

LETTER

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Matrix metalloproteinase-8: a useful biomarker to refine the diagnosis of community-acquired pneumonia upon intensive care unit admission?

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The optimal management of severe community-acquired pneumonia (CAP) requires a prompt and accurate diagnosis [1]. Since clinical, radiological, and biological findings are poorly sensitive or specific, microbiological documentation often slow and unavailing, biomarkers could help to safely withhold antibiotics when the risk of bacterial infection is minimal and steer the diagnostic process towards non-infectious causes of respiratory failure [2]. In our previous study deriving the *FAIM3:PLAC8* molecular biomarker, we noticed that *MMP8*, encoding matrix metalloproteinase-8 (MMP-8), was the most overexpressed gene in confirmed CAP relative to non-infectious differential diagnoses (no-CAP) [3]. We investigated in the same cohort if plasma levels of MMP-8 could be a valuable candidate biomarker for the diagnosis of CAP.

Similar to *MMP8* whole blood gene expression (Fig. 1a), plasma MMP-8 (measured by Luminex assay [BioRad, Hercules, CA, USA]) was increased in patients with a suspicion of CAP compared to healthy volunteers and further increased in patients with confirmed CAP (median 3.45 ng/mL; interquartile range [IQR], 0.93–

15.40 ng/mL, $n = 86$) compared to no-CAP (0.76 ng/mL; IQR, 0.35–2.64 ng/mL, $p < 0.001$, $n = 31$, Fig. 1b). *MMP8* expression correlated with plasma levels of MMP-8 ($\rho = 0.73$, $p < 0.001$, Fig. 1c). The receiver operating characteristic area under the curve (AUC) of plasma MMP-8 for the prediction of infection was 0.71 (95% CI 0.59–0.81) (Fig. 1d). A numerical threshold set at 0.25 ng/mL to minimize the risk of false-negative diagnosis allowed the identification of infection with a 97% sensitivity at the expense of a low specificity (19%). AUCs for plasma MMP-8, *MMP8* expression, and procalcitonin (widely used for the diagnosis of CAP [4]) were not statistically different (Fig. 1d). In the independent validation cohort comprising 57 CAP and 26 no-CAP patients, the AUC for MMP-8 was 0.83 (95% CI 0.73–0.91, Fig. 1e). A numerical threshold of 0.30 ng/mL favoring a >97% sensitivity yielded a specificity of 15%. The combination of MMP-8 (cutoff 0.25 ng/mL) with a reference model including variables routinely used for the diagnosis of infection (body temperature ≥ 37.5 °C and procalcitonin > 1.0 ng/mL [5]) significantly but modestly improved the prediction of infection (net reclassification improvement 0.36 [95% CI 0.03–0.70], $p = 0.033$).

In conclusion, MMP-8 slightly improved patient classification compared to a routine care reference strategy. However, its poor specificity precludes its use as a stand-alone diagnostic biomarker to safely withhold antibiotics in this critically ill population. Further studies are needed to establish the potential add-on value of plasma MMP-8 in diagnostic tests including multiple biomarkers.

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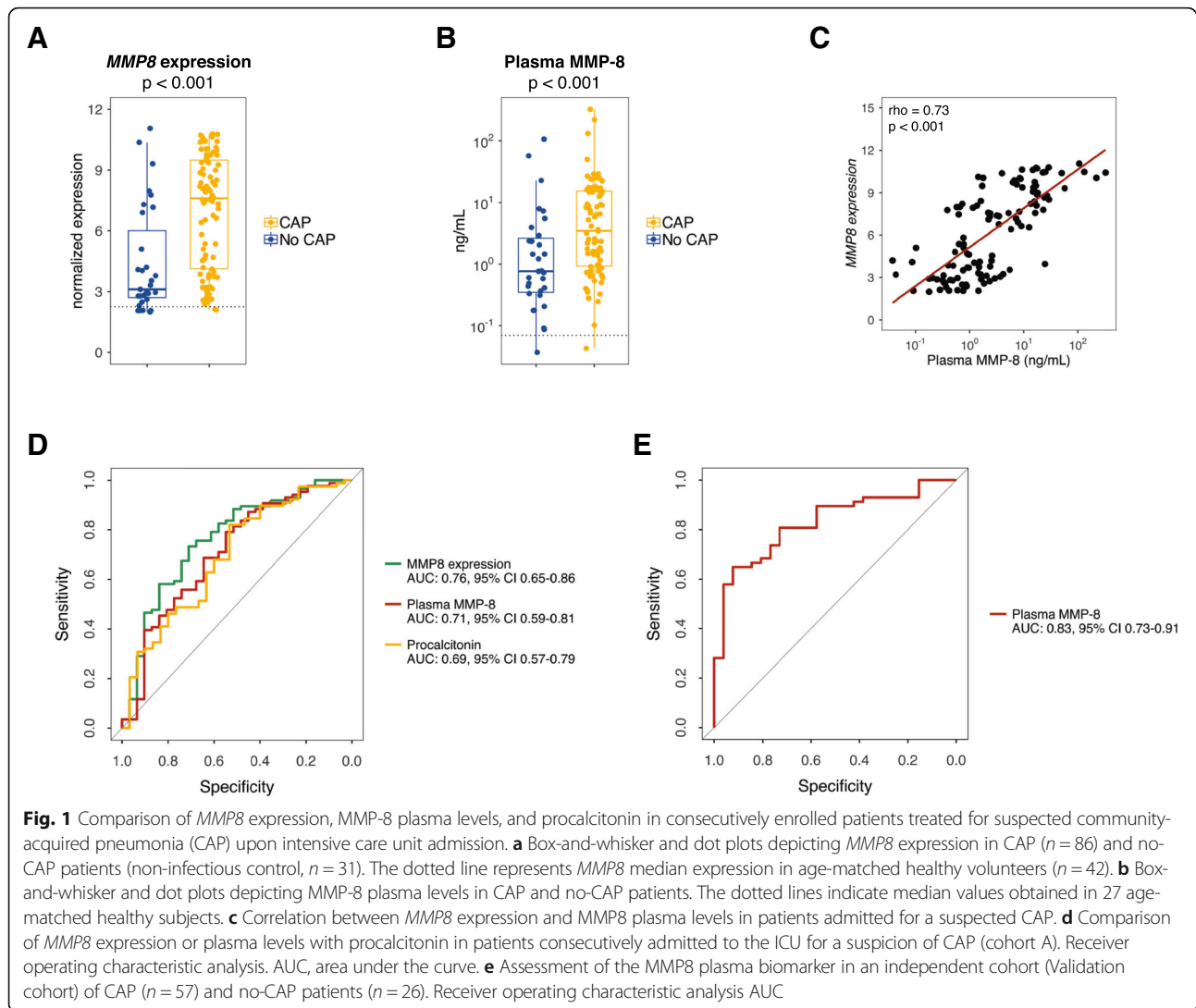
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Abbreviations

AUC: Area under the curve; CAP: Community-acquired pneumonia; IQR: Interquartile range; MMP-8: Matrix metalloproteinase-8; ROC: Receiver operating characteristic

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Authors' contributions

FU, BPS, and TvdP designed the paper and wrote the manuscript. All authors participated in collecting and analyzing the data. All authors read and approved the final version of the manuscript.

Authors' information

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Availability of data and materials

Gene expression datasets are available at the Gene Expression Omnibus public repository of NCBI under accession number GSE65682. Other data generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Patients were included via an opt-out consent method approved by the institutional review boards of both hospitals (Academic Medical Center, Amsterdam; University Medical Center Utrecht, Utrecht, IRB No. 10-056C).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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