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

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Running title: AVSc and increased risk of recurrent AMI.

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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/BioinfoMozino/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 (χ²) 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 recurrence 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


Tables and Figure Legends.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Cohort n=1070</th>
<th>Test Cohort n=966</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66.2 ± 12.6</td>
<td>66.5 ± 11.9</td>
<td>0.600</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>811 (75.8%)</td>
<td>724 (74.9%)</td>
<td>0.680</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.4 ± 4.16</td>
<td>26.7 ± 4.29</td>
<td>0.279</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>213 (19.9%)</td>
<td>213 (22.0%)</td>
<td>0.252</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>673 (62.9%)</td>
<td>603 (62.4%)</td>
<td>0.854</td>
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<tr>
<td>Smoking, n (%)</td>
<td>602 (56.3%)</td>
<td>505 (52.3%)</td>
<td>0.075</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>505 (47.2%)</td>
<td>456 (47.2%)</td>
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<tr>
<td>Prior AMI, n (%)</td>
<td>245 (22.9%)</td>
<td>211 (21.8%)</td>
<td>0.595</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>109 (10.2%)</td>
<td>89 (9.2%)</td>
<td>0.500</td>
</tr>
<tr>
<td>Prior PCI, n (%)</td>
<td>264 (24.7%)</td>
<td>218 (22.6%)</td>
<td>0.273</td>
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<tr>
<td>STEMI, n (%)</td>
<td>551 (51.5%)</td>
<td>517 (53.5%)</td>
<td>0.374</td>
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<tr>
<td>Left ventricular ejection fraction, (%)</td>
<td>50.4 ± 11.2</td>
<td>50.5 ± 10.9</td>
<td>0.896</td>
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<tr>
<td>Treated vessels</td>
<td>1.06 ± 0.64</td>
<td>1.10 ± 0.64</td>
<td>0.150</td>
</tr>
<tr>
<td>AVSc presence, n (%)</td>
<td>495 (46.3%)</td>
<td>447 (46.3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Recurrent AMI</td>
<td>149 (14)</td>
<td>135 (14)</td>
<td>1.000</td>
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Admission laboratory values

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<th>Test Cohort n=966</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>178 ± 43.1</td>
<td>177 ± 43.7</td>
<td>0.750</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>111 ± 38.5</td>
<td>111 ± 39.3</td>
<td>0.877</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>42.8 ± 12.7</td>
<td>43.2 ± 13.4</td>
<td>0.688</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>126 ± 76.2</td>
<td>117 ± 63.2</td>
<td>0.029</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.04 ± 0.503</td>
<td>1.05 ± 1.47</td>
<td>0.984</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>78.4 ± 24.9</td>
<td>78.5 ± 23.9</td>
<td>0.743</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.9 ± 1.79</td>
<td>13.8 ± 1.81</td>
<td>0.913</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein, mg/dL</td>
<td>16.6 ± 43.2</td>
<td>15.6 ± 37.1</td>
<td>0.890</td>
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In-hospital complications

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<th>Test Cohort n=966</th>
<th>p-Value</th>
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</thead>
<tbody>
<tr>
<td>Cardiogenic shock, n (%)</td>
<td>40 (3.7%)</td>
<td>45 (4.7%)</td>
<td>0.319</td>
</tr>
<tr>
<td>Ventricular fibrillation/ventricular tachycardia, n (%)</td>
<td>66 (6.2%)</td>
<td>74 (7.7%)</td>
<td>0.189</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>114 (10.7%)</td>
<td>106 (11.0%)</td>
<td>0.831</td>
</tr>
<tr>
<td>Acute pulmonary edema, n (%)</td>
<td>74 (6.9%)</td>
<td>75 (7.8%)</td>
<td>0.496</td>
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<tr>
<td>Acute kidney injury, n (%)</td>
<td>96 (9.0%)</td>
<td>84 (8.7%)</td>
<td>0.876</td>
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Discharge therapy

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<tr>
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<th>Test Cohort n=966</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins, n (%)</td>
<td>994 (92.9%)</td>
<td>903 (93.5%)</td>
<td>0.786</td>
</tr>
<tr>
<td>Dual antiplatelet therapy, n (%)</td>
<td>1036 (96.8%)</td>
<td>936 (96.9%)</td>
<td>0.889</td>
</tr>
<tr>
<td>Beta-blockers, n (%)</td>
<td>846 (79.1%)</td>
<td>777 (80.4%)</td>
<td>0.503</td>
</tr>
<tr>
<td>ACE/ARB, n (%)</td>
<td>711 (66.4%)</td>
<td>643 (66.6%)</td>
<td>1.000</td>
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</table>

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.
Patients enrolled
\[ n = 2350 \]

Random splitting

Patients Excluded
lost at follow up (\( n = 230 \))
> 5 missing values (\( n = 84 \))

Dataset consolidation
missing value imputation

Analysed Dataset
\[ n = 1070 \]

Topological Data Analysis (TDA)

Study Cohort
\[ n = 1070 \]

Test Cohort
\[ n = 966 \]

Figure 1

\textit{Figure 1}

267x356 mm (\textit{x} DPI)
Figure 2

Figure 2
267x356 mm (x DPI)
Figure 3

267x356 mm (x DPI)
Figure 4

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**Graphical Abstract**

267x356 mm (x DPI)

**CLINICAL IMPLICATIONS**

- Non-stenotic fibro-calcific aortic valve (AVSc) was an important and independent risk predictor of recurrent AMI, starting at the second year of follow-up after the indexed AMI, in both the study and the external validation cohorts.

- Incorporating AVSc into risk stratification models may improve the accuracy of predicting recurrent AMI and could enhance personalized treatment decisions for AMI patients.