

ORIGINAL CONTRIBUTION

Diagnosis of Myocardial Infarction: Integration of Serum Markers and Clinical Descriptors Using Information Theory

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Objective: We examine the use of information theory applied to a single cardiac troponin T (cTnT) (first generation monoclonal; Boehringer Mannheim Corp., Indianapolis, Indiana) used with the character of chest pain, electrocardiography (ECG) and serial ECG changes in the evaluation of acute myocardial infarction (AMI). We combined a single measure of cTnT (blinded to the investigators) with a creatine kinase MB isoenzyme (CK-MB) measurement to discover the best decision value for this test in a study of 293 consecutive patients presenting to the emergency department with symptoms warranting exclusion of AMI.

Methods: The decision value for determining whether cTnT is positive or negative was determined independently of the final diagnosis by examining the information in the cTnT and CKMB data. Using information theory, an autocorrelation matrix with a one-to-one pairing of the CKMB and troponin T was constructed. The effective information, also known as Kullback entropy, assigned the values for troponin T and for CKMB that have the lowest frequency of misclassification error. The Kullback entropy is determined by subtracting the data entropy from the maximum entropy of the data set in which the information has been destroyed. The assignment of the optimum decision values was made independently of the clinical diagnoses without the construction of a receiver-operator characteristic curve (ROC). The final diagnosis of AMI was independently determined by the clinicians and entered into the medical record.

Results: The decision value for cTnT was 0.1 ng/ml as determined by the the information in the data. The method was validated within the same study by mapping the results so obtained into the diagnoses obtained independently by the clinicians using all of the methods at their disposal. The cTnT was different in AMI ($n = 60$) compared with non-AMI patients ($n = 233$) (2.08 ± 0.21 vs. 0.07 ± 0.10 ; $p < .0001$).

Conclusion: Information theory provides a strong framework and methodology for determining the decision value for cTnT, which minimizes misclassification errors at 0.1 ng/ml. The result has a strong correlation with other features in detecting AMI in patients presenting with chest pain.

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^dAbbreviations: AMI, acute myocardial infarction; cTnT, cardiac troponin T; ECG, electrocardiography; CK-MB, creatine kinase MB; ROC, receiver-operator characteristic curve. Received February 6, 1998; Returned for revision September 15, 1998; Accepted April 1, 1999.

INTRODUCTION

The enzymatic diagnosis of acute myocardial infarction (AMI)^d has for the past decade or more been based on measurement of at least two creatine kinase isoenzymes (CK-MB) drawn six or more hours apart to detect abnormal elevation signifying myocardial necrosis.

An assay for a new biochemical marker, cardiac troponin T (cTnT), has been developed for the diagnosis of AMI. Preliminary studies have shown that cTnT rises to abnormal levels in serum within four to six hours after the onset of myocardial damage, remains elevated for a week or longer [1-3] and may be associated with a greater likelihood of cardiac complications and death in patients with acute coronary ischemia, even when myocardial necrosis is not detected by CK-MB assay [4-6]. Proper clinical use of this new test first demands selection of the optimum cutoff for medical decision-making; that is, the serum level drawn at a certain time-point that best confirms or excludes myocardial necrosis. The traditional method for selecting such a cutoff value would involve performing the assay in a group of patients, comparing it to other enzymatic and clinical descriptors and constructing receiver operator curves (ROC) to determine the value producing optimal sensitivity and specificity. One would then perform a validation study in a separate population to minimize errors from bias that might occur in the initial population.

In this study, we examine an alternative approach that does not require the use of separate training and validation studies by examining for the information characteristics of the study data set using the information-induction method described by Rudolph et al. [7]. Moreover, we examined this methodology to determine a cTnT value at the time of presentation to the emergency department that would optimally confirm or exclude the presence of acute myocardial damage. Information theory allows us to treat the cTnT, CK-MB

and clinical data as an encrypted message without reliance on a supervisory classification, which is what is done when prior diagnostic categories are assigned (dependent variables) separately (by an expert or using a reference method), and which is used for constructing the ROC curves. Thus, this relies on no assumptions about the nature and distribution of the data or the diagnostic tests, and it partially eliminates the need for supervisory classes to determine cutoff values [7]. We, thereby, resolve uncertainty in the available data used for decision making to the greatest extent.

METHODS

We used information induction as described by Rudolph et al. [7] to classify patients using cTnT and CKMB, with or without ECG characteristics to form a classification matrix.

Study Sample

A single cTnT was measured on the first specimen submitted for CK-MB isoenzyme analysis in 293 patients who presented to the Emergency Department with chest pain or symptoms suspicious of AMI. The results of cTnT were not reported to the clinicians caring for the patient (the assays were run in batches after patients had received their care).

All patient's records, ECGs and hospital discharge diagnoses were reviewed without knowledge of the serum cTnT results. A standard questionnaire was utilized by one author (AQ) to obtain historical data and classify patients as having typical or atypical chest pain or other symptoms at presentation. World Health Organization criteria (two of three of the following criteria) were used as the criterion for the diagnosis of AMI. For the purpose of this study, patients were classified as having suffered acute MI if, based on all available clinical information this was the discharge diagnosis of the attending physician. We felt this would optimize specificity of the clinical diagnosis since it did not

rely solely on ECG and CK-MB criteria, which are subject to false positive results. Unstable angina was defined as chest pain or symptoms suspicious for myocardial ischemia with ECG abnormalities but no elevation of CK-MB.

Cardiac markers

The cTnT was measured on the ES300 using the first generation ELISA one-step sandwich assay from Boehringer Mannheim Corporation (BMC, Indianapolis, Indiana). The CK-MB was measured on the Vitros 950 using an immunoinhibition assay (Johnson & Johnson Diagnostics, Rochester, New York). Based on previous work in our laboratory, a CK-MB of 17 U/l was considered abnormal [7].

Statistical methods

Descriptive statistics included histograms and normal probability plots. Parametric and nonparametric analyses included: one-way analysis of variance, stepwise linear regression with selection of variables, Kruskal-Wallis analysis by rank, crosstabulation analyses. These were done with Statgraphics Plus software (Manugistics Corp., Rockville, Maryland) on a DEC Starion 586 PC. Shannon and Kullback entropy used to determine decision points for each test were done using Statgraphics apl Plus (Manugistics Corp., Rockville, Maryland) software written by Rosser Rudolph. The method allows us to classify the data and map the patterns into the independently determined diagnoses. The optimum medical decision cutoffs were assigned using the method of group-based reference as determined by the method of Rudolph et al. [24].

Minimum feature set and attribute extraction: A primary data base is expressed in a matrix format with each patient a row and each attribute, characteristic or predicate variable a column. Rypka [8] describes a method for extracting features over all of the elements in a paired comparison such that the minimum fea-

tures can be found that separate all possible pairs of elements.

The minimum feature set, called variety in cybernetics and minimum test set in diagnosis is:

$$h = \log_R N$$

where h is the theoretical number of features required to separate N elements in a radix of R and all elements (rows) are separable into some combination of N elements taken h (H) at a time by at least one distinguishing feature. The combination of features that maximizes s , separation, maximizes entropy (H). The process of maximizing information content and optimizing separation is tied to uncertainty in information theory. Information is the uncertainty that is resolved by the data.

"Group-Based Reference": We previously described an information based model [7] in which the disease and normal reference populations are distinct subsets. These groups can be differentiated even without a supervisory classification by using a defining set of features (tests) that allow classification of each individual. We used CK-MB, LD1, and %LD1 to assign patients into any of eight groups that fit either AMI or non-AMI diagnosis with less than one percent misclassification error (000, 001, 010, 100)/(111, 110, 011, 101) based on the occurrence of at least two positive results [7]. The problem now is fitting ordinal classes to likelihoods of diagnoses.

We examined the entropy of the data set and found decision limits for each variable. The decision values for each test create binary pattern classes of the combined variables, which allows minimum error assignment to the classes [7].

We take the frequency distribution and probabilities of the classes using incremented values assigned to each variable paired with the median or optimum value of the other variables. The maximum entropy of the data is found by destroying correlation in the data, randomizing the variables. We take the frequency distribu-

tion and probabilities of the binary classes produced. The entropy distribution is flat when there is no information in the data. If there is information in the data, the frequency of all positive and all negative patterns is greater. The point of maximum effective information (Kullback entropy) is that which relieves the most uncertainty in the data base and yields the fewest errors in discrimination [9, 10].

Scaling the Data and Partitioning the Population into Pattern Classes: The data were used in a classifying matrix to find optimum decision points [7]. This method

treats information gained by a test as equivalent to reduction of uncertainty.

For any variable the optimum decision point is that at which uncertainty is minimized. Once the optimum decision points are determined, the data is scaled to a truth table with n-classes [8]. The all positive (disease) and all negative (normal reference) patterns are the most frequent. The data separated the population into AMI and non-AMI, based on the following values: cTnT < 0.1 ng/ml or ≥ 0.1 ng/ml. Initial CKMB was scaled to 0 if less than 17 U/l, and 1, if above. The normal population,

Table 1. Paired comparisons of cTnT and CKMB with combinatorial classes.

cTnT	CKMB	Pattern
0	5	0
0	9	0
0	4	0
0	13	0
0	4	0
0.01	1	0
0.01	4	0
0.01	12	0
0.02	12	0
0.02	7	0
0.02	7	0
0.03	16	0
0.03	14	0
0.03	8	0
0.04	10	0
0.05	8	0
0.05	8	0
0.05	6	0
0.06	15	0
0.07	13	0
0.08	7	0
0.08	10	0
0.09	15	0
0.10	9	0
0.11	7	0
0.11	7	0
0.12	25	11
0.14	12	10
0.14	12	10
0.15	3	10
0.16	158	11
0.16	33	11
0.16	23	11
0.18	1	10
0.18	46	11

defined by Rudolph et al. [7] as that which has no information, is characterized by values of the tests below the critical cutoffs. Analysis of the population above the maximum entropy decision level and also below it again partitioned the AMI and the non-AMI populations.

Data that was extracted from the medical record and review of ECGs was scaled. The clinical and laboratory features were both used to form additional classes. The CKMB evolution was 0 if negative and 1 if there was typical evolution of AMI. The ECG data was scaled to presence of: 3, ST segment elevation; 2, Q waves; 1, ST segment depression/T wave inversion; 0, normal; -1, other. The characteristics of the chest pain was scaled: 1, typical; 0, atypical; -1, other presenting feature.

There are four theoretical classes that can be formed by two tests, CKMB and cTnT, each having a 0 or 1 value. The partitioning results in 16 pattern classes based on a maximum scale of 4 levels for a test if clinical features are used with the laboratory tests. That is less than the theoretical number of classes that can arise from three tests and four values ($34 = 81$). A total of 293 patients should be adequate to capture the patterns that would be expected to occur from combining the test results (typical chest pain, ECG, cTnT). This is not surprising because there is information in the data as demonstrated by a high frequency of redundant patterns (000, 111, 221). If there were no information in the data, then the frequency of all the patterns would be the same. Evaluation of the pattern classes formed using cTnT, ECG and chest pain allows the compression of these into seven or eight classes with some loss of information. The final diagnoses are not used in the final classification. The approach described uses these variables to form classes that occur at expected frequencies. The classification described may be referred to as a "self-classifying" matrix [8], which has a relationship to the clinical classification that is used for ROC analysis.

RESULTS

Having examined the information contribution and optimum decision value of cTnT using the method of Rudolph et al. [7], we illustrate the principle first and simply by listing some of the paired values of cTnT and CKMB in ascending order with the assignment of a class defined by the optimum decision value for the test (Table 1). The maximum entropy is the entropy of the data after removing the association between the variables (cTnT, chest pain, ECG, serial CKMB) so that it has no information. The data entropy is the endogenous information in the data. In exploring for the information in the cTnT and CK-MB matrix, the median of CK-MB is used to examine the cTnT, and the median of the cTnT is used while examining the CK-MB, respectively, for information. The effective information or Kullback entropy is the difference curve obtained by subtracting the data entropy from the maximum entropy [7, 9]. It is the information added to resolve uncertainty. Figure 1 plots the maximum, data and Kullback entropy (effective information) from the difference curve. The decision level at 0.1 ng/ml is the highest point on the effective information plot. It is the point at which the information is greatest and results in the fewest errors if the cTnT is scaled to a binary result in a truth table. It is of great interest that a decision value of 0.2 ng/ml was assigned for the kit assay at the time of the study. It has subsequently been changed to 0.1 ng/ml based on continuing validation studies.

The cTnT decision level has a strong relationship, indeed, to the clinical features that are necessary for a clinical decision about AMI. Table 2 is a crosstabulation of the association of cTnT with the ECG findings. 11.1 percent of negative cTnT results occur with ST elevation, Q wave, ST depression or T wave inversion. 70.6 percent of cTnT elevations are associated with ST elevation, Q-waves, and ST depression or T wave inversion. The crosstabulation is an important representa-

Cardiac troponin T vs entropies

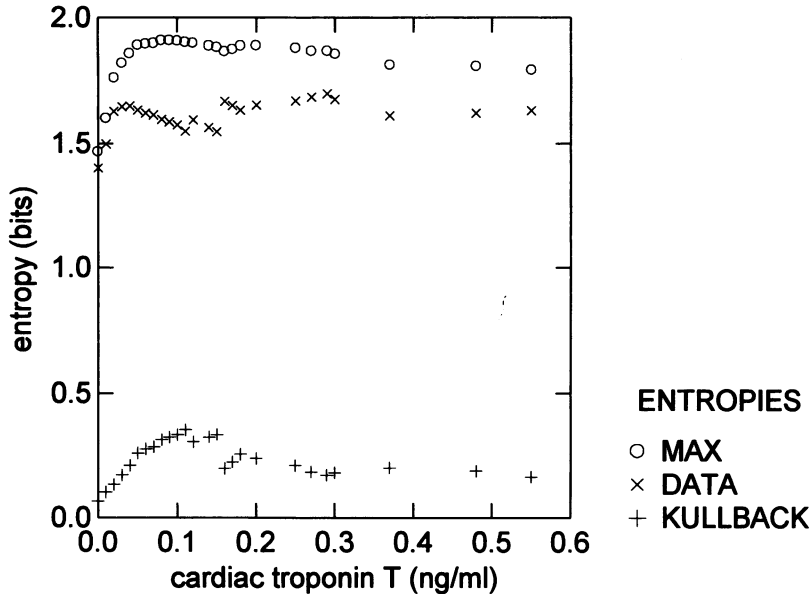


Figure 1. Entropy plot of total, data and Kullback entropy (effective information) (bits) for troponin T (Tnt) in incremented values.

tion of the data because the frequencies can readily be converted to likelihoods. The data compared is both nominal and ordinal, and the chi-square is the test of significance for the relationship. We see here that both ECG and cTnT are features, not diagnoses. What is compared here is the relationship of two features that are each associated with a classifying decision.

Table 3 is a crosstabulation of the cTnT levels associated with the final diagnoses: 96.4 percent negative with a non-AMI diagnosis, and 76.4 percent of positives associated with Q-wave or non-Q-wave AMI, with the remaining 16 of 68 associated with angina or other clinical findings. This has the appearance of an $N \times 2$ frequency table, revealing more detail than the traditional 2×2 table. This presen-

tation can be collapsed into a 2×2 table to obtain the usual sensitivity and specificity calculations. The false-negative diagnoses, with the exception of one patient seen 10 days after the infarct, were specimens taken too early (less than three hours after the onset of chest pain).

We can also move into a frequency table in which the same data is a string of data (features), each component of which has an association with the described classification. One might imagine constructing a frequency table using the same cTnT cutoff in which the message was cTnT [0 h, 3 h]. The frequency table would show more GRANULARITY of the information, capturing the stochastic behavior of the cardiac marker elevation. On the other hand, it immediately comes to mind that one would like to see the frequencies of

Table 2. Crosstabulation of cardiac troponin T and electrocardiographic findings.

cTnT	Negative	Positive
ST elevation	4 (1.8%)	23 (33.8%)
Q wave	7 (3.1%)	3 (4.4%)
ST depression/T wave inversion	14 (6.2%)	22 (32.4%)
Other abnormality	140 (62.2%)	20 (29.4%)
Normal ECG	60 (26.7%)	0

Table 3. Crosstabulation of cardiac troponin T concentration vs. final diagnoses.

cTnT	Negative	Positive
Q-wave AMI	3 (1.3%)	26 (38.2%)
Non Q-wave AMI	5 (2.2%)	26 (38.2%)
Angina	16 (7.1%)	10 (14.4%)
Other clinical findings	201 (89.3%)	6 (8.8%)

the message cTnT with ECG. The cTnT has binary choices as here defined by the 0.1 ng/ml cutoff, but the ECG can be either binary (problematic for the selection of ST depression) or ternary. If the data were continuous, it would be appropriate to model it using ANOVA1, MANOVA and stepwise or general linear regression. The logistic regression model was designed to fit the data to a simple binary outcome, assuming that the outcome can be so simplified (non-Q-wave AMI/unstable angina confounds our assumption that this is the case).

Table 4 illustrates the classes formed by three (binary) variables using chest pain, ECG and cTnT as classifiers. In the case of ECG, the data are scaled to a binary result in the truth table: 1, ST elevation, Q-waves, or ST depression and T inversion; 2, other pattern and normal ECG. One might justifiably argue that it should be a ternary outcome with ST elevation or Q-wave (1), ST depression/T wave inversion (2), and other pattern or normal ECG (3). The truth table is mapped into AMI and not AMI. The diagnoses, not AMI (NAMI) and AMI are in the first column. The diagnoses are described by the pattern classes in column 2 formed from troponin

T, chest pain, and ECG. The results of each of the three tests have a value of 0 or 1. The counts for each pattern is column 3, and the percent frequency is column 4. Two or more 0 values occur 95.7 percent of the time in NAMI, and two or more 1 values occur 81.6 percent of the time in AMI. The odds-ratio is in column 4. The likelihood of each pattern is a product of three likelihoods. The likelihoods are easily calculated for each feature using the frequency tables we have described or shown. Therefore, a 000 is $0.913 \times 0.8884 \times 0.9270 = 0.7519$. The most common pattern is the 000 pattern in non-AMI, and the 111 pattern in AMI. The last column of the table is the odds-ratio for each class. The odds-ratio is a measure of the ratio of likelihood for versus the likelihood against an event.

DISCUSSION

This study shows the information contribution of a single cTnT measured on a serum taken for CKMB at presentation with symptoms suspicious of AMI. The presenting cTnT alone has early false-negative values, but the cTnT is used

Table 4. Classes formed by Troponin T, chest pain, ECG.

Diagnosis	Pattern	Frequency Number	(%)	Likelihood 0.913 0.8884 0.9270	Odds ratio
NAMI	000	189	64.5	0.7519	1.5
	001	10	3.4	0.0592	1.1
	010	17	5.5	0.0944	0.98
	100	7	2.4	0.0716	0.84
	011	1	0.3	0.0074	0.72
	110	3	1.0	0.0090	0.60
	101	1	0.3	0.0056	0.45
	111	5/233	1.7	0.0007/0.9998	0.32
				0.2353 0.4706 0.3823	
AMI	001	3	1.0	0.0684	0.70
	010	3	1.0	0.0476	1.5
	100	5	1.7	0.1376	2.0
	011	2	0.7	0.0769	5.9
	110	5	1.7	0.1548	11.9
	101	8	2.7	0.2223	26.2
	111	34/60	11.6	0.2501/0.9677	49.0

The diagnoses, not AMI (NAMI) and AMI are in the first column. The diagnoses are described by the pattern classes in column 2 formed from troponin T, chest pain and ECG. The results of each of the three tests have a value of 0 or 1. The counts for each pattern is column 3, and the percent frequency is column 4. Two or more 0 values occur 95.7% of the time in NAMI, and two or more 1 values occur 81.6% of the time in AMI. The odds-ratio in column 4.

combined with chest pain and ECG. We did not show the information contribution of sampling time, which is optimized at 3.5 hours after onset of chest pain by the entropy formalism.

We further elaborate on a thesis previously described: The maximum entropy formalism has relevance to current discussions about decision values for medical tests and for the construction of highly rich and meaningful models of clinical processes. The models constructed are based on the treatment of a clinical presenting event as the resolution of an encrypted message. The model is highly consistent with the actual way in which information is used in making clinical decisions in situations with chest pain or atypical findings suspicious of AMI.

We have shown how the use of information theory allows for the measurement of a decision value for a test without the construction of an ROC curve because the value is elicited from an autocorrelation matrix. We have also examined first how simple frequency tables are useful for describing the relationships between event likelihoods, and then how combined features are displayed as frequencies to map the most descriptive features to their likelihoods in rule-in/rule-out AMI. Frequency tables when they are collapsed into the 2x2 format suffer enormous loss of information, which imposes the major problem of the Bayesian approach. If all of the information available is used in examining the data set then there is minimum loss of information, better resolution, and

the data becomes a "self-classifying" matrix. The self classifying behaviour is revealed in the emergence of stable frequencies for the $N \times N$ table of features against the selection of diagnoses.

We believe that our study is unique in several ways: We studied a broad group of emergency department patients presenting with symptoms consistent with ischemia or infarction in whom CK-MB determinations were ordered. Our cohort represents not only the typical patient seen in an emergency room with chest pain, but rather the whole spectrum of patients presenting with a suspicion for AMI. In fact, in half the patients chest pain was not the major presenting symptom. As such a large percentage of patients present with atypical complaints, the role of biochemical markers in the diagnosis of AMI becomes paramount.

Secondly, the cTnT results were blinded to the treating physicians and did not influence decision making or diagnosis. Finally, the role of serum markers in the diagnosis of AMI was assessed 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 information theory based model clarifies the underlying relationship between the serum markers, clinical features and outcomes.

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