

ORIGINAL CONTRIBUTION

Evaluating a New Graphical Ordinal Logit Method (GOLDminer) in the Diagnosis of Myocardial Infarction Utilizing Clinical Features and Laboratory Data

Larry H. Bernstein^a, Asad Qamar^b, Craig McPherson^b, and Stuart Zarich^b

Departments of ^aPathology and Laboratory Medicine and ^bInternal Medicine, Yale University School of Medicine, Bridgeport Hospital, Bridgeport, Connecticut

Objective: We used a new graphical ordinal logit method (GOLDminer) to assess a single cardiac troponin T (cTnT) analysis at the time of admission (first generation monoclonal; Roche BMC Corp., Indianapolis, Indiana), the character of chest pain, and electrocardiographic (ECG) findings in predicting the likelihood of acute myocardial infarction (AMI) in patients presenting with suspected myocardial ischemia. The final diagnosis of AMI was based on serial ECG findings and evolution of CKMB isoenzyme levels in conjunction with clinical findings.

Subjects: The study population consisted of 293 consecutive patients who presented at a mean of six hours after onset of chest pain or associated symptoms warranting a "rule-out" for AMI assessment to a university-affiliated community hospital.

Results: The odds-ratio for an elevated cTnT (> 0.1 ng/ml) in AMI was 22.2:1. There was an association between typical chest pain and cTnT (chi square = 78.23, $p < .0001$) and between abnormal ECG findings and cTnT (chi square = 108, $p < .0001$). The cTnT yielded diagnostic benefit in addition to chest pain characteristics and ECG findings in AMI. We present the odds-ratios for the combined features in GOLDminer plots.

Conclusion: We demonstrate how the odds-ratios for AMI are obtained after scaling continuous to ordinal the values for a single cTnT determination alone and with other features in patients presenting with chest pain.

INTRODUCTION

The diagnosis of acute myocardial infarction (AMI)^b is problematic for many patients who present with equivocal symp-

toms or electrocardiographic (ECG) findings. Chest pain is associated with an over-triage of patients to the coronary care unit since less than one-third of chest pain patients demonstrate creatine kinase

^a To whom all correspondence should be addressed: Larry H. Bernstein, M.D., Department of Pathology and Laboratory Medicine, Bridgeport Hospital/Yale-New Haven Health, 267 Grant Street, Bridgeport, CT 06610.

^c Abbreviations: cTnT, cardiac troponin T; AMI acute myocardial infarction; CKMB, creatine kinase isoenzyme MB; ECG, electrocardiographic.

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isoenzyme MB (CKMB) changes [1-4]. Additionally, in nearly 10 percent of patients, the diagnosis of AMI cannot be definitively confirmed or excluded [5].

Although serial measurement of blood CKMB is a widely used biochemical marker in the diagnosis of AMI [6, 7], CKMB levels typically are not increased until nine hours after the onset of chest pain. Given the late rise of CKMB, the CKMB mass assay has less than 70 percent sensitivity in the diagnosis of AMI at the time of presentation to the emergency department [8]. Newer biochemical markers have been utilized to aid in the diagnosis of AMI, including cTnT, which rises to abnormal levels in serum within four to six hours after the onset of myocardial damage, remains elevated for a week or longer, and is associated with a significant likelihood of cardiac events [9-14]. Despite conflicting views about which troponin is best to use, there is now a recommendation for incorporating them in the WHO guidelines for AMI diagnosis, with special interest in their value for risk stratifying patients with unstable angina [15]. There has also been a recommendation to integrate the troponins with the Goldman algorithm [16, 17]. We specifically chose troponin T to study because there was already a substantial literature about the sensitivity of the assay and its value in identifying a subset of unstable angina patients with the same risk as AMI. The value of the cardiac marker was not proved for emergency room decisions based on an initial blood sample taken at the time patients present with chest pain. We carried out this study by blinding the physicians to the troponin results and proposed that the laboratory can incorporate this method in a clinical pathway for decisions about the disposition of patients presenting with clinical features suggestive of AMI [18].

We describe a novel method for interpreting the clinical, electrocardiographic,

and the laboratory features of patients presenting with suggested myocardial infarction. The result is not a binary response, but rather a graded relationship that is most useful for fitting the data to observed outcomes and for predicting expected responses. The decision-making method described can reduce medical treatment failure rates, lower the cost of managing chest pain patients, and improve the delivery of health care.

We examine cTnT levels at the time of first sample as compared with chest pain characteristics, ECG findings, and serial CKMB determinations in consecutive patients presenting to the emergency department with symptoms and/or signs suggestive of myocardial injury. Clinicians blinded to the results of cTnT values evaluated patients for the diagnosis of AMI on clinical grounds in conjunction with serial ECG findings and CKMB results according to World Health Organization criteria. We applied a universal probability model under bivariate normality to estimate the odds-ratios for either dichotomous or for polytomous outcomes in this study.

METHODS

Study sample

cTnT was measured on the first specimen submitted for CKMB isoenzyme analysis from each of 293 patients presenting to the Bridgeport Hospital emergency department with chest pain or symptoms suspicious for AMI. The results of cTnT were not provided to the Bridgeport Hospital emergency department physicians and clinicians caring for the patient during their hospitalization.

All patients' records, ECGs, and hospital discharge diagnoses were reviewed without knowledge of the serum cTnT results. A standard questionnaire was uti-

lized to obtain historical data and classify patients as having typical or atypical chest pain or other findings at presentation. World Health Organization criteria were used as the criterion for the diagnosis of AMI.

Cardiac markers

cTnT was measured using the first generation assay (Roche/BMC, Indianapolis, IN). A cTnT level of 0.1 ng/ml or above was considered abnormal.

Statistical methods

We converted continuous data by scaling to ordinal and examined relationships between interval data and outcomes [19, 20]. The World Health Organization criteria depend on more than one feature for diagnosis: clinical, ECG, and release of enzymes or proteins from damaged myocardium. The optimum medical decision cutoffs were assigned using Rudolph et al.'s [21] method of group-based reference.

Scaling the data and partitioning the population into pattern classes: The data were used to classify the patients whose diagnoses were known (AMI, unstable angina, and nonischemic chest pain). These data were used in a classifying matrix separating the population into two classes, AMI or not, based on cTnT less than 0.1 ng/ml, or equal to or greater than 0.1 ng/ml. The other clinical and laboratory

features were scaled: initial CKMB was scaled to 0 if less than 17 U/l, and 1 if equal to or above 17 U/l [21]; and the CKMB evolution was 0 if negative, and 1 if there was typical evolution of AMI. The ECG data were scaled to: 3, ST segment elevation; 2, Q waves; 1, ST segment depression/T wave inversion; 0, normal; -1, other. The characteristics of the chest pain were scaled to: 2, typical; 1, atypical; 0, other presenting feature. cTnT was scaled to: -1, < 0.05; 0, 0.05 to 0.099; 1, 0.1 to 0.2; 2, 0.2 to 0.5; 3, 0.5 to 1; 4, > 1 ng/ml.

Statistical analyses: The relationship of scaled tests to diagnoses and clinical features were examined using a universal regression model under bivariate normality with estimation of generalized odds-ratios. The model was developed by Jay Magidson (Statistical Innovations, Inc., Belmont, Massachusetts) [19, 20] and is available from Statistical Package for Social Science with a graphical ordinal logit display (GOLDminer™). The universal regression model is a unified maximum likelihood method for simultaneously assessing the statistical significance of treatment effects and the model fit when the response variable is ordered. It uses a "parallel log-odds" model based on adjacent odds to describe the data.

Justification of the universal regression model: The "universal" probability model overcomes errors that arise from using linear regression for ordered variables. The scaled data form a cross-table that is used in the universal regression

Table 1. Observed frequency of cardiac troponin T concentration in ECG categories.

TnT/ECG	Normal	Other	Q-wave	ST dep	ST ele
< 0.05	56	125	6	12	4
0.05 – 0.1	4	15	1	2	0
0.1 – 0.2	0	6	0	4	1
0.2 – 0.5	0	6	0	5	5
0.5 – 1	0	2	1	3	8
> 1	0	6	2	10	9

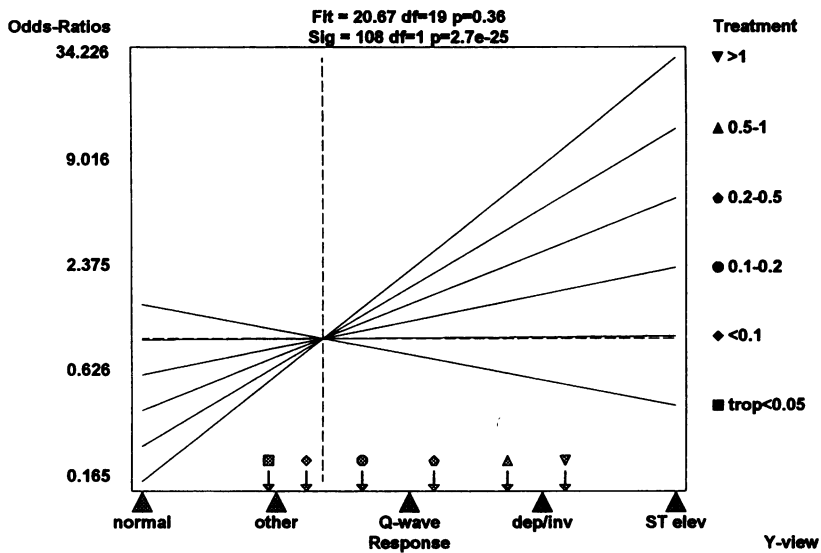


Figure 1. GOLDminerTM Y-view of cTnT (ng/ml) against ECG findings. The Y-view displays the cardiac troponin T (trop) in ng/ml at intervals of: < 0.05, 0.05 to 0.099, 0.1 to 0.2, 0.2 to 0.5, 0.5 to 1, and >1 on the Y-axis versus the ECG finding on the X-axis. The ECG findings are normal, other finding, Q-wave, ST depression or T-wave inversion (dep/inv), and ST elevation (ST elev). The result of Y variable are regressed against X. The fit is significant at chi-square = 108 ($p = 2.7 \times 10^{-25}$). The odds-ratios are equally spaced opposite the troponin T values on the Y-axis. The crossing lines show the relationship of the value on the Y-axis to the odds-ratio. A troponin T > 1 has an odds-ratio of 0.165 versus 34.226 against a normal ECG with a likelihood of ST-elevation. The symbols on the Y-axis are arranged in order by relative distance on the X-axis.

analysis. The method allows us to look at more than two values of the dependent variable when the variable values are ordered. When there are only two values, the result is a logistic regression. The odds-ratio represents the increase in the odds associated with a change in condition from baseline with respect to AMI.

RESULTS

A total of 141 patients (48 percent) presented with chest pain (typical for 70 [24 percent]), and 152 (52 percent) had associated symptoms (dyspnea, abdominal discomfort, congestive heart failure, etc.). Among the 60 patients (21 percent) with a final diagnosis of AMI, there was an even

distribution between Q-wave (QMI) and non Q-wave AMI (non QMI). ECG features clinically diagnostic of myocardial ischemia or infarction were present in 73 patients (24 percent), while 160 patients (55 percent) had non-diagnostic ECGs. Sixty patients (21 percent) had a normal presenting ECG.

A GOLDminer™ plot can be constructed in many ways. For example, when the dependent variable is the ECG, ECG findings are predicted by the cTnT, and the association between AMI is significant ($p = 2.7 \times 10^{-25}$). The predictor is scaled to the intervals described. Table 1 is the observed frequencies that give rise to the GOLDminer™ plot (Y-view) shown in Figure 1.

Table 2. Odds for cardiac troponin T concentration versus ECG findings.

TnT/ECG	Normal	Other	Q-wave	ST dep	ST ele
< .05	1.023	2.457	0.120	0.244	0.067
.05 - .1	0.654	2.187	0.148	0.421	0.160
.1 - .2	0.418	1.947	0.184	0.726	0.384
.2 - .5	0.268	1.733	0.228	1.252	0.921
.5 - 1	0.171	1.543	0.282	2.160	2.212
> 1	0.109	1.374	0.350	3.725	5.310
ref	0.664	2.196	0.147	0.413	0.155

We review the steps required to get to Figure 1. Each cell has an observed and expected frequency. The probabilities of each cell are obtained by dividing the expected (or observed) frequency by the total frequency for the column. The probabilities add to 1. The odds-ratio is calculated by comparing the ratio of the Y-reference odds to the baseline or X-reference odds. The odds are obtained by taking the ratio of the frequency count for an outcome category to that of the outcome reference. In this case the outcome reference is the column "normal ECG." Consider the example of "cTnT < 0.05," and "cTnT > 1 with ST elevation" as the outcome and "normal ECG" as the reference. The expected odds for "cTnT < 0.05" or for "cTnT > 1 with ST elevation" are 3.46/3.47 (= 1) and 13.19/3.47 (= 3.80) using the axis-reference of 3.47. The expected odds for "normal ECG" versus "ST elevation with cTnT < 0.05" are 53.09/51.92 (= 1.02) and 3.46/51.92 (= 0.07) using the axis-reference of 51.92. The axis-reference frequencies are hidden from view in this presentation. The expected odds for the cells are calculated before calculating the odds-ratios. The Y-reference may be displayed on the right for each row, and the X-reference may be displayed at the bottom of each column, but the variables may also be reversed, particularly in this example. The important point is that calculation of odds prior to calcu-

lating the odds-ratio requires that the entire Y-reference be converted to a value of 1 by dividing all the cell frequencies by the reference frequency. The odds-ratio is next calculated by converting the X-reference to a baseline of 1.

Table 2 is the calculated odds that are used for the odds-ratios shown in Figure 1 using a cTnT reference of 0.1 ng/ml. The reference odds listed in the last row of each column coincides with the odds at cTnT < 0.1 (0.05 to 0.1). There is a reference odds for each column, or ECG category. The odds-ratio is calculated for any cTnT value in an ECG category with the odds-ratio for cTnT < 0.1 as 1 by dividing the odds by the reference odds. For example, the expected odds-ratio for the table cell cTnT > 1 and ST elevation is calculated as 5.310/0.155 = .26. Likewise, the odds-ratio for cTnT < 0.05 and normal ECG is calculated as 1.023/0.654 = 1.54. The odds-ratio for cTnT 0.2 to 0.5 and Q-wave is calculated as 0.228/0.147 = 1.55.

Figure 1 is a GOLDminer™ Y-view of the scaled cTnT versus ECG findings [15, 16], a graphical representation of the results of the universal regression with the odds-ratios displayed on the left side and the cTnT scaled values evenly spaced on the right side. The chi-square (108), significant at $p = 2.7 \times 10^{-25}$, shows that the uniform spacing fits the table. The significance chi-square is the difference between the chi-square for independence and the

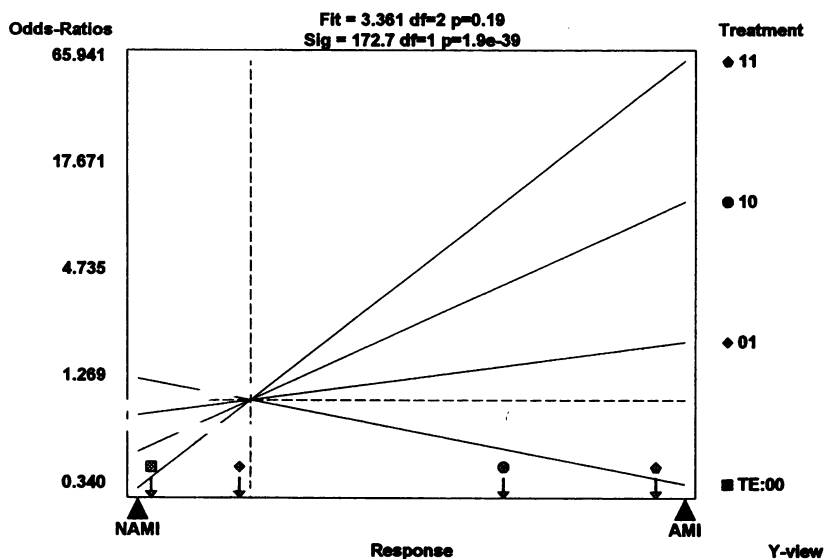


Figure 2. GOLDminer™ Y-view of binary 2 variable pattern versus AMI or non-AMI. The pattern classes, as in Table 1, are displayed on the Y-axis. The troponin T and ECG have binary values. The equally spaced odds-ratios are opposite the pattern classes. The only classes represented on the X-axis are non-AMI (NAMI) and AMI. The symbols are arranged in order by relative distance on the X-axis. The crossed lines show the expected odds-ratios of the classes for and against NAMI/AMI. The fit of the classification is significant at chi-square = 182.3 ($p = 1.6 \times 10^{-41}$).

Table 3. Observed and expected frequencies for cTnT, ECG versus diagnoses.

TnT,ECG/Dx (obs/exp)	0	1	2	3
2,4	0/0.09	0/0.56	0/5.56	21/14.79
1,4	0/0.10	0/0.23	0/0.84	2/0.84
2,3	3/2.26	6/4.37	22/13.39	0/10.98
0,4	3/1.40	0/1.23	0/1.72	2/0.64
1,3	2/3.56	4/2.57	4/2.96	0/0.91
2,2	0/1.31	0/0.78	0/0.73	3/0.19
0,3	49/47.81	13/12.96	5/5.59	0/0.64
2,1	1/0.81	0/0.15	0/0.04	0/0
0,2	5/6.39	1/0.53	0/0.07	1/0
0,1	85/83.76	1/2.16	0/0.09	0/0
0,0	59/59.52	1/0.47	0/0.01	0/0

chi-square for fit. The values for the pairings for cTnT and categorical ECG results are calculated from the expected odds as described above.

The GOLDminer™ plot is constructed by converting the cTnT results from

continuous to ordinal data by definition in intervals. cTnT is a treatment variable and ECG findings is the effect or outcome variable. The effect is not dichotomous, but polytomous as the ECG finding is not simply a positive or negative result. It is cus-

Table 4. Expected odds and odds ratios from Table 3.

TnT,ECG/Dx (odds/OR)	0	1	2	3
2,4	1/1	6.26/789.22	62.29/622865	166/4.6x10 ⁸
1,4	1/1	2.35/295.91	8.76/87560	8.7/2.6x10 ⁷
2,3	1/1	1.93/243.18	5.91/59134	4.8/1.4x10 ⁷
0,4	1/1	0.88/110.95	1.23/12309	0.5/1.4x10 ⁶
1,3	1/1	0.72/91.18	0.83/8313	0.3/7.6x10 ⁵
2,2	1/1	0.59/74.93	0.56/5614	0.1/4.2x10 ⁵
0,3	1/1	0.27/34.18	0.12/1169	0.01/4x10 ⁴
2,1	1/1	0.18/23.09	0.05/533	0/1.2x10 ⁴
0,2	1/1	0.08/10.53	0.01/111	0/1169
0,1	1/1	0.03/3.25	0/10.53	0/34.2
0,0	1/1	0.01/1	0	0

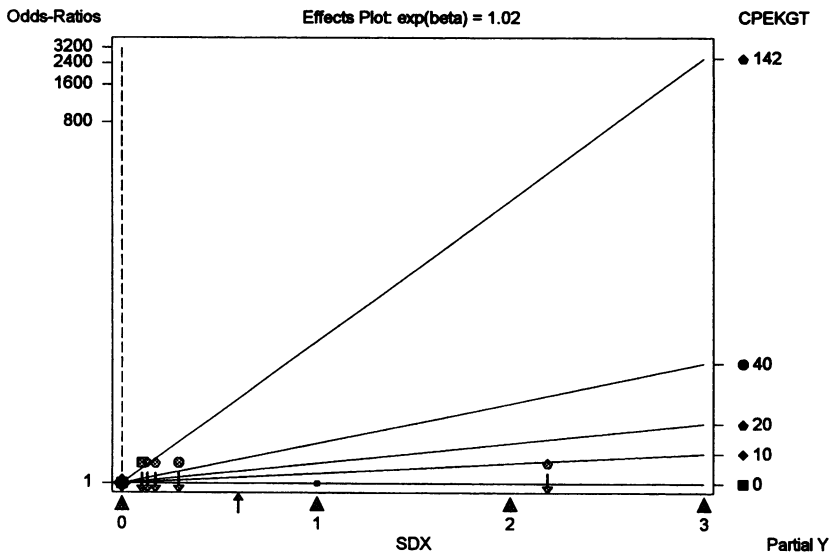


Figure 3. GOLDminer™ Y-view of the CP/ECG/cTnT coded classes versus the full diagnoses (0[other], 1[angina], 2[non QMI], 3[QMI]). The pattern classes are formed using typical or atypical chest pain combined with the features used in Figure 1 that describe cTnT and ECG.

tomary to do a logistic regression for a binary valued outcome, but the choices are normal ECG, ST elevation, Q-wave, ST depression/T wave inversion, and other. It is not easy to examine multiple alternatives with the logistic regression model. The

square, diamond, circle, pentagon, and triangle symbols in the plot are opposite the observed odds-ratios, displayed on the opposite Y-axis. The solid lines show the expected odds-ratios under the model. The cTnT values on the Y-axis are compared

with the ECG findings as the response variables on the X-axis. The symbols are aligned at the bottom showing the relative closeness of the cTnT result to the expected ECG finding. The arrows show their positions relative to the outcome categories. cTnT values above 0.1 ng/ml have odds-ratios from 2 to 34 with increasing relationship to diagnostic ECGs.

Figure 2 is a GOLDminer™ plot [19, 20] Y-view of the odds-ratios for and against AMI using the syndromic classes formed by the cTnT at a cutoff of > 0.1 ng/ml with diagnostic versus non-diagnostic ECG findings. The chi square = 172.7 is significant at $p = 1.9 \times 10^{-39}$. The patterns with both 0 versus both 1's of cTnT (0.1 ng/ml) and ECG positive have odds-ratios for AMI of 0.358 and 65.941, respectively. In the case of the cTnT(-) and ECG(-) or "0,0" with AMI the odds is calculated as $6/100.63 (= 0.06)$, for cTnT(+) and ECG(-) or 1,0 without AMI is calculated as $16/17.67 (= 0.91)$, and for the 0,1 without AMI is $9/6.61 (= 1.36)$. The odds-ratio for TREATMENT = cTnT(+), ECG(+) or "1,1" and EFFECT = "AMI" is calculated as $9.914/0.150 (= 66.07)$. Likewise, the odds-ratio for TREATMENT = cTnT(-), ECG(-) or "0,0" and EFFECT = "AMI" is calculated as $0.054/0.150 (= 0.36)$. The odds of having AMI (versus no AMI) is 184 times as high for the 1,1 than for the 0,0 combination of features.

We now introduce the multivariable GOLDminer™, which uses two or more predictor variables regressed to a multivalued dependent variable. The full range of values for the dependent variable, diagnoses (0,1,2,3), and two predictors, cTnT (0 to 2) (left) and ECG (0 to 4) (right) are considered. The association is significant at chi square = 246.10 ($p = 3.6 \times 10^{-54}$). Table 3 is the observed (obs) and expected (exp) frequencies for the predictor classes vs. the diagnoses (Dx), and Table 4 is the expected odds and odds ratios from Table

3. If we use three features cTnT, chest pain, and ECG with the full range of ECG findings and the cTnT intervals as defined in Figure 1, we construct a three-letter word using CP/ECG/cTnT with the value of the variable in its assigned position. Figure 3 is the GOLDminer™ plot Y-view of odds ratios for the full regression vs the diagnoses.

Constructing GOLDminer plots yields a quantitative analysis of outcomes that can aid in the diagnosis of AMI in patients with equivocal ECG or clinical findings. For instance, 26 patients without a final diagnosis of AMI presented with atypical chest pain and non-specific ECG findings (ST segment depression or T wave inversions) and had normal cTnT values. The normal cTnT values allows us to exclude the diagnosis of AMI at the time of presentation and allow rapid triage of the patient in the emergency department. Conversely, in a group of patients with typical chest pain with equivocal ECG findings, an abnormal cTnT value allows rapid triage for admission and potential aggressive early intervention in this high-risk subgroup.

DISCUSSION

Our study validates the diagnostic utility of cTnT values at the time of presentation and is unique in several ways. We studied the entire spectrum of patients presenting to the emergency department with a suspicion of AMI and not just patients with chest discomfort. Secondly, the cTnT results and the decision-making process were separated. This had implications for test validation. The test cutoff was determined by a process independent of the clinical decisions used in patient care. We then evaluated the role of serum cTnT in the diagnosis of AMI in relationship to the other features in the diagnosis of AMI. We argue that cTnT has great

value for relieving uncertainty when the clinical features are not definitive for excluding AMI. The universal regression model clarifies the underlying relationship between the serum markers, clinical features, and outcomes. This type of modeling allows us to form a classification with features that can be displayed in a truth table. Instead of the individual tests or symptoms, the combinations of features resolve uncertainty, just as the pixels on a screen give resolution in picture definition.

The GOLDminer™ method unmask the underlying autocorrelation between cTnT and ECG findings in the data. We use the GOLDminer™ to examine the probability characteristics of the feature combinations as more and more uncertainty is relieved. This approach is considerably more satisfying than other models currently in use and may have future implications for medical practice and decision making. This is especially important in the case where there are equivocal clinical and ECG findings. The diagnostic efficiency of cTnT values at the time of presentation coupled with clinical and electrocardiographic findings allows rapid decision making and patient triage resulting in potential enormous healthcare savings.

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