Prediction of the onset of cardiovascular diseases from electronic health records using multi-task gated recurrent units

Fernando Andreotti 1, Frank S. Heldt 1, Basel Abu-Jamous 1, Ming Li 1, Avelino Javer 1, Oliver Carr 1, Stojan Jovanovic 1, Nadezda Lipunova 1, Benjamin Irving 1, Rabia T. Khan 1, Robert Dürichen 1*

Abstract

In this work, we propose a multi-task (MT) recurrent neural network with attention mechanism for predicting cardiovascular events from electronic health records (EHRs) at different time horizons. The proposed approach is compared to a standard clinical risk predictor (QRISK) and machine learning alternatives using 5-year data from a NHS Foundation Trust. The proposed model outperforms standard clinical risk scores in predicting stroke (AUC = 0.85) and myocardial infarction (AUC = 0.89), considering the largest time horizon. Benefit of using an MT setting becomes visible for very short time horizons, which results in an AUC increase between 2−6%. Further, we explored the importance of individual features and attention weights in predicting cardiovascular disease (CVD) events. Our results indicate that the recurrent neural network approach benefits from the hospital longitudinal information and demonstrates how machine learning (ML) techniques can be applied to secondary care.

1. Introduction

Cardiac events are associated with high mortality rates as well as long-lasting morbidities. They represent a significant burden to healthcare systems such as the UK’s National Health Service (NHS) and continued efforts to improve risk prediction are of great importance as they allow preventive interventions (Pike et al., 2016). Existing clinical guidelines such as the QRISK2 (Hippisley-Cox et al., 2008) score are often used in primary care settings for 10-year cardiovascular risk for an individual. These guidelines are derived from populational studies and take into account well-established risk factors such as hypertension, cholesterol, age, smoking, and diabetes.

EHR systems have become ubiquitous, with hospitals routinely collecting data at high frequencies and large numbers of variables (Pike et al., 2016). These systems contain longitudinal patient information like demographics, laboratory results, medications and diagnoses. Such rich information may provide a patient-tailored training set for predicting near-term risk of events when using state-of-the-art ML approaches (Goldstein et al., 2017). However, EHR analysis remains challenging due to its high dimensionality, noise, heterogeneity, sparsity and systematic biases. A large number of studies exist on ML–based risk prediction approaches for patient deterioration in intensive care (RCP, 2017; Johnson et al., 2013) and population studies for primary care usage (Hippisley-Cox et al., 2008).

Various approaches have been investigated to predict disease unspecific endpoints from EHR such as length of stay, risk of re-admission or mortality. While many works attempt to predict future diagnoses from previous ones (Lipton et al., 2015) or from clinical notes, few predict the risk of CVDs based on EHR data, such as stroke (Teoh, 2018) or heart failure (Choi et al., 2017). In Teoh (2018), the author used recurrent neural networks (RNNs) to predict the onset of stroke within a year of the last admission, reporting an area under the curve (AUC) of 0.667 by using temporal information of diagnoses codes and laboratory values of 8,000 patients. In a recent study, Xu et al. (2019) applied an attention mechanism on top of a RNN and evaluated their models in a multi-task learning setting for predicting the risk of stroke, myocardial infarction (MI) and death within a year. Adding attention resulted only in minor improvements, with the authors reporting an average increase of AUC by 0.065. Choi et al. (2017) also proposed a RNN with an attention mechanism to predict onset of heart failure. Common factors amongst these studies are i) use of limited number of features, e.g. only diagnoses and laboratory results, ii) the focus on a single prediction horizon, e.g. the risk of having an event within a year after admission, and iii) no analysis...
of which features are most relevant for prediction.

In this work, we propose an algorithm to predict a patient’s first diagnosis of ischemic stroke or MI. For this purpose, a multi-task attention RNN is proposed. The method takes as input the established risk factors as well as data of multiple EHR modalities for prediction, including diagnoses, procedures, medications, encounter, demographic, laboratory and vital signs information. The main contributions of this paper are three-fold: (i) Prediction of the onset of ischemic stroke or MI for different time horizons in a single and multi-task setting; (ii) evaluation of the relevance of heterogeneous input data e.g. laboratory results and vital signs; and (iii) exploration of relevant observed events which lead to positive prediction using attention weights.

2. Material and Methods

Data was collected by the Oxford University Hospitals NHS Foundation Trust between 2014 – 2019 as part of routine care. The longitudinal secondary care EHR includes demographic information (i.e. sex, age), admission information (start/end dates, discharge method/destination, admission types - e.g. in-patient, outpatient, emergency department), ICD-10 coded diagnoses, OPCS-4 coded procedures, medications as British National Formulary (BNF) codes (prescribed both during visits and take-home), Laboratory Information Management System (LIMS) (e.g. blood and urine tests), digital bedside observations of vital signs (e.g. systolic blood pressure, temperature, etc) as well as demographic measurements such as body-mass index (BMI).

In this study, we focus on two highly prevalent CVDs, namely ischemic stroke (defined by ICD-10 codes I63.X or I69.3) and myocardial infarction (MI - code I21.X or I25.2). In particular, we include patients who have at least one observation at least 2 weeks prior to the CVD event. Both cohorts are summarised in Table 1. For each cohort, we construct a case-control group of patients who had never been diagnosed with the case CVD (neither primary nor secondary reasons for admission). Controls were assigned by nearest neighbour matching on diseased patients on age, sex, and number of days containing observations.

### Table 1. PATIENT NUMBERS IN EACH TARGET COHORT.

| TIME HORIZON | STROKE COHORT | MI COHORT |
|--------------|---------------|-----------|
| 1 MONTH      | 339           | 337       |
| 3 MONTH      | 910           | 951       |
| 12 MONTH     | 1,727         | 1,959     |
| > 12 MONTH   | 2,133         | 2,732     |

2.1. Data representation

Each patient is represented by a sequence of days in which observations are available, to which we refer as observation days. Data was aggregated into a single feature vector for each day. Continuous variables (e.g. vital signs and laboratory results) are represented by the median, median absolute deviation, count of observations and an abnormality flag (indicating if values outside physiological ranges), whereas categorical variables (i.e. medication prescription) were counted and the 300 most common diagnoses and procedure codes were sparse encoded. Additional features representing the existence or absence of co-morbid conditions were incorporated by utilising the ICD-10 definition of the Charlson’s co-morbidity score. Therefore, each patient is represented by a single 2D vector of $n_{\text{days}}$ and $n_{\text{features}}$, representing the number of observed days and features, respectively. Features with less than 1 % prevalence were excluded from our analysis. All features were scaled between $[0,1]$ and populational mean imputation was used on missing data points.

2.2. Patient trajectory prediction algorithms

For the task of predicting CVD events from a sequence of $n_{\text{days}}$ containing hospital observations, the following approaches are evaluated.

2.2.1. Baseline clinical approach

The QRISK2 (QRISK) algorithm (Hippisley-Cox et al., 2008) is the UK primary care standard clinical assessment tool, which calculates 10-year risk of cardiovascular disease. The score is based on Cox proportional hazards models and trained on well known populational risk factors. Since secondary care EHR does not contain all risk factors from the QRISK model, missing coefficients were set to zero. The method focuses on a single observation, therefore the last observation of each subject before the event was used.

2.2.2. Baseline ML approach

Logistic regression (LR) was used as baseline ML method using L1 regularisation to account for the sparse feature space. To allow a fair comparison and make use of the information contained on multiple past observed days, observations from previous timesteps were concatenated as additional features. We evaluated the inclusion of 1, 50 and 100 days, here denoted as LR-1, LR-50 and LR-100.

2.2.3. Proposed Recurrent Neural Network

In order to leverage the longitudinal EHR data, we propose a multi-task GRU (MT-GRU) RNN-based approach. In the single-task scenario, the model predicts CVD in a single time horizon based on historical information provided. We
Prediction of CVDs from EHR using MT-GRU

Table 2. Model performances for predicting myocardial infarction and ischemic stroke throughout all time horizons. Shown are average and standard deviation of area under the curve (AUC), sensitivity (SEN), and precision (PRE) of 5-fold cross validation. Best average results per time horizon and disease are highlighted in bold.

| Time horizon | Method      | Myocardial Infarction | Stroke |
|--------------|-------------|-----------------------|--------|
|              | AUC | SEN | PRE | AUC | SEN | PRE |
| 1 month      |    |     |     |     |     |     |
| MT-GRU       | 0.783 ± 0.032 | 0.698 ± 0.124 | 0.138 ± 0.018 | 0.722 ± 0.014 | 0.608 ± 0.087 | 0.188 ± 0.033 |
| MT-Att-GRU   | 0.756 ± 0.033 | 0.696 ± 0.136 | 0.131 ± 0.013 | 0.733 ± 0.025 | 0.684 ± 0.101 | 0.165 ± 0.024 |
| GRU          | 0.703 ± 0.038 | 0.611 ± 0.155 | 0.727 ± 0.082 | 0.703 ± 0.047 | 0.694 ± 0.144 | 0.675 ± 0.040 |
| QRISK        | 0.753 ± 0.023 | 0.838 ± 0.155 | 0.516 ± 0.013 | 0.486 ± 0.041 | 0.567 ± 0.031 | 0.564 ± 0.038 |
| 3 months     |    |     |     |     |     |     |
| MT-GRU       | 0.773 ± 0.010 | 0.707 ± 0.084 | 0.355 ± 0.043 | 0.734 ± 0.025 | 0.698 ± 0.086 | 0.314 ± 0.018 |
| MT-Att-GRU   | 0.788 ± 0.008 | 0.682 ± 0.032 | 0.769 ± 0.012 | 0.726 ± 0.037 | 0.654 ± 0.122 | 0.711 ± 0.066 |
| GRU          | 0.740 ± 0.024 | 0.678 ± 0.094 | 0.693 ± 0.020 | 0.679 ± 0.032 | 0.699 ± 0.092 | 0.641 ± 0.034 |
| QRISK        | 0.474 ± 0.037 | 0.601 ± 0.205 | 0.516 ± 0.013 | 0.479 ± 0.035 | 0.431 ± 0.326 | 0.556 ± 0.058 |
| 12 months    |    |     |     |     |     |     |
| MT-GRU       | 0.811 ± 0.018 | 0.794 ± 0.045 | 0.594 ± 0.041 | 0.801 ± 0.010 | 0.765 ± 0.065 | 0.657 ± 0.033 |
| MT-Att-GRU   | 0.797 ± 0.012 | 0.718 ± 0.055 | 0.610 ± 0.042 | 0.780 ± 0.013 | 0.647 ± 0.033 | 0.672 ± 0.015 |
| GRU          | 0.850 ± 0.011 | 0.769 ± 0.035 | 0.789 ± 0.029 | 0.793 ± 0.024 | 0.724 ± 0.089 | 0.714 ± 0.024 |
| QRISK        | 0.758 ± 0.005 | 0.660 ± 0.034 | 0.714 ± 0.014 | 0.737 ± 0.018 | 0.691 ± 0.064 | 0.695 ± 0.034 |
| > 12 months  |    |     |     |     |     |     |
| MT-GRU       | 0.885 ± 0.014 | 0.769 ± 0.028 | 0.824 ± 0.029 | 0.853 ± 0.010 | 0.749 ± 0.058 | 0.791 ± 0.027 |
| MT-Att-GRU   | 0.881 ± 0.015 | 0.775 ± 0.027 | 0.847 ± 0.030 | 0.844 ± 0.016 | 0.774 ± 0.030 | 0.763 ± 0.018 |
| GRU          | 0.881 ± 0.000 | 0.775 ± 0.003 | 0.847 ± 0.002 | 0.844 ± 0.009 | 0.774 ± 0.030 | 0.763 ± 0.018 |
| QRISK        | 0.473 ± 0.017 | 0.775 ± 0.248 | 0.506 ± 0.003 | 0.468 ± 0.021 | 0.577 ± 0.293 | 0.53 ± 0.041 |

Further extend the model into a MT-GRU prediction model such that, given the past history, the model predicts a sequence of $n_t$ time horizons simultaneously. Further, we use attention (Luong et al., 2015) to assign weights to each day of a patient’s health record when predicting the target disease. The final model is referred to as MT attention GRU (MT-Att-GRU). Hyperparameter search was performed using Bayesian optimisation. Zero padding was applied to pad sequences to $n_{days}$ which is also a hyperparameter of each model. Implementation details are available as Supplementary Material.

2.2.4. PERFORMANCE EVALUATION

ML and clinical approaches were assessed for 1, 3, 12, and > 12 months time horizons using 5-fold cross-validation. Prediction accuracy is measured in terms of AUC of the receiver operating characteristic (ROC) as well as sensitivity (SEN), and precision (PRE). To further characterise the models, we calculated the permutation feature importance post-hoc as the change in F1 score after randomising each feature individually. In addition, we qualitatively assessed the attention weights of MT-Att-GRU trained models to demonstrate how the models incorporate information about previous observation days.

3. Results

Table 2 lists the AUC, SEN and PRE for all four investigated time horizons and both diseases. Due to space limitations, only the results for LR-50 are shown in Table 2. Extended results are shown in Supplementary Materials. Overall, the proposed gated recurrent unit (GRU) models outperform LR and QRISK in all tasks. In shorter time horizons, in which data is limited (see Table 1), both MT-GRU and MT-Att-GRU outperform the single-task GRU. In case of estimating the risk of having MI (Figure 1(a)) the mean AUC values for GRU, MT-GRU, and MT-Att-GRU are 0.703, 0.763, and 0.756, respectively. Whereas in longer horizons GRU methods perform comparably.

Next, we aim to further understand the model’s decision. Figure 2(a) shows the feature importance for the MT-GRU model evaluated on the MI cohort with a > 12 months prediction horizon. Features such as age, previous albumin levels, diagnoses of pleural effusion (J90) and procedure codes for 24h Holter electrocardiogram (U19.2) are deemed important. Last, to explore the relevance of past EHR information, we refer to the attention weights of MT-Att-GRU in Fig. (2(b)). The model focuses on specific observation days throughout a patient’s history. Overall, the model seems to weigh more recent observations higher.

4. Discussion

An important aspect of the proposed GRU-based approaches is that they are able to incorporate the longitudinal information present in EHR. The proposed approaches outperform consistently clinical and ML baselines. While multi-task approaches leverage the availability of data in shorter time horizons, in longer time frames they are not as helpful. The addition of attention does not improve model performance. Meanwhile, the QRISK AUC values are close to 0.5 as expected due to the following reasons: i) the fact that some of the features are not available in EHR and; ii) the algorithm is trained for population studies and should indeed under-perform in an age- and sex-matched setup.

Population models such as the QRISK make use of features such as age, systolic blood pressure and BMI as well-known indicators of future CVD. Consequently, we expect models to use these variables. The feature importance analysis
highlights potentially important predictors of future cardiac events. Reassuringly, the most important features broadly align with the current standard of care. Our results confirm the high relevance of diagnoses and procedure codes as used in previous studies (Xu et al., 2019), but also indicate the benefit of integrating further EHR modalities such as laboratory values and vital signs. This might be one reason why our GRU models achieve an AUC between 0.8 – 0.85 for predicting the risk of MI within a 12 month time horizon, in contrast to (Xu et al., 2019) who reported AUC values of 0.78.

In addition to relevant features, attention is able to highlight past observation days which were most important in a model’s decision as shown in Fig. 2(b). It is reassuring to notice the MT-Att-GRU does not only focus on recent observations, but also on historical observations.

Although the results here presented are promising, our approach has several limitations, which we plan to address in the future. These limitations include:

- **Data representation**: Secondary care data is highly sparse. Hence, embeddings or graph networks may help to better represent intrinsic structures of EHR data and improve predictions.

- **Multi-task learning**: Our results indicate that the MT-GRU model can learn similarities across time horizons, which results in a superior prediction performance, in particular for scenarios with scarce training data. In the future, we plan to extend this approach for the task of predicting multiple diseases.

![Figure 1](image1.png)  
**Figure 1.** Average ROC for the proposed models in comparison to LR and QRISK to predict the risk of having myocardial infarction. Predicted time horizons shown (a) 1 and (b) > 12 months. Shaded areas represent the standard deviation based on 5-fold cross-validation.

![Figure 2](image2.png)  
**Figure 2.** Feature importance (a) and attention weights (b) for MI cohort with a > 12 months time horizon. In (a) asterisks mark significance from zero with t-test p-value thresholds of 5% (*) and 1% (**). At most, the top 10 features for each category is shown.
• **Multiple hospitals**: As most studies in the field (Xu et al., 2019; Teoh, 2018) our evaluation is restricted to a single NHS trust. To increase robustness of ML models and assess generalisability, we plan to evaluate on further datasets and potentially investigate the usage of transfer learning approaches.

### 5. Conclusion

This contribution presents a multi-task attention RNN approach (MT-Att-GRU) for predicting MI and stroke events from the rich and longitudinal data available in EHR. The method was evaluated using multivariate information from a NHS trust. The proposed method outperforms baseline approaches and standard clinical tools for predicting CVDs at different time horizons.

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