EXPERT REVIEWS

Prediction of prognosis by markers in community-acquired pneumonia

Expert Rev. Anti Infect. Ther. 11(9), 917–929 (2013)

Diego Viasus[1,2], Antonella Simonetti[1], Carolina Garcia-Vidal[1,2] and Jordi Carratalà*[1,2,3]

[1]*Department of Infectious Diseases, Hospital Universitari de Bellvitge – IDIBELL, Barcelona, Spain*
[2]*Spanish Network for Research on Infectious Diseases (REIPI), Instituto de Salud Carlos III, Madrid, Spain*
[3]*Department of Clinical Sciences, University of Barcelona, Barcelona, Spain*
**Author for correspondence:*
Tel.: +34 932 607 625
Fax: +34 932 607 637
jcarratala@ub.edu

Early identification of patients with community-acquired pneumonia (CAP) at risk of poor outcome is critical for defining site of care and may impact on hospital resource consumption and prognosis. The Pneumonia Severity Index and CURB-65 are clinical rules that accurately identify individuals at risk of death. However, these scores have some limitations. Therefore in recent years, increasing attention has been being paid to research on biomarkers, since they have the potential to resolve fundamental issues regarding prognostic prediction that cannot be readily addressed using CAP-specific scores. Nevertheless, the use of biomarkers in this context needs to be validated in prospective trials so as to elucidate how they can best be applied in practice. This review examines the usefulness of biomarkers, whether used alone or in conjunction with other clinical severity of illness scores, for identifying CAP patients at risk of short- and long-term mortality and for predicting both the need for intensive care unit admission and the potential for treatment failure.

KEYWORDS: biomarker • clinical stability • community-acquired pneumonia • intensive care unit • mortality • prognosis • treatment failure

Community-acquired pneumonia (CAP) is one of the most important public health problems worldwide [1]. In industrialized countries, CAP is the most frequent cause of mortality among infectious diseases, and it accounts for a substantial use of healthcare resources [2]. In Europe, studies have reported the incidence of CAP to be between 1.2 and 11.6 cases per 1000 population per year [3,4], a figure that increases at least 10-fold in certain risk groups such as the elderly or patients with chronic obstructive pulmonary disease.

Stratifying the severity and prognosis of CAP is very important. Existing severity assessment scores have been used to assess the need for hospitalization and to identify patients requiring intensive care unit (ICU) admission [5,6]. The Pneumonia Severity Index (PSI) [7] and CURB-65 (confusion, urea >7 mmol/l, respiratory rate 30/min, low systolic (<90 mm Hg) or diastolic (≤60 mm Hg) blood pressure and age 65 years) [8] are clinical rules that identify individuals at low risk of death who are candidates for outpatient care [7–9]. However, patients defined as low-risk by these scores may occasionally require hospital admission. Conversely, although patients classified as high-risk of death usually require prompt admission to hospital and treatment with parenteral antibiotics, a large proportion of them have good evolution [10]. Notably, investigators have documented that these scores perform less well when it comes to predicting the need for ICU admission [11]. They are also limited by the fact that i) physicians may misapply or fail to remember them, ii) a given risk group can present a significant range of outcomes and iii) under certain circumstances the risk of death or need for ICU admission may be overestimated or underestimated. Consequently, these severity assessment tools should be used with caution and in conjunction with clinical judgment.

Biological markers (biomarkers) have been defined as cellular, biochemical or molecular characteristics that are objectively measurable in biological media such as human tissues, cells or fluids and which may be used as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a

 10.1586/14787210.2013.825442 ISSN 1478-7210

therapeutic intervention [12,13]. In the context of CAP, biomarkers could be useful in numerous areas: establishing diagnosis, identifying etiology, assessing severity and prognosis and for therapeutic interventions. Given the limitations of existing CAP severity scores there has been considerable interest in the development of rapidly available biomarkers that might confer additional and reliable prognostic information.

In this review, the authors focus on the recent literature concerning the usefulness of biomarkers, whether used alone or in conjunction with other clinical severity of illness scores, for identifying CAP patients at risk of short- and long-term mortality and for predicting both the need for ICU admission and the potential for treatment failure. For this purpose, a comprehensive literature search has been conducted in PubMed/MEDLINE database, using the following search terms: community-acquired pneumonia, biomarker, marker, prognosis, treatment failure, intensive care unit and mortality. Studies evaluating composite end points were excluded.

Biomarkers for predicting short- & long-term mortality

Although mortality in patients with CAP fell dramatically with the introduction of antibiotics in the 1950s, it has changed very little over the past 50 years. Recent studies have reported overall mortality rates of 8–15% [14,15], although in those patients who require ICU admission, mortality can be as high as 30%, despite prompt and appropriate antibiotic therapy [16]. Importantly, it has been shown that CAP may have significant longer-term effects and that hospitalization for this infection is associated with higher long-term mortality compared with other major medical conditions. This increased mortality appears to be due to several factors, including acute cardiovascular events and alterations in immune function [17,18].

Current guidelines [5,6,19] recommend the use of severity scores to classify CAP patients according to the risk of mortality. The main tools used for this purpose are the PSI and CURB-65. A recent meta-analysis reported that these scores had similar overall test performance for predicting mortality in patients with CAP [20].

Numerous studies have been conducted to determine the relationship between certain biomarkers and both severity and mortality in CAP. Biomarkers of all types have been used by investigators to study the prognostic in CAP, and evaluate several biological pathways that are altered in these patients, such as the cardiovascular, coagulation, endocrine or immune systems. The most common biomarkers investigated to predict mortality are procalcitonin, C-reactive protein (CRP), pro-adrenomedullin, inflammatory cytokines and D-dimer.

Most of the studies evaluating the utility of biomarkers have focused on CAP patients requiring hospitalization, followed by those seen in the emergency department and, finally, those admitted to an ICU. Sample size has varied from 30 [21] to 3463 patients [22]. The majority of studies provide information on short-term mortality (28- and 30-day mortality) as their primary end point, while others use long-term mortality (from 60-day to 18-month mortality) or ICU mortality. Most studies have conducted multivariate analyses to determine the association between biomarkers and mortality, with the area under the receiver operating characteristic (AUROC) curve being used to assess predictive power. Importantly, the majority of studies have compared the AUROC curves of biomarkers and CAP-specific severity scoring systems, mainly PSI and CURB-65. The utility of adding biomarkers to CAP-specific severity scores has also been evaluated. The best operating point of the biomarker for predicting mortality is reported by the majority of manuscripts.

As shown in Table 1, most of the biomarkers evaluated to date have been found to be independent predictors of short- and long-term mortality in patients with CAP. However, serum angiotensin-converting enzyme (ACE) activity, which is significantly decreased during the acute phase of CAP, was not associated with mortality in hospitalized patients, even despite correction for ACE insertion/deletion polymorphism [23,24]. It is important to note that most AUROC curve values generated by biomarkers were not significantly higher than those obtained from CAP-specific severity scores. Thus, the ability of biomarkers alone to predict mortality was no better than that of existing clinical scores for CAP, although adding biomarkers to scores such as the PSI, CURB-65, APACHE II and SOFA did improve their predictive capability, as evidenced by a significant increase in the AUROC curve. However, studies are not consistent in relation to these findings. N-terminal pro-brain natriuretic peptide, D-dimer and mid-regional pro-adrenomedullin improved the AUROC curve for scores in some studies but not in others [25–27]. Similarly, visfatin [28] did not improve the mortality prediction of scores in hospitalized patients with CAP, and pro-adrenomedullin [29] did not increase the mortality prediction of scores in ICU patients with CAP. Importantly, reclassification analysis was performed in only four of the studies reviewed. One of these reported no benefit from the combination of CURB-65 score and D-dimer in reclassification of risk for clinical success at day 30, 30-day mortality or need for mechanical ventilation [26], whereas the other two found that a combination of the PSI and pro-adrenomedullin did enable better risk assessment for mortality than PSI alone [30,31]. Finally, a reclassification analysis comparing the PSI class model with a combined model with PSI class and initial endothelin-1 levels found a significant improvement in classification of risk of mortality [32].

Interestingly, some studies report kinetic information regarding biomarkers. One study evaluated the usefulness of re-evaluating CRP for predicting mortality in hospitalized patients with CAP [33]. CRP <100 mg/l was found to be independently associated with a lower risk of mortality. In addition, a CRP level that fails to fall by 50% was independently associated with mortality. Furthermore, a study found that the changes of endothelin-1 levels on day 3 significantly improved classification of patients compared with initial PSI and endothelin-1 levels [32].

Other studies have evaluated the predictive value of combining biomarkers from distinct biological pathways. One multicenter study assessed the prognostic accuracy of five prohormones (adrenomedullin, endothelin-1, atrial-natriuretic

Table 1. Biomarkers for predicting mortality in patients with community-acquired pneumonia.

Study	N	Serum level	Patients	End point	Comment	Ref.
Visfatin	176	48.6 ng/ml	Hospitalized	30-day mortality	Independent predictor of 30-day mortality. AUROC for visfatin was similar to that of PSI and APACHE II. Visfatin did not increase the predictive value of scores	[28]
Kallistatin	54	>8.3 μg/l	ICU	60-day mortality	Associated with a decreased risk of mortality ($p = 0.05$)	[35]
Albumin	3463	-5 g/l decrease	Hospitalized	30-day mortality	Independently associated with higher risk of mortality. Hypoalbuminemia (<30 g/l) significantly increased the AUROC of PSI and CURB-65	[22]
Thrombocytopenia	822	$\leq 50 \times 10^9$/l	ICU	ICU mortality	Independent predictor of mortality	[36]
RDW	744	>15.2	Hospitalized	30-day mortality	Independently associated with mortality. Improved mortality prediction when RDW was added to PSI or CURB-65	[75]
Pro-adrenomedullin	109	>1.8 nmol/l	ED	30-day mortality	Significantly predictive of risk of death. Reclassification analysis of combination of PSI and proADM allows better risk assessment	[30]
Cortisol	984	IQR increase	Hospitalized	30-day survival	Independently associated with 30-day mortality. Combined use of cortisol and CRB-65 significantly improved prediction of mortality	[76]
Pro-adrenomedullin	49	>4.86 nmol/l	ICU	Hospital mortality	ProADM levels were not an independent predictor of hospital mortality. AUROC for proADM was similar to that of PSI. Adding proADM to PSI slightly increased AUROC	[29]
Soluble RAGE	30	NR	Hospitalized	28-day mortality	sRAGE was independently associated with mortality ($p = 0.05$)	[21]
Procalcitonin	102	NR	Hospitalized	30-day mortality	AUC value of PCT for predicting mortality was 0.92, which was lower than that for A-DROP (0.97)	[77]
Procalcitonin	126	0.35 ng/ml	ED	28-day mortality	PCT had similar AUROC to that of PSI, CURB-65 and IDSA/ATS guidelines for severe CAP. Addition of PCT improves prediction rules	[78]
Hemostasis markers	893	NR	Hospitalized	1-year mortality	D-dimer and thrombin–antithrombin complexes were independently associated with 1-year mortality	[41]
RDW	637	>14.5	Hospitalized	90-day mortality	Elevated RDW was associated with increased 90-day mortality	[42]
ACE activity	265	<24 U/l	Hospitalized	Hospital mortality	Low serum ACE activity was not prognostic for mortality	[24]
Coagulation parameters	90		ICU	Hospital mortality	D-dimer was independently associated with mortality. AUROC of D-dimer was similar to that of the APACHE II and SOFA. Adding D-dimer to APACHE II or SOFA improved AUROC significantly	[37]
Albumin and CRP	424	Albumin 3.3 mg/dl and CRP 14.3 mg/dl	Hospitalized	28-day mortality	Independently associated with mortality. AUROC showed improved mortality prediction when adding albumin or CRP	[79]
Inflammatory markers	877	>1.97 nmol/l (ProAMD)	Post-discharge	18-month mortality	ProADM was independently associated with mortality	[43]

ACE: Angiotensin-converting enzyme; AUROC: Area under receiver operating characteristic curve; CRP: C-reactive protein; ED: Emergency department; ICU: Intensive care unit; IQR: Interquartile range; NR: Not reported; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCT: Procalcitonin; PSI: Pneumonia Severity Index; RDW: Red blood distribution width.

Table 1. Biomarkers for predicting mortality in patients with community-acquired pneumonia (cont.).

Study	N	Serum level	Patients	End point	Comment	Ref.
Mid-regional pro-atrial natriuretic peptide and C-terminal pro-atrial vasopressin	1740	MR-proANP >102 pmol/l and CT-proAVP >22.3 pmol/l	Hospitalized	28- and 180-day mortality	MR-proANP and CT-proAVP were independent predictors of short- and long-term mortality. AUROC for MR-proANP and CT-proAVP were superior to AUROC of CURB-65. PSI was not evaluated	[44]
N-terminal pro-brain natriuretic peptide	502	NR	Hospitalized	30-day mortality	NT-proBNP was an independent predictor of mortality. AUROC similar to that of PSI and CURB-65. Adding NT-proBNP to PSI and CURB-65 scores did not increase significantly the AUROC	[25]
Platelets	500	<100,000/l or >400,000/l	Hospitalized	30-day mortality	Thrombocytopenia and thrombocytosis were independently associated with mortality	[80]
B-type natriuretic peptide	58	282 pg/ml	ED	30-day mortality	BNP was independent predictor of death. AUROC of BNP was greater than that of the PSI (p-value not reported)	[81]
Procalcitonin	100	Increased PCT from day 1 to day 3	ICU	ICU mortality	PCT increase was associated with death	[38]
Pro-adrenomedullin	302	1.8 mmol/l	ED	Mortality during follow up (mean 6.9 weeks)	AROUC for pro-AMD was 0.76, which was significantly better compared with procalcitonin but similar to the AUROC of the PSI	[56]
Copeptin	373	53 pmol/l	ED	Mortality during follow-up (mean 6 weeks)	Copeptin was independently associated with survival. AUROC for copeptin was in the same range as that of the PSI	[82]
ACE activity and ACE I/D polymorphism	134	NR	Hospitalized	28-day mortality	ACE activity and ACE I/D polymorphism were not associated with mortality	[23]
Procalcitonin	1671	IQR increase	ED	28-day mortality	The AUROC of PCT was 0.80, which was not significantly different compared with CRB-65. PCT was independently associated with mortality. PCT identified low-risk patients across CRB-65 classes 0 – 4	[83]
Mid-regional pro-atrial natriuretic peptide and C-terminal pro-atrial vasopressin	173	CT-proAVP >18.9 pmol/l and MR-proANP >227 pmol/l	ED	Death during follow-up (4 weeks)	CT-proAVP was an independent predictor of death. MR-proANP was not independently associated with mortality	[84]
Mid-regional pro-atrial natriuretic peptide and C-terminal pro-atrial vasopressin	589	CT-proAVP >28.8 pmol/l and MR-proANP >116 pmol/l	ED	28-day mortality	CT-proAVP and MR-proANP were the strongest predictors of mortality. AUROC for CT-proAVP and MR-proANP were similar to that of CURB-65	[85]
CRP	53	Daily CRP measurement	ICU	ICU mortality	On day 3 of antibiotic therapy, a decrease in CRP was a marker of good prognosis	[39]
CRP	391	NR	Hospitalized	30-day mortality	Older patients (>65 years old). CRP was not associated with mortality	[48]
	1653	Quartiles	ED	30-day mortality		[27]

ACE: Angiotensin-converting enzyme; AUROC: Area under receiver operating characteristic curve; CRP: C-reactive protein; ED: Emergency department; ICU: Intensive care unit; IQR: Interquartile range; NR: Not reported; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCT: Procalcitonin; PSI: Pneumonia Severity Index; RDW: Red blood distribution width.

Table 1. Biomarkers for predicting mortality in patients with community-acquired pneumonia (cont.).

Study	N	Serum level	Patients	End point	Comment	Ref.
Mid-regional pro-adrenomedullin					MR-proADM had a greater AUROC for mortality (0.76) but did not improve performance of PSI or CURB-65	
D-dimer	314	>500 ng/ml	ED	30-day mortality	D-dimer had an AUROC of 0.7, similar to that of CURB-65 and PSI	[57]
Inflammatory markers (IL-6, IL-8, PCT and CRP)	453	NR	Hospitalized	30-day mortality	CRP and IL-6 were independently associated with mortality. CRP improves ability of PSI and CURB-65 to predict mortality. The addition of several biomarkers to scores significantly increased AUROC	[34]
CRP	570	CRP at day 1 and day 4	Hospitalized	30-day mortality	CRP <100 mg/l was independently associated with a lower risk of mortality. A CRP level that fails to fall by 50% was independently associated with mortality. The AUROC for CRP was smaller than that of PSI and CURB-65	[33]
B-type natriuretic peptide	302	Increase 100 pg/ml	ED	Mortality during follow-up (mean 6.9 weeks)	BNP increase was independently associated with mortality. AUROC for BNP was comparable with AUROC of PSI. Adding BNP to PSI significantly improved the prognostic accuracy of the PSI alone	[69]
Pro-adrenomedullin	72	0.64 nmol/l	ED	30- and 180-day mortality	MR-proADM has high short- and long-term prognostic accuracy, and increases the accuracy of clinical scores	[46]
Cortisol	72	25.7 µg/l	ICU	Hospital mortality	Greater AUROC curve, but non-statistically significant differences for the comparison of baseline cortisol with APACHE II, CURB-65 and D-dimer	[40]
Prohormones	925	NR	ED	30-day mortality	AUROC for biomarkers ranged between 0.60 for PCT and 0.79 for proANP. The addition of proADM to scores significantly increased AUROC. Reclassification methods showed benefit from adding biomarkers	[31]
D-dimer	147	NR	Hospitalized	30-day mortality	AUROC for D-dimer was smaller than for CURB-65 and adding D-dimer to CURB-65 did not improve the accuracy. Reclassification methods did not show benefit	[36]
25-Hydroxyvitamin D	272	50 nmol/l	Hospitalized	30-day mortality	Vitamin D status was an independent predictor of 30-day mortality and added prognostic value to prognostic scores	[86]
Endothelin-1	925	NR	ED	30-day mortality	Initial proET1 levels improved the PSI in reclassification statistics. Changes of proET1 on day 3 improved the C-statistic of the combined model of PSI and initial proET1 and reclassification tables demonstrated a significant improvement	[32]
Natriuretic peptides	341	NT-proBNP increase of 300 pg/ml	ED	30-day mortality and long-term mortality	AUROC for natriuretic peptides were comparable with PSI for short- and long-term mortality. NT-proBNP was an independent mortality predictor	[45]

ACE: Angiotensin-converting enzyme; AUROC: Area under receiver operating characteristic curve; CRP: C-reactive protein; ED: Emergency department; ICU: Intensive care unit; IQR: Interquartile range; NR: Not reported; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PCT: Procalcitonin; PSI: Pneumonia Severity Index; RDW: Red blood distribution width.

peptide, antidiuretic hormone and procalcitonin) [31]. Adding all these biomarkers instead of just one (pro-adrenomedullin) led to a significant improvement in the model for CURB-65 but not for the PSI. In another study [34], CRP and IL-6 were independently associated with mortality. Furthermore, the AUROCs of the different logistic regression models with combinations of markers and cytokines added to any or both PSI and CURB-65 prognostic scales were calculated. The addition of several biomarkers has been found to increase the AUROC curves of CAP-specific scores.

Some studies have assessed the utility of biomarkers for predicting mortality in CAP patients admitted to the ICU [29,35-40]. Each of these studies evaluated a different biomarker (kallistatin, thrombocytopenia, pro-adrenomedullin, D-dimer, procalcitonin, CRP and cortisol). All these biomarkers were independently associated with an increased risk of mortality, except for pro-adrenomedullin and cortisol. Two of these studies evaluated kinetic data from procalcitonin and CRP in this context, reporting that an increased concentration during the first few days after ICU admission was associated with a higher risk of mortality [38,39].

Hospitalization for CAP has also been found to be related to higher long-term mortality than is the case for many other main medical disorders [17,18]. Several studies have evaluated the usefulness of biomarkers for predicting long-term mortality [35,41–46]. Although this is not the optimal guide for early management during hospital admission, it is useful for identifying patients who need closer monitoring after hospital discharge, and it could therefore have a favorable impact on long-term mortality. Pro-adrenomedullin, D-dimer, thrombin–antithrombin complexes, kallistatin, red blood cell distribution width, mid-regional pro-atrial natriuretic peptide, C-terminal pro-atrial vasopressin and B-type natriuretic peptide have been found to be significantly associated with long-term mortality.

Despite the interest of all these findings, it is important to note several limitations of the studies from which they are derived:

- The number of patients is limited in some studies, and further research with larger samples is therefore necessary to confirm the results. CAP prediction rules, such as the PSI and CURB-65, were, of course, developed and validated in larger cohorts. There is also a need for interventional trials that assess the usefulness of biomarkers for identifying those patients who require more intensive monitoring.
- Timing of biomarkers was not standardized in the majority of studies. One study found that different timing of measurements of leukocyte count and serum creatinine level in patients with *Clostridium difficile* infection led to a different severity classification in many cases [47]. A further point is that most studies did not examine biomarker kinetics.
- The majority of studies did not control for factors that could influence biomarker levels, such as age, corticosteroids, prior antibiotic therapy, etiology of CAP or acute renal failure. Interpretation is difficult because the observed concentrations of some biomarkers might, in part, be a result of these factors. In this regard, one study reported that in elderly (>65 years old) hospitalized patients with CAP the measurement of CRP levels at admission was not associated with prediction of prognosis [48]. In addition, although cytokine activation patterns and certain biomarker are influenced by microorganisms in CAP, the prognostic value of mid-regional pro-adrenomedullin is not modified by different possible CAP etiologies [46].
- An analysis of causes of death was not performed. The main causes of mortality in patients hospitalized with CAP are respiratory failure, septic shock, multiorgan failure, acute cardiovascular events or decompensation of underlying diseases. However, causes of death differ between short- and long-term mortality [17,18]. Importantly, the biomarkers evaluated correspond to several biological pathways and, therefore, it is likely that their predictive value will differ depending on the cause of death. In addition, some patients with CAP usually receive 'do not resuscitate' orders and present therapeutic limitations. Evidently, these patients have to be excluded from any analysis designed to identify the utility of prognostic biomarkers.
- When a novel biomarker becomes available to help in risk prediction, it is essential to measure the improvement over existing practice tools. Current evidence based on AUROC curves suggests that biomarkers alone have no clear advantage over validated clinical prediction rules for measuring severity of CAP or predicting mortality. Importantly, most studies did not perform reclassification analyses. Several novel methods have recently been proposed that can be seen as refinements of discrimination measures, including variants of the C-statistic for survival, reclassification tables, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [49].
- Adding biomarkers to scores, mainly the PSI and CURB-65, improved the predictive capability of scores, as evidenced by a significant increase in the AUROC curves. However, the usefulness of other available scores has not been extensively reviewed.
- Finally, as most studies did not include outpatients with CAP the results cannot be extrapolated to this population.

Biomarkers for predicting ICU admission

ICU admission criteria and the characteristics of patients vary considerably between different centers and different healthcare systems [11]. Approximately 10% of hospitalized patients with CAP require ICU admission [50].

The decision to admit a patient to the ICU remains one of the most significant steps in the management of CAP. Patients who require mechanical ventilation and/or vasopressors are easily identified as patients requiring ICU admission. Notably, studies have documented that an important number of patients with severe disease but without the abovementioned

characteristics are first transferred to general wards [51,52]. Recently, it was reported that in patients with severe CAP, delayed admission to the ICU is a risk factor associated with higher mortality [52]. Consequently, several scores have been developed to identify patients with severe CAP who require prompt admission to the ICU [53,54], the goal being to allow earlier intensive management of their condition. One of the problems is that when ICU admission is taken into account, scoring systems originally designed to predict 30-day mortality (PSI and CURB-65) perform less well, achieving poor to moderate predictive accuracy [11]. A recent meta-analysis [11] found that the 2007 ATS/IDSA and 2001 ATS criteria were more sensitive predictors of the need for ICU admission than were PSI and CURB-65 scores. Interestingly, the investigators documented that 30–70% of patients requiring ICU admission are not adequately classified. Other scores designed to identify patients requiring ICU admission, such as SMART-COP and Risk of Early Admission to ICU (REA-ICU), need further and more extensive validation.

A few studies have evaluated the usefulness of biomarkers for predicting the need for ICU admission among patients with CAP. The characteristics of the reviewed studies are detailed in Table 2. Ramírez *et al.* [55] documented that inflammatory biomarkers identified patients requiring ICU admission. However, ATS/IDSA criteria for severe disease predicted ICU admission more accurately than did biomarkers. Interestingly, CRP and procalcitonin were higher in patients initially located on a ward and subsequently transferred to an ICU. Other studies have linked pro-adrenomedullin and albumin levels to ICU admission [25,56]. Chalmers *et al.* [57,58] evaluated the utility of D-dimer and CRP for predicting the need for mechanical ventilation or vasopressor support. D-dimer had an AUROC curve of 0.66, which was lower than that of CURB-65 but similar to the value for PSI. CRP <100 mg/l was independently associated with a lower risk of the need for mechanical ventilation or vasopressor support. It has recently been reported that serum ACE activity has no prognostic value for predicting ICU admission [24]. Finally, albumin had an additive role with PSI, but CRP did not, for predicting ICU admission, mechanical ventilation or vasopressor support [59].

Although studies have evidenced that some biomarkers might be useful for predicting ICU admission in patients with CAP, biomarkers are no better than CAP-specific scores, as evidenced by AUROC curves. Importantly, research has documented that both the PSI and CURB-65 have limited accuracy as predictors of ICU admission [11]. Other ICU admission tools, such as the minor criteria of ATS/IDSA guidelines or SMART-COP, are probably more helpful in patients who do not immediately require mechanical ventilation or vasopressors [53,60]. It should be noted, however, that studies which evaluated the utility of biomarkers for predicting ICU admission in CAP did not compare the performance characteristics of biomarkers with these ICU admission scores. Finally, the majority of reviewed studies investigated the performance of scores for 30-day mortality and reported ICU admission as a secondary outcome. Thus, further studies evaluating the relationship between biomarkers and the need for ICU admission in CAP are required. Interestingly, Renaud *et al.* [61] evaluated whether pro-adrenomedullin improved the performance of the REA-ICU score in predicting the composite outcome of requirement for mechanical ventilation or vasopressive drugs or occurrence of death within 3 days of emergency department presentation. Combining pro-adrenomedullin with the REA-ICU score improved the AUROC compared with either parameter and resulted in a significant NRI.

Biomarkers for predicting treatment failure or clinical stability

Recognition of treatment failure and clinical stability are important components in the management of CAP.

Clinical stability is usually defined according to the criteria proposed by Halm *et al.* [62]. Once stability is achieved, clinical deterioration occurs in 1% of cases or fewer. Clinical stability is useful for deciding when to switch from intravenous to oral antibiotics, when to recommend discharge from hospital and as a measure of outcome after hospitalization [63,64].

Treatment failure is defined as a lack of response or clinical deterioration. It is considered to be early when it occurs within the first 72 h and late when it occurs more than 72 h after hospital admission. The incidence of treatment failure among hospitalized patients with CAP ranges from 2.4 to 31% for early failure and from 3.9 to 11% for late failure. Factors associated with treatment failure include high-risk pneumonia, liver disease, multilobar infiltrates, *Legionella* pneumonia, Gram-negative pneumonia, pleural effusion, cavitation, leucopenia and discordant antimicrobial therapy. Conversely, influenza vaccination, initial treatment with fluoroquinolones and chronic obstructive pulmonary disease have been linked to a lower risk of failure. Importantly, most cases of early failure occur because of inadequate host–pathogen responses [65]. Since treatment failure is associated with high morbidity and mortality rates, its detection and management require careful clinical assessment.

Studies evaluating the utility of biomarkers for predicting treatment failure or determining clinical stability in patients with CAP are detailed in Table 3. Menéndez *et al.* [66] evaluated the cytokine profile in 84 hospitalized CAP patients with treatment failure. IL-6, IL-8 and CRP on day 1 after admission were independently associated with treatment failure. In addition, CRP and procalcitonin on day 1 were predictors of early failure, while IL-6 and CRP on day 3 were predictors of late failure. In another study [26], higher D-dimer concentrations were documented in patients with clinical failure and severe CAP. Patients with early failure had higher D-dimer concentrations than did patients without early failure. However, there were no significant differences in D-dimer concentrations among patients with late treatment failure.

Kolditz *et al.* [67] documented that increased copeptin and pro-adrenomedullin levels were associated with persistent clinical instability in hospitalized CAP patients. Clinical instability was defined as failure to fulfill one or more of the Halm criteria for clinical stability after 72 h of admission. In another study,

Table 2. Biomarkers for predicting ICU admission in patients with community-acquired pneumonia.

Study	N	Serum level	Patients	End point	Comment	Ref.
Inflammatory biomarkers (CRP, procalcitonin, TNF, IL-1, -6, -8, -10)	685		Hospitalized	Direct and delayed ICU admission	CRP and procalcitonin were higher in patients initially located on a ward and subsequently transferred to an ICU. ATS/IDSA guidelines predict ICU admission more accurately than do biomarkers	[55]
ACE activity	265	<24 U/l	Hospitalized	ICU admission	Low serum ACE activity was not prognostic for ICU admission	[24]
Pro-adrenomedullin	302	NR	ED	ICU admission	AUROC for pro-AMD was 0.65, which was similar to that of pro-calcitonin, CRP, leukocyte count and PSI	[56]
D-dimer	314	>500 ng/ml	ED	Mechanical ventilation or vasopressor support	D-dimer had an AUROC of 0.66, which was lower than that of CURB-65 but similar to PSI	[57]
CRP	570	CRP at days 1 and 4	Hospitalized	Mechanical ventilation or vasopressor support	CRP < 100 mg/l was independently associated with a lower risk of the need for mechanical ventilation or vasopressor support. The AUROC for CRP was lower than those of PSI and CURB-65	[58]
Albumin	3463	-5 g/l decrease	Hospitalized	ICU admission	Independently associated with higher risk of ICU admission	[22]
Albumin and CRP	424	Albumin 3.3 mg/dl and CRP 14.3 mg/dl	Hospitalized	ICU admission, mechanical ventilation or vasopressor support	Albumin had an additive role with PSI, but CRP did not	[59]
CRP	391	NR	Hospitalized	ICU admission	Older patients (> 65 years old). CRP was not associated with ICU admission	[48]
D-dimer	147		Hospitalized	Need for mechanical ventilation	AUROC for D-dimer was lower than that of CURB-65, and adding D-dimer to CURB-65 did not improve the accuracy. Reclassification methods did not show benefit	[26]

AUROC: Area under receiver operating characteristic curve; CRP: C-reactive protein; ED: Emergency department; ICU: Intensive care unit; NR: Not reported; PSI: Pneumonia Severity Index; TNF: Tumor necrosis factor.

CRP was found to be an independent predictor of treatment failure, whereas procalcitonin was not independently related to the absence of severe complications after 72 h of treatment [68]. Interestingly, when clinical stability and low levels of CRP (3 mg/dl) and procalcitonin (0.25 ng/ml) were presented at 72 h, no complications occurred later. Finally, Christ-Crain *et al.* documented that pro-adrenomedullin and B-type natriuretic peptide were good predictors of treatment failure [56,69], and AUROC for copeptin was in the same range as that of the PSI for detecting treatment failure during follow-up (mean 6 weeks) [70].

Only a few studies have assessed the utility of biomarkers for predicting treatment failure or clinical stability, and they include a low number of patients at the clinical end point. In addition, there is no standard definition of treatment failure across these studies. These limitations mean that the results are not yet applicable in clinical practice. Indeed, there is a need not only for existing findings to be validated by large studies but also for further studies evaluating the relationship between other biomarkers and treatment failure or clinical stability in CAP.

Expert commentary & five-year view

Current CAP-specific severity scores have certain limitations when it comes to predicting prognosis. Consequently, there has been substantial interest in finding biomarkers that might offer supplementary prognostic information. Several biomarkers

Table 3. Biomarkers for predicting treatment failure and clinical stability in patients with community-acquired pneumonia.

Study	N	Serum level	Patients	End point	Comment	Ref.
Copeptin, pro-adrenomedullin and procalcitonin	51	>25 pmol/l	Hospitalized	Clinical instability after 72 h	AUROC of copeptin was 0.74 for predicting clinical instability, and similar to that of PSI and CURB-65. The addition of copeptin to the PSI score did not improve prognostic accuracy, whereas its addition to CURB-65 did	[67]
D-dimer	147		Hospitalized	Early and late failure (72 h)	Patients with early failure had higher D-dimer. No significant differences were found in patients with late failure	[26]
CRP and procalcitonin	394	CRP <3 mg/dl and procalcitonin <0.25 ng/ml	Hospitalized	Complications after 72 h	CRP was independent predictor of complications. PCT was not predictive of complications. When CRP or PCT were added to clinical stability criteria, AUROC did not increase significantly	[68]
Pro-adrenomedullin	302	NR	ED	Treatment failure at follow-up	AUROC for pro-AMD was 0.73, similar to the AUROC of the PSI	[56]
TNF, IL-1, -6, -8, CRP, PCT	453	IL-6 >169 pg/ml, IL-8 >14 pg/ml, CRP >21.9 mg/dl, PCT >2.2 ng/ml	Hospitalized	Treatment failure, early and late treatment failure	IL-6, IL-8 and CRP were independently associated with treatment failure and late failure. CRP and PCT were independent predictors of early failure	[66]
B-type natriuretic peptide	302	Increase 100 pg/ml	ED	Treatment failure during follow-up (mean 6.9 weeks)	BNP increase was independently associated with treatment failure. Prognostic accuracy was comparable with that of the PSI	[69]
Copeptin	373	53 pmol/l	ED	Treatment failure during follow-up (mean 6 weeks)	AUROC for copeptin was in the same range as that of the PSI	[70]

AUROC: Area under receiver operating characteristic curve; CRP: C-reactive protein; ED: Emergency department; NR: Not reported; PCT: Procalcitonin; PSI: Pneumonia Severity Index; TNF: Tumor necrosis factor.

representing distinct biological pathways have been evaluated for predicting outcomes in CAP, with promising results. The majority of these biomarkers have been shown to be independently associated with short- and long-term mortality, with the need for ICU admission, and with treatment failure in patients with CAP. In addition, several studies have demonstrated that in terms of predicting mortality, biomarkers perform on a par with conventional CAP-specific scores. However, studies are inconsistent regarding whether biomarkers are better than CAP-specific scores for predicting prognosis, as evidenced by the results of AUROC curves. Importantly, when biomarkers are added to scores, an improvement in performance for predicting mortality has been documented. Thus, none of the biomarkers should ever be used in isolation to make clinical decisions.

Studies in this field also present other limitations that question the applicability of their findings in clinical practice. Specifically, the number of patients was low in most studies, the timing of biomarkers was not standardized, factors that could influence the levels of biomarkers were not controlled for, an analysis of causes of death was not performed and most studies did not perform reclassification analyses. The use of biomarkers therefore needs to be validated in prospective trials so as to elucidate how they can best be applied in practice and to determine which ones are the most appropriate – and which cut-off levels should be used – to predict prognosis in CAP. In addition, studies should evaluate the predictive value of combinations of biomarkers from distinct biological pathways, and also examine whether changes in biomarker levels during the course of the disease may help physicians to identify patients at higher risk of deterioration and poor outcomes. Reclassification analysis should obviously be performed. This new research should aim to optimize discharge strategies, enable the application of intensified monitoring and treatment and consider adjuvant treatment options for CAP patients. In addition, investigators should keep in mind the purpose of the biomarker and the setting in which it is to be used.

Interestingly, a study aimed to derive a practical algorithm combining the CURB-65 score with pro-adrenomedullin levels in patients with CAP [71]. The new risk classification offers improved risk prediction with regard to both adverse events and mortality in CAP patients. However, this study used a composite of adverse events defined as all-cause mortality, ICU

admission or any disease-specific complications as primary end point and there is need for further validation studies.

Recently, an expert consensus proposed the possible application of the PIRO model (predisposition and comorbidities, nature of the infection, host response, and extent of organic dysfunction) to stratify patients with sepsis [72]. This model is innovative because it takes into account the heterogeneity of patients with sepsis. The potential applications of the model include the assessment of prognosis, the provision of an aid to therapeutic decision-making and the assessment of treatment response. Notably, the experts considered the need to incorporate biomarkers so as to optimize their clinical utility. The PIRO model has been evaluated in ICU patients with CAP, although the study in question had a retrospective design and only considered the clinical characteristics of patients rather than the determination of biomarkers [73]. The PIRO model therefore needs to be assessed in a prospective cohort of hospitalized patients with CAP so as to clarify whether the concepts on which it is based could enable an individualized stratification and management approach to be developed for CAP. In the near future, genomic, proteomic and metabolomic methods may also prove useful for developing clinically applicable tools for identifying patients with high-risk profiles and the genotypes that underlie them [74].

In conclusion, recent years have seen increasing attention being paid to research on biomarkers, since they have the potential to resolve fundamental issues regarding prognostic prediction that cannot be readily addressed using CAP-specific scores. Current findings support the use of biomarkers in conjunction with scores as a way of significantly improving their prediction performance. However, the usefulness of biomarkers in clinical practice is still to be determined.

Financial & competing interests disclosure

This work was supported by the Fondo de Investigación Sanitaria de la Seguridad Social (grant 11/01106) and by Spain's Ministerio de Economia y Competitividad, Instituto de Salud Carlos III – co-financed by the European Regional Development Fund (ERDF) 'A way to achieve Europe', Spanish Network for Research in Infectious Diseases (REIPI RD12/0015). Viasus D is the recipient of a research grant from the REIPI. Garcia-Vidal C is the recipient of a Juan de la Cierva research grant from the Instituto de Salud Carlos III, Madrid, Spain. Simonetti A is the recipient of a research grant from the IDIBELL – Bellvitge Biomedical Research Institute. The funding sources had no role in the study design, in the collection, analysis and interpretation of data, or in the writing of the manuscript. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- The majority of biomarkers have been found to be independent predictors of short- and long-term mortality, intensive care unit (ICU) admission and treatment failure in patients with community-acquired pneumonia (CAP).
- Importantly, studies are inconsistent regarding whether biomarkers are better than CAP-specific scores for predicting prognosis, as evidenced by the results of area under the receiver operating characteristic (AUROC) curves.
- Adding biomarkers to scores such as Pneumonia Severity Index, CURB-65, APACHE II and SOFA improved their predictive capability, as indicated by a significant increase in the AUROC curves.
- There is a need not only for existing findings to be validated by large studies but also for further studies evaluating the relationship between biomarkers and the need for ICU admission and treatment failure or clinical stability in CAP.
- Future research should seek to elucidate how biomarkers can best be used in clinical practice, which ones are the most appropriate and which cut-off levels should be applied for predicting prognosis in CAP.
- Future studies should evaluate the predictive value of combinations of biomarkers from distinct biological pathways and also examine whether changes in biomarker levels during the course of the disease may help physicians to identify patients at higher risk of deterioration and poor outcomes.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Mandell LA, Wunderink RG, Anzueto A *et al.* IDSA/ATS consensus guidelines on the management of community-acquired pneumonia in adults. *Clin. Infect. Dis.* 44(Suppl. 2), S27–S72 (2007).

2 Heron M, Hoyert DL, Murphy SL *et al.* Deaths: final data for 2006. *Natl Vital. Stat. Rep.* 57, 1–134 (2009).

3 Almirall J, Bolíbar I, Vidal J *et al.* Epidemiology of community-acquired pneumonia in adults: a population based study. *Eur. Respir. J.* 15, 757–763 (2000).

4 Jokinen C, Heiskanen L, Juvonen H *et al.* Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am. J. Epidemiol.* 137, 977–988 (1993).

5 Woodhead M, Blasi F, Ewig S *et al.* Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections–full version. *Clin. Microbiol. Infect.* 17(Suppl. 6), E1–59 (2011).

6 Mandell LA, Wunderink RG, Anzueto A *et al.* Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired

pneumonia in adults. *Clin. Infect. Dis.* 44(Suppl. 2), S27–72 (2007).

7 Fine MJ, Auble TE, Yealy DM *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N. Engl. J. Med.* 336, 243–250 (1997).

8 Lim WS, van der Eerden MM, Laing R *et al.* Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 58, 377–382 (2009).

9 Carratalà J, Fernández-Sabé N, Ortega L *et al.* Outpatient care compared with hospitalization for community-acquired pneumonia: a randomized trial in low-risk patients. *Ann. Intern. Med*. 142, 165–172 (2005).

10 Huang DT, Weissfeld LA, Kellum JA *et al.*; GenIMS Investigators. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann. Emerg. Med*. 52, 48–58 (2008).

11 Chalmers JD, Mandal P, Singanayagam A *et al.* Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. *Intensive Care Med*. 37, 1409–1420 (2011).

12 Mayeux R. Biomarkers: Potential Uses and Limitations. *NeuroRx*. 1, 182–188 (2004).

13 Naylor S. Biomarkers: current perspectives and future prospects. *Expert. Rev. Mol. Diagn*. 3, 525–529 (2003).

14 Rosón B, Carratalà J, Dorca J *et al.* Etiology, reasons for hospitalization, risk classes, and outcomes of community-acquired pneumonia in patients hospitalized on the basis of conventional admission criteria. *Clin. Infect. Dis*. 33, 158–165 (2001).

15 Blasi F, Garau J, Medina J, Avila M, McBride K, Ostermann H. Current management of patients hospitalized with community-acquired pneumonia across Europe: outcomes from REACH. *Respir. Res*. 14, 44 (2013).

16 Rodriguez A, Lisboa T, Blot S *et al.* Mortality in ICU patients with bacterial community-acquired pneumonia: when antibiotics are not enough. *Intensive Care Med*. 35, 430–438 (2009).

17 Bruns AH, Oosterheert JJ, Cucciolillo MC *et al.* Cause-specific long-term mortality rates in patients recovered from community-acquired pneumonia as compared with the general Dutch population. *Clin. Microbiol. Infect.* 17, 763–768 (2011).

18 Reade MC, Yende S, D'Angelo G *et al.*; Genetic and Inflammatory Markers of Sepsis Investigators. Differences in immune response may explain lower survival among older men with pneumonia. *Crit. Care Med.* 37, 1655–1662 (2009).

19 Lim WS, Baudouin SV, George RC *et al.* Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 64 (Suppl. 3), iii1–iii55 (2009).

20 Chalmers JD, Singanayagam A, Akram AR *et al.* Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia. Systematic review and meta-analysis. *Thorax*. 65, 878–883 (2010).

21 Narvaez-Rivera RM, Rendon A, Salinas-Carmona MC, Rosas-Taraco AG. Soluble RAGE as a severity marker in community acquired pneumonia associated sepsis. *BMC Infect. Dis*. 12, 15 (2012).

22 Viasus D, Garcia-Vidal C, Simonetti A *et al.* Prognostic value of serum albumin levels in hospitalized adults with community-acquired pneumonia. *J. Infect*. 66, 415–423 (2013).

23 van de Garde EM, Endeman H, Deneer VH *et al.* Angiotensin-converting enzyme (ACE) I/D corrected serum ACE activity and severity assessment of community-acquired pneumonia. *Clin. Chem. Lab. Med*. 45, 1326–1331 (2007).

24 Meijvis SC, Cornips MC, Endeman H *et al.* Prognostic value of serum angiotensin-converting enzyme activity for outcome of community-acquired pneumonia. *Clin. Chem. Lab. Med.* 49, 1525–1532 (2011).

25 Jeong KY, Kim K, Kim TY *et al.* Prognostic value of N-terminal pro-brain natriuretic peptide in hospitalised patients with community-acquired pneumonia. *Emerg. Med. J*. 28, 122–127 (2011).

26 Snijders D, Schoorl M, Schoorl M, Bartels PC, van der Werf TS, Boersma WG. D-dimer levels in assessing severity and clinical outcome in patients with community-acquired pneumonia. A secondary analysis of a randomised clinical trial. *Eur. J. Intern. Med.* 23, 436–441 (2012).

27 Huang DT, Angus DC, Kellum JA *et al.* Midregional proadrenomedullin as a prognostic tool in community-acquired pneumonia. *Chest*. 136, 823–831 (2009).

28 Hu W, Liu CW, Su J, Lu J, Zhu Y, Liu BW. Elevated plasma visfatin concentrations in patients with community-acquired pneumonia. *Peptides*. 43, 8–12 (2013).

29 Suberviola B, Castellanos-Ortega A, Llorca J, Ortiz F, Iglesias D, Prieto B. Prognostic value of proadrenomedullin in severe sepsis and septic shock patients with community-acquired pneumonia. *Swiss. Med. Wkly* 142, w13542 (2012).

30 Courtais C, Kuster N, Dupuy AM *et al.* Proadrenomedullin, a useful tool for risk stratification in high Pneumonia Severity Index score community acquired pneumonia. *Am. J. Emerg. Med.* 31, 215–221 (2013).

31 Schuetz P, Wolbers M, Christ-Crain M *et al.* ProHOSP Study Group. Prohormones for prediction of adverse medical outcome in community-acquired pneumonia and lower respiratory tract infections. *Crit. Care* 14, R106 (2010).

•• **Finding of adding several biomarkers instead of just one lead to a significant improvement in the current community-acquired pneumonia (CAP)-specific scores.**

32 Schuetz P, Christ-Crain M, Zimmerli W, Mueller B. Repeated measurements of endothelin-1 precursor peptides predict the outcome in community-acquired pneumonia. *Intensive Care Med.* 37, 970–980 (2011).

33 Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am. J. Med*. 121, 219–225 (2008).

34 Menéndez R, Martínez R, Reyes S *et al.* Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. *Thorax*. 64, 587–591 (2009).

•• **Finding of adding several cytokines and biomarkers to current CAP-specific scores improve their performance for predicting prognosis.**

35 Lin WC, Lu SL, Lin CF *et al.* Plasma kallistatin levels in patients with severe community-acquired pneumonia. *Crit. Care*. 17, R27 (2013).

36 Brogly N, Devos P, Boussekey N, Georges H, Chiche A, Leroy O. Impact of thrombocytopenia on outcome of patients admitted to ICU for severe community-acquired pneumonia. *J. Infect.* 55, 136–140 (2007).

37 Salluh JI, Rabello LS, Rosolem MM *et al.* The impact of coagulation parameters on the outcomes of patients with severe community-acquired pneumonia requiring intensive care unit admission. *J. Crit. Care*. 26, 496–501 (2011).

38 Boussekey N, Leroy O, Alfandari S, Devos P, Georges H, Guery B. Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. *Intensive Care Med*. 32, 469–472 (2006).

39 Coelho LM, Salluh JI, Soares M *et al.* Patterns of C-reactive protein RATIO response in severe community-acquired pneumonia: a cohort study. *Crit. Care*. 16, R53 (2012).

40 Salluh JI, Bozza FA, Soares M *et al.* Adrenal response in severe community-acquired pneumonia: impact on outcomes and disease severity. *Chest*. 134, 947–954 (2008).

41 Yende S, D'Angelo G, Mayr F *et al.*; GenIMS Investigators. Elevated hemostasis markers after pneumonia increases one-year risk of all-cause and cardiovascular deaths. *PLoS One*. 6, e22847 (2011).

42 Braun E, Domany E, Kenig Y, Mazor Y, Makhoul BF, Azzam ZS. Elevated red cell distribution width predicts poor outcome in young patients with community acquired pneumonia. *Crit. Care*. 15, R194 (2011).

43 Guertler C, Wirz B, Christ-Crain M, Zimmerli W, Mueller B, Schuetz P. Inflammatory responses predict long-term mortality risk in community-acquired pneumonia. *Eur. Respir. J*. 37, 1439–1446 (2011).

44 Krüger S, Ewig S, Kunde J, Hartmann O, Suttorp N, Welte T; CAPNETZ Study Group. Pro-atrial natriuretic peptide and pro-vasopressin for predicting short-term and long-term survival in community-acquired pneumonia: results from the German Competence Network CAPNETZ. *Thorax* 65, 208–214 (2010).

45 Nowak A, Breidthardt T, Christ-Crain M *et al.* Direct comparison of three natriuretic peptides for prediction of short- and long-term mortality in patients with community-acquired pneumonia. *Chest* 141, 974–982 (2012).

46 Bello S, Lasierra AB, Mincholé E *et al.* Prognostic power of proadrenomedullin in community-acquired pneumonia is independent of aetiology. *Eur. Respir. J*. 39, 1144–1155 (2012).

47 Bauer MP, Hensgens MP, Miller MA *et al.* Renal failure and leukocytosis are predictors of a complicated course of *Clostridium difficile* infection if measured on day of diagnosis. *Clin. Infect. Dis*. 55(Suppl, 2), S149–153 (2012).

48 Thiem U, Niklaus D, Sehlhoff B *et al.* C-reactive protein, severity of pneumonia and mortality in elderly, hospitalised patients with community-acquired pneumonia. *Age Ageing* 38, 693–697 (2009).

49 Steyerberg EW, Pencina MJ, Lingsma HF, Kattan MW, Vickers AJ, Van Calster. Assessing the incremental value of diagnostic and prognostic markers: a review and illustration. *Eur. J. Clin. Invest*. 42, 216–228 (2012).

•• **Comprehensive recent review on various measures to quantify the incremental value of markers over standard, readily available characteristics.**

50 Marrie TJ, Shariatzadeh MR. Community-acquired pneumonia requiring admission to an intensive care unit: a descriptive study. *Medicine (Baltimore)*. 86, 103–111 (2007).

51 Brown SM, Jones JP, Aronsky D, Jones BE, Lanspa MJ, Dean NC. Relationships among initial hospital triage, disease progression and mortality in community-acquired pneumonia. *Respirology*. 17, 1207–1213 (2012).

52 Phua J, Ngerng WJ, Lim TK. The impact of a delay in intensive care unit admission for community-acquired pneumonia. *Eur. Respir. J*. 36, 826–833 (2010).

53 Charles PG, Wolfe R, Whitby M *et al.* SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin. Infect. Dis*. 47, 375–384 (2008).

54 Renaud B, Labarère J, Coma E *et al.* Risk stratification of early admission to the intensive care unit of patients with no major criteria of severe community-acquired pneumonia: development of an international prediction rule. *Crit. Care*. 13, R54 (2009).

55 Ramírez P, Ferrer M, Martí V *et al.* Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. *Crit. Care Med*. 39, 2211–2217 (2011).

56 Christ-Crain M, Morgenthaler NG, Stolz D *et al.* Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia. *Crit. Care* 10, R96 (2006).

57 Chalmers JD, Singanayagam A, Scally C, Hill AT. Admission D-dimer can identify low-risk patients with community-acquired pneumonia. *Ann. Emerg. Med*. 53, 633–638 (2009).

58 Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am. J. Med*. 121, 219–225 (2008).

59 Lee JH, Kim J, Kim K *et al.* Albumin and C-reactive protein have prognostic significance in patients with community-acquired pneumonia. *J. Crit. Care*. 26, 287–294 (2011).

60 Chalmers JD, Taylor JK, Mandal P *et al.* Validation of the Infectious Diseases Society of America/American Thoratic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. *Clin. Infect. Dis*. 53, 503–511 (2011).

61 Renaud B, Schuetz P, Claessens YE, Labarère J, Albrich W, Mueller B. Proadrenomedullin improves Risk of Early Admission to ICU score for predicting early severe community-acquired pneumonia. *Chest* 142, 1447–1454 (2012).

62 Halm EA, Fine MJ, Marrie TJ *et al.* Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* 279, 1452–1457 (1998).

63 Oosterheert JJ, Bonten MJM, Schneider MME *et al.* Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *BMJ*. 333, 1193 (2006).

64 Carratalà J, Garcia-Vidal C, Ortega L *et al.* Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. *Arch. Intern. Med*. 172, 922–928 (2012).

65 Garcia-Vidal C, Carratalà J. Early and late treatment failure in community-acquired pneumonia. *Semin. Respir. Crit. Care Med*. 30, 154–160 (2009).

66 Menéndez R, Cavalcanti M, Reyes S *et al.* Markers of treatment failure in hospitalised community acquired pneumonia. *Thorax*. 63, 447–452 (2008).

67 Kolditz M, Halank M, Schulte-Hubbert B, Bergmann S, Albrecht S, Höffken G. Copeptin predicts clinical deterioration and persistent instability in community-acquired pneumonia. *Respir. Med*. 106, 1320–1328 (2012).

68 Menéndez R, Martinez R, Reyes S *et al.* Stability in community-acquired pneumonia: one step forward with markers? *Thorax* 64, 987–992 (2009).

69 Christ-Crain M, Breidthardt T, Stolz D, *et al.* Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. *J. Intern. Med.* 264, 166–176 (2008).

70 Müller B, Morgenthaler N, Stolz D *et al.* Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. *Eur. J. Clin. Invest.* 37, 145–152 (2007).

71 Albrich WC, Dusemund F, Rüegger K *et al.* Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: derivation of a clinical algorithm. *BMC Infect. Dis.* 11, 112 (2011).

72 Levy MM, Fink MP, Marshall JC, Abraham E *et al.*; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit. Care Med.* 31, 1250–1256 (2003).

73 Rello J, Rodriguez A, Lisboa T, Gallego M, Lujan M, Wunderink R. PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. *Crit. Care Med.* 37, 456–462 (2009).

74 Waterer GW. Community-acquired pneumonia: genomics, epigenomics, transcriptomics, proteomics, and metabolomics. *Semin. Respir. Crit. Care Med.* 33, 257–265 (2012).

• **Comprehensive recent review on the use of genomic, epigenomic, transcriptomic, proteomic and metabolomic approaches in CAP.**

75 Lee JH, Chung HJ, Kim K *et al.* Red cell distribution width as a prognostic marker in patients with community-acquired pneumonia. *Am. J. Emerg. Med.* 31, 72–79 (2013).

76 Kolditz M, Höffken G, Martus P *et al.*; CAPNETZ study group. Serum cortisol predicts death and critical disease independently of CRB-65 score in community-acquired pneumonia: a prospective observational cohort study. *BMC Infect. Dis.* 12, 90 (2012).

77 Horie M, Ugajin M, Suzuki M *et al.* Diagnostic and prognostic value of procalcitonin in community-acquired pneumonia. *Am. J. Med. Sci.* 343, 30–35 (2012).

78 Park JH, Wee JH, Choi SP, Oh SH. The value of procalcitonin level in community-acquired pneumonia in the ED. *Am. J. Emerg. Med.* 30, 1248–1254 (2012).

79 Lee JH, Kim J, Kim K *et al.* Albumin and C-reactive protein have prognostic significance in patients with community-acquired pneumonia. *J. Crit. Care.* 26, 287–294 (2011).

80 Mirsaeidi M, Peyrani P, Aliberti S *et al.* Thrombocytopenia and thrombocytosis at time of hospitalization predict mortality in patients with community-acquired pneumonia. *Chest.* 137, 416–420 (2010).

81 Mueller C, Laule-Kilian K, Scholer A, Perruchoud AP. B-type natriuretic peptide for risk stratification in community-acquired pneumonia. *J. Intern. Med.* 258, 391–393 (2005).

82 Müller B, Morgenthaler N, Stolz D *et al.* Circulating levels of copeptin, a novel biomarker, in lower respiratory tract infections. *Eur. J. Clin. Invest.* 37, 145–152 (2007).

83 Krüger S, Ewig S, Marre R *et al.*; CAPNETZ Study Group. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur. Respir. J.* 31, 349–355 (2008).

84 Masiá M, Papassotiriou J, Morgenthaler NG, Hernández I, Shum C, Gutiérrez F. Midregional pro-A-type natriuretic peptide and carboxy-terminal provasopressin may predict prognosis in community-acquired pneumonia. *Clin. Chem.* 53, 2193–2201 (2007).

85 Krüger S, Ewig S, Kunde J, Hartmann O, Suttorp N, Welte T; CAPNETZ Study Group. Pro-atrial natriuretic peptide and pro-vasopressin for predicting short-term and long-term survival in community-acquired pneumonia: results from the German Competence Network CAPNETZ. *Thorax* 65, 208–214 (2010).

86 Remmelts HH, van de Garde EM, Meijvis SC *et al.* Addition of vitamin D status to prognostic scores improves the prediction of outcome in community-acquired pneumonia. *Clin. Infect. Dis.* 55, 1488–1494 (2012).