ 0.05 ng/mL [0.05 $\mu\text{g/L}$]) was used as the AMI cutoff, the number of missed AMI cases dropped to 4, resulting in an NPV of 99.9% (Table 3). However, the PPV for the diagnosis of AMI using TnI only was poor, 36.4% (Table 3).

Concurrently with the diagnostic and analytic data, outcomes data were obtained from the hospitals' information systems to evaluate the ED LOS and ED discharge rates for the patients and timeframes associated with the study. From February 2004, when the multimarker POC protocol was first implemented, through May 2004, the mean ED LOS showed a downward trend at all 3 centers (Figure 3). At Medical City Dallas, a 1.8-hour statistically significant decrease in the ED LOS was observed ($P = .002$). The weighted average ED LOS for all 3 centers declined 1.5 hours, from 5.8 hours in February 2004 to 4.3 hours in May 2004 ($P = .02$).

Additional analysis of outcomes data indicated a statistically significant increase in the proportion of patients with chest pain in the study population (February through May 2004) who were discharged in less than 24 hours compared with a population from a comparable 4-month baseline period 1 year earlier (January to April 2003) when no POC multimarker protocol was in place (Figure 4). At Medical City Dallas, the percentage of patients discharged in less than 24 hours increased from 51% to 56% ($P < .05$). At Medical Center of Arlington, there was an increase from 40% to 52%

of all patients with chest pain discharged in less than 24 hours ($P < .05$). The 2003 baseline data were not available for Plaza Medical Center.

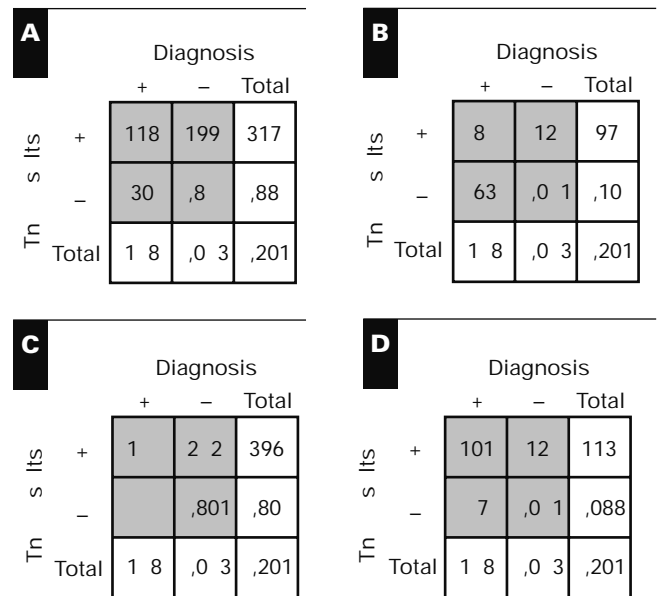


Figure 2 Comparison between single (A, B) and serial (C, D) specimen methods for POC testing of troponin I (TnI) as a single cardiac marker in diagnosis of acute myocardial infarction. A and C show the data using a 0.05 ng/mL (0.05 $\mu\text{g/L}$) cutoff, and B and D show data using a 0.4 ng/mL (0.4 $\mu\text{g/L}$) cutoff.

Table 3
Statistical Comparison of Point-of-Care Testing of TnI Levels for Diagnosis of Acute Myocardial Infarction*

	Single Specimen, TnI Only		Serial Specimen, TnI Only	
	0.05 ng/mL (0.05 $\mu\text{g/L}$)	0.4 ng/mL (0.4 $\mu\text{g/L}$)	0.05 ng/mL (0.05 $\mu\text{g/L}$)	0.4 ng/mL (0.4 $\mu\text{g/L}$)
Sensitivity (%)	79.7 (73.3-86.2)	57.4 (49.5-65.4)	97.3 (94.7-99.9)	68.2 (60.7-75.7)
Specificity (%)	96.1 (95.5-96.6)	99.8 (99.6-99.9)	95.0 (94.4-95.6)	99.8 (99.6-99.9)
Accuracy (%)	95.6 (95.0-96.2)	98.6 (98.2-98.9)	95.1 (94.5-95.7)	98.9 (98.6-99.2)
Positive predictive value (%)	37.2 (31.9-42.5)	87.6 (81.1-94.2)	36.4 (31.6-41.1)	89.4 (83.7-95.1)
Negative predictive value (%)	99.4 (99.2-99.6)	98.8 (98.5-99.1)	99.9 (99.8-100.0)	99.1 (98.8-99.3)

TnI, troponin I.

* Data are expressed as the mean (95% confidence interval).

Discussion

Despite the remarkable recent advances in the prevention, diagnosis, and treatment of AMI and the resultant decline in AMI-related morbidity and mortality, the differential diagnosis and complications of AMI remain as much of a challenge now as they were a half-century ago.¹¹ Any delay in diagnosis of AMI may significantly affect the quality of care for patients. Recent studies conducted by Graff et al¹² on age, comorbidities, procedures during hospitalization, and discharge status for 42,406 Connecticut Medicare recipients (between 1992 and 2001) demonstrated a significant delay in AMI diagnosis after ED admission. In addition, the patients received care that

was measured to be of lower quality, perhaps attributable to the lack of timely and accurate diagnosis.¹²

The advent of unique kinetic release data for various cardiac biomarkers and the availability of POC testing devices for these markers have proven to be extremely valuable in diagnosis and risk stratification of patients admitted to the ED with chest pain.^{4,6,13-21} Although POC testing for cardiac markers is increasingly prevalent in EDs, the use of single biomarkers may underdiagnose the cardiac condition owing to variations in sensitivity and specificity, and they may be inadequate to make triage decisions as noted by several researchers.^{22,23} Current findings from the American College of Emergency Physicians also state that no single serum

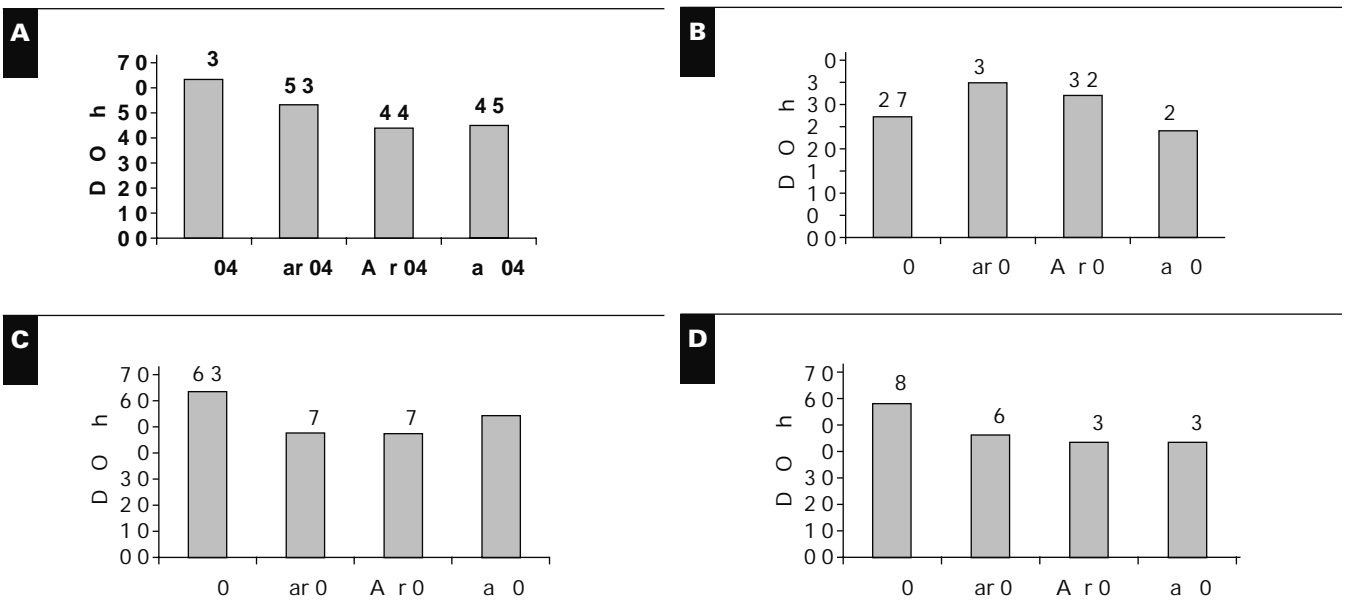


Figure 3 Clinical outcome data for emergency department (ED) length of stay (LOS) in 3 urban centers in Texas during the study period, February 2004 through May 2004: Medical City Dallas, Dallas (**A**); Plaza Medical Center, Fort Worth (**B**); and Medical Center of Arlington, Arlington (**C**). **D**, Combined weighted average data for all 3 centers. Data show the mean number of hours as LOS by month.

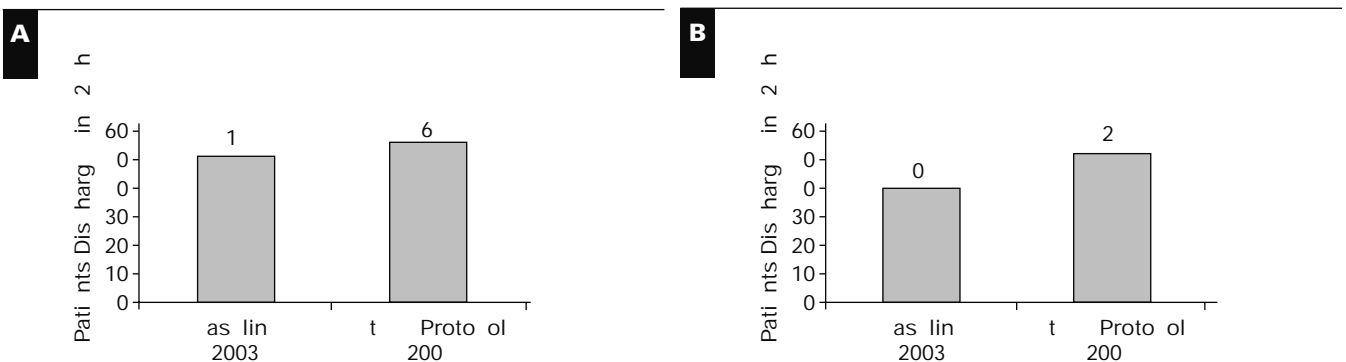


Figure 4 Clinical outcome data for patient discharge rate at Medical City Dallas, Dallas, TX (**A**), and Medical Center of Arlington, Arlington, TX (**B**), during the baseline period (2003) and the study period (2004). Data show the mean percentage of patients discharged in fewer than 24 hours for each period.

marker reliably identifies or excludes AMI within 6 hours of symptom onset.²⁴

Therefore, in the present study, we used a multimarker algorithm along with results from serial testing to improve the sensitivity and PPV for AMI diagnosis. Results of elevated biomarker levels were obtainable within approximately 15 minutes of obtaining the blood specimen when using this POC system, allowing us to translate these findings into earlier treatment or triage. Additional advantages of using this multimarker algorithm strategy are its high NPV (99.9%) and PPV (92.4%) using serial and multimarker testing. The use of cardiac troponin as a single marker (for the first specimen or serial specimens) resulted in a lower PPV compared with the PPV from using all 3 POC markers, a finding that is similar to that reported by Kratz et al.²⁵

Several investigators have also focused on the rapid diagnosis of AMI in the ED by using multiple markers.²⁵⁻³⁰ McCord et al²⁶ described a pathway for 90-minute exclusion of AMI using quantitative POC testing for CK-MB, cTnI, and myoglobin with an NPV of 99.6% for cTnI and myoglobin at 90 minutes after admission. Ng et al²⁷ developed an algorithm to diagnose all AMIs within 90 minutes of admission. However, the overall PPV using their algorithm was 47%, even with serial testing, similar to the PPV (36%) obtained by Kratz et al²⁵ using 1-time, qualitative POC testing for the same markers with a different assay system. Contrary to the strategies used previously, we incorporated a 100% Δ myoglobin between sequential specimens as a major criterion in the diagnosis of AMI. This approach allowed us to eliminate the FP AMI diagnoses caused by elevated myoglobin levels in patients who did not have a "significant change" in the concentration of myoglobin between 2 sequential specimens. It is essential to note that our PPV and NPV were determined using a heterogeneous population of all ED patients admitted with chest pain from 3 medical centers in an attempt to eliminate possible bias introduced from retrospective analyses of homogeneous, single-center populations, preselected for AMI leading to a higher prevalence and PPV.

An additional possible novel aspect of our multimarker algorithm is the exclusive reliance on time changes in myoglobin values during an abbreviated interval as opposed to the more traditional approach of relying on a value exceeding the normalcy threshold. As noted in a review article by Fesmire,²⁴ owing to the increasing precision and sensitivity of cardiac biomarker assays, this Δ approach has the potential for identifying and excluding AMI at earlier times without compromising specificity. Our approach of using the Δ myoglobin value is similar to that reported by Sallach et al,³¹ in which an increase of 20 $\mu\text{g/L}$ (1.1 nmol/L) in the myoglobin level from 0 to 90 minutes provided maximal diagnostic usefulness in patients who did not have increased myoglobin or troponin levels at admission. A change in the myoglobin level of 20

$\mu\text{g/L}$ (1.1 nmol/L) or more at 90 minutes in their study produced an 83.3% sensitivity, an 88.6% specificity, and a 99.5% NPV, resulting in a highly accurate diagnosis of AMI within 90 minutes,³¹ similar to the results reported from the use of our multimarker algorithm. Fesmire et al²⁴ have shown that Δ CK-MB outperforms myoglobin at 2 hours during the ED identification and exclusion of troponin-positive non-ST segment elevation ACS. Although our study included CK-MB as one of the cardiac markers for analysis using the multimarker algorithm, we did not attempt to evaluate or compare the role of Δ CK-MB in the diagnosis of AMI.

Several studies have shown that the use of multiple cardiac biomarkers, as well as B-type natriuretic peptide, most strongly predicts the first major cardiovascular event and the risk of death³³ and reduces LOS and laboratory costs for cardiac patients.^{7,34,35} Likewise, data from our studies demonstrate a trended, statistically significant reduction in the ED LOS after initiation of the POC cardiac marker protocol at 1 center and a statistically significant increase in patients with chest pain discharged in less than 24 hours at 2 centers. The lack of statistical significance in the reduction of the ED LOS at the other centers may be due to an inconsistency in physician adoption of the protocol. Because this was a pilot study, many of the participating ED physicians were reluctant to triage patients based on the POC results until they became more confident in the diagnostic accuracy of the new testing protocol.

The use of serial testing of multiple markers using our proposed rapid algorithm strategy, compared with a TnI-only strategy, resulted in increased sensitivity, PPV, and NPV for an AMI diagnosis and faster patient discharge, especially when an AMI was ruled out. Also, the present study seems to be the first to evaluate the use of POC multimarker testing with a Δ myoglobin value in combination with a rapid algorithm method to diagnose AMI in the ED. Although more studies are needed to further validate our findings, the routine use of such a POC multimarker algorithm approach in the ED seems to have the potential to improve the accuracy and speed of non-STEMI diagnosis and, at the same time, assist in the accuracy of ruling out AMI in patients with chest pain who have not had an AMI.

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