Non-stenotic fibro-calcific aortic valve as a predictor of myocardial infarction recurrence

Myasoedova Veronika A. MD, PhD[1#], Chiesa Mattia PhD[1,2#], Cosentino Nicola MD, PhD[1,3], Bonomi Alice PhD[1], Ludergnani Monica MSc[1], Bozzi Michele MSc[1], Valerio Vincenza PhD[1], Moschetta Donato MSc[1], Massaiu Ilaria PhD[1], Mantegazza Valentina MD[1,3], Marenzi Giancarlo MD[1], Poggio Paolo PhD[1,4*]

1. *Centro Cardiologico Monzino, IRCCS, Milan Italy.*
2. *Department of Electronics, Information and Biomedical engineering, Politecnico di Milano, Milan, Italy.*
3. *Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Milan, Italy.*
4. *Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milano, Italy.*

Running title: AVSc and increased risk of recurrent AMI.

#Equal contribution (co-first authors)

***Corresponding author**

Paolo Poggio, PhD (ORCID: 0000-0002-7225-3379)

Department of Biomedical, Surgical and Dental Sciences

University of Milan, Milano, Italy.

and

Unit for the Study of Aortic, Valvular, and Coronary Pathologies

Centro Cardiologico Monzino IRCCS

Via privata Carlo Parea, 4

20138 Milan, Italy

TEL: +390258002853; Fax: +390258002342

Email: paolo.poggio@unimi.it

Email: paolo.poggio@cardiologicomonzino.it

ABSTRACT

Background: Patients with acute myocardial infarction (AMI) are at increased risk of recurrent cardiovascular events. Non-stenotic aortic valve fibro-calcific remodeling (AVSc), reflecting systemic damage, may serve as a new marker of risk.

Objectives: To stratify subgroups of AMI patients with specific probabilities of recurrent AMI and to evaluate the importance of AVSc in this setting.

Methods: Consecutive AMI patients (n=2530) were admitted at Centro Cardiologico Monzino (2010-2019) and followed up for 5 years. Patients were divided into study (n=1070) and test (n=966) cohorts. Topological data analysis (TDA) was used to stratify patient subgroups, while Kaplan-Meier and Cox regressions analyses were used to evaluate the significance of baseline characteristics.

Results: TDA identified 11 subgroups of AMI patients with specific baseline characteristics. Two subgroups showed the highest rate of reinfarction after 5 years from the indexed AMI with a combined hazard ratio (HR) of 3.8 (95%CI: 2.7-5.4) compared to the other subgroups. This was confirmed in the test cohort (HR=3.1; 95%CI: 2.2-4.3). These two subgroups were mostly men, with hypertension and dyslipidemia, who exhibit higher prevalence of AVSc, higher levels of high-sensitive c-reactive protein and creatinine. In the year-by-year analysis, AVSc, adjusted for all confounders, showed an independent association with the increased risk of reinfarction (odds ratio of ~2 at all time-points), in both the study and the test cohorts (all $p<0.01$).

Conclusions: AVSc is a crucial variable for identifying AMI patients at high risk of recurrent AMI and its presence should be considered when assessing the management of AMI patients. The inclusion of AVSc in risk stratification models may improve the accuracy of predicting the likelihood of recurrent AMI, leading to more personalized treatment decisions.

Keywords: acute myocardial infarction; aortic valve fibro-calcific remodeling; predictors; topological data analysis.

Lay Summary:

We wanted to understand the factors that make some acute myocardial infarction (AMI) patients more likely to experience recurrent infarction after leaving the hospital. Specifically, we asked whether a heart valve condition called non-stenotic aortic valve fibro-calcific remodeling (AVSc) could be a crucial factor.

Our study used advanced data analysis techniques, including topological data analysis (TDA), to explore this question. We unveil that AVSc is indeed a significant predictor of recurrent infarction in AMI patients. Our findings suggest that the presence of aortic valve remodeling should be taken into account when assessing the risk of recurrent AMI and managing these patients.

INTRODUCTION

Patients with acute myocardial infarction (AMI) are at increased risk of recurrent cardiovascular events after hospital discharge (1) and data from recent real-world registries reported an average 5-year all-cause mortality rate, after the index AMI, of ~25% (2) and 5-year recurrent AMI rate of ~ 30% (3). It cannot be excluded that in a heterogeneous population such as patients with AMI, there are no particular groups of patients, with a specific risk of re-infarction. Therefore, it is imperative to identify the precise phenotype(s) that characterize(s) patients who will encounter adverse events after AMI also because some risk factors are already known as predictors of re-infarction, while other variables have not yet been associated with recurrent AMI.

In this context, the application of unsupervised methodologies has been proven to be convincing in identifying (sub-)phenotypes of patients, in the cardiovascular field (4, 5). Among them, topological data analysis (TDA) is a robust and effective unsupervised methodology, representing complex data in a low-dimensional space and preserving the intrinsic characteristics of data and the mutual relations among observations (6, 7).

Non-stenotic aortic valve fibro-calcific remodeling (AVSc) may serve as a marker of reinfarction risk. AVSc is the earliest manifestation of aortic stenosis (AS), characterized by non-uniform thickening of the aortic leaflets without obstruction to the left ventricular outflow tract (8). The estimated prevalence of AVSc is around 25-30% in subjects over 65 years of age (8, 9). The initial mechanisms involved in AVSc development, such as

lipid deposition, oxidative stress, inflammation, and calcification are very similar to those of atherosclerosis (10). Results of our previous studies demonstrated that the atherosclerosis risk factors, such as age, hypertension, dyslipidemia, and diabetes mellitus, are associated with AVSc (11), while epidemiological studies suggested that AVSc is a predictor of both all-cause and cardiovascular mortality (12, 13). Thus, it is not surprising that atherosclerotic diseases (*e.g.*, carotid or coronary atherosclerosis) and AVSc often coexist in the same subject (14, 15).

To better stratify subgroups of patients with AMI with specific probabilities of recurrent AMI and to assess the importance of AVSc in this context, we employed unsupervised TDA. In addition, we validated the results obtained from TDA using study and test cohorts in order to explore whether AVSc could be an independent prognostic predictor in patients with AMI or a biomarker reflecting their comorbidity burden at 5 years after hospitalization.

METHODS

Study population

This is a large prospective cohort study that consecutively recruited AMI patients, hospitalized at Centro Cardiologico Monzino IRCCS (CCM), Milan, Italy, between June 2010 and December 2019. Both ST-elevation (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) patients were included in the study. Patients with significant valvular pathologies, intended as ≥ moderate valvular stenosis and/or regurgitation, major concomitant systemic conditions (*e.g.*, malignancies), or poor echocardiographic images were excluded from the study. All examined patient underwent primary percutaneous coronary intervention (PCI) revascularization, coronary artery by-pass surgery (CABG) patients or patients not eligible for PCI were not enrolled. The study was approved by the Institutional Review Board and by the Ethical Committee of CCM (R1348/20-CCM 1418).

Topological data analysis (TDA)

Building topological models as networks, TDA allows complex diseases to be inspected in a continuous space, where subjects can 'fluctuate' over the graph, sharing more than one node of the network

(**Supplementary Methods**). In addition, TDA allows the identification of specific connected clusters (called 'communities') in the network, sharing similar features (16).

We pre-processed the original dataset for TDA as follows: 1) features with more than 5% missing values were removed; 2) binary variables where minority class exhibits a frequency lower than 2% were removed; 3) samples with more than 5 missing values were discarded; and 4) data imputation was performed on the remaining dataset, composed by 1070 of samples and 34 features for "study cohort". The first 2 dimensions extracted from the Principal Component Analysis (PCA) have been chosen as lenses, while the number of TDA bins (NB) and the bin overlapping ratio (BO) have been selected via a 'grid search' approach, ranging NB between [18 - 28] and BO between [0.3 - 0.6]. To ensure a scale-free configuration of the resulted network, the lowest Pearson's R correlation index between node rank (k) and the frequency of node rank (p(k)) has been chose as evaluation metrics. The best parameters' set was: NB=24 and OB=0.3. TDA was performed in R using the 'PIUMA' (https://github.com/BioinfoMonzino/PIUMA) packages. Networks have been plotted by Cytoscape (17).

To verify the reliability of the data obtained with TDA test model was performed, including the cohort of patients that represent the "real-world" scenario without imputation of unavailable data (test cohort). All patients underwent 2-dimensional transthoracic echocardiographic evaluation during the index event, and demographic and clinical characteristics were collected during hospitalization (*i.e.*, at baseline). The primary endpoint of the study was rehospitalization for recurrent AMI which was obtained from the medical records of all hospitalizations and outpatient visits, collected during follow-up.

Echocardiographic evaluation

Two experienced cardiologists reviewed all recorded transthoracic echocardiographic images performed during index hospitalization and assessed the morphology and function of the aortic valve to evaluate the presence of AVSc, expressed as a dichotomous variable (yes or no). The AVSc was identified according to criteria described by Gharacholou *et al.* (8), irregular, non-uniform thickening of portions of the aortic valve leaflets or commissures, or both; thickened portions of the aortic valve with an appearance suggesting

calcification (*i.e.*, bright echoes); non-restricted or minimally restricted opening of the aortic cusps; and peak continuous wave Doppler velocity across the valve < 2 m/s.

Statistical analysis

Continuous variables are presented as mean ± SD, while categorical data are reported as frequencies and percentages. Group comparisons for continuous and categorical variables were performed by Student t-test for independent samples and by chi-square ($\chi 2$) test, respectively. Kaplan-Meier analysis was used to generate time-to-event curves and the log-rank test was used to compare strata. Univariate and multivariate Cox regressions and the related hazard ratios (HR), were calculated exploiting the 'survival' (v. 3.2-13) and 'survminer' (v. 0.4.9) R packages, while plots were generated by the 'ggplot2' (v. 3.3.5) R package. Univariate and multivariate logistic regression models were implemented to assess the odd ratio (OR) of each variable versus the outcome. A p-Value < 0.05 was considered statistically significant. The data imputation and the features importance assessment were performed by 'randomForest' R package (18).

RESULTS

The 2350 patients initially examined were randomly divided into the study cohort and the test cohort, after excluding patients lost to follow-up and those with more than five missing values at baseline (n=314), 2036 patients were analyzed. The study cohort comprise of 1070 patients, while the test cohort include 966 patients, well-balanced by baseline clinical and demographic characteristics (**Figure 1** and **Table 1**).

Using only variables collected at baseline, we generated a network where each node represents a group of patients with similar characteristics, while edges thickness depicts the number of samples shared by nodes. The TDA highlighted the presence of 11 clusters of patients with specific baseline clinical characteristics (**Figure 2A**). The year-by-year analysis emphasized that recurrent AMI occurred in specific group of patients (**Supplementary Figure S1**). Since the greatest number of events occurred in the first few years after the indexed AMI, we focused our subsequent analysis on the 5-year follow-up period.

Performing the survival analysis, we found that samples belonging to clusters c1 and c2 were at higher risk of adverse events than all other clusters, where the rate of myocardial infarction gradually decreases in the

study cohort (**Figure 3A**). In particular, patients that belong to clusters c1-c2 were mostly men, with hypertension and dyslipidemia, who exhibit higher prevalence of AVSc, higher levels of high-sensitive c-reactive protein and creatinine (**Figure 2B**). Taking in to account this finding, we combined cluster c1 and c2 into the high-risk group and all others were combined into the moderate-risk group. The Kaplan-Meier demonstrated that the average risk of event-free rate after 5 years from discharge was approximately 82% and 58% when aggregating c3-11 (moderate-risk group), and c1 and c2 (high-risk group), respectively in the study cohort with a HR of 3.8 (95% CI: 2.7-5.4, $p < 0.001$; **Figure 3C**).

We applied the same TDA procedure and Kaplan-Meier analysis to the test cohort, and we found that the average risk was approximately 86% in the moderate-risk group and 60% in the high-risk group, in test cohort with a HR of 3.1 (95% CI: 2.2-4.3, $p < 0.001$; **Figure 3B** and **3D**).

To corroborate our findings, we compare the 5-year event frequency of the study cohort with those of the test cohort, obtaining Pearson correlation indexes equal to 0.9 ($p < 0.001$; **Supplementary Figure S2**).

Finally, we compared which variables were the most relevant to predict the year-by-year risk of reinfarction in the study and the test cohorts. As summarized in **Figure 4A**, age and AVSc showed a significant positive association (OR > 2) with risk of reinfarction, while eGFR and hemoglobin showed a significant negative association (OR < 0.5). Interestingly, adjusting AVSc for all significant confounders, we found that it was independently associated with the increased risk of recurrent AMI for both the study and test cohorts, starting from second year after the indexed AMI (**Figure 4B** and **Supplementary Table S1**, **S2**, and **S3**).

DISCUSSION

A large AMI patient cohort was evaluated by applying TDA and two patient groups of recurrent AMI risk were identified with this unsupervised methodology. Patients in the high-risk group were mostly male and had a higher prevalence of classic cardiovascular risk factors, such as hypertension, and dyslipidemia, whereas the moderate-risk group had fewer comorbidities. Of note, we found that AVSc was an important and independent risk predictor of recurrent AMI, starting at the second year of follow-up after the indexed AMI. This was true for both the study and the test cohorts.

Patients with AMI remain at very high risk of experiencing recurrent cardiovascular events after discharge and it is very important to better identify and stratify their risk. To this goal, Steen *et al.* (1) conducted an elegant study of event rates and risk factors for recurrent cardiovascular events using several approaches in a large and well-characterized population of more than 240000 AMI patients. The authors suggested that the combined 5-year incidence of non-fatal AMI, non-fatal ischemic stroke, or cardiovascular death was 33% and the risk of recurrence of these events was higher immediately after discharge. According to other studies, the likelihood of experiencing a reinfarction increased over time and reached 7-12% after three years of the indexed AMI (19, 20) and up to 30% after five years (3). Even if our cohort was considerably smaller, we observed that the majority of recurrent events occurred within the first two years after discharge and the incidence of recurrent AMI after 5 years was 16%.

It is widely recognized that various clinical factors, including diabetes and smoking habits, can contribute to the risk of recurrent AMI (21). Our TDA analysis has further revealed that there are two major groups that exhibit an increased risk for such events. Remarkably, our analysis suggests that different combinations of clinical features can result in the same probability of adverse events, as separate clusters have been found to belong to the same risk group. Of note, impaired renal function, known to be a contributing factor for reinfarction (22), has been identified as a crucial component of the high-risk group in our analysis. Our results also highlight the importance of well-known cardiovascular risk factors such as age, previous AMI, dyslipidemia, low levels of glomerular filtration rate, and hemoglobin in predicting the year-by-year increased risk of reinfarction. Furthermore, we have identified a previously unrecognized factor, AVSc, that significantly associates to the risk of reinfarction.

Recently published data showed the association between AVSc and preclinical left ventricular (LV) systolic and diastolic function in subjects with normal LV geometry free of cardiac disease, indicating AVSc as a marker of LV functional alteration even before LV morphological changes (23, 24). Furthermore, previous results of a meta-analysis on more than 30 studies, which included 10537 patients with AVSc and 25005 controls, showed that the presence of AVSc was associated with coronary artery disease (CAD), stroke, and cardiovascular mortality (12). Indeed, the prevalence of AVSc in patients with CAD is approximately 45% and

even higher (> 60%) in patients with carotid atherosclerosis, and after coronary or carotid revascularization these patients had increased overall mortality compared with patients without AVSc (14, 15). Moreover, in patients who underwent coronary artery bypass graft (CABG), the 90-day survival was significantly lower in AVSc patients and the addition of AVSc to the EuroSCORE II improved the stratification of these high-risk patients (13). However, only Dursan *et al.* (25) reported, in a small cohort, that patients with previous AMI were more likely to have AVSc at the indexed AMI event. We directly associated AVSc presence and AMI recurrency following these patients up to 5 years after the indexed event. Therefore, to improve the life-expectancy of patients after an AMI, new markers associated with recurrent events such as AVSc should be considered and included in overall clinical management. Thus, to date, in AMI patients that present AVSc, the risk factors associated with several comorbidities must be brought to target, using the latest pharmacological tools. In addition, since AVSc could be seen as a marker of systemic damage, the patients' management approach should include a deeper diagnostic evaluation to uncover other possible silent associated disorders, such as peripheral artery disease (11, 14).

The incorporation of novel biomarkers for patient risk stratification is crucial in modern medical practice. Presently, routine echocardiography is performed on all patients admitted to hospitals with AMI, providing a simple and effective means of assessing AVSc. The identification of AVSc through echocardiography has the potential to enable early identification of patients at high risk of recurrent cardiovascular events. Nevertheless, recently published meta-analysis study by Chen and colleagues (26) suggested that poor adherence to guideline-recommended therapies contributes to a considerable proportion of all cardiovascular disease events and mortality in patients with CAD. Indeed, results from another study indicate that full adherence to guideline-recommended therapies associated with a lower rate of major adverse cardiovascular events (MACE) and cost savings (27).

Thus, prior to the implementation of AVSc in patient management decisions, dedicated clinical trials are necessary. These trials should examine the specific pharmacological treatment of AMI patients with AVSc and compare their outcomes to those of non-AVSc patients with AMI. Finally, opening to the pool of omics-type variables, such as genomics, transcriptomics, proteomics, and metabolomics, will further enhance the

understanding of the molecular mechanisms underlying the disease and the identification of potential therapeutic targets, contributing to the advancement of precision medicine in this filed.

Limitations

Several limitations of the study should be acknowledged. First, this is a single-center study, which may limit the generalizability of the findings. However, the large number of participants enrolled in the study and the random division into two independent cohorts helps to reduce potential bias. Nevertheless, a new study, involving a sizable multi-center population, is warranted to confirm our findings and to translate our model in a clinical setting. Second, the models used in the study do not account for changes in baseline treatment that may have occurred during the lengthy follow-up period. Third, the assessment of AVSc was conducted using a dichotomous variable, as the most commonly used definition is still too broad. Indeed, more accurate and unbiased methods for quantifying AVSc are needed. Fourth, different coronary stents and antithrombotic agents were used. Yet, this corresponds to a "real-world" scenario where patients are treated with different antiplatelet drugs and stents according to clinical setting, operator choice, and drug/device availability. Lastly, no information was available regarding patients' adherence to treatment during follow-up. In particular, patients were considered to be on dual antiplatelet therapy according to the discharge treatment.

Conclusion

Our study provides evidence that non-stenotic aortic valve fibro-calcific remodeling is a crucial variable for identifying AMI patients at high risk of recurrent AMI. Therefore, our findings suggest that the presence of aortic valve remodeling should be taken into account when assessing the risk of recurrent AMI and managing AMI patients. Including non-stenotic aortic valve fibro-calcific remodeling in risk stratification models may significantly enhance the accuracy of predicting the likelihood of recurrent AMI. This, in turn, could lead to more personalized treatment decisions for AMI patients.

Authors contributions: MVA, CM, CN, ML, MG and PP substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. BA, ML, VV, BM, MI, MV drafting

of the work or reviewing it critically for important intellectual content. All authors approved the final version to be published, and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest:

All the authors have nothing to disclose.

Data availability:

The data underlying this article will be shared upon reasonable request to the corresponding author.

Fundings:

This work was supported by the Italian Ministry of Health funds (Ricerca Finalizzata: GR-2019-12370560 and GR-2018-12366423) and Ricerca Corrente. P.P. is supported by Fondazione Gigi e Pupa Ferrari ONLUS (FPF-14).

References

1. Steen DL, Khan I, Andrade K, Koumas A, Giugliano RP. Event Rates and Risk Factors for Recurrent Cardiovascular Events and Mortality in a Contemporary Post Acute Coronary Syndrome Population Representing 239 234 Patients During 2005 to 2018 in the United States. *J Am Heart Assoc*. 2022 May 3;**11**(9):e022198. PubMed PMID: 35475346. Pubmed Central PMCID: PMC9238606. Epub 2022/04/28.

2. Lim S, Choo EH, Choi IJ, Lee KY, Lee SN, Hwang BH, et al. Risks of Recurrent Cardiovascular Events and Mortality in 1-Year Survivors of Acute Myocardial Infarction Implanted with Newer-Generation Drug-Eluting Stents. *J Clin Med*. 2021 Aug 17;**10**(16). PubMed PMID: 34441938. Pubmed Central PMCID: PMC8396866. Epub 2021/08/28.

3. Plakht Y, Gilutz H, Shiyovich A. When More Means Less: The Prognosis of Recurrent Acute Myocardial Infarctions. *J Clin Med*. 2021 Dec 15;**10**(24). PubMed PMID: 34945184. Pubmed Central PMCID: PMC8706169. Epub 2021/12/25.

4. Casaclang-Verzosa G, Shrestha S, Khalil MJ, Cho JS, Tokodi M, Balla S, et al. Network Tomography for Understanding Phenotypic Presentations in Aortic Stenosis. *JACC Cardiovasc Imaging*. 2019 Feb;**12**(2):236-48. PubMed PMID: 30732719. Epub 2019/02/09.

5. Li L, Cheng WY, Glicksberg BS, Gottesman O, Tamler R, Chen R, et al. Identification of type 2 diabetes subgroups through topological analysis of patient similarity. *Sci Transl Med*. 2015 Oct 28;**7**(311):311ra174. PubMed PMID: 26511511. Pubmed Central PMCID: PMC4780757.

6. Lum PY, Singh G, Lehman A, Ishkanov T, Vejdemo-Johansson M, Alagappan M, et al. Extracting insights from the shape of complex data using topology. *Sci Rep*. 2013;**3**:1236. PubMed PMID: 23393618. Pubmed Central PMCID: PMC3566620. Epub 20130207.

7. CARLSSON G. TOPOLOGY AND DATA. *BULLETIN (New Series) OF THE AMERICAN MATHEMATICAL SOCIETY*. 2009;**46**(2):255-308.

8. Gharacholou SM, Karon BL, Shub C, Pellikka PA. Aortic valve sclerosis and clinical outcomes: moving toward a definition. *Am J Med*. 2011 Feb;**124**(2):103-10. PubMed PMID: 21295189. Epub 2011/02/08.

9. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med*. 1999 Jul 15;**341**(3):142-7. PubMed PMID: 10403851. Epub 1999/07/15.

10. Myasoedova VA, Ravani AL, Frigerio B, Valerio V, Moschetta D, Songia P, et al. Novel pharmacological targets for calcific aortic valve disease: Prevention and treatments. *Pharmacol Res*. 2018 Oct;**136**:74-82. PubMed PMID: 30149054. Epub 2018/08/28.

11. Di Minno MND, Di Minno A, Songia P, Ambrosino P, Gripari P, Ravani A, et al. Markers of subclinical atherosclerosis in patients with aortic valve sclerosis: A meta-analysis of literature studies. *Int J Cardiol*. 2016 Nov 15;**223**:364-70. PubMed PMID: 27543711. Epub 2016/08/21.

12. Di Minno MND, Di Minno A, Ambrosino P, Songia P, Pepi M, Tremoli E, et al. Cardiovascular morbidity and mortality in patients with aortic valve sclerosis: A systematic review and meta-analysis. *Int J Cardiol*. 2018 Jun 1;**260**:138-44. PubMed PMID: 29622430. Epub 2018/04/07.

13. Poggio P, Cavallotti L, Myasoedova VA, Bonomi A, Songia P, Gripari P, et al. Aortic Valve Sclerosis Adds to Prediction of Short-Term Mortality in Patients with Documented Coronary Atherosclerosis. *J Clin Med*. 2019 Aug 5;**8**(8). PubMed PMID: 31387275. Pubmed Central PMCID: PMC6722808. Epub 2019/08/08.

14. Myasoedova VA, Saccu C, Chiesa M, Songia P, Alfieri V, Massaiu I, et al. Aortic Valve Sclerosis as an Important Predictor of Long-Term Mortality in Patients With Carotid Atheromatous Plaque Requiring Carotid Endarterectomy. *Front Cardiovasc Med*. 2021;**8**:653991. PubMed PMID: 34124193. Pubmed Central PMCID: PMC8193358. Epub 2021/06/15.

15. Myasoedova VA, Genovese S, Cavallotti L, Bonomi A, Chiesa M, Campodonico J, et al. Aortic Valve Sclerosis in High-Risk Coronary Artery Disease Patients. *Front Cardiovasc Med*. 2021;**8**:711899. PubMed PMID: 34386534. Pubmed Central PMCID: PMC8354333. Epub 2021/08/14.

16. Dagliati A, Geifman N, Peek N, Holmes JH, Sacchi L, Bellazzi R, et al. Using topological data analysis and pseudo time series to infer temporal phenotypes from electronic health records. *Artif Intell Med*. 2020 Aug;**108**:101930. PubMed PMID: 32972659. Pubmed Central PMCID: PMC7536308. Epub 2020/09/26.

17. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res*. 2003 Nov;**13**(11):2498-504. PubMed PMID: 14597658. Pubmed Central PMCID: PMC403769. Epub 2003/11/05.

18. Breiman L. Random Forests. *Machine Learning*. 2001;**45**:5-32.

19. Zeymer U, Riedel K, Hahn M. Medical Therapy and Recurrent Ischemic Events in High Risk Patients Surviving their Myocardial Infarction for at Least 12 Months: Comparison of Patients with ST Elevation Versus Non-ST Elevation Myocardial Infarction. *Cardiol Ther*. 2017 Dec;**6**(2):273-80. PubMed PMID: 28616861. Pubmed Central PMCID: PMC5688970. Epub 2017/06/16.

20. Stone SG, Serrao GW, Mehran R, Tomey MI, Witzenbichler B, Guagliumi G, et al. Incidence, predictors, and implications of reinfarction after primary percutaneous coronary intervention in ST-segment-

elevation myocardial infarction: the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction Trial. *Circ Cardiovasc Interv*. 2014 Aug;**7**(4):543-51. PubMed PMID: 24939928. Epub 2014/06/19.

21. Schmitz T, Harmel E, Heier M, Peters A, Linseisen J, Meisinger C. Long-Term Predictors of Hospitalized Reinfarction after an Incident Acute Myocardial Infarction. *Life (Basel)*. 2022 Dec 13;**12**(12). PubMed PMID: 36556454. Pubmed Central PMCID: PMC9784794. Epub 2022/12/24.

22. Amon J, Wong GC, Lee T, Singer J, Cairns J, Shavadia JS, et al. Incidence and Predictors of Adverse Events Among Initially Stable ST-Elevation Myocardial Infarction Patients Following Primary Percutaneous Coronary Intervention. *J Am Heart Assoc*. 2022 Sep 6;**11**(17):e025572. PubMed PMID: 36056738. Pubmed Central PMCID: PMC9496426. Epub 2022/09/04.

23. Yoshida Y, Nakanishi K, Daimon M, Hirose K, Ishiwata J, Kaneko H, et al. Aortic valve sclerosis and subclinical LV dysfunction in the general population with normal LV geometry. *Eur J Prev Cardiol*. 2022 Nov 22. PubMed PMID: 36416216. Epub 2022/11/24.

24. Kardos A. Invited Editorial: Professor Attila Kardos MD PhD FRCP FESC In search for a mechanism of poor outcome in patients with aortic valve sclerosis without aortic stenosis and left ventricular hypertrophy. Results of a Populational Observational Study with normal LV geometry. *Eur J Prev Cardiol*. 2023 Feb 23. PubMed PMID: 36821698. Epub 2023/02/24.

25. Dursun I, Kul S, Bayraktar A, Erkan H, Turan T, Sayin MR, et al. Association of Aortic Valve Sclerosis and Clinical Factors in Patients With Acute Myocardial Infarction. *Am J Med Sci*. 2019 Jun;**357**(6):474-82. PubMed PMID: 31000422. Epub 2019/04/20.

26. Chen C, Li X, Su Y, You Z, Wan R, Hong K. Adherence with cardiovascular medications and the outcomes in patients with coronary arterial disease: "Real-world" evidence. *Clin Cardiol*. 2022 Dec;**45**(12):1220-8. PubMed PMID: 36116032. Pubmed Central PMCID: PMC9748759. Epub 2022/09/19.

27. Bansilal S, Castellano JM, Garrido E, Wei HG, Freeman A, Spettell C, et al. Assessing the Impact of Medication Adherence on Long-Term Cardiovascular Outcomes. *J Am Coll Cardiol*. 2016 Aug 23;**68**(8):789-801. PubMed PMID: 27539170. Epub 2016/08/20.

Tables and Figure Legends.

Table 1. Baseline clinical characteristics and in-hospital outcomes of study cohort and test cohort.

Variable	Study Cohort n=1070	Test Cohort n=966	p-Value
Age, years	66.2 ± 12.6	66.5 ± 11.9	0.600
Male sex, n (%)	811 (75.8%)	724 (74.9%)	0.680
Body mass index, kg/m^2	26.4 ± 4.16	26.7 ± 4.29	0.279
Diabetes mellitus, n (%)	213 (19.9%)	213 (22.0%)	0.252
Hypertension, n (%)	673 (62.9%)	603 (62.4%)	0.854
Smoking, n (%)	602 (56.3%)	505 (52.3%)	0.075
Dyslipidemia, n (%)	505 (47.2%)	456 (47.2%)	1.000
Prior AMI, n (%)	245 (22.9%)	211 (21.8%)	0.595
Prior CABG, n (%)	109 (10.2%)	89 (9.2%)	0.500
Prior PCI, n (%)	264 (24.7%)	218 (22.6%)	0.273
STEMI, n (%)	551 (51.5%)	517 (53.5%)	0.374
Left ventricular ejection fraction, (%)	50.4 ± 11.2	50.5 ± 10.9	0.896
Treated vessels	1.06 ± 0.64	1.10 ± 0.64	0.150
AVSc presence, n (%)	495 (46.3%)	447 (46.3%)	1.000
Recurrent AMI	149 (14)	135 (14)	1.000
Admission laboratory values			
Total Cholesterol, mg/dL	178 ± 43.1	177 ± 43.7	0.750
LDL, mg/dL	111 ± 38.5	111 ± 39.3	0.877
HDL, mg/dL	42.8 ± 12.7	43.2 ± 13.4	0.688
Triglycerides, mg/dL	126 ± 76.2	117 ± 63.2	0.029
Creatinine, mg/dL	1.04 ± 0.503	1.05 ± 1.47	0.984
eGFR, mL/min/1.73 m^2	78.4 ± 24.9	78.5 ± 23.9	0.743
Hemoglobin, g/dL	13.9 ± 1.79	13.8 ± 1.81	0.913
High-sensitivity C-reactive protein, mg/dL	16.6 ± 43.2	15.6 ± 37.1	0.890
In-hospital complications			
Cardiogenic shock, n (%)	40 (3.7%)	45 (4.7%)	0.319
Ventricular fibrillation/ventricular tachycardia, n (%)	66 (6.2%)	74 (7.7%)	0.189
Atrial fibrillation, n (%)	114 (10.7%)	106 (11.0%)	0.831
Acute pulmonary edema, n (%)	74 (6.9%)	75 (7.8%)	0.496
Acute kidney injury, n (%)	96 (9.0%)	84 (8.7%)	0.876
Discharge therapy			
Statins, n (%)	994 (92.9%)	903 (93.5%)	0.786
Dual antiplatelet therapy, n (%)	1036 (96.8%)	936 (96.9%)	0.889
Beta-blockers, n (%)	846 (79.1%)	777 (80.4%)	0.503
ACE/ARB, n (%)	711 (66.4%)	643 (66.6%)	1.000

CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; Treated vessels: number of treated coronary arteries; AVSc: aortic valve sclerosis; AMI: acute myocardial infarction; LDL: low density lipoprotein; HDL: high density lipoprotein; eGFR: estimated glomerular filtration rate; ACE/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Figure 1. Flow diagram of the study.

Figure 2. (**A**) AMI patients and sub-phenotypes identification. Topological data analysis results shown as network. Each node represents a group of patients with similar clinical characteristics, while edges thickness depicts the Jaccard's index (*i.e.*, the number of samples shared by nodes). (**B**) AMI patients and sub-phenotypes characterization. Bubble plots were performed for each cluster; different colors belong to different clusters (c01-c11). The size of the circle indicates the frequency of samples with a specific characteristic in each cluster, where the larger the size the higher the frequency. Circles with a frequency less than 0.6 were removed. The variables are shown in alphabetic order divided in two blocks, dichotomous and continuous variables. AVSc: aortic valve sclerosis; Prior MI: previous myocardial infarction; STEMI: ST-elevation myocardial infarction; VF/VT: Ventricular fibrillation/ventricular tachycardia; BMI: body mass index; AKI: Acute kidney injury; eGFR: estimated glomerular filtration rate; HsCRP: High-sensitivity C-reactive protein; LDL: low-density lipoprotein; LVEF: Left ventricular ejection fraction; Treated vessels: number of treated coronary arteries.

Figure 3. (**A**) Kaplan-Meier (KM) curves show the incidence of re-infarction of AMI patients for each cluster at 5 years follow-up in study cohort. (**B**) Kaplan-Meier curves show the incidence of re-infarction of AMI patients for each cluster at 5 years follow-up in test cohort. (**C**) Kaplan-Meier curves show the incidence of re-infarction of AMI patients for high-risk (clusters c1-c2) and moderate-risk (clusters c3-c11) group in study cohort. (**D**) Kaplan-Meier curves show the incidence of re-infarction of AMI patients for high-and moderate-risk group in test cohort. Tables under the KM curves indicated the patients at risk and numbers of event for each year of follow up in high- and moderate risk groups. HR: hazard ratio; CI: confidence interval.

Figure 4. (**A)** Clinical variables associated with re-infarction in AMI patients. Variation trend of Odds ratio (OR) during the time. (**B**) The plots show the strength of the associations between re-infarction and AVSc at 2, 3, 4 and 5-year follow-up (Odds ratio - OR) and their distribution in unadjusted and full adjusted model for all significantly associated variables with re-infarction in both, study and test cohorts. MI: myocardial infarction; STEMI: ST-elevation myocardial infarction; eGFR: estimated glomerular filtration rate.

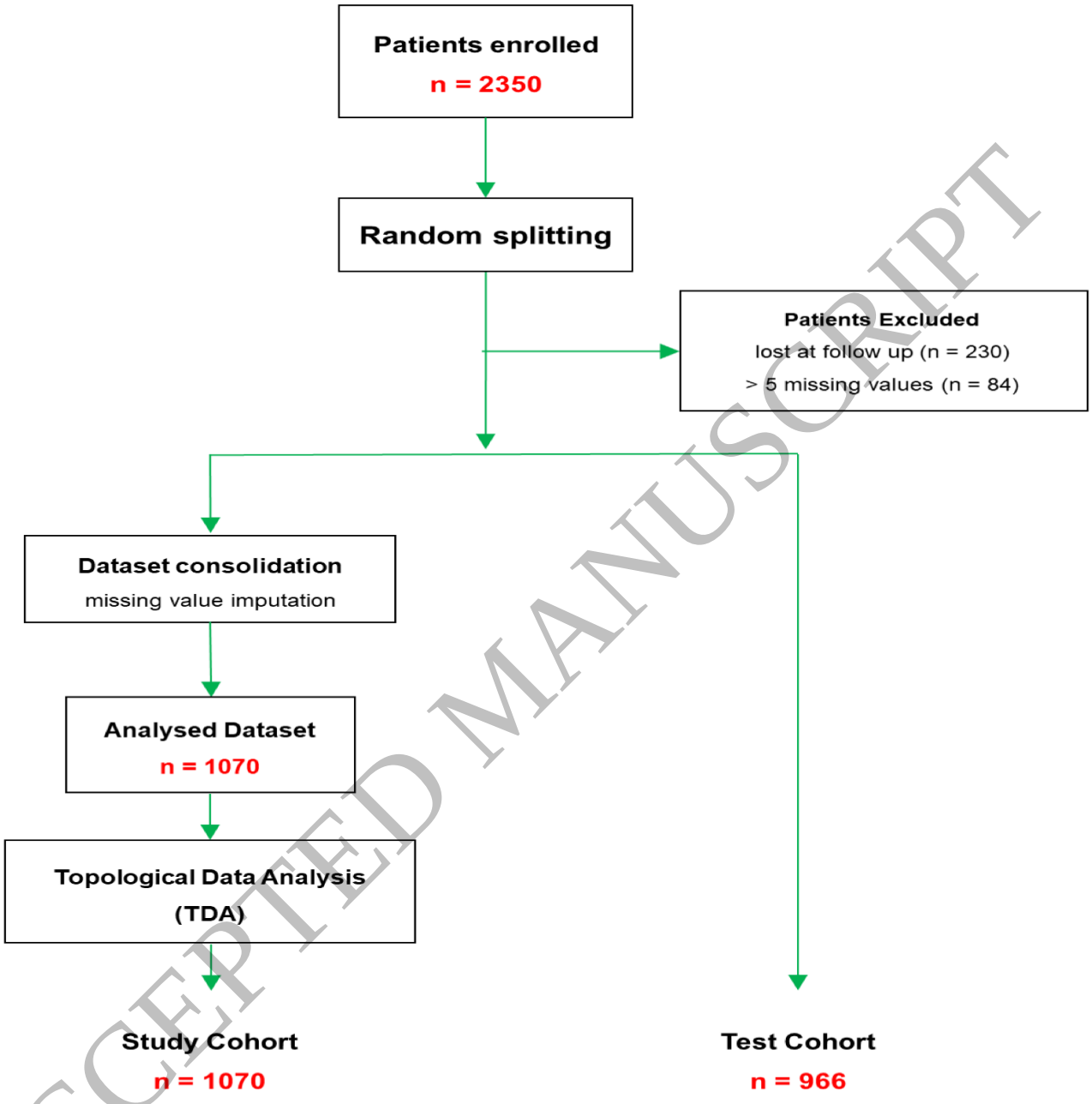


Figure 1

Figure 1
267x356 mm (x DPI)

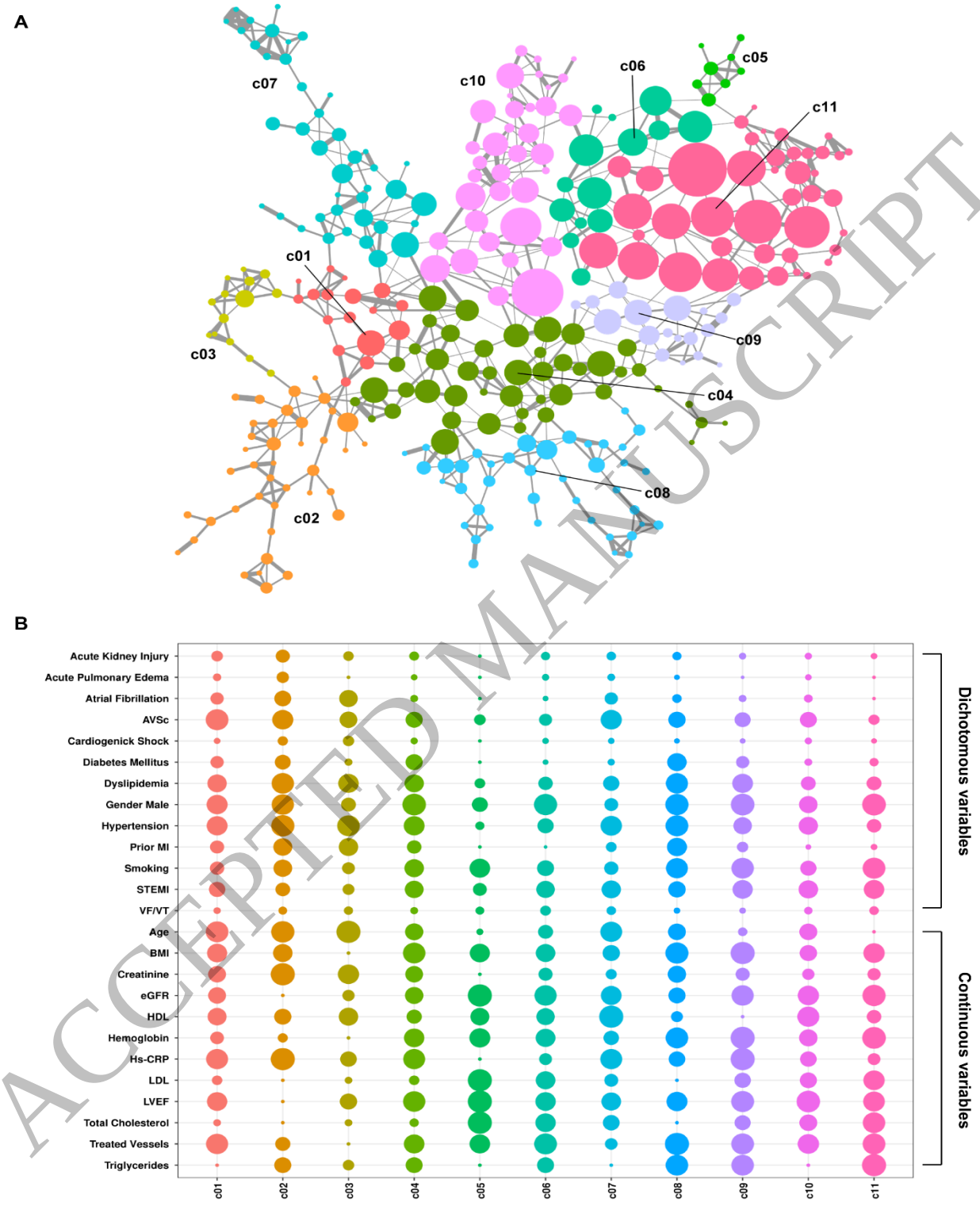


Figure 2

Figure 2
267x356 mm (x DPI)

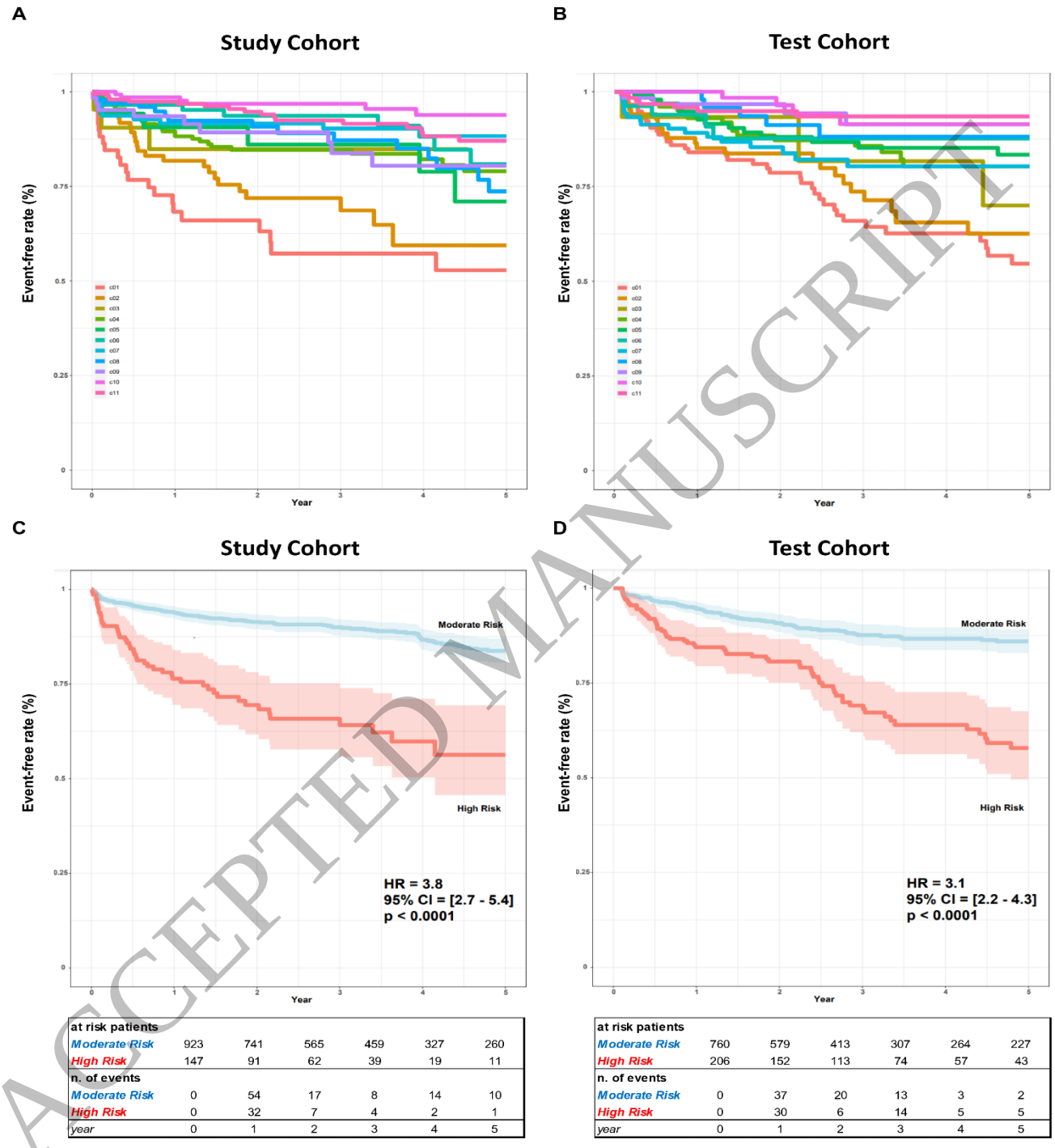


Figure 3

Figure 3
267x356 mm (x DPI)

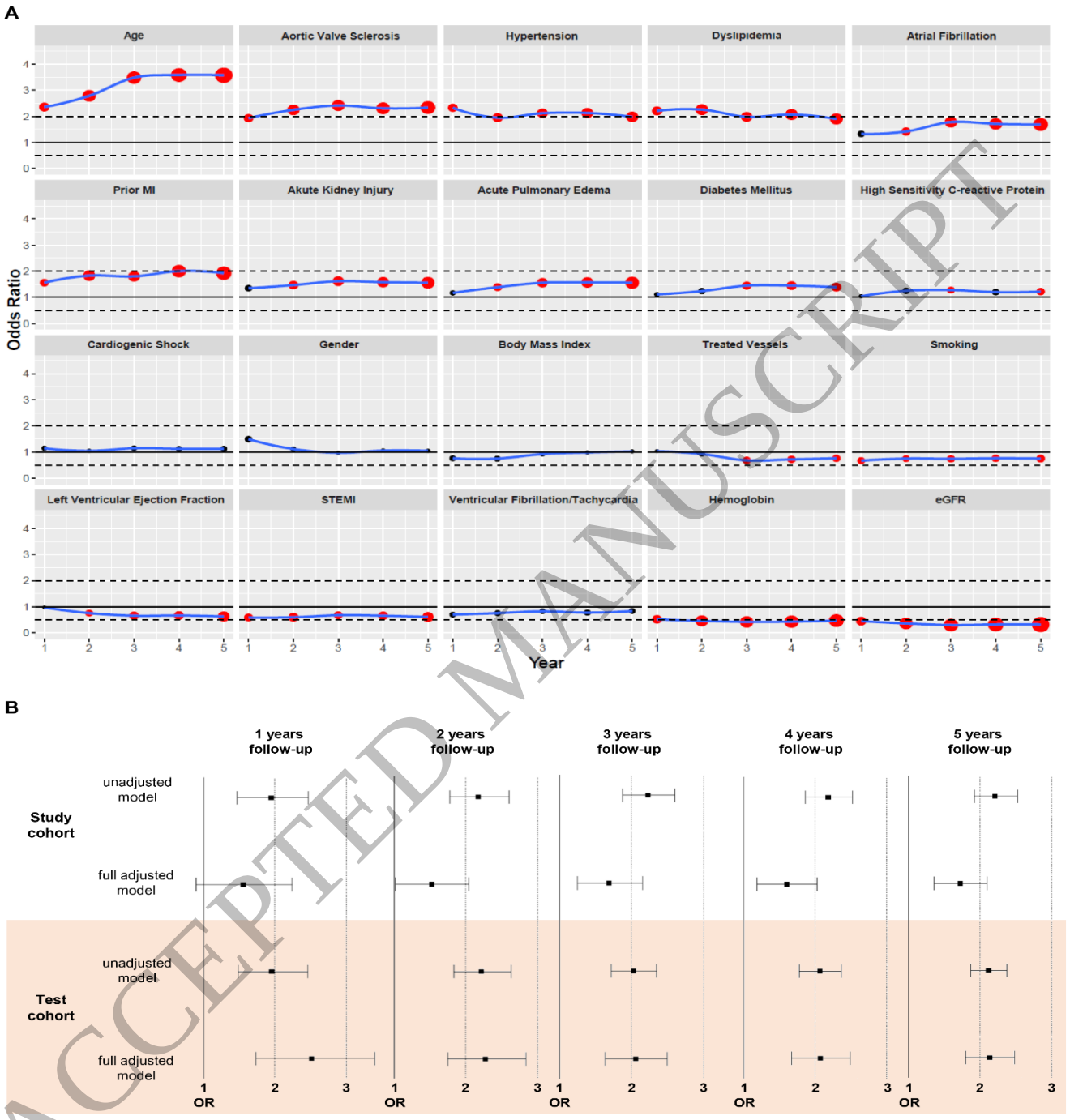
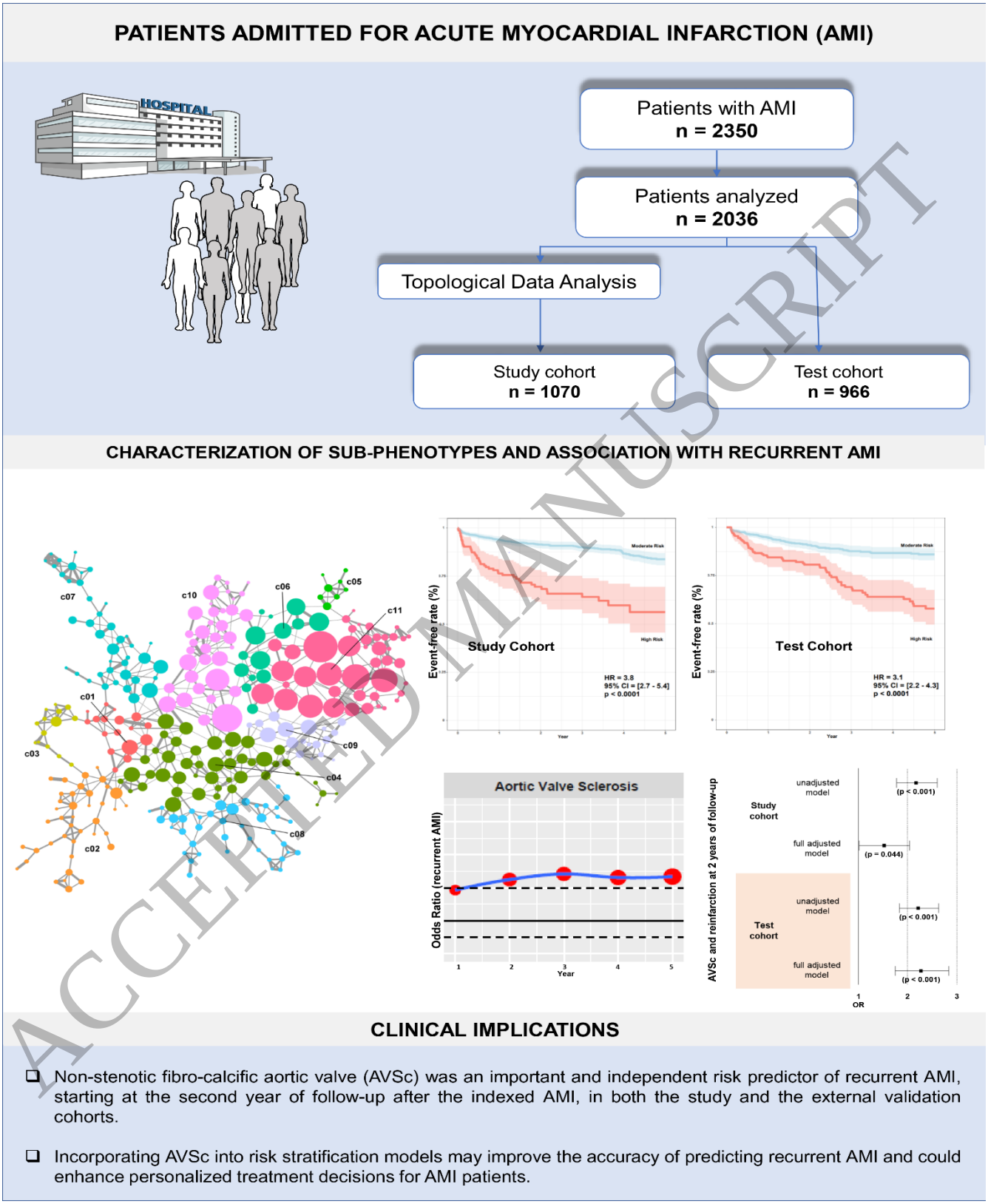


Figure 4

Figure 4
267x356 mm (x DPI)



Graphical Abstract
267x356 mm (x DPI)