Adrenomedullin refines mortality prediction by the BODE index in COPD – The "BODE-A" index

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Online Data Supplement

METHODS

Study Design: Inclusion Of Other Plasma Biomarkers Besides Proadrenomedullin

Besides proadrenomedullin, we examined the relationships of three other plasma biomarkers, procalcitonin, copeptin, and pro-atrial natriuretic protein, with 1-year and 2-year mortality in the analyzed cohort (N = 549). Observations from single-center studies of these analytes in adverse outcome prediction in chronic obstructive pulmonary disease (COPD) and other illnesses, summarized in the "Other biomarkers: description and use in adverse outcome prediction" subsection below, provided the rationale for inclusion of procalcitonin, copeptin, and pro-atrial natriuretic peptide in the present study.

Each biomarker was studied alone and together with either the Body-mass, airflow Obstruction, Dyspnea and Exercise capacity index (BODE)[1] or the non-6-minute-walk test (6MWT) BODE components (BOD). The identical univariate and multivariate Cox regression proportional-hazard regression modelling techniques were used to examine these relationships, and the data are reported in the same fashion, as are described in the "Statistics" subsection of the "Methods" section of the main manuscript.

Other Biomarkers: Description And Previous Use In Adverse Outcome Prediction

Procalcitonin is the stable prohormone of the regulator of calcium metabolism, calcitonin. Procalcitonin production and secretion are markedly up-regulated in response to bacterial toxins and cytokines expressed due to systemic bacterial infection, but are down-regulated by cytokines evoked by viral infection.[2] Therefore, procalcitonin has gained widespread use to help guide whether to start or how long

to continue antibiotic therapy, or both decisions, in patients with lower respiratory infections,[3,4] including chronic obstructive pulmonary disease (COPD) exacerbations[5] and sepsis.[3]

Copeptin is the stable co-terminal fragment of the prohormone of arginine vasopressin, and as such, a surrogate for the mature hormone. The primary function of arginine vasopressin is fluid regulation, but levels of this mature hormone are elevated in response to systemic stress, including acute myocardial infarction,[6] hemorrhage, and sepsis.[7]

Pro-atrial natriuretic peptide is the mid-regional fragment of the prohormone of, and thus a surrogate for, atrial natriuretic peptide, a biomarker of cardiovascular stress.[8] The relationship of admission procalcitonin and copeptin measurements with 14-day and 6-month clinical failure, including mortality, previously was examined in a single-center observational study[9] of inpatients with COPD exacerbation. The study found copeptin, but not procalcitonin, to have predictive value with respect to 6-month clinical failure.[9] Significantly higher mean pro-atrial natriuretic peptide concentrations were observed in 2-week non-survivors than in 2-week survivors in a large single-center study in patients with lower respiratory tract infections including those with COPD exacerbations, who comprised11% of the study sample.[10]

Plasma Biomarker Measurement

Blood for proadrenomedullin, procalcitonin, copeptin, and pro-atrial natriuretic peptide measurements was collected via indwelling venous catheter into vacutainer tubes, which were centrifuged at 3000 x *g* for 10-15 minutes to obtain plasma. Samples were stored at –80°C until analyzed. For all four analytes, quantification was performed in duplicate within one run in a central, accredited laboratory by technicians unaware of patients' clinical data, using automated sandwich

immunoassays based on time-resolved amplified cryptate emission technology (KRYPTOR®; Thermo Scientific Biomarkers, Hennigsdorf, Germany). The procalcitonin assay had a lower detection limit of 0.02 µg/L and functional assay sensitivity of 0.06 µg/L, i.e., 3–10-fold over mean values in healthy volunteers.[11] The copeptin assay had a 0.4 pmol/L lower detection limit and an <1 pmol/L functional assay sensitivity.[12] The pro-atrial natriuretic peptide assay had a 4.3 pmol/L lower detection limit and a 11.0 pmol/L functional sensitivity, with an interassay coefficient of variation <20%.[8]

For each studied plasma biomarker, measurements below the limit of quantitation were imputed to that value.

Outcome Assessment and Statistics: Additional Information

Otherwise undeterminable death dates were imputed to halfway between the latest study visit and the date that the investigator learned of the death. All statistical analyses were performed using R version 2.5.1 (http://www.r-project.org) or Statistical Package for the Social Sciences version 19.0 (IBM, Armonk, NY).

Online Data Supplement References

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SUPPLEMENTARY FIGURE LEGEND

Figure E1A-C. Dichotomized Kaplan-Meier 2-year survival curves based on optimized cut-offs for (A) procalcitonin (0.1 µg/L), (B) copeptin (15 pmol/L), and (C) pro-atrial natriuretic peptide (145 pmol/L) in the 594 patients (93.1%) from the PROMISE-COPD cohort who had complete data for these biomarkers. ANP = pro-atrial natriuretic peptide; PCT = procalcitonin.

SUPPLEMENTARY TABLES

TABLE E1. COX REGRESSION MODELS FOR 1-YEAR ALL-CAUSE MORTALITY PREDICTION

Variable(s)	Hazard ratio (95% CI)	*P*	C statistic	Model chi-square	*P*
Univariate analyses					
BODE	3.30 (2.04-5.35)	<0.001	0.745	23.24	<0.001
BOD	3.74 (1.90-7.34)	<0.001	0.690	15.25	<0.001
Procalcitonin	1.37 (0.94-1.99)	0.110	0.591	2.45	0.117
Copeptin	3.30 (2.04-5.35)	<0.001	0.620	9.44	0.002
ProANP	2.22 (1.31-3.75)	0.003	0.611	8.38	0.004
Multivariate analyses					
BODE plus:					
Procalcitonin	1.41 (0.98-2.02)	0.070	0.739	26.34	<0.001
Copeptin	2.96 (1.38-6.36)	0.005	0.765	31.10	<0.001
ProANP	2.30 (1.37-3.86)	0.002	0.774	32.90	<0.001
BOD plus:					
Procalcitonin	1.41 (0.97-2.05)	0.072	0.692	18.28	<0.001
Copeptin	3.36 (1.55-7.25)	0.002	0.741	24.76	<0.001
Pro-ANP	2.54 (1.49-4.32)	<0.001	0.750	26.72	<0.001

Definition of abbreviations: BOD = Body mass, airflow Obstruction, and Dyspnea index; BODE = Body mass, airflow Obstruction, Dyspnea, Exercise capacity index;

ProANP= pro-natriuretic peptide; CI = confidence interval. Increment one quartile for BODE, BOD, and biomarkers. P-values compare variables with hazard ratio=1 or C-statistics=0.5 (null hypothesis).

BOD comprises BODE without the exercise capacity measurement. These three components are scored according to the same cut-offs as is the BODE index.[1] The "BOD index" therefore ranges, in increasing severity, ranging, in increasing severity, from 0 to 7.

TABLE E2. COX REGRESSION MODELS FOR 2-YEAR ALL-CAUSE MORTALITY PREDICTION

Variable(s)	Hazard ratio (95% CI)	*P*	C statistic	Model chi-square	*P*
Univariate analyses					
BODEII	2.53 (1.73-3.69)	<0.001	0.679	22.07	<0.001
BODII	3.74 (1.90-7.34)	<0.001	0.649	15.26	<0.001
Procalcitonin	1.37 (1.02-1.84)	0.030	0.607	4.16	0.040
Copeptin	2.53 (1.73-3.69)	0.002	0.602	9.38	0.002
ProANP	2.04 (1.34-3.11)	0.001	0.609	10.63	0.001
Multivariate analyses					
BODE plus:					
Procalcitonin	1.40 (1.05-1.86)	0.020	0.697	26.98	<0.001
Copeptin	2.28 (1.27-4.11)	0.006	0.710	29.63	<0.001
ProANP	2.07 (1.37-3.12)	<0.001	0.734	33.62	<0.001
BOD plus:					
Procalcitonin	1.40 (1.05-1.87)	0.02	0.673	20.10	<0.001
Copeptin	2.49 (1.37-4.50)	0.003	0.696	24.24	0.001
ProANP	2.23 (1.46-3.39)	<0.001	0.718	28.85	<0.001

Definition of abbreviations: BOD = Body mass, airflow Obstruction, and Dyspnea index; BODE = Body mass, airflow Obstruction, Dyspnea, Exercise capacity index; ProANP= pro-natriuretic peptide; CI = confidence interval. Increment one quartile for BODE, BOD, and biomarkers, P-values compare variables with hazard ratio=1 or C-statistics=0.5 (null hypothesis). BOD comprises BODE without the exercise capacity measurement. These three components are scored according to the same cut-offs as

is the BODE index.[1] The “BOD index” therefore ranges, in increasing severity, ranging, in increasing severity, from 0 to 7.

Figure E1- A.

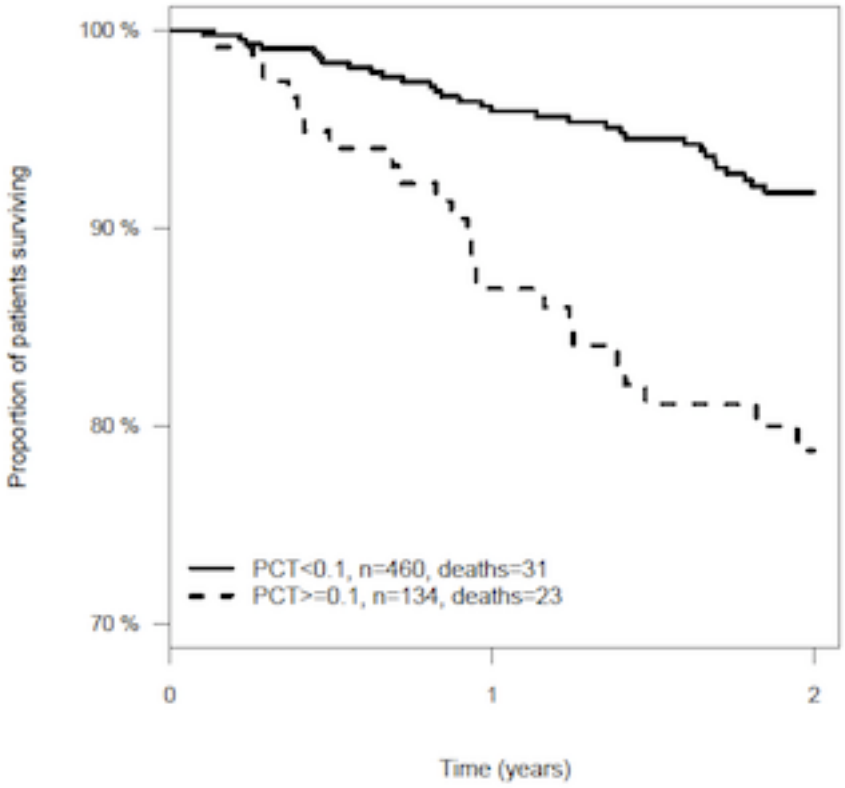


Figure E1- B.

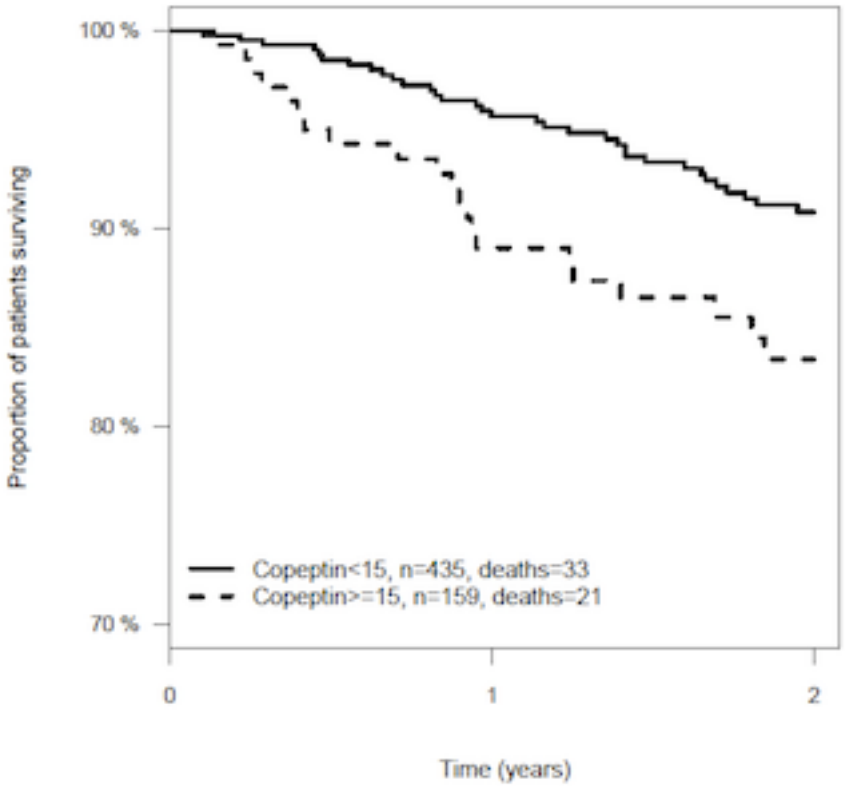
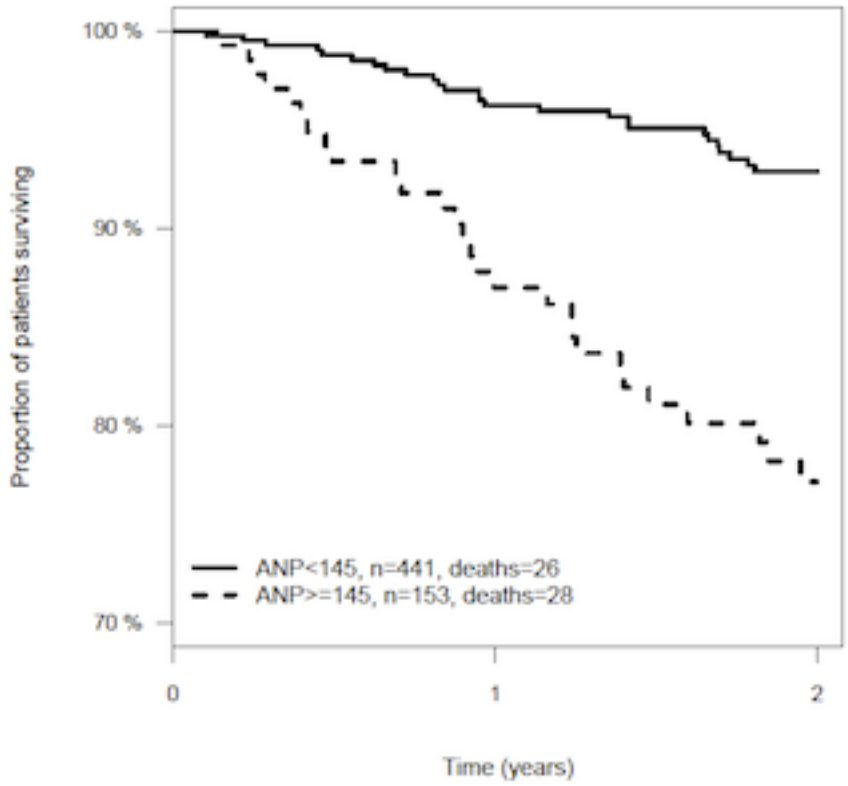


Figure E1- C.


100 %
90 %
80 %
70 %
Proportion of patients surviving
ANP<145, n=441, deaths=26
ANP>=145, n=153, deaths=28
0
1
2
Time (years)