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Usefulness of Midrange-Proadrenomedullin as a Predictor of Mortality in Patients With COPD

To the Editor:

In a recent article in *CHEST* (March 2014) by Zuur-Telgen et al[1] about the usefulness of midrange-proadrenomedullin (MR-proADM) in predicting mortality in patients with COPD, the authors confirm previous findings by Stolz et al[2] that higher MR-proADM levels during hospitalization for an acute exacerbation of COPD are associated with increased mortality. In addition, Zuur-Telgen et al[1] demonstrate the association between high levels of MR-proADM in the stable state and increased mortality, even after adjustment for comorbidities. These results provide hopeful evidence for the use of MR-proADM measurement in the prognosis of COPD. However, several steps must be taken before this biomarker can be accepted as a strong predictor of mortality in COPD.

The authors discuss an existing measure of prognosis used in COPD, an index of BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) and compare the C statistic for each test. However, they do not provide a test of the incremental usefulness of MR-proADM. Therefore, it is not clear whether the MR-proADM is measuring the same risk as the BODE index or if it is predicting risk that is not measured by the BODE index. The construction of a composite receiver operating characteristic curve that includes both the BODE index and MR-proADM level and calculation of that C statistic is an important step. This would provide insight into how much information the use of MR-proADM is adding to prognosis, in terms of the improvement in net benefit. This information could help guide the decision about whether to use MR-proADM as an adjunct or potential replacement to the BODE index.

Another important step in evaluating the usefulness of a new biomarker as a prediction tool is replication. The Prognosis Research Strategy (PROGRESS) group set forth recommendations for the conduct and reporting of prognostic factor research, a major component of which is replication.[3] Much like Zuur-Telgen et al[1] confirmed

the results of Stolz et al,[2] it is necessary to validate the results of the study in a different cohort of patients, in the initial study when possible. This is especially important because of the limitations inherent in the study, especially selection bias. As noted by the authors, patients included in the study were hospitalized for acute exacerbations of COPD, meaning they may have only included patients with a higher severity of disease necessitating hospitalization. This could have an effect on both the levels of MR-proADM and the mortality rate.

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References

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2. Stolz D, Christ-Crain M, Morgenthaler NG, et al. Plasma pro-adrenomedullin but not plasma pro-endothelin predicts survival in exacerbations of COPD. *Chest*. 2008;134(2):263-272.
3. Riley RD, Hayden JA, Steyerberg EW, et al; PROGRESS Group. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med*. 2013;10(2):e1001380.

Response

To the Editor:

We would like to respond to the letter in which Mr Khorfan remarks that several steps are required before proadrenomedullin (proADM) can be accepted as a strong predictor of mortality in COPD. Indeed, as he suggests, before the cutoff value of proADM that was observed in our study can be used in clinical practice it needs to be validated. We already started the validation

study in the Cohort of Mortality and Inflammation in COPD (COMIC). The determination of the cutoff has also been done in the COMIC study, but this was performed in only a subset of patients for whom a paired blood sample (in stable state and at hospitalization for an acute exacerbation of COPD) was available.[1] In this validation study we obtained 490 blood samples in stable state and 101 blood samples at hospitalization for an acute exacerbation of COPD from 545 patients that did not participate in the already published analysis. In addition, we are validating the cutoff values as suggested by Stolz et al.[2,3]

We agree with Mr Khorfan that it would be interesting to analyze the incremental value of proADM to current multidimensional indexes for prediction of mortality in COPD, such as the BMI, airflow obstruction, dyspnea, and exercise capacity (BODE) index as he suggests. We hypothesize that proADM has additional value because it could reflect the systemic component of COPD, which is currently not sufficiently done in indexes such as the BODE. Stolz et al[3] already showed that proADM plus BODE predicts mortality more accurately than BODE alone. We are currently completing the analyses on the incremental value of proADM to currently used indexes in a pooled assessment of two large European, prospective, observational cohort studies of patients with COPD in stable state. We believe that these additional steps will bring the use of proADM in the clinic even closer to implementation.

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References

1. Zuur-Telgen MC, Brusse-Keizer MGJ, VanderValk PDLPM, van der Palen J, Kerstjens HAM, Hendrix MGR. Stable-state midrange-proadrenomedullin level is a strong predictor of mortality in patients with COPD. *Chest*. 2014;145(3):534-541.
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3. Stolz D, Kostikas K, Blasi F, et al. Adrenomedullin refines mortality prediction by the BODE index in COPD: the "BODE-A" index. *Eur Respir J*. 2014;43(2):397-408.