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REVIEW

Management-based risk prediction in community-acquired pneumonia by scores and biomarkers

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ABSTRACT: Community-acquired pneumonia (CAP) represents a major life-threatening infection, but disease course and outcome is highly variable. Major drivers of prognosis are respiratory failure, sepsis-related organ dysfunction and unstable comorbidities.

Current risk stratification tools have been primarily designed to predict mortality and identify low risk patients potentially suitable for ambulatory management. Detection of patients at high risk for clinical deterioration by current scores remains suboptimal.

Therefore, management-related risk stratification tools designed to predict benefit from early intensified monitoring and treatment strategies in hospitalised CAP are advocated. An approach including early and repeatedly evaluated clinical markers of respiratory failure, sepsis-related organ dysfunction or decompensating comorbidity combined with individual definition of treatment goals is suggested.

Inflammatory biomarkers can add prognostic information. New cardiovascular or stress-related biomarkers like copeptin, midregional proadrenomedullin and cortisol have been repeatedly linked with outcome and disease course in CAP and improved clinical scoring in observational studies. Thus they represent promising tools for individualised risk stratification. A major task in future CAP research will be the evaluation of their additional value in large interventional trials with control groups incorporating strict management guidance by clinical criteria.

KEYWORDS: Acute respiratory failure, biomarkers, community-acquired pneumonia, early intervention, risk group, sepsis

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Community-acquired pneumonia (CAP) is the number one severe infectious disease in the western world, and disease course and outcome is highly variable. Whereas mortality and complication rates remain low in non-severe CAP managed in the community [1], hospitalised CAP is associated with a high risk of respiratory failure or sepsis-related organ dysfunction. Recent population-based data showed an overall mortality rate of 13% in hospitalised CAP, rising to more than 35% in severe CAP [2]. Thus, prognosis resembles that of well-recognised acute emergencies in internal medicine, such as acute myocardial infarction [3], but comparable structured management approaches regarding pre- and early hospital management to improve outcome have not yet been established.

Real life data from Germany illustrate that 39% of patients receiving mechanical ventilation (and thus dedicated intensive management) do not survive the hospital stay; conversely, only a minority (16%) of patients dying in the hospital have been mechanically ventilated [2]. Accordingly, a multicentre database in the USA previously found that only a small proportion of patients experiencing cardiac arrest while hospitalised with pneumonia showed features of severe CAP, such as shock (33%) or mechanical ventilation (36%), and 38% of arrests occurred in a normal ward with only 52% being under cardiorespiratory monitoring [4]. Clinical deterioration, septic organ dysfunction or death predominantly occur within a well-defined time frame of 24–72 h after hospitalisation [2, 4–6]. For this vulnerable early period, interventions like intensive monitoring and management in the intensive care unit (ICU) [6–8], optimised sepsis management (''sepsis bundles'') [9] and early adequate antibiotic therapy [10, 11] potentially

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translate into substantial prognosis improvement. However, CAP is a disease of very elderly patients and is frequently considered and managed as a terminal event of severe comorbid conditions. Definition of individual therapeutic goals in this setting is important but little accounted for so far in current guidelines. Additionally, a substantial proportion of CAP mortality is related to unstable or exacerbating pre-existing comorbidities as major risk factors of adverse CAP outcome [2, 12, 13]. A recent prospective study reported acute cardiac events in 27% of hospitalised CAP patients. Risk was highest within the first 24 h and cardiac events were associated with poor outcome independent of CAP severity [14]. From these data it seems plausible to argue for routine comorbidity screening and monitoring in early hospitalised CAP. Although the Pneumonia Severity Index (PSI) score implements the presence of comorbidities [13], none of the established risk stratification recommendations accounts for this major prognostic factor in a standardised manner.

Together, these data highlight a gap between current risk stratification approaches and real life situations. The implementation of individualised management-based tools designed to predict benefit from early intensified management and monitoring strategies like early goal directed treatment or monitoring for organ failure is needed.

CLINICAL RISK STRATIFICATION

Established scores for risk stratification at hospital admission

International guidelines recommend different clinical scores to support grading of CAP severity. Most established are the PSI score [13], consisting of 20 clinical, laboratory and radiographic variables, and the CRB-65 (confusion, respiratory rate $\geqslant$ 30 min^{-1}, blood pressure $<90/\geqslant 60$ mmHg, age >65 years) [1] and the CURB score (urea >7 $mmol \cdot L^{-1}$ instead of age) [15] criteria, which include only four parameters. The CRB-65 score is the most easy to calculate and thus widely used in Europe [16, 17]. Both proved to be comparable tools for mortality prediction and identification of low risk patients suitable for ambulatory management, and mortality in low risk patients (PSI score I–III; CURB/CRB-65 score 0) consistently is below 2% [1, 18, 19].

For prediction of severe CAP, studies frequently use the clinical surrogate of ICU admission. Here, the 2001 American Thoracic Society (ATS)- [20] and 2007 ATS/Infectious Diseases Society of America (IDSA)-rules [21] indicating features of sepsis-related organ dysfunction or respiratory disturbance performed best and are widely recommended [21–23]. The 2001 rule consists of two major criteria (requirement for mechanical ventilation, presence of septic shock) and three minor criteria (systolic blood pressure <90 mmHg, multilobar infiltrate, arterial oxygen tension/inspiratory oxygen fraction <250), while the 2007 rule added six more minor criteria (respiratory rate >30 min^{-1}; confusion; blood urea nitrogen >20 $mg \cdot dL^{-1}$; leukopenia; thrombocytopenia; hypothermia). Both have a superior performance to the PSI or CURB scores for prediction of ICU admission (pooled sensitivity of 61–67%, positive likelihood ratio 6.2–7.1) [22]. Other scoring systems, such as the SMART-COP rule [24], the SCAP/Espana rule [25, 26], the CORB score [27] and the REA-ICU rule [28] have been introduced and incorporate variations of the ATS minor criteria and/or additional factors such as low arterial pH, albumin, tachycardia and hyponatraemia. While their prediction of severe CAP showed accuracies comparable to those of the ATS rules [23, 29], the latter three have not been validated in external cohorts so far. A recent study compared most of these scores with a rigorous design, excluding patients with immediate need for vasopressor use and/or mechanical ventilation as well as patients not suitable for ICU care owing to advanced directives or major comorbid illnesses [23]. Evaluated end-points included the need for mechanical ventilation or vasopressor use, and the 2007 minor criteria achieved the highest prediction (area under the curve 0.85: sensitivity 79%, positive predicted value 23%).

Problems with current risk scores

Most studies evaluated prognostic scores by observational design. To prove clinical utility, interventional trials demonstrating improvement of clinical end-points, such as prognosis, treatment failure, treatment allocation, hospital stay or cost, would be required. So far trials proving accurate identification of low risk patients suitable for ambulatory treatment without compromising their safety have been performed only for the PSI score [30–33], and no clinical end-point studies exist for high risk prediction.

Evidence from observational studies suggests that both the CURB/CRB-65 and PSI scores perform more poorly in predicting high risk patients, as they show low positive likelihood ratios at the recommended cut-off points for the prediction of 30-day mortality (PSI $\geqslant$4: positive likelihood ratio 1.9; CRB-65 $\geqslant$2: positive likelihood ratio 2.4) [18, 19]. Moreover, accurate mortality prediction does not always lead to accurate identification of patients developing severe CAP and who are in need of intensified management strategies. As there is no generally accepted definition for severe CAP, the most widely used surrogate for high risk prediction is ICU admission. This end-point is vulnerable to bias by ICU admission policy and highly dependent on individual physician decisions. Treatment restrictions bias this end-point further. In a recent study 35% (563 out of 1,625) of consecutive patients showed ''contraindications'' for ICU admission [23]. Both the CRB-65/CURB (pooled sensitivity only 49%) and PSI scores (pooled specificity only 48%) lack accuracy for prediction of ICU admission [22]. Even the 2007 ATS/IDSA rule showed a pooled sensitivity of only 61% in a recent meta-analysis, meaning that 39% of patients deteriorating in the course would be missed [22]. Additionally, the two major criteria of the ATS rules rather reflect critical disease by themselves instead of being risk factors for it, and ICU referral for patients presenting with manifest respiratory failure or septic shock is self-evident. Consequently, recent studies used the major criteria as end-points [23–25, 27, 34, 35]. By this approach, the 2007 ATS minor criteria achieved a positive likelihood ratio of 4.3 and a negative likelihood ratio of 0.26 [23], clearly missing the recommended threshold of 10/0.1 for diagnostic instruments [36]. Their sensitivity of 79% still means that 21% of patients deteriorating in the course are missed [23]. Moreover, prediction of vasopressor use or mechanical ventilation still represents only a subgroup of patients in need of intensified management strategies for sepsis-related organ

failure, such as fluid resuscitation responsive hypotension or instable comorbidities. Thus, optimal prediction of severe CAP should primarily aim to identify all patients who benefit from intensified monitoring and management strategies rather than a specific site of care prediction, as recently suggested [29].

Risk of unstable comorbidities

Pre-existing comorbidities, such as chronic renal, hepatic, cardiac, cerebrovascular and neoplastic disease or diabetes mellitus, have been independently associated with adverse prognosis in CAP [2, 13, 14, 37–40]. Acute systemic inflammatory and pro-coagulatory changes caused by CAP increase the risk for decompensation of organ function [14, 38–40]. Non-pulmonary acute organ dysfunction occurs in about 40% of hospitalised CAP patients and is already present in half of them at hospital admission [41]. For acute cardiac events it has been shown that risk is elevated in patients with pre-existing cardiac disease (OR 4.3) and associated with pneumonia severity (37%/43% in PSI class IV/V); risk is highest during the first 24 h of hospitalisation [14]. Therefore, the presence of unstable or decompensating comorbidities should be evaluated routinely as a marker of severe CAP requiring intensified monitoring and management.

Risk stratification in elderly patients and patients from nursing homes

Increasingly CAP has become a disease of elderly and multimorbid patients, and efforts have been made to describe and categorise special aspects of CAP in this patient group [42, 43]. From several recent European studies it has been consistently shown that the main drivers of poor prognosis in nursing home patients are: 1) poor functional status due to severe and often multiple comorbidities; and 2) hidden or open treatment restrictions rather than treatment failure due to inadequate therapy of multiresistant or rare pathogens [12, 44–46]. Thus, routine assessment of functional status, preferentially defined by a validated score like activities of daily living ($\geqslant$14) or World Health Organization performance status ($\geqslant$3) has been suggested to account for this important patient group more adequately [43, 47]. Established risk stratification tools like the CRB-65 and PSI scores work less well in elderly and severely disabled patients, but can be significantly improved by including oxygenation measurement and assessment of functional status [47–50]. A recent population-based study from Germany showed that especially the negative predictive value of the CRB-65 score for mortality in nursing home patients is insufficient as hospital mortality of identified ''low risk'' patients was still about 20%, but prediction could be improved by the evaluation of functional status (''bedridden'') and comorbidities [50].

Therefore, any risk stratification approach should account for the special requirements in this important patient group by including assessment of comorbidities and functional status, as well as the initial definition and continuous review of individual treatment goals.

Risk stratification in the hospital course

Existing risk scores have been evaluated for admission scoring only. However, there is an obvious need for repeated evaluation of hospitalised patients to account for the risk of deterioration in the course. Risk of clinical deterioration or death is highest within the first 24–72 h and fades over the following days [2, 4–6]. In a recent study, patients with delayed ICU transfer showed an increase of positive minor criteria from two at admission to four at the time of ICU transfer, resulting in a significantly elevated mortality (51 *versus* 20%) after late referral [6]. Sepsis-related organ dysfunction in about 50% of patients only develops after hospital admission [41]. Therefore, repeated clinical re-evaluation in hospitalised CAP patients should be performed until clinical improvement with therapy is evident.

After response to treatment, a simple clinical score can evaluate the risk of subsequent clinical deterioration. These clinical stability criteria consist of five parameters: temperature $\leqslant$37.8°C, heart rate $\leqslant$100 min^{-1}, respiratory rate $\leqslant$24 min^{-1}, systolic blood pressure $\geqslant$90 mmHg and arterial oxygen saturation $\geqslant$90% on breathing room air [51]. If these criteria are fulfilled, the risk of serious deterioration with ICU admission or in-hospital death decreases to $<$1% [51, 52] and risks for mortality or readmission after discharge to $<$3% and 9%, respectively [53]. These criteria also have been successfully used to guide a switch to oral therapy [54], treatment duration [55] and discharge management [53].

Suggested clinical risk stratification approach for CAP in the hospital

Because of the limitations of current clinical high risk stratification in hospitalised CAP, a management-based approach has been advocated to identify the need for intensified monitoring and treatment strategies rather than ICU admission or mortality [29]. The basis of this approach constitutes the evaluation of critical organ dysfunction as a consequence of respiratory, cardiocirculatory or comorbidity-related deterioration. Therefore, individual clinical recognition of organ dysfunction by the experienced physician appears to be crucial. Such organ dysfunction should be objectively assessed by the presence of parameters incorporated into evaluated risk scores indicating respiratory failure, sepsis-related organ dysfunction or decompensating comorbidities, which need to be integrated within the individual clinical picture indicating the need for intensified management. Screening for unstable comorbidities should be implemented in all patients with either pre-existing comorbidities or high CAP severity. Additionally, the dynamic nature of pneumonia urges repeated re-evaluation of organ function and minor criteria during the first days of hospitalisation. This algorithm must be supplemented by the continuous evaluation of individual treatment goals.

Resulting management decisions in high risk patients should include: 1) repeated (*e.g.* every 4–6 h) evaluation of clinical and vital signs and cardiovascular monitoring; 2) application of recommended management for severe sepsis and septic shock, according to sepsis guidelines [9], including fluid resuscitation with early goal directed treatment within the first 6 h and early (within the first hours) intravenous broad spectrum antibiotic therapy; 3) repeated evaluation of respiratory function by respiratory rate, oxygenation monitoring and/or blood gas analysis to guide oxygen or ventilator assistance; and 4) regular monitoring of organ function by laboratory parameters and urine output.

Ambulatory management could be considered in patients: 1) not presenting with the above described features of severe CAP; and 2) showing a low mortality risk according to established risk scores; which 3) should be supplemented by functional assessment in comorbid and elderly patients. After clinical response to treatment, documentation of clinical stability criteria should precede hospital discharge. A resulting algorithm is illustrated in figure 1.

BIOMARKERS TO IMPROVE RISK PREDICTION

With the described limitations of clinical risk stratification in hospitalised CAP in mind, efforts have been undertaken to improve current strategies by including biomarkers, given their theoretical capability to detect underlying mechanisms of CAP progression in a more accurate and timely manner.

Inflammatory biomarkers

Inflammatory biomarkers like C-reactive protein (CRP) [56, 57], procalcitonin (PCT) [58–60] and cytokines, such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α [56, 60, 61] are associated with mortality and disease severity in CAP; however, their predictive accuracy does not allow their use for high risk prediction by themselves. The most established markers PCT and CRP provide additional information to the clinical scores by identifying low risk patients with low admission levels [56–59] and monitoring treatment response using kinetic data [57, 62–65]. Adequate antibiotic therapy and good prognosis has been demonstrated by decreasing CRP levels after 3–4 days [57, 64, 65]. Persistent or rising CRP at day 3–4 [64, 65] or PCT at day 3 [62, 63] indicates inadequate treatment and poor prognosis. In clinical treatment failure low PCT levels might raise suspicion of a non-infectious cause, like organising pneumonia [66]. Additionally PCT can be used to guide antibiotic treatment duration. Stopping antibiotics on the basis of low PCT levels in the course has been proven to shorten antibiotic treatment without compromising patient safety in a variety of interventional trials and even in an ICU setting [67–69]. Unfortunately, for demonstrating superiority of a biomarker-guided strategy these studies are limited by the absence of rigorous treatment guidance by established clinical criteria in the control group, but they support the prognostic value of kinetic PCT data. Consequently, re-evaluation of inflammatory biomarkers after 3–4 days to validate treatment response or monitor infectious causes of treatment failure in hospitalised patients has been recommended [17, 70].

The main advantage of PCT over CRP in CAP lies in its faster kinetics. However, false-negative admission PCT in patients with severe sepsis or even septic shock has been reported [71]. One possible explanation is a delayed PCT rise after septic stimulus, which can cause a diagnostic gap requiring repeated measurements. Although PCT is more specific than CRP for bacterial infections, its accuracy still does not allow individual prediction of aetiology [72]. Another problem of both markers is their poor prediction of high risk patients. For PCT the positive likelihood ratio for mortality has been as low as 1.4–1.5 in recent

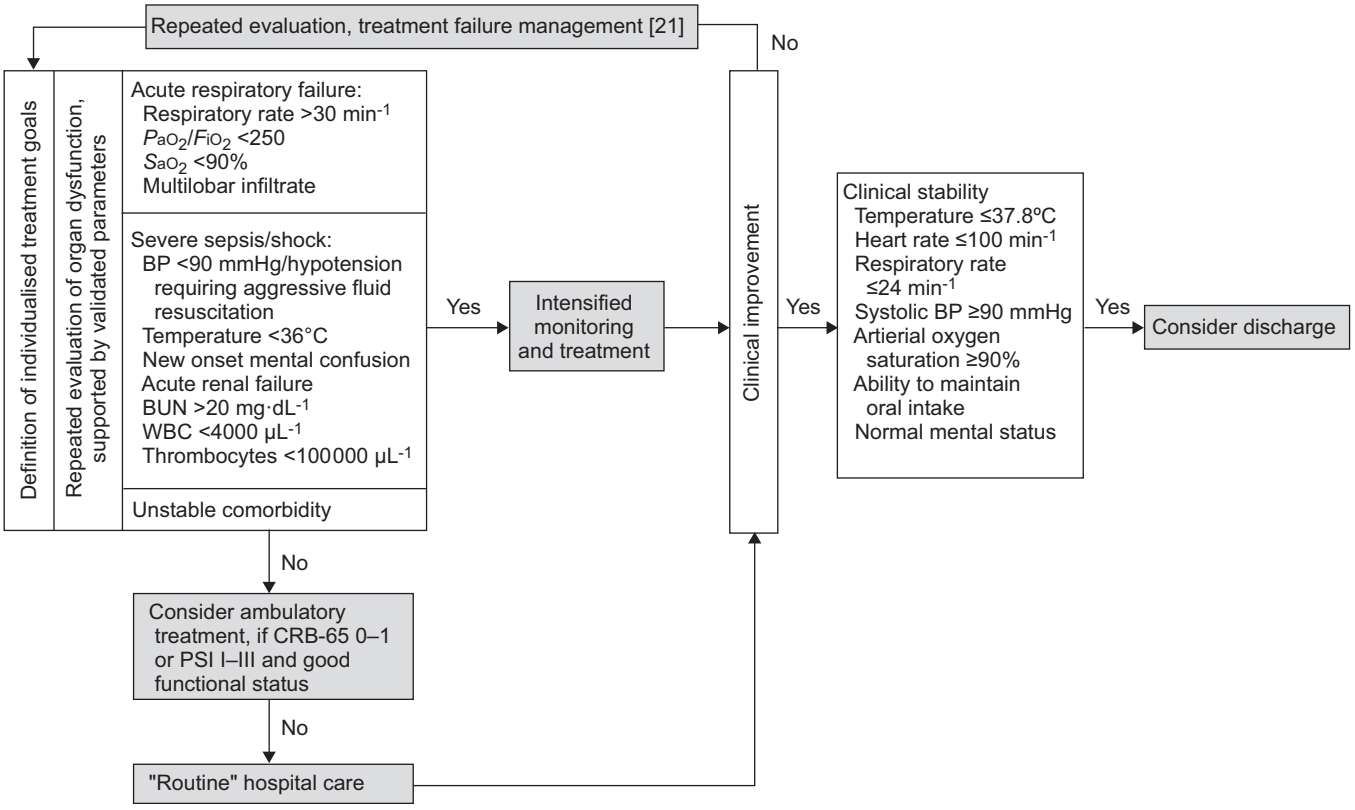

FIGURE 1. Proposed management-based risk stratification algorithm in hospitalised community-acquired pneumonia. P_{aO_2}: arterial oxygen tension; F_{iO_2}: inspiratory oxygen fraction; S_{aO_2}: arterial oxygen saturation; BP: blood pressure; BUN: blood urea nitrogen; WBC: white blood cell; CRB-65: confusion, respiratory rate $\geqslant$30 min^{-1}, blood pressure $<$90/$\geqslant$60 mmHg, age $>$65 years; PSI: Pneumonia Severity Index. Modified from [29].

large studies [59, 73]. With these limitations in mind, it is important to emphasise that management decisions primarily have to be driven by clinical criteria, and biomarkers should be evaluated for their additional but not exclusive contribution in guiding management decisions. This has been underlined by a recent interventional study, where the implementation of antibiotic escalation purely based on a PCT-guided protocol lead to antibiotic overtreatment and a worse outcome in ICU patients [74].

Biomarkers reflecting cardiovascular and stress response

Causes of clinical deterioration in CAP are heterogeneous and include mechanisms reflecting local and systemic inflammation, septic organ dysfunction, underlying or decompensating chronic diseases and stress response. To account for this heterogeneity, it has been emphasised that optimal risk prediction probably should incorporate not only markers reflecting inflammatory status, but also cardiovascular and stress mechanisms of disease progression. From a theoretical point of view it seems attractive to use objective assessment tools of current disease impact to the cardio-circulatory and endogenous stress systems to graduate disease severity and the state of these potential (de)compensating systems.

Accordingly, cardiovascular markers like N-terminal B-type natriuretic peptide (NT-proBNP) [75], proendothelin-1 (proET-1) [76–78], midregional proatrial natriuretic peptide (MR-proANP) [77–79], proarginin-vasopressin (copeptin) [78, 80–84] and midregional proadrenomedullin (MR-proADM) [77, 78, 85–91], coagulatory markers like D-dimer [92, 93] or thrombocytes [94] and markers reflecting stress response like cortisol [61, 95–99] and again copeptin have been repeatedly associated with prognosis in CAP.

The most convincing data accumulated from this evidence currently exists for the markers MR-proADM, copeptin and cortisol. Whereas MR-proADM is a potent vasodilator with immunomodulatory and bactericidal effects, cortisol reflects stress response and immunomodulatory regulation of inflammatory processes and the vasopressin precursor copeptin combines response to stress and fluid balance. Several large, non-interventional studies suggest that these markers improve risk prediction by clinical scores and inflammatory biomarkers. Published results for CAP including used end-points and predictive accuracies are summarised in tables 1–3.

The accuracy of MR-proADM to predict mid- and long-term mortality in CAP repeatedly was superior when compared to

TABLE 1 Studies evaluating midregional proadrenomedullin (MR-proADM) as a prognostic parameter in community-acquired pneumonia (CAP)

Study	Patients n	Design	End-point	MR-proADM cut-off nmol·L^{-1}	AUC	Comments on prognostic value of MR-proADM
Christ-Crain [85]	302	Prospective, CAP in ED	7-week mortality	1.8	0.76	Superior to CRP, PCT; improved PSI score
			ICU admission	Not given	0.65	
Huang [86]	1653	Prospective, hospitalised CAP	30-day mortality	1.3	0.76	Superior to PCT, but improved PSI score only in high risk patients
Kruger [77]	728	Prospective, in- and outpatients with CAP	28-day mortality	0.96	0.85	Superior to CRP, PCT, copeptin, proANP, CT-proET1; independent of CRB-65 score
			180-day mortality	0.96	0.79	
Schuetz [78] and Albrich [87]	925	Prospective, CAP in ED	Combined death, ICU admission, empyema within 30 days	0.75–1.5	0.72	Improved PSI score and CURB-65 score, proposal of new CURB65-A score to improve low-risk prediction
Guertler [88]	877	Prospective, hospitalised CAP after discharge	Mortality at 18 months after discharge	1.97		A new clinical score including MR-proADM was superior to the PSI score for long-term risk prediction
Bello [89]	228	Prospective, CAP in ED	Complications at 30 days	0.83	0.71	Improved PSI score and CURB-65 score for mortality, but not for complications
			30-day mortality	1.07	0.86	
			180-day mortality	Not given	0.80	
Suberviola [90]	49	Prospective, severe CAP in ICU	In-hospital mortality	4.86	0.72	Superior to CRP and PCT, in multivariate analysis only APACHE-II predictive
Renaud [91]	877	Prospective, CAP in ED	Combined 3-day mortality, vasopressor use or mechanical ventilation	1.8	0.73	Improved REA-ICU score
Kolditz [84]	51	Prospective, hospitalised CAP	Combined 7-day mortality/ICU admission	1.05	0.67	Inferior to copeptin for short-term outcome
			Clinical instability on day 4	Not given	0.61	

AUC: area under the curve; ED: emergency department; ICU: intensive care unit; CRP: C-reactive protein; PCT: procalcitonin; PSI: Pneumonia Severity Index; proANP: proatrial natriuretic peptide; CT-proET1: C-terminal proendothelin-1; C(U)RB-65: confusion, (urea>7 mmol·L^{-1}) respiratory rate $\geqslant$30 min^{-1}, blood pressure <90/$\geqslant$60 mmHg, age >65 years.

TABLE 2 Studies evaluating copeptin as a prognostic parameter in community-acquired pneumonia (CAP)

Study	Patients n	Design	End-point	Copeptin cut-off pmol·L^{-1}	AUC	Comments on prognostic value of copeptin
Muller [80]	373	Prospective, CAP in ED	6-week mortality	53	0.68	Independent of PSI score, superior to CRP, PCT
Kruger [81]	589	Prospective, in- and outpatients with CAP	28-day mortality	29	0.86	Independent of CRB-65 score, predicted shock or mechanical ventilation
Masia [82]	173	Prospective, in- and outpatients with CAP	28-day mortality	19	0.75	Independent of PSI score, predicted ICU admission/complications
Schuetz [78]	925	Prospective, CAP in ED	Combined death, ICU admission, empyema within 30 days	36	0.70	
Kruger [79]	1740	Prospective, in- and outpatients with CAP	28-day mortality	29	0.84	Superior to CRB-65, CRP, PCT
Kolditz [84]	51	Prospective, hospitalised CAP	Combined 7-day mortality/ICU admission	35	0.81	Superior to CRB-65 score, proADM, PCT; Improved 2007 ATS/IDSA minor criteria
			Clinical instability on day 4	25	0.74	

AUC: area under the curve; ED: emergency department; PSI: Pneumonia Severity Index; CRP: C-reactive protein; PCT: procalcitonin; CRB-65: confusion, respiratory rate $\geqslant$30 min^{-1}, blood pressure <90/$\geqslant$60 mmHg, age >65 years; ICU: intensive care unit; proADM: proadrenomedullin; ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America.

clinical scores or inflammatory and other cardiovascular biomarkers (table 1). One study compared MR-proADM to a large set of biomarkers including CRP, PCT, copeptin, proANP and C-terminal proET1 and found MR-proADM best for prediction of 28- and 180-day mortality [77]. Another group demonstrated its ability to identify patients at risk of poor long term outcome after hospital discharge with CAP [88]. Furthermore, the addition of MR-proADM significantly improved the CURB-65 score to predict a combined end-point of death and pneumonia complications [87]. From this evidence it can be concluded that MR-proADM represents a promising marker to stratify patients according to their mid- and long-term risk for death and complications during and after hospitalisation for CAP. Accordingly, it is currently evaluated as an adjunctive tool in combination with clinical criteria to guide hospital discharge decisions within a first interventional study [87]. Further large interventional trials implementing well-defined clinical discharge criteria in the control group are needed to prove the safety and additional benefit of such a biomarker-supplemented management decision strategy.

Prediction of mortality and complications after 28 or even 180 days might provide identification of low risk patients but it does not reflect an optimal strategy to guide early intensified

TABLE 3 Studies evaluating cortisol as a prognostic parameter in community-acquired pneumonia (CAP)

Study	Patients n	Design	End-point	Cortisol cut-off nmol·L^{-1}	AUC	Comments on prognostic value of cortisol
Christ-Crain [95]	251	Prospective, CAP in ED	7-week mortality	960	0.76	Independent of PSI score, superior to CRP, PCT
Gotoh [96]	64	Prospective, hospitalised CAP	Length of hospital stay	820	0.82	
Salluh [97]	72	Prospective, severe CAP on ICU	In-hospital mortality	709	0.77	Superior to APACHE-II, CURB-65, SOFA, D-dimer, CRP
Kolditz [61]	59	Prospective, hospitalised CAP	In-hospital mortality	734	0.83	Independent of PSI score and CRB-65 score, superior to CRP, PCT
			Clinical instability on day 4	571	0.83	
Remmelts [98]	270	Prospective, hospitalised CAP	Combined in-hospital mortality/ICU admission	657–994	0.63	Delta cortisol day 0–2 and 0–4 with superior prediction
Kolditz [99]	984	Prospective, hospitalised CAP	30-day mortality	795	0.70	Improved CRB-65 score, CURB-65 score and 2007 ATS/IDSA minor criteria
			Critical CAP$^{\#}$	795	0.71	

AUC: area under the curve; ED: emergency department; PSI: Pneumonia Severity Index; CRP: C-reactive protein; PCT: procalcitonin; ICU: intensive care unit; C(U)RB-65: confusion, (urea >7 mmol·L^{-1}) respiratory rate $\geqslant$30 min^{-1}, blood pressure <90/$\geqslant$60 mmHg, age >65 years; ATS: American Thoracic Society; IDSA: Infectious Diseases Society of America. $^{\#}$: critical CAP: combined death occurring during antibiotic treatment, mechanical ventilation, catecholamine treatment or ICU admission.

management for patients with clinical deterioration or persistent instability. In a recent large study re-evaluating patients from a prospective trial, MR-proADM identified patients dying or in need of mechanical ventilation/vasopressors within the first 3 days with a sensitivity of 61% and a specificity of 77% and significantly improved prediction by one clinical high risk score (REA-ICU) [91]. However, data on prediction of other short term outcomes like ICU admission [85] or clinical deterioration after 7 days and persistent clinical instability [84] by MR-proADM have been less convincing, and one small study showed the superior value of copeptin in that setting [84]. More studies including a comparison to the 2007 ATS/IDSA minor criteria and other proposed biomarkers, like copeptin and cortisol, for short term prediction are needed.

In principle, markers of stress like cortisol and copeptin might provide another option for high risk evaluation. Physiologically, acute stress like severe illness leads to an activation of the hypothalamic–pituitary–adrenal axis which protects the organism against excessive inflammatory responses [100]. Studies have shown an increase of cortisol that parallels the severity of infection and prognosis of patients with severe sepsis and septic shock [101]. Copeptin might mirror the individual stress level even more subtly and was found to be associated with disease severity and to discriminate patients with unfavourable outcomes for a variety of conditions [102]. In CAP, copeptin has repeatedly been shown to accurately predict mortality independently of clinical risk prediction by various scores (table 2). The largest study included 1,740 patients and showed the superior accuracy of copeptin for 28-day mortality when compared to the CRB-65 score and the inflammatory biomarkers CRP and PCT. In a recent smaller study, copeptin additionally performed superiorly to PCT and MR-proADM in prediction of clinical instability after 72 h or early deterioration including death or ICU admission within 1 week and improved clinical prediction by the 2007 minor criteria [84].

Also for cortisol all published studies in CAP demonstrated an association with prognosis independent of clinical risk stratification (table 3). High cortisol levels also predict short term outcomes like persistent clinical instability after 72 h [61] and early disease deterioration defined as death during antibiotic treatment, ICU admission, mechanical ventilation or vasopressor use [99]. For the latter composite end-point, in a study

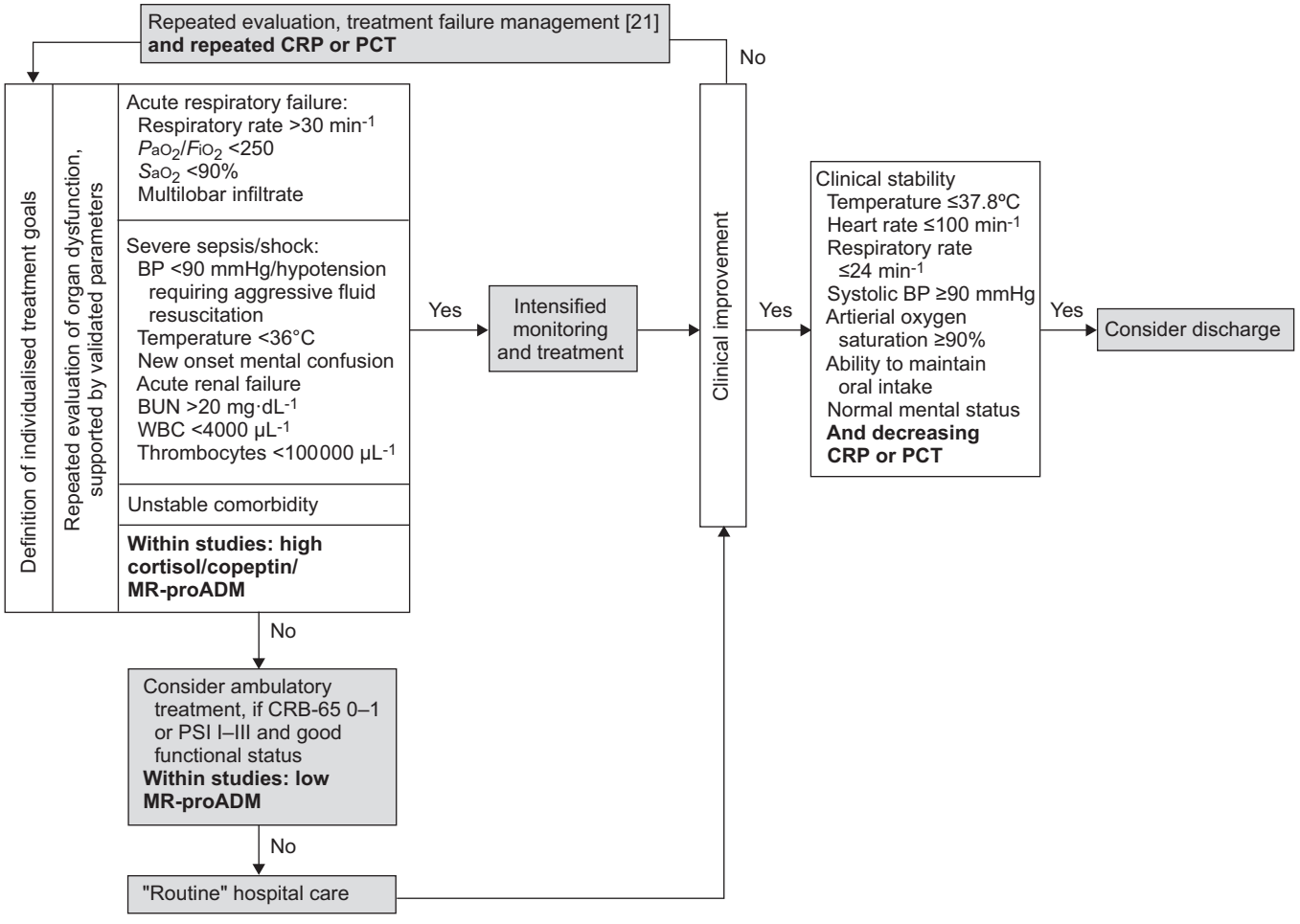

FIGURE 2. Proposed management-based risk stratification algorithm including potential indications for biomarkers in hospitalised community-acquired pneumonia (highlighted in bold type). CRP: C-reactive protein; PCT: procalcitonin; P_{aO_2}: arterial oxygen tension; F_{iO_2}: inspiratory oxygen fraction; S_{aO_2}: arterial oxygen saturation; BP: blood pressure; BUN: blood urea nitrogen; WBC: white blood cell; MR-proADM: midregional proadrenomedullin; CRB-65: confusion, respiratory rate $\geqslant$30 min^{-1}, blood pressure $<$90/$\geqslant$60 mmHg, age $>$65 years; PSI: Pneumonia Severity Index. Modified from [29].

including 984 hospitalised CAP patients, cortisol significantly improved the predictive properties of the CRB-65 score and the 2007 minor criteria and was superior to inflammatory biomarkers such as CRP and PCT. Measurement of routinely available total cortisol was at least as good as the more complicated measurement of free cortisol [95]. An unresolved question remains the impact of the blood sampling time point, as cortisol exhibits diurnal concentration changes; however, during infectious diseases this circadian pattern is often lost [103]. Furthermore, its prognostic value certainly would be limited in patients with steroid co-medication.

Strategies to implement biomarkers for risk stratification of CAP in hospital

Taking these data together, it could be hypothesised that different biomarkers might be used as complementary tools to predict different management decisions in CAP.

The inflammatory biomarkers PCT or CRP have been recommended to validate treatment response in CAP from repeated measurements, with decreasing levels indicating adequate treatment response while persistently elevated or even rising concentrations after 3–4 days of antibiotic treatment together with clinical nonresponse should prompt the evaluation of infectious treatment failure. Very low PCT levels in a patient achieving clinical stability justify the consideration to stop antibiotics.

MR-proADM might be a tool to predict low risk for mortality or complications in patients with a low biomarker concentration. The addition of this marker to clinical scores like the CURB-65 in the future might allow earlier hospital discharge or ambulatory treatment and possibly tailored follow-up concepts, if the first promising study data [87] are confirmed by further trials.

Most work remains to be done for better identification of patients at risk of early clinical deterioration. Here the stress dependent markers copeptin and cortisol are promising candidates for better prognostication, but further comparison to MR-proADM and an optimal combination of minor criteria reflecting respiratory failure and septic organ dysfunction remains to be performed. Also the evaluation and significance of repeated measurements of cardiovascular and stress-dependent biomarkers in this setting are subject to study, as nearly no data exist.

Currently, all these markers are limited by absent rapid or even on-site availability and high costs. Furthermore, any additional benefit of such biomarker complemented strategies over control groups guided by clinical management decision criteria and the optimal combination of biomarkers and clinical scores as well as cut-off points for different clinical settings still have to be confirmed by large interventional trials. Evolving study indications for biomarkers within such concepts are proposed in figure 2. Relevant interventions would include biomarker-guided application of intensified monitoring and management, as well as optimised discharge strategies, and probably further, less defined interventions such as follow-up and secondary prevention measures, or yet to be identified adjuvant treatment options to improve CAP outcome. In the future, such a concept might lead to an individualised stratification and management approach of CAP analogous to the recent progress made in oncology. A first step towards such a scenario is underway in a large German multicentre study, the ''Pneumonia Research Network on Genetic Resistance and Susceptibility for the Evolution of Severe Sepsis (PROGRESS)'' trial, which is evaluating genomic, transcriptomic and proteomic markers of pneumonia progression to better understand the pathophysiology of CAP progression and derive potential new diagnostic and therapeutic tools to improve the prognosis of this disease.

SUMMARY

In patients hospitalised for CAP, a management-based risk stratification approach to predict benefit from early intensified monitoring and treatment strategies is advocated. The central tool to rapidly identify patients with severe disease or at risk of deterioration constitutes the early and repeated evaluation of clinical markers for respiratory failure, sepsis-related organ dysfunction or decompensating comorbidity, which should prompt intensified management strategies including close monitoring of organ functions, adequate sepsis management and early intravenous antibiotic therapy. In elderly and severely disabled patients this has to be complemented by the repeated individual definition of treatment goals. Ambulatory management could be considered in patients without features of severe CAP and presenting with a low mortality risk according to established risk scores, which should be supplemented by functional assessment in comorbid and elderly patients. Inflammatory biomarkers, such as CRP and PCT, supplement clinical criteria for monitoring treatment response by follow-up measurements. New cardiovascular or stress-related biomarkers like copeptin, MR-proADM and cortisol represent promising tools for further individualised risk stratification by possibly identifying and validating clinical prognostication of low and high risk patients in the future. A major task in CAP research will be the evaluation of their additional value in large interventional trials with control groups incorporating strict management guidance by clinical criteria.

STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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