U-shaped relationship between vitamin D levels and long-term outcome in large cohort of survivors of acute myocardial infarction

Aneta Aleksova [a,*], Antonio Paolo Beltrami [b], Rita Belfiore [a], Giulia Barbati [a], Milena Di Nucci [c], Sara Scapol [a], Valerio De Paris [a], Cosimo Carriere [a], Gianfranco Sinagra [a]

[a] Cardiovascular Department, "Ospedali Riuniti" and University of Trieste, Trieste, Italy
[b] Department of Medical and Biological Sciences, University of Udine, Italy
[c] Department of Internal Medicine and Degenerative-Atherothrombotic Diseases, University Hospital of Verona, Italy

A R T I C L E   I N F O

A B S T R A C T

Background: Previous studies in the setting of patients with acute myocardial infarction (AMI) have demonstrated that hypovitaminosis D is associated with increased mortality risk during a follow-up whose median did not exceed two years.

Objective: To evaluate the impact of vitamin D levels on long-term mortality in patients with AMI.

Results: In our study 477 patients with AMI were included. During a median follow-up period of 57 (IQR 53–64) months, 93 patients (20%) died. A non-linear U-shaped relationship between 25(OH)D levels and long-term mortality was observed; patients with vitamin D < 10 ng/mL and >30 ng/mL had higher mortality rate than those with intermediate values. After adjustment for differences in baseline features and treatment, it was confirmed that extreme values of vitamin D (<10 or >30 ng/mL) are independent predictors of mortality with HR of 3.02 (95% CI 1.78–5.11). Other independent predictors of outcome were age, NYHA class at discharge, treatment with ACE inhibitors and statins. The estimated time-dependent ROC curve of the multivariable model including vitamin D showed an AUC significantly higher than the model without vitamin D: AUC 0.82 (95% CI 0.76–0.87) vs. 0.77 (95% CI 0.71–0.83), p = 0.005. Addition of vitamin D to the model that included all significant factors for mortality improved the prognostic accuracy as showed by the metrics of reclassification (NRI 0.34 (95% CI 0.14–0.48), p = 0.003 and IDI 0.06 (95% CI 0.01–0.12, p = 0.005 p = 0.03).

Conclusions: We report a U-shaped relationship between vitamin D levels and long-term outcome of patients surviving AMI.

1. Introduction

Worldwide, the deficiency of vitamin D, or that of 25-hydroxyvitamin D (25[OH]D), its main circulating form in the blood, currently exceed 50% [1]. Additionally, vitamin D deficiency has been described to be frequent in patients with myocardial infarction [2–4] and to correlate with markers of unfavorable cardiac remodeling and mortality following the acute cardiac event [5,6].

Many observational studies have associated low vitamin D status with increased risk of death [7–9]. Some of these studies, as well as a recently published Cochrane review [10] of 56 randomized trials with 95,286 participants, suggested a beneficial effect of vitamin D3 on mortality. These findings suggest the potential utility of vitamin D supplementation as a therapeutic intervention to decrease mortality.

Nevertheless, more recent community based studies, such as Copenhagen Vitamin D study (CopD-study) [1,11] and U.S. Nationally Representative NHANES [12] have suggested a reverse J-shaped association between serum 25-hydroxyvitamin D, cardiovascular and all-cause mortality.

In the setting of survivors from acute myocardial infarction, two recent studies [4,13] have shown that patients from the lowest vitamin D quartile (<7.3 ng/mL and <9 ng/mL, respectively) have higher major adverse events (MACE) and mortality risk during a follow-up whose median did not exceed two years.

In this study, we newly analyzed whether vitamin D levels are associated with the long-term all-cause mortality of patients with previous myocardial infarction.

2. Materials and methods

2.1. Study population

A total of 477 consecutive patients admitted for acute myocardial infarction (AMI) from June 2009 to December 2010 were included in this study. The diagnosis of

myocardial infarction (ST segment elevation (STEMI)) and non-ST segment elevation (NSTEMI) was made according to ECS guidelines [14]. At enrollment all patients underwent coronary catheterization and transthoracic echocardiogram and were subjected to blood count, fasting plasma glucose tests, liver and kidney function tests, lipid profile, parathyroid hormone (PTH), serum calcium and phosphorus determinations.

Vitamin D was measured from fresh plasma samples. A chemiluminescent test (CLIA) was performed using Liaison (DiaSorin Inc., Saluggia, Italy) instrument.

The end of the follow-up was set to 11 June 2015 or the date of death of the patient. Information regarding endpoints was obtained by reviewing the local hospital database Cardionet (INSIEL, Trieste). This study was approved by the Institutional Hospital Ethics Committee and was performed in accordance with the declaration of Helsinki. All subjects provided a written informed consent prior to inclusion in the study.

2.2. Statistical analysis

Continuous variables are presented as mean (standard deviation) or median and interquartile range, as appropriate. Baseline characteristics of patients in different vitamin D groups were compared by means of the ANOVA or Kruskal–Wallis tests according to the parameter's distribution. Post-hoc comparisons between groups were reported using the Bonferroni or Tamhane correction respectively. Categorical variables are presented as percentages and were compared using the Chi-square test or the Fisher exact test if necessary.

Cox proportional hazards regression was used to evaluate the relationship between baseline data and long-term outcome and to assess prognostic value of vitamin D status. Covariates were selected from univariable Cox regression models performed on all parameters recorded at baseline, and those with a p value ≤ 0.1 were retained in the final list. A full initial 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 checked the linearity assumption. The proportional hazard assumption for covariates selected in the multivariable model was checked by means of the and Therneau and Grambsch test [15]. Time-Dependent Area Under Receiver-Operating-Characteristic curves for censored data (TD-ROC) [16] were estimated both to evaluate the Cox model predictive accuracy at different follow up times and to evaluate the incremental prognostic value of adding vitamin D. The discriminative additive value of vitamin D on mortality was also assessed using the category-free Net Reclassification Improvement (cfNRI) and the Integrated Discrimination Improvement (IDI) indexes for censored data. The predicted probabilities of event estimated by the Cox multivariable models with or without vitamin D were considered as markers [17].

A two-tailed $p < 0.05$ was considered statistically significant for all test results. All analyses were performed using the software IBM SPSS Statistical Package for Windows, version 19, and the R statistical software, version 3.02, libraries "survival", "timeROC" and "survIDINRI".

3. Results

3.1. Patients characteristics

A total of 477 patients (mean age 66.8 (11.6) years; male 69.6%) were included in the present study (STEMI 47.2%; NSTEMI 52.8%).

At admission 93.9% were in Killip class I–II. The mean GRACE score was 140.2 (35.6). All patients included in our study underwent coronary angiography within 24 h of hospital admission. Coronary revascularization was performed in the majority of them; of the 226 presenting with STEMI, 79.2% underwent primary percutaneous coronary angioplasty (success rate > 99%); among the 251 patients with NSTEMI, 80.2% received percutaneous coronary intervention or coronary artery bypass surgery (CABG) (success rate > 99%) during the index hospitalization. The modality of the revascularization was made according to current guidelines. In particular, the clinical presentation, comorbidities, risk stratification, presence of high-risk features specific for a revascularization modality, and functional and anatomic severity, as well as pattern of coronary artery disease (CAD), together with the risk in terms of morbidity/mortality associated with the proposed strategy (PCI or CABG), were taken into account. Conservative treatment after coronary angiography was performed in patients with acute myocardial infarction not amenable to revascularization (17% of patients) for: 1) presence of nonobstructive CAD, 2) presence of peripheral CAD (<2 mm), 3) presence of normal coronary angiogram (non-CAD-associated coronary thromboembolism, vasospasm and microvascular disease) or 4) prolonged delay between the onset of symptoms and hospital admission (>12 h) in patients with STEMI.

The mean serum 25-OH D concentration was 16.6 (11.1) ng/mL. According to different 25(OH)D plasma levels, we distinguished 4 groups of patients: group 1 — below 10 ng/mL, group 2 — between 10 and 20 ng/mL, group 3 — between 20 and 30 ng/mL and group 4 — above 30 ng/mL. Clinical and instrumental characteristics of patients stratified according to vitamin D levels are described in Table 1.

Patients with lower levels of 25(OH)D (groups 1–2) were predominantly females and were more likely to have higher levels of alkaline phosphatase and PTH.

There were no significant differences in past medical history of hypertension, dyslipidemia or diabetes mellitus, previous myocardial infarction or percutaneous coronary intervention/CABG, type of myocardial infarction (STEMI vs. NSTEMI), Killip class and GRACE score range between the 4 groups of patients stratified by serum vitamin D levels.

At hospital-discharge, there were no significant differences among groups regarding principal cardiac factors influencing survival such as NYHA functional class, mitral regurgitation, left ventricular function, size and wall motion score index. The majority of patients had normal renal function too. The four groups differed regarding the treatment with loop diuretics at discharge, while there were no differences regarding treatment with ACE inhibitors, beta blockers and statins.

3.2. Vitamin D levels and long-term all-cause mortality

During a median follow-up period of 57 (IQR 53–64) months, 93 patients (20%) died. A non-linear U-shaped relationship between 25(OH)D levels and long-term mortality was observed (Fig. 1A). Patients with vitamin D lower than 10 ng/mL and higher than 30 ng/mL had higher long-term mortality rate than those with intermediate values (Fig. 1A and B).

The independent prognostic value of serum 25(OH)D level for the end-point total mortality was tested in the Cox proportional hazard model (Table 2). After adjustment for differences in baseline features and treatment, our previous observation that extreme values of vitamin D (below 10 ng/mL or above 30 ng/mL) are independent predictors of long-term mortality with HR of 3.02 was confirmed. Other independent predictors of outcome were age, NYHA class at discharge, treatment with ACE inhibitors and statins (Table 2). The proportional hazard assumption for the covariates selected in the multivariable model was satisfied (Grambsch and Therneau test global p value = 0.638, for each covariate p > 0.12). The estimated time-dependent ROC curve at 48 months of the multivariable model including vitamin D showed an AUC significantly higher than the model without vitamin D: AUC 0.82 (95% CI 0.76–0.87) with respect to AUC 0.77 (95% CI 0.71–0.83), p = 0.005 (Fig. 2). Addition of vitamin D to the model that included all significant factors for mortality improved the prognostic accuracy as showed by the metrics of reclassification; for early outcomes NRI and IDI were respectively 0.27, 95% CI 0.08–0.47, p = 0.001, and 0.041, 95% CI 0.01–0.10, p = 0.006. For the long-term follow-up (48 months) NRI and IDI were respectively 0.34 (95% CI 0.14–0.48), p = 0.003 and 0.06 (95% CI 0.01–0.12), p = 0.005. This reclassification was mainly driven by the event component of the NRI, respectively for early outcome NRI for events 0.64 vs NRI non-events 0.37, for long-term outcomes NRI for events 0.69 vs NRI non-events 0.35.

4. Discussion

This study showed a non-linear U-shaped relationship between 25(OH)D levels and long-term mortality in a large cohort of survivors after acute myocardial infarction. During a follow-up period of approximately five years, patients with 25(OH)D plasma concentration lower than 10 ng/mL and higher than 30 ng/mL had the worse outcome, in comparison to patients with intermediate values of vitamin D.

Our findings are in accordance with the recent observation from the large community based studies with long-term follow-up [1,11,12], but

Table 1

Baseline characteristics of the study patients according to vitamin D.

	All n = 477	Vit D < 10 ng/mL n = 162	Vit D 10–20 ng/mL n = 162	Vit D 20–30 ng/mL n = 106	Vit D >30 ng/mL n = 47	Global p value
Age (years)	66.8(11.6)	69.8(10.9)	64.8(12)	65.2(10.6)	66.7(12.7)	0.001
Male gender (%) [.,‡,∞]	69.6	59.3	69.1	80.2	83.0	<0.001
Smoking (%)						
Present	33.8	34.0	35.2	34.9	25.5	0.93
Past	20.3	19.8	19.8	19.8	25.5	
Hypertension (%)	66.5	65.4	67.3	66.0	68.1	0.98
DM (%)	28.5	31.5	30.2	23.6	23.4	0.42
Dyslipidemia (%)	59.5	57.4	65.4	52.8	61.7	0.19
Previous IMA/PCI/CABG (%)	21.2	21.6	19.8	17.9	31.9	0.25
BMI (kg/m²)	26.8(4.3)	26.8(4.7)	27.4(4.4)	26.3(3.7)	25.8(3.6)	0.08
SBP/DBP (mm Hg)	140(26)/77(13)	137(25)/77(13)	142(26)/79(13)	140(26)/77(12)	139(27)/79(14)	0.48/0.37
STEMI/NSTEMI (%)	47.2/52.8	46.3/53.7	50/50	48.1/51.9	40.4/59.6	0.69
Killip class 1–2 (%)	93.9	92.5	93.2	96.2	95.7	0.61
GRACE score[†,.]	140.2 (35.6)	149.3 (35.4)	134.3 (39.1)	136.2 (28.8)	138.7 (32.5)	0.001
Acute treatment (%)						
Medical therapy	17.0	16.7	17.9	16.0	17.0	0.92
PCI	64.2	60.5	64.8	65.1	72.3	
CABG	18.9	22.8	17.3	18.9	10.6	
Creatinine (mg/dL)	0.8 [0.7–1]	0.9 [0.7–1.2]	0.9 [0.7–1.1]	0.8 [0.7–1]	1.0 [0.8–1.2]	0.18
GFR (mL/min/m²)[†]	93.3(40)	84.8(40.3)	102.5(41.1)	95.1(38)	86.7(32.9)	0.001
Hb (g/dL)	13 [11.7–14]	12.1 [11–13.5]	13.1 [12–14]	13.5 [12.7–14.2]	13.4 [11.8–14.3]	<0.001
Total cholesterol (mg/dL)	181.8(49.7)	178.8(53.3)	186.7(48.0)	183.3(44.2)	171.5(54.2)	0.24
HDL (mg/dL)	44.8(12.1)	45.5(14.6)	43.8(11.3)	45.3(9.6)	44.6(11.3)	0.61
TG (mg/dL)	121.7(66.2)	120(69.5)	125.9(58.4)	123.3(70.3)	109.7(70.4)	0.50
HbA1C (%)	5.9 [5.5–6.4]	5.9 [5.6–6.5]	5.8 [5.5–6.3]	5.8 [5.5–6.2]	5.8 [5.5–6.3]	0.22
TnI max (mcg/dL)	7.9 [1.2–38.9]	10 [2–46.1]	7.4 [1.3–36.9]	8.3 [0.5–35.4]	4.6 [0.4–39.2]	0.18
S-albumin (g/dL)	3.7(0.5)	3.5(0.6)	3.8(0.4)	3.8(0.3)	3.8(0.4)	0.004
PTH (pg/mL)	88.2 [66.9–133]	111 [77.6–172.7]	85 [67.2–115.2]	76.1 [59.5–117]	79.7 [57.7–129.2]	<0.001
Vit. D (ng/mL)	16.6(11.1)	6.4(1.8)	14.9(3.1)	24.2(2.6)	40.4(11.7)	<0.001
Calcium (mg/dL)	9(0.8)	8.9(0.8)	9.1(0.4)	9.1(1.1)	9.2(0.6)	0.003
Phosphate (mg/dL)	3.2(0.7)	3.3(0.8)	3.2(0.7)	3.2(0.7)	3.1(0.7)	0.28
CRP (mg/L)	8.9 [3–25.7]	10.2 [3.2–36.6]	8.4 [2.9–21.1]	8.0 [3.3–24.3]	9.1 [1.9–25]	0.75
ALP (U/L)	67.4(30.3)	71.9(30)	68.8(38.4)	60.1(16.9)	63.6(18.9)	0.01
Fibrinogen (mg/dL)	341 [289–401]	347 [297–432.5]	347.5 [302.7–401.7]	331 [280–380]	316 [281–391]	0.50
EDVI (mL/m²)	48.9(16.4)	49.4(17.7)	49.5(17.3)	46.7(11.9)	50.1(17.5)	0.5
ESVI (mL/m²)	24(13.3)	24.8(14.5)	23.9(13.6)	22.3(10.0)	25.3(14.9)	0.61
EF (%)	52.9(11)	52.2(11.7)	53.5(11.9)	53.4(11.4)	52.4(12)	0.80
WMSI	1.4(0.4)	1.5(0.4)	1.4(0.4)	1.4(0.4)	1.5(0.5)	0.30
IVS (cm)	1.2(0.2)	1.3(0.2)	1.2(0.2)	1.2(0.2)	1.2(0.2)	0.24
MR (%)						
Mild	48.4	51.9	47.2	47	43.2	0.14
Moderate	6.5	7.6	4.4	4	15.2	
Severe	0.7	0.6	0.6	0	2.3	
NYHA at discharge						
1	90.4	88.3	91.4	92.5	89.4	0.92
2	6.7	8.0	6.2	4.7	8.5	
3	2.9	3.7	2.5	2.8	2.1	
ACEI/ARBs (%)	68.6	67.7	70.8	67.9	65.9	0.91
Beta blockers (%)	79.2	76.2	81.8	79.8	79.5	0.73
Loop diuretics (%)[†]	19.5	26.9	13.9	16.7	20.5	0.51
Insulin (%)	5.8	7.7	5.1	4.8	4.5	0.74
Oral antidiabetics (%)	14.2	13.1	15.4	13.1	15.9	0.92
Statins (%)	84.1	84.6	81.8	83.3	90.9	0.54
ASA (%) ∞	95.7	96.9	92.0	98.8	97.7	0.06

Legend: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFR: glomerular filtration rate; Hb: hemoglobin; HDL: high density lipoprotein; TG: triglycerides; HbA1C: glycated hemoglobin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CK-MB: creatinine phosphokinase MB; TnI max: troponin I maximum; CRP: C-reactive protein; ALP: alkaline phosphatase; EDVI: end diastolic volume indexed; ESVI: end systolic volume indexed; EF: ejection fraction; IVS: interventricular septum; ACEI/ARBs: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; ASA: acetylsalicylic acid; MR: mitral regurgitation.

† p value showing statistical significance in comparison between subgroup 1 and 2.

. p value showing statistical significance in comparison between subgroup 1 and 3.

‡ p value showing statistical significance in comparison between subgroup 1 and 4.

∞ p value showing statistical significance in comparison between subgroup 2 and 3.

newly extend these observations in the setting of acute myocardial infarction. Previously cited works described a reverse J-shaped relationship between serum levels of vitamin D and mortality in general population, thus indicating that not only a lower limit, but also an upper one, is necessary to preserve cardiovascular health.

Numerous mechanisms may be implicated into the causal relationship between vitamin D deficiency and augmented cardiovascular risk and mortality. Vitamin D acts at different levels in the cardiovascular homeostasis, by controlling cell proliferation, inhibiting the activity of the renin–angiotensin–aldosterone system (RAAS), thus preventing adverse left ventricular remodeling after myocardial infarction [18–23], and exerting an anti-inflammatory and anti-coagulant effect [24–26]. Low levels of vitamin D may have also adverse effects on outcome through secondary hyperparathyroidism. High levels of PTH are associated with increases in arterial pressure and myocardial contractility, which can ultimately lead to apoptosis, fibrosis, and vascular
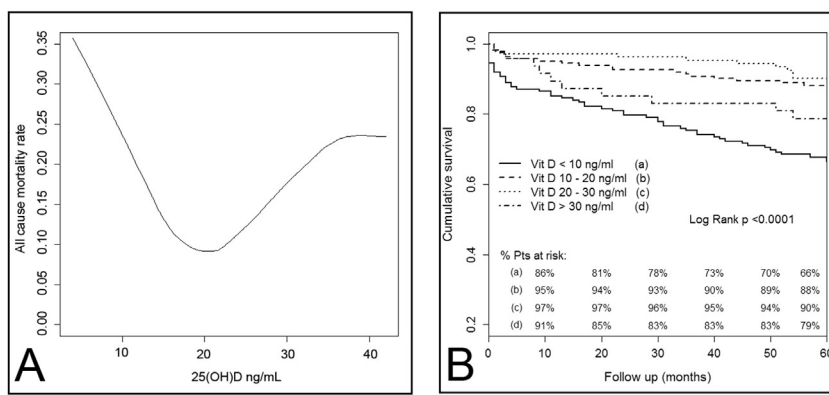
Fig. 1. Panel A. Effect of vitamin D levels on long-term outcome. Panel B. Kaplan–Meier curves of overall survival for patients stratified according to 25(OH)D plasma levels.

smooth muscle cell hypertrophy as well as left ventricular hypertrophy [19,27,28]. In several clinical studies hypovitaminosis D was associated with an increased mortality risk in survivors after an acute myocardial infarction [4,13].

While the link between low vitamin D plasma levels and cardiovascular adverse events has been largely investigated and observed in clinical studies, on the contrary, the mechanisms of the association between higher vitamin D levels and unfavorable outcome remain unclear. One possible explanation may lay in the recognized vitamin D role in calcium metabolism regulation, by inducing its absorption from renal distal tubules (1% out of 7 g daily filtered by glomerulus) [29]. A work by De Boer et al. assessed an inverse relationship between circulating 25(OH)D levels and CAC score [30]. Considering the complex nature of the homeostatic mechanism, we could speculate that this kind of relationship pertains also to higher vitamin D levels. In line, hypervitaminosis D is associated with extensive arterial calcium phosphate deposits. Moreover, in experimental animal models, the administration of vitamin D can lead to widespread vascular calcification, especially in the presence of comorbidities, such as diabetes, atherosclerosis and renal disease [31,32]. The presumptive mechanisms include the increase of serum calcium and phosphate, the formation of fetuin-A mineral complexes, and the induction of an osteochondrogenic program in vascular smooth muscle cells [31,32]. Additionally, 25(OH)D may alter the ratio between osteoprotegerin and RANKL [33], thus modulating the egress of mesenchymal stromal cell from bone marrow [34,35], an event that may positively impact post-ischemic myocardial remodeling [34].

Intriguingly, while in the U.S. Nationally Representative NHANES [12] the reverse J-shaped association between vitamin D and mortality became stronger with longer follow-up (>3 years), in our case study, the major increase in mortality is observed within 30 months post-MI. However, we also observed a shift in the events towards later time points in patients with >30 ng/mL versus patients <10 ng/mL. This finding suggests that the mechanisms for mortality may differ between the two groups of patients. With regard to previous studies, we should point out that NHANES and CopD studies were conducted on cohorts of civilian, non-institutionalized populations [11,12]. Regarding works evaluating the effects of vitamin D on the outcome of AMI patients,

both Ng et al. and De Metrio and coll. divided the patients according to vitamin D quartile groups, which include the IV quartile, patients with >20 ng/mL vitamin D. Intriguingly, our case study suggests that a cutoff of 30 ng/mL is required to identify patients with the highest risk for AMI-related mortality.

Indeed, the last crucial issue regards the correct definition of the range of adequacy. Although it has been not yet clearly defined a potentially harmful level of vitamin D [36], currently many laboratories consider 30 ng/mL as the cut off to define a sufficient provision of 25(OH)D [37] and 50 ng/mL as the upper limit for possible detrimental effects [38]. In our population, though, the range of adequacy appears to be even narrower, between 20 and 30 ng/mL.

The strengths of the present study are: its large, sample size from a single center and its long-term follow-up. The main limitation of this study is principally due to its observational nature. Blood samples for vitamin D determination were drawn only at study entry, so we have not considered potential alterations of vitamin D status during follow-up. However, McKibben et al. in community-based sample have shown that 25(OH)D levels remain relatively stable over time [39]. Last, although the heterogeneous population of AMI patients may be viewed as a potential limitation of our study, that reflects a "real life" scenario; it has been observed that, while short-term (in-hospital or one month) mortality is lower in NSTEMI compared to STEMI, long-term mortality is similar.

In conclusion, data from our study suggests that too low and too high vitamin D levels in patients with myocardial infarction are associated

Table 2
Multivariable Cox proportional hazards regression analysis.

Variables	HR	95% CI	p
Age (for 1 year increase)	1.068	1.040–1.098	<0.001
NYHA class at discharge (for 1 class increase)	2.142	1.415–3.241	<0.001
Statin (yes vs.no)	0.507	0.293–0.878	0.015
ACEI/ARBs (yes vs. no)	0.450	0.273–0.742	0.002
Vitamin D (below 10 ng/mL or above 30 ng/mL vs. intermediate values)	3.019	1.782–5.113	<0.001

NYHA: New York Heart Association Functional Classification; ACEI: Angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers.
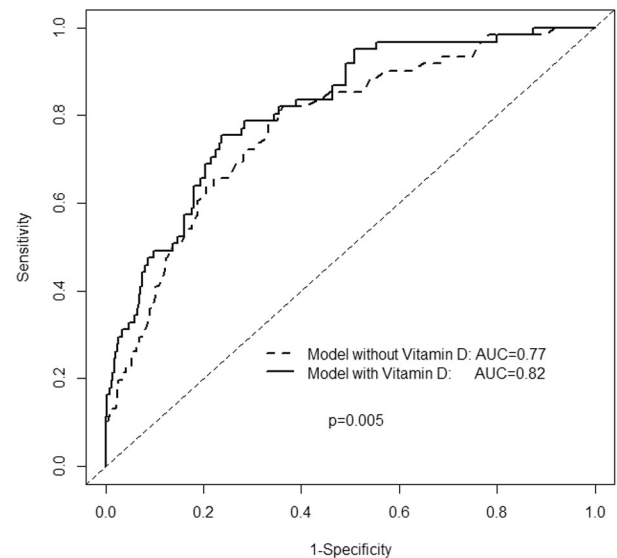

Fig. 2. Time-dependent ROC curves.

with a poor long-term outcome. The exact biological mechanisms as possible explanation for increased mortality among infarcted patients with altered vitamin D levels are not clear. Vitamin D dysregulated status may be considered as a surrogate marker for general health and for unknown risk factors that could possibly explain worse outcome. Further studies are needed to better explain the relationship between levels of vitamin D and cardiovascular mortality.

Conflict of interest

The authors have no conflict of interest to disclose.

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