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Chapter 5

Clinical Diagnosis and Severity Assessment in Immunocompetent Adult Patients with Community-Acquired Pneumonia

Fernando Peñafiel Saldías, Orlando Díaz Patiño and Pablo Aguilera Fuenzalida

Additional information is available at the end of the chapter

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1. Introduction

Community-acquired pneumonia (CAP) is a common and potentially serious illness [1]. It is defined as an acute infection of the pulmonary parenchyma, occurring outside the hospital, with clinical symptoms accompanied by the presence of pulmonary infiltrates on chest radiograph. With a prevalence estimated at nearly five million cases annually in United States, emergency physicians and general practitioners diagnose and treat CAP on a regular basis [2]; nearly one third of CAP patients arrived by emergency medical services, and half eventually were admitted [3].

Community-acquired pneumonia is the major infection-related cause of death in developed countries [4] and ranks as the third leading cause of all deaths in the world after ischaemic heart disease and cerebrovascular disease [5]. Mortality from CAP ranges from less than 1% in patients without risk factors treated as outpatients to 5-15% in hospital admitted patients to greater than 20-30% in intensive care unit patients [6]. Pneumonia increases in frequency with advancing age, and with associated comorbid medical illnesses (specially cardiovascular, metabolic, neoplastic, respiratory and neurological disease) there is a significant increase in morbidity and mortality [7].

Acute respiratory infections are a prevalent problem, affecting children, adults and the elderly, the main pathogens involved are respiratory viruses (*rhinovirus*, *influenza*, *parainfluenza*, *adenovirus*, *respiratory syncytial virus*, *metapneumovirus*) and secondly bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Le-*

gionella pneumophila, gram negative bacilli, and others), they are an important cause of school and labor absenteeism, especially during the cold seasons [1,8].

The clinical manifestations associated with respiratory infections, such as malaise, fever, chills, myalgia, sore throat, runny nose, cough, sputum production, chest pain and dyspnea, can occur in different clinical contexts that differ in etiology, pathogenesis, clinical course, treatment and prognosis [8,9]. Thus, the clinical picture may correspond to a mild self-limited upper respiratory tract infection to a severe lung parenchyma infection that requires specific treatment, as in cases of pneumonia and tuberculosis [10].

The reference standard to diagnose CAP is a new infiltrate on chest radiograph in the presence of recently acquired respiratory signs and symptoms [11]. These include cough, increased sputum production, dyspnea, fever and abnormal auscultatory findings [12]. Unfortunately, clinical findings do not reliably predict radiologically confirmed pneumonia [13]. Especially elderly people often present with atypical symptoms and without fever [14]. However physicians, especially in primary care, may not perform chest radiography and rely on the patient's history and physical examination [15].

The initial management of patients suspected of having community-acquired pneumonia is challenging because of the broad range of clinical presentations, comprehensive differential diagnosis, potential life-threatening nature of the illness, the need for antibiotic treatment and associated high costs of care [16,17]. The initial testing strategies should accurately establish a diagnosis and prognosis in order to determine the optimal treatment strategy, such as decisions about the site of care (ambulatory or in-hospital), extension of microbiology and laboratory assessments and antimicrobial recommendations.

The diagnosis is important to implement specific management measures, such as empirical antibiotic treatment and prevention of complications, and the prognosis is important in determining the site of care (ambulatory, general ward or intensive care facilities) and define treatment strategies to be implemented in each particular case [16,17]. This paper reviews the sensitivity, specificity and accuracy of the history, physical examination, and laboratory findings, individually and in combination, in diagnosing community-acquired pneumonia and predicting short-term risk for complications and death from the infection.

2. Diagnosis of pneumonia

Primary-care physicians usually rely on patient history, and signs and symptoms to diagnose or exclude pneumonia [10]. However, most signs and symptoms traditionally associated with pneumonia (e.g. malaise, fever, cough, sputum production and dyspnea) are not predictive of pneumonia in general practice [18]. Chest radiography (CXR) is the most frequently performed diagnostic investigation requested by general practitioners in the ambulatory setting (primary care and emergency department) [19]. The history and physical examination cannot provide a high level of certainty in the diagnosis of community-acquired pneumonia, but the absence of vital sign abnormalities and abnormal chest examination findings substantially reduces the probability of the infection [20].

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The differential diagnosis of CAP includes several noninfectious causes, including pulmonary embolism, malignancy and congestive heart failure, among others [21]. The presence of a non-infectious differential diagnosis is usually suspected only after failure of antibiotic therapy, with the ensuing risks related to untreated, potentially life threatening non-bacterial disease [22]. Conversely, a delay of antibiotic treatment of more than 4-8 hours after hospital admission is associated with increased mortality [23]. Hence, both a rapid diagnosis of CAP and an accurate differentiation from viral respiratory illnesses and non-infectious causes has important therapeutic and prognostic implications [24].

2.1. Medical history

In the initial diagnosis of the patient who complains of acute respiratory symptoms or fever is necessary to establish the correct diagnosis based on clinical manifestations (history and physical examination) and laboratory tests (e.g., blood cell count, chest radiograph, C-reactive protein, procalcitonin, etc.) that are available in ambulatory practice. This requires knowledge of the epidemiology of respiratory infections in the geographic area, together with the sensitivity and specificity of the clinical history and physical signs abnormalities in diagnosing pneumonia [18].

The primary care physicians are often being confronted with patients presenting with nonspecific constitutional symptoms (e.g., malaise, fever, chills, myalgia, headache, anorexia) or respiratory symptoms (e.g., cough, sputum production, chest pain, dyspnea), and must to establish a presumptive diagnosis based on their knowledge of the local epidemiology of acute respiratory infections and the main findings on clinical history and physical examination. Unfortunately clinical manifestations at presentation distinguish poorly between community-acquired pneumonia and other causes of respiratory illnesses (view differential diagnosis on Table 1). The likelihood ratio (LR) for these findings ranges between 1 and 3, which is not useful to confirm the diagnosis of pneumonia (Table 2) [25-29]. In general, the presence or absence of preexisting diseases, respiratory or constitutional symptoms does not have a substantial effect on the probability of pneumonia.

Five studies based in emergency departments have assessed the characteristics of individual items in the clinical history in the diagnosis of community-acquired pneumonia in adult patients [25-29]. In each of these studies, the reference standard for the diagnosis of pneumonia was a new infiltrate on a chest radiograph with or without clinical monitoring during one month. Table 2 summarizes the likelihood ratios associated to main clinical findings obtained from the history, including general manifestations, preexisting diseases and respiratory symptoms. Differences on results reflect, in part, variation in the selection criteria for each study. For example, chest radiographs were obtained for all patients presenting with acute cough in one study [25], while the other studies obtained chest radiographs only when the emergency physician previously determined a need for them, often to confirm or exclude a suspected diagnosis of pneumonia [26-29]. The latter approach provides a more highly selected population of patients with acute respiratory complaints that may change the measured test characteristics of individual clinical findings. Thus, the prevalence of pneumonia in study populations ranged from as low as 2.6% [25] to as high as 38.3% [26].

There are no individual items from the clinical history whose presence or absence would reduce or increase the odds of disease sufficiently to exclude or confirm the diagnosis of pneumonia without obtain a chest radiograph [18,20]. Though the presence of fever, comorbidities, history of dementia or immunosuppression may be helpful, they are not confirmatory, particularly given the typically low prevalence of pneumonia in the primary health services (2-5%) [1-3]. For example, when the estimated prevalence of pneumonia in primary care services is around 2-3%, the presence of subjective fever (LR^+=1.3-2.1) had a positive predictive value (PPV) ranging between 2.6% and 6.2% [25,28,29], reflecting the low prevalence of pneumonia in the ambulatory care setting. Meanwhile the presence of odynophagia or rhinorrhea (LR^+=0.5-0.7) in the same context had a positive predictive value ranging between 1.0% and 2.1% [25,29].

Common causes
Upper respiratory tract infections
Acute bronchitis and bronchiolitis
Influenza - Flu
Exacerbations of asthma and COPD
Pulmonary tuberculosis
Congestive heart failure
Pulmonary embolism
Primary neoplastic disease and metastatic lung disease
Pulmonary atelectasis
Rare causes
Hypersensitivity pneumonitis
Drug-induced lung diseases
Radiation-induced lung disease
Carcinomatous lymphangiosis
Collagen vascular disease: Systemic lupus erythematosus, rheumatoid arthritis, Wegener granulomatosis, Churg-Strauss syndrome.
Sarcoidosis
Eosinophilic pneumonia
Cryptogenic organizing pneumonia (COP)

Table 1. Differential diagnosis of adult patients with community-acquired pneumonia in the primary health care system.

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Variables	Diehr et al	Gennis et al	Singal et al	Heckerling et al	Saldías et al
Cough	---	NS	1.8	NS	NS
Sputum production	1.3	NS	—	NS	1.2
Dyspnea	—	1.4	NS	NS	NS
Fever	2.1	NS	—	1.7	1.3
Chills	1.6	1.3	—	1.7	1.4
Myalgias	1.3	NS	—	—	NS
Odynophagia	0.7	NS	—	—	0.5
Rhinorrhea	0.7	NS	—	—	0.5
HR > 100/min	NS	1.6	NS	2.3	1.4
RR > 20/min	—	1.2	—	—	1.3
T > 37.8 °C	4.4	1.4	2.4	2.4	2.2
Normal vital signs	—	0.2	—	—	0.3
Dullness to percussion	NS	2.2	—	4.3	3.8
Ronchi	NS	1.5	—	1.4	NS
Bronchophony	—	—	—	3.5	9.5
Crackles	2.7	1.6	1.7	2.6	2.0
Normal lung exam	—	0.5	—	—	0.4

LR^+: positive likelihood ratio for pneumonia (sensitivity/1-specificity). HR: heart rate, RR: respiratory rate, T: temperature. Normal vital signs: heart rate < 100 beats/min, respiratory rate < 20 breaths/min and temperature < 37.8 °C. NS: result not significant.

Table 2. Predictive value of clinical manifestations (symptoms and signs) associated with the diagnosis of community-acquired pneumonia in adults (LR^+)[25-29].

2.2. Physical examination

The effect of vital sign abnormalities (e.g., tachycardia, tachypnea, fever) or pulmonary exam findings (e.g., decreased breath sound, bronchophony, dullness on percussion, rhonchus, crackles) on the probability of pneumonia depends on the cut-off value to define an abnormal result. For example, a respiratory rate greater than 20 breaths/min had a LR^+ of 1.2 to 1.3 [26,29], whereas a respiratory rate greater than 25 breaths/min had a LR^+ of 1.5 to 3.4 [25,28] (Table 2). When the estimated prevalence of pneumonia in primary care services is around 2-3%, the presence of crackles on pulmonary examination (LR^+=1.6-2.7) had a positive predictive value ranging between 3.2% and 8.1% [25-29]. In contrast, two studies have

shown that having a normal heart rate (below 100 beats/min) without fever (temperature < 37.8 °C) and tachypnea (respiratory rate < 20 breaths/min) reduces significantly the probability of community-acquired pneumonia (LR^- = 0.18), thereby reducing the pretest odds of pneumonia by more than fivefold [26,29].

In the Chilean study [29], the major clinical predictors of pneumonia were fever (≥38 °C), tachypnea (≥20 breaths/min), mental confusion, orthopnea, cyanosis, dullness on percussion, bronchophony, crackles and oxygen saturation less than 90% breathing room air (LR^+: 2.0 to 9.5). In contrast, sore throat, runny nose, normal vital signs and lung auscultation without clinical abnormalities were less frequent in patients with final diagnosis of pneumonia (LR^+: 0.3-0.5). Unlike other studies, Saldías et al. examined some combinations of symptoms and signs showing that significantly increases the pretest probability. The combination of clinical variables increase the probability of pneumonia, such as the presence of fever and tachypnea associated with orthopnea, dullness on percussion, crackles or oxygen saturation below 90% (LR^+: 4.9 to 14.7). At the same time, the probability of pneumonia is very low in patients presenting with respiratory symptoms and normal vital signs and lung auscultation (LR^+: 0.1).

In summary, individual symptoms and signs at presentation distinguish poorly between community-acquired pneumonia and other causes of respiratory illnesses [13,18,20]. Thus, in 10-20% of ambulatory patients with a suspected lower respiratory tract infection CXR is requested [19]. CXR can diagnose pneumonia in cases with the presence of pulmonary infiltrates and differentiate pneumonia from other conditions that may present with similar symptoms (e.g., acute bronchitis or influenza) [2,3]. In addition, the results may suggest specific aetiologies (e.g., lung abscess, TB infection), identify coexisting conditions (e.g., bronchial obstruction, pleural effusion, neoplasms) and evaluate the severity of illness (e.g., multilobar or bilateral infiltrates, rapid progression of infiltrates, pleural effusion) [6,8]. Although chest radiography is frequently used for diagnosing pneumonia, little is known about the influence of CXR on the probability estimation of pneumonia by general practitioners and on change in patient management [18,20]. Chest radiography is considered the gold standard for pneumonia diagnosis; however, we do not know its sensitivity and specificity, and we have limited data on the clinical implications of false-positive and false-negative results [18]. In the absence of empirical evidence, the decision to order a chest radiograph needs to rely on expert opinion in seeking strategies to optimize the balance between harms and benefits [16,17].

2.3. Clinical judgment and decision guidelines

Although physicians often planning the diagnostic and laboratory exams considering the prevalence of the disease and its estimate of the probability in the population being evaluated, the diagnostic threshold of professionals varies considerably even when faced with similar clinical situations [30,31]. As the predictive value of individual signs and symptoms to the diagnosis of pneumonia is relatively low, to resolve this problem, it has been designed some predictive rules or decision guidelines incorporating the presence or absence of specific clinical findings intended to guide clinicians in the management of patients with similar

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clinical features [18,20]. In the literature we find several protocols or decision rules that are designed specifically to help primary care physicians in the assessment of adult patients with lower respiratory tract infections (Table 3) [25-29,32-34]. Thus, in the clinical practice guidelines is often recommended to primary care physicians request of chest radiography in patients presenting respiratory symptoms based on some of these decision rules, in order to optimize patient`s care [16,17,35].

Clinical prediction rules for pneumonia diagnosis in adults	
Diehr et al.	**Score**
Rhinorrhea	-2 points
Sore throat	-1 point
Night sweats	1 point
Mialgyas	1 point
Sputum production	1 point
RR > 25 breaths/min	2 points
Tº ≥ 37.8 °C or 100 °F	2 points
Heckerling et al. Each variable scores a point.	
Heart rate > 100 beats/min	
Temperature > 37.8 °C or 100 °F	
Decreased breath sounds	
Crackles	
Absence of asthma	
Gennis et al. If one or more variables are present requesting chest radiograph.	
Heart rate > 100 beats/min	
Respiratory rate > 20 breaths/min	
Temperature > 37.8 °C	
Singal et al. Estimating the probability of pneumonia.	
Probability = $1/(1 + e^{-Y})$	
Where Y: -3.095 + 1.214 x Cough + 1.007 x Fever + 0.823 x Crackles	
Each variable = 1 if present	
Melbye et al. A logistic regression model is proposed for the diagnosis of pneumonia.	
Y= + 4.7 for fever (reported by patient) with duration of illness of one week or more; – 4.5 for coryza; – 2.1 for sore throat; + 5.0 for dyspnea; + 8.2 for lateral chest pain; + 0.9 for crackles.	
González Ortiz et al. A logistic regression model is proposed for the diagnosis of pneumonia.	
Y= –1.87; + 1.3 for pathologic auscultation; + 1.64 for neutrophilia; + 1.70 for pleural pain; + 1.21 for dyspnea.	
Hopstaken et al. A logistic regression model is proposed for the diagnosis of pneumonia.	
Y= –4.15; + 0.91 for dry cough; + 1.01 for diarrhea; + 0.64 for temperature ≥ 38 °C; + 2.78 for C-reactive protein ≥ 20 mg/L.	

Table 3. Clinical predictive rules for pneumonia diagnosed by chest radiography in the ambulatory care setting[25-28,32-34].

Prediction rules based on clinical information have been developed to support the diagnosis of pneumonia and help limit the use of expensive diagnostic tests [36,37]. However, these prediction rules need to be validated in the primary care setting. Several clinical prediction rules have been developed to predict pneumonia in adults but they were not superior to clinical judgment to predict pneumonia in the ambulatory setting [20,36,37]. In summary, combination of history and physical examination findings at presentation only moderately increase the probability of pneumonia. Thus, the clinical guidelines endorse the need for chest radiography to confirm all diagnoses of community-acquired pneumonia [16,17,35].

In two predictive rules, described by Diehr et al. [25] and Heckerling et al. [28], the pretest probability of pneumonia is amended according to the presence or absence of certain specific symptoms. While other rule, described by Singal et al. [27], was designed using a logistic regression analysis and provides a probability of pneumonia ranging from 4% (absence of symptoms and signs) to 49% (presence of cough, fever and crackles). On the other hand, Gennis et al. [26] suggested applying chest radiograph in patients with suspected of CAP and alteration in any vital signs (heart rate above 100 beats/min, respiratory rate above 20 breaths/min or temperature higher than 37.8 °C). Melbye et al [32], González Ortiz et al. [33] and Hospstaken et al. [34] proposed a logistic regression model for diagnosis of pneumonia based on clinical and laboratory variables.

Two prospective studies have examined the predictive value of clinical judgment and four clinical predictive rules in the diagnosis of community-acquired pneumonia in adults [37,38]. Emerman et al. [37] compared physician judgment in the use of chest radiographs for diagnosing pneumonia with decision rules developed by Diehr, Singal, Heckerling, and Gennis in the emergency department and medical outpatient clinic of a major urban teaching hospital. The prevalence of pneumonia in this study was 7%, they found that clinical judgment allowed to reduce the application of unnecessary chest radiographs better than the four predictive rules (LR^-= 0.25, 95%CI: 0.09 to 0.61) while clinical judgment allowed to increase the likelihood of pneumonia to around 13% (LR^+ = 2.0, 95%CI: 1.5 to 2.4), which would have led to demand many unnecessary radiographic examinations. Among the four examined predictive rules, the application of x-ray only to patients with abnormal vital signs recommended by Gennis et al. [26] had higher diagnostic yield with a LR^+ of 2.6 (95%CI: 1.6 to 3.7), which would have reduced by 40% the application of unnecessary radiographic examinations but would not have detected 38% of pneumonias confirmed by radiology (LR^- = 0.50, 95%CI: 0.27 to 0.78 compared with LR^- = 0.18 of the original study of Gennis et al.) [34]. The sensitivity of physician judgment (86%) exceeded that of all four decision rules (62-76%), but the higher specificity and accuracy of two of the decision rules [26,28] suggested that they may have a role in patient evaluation.

Saldías et al. [29,38] have shown that clinical diagnosis of pneumonia made by physicians in the emergency department had better sensitivity (range: 75-83%) than specificity (range: 47-83%) and better negative predictive value (NPV) (range: 85-91%) than PPV (range: 36-70%) (Table 4). In fact, a less experienced emergency physician had lower PPV and specificity compared to internal medicine and respiratory disease physicians (Table 5). The chance to change the initial diagnosis of pneumonia or positive likelihood ratio of three

emergency physicians ranged between 1.5 and 4.8. Similar findings were described by Wipf et al. [39], who determined the accuracy of various physical examination maneuvers in diagnosing pneumonia and compared the interobserver reliability of the maneuvers among three examiners. The authors concluded that the clinical findings investigated in chest examination does not confirm or exclude with certainty the diagnosis of pneumonia, and the degree of interobserver agreement was highly variable for different physical examination findings.

Variables	Clinical diagnosis	Diehr et al	Singal et al	Heckerling et al	Gennis et al
	%, (95% CI)	%, (95% CI)	%, (95% CI)	%, (95% CI)	%, (95% CI)
Sensitivity	0.79 (0.72-0.84)	0.77 (0.70-0.83)	0.76 (0.69-0.82)	0.84 (0.78-0.90)	0.92 (0.87-0.96)
Specificity	0.66 (0.63-0.69)	0.64 (0.61-0.68)	0.54 (0.51-0.58)	0.41*(0.38-0.44)	0.31*(0.28-0.33)
PPV	0.55 (0.50-0.59)	0.54 (0.49-0.58)	0.46 (0.42-0.50)	0.43 (0.39-0,45)	0.42 (0.39-0.44)
NPV	0.85 (0.81-0.89)	0.84 (0.79-0.88)	0.81 (0.76-0.86)	0.84 (0.77-0.89)	0.88 (0.80-0.94)
Accuracy	0.70 (0.65-0.75)	0.69 (0.67-0.74)	0.62 (0.57-0.67)	0.56*(0.50-0.62)	0.53*(0.47-0.59)
LR^+	2.3 (1.9-2.7)	2.2 (1.8-2.6)	1.7 (1.4-1.9)	1.4* (1.2-1.6)	1.4* (1.2-1.4)

Note: 95% CI: confidence interval of 95%, PPV: positive predictive value; NPV: negative predictive value. * p <0.05 compared with clinical judgment.

Table 4. Predictive value of clinical judgment and four predictive rules in the diagnosis of community-acquired pneumonia in adults[38].

Clinical diagnosis	Sensitivity	Specificity	PPV	NPV	LR^+
Physician A	**83%**	**83%**	**70%**	**91%**	**4.8**
Physician B	**75%**	**73%**	**56%**	**86%**	**2.8**
Physician C	**77%**	**47%**	**36%**	**85%**	**1.5**
Average	**79%**	**66%**	**55%**	**85%**	**2.3**

Note: Physicians A and B were specialists in internal medicine and respiratory disease over five years of professional practice. Physician C was an emergency medicine specialist with less than three years of clinical practice.

Table 5. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive likelihood ratio (LR^+) for clinical diagnosis of community-acquired pneumonia[29].

Lieberman et al. [40] evaluated the reliability of physicians' judgement relating to the presence of pneumonia in adult patients with acute respiratory symptoms by clinical assessment alone compared with chest X-ray. Physicians' judgements of pneumonia had a sensitivity of 74% (95% CI 49-90%), a specificity of 84% (95% CI 78-88%), a NPV of 97% (95% CI 94-99%)

and a PPV of only 27% (95% CI 16-42%). They concluded that the ability of physicians to negate radiologically confirmed pneumonia by clinical assessment in febrile adult respiratory tract infection patients was good, but that their ability to successfully predict this condition was poor.

In other study developed in two emergency departments from Madrid, Spain; Gonzalez et al. [33] showed that the clinical judgment had low sensitivity for the diagnosis of pneumonia (45%) with a moderate PPV (80%). The sensitivity and specificity of clinical diagnosis of pneumonia established by emergency medicine physicians were similar or slightly higher compared with the four clinical predictive rules described in the literature [37,38]. The area under the curve (AUC) of clinical judgment and the clinical decision rule described by Diehr et al. for diagnosis of pneumonia were similar (AUC = 0.79 and 0.75, respectively), and both were higher than those described by Heckerling (AUC = 0.70), Singal (AUC = 0.70) and Gennis et al. (AUC = 0.67) [38].

In summary, the clinical findings (history and physical examination) have only moderate sensitivity and specificity for diagnosis of pneumonia in immunocompetent adult patients presenting with fever or respiratory symptoms in the ambulatory care setting (Table 6). None of the decision rules described in the literature have been superior to clinical judgment in the diagnosis of pneumonia, yet no studies have examined its real contribution in the evaluation and management of patients presenting with respiratory symptoms or fever in the primary care services.

Clinical diagnosis	Sensitivity	Specificity	PPV	NPV	LR^+
González et al.	45%	93%	80%	74%	6.6
Wipf et al.	47-69%	58-75%	48-64%	57-72%	1.1-2.0
Emerman et al.	86%	58%	14%	98%	2.0
Lieberman et al.	49-90%	78-88%	16-42%	94-99%	____
Saldías et al.	75-83%	47-83%	36-70%	85-91%	1.5-4.8

Note: PPV: positive predictive value, NPV: negative predictive value, LR: likelihood ratio.

Table 6. Predictive value of clinical judgment in diagnosing community-acquired pneumonia in adults[29,37,39-41].

2.4. Biomarkers and lower respiratory tract infection diagnosis

Numerous non-infectious processes can produce respiratory symptoms and new pulmonary infiltrates with systemic inflammatory signs and symptoms that can be easily confused with bacterial pneumonia (Table 1). Typically, Gram stains of respiratory secretions are often unavailable or are difficult to evaluate, and microbiological culture reports take at least 24 to 48

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hours. A negative sputum or blood culture in a patient suspected of having community-acquired pneumonia does not rule out the possibility of a severe lower respiratory tract infection [41]. Given these areas of uncertainty in clinical decision-making, a concerted effort has been undertaken to develop reliable and practical biomarkers for the diagnosis, risk prediction and management of CAP. To be helpful in routine clinical practice, a biomarker should provide additional actionable information – not already available by standard methods – that accomplishes at least one or more of the following: a) Assists in establishing a rapid and reliable diagnosis; b) Provides an indication of prognosis; c) Selects those patients most likely to benefit from a specific intervention; d) Reflects the efficacy or lack of efficacy of specific interventions.

The usefulness of biomarkers for diagnosing lower respiratory tract infections (LRTI), and identifying particular disease entities amongst LRTIs (e.g., acute bronchitis, influenza, COPD exacerbation, pneumonia) is still a matter of controversy.

2.4.1. C- reactive protein

Some observational studies indicate that C-reactive protein (CRP) may have some role in identifying patients with community-acquired pneumonia. Almirall et al. found significantly higher CRP values in adult patients with confirmed CAP compared to healthy controls and suspected CAP [42]. Flanders et al. evaluated CRP as a possible tool in the differential diagnosis of 168 adults with acute cough less than three weeks [43]. CRP levels correlated with the presence of pneumonia but not with its severity. A serum CRP level over 40 mg/L had a sensitivity of 70% and specificity of 90% to identify pneumonia. Holm et al. confirmed the low sensitivity (73%) and specificity (65%) of serum CRP in the differential diagnosis of LRTIs [44]. The authors concluded that only very high CRP levels (>100 mg/L) can be used as indicator for the presence of CAP. Accordingly, Stolz et al. showed that the specificity of CRP at the cut-off value of 100 mg/L to predict radiological confirmed pneumonia reaches 91.2% [45].

Falk et al. [46] assessed the diagnostic value of CRP in primary care and emergency departments in terms of ruling in or ruling out CAP. Eight studies incorporating 2,194 patients were included. The median prevalence of CAP was 14.6% (range 5%-89%). At a CRP cut-point of less than 20 mg/L, the pooled positive LR^+ was 2.1 (95%CI 1.8-2.4] and the pooled negative LR^- was 0.33 (95% CI 0.25-0.43). In conclusion, CRP may be of value in ruling out a diagnosis of CAP in situations where pneumonia probability exceeds 10%, typically in emergency departments. However, in primary care services, additional diagnostic testing with CRP is unlikely to alter the probability of CAP sufficiently to change subsequent management decisions such as antibiotic prescribing or referral to hospital.

2.4.2. Procalcitonin

Procalcitonin (PCT) is a 116 amino acid protein, precursor of calcitonin, which is physiologically produced by the C-cells of the thyroid after intracellular processing of the prohormone. The half-life of PCT is around 20-24 h and the plasma concentration in healthy individuals is

typically below 0.1 μg/L. In some studies procalcitonin does not appear to be a significant marker for CAP [47,48]. However, a more recent evaluation of the role of highly sensitive CRP and PCT measurements showed a better discriminatory value of these biomarkers compared to clinical signs [49]. The diagnostic accuracy of clinical signs and symptoms and a range of laboratory markers were assessed in 545 patients with suspected lower respiratory tract infection admitted to the emergency department. The area under the curve of a clinical model including fever, cough, sputum production, abnormal chest auscultation and dyspnea was 0.79 (95%CI, 0.75-0.83). Combining the values for procalcitonin and highly sensitive C-reactive protein together increased the AUC to 0.92 (95%CI, 0.89-0.94), which was significantly better than the AUC for PCT, CRP and clinical signs and symptoms alone. The contribution to diagnostic reliability made by PCT was substantially greater than that made by CRP, which in turn performed better than the total leukocyte count. Clinical criteria such as sputum production and physical examination with chest auscultation were poor predictors for the diagnosis of CAP. To predict bacteremia, PCT also had a higher AUC (0.85, 95%CI 0.80-0.91) as compared to CRP (0.71, 95%CI 0.62-0.80; p =0.01), leukocyte count (0.68, 95%CI 0.59-0.77; p = 0.002) and elevated body temperature (0.46, 95%CI 0.37-0.56; p < 0.001). The added value of the PCT biomarker as a clinical decision-making tool has been evidenced in several studies involving PCT measurement [50-57].

Circulating levels of the precursor hormone PCT, derived primarily from nonthyroidal tissues, can rise several thousand times above normal in various inflammatory conditions, but most notably in bacterial infection [54]. In differentiating bacterial infection from non-infective causes of inflammation in hospitalized patients, a meta-analysis concluded that PCT was both more sensitive (85% vs. 78%) and more specific (83% vs. 60%) compared with CRP. PCT was also more sensitive (92% vs. 86%) in differentiating between a bacterial etiology and a viral etiology [55].

PCT and ventilator-associated pneumonia: The utility of PCT levels to improve the early diagnosis of ventilator-associated pneumonia (VAP) has been evaluated in different studies. Due to the use of dissimilar thresholds the results were not consistent [56-58]. Ramirez et al. report a cohort study with sequential measurement of PCT and CRP in well characterized patients with VAP [59]. The results of this study showed that PCT and CRP plasma levels were statistically higher in patients with confirmed VAP, PCT being the more accurate marker. The combination of the simplified clinical pulmonary infection score (CPIS) and serum PCT was able to exclude all false-positive diagnosis of VAP thus resulting in 100% specificity.

2.4.3. Soluble triggering receptor expressed by myeloid cell

The soluble triggering receptor expressed by myeloid cells-1 (sTREM) has been proposed as another potentially useful diagnostic tool for CAP and VAP [58, 60-62]. The sTREM is upregulated by microbial products, it accurately identifies bacterial or fungal pneumonia in bronchoalveolar lavage fluid (BAL) from mechanically ventilated patients, and is superior in this regard to clinical findings or other laboratory values. Such intervention is not appropriate, however, in the routine care of patients with community-acquired pneumonia. In this

setting, measurement of soluble triggering receptor expressed on myeloid cells-1 in plasma or serum has proved unhelpful as a guide to either etiology or outcome [61].

The first study on 148 patients suffering from suspected CAP or VAP and receiving mechanical ventilation, sTREM was assessed in the BAL fluid and its levels were a better predictor for bacterial infection than CPIS, TNF-alfa and IL-1 levels [58]. The authors also analyzed the behavior of PCT and did not find any role for this biomarker in identifying pneumonia. Another group evaluated the presence of sTREM in exhaled ventilator condensate (EVC) and in BAL fluid from 23 patients clinically suspected of having VAP [60]. In contrast with the first report, sTREM-1 was detected in the BAL fluid of all 14 VAP subjects but also in 8 of 9 subjects without pneumonia, and sTREM levels did not differ in the VAP subjects compared to the non-pneumonia subjects. However, sTREM-1 was detected in the EVC from 11 of 14 subjects with VAP, but from only 1 of 9 subjects without VAP, and was significantly higher in the pneumonia patients. Another study tends to rule out the value of sTREM detection in BAL as a useful tool in VAP diagnosis [62]. In this study, 105 consecutive patients receiving mechanical ventilation and undergoing BAL were enrolled. Of those, 19 patients (18.1%) met definite microbiologic criteria for bacterial or fungal VAP. All the statistical analysis performed showed that measurement of sTREM-1 was inferior to clinical parameters for the diagnosis of VAP.

In patients with community-acquired pneumonia, traditional criteria of infection based on clinical signs and symptoms, clinical scoring systems, and general inflammatory indicators (for example, leukocytosis, fever, sputum and blood cultures) are often of limited clinical value and remain an unreliable guide to diagnosis lower respiratory tract infections. Procalcitonin is superior to other commonly used markers in its specificity for bacterial infection, allowing alternative diagnoses to be excluded, mainly as a guide to the necessity for antibiotic therapy [63-65]. It can therefore be viewed as a diagnostic and prognostic test. It more closely matches the criteria for usefulness than other candidate biomarkers such as C-reactive protein, which is rather a nonspecific marker of acute phase inflammation, and proinflammatory cytokines such as plasma IL-6 levels that are highly variable, cumbersome to measure, and lack specificity for systemic infection.

2.5. Pneumonia in elderly

The clinical presentation of pneumonia in the elderly may be subtle, lacking the typical acute symptoms observed in younger adults. Riquelme et al. [66] reported the initial clinical presentation of 101 elderly patients with CAP (mean age, 78 years; 66.3% men) who were admitted to a 1000-bed teaching hospital in Barcelona, Spain. The most frequently observed symptoms were dyspnea (72.3%), cough (66.3%), fever (63.4%), asthenia (57.4%), purulent sputum (51.5%), anorexia (49.5%), altered mental status (44.6%), and pleuritic chest pain (33.7%). The classic triad of symptoms of pneumonia − cough, dyspnea, and fever − was observed in only 30.7% of these elderly patients. Nineteen patients (18.8%) did not have cough, purulent sputum, or pleuritic chest pain. In a prospective study [67] designed to assess the clinical characteristics of 503 elderly patients (mean age, 76.3 years; 63.4% men) admitted for CAP to 16 hospitals across Spain, the most frequently observed symptoms were cough

(80.9%), fever (75.5%), dyspnea (69.8%), sputum production (65.8%), chills (53.1%), pleuritic chest pain (43.3%), asthenia (38.6%), and altered mental status (25.8%). The typical constellation of symptoms of pneumonia (cough, purulent sputum, and pleural pain) was noted in only 152 patients (30.2%). Metlay et al. [68] studied the influence of age on symptoms at presentation in 1,812 patients with CAP. Cough, dyspnea, and pleuritic chest pain were significantly less common among elderly patients than among younger patients (81.7% vs. 87.8%, 68.8% vs. 73.9%, and 31.6% vs. 53.3%, respectively). After controlling for patient demographics, comorbidities, and severity of illness, elderly patients exhibited significantly fewer respiratory symptoms than did younger patients (respiratory symptom score, 7.21 vs. 9.79, respectively; $p < 0.01$). In other study, altered mental status and the absence of fever were observed more frequently in patients over 80 years of age than in those under 80 years of age (21.0% vs. 10.7%; $p < 0.001$ and 32.1% vs. 21.9%; $p < 0.001$, respectively). These findings are consistent with Saldías et al. study [69], which reported a higher incidence of dyspnea and confusion (71% vs. 53%; $p < 0.001$ and 28% vs. 8%; $p< 0.001$, respectively) but a lower incidence of fever, chills and pleuritic chest pain in the older patients (63% vs. 76%; $p = 0.007$, 21% vs. 41%; $p < 0.001$ and 12% vs. 32%; $p< 0.001$, respectively). Compared to adults below 65 years of age hospitalized for CAP during the same period, the following clinical findings were more prevalent among the elderly population: the presence of comorbidity, dyspnea, decreased level of consciousness, suspected aspiration, hypoxemia and high serum urea nitrogen on admission to hospital. In the elderly, admission to intermediate and intensive care units was more frequent (47.7% vs. 29.2%, $p< 0.001$), and the length of hospital stay was longer (10.6 vs. 8.6 days, $p= 0.03$). Multilobar radiographic involvement, pleural effusion, the hospital complication rate and the need for mechanical ventilation were similar in both groups, but mortality, both in-hospital and at 30-days follow-up, was higher in the elderly population (9.8% vs. 3.2%; $p= 0.03$ and 13.1% vs. 4.8%; $p= 0.02$, respectively). Furthermore, it has been suggested that the local inflammatory response to infection of the lungs is decreased in the elderly, resulting in less cough and sputum production [70]. The systemic inflammatory response (e.g., fever, leukocytosis, high serum C-reactive protein) is also reduced secondary to decreased production of cytokines. Nevertheless, the decrease in interleukin-6 (IL-6), the most prevalent mediator of fever, did not reach statistical significance in a study that measured IL-6 levels in 59 elderly patients and 21 younger patients with CAP (211.6 vs. 284.5 pg/mL, respectively) [71]. In contrast, tachypnea remains prevalent and appears to be a sensitive indicator of lower respiratory tract infection in the elderly [69,72]. Altered mental status, confusion, a sudden decline in functional physical capacity, and comorbidity decompensation may be the only symptoms of an infection (including pneumonia) in the elderly [66]. Clinicians should be cognizant of those symptoms to avoid delay in establishing the diagnosis and initiating antibiotic therapy.

2.6. Recommendation

The clinical diagnosis of pneumonia without radiological confirmation lacks specificity because the clinical feature (history and physical examination) does not allow differentiating the patient with pneumonia from other acute respiratory diseases (e.g., upper respiratory tract infections, bronchitis, bronchiolitis, influenza). The diagnosis of pneumonia based sole-

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ly on clinical criteria is also hampered by the large variability in the ability to detect focal signs on chest examination between different examiners. Pneumonia remains foremost a clinical diagnosis. However, symptoms of lower respiratory infection, including fever, cough, purulent sputum, dyspnea, and pleuritic chest pain as well as the clinical findings of fever, tachypnea, tachycardia, hypoxemia, and auscultatory signs of consolidation, are not unique to pneumonia.

Although most patients with CAP can be managed successfully in the community by their general practitioner without additional investigations, distinguishing CAP from other causes of respiratory symptoms and signs can be difficult, particularly where the presence of comorbidities such as congestive heart failure, chronic lung disease, or COPD complicate the clinical picture. The elderly can present a particularly difficult diagnostic challenge because they more frequently present with non-specific or atypical symptoms and signs. Chest radiographs are therefore routinely required to confirm the clinical suspicion of pneumonia: The clinical history and physical examination suggest the presence of a lower respiratory tract infection, but the diagnosis is established when demonstrating the presence of new onset pulmonary infiltrates on chest radiography.

3. Prognosis of pneumonia

3.1. Severity assessment in adult patients with community acquired pneumonia

Once community-acquired pneumonia is diagnosed, a combination of history, physical examination, and laboratory exams can help estimate the short-term risk for torpid evolution or death and, along with the patient's psychosocial characteristics, determine the appropriate site of treatment [6,16,17,32]. These decisions, including the need for parenteral therapy and supportive care, ultimately relate to the decision on whether to hospitalize the patient.

The wide spectrum of severity in patients presenting in the ambulatory care setting explains the wide variation in case fatality rates for pneumonia reported in the national and international literature in different clinical contexts [1,4,6,8]. Thus adult patients with pneumonia without risk factors treated in the ambulatory setting has a low mortality risk (1-2%), rising to 5-15% in patients with comorbidities or specific risk factors that are admitted to hospital ward and increases to 20-50% in those admitted to the intensive care unit. The severity assessment allow us to decide the site of care (outpatient or in-hospital: general ward, intermediate care unit or ICU), the extension of laboratory and microbiological examination, coverage of empiric antibiotic treatment, route and length of treatment and level of medical and nursing care that requires the particular case. Recognition of patients at low risk of complications that can be managed as outpatients would significantly reduce the costs of health care, minimizing risks, without compromising the evolution and prognosis of CAP patients [73]. Hospital admission rates of adult patients with community-acquired pneumonia reported in the literature vary considerably, suggesting that physicians do not use uniform criteria to assess the risk of morbidity and mortality of patients. It has been reported that primary care physicians often overestimate the risk of complications and death in patients

with CAP, hospitalizing consequently a significant number of patients at low risk [74]. The risk stratification of patients should help to reduce this variability and improve the decision of admission and cost effective management of the disease.

3.2. Clinical, radiographic and laboratory prognostic factors in community-acquired pneumonia

Numerous studies have examined hospital or ICU admission risk factors associated with complicated clinical course or poor prognosis in CAP patients, particularly related to hospital or short-term mortality [6,16,17,69]. Univariate studies have described more than 40 clinical and laboratory parameters associated with mortality [6,36,69,75-77]. However, an independent association with short-term risk of death or hospital complication rate was found only for some clinical variables using multivariate analysis.

To facilitate handling of short-term prognostic factors in pneumonia, it is convenient to group them in different categories: a) Sociodemographic factors: age, gender, origin, ethnicity, social factors; b) Clinical history: preexisting disease, immunosuppression, altered mental status, fever, cough, sputum production, dyspnea, chills, chest pain; c) Physical examination: tachycardia, hypotension, tachypnea, hypothermia, hyperthermia, confusion, or pulmonary exam abnormalities; d) Chest radiograph: multilobar or bilateral pulmonary infiltrates, cavitation or pleural effusion; e) Laboratory tests: hypoxemia, hypercapnia, acidosis, high blood urea nitrogen, anemia, leukopenia, leukocytosis, hypoalbuminemia, hyperglycemia, and raised biomarkers of inflammation; f) Microbiological exams: bacteremic pneumonia, lung infection by pneumococcus, anaerobic, atypical microorganisms, gram-negative bacilli or *S. aureus* [6].

Age: Several studies have demonstrated an association between extreme ages (below one year and over 65 years) and the risk of death in the hospital [4-6,14,23,78,79,82,83]. The community-acquired pneumonia in the elderly usually manifests with atypical or nonspecific symptoms (e.g., mental confusion, anorexia, arrhythmias, congestive heart failure), difficulting the diagnostic process and delaying specific treatment adversely compromising the prognosis of patients [14,66,69,70]. The absence of fever, prostration, multiple comorbidities, nutritional disorders and institutionalization are poor prognostic factors in the elderly [14,66,72]. However, based on evidence from clinical studies, there are not reasons that support the use of different clinical variables to assess the severity in elderly people.

Comorbidity: The presence of coronary heart disease, congestive heart failure, cerebrovascular disease with motor dysfunction or dementia, diabetes mellitus, chronic respiratory disease (COPD, bronchiectasis), cancer, immunosuppression, chronic renal failure, alcoholism, malnutrition and chronic hepatic disease are associated to increased hospital mortality in adult patients with pneumonia [6,69,75-77,83,85]. However, the contribution of different comorbidities to severity of community-acquired pneumonia in adults has been difficult to establish, due to lack of uniformity in the definition of chronic diseases in different studies and stratification problems with the severity of various comorbidities. This could partly explain the low predictive power of specific comorbidities as risk factors of death in multivari-

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ate analysis, despite that large number of studies have shown its importance in the univariate analysis.

Respiratory rate: Regardless of age of the patient, the presence of tachypnea is one of the most reliable indicators of severity of pneumonia in univariate and multivariate analysis [6,69,75-77,79,81-83,86,87]. There is a linear relationship between respiratory rate and mortality in pneumonia patients, but in the clinical practice, it is recommended that the respiratory rate above of 20 breaths/min should be considered a reliable sign of severity in patients with pneumonia.

Mental status: Altered mental status has been identified as an independent risk factor of death in several studies, including elderly population [6,14,66,69,72,79,82]. However, the definition of altered mental status has varied in different studies, thus complicating their integration as a prognostic factor. Despite this, the quantitative or qualitative impairment of consciousness are an excellent predictor of prognosis in patients with community-acquired pneumonia.

Blood pressure: Systolic hypotension (SBP <90 mmHg) or low diastolic blood pressure (DBP ≤ 60 mmHg) and the presence of septic shock on admission to hospital are independent factors of poor prognosis in multivariate analysis of several studies [6,69,75-82,84]. In the ICU, the presence of septic shock or prolonged systolic hypotension for more than 12 hours which does not improve with adequate volume replacement and/or vasopressor drugs prescription is another sign of poor prognosis.

Oxygenation: Hypoxemia and oxygen administration with a $FiO_2 \geq 0.5$ to maintain adequate tissue oxygenation or the application of PEEP are indicators of poor prognosis [6,78,79,83]. The severe acute respiratory failure and the need for mechanical ventilation in ICU admission or during hospital stay are also predictors of mortality. The presence of hypoxemia or hypercapnia should be corrected immediately and is a determining factor in deciding hospitalization of a particular case.

Chest radiography: Bilateral or multilobar pulmonary opacities, rapid progression of pulmonary infiltrates over 72 hours, the presence of cavitation or pleural effusion are poor prognostic factors associated to hospital complications and short-term mortality [6,74-77,82-84]. The performance of serial chest radiographs to assess the clinical evolution of hospitalized patients with pneumonia is not recommended outside the ICU, unless there is clinical evidence suggestive of treatment failure or a complication.

Leukocytes count: The presence of leukopenia (less than 4,000 leukocytes per mm^3) or leukocytosis (greater than 20,000 leukocytes per mm^3) on admission to hospital was associated with high mortality in univariate analysis. However, multivariate analysis results have been controversial and suggest that leukopenia may be a better predictor of mortality [6,79].

Renal function: The high blood urea nitrogen on admission to hospital has been recognized as a poor prognostic factor in patients with community acquired pneumonia in the univariate and multivariate analysis, probably reflecting the deterioration of tissue perfusion [6,69,75-77, 79,81,82]. It is important to emphasize, the main prognostic laboratory tests

measured at admission in hospitalized adult patients with community-acquired pneumonia are the arterial blood gases and measurement of uremia.

Microbiology: Bacteremic pneumonia with positive blood cultures has two to three times greater risk of death [6,75-77,83]. Pneumonia caused by gram negative bacilli, *Staphylococcus aureus* and *Pseudomonas aeruginosa* tend to have more complications during the evolution and increased lethality [6,83]. Pulmonary infection by *Legionella spp* is a common cause of severe pneumonia and admission to the intensive care unit, specially reported in Europe. However, the clinical-radiographic features has failed to differentiate between the different etiologic agents of pneumonia; in this way, the late microbiological information has not been useful for assessing the severity of the individual patient on admission to hospital or in the context of attention in primary health care services (outpatient clinics or emergency departments). Nevertheless, microbiological tests are useful for evaluating the severity and guide antimicrobial therapy in patients hospitalized with community-acquired pneumonia.

3.3. Clinical predictive rules to assess the severity of the patient with pneumonia

The evaluation of the severity of the patient with pneumonia depends on the experience of the clinician, who has been reported often underestimate the seriousness of the disease [78]. No prognostic factor is sufficiently sensitive and specific for predicting the evolution of the individual patient. Thus, in the medical literature have been described several prognostic indices that would help the clinician to identify patients with community acquired pneumonia that have low or high risk of complications and/or death during the evolution (Table 7) [76,79-82]. None of the developed predictive models has allowed stratifying patients into well-defined risk categories. The development and dissemination of clinical guidelines that examine the severity of the patient with pneumonia by objective criteria, have reduced the hospitalization of low risk patients, significantly reducing the cost of medical resources without affecting the evolution and prognosis of patients [16,17,35,88,89]. Severity predictive models based on clinical and laboratory exams are best viewed as adjunctive tools for the clinical evaluation of patients. In general, predictive models should be used with care and should never override clinical judgment. The periodic assessment of severity during the course of hospital stay is mandatory to allow adjustment of empirical antibiotic treatment to avoid adverse events associated to it.

Significant variation in admission rates among hospitals and among individual physicians has been well documented. Physicians often overestimate severity and hospitalize a significant number of patients at low risk for death [90,91]. Because of these issues, interest in developing simple and objective clinical criterias available at primary health care has stimulated to develop such predictive rules by several research groups [76,79-82]. The relative merits and limitations of various proposed criteria have been carefully evaluated [92]. The two most interesting predictive rules are the Pneumonia Severity Index (PSI) described by Fine et al. [81] for screening of patients at low risk for outpatient treatment, and the British Thoracic Society criteria (CURB-65) for screening of high risk patients with severe CAP [79,80].

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Patient characteristics	Score (points)
Demographic factors	
Age (in years)	
Male	Age
Female	Age - 10
Nursing home resident	10
Coexisting conditions	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Initial physical examination findings	
Altered mental status	20
Respiratory rate ≥30 breaths/min	20
Systolic blood pressure < 90 mmHg	20
Temperature < 35 °C or ≥40 °C	15
Heart rate ≥125 beats/min	10
Initial laboratory findings	
pH < 7.35	30
BUN > 30 mg/dL	20
Sodium < 130 mEq/L	20
Glucose ≥250 mg/dL	10
Hematocrit < 30%	l10
PaO_2 < 60 mmHg or O_2 sat < 90%	10
Pleural effusion	10

Risk class	Score	Mortality	Site of care recommendation
I	50	0.1 – 0.4%	Outpatient
II	51 – 70	0.6 – 0.7%	Outpatient
III	71 – 90	0.9 – 2.8%	Short stay inpatient
IV	91 – 130	8.2 – 12.5	Inpatient
V	> 130	27.1 – 31.1%	Inpatient

British Thoracic Society criteria (CURB-65)
Confusion
BUN > 7 mmol/L or 20 mg/dL
Systolic BP < 90 mmHg or Diastolic BP ≤60 mmHg
Respiratory rate ≥30 breaths/min
Age ≥65 years

Risk categories	Score	Mortality	Site of care recommendation
I	0 – 1	1.5%	Outpatient
II	2	9.2%	Inpatient
III	3	22%	Inpatient (ICU admission)

Severe Community Acquired Pneumonia score (SCAP)		
Variables	*Score*	
Age ≥80 years	5	
Systolic blood pressure < 90 mmHg	11	
Respiratory rate > 30 breaths/min	9	
Confusion	5	
Blood urea nitrogen > 30 mg/dL	5	
Multilobar or bilateral pulmonary infiltrates	5	
PaO_2 < 54 mmHg or PaO_2/FiO_2 < 250	6	
pH < 7.30	13	
Risk categories	**Score**	**Severe CAP ***
Low	0 – 9	0.19 - 3.4%
Intermediate	10 – 19	9.2 - 11.2%
High	20	36.6 - 75.8%

* *Severe CAP was defined by hospital* mortality, mechanical ventilation use and/or septic shock.

Table 7. Prognostic rules in adults patients with community-acquired pneumonia[79-81].

3.3.1. Pneumonia severity index

The PSI is based on derivation and validation cohorts of 14,199 and 38,039 hospitalized patients with CAP, respectively, plus an additional 2,287 combined inpatients and outpatients [81]. The Pneumonia Severity Index allows us stratify patients into five risk categories. Patients with pneumonia risk class I have low risk of death and adverse events, with a mortality rate ranging between 0.1% and 0.4%. In an observational study, low-risk patients susceptible to ambulatory care had a 30-days hospitalization rate around 5.5% [93]. The model described by Fine et al. was developed as a two-stage predictive tool to identify low risk patients for ambulatory management. In a first step, we consider some epidemiological variables (age, gender, nursing home residence), the presence of certain specific comorbidities (congestive heart failure, malignancy, chronic liver disease, cerebrovascular disease and chronic kidney disease) and some physical examination abnormalities (mental status, heart rate, blood pressure, respiratory rate and temperature). In a second step, we consider some laboratory and radiographic findings (for example, anemia, hypoxemia, azotemia, hyperglycemia and pleural effusion). On the basis of associated mortality rates, it has been suggested that risk class I and II patients should be treated as outpatients, risk class III patients should be treated in an observation unit or with a short hospitalization, and risk class IV and V patients should be treated as inpatients (Table 7). In general, patients younger than 60 years without comorbidities and abnormalities in mental status and vital signs are classified into low risk categories, which could be treated as outpatients unless there are social factors that hinder their control or adherence to treatment (e.g., alcoholism, drug addiction, psychiatric disorders or, rural origin).

3.3.2. British thoracic society rule

To identify high-risk patients has been useful the discriminant rule developed by the British Thoracic Society, confirming that advanced age, altered mental status or confusion, respiratory rate above 30 breaths/min, diastolic blood pressure below 60 mmHg and blood urea nitrogen greater than 20 mg/dL are associated with increased mortality [79,80]. The BTS original criteria of 1987 have subsequently been modified [78-80]. In the initial study, risk of death was increased 21-fold if a patient, at the time of admission, had at least 2 of the following 3 conditions: tachypnea, diastolic hypotension, and an elevated blood urea nitrogen level. These criteria appear to function well except among patients with chronic renal failure and among elderly patients [94,95]. The most recent modification of the BTS criteria includes five easily measurable factors [80]. Multivariate analysis of 1,068 patients identified the following factors as indicators of increased mortality: confusion (based on a specific mental test or disorientation to person, place, or time), BUN level above 17 mmol/L (20 mg/dL), respiratory rate over 30 breaths/min, low blood pressure (systolic, below 90 mm Hg; or diastolic, below 60 mmHg), and age over 65 years; this gave rise to the acronym CURB-65. In the derivation and validation cohorts, the 30-day mortality among patients with 0, 1, or 2 factors was 0.7%, 2.1%, and 9.2%, respectively. Mortality was higher when 3, 4, or 5 factors were present and was reported as 14.5%, 40%, and 57%, respectively. The authors suggested that patients with a CURB-65 score of 0-1 be treated as outpatients, that those with a score of 2 be admitted to the wards, and that patients with a score of ≥ 3 often required ICU care. A simplified version (CRB-65), which does not require testing for BUN level, may be appropriate for decision making in the primary care practitioner's office [96].

3.3.3. Severe CAP rule

Severe CAP (SCAP) is a life-threatening condition that requires intensive care. Estimates of the frequency of severe CAP range from 5 to 35%, with mortality ranging from 20 to 50% [6]. These relatively wide ranges indicate disparities between definitions of SCAP. There is no universally accepted definition of SCAP. During the last decade, the term has been used for cases that ultimately result in death, and/or patients requiring admission to an intensive care unit. Such practical definitions seem to be insufficient because the risk of death from CAP is not the same as the need for inpatient care. On the other hand, the decision to admit a patient to the ICU depends on the clinical judgment of individual clinicians and the local practices of their hospitals, differences that could account for much of the variability regarding ICU admission. Studies focused on the evaluation of patients admitted to the ICU mix some variables evident at the time of admission with other potentially evolutionary criteria, which are not applicable to early hospital admission. Other criteria, such as mechanical ventilation and septic shock, are less subject to interpretive variability and better reflect illness severity [97]. España et al. [82] developed a clinical prediction rule for severe community-acquired pneumonia (SCAP) in 1,057 adult patients visiting the emergency department from one hospital, which was then validated in two different populations: 719 patients from the same center and 1,121 patients from four other hospitals. In the multivariate analyses, eight independent predictive factors were correlated with severe community-acquired pneumonia: ar-

terial pH below 7.30, systolic blood pressure under 90 mmHg, respiratory rate above 30 breaths/min, altered mental status, blood urea nitrogen over 30 mg/dL, oxygen arterial pressure under 54 mmHg or ratio of arterial oxygen tension to fraction of inspired oxygen under 250 mmHg, age greater than or equal to 80 years, and multilobar or bilateral lung affectation. The SCAP score was designed to identify high risk patients at admission, by predicting the hospital mortality, need for mechanical ventilation, and risk for septic shock.

The Severe Community Acquired Pneumonia score described by España et al. was validated to predict 30-day mortality in an internal validation cohort of consecutive adult patients admitted to one hospital [98]. Consecutive inpatients from other three hospitals were used to externally validate the score and compare the SCAP with the PSI and CURB-65. The discriminatory power of these rules to predict 30-day mortality was tested by the area under curve (AUC), and their predictive accuracy with the sensitivity, specificity and predictive values. The 30-day mortality rate increased directly with increasing SCAP score (class 0: 0.5%, to class 4: 66.5% risk) in the internal validation cohort, and from 1.3% to 29.2% in external cohort ($p < 0.001$) with an AUC of 0.83 and 0.75, respectively ($p = 0.024$). The SCAP score identified 62.4% (95%CI 58.8-66.0) low-risk patients, 52.5% (95%CI 48.8-56.2) the PSI and 46.2% (95%CI 42.5-49.9) the CURB-65 in the external cohort. Patients classified as low risk by the three rules had similar 30-day mortality (SCAP: 2.5%, PSI: 1.6% and CURB-65: 2.7%). The SCAP score was valid to predict 30-day mortality among low-risk patients and to identify patients at low-risk was similar or greater than the other studied rules.

3.3.4. Generic sepsis scores

Generic scoring systems such as the systemic inflammatory response syndrome (SIRS) criteria and standardized early warning score (SEWS) have been extensively assessed in critically ill patients and are relatively simple to calculate [99,100]. However, it has been reported that SIRS and SEWS perform less favourably than CURB-65 and PSI scores for severity assessment in CAP and prediction of progression to sepsis in severe CAP [101,102]. Considering the limited number of studies to date does not support use of generic sepsis scores over pneumonia-specific scores in CAP.

The clinical pulmonary infection score (CPIS) - original or modified - has been proposed for the diagnosis and management of ventilator-associated pneumonia [103, 104]. The clinical pulmonary infection score has low diagnostic accuracy; however, incorporating gram stains results into the score may help clinical decision making in patients with clinically suspected pneumonia [105].

The use of APACHE II predictive model in the evaluation of patients with severe pneumonia in the ICU has demonstrated its usefulness as a predictor of mortality [106,107]. However, it has not been proved applicable in units of lower complexity of the hospital. The application of this prognostic tool out of the ICU is difficult, time consuming and impractical.

3.3.5. Clinically relevant adverse outcome prediction

Severity scores provide pivotal direction for the management of community-acquired pneumonia, helping guide decisions such as the appropriate venue for care, diagnostic strategies,

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and antibiotic therapies. The most popular severity scores, the pneumonia severity index and CURB-65 are accurate for predicting pneumonia-related mortality [108-114]. But clinical care should be based on a broader set of medical outcomes than just mortality, such as ICU admission, need for mechanical ventilation, progression to severe sepsis, or treatment failure [115,116]. Unfortunately, there is no consensus surrounding serious complications that warrant hospitalization for patients with pneumonia.

It has been reported that the SCAP score is slightly better than the PSI and CURB-65 in predicting adverse outcomes other than mortality in two independent cohorts [117]. In the external validation cohort, the rate of adverse outcomes increased steadily from low- to high-risk classes for the SCAP score as well as for the PSI and CURB-65 ($p < 0.001$). In the internal validation cohort, there were no significant differences in outcomes such as ICU admission and mechanical ventilation for the PSI and CURB-65. All three scores predicted treatment failure with low to moderate discrimination in the external validation cohort. It must be noted that the initial severity of CAP is only one factor predicting treatment failure. Other factors, such as the causal microorganism and treatment-related factors, are not part of the three prediction tools. The SCAP score classified a significantly higher proportion of patients as low risk in both cohorts than the PSI and CURB-65, with lower rates of all adverse outcomes. Another goal of the tool is its negative predictive value. If the score is low, ICU admission and others adverse outcomes are very unlikely. In addition, patients identified as high risk by the SCAP score had somewhat higher rates of ICU admissions, need for mechanical ventilation, and severe sepsis compared with the PSI and CURB-65. Thus, applying the SCAP score would identify CAP patients who should receive closer monitoring and more aggressive treatment. Given the somewhat poorer predictive power of the PSI and CURB-65 in the internal validation cohort, the sensitivity, specificity, and AUC of the three scores were compared in the external validation cohort. Although the SCAP score had significantly better sensitivities and specificities than the PSI and CURB-65, the differences were small and of uncertain clinical relevance.

Saldías et al. [77] assessed the accuracy and discriminatory power of three validated rules (PSI, CURB-65 and SCAP) for predicting clinically relevant adverse outcomes (ICU admission, need for mechanical ventilation and hospital complications rate) in patients hospitalized with community-acquired pneumococcal pneumonia. The rate of all adverse outcomes and hospital length of stay increased directly with increasing PSI, CURB-65 and SCAP scores. The three severity scores allowed us to predict the risk of in-hospital complications and 30-day mortality. The PSI score was more sensitive and the SCAP was more specific to predict hospital complications and the risk of death. However, the SCAP was more sensitive and specific in predicting the use of mechanical ventilation. Thus, the severity scores validated in the literature allow us to predict the risk of complications and death in adult patients hospitalized with pneumococcal pneumonia. Nevertheless, the clinical indexes differ in their sensitivity, specificity and discriminatory power to predict different adverse events.

3.4. Biomarkers of inflammation for the severity assessment of CAP

The clinical guidelines for the management of adult patients with CAP suggest the use of severity-based approach for the purpose of guiding therapeutic options, such as the need for hospital or ICU admission, suitability for ambulatory care, and choice and route of an-

timicrobial agents. The use of prognostic scores, like CURB-65 and PSI, is recommended to support clinical judgment [16,17,35]. Despite their widespread use in clinical routine, traditional markers, such as severity of disease assessment by the patient`s fever, white blood cell count and also CRP level are not reliable for the assessment of disease severity and mortality risk in CAP. The pneumonia severity index (PSI) is a widely accepted and validated severity scoring system that assesses the risk of mortality for pneumonia patients in a two step algorithm, combining clinical signs, demographic data and laboratory values [81]. However, its complexity is high, jeopardizing its dissemination and implementation, especially in everyday clinical practice. Therefore, the CURB-65 score has been proposed as a simpler alternative [79,80].

A number of studies have explored the prognostic value of biomarkers in patients with CAP. Muller et al. [49] reported a significant relationship between procalcitonin levels and PSI categories, with PCT being markedly elevated in the highest PSI class. However, it must be taken into account that many PSI class V patients had low PCT values. Huang et al. [118], report a multicenter, prospective, observational cohort study in a large population of 1,651 patients admitted to 28 community or teaching emergency departments for CAP to determine whether procalcitonin can provide prognostic information beyond the Pneumonia Severity Index and CURB-65. In this study procalcitonin levels did not add relevant prognostic information for most pneumonia patients. Used alone, procalcitonin had modest test characteristics: specificity (35%), sensitivity (92%), positive likelihood ratio (1.41), and negative likelihood ratio (0.22). However, among higher-risk groups as assessed by the Pneumonia Severity Index score, low procalcitonin level reliably predicted lower mortality.

The predictive value of procalcitonin was compared to CRP, leukocyte count and CRB-65 score in a large study of the CAPNETZ competence network [119] involving 1,671 patients with proven CAP, clinical and laboratory variables were determined at admission and patients were followed-up for 28 days for outcome. The PCT levels at admission were a better predictor of CAP severity and outcome than leukocyte count and CRP levels, with a similar prognostic accuracy as the CRB-65 score. The area under the curve for PCT and CRB-65 was comparable (0.80, 95%CI 0.75-0.84 versus 0.79, 95%CI 0.74-0.84), but each significantly higher compared with CRP (0.62, 95%CI 0.54-0.68) and leukocyte count (0.61, 95%CI 0.54-0.68). Another finding from this study, a PCT threshold of ≤ 0.228 ng/mL identified low-risk patients within all CRB-65 risk groups.

Another study from the CAPNETZ network explored the role of pro-atrial natriuretic peptide (MR-proANP), pro-vasopressin (CT-proAVP), PCT and CRP for severity assessment and outcome prediction in 589 adult patients with CAP [120]. MR-proANP, CT-proAVP and PCT levels, but not CRP, increased with increasing severity of CAP, classified according to the CRB-65 score. The area under the curve values for CT-proAVP (0.86, 95%CI 0.83-0.89) and MR-proANP (0.76, 95%CI 0.72-0.80) were similar to the AUC of CRB-65 (0.73, 95%CI 0.70-0.77). In multivariate Cox proportional hazards regression analyses high levels of MR-proANP and CT-proAVP were the strongest predictors of mortality. Thus, the authors concluded that MR-proANP and CT-proAVP are predictors of CAP severity and 28-day mortality comparable to the clinical CRB-65 score.

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4. Conclusion

In assessing the probability of death in adult patients with community-acquired pneumonia, the clinical history and physical examination abnormalities significantly influenced the prognosis [4,6,49,69,75-87]. In medical history, advanced age (over 65-70 years), specific comorbidities, symptoms of dyspnea and confusion were associated with increased risk of death. Among comorbid conditions, the strongest predictors of death were neurologic disease, cancer, immunosuppression, alcoholism, malnutrition, renal disease, liver disease and congestive heart failure. In physical examination, altered mental status, hypotension, tachypnea and hypothermia were associated with increased odds of death. Laboratory abnormalities significantly associated to bad prognosis are azotemia (blood urea nitrogen level above 20 mg/dL), hypoxemia, leukopenia (≤ 4,000 cells/mm^3) and leukocytosis (≥ 20,000 cells/mm^3). Pleural effusion, rapid progression of pulmonary infiltrates and multilobar or bilateral infiltrates on chest radiograph were also associated to increased risk of complications and death.

Individual clinical and laboratory abnormalities are associated with only moderate increases in the odds of death [6,49,75-87]. Thus, combinations of factors are necessary to accurately assess short-term risk for death and guide site-of-care decisions. These prognosis rules include demographic factors (age, gender and nursing home residence), comorbid conditions (for example, neoplastic disease, diabetes, pulmonary disease, and heart disease), symptoms and signs (for example, altered mental status, lack of pleuritic chest pain or fever, tachypnea, and hypotension), and laboratory and radiographic findings (for example, hypoxemia, azotemia, leukopenia, acidosis, hypoalbuminemia and multilobar infiltrates). The Pneumonia Patient Outcomes Research Team (PORT) Severity Index and CURB-65 are well validated prognostic rules recommended in the clinical guidelines [16,17,35] to assess severity of pneumonia patients in the ambulatory care setting. In evaluating clinical findings as a guide to initial site of treatment, most studies on prognosis have focused on mortality as the sole outcome, which is problematic because a high risk for death may not be the only reason for hospitalization. Increased risk for other serious adverse events (e.g., ICU admission, mechanical ventilation support, progression to septic shock), reliability in adhering to therapy, returning for follow-up, and availability of supportive care at home are also important determinants for hospitalization. Therefore, clinical judgment should always prevail over the severity index calculation in clinical decision for site of care and treatment planning.

4.1. Pneumonia severity assessment in the ambulatory setting

Clinicians are advised to implement a simple and practical strategy for assessing the severity and risk of complications in patients with community-acquired pneumonia assisted in the ambulatory care setting (outpatient clinics and emergency departments). It is suggested to classify patients into three risk categories:

a. Low-risk patients (short-term mortality less than 1-2%) susceptible to ambulatory treatment or brief hospitalization.

b. High-risk patients (short-term mortality around 20-30%) that must be managed in the hospital and probably in specialized units (Intermediate Care Unit or ICU) with severe pneumonia criteria.

c. Intermediate-risk patients with advanced age, comorbidities or independent risk factors of death, but they cannot be classified into a specific category.

Clinical judgment is essential to decide the setting of care and treatment of patients with community-acquired pneumonia, especially those located in the intermediate risk category. In general, patients younger than 65 years without preexisting diseases, abnormal vital signs or altered mental status at admission, could be managed as outpatients considering its low risk of death and complications. Elderly patients (aged above 65 years) with specific comorbidities and two or more risk factors from the British Thoracic Society rule (CURB-65), it is recommended to handle them in the hospital with severe pneumonia criteria.

In primary health care services, we recommend to assess the severity of adult patients with community acquired pneumonia considering only clinical variables available in primary care services:

- Age over 65 years.
- Comorbidity: coronary heart disease, congestive heart failure, chronic pulmonary disease (COPD, bronchiectasis), diabetes mellitus, cerebrovascular disease with motor dysfunction or dementia, chronic renal failure, chronic liver disease, alcoholism, malignancies, malnutrition.
- Altered mental status: drowsiness, stupor, coma or mental confusion.
- Tachycardia or heart rate ≥ 120 beats/min.
- Low blood pressure or hypotension (BP < 90/60 mmHg).
- Tachypnea or respiratory rate ≥ 20 breaths/min.
- Chest X-ray: bilateral or multilobar pulmonary infiltrates, cavitation or pleural effusion.
- Pulse oximetry: SpO_2 saturation less than 90% on room air.
- Presence of decompensated comorbidity (e.g., COPD exacerbation, congestive heart failure, myocardial infarction, hyperglycemia, arrhythmias).

In general terms, in young adults without risk factors it is recommended outpatient management, in presence of one risk factor it is recommended ambulatory or short-term hospital care depending on previous experience and clinical judgment, in presence of two or more risk factors it is recommended to refer the patient to the hospital (Figure 1).

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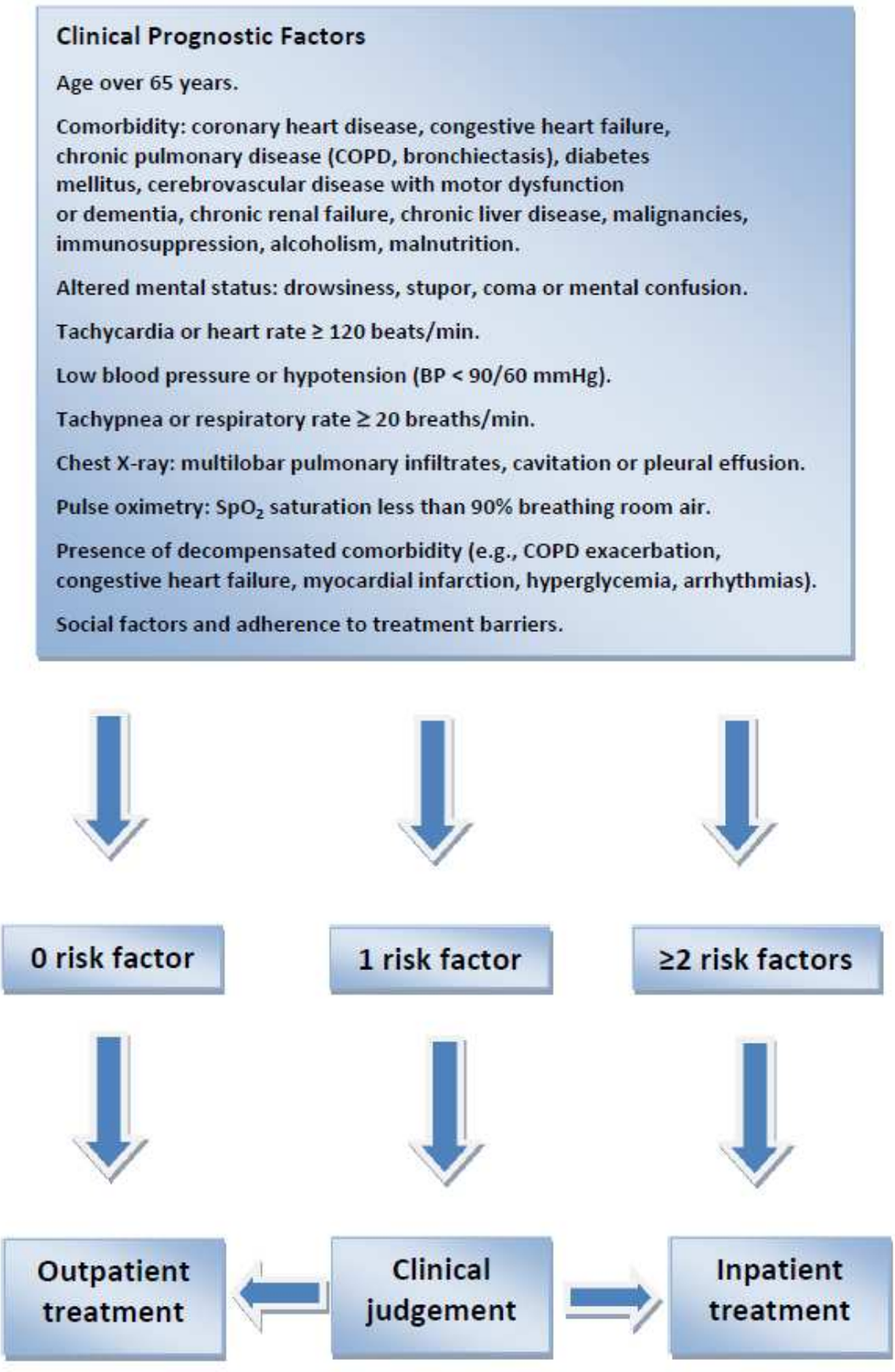

Figure 1. Severity assessment in adult patients with community-acquired pneumonia attended in primary health care services (outpatient clinics and emergency departments).

Nevertheless, after evaluating the severity of the case, when the clinician needs to decide the site of care (outpatient or hospital admission), it is important to consider the clinical and social variables involved in each particular case. We should especially avoid that high-risk patients receive outpatient treatment, but it is also important to minimize the number of low-risk patients that are unnecessarily admitted to hospital. Different studies have allowed developing a list of risk factors that determine the need for hospital admission and aid the clinicians in estimating the severity of CAP patients. Clinical judgment and experience of the physician must predominate over predictive models, which are not infallible, and should always consider the aspirations and concerns of patients in making decisions about the site of care and treatment prescribed.

Author details

Fernando Peñafiel Saldías[1*], Orlando Díaz Patiño[2] and Pablo Aguilera Fuenzalida[3]

*Address all correspondence to: fsaldias@med.puc.cl

1 Departamento de Enfermedades Respiratorias y Programa de Medicina de Urgencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Chile

2 Departamento de Enfermedades Respiratorias y Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Chile

3 Programa de Medicina de Urgencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Chile

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