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Community-Acquired Pneumonia Patients at Risk for Early and Long-term Cardiovascular Events Are Identified by Cardiac Biomarkers

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BACKGROUND: Community-acquired pneumonia (CAP) increases the risk of cardiovascular complications during and following the episode. The goal of this study was to determine the usefulness of cardiovascular and inflammatory biomarkers for assessing the risk of early (within 30 days) or long-term (1-year follow-up) cardiovascular events.

METHODS: A total of 730 hospitalized patients with CAP were prospectively followed up during 1 year. Cardiovascular (proadrenomedullin [proADM], pro-B-type natriuretic peptide (proBNP), proendothelin-1, and troponin T) and inflammatory (interleukin 6 [IL-6], C-reactive protein, and procalcitonin) biomarkers were measured on day 1, at day 4/5, and at day 30.

RESULTS: Ninety-two patients developed an early event, and 67 developed a long-term event. Significantly higher initial levels of proADM, proendothelin-1, troponin, proBNP, and IL-6 were recorded in patients who developed cardiovascular events. Despite a decrease at day 4/5, levels remained steady until day 30 in those who developed late events. Biomarkers (days 1 and 30) independently predicted cardiovascular events adjusted for age, previous cardiac disease, $Pao_2/Fio_2 < 250$ mm Hg, and sepsis: ORs (95% CIs), proendothelin-1, 2.25 (1.34-3.79); proADM, 2.53 (1.53-4.20); proBNP, 2.67 (1.59-4.49); and troponin T, 2.70 (1.62-4.49) for early events. For late events, the ORs (95% CIs) were: proendothelin-1, 3.13 (1.41-7.80); proADM, 2.29 (1.01-5.19); and proBNP, 2.34 (1.01-5.56). Addition of IL-6 levels at day 30 to proendothelin-1 or proADM increased the ORs to 3.53 and 2.80, respectively.

CONCLUSIONS: Cardiac biomarkers are useful for identifying patients with CAP at high risk for early and long-term cardiovascular events. They may aid personalized treatment optimization and for designing future interventional studies to reduce cardiovascular risk.

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KEY WORDS: biomarkers; cardiovascular events; pneumonia

ABBREVIATIONS: AMI = acute myocardial infarction; AUROC = area under the receiver-operating curve; CAP = community-acquired pneumonia; CRP = C-reactive protein; PCT = procalcitonin; proADM = proadrenomedullin; proBNP = pro-B-type natriuretic peptide

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Community-acquired pneumonia (CAP), with an incidence of three to five cases per 1,000 adults per year, is one of the most prevalent infectious diseases and causes high morbidity and mortality.[1] A striking fact is that, during the 10 years following the acute episode, patients who survive CAP continue to present a higher risk of cardiovascular complications and mortality than patients with similar age and comorbidities.[2-4]

Serious cardiovascular complications (during and following pneumonia) include acute myocardial infarction (AMI),[5,6] cardiogenic edema, acute or worsening arrhythmia, and stroke; these complications have been reported more frequently in patients with previous chronic cardiovascular diseases and/or more severe CAP episodes.[7-9] However, they may also appear in patients without known previous cardiovascular disease,[10] and it has been stated that pneumonia itself should be considered a cardiovascular risk factor.[10-13] Several mechanisms have been proposed to be involved[14] such as destabilization of the vascular endothelium, imbalance between proinflammatory and antiinflammatory factors, and acceleration of the progression of atherosclerosis, among others.[11-15] One important aspect is that the severity and duration of cardiovascular stress in CAP is not well known. Direct injury to myocardial tissue caused by *Streptococcus pneumoniae* has been shown in animal models,[16] leaving residual fibrosis following initial myocyte necrosis.[17]

We hypothesized that cardiac and inflammatory biomarkers, as an expression of cardiovascular stress and inflammation, measured during and following the acute phase would help to identify patients with CAP at high risk for early and long-term cardiovascular events. The selected inflammatory and cardiac biomarkers are those widely validated[18,19] and most frequently available in hospitals; proendothelin-1 was added as a newer promising marker in sepsis and endothelial damage.[20] We considered that both the initial severity and the possible residual cardiovascular damage and inflammation at 30 days may influence the development of cardiovascular events, and there is a lack of studies monitoring biomarkers beyond hospitalization.

The goal of the current study was to determine the usefulness of several cardiac (proadrenomedullin [proADM], pro-B-type natriuretic peptide [proBNP], proendothelin-1, and troponin T) and inflammatory(interleukin 6 [IL-6], C-reactive protein (CRP], and procalcitonin [PCT]) biomarkers at day 1, day 4/5, and day 30 to predict early (within the first 30 days) and long-term (> 30 days to 1 year) cardiovascular events in hospitalized patients with CAP.

Patients and Methods

Prospective Cohort Multicenter Study

A prospective multicenter study was performed of patients with CAP hospitalized at three hospitals affiliated with the Spanish National Health Service. The inclusion criterion was a diagnosis of pneumonia based on a new radiological infiltrate with at least two compatible clinical symptoms. Exclusion criteria were admission in the previous 15 days, residence in a nursing home, immunosuppressive treatments, and HIV-positive status. The study complied with the Declaration of Helsinki, it was approved by the ethics committee at each hospital, and patients signed an informed consent (Code 2013/0204). Patients were followed up for 1 year. The follow-up was conducted at day 30 in the outpatient clinics and through revision of both hospital and primary care electronic health records and a telephone interview at 1 year.

The data collected data included age, sex, smoking habit, vaccination status, comorbidities, analytical results at admission, and previous treatments. Comorbidities were defined as published in previous studies[21]: cardiac (coronary artery disease, congestive heart failure, arrhythmia, or valvular heart disease); pulmonary (treatment for asthma, COPD, or interstitial lung disorders); renal (preexisting kidney disease with documented anomalous serum creatinine levels outside the pneumonia episode); hepatic (preexisting viral or toxic liver disease); neurologic (presence of symptomatic acute or chronic vascular or nonvascular encephalopathy, with or without dementia); and diabetes mellitus (diagnosis of glucose intolerance and treatment with oral antidiabetic drugs or insulin). Pneumonia severity index,[22] sepsis status, and respiratory failure were also recorded.

Cardiac Biomarker Determinations

Blood samples were taken the morning following admission, day 1, at day 4/5, and at day 30. The serum and plasma samples were frozen at −80°C until analysis. CRP was measured by using a microparticle-enhanced turbidimetric assay (CRP Gen.3, Cobas 8000, c701; Roche Diagnostics). PCT (Elecsys BRAHMS PCT test), IL-6 (Elecsys IL-6 test), NT-proBNP (Elecsys proBNP II STAT test), and troponin T (Elecsys troponin T high-sensitivity STAT test) were determined by electrochemiluminescence immunoassay with Cobas 8000, e602

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(Roche Diagnostics). ProADM and proendothelin-1 were determined by using immunofluorescent assays according to manufacturer's instructions (Thermo Scientific BRAHMS through TRACE technology in KRYPTOR systems). With the exception of proendothelin-1, all analytes were characterized by good ex vivo stability for days at room temperature (endothelin-1, 4 h). In case of levels below the limit of detection, the data included were the inferior limit as follows: proendothelin-1, 2.94 pmol/L; proADM, 0.05 nmol/L; PCT, 0.02 ng/mL; troponin T, 3 ng/L; proBNP, 5 pg/mL; IL-6, 1.5 pg/mL; and CRP, 0.3 mg/L.

Definitions of Cardiovascular Events and Outcome

The definition of cardiovascular events was pre-established in the design protocol, and they were registered systematically. A cardiologist was involved during the whole process. The occurrence of cardiovascular events was considered if any of the following appeared within the first 30 days (early cardiovascular events) or between day 31 and 1 year of follow-up (late events): acute coronary syndrome (AMI or unstable angina), new or worsening heart failure, de novo or recurrent arrhythmia requiring hospital admission or ED care, and cerebrovascular accident (stroke or transient ischemic attack). Criteria for AMI were the detection of a rise and/or fall in troponin T with at least one value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischemia with at least one of the following: (1) symptoms of ischemia; (2) development of abnormal Q waves in the ECG; (3) new, or presumed new, significant ST-segment T-wave changes or new left bundle-branch block; and (4) imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality. New or worsening heart failure was considered by the simultaneous presence of clinical signs of new or worsening pulmonary edema or acute congestive heart failure (eg, rales, increased jugular venous pressure, S3 gallop, peripheral edema) detected by the managing physician on physical examination and documented in the medical record, and a chest radiograph read by the local radiologist as showing pulmonary edema, cardiomegaly, vascular congestion, or congestive heart failure. De novo arrhythmia or worsened chronic arrhythmia was registered. Worsened arrhythmia was considered if there was any hemodynamic repercussion, including heart failure, severe hypotension usually requiring cardiologic assessment, or a change in usual treatment.

Mortality was recorded at three periods: in-hospital, at 30 days, and at 1 year. Mortality for any reason was also recorded.

Statistical Analysis

The analysis was conducted by using IBM SPSS 20.0 software (IBM SPSS Statistics, IBM Corporation). Cardiac and inflammatory biomarkers are presented as medians and interquartile ranges. They were compared by using the Mann-Whitney U test; P values $< .05$ were considered significant. Nonparametric Spearman correlation between cardiac and inflammatory biomarkers was studied to assess collinearity. The areas under the receiver-operating curves (AUROCs) to determine the accuracy of biomarkers for early and late cardiovascular events were calculated by using SPSS. The thresholds for cardiac biomarkers (the highest sensitivity and specificity) were estimated from AUROCs. Using these thresholds, biomarkers were dichotomized for inclusion in the multivariate analyses.

Several logistic regression analyses were performed to predict early and late cardiovascular events (dependent variables). We included as independent variables clinically relevant factors such as age > 65 years, cardiac disease, cerebrovascular disease, respiratory failure ($Pao_2/Fio_2 < 250$ mm Hg), and sepsis along with biomarkers. The dichotomized cardiac and inflammatory biomarkers were evaluated separately one by one in different models to calculate their adjusted ORs. To evaluate the potential improvement of prediction with a combination of biomarkers, several additional logistic regression analyses adjusting for the same clinical relevant variables were performed. Due to the high collinearity between cardiac biomarkers, we explored the combination of each cardiac biomarker along with one inflammatory biomarker (IL-6, because it was found to be significant in univariate analysis).

Results

Patients' Characteristics and Cardiovascular Events

We recruited 920 patients and ultimately included 730 patients, with a median age of 70 years (interquartile range, 55-80 years). Ninety-five patients presented with an early event and 67 with late cardiovascular events (Table 1); 20 patients had both early and late events. Patients with early cardiovascular events were older and presented more previous cardiac diseases, more sepsis, and more previous treatment with statins (Table 2).

Mortality in the whole cohort was as follows: 4.7% (n = 34) in-hospital, 5.3% (n = 39) at 30 days, and 9.9% (n = 72) at 1-year follow-up. One-year mortality was significantly higher in patients with early cardiovascular events (22.8% vs 8%; $P < .0001$).

Cardiac Biomarkers and Early Cardiovascular Events

Patients who developed early cardiovascular events exhibited initial higher proendothelin-1, troponin T, proADM, and proBNP levels (Table 3). A significant strong correlation was found between the different cardiac biomarkers at day 1 (e-Table 1). At day 4/5, levels of cardiac biomarkers had fallen with respect to initial levels, although they remained significantly higher in patients with cardiovascular events. Patients with higher initial severity and sepsis also experienced more early events.

In the subset of patients with no previous chronic cardiac disease, biomarkers also showed initial higher levels in patients who developed early cardiovascular events (e-Table 2).

The AUROCs of biomarkers at day 1 for estimating early events ranged from 0.71 (proendothelin-1) to 0.75 (proBNP) (e-Fig 1A). The cutoff points selected were: CRP > 157.8 mg/L, PCT > 0.72 ng/mL, IL-6 > 33.7 pg/mL, proADM > 1.2 nmol/L, proendothelin-1 > 104 pmol/L, troponin T > 21.9 ng/mL, and proBNP > 1,619 pg/mL. In the subset of patients with no previous cardiac disease, the AUROCs were similar, ranging from 0.73 (proADM) to 0.78 (proBNP).

TABLE 1] Number of Early and Late Cardiovascular Events in the 730 Patients

Event	Early[a]: n = 95 (13%) Patients	Late[a]: n = 67 (9.2%) Patients
No. of events[b]	113 (100)	71 (100)
Acute coronary syndrome	4 (3.5)	4 (5.6)
Acute myocardial infarction	2 (1.8)	3 (4.2)
Unstable angina	2 (1.8)	1 (1.4)
New or worsening arrhythmia	52 (46)	19 (26.8)
Atrial fibrillation	40 (35.4)	15 (21.1)
Atrial flutter	13 (11.5)	3 (4.2)
Other	4 (3.6)	1 (1.4)
Acute heart failure	56 (50)	41 (57.7)
Cerebrovascular accident	1 (0.9)	7 (9.9)
Stroke	0	5 (7.0)
Transient ischemic attack	1 (0.9)	2 (2.8)

Data are presented as No. (%).
[a]Number of patients with at least one event.
[b]Number of events (some patients had more than one event).

Cardiac Biomarkers and Late Cardiovascular Events

Sixty-seven of 691 patients (9.4%) alive at 30 days developed late cardiovascular events, 47 of whom had not had early events. The characteristics of patients without early events are shown in Table 2. Levels of biomarkers during (day 1 and day 4/5) and after (day 30) CAP hospitalization are depicted in Figure 1. A significant strong correlation was also found between the different cardiac biomarkers at day 30 (e-Table 1).

Despite a decrease at day 4/5, levels of proADM, troponin T, and proendothelin-1 remained steady until 30 days in those who developed late events. At day 30, the median levels were still higher in patients who developed cardiovascular events (Table 3). In the subset of patients with no previous chronic cardiac disease, biomarker results also exhibited higher levels at 30 days in patients who developed late cardiovascular events (e-Table 2).

The AUROCs of biomarkers at day 30 to estimate late events in the whole cohort ranged from 0.73 (troponin T) to 0.78 (proendothelin-1) (e-Fig 1B). The best cutoff points were: CRP > 3.4 mg/mL, PCT > 0.05 ng/mL, IL-6 > 5.45 pg/mL, proADM > 0.83 nmol/L, proendothelin-1 > 70.7 pmol/L, troponin T > 16 ng/mL, and proBNP > 315 pg/mL. The AUROCs of biomarkers at day 30 were also calculated after excluding patients with previous cardiac disease; the AUROCs ranged from 0.76 (proendothelin-1) and 0.77 (IL-6) to 0.81 (troponin T).

Multivariable Analyses for Early and Late Cardiovascular Events

Early Events: The ORs for each cardiac biomarker analyzed separately and adjusted for independent associated factors were statistically significant (Fig 2). Age > 65 years, previous chronic cardiovascular disease, Pao_2/Fio_2 < 250 mm Hg, and PCT were also found to be independent risk factors. For each model, the AUROCs were calculated and yielded similar figures, approximately 0.74 (e-Table 3). The combination of each cardiac biomarker with IL-6 did not improve ORs or AUROCs.

Late Events: The corresponding results for prediction of late events (excluding patients with early events) are shown in Figure 3. Again, cardiac biomarkers (except troponin T) were independent risk factors along with age > 65 years and previous chronic cardiovascular disease. In the regression statistical analyses performed with combinations of each cardiac biomarker with IL-6, the highest OR (3.53; 95% CI, 1.51-8.26) was reached by proendothelin-1 and IL-6 at day 30, with an AUROC of 0.83 (e-Table 4).

Discussion

The most relevant results of our study are as follows: (1) cardiac biomarkers are independently related to early and long-term cardiovascular events after controlling for age, sepsis, Pao_2/Fio_2 < 250 mm Hg, and previous heart diseases; (2) for early events, cardiac biomarkers measured on day 1 show similar ORs (proBNP, 2.67; troponin T, 2.70; proADM, 2.53; and proendothelin-1, 2.25); and (3) for late cardiovascular events, a combination of IL-6 levels at day 30 to proendothelin-1 or proADM achieved the highest OR (3.53 and 2.80, respectively).

In the current study, cardiovascular events appeared in 11.4% of patients during hospitalization, 1.6% following hospital discharge and within 30 days, and 9.2% more during the first year of follow-up.[23] Cardiovascular events were more frequent in elderly patients with previous cardiac risk factors, hypertension, COPD, and renal chronic diseases, and in those with more severe CAP, as previously reported.[24] Pneumonia may worsen a preexisting chronic condition, and it may also

TABLE 2] Baseline Characteristics According to the Development of Early and Late Cardiovascular Events Excluding Those With Early Events

Characteristic	Early Cardiovascular Events				Late Cardiovascular Events (Excluding Those With Early Events)			
	Overall	No	Yes	*P* Value	Overall	No	Yes	*P* Value
No.	730	635 (87%)	95 (13%)		611	564 (92.3%)	47 (7.7%)	
Demographic and toxic habits								
Age, y	70 (55-80)	68 (54-80)	78 (69-84)	< .001	68 (53-79)	67 (52-78)	77 (71-84)	< .001
Sex (male)	63.8%	62.4%	73.7%	.032	62.5%	62.8%	59.6%	.664
Pneumococcal vaccine	4.3%	4.3%	4.7%	.850	4.2%	4%	6.7%	.396
Influenza vaccine	42.5%	39.8%	60.9%	< .001	39%	38.4%	46.8%	.255
Smoker	17.9%	19.1%	10.5%	.043	19.6%	20.2%	12.8%	.217
Former smoker	33.3%	31.3%	46.3%	.004	31.4%	31%	36.2%	.466
Comorbidities								
Dyslipidemia	33.3%	31.9%	43.2%	.029	32%	30.7%	47.8%	.023
Arterial hypertension	49.4%	45.5%	71.7%	< .001	55.1%	41.8%	80%	< .001
Diabetes mellitus	22.6%	21.1%	32.6%	.012	21.3%	21.1%	23.9%	.711
Obesity	13.4%	12.6%	19.1%	.080	12.9%	12.6%	17.4%	.379
Chronic heart disease	31.1%	28%	51.6%	< .001	27%	24.3%	58.7%	< .001
Acute coronary syndrome	3.2%	2.7%	6.3%		2.8%	2.8%	2.2%	
Arrhythmia	10.5%	8.7%	23.2%		8.2%	7%	28.3%	
Heart failure	8.8%	6.5%	24.2%		6.4%	5.5%	17.4%	
Valvulopathy	2.1%	1.9%	3.2%		2%	1.8%	4.3%	
Other[a]	6.5%	8.2%	5.9%		7.6%	7.2%	12.1%	
Cerebrovascular disease	6.7%	6.3%	9.5%	.249	6.2%	6.4%	4.3%	.562
COPD	20.6%	18.8%	33%	.002	18.7%	17.6%	31.9%	.015
Chronic renal disease	11.2%	9.6%	22.1%	< .001	9.2%	8.3%	19.1%	.014
Liver disease	2.9%	3%	2.1%	.630	3.1%	3%	4.3%	.638
Initial severity								
Sepsis	47.8%	46.1%	60%	.012	45.6%	44%	66%	.004
Pneumonia Severity Index				< .001				< .001
I	15.1%	17.1%	2.1%		17.8%	19.3%	0%	
II	17.5%	19.6%	3.2%		20.4%	21%	12.8%	
III	23.1%	23.6%	20%		24%	24.4%	19.1%	

(Continued)

TABLE 2] *(Continued)*

Characteristic	Early Cardiovascular Events				Late Cardiovascular Events (Excluding Those With Early Events)			
	Overall	No	Yes	*P* Value	Overall	No	Yes	*P* Value
IV	32.6%	31%	43.2%		30.9%	29.4%	48.9%	
V	11.7%	8.7%	31.6%		6.9%	5.9%	19.1%	
Physical examination, laboratory, microbiology and radiographic findings								
Altered mental status	7.7%	6.7%	14%	.015	6.1%	5.7%	10.9%	.414
Heart rate, beats/min	98 (85-111)	97 (85-110)	100 (86-119)	.034	97 (85-110)	98 (85-110)	97 (84-112)	.760
Respiratory rate, breaths/min	18 (16-24)	18 (16-24)	20 (18-28)	< .001	17 (16-22)	17 (16-22)	19 (16-25)	.097
Pao_2/FIo_2 < 250 mm Hg	25.1%	22.6%	41.1%	< .001	21%	19.9%	34.8%	.015
Hematocrit, %	39 (36-42)	39 (36.1-42)	38 (35.2-42.3)	.241	39.1 (36.4-42)	39.3 (36.6-42.1)	38 (34.7-40.5)	.027
Glucose, mg/dL	128 (109-158)	128 (108-156)	140 (112-185)	.016	127 (108-156)	126 (108-155)	142 (123-196)	.007
Creatinine, mg/dL	0.96 (0.78-1.29)	0.93 (0.77-1.23)	1.1 (0.93-1.76)	< .001	0.93 (0.76-1.23)	0.92 (0.75-1.20)	1.15 (0.83-1.63)	.002
Bacteremia	10.4%	10.2%	11.7%	.820	9.2%	9.5%	6.1%	.681
Pneumococcal disease	20.6%	20.3%	22.1%	.693	20.2%	19.5%	28.3%	.143
Pleural effusion	16.7%	15.3%	26.3%	.019	15.4%	14.9%	21.3%	.380
Previous treatments								
Statins	29.9%	28.9%	36.8%	.115	29.1%	27.8%	44.7%	.031
Aspirin	17.1%	16.1%	23.3%	.089	16.1%	14.8%	31.8%	.002
Antibiotic treatment								
Fluoroquinolone	45.8%	45.6%	46.6%	.906	45.8%	46.1%	42.1%	.639
Macrolide + β-lactam	39.5%	39.1%	42.5%	.571	39.4%	39%	43.9%	.444

Data are presented as median (interquartile range) unless otherwise indicated.
[a]Includes congenital heart disease, bundle-branch block, hypertrophic cardiomyopathy, and/or dilated cardiomyopathy.

TABLE 3] Biomarker Levels According to the Development of Early and Late Cardiovascular Events

	Early Cardiovascular Event			Late Cardiovascular Event		
	No	Yes	*P* Value	No	Yes	*P* Value
Day 1						
Proendothelin-1	81.2 (55.2-126.3)	144.2 (92-214.7)	< .001	78.8 (54.1-122.3)	123.8 (88.4-163.9)	< .001
ProADM	1 (0.7-1.5)	1.6 (1.1-2.3)	< .001	0.9 (0.7-1.4)	1.3 (1-1.7)	< .001
PCT	0.4 (0.1-2.2)	1.1 (0.2-5.3)	.005	0.4 (0.1-2.3)	0.5 (0.1-1.4)	.846
Troponin T	13.6 (6.2-30.4)	27 (17-55.2)	< .001	12.6 (5.6-26.4)	29.8 (16.1-44.2)	< .001
ProBNP	671.3 (229.4-2,062.5)	2811.5 (1,156-8,019)	< .001	5,72.1 (217.2-1,843)	2,080.5 (1,369-4,762)	< .001
IL-6	36.3 (12.1-113.8)	60.1 (12-168.9)	.250	36.3 (12.1-117.6)	37.4 (13.8-92.6)	.898
CRP	161.5 (77.8-274.1)	154.3 (81.5-296.4)	.621	165.3 (80.3-284.8)	118.3 (46.9-228)	.026
Day 4/5						
Proendothelin-1	62.1 (45-83.7)	93.6 (63.7-121.4)	< .001	61.3 (44.9-81)	90.5 (65.6-107.7)	< .001
ProADM	0.8 (0.6-1.1)	1.2 (0.9-1.6)	< .001	0.8 (0.6-1.1)	1 (0.8-1.6)	.001
PCT	0.2 (0.1-0.5)	0.2 (0.1-0.7)	.141	0.2 (0.1-0.5)	0.2 (0.1-0.4)	.855
Troponin T	12.5 (5.3-26.1)	25.3 (15.9-50)	< .001	11.2 (4.8-24.2)	25 (14.4-36.3)	< .001
ProBNP	473.8 (125.3-1,577)	1,509 (613-4,396)	< .001	419.1 (112.9-1510)	1,427 (429.6-3,299)	.001
IL-6	13.3 (4.6-32.9)	11.1 (4.5-52.6)	.698	13.4 (4.5-33.1)	8.2 (5.2-20.8)	.770
CRP	47.9 (20.6-95.7)	48.6 (25.2-110.7)	.880	49.9 (21.1-102.6)	33.8 (15-64.9)	.043
Day 30						
Proendothelin-1	…	…	…	55 (43.6-74.6)	85.6 (67.6-95.3)	< .001
ProADM	…	…	…	0.6 (0.5-0.9)	0.9 (0.7-1.3)	< .001
PCT	…	…	…	0.1 (0-0.1)	0.1 (0-0.1)	.465
Troponin T	…	…	…	10.1 (4.3-19.7)	22.3 (11.9-38.8)	< .001
ProBNP	…	…	…	132.6 (52.5-421.9)	692.7 (227.7-1461)	< .001
IL-6	…	…	…	4.1 (1.8-7.3)	6.7 (4.3-12.7)	.001
CRP	…	…	…	2.9 (1.3-7)	3.8 (1.2-9)	.470

Data are presented as median (interquartile range). CRP = C-reactive protein; IL-6 = interleukin 6; PCT = procalcitonin; proADM = proadrenomedullin; ProBNP = pro-B-type natriuretic peptide.

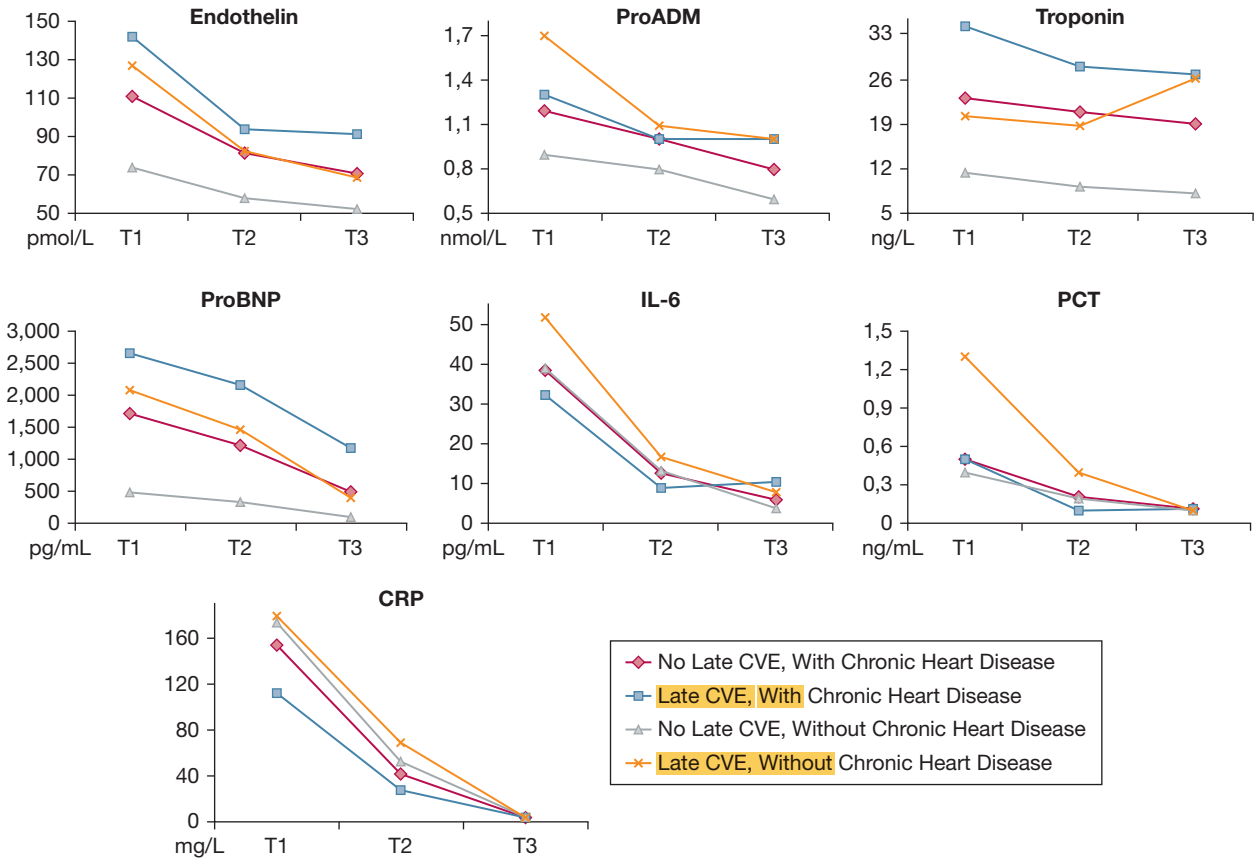

Figure 1 – *Evolution of biomarkers during hospital stay and at 30 days. CRP = C-reactive protein; CVE = cardiovascular events; IL-6 = interleukin-6; PCT = procalcitonin; ProADM = proadrenomedullin; ProBNP = pro-B-type natriuretic peptide; T1 = Day 1; T2 = Day 4/5; T3 = Day 30.*

contribute to deterioration of a prior unknown structural comorbid condition.

Cardiac biomarker levels at day 1 were higher in patients developing cardiovascular complications, reflecting the more intense damage and cardiovascular stress at that initial infection phase, as it corresponds with the highest inflammation. It should also be recognized that biomarker levels may also reflect a greater degree of multisystem organ failure. In patients developing early events, cardiac biomarker levels were similar in patients with or without previous cardiac diseases, revealing a comparable degree of cardiovascular dysfunction. Cardiac biomarkers reflect deterioration in several aspects such as ventricular cardiac stress, myocyte injury, myocardial supply-demand mismatch, or heart failure, and they therefore allow recognition of cardiovascular dysfunction in CAP. The relevance of cardiac biomarkers has been shown even in patients with no evidence of acute ischemic cardiac disease.[25] In fact, high levels of cardiac biomarkers are showing some degree of subclinical dysfunction despite no cardiovascular events appear, whereas low levels represent a low risk for them.

The independent value of cardiac biomarkers to predict early cardiovascular events was confirmed in multivariable analyses after adjusting for age, sepsis, PaO_2/FIO_2,[26] and previous cardiovascular diseases, as all these conditions are well known to be associated with more cardiovascular complications and/or mortality.[23] The various multivariable analyses and the AUROCs showed that proADM, proBNP, proendothelin-1, and troponin T present similar accuracy (in fact, there was a high correlation between the biomarkers) and that they can be used interchangeably, depending on their availability, cost, or the results of other future studies. A combination of cardiac biomarkers was not assessed due to high collinearity among them; instead, combinations of each cardiac biomarker with inflammatory biomarkers were evaluated. However, the addition of IL-6 levels at day 1 to each cardiac biomarker did not improve prediction, indicating the better performance of cardiac biomarkers to predict early events.

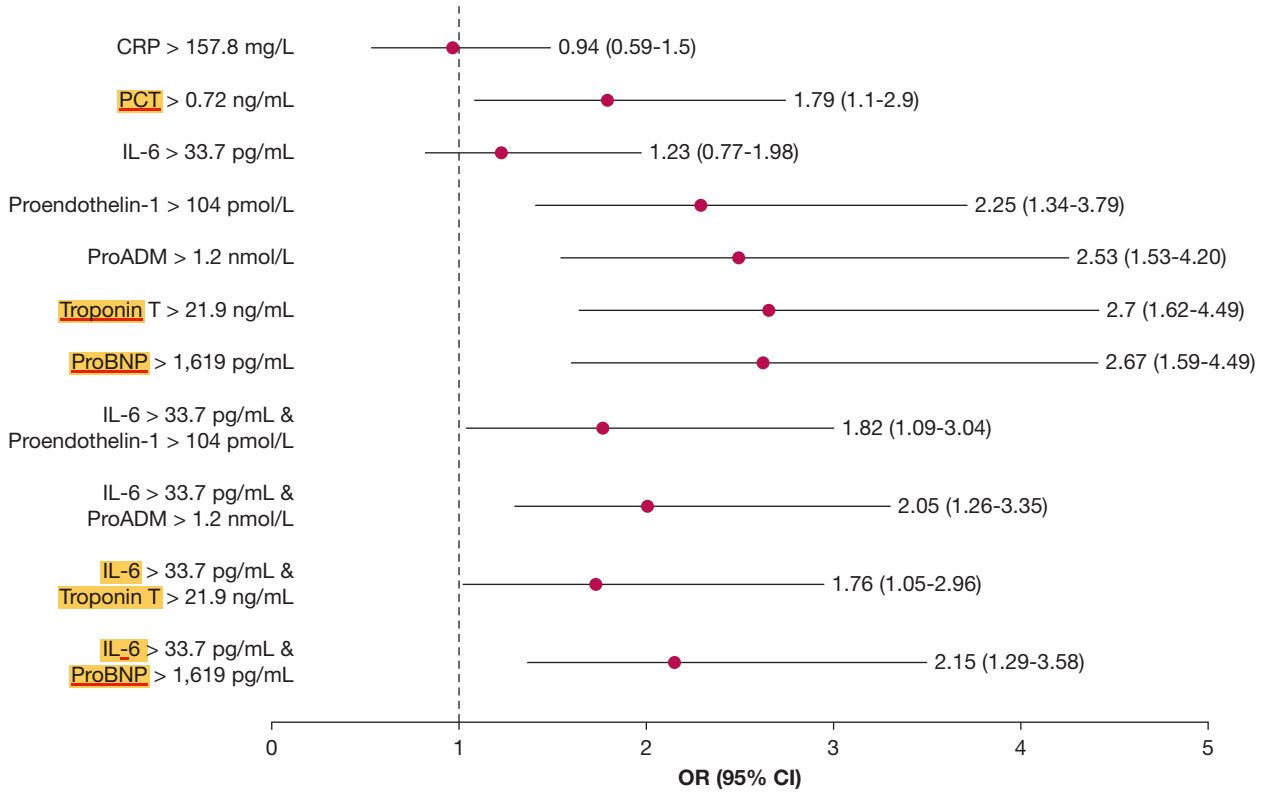

Figure 2 – *Multivariable analysis for early cardiovascular events. Adjusted for age, chronic heart disease, cerebrovascular disease, sepsis, and* $Pao_2/Fio_2 < 250$ *mm Hg. See Figure 1 legend for expansion of abbreviations.*

Cardiac biomarker levels decreased from day 1 to day 4/5 even in those with cardiovascular events, but they remained steady between day 4/5 and day 30, especially proendothelin-1, proADM, and troponin T, in those who subsequently developed late events. Previous studies have reported the negative consequences due to the ongoing subclinical inflammatory[19] and/or prothrombotic state[27] at hospital discharge, but there is scarce information on later periods.

Increased proADM, proBNP, or proendothelin-1 levels at day 30 were independently associated with long-term cardiovascular events after adjusting for clinical factors. To our knowledge, the identification of remaining cardiovascular stress at 30 days in patients with CAP through cardiac biomarkers has not been previously reported, although it has been evaluated during hospital stays.[28-30] Using proBNP, a biomarker commonly available in hospitals, our results showed that a level > 315 pg/mL at 30 days increases more than twofold the risk of late cardiac events following discharge.[31] The AUROCs calculated for each cardiac biomarker separately were similar, indicating that they may offer comparable information regarding cardiovascular stress and making possible use of any of them depending on their availability in different hospitals. Nevertheless, proendothelin-1, which is secreted by endothelial cells and expresses shear stress, exhibited the highest accuracy. Remarkably, the strongest risk for late cardiovascular events was found when both inflammation and cardiovascular damage concurred, as expressed by increased proendothelin-1 or proADM along with increased IL-6 levels. Our findings imply that the worst scenario seemed to occur in patients with remaining cardiovascular stress and concurrent persistent inflammation at day 30. In fact, in the general population without pneumonia, raised levels of IL-6 and troponin are associated with higher increased cardiovascular risk.[32,33] A meta-analysis performed by Li et al[34] on an elderly population showed more cardiovascular risk when IL-6 levels were elevated.

Our study has some limitations. First, individual cardiac biomarkers might be more useful for predicting different cardiovascular events, and we considered any cardiovascular events as the end point variable. Second, the cause of mortality at 1 year was not identified in most patients, and no control group was included. In terms of the strengths of the study, we stress that CAP could represent an opportunity to identify individuals at

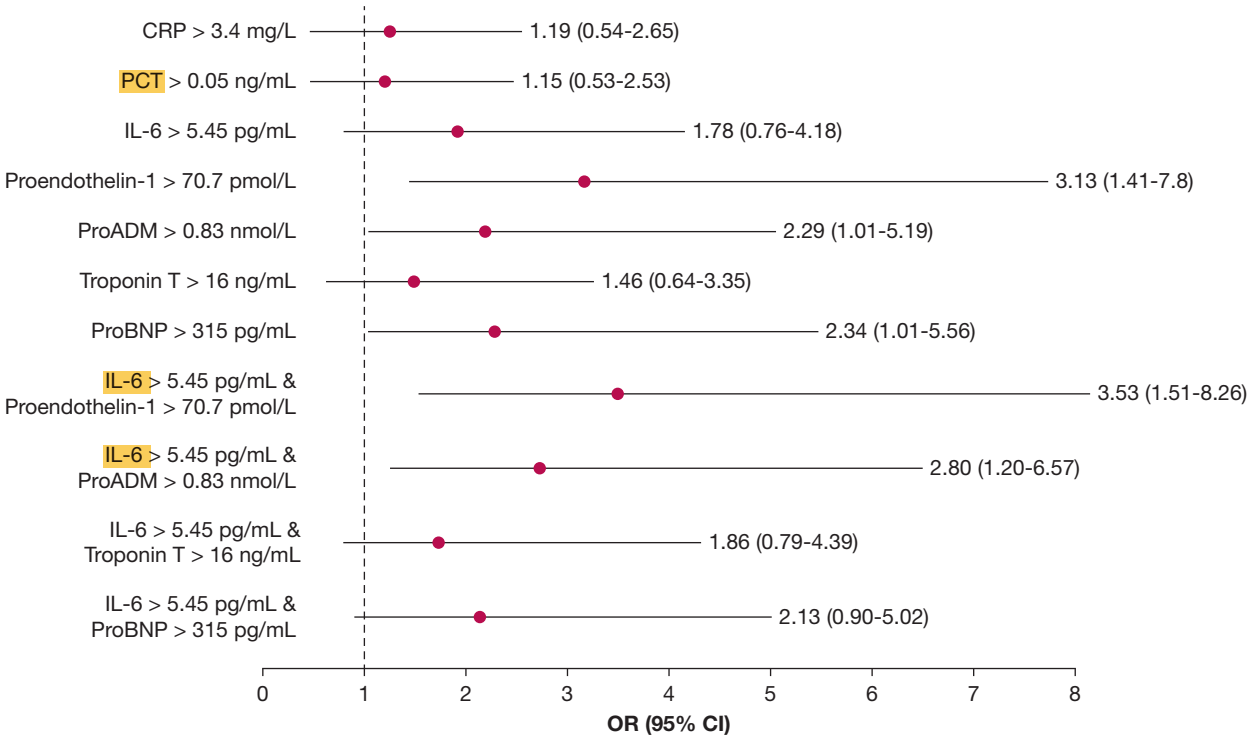

Figure 3 – *Multivariable analysis for late cardiovascular events (excluding patients with early events). Adjusted for age, chronic heart disease, cerebrovascular disease, sepsis, and* $Pao_2/Fio_2 < 250$ *mm Hg. See Figure 1 legend for expansion of abbreviations.*

risk for posterior cardiovascular events and thus to develop strategies for early intervention programs. Therapy can be optimized during hospitalization, and patients at risk should receive full assessment; at hospital discharge, they should be referred for cardiac rehabilitation programs to reduce cardiovascular risk.[35] Cardiac biomarkers may also help in selection of high-risk patients with CAP to design future interventional studies with treatments (statins, aspirin, polypill strategy, anticoagulants, or others) for reducing cardiovascular events, as has occurred in other conditions.[9,36-38]

Conclusions

The current study shows the usefulness of cardiac biomarker levels at day 1 to predict early cardiovascular events and at day 30 to predict late cardiovascular events even in patients with no previous cardiac diseases. Some patients still have high levels of inflammatory and cardiac biomarkers at 30 days, when they are usually referred to primary care without receiving any specific additional recommendations. Our results suggest that a change in usual practice is needed to reduce current and further cardiovascular CAP complications. ProADM, proBNP, proendothelin-1, and IL-6 levels may help in the individual assessment of risk, and they may therefore guide the design of personalized cardiovascular rehabilitation programs and treatment optimization in patients both with and without known previous cardiac disorders. Cardiac biomarkers may also help in the selection of high-risk patients to design future interventional studies. Prevention strategies in patients with CAP to reduce cardiovascular risk are required.

Acknowledgments

Author contributions: R. Menéndez conceived the study design. R. Méndez, I. A., S. R., P. G.-J., P. P. E., and J. A. developed and recruited cohorts that were used in the study. R. Méndez, I. A., S. R., P. G.-J., P. P. E., and J. A. collected the data used in the study. M. S. and R. A. performed the laboratory analysis of the biological samples. R. Menéndez, R. Méndez, and L. M.-D. analyzed the data. L. M.-D. and A. T. contributed to interpretation of results. R. Menéndez wrote the manuscript. All authors reviewed, revised, and approved the manuscript for submission. R. Menéndez had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Additional information: The e-Figure and e-Tables can be found in the Supplemental Materials section of the online article.

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