

A Feature Selection for Detection of Non ST Elevation Myocardial Infarction

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Abstract

A feature selection (FS) process of biomarkers for detecting Acute Myocardial Infarction (AMI) for Non ST Elevation patients (NSTEMI) is presented. FS has been applied by a retrospective analysis of biomarkers - high sensitivity cardiac troponin T (hs-cTnT), heart-type fatty acid-binding protein (H-FABP), creatine kinase-MB (CK-MB), myoglobin, GPBB, CA3 and NTproBNP which are measured at different times from presentation. ECG anomalies at presentation which are key for diagnosis were not considered for FS since they are routinely assessed in the emergency department (ED). Biomarkers measurements and additional data were collected at the ED from patients with chest pain of suspected cardiac origin comprising 478 cases (97 NSTEMI).

hs-cTnT, H-FABP and CK-MB are statistically significant biomarkers to detect AMI according to ROC curve analysis and logistic regressions using data at different time windows. Overall, hs-cTnT as a sole marker is superior for AMI detection. However, H-FABP can be detected earlier and it demonstrates net gains in classification for non-AMI that makes it relevant for AMI rule-out approaches.

1. Introduction

Chest pain is one of the most common complaints with patients arriving at Emergency Department (ED) with approximately 6 million patients presenting annually in the United States [1]. Of those admitted, only 10% to 13% have a confirmed Acute Myocardial Infarction (AMI) [2]. Challenges exist in providing early and accurate diagnosis of AMI in patients admitted to ED with chest pain of suspected cardiac origin. Additionally, many current standard diagnostic tests are not accurate enough to rule-out MI at presentation [3] or under 3 hours in ECG negative patients providing a burden to overcrowded ED. Inappropriate discharge however is associated with a 5-fold increase in mortality and morbidity [4].

AMI is diagnosed by history, clinical examination,

electrocardiogram (ECG) and measurement of cardiac biomarkers including high sensitive troponin T (hs-cTnT).

This study aimed to explore additional biomarkers that could add more diagnostic capabilities to hs-cTnT (which is the gold standard) in the detection of AMI in patients presented to ED with chest pain of suspected cardiac origin. This retrospective analysis for feature selection takes biomarkers measured at multiple timepoints after presentation apart from the initial ECG to assist in the detection of AMI.

2. Methods

2.1. Recruitment of patients and data

Consecutive patients (age>18 years) with chest pain of presumed ischaemic origin were recruited at Craigavon Area and Daisy Hill hospitals in Northern Ireland between October 2009 and October 2011. Exclusion criteria comprise symptom onset >12 hours prior to recruitment, had a terminal malignancy, had received thrombolysis prior to recruitment, were receiving chronic anticoagulant therapy or had been previously recruited into the study. Time of symptom onset was determined following patient interview. The study complies with the Declaration of Helsinki and was approved both by the Office for Research Ethics Northern Ireland and the Southern Health and Social Care Trust Research and Development Department. Written informed consent was obtained from all participating patients.

A 12-lead ECG was obtained on presentation and indicators of anomalies were annotated (abnormal Q wave, ST shift and T wave inversion). Blood was drawn on presentation (time 0 hour) and at subsequent timepoints if required (1, 2, 3, 6, 12 and 24 hours) for the measurement of biomarkers hs-cTnT, Creatine Kinase-MB (CK-MB), Myoglobin, GPBB, Heart-type Fatty Acid-Binding Protein (H-FABP), CAIII, Troponin I (cTnI), Troponin T (cTnT) and NTproBNP.

Diagnosis of AMI was established according to the universal definition of MI at the time [5]. The final diagnosis was adjudicated by two independent clinicians

who had all the clinical, laboratory and imaging data available.

548 cases were recruited and 70 cases of ST Elevation MI (STEMI) were not included in the analysis since those cases are treated by PCI (in hospitals where it is available) and would not routinely have biomarkers measured. Thus the number of cases was reduced from 548 to 478 including 97 Non ST Elevation MI (NSTEMI).

2.2. Feature selection

Measured biomarkers for segregating cases of MI from non-MI were analysed by the area under the receiver operator characteristic curve (AUROC) and logistic regression. Calculations were carried out using R version 3.1.0 and for AUROC analysis the package “pROC” [6] was used. Level of statistical significance was fixed at 0.05 for comparisons. Values were rounded to four decimal places. The biomarkers exhibiting the highest AUROC with no statistical significant difference were chosen as candidate markers for further exploration. Cases with missing values were excluded and no imputation of the data was carried out.

3. Results

3.1. AUROC

H-FABP, hs-cTnT, CK-MB, GPBB, CAIII, Myoglobin, c-TnI, NTproBNP and c-TnT were analysed using AUROC at different times from presentation.

According to table 1, hs-cTnT at presentation had the highest AUROC of all the biomarkers but was not statistically different to H-FABP ($p=0.0587$).

Table 1. AUROC for biomarkers associated to AMI at presentation. Lower and upper CI 95% and p value compared to hs-cTnT.

Biomarker	Area	Std e	Lower	Upper	p
hs-cTnT	0.9083	0.021	0.867	0.9495	NA
CK-MB	0.7973	0.027	0.7443	0.8503	0.0013
Myoglobin	0.7297	0.0314	0.6682	0.7911	0
GPBB	0.5767	0.0343	0.5095	0.644	0
H-FABP	0.8483	0.0237	0.8019	0.8947	0.0587
CAIII	0.5231	0.0326	0.4592	0.587	0
cTnI	0.6576	0.0266	0.6054	0.7097	0
NTproBNP	0.6499	0.0333	0.5847	0.7151	0
cTnT	0.8195	0.0261	0.7682	0.8707	0.0083

The pattern of superiority for AUCROC of hs-cTnT is repeated at 3 hours (table 2) but it is not statistically different to H-FABP ($p=0.1239$).

Table 2. AUROC for biomarkers associated to AMI at 3 hours. Lower and upper CI 95% and p value compared to hs-cTnT.

Biomarker	Area	Std e	Lower	Upper	p
hs-cTnT	0.9155	0.023	0.8705	0.9605	NA
CK-MB	0.8438	0.0262	0.7926	0.8951	0.0397
Myoglobin	0.7142	0.0341	0.6475	0.781	0
GPBB	0.6004	0.0341	0.5335	0.6673	0
H-FABP	0.8676	0.021	0.8265	0.9088	0.1239
CAIII	0.5643	0.0343	0.497	0.6315	0
cTnI	0.7676	0.0281	0.7126	0.8226	0
cTnT	0.4737	0.0301	0.4147	0.5327	0

3.2. Logistic regression

Logistic regressions were used to show the predictive capabilities of combinations of biomarkers collected at different timepoints. hs-cTnT, H-FABP and CK-MB were included as predictors of AMI in two models for data collected up to 1 hour and 3 hours.

A model is presented in table 3 with data collected up to 1 hour from presentation (0 hour) that used biomarkers from 335 patients, 67 NSTEMIs and without missing values for the biomarkers involved. A corresponding label for the timepoint was added to the name of the biomarker for naming the variables.

Table 3. Logistic regression model with data collected up to 1 hour from presentation. 335 patients, 67 NSTEMIs.

	estimate	Std e	t-val	p
Intercept	-2.5318	0.2754	-9.193	0
hs-cTnT_0	0.0164	0.00851	1.928	0.0539
hs-cTnT_1	0.00071	0.006	0.118	0.9062
H-FABP_0	-0.4546	0.1225	-3.71	0.0002
H-FABP_1	0.6614	0.1678	3.941	0
CK-MB_0	0.0678	0.2177	0.312	0.7554
CK-MB_1	-0.1862	0.1724	-1.08	0.28

F critical 5% = 2.13, null deviance (total): 335.27 on 334 degrees of freedom (df) and residual deviance: 231.22 on 328 df. Model residual: 104.05 on 6 df, $F(6,328) = 24.6$, then the null hypothesis H_0 of all coefficients equal to zero is rejected. It also can be concluded that coefficients for H-FABP at presentation and at 1 hour are significantly different to zero, suggesting this biomarker is a significant predictor of MI at presentation and 1 hour in the logistic regression model.

Additionally, a model is shown with data collected up to 3 hours from presentation, using biomarkers from 272 patients (without missing values), 55 NSTEMIs, for timepoints at presentation (0 hour), 1 hour, 2 hour and 3 hour (table 4).

Table 4. Logistic regression model with data collected up to 3 hours from presentation. 272 patients, 55 NSTEMIs.

	estimate	Std e	t -val	p
Intercept	-3.6085	0.5031	-7.173	0
hs-cTnT_0	0.015	0.0288	0.522	0.602
hs-cTnT_1	-0.0527	0.0396	-1.328	0.1841
hs-cTnT_2	-0.0377	0.048	-0.786	0.432
hs-cTnT_3	0.1142	0.0432	2.646	0.0081
H-FABP_0	-0.8702	0.2753	-3.161	0.0016
H-FABP_1	0.173	0.4364	0.396	0.6919
H-FABP_2	0.4071	0.5006	0.813	0.416
H-FABP_3	0.3553	0.3128	1.136	0.2559
CK-MB_0	0.0608	0.5324	0.114	0.9091
CK-MB_1	-1.1973	0.8542	-1.402	0.161
CK-MB_2	2.6305	0.875	3.006	0.0026
CK-MB_3	-1.4567	0.7446	-1.956	0.0504

F critical 5% = 1.79, null deviance (total): 273.87 on 271 df and residual deviance of 123.14 on 259 df. Model residual: 150.73 on 12 df, $F(12,259) = 26.42$, then reject H_0 . Individually, coefficients for H-FABP at presentation, CK-MB at 2 hour and hsTnT at 3 hours are significantly different to zero, suggesting these biomarkers are significant predictors of MI in this logistic regression model.

3.3. Peaking times for AMI

Figure 1 shows normalized averages for hs-cTnT, H-FABP and CK-MB for the timepoints considered. The steady values below 0.2 correspond for averages of non-MI and are displayed for reference.

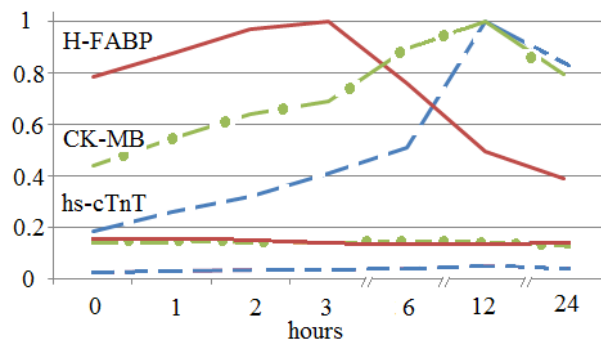


Figure 1. Normalized averages for most relevant biomarkers showing different peaking times for AMI. “0” hour is time of presentation.

3.4. Comparison of algorithms

Algorithms to detect MI based on biomarkers at different thresholds were compared using the Pencina’s

Net Reclassification Improvement (NRI) [7]. The initial focus was towards algorithms at presentation. H-FABP and hs-cTnT are preferred over CK-MB according to the AUROC and logistic regression models. Some comparisons to the gold standard $hs-cTnT \geq 14ng/l$ are shown in Table 5. The threshold of $14ng/l$ is the 99th percentile widely used for AMI detection and it is used here as a reference. For instance, according to the first row in table 5, an algorithm based on $H-FABP \geq 1.5\mu g/l$ to detect MI at presentation is more sensitive than one based on $hs-cTnT \geq 14ng/l$ (net gain with MI of 0.0462) but less specific (negative net gain with non-MI of -0.3765), and the probability of $|NRI|$ (absolute value of the sum of the two net gains) higher than $|-0.3303|$ is low ($p < 0.00005$) if the hypothesis of NRI zero is assumed. Thus it can be concluded that these two algorithms are statistically different in terms of NRI and the negative value shows no overall improvement of the algorithm. However it is not the case when comparing $H-FABP \geq 3.8\mu g/l$ against $hsTnT \geq 14ng/l$ ($p = 0.1073$) (third row in table 5). The cut-off of $3.8\mu g/l$ was used to show no difference.

Table 5. Pencina’s NRI comparing algorithms with $hs-cTnT \geq 14ng/l$ at presentation to detect MI. 360 patients were included in the analysis without missing values and 72 NSTEMIs. Concentrations are in ng/l and in $\mu g/l$ for hs-cTnT and H-FABP respectively.

Algorithm	Net MI	Net non-MI	NRI	p
H-FABP ≥ 1.5	0.0462	-0.3765	-0.3303	0
H-FABP ≥ 2.5	-0.1231	-0.0196	-0.1427	0.0193
H-FABP ≥ 3.8	-0.2462	0.1373	-0.1089	0.1073
H-FABP ≥ 5.3	-0.3846	0.2078	-0.1768	0.0328
H-FABP ≥ 7	-0.4462	0.2235	-0.2226	0.0119
hs-cTnT ≥ 14 OR H-FABP ≥ 2.5	0.0154	-0.0941	-0.0787	0.0014
hs-cTnT ≥ 14 OR H-FABP ≥ 3.8	0	-0.0314	-0.0314	0.0047
hs-cTnT ≥ 14 OR H-FABP ≥ 5.3	0	-0.0157	-0.0157	0.0455
hs-cTnT ≥ 14 AND H-FABP ≥ 1	0	0.0039	0.0039	0.3173
hs-cTnT ≥ 14 AND H-FABP ≥ 1.5	-0.0154	0.0314	0.0160	0.3992
hs-cTnT ≥ 14 AND H-FABP ≥ 2.5	-0.1538	0.1020	-0.0519	0.3239

4. Discussion

Cardiac troponin is currently the main biomarker assisting in the detection of AMI. With the dataset used (focused on NSTEMI only) the analysis demonstrated that hs-cTnT consistently had a higher AUROC than the other biomarkers but the statistical difference to H-FABP

could not be established at presentation ($p=0.0587$) (table 1) and at 3 hours after presentation ($p=0.1239$) (table 2).

H-FABP was also a strong predictor of AMI according to logistic regression models especially at 0 and 1 hour (tables 3 and 4). In those models H-FABP was combined with hs-cTnT and CK-MB.

H-FABP, measured at presentation and acting as a sole biomarker at different thresholds, did not outperform hs-cTnT $\geq 14\text{ng/l}$ for detecting MI as shown in table 5. In this comparison it is worth considering that hs-cTnT at 14ng/l is used to aid in the diagnosis itself. At best, H-FABP $\geq 3.8\mu\text{g/l}$ used to diagnose MI showed no statistical difference to hs-cTnT at 14ng/l (row 3). There were other thresholds tested for H-FABP and some of them are shown in table 5 and none of them exhibit $\text{NRI} > 0$ when compared to hs-cTnT at 14ng/l .

Nevertheless, the comparisons of algorithms in table 5 show net gains when a diagnosis of non-MI is made when H-FABP at thresholds of 3.8, 5.3 and $7\mu\text{g/l}$ are compared to hs-cTnT $\geq 14\text{ng/l}$ (rows 3, 4 and 5). However, $\text{NRI} < 0$ for those algorithms at presentation since the net gains when non-MI are surpassed by net gains in detecting MI.

Additionally in table 5 there are comparisons for some of the possible combinations of H-FABP and hs-cTnT. There were cases of $\text{NRI} > 0$ when compared to hs-cTnT $\geq 14\text{ng/l}$ but without statistical significance. It seems that by enforcing the two markers over a threshold (combinations AND instead of OR) it is possible to get $\text{NRI} > 0$ with net gains without MI (rows 9 and 10 in table 5). There is still ongoing research in order to establish how combining H-FABP with hs-cTnT at different thresholds would help to improve on MI detection.

H-FABP is present in high concentrations in the myocardium 30 minutes after an ischemic episode [8]. Additionally, its relative tissue specificity [9] makes it a suitable biomarker to be investigated. Following H-FABP's advantage of early expression (Figure 1) and net gains in non-MI as a sole marker and in combinations with hs-cTnT, we aimed to combine this biomarker with hs-cTnT and ECG anomalies as a rule-out approach, especially under 3 hours of presentation in line with Body et al. [10]. They demonstrated a model of eight variables including hs-cTnT, H-FABP, an indication of ischaemia from ECG and the outcomes of a clinical assessment. In future work we aim to simplify Body's approach using fewer variables and concentrating uniquely in NSTEMIs. Additionally we aim to use the time for onset of symptoms, which is subjective but could be a very important piece of information.

It is important to note the limitation of the study which includes the use of a relatively small dataset.

5. Conclusions

H-FABP has shown promise among other biomarkers investigated to pair with hs-cTnT according to AUROC

and logistic regressions. It does not outperform hs-cTnT for the detection of AMI in the dataset investigated. However, its earlier detection in blood following an ischaemic event, and net gains in classification when a diagnosis of non-MI is made, suggest its use as a rule-out test for suspected AMI patients. If effective, this would allow risk stratification and a more efficient use of resources to the health care system.

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