An Interpretable Analysis of Inflammation Biomarkers to Improve Cardiovascular Risk Evaluation

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Abstract

Cardiovascular diseases (CVDs) are the primary global cause of death, imposing substantial clinical, and economic burdens. Accurate risk stratification tools are crucial for guiding clinical decisions and preventive care. In this study, we've employed Machine Learning techniques to integrate inflammation biomarkers with well-established Acute Coronary Syndrome (ACS) risk factors, to enhance the Global Registry of Acute Coronary Events (GRACE) stratification tool. The developed approach combines clinical knowledge with data-driven techniques, ensuring interpretability and personalization without compromising performance. To validate our approach, we collaborated with the Cardiology Unit of Coimbra Hospital and University Centre (CHUC) and analyzed a dataset of 1544 ACS patients. Our approach improved ACS Risk Scores by 5% when compared to the widely used GRACE, offering clinicians a comprehensive and personalized tool to make informed decisions and provide better patient care.

1 Introduction

CVDs are a major global health concern, responsible for 32% of global deaths in 2019 [1]. Despite some governmental efforts to reduce mortality, non-fatal Acute Coronary Syndrome (ACS) remains prevalent, leading to substantial economic costs. The most used model in Portugal is the GRACE risk score, which uses a limited range of variables to indicate short-term prognosis. Furthermore, some recent research suggests that inflammatory processes in the human body may be associated with adverse cardiac occurrences [2]. Considering that, our study explores the potential of inflammation biomarkers combined with the GRACE known risk factors. By using Machine Learning (ML) techniques, we combine clinical evidence with data, ensuring interpretability and personalization without compromising accuracy. The main goal of this study is to develop a new risk stratification model with improved efficacy.

2 Methodology

Our study aims to achieve two goals: i) incorporate Inflammation Biomarkers into the accepted models in order to improve mortality prediction accuracy, and ii) develop a system prioritizing personalization and interpretability in Cardiovascular Risk assessment without compromising performance. Regarding the former, three models were implemented and a statistical analysis comparing the model's performance was conducted: i) GRACE Risk Score, ii) ML classifier with GRACE features, and iii) ML classifier with GRACE risk factors and selected inflammation biomarkers (C Reactive Protein, Leukocyte Count, Albumin serum). Moreover, the GRACE Risk Score was employed as a reliable benchmark to evaluate our system's ability to measure a patient's risk accurately.

2.1. GRACE Risk Score

The GRACE Risk Score is a scoring system built with a prospective observational registry as a basis. It enrolled patients with all diagnoses in the entire spectrum of ACS. Consequently, it aimed to analyze an unbiased population from varied geographical areas.

This model comprises the well-established risk factors values of each patient and calculates a final risk score (2-383) by summing the scores from each variable. Moreover, the patients were classified into three groups based on their final calculation: i) Low risk: patients diagnosed with no ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) with a score ≤ 108.

For ST-elevation myocardial infarction (STEMI) diagnoses, the score should be ≤ 125; ii) Intermediate risk: patients diagnosed with NSTEMI and UA with a final score ranging from 109 to 140. For STEMI diagnoses, the score ranges from 126 to 154, and iii) High-risk: patients diagnosed with NSTEMI and UA with a GRACE score of ≥ 141, and for STEMI diagnosis, a score of ≥ 155.

2.2. Machine Learning Model with GRACE Risk Factors

The first step in our approach was to employ an ML classifier to predict cardiovascular mortality, using just the established risk factors from the GRACE Risk Score as inputs. The classifier employs a supervised approach with patient data *(X)* and predicts mortality outcomes *(t_i)* in a binary classification *(survival or death).* High-risk patients are expected to die, while low and medium-risk patients are associated with survival.

2.3. Machine Learning Model with GRACE Risk Factors and Inflammation Biomarkers

In the context of ACS development, inflammation is a recognized risk factor due to its presence in atherosclerotic plaques [3]. Its role in sudden coronary instability is acknowledged, but its impact on ACS outcomes remains uncertain [4]. Notably, C-Reactive Protein (CRP), Albumin Serum (AS), and White Blood Cell (WBC) count are robust biomarkers indicating inflammation. During acute infection responses, these biomarkers can display significant fluctuations in the bloodstream. For this study, the clinical partner selected and validated these biomarkers for analysis. To analyze their impact, we employed a classifier identical to 2.2 but also considered the inflammation biomarkers as input variables.

2.4. Interpretable and Personalized Approach

In order to create a valuable risk score tool for physicians, we thoroughly studied the GRACE model and its risk factors. While ML models can perform well, they lack interpretability and personalization, essential for medical decision-support systems [5]. Consequently, our three-phase strategy begins with the creation of a set of interpretable clinical knowledge-based rules. Secondly, we employ an ML-based classifier to identify the most suitable rule subset for each patient and, finally, we combine the chosen rules to estimate the cardiovascular mortality risk for individual patients, ensuring a more effective and personalized approach.

Rule Definition. The first phase in our model development was the construction of several interpretable rules following clinical guidelines, relying on specific risk factors' binary associations. These rules were created using two strategies: knowledge-driven, by incorporating clinical expertise and literature, and data-driven, by using available data to generate rules.

Virtual Patients. A data-driven method used virtual patients created by clustering similar symptoms and characteristics, establishing two centroids for each risk factor (including GRACE and inflammation biomarkers). These centroids represented two classes: one for surviving patients and another for deceased patients, calculated as the average of the respective virtual patient groups. The core of the clustering methodology (Fig. 1) involved combining two risk factors. In this case, patient mortality risk was classified as binary class 1, as their distance to the death centroid *(d_1)* was smaller than to the survival centroid *(d_0)*.

$$d_n = \frac{d_0}{d_1 + d_0} \quad (1)$$

A normalized distance (Eq. 1) was used to quantify dissimilarity between survivors *(dn = 0)* and deceased *(dn = 1)* virtual patients due to diverse scalarization in ACS risk factors.

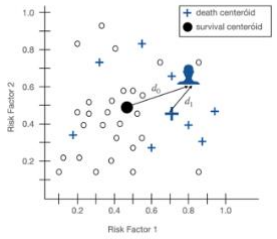

Figure 1: Clustering example with the combination of 2 Risk Factors.

Optimal threshold. The patient's categorization as survival or death is determined by a threshold value *(L)*. Typically, L is set to the mean distance between the two centroids *(L=0.5)*. However, optimizing the threshold for each risk factor can improve accuracy while also complying with clinical guidelines. To validate our approach, we used the Geometric Mean (Eq. 2) performance metric, comparing our calculated risk vector ($\hat{t}$) with the transposed target-risk vector *(t')*. The number of survivals (T_0) and deaths (T_1) is obtained directly from the target.

$$GM = \sqrt{\frac{1}{T_1} \cdot (t' \cdot \hat{t}) \cdot \frac{1}{T_0} \cdot ((1 - t') \cdot (1 - \hat{t}))} \quad (2)$$

In summary, we can describe the maximization of each risk factor rule as the following (Eq. 3). The estimated mortality probability for patient *i* using rule j is denoted as t_{ij}. Here, d_{ni} refers to the normalized distance of the *ith* risk factor *(i = 1, ..., M)*, and Li represents the corresponding threshold.

$$if\ dn \geq L\ then\ t\hat{} = 1\ i = 1, \ldots, M \quad (3)$$

Rule selection process. The second step selects patient-specific rules using an ML classifier. Only relevant rules are employed, estimating their accuracy beyond mortality data. The target matrix r_{ik} indicates the rule *k's* accuracy for patient *i*, with 1 denoting relevance and 0 indicating the contrary.

Patient Mortality Prediction. This study proposes a method to predict patient mortality by utilizing a subset of rules *(N)* obtained earlier.

The method employs Eq. 4, where a patient's mortality score is determined by the ratio of accepted rules indicating mortality probability $(\hat{r}_{ik} = 1 \wedge \hat{t}_{ik} = 1)$ to the total accepted rules *(N)*. This score ($\hat{t}_i$) correlates with the final prognosis in Eq. 5.

$$\hat{t}_i = \frac{1}{N} \sum_{j=1}^{N} \hat{r}_{ij} \cdot \hat{t}_{ij} \quad (4)$$

$$\hat{t}_i = \begin{Bmatrix} 1\ (death)\ if\ \hat{t}_i \geq 0.5 \\ 0\ (death)\ if\ \hat{t}_i < 0.5 \end{Bmatrix} \quad (5)$$

3 Results

3.1. Dataset

The dataset (Table 1) includes records of 1544 patients admitted to Hospital dos Covões Cardiology ICU from 2009 to 2016, covering various ACS diagnoses (STEMI, NSTEMI, and UA). It also includes information on all-cause death/survival and date of death.

	Survival Mean (n=1359)	Survival IQR Range	Death Mean (n=1359)	Death IQR Range
Age	66.87	57-77	77.49	74-83
Systolic Pressure*	135.05	119.5-150	123.07	104.25-140.75
Cardiac frequency*	75.73	64–85	84.02	70–90
Troponin	19.47	0.11-9.61	29.58	0.80-24.77
Maximum Creatinine	125.71	78 –111.6	241.34	112.35-310.35
STEMI*	0.36	-	0.46	-
Maximum Killip	1.35	-	2.53	-
C Reactive Protein*	2.28	0.5-2.6	5.6	0.7-6.77
Leukocyte count *	10186	7180-11450	11576.8	8100-13250
Albumin	36.11	34-38.2	33.36	31-35.95

Table 1: Dataset.

3.2. Evaluation of Inflammation Biomarkers Effect

GRACE Risk Score. The study assesses inflammation markers' impact on the GRACE score in predicting survival after ACS within six months. Sensitivity (SE), specificity (SP), geometric mean (GM), and area under the curve (AUC) values are 0.61, 0.63, 0.62, and 0.63, respectively, aligning with conventional GRACE approach results (AUC: 60%-70%).

ML classifier: GRACE Risk Factors. The chosen model was a random forest, with optimal settings of 200 estimators, 2 minimum sample leaves, and 2 minimum samples split. The resulting model had a very acceptable performance with SE, SP, GM, and AUC values of 0.75, 0.85, 0.80, and 0.88, respectively. The random forest's non-linear approximation abilities led to higher accuracy compared to the original GRACE score.

ML classifier: GRACE Risk Factors and Inflammation Biomarkers. A similar random forest classifier was employed, but three variables were added (CRP, AS, WBC), achieving SE: 0.83, SP: 0.84, GM: 0.83, and AUC: 0.91.

Estimation of the impact of inflammation markers. Comparing AUC values, incorporating inflammation markers with GRACE risk scores improves results by approximately 3% (from 88% to 91%).

3.3. Interpretable and Personalized Approach

A random forest model was chosen for two scenarios: using only GRACE risk scores and incorporating inflammation biomarkers. The model's hyperparameters were fine-tuned through grid search. Performance metrics are shown in Table 2 during the training and testing phases.

Approach		SE	SP	GM	AUC
GRACE ML	Training	0.633	0.81	0.716	0.721
	Testing	0.846	0.644	0.720	0.729
GRACE ML + Inflammation	Training	0.808	0.752	0.780	0.780
	Testing	0.763	0.778	0.770	0.770

Table 2: Performance metrics.

4 Conclusions

Inflammation biomarkers' impact on Acute Coronary Syndrome outcomes is a growing research interest. Identifying strong risk factors is crucial for accurate cardiovascular disease diagnosis and prognosis. This study developed a hybrid approach, combining machine learning and clinical knowledge to integrate inflammation biomarkers into existing risk scores. Results indicate that biomarkers (Albumin, C-Reactive Protein, and Leukocyte Count) influence ACS outcomes, potentially improving the GRACE risk score's assessment. The approach offers interpretability and personalization, fostering trust in explainable AI. Further research with additional datasets could enhance its potential.

References

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