# Post-infarct cardiac remodeling predictions with machine learning

Xavier Dieu, Floris Chabrun, Fabrice Prunier, Denis Angoulvant, Nathan Mewton, François Roubille, Pascal Reynier, Marc Ferre, Valérie Moal, Laurane Cottin, et al.

# Post-infarct cardiac remodeling predictions with machine learning

Xavier Dieu [a,1,2,*], Floris Chabrun [a,1,2], Fabrice Prunier [b,1], Denis Angoulvant [c,1], Nathan Mewton [d,1], François Roubille [e,1], Pascal Reynier [a,1], Marc Ferre [a,1], Valérie Moal [a,1], Laurane Cottin [f,1], Alain Furber [b,1], Gabriel Garcia [b,1], Loïc Bière [b,1], Delphine Mirebeau-Prunier [a,1]

[a] *Univ Angers, Service de Biochimie et Biologie Moléculaire, CHU Angers, Inserm, CNRS, MITOVASC, F-49000 Angers, France*
[b] *Univ Angers, Service de Cardiologie, CHU Angers, Inserm, CNRS, MITOVASC, F-49000 Angers, France*
[c] *CHU Tours, Equipe d'Accueil 4245 Transplantation Immunité Inflammation, Université Tours, Tours, France*
[d] *Hôpital Cardiologique Louis Pradel, Service d'insuffisance cardiaque, Centre d'Investigation Clinique, Inserm 1407, CarMeN Inserm 1060, Université Claude Bernard Lyon 1, Hospices Civils de Lyon, Lyon, France*
[e] *PhyMedExp, Université de Montpellier, INSERM, CNRS, Service de Cardiologie, CHU de Montpellier, INI-CRT, France*
[f] *Univ Angers, Laboratoire d'hématologie, CHU Angers, Inserm, CRCINA, F-49000 Angers, France*

ARTICLE INFO

*Keywords:*
Left ventricular remodeling
Myocardial infarction
Machine learning
Deep learning
Neural networks
Cardiac magnetic resonance

ABSTRACT

*Background:* We sought to improve the risk prediction of 3-month left ventricular remodeling (LVR) occurrence after myocardial infarction (MI), using a machine learning approach.
*Methods:* Patients were included from a prospective cohort study analyzing the incidence of LVR in ST-elevation MI in 443 patients that were monitored at Angers University Hospital, France. Clinical, biological and cardiac magnetic resonance (CMR) imaging data from the first week post MI were collected, and LVR was assessed with CMR at 3 month. Data were processed with a machine learning pipeline using multiple feature selection algorithms to identify the most informative variables.
*Results:* We retrieved 133 clinical, biological and CMR imaging variables, from 379 patients with ST-elevation MI. A baseline logistic regression model using previously known variables achieved an AUC of 0.71 on the test set, with 67% sensitivity and 64% specificity. In comparison, our best predictive model was a neural network using seven variables (in order of importance): creatine kinase, mean corpuscular volume, baseline left atrial surface, history of diabetes, history of hypertension, red blood cell distribution width, and creatinine. This model achieved an AUC of 0.78 on the test set, reaching a sensitivity of 92% and a specificity of 55%, outperforming the baseline model.
*Conclusion:* These preliminary results show the value of using an unbiased data-driven machine learning approach. We reached a higher level of sensitivity compared to traditional methods for the prediction of a 3-month post-MI LVR.

## 1. Introduction

Myocardial infarction (MI) morbidity and mortality is broadly driven by post-MI left ventricular remodeling (LVR) occurrence which associates functional and structural changes in both the ischemic and non-ischemic regions of the heart [1,2]. Even in the present era in which ST-elevation segment myocardial infarction (STEMI) is largely treated with acute revascularisation and optimal pharmacotherapy, a large number of patients show post-infarct LVR at 3 months after MI [3]. It more likely occurs in large infarcts and leads to the development of heart failure and cardiac death [1,2,4]. Early detection of patients likely to experience LVR may help to optimize therapeutic strategies aiming at preventing or reverting LVR and its subsequent clinical consequences [5].

In recent years, artificial intelligence based on machine and deep learning algorithms has been used to tackle the challenge of integrating

* Corresponding author at: Service de Biochimie et Biologie Moléculaire, Centre Hospitalier Universitaire Angers, 49933 Angers, France.
*E-mail address:* xavier.dieu@chu-angers.fr (X. Dieu).
[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] Contributed equally.

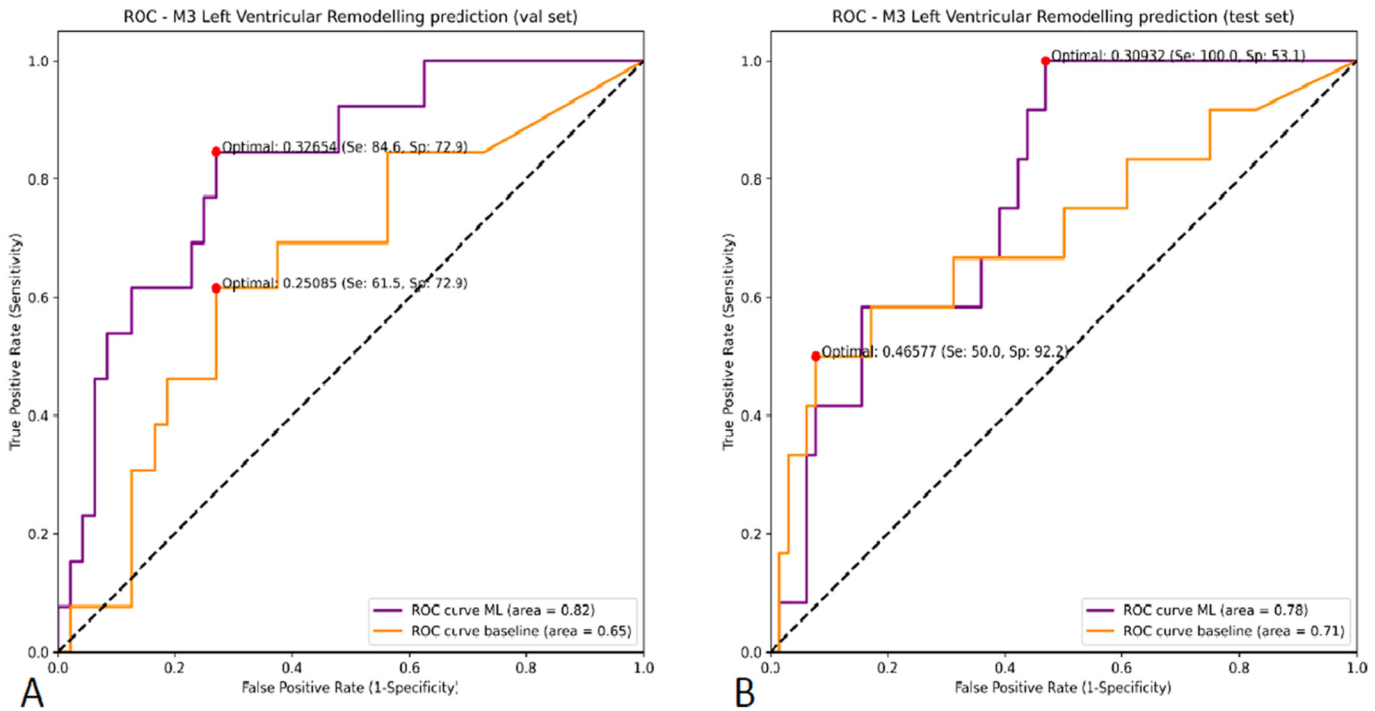


**Fig. 1.** Receiver Operating Characteristic plot of the baseline logistic regression model (in orange) and our proposed machine learning approach combining feature selection and a neural network (in purple). Performances on the validation set (61 patients) and on the test set (76 patients) is displayed on the left (A) and right (B) plots respectively. Thresholds for computing sensitivity and specificity are represented for default value (50%) and for the optimal threshold determined at the maximal Youden's index. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and analyzing the ever increasing accumulation of measured parameters produced by patient care [6]. A machine learning approach has the potential to allow increased performance in prediction compared to traditional statistical methods that are still largely used to this day. It could identify new potential candidates for prediction, without any preconceived ideas often based on established parameters or pathophysiological considerations. We therefore aimed to apply machine learning algorithms to common or potentially accessible markers that could help predict LVR at three month in patients following acute MI.

## 2. Methods

### 2.1. Patients

443 patients were included at Angers University Hospital, France in a prospective cohort study analyzing the incidence of LVR in STEMI (PHRC, N° 2006/0070, more details in Supplementary Method). Time period of inclusion span from 2004 to 2018. The protocol was approved by the institutional ethics committee of the University Hospital of Angers (CCPPRB agreement 15/11/2005).

### 2.2. Biological data and CMR data

We retrospectively collected biological results available in the first week post-MI as part of medical care (detailed list in Supplementary Table 1). All patients underwent CMR at baseline and after follow-up at 3 month. CMR was performed using either 1.5 or 3.0 T imager (Avanto or Skyra, Siemens, Erlangen, Germany, details in Supplementary Method).

### 2.3. Machine learning pipeline

LVR was defined as LV end systolic dilation superior or equal to 10% between baseline CMR and the 3-month follow-up [7]. Data was splitted in a train (64%), val (16%) and test set (20%) with random stratified sampling. Missing values were imputed (detailed list of variables and their corresponding amount of imputed missing values in Supplementary Table 1). Three feature selection algorithms (ElasticNet [8], BORUTA [9] and MULTISURF [10]) were used to select the most relevant variables. We then trained multiple machine learning algorithms. The role and impact of each feature value on the model's prediction was also assessed using SHAP (SHapley Additive exPlanation) values [11] (code for the analysis available at: https://www.github.com/XavierDieuRenard/LVR_prediction_with_ML).

## 3. Results

### 3.1. Cohort description

From the 443 patients initially included in our STEMI cohort, 379 for whom we could cross match our clinical, CMR and biological data were finally included in our study (patients' description in Supplementary Table 2). We collected 133 variables: 41 clinical and 12 CMR features as well as 80 biological parameters. Of those 379 patients, 78 (20.5%) had a LVR at 3 month. After random stratified sampling, the final training set comprised 242 patients, the validation set comprised 61 patients and the test set comprised the remaining 76.

### 3.2. Feature selection

We applied three feature selection algorithms to remove non-informative features, and used them to highlight the most important features to keep (Supplementary Table 3). Accordingly, 7 features were finally selected: median value of creatine kinase (CK), maximum value of mean corpuscular volume, maximum value of red blood cell distribution width, maximum value of creatinine, baseline left atrial surface, presence or absence of hypertension and presence or absence of diabetes.

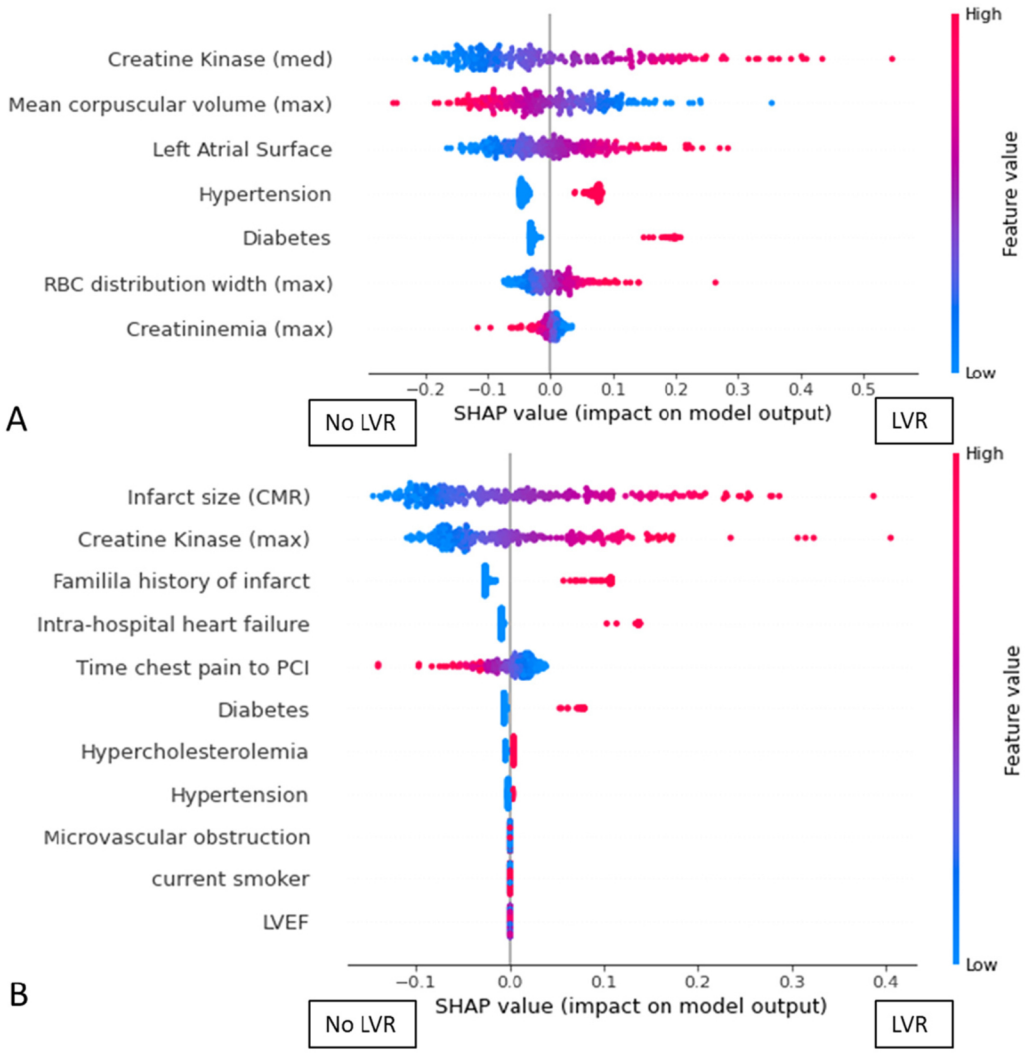


**Fig. 2.** SHAP value plot of the neural network (A) and baseline model (B) results on the train set. Each patient's feature value is represented as a dot, with colours varying from blue for lower values to red for higher values of that feature. The X-axis displays the impact of each feature value on the model output (the probability score that the model output when a feature takes a certain value). As a result, a feature value with a high SHAP value indicates a higher probability for a patient with this feature value to have LVR at 3 months. CMR and biological features are continuous but clinical features are qualitative (i.e. 0 when absent and 1 when present). "med": median; "max": maximum. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

### *3.3. Model training and results*

For comparison purposes we first started by training a baseline logistic regression model which used previously described variables [12] such as: infarct size, microvascular obstruction, CK peak, hypertension, diabetes, family history of MI, hypercholesterolemia, tobacco smoking, alcohol consumption, time interval between chest pain and angioplasty and intra-hospital heart failure. This model achieved an AUC-ROC of 0.71, 0.65 and 0.71 on the train, validation and test sets respectively. When using the optimal threshold found on the validation set on the test set, this model had a sensitivity of 67% and a specificity of 64% for the prediction of 3-month post MI LVR.

In comparison, our best model (a neural network) fitted on our 7 variables achieved an AUC-ROC of 0.78, 0.81 and 0.78 on the train, validation and test sets respectively (Figure 1). When using the optimal threshold of the validation set on the test set, we obtained a sensitivity of 92% and the specificity was at 55%. The importance of each feature for the models was assessed on the train set through the computation of SHAP values (Figure 2).

We tested our model's prediction against different thresholds recently proposed in the literature. When using a threshold of a 10% dilation of the left ventricular end-diastolic volume (LVEDV) [13], none of the approaches could predict LVR. However when using a threshold of a dilation superior to 12% in both left ventricular end systolic volume (LVESV) and LVEDV [14], we did achieve similar performance (Supplementary Fig. 1).

## 4. Discussion

We have developed a machine learning pipeline which selected seven variables that are easily accessible and/or already routinely measured and achieved a good sensitivity for the prediction of 3-month post MI LVR, enabling a better detection of patients at risk of LVR than classical statistical approaches. Our results showcase that this type of unbiased approach could lead to better results than a baseline model that rely solely on established parameters or pathophysiological considerations. This approach could be the basis for the future development of more effective models that could help with adapting treatments or follow-up for patients after MI [15].

A pivotal aspect when trying to predict LVR is how we define it. The threshold we used presents the theoretical appeal of combining information on both volumetric assessment and systolic function. However, we tried to apply our model's predictions to recently proposed thresholds. We did achieve similar performances when using the threshold proposed by Bulluck et al [14] but not when using the threshold of Reindl et al. [13] Bulluck et al [14] had observed similar results, where isolated LVEDV dilation was not associated with clinical outcomes. It illustrates the difficulty to dichotomize LVR in a generalizable way across different centers.

As health care produce large amounts of data from diverse

modalities, model performance will decrease without feature selection. Fewer features selected enables better model explainability and easier use by other centers. As there is no best way to select the best features for a prediction task, the concept of ensemble feature selection (combining the strength of different algorithms) recently emerged [16]. Leveraging this approach and consistently with the literature, we have found that our model selected known predictors of post-MI LVR remodeling such as CK [4], hypertension or diabetes, which helps in validating the relevance of this approach. Interestingly, LAS is also among our selected predictors. We used CMR to obtain its surface in our patients, however it could also be obtained by standard cardiac echocardiography. In the literature, LA volume increase has been shown to be an early predictor of death and heart failure in patients with a high risk MI [17]. Our model also selected some unexpected biological biomarkers. Specifically, RBCDW and mean corpuscular volume (MCV) have been linked with cardiovascular diseases in the literature, however the link between these variables and post-MI LVR is unclear and should be explored. An increase in RBCDW has previously been reported to correlate with poor clinical outcomes in cardiovascular diseases [18]. Similarly, changes in MCV levels have been reported as a marker of poorer outcomes in patients with MI but not as a predictor of LVR [19].

Our study has certain limitations. The modest specificity of our model may be due to other unknown factors involved in LVR pathophysiology which could limit the extrapolation of our results for clinical use. It also could be due to the size of our cohort which prompted us to use drastic feature selection and limited our ability to create a more complex model including more variables. Additionally, our results were obtained on a monocentric cohort and should be validated on external data. However, our approach may be pushed even further thanks to the relative simplicity and the good availability of the parameters making it suitable for additional testing on multicentric cohorts, necessary for validating the relevance of our methodology.

## 5. Conclusion

In this preliminary study, the use of a "big data" and machine learning approach, i.e. using highly and easily available common biological, clinical and imaging markers as inputs for a model capable of complex modelling without making assumptions about data, allowed us to achieve better results than traditional statistical approach for the prediction of a 3-month LVR post-MI.


## Funding

This work was supported by the Institut National de la Santé et de la Recherche Médicale (INSERM), the Centre National de la Recherche Scientifique (CNRS), and the University Hospital of Angers.


## Data availability

The original data used to support the findings of this study are available from the corresponding author upon request.

## Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.


## Acknowledgements

The authors do not report specific acknowledgements regarding this study.


## References


[1] G.W. Reed, J.E. Rossi, C.P. Cannon, Acute myocardial infarction, Lancet 389 (2017) 197–210.

[2] J.N. Cohn, R. Ferrari, N. Sharpe, Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling, J. Am. Coll. Cardiol. 35 (2000) 569–582.

[3] P. van der Bijl, R. Abou, L. Goedemans, B.J. Gersh, D.R. Holmes, N. Ajmone Marsan, V. Delgado, J.J. Bax, Left ventricular post-infarct remodeling: implications for systolic function improvement and outcomes in the modern era, JACC Heart Fail. 8 (2020) 131–140.

[4] M.A. Konstam, D.G. Kramer, A.R. Patel, M.S. Maron, J.E. Udelson, Left ventricular remodeling in heart failure, JACC Cardiovasc. Imaging 4 (2011) 98–108.

[5] D.V. Cokkinos, C. Belogianneas, Left ventricular remodelling: a problem in search of solutions, Eur. Cardiol. 11 (2016) 29–35.

[6] K. Shameer, K.W. Johnson, B.S. Glicksberg, J.T. Dudley, P.P. Sengupta, Machine learning in cardiovascular medicine: are we there yet? Heart 104 (2018) 1156–1164.

[7] L. Bière, E. Donal, A. Jacquier, P. Croisille, O. Genée, L. Christiaens, F. Prunier, P. Gueret, L. Boyer, A. Furber, A new look at left ventricular remodeling definition by cardiac imaging, Int. J. Cardiol. 209 (2016) 17–19.

[8] H. Zou, T. Hastie, Regularization and variable selection via the elastic net, J. R. Stat. Soc. Ser. B Stat Methodol. 67 (2005) 301–320.

[9] M.B. Kursa, W.R. Rudnicki, Feature selection with the Boruta package, J. Stat. Softw. 36 (2010).

[10] R.J. Urbanowicz, R.S. Olson, P. Schmitt, M. Meeker, J.H. Moore, Benchmarking relief-based feature selection methods for bioinformatics data mining, J. Biomed. Inform. 85 (2018) 168–188.

[11] S.M. Lundberg, B. Nair, M.S. Vavilala, M. Horibe, M.J. Eisses, T. Adams, D. E. Liston, D.K.-W. Low, S.-F. Newman, J. Kim, S.-I. Lee, Explainable machine-learning predictions for the prevention of hypoxaemia during surgery, Nat. Biomed. Eng. 2 (2018) 749–760.

[12] P.C. Westman, M.J. Lipinski, D. Luger, R. Waksman, R.O. Bonow, E. Wu, S. E. Epstein, Inflammation as a driver of adverse left ventricular remodeling after acute myocardial infarction, J. Am. Coll. Cardiol. 67 (2016) 2050–2060.

[13] M. Reindl, S.J. Reinstadler, C. Tiller, H.-J. Feistritzer, M. Kofler, A. Brix, A. Mayr, G. Klug, B. Metzler, Prognosis-based definition of left ventricular remodeling after ST-elevation myocardial infarction, Eur. Radiol. 29 (2019) 2330–2339.

[14] H. Bulluck, J. Carberry, D. Carrick, M. McEntegart, M.C. Petrie, H. Eteiba, S. Hood, S. Watkins, M. Lindsay, A. Mahrous, I. Ford, K.G. Oldroyd, C. Berry, Redefining adverse and reverse left ventricular remodeling by cardiovascular magnetic resonance following ST-segment–elevation myocardial infarction and their implications on long-term prognosis, Circ. Cardiovasc. Imaging 13 (2020).

[15] A.S. Bhatt, A.P. Ambrosy, E.J. Velazquez, Adverse remodeling and reverse remodeling after myocardial infarction, Curr. Cardiol. Rep. 19 (2017).

[16] E. Alhenawi, R. Al-Sayyed, A. Hudaib, S. Mirjalili, Feature selection methods on gene expression microarray data for cancer classification: a systematic review, Comput. Biol. Med. 140 (2022), 105051.

[17] A. Meris, M. Amigoni, H. Uno, J.J. Thune, A. Verma, L. Kober, M. Bourgoun, J. J. McMurray, E.J. Velazquez, A.P. Maggioni, J. Ghali, J.M.O. Arnold, S. Zelenkofske, M.A. Pfeffer, S.D. Solomon, Left atrial remodelling in patients with myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: the VALIANT Echo Study, Eur. Heart J. 30 (2008) 56–65.

[18] E. Danese, G. Lippi, M. Montagnana, Red blood cell distribution width and cardiovascular diseases, J. Thorac. Dis. 7 (2015) E402–E411.

[19] L. Cheng, L. Zhang, J. Liu, W. Li, X. Bai, R. Li, B. Li, L. Wang, J. Zhou, Y. Wu, Z. Yuan, Prognostic value of admission mean corpuscular volume for major adverse cardiovascular events following stent implantation in nondiabetic and diabetic patients with acute coronary syndrome, Dis. Markers 2020 (2020), 7054596.