



Left ventricular adverse remodeling after myocardial infarction and its association with vitamin D levels

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ABSTRACT

Background: Vitamin D, a potential cardiovascular risk biomarker, has an unclear role in the adverse left ventricle remodelling (LVAR) after acute myocardial infarction (AMI).

Methods: To evaluate the impact of Vitamin D levels on LVAR in a prospective cohort study of patients with AMI.

Results: 253 patients with AMI were studied, 81 of which (32%) developed, in median 4.1 months after AMI, LVAR. Age, sex, risk factors, type and location of the infarction, clinical presentation, timing and mode of revascularization did not differ between patients with and without LVAR. However, patients with LVAR had lower Vitamin D levels (12.6 vs. 18.7 ng/mL, $p < 0.001$), while higher Vitamin D at baseline protected against LVAR (for increase of 10 ng/mL HR 0.74, CI 0.61–0.90, $p < 0.001$). Plasma levels of C Reactive Protein (CRP), peak Troponin I, indexed left ventricular end systolic volume (LVESVI) and NYHA class at discharge predicted, in multivariate analysis, LVAR occurrence at follow-up. Moreover, the inclusion of Vitamin D improved the multivariate model, as shown by the area under the ROC curve (HR 0.82; CI 0.76–0.88, $p < 0.001$). During the follow-up of 25.5 (7–77) months, patients with LVAR had a worse event-free survival rate (HF, $p = 0.012$; combined event HF/mortality, $p = 0.006$), even when the analysis was restricted to patients with ST-elevation MI ($p = 0.006$).

Conclusions: Low Vitamin D levels are associated with post-infarct LVAR.

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1. Introduction

Acute myocardial infarction (AMI) determines a series of geometric and structural changes in the myocardium, involving both the infarcted and noninfarcted zone, which are collectively defined as adverse ventricular remodelling (LVAR) [1,2]. Specifically, cardiomyocyte hypertrophy, together with ongoing cell death, fibrosis, vascular rarefaction, metabolic changes, and inflammation have been associated with the progressive dilation of the left ventricle and predispose to cardiovascular morbidity and mortality [1].

During the last years, several studies tried to establish specific factors that could help in predicting LVAR after the acute ischemic phase. Some predictors were related to patient's characteristics, such as age [3], presence of hypertension [4] or diabetes mellitus [5], but most of all

were related to the time for reperfusion [6], the extension of the ischaemic area (also associated with peak of Troponin I) [7] and to the intensity of inflammatory response [8].

Nevertheless, in spite of the intense research in this area, the identification of specific factors that could predict more accurately the degree of left ventricular dilatation and remodelling after MI is still an unsatisfied need.

Vitamin D is a possible prognostic marker in patients with AMI [9] that has been associated with both the degree of ventricular dilation in HF [10] and with left ventricular geometry in the healthy population [11].

However, the exact pathophysiologic mechanism exerted by Vitamin D deficiency in the development of adverse LV remodelling after myocardial infarction remains unclear. Several studies, conducted in different pathologic settings, revealed an association between Vitamin D levels and: the activation status of the Renin-Angiotensin-Aldosterone System (RAAS), the function endothelial cells and platelets, inflammation, insulin resistance and blood pressure, emphasizing a possible benefit of Vitamin D supplementation in patients with intolerance to ACE-I or ARBs [12,13].

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In the current study, we therefore aimed to evaluate, in patients with AMI, the impact of Vitamin D levels on LVAR, a condition that exerts a negative impact on all-cause death and/or development of heart failure during the follow-up.

2. Materials and methods

2.1. Study population

In this study were prospectively enrolled 253 patients, admitted or transferred to the Cardiovascular Department of the University Hospital in Trieste for both ST segment elevation-MI (STEMI) and non-ST segment elevation-MI (NSTEMI). The diagnosis of AMI was made according to the European Society of Cardiology (ESC) guidelines [14,15]. Each enrolled patient underwent coronary angiography and further received appropriate treatment as recommended by the ESC guidelines (PTCA, bypass surgery, conservative medical therapy) [14,15]. All patients underwent at least one transthoracic echocardiography during the hospitalization.

Vitamin D status was determined by measuring 25(OH)D levels, from fresh plasma samples in a single laboratory. A chemiluminescent test (CLIA) was performed using Liaison (DiaSorin Inc., Saluggia, Italy) instrument.

Clinical data of patients during the hospital stay and at hospital discharge were prospectively entered into database and retrospectively analyzed. Data recorded for each enrolled patient include demographic information, past history, baseline characteristics, medical treatment, procedures, hospital course, and outcomes.

Data on patients' follow-up were obtained by consulting the electronic health records software Cardionet (INSIEL, Trieste) and G2 Clinical (INSIEL, Trieste). The data for those who came from other provinces (Udine and Gorizia), were obtained thanks to the collaboration of the reference hospitals.

The end of the follow-up was either fixed on March 10th, 2017 or the date of death of the patient.

Informed consent was obtained from each patient. The study fulfills the requirements of the Helsinki Declaration and has been approved by the Institutional Review Board of the Hospital-University Hospital and the Regional Ethic Committee. All personal data have been processed in accordance with the current privacy law D.Lgs. 196/2003.

The primary endpoint of the study was the development of LVAR during the follow-up. An increase in left ventricular end-systolic volume (LVESV) greater or equal to 15% with respect to the pre-discharge evaluation was defined as LVAR. In the absence of a consensus, within the scientific community, on the definition of LVAR, we considered LVESV changes as a measure for LVAR since it is one of the major determinants of survival after recovery from AMI [16].

The secondary endpoint was defined as the impact of LVAR on the composite outcome of all-cause death and/or development of heart failure during the follow-up.

Heart failure was diagnosed by the cardiologist only if there was at least one symptom of heart failure (shortness of breath, fatigue, leg oedema with increased central venous pressure) at rest or on exertion and necessity of diuretic prescription or an increase in the daily dosage of the ongoing treatment with diuretics or necessity for hospitalization for heart failure [17].

Left Ventricular Ejection Fraction (LVEF) was estimated with transthoracic echocardiography using the Simpson method. The presence of valvular regurgitation was evaluated using the Doppler color technique. Mitral regurgitation (MR) was assessed semiquantitatively (classified as none, mild, or moderate to severe) by color Doppler analysis of the regurgitant jet area.

All echocardiographic measurements were obtained by cardiologists without knowledge of the clinical status of the patient, from the mean of 3 beats (sinus rhythm) or 5 beats (atrial fibrillation). For interobserver variability two different operators and in a double evaluation by each analyzed echocardiographic images and measured LVESV and left ventricular end-diastolic volume (LVEDV) independently. For intra-observer variability, echocardiographic images were reanalyzed after an average period of 2 weeks. Inter-observer and intra-observer agreement were as follows: 93% and 94% for LVEDV and 92% and 93% for LVESV, respectively.

Creatinine clearance was calculated using MDRD. Vitamin D deficiency was defined as a 25(OH)D level < 20 ng/mL. The maximum Troponin I concentration corresponds to the highest value determined during the hospitalization. Patients with hemoglobin levels lower than 13 g/dL for male and 12 g/dL for females have been identified as anemic.

The GRACE Score (Global Registry of Acute Cardiac Events Risk Score) was calculated by using the official calculator (www.gracescore.org).

2.2. Statistical analyses

Data are presented as mean values (with the SD), as median values (with the interquartile range), or as proportions. Characteristics of patients with or without LVAR were compared by means of the ANOVA or Kruskal–Wallis tests according to the parameter distribution. Post-hoc comparisons between groups were reported using the Bonferroni or Tamhane correction respectively. Categorical variables were compared using the Chi-square test or the Fisher exact test if necessary.

Cox proportional hazard models were used to assess univariate and multivariate predictors of LVAR. The multivariable Cox model included all variables with a p value ≤ 0.2 at univariable Cox regression model (performed on all recorded parameters at baseline

and discharge). Initially, a full multivariable model was estimated and then reduced by means of a backward conditional stepwise procedure in order to minimize collinearity among predictors. Plotting smoothed estimates of covariates versus the probability of event, we checked the linearity assumption. The proportional hazard assumption for covariates selected in the multivariable model was checked by means of the Therneau and Grambsch test.

Receiver-operating characteristics (ROC) analysis was performed to assess the performance of Vitamin D to predict LVAR. Areas under the ROC curve were calculated also for the final multivariable model for LVAR, at Cox regression analysis, with and without Vitamin D. Areas under the ROC curves for these models were compared using DeLong test.

The cumulative probability of events during the follow-up was estimated by the Kaplan–Meier method and curves were compared by the log-rank test.

All statistical tests were two-sided, and statistical significance was set at $p < 0.05$. Statistical analyses were performed using the software IBM SPSS Statistical Package for Mac, version 19, and the R statistical software, version 3.02.

3. Results

3.1. Patients characteristics

The main characteristics of the study population, stratified by the development of LVAR during follow-up, are described in Table 1.

The enrolled population had an average age of 66 years; the diagnosis was STEMI in 174 (68.8%) of cases. In the majority of patients PCI was performed. Of 153 patients with STEMI who underwent primary PCI, post-procedure TIMI flow grades 2–3 occurred in 94% of cases. Emergent/urgent bypass surgery was performed in 7 patients with STEMI and 20 patients with NSTEMI. Conservative treatment after coronary angiography was performed in case of non-obstructive coronary artery disease (CAD), peripheral CAD (<2 mm) or normal coronary angiogram (non-CAD-associated coronary thromboembolism, vasospasm and microvascular disease).

The majority of patients were discharged from the hospital in NYHA class I, in optimized medical therapy and with a median LVEF of 53%.

The median level of Vitamin D in the enrolled population was 16.9 (10.4–23.6) ng/mL.

3.2. Adverse remodelling

Of the 253 patients included in the study, 81 (32%) developed LVAR, in median after 4.1 (3.4–6.2) months from the acute event. We did not find any statistically significant difference between the two groups (with and without LVAR) in terms of age, sex, risk factors, type and location of the infarction, clinical presentation, timing and mode of revascularization, and acute arrhythmic complications. In both groups, there was a comparable proportion of patients with pre-existing myocardial infarction ($p = 0.2$) and with history of coronary angioplasty or coronary artery bypass surgery. There were no significant differences, between the two groups, at pre-discharge echocardiographic evaluation, as well in the frequency of use of ACE-I/ARBs and Beta-Blockers (Table 1).

Compared with the group without LVAR, patients with LVAR had significantly lower Vitamin D levels (12.6 vs. 18.7 ng/mL, $p < 0.001$) (Fig. 1). In addition, CRP levels were higher in the group with LVAR ($p = 0.02$) (Table 1). The group with adverse remodelling had also a slightly higher peak Troponin I ($p = 0.07$) (Table 1).

The receiver operating characteristic curve of Vitamin D at admission showed a cut-off level of 14.5 pg/mL for predicting LVAR, with an area under the curve of 0.73, sensitivity of 69%, and specificity of 62% (95% CI 0.65–0.8, $p < 0.001$) (Fig. 2a).

The results of univariate and multivariate Cox analyses to predict LVAR are listed in Table 2.

At multivariate analysis, higher Vitamin D at baseline was independently associated with a lower likelihood of LVAR (for increase of 10 ng/mL HR 0.74, CI 0.61–0.90, $p < 0.001$) (Table 2). Other parameters significantly associated with development of LVAR during the follow-up

Table 1
Baseline characteristics of patients stratified by left ventricular adverse remodelling (LVAR) during the follow-up.

	All patients n = 253 (100%)	Pts with LVAR n = 81 (32%)	Pts without LVAR n = 172 (68%)	p*
Age (years)	66.3 (10.9)	66.7 (11.1)	66.2 (10.9)	0.7
Gender (male) (%)	79.8	77.8	80.8	0.6
BMI (kg/m ²)	26.9 (3.9)	27 (3.6)	26.8 (3.9)	0.7
Systolic blood pressure (mm Hg)	137.5 (25.2)	138.8 (28.2)	136.9 (23.7)	0.6
Diastolic blood pressure (mm Hg)	78.7 (13.2)	77.8 (14.6)	79.2 (12.5)	0.4
Heart rate (bpm)	75.1 (15.1)	76.3 (15.7)	74.5 (14.8)	0.4
Cardiac arrest (%)	1.6	1.2	1.7	0.8
LBBB (%)	6.5	7.7	6.1	0.7
STEMI (%)	68.8	70.4	68	0.7
NSTEMI (%)	31.2	29.6	32	
KILLIP class > I (%)	25.3	8.3	17	0.9
Season (%)				
Spring	13.8	17.1	12.3	0.6
Summer	31.4	32.9	30.7	
Autumn	39.7	34.2	42.3	
Winter	15.1	15.8	14.7	
Hypertension (%)	67.1	69.1	66.1	0.6
Diabetes mellitus (%)	26.6	24.7	27.5	0.6
Dyslipidemia (%)	56.9	58	56.4	0.81
Smoking (%)	51.8	53.1	51.2	0.8
Familiarity for premature MI (%)	28.9	28.4	29.1	0.9
CKD at admission (%)	10.7	3.2	7.5	0.8
PAOD (%)	9.1	9.9	8.7	0.8
Previous MI (%)	16.6	21	14.5	0.2
Previous PTCA (%)	15.4	19.8	13.4	0.2
Previous CABG (%)	3.6	0.8	2.8	0.5
Anemia at admission (%)	30	35.8	27.3	0.2
Total cholesterol (mg/dL)	188.0 (48.2)	185.3 (53.6)	189.3 (45.5)	0.5
HDL cholesterol (mg/dL)	44.7 (11.5)	44 (12.1)	45.1 (11.2)	0.9
LDL cholesterol (mg/dL)	117.9 (40.2)	116.4 (45)	118.3 (37.8)	0.5
Triglyceride (mg/dL)	111 (83.3–151.5)	113 (82–143)	109 (84.5–161)	0.1
Albumin (mg/dl)	3.7 (0.4)	3.6 (0.3)	3.7 (0.4)	0.6
Troponin I max (ng/mL)	26 (6.1–69)	37.2 (6.4–104.2)	23.6 (5.7–57.5)	0.07
Hb1AC (%)	5.9 (5.6–6.3)	5.9 (5.6–6.3)	5.8 (5.6–6.3)	0.04
Vitamin D (ng/mL)	16.9 (10.4–23.6)	12.6 (6.8–19)	18.7 (13.1–26.1)	< 0.001
CRP (mg/L)	7.94 (3.2–21.8)	13.2 (4.6–37.5)	6.9 (2.7–17.6)	0.02
Sodium at discharge (mEq/L)	139 (2.2)	138.8 (7.7)	139.1 (2.1)	0.6
Hb at discharge (g/dL)	12.7 (2.3)	12.5 (1.7)	12.8 (2.5)	0.3
GFR at discharge (mL/min/m ²)	78.4 (25.8)	77.8 (26.6)	78.8 (25.4)	0.1
GRACE Score at six months	130.6 (33.9)	138.5 (40.9)	126.9 (29.5)	0.01
Left atrial diameter (cm)	3.9 (0.7)	3.9 (0.7)	3.9 (0.7)	0.9
Left atrial area (cm ²)	22.2 (5.4)	21.8 (5.3)	22.3 (5.5)	0.6
LVEDDI (cm/m ²)	2.6 (2.4–2.9)	2.7 (2.6–3)	2.6 (2.4–2.9)	0.5
LVESDI (cm/m ²)	1.7 (1.5–2)	1.6 (1.4–2.1)	1.7 (1.5–2)	0.4
IVS (cm)	1.3 (1.1–1.4)	1.4 (1.1–1.5)	1.3 (1.1–1.4)	0.3
FS (%)	35.5 (11.2)	37 (15.4)	35.1 (9.9)	0.5

Table 1 (continued)

	All patients n = 253 (100%)	Pts with LVAR n = 81 (32%)	Pts without LVAR n = 172 (68%)	p*
LVEDVI (mL/m ²)	48.9 (39.1–57.5)	45.6 (36.6–57.9)	49.8 (39.5–57.5)	0.5
LVESVI (mL/m ²)	21.5 (15.4–28.8)	22.1 (13.6–29.5)	22.2 (17.5–30.6)	0.6
E/A	1.1 (0.9)	1 (0.5)	1.2 (0.7)	0.4
E/E'	12.5 (5.3)	13.6 (5.2)	12.2 (5.3)	0.3
WMSI	1.4 (1.1–1.8)	1.4 (1.2–1.9)	1.4 (1.1–1.8)	0.4
LV mass (g)	236.7 (66.1)	260.7 (58.2)	230.5 (66.9)	0.08
LVEF (%)	54 (46–60.5)	54 (45–64)	54 (47–60)	0.4
MR (%)	68.5	69.2	68.4	0.9
Mild	62.9	65.4	62.2	0.9
Moderate	4.8	3.8	5.1	
Severe	0.8	0	1	
Acute treatment (%)				
PTCA	76.2	80.2	74.3	0.4
CABG	10.7	11.1	10.5	
Medical therapy	13.1	8.6	15.2	
Time for PTCA (h)	4.02 (4.4)	4.1 (4.1)	3.4 (4.5)	0.9
GP IIb/IIIa inhibitors (%)	14.8	16.9	13.9	0.6
Multivessel disease > 70% (%)	41.4	41.3	41.4	0.9
Supraventricular arrhythmias (%)	11.5	8.6	12.8	0.3
Ventricular arrhythmias (%)	13.5	17.3	11.7	0.3
Bradiarrhythmias (%)	8.7	6.2	9.9	0.3
ACE-I/ARBs (%)	77.7	82.7	75.3	0.2
Beta-blockers (%)	84.5	88.9	82.4	0.2
Digitalis (%)	1.2	1.2	1.2	0.9
Amiodarone (%)	7.2	4.9	8.3	0.3
Antialdosteronic therapy (%)	8.8	12.3	7.1	0.2
Loop diuretics (%)	19.9	8.8	11.2	0.1
Acetylsalicylic acid (%)	95.6	96.3	95.3	0.7
P2Y12 receptor inhibitors (%)	86.9	27.9	59	0.9
Clopidogrel (%)	62.4	68.8	59.4	0.5
Prasugrel (%)	18.8	13.8	21.2	
Ticagrelor (%)	6	5	6.5	
Statins (%)	90.4	85.2	92.9	0.1
Oral antidiabetics (%)	14.7	12.3	15.9	0.5
Insulin (%)	8.5	9.9	7.7	0.6
Oral anticoagulants (%)	9.2	4.9	11.2	0.1
NYHA class at discharge (%)				
I	88.1	81.5	91.3	0.1
II	7.1	9.9	5.8	
III	4.7	8.6	2.9	

Legend: BMI: Body Mass Index; STEMI: ST-segment elevation myocardial; NSTEMI: Non-ST-segment elevation myocardial infarction; MI: myocardial infarction; CKD: Chronic Kidney Disease; PAD: Peripheral arterial occlusive disease; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass grafting; HbA1C: Hemoglobin A1c (glycated hemoglobin); CRP: C-reactive Protein; Hb: haemoglobin; GFR: estimated glomerular filtration rate; LBBB: Left Bundle Branch Block; LVEDDI: left ventricular end diastolic diameter indexed; LVESDI left ventricular end systolic diameter indexed; IVS: interventricular septum; FS: Fractional Shortening; LVEDVI: left ventricular end diastolic volume indexed; LVESV: left ventricular end systolic volume indexed; LV: left ventricular; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; ACEi/ARBs: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; NYHA: New York Heart Association.

* p value showing statistical significance in comparison between subgroup with and without left ventricular adverse remodelling.

at multivariate analysis were: plasma levels of CRP, peak Troponin I, indexed LVESV and NYHA class at discharge (Table 2).

Further, the C-statistics of the Cox multivariate model predicted probability with and without Vitamin D was tested; Fig. 2b illustrates improvement in area under the ROC curve for inclusion of Vitamin D in the multivariate model (De Long test p = 0.01).

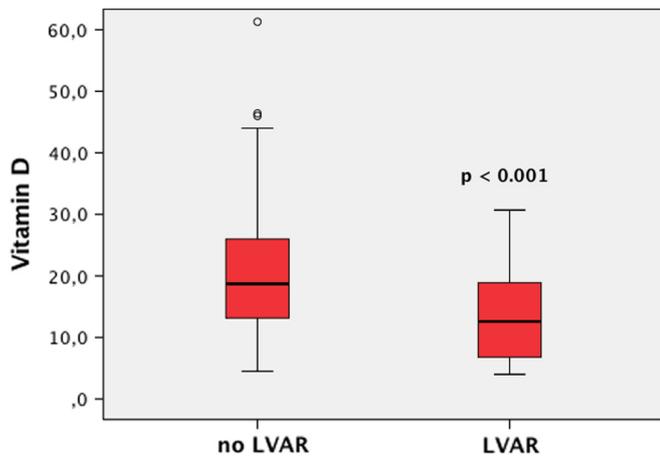


Fig. 1. Median level of Vitamin D in the enrolled population stratified by left ventricular adverse remodelling (LVAR) during the follow-up.

3.3. Death/Heart Failure

During the median follow-up of 25.5 (7–77) months after enrollment, there were 64 events (25 patients died, 39 had heart failure, 9 patients had first admission for heart failure and subsequently died). When stratified according to the subsequent development of LVAR, the event-free survival rate was significantly worse in the patients with LVAR than in those without LVAR (heart failure, $p = 0.012$; combined event heart failure/mortality, $p = 0.006$, Supplementary Figs. 1a, 2a), whereas there was no significant difference in mortality between the LVAR and non LVAR group ($p = 0.103$, Supplementary Fig. 3a). The same trend was observed if analyses were limited only to patients with STEMI (Supplementary Figs. 1b, 2b, 3b).

4. Discussion

The main novel finding of the current study is that low Vitamin D plasma levels are associated with the development of LVAR. In line with literature data, we observed that patients with LVAR had a higher rate of events during the follow-up. The population included in this study is highly representative of patients with myocardial infarction, as it is largely in line with the worldwide and Italian epidemiological

data, not only from a demographic point of view (age, gender), but also the frequency of major risk factors associated with ischemic heart disease [18,19]. Also, the trend of events occurring during the follow-up period faithfully reproduces what emerged in other studies [20].

4.1. Left ventricular remodelling

Adverse LV remodelling occurs frequently after acute MI, and its prevalence ranges from 12 to 44% [21], depending on the included population, timing of imaging and revascularization mode. In line with literature data, 32% of our study patients developed LVAR. Adverse remodelling is usually defined by an increase in LVEDV/LVESV of 15 to 20% from baseline. Since LVESV is one of the major determinants of survival after AMI [16], we assessed LVAR from the change in LVESV between pre-discharge and follow-up examinations.

Left ventricular (LV) remodelling occurs over a series of steps, such as: infarct expansion, myocardial wall thinning, cardiomyocyte hypertrophy and lengthening, and progresses to LV dilatation [22]. According to White et al., patients with a LV dilation after AMI have a significantly reduced survival, so that enlarged and weakened LV could be used as a predictor of survival in patients with coronary heart disease [16]. Several studies have investigated the importance of early reperfusion therapy and patency of the infarct-related artery for reducing infarct expansion and LV enlargement. It has also been suggested that early reperfusion therapy could help improving patients survival by decreasing infarct size and, consequently, preserving LV function [6,16,23].

4.2. Vitamin D and post-infarction adverse left ventricular remodelling

Vitamin D deficiency is highly prevalent among patients with myocardial infarction [24]. A growing body of literature already exists on the negative impact exerted by Vitamin D deficiency on the prognosis of patients affected by acute myocardial infarction [9,25,26]. However, the association between Vitamin D deficiency and the occurrence of LV remodelling following acute myocardial infarction has not been adequately investigated yet, in spite of the major role played by LVAR in heart failure and death [21,27,28].

The correlation, that we report in this work, between Vitamin D and post-infarction adverse left ventricular remodelling, strongly supports the important role played by Vitamin D in the cardiovascular system physiology [29,30]. In line, although Vitamin D is mainly produced *de novo* through scission of cholesterol precursors in the skin by ultraviolet

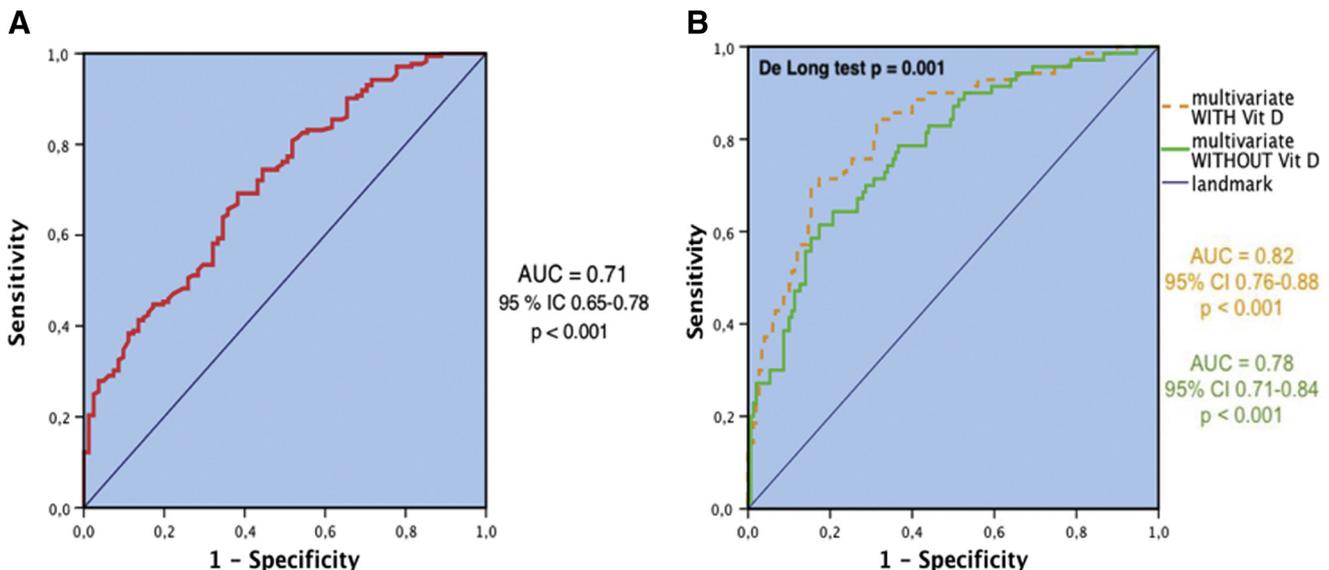


Fig. 2. a. ROC curve of Vitamin D levels and LVAR: higher Vitamin D at baseline was independently associated with a lower likelihood of LVAR. b. ROC curves of multivariate models: improvement of the area under the ROC curve resulting from the inclusion of Vitamin D in the multivariate model.

Table 2

Predictors of left ventricular adverse remodelling (LVAR) at univariate and multivariable Cox proportional hazards regression analysis.

	UNIVARIATE		MULTIVARIATE	
	HR (95% CI)	p	HR (95% CI)	p
Age	1.01 (0.98–1.03)	0.70	–	–
Male gender	1.20 (0.63–2.29)	0.85	–	–
BMI	1.01 (0.95–1.08)	0.72	–	–
STEMI	0.89 (0.50–1.59)	0.71	–	–
Obesity	0.86 (0.45–1.66)	0.67	–	–
Cardiac arrest	1.42 (0.15–13.87)	0.76	–	–
KILLIP class > I	0.95 (0.52–1.74)	0.87	–	–
Hypertension	0.87 (0.49–1.54)	0.63	–	–
Diabetes mellitus	1.16 (0.63–2.12)	0.64	–	–
Dyslipidemia	0.94 (0.55–1.59)	0.81	–	–
Smoking	0.93 (0.55–1.57)	0.78	–	–
Familiarity for premature MI	1.03 (0.58–1.85)	0.91	–	–
CKD at admission	1.13 (0.47–2.71)	0.78	–	–
Previous MI	0.64 (0.32–1.27)	0.20	–	–
Previous PTCA	0.63 (0.31–1.27)	0.19	–	–
Troponin I max (for increase of 10 unit)	1.00 (1.00–1.01)	0.02	1.04 (1.02–1.06)	<0.001
Hb1AC %	0.99 (0.79–1.23)	0.89	–	–
Vitamin D (for increase of 10 unit)	0.90 (0.87–0.94)	<0.001	0.74 (0.61–0.90)	<0.001
CRP (for increase of 10 unit)	1.01 (1.00–1.01)	0.01	1.05 (1.01–1.09)	0.02
Sodium at discharge	0.94 (0.78–1.15)	0.55	–	–
Creatinine at discharge	1.15 (0.73–1.81)	0.55	–	–
Hb at discharge	0.93 (0.80–1.07)	0.29	–	–
Anemia at discharge	0.67 (0.39–1.15)	0.14	–	–
Serum albumin	1.03 (0.47–2.26)	0.9	–	–
Season of enrolment	1.1 (0.8–1.4)	0.5	–	–
CKD at discharge	1.00 (0.54–1.87)	0.99	–	–
GFR at discharge	0.99 (0.99–1.01)	0.79	–	–
LVESVI at discharge (for increase of 5 mL/BSA)	0.98 (0.97–0.99)	0.01	0.84 (0.77–0.92)	<0.001
LVEF at discharge	1.01 (0.99–1.04)	0.31	–	–
ACE-I/ARBs	0.67 (0.33–1.25)	0.19	–	–
Beta-blockers	0.58 (0.26–1.29)	0.19	–	–
Loop diuretics	0.53 (0.28–0.99)	0.05	–	–
Antidopaminergic therapy	0.54 (0.22–1.31)	0.17	–	–
NYHA class I vs II-III	0.42 (0.19–0.91)	0.03	0.07 (0.01–0.33)	0.001

Legend: BMI: Body Mass Index; STEMI: ST-segment elevation myocardial; CKD: Chronic Kidney Disease; AMI: acute myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; HbA1C: Hemoglobin A1c (glycated hemoglobin); CRP: C-reactive Protein; Hb: GFR: estimated glomerular filtration rate; LVESVI: left ventricular end systolic volume indexed; LVEF: left ventricular ejection fraction; ACEi/ARBs: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; NYHA: New York Heart Association.

light [31], Vitamin D-dependent signaling systems are present in cardiac myocytes and fibroblasts [32]. Importantly, Vitamin D deficiency has been shown to lead to alterations in: cardiac myocyte contractility, abnormal cardiac relaxation, protein expression, and increased cardiac renin gene expression [30,33,34].

Furthermore, Vitamin D can decrease the RAAS activity both in animal models and in humans [33,34]. This implies that deficiency of Vitamin D or Vitamin D receptor signaling may amplify the pathologic response to a variety of metabolic or physiological perturbations associated with cardiovascular disease. Moreover, evidence has been accumulated indicating that chronic Vitamin D deficiency causes an increase in Parathyroid Hormone concentrations, and that this latter can elevate the risk of different cardiovascular diseases, enhancing inflammation [35]. Bae et al. [36] showed, in a murine model, that the administration of the activated Vitamin D analogue Paricalcitol attenuates the development of heart failure following AMI. Specifically, Paricalcitol reduced RAAS activation, cardiomyocyte apoptosis, and both inflammation and fibrosis. On the contrary, a dramatic progression of ventricular remodelling to heart failure has been observed in mice lacking the Vitamin D receptor [37]. These results are of clear importance, since

they highlight a link between Vitamin D and some of the most important promoters of post-infarction LVAR in humans; inflammation and the RAAS, where the latter potently promotes ventricular remodelling, as shown by the protective effects exerted by ACE-I and ARBs [37]. Moreover, experimental data obtained on Vitamin D receptor null mice have shown that Vitamin D is an endocrine suppressor of renin biosynthesis [35], supporting the observation that, in our study, those patients with lower levels of Vitamin D subsequently developed adverse remodelling. In line, Ameri et al. explored a possible link between hypovitaminosis D and ventricular geometry alteration, especially hypertrophy, in healthy patients [11]. The authors noted a remarkable relation between hypovitaminosis D, hypertension (one of the main consequences of RAAS activation) and ventricular hypertrophy (possibly due to Angiotensin II activity) [11,38]. Last, with regard to the effect of Vitamin D on inflammation, it is well assessed that it exerts potent immunomodulatory effects, linking innate and adaptive immunity [29].

4.3. Inflammation and ventricular remodelling

Inflammation plays a significant role in the development of adverse remodelling. In our study, patients with adverse remodelling had higher CRP levels and it was independent predictor at Cox multivariate model. According to this relation, the patients enrolled in this study who develop adverse remodelling not only show higher CRP levels (and thus a greater inflammatory response) in comparison to the other group, but also have a lower Vitamin D level, which is a mediator that can down regulate the inflammation and so restraining the unfavourable remodelling. Eren et al. [39] did not observed a significative correlation between Vitamin D, CRP and other markers of inflammation, but this study included a restricted number of patients with STEMI. The relationship highlighted in our report is supported by the work of Arnson et al. [40], that has evaluated patients suffering from AMI and hypovitaminosis D. The aim was to examine the levels of inflammatory cytokines and their modification following the administration of supplemental Vitamin D. The result was a significant reduction of both levels of CRP and mediators such as Tumor necrosis factor (TNF)-alpha, Interleukin (IL)-6 and IL-8, which are some of the most involved cytokines in the induction of left ventricular adverse remodelling [40]. Other studies, that did not focus on myocardial ischemia, showed the protective role of Vitamin D against inflammation and oxidative stress. Specifically, vitamin supplementation of otherwise healthy subjects, affected by hypovitaminosis D, reduced oxidative stress markers [41]. Further, a recent meta-analysis [42] confirmed that vitamin D supplementation, significantly reduce the levels of inflammatory markers such as hs-CRP and oxidative stress in patients with diabetes mellitus. Similarly, experimental models conducted on mice exposed to cigarette smoke demonstrated a protective role for Vitamin D against oxidative stress, inflammation and subsequent ventricular remodelling [43]. Last, observational studies conducted on a healthy population showed that people with lower Vitamin D levels presented more signs of endothelial dysfunction and higher concentrations of pro-inflammatory cytokines [44].

Another essential connection between Vitamin D and adverse remodelling regards matrix metalloproteinase (MMP)-9 [45]. This latter, whose expression is activated by inflammatory cytokines, can degrade the extracellular matrix and is a strong and early marker of left ventricular remodelling [46]. However, according to the study led by Khalili et al. [45] among patients with acute myocardial infarction has been revealed an inverse relationship between serum levels of Vitamin D and MMP-9. This result suggests the existence of a further role of Vitamin D in the regulation of the events that lead to post-infarct left ventricular adverse remodelling.

Therefore, taking into account both the cited literature data, obtained in animal models and in humans, and considering the evidence provided from our study on the pathophysiological connections between Vitamin D and adverse remodelling, it would be very important

to prospectively assess if the supplementation of Vitamin D can prevent LVAR in patients with AMI. In this regard, Polat et al. carried out a study including patients with dilated cardiomyopathy [47] and observed that those with lower Vitamin D plasma levels had more conspicuous left ventricular dilatation and dysfunction. Moreover, Witte et al., [48] evaluated the effect of Vitamin D supplementation in patients affected by heart failure (both of ischemic and non-ischemic origin) and hypovitaminosis D. Despite the intervention did not lead to a significant recovery from symptoms, a significant improvement of cardiac morphology and function, in terms of both left ventricle ejection fraction and volumetric parameters, was documented [48]. These results suggest a role for Vitamin D on reverse ventricular remodelling.

Last, the results of our study are novel, hypothesis generating and could have some remarkable implications on clinical practice. In fact, if lower levels of Vitamin D were linked to the development of LVAR, then the supplementation therapy could prove to be useful to reduce the occurrence of changes in the left ventricular structure early after AMI. In particular, it could be possible to take advantage of the role of Vitamin D as RAAS inhibitor, most of all for those patients who cannot be treated with optimal doses of ACE-I/ARBs because of their side effects, such as hypotension or intolerance. So, an early administration of Vitamin D could probably help to complete the inhibition of RAAS, even in those cases in which the administration of ACE-I/ARBs at their most effective doses would not be possible. Clinical trials in those patients with insufficient Vitamin D status may also be useful to assess any beneficial effect of Vitamin D supplementation on insulin resistance. Moreover, the administration of supplemental Vitamin D should be thoroughly evaluated, in light of the results emerged from our study, in its ability to restrain the development of adverse remodelling in patients affected by AMI. In particular, the next step would be to measure Vitamin D plasma levels among AMI patients as soon as they are admitted in the hospital, in order to identify precociously those who need an optimization and start it soon, with the purpose to reduce the incidence of LVAR. In line, we are intrigued by the future results of the clinical trial VITDAMI, whose purpose is to investigate whether post-infarction left ventricular remodelling would be affected or not by a supplemental administration of Vitamin D [49].

4.3.1. Study limitation

Possible limits of our study are related to the fact that not all the patients suffering from acute myocardial infarction are subjected to an echocardiographic assessment during follow-up. However, the very same issue can nevertheless be found in other studies aimed to investigate ventricular remodelling post-infarction [21,28]. Moreover, a potential concern is that we used echocardiography for the study of LV remodelling, instead of Cardiac Magnetic Resonance (CMR). Nevertheless, CMR is not yet a technique applicable as a routine exam for follow-up of patients with AMI because of some significant limitations, such as limited availability, higher costs, duration of the exam etc. Another possible limitation could be that the levels of Vitamin D have been measured only once at the admission, without studying its possible fluctuations during the follow-up period. However it has been already demonstrated that no significant changes of Vitamin D levels can be documented in the months following an acute myocardial infarction [50]. Further, we did not consider variables as latitude, sunlight exposure, skin color and vitamin D intake. However, we enrolled Caucasian patients from the same geographic area, including Trieste, Gorizia and Udine, so we do not expect variations in Vitamin D related to the skin color and latitude. Finally, BNP was assessed only in a small subgroup patient presenting signs of heart failure during the hospital stay and it was not included in the multivariate analysis.

5. Conclusions

In the present study we have shown, for the first time, that low levels of Vitamin D are associated with adverse ventricular remodelling after

myocardial infarction. This finding underlines the need to better clarify the main mechanism of action of Vitamin D, that could be able to prevent LVAR after AMI. Furthermore, it remains to be clarified whether the association emerged in our study may also have therapeutic implications, and therefore if optimization of Vitamin D levels can actually help reduce the frequency of unfavourable remodelling post-AMI.

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Disclosure

The authors have no conflict of interest to disclose.

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