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Title: Proadrenomedullin improves the prognostic property of the BODE index

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Body: BACKGROUND: The BODE index, a multidimensional grading system assessing the respiratory and systemic expressions of COPD, proved helpful in the prognostic assessment in COPD. We hypothesize that systemic biomarkers might additionally improve categorization and outcome prediction in COPD. METHODS: We prospectively evaluated 638 patients with stable COPD for $\geq$ 6 weeks, > 10 PY and GOLD II-IV seeking care in pulmonary tertiary hospitals in 8 European countries and included in the PROMISE cohort. The primary outcome of the study was death from any cause and from respiratory causes. Median observation time was 24 months. RESULTS: There were 63 deaths among the 638 patients (9.9%). 32 (51%) of the deaths were attributed mainly to COPD. Patients with higher proadrenomedullin values were at higher risk for death (p<0.0001). In the multivariate analysis, proadrenomedullin HR (95% CI) 1.83 (1.34-2.51, p=0.0002), BMI 0.48 (0.32-0.72, p=0.0004) and 6 MWD 0.6 (0.4-0.91, p=0.0152) but not MMRC 1.31 (0.94-1.84, p=0.113) and FEV1%pred 1.17 (0.68-2, p=0.5727) were significantly associated with 2 year survival. The C-index for the prediction of mortality in the Cox-regression analysis was 0.676 for the BODE index and 0.658 for proadrenomedullin (p<0.0001 both). The addition of proadrenomedullin to the BODE index improved its performance significantly (C-index 0.743, p=0.00020). In combination with

proadrenomedullin, the BMI (B), the degree of airflow obstruction (O) and dyspnea (D) domains by itself (e.g. without exercise capacity) performed similarly to the BODE index (C-index 0.772). CONCLUSION: Proadrenomedullin improves the performance of the BODE index at predicting the risk of death from any cause among patients with COPD.