The CardioRisk project: Improvement of cardiovascular risk assessment

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1. Introduction

Cardiovascular diseases are the world's primary cause of death, responsible for 17.1 million deaths per year. According to the World Health Organization (WHO) estimates, the number of people who die from CVD will increase to reach 23.3 million by 2030, remaining the single leading cause of death [18].

Risk assessment, i.e. the evaluation of the probability of occurrence of an event given the patient's past and current exposure to risk factors, is critical to improve diagnosis and prognosis. In fact, clinical guidelines recommend the use of cardiovascular risk assessment tools[1] (risk scores) to predict the risk of a cardiovascular disease (CVD) event; e.g., death [13]. Thus, it is clinically recognized that the research and development of practical and accurate CV risk assessment tools/models are of fundamental importance.

CV risk assessment tools are usually developed on the basis of population samples monitoring over a long period of time. Two categories of CV risk tools can be derived: long-term (years) and short-term (months) tools. Long term tools are widely available,

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[1] In order to clarify, risk assessment models that have been statistically validated and are availablein literature are going to be designated through this work as risk assessment tools.

while only a few studies have been conducted for short-term tools [10].

FRAMINGHAM [7], SCORE [5], QRISK [6] projects can be identified as examples of long-term risk assessment tools. GRACE [15], TIMI [1] and PURSUIT [4] should be mentioned among the short-term risk assessment tools. These short-term tools have been specifically developed to address CAD patients, specifically focusing on MI condition (the CV condition under study).

Although useful, they present some important weaknesses as they: (i) may present some lack of performance; (ii) ignore the information provided by other risk assessment tools that were previously developed; (iii) consider (each individual tool) a limited number of risk factors; (iv) have difficulty in coping with missing risk factors; (v) do not allow the incorporation of additional clinical knowledge; (vi) do not assure the clinical interpretability of the respective parameters; (vii) impose a selection of a standard tool to be applied in the clinical practice.

To reduce the aforementioned limitations, some approaches have been proposed, including combination strategies [14,17]. Recently, as a result of the HeartCycle project, a Bayesian strategy for the fusion of several risk tools has been developed [11]. Using this approach a higher number of risk factors can be simultaneously considered and missing information can be dealt with (a characteristic of Bayes' probability theory).

In this context, the improvement of CV risk assessment is the main scientific challenge of this project (CardioRisk project). To achieve this goal, three different research lines have been followed: (i) fusion methodologies extracting information from different sources (individual models, clinical evidence); (ii) grouping of patients to achieve a more personalized prognosis; (iii) biosignals processing techniques (e.g., ECG; HRV) to extract significant information that can contribute to improve the CV risk assessment.

The CardioRisk project also comprises an observational study focused on patients admitted in the intensive cardiac care unit (ICCU) with a first episode of acute MI, managed according to the current European guidelines. Three exclusion criteria are considered: artificial pacing, previous heart failure and valvular heart disease. The primary endpoints are death or a new hospitalization due to heart failure, 30 days after the event.

An integrated clinical platform, including the developed algorithms/models, has been implemented to support this observational study that is being carried out under real conditions in Leiria Hospital Centre. This platform considers as inputs historic data, such as demographics, biomarkers and clinical exams that can be obtained from the hospital information system. The ECG signal is acquired using a Holter device (consisting of 12 leads, during 24 h).

The paper is organized as follows: Section 2 describes the CardioRisk project. Section 3 presents the methodologies as well as some preliminary results. Section 4 details the developed software while Section 5 depicts the validation strategy. Some final considerations are drawn in Section 6.

2. CardioRisk project

2.1. CardioRisk approach

As mentioned, the CardioRisk project addresses the coronary artery disease (CAD), namely, the management of myocardial infarction (MI) patients.

The scientific goals of the project can be defined as the development of personalized clinical models for cardiovascular (CV) risk assessment of acute events (e.g., death and new hospitalization), in order to stratify patients according to their care needs. Here, three main issues can be identified: (i) Combination of available CVD risk assessment tools; (ii) grouping of patients; (iii) incorporation of parameters resulting from heart rate variability (HRV) analysis.

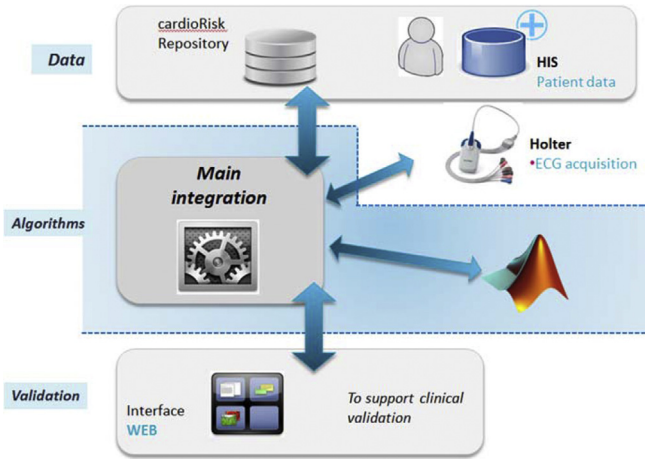

Fig. 1. CardioRisk architecture.

From the technical perspective, the development of a clinical platform integrating the patient data (Hospital Information System), the ECG acquisition (Holter device) as well as the developed algorithms is the main achievement. Fig. 1 presents the CardioRisk architecture.

The integrated clinical application comprises three main levels: (i) data acquisition; (ii) data analysis algorithms and (iii) physician interface and clinical validation.

The first level involves the development of an application to collect the necessary information, namely, the relevant information from HIS and ECG collected by means of the Holter devices.

The second is devoted to the development of models for short-term risk assessment, incorporating the developed algorithms for fusion of tools, personalization of patients, and HRV analysis. This module uses as input the data from the first module and generates the required outcomes to be used by module 3. This third module presents the algorithms' results to the physicians and supports all the necessary functionalities for the clinical validation.

2.2. Organization

The CardioRisk consortium involves three partners from two different countries (Portugal, Italy). The team is composed of two research institutions, the University of Coimbra and the Politecnico di Milano, and a public hospital, Leiria Hospital Centre.

The project started in July 2013 and has a total duration of 24 months (until June 2015). It is structured in 5 main tasks: (i) Clinical application (ECG acquisition; repository of data; integration of applications); (ii) Fusion of risk assessment tools and personalization methods (Combination models; Grouping strategies); (iii) HRV analysis algorithms (new parameters for CV risk assessment); (iv) Clinical assessment (validation in hospital, 100 patients); (v) Project Management and dissemination.

3. Methodologies

3.1. Fusion of individual models

Fig. 2 presents the main concept of this approach: combine available information/merge information from different sources.

A Common representation of individual tools

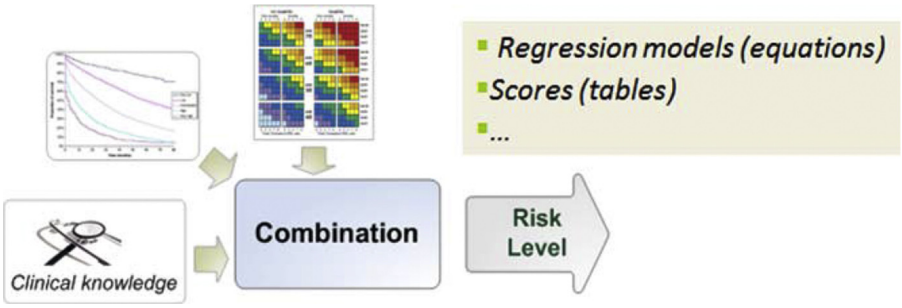

Fig. 2. Fusion of individual models.

The first step is to create a common representation (representation based on the same classifier) such that it can ease the combination of individual risk tools that are diversely represented.

The naïve Bayes was the selected classifier. In fact, the naïve Bayes has a competitive performance with the remaining classifiers, is simple and can deal with missing risk factors. [8].

If $X = [X_1 \ldots X_p]$ is a set of observations (risk factors: e.g., clinical examination; demographic data, etc), C is the hypothesis (e.g., risk level is "High"), then the inference mechanism is given by Eq. (1):

$$P(C|X) = P(C|X_1, \ldots, X_p) = \alpha P(C) \prod_{i=1}^{p} P(X_i|C) \tag{1}$$

The term $P(C|X)$ is the probability that the hypothesis is correct after observations have occurred (e.g., the probability that risk is "High" given the results of a clinical examination). $P(C)$ is the probability that the hypothesis is correct before seeing any observation (the prevalence of the risk level), α is a normalization constant. $P(X_i|C)$ is a likelihood expressing the probability of the observation X_i being made if the hypothesis is correct (equivalent to the sensitivity of the clinical examination).

The estimation of conditional probabilities $P(X_i|C)$ is a central issue in the implementation of a naïve Bayes. A training dataset was applied to the selected CVD risk assessment tools to obtain a complete labelled dataset. In fact, the Bayesian model has to learn from the training data set, the conditional probability $P(X_i|C)$ of each attribute X_i given the class C as well as the prior probability $P(C)$ of the class C. Thus, the process of representing an individual risk assessment tool as a naïve Bayes classifier can be systematized as follows: (i) a training dataset (N instances $\boldsymbol{x} = [x_1 \ldots x_p]$ composed of p attributes) is generated; (ii) this training dataset is applied to a given risk assessment tool in order to obtain a complete labelled dataset $J = \{(\mathbf{x}_1, c_1), \ldots., (\mathbf{x}_N, \mathbf{c}_N)\}$; (iii) based on J it is possible to derive a naïve Bayes classifier that resembles the behavior of that specific risk assessment tool (Eq. (2)).

$$P(X_i = x_i|C = c) = \frac{\sum_{1}^{N}(X_i = x_i \wedge C = c)}{\sum_{1}^{N}(C = c)} \tag{2}$$

B Combination of individual models

This phase is responsible for the combination of the naïve Bayes classifiers that resemble the behavior of each one of the risk assessment tools. If l individual models $\{M_1, \ldots, M_l\}$ integrate the combination scheme, where a classifier j is characterized by a specific conditional probability table of attribute i of model j, , and by the respective prior probability of output class $P(C_j)$, the combination scheme is represented by Eq. (3):

$$\begin{aligned} P(C) &= \sum_{j=1}^{l} P(C_j) \times \frac{w_j}{\Phi}; \Phi = \sum_{j=1}^{l} w_j \\ P(X_i|C) &= \sum_{j=1}^{b} P(X_i^j|C_j) \times \frac{w_j}{\Psi}; \Psi = \sum_{j=1}^{b} w_j \end{aligned} \tag{3}$$

where l is the number of individual models, b is the number of individual models that contain the attribute $X_i \in X$, C_j denotes each individual model that contains X_i, w_j is the weight of model j [11].

C Optimization

An additional optimization step can be performed to improve the performance of the global model. Conditional probability tables $P(X_i|C)$ of the global model can be optimized by means of an optimization strategy, such as genetic algorithms (GA). This algorithm focuses on the parameters $P(X_i|C)$; $P(C)$ of the global model that was created through Eq. (3) [11].

3.2. Personalization through grouping strategies

The personalization of CVD risk assessment based on grouping of patients is based on the evidence that risk assessment tools perform differently among different populations, which originates the following hypothesis: if the patients are properly grouped it is possible to find the best model (classifier) for each group.

A Clustering Patients Approach

Clustering algorithms are unsupervised learning algorithms, i.e. they try to find hidden structures in unlabeled data. Thus, the identification of groups of patients is exclusively based on the values of the considered risk factors/inputs. Fig. 3 presents the two main phases of clustering patients approach: (i) training process; (ii) classification.

The training process involves the creation of a set of clusters. Initially the data is pre-processed and then a clustering algorithm is applied (subtractive clustering algorithm) [12]. So, patients are grouped based on the values of respective risk factors, which require the adoption of a distance metric that allows the quantification of the distance between patients.

After the clusters creation, CVD risk assessment tools are assigned to the several clusters based on the respective performance, i.e. the tool with the best performance in a specific cluster is assigned to that cluster. The classification of a new patient can be simply described in two steps: (i) the patient is assigned to a specific cluster (the closest one); (ii) the patient is classified by the CVD risk assessment tool with the best performance in that cluster.

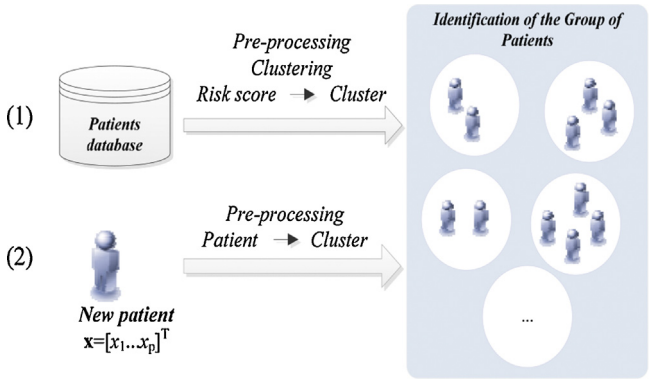

Fig. 3. Clustering patients approach.

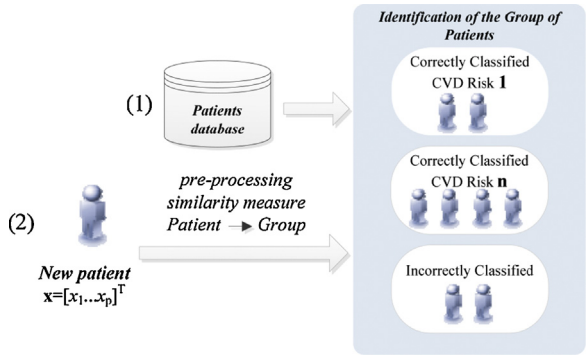

Fig. 4. Similarity measures approach.

B Similarity Measures Approach

This methodology proposes a simpler strategy to form groups of patients (Fig. 4).

The classification of a new patient is based on a similarity measure, assuming that if a new patient is closest to one that is correctly classified by a CVD risk assessment tool; it is probable that the same tool will also be able to classify it accurately. In this way, the groups of patients are formed by the patients correctly classified by each CVD risk tool which is different from the clustering algorithm where the classification of each CVD risk assessment tool is not considered for the creation of those groups. If a patient is not correctly classified by any of the individual CVD risk assessment tools, it is assigned to a group that is classified by the CVD risk tool with highest sensitivity [12].

However, the identification of the closest patient is not obvious, which imposes a comparison among several distance metrics (e.g., Euclidean, Hamming). Additionally, with the goal of improving the identification of the closest patient, a specific weight was assigned to each risk factor. An optimization procedure, based on genetic algorithms, was carried out to adjust those weights.

3.3. Heart rate variability analysis

The HRV signal can be easily derived from the ECG and consists in the oscillation in the interval between consecutive heart beats. Since cardiac rhythmicity is controlled by the autonomic nervous system (ANS), by analyzing the HRV, some information about autonomic functionality can be obtained.

A significant correlation between autonomic functionality and cardiovascular mortality has been identified [16]. In fact, depressed HRV has been reported in several cardiovascular diseases, including coronary heart disease and heart failure. In fact, HRV is depressed in patients following acute myocardial infarction (MI) [9].

A Algorithms for HRV metrics extraction

Both spectral and non-linear HRV derived parameters are taken into consideration in the CardioRisk project.

In the frequency domain, three main spectral components can be identified on the HRV signal spectrum: the very low frequency (VLF: 0.01–0.04 Hz), the low frequency (LF: 0.04–0.15 Hz) and the high frequency (HF: 0.15–0.4 Hz) components. In healthy subjects, LF and HF can increase under different conditions. In normal subjects, LF and HF exhibit a circadian pattern, with higher values of LF during the day and of HF at night. Moreover, an increased LF is observed during standing, mental stress and moderate exercise, while an increase in HF is induced by controlled respiration. As for the VLF component, its physiological significance is not completely understood yet. Characteristic changes in the VLF, LF and HF bands were found in MI patients.

The algorithm uses an autoregressive (AR) model to calculate the power spectral density (PSD) of the signal. The PSD is decomposed into single spectral components, according to the method described in [2]. The frequency and power values associated to each rhythmic component can subsequently be calculated. Parameters that can be derived include the normalized power of the LF and the HF components along with the LF/HF ratio.

B Non-linear HRV complexity analysis

Cardiac activity is determined and modulated by non-linear mechanisms, thus non-linear analysis might provide a more insightful description of the HRV dynamics than the traditional spectral approaches in conditions of reduced variability (which characterizes, for instance, the cardiac activity of heart failure patients) [3].

The Detrended Fluctuation Analysis (DFA) algorithm has proven that is useful in discriminating between physiological and pathological conditions. Due to its potential, the DFA algorithm is applied in this project [3].

The $1/f$ slope is defined as the power-low regression line fitted to the HRV power spectrum, typically for the frequency range $0.0001\,\text{Hz} < f < 0.01\,\text{Hz}$. The $1/f$ physiopathological significance is not completely clear, but altered values with respect to the ones normally observed in healthy subjects may suggest adverse implications in pathological conditions.

The Lempel-Ziv Complexity (LZC) is a popular measure used to characterize the randomness of finite sequences. This index gives a measure of the algorithmic complexity, which refers to the irregularity of a dynamic process.

3.4. Preliminary results

As mentioned, the project started in June 2013 and it will finish in June 2015, so the final results are not yet available. However, some preliminary (partial) results obtained with Santa Cruz dataset (460 acute coronary syndrome patients with non-ST segment elevation[2]) can be presented.

The developed methodologies were validated based on 10 fold cross validation where the 460 patients were partitioned in 10 folds, each one with 46 patients. Table 1 comprises the performance of the three individual risk assessment tools in the Santa Cruz dataset.

[2] A detailed description of this dataset can be found in [11].

Table 1
Performances comparisons of individual CVD risk tools – Santa Cruz (death/MI).

%	GRACE	PURSUIT	TIMI
SE	81.82	69.70	48.58
SP	53.40	43.80	72.60
G_{mean}	66.10	55.24	59.33

Table 2
Performance of fusion and grouping models before optimization.

%	Fusion model	Grouping model
SE	66.67	75.83
SP	46.60	65.24
G_{mean}	55.74	70.34

Table 3
Performance of both methodologies after optimization.

%	Fusion				Grouping			
Scenarios	S1F	S2F	S3F	S4F	S1G	S2G	S3G	S4G
SE	87.88	81.82	78.79	75.76	78.79	75.76	72.73	69.70
SP	63.0	68.38	73.07	74.71	63.23	69.79	75.41	75.64
G_{mean}	74.41	74.8	75.87	75.23	70.58	72.71	74.06	72.61

The GRACE tool presents high sensitivity, but low specificity. The TIMI model behaves in the same way but with even lower values. On the contrary, the PURSUIT model has high specificity but low sensitivity. Table 2 presents the results for the fusion and grouping algorithms before the optimization procedure. The three models (GRACE, TIMI, PURSUIT) were combined, and their performance was assessed based on the sensitivity (SE), specificity (SP) and geometric Mean (G_{mean}).

The grouping approach (similarity measures approach registered better results than the clustering patients approach), even without optimization, obtained an improvement of the metrics when compared with the individual tools (Table 1). Considering the GRACE tool (the best individual risk assessment tool), the sensitivity slightly decreased but on the other hand, the specificity increased.

However, the performances of the developed algorithms have to be improved. Then, an optimization procedure based on genetic algorithms was applied. Table 3 presents the 4 test cases (scenarios-Si, $i = 1, \ldots, 4$) with the best performance in each approach (F – fusion and G – grouping)

The optimization results corresponding to the fusion models are presented in Table 3. These values are compared with the values of GRACE tool. The best SE value (87.88%) was achieved in column 1, while the SP also increased, around 9.6%. Column 3 contains the best G_{mean}, which is explained by the balance between SE and SP. Both situations represent an improvement when compared with the performance obtained with GRACE. Table 3 also presents the results corresponding to the optimization of the grouping strategy (similarity approach). Here, the optimization was applied to the weights of each risk factor but it was not as efficient as in the previous situation (fusion of individual models). However, these preliminary results suggest the potential of the proposed strategies.

4. Developed software

To support the project, the need for a computer application arose with the following requirements: (i) an integrated clinical application for short-term risk assessment, incorporating the developed algorithms for fusion of tools, personalization of patients and HRV analysis; (ii) support the ECG collection performed during the observational study; (iii) support the integration with the HIS, Hospital Information System, to access the necessary data. The application should be highly modular to allow the development and easy integration of additional modules. Since the algorithms used for fusion of risk assessment tools, personalization methods and HRV analysis were coded in MATLAB, the whole application should be coded in the same programming language to facilitate module integration.

4.1. Architecture

The system is based on a three-tier architecture: (i) presentation tier, (ii) logic tier and (iii) data tier. The presentation tier is the topmost level of the application. It interfaces with the user, displaying relevant information while providing a simplified interaction to edit the patient's data.The logic tier, controls all the application functionalities by performing all data processing (developed algorithms). The data tier includes data persistence mechanism (database servers, file shares, text files, etc.) and a data access layer responsible for the encapsulation of that mechanism while exposing the data.

The current CardioRisk application uses a proper database engine while maintaining compatibility with previously generated files that can be both easily imported and exported. It uses SQLite engine as it was considered adequate for the storage of relatively small sets of data. Furthermore, SQLite allows the application to be easily portable.

4.2. Graphical user interface

The resulting interface was designed to be used intuitively and without the help of an operating manual. The screenshot (Fig. 5) presents the main screen, right after the application launch and after the auto-loading of the first acquisition data.

5. Validation

The algorithms developed under CardioRisk project have to be validated. In order to achieve this goal, two main strategies have been followed: (i) initial validation (Section 3.4), (ii) final validation based on an observational study performed in the Leiria Hospital Centre.

5.1. Clinical study

The observational study addresses patients admitted in the ICCU/CHL with a first episode of acute MI, managed according to the current European guidelines. Three exclusion criteria are being considered: artificial pacing, previous heart failure and valvular heart disease. The primary endpoints are death or a new hospitalization due to heart failure, 30 days after the event.

The number of patients to be enrolled in the clinical study is approximately 100 (during one year). The clinical study has started during May 2014 (month 10). As a consequence, so far (January 2015), 87 patients have been enrolled and the respective data collected.

Currently, the validation/improvement of the algorithms is the main focus of the CardioRisk Project. Further research is being performed to merge the information provided by the heart rate variability (HRV) parameters in the global CV risk prediction scheme. These tasks are being conducted based on the data gathered in the clinical observational study.

6. Final considerations

This project addresses the coronary artery disease (CAD) and, specifically, the management of myocardial infarction (MI)

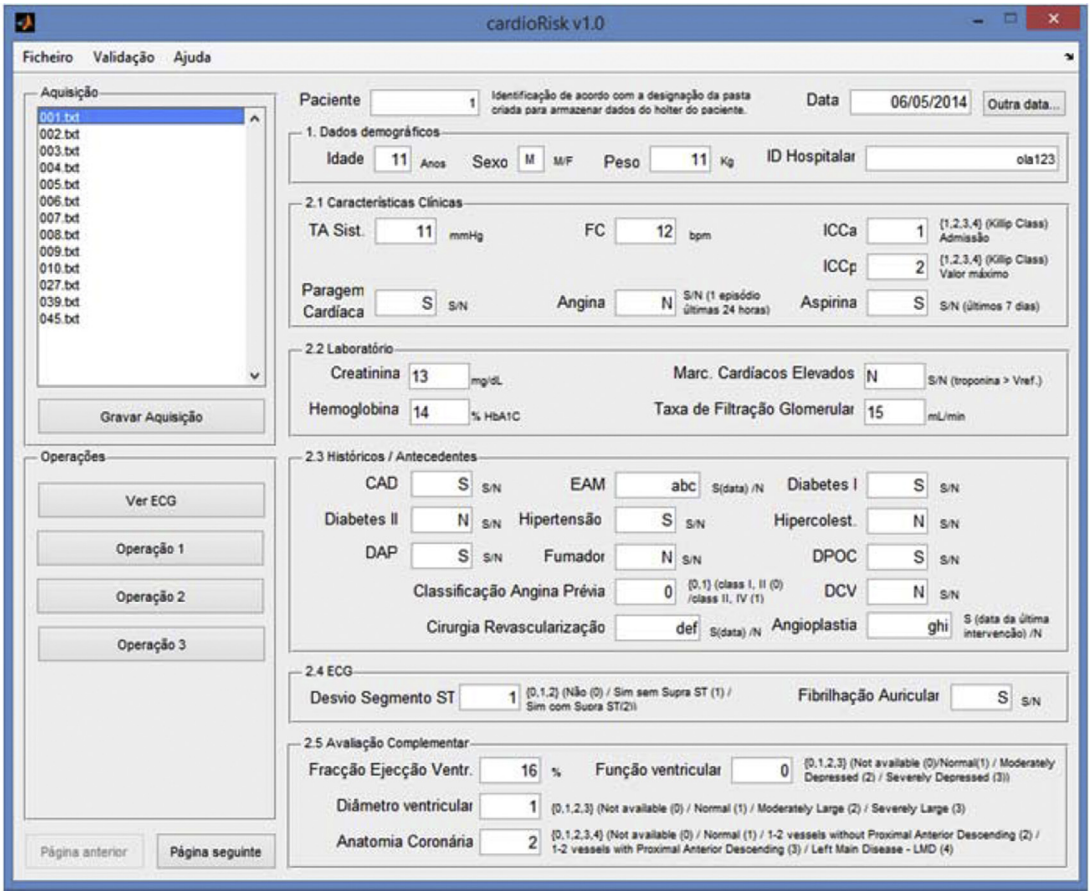

Fig. 5. Graphical user interface (application launch).

patients. The main goal is the development of personalized clinical models for short-term (30 days) cardiovascular risk assessment of acute events (death and new hospitalization).

Up to this moment, all the algorithms were developed and some of them were partially validated. The obtained results are very promising, suggesting the potential of the proposed approaches to improve CV risk assessment.

An in-hospital observational study, addressing patients admitted in the Intensive Cardiac Care Unit with a first episode of acute MI, is being carried out in Leiria Hospital Centre to validate all the algorithms. An integrated clinical platform was implemented to support the observational study, therefore the entire validation. It comprises all the required data (demographics, biomarkers, clinical exams, ECG from Holter device) and the developed models and algorithms.

Additional testing datasets would be very useful to improve the proposed strategy. Thus, the collaboration with clinical partners must be one of the main objectives of future work.

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