Biomarkers in community-acquired pneumonia: still searching for the one

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Fibroblast growth factor 21 (FGF21) predicts severity of illness, clinical stability and mortality in community-acquired pneumonia. Validation is needed to confirm the application of FGF21 in clinical practice. http://ow.ly/SYI730nuRc1

Community-acquired pneumonia (CAP) remains a major cause of morbidity and mortality worldwide [1]. Despite advances in antibiotic treatment and medical care, the mortality of CAP is still high in hospitalised patients, especially in those with severe illness [2]. Appropriate initial severity assessment is a crucial step in pneumonia management, since it has been demonstrated that an early recognition of severe CAP patients improves their clinical outcomes [3]. Several tools have been developed to evaluate disease severity, in particular focusing on predicting hospital admission and mortality [4]. However, recent studies have showed that most of these scores are not used routinely in clinical practice and may be inadequate tools to guide appropriate antibiotic treatment [5, 6].

Biomarkers are biological markers that can be measured accurately and reproducibly from patients' samples. In pneumonia, several studies have evaluated the role of biomarkers in different important clinical areas, such as diagnosis of pneumonia, aetiology, risk stratification and triage decision, severity of illness and initiation/duration/discontinuation of antibiotic therapy [7]. Most of these studies focused on inflammatory markers that reflect the interaction between the micro-organism and the host, which is crucial in CAP prognosis and severity of disease [8]. The two most common inflammatory biomarkers are C-reactive protein (CRP) and procalcitonin (PCT). However, other biomarkers with less available evidence have been tested for a wide range of clinical outcomes, and include sTREM (soluble triggering receptor expressed on myeloid cells) [9, 10], pro-adrenomedullin [11, 12], pro-atrial natriuretic peptide [13, 14], pro-vasopressin [15, 16], surfactant protein-D, human cartilage glycoprotein YKL-40 and chemokine ligand 18 [17], endocan [18], barrier-stabilising angiopoietins 1 and 2 [19], or markers of neutrophil extracellular traps [20]. Figure 1 summarises the most common biomarkers evaluated and their potential role in assessing different clinical outcomes in patients with CAP.

In this issue of *European Respiratory Journal*, EBRAHIMI *et al.* [21] studied the prognostic value in CAP patients of fibroblast growth factor 21 (FGF21), a peptide hormone that has been shown to act as a metabolite regulator of glucose homeostasis, ketogenesis, insulin sensitivity and lipid metabolism [22]. Several organs synthesise FGF21, including the liver, brown adipose tissue, inguinal white adipose tissue, gonadal white adipose tissue, muscle, pancreas and heart. Therefore, it can act on multiple target tissues in either a paracrine or an endocrine fashion. It is postulated that FGF21 may play an important role in the
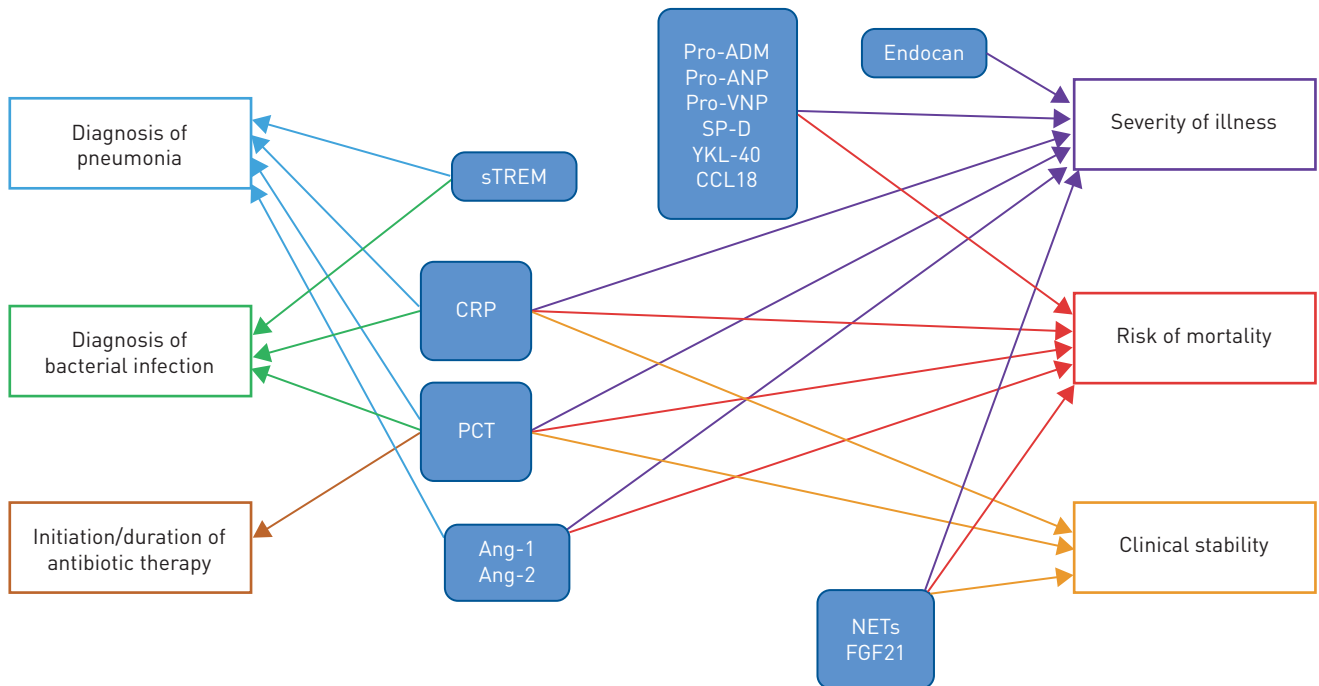
FIGURE 1 Inflammatory biomarkers and their relationship with community-acquired pneumonia outcomes most studied in the past 10 years. sTREM: soluble triggering receptor expressed on myeloid cells; CRP: C-reactive protein; PCT: procalcitonin; Ang: barrier-stabilising angiopoietin; pro-ADM: pro-adrenomedullin; pro-ANP: pro-atrial natriuretic peptide; pro-VNP: pro-vasopressin; SP-D: surfactant protein-D; YKL-40: human cartilage glycoprotein YKL-40; CCL18: chemokine ligand 18; NET: neutrophil extracellular trap.

immunoregulation of pro- and anti-inflammatory mediators in systemic inflammatory states such as pneumonia. Using samples and clinical data of two previous well-defined cohorts of hospitalised CAP patients, the authors found that FGF21 levels at admission were related to disease severity and identify patients at risk of 30-day all-cause mortality with superior discriminate power compared to than routine markers such as CRP, PCT or white cell count. The prognostic performance of FGF21 for the prediction of 30-day mortality was better than commonly used clinical scores such as CURB-65 and comparable to the Pneumonia Severity Index (PSI). In addition, adjunct treatment with corticosteroids, which potentially improved clinical outcomes in these patients [23], led to decreasing FGF21 levels, which is related to clinical stability. These findings are novel and suggest that the determination of FGF21 on admission and during hospitalisation might provide information regarding the severity of CAP, time to clinical stability and risk of short-term mortality.

However, it is important to remark that the use of FGF21 as a CAP biomarker in clinical practice is still undermined by many uncertainties and questions. First, it is unclear the equipment that would be needed and the cost related to measure FGF21. This may bring difficulties with implementation in a "real world scenario" compared to the easily accessible and cost-effective. Second, the identification of clinically relevant cut-off values is critical in the interpretation and adoption of this new biomarker. Third, as seen with corticosteroids, comorbid conditions or other concomitant treatments may potentially affect FGF21 levels. And finally, validation studies are needed in order to prove that FGF21 is here to compete against other biomarkers, before final adoption in clinical practice.

In summary, FGF21 is a novel biomarker tested to predict CAP severity. However, time and new evidence will tell whether FGF21 will become a biomarker that will assist clinicians in decision-making regarding care for patients with CAP, and to help improve patients' clinical outcomes. It is encouraging to see a growing trend in identifying new molecules and novel biomarkers for a neglected disease that affects millions of patients around the world [24].

Conflict of interest: None declared.

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