

Biomarkers improves prognostic and mortality prediction in pneumonia

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Abstract

Pneumonia exhibits mortality rates, between 20% and 50% in severe cases. Biomarkers are useful tools for antibiotic therapy modifications as well as diagnosis, prognosis and follow-up treatment of pneumonia. This review presents the biological and clinical features of various biomarkers in Pneumonia patients, including C-reactive protein, Procalcitonin, Coceptin, D-dimers, MRpro-ADM, (Mid-regional pro adrenomedullin), Corisol, Endothelin-1, Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1), Adrenomedullin, Endotoxin, Mid regional Pro-Atrial Natriuretic Peptide (MR-proANP), TNF- α Polymorphisms, Pentraxin 3.

Keywords: Pneumonia, Community-acquired, Hospital-acquired, Ventilator-associated pneumonia (VAP), Biomarkers, Point of care testing.

Introduction

Pneumonia, one of the most common infectious diseases, associated with high morbidity and mortality worldwide.¹ Pneumonia is one of the cause of death in children, killing more than 2,500 children a day globally and 7% of all deaths in adults.²

Pneumonia is considered to be the most prevalent cause of sepsis associated with the highest mortality rates.¹ Since infectious diseases are related to immune-mediated disorders, genetic susceptibility loci for immune traits can be considered as good candidates in genetic association studies of pneumonia and its complications.³

Pneumonia is classified according to the site of acquisition as community-acquired (CAP) and hospital-acquired (or nosocomial) pneumonia (HAP or NP), which includes healthcare-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP). HAP tends to be a more serious problem than CAP, since HAP patients have an increased risk of infection caused by antibiotic-resistant organisms, besides they are often burdened by comorbidities.

The first line of defence of the innate immune system is represented by pattern-recognition receptors that sense bacterial, viral or fungal molecular structures and induce systemic inflammation. Various ongoing research is being done in this field so as to put an array of biomarkers at the disposal of doctors to improve the diagnosis of pneumonia when patients present to them with cough or nonspecific symptoms which could easily be misinterpreted as symptoms of other conditions.

Some biomarkers which are still being studied for their feasible use in pneumonia; these include endotoxin, proadrenomedullin, procalcitonin soluble triggering receptor expressed on myeloid cells-1, C-

reactive protein, leukocyte count, and pro inflammatory cytokines. An optimal biomarker for bacterial pulmonary infections should grant a rapid diagnosis, have a prognostic value and expedite therapeutic determination making. The two biomarkers currently in clinical use are C-reactive protein and procalcitonin. C-reactive protein is very unspecific and elevated in bacterial as well as viral infections.⁴

Procalcitonin

The peptide PCT is a prohormone of the active hormone calcitonin that is synthesized in the C-cells of the thyroid. PCT is encoded by the *CALC-I* gene.⁵ Microbial toxins and proinflammatory mediators (IL-1 β , TNF- α , IL-6) induce a significant increase of PCT release from parenchymal organs. Increased PCT concentrations are detectable within 2 h of an infectious bacterial stimulus, which is a more prompt increase compared with CRP, but slower when compared with cytokines biomarkers.

PCT levels are not elevated in viral infections, because in contrast to bacterial infections a viral infection does not lead to a ubiquitous increase of *CALC-I* gene expression and a constitutional release of PCT from entire parenchymal tissues and extricate cell types around the body. In a meta-analysis of hospitalized patients, PCT has higher sensitivity and specificity when compared with CRP in the differential diagnosis of bacterial infections from noninfectious causes of inflammation. PCT also shows a higher sensitivity to differentiate between viral and bacterial infections.⁶

Anokhi et al⁷ (2016) as reported that PCT biomarker had area under curve of about 0.79 with the cut off range 1 to 1.25 ug/ml. The sensitivity and specificity about 80% and 96% respectively which is

statistically significant ($p < 0.001$). A Nicola et al² in 2017 as reported that PCT biomarker had Area under curve of about 0.04. The sensitivity and specificity was

found to be 95 % and 100% respectively which is statistically significant ($p < 0.001$).⁸ [Table 1] & [Fig. 1]

Table 1: Shown biomarkers in various studies & their AUC

(Biomarker) PCT	AUC (95% CI)	% Sensitivity Range (No. studies)(95% CI)	% Specificity Range (No. studies) (95% CI)	P-Value
Anokhi ⁷ et al 2016	0.79	80.0%	96%	0.001
Nicola ² et al 2017	0.04	95%	100%	0.001
sTERM-1				
Anokhi J ⁷ et al 2016	0.082	53.2%	86.3%	0.001
Yuetian ¹⁴ et al 2017	0.0831	85.5%	73.1%	0.05
MRpro-ADM				
S Akpinar ²⁰ et al 2014	0.513	66.7%	86.8%	<0.001
Bello ⁸ et al 2012	0.851	92.1%	55.1%	<0.001

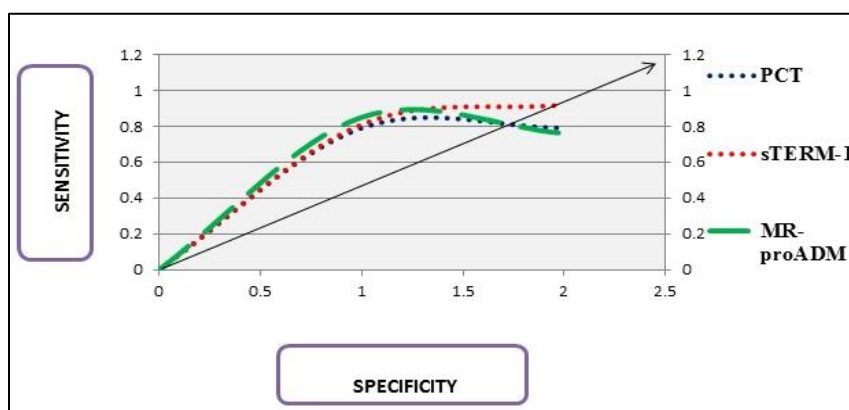


Fig. 1: AUC curves for the biomarkers used in respiratory failure
The AUC curves shown are the PCT, s TERM-1, MR-pro. ADM

Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1)

Soluble Triggering receptor expressed on myeloid cells-1 (TREM-1) is another biomarker which holds great promise when it comes to pneumonia. sTREM-1 belongs to the immunoglobulin superfamily and is involved in inflammatory response.⁹

It has the advantage of being increased during infectious processes but not in noninfectious inflammatory conditions like psoriasis, ulcerative colitis, and vasculitis. sTREM-1 exists in both amembranous and a soluble form (soluble triggering receptor expressed on myeloid cells-1; sTREM-1).¹⁰ Altitude of sTREM-1 have been created to be exalted in bronchoalveolar lavage fluids of patients with pneumonia, in the plasma of septic patients, and in the exhaled breath condensate in VAP patients.¹¹

Gibot¹¹ study documents sTREM-1 levels ≥ 5 pg/mL in bronchoalveolar lavage fluids (BAL), they approximate to 100% of VAP patients, 95% CAP patients and only 10% patients without pneumonia. A cut-off value of 5 pg/mL had a sensitivity of 98% and a specificity of 90% to predict pneumonia.¹² However, no

significant difference has been found in the levels obtained from CAP and VAP patients.

In patients who developed VAP, sTREM-1 levels in BAL were found to start rising 6 days prior to VAP diagnosis. sTREM-1 Early treatment can be started in VAP patients when sTREM-1 is used. Furthermore, Gibot et al. stated that combined measurement of serum PCT and BAL sTREM-1 can be useful in differentiating VAP from extrapulmonary infection.¹³

Anokhi et al⁷ (2016) as reported that sTREM-1 biomarker had Area under curve of about 0.082 with the cut off range 755pg/ml. The sensitivity and specificity was found to be 53.2% and 86.3% respectively and statistically significant ($p < 0.001$). Youtian et al¹⁴ (2017) as reported that sTREM-1 biomarker had Area under curve of about 0.0831 with the cut off range 23.61 ug/ml. The sensitivity and specificity was found to be 85.5% and 73% respectively which is statistically significant ($p < 0.05$) with r-ratio-0.78. [Table 1]

Mid-regional Proadrenomedullin

Human adrenomedullin (ADM) is a 52-amino acid peptide that is synthesized as part of pre-pro-

adrenomedullin, a larger precursor molecule.¹⁵ This peptide is a secretory product of the vascular endothelium, the ADM gene is expressed in a wide range of tissues but initial studies on the distribution of this gene have suggested that the highest levels of expression are observed in the adrenal medulla, ventricular chambers, kidneys and lungs.¹⁶ MR-proADM is a stable, functionally irrelevant fragment of ADM degradation that is used in some studies because of its better technical viability.¹⁶

The ADM levels upon admission were significantly higher in the patients who died during the follow-up compared to the patients who survived: 2.1 (1.5–3.0 nmol/L) vs. 1.0 (0.6–1.6 nmol/L) (p,0.001). An analysis of the “treatment failure” and “death” outcomes demonstrated that the prognostic accuracy of ADM was similar to the PSI score but higher than other parameters.¹⁷

R Cavallazzi et al¹⁸ -2014 in his study proved elevated MR-proADM was associated with an increase in short-term mortality (OR Z 6.8; 95% CI: 4.65e10.13; P value < 0.001) and complications (OR Z 5.0; 95% CI: 3.86 to 6.49; P value < 0.001). The sensitivity ranged from 0.62 to 0.80, while the specificity ranged from 0.53 to 0.86. [Table 1]

According to S Akpınar et al¹⁹ 2014, the values of area under the ROC curve for each parameter MR-proADM AUC, area under the curve; 0.513, Standard error 0.081, P-value P<0.001 MR-ProADM and PSI combination had 92.1% specificity and 50.1% sensitivity to predict mortality in 4 weeks. When MR-proADM and Pneumonia Severity Index (PSI)

combination showed 71% specificity and 84% sensitivity to expect 8-week mortality.

D-dimers

D-dimers are released into the blood during the dissolution process of fibrin emboli in the fibrinolytic system. D-dimers are the smallest fragments of the fibrin degradation, and these proteins are detectable in blood plasma.

The most important application of D-dimers is related to thrombotic events. D-dimers have been studied extensively as a diagnostic method for deep vein thrombosis (DVT) and pulmonary embolism (PE).²⁰ A negative result has diagnostic utility that is comparable to normal lung scans or negative duplex ultrasound findings.²¹ The application of the D-dimers analysis to CAP is a novel approach.

According to Fruchter et al²² and Jose. M et al D-dimer biomarker had area under curve 0.0862 and 0.78 cut off range 1.52 µg/ml and 0.91 µg/ml respectively. A Karalezli et al²³ (2009) as reported that D-dimer biomarker had Area under curve of about 0.82. The sensitivity and specificity were 60.2% and 94.2% respectively which was statistically significant (p<0.001). [Table 2]

Jose. M et al²⁴ as reported that D-dimer biomarker had Area under curve of about 0.86 with the cut off range 0.91/ml. The sensitivity and specificity was found to be high about 97.4% and 98.1% respectively which is statistically significant (p<0.001). [Fig. 2]

Table 2: Area under curve values for D-dimer, Endotoxin, TNF- α, Pentraxin-3.

Area Under Curve Values Based On Different Biomarkers			
Author	Biomarker	AUC Values	P-values
O Fruchter et al ³⁸	D-dimer	0.086	p<0.011
Jose M et al ²⁴	D-dimer	0.86	p<0.001
Ledox D et al ²⁸	Endotoxin	0.92	p<0.001
Kilmiec E et al ²⁹	Endotoxin	4.23	p<0.001
Menedez R et al ³⁷	TNF-α	0.88	p<0.001
Kao SJ et al ⁴¹	Pentraxin-3	0.29	p<0.001
Tommaso et al ⁴²	Pentraxin-3	0.82	p<0.001

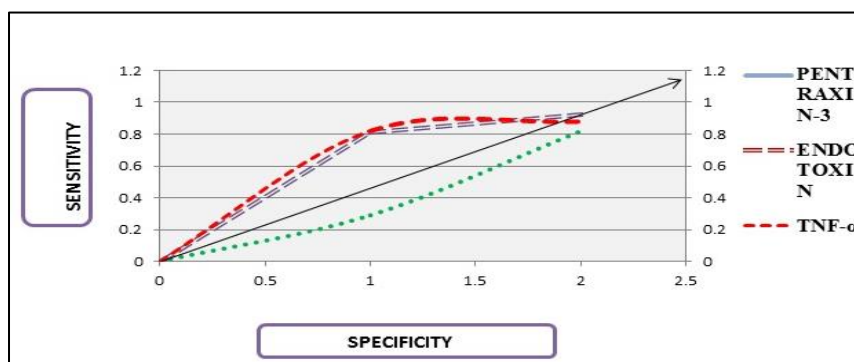


Fig. 2: AUC curves for the biomarkers used in respiratory failure
The AUC curves shown are the pentrasin-3, Endotoxin, TNF-α

Endotoxin

Endotoxin measurements in BAL showed a relation between its concentration and the quantity of Gram-negative bacteria in BAL fluids of VAP patients. Endotoxin allows rapid diagnosis of Gram-negative bacterial pneumonia.²⁵

Flanagan et al found that endotoxin level within four days of starting mechanical ventilation is an accurate as well as a rapid way for diagnosing VAP.²⁶ In a study conducted by Nys M et al., it was established that antimicrobial Gram-negative therapy may be justified according to the results of endotoxin level in BAL fluids of ventilated patients having pneumonia.²⁷

Ledox D et al²⁸ reported that Endotoxin biomarker had Area under curve of about 0.92. The sensitivity and specificity were 82.2% and 95.6% respectively which is statistically significant ($p < 0.001$). [Fig. 2] Kilmiec E et al²⁹ in 2018 has documented that Endotoxin biomarker had Area under curve of about 4.23. The sensitivity and specificity were 93% and 95% and statistically significant ($p < 0.001$) [Table 2].

TNF- α Polymorphisms

TNF- α is a potential proinflammatory cytokine that plays a critical role in inflammatory and immune responses. Excessive TNF- α production contributed to lung injury in a variety of diseases^{30,31} and increased the risk of sepsis.³² Furthermore, Puren et al³⁶ As a biomarker, levels of TNF- α in plasma indicates the severity of pneumonia.⁴⁷

In mechanically ventilated patients, Monto'n and colleagues found that serum TNF- α level was significantly higher in patients with pneumonia compared with controls.³³ In addition, Bauer et al. showed that levels of serum TNF- α was strongly associated with the degree of lung injury.^{34,35}

According to Kilmiec et al,²⁹ TNF- α sensitivity and specificity were 93% and 95% respectively statistical significance $P < 0.03$. Menede et al³⁷ reported that TNF- α biomarker had Area under curve of about 0.88. The sensitivity and specificity about 95% and 98% and statistically significant ($p < 0.001$) [Table 2]

Pentraxin 3

In Bronchoalveolar lavage fluid PTX3 levels and diagnosis of pneumonia represents one of the most widespread infections in intubated ICU patients and is associated with significant morbidity (for example, prolonged mechanical ventilation, end-stage organ failure), costs and mortality.³⁸ Timely and accurate diagnosis of pneumonia is crucial to starting appropriate treatment and improving patients' recovery and survival. However, to date, a rapid and accurate approach to diagnose pneumonia in intubated critically ill patients is lacking.³⁹

In the subset of patients, pretest probability was higher and the diagnostic accuracy of a screening test such as PTX3 was expected to be poorer and

oxygenation did not differ between infected and uninfected patients. Other studies have proved that plasma PTX3 level is correlated with the severity of ARDS.⁴⁰

Earlier in 2013 Kao SJ et al⁴¹ reported that Penraxis-3 biomarker had Area under curve of about 0.290. The sensitivity (85%) and specificity (93%) and statistically significant ($p < 0.001$) [Fig. 2]. In 2015 Tommaso et al⁴² as reported that Penraxis-3 biomarker had Area under curve of about 0.827. The sensitivity (92%) and specificity (60%) and statistically significant ($p < 0.001$).

Disadvantages

Today, no biomarker is sensitive enough in LRTI to definitely exclude bacterial infection. And it is not possible to withhold an antibiotic therapy in a critically ill patient with suspected severe respiratory infection on the basis of a single measurement of a biomarker. If the biomarker values remain unremarkable or low at follow-up measurements, a relevant severe infection is very unlikely.⁴³

Earlier study done by documents even the PCT-guided antimicrobial escalation strategy with daily measurements of PCT in the ICU were not superior to a standard strategy of antimicrobial escalation and did not improve survival.⁴⁴ Thus, in the ICU setting PCT is valuable for the management of de-escalation but not escalation of antibiotic therapy.

Advantages: Biomarkers show improved validation in the diagnosis of pulmonary infections than, imaging techniques.⁴⁵ Biomarkers can also be used in a broad setting as a point-of-care diagnostic and without any risk to the patient compared with radiation exposure during chest x-ray or computed tomography. The serial measurements of biomarkers can reflect the dynamics of CAP.⁴⁶ They are a useful tool to monitor resolution of Pneumonia, which goes along with a decrease in elevated biomarker levels.

Conclusion

Biomarkers are used as Point-of-care tests in emergency rooms and out patients department. Clinicians can make real-time decisions about the care and the admission path of patients. Once there is a complete understanding of all the information that can be gained from these simple tests, there will be greater insight into the future management of patients with Pneumonia.

The combination of several biomarkers reflecting different pathophysiological aspects of Pneumonia, such as PCT for bacterial infection and Pentraxin 3, MRproADM for inflammation and circulation, could offer future potential for improved management in Pneumonia. In near future biomarkers will reflect in improved patients outcome.

Conflict of Interest: None

Key Issues

1. Procalcitonin (PCT) improves the diagnosis of clinically-relevant bacterial pulmonary infections compared with C-reactive protein or leukocytes.
2. In lower respiratory tract infections in general a PCT-guided algorithm significantly reduces antibiotic exposure without a negative influence on clinical outcome compared with standard therapy.
3. Inflammatory biomarkers are not helpful for the individual diagnosis of microbiological etiology of pneumonia.
4. In Pneumonia, cardiovascular biomarkers have a higher prognostic value compared with inflammatory biomarkers.

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