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A statistical approach to evaluate the performance of cardiac biomarkers in predicting death due to acute myocardial infarction: time-dependent ROC curve

Eda KARAİSMAİLOĞLU[1,*], Zeliha Günnur DİKMEN[2], Filiz AKBIYIK[2], Ahmet Ergun KARAAĞAOĞLU[3]

[1]Department of Biostatistics, Faculty of Medicine, Kastamonu University, Kastamonu, Turkey
[2]Department of Medical Biochemistry, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[3]Department of Biostatistics, Faculty of Medicine, Hacettepe University, Ankara, Turkey

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Background/aim: Myoglobin, cardiac troponin T, B-type natriuretic peptide (BNP), and creatine kinase isoenzyme MB (CK-MB) are frequently used biomarkers for evaluating risk of patients admitted to an emergency department with chest pain. Recently, time-dependent receiver operating characteristic (ROC) analysis has been used to evaluate the predictive power of biomarkers where disease status can change over time. We aimed to determine the best set of biomarkers that estimate cardiac death during follow-up time. We also obtained optimal cut-off values of these biomarkers, which differentiates between patients with and without risk of death. A web tool was developed to estimate time intervals in risk.

Materials and methods: A total of 410 patients admitted to the emergency department with chest pain and shortness of breath were included. Cox regression analysis was used to determine an optimal set of biomarkers that can be used for estimating cardiac death and to combine the significant biomarkers. Time-dependent ROC analysis was performed for evaluating performances of significant biomarkers and a combined biomarker during 240 h. The bootstrap method was used to compare statistical significance and the Youden index was used to determine optimal cut-off values.

Results: Myoglobin and BNP were significant by multivariate Cox regression analysis. Areas under the time-dependent ROC curves of myoglobin and BNP were about 0.80 during 240 h, and that of the combined biomarker (myoglobin + BNP) increased to 0.90 during the first 180 h.

Conclusion: Although myoglobin is not clinically specific to a cardiac event, in our study both myoglobin and BNP were found to be statistically significant for estimating cardiac death. Using this combined biomarker may increase the power of prediction. Our web tool can be useful for evaluating the risk status of new patients and helping clinicians in making decisions.

Key words: Time-dependent ROC curve, cardiac biomarkers, B-type natriuretic peptide, creatine kinase isoenzyme MB, troponin T, myoglobin

1. Introduction

Acute myocardial infarction (AMI) is one of the most important cardiovascular diseases, and it remains a leading cause of morbidity and mortality worldwide. The maximum risk of death occurs within the initial hours following the onset of AMI. Lower mortality depends on the early diagnosis of cardiac disease, which is important for effective treatment. Electrocardiography produces a physiological signal that is frequently used for diagnosing heart problems, but it is incapable of adequately diagnosing AMI. To overcome this limitation, cardiac biomarkers have been used in the detection of AMI. Myoglobin, cardiac troponin T, B-type natriuretic peptide (BNP), and creatine kinase isoenzyme MB (CK-MB) are cardiac biomarkers that are frequently used to assess cardiac risk factors (1,2).

Myoglobin is a sensitive early biomarker of myocardial cell injury and is found in cardiac and skeletal muscle. It appears in the blood 1 h after myocardial infarction, peaks at 4–12 h, and then returns to the baseline level (3). It is not cardiac-specific; myoglobin released from the skeletal muscles cannot be distinguished from that released as a result of cardiac injury (4). CK-MB levels increase in the serum 4–9 h after chest pain begins, reach peak values within 24 h, and return to baseline values within 48–72 h. CK-MB is not sensitive enough for diagnosis within 4 h from the time of symptom onset, but test sensitivity rises 6 h or more after the onset of chest pain (5). Troponin

* Correspondence: eda.ozturk@hacettepe.edu.tr

is a regulatory complex of 3 protein subunits (C, I, and T) located on the contractile apparatus of the cardiac and skeletal muscle fibers. Troponin T found in the cardiac muscle is genetically different from that found in the skeletal muscle (6). Therefore, cardiac troponin T is a more specific biomarker for the diagnosis of cardiac damage. Cardiac troponin T appears in the blood 6–8 h after the acute episode, peaks at 24–48 h, and remains elevated for a week or more (7). BNP is a cardiac neurohormone that is synthesized in cardiac cells. It is used as a diagnostic biomarker for congestive heart failure and can predict outcomes in patients with AMI (8,9). Myoglobin, cardiac troponin T, BNP, and CK-MB have all been used as cardiac biomarkers, but none meet all the criteria for an "ideal" biomarker of AMI.

There are several methods for evaluating the performance of the biomarkers that are used to classify an individual as healthy or diseased. Receiver operating characteristic (ROC) curve analysis is frequently used for this purpose because it is easy to calculate and is available in several software packages. The classical ROC curve assumes that disease status does not change over time. However, predicting whether a subject will or will not experience an event (death, in this study) during follow-up time is also of interest. Since an event may or may not occur during follow-up time, the data are not complete as in classical ROC analysis, but rather are censored. The performance of a single biomarker or a combination of biomarkers measured at baseline for predicting the occurrence of an event within a time period can be evaluated by time-dependent ROC analysis, as proposed by Heagerty et al. (10).

Cardiac-specific biomarkers can be used for clinical assessment of risk to patients with poor prognoses. In this study, we aimed to evaluate the prognostic performance of myoglobin, CK-MB, cardiac troponin T, and BNP in patients presenting with chest pain to the emergency department (ED) using time-dependent ROC analysis. We combined the biomarkers to determine which biomarker or combination of biomarkers was best for predicting death within a specified time period. We also aimed to obtain cut-off values for the combined biomarker that would indicate the highest performance, and we proposed a new method that involves obtaining the confidence intervals of areas under time-dependent ROC curves for comparing the performance of the biomarkers. Finally, we developed a web tool designed to help clinicians evaluate the risk status of new patients based on the information obtained in the study.

2. Materials and methods

2.1. Study population and variables

Patients admitted to the Department of Emergency Medicine at the Hacettepe University Faculty of Medicine with shortness of breath and chest pain (n = 410) between January 2010 and October 2012 were included in the study retrospectively. The age, sex, and diagnosis of the patients after hospitalization, as well as their CK-MB, myoglobin, cardiac troponin T, and BNP biomarker levels at admission, were retrieved from the hospital database.

Myoglobin, CK-MB (mass), and high-sensitivity troponin T (hs-TnT) electrochemiluminescence immunoassays were used to determine serum myoglobin, CK-MB, and cardiac troponin T levels, respectively (Roche Diagnostics, Mannheim, Germany). EDTA-plasma samples were used for the quantitative measurement of BNP on an Architect i2000SR analyzer (Abbott Diagnostics, Abbott Park, IL, USA) by chemiluminescent microparticle immunoassay.

Because the biomarker data were not normally distributed, we applied a logarithmic transformation. After achieving normality, the results of the analyses were presented with the transformed data. The event was defined as death from cardiac reasons. Patient follow-up lasted for 10 days (240 h) after admittance to the ED. The data consisted of survival times of patients recorded in terms of hours after admission and were right-censored.

2.2. Statistical analysis

The data were expressed as mean and standard deviation for quantitative variables and as frequency and percent for qualitative variables. Cox proportional hazards regression analysis was performed to identify independent variables of cardiac death. Significant variables were identified using univariate Cox proportional hazards regression analysis. $P < 0.20$ identified potential variables for multivariate analysis (11). Multivariate Cox proportional hazards regression was carried out with the candidate variables. The nearest neighbor estimation method was used for estimating time-dependent ROC curve analysis. This curve is drawn using sensitivity (t) and 1 – specificity (t), which are obtained from various cut-off values of a biomarker at time t. By using these measurements, a time-dependent ROC curve can be drawn at any time t. The Youden index method was used to calculate optimal cut-off values.

We proposed a new method for testing differences between the areas under time-dependent ROC curves of biomarkers. Bootstrap confidence intervals were used to determine whether the performances of the biomarkers, measured in terms of areas under time-dependent ROC curves, were significantly different from each other. For this purpose, an R code was developed (R 3.1.2; Foundation for Statistical Computing, Vienna, Austria). Samples were taken with replacement (n = 410) and repeated 1000 times by holding the proportion of censored data unchanged for each of the follow-up time points (240 h). First, time-dependent ROC curves were obtained for each time point. Then areas under time-dependent ROC curves were

calculated using these bootstrap samples. Confidence intervals were obtained using the percentile confidence interval method (12).

Statistical analysis was performed using IBM SPSS 21 (IBM Corp., Armonk, NY, USA). A significance level of 0.05 was used for multivariate Cox proportional hazards regression analysis. This study protocol was approved by the Noninvasive Clinical Research Ethics Committee of Hacettepe University.

3. Results

During the follow-up time (240 h), 344 patients were identified as censored and 66 patients died from cardiac causes. Descriptive statistics for patients who died or were censored during the follow-up time are presented in Table 1. The areas under time-dependent ROC curves of the biomarkers during the follow-up time are shown in Figure 1.

The x-axis of the graph indicates the follow-up time (240 h) and the y-axis refers to the area under the time-dependent ROC curve (AUC), calculated for all time points. The AUC value varies between 0 and 1. A value of 0.5 indicates that the biomarker distinguishes the individuals with and without the event completely by chance. The curves that are drawn against follow-up time close to 1 indicate better performance. Although comparison of the performance of the biomarkers showed a slight variance over time, changes in trends were similar. Areas under the ROC curves were around 0.80 during the follow-up time (Figure 1).

The biomarkers and covariates (sex, age, and diagnosis after admittance to the hospital) were combined to improve the ability of the biomarkers to estimate the event (death). Whereas the covariates of age, sex, and diagnosis were insignificant, all the log-transformed biomarkers were highly significant according to Cox proportional hazards regression analysis ($P < 0.001$) (Table 2).

Statistically significant biomarkers were examined to determine whether they satisfied the proportional hazards assumption. According to the test of proportionality assumption based on the Schoenfeld residuals, only myoglobin did not meet the assumption and the hazard was not constant over the course of time ($P = 0.006$) (Table 3). Therefore, the interaction between time and myoglobin was included in the model in multivariate Cox proportional hazards regression analysis.

The results of reduced multivariate Cox proportional hazards regression analysis including the time factor showed that myoglobin, myoglobin–time interaction, and BNP biomarkers were statistically significant (Table 4).

The results of the final model (Table 5), which was obtained from the significant variables in Table 4, indicated that the risk of death increased by approximately 6.9 times when the log (myoglobin) value increased by 1 unit. Likewise, when log (BNP) increased by 1 unit, the risk of death increased by approximately 3 times.

The score for each individual was obtained from the following equation, using beta coefficients:

Score = (1.928 × log (myoglobin)) + (1.109 × log (BNP)) + (–0.008 × log (myoglobin) × time).

These scores will be referred to as "the combined biomarker". Time-dependent ROC curves were obtained to determine whether the combined biomarker showed

Table 1. Descriptive statistics for patients who died or were censored during the follow-up time.

Variable		Death	Censored
		frequency (%)	frequency (%)
Sex	Female	29 (15.3)	160 (84.7)
	Male	37 (16.7)	184 (83.3)
Diagnosis	Cardiological	33 (14.5)	194 (85.5)
	Pulmonary/respiratory	26 (16.0)	136 (84.0)
	Other	7 (33.3)	14 (66.7)
Variable		Mean ± standard deviation	
Age		71.95 ± 13.22	69.89 ± 11.21
Log (CK-MB)		0.72 ± 0.45	0.43 ± 0.28
Log (myoglobin)		2.42 ± 0.66	1.77 ± 0.36
Log (troponin T)		–0.87 ± 0.72	–1.58 ± 0.55
Log (BNP)		3.09 ± 0.54	2.65 ± 0.54

CK-MB: Creatine kinase isoenzyme MB; BNP: B-type natriuretic peptide; Log: logarithm.

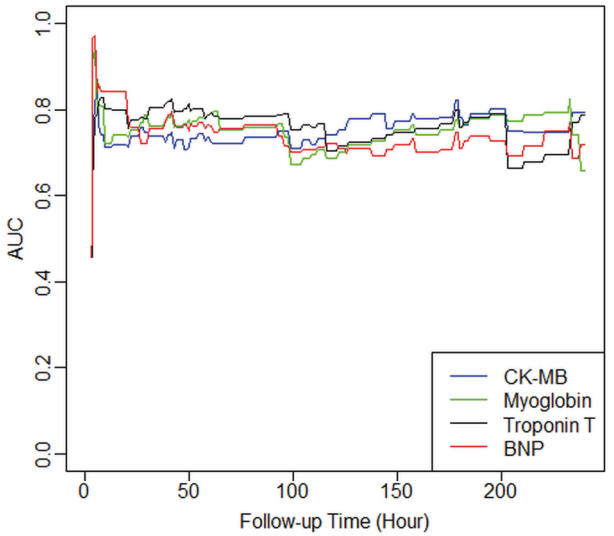

Figure 1. Areas under time-dependent ROC curves based on the biomarkers for the first 10 days.

better performance than the individual myoglobin and BNP biomarkers (Figure 2A). We found that the combined biomarker performed better than individual biomarkers from the beginning of the follow-up time to approximately the 180th hour. The AUCs varied from 0.75 to 0.97. After 180 h, performance of the combined biomarker declined, and the advantage swung towards myoglobin. The AUCs for myoglobin varied between 0.74 and 0.82.

Even though the combined biomarker had a visually better performance than other biomarkers in the first 180 h of follow-up time, differences between curves should also be checked for statistical significance. Therefore, bootstrap confidence intervals were used to assess differences between curves. Confidence intervals were calculated by taking the 2.5 and 97.5 percentiles of 1000 bootstrap samples. A comparison of the combined and individual biomarkers by using the confidence intervals is presented in Figure 2B. Confidence intervals of the three biomarkers overlapped with each another. Accordingly, although the combined biomarker showed better performance than the individual ones, the difference was not statistically significant.

Optimal cut-off values that are used to decide whether a subject will or will not experience an event also vary because the AUCs vary during the follow-up time. Therefore, cut-off values should be evaluated individually for every follow-up time point. In this study, cut-off values were calculated using the Youden index method. Cut-off values were obtained for the combined biomarker because it performed best. Cut-off values were calculated using the following method: when c was the cut-off value, sensitivity (c) + specificity (c) – 1 values were obtained for all time points (with 1-h intervals) by taking into account all available patients at that time point. The highest value was determined to be the cut-off point. In the graph, the y-axis indicates the scores of the combined biomarker that were calculated from log (myoglobin) and log (BNP) by using the equation mentioned above. The cut-off values remained constant for the first 120 h (approximately between 6 and 6.5) but decreased after 120 h until the end of the follow-up time. The percentile bootstrap method was used for analyzing the variability of cut-off values. Confidence intervals of the cut-off values were narrow for the first 200 h but gradually widened after 200 h (Figure 3).

Table 2. Results of univariate Cox proportional hazards regression analysis.

Variable		B	Standard error	Wald χ^2	P-value	Exp (β)	Confidence interval exp (β)
Age		0.010	0.011	0.710	0.399	1.010	0.987–1.033
Sex	Female	-	-	-	-	-	-
	Male	0.101	0.249	0.164	0.685	1.106	0.679–1.801
Diagnosis	Cardiological	-	-	1.909	0.385	-	-
	Pulmonary/respiratory	–0.053	0.263	0.041	0.839	0.948	0.566–1.588
	Other	0.525	0.418	1.574	0.210	1.690	0.744–3.839
Log (CK-MB)		1.057	0.187	32.084	<0.001	2.876	1.996–4.146
Log (myoglobin)		1.406	0.182	59.528	<0.001	4.078	2.853–5.828
Log (troponin T)		0.714	0.128	31.043	<0.001	2.042	1.589–2.626
Log (BNP)		1.466	0.250	34.355	<0.001	4.330	2.653–7.069

CK-MB: Creatine kinase isoenzyme MB; BNP: B-type natriuretic peptide; β: beta coefficient; Log: logarithm.

Table 3. Results of proportional hazards assumption test based on Schoenfeld residuals.

Variable	Chi-square	P-value
Log (CK-MB)	2.59	0.108
Log (myoglobin)	7.41	0.006
Log (troponin T)	0.56	0.454
Log (BNP)	0.18	0.669

CK-MB: Creatine kinase isoenzyme MB; BNP: B-type natriuretic peptide; Log: logarithm.

3.1. Web tool

We developed a web tool (http://www.biosoft.hacettepe.edu.tr/tdROC/) to evaluate the risk of death in patients admitted to the ED with shortness of breath and chest pain. The model was established with myoglobin and BNP by using Cox proportional hazards regression analysis, but time interaction with myoglobin was ignored because the follow-up time for new patients is uncertain. When the data for BNP and myoglobin are entered into the web tool, a patient's risk score is calculated using the following equation:

Score = (1.234 × log (myoglobin) + (1.175 × log (BNP))).

A time-dependent cut-off graph is constructed using this score. In the graph, the patient's risk score, obtained using the formula above, is marked on the y-axis as a horizontal bar that is parallel to the x-axis. In the same graph, the cut-off values that distinguish mortality from survival are represented by a black line. The distance between the horizontal bar (green, brown, and red dots) and the black line represents the mortality risk of the patients. When the horizontal bar is below the black line, the mortality risk decreases as the distance increases. However, when the horizontal bar is above the black line, the mortality risk increases with distance. Patient risk is indicated by colors that are formed by the cut-off values on the horizontal bar and the colors vary between red and green: green indicates low risk and red indicates high risk. Shades of brown represent an area where the horizontal bar and black lines are close.

The time intervals for patients at risk are given in the result section of the web page. The confidence intervals of cut-off values are obtained using the bootstrap method and are represented by dotted blue lines on the graph. When the "Show Confidence Intervals" option is selected, blue dotted lines appear. Mean, median, and 2.5% and 97.5% confidence interval values of 1000 bootstrap iterations for all time points are presented on the web page. If the duration of follow-up is entered in the "Follow-up Time" option, the graph can be drawn from the beginning to the

Table 4. Results of reduced multivariate Cox proportional hazards regression analysis.

Variable	B	Standard error	Wald (χ^2)	P-value	Exp (β)	Confidence interval exp (β)
Log (myoglobin) × time	–0.008	0.003	7.557	0.006	0.992	0.987–0.998
Log (myoglobin)	1.892	0.359	27.828	<0.001	6.632	3.284–13.393
Log (troponin T)	–0.172	0.216	0.632	0.427	0.842	0.551–1.287
Log (BNP)	1.204	0.270	19.856	<0.001	3.332	1.962–5.657
Log (CK-MB)	0.286	0.371	0.596	0.440	1.332	0.644–2.755

CK-MB: Creatine kinase isoenzyme MB; BNP: B-type natriuretic peptide; β: beta coefficient; Log: logarithm.

Table 5. Results of multivariate Cox proportional hazards regression analysis.

Variable	B	P-value	Exp (β)	Confidence interval exp (β)
Log (myoglobin)	1.928	<0.001	6.876	3.686–12.824
Log (BNP)	1.109	<0.001	3.032	1.866–4.928
Log (myoglobin) × time	–0.008	0.006	0.992	0.987–0.998

BNP: B-type natriuretic peptide; β: beta coefficient; Log: logarithm.

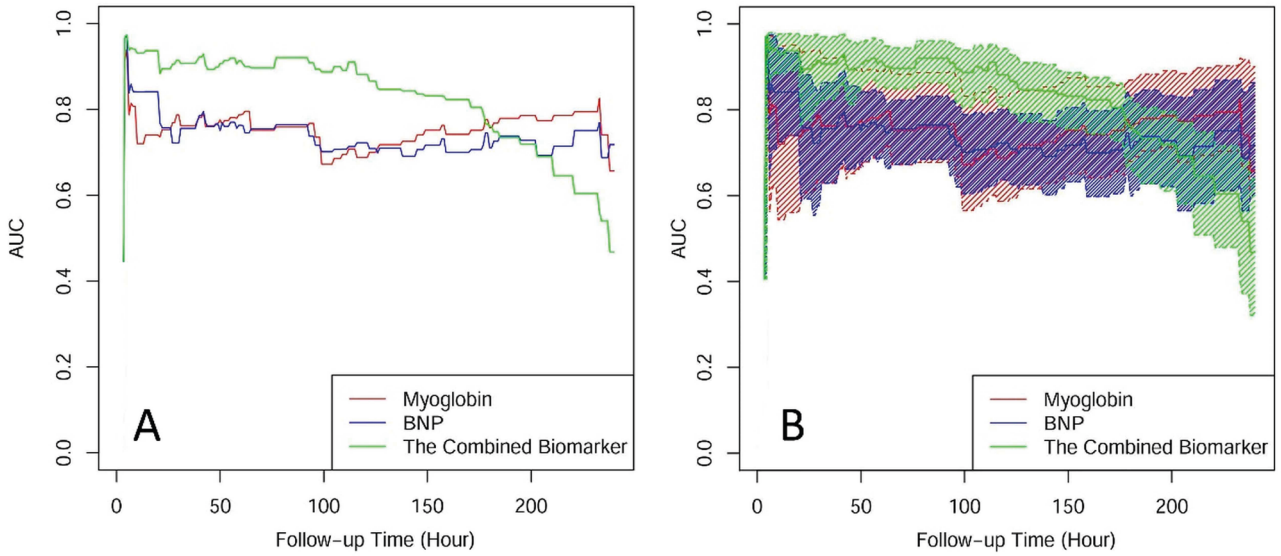

Figure 2. Areas under time-dependent ROC curves based on the combined biomarker and individual biomarkers (A) and their confidence intervals (B) for the first 10 days.

end of follow-up. The scale of the y-axis of the graph can be modified by using the "Zoom in/out" option. Sample data and results are shown in Figure 4.

Disclaimer: This method and the web tool are intended for research purposes only and may not be used commercially; the authors cannot be held liable in any way for the service provided here.

4. Discussion

Time-dependent ROC curve analysis has been performed in several investigations, including oncological and cardiovascular disease studies with long follow-up times. Our study evaluated situations in which patient follow-up times were comparatively short. Although AUC analysis is often used to evaluate the performances of BNP, myoglobin, CK-MB, and cardiac troponin T, no study on how the performances of these biomarkers change over follow-up time has been reported in the literature. In this study, our objective was to use time-dependent ROC curves to evaluate the effectiveness of cardiac biomarkers for determining the risk of death for 10 days (240 h) following admission to the ED.

Some studies have shown that BNP can be a useful biomarker for estimating mortality in acute coronary syndrome (ACS). Morrow et al. indicated that risk of death increases with rising BNP levels (13). Fazlinezhad et al. also stated that individual BNP might be an important biomarker for determining the risk of cardiac death after AMI (14). Other studies showed that BNP can be used to estimate all-cause mortality, heart failure, and myocardial infarction (15,16). Brown et al. concluded that BNP performs better when used with troponin I, CK-MB,

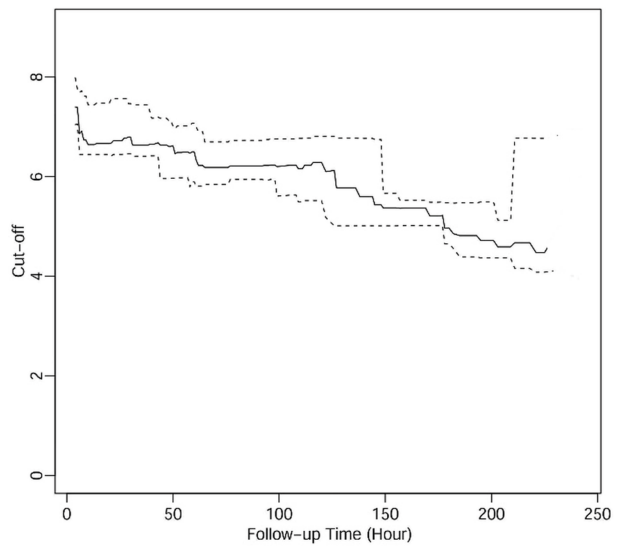

Figure 3. Optimal cut-off values for the combined biomarker during the follow-up time.

and myoglobin for the prediction of death and ACS (17). In the current study, we found that BNP is a promising predictor, either used individually or adjusted for other (myoglobin, CK-MB, and cardiac troponin T) biomarkers. The AUCs of BNP and myoglobin (used individually) were approximately 0.80, and the corresponding area for the combined biomarker was approximately 0.90 during the follow-up time.

Previous studies have indicated that myoglobin can predict death in patients with chest pain over both short

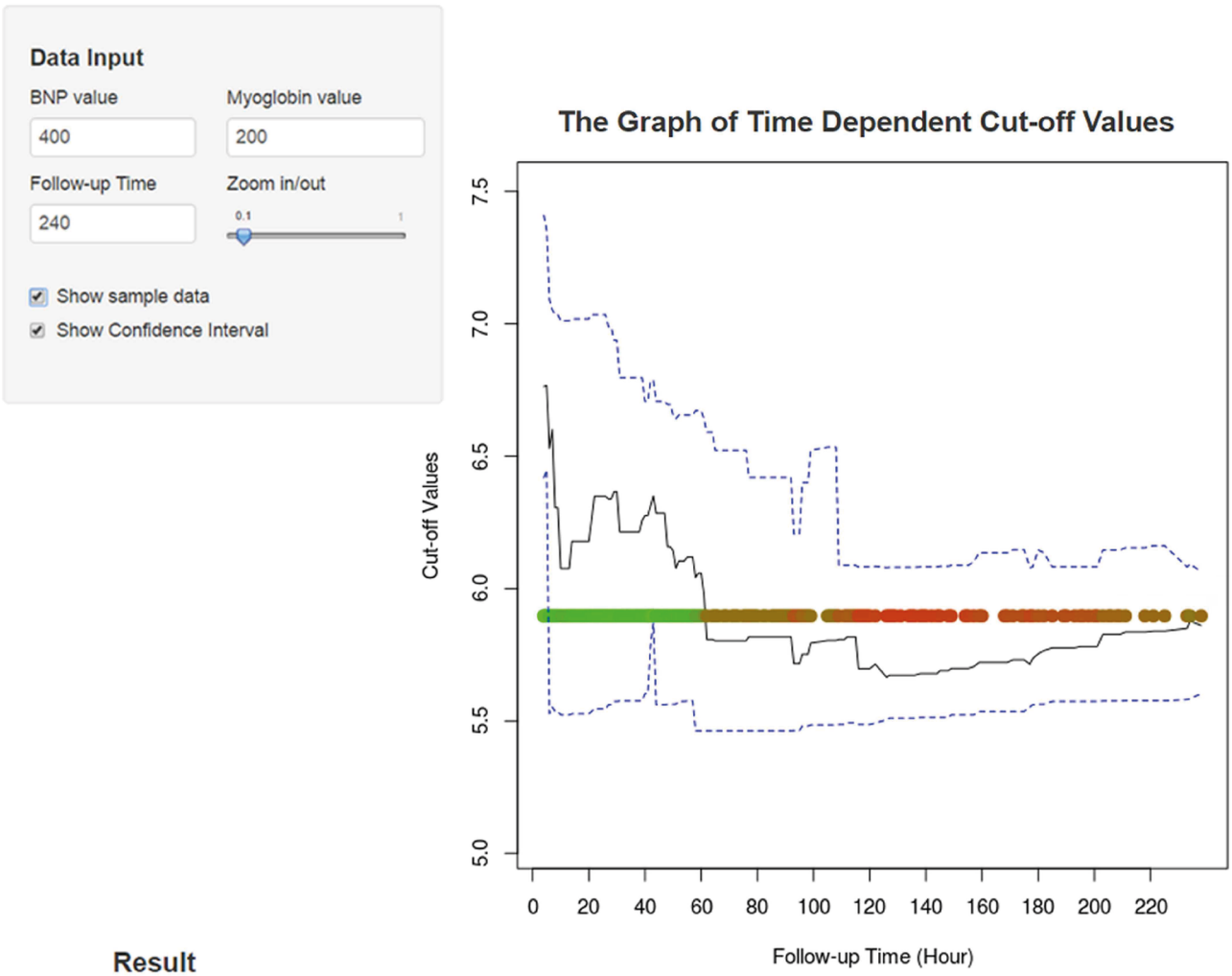

Figure 4. Output of sample data.

and long follow-up times with significant success (18,19). In the current study, we also found that myoglobin could predict cardiac death with significant success, although the combined biomarker (myoglobin and BNP) performed better.

Murty et al. stated that CK-MB should not be used by itself to estimate mortality in patients with heart failure (20), and Jaffery et al. reported similar results for patients with chest pain who were admitted to an ED (18). Newby et al. indicated that CK-MB performed better when used

in combination with myoglobin or troponin I (21). In the current study, we found that although the success of CK-MB was significant, the significance was lost after multivariate Cox proportional hazards regression analysis.

Some studies have shown inconsistencies in the ability of cardiac troponin T to estimate mortality. Whereas O'Donoghue et al. showed that cardiac troponin T could be useful after adjustment for covariates such as age, sex, and previous MI (22), other studies indicated that it should be used by itself to estimate death in patients with acute heart failure (23–25).

Recent studies have indicated that an hs-TnT assay performed better than the conventional troponin assay (26–28), and hs-TnT was significant for predicting death and/or AMI (29–34).

Jaffery et al. estimated that sex did not have a significant effect on 5-year mortality, but age did. Being over 65 years of age increased the risk of death by 2.11 times compared with being less than 65 years of age (18). In the current study, we found that sex and age had no effect on survival.

Our study has several limitations. Because the study was retrospective, some covariates, such as smoking status, body mass index, and frequency of physical activity, were absent from the hospital database, which could have affected mortality. We suggest that a larger sample size will provide more reliable results. We recommend comparing new biomarkers such as copeptin and fatty acid-binding proteins with standard biomarkers.

In summary, the data from the statistical analyses presented here indicate that myoglobin and BNP can be used individually as cardiac biomarkers. However, myoglobin or BNP should not be used as single diagnostic biomarkers, according to clinical practice. Thus, using the biomarker combination is preferred in clinics, and our analyses indicate that myoglobin and BNP perform better when combined. Our study proposes a new testing method, which is developed with a percentile confidence interval method and a web tool. The method can be used by clinicians to estimate time intervals in the risk status of newly admitted patients. Although our investigation has some limitations, we think that it is the first study to evaluate the performance of cardiac biomarkers using time-dependent ROC curve analysis in an ED.

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