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D-Dimer: A Potential Prognostic Biomarker for Community Acquired Pneumonia in Children

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ABSTRACT

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

Community-acquired Pneumonia (CAP):

Community-acquired pneumonia (CAP) is acquired in the community, outside of health care facilities. Compared with health care–associated pneumonia, it is less likely to involve multidrug-resistant bacteria. Although the latter are no longer rare in CAP, they are still less likely.

Community-acquired pneumonia (CAP) is one of the most important public health problemsworldwide **[1]**. In industrialized countries, CAP is the most frequent cause of mortality among infectious diseases, and it accounts for a substantial use of healthcare resources **[2]**. In Europe, studies have reported the incidence of CAP to be between 1.2 and 11.6 cases per 1000 population per year **[3,4]**, a figure that increases at least 10-fold in certain risk groups such as the elderly or patients with chronic obstructive pulmonary disease. Stratifying the severity and prognosis of CAP is very important. Existing severity assessment scores have been used to assess the need for hospitalization and to identify patients requiring intensive care unit (ICU) admission **[5,6]**. The Pneumonia Severity Index (PSI) **[7]** and CURB-65 (confusion, urea >7 mmol/l, respiratory rate ‡30/min, low systolic (<90 mm Hg) or diastolic (£60 mm Hg) blood pressure and age ‡65 years) **[8]** are clinical rules that identify individuals at low risk of death who are candidates for outpatient care **[7–9]**. However, patients defined as low-risk by these scores may occasionally require hospital admission.

Conversely, although patients classified as high-risk of death usually require prompt admission to hospital and treatment with parenteral antibiotics, a large proportion of them have good evolution **[10]**. Notably, investigators have documented that these scores perform less well when it comes to predicting

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the need for ICU admission **[11]**. They are also limited by the fact that i) physicians may misapply or fail to remember them, ii) a given risk group can present a significant range of outcomes and iii) under certain circumstances the risk of death or need for ICU admission may be overestimated or underesti-mated. Consequently, these severity assessment tools should be used with caution and in conjunction withclinical judgment. Biological markers (biomarkers) have been defined as cellular, biochemical or molecular characteristics that are objectively measurable in biological media such as human tissues, cells or fluids and which may be used as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention **[12,13]**.

In the context of CAP, biomarkers could be useful in numerous areas: establishing diagnosis, identifying etiology, assessing severity and prognosis and for therapeutic interventions. Given the limitations of existing CAP severity scores there has been considerable interest in the development of rapidly available biomarkers that might confer additional and reliable prognostic information. In this review, the authors focus on the recent literature concerning the usefulness of biomarkers, whether used alone or in conjunction with other clinical severity of illness scores, for identifying CAP patients at risk of short- and long-term mortality and for predicting both the need for ICU admission and the potential for treatment failure. For this purpose, a comprehensive literature search has been conducted in PubMed/MEDLINE database, using the following search terms: community-acquired pneumonia, biomarker, marker,prognosis, treatment failure, intensive care unit and mortality. Studies evaluating composite end points were excluded.

Pneumonia Severity Assessment

	Mild	Severe
Infants	Temperature <38.5 C RR < 50 breaths/min Mild recession Taking full feeds	Temperature >38.5 C RR > 70 breaths/min Moderate to severe recession Nasal Flaring Cyanosis Intermittent Apnea Grunting Respirations Not feeding
Older Children	Temperature <38.5 C RR < 50 breaths/min Mild breathlessness No vomiting	Temperature >38.5 C RR > 50 breaths/min Severe difficulty in breathing Nasal Flaring Cyanosis Grunting Respirations Signs of dehydration

Fig. (1): Pneumonia severity assessment **[67].**

Biomarkers for predicting short- & long-term mortality:

Although mortality in patients with CAP fell dramatically withthe introduction of antibiotics in the 1950s, it has changed very little over the past 50 years. Recent studies have reportedoverall mortality rates of 8–15% **[14,15]**, although in those patients who require ICU admission, mortality can be as

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highas 30%, despite prompt and appropriate antibiotic therapy **[16]**. Importantly, it has been shown that CAP may have significant longer-term effects and that hospitalization for this infection is associated with higher long-term mortality compared with other major medical conditions.

This increased mortality appears to be due to several factors, including acute cardiovascular events and alterations in immune function **[17,18]**. Current guidelines **[5,6,19]** recommend the use of severity scores to classify CAP patients according to the risk of mortality. The main tools used for this purpose are the PSI and CURB-65. A recent meta-analysis reported that these scores had similar overall test performance for predicting mortality in patients with CAP **[20]**. Numerous studies have been conducted to determine the relationship between certain biomarkers and both severity and mortality in CAP. Biomarkers of all types have been used by investigators to study the prognostic in CAP, and evaluate several biological pathways that are altered in these patients, such as thecardiovascular, coagulation, endocrine or immune systems. The most common biomarkers investigated to predict mortality are procalcitonin, C-reactive protein (CRP), pro-adrenomedullin, inflammatory cytokines and D-dimer.

Most of the studies evaluating the utility of biomarkers have focused on CAP patients requiring hospitalization, followed by those seen in the emergency department and, finally, those admitted to an ICU. Sample size has varied from 30 **[21]** to3463 patients **[22]**. The majority of studies provide information on short-term mortality (28- and 30-day mortality) as their primary end point, while others use long-term mortality (from 60-day to 18-month mortality) or ICU mortality.

Most studies have conducted multivariate analyses to determine the association between biomarkers and mortality, with the area under the receiver operating characteristic (AUROC) curve being used to assess predictive power. Importantly, the majority of studies have compared the AUROC curves of biomarkers and CAP-specific severity scoring systems, mainly PSI and CURB-65. The utility of adding biomarkers to CAP-specific severity scores has also been evaluated. The best operating point of the biomarker for predicting mortality is reported by the majority of manuscripts.As shown in TABLE 1, most of the biomarkers evaluated to date have been found to be independent predictors of shortandlong-term mortality in patients with CAP. However, serum angiotensin-converting enzyme (ACE) activity, which is significantly decreased during the acute phase of CAP, was not associated with mortality in hospitalized patients, even despite correction for ACE insertion/deletion polymorphism **[23,24]**.

It is important to note that most AUROC curve values generated by biomarkers were not significantly higher than those obtained from CAP-specific severity scores. Thus, the ability of biomarkers alone to predict mortality was no better than that of existing clinical scores for CAP, although adding biomarkers to scores such as the PSI, CURB-65, APACHE II and SOFA did improve their predictive capability, as evidenced by a significant increase in the AUROC curve. However, studies are not consistentin relation to these findings. N-terminal pro-brain natriuretic peptide, D-dimer and mid-regional pro-adrenomedullinimproved the AUROC curve for scores in some studies but not in others **[25–27]**. Similarly, visfatin**[28]** did not improve themortality prediction of scores in hospitalized patients with CAP, and pro-adrenomedullin **[29]** did not increase the mortality prediction of scores in ICU patients with CAP. Importantly, reclassification analysis was performed in only four of the studies reviewed. One of these reported no benefit from the combination of CURB-65 score and D-dimer in reclassification of risk for clinical success at day 30, 30-day mortality or need for mechanical ventilation **[26]**, whereas the other two found that a combination of the PSI and pro-adrenomedullin did enable better risk assessment for mortality than PSI alone **[30,31]**.

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Finally, a reclassification analysis comparing the PSI class model with a combined model with PSI class and initial endothelin-1 levels found a significant improvement in classification of risk of mortality [32]. Interestingly, some studies report kinetic information regarding biomarkers. One study evaluated the usefulness of reevaluating CRP for predicting mortality in hospitalized patients with CAP [33]. CRP <100 mg/l was found to be independently associated with a lower risk of mortality. In addition, a CRP level that fails to fall by 50% was independently associated with mortality. Furthermore, a study found that the changes of endothelin-1 levels on day 3 significantly improved classification of patients compared with initial PSI and endothelin-1 levels **[32]**.Other studies have evaluated the predictive value of combining biomarkers from distinct biological pathways. Onemulticenter study assessed the prognostic accuracy of five prohormones (adrenomedullin, endothelin-1, atrial-natriuretic.

D-DimerDescription:

D-dimer is the degradation product of cross linked (by factor XIII) fibrin. It reflects ongoing activation of the hemostatic system.Upon activation of either the intrinsic or extrinsic pathway of the coagulation cascade, thrombin forms and cleaves fibrinopeptide A and B from fibrinogen, resulting in soluble fibrin monomers, which then associate and form fibrin polymers. The D domains of these fibrin polymers are crosslinked by activated factor XIII, producing an insoluble crosslinked fibrin clot **[33].**Owing to the parallel activation of the fibrinolytic system to maintain proper balance between coagulation and fibrinolysis, plasmin, the end product of the fibrinolytic system, cleaves insoluble fibrin polymers, resulting in the production of fibrin degradation products (FDPs). If the polymers were crosslinked between two D domains (hence the name) of the fibrinopeptides, D-dimer is produced **[34].**

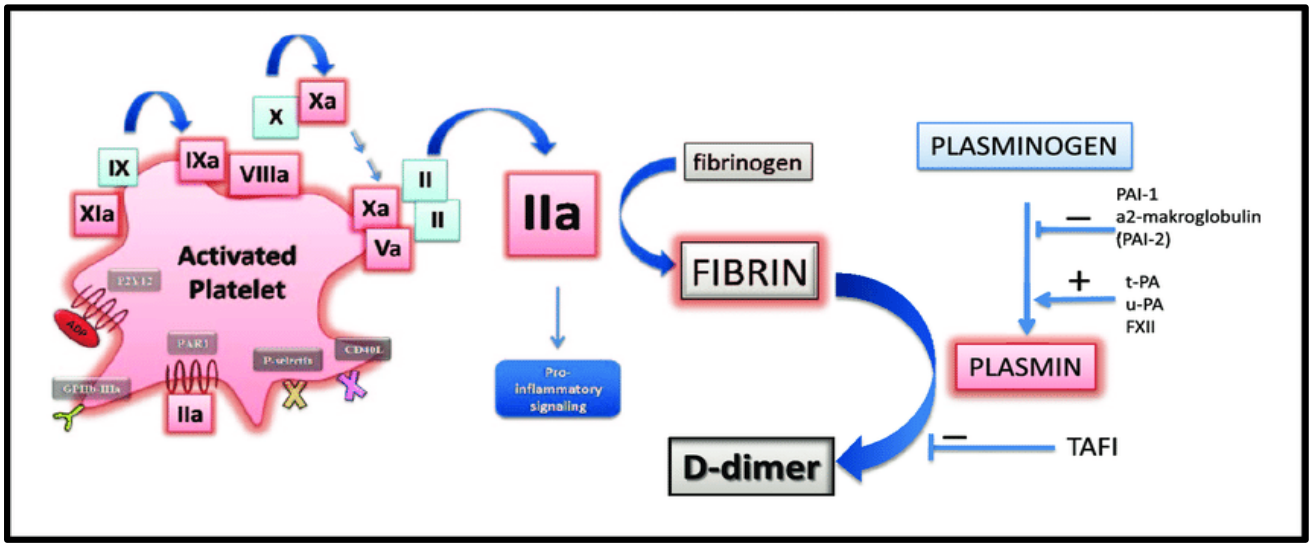

Fig. (2): D-dimer formation **[34].**

Indications and Applications of D-Dimer Test:

The principal utility of measuring D-dimer is the diagnosis of deep venous thrombosis (DVT) in an appropriate clinical setting. The clinical (pretest) probability of DVT is determined by assessing multiple factors, such as recent or ongoing therapy for cancer, immobilization of the lower extremities, recent major surgeries, localized tenderness, edema, and history of previous DVT. Based on this score, the

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probability for developing DVT is categorized as low (unlikely to develop) or high (likely to develop) **[35].**

Since D-dimer assumes activation of the coagulation and fibrinolytic systems, it is valuable in the diagnosis and the monitoring of DIC in combination with other parameters **[36]. Swanson et al.(2010) [37]**showed that a low plasma D-dimer level in pediatric patients correlates well with the absence of traumatic brain injury .In the appropriate setting, the D-dimer test yields a good test in the diagnosis of aortic dissection **[38]**In combination with other markers, D-dimer may be useful to differentiate between acute stroke and stroke-mimic conditions**[39]**.

Considerations:
The D-dimer test has a high sensitivity but low specificity. It may be increased in association with the following: **[40].** After surgical proceduresThe D-dimer test has a high sensitivity but low specificity. It may be increased in association with the following: **[40].**

- Inflammation
- Malignancy
- Trauma
- Liver disease (decreased clearance)
- Heart disease
- Hospitalized patients

Venous thromboembolic diseases are common complications in patients with cancer. Therefore, it is important to keep in mind that false-negative D-dimer results more commonly occur in this patient population.The major advantage of the D-dimer test is the excellent NPV in the appropriate clinical setting. However, since the positive predictive value (PPV) of the test is low, positive results cannot be used alone in the diagnosis of DVT/pulmonary embolism **[41].**From a practical standpoint, the D-dimer assay only measures the neo-epitope, which is formed after the crosslinking process of the fibrin polymers by factor XIII. Therefore, although it has limited importance in the assessment of primary fibrinolysis, there is no interference with fibrinogen, if it is present in the sample **[42].**

Reference Range:
The reference concentration of D-dimer is less than 0.5 µg/mL fibrinogen-equivalent units (FEU).Units are also expressed as mg/L, µg/L, or ng/Ml **[43].**The reference range/cutoff value for D-dimer is ideally established by the performing laboratory, or, if a cutoff value published in the literature is used, the value has to be determined with the same methodology, preferably from the same manufacturer.A quantitative, automated point-of-care D-dimer test has recently been developed, providing an excellent, cost-effective, and rapid tool, especially in the setting of ruling out pulmonary embolism among patients with a low probability of the condition **[44].**

The Association between Plasma D-dimer Levels and Community-Acquired Pneumonia Community-acquired pneumonia (CAP) is a significant cause of respiratory morbidity and mortality in children, especially in developing countries **[45]**. Worldwide, CAP is the leading cause of death in

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children younger than five years . Factors that increase the incidence and severity of pneumonia in children include prematurity, malnutrition, low socioeconomic status, exposure to tobacco smoke**[46]**.

D-dimer (DD) is a metabolic substance produced during the catabolization of fibrin by plasmin.D-dimer (DD) levels have been shown to increase in patients who have disorders that trigger fibrin production and catabolization; these disorders include pulmonary emboli (PE), deep vein thrombosis (DVT), solid tumors, leukemia, severe infections, trauma or a post-operative state, disseminated intravascular coagulation (DIC), pregnancy, acute stroke, sickle-cell anemia, congestive heart failure and chronic kidney failure **[47]**.

Several studies have examined the relationship between plasma D-dimer levels and the extent of disease in the lungs of CAP patients **[48]**. **Levi et al., (2003) [49]** reported a correlation between the extent of pulmonary disease, radiological appearance and plasma DD levels in severe pneumonia patients. **Ribelles et al., (2004) [50]** suggested that plasma D-dimer levels were higher in patients with lobar or multilobar pneumonia than in patients with segmental pneumonia. An increase in plasma D-dimer levels may result from the activation of the fibrinolytic system and from fibrin catabolization within the alveoli. In addition, plasma D-dimer levels may be increased by the activation of the blood coagulation process; this activation is caused by endotoxins in the Gram-negative pathogens that trigger CAP **[51].**

Plasma D-dimer levels are increased even in community-acquired pneumonia patients who did not have an accompanying disease that would normally cause such an increase**)[52]**.Multiple studies have examined the relationship between Community-acquired pneumonia (CAP) and plasmaD-dimer (DD) levels. Some of these studies suggest that an increase in D-dimer is directly related to the intra- and extra-vascular coagulation that occurs in acute and chronic lung damage in CAP cases **[53].**

Blood levels of D-dimer reflect the pathological role of coagulation and fibrinolysis in the development of acute lung injury **[54].**Coagulation abnormalities were presented in older children with severe infections and comorbidity. Plasma D-dimer correlated better than standard inflammatory markers with severity of disease and risk of mortality in patients with CAP. In predicting mortality risk, D-dimer did not show difference among the PSI score**[54]**.

During pneumonia, vascular congestion develops and the alveolar cavity fills with fibrin, due to enzymatic degradation of this fibrin by the fibrinolytic system, fibrin degradation products can be released into the circulation**[55].** Alveolar fibrin deposition is the characteristic of diverse forms of acute lung injury. Intravascular thrombosis can also occur in an acutely injured lung**[55].**

Therefore, being one of the fibrin degradation products,D-dimer levels can be increased in pneumonia**[56].**Proposed scoring systems helped to distinguish patients with CAP who can be managed at home and those with high mortality risk who need intensive care treatment **[57].**Recommended score systems are accurate, but not always easy to apply in clinical practice on admission **[58].**

Querol-Ribelles et al., (2004) [59]showed thata significant relationship was found between the presence of elevated D-dimer levels and the PSI. Elevated D-dimer levels were associated with radiologic pneumonia extension. D-dimer plasma levels could be useful for predicting clinical outcome in patients with

CAP.**Guneysel et al., (2004)[60]** found that Plasma D-dimer levels increases significantly with the severity of the CAP, A rapid quantitative D-dimer assay at admission correlates with the severity of community acquired pneumonia. D-dimer levels at admission may predict the severity of CAP, and the patients with severe CAP were associated with increased plasma D-dimer levels **[61]**.

In severe CAP, activation of the coagulation process because of the vascular damage in association with the necrosis may increase the plasma D-dimer levels**[62]**.The admission with low levels of D-dimer is associated with low risk of short term death and the major morbidity with community acquired pneumonia **[63]**.

It is well-known that D-dimer results from the breakdown of intravascular fibrin and can serve as a marker for fibrinolytic system activity. Additionally, growing evidence suggests that fibrin degradation products may enter into the circulation by the action of the alveolar space fibrinolyticactivity.Under inflammatory conditions, the alveolar hemostatic balance is shifted toward a predominance of procoagulant activity.In contrast, the fibrinolytic activity of the alveolar space was found to be markedly reduced under these conditions **[64].**D-dimer has been found to be a clinically significant marker for lymphovascular invasion and early tumor invasion in patients with solid tumors **[65].**In addition, several investigators have demonstrated that elevated D-dimer levels on the admission of critically ill patients to the ICU is associated with an increased risk of mortality **[66]**.

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