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Original article

Meteorin-like protein is associated with a higher risk profile and predicts a worse outcome in patients with STEMI

Gemma Ferrer-Curriu,[a,◇] Ferran Rueda,[b,c,◇] Elena Revuelta-López,[a,d] Cosme García-García,[b,c,d] Pau Codina,[b,c] Carolina Gálvez-Montón,[a,c,d] Santiago Roura,[a,d,e] Alberto Aimo,[f] Michele Emdin,[f] Anna Planavila,[g,h] and Antoni Bayés-Genís[a,b,c,d,*]

[a] *ICREC Research Program, Institut de Recerca Germans Trias i Pujol (IGTP), Can Ruti Campus, Badalona, Barcelona, Spain*
[b] *Servicio de Cardiología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain*
[c] *Institut del Cor, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain*
[d] *Centro de Investigación en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*
[e] *Facultat de Medicina, Universitat de Vic – Universitat Central de Catalunya (UVic-UCC), Vic, Barcelona, Spain*
[f] *Interdisciplinary Center of Health Science, Scuola Superiore Sant'Anna, Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy*
[g] *Departament de Bioquímica i Biologia Molecular; Institut de Biomedicina (IBUB), Universitat de Barcelona, Barcelona, Spain*
[h] *Centro de Investigación en Red de Fisiopatología de la Obesidad y Nutrición (CIBERON), Spain*

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ABSTRACT

Introduction and objectives: Meteorin-like protein (Metrnl) is a cytokine involved in the attenuation of inflammation. In patients with heart failure, high levels of this biomarker are associated with a worse outcome. In this study, we evaluated the circulating levels and prognostic value of Metrnl in patients with ST-segment elevation myocardial infarction (STEMI).

Methods: We enrolled STEMI patients undergoing primary percutaneous coronary intervention. Circulating Metrnl levels were measured in peripheral blood 12 hours after symptom onset. The primary endpoint was a composite of all-cause mortality or nonfatal myocardial infarction (MI) at 3 years.

Results: We studied 381 patients (mean age 61 years, 21% female, 8% Killip class III/IV). Metrnl levels were associated with age, cardiovascular risk factors and the extent of coronary artery disease, as well as with STEMI complications, particularly heart failure and cardiogenic shock. Multivariable Cox regression analysis revealed that Metrnl independently predicted all-cause death or nonfatal MI at 3 years (HR, 1.86; 95%CI, 1.23-2.81; $P = .003$). Moreover, patients in the highest tertile (> 491.6 pg/mL) were at higher risk for the composite endpoint than those in the lowest tertiles (HR, 3.24; 95%CI, 1.92-5.44; $P < .001$), even after adjustment by age, diabetes mellitus, cardiac arrest, Killip-Kimball III/IV class, left ventricular ejection fraction, and creatinine clearance (HR, 1.90; 95%CI, 1.10-3.29; $P = .021$).

Conclusions: Circulating Metrnl levels are associated with complications during the acute phase of STEMI and independently predict a worse outcome in these patients.

La proteína *meteorin-like* se asocia a un perfil de mayor riesgo y predice un peor pronóstico en pacientes con IAMCEST

Palabras clave:
Meteorin-like (Metrnl)
Infarto de miocardio
Infarto agudo de miocardio con elevación del segmento ST (IAMCEST)
Angioplastia primaria
Biomarcador

RESUMEN

Introducción y objetivos: La proteína *meteorin-like* (Metrnl) es una citocina implicada en la atenuación de la inflamación asociada a mal pronóstico en la insuficiencia cardiaca. En este estudio se evalúan los niveles circulantes de Metrnl y su valor pronóstico en el infarto agudo de miocardio con elevación del segmento ST (IAMCEST).

Métodos: Se incluyó a pacientes con IAMCEST tratados con angioplastia primaria. Se determinaron los niveles de Metrnl en sangre periférica a las 12 horas del inicio de los síntomas. El criterio de evaluación primario fue muerte por cualquier causa o infarto de miocardio no mortal a 3 años.

Resultados: Se estudiaron 381 pacientes (edad media 61 años, 21% mujeres, 8% clase Killip III/IV). Los niveles de Metrnl se asociaron con la edad, los factores de riesgo cardiovascular y la extensión de la

* Corresponding author.
E-mail address: abayesgenis@gmail.com (A. Bayés-Genís).
@GTRecerca @hgermanstrias @IcorCat @santi_roura

◇ Both authors contributed equally.

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enfermedad coronaria, pero también con complicaciones del infarto, especialmente insuficiencia cardíaca y shock cardiogénico. En la regresión multivariante de Cox Metrnl fue un predictor independiente del criterio de evaluación combinado (HR = 1,86; IC95%, 1,23-2,81; p = 0,003). Además, los pacientes en el tercil más alto (> 491,6 pg/ml) presentaron mayor riesgo que en los terciles inferiores (HR = 3,24; IC95%, 1,92-5,44; p < 0,001), incluso después de ajustar por edad, diabetes, paro cardíaco, clase Killip-Kimball III/IV, fracción de eyección y aclaramiento de creatinina (HR = 1,90; IC95%, 1,10-3,29; p = 0,021).

Conclusiones: En los pacientes con IAMCEST, los niveles circulantes de Metrnl se asocian con las complicaciones durante la fase aguda y predicen de forma independiente un peor pronóstico.

Abbreviations

Metrnl: Meteorin-like protein
STEMI: ST-segment elevation myocardial infarction
MI: myocardial infarction

INTRODUCTION

Outcomes of patients with ST-segment elevation myocardial infarction (STEMI) have considerably improved over the last few decades, mainly as a result of the widespread use of primary percutaneous coronary intervention (PCI) and evidence-based treatments.[1,2] However, patients still face a substantial risk of death and further cardiovascular events, in both the short- and long term. Thus, there is a need to optimize early risk stratification and identify new therapeutic targets.

Meteorin-like (Metrnl) is a secreted protein expressed by multiple tissues.[3] This protein was first identified as a hormone produced by skeletal muscle and adipose tissue upon stimulation by exercise and exposure to cold, respectively, stimulating energy expenditure and attenuating inflammation and insulin resistance.[4,5] Therefore, it is not surprising that it has been reported to be involved in diseases like obesity[6] and type 2 diabetes mellitus (T2D).[7] Preclinical studies also showed that Metrnl is produced by cardiomyocytes after cardiac injury. In a rodent model of cardiac hypertrophy, lack of Metrnl was associated with left ventricular dysfunction and enhanced interstitial fibrosis together with reduced expression of fatty acid oxidation genes and anti-inflammatory type 2 cytokines signalling components, while its overexpression prevents the development of cardiac remodelling.[8] Very recently, Reboll et al.[9] have shown that Metrnl is a driver of postinfarction angiogenesis. All these data point to a prominent protective role of Metrnl in the myocardium. In addition, Metrnl has also been associated with inflammatory diseases and is strongly induced in activated macropahges.[10] Finally, we previously reported that Metrnl is a new prognostic biomarker in heart failure (HF) patients.[8]

The aim of the present study was to evaluate circulating Metrnl levels in the acute phase of STEMI treated by primary PCI and to assess its predictive value for adverse events.

METHODS

Study design and population

In this prospective observational study, we enrolled patients with STEMI who were admitted to a tertiary university center within a primary PCI network from February 2011 to January 2016. STEMI was diagnosed and managed according to contemporary guidelines.[11,12] Baseline demographics and clinical data were recorded during hospital admission in a database. Left ventricular ejection fraction (LVEF) was assessed before discharge with echocardiography using the Simpson method.

The protocol was approved by the institutional ethics committee (reference EO-11-061) and patients or their representatives provided written informed consent.

Measurement and laboratory data

Blood samples were obtained by venepuncture 12 hours after symptom onset. Samples were processed in a central laboratory for biomarker measurements. Serum was obtained by centrifugation and stored at − 80 °C until assayed.

Metrnl was measured by Human Meteorin-like/METRNL DuoSet ELISA (R&D Systems, United States; reference DY7867-05, lot P100731) (n = 381) using spectrophotometry immunoassay according to the manufacturers' protocols; the assay range was 15.6 to 1000 pg/mL. High-sensitivity troponin T (hs-Troponin T; n = 354) and N-terminal pro B-type natriuretic peptide (NT-proBNP; n = 318) were measured using electrochemiluminescence immunoassays (Troponin T hs[13] and Elecsys proBNP,[14] Roche Diagnostics, Germany) with a Modular Analytics E170 system (Roche Diagnostics).

All other laboratory values (hemoglobin, creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and creatine kinase-MB) were measured at the time of admission.

Study outcomes and follow-up

The primary outcome was the composite of all-cause mortality or nonfatal myocardial infarction (MI) at 3 years. For patients with recurrent events, the time to the first event was recorded. The secondary outcome was all-cause mortality at 3 years. Outcome events were adjudicated based on electronic clinical records and/or directly contacting patients or relatives by telephone.

Statistical analyses

Categorical variables are presented as absolute numbers and percentages. Continuous variables are expressed as the mean ± standard deviation or median [interquartile range], according to normal or nonnormal data distribution. Departures from normality were evaluated using normal QQ-plots. Between-group comparisons were performed with the chi-square and Fisher test for categorical variables, and the Student *t*-test, Wilcoxon rank sum test or Kruskal-Wallis test for continuous variables, as appropriate. Correlations between Metrnl levels and other continuous variables were performed using the Pearson or Spearman method, as appropriate.

Survival analyses were performed using Cox proportional hazards models (using the backward stepwise method) after assessment of proportional assumptions. Nonnormally distributed variables were $\log_2$-transformed prior to analyses. Hazard ratios (HR) with 95% confidence intervals (95%CI) are reported. Multivariate models included major outcome predictors according to prior knowledge[15,16] which, in turn, were statistically significant ($P < .05$) on univariate analysis, avoiding overfitting. The following variables were incorporated into the regression model for the primary outcome: Metrnl levels, age, diabetes mellitus, cardiac arrest, Killip-Kimball class III/IV, LVEF, and creatinine clearance on admission estimated from the Cockroft–Gault formula. Similarly, the model for secondary outcome included Metrnl levels, age, cardiac arrest, Killip-Kimball class III/IV, and LVEF. In a sensitivity analysis, models that included hs-troponin T and NT-proBNP were run for both endpoints. The improvement in discrimination when adding Metrnl to the clinical models was assessed by comparing the resulting Harrell c-indexes. Cox survival curves were performed to depict how the occurrence of the primary endpoint was related to the distribution of Metrnl levels over time.

Differences were considered statistically significant at $P < .05$. Statistical analyses were performed with SPSS Statistics 24 (IBM, United States) and STATA V.15.1 software (StataCorp., United States).

RESULTS

Patient characteristics

A total of 381 patients were enrolled during the study period (table 1). The mean age was 61.4 ± 13.0 years, 21% were women, and 43% had an anterior MI. Killip-Kimball class III to IV was present in 8% patients and 97% were treated with successful primary PCI at a median time of 180 minutes from symptom onset.

More than 98% of the patients completed the 3-year follow-up. Only 7 patients (1.8%) were lost to follow-up: 4 after discharge, who were excluded from the survival analyses, and 3 after a median follow-up of 1.7 years, who were included. At the 3-year time point, 40 patients had died, 24 had been readmitted due to MI, and 59 (16%) had had the composite endpoint (35 deaths and 24 nonfatal MI, of whom 5 subsequently died). Patients with events were older and were more likely to have a history of hypertension, diabetes, cerebrovascular disease, HF, MI, or PCI. Moreover, they were reperfused later, exhibited greater disease severity (higher Killip-Kimball class and Global Registry of Acute Coronary Events [GRACE] score), more complications related to acute myocardial infarction (AMI), worse LVEF, lower hemoglobin and creatinine clearance values on admission, and higher NT-proBNP and Metrnl levels (table 1 of the supplementary data).

Predictors of Metrnl levels

The median concentration of Metrnl 12 hours after STEMI was 413.2 pg/mL [320.9-559.7 pg/mL]. Table 1 shows patients stratified into Metrnl above and below the median and table 2 shows Metrnl medians according to the presence of each variable. Metrnl levels were associated with the presence of cardiovascular risk factors, a history of HF and PCI, and the number of diseased coronary arteries at the time of STEMI. Furthermore, Metrnl was positively correlated with age, GRACE score and levels of hs-Troponin T and NT-proBNP, and inversely correlated with systolic blood pressure and values of hemoglobin, creatinine clearance, total cholesterol and LDL-cholesterol on admission (table 3; figure 1 of the supplementary data).

Metrnl and acute complications in STEMI

Metrnl levels were also associated with in-hospital complications of MI. Thus, concentrations were higher in patients with ventricular tachycardia ($P = .021$), atrial fibrillation ($P = .008$), intraventricular conduction disturbances ($P = .007$), right ventricular infarction ($P = .001$), HF ($P = .001$), shock ($P < .001$) and in-hospital death ($P < .001$) (table 4; table 2 of the supplementary data). There was an increasing trend for Metrnl that was related to Killip class (figure 1). Interestingly, we found no relationship between Metrnl and LVEF or other serious complications as ventricular fibrillation or cardiac arrest.

Metrnl as a predictor of outcomes

Compared with participants in the 2 lowest tertiles, those in the highest tertile had a 3 times higher risk of 3-year all-cause death or nonfatal MI (HR, 3.24; 95%CI, 1.92-5.44) (figure 2). Multivariable Cox proportional hazard regression models (table 5) showed that Metrnl was an independent predictor of the primary endpoint (HR, 1.86; 95%CI, 1.23-2.81), together with age, the occurrence of cardiac arrest, Killip-Kimball class III or IV, and LVEF. The addition of Metrnl levels to a predictive model including these variables improved discrimination with an increase in the c-index from 0.764 (95%CI, 0.690-0.838) to 0.776 (95%CI, 0.704-0.848), although this difference was not statistically significant ($P = .328$), as depicted in figure 2 of the supplementary data. Further, Metrnl independently predicted 3-year all-cause mortality alone (HR, 1.84, 95%CI, 1.11-3.04). Sensitivity analyses with models that included hs-Troponin T and NT-proBNP revealed similar results for both outcomes (table 3 of the supplementary data).

DISCUSSION

This observational study evaluated circulating Metrnl levels and their prognostic value in a cohort of unselected patients with STEMI. Higher values in the acute phase were associated with age, cardiovascular risk factors and certain MI complications, especially those related to HF but independently of LVEF. In addition, Metrnl was an independent predictor of all-cause death or nonfatal MI after a 3-year follow-up (figure 3).

Our study identified higher levels of Metrnl in older patients and in those with a history of cardiovascular risk factors and, consequently, more extensive coronary artery disease. Metrnl has been reported to be involved in metabolic disorders such as T2D and inversely related to cardiovascular risk factors.[17] T2D is characterized by molecular changes in various tissues such as adipose tissue, liver, skeletal muscle and heart, impairing the glucose homeostasis. In adipose tissue, Metrnl stimulates energy expenditure and improves glucose tolerance by activating thermogenesis.[5] Other metabolic effects have been described in skeletal muscle, increasing glucose uptake via AMPKα2 in obese or T2D mice.[18] Some studies showed increased Metrnl levels in diabetic patients,[7,17] while others showed the opposite results.[19] These discrepancies may be due to confounding factors.[20] The higher levels of Metrnl could act as a defensive response to counteract metabolic stress or resistance to Metrnl, similar to insulin or leptin resistance.[17] In our study, the higher levels could also be explained because patients with diabetes, a well-known risk factor for AMI,[21] could be sicker and have greater activation of other Metrnl-related pathophysiological pathways, such as in-

Table 1
Baseline characteristics of the study population according to median circulating Metrnl levels 12 hours after STEMI onset

Variable	All patients (N = 381)	Metrnl < 413.2 pg/mL	Metrnl > 413.2 pg/mL	*P*
Demographics				
Age, y	61.4 ± 13.0	57.2 ± 12.3	65.6 ± 12.3	< .001
Sex, female	80 (21.0)	40 (21.1)	40 (20.9)	.979
BMI, kg/m²	27.0 [24.8-29.8]	27.3 [25.0-29.8]	26.6 [24.6-29.9]	.197
History				
Smoking				.022
Never	91 (23.9)	41 (21.6)	50 (26.2)	
Former	104 (27.3)	43 (22.6)	61 (31.9)	
Active	186 (48.8)	106 (55.8)	80 (41.9)	
Hypertension	203 (53.3)	82 (43.2)	121 (63.4)	< .001
Diabetes mellitus	99 (26.0)	40 (21.1)	59 (30.9)	.029
Diabetes mellitus				.061
No	282 (74.0)	150 (78.9)	132 (69.1)	
Noninsulin treatment	64 (16.8)	28 (14.7)	36 (18.8)	
Insulin treatment	35 (9.2)	12 (6.3)	23 (12.0)	
Dyslipidemia	202 (53.0)	88 (46.3)	114 (59.7)	.009
Cerebrovascular disease	20 (5.2)	8 (4.2)	12 (6.3)	.365
Peripheral arterial disease	21 (5.5)	7 (3.7)	14 (7.3)	.119
End-stage chronic kidney disease	4 (1.0)	1 (0.5)	3 (1.6)	.317
Previous heart failure	3 (0.8)	0	3 (1.6)	.083
Previous MI	35 (9.2)	13 (6.8)	22 (11.5)	.114
Previous PCI	32 (8.4)	9 (4.7)	23 (12.0)	.010
Previous CABG	1 (0.3)	0	1 (0.5)	.318
Clinical presentation				
GRACE score	148.9 ± 39.3	135.6 ± 27.1	162.2 ± 44.7	< .001
Anterior infarct location	163 (42.8)	107 (56.3)	111 (58.1)	.723
Killip-Kimball class				< .001
I	311 (81.6)	169 (88.9)	142 (74.3)	
II	39 (10.2)	16 (8.4)	23 (12.0)	
III	7 (1.8)	4 (2.1)	3 (1.6)	
IV	24 (6.3)	1 (0.5)	23 (12.0)	
Coronary angiography	380 (99.7)			
Main epicardial coronary arteries ≥70% stenosis				.011
1	192 (50.5)	97 (51.1)	95 (50.0)	
2	111 (29.2)	65 (34.2)	46 (24.2)	
3	77 (20.3)	28 (14.7)	49 (25.8)	
Left main ≥ 50% stenosis	15 (3.9)	4 (2.1)	11 (5.8)	.065
Successful primary PCI	369 (96.9)			
Symptom onset-to-balloon, min	180 [123-295]	184 [130-295]	179 [117-299]	.839
Staged PCI	34 (8.9)			
Staged CABG	2 (0.5)			
LVEF, %	51.0 ± 10.7	51.6 ± 9.9	50.4 ± 11.4	.246
Laboratory results				
Hemoglobin on admission, g/dL	13.0 ± 1.8	13.3 ± 1.6	12.7 ± 2.0	.001
Creatinine clearance on admission, mL/min *	89.2 ± 37.7	103.0 ± 37.0	75.5 ± 33.2	< .001
Total cholesterol, mg/dL	175.8 ± 40.1	183.3 ± 38.0	168.4 ± 41.0	< .001
HDL-cholesterol, mg/dL	43.2 ± 11.3	42.6 ± 10.4	43.7 ± 12.0	.379
LDL-cholesterol, mg/dL	105.0 ± 34.9	110.6 ± 33.9	99.5 ± 35.1	.003
Triglycerides, mg/dL	112 [83-158]	121 [88-168]	106 [81-144]	.007
CK-MB peak, ng/mL	176.0 [73.2-337.1]	176.1 [95.6-292.3]	175.3 [67.0-372.6]	.766
hs-Troponin T at 12 h, pg/mL	3714.5 [1196.6-7115.3]	2867.6 [1324.6-5990.2]	4455.3 [1094.1-8474.4]	.021
NT-proBNP at 12 h, pg/mL	576.2 [254.9-1533.3]	455.4 [230.1-1008.9]	818.4 [343.8-2740.8]	< .001

BMI, body mass index; CK-MB, creatine kinase-MB; GRACE, Global Registry of Acute Coronary Events; HDL, high density lipoprotein; HR, heart rate; LDL; low density lipoprotein; LVEF; left ventricular ejection fraction; NT-proBNP; inactive proform of natriuretic peptide B; SBP, systolic blood pressure.
Data are expressed as No. (%), mean ± standard deviation, or median [interquartile range: Q1-Q3].
* Estimated with the Cockroft-Gault formula.

Table 2
Circulating Metrnl levels 12 hours after STEMI onset according to baseline characteristics

Variable		Metrnl at 12 hours, pg/mL	*P*
Demographics			
Age, y	< 61 ≥ 61	368.2 [297.2-471.2] 483.1 [361.1-666.7]	< .001
Sex	Female Male	412.8 [313.8-562.7] 413.2 [321.2-559.7]	.868
BMI	< 27.0 kg/m^2 ≥ 27.0 kg/m^2	438.7 [320.9-579.7] 399.5 [319.6-528.9]	.293
History			
Smoking	Never Former Active	432.3 [342.6-592.4] 447.8 [339.9-630.8] 389.79 [299.4-515.3]	.006
Hypertension	No Yes	378.5 [305.4-484.4] 457.4 [341.1-629.5]	< .001
Diabetes mellitus	No Noninsulin treatment Insulin treatment	402.6 [306.3-531.5] 442.8 [339.1-631.1] 466.0 [358.0-685.8]	.015
Dyslipidemia	No Yes	394.5 [307.4-519.5] 443.0 [330.8-589.6]	.034
Cerebrovascular disease	No Yes	410.3 [320.9-557.0] 490.3 [338.1-696.6]	.319
Peripheral arterial disease	No Yes	409.4 [319.5-549.5] 526.2 [394.4-700.4]	.033
End-stage chronic kidney disease	No Yes	412.4 [320.9-557.0] 594.4 [392.0-914.9]	.292
Previous heart failure	No Yes	411.3 [319.6-554.6] 805.1 [771.6-870.9]	.014
Previous MI	No Yes	409.2 [320.9-559.7] 472.0 [319.4-559.7]	.289
Previous PCI	No Yes	407.8 [319.4-559.7] 483.5 [397.1-584.9]	.069
Previous CABG	No Yes	412.8 [320.2-558.4] 828.2 [828.2-828.2]	.148
Clinical presentation			
GRACE score	< 140 ≥ 140	368.22 [290.0-463.9] 483.1 [361.1-669.4]	< .001
Anterior infarct location	No Yes	409.0 [319.4-579.7] 418.9 [321.2-554.2]	.944
Killip-Kimball class	I II III IV	400.0 [309.9-519.5] 468.9 [327.9-669.4] 402.4 [299.2-672.3] 829.6 [507.3-1094.6]	< .001
Main epicardial coronary arteries ≥70% stenosis	1 2 3	409.4 [321.6-536.9] 390.2 [302.4-515.3] 483.7 [360.7-650.1]	.012
Left main ≥ 50% stenosis	No Yes	409.3 [320.9-554.2] 518.7 [304.0-700.4]	.151
Successful primary PCI	No Yes	374.1 [308.0-678.6] 415.5 [321.2-554.6]	.921
Symptom onset-to-balloon, min	< 181 min ≥ 181 min	427.7 [321.2-574.5] 409.3]319.6-526.6]	.491
LVEF	< 53% ≥ 53%	406.5 [318.0-587.9] 422.6 [327.4-539.6]	.962
Laboratory results			
Hemoglobin on admission	< 13.2 g/dL ≥ 13.2 g/dL	450.4 [333.9-610.5] 378.7 [305.8-492.9]	.001
Creatinine clearance on admission*	< 85.5 mL/min ≥ 85.5 mL/min	487.5 [376.1-676.2] 360.7 [288.9-463.6]	< .001
Total cholesterol	< 171 mg/dL ≥ 171 mg/dL	447.2 [330.8-615.5] 401.1 [308.6-503.4]	.026
HDL-cholesterol	< 42 mg/dL ≥ 42 mg/dL	416.3 [321.2-564.4] 413.2 [315.0-554.2]	.381
LDL-cholesterol	< 100 mg/dL ≥ 100 mg/dL	456.3 [330.8-608.8] 394.4 [312.6-491.1]	.007

Table 2 *(Continued)*
Circulating Metrnl levels 12 hours after STEMI onset according to baseline characteristics

Variable		Metrnl at 12 hours, pg/mL	*P*
Triglycerides	< 112 mg/dL ≥ 112 mg/dL	439.7 [332.2-603.6] 397.3 [303.3-518.7]	.015
CK-MB peak, ng/mL	< 176.0 ng/mL ≥ 176.0 ng/mL	415.3 [327.5-559.7] 412.4 [309.9-564.4]	.899
hs-troponin T at 12 h, pg/mL	< 3714.5 pg/mL ≥ 3714.5 pg/mL	392.4 [318.0-503.4] 439.9 [319.6-608.8]	.025
NT-proBNP at 12 h, pg/mL	< 576.2 pg/mL ≥ 576.2 pg/mL	390.2 [302.5-493.6] 457.4 [342.6-668.8]	< .001

BMI, body mass index; CK-MB, creatine kinase-MB; GRACE, Global Registry of Acute Coronary Events; HDL, high density lipoprotein; HR, heart rate; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, inactive proform of natriuretic peptide B; SBP, systolic blood pressure.
Metrnl levels are presented as median [interquartile range: Q1-Q3]. Quantitative variables are categorized according to the median.
* Estimated with the Cockroft-Gault formula.

Table 3
Correlations between circulating Metrnl levels, clinical variables, and laboratory values.

Variable	Correlation coefficient	*P*
Age	r = 0.248	< .001
BMI	r = −0.005	.926
GRACE score	r = 0.377	< .001
SBP on admission	r = −0.145	.004
HR on admission	r = −0.008	.883
Symptom onset-to-balloon time	r = 0.067	.196
LVEF	r = −0.067	.195
hs-troponin T at 12 h	r = 0.279	< .001
NT-proBNP at 12 h	r = 0.363	< .001
CK-MB peak	r = 0.078	.131
Hemoglobin on admission	r = −1.174	< .001
Creatinine clearance on admission*	r = −0.322	< .001
Total cholesterol	r = −0.220	< .001
HDL-cholesterol	r = −0.065	.216
LDL-cholesterol	r = −0.208	< .001
Triglycerides	r = −0.037	.479

BMI, body mass index; CK-MB, creatine kinase-MB; GRACE, Global Registry of Acute Coronary Events; HDL, high density lipoprotein; HR, heart rate; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, inactive proform of natriuretic peptide B; SBP, systolic blood pressure.
* Estimated with the Cockroft-Gault formula.

flammation. In accordance, studies in humans and rodents demonstrate that Metrnl levels are associated with HDL-cholesterol as well as being inversely associated with blood pressure, total cholesterol, LDL-cholesterol, and triglycerides.[17,22] Such correlations were also observed in our study, although patients with hypertension and dyslipidemia showed higher Metrnl levels, probably due to an upregulated response to metabolic stress.

Given the relationship between atherosclerosis, metabolic syndrome and inflammation, some authors have proposed a link between Metrnl and coronary artery disease. Thus, studies in outpatients have reported an inverse association between circulating Metrnl levels and inflammatory cytokines, insulin resistance, markers of atherosclerosis and severity of coronary artery disease.[23–25] These results contrast with our findings showing that Metrnl levels increased in parallel with the number of diseased vessels. Unlike the aforementioned studies, ours included patients with AMI, a condition in which multivessel disease is known to be a predictor of mortality and the development of HF both in the short- and long-term[26–29]; therefore, this elevation of Metrnl levels could be explained by increased disease severity.

The second main finding of our study was the association between high Metrnl levels and STEMI severity, especially with regard to the development of HF, both left and right, and cardiogenic shock. Overall, it is recognized that the inflammatory response plays a critical role in determining AMI size and subsequent post-MI adverse left ventricular remodelling.[30,31] Moreover, inflammation has been linked to disease development, progression and complications, and is predictive of poor outcomes in acute HF and cardiogenic shock independent of LVEF.[32,33] Metrnl has also been associated with several inflammatory diseases such as psoriasis, atopic dermatitis and rheumatoid arthritis,[10] and a consistent finding is that a lack of Metrnl in mice impaired their response in a sepsis model.[34] In the present study, Metrnl was determined 12 hours after STEMI onset. Therefore, our data suggest that, during the proinflammatory phase, Metrnl plays a key role in modulating inflammatory response to ischemia/reperfusion injury, which could contribute to post-MI adverse left ventricular remodelling.

Finally, we identified increased Metrnl levels at the time of STEMI as an independent predictor of adverse outcomes in a model that included strong predictors such as Killip-Kimball class and LVEF. These findings are consistent with our previous study, which identified Metrnl as a prognostic biomarker in HF.[8] Again, the higher Metrnl levels may be a reactive response to cardiac damage, identifying high-risk individuals. Similar observations have been made for other cardioprotective cardiokines such as ANF and FGF21.[35]

Limitations

This study has some limitations. This is a single-center, observational study, although the sample size is relatively large and the follow-up was 3 years. Blood samples were drawn at a single time point and consequently we were unable to evaluate dynamic changes over time and their association with the clinical picture and outcomes.

Likewise, the study design *per se* does not provide sufficient data for a full understanding of the pathophysiology of Metrnl in AMI. Finally, although this study is the first to provide evidence of an association between Metrnl levels and prognosis in MI, more studies are needed to validate our results, establish their clinical usefulness, and evaluate the role of Metrnl in the acute phase of MI.

Table 4
Circulating Metrnl levels at 12 hours by STEMI complications

Complication		Patients	Metrnl at 12 hours, pg/mL	*P*
Postinfarction angina	No	370 (97.1)	412.8 [320.9-557.0]	.852
	Yes	11 (2.9)	525.8 [275.6-592.0]	
Reinfarction	No	377 (99.0)	413.2 [320.9-557.0]	.364
	Yes	4 (1.0)	938.5 [327.0-1653.3]	
Pericarditis	No	373 (97.9)	413.2 [321.9-557.0]	.977
	Yes	8 (2.1)	392.9 [295.7-685.5]	
Primary VF	No	362 (95.0)	412.8 [321.2-564.4]	.610
	Yes	21 (5.0)	427.5 [287.8-528.9]	
Sustained VT	No	360 (94.5)	408.8 [320.2-547.6]	.021
	Yes	21 (5.5)	545.8 [415.5-828.2]	
2nd/3rd degree atrioventricular block	No	363 (95.3)	409.4 [319.4-559.7]	.413
	Yes	18 (4.7)	434.0 [333.9-616.1]	
Atrial fibrillation	No	358 (94.0)	409.9 [318.0-539.6]	.008
	Yes	23 (6.0)	587.9 [359.9-1051.8]	
Intraventricular conduction disturbances	No	375 (98.4)	410.3 [319.4-554.6]	.007
	Yes	6 (1.6)	762.1 [532.0-1112.8]	
Mechanical complications	No	378 (99.2)	412.8 [320.9-557.0]	.468
	Yes	3 (0.8)	678.1 [204.9-1718.9]	
Right ventricular infarction	No	367 (96.3)	409.3 [318.0-541.9]	.001
	Yes	14 (3.7)	678.3 [473.7-887.6]	
Heart failure	No	344 (90.3)	405.8 [315.9-540.8]	.001
	Yes	37 (9.7)	531.2 [406.5-805.1]	
Shock	No	361 (94.8)	406.4 [316.9-534.0]	<.001
	Yes	20 (5.2)	827.4 [477.5-1015.9]	
Cardiac arrest	No	356 (93.4)	409.4 [320.2-558.4]	.356
	Yes	25 (6.6)	466.0 [338.2-676.2]	
In-hospital death	No	365 (95.8)	408.6 [319.4-532.0]	<.001
	Yes	16 (4.2)	828.8 [686.5-975.4]	

VF, ventricular fibrillation; VT, ventricular tachycardia.
Data are expressed as No. (%) or median [interquartile range: Q1-Q3].

Table 5
Cox regression analyses of outcomes

3-year all-cause death or nonfatal MI				
	Univariable		Multivariable	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Metrnl	2.22 (1.62-3.06)	<.001	1.86 (1.23-2.81)	.003
Age	1.06 (1.04-1.09)	<.001	1.07 (1.04-1.10)	<.001
Diabetes mellitus	1.90 (1.13-3.21)	.016	-	-
Cardiac arrest	3.72 (1.88-7.35)	<.001	3.48 (1.67-7.23)	.001
Killip-Kimball III/IV class	5.47 (3.04-9.85)	<.001	2.14 (1.08-4.23)	.028
LVEF	0.94 (0.92-0.96)	<.001	0.96 (0.94-0.98)	.001
Creatinine clearance on admission*	0.98 (0.98-0.99)	<.001	-	-
3-year all-cause-death				
	Univariable		Multivariable	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Metrnl	2.80 (1.94-4.03)	<.001	1.84 (1.11-3.04)	.017
Age	1.12 (1.08-1.15)	<.001	1.10 (1.07-1.14)	<.001
Cardiac arrest	4.28 (1.97-9.30)	<.001	4.73 (1.99-11.22)	<.001
Killip-Kimball III/IV class	9.42 (4.96-17.92)	<.001	2.59 (1.20-5.60)	.016
LVEF	0.92 (0.90-0.95)	<.001	0.95 (0.93-0.98)	.002

MI, myocardial infarction; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction.
Analyses included only the 373 patients with complete data on all variables.
* Estimated with the Cockroft-Gault formula.

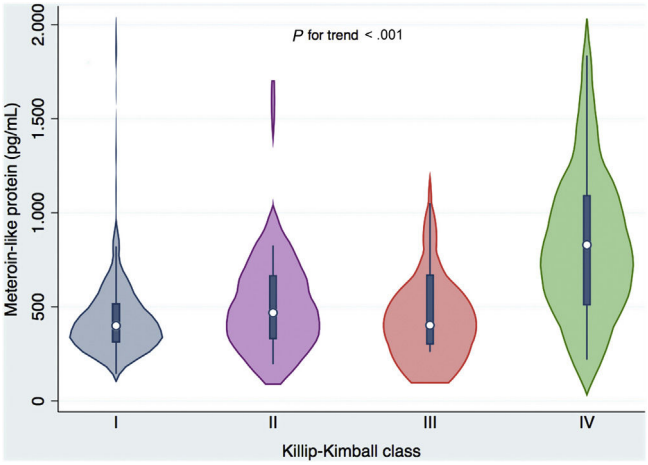

Figure 1. Violin-plot of circulating Metrnl levels 12 hours after STEMI onset according to Killip-Kimball class. STEMI, ST-segment elevation myocardial infarction.

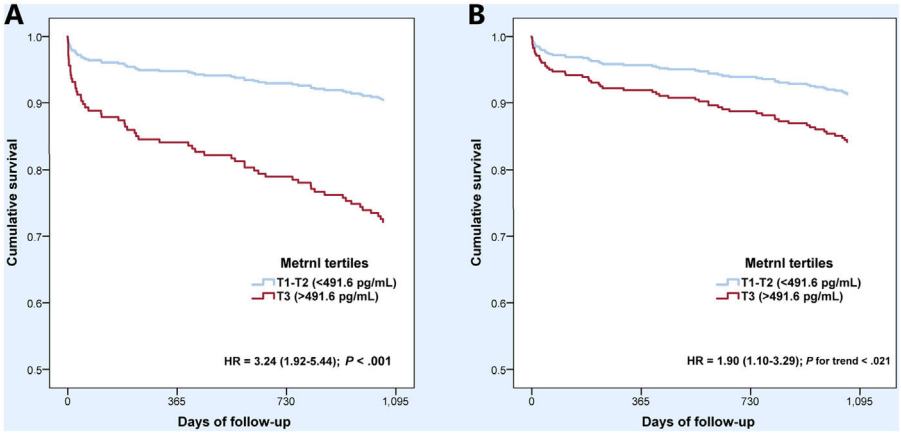

Figure 2. Unadjusted (A) and adjusted (B) Cox survival curves for the primary endpoint (3-year all-cause death or nonfatal myocardial infarction) according to tertiles of Metrnl levels (T3 vs T1-T2). Curves adjusted by age, history of diabetes mellitus, cardiac arrest at admission, Killip-Kimball III/IV class, left ventricular ejection fraction and creatinine clearance on admission estimated by the Cockroft-Gault formula.

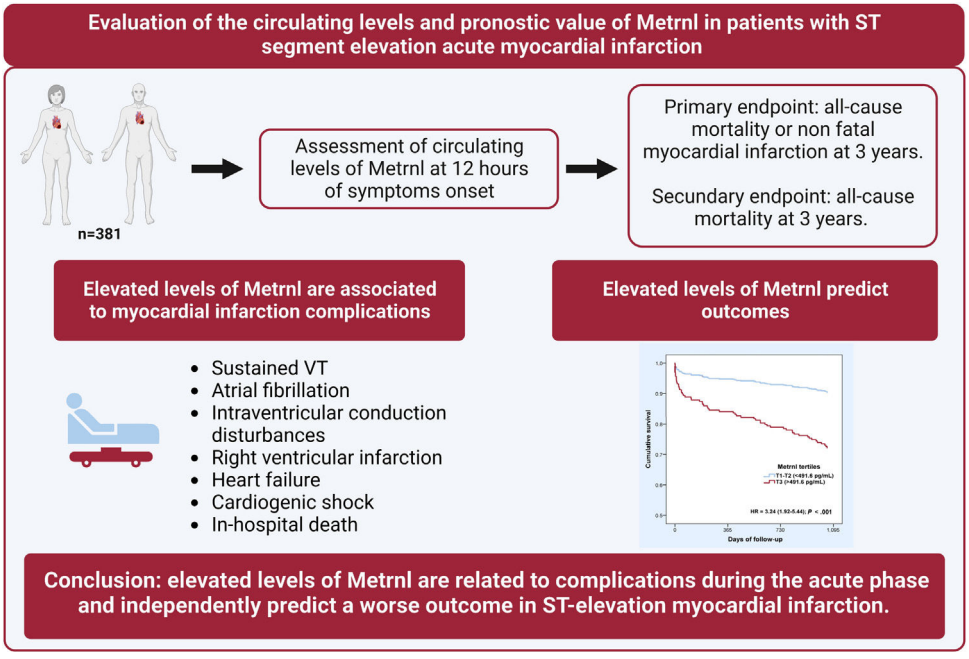

Figure 3. Central illustration. Deciphering the prognostic value of Metrnl in patients with ST-segment elevation acute myocardial infarction. Metrnl, meteorin-like; VT, ventricular tachycardia.

CONCLUSIONS

In patients with STEMI treated by primary PCI, circulating Metrnl levels during the first few hours are related to disease severity and are a predictor of adverse outcomes. In addition to their possible use in risk stratification, the cardioprotective and inflammatory modulator functions of Metrnl suggest the advisability of exploring its role as a new therapeutic target.

WHAT IS KNOWN ABOUT THE TOPIC?

- Metrnl is a secreted protein with an anti-inflammatory role.
- Clinical studies have described the relationship between circulating Metrnl levels and metabolic diseases.
- Circulating Metrnl levels have a prognostic value in HF patients.

WHAT DOES THIS STUDY ADD?

- Metrnl was associated with acute phase complications of STEMI.
- Metrnl was an independent predictor of all-cause death and nonfatal myocardial infarction after a 3-year follow-up in STEMI patients.

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AUTHORS' CONTRIBUTIONS

G. Ferrer-Curriu: investigation, writing original draft, revising, and editing; F. Rueda: investigation, writing original draft, revising, and editing; E. Revuelta-López: investigation, writing original draft, and funding acquisition; C. García-García: writing, revising, and editing; P. Codina: writing, revising, and editing; C. Gálvez-Montón: writing, revising, and editing; S. Roura: writing, revising, and editing, funding acquisition; A. Aimo: writing, revising, and editing; M. Emdin: writing, revising, and editing; A. Planavila: investigation, writing original draft, revising, and editing; A. Bayés-Genís: conceptualization, writing, revising, and editing, supervision, funding acquisition. G. Ferrer-Curriu and F. Rueda share authorship.

CONFLICTS OF INTEREST

The authors have no disclosures.

APPENDIX. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2023.03.015

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