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Title: Predicting Mortality, Thrombus Recurrence and Persistence In Patients With Post-Acute Myocardial Infarction Left Ventricular Thrombus

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Abstract

Introduction

Left ventricular thrombus (LVT) is a common complication of acute myocardial infarction and is associated with morbidity from embolic complications. Predicting which patients will develop death or persistent LVT despite anticoagulation may help clinicians identify high-risk patients. We developed a random forest (RF) model that predicts death or persistent LVT and evaluated its performance.

Methods

This was a single-center retrospective cohort study in an academic tertiary center. We included 244 patients with LVT in our study. Patients who did not receive anticoagulation (n=8) or had unknown (n=31) outcomes were excluded. The primary outcome was a composite outcome of death, recurrent LVT and persistent LVT. We selected a total of 31 predictors collected at the point of LVT diagnosis based on clinical relevance. We compared conventional regularized logistic regression with the RF algorithm.

Results

There were 156 patients who had resolution of LVT and 88 patients who experienced the composite outcome. The RF model achieved better performance and had an AUROC of 0.700 (95% CI 0.553-0.863) on a validation dataset. The most important predictors for the composite outcome were receiving a revascularization procedure, lower visual ejection fraction (EF), higher creatinine, global wall motion abnormality, higher prothrombin time, higher body mass index, higher activated partial thromboplastin time, older age, lower lymphocyte count and higher neutrophil count.

Conclusion

The RF model accurately identified patients with post-AMI LVT who developed the composite outcome. Further studies are needed to validate its use in clinical practice.

Introduction

Left ventricular thrombus (LVT) is a common complication of acute myocardial infarction (AMI) occurring in 3-20% of patients.[1–3] The varying incidence of post-AMI LVT is affected by several factors, including the imaging modality used, with cardiac magnetic resonance imaging having increased sensitivity compared to conventional transthoracic echocardiography.[1] Increased use of primary percutaneous coronary intervention as compared to thrombolysis may have resulted in lower incidence in LVT in recent years.[4] LVT can lead to devastating embolic complications including acute ischemic stroke and acute limb ischemia.[3,5–7]

At present, the optimum duration of anticoagulation for LVT is unclear.[8] The currently recommended treatment regimen is oral anticoagulation (OAC) for 3 to 6 months with repeat echocardiography at 6 months.[9,10] Previous studies have identified the presence of apical dyskinesis 6 weeks after myocardial infarction and absence of anticoagulation as risk factors for persistent LVT.[11,12] It remains difficult to predict which patients will have persistent LVT despite anticoagulation especially at the point of diagnosis. To the best of our knowledge, no prediction system for post-AMI LVT has been developed.

Predicting which patients have high-risk of death or persistent post-AMI LVT despite anticoagulation could potentially help clinicians identify patients who require closer follow-up and monitoring. We postulate that LVT resolution can be predicted using clinical and objective variables that can be measured at the point of the diagnosis. In this study, we developed a random forest (RF) model to predict death or persistent LVT using variables measured at the point of diagnosis of post-AMI LVT.

Methods

We performed a retrospective, single-center observational study at the National University Hospital in Singapore, a tertiary academic medical center. We included post-AMI patients who developed acute LVT formation, defined as within 7 days of the AMI event, from 1st August 2006 to 2nd September 2017. AMI was defined based on cardiac biomarker values (cardiac troponin I above 99th percentile upper reference limit) with symptoms of ischemia or electrocardiogram (ECG) changes. Ethics approval for the study was obtained from the local institutional review board (2013/00442). We excluded patients with a known history of LVT thrombus or prior use of anticoagulation.

Patients with AMI in our center typically receive a transthoracic echocardiogram (TTE) examination by a trained echo-sonographer within 72 hours of diagnosis. LVT was diagnosed by the presence of an echo-dense mass present in the left ventricular (LV) cavity in at least two views while a protruding thrombus was defined as the project of thrombus into the LV cavity[13,14]. The echocardiograms were interpreted by an independent cardiologist in accordance with published guidelines[15]. Contrast TTE or cardiac magnetic resonance imaging (MRI) was performed to confirm the diagnosis of LVT if the initial TTE was inconclusive. Initial repeat echocardiograms were performed at between 3 to 6 months after the diagnosis of LVT, while subsequent echocardiograms were performed based on the managing clinician's discretion.

We collected demographic and clinical data for each patient including comorbidities such as diabetes mellitus or prediabetes, chronic kidney disease, venous thromboembolism, stroke or transient ischemic attack, and congestive cardiac failure. We also recorded the most recent laboratory values including complete blood count, creatinine, liver function tests, international normalized ratio, prothrombin time and activated partial thromboplastin time. Other variables collected include the number of vessels with coronary artery disease, revascularization therapy (including both percutaneous coronary intervention and coronary artery bypass graft), antiplatelet and anticoagulation therapy. A total of 31 variables were included in the model.

Our primary endpoint was defined as a composite of mortality, recurrence of LVT and persistent LVT. Recurrence of LVT was defined as the presence of LVT on the final echocardiogram following an initial negative repeat echocardiogram. Persistent LVT was defined as the presence of LVT on both repeat and final echocardiograms. These three outcomes were combined as they represent an adverse clinical course following a diagnosis of LVT.

Descriptive statistics were computed using the TableOne python packages.[16] Statistical testing for continuous variables was performed using two-sample t-tests. Statistical testing for categorical variables was performed using the fisher's exact test or chi-square tests depending on sample size.

Missing data for predictor variables were handled by univariate imputation without stratification of the most frequent category for categorical variables and sample median for continuous variables. An indicator variable was added to indicate if a particular data point is missing prior to the imputation process. Categorical variables were one-hot encoded with the first category dropped. The data were randomly split into a training set (75% of the sample, n=183) and validation set (25% of the sample, n=61). Training and validation sets are terminology used in machine learning to denote the data used to develop the model and data used to evaluate the performance of the model respectively.

We experimented using regularized logistic regression,[17–19] and compared it to the RF algorithm.[20] RF is a machine learning method that fits a series of weak tree-based learners to randomly sample splits of the original data. The method has been shown to be highly effective in clinical prediction tasks, where data is often complex and messy. We performed model selection using the mean area under the receiver operating curve (AUROC) obtained by repeated cross-validation[21] using a randomized search algorithm.[22] Cross-validation was used to estimate the generalizability of a model to an independent data set by partitioning the training data into a training set and validation set, fitting the model on the training set and estimating the performance on the validation set. This procedure is repeated many times and the performance on the validation sets are averaged to select for the model with the greatest external validity. The best model was then evaluated on the testing set where 95% confidence intervals were computed using nonparametric bootstrap resampling. The reliability of the model was then evaluated using a calibration plot. We used SHapley Additive exPlanations (SHAP),[23] a game-theoretic approach to identify the importance of risk factors in a model. The use of SHAP allows for human interpretable presentations of clinical features driving the prediction for individual patients. The full source code used to reproduce the analysis can be found at: https://github.com/wesleyyeung/lvtres/

Results

There were 289 patients who had post-AMI LVT during the study period. We excluded 14 patients who did not receive anticoagulation and 31 patients whom the outcome was unknown. There were 244 patients with post-AMI LVT included in our study (Figure 1). The median follow-up duration was 807 days (IQR: 265 -1746) from diagnosis of LVT. The median time to the repeat echocardiogram was 5.0 months (IQR: 3.0-7.0). There were 12 patients who received cardiac MRI for their follow-up scan. Most patients in the cohort received warfarin as their primary anticoagulation therapy (98.0%, n=239) compared to heparin (1.2%, n=3) and novel oral anticoagulants (0.8%, n=2). There were 88 patients who had the composite endpoint of death (n=53), persistent (n=21), or recurrent LVT (n=14) at the end of the observation period. Patient characteristics of the top 10 most important variables are presented in Table 1. A full list of patient characteristics used in the prediction model is included in the Data Supplement as Table S1.

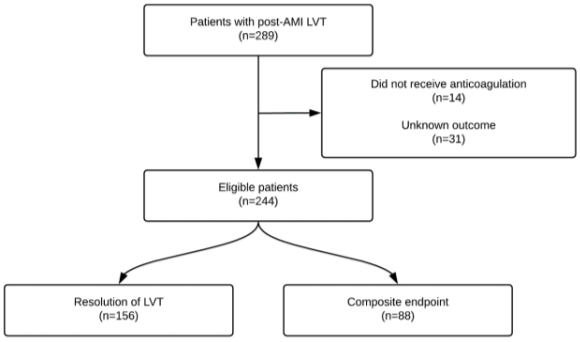

Figure 1. Cohort Flow Diagram

The patients were approximately in their 6th decade of life. There was a male predominance (n=212, 86.9%) in both groups. Most patients in the cohort were of Chinese ethnicity (n=127, 52.0%). Past medical history of stroke or transient ischemic attack (22.7%, n=20 vs 9.0%, n=17; p=0.022) and global wall motion abnormality (67.0%, n=59 vs 37.2%, n=58; p < 0.001) was more common in patients with the composite endpoint. Patients who developed the composite endpoint had higher mean neutrophil counts (9.9x10^9/L vs 8.6x10^9/L; p=0.036), prothrombin time (14.7s vs 13.6s; p=0.006), international normalization ratio (1.2 vs 1.1; p=0.009), creatinine (136mmol/L vs 96.5mmol/L; p=0.013) and left ventricular internal diameter at end-systole (LVIDs) (45.0mm vs 42.1mm; p=0.036). Fewer patients in the composite end point group had ST-segment elevation myocardial infarction (STEMI) (63.6%, n=56 vs 80.1%, n=125; p=0.007) and fewer patients received a revascularization procedure (48.9%, n=43 vs 84.0%, n=131; p<0.001). Patients with the composite endpoint had lower mean weight (66.0kg vs 70.4kg; p=0.045), lymphocyte count (2.0x10^9/L vs 2.5x10^9/L; p=0.025) and visual ejection fraction (EF) (29.3% vs 35.4%; p<0.001).

The RF model obtained a better training set cross-validation AUROC of 0.712 (Table 2). It had an AUROC of 0.700 (95% CI 0.553-0.863) on the held-out test set (Figure 2a). A model calibration curve showed good calibration across predicted probabilities (Figure 2d). The model had a sensitivity of 0.364 (95% CI 0.167-0.571), specificity: 0.872 (95% CI 0.757-0.972) and a positive predictive value: 0.615 (95% CI 0.333-0.889).

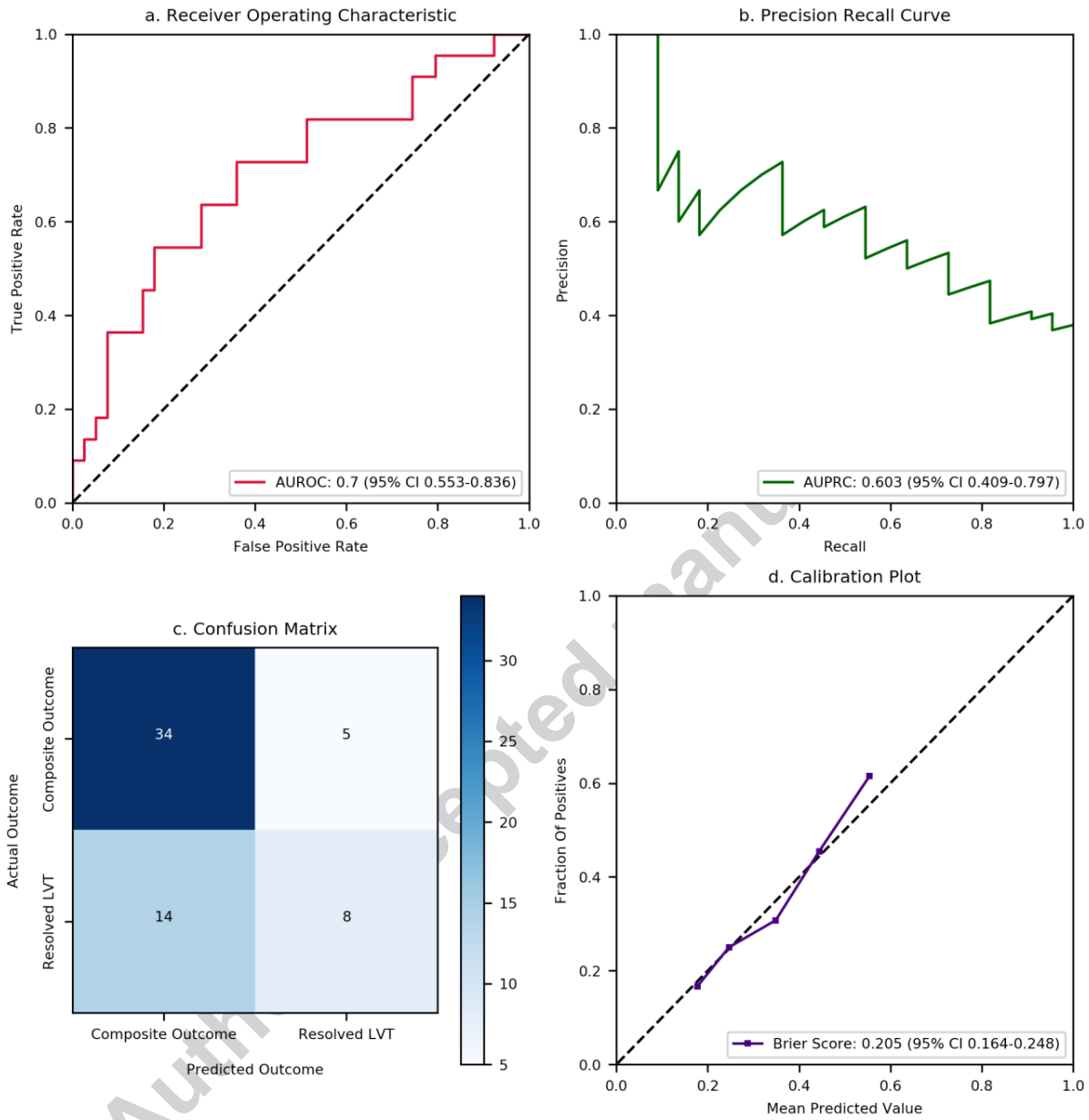

Figure 2. Model Performance. Figure 2a shows the receiver operating characteristic of the final model (red line) on the held-out test set compared to a baseline random classifier (black dotted line). Figure 2b shows the precision recall curve of the final model on the held-out test set. Figure 2c is a confusion matrix which cross-tabulates the predicted outcome versus the actual outcome. Figure 2d shows the calibration curve of the final model (purple line) versus a theoretical classifier with perfect calibration (dotted line); the closer the calibration curve is to the diagonal line, the better the calibration of the model.

We calculated feature importance on the test data set using SHAP values with the RF model (Figure 3). The top 10 variables ranked in order by relative importance were revascularization procedure, lower visual ejection fraction (EF), higher creatinine, global wall motion abnormality, higher prothrombin time, higher body mass index, higher activated partial thromboplastin time, older age, lower lymphocyte count and higher neutrophil count.

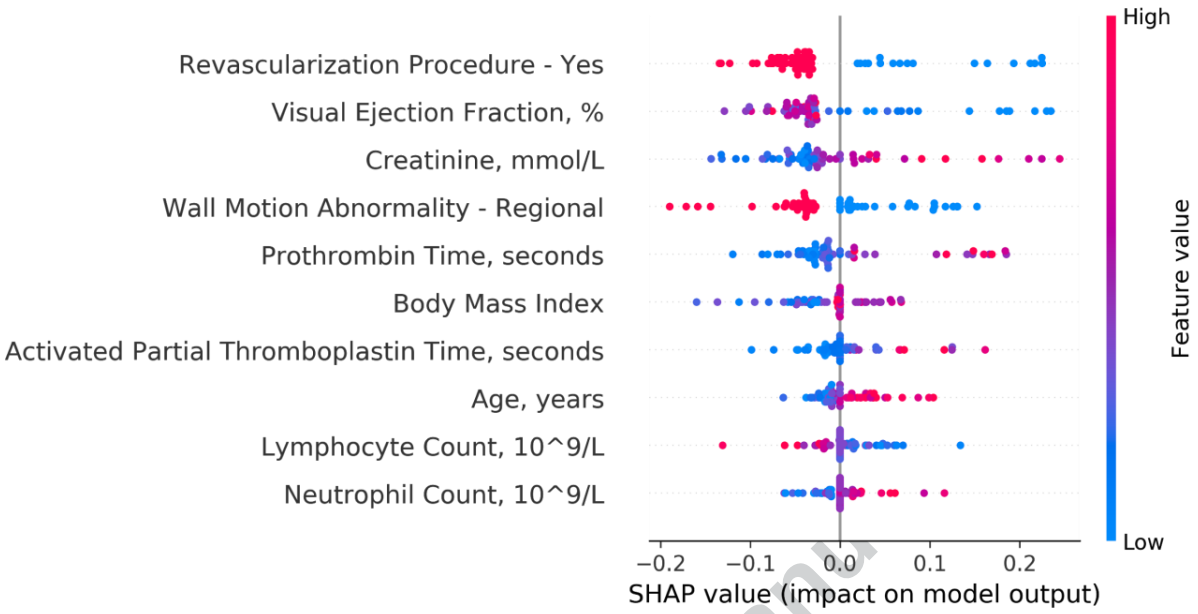

Figure 3. SHAP values of individual features ranked by variable importance. Individual samples are represented as dots in a scatter plot. For categorical variables, the presence of the feature would lead to red color while the absence of the feature would lead to blue color. For numeric variables, higher values have a color closer to red while lower values have a color closer to blue. Features with a stronger contribution to a prediction of the composite endpoint have a higher SHAP value. For example, higher values of creatinine (seen as colors ranging from purple to red) were associated with a positive SHAP value which indicates that higher creatinine is associated with a prediction of the composite endpoint.

Discussion

Our model was able to identify patients with post-AMI LVT who developed the composite endpoint with good discrimination. using a combination of clinical, laboratory and echocardiographic measurements that can be obtained at the point of diagnosis. The AUC of our model was 0.700 (95% CI 0.553-0.863) and it was well-calibrated. We found that receiving a revascularization procedure, lower visual ejection fraction (EF), higher creatinine, global wall motion abnormality, higher prothrombin time, higher body mass index, higher activated partial thromboplastin time, older age, lower lymphocyte count and higher neutrophil count were the most important variables in predicting the composite endpoint.

The mechanism of LVT formation is still unclear but has been postulated to be due to a combination of endothelial injury, coagulopathy as well as stasis from mechanical dysfunction of the ventricle.[2] There is little existing literature investigating the mechanisms for LVT resolution. Left ventricular ejection fraction is a marker of the mechanical function of the heart and might contribute to stasis and persistence and recurrence of thrombus and is also a strong predictor of mortality.[24–26] Therapeutic interventions such as revascularization therapy have well-documented survival benefits in acute coronary syndrome and may also improve the mechanical function of the heart and are the cornerstone of current ACS treatment.[27,28]

Chronic kidney disease is associated with increased risk of venous thromboembolism and serum creatinine is a marker of severity of renal dysfunction.[29] Coagulation markers such as PT and aPTT were also important predictors of the composite outcome in this cohort. We postulate that coagulopathy might predispose patients to both increased mortality and possibly represent a reduction in clotting factors production that might lead to a hypercoagulable state. Unsurprisingly, older age was associated with the composite outcome. Lower leukocyte count and higher neutrophil count were predictive of the composite outcome in this cohort which may be indicative of greater inflammatory response.[30]

The relationship between BMI and the composite outcome is less straightforward. In the univariate analysis, the composite outcome group had a lower mean BMI, although this did not reach statistical significance. However, upon inspecting the impact of BMI on model prediction, there appears to be a non-linear relationship between BMI and the composite outcome (Figure S1). Values of BMI between the mean and up to one standard deviation above the mean appeared to contribute positively to a prediction of the composite outcome whereas BMI higher than one standard deviation above the mean did not contribute to the prediction. Values of BMI below the cohort mean had a negative contribution to the prediction of the composite outcome. While existence of an "obesity paradox" in post-AMI mortality has been reported in some studies,[31] patients at lower BMI and very higher BMI (above 40) had increased hazards of mortality whereas the relationship between BMI and the composite outcome in our cohort had the opposite effect. This relationship deserves further investigation in future studies.

From a clinical perspective, prediction of the composite outcome in patients with post-AMI LVT is important as it allows clinicians to identify patients who may need to be monitored more carefully with closer surveillance or may potentially benefit from alternative treatment strategies. After appropriate validation studies and calibration on the desired target population, the model can be implemented into electronic medical records systems and clinical decision support systems to provide clinicians with the estimated probability of post-AMI LVT resolution. This individualized probability estimate could potentially assist physicians plan for follow-monitoring and improve the collaborative patient-physician decision making. Other studies investigating the use of machine learning in cardiology practice have shown promising results in a wide range of applications from studies predicting mortality of patients undergoing cardiac computed tomography angiography[32] to automated echocardiographic assessment of mitral regurgitation.[33]

As our model only utilizes measurements at the point of diagnosis, it does not require serial measurements over time and as such improves its ease of use. It also does not require special biomarkers or imaging data

that is not already routinely used in the management of acute coronary syndrome. This study has several important limitations. The sample size used for model training is small by modern machine learning standards. However, as post-AMI LVT is a relatively rare condition, this data set remains one of the largest in the available literature. Also, we used robust machine learning methodology to reduce the risk of bias and information leakage, these include model selection using repeated cross-validation and performance estimation on a held-out test set which was not used for model development. Although RF is a black box technique, the use of SHAP allowed us to infer the relationship between the clinical variables and the final prediction generated by the model. As the dataset used was collected in a single center, our model requires external validation in other populations. The use of real-world data and lack of protocolized follow-up means that we could not fix the times at which repeat imaging tests were performed, although this could be a focus of future studies. The lack of protocolized follow-up also exposes our findings to length time bias, which is a limitation of this study. Another limitation is the small number of patients who received cardiac MRI to confirm resolution of LVT. While cardiac MRI has superior sensitivity and specificity in detecting LVT, there is limited use in our center due to cost and availability and was reserved for patients who had inconclusive transthoracic echocardiograms. Lastly, this study did not address whether resolution of LVT led to any change in anticoagulation practice.

Clinical prediction models are useful only if they can positively impact clinical practice and patient outcomes. Apart from validation studies described above, prospective evaluation in a clinical setting is required to measure the impact the model has on clinical decision making by clinicians, and whether such changes in practice translate to actual patient outcomes such as thrombus recurrence, embolic events and mortality. The source code used to develop the model is provided in an open access code repository described above to facilitate replication of this experiment in other patient populations and prospective evaluation in clinical settings.

Conclusion

The developed model incorporates simple and objective variables including patient demographics, laboratory values, past medical history and echocardiography measurements to estimate the likelihood of post-AMI LVT resolution and can be used to individualize the risk assessment of patients with LVT. Further clinical studies are needed to determine its performance in real-world clinical practice.

Contributors

WY and CHS conceived of the presented idea. WY developed the theory and performed the computations. TP provided technical assistance during the analysis. MC, JL, BT and LY supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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Conflicts of interest

We declare no conflicts of interest.

Table 1. Patient Characteristics Of Top Ten Variables Ranked By Importance

Rank	Measurement	Category	Count	No Composite Outcome (n=156)	Composite Outcome (n=88)	p-value
1	Revascularization Procedure	No	244	25 (16.0)	45 (51.1)	<0.001
		Yes		131 (84.0)	43 (48.9)	
2	Visual Ejection Fraction, %		244	35.4 (9.7)	29.3 (10.8)	<0.001
3	Creatinine, mmol/L		239	96.5 (68.9)	136.0 (135.9)	0.013
4	Wall Motion Abnormality	Regional	244	98 (62.8)	29 (33.0)	<0.001
		Global		58 (37.2)	59 (67.0)	
5	Prothrombin Time, seconds		227	13.6 (1.7)	14.7 (3.1)	0.006
6	Body Mass Index		193	26.2 (6.0)	25.0 (4.4)	0.121
7	Activated Partial Thromboplastin Time, seconds		200	33.7 (20.4)	38.7 (22.0)	0.129
8	Age, years		244	58.4 (12.1)	61.5 (14.3)	0.090
9	Lymphocyte Count, 10^9/L		185	2.5 (1.3)	2.0 (1.3)	0.025

10	Neutrophil Count, 10^9/L		183	8.6 (3.7)	9.9 (4.3)	0.036

Table 2. Comparison Of Models

Rank	Model	Cross-validation Area Under Receiver Operator Curve
1	Random Forest	0.729
2	Regularized Logistic Regression	0.723

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