Biomarkers in the management of COPD

A. Lacoma*,#, C. Prat*,#, F. Andreo*# and J. Domínguez*#

ABSTRACT: Chronic obstructive pulmonary disease (COPD) is still a leading cause of morbidity and mortality worldwide, with a huge socioeconomic impact. New strategies for the management of COPD are required, not only for identifying the origin of the exacerbation episodes, but also to assess an individual risk for each patient. A promising approach is to measure systemic biomarkers and correlate their levels with exacerbation characteristics and clinical prognosis of the disease. Several biomarkers have clearly correlated with the aetiology of lower respiratory tract infections and the response to antibiotic treatment, indicating a potential utility in COPD exacerbation. Nevertheless, the results available at the moment, together with the absence of a gold standard for identifying the aetiological origin of an exacerbation, impedes establishing the real utility of these biomarkers for this concrete task. Regarding the clinical evolution and prognosis, several clinical characteristics have been correlated to biomarker levels. The potential influence of many factors (severity of the disease, presence of comorbidities and treatment) leads to the conclusion that, in the future, the best option would be to monitor levels individually, rather than establishing cut-off points for the general COPD population.

KEYWORDS: Biomarker, chronic obstructive pulmonary disease, exacerbation, inflammation

Chronic obstructive pulmonary disease (COPD) is the leading respiratory disease in terms of prevalence and socioeconomic impact worldwide [1]. The prevalence and burden will continue to increase in the coming years, owing to the continued exposure to risk factors, such as tobacco, and the ageing of the world’s population. The disease is characterised by the presence of an airflow limitation that is not fully reversible, and is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases [2]. Until recently, COPD was thought to cause only pulmonary abnormalities, but recent studies have demonstrated the presence of systemic and extrapulmonary effects [3].

Exacerbation episodes are an important problem for healthcare systems, because of the morbidity and mortality rates. The frequency and severity of these episodes have a significant impact on the patient’s quality of life and the course of the disease. In addition, the identification of the aetiological origin of the exacerbation based on the culture of respiratory samples remains controversial, due to the colonisation present in some patients. The traditional marker for COPD progression, in the absence of other validated markers, has been lung function measurement: specifically, forced expiratory volume in 1 s (FEV1). However, these measurements correlate poorly with the presence of some symptoms and do not take into account extrapulmonary effects [4].

For these reasons, new strategies for the management of COPD patients are required, not only for identifying the origin of the exacerbation episodes, but also to assess individual risk for each patient. Measurement of circulating biomarkers in peripheral blood of COPD patients has emerged as a new tool, having mainly two applications. One would consist of assessing its utility for exacerbation episodes and use a combination of biomarkers and clinical symptoms to identify the aetiological origin and degree of severity. The second would be to monitor and assess the clinical evolution of the disease, correlating biomarker levels with the response to therapy interventions (inhaled corticosteroids and oxygen-therapy) and also with the potential development of complications that might arise. Both approaches would enable a better risk stratification and correct management of COPD patients.

BIOMARKERS

A huge amount of biomarkers has been evaluated in COPD patients, but this review summarises the main findings from those used most frequently or those regarded as the most promising.
The measurement of cytokines in lower respiratory tract infections and inflammatory conditions is not sufficiently useful. This is mainly due to short plasma half-life, rapid turnover, presence of blocking factors, and compartmentalised production in the lung. In addition, when they are detected in serum, they undergo a fast downregulation. Therefore, acute phase proteins and the so-called hormokines seem to be more reliable, owing to their longer plasma half-life, fewer variations in daily levels and stability in vivo and ex vivo.

An acute phase reactant extensively evaluated in clinical situations is C-reactive protein (CRP). Its levels are increased in the presence of localised bacterial and viral infections, and also in chronic inflammatory conditions [5]. Another promising inflammatory mediator is neopterin. It is a 2-amino-4-hydroxypteridine synthesised by macrophages and monocytes after induction by interferon-γ secreted by T-lymphocytes [6]. It has been reported to act as a mediator of cell immunity against intracellular pathogens, such as viruses, parasites and intracellular bacteria [7]. The soluble form of the triggering receptor expressed on myeloid cells (sTREM)-1 is expressed on neutrophils, mature monocytes and macrophages, its levels being increased during sepsis, and not during noninfectious inflammatory conditions [8].

The following markers are also known as hormokines, unlike CRP, neopterin or sTREM-1. They can follow either a classical hormonal expression, or under specific inflammatory and infectious conditions show a cytokine-like behaviour [9, 10]. Procalcitonin (PCT) is a precursor peptide of the hormone calcitonin, and its levels have shown to help in differentiating patients with relevant bacterial infections from the ones with viral infections, the latter ones not requiring antibiotic treatment, or from inflammation not of infectious origin [11]. Adrenomedullin (ADM), whose precursor is pro-ADM, is a potent vasodilator, encoded in the CALC family gene and is mainly produced by the vascular endothelium [12]. Its properties are immunological, metabolic and bactericidal. Copetin is the stable C-terminal fragment of arginin vassopresin (AVP). AVP is a peptide hormone produced in the hypothalamus and its stimuli for release are hyperosmolality and hypovolaemia [13]. Finally, endothelin (ET)-1, whose precursor is pro-ET1, is a potent vasoconstrictor, mainly endothelium derived. Stimuli are multiple and include hypoxia and pulmonary infections [14].

From the family of natriuretic peptides, two biomarkers are also candidates: atrial natriuretic peptide (ANP), whose precursor is pro-ANP, and brain natriuretic peptide (BNP). ANP plays a key role in homeostasis regulation and it is released from the heart upon increased stretch of the myocardium, serving as a marker of congestive heart failure [15]. BNP is mainly synthesised in the left and right cardiac ventricles, and plays a role in the regulation of natriuresis, diuresis and vasodilation [15].

The aforementioned markers have been evaluated, particularly in community-acquired pneumonia (CAP), stating for some of them significant correlation with aetiology, severity and prognosis.

In a systematic review, CRP was found to be not sensitive enough for the detection of radiologically proved pneumonia, and its usefulness for guiding antibiotic prescription was not consistently supported [16]. Conversely, the measurement of neopterin levels in patients with CAP has improved the discrimination between bacterial and viral aetiology [17] and has also shown a correlation with the severity of the infection [18, 19]. In turn, PCT has been extensively evaluated in the clinical context of CAP, its levels correlating with severity scores such as the pneumonia severity index [18, 20]. Regarding aetiological origin, PCT has also been shown to be a specific and sensitive marker of bacterial pneumonia [18-20]. In addition, two interventional trials of PCT-guided therapy in lower respiratory tract infections [21] and CAP [22] have suggested that measuring PCT in some groups of patients might help to reduce antibiotic prescriptions without negative effects on patient recovery. ADM, copeptin, pro-ANP, BNP, ET-1 and sTREM-1 have also been evaluated in CAP, and have been found to be useful for risk stratification [23-29]. Cytokines have also been tested with the purpose of measuring the inflammatory response associated with pneumococcal pneumonia [30, 31]. Table 1 comprises a list of biomarkers and their potential use in the management of COPD.

**BIOMARKERS AND MANAGEMENT OF THE EXACERBATION**

**Inflammation: stable state versus exacerbation**

The COPD definition includes a reference to its inflammatory and systemic component. For this reason a wide range of inflammatory mediators, cytokines, acute phase reactants and biomarkers are found in COPD patients [32]. It is widely accepted that COPD is associated with an increased systemic inflammatory response in comparison with control individuals [33] and that this inflammatory response is amplified during exacerbation episodes, increasing the levels of cytokines and other inflammatory markers [34-37]. Takabatake et al. [38] reported higher levels of neopterin in stable COPD patients in comparison with a control group. Radsak et al. [39] found that serum levels of sTREM-1 were increased in COPD patients in a clinically stable state, reflecting an inflammatory process. In addition, levels seemed to correlate negatively with the degree of severity. However, the study only included a small number of patients. It has been observed that high levels of PCT, CRP and pro-ANP present during an exacerbation episode tend to decrease once the patient is back in a stable state. On the contrary, in our experience, levels of neopterin tend to be higher once the patient was in a stable state (unpublished data). Indeed, the “vicious circle hypothesis” explains how bacterial colonisation in the lower airways of COPD patients can perpetuate the inflammation and contribute to the disease progression [40].

**Aetiological diagnosis**

Exacerbations can be precipitated, among other causes, by bacterial and viral infections, and by common pollutants, such as tobacco and air pollution. But in up to 30% of cases, an aetiological diagnosis cannot be achieved [41]. In addition to this, 25–50% of COPD patients are colonised with potential respiratory pathogens, especially Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis [40–43]. In fact, in some COPD patients it is possible to isolate potential pathogenic bacteria in sputum, not only during an exacerbation but also during a stable state, so the presence of
pathogenic bacteria does not prove its direct implication in the episode.

This is one of the reasons why the identification of exacerbations of infectious origin is difficult and challenging. According to the culture result, it is not possible to differentiate between infection and colonisation. Therefore, taking into account that bacterial colonisation is present in the stable state, and that sputum microbiology is considered of limited value in exacerbation, there is a need for new tools for identifying episode origin.

Even though the presence of mucopurulent sputum expectoration is associated with isolation of pathogenic bacteria, it is difficult, or even impossible, to differentiate colonisation from infection. In addition, sputum samples can also be contaminated with oropharyngeal flora. Thus, a negative result or a normal flora result does not exclude the presence of a microorganism responsible for the exacerbation. The criteria published by Anthonisen et al. [44] and the presence of other clinical symptoms are likelihood criteria, and as such are subjective and prone to interobserver variation. In contrast, the measurement of biological markers offers objective data, although it has to be considered in combination with the clinical criteria.

Information from different surveys indicates that although antibiotic prescription is a common practice in COPD patients undergoing an exacerbation, there is no clear evidence of its efficacy in all cases [45]. An inappropriate and uncontrolled use of antibiotics increases health-related costs but also contributes to the spread of resistant microorganisms [46]. Therefore, identifying the origin of the exacerbation would have direct clinical and therapeutic consequences, and also a reduction of antibiotic prescriptions and a lesser selective pressure for resistant bacteria.

The direct consequence of identifying the aetiological origin of an exacerbation episode is that the treatment can be chosen in accordance to the triggering factor. So, the usefulness of biomarkers in this field is to help detect which are the exacerbations that require antibiotic treatment.

PCT, which has been extensively reported to be a specific marker of bacterial infection, has also been evaluated in COPD patients. However, in exacerbations with isolation of pathogenic bacteria in the sputum, its levels were not significantly increased [47, 48]. A probable explanation would be that in COPD patients the infection might be locally restricted and too nonspecific to result in a remarkable increase of PCT. Since there is an absence of a gold standard for identifying probable infectious exacerbations, it is possible that some positive culture might be colonisation and, in contrast, that some negative culture might be infectious exacerbations.

An interventionist study has found, in patients undergoing an acute exacerbation, that antibiotic guidance according to PCT levels significantly reduced the antibiotic prescription, with no consequences for the short- and long-term prognosis [47]. Although PCT levels are not significantly elevated during exacerbations with isolation of pathogenic bacteria, it might somehow have an influence, as it allows a substantial reduction in antibiotic prescription. In fact, for documented pneumonia clearly associated with bacterial aetiology, PCT levels were significantly increased [18]. Daubin et al. [49], in a set of COPD patients admitted to the intensive care unit, found that the likelihood of bacterial infection during acute exacerbations was low, as ~40% of the patients had values of PCT <0.1 μg·L⁻¹, suggesting probable inappropriate antibiotic use.

Hurst et al. [36] have proposed CRP to be a tool for identifying exacerbation episodes. Using a proteome array, they analysed the potential utility of 36 analytes in identifying and confirming the diagnosis of exacerbation, without considering the aetiological origin. They found that the most effective combination was CRP levels with the presence of a major symptom, such as dyspnoea, sputum volume or sputum purulence, even though it was not helpful for predicting severity. Weis et al. [50] reported, for 166 patients admitted owing to exacerbation of COPD, that there was large variation of CRP levels, including values in the normal range. Interestingly, patients that reported mucopurulent expectoration had higher levels of CRP than patients with mucoid expectoration. In addition, patients meeting one of the Anthonisen criteria had lower levels than patients with two or more. Stolz et al. [51] also found significant differences when comparing CRP levels according to the Anthonisen classification, with higher values during Anthonisen type I exacerbations. Bircan et al. [52] also evaluated CRP levels and

| TABLE 1 | Current biomarkers, biological interest and potential use in chronic obstructive pulmonary disease (COPD) |
| --- | --- |
| Biomarkers | Biological interest | Potential use in COPD |
| CRP | Marker of systemic inflammation | Identify aetiological origin of exacerbation |
| PCT | Marker of systemic bacterial infection | Identify bacterial exacerbations |
| Neopterin | Marker of infection by pathogens activating cellular immunity | Assess treatment effect |
| Copeptin | Marker of homeostasis deregulation | Identify aetiological origin of exacerbation |
| Pro-ANP | Marker of cardiovascular/renal dysfunction | Assess treatment effect |
| Pro-ADM | Marker of cardiovascular/renal dysfunction | Monitor short- and long-term prognosis |

CRP: C-reactive protein; PCT: procalcitonin; pro-ANP: pro-atrial natriuretic peptide; pro-ADM: pro-adrenomedullin.
found that they correlated with sputum purulence and increased serum white blood cell counts, possibly indicating an infectious origin. Phua et al. [53] found that patients undergoing a type I exacerbation had higher levels of sTREM-1. The authors hypothesised that the patient group with type I Anthonisen criteria might have had a higher airway bacterial load, which triggers systemic inflammation [34, 44], and so increased sTREM-1 levels.

In our experience, COPD exacerbation patients with normal flora or a negative sputum culture result have higher neopterin levels than patients with isolation of pathogenic bacteria [48]. Given that viruses such as rhinovirus, influenza and adenovirus play a role in stable COPD and during exacerbation episodes [54, 55], these higher levels could reflect episodes of viral aetiology [17].

Interestingly, neopterin and pro-ANP are influenced by the presence of arterial hypertension and renal disease, in that their levels are higher in patients with these underlying diseases [7, 15]. In contrast, pro-ANP is a marker of disease severity and its levels have shown no correlation with aetiology [27]; levels could merely reflect the homeostasis dysfunction. The association between aetiology and other biomarkers involved in cardiovascular and renal regulation has not been reported, but it seems that these mediators would not show a reliable association.

Up to now, markers such as CRP help in confirming the diagnosis of exacerbation. However, what remains unclear, due to the absence of a gold standard, is the real utility they can have for identifying the aetiological origin of the exacerbations, unless we extrapolate the good correlation of some biomarkers with bacterial infection.

Corticosteroid therapy

COPD patients are also treated with corticosteroids, not only during clinical stability, but also when undergoing an exacerbation episode. As has been reported, corticosteroid therapy decreases the levels of inflammatory markers, with the exception of PCT [56, 57]. The fact that PCT is not influenced by corticosteroid therapy means that it retains its usefulness as a marker of bacterial infection, and allows monitoring of the effectiveness of the antibiotic treatment.

BIOMARKERS AND PROGNOSIS

Influence and impact of comorbidities

Comorbidity is frequently related to COPD, affecting the disease progression and prognosis [58]. COPD patients are at increased risk of having other coexisting illnesses, mainly cardiovascular disease and lung cancer, even though other chronic conditions such as renal failure and hypertension may also contribute. Theoretically, circulating biomarkers might be affected by the presence of comorbidities. In particular, attention should be focused on renal and cardiovascular diseases, as some of the biomarkers presented are mediators of cardiovascular and renal dysfunction.

Interestingly, neopterin and pro-ANP are influenced by the presence of arterial hypertension and renal disease, in that their levels are higher in patients with these underlying diseases [7, 15]. In addition, pro-ANP levels are also higher in patients with congestive heart failure [27]. ANP, BNP, copeptin, pro-ADM and ET-1 are markers of renal and/or cardiovascular dysfunction, so levels are understandably increased in patients with these conditions [15]. To our knowledge, PCT levels are not related to chronic and neoplastic disorders, with the exception of the C-cell carcinoma of the thyroid and the small cell carcinoma of the lung [9].

Smoking habits also have to be considered, as smoking causes a low-grade inflammatory response in COPD patients and may influence the levels of some biomarkers [59].

Prognosis and clinical evolution

Several parameters and characteristics that can be obtained in clinical practice have been proposed to be prognostic markers of morbidity and mortality for exacerbations [60], but their predictive value varied across studies. One example is the BODE (body mass index, airway obstruction, dyspnoea and exercise tolerance) index, which has been recently been proposed to be a long-term prognosis marker for COPD patients [61]. Furthermore, the severity and rate of exacerbation have also been evaluated as prognostic factors for mortality [62].

The search for biological markers that may assess different aspects of COPD, such as the pathogenesis, severity, prognosis and response to therapy, has been investigated. Inflammatory cell and cytokine concentrations have been measured in urine, sputum, bronchoalveolar lavage, bronchial biopsy and exhaled breath condensate [63]. But specifically, the search for systemic biomarkers detectable in the peripheral blood has gained interest in the field of COPD in the past years.

Some authors have proposed that measuring some biomarkers during an exacerbation or during a clinically stable state can also be informative about the prognosis at short- and long-term [51, 64–66]. Results may vary, depending not only on the biomarker considered, but also on the characteristics of the COPD population evaluated.

Using a protein microarray platform, it has been possible to establish serum protein expression profiles in COPD patients [64]. A subset of 24 markers showed significant differences between COPD patients and controls and they had different pathobiological functions, being chemoattractants, inflammation mediators and markers of destruction and repair. These selected biomarkers correlated with FEV₁, diffusing capacity for carbon monoxide, 6-min walk test, BODE index and exacerbation frequency.

CRP is one of the most studied biomarkers, having been evaluated in different settings of COPD patients in order to establish a possible association with basal systemic inflammation in the stable period, cardiovascular risk events, disease prognosis and identification of infectious exacerbations [50–52, 64–66]. When considering the stable state, CRP levels tend to be independent of smoking, lung function and BODE index, while being strongly associated with arterial oxygen tension and 6-min walk distance [67, 68]. Regarding mortality as the primary outcome, for patients with mild to moderate disease, CRP may accurately detect patients with high risk of mortality [69]. However, when patients had moderate-to-severe COPD, CRP was not found to be associated with the survival status [70].

Hormokines have also been evaluated in COPD patients, showing promising results. Specifically, copeptin and pro-ADM levels measured during an acute exacerbation independently predicted survival, and so might be candidate prognostic
| First author [ref.] | Participants n | Plasma/serum biomarkers | Main findings |
|---------------------|----------------|------------------------|---------------|
| TAKABATAKE [38]    | 35 patients    | IFN-γ, sIL-2R          | Impaired systemic cell-mediated immunity is present in COPD patients and is associated with an increased susceptibility to acute respiratory tract infections. Neopterin levels are increased in stable COPD patients in comparison to the control subjects. |
| 22 controls         | Neopterin      |                         |               |
| sICAM-1             |                |                         |               |
| PHUA [53]           | 43 patients     | sTREM-1                 | Serum levels of the sTREM-1 are significantly higher in COPD patients than in the control group. Anthonisen type 1 exacerbations had higher levels than types 2 and 3 and might also have a higher airway bacterial load. |
| 62 controls         |                |                         |               |
| HURST [36]          | 90 patients    | Levels of CRP, IL-6 and sICAM-1 levels are increased during exacerbations in comparison to the stable state. CRP concentration and the presence of a major exacerbation symptom are useful in confirming COPD exacerbation. Systemic biomarkers were not useful for predicting severity. |
| 36 analytes         |                |                         |               |
| PINTO-PLATA [71]    | 88 patients    | CRP                     | CRP may be a systemic marker of the underlying inflammatory process seen in stable COPD. CRP levels are raised independently of tobacco consumption, and reduced in patients using inhaled corticosteroids. |
| MAN [69]           | 4803 patients  | CRP                     | For patients with mild-to-moderate COPD, CRP may accurately detect patients at high risk mortality. |
| WEIS [50]           | 166 patients   | CRP                     | CRP values are in the normal range in ~50% of patients admitted with COPD exacerbation. Patients with increased sputum purulence had higher CRP levels. CRP may be used as a marker of significant bacterial infection in exacerbation episodes. |
| DE TORRES [68]      | 130 patients   | CRP                     | CRP levels in stable COPD patients are strongly associated with arterial oxygen tension and 6-min walk distance. Levels correlated independently with FEV1, GOLD stage and BODE index. |
| MULLER [26]         | 60 patients    | Pro-ANP                 | Levels of pro-ANP were higher in the group of patients with exacerbation in comparison to the control group. There was no difference in pro-ANP levels according to the Anthonisen criteria and the severity of COPD. |
| 50 controls         |                |                         |               |
| HURST [34]          | 41 patients    | IL-6, CRP               | The systemic inflammatory response observed during an exacerbation is proportional to the inflammation present in the lower airways, and is greater in the presence of a bacterial pathogen in the sputum. |
| PINTO-PLATA [64]    | 48 patients    | 143 analytes            | Some of the biomarkers analysed are associated with clinical variables, such as degree of airflow limitation, lung transfer factor, BODE index and exacerbation frequency. |
| 48 controls         |                |                         |               |
| DAHL [67]           | 1302 patients  | CRP                     | CRP levels in the stable state are a strong long-term predictor of future outcomes in COPD patients, independent of smoking and lung function. |
| STOLZ [47]          | 208 patients   | PCT                     | PCT guidance for acute exacerbations offers an advantage over standard therapy in reducing antibiotic use without negative consequences for patient recovery. |
| STOLZ [51]          | 167 patients   | Copeptin, CRP, PCT      | Copeptin might be a better prognostic factor than CRP and PCT for short- and long-term prognosis in patients undergoing exacerbations requiring hospitalisation. |
| RADSAK [39]         | 12 patients    | sTREM-1                 | Serum concentrations of sTREM-1 are increased in patients with COPD, compared with levels in the control group. Levels of sTREM-1 during the stable state showed a significant negative correlation with lung function impairment. |
| 10 controls         |                |                         |               |
| MULLER [25]         | 60 patients    | Copeptin                | Levels of copeptin were higher in the group of patients with exacerbation in comparison to the control group. There was no difference in copeptin levels according to the Anthonisen criteria and the severity of COPD. |
| 50 controls         |                |                         |               |
| PERERA [37]         | 73 patients    | IL-6, CRP               | Non-recovery of symptoms at exacerbation is associated with persistently increased systemic inflammation. The time course of systemic inflammation following the exacerbation episode is different between frequent and infrequent exacerbators. |
markers for short- and long-term prognosis [51, 66]. However, these are single-centre studies, so further studies are required to confirm these data. Table 2 summarises the main findings reported for the aforementioned biomarkers in the management of COPD.

**CONCLUSION**

Establishing systemic biomarker cut-off values for the general COPD population is probably not the right approach. On one hand, there is too much heterogeneity among COPD patients, in terms of disease severity and progression, presence of comorbidities and clinical presentation. On the other hand, there is no general agreement on the real influence of covariates on biomarker levels. It seems that it would be more appropriate to individually monitor patients and assess the intra-individual biomarker variation/kinetics in the long term. To that effect, it would be possible to correlate the changes in biomarker levels with the appearance and severity of new exacerbation episodes and with complications that may arise from COPD, either from the underlying coexisting diseases or interventions (i.e. long-term treatment with corticosteroids or oxygenotherapy); in other words, to assess COPD prognosis by combining clinical data and serial biomarker measurement. However, in order to validate the clinical utility of biomarkers in COPD patients, further multi-institutional and longitudinal studies are required.

There is a wide range of biomarkers, several kinds of clinical samples and different methods of detection available, each with its range of sensitivity. In addition, the clinical moment when the sample is collected (stable disease or exacerbation episode), and the degree of severity of the disease has also to be considered. All these factors impede stating conclusive affirmations and generalising study findings.

The introduction of biomarkers for the clinical routine management of COPD relies principally on the resources available. In addition, biomarker concentrations should be measured within the first hours of admission, preferably before starting treatment. Serial measurements during the hospitalisation and follow-up determinations could also be recommended. Up to the present time, these factors limit the use of biomarkers to patients requiring hospitalisation, so patients treated in primary care and at home would be excluded. It seems that the combination of diverse biomarkers is clinically informative, and at the moment only available in hospital. Therefore, a substantial investment in the development of easy and reliable immunological assays is required. One answer to this problem would be the implementation of quantitative, quick, point of care tests for the different biomarkers [72] that would be apt for both family physicians and hospital specialists.

In summary, the absence of a gold standard for identifying exacerbations of infectious origin with certainty impedes, for the time being, the understanding of the real usefulness of inflammatory markers in distinguishing between infectious (bacterial) and noninfectious origin. In the forthcoming years, it would be interesting to have at one’s disposal a set of biological markers that, combined with clinical symptoms, would identify exacerbation origin according to its aetiology. This would mean that a more rational therapeutic approach, combining antibiotherapy and immunomodulatory treatment,

| First author [ref.] | Participants n | Plasma/serum biomarkers | Main findings |
|---------------------|----------------|------------------------|--------------|
| **PINTO-PLATA [35]** | 20 patients | IL-6, IL-8, LTB₄, TNF-α, SLPI | Patients admitted to the hospital because of an exacerbation experience significant changes in systemic cytokine levels that correlate with symptoms and lung function. During the episode there is a worsening of the airflow obstruction and an increased systemic demand. |
| **PHAT [27]** | 135 patients* | Pro-ANP | Levels of pro-ANP are increased in COPD patients with pneumonia, and its levels correlate with PSI. |
| **BIRCAN [52]** | 113 patients | CRP | A high level of serum CRP may indicate infectious exacerbation origin in COPD patients and correlates with sputum purulence and increased serum WBC counts. |
| **DE TORRES [70]** | 218 patients | CRP | For patients with moderate-to-severe COPD, CRP levels measured during clinical stability are not associated with survival and do not add information to the risk assessment provided by the BODE index. |
| **STOLZ [65]** | 208 patients | BNP | BNP levels predicted independently the need for intensive care, but failed to adequately predict short- and long-term prognosis in patients admitted with acute exacerbation. |
| **STOLZ [66]** | 167 patients | Pro-ADM, Pro-ET1 | Levels of pro-ADM, but not pro-ET1, on admission because of an acute exacerbation, independently predicted 2-yr survival, suggesting it could be useful for predicting prognosis. |

**TABLE 2** Continued.

| First author [ref.] | Participants n | Plasma/serum biomarkers | Main findings |
|---------------------|----------------|------------------------|--------------|
| **PINTO-PLATA [35]** | 20 patients | IL-6, IL-8, LTB₄, TNF-α, SLPI | Patients admitted to the hospital because of an exacerbation experience significant changes in systemic cytokine levels that correlate with symptoms and lung function. During the episode there is a worsening of the airflow obstruction and an increased systemic demand. |
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IFN: interferon; sIL-2R: soluble interleukin-2 receptor; sICAM: soluble intercellular adhesion molecule; sTREM: soluble triggering receptor expressed on myeloid cells; CRP: C-reactive protein; IL: interleukin; FEV1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; BODE: body mass index, airway obstruction, dyspnoea and exercise capacity; pro-ANP: pro-atrial natriuretic peptide; PCT: procalcitonin; LTB₄: leukotriene B₄; TNF: tumour necrosis factor; SLPI: secretory leukocyte protease inhibitor; PSI: pneumonia severity index; WBC: white blood cells; BNP: brain natriuretic peptide; pro-ADM: pro-adrenomedullin; pro-ET1: pro-endothelin-1. *: the total population included a subgroup of COPD patients.
could be performed. In addition, the correlation of certain biomarker levels/variation with prognostic markers of COPD progression might help us to identify patients with poorer prognosis and higher risk of treatment failure. Consequently, with the combination of clinical data and biomarker levels, medical and treatment decisions might be taken in accordance.

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