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The Diagnostic Value of Procalcitonin in Differentiation of Exacerbation and Pneumonia in Patients with Idiopathic Pulmonary Fibrosis

İdiyopatik Pulmoner Fibrozis Hastalarında Alevlenme ve Pnömoni Ayrımında Prokalsitoninin Tanısal Değeri

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ABSTRACT

Background: It is often difficult to distinguish between acute exacerbations of idiopathic pulmonary fibrosis (IPF-AE) and pneumonia occurring in patients with IPF (IPF-PNA). Procalcitonin (PCT) is a highly specific biomarker for bacterial infections. The diagnostic value of PCT in differentiating IPF-AE and IPF-PNA was investigated in the study.

Materials and Methods: All hospitalized patients with IPF-AE and IPF-PNA between January 2015 and June 2018 were evaluated. Demographic data, C-reactive protein (CRP) and PCT levels, the duration of hospitalization was recorded.

Results: A total of 44 eligible patients were randomized into two groups at a 1:1 ratio. The PCT and CRP levels were significantly higher in IPF-PNA group than in IPF-AE group (1.727±3.549 ng/mL vs. 0.642±0.049 ng/mL, p<0.001 for PCT, and 148.4±97.7 mg/L vs. 55.4±47.2 mg/L, p<0.001 for CRP). The duration of hospitalization was longer in IPF-PNA group (15.18±8.3 days vs. 8.54±2.5 days, p=0.001) than in IPF-AE group. Furthermore, when 0.1065 ng/mL was accepted as the cut-off value for PCT, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 0.955, 0.773, 0.808, and 0.944, respectively. When 35 mg/L was accepted as the cut-off value for CRP, the sensitivity, specificity, PPV and NPV were 0.955, 0.500, 0.656 and 0.917, respectively.

Conclusion: PCT and CRP levels were significantly higher in IPF-PNA group than in IPF-AE group. Compared with CRP, PCT was found to be a more sensitive biomarker in differentiating IPF-PNA from IPF-AE.

Keywords: Differential diagnosis, idiopathic pulmonary fibrosis, exacerbation, pneumonia, procalcitonin

ÖZ

Amaç: İdiyopatik pulmoner fibrozis (İPF) tanılı olgularda, İPF akut alevlenmesi (İPF-AA) ile pnömoninin (İPF-pnömoni) ayrımını yapmak genellikle zordur. Procalcitonin (PKT) bakteriyel pnömoniler için oldukça spesifik bir biyobelirteçtir. Bu çalışmada PKT'nin İPF-AA ile İPF-pnömoni ayrımındaki tanısal değeri araştırılmıştır.

Gereç ve Yöntemler: Ocak 2015 ile Haziran 2018 tarihleri arasında İPF-AA ve İPF-pnömoni tanıları ile hastaneye yatırılan olgular çalışmaya alınmış; demografik özellikleri, C-reaktif protein (CRP) ve PKT seviyeleri ile hastane yatış süreleri kaydedilmiştir.

Bulgular: Toplam 44 uygun hasta 1:1 oranında iki gruba randomize edilmiştir. PKT ve CRP seviyeleri İPF-pnömoni grubunda İPF-AA grubuna göre anlamlı olarak daha yüksek saptandı (PKT için 1.727±3.549 ng/mL'ye karşılık 0.642±0.049 ng/mL, p<0.001, ve CRP için 148.4±97.7 mg/L'ye karşılık 55.4±47.2 mg/L, p<0.001). Hastane yatış süresi İPF-pnömoni grubunda anlamlı olarak daha uzundu (15.18±8.3 gün'e karşılık 8.54±2.5 gün, p=0.001). Ayrıca, PKT için 0.1065 ng/mL eşik değer kabul edildiğinde, sensitivite, spesifisite,

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pozitif prediktif değer (PPD) ve negatif prediktif değer (NPD) sırası ile 0.955, 0.773, 0.808 ve 0.944 saptandı. CRP için eşik değer 35 mg/L olarak kabul edildiğinde ise sensitivite, spesifisite, PPD ve NPD sırası ile 0.955, 0.500, 0.656 ve 0.917 idi.

Sonuç: PKT ve CRP düzeyleri İPF-pnömoni grubunda İPF-AA grubuna göre anlamlı olarak yüksek saptandı. CRP ile karşılaştırıldığında PKT'nin, İPF-AA ile İPF-pnömoniyi ayırmada daha sensitif bir biyobelirteç olduğu gözlendi.

Anahtar Kelimeler: Ayırıcı tanı, idiyopatik pulmoner fibrozis, alevlenme, pnömoni, prokalsitonin

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease with a poor prognosis which is frequently diagnosed in older ages (1). Patients with IPF may experience sudden onset respiratory worsening, most of which is idiopathic and defined as acute exacerbation of IPF (IPF-AE). It is usually challenging to differentiate IPF-AE from heart failure, bilateral pneumonia (PNA), or pulmonary embolism (2). Cough, increased expectoration, dyspnea, hypoxemia, and newly formed parenchymal infiltrations on chest imaging are non-specific for IPF-AE; moreover, these observations can also be seen in bacterial PNA (3). Procalcitonin (PCT), the precursor of calcitonin, is produced by neuroendocrine cells when confronted with microbial toxins and inflammatory mediators. It is a highly specific biomarker for severe bacterial infections in suspected cases of sepsis (4,5). The objective of the study was to investigate the diagnostic value of PCT in the differential diagnosis of acute exacerbation and pneumonia in IPF patients.

Material and Methods

The data of IPF inpatients were retrospectively analyzed at a tertiary referral hospital between January 2015 and June 2018. Age, gender, presenting symptoms, duration of hospitalization, vital signs, biochemical markers [including C-reactive protein (CRP) and PCT levels], and radiological findings were recorded. Patients with incomplete data such as absence of thorax computerized tomography/high-resolution computerized tomography (CT/HRCT) and those who were hospitalized for other conditions such as pulmonary embolism, decompensated heart failure, pneumothorax, and acute renal failure were excluded from the study. Since the study was retrospective, patient consent was not obtained.

The diagnosis of IPF-AE was made according to the criteria suggested by the ATS/ERS/JRS/ALAT committee and the International Working Group Report by Collard et al. (6,7). The presence of fever (>37.5 °C), pneumonic consolidation in thoracic imaging, and positive sputum and/or blood culture were suggestive of PNA. On the other hand, if the patients had progressive dyspnea in the previous month, recently developed bilateral ground-glass opacities, and/or consolidations with a usual interstitial PNA pattern without heart failure or fluid retention, the diagnosis was IPF-AE (7).

CRP and PCT levels were measured using an immunoturbidimetric assay via Beckman Coulter AU Analyzer (US).

Study approval was taken from the Karabük University Ethics Committee on 03.01.2018 with verdict number 1/2.

Power Analysis

In the a priori power (G*Power Version 3.0) analysis in independent groups based on the data (effect size d=0.926, α=0.05, power=0.80) of a study by Ding et al. (8) on procalcitonin-guided antibiotic use in IPF-AE, it was calculated that at least 16 independent control and 16 experimental subjects were required for a study investigating procalcitonin testing. Each group of this independent study consisted of 22 subjects.

Statistical Analysis

The minimum (min), maximum (max), and mean ± standard deviation (SD) was calculated for all variables. The SPSS for Mac 20.0 package program (SPSS Inc, Chicago, IL, USA) was used to analyze the data. Frequency and percentage for discrete data and mean ± SD for continuous data were used in descriptive statistics. Normally distributed continuous data were analyzed by the Kolmogorov-Smirnov test while all nominal data were analyzed by the chi-square test. Non-parametric distributions were compared with the Mann-Whitney U test, and mean values with parametric distribution between groups were analyzed with Student's t-test. Receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off values of the PCT and CRP to predict PNA. A p-value <0.05 was considered as statistically significant.

Results

Fifty-seven IPF patients were evaluated; 13 of them were excluded due to pulmonary embolism (n=1), decompensated heart failure (n=3), absence of HRCT scans (n=3), and failure to obtain laboratory work-up (n=6). A total of 44 eligible

patients were randomized into two groups at a 1:1 ratio. The mean age was 62.9±7.6 years in the pneumonia in patients with IPF (IPF-PNA) group and 67.3±6.6 years in the IPF-AE, with a statistically significant difference (p=0.049). The number of male patients was significantly higher in the IPF-PNA group (p=0.007) than in the IPF-AE.

The PCT levels were significantly higher in the IPF-PNA group than in the IPF-AE [0.253 ng/mL (0.10-12) vs. 0.05 ng/mL (0-0.15), p<0.001]. Additionally, the CRP levels were significantly higher in the IPF-PNA group than in the IPF-AE [129 mg/L (33.6-413) vs. 37.9 mg/L (4-152), p<0.001] (Figure 1). Also, the hospital stay was significantly higher in the IPF-PNA group (15.18±8.3 days vs. 8.54±2.5 days, p=0.001). Demographical data and laboratory results are summarized in Table 1.

ROC analysis was performed for identification of the PCT and CRP cut-off values to predict PNA in worsening IPF (Figure 2). When 0.1065 ng/mL was taken as the cut-off for PCT, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 0.955, 0.773, 0.808, and 0.944, respectively. When 35 mg/L was taken as the cut-off for CRP, the results were 0.955, 0.500, 0.656, and 0.917, respectively (ROC graphic, Table 2).

Regarding sputum analyses, the causative pathogens identified in the IPF-PNA group were *Klebsiella pneumoniae* (n=3), *Pseudomonas aeruginosa* (n=1), and *Escherichia coli* (n=1).

Discussion

In our study, the PCT and CRP levels were significantly higher in the IPF-PNA group when compared with the IPF-AE group. Also, the IPF-PNA group had a longer hospital stay. When the cut-off values of the CRP and PCT levels were specified, PCT was found to be a more sensitive biomarker for differentiating between IPF-PNA and IPF-AE.

The fact that both IPF-PNA and IPF-AE groups have similar clinical, laboratory, and radiologic findings makes it difficult to decide on antibiotic use. The differentiation between patients who require antibiotic treatment and

Table 1. General characteristics of the IPF-PNA and IPF-AE study groups

Characteristics	IPF-AE (n=22)	IPF-PNA (n=22)	[a]p-value
Age, years	62.9±7.6	67.3±6.6	0.049
Female/male	10/12	2/20	0.007
PCT, ng/mL	0.0642±0.049	1.727±3.549	<0.001
CRP, mg/L	55.4±47.2	148.4±97.7	<0.001
ESR, mm/hr	48.7±28.8	64.8±24.6	0.157
NLR	6.08±4.5	9.56±7.9	0.110
PLR	21.93±19.8	38.06±48.6	0.054
WBC	11.83±3.57	14.0±6.38	0.051
Neut	72.4±18.3	74.3±22.2	0.764
Lymph	18.9±14.4	12.3±7.1	0.059
Eos	1.4±1.5	1.3±1.5	0.571
Plt.	279.7±101.1	284.0±30.5	0.904
Length of stay, day	8.54±2.5	15.18±8.3	0.001

[a]: Mann-Whitney U test, IPF: Idiopathic pulmonary fibrosis, IPF-PNA: Pneumonia in patients with IPF, IPF-AE: Acute exacerbation of IPF, PCT: Procalcitonin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, WBC: White blood cells, Neut: Neutrophil, Lymph: Lymphocyte, Eos: Eosinophil, Plt: Platelet

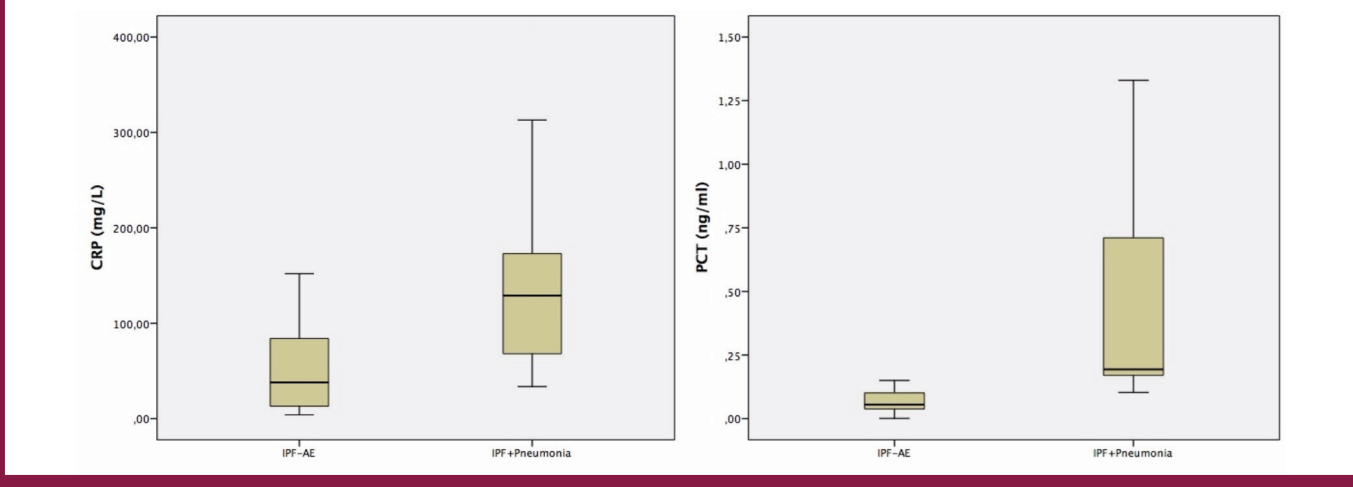

Figure 1. Distribution of PCT and CRP levels between study groups
PCT: Procalcitonin, CRP: C-reactive protein, IPF-AE: Acute exacerbation of IPF, IPF: Idiopathic pulmonary fibrosis

those who do not remains a challenge, as reliable clinical and/or microbiological parameters that are easily accessible during sampling are still inadequate. At this stage, the delayed availability of culture results, low sensitivities of some tests, and the contamination risk, especially in sputum cultures, pose challenges in making decisions regarding antibiotic usage. Inflammatory markers like CRP or white blood cells (WBC) are faster and more easily accessible indicators for indicating infection in daily practice, yet lack specificity for bacterial infections. This scenario has prompted the exploration of new biomarkers that are more discriminative. One of these biomarkers mentioned is PCT.

Procalcitonin is produced by the medullary C glands of the thyroid and neuroendocrine cells of the lung in the healthy population (9,10). It is a member of the CAPA protein family and is a 116 amino acid polypeptide (11). It rapidly converts into the 32 amino acid hormone calcitonin, which plays an important role in calcium hemostasis, and therefore presents in very small amounts in circulation (<0.01 ng/mL) (12). Depending on the type and severity of infection, varying amounts of PCT are released into the circulation from other parenchymal tissues and differentiated cell types (13,14). PCT serum levels are increased in bacterial, fungal, and parasitic infections, but do not rise or slightly increase during viral infections and non-infectious inflammatory reactions (14). It is also critical to differentiate between infectious and non-infectious exacerbations in IPF patients because bacterial PNA stands as a well-known leading cause of mortality in patients with IPF (7,15). Additionally, the treatments for these two conditions are very different from each other; while antibiotherapy is required for infectious exacerbations, systemic glucocorticoids are suggested for non-infectious exacerbations (16). Ding et al. (8) showed that PCT-guided antibiotic use in IPF-AE reduced antibiotic exposure and duration of antibiotic treatment, indicating that PCT is a useful biomarker in the management of these patients. In the light of this information, PCT, which gives quick result and provides practical approach, was preferred in our study design. The outcomes of our study also demonstrate that PCT can be employed as a biomarker to differentiate between IPF-AE and IPF-PNA.

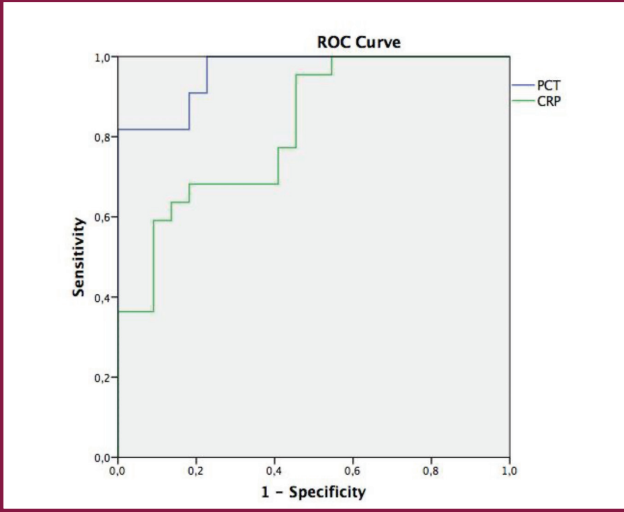

Figure 2. ROC curve for defining the PCT and CRP cut-off point predicting pneumonia

PCT: Procalcitonin, CRP: C-reactive protein, ROC: Receiver operating characteristic

Procalcitonin emerges as a more specific biomarker for the identification of bacterial infections. PCT is produced in response to endotoxins or bacterial infections, triggered by cytokines like interleukin (IL)-1b, tumor necrosis factor (TNF)-a, and IL-6 (17). The elevation of PCT levels is attenuated by interferon (INF)-ɣ released in viral infections, rendering it lower in viral infections and more specific for bacterial infections, allowing for the differentiation between bacterial and viral illnesses. A meta-analysis performed by Simon et al. (18) showed that PCT is more sensitive and specific than CRP for the differential diagnosis of viral and bacterial infection. It also helps in planning to start or cease antibiotic treatments (19). Because unnecessary and prolonged use of antibiotics increases antibiotic resistance and the risk of fungal infections (20,21). The widespread use of antibiotics is also a public health issue due to increased healthcare costs (22). However, avoiding antibiotics when PNA is suspected, is as dangerous as the overuse of antibiotics (23,24). The role of PCT has been researched in many different infectious diseases. ProHOSP study has shown that using PCT may reduce antibiotic use in emergency departments in infections of lower respiratory tract such as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbations of chronic obstructive pulmonary disease (25). Jain et al. (26) have illustrated

Table 2. Diagnostic accuracy rates of PCT and CRP in the differential diagnosis of IPF-PNA and IPF-AE study groups

	Cut-off	AUC	95% CI	Sensitivity/specifity	PPV	NPV	NLR	Accuracy	p-value
PCT, ng/mL	0.1065*	0.963	95% CI: 0.916-1.000	0.955/0.773	0.808	0.944	0.05	0.863	<0.001
CRP, mg/L	35**	0.820	95% CI: 0.699-0.942	0.955/0.500	0.656	0.917	0.09	0.727	<0.001

IPF: Idiopathic pulmonary fibrosis, IPF-PNA: pneumonia in patients with IPF, IPF-AE: Acute exacerbation of IPF, AUC: The area under the ROC curve, PPV: Positive predictive value, NPV: Negative predictive value, NLR: Negative likelihood ratio, PCT: Procalcitonin, CRP: C-reactive protein, *: ng/mL, **: mg/L

that PCT may be helpful in antibiotic decision-making for CAP. Moisa et al. (27) evaluated hematological biomarkers in distinguishing viral and bacterial sepsis and found that PCT was the best discriminative parameter among all measured parameters. Another retrospective study showed that PCT and CRP levels in non-neutropenic lung cancer patients with tumor fever to differentiate localized bacterial infection from bacteremia, and compared with CRP, PCT was to be more accurate in differentiating tumor fever from bacterial infections (28). Wang et al. (29) found that PCT was a more useful biomarker than CRP to differentiate acute radiation pneumonitis from bacterial PNA in patients with lung cancer. In a study examining WBC, CRP, and PCT levels of patients with cryptogenic organizing pneumonia (COP), another interstitial lung disease, were compared with CAP patients; PCT was shown to be a more useful biomarker in differentiating COP from CAP (30). In our study, which aimed to differentiate pneumonia from exacerbation according to inflammatory biomarkers measured on the first day of hospitalization, PCT was found to be more sensitive than CRP in predicting exacerbation in patients with IPF, which is consistent with the literature.

A systematic review assessing PCT's role as a predictor of sepsis has indicated that surpassing threshold levels in PCT could be a superior indicator compared to CRP. Nonetheless, it's noted that the cut-off values for patients can vary due to diverse surgical procedures, medication use, and immune system conditions (31). Ding et al. (8) have evaluated the feasibility of PCT in navigating antibiotic use in IPF-AE. One group of patients with IPF-AE was given antibiotics according to daily routine practice, whereas the other group was treated with the guidance of PCT levels. This study concluded that the use of 0.25 ng/mL as a threshold level for PCT decreased the length of antibiotic treatment and the number of patients receiving antibiotics (8). Sim et al. (3) have retrospectively evaluated 21 cases with interstitial lung disease who had recently increased dyspnea and worsened radiological findings. In nine of 21 patients, the cause of deterioration was bacterial PNA. They concluded that a cut-off value of 0.1 ng/mL for PCT may clearly indicate IPF-AE and facilitate clinical decision-making. At this threshold, the sensitivity, specificity, and NPV of serum PCT level are 88.9%, 100.0%, and 92.3%, respectively (3). In our study, when 0.1065 ng/mL was taken as the cut-off for PCT, the results were 95.5%, 77.3%, and 94.4%, respectively. Our findings are consistent with the previous study. Further large-scale studies are still needed to identify the exact cut-off values in more homogenous patient populations.

IPF is more common in older adult men and Kärkkäinen et al. (32) have reported that this is a risk factor for mortality in IPF-PNA patients. As far as we know, there is no data regarding the higher frequency of IPF-PNA cases in males compared to IPF-AE cases. A statistically significant predominance of male-sex in the IPF-PNA group was seen in this study.

Study Limitations

The limitations of the study can be described as the retrospective structure and the small sample size. Given the retrospective nature of our study, decisions regarding antibiotic initiation and cessation were not solely based on PCT. In order to comprehensively understand the role of this biomarker in guiding the clinical decision-making process, prospective studies are imperative. Additionally, it's noteworthy that most patients received PNA diagnoses through multidisciplinary evaluations and clinical and radiological assessments. Although this approach proves satisfactory in diagnosis, the absence of comprehensive microbiological confirmation constitutes another limitation of our study.

Conclusion

PCT and CRP levels were higher in the IPF-PNA than in the IPF-AE. Compared with CRP, PCT was found to be a more sensitive biomarker in differentiating IPF-PNA from IPF-AE. Future studies with larger study populations are essential on this issue.

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Ethics

Ethics Committee Approval: Study approval was taken from the Karabük University Ethics Committee on 03.01.2018 with verdict number 1/2.

Informed Consent: Since the study was retrospective, patient consent was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.D., E.T., B.Z.Y., D.D., E.G.U.C., D.T., H.Ç., E.Ç., Concept: B.D., E.T., B.Z.Y., D.D., D.T., F.E.G., H.Ç., E.Ç., Design: B.D., E.T., B.Z.Y., D.D., E.G.U.C., F.E.G., H.Ç., E.Ç., Data Collection or Processing: B.D., E.G.U.C., D.T., F.E.G., Analysis or Interpretation: B.D., E.T., B.Z.Y., D.D., E.G.U.C., D.T., F.E.G., E.Ç., Literature Search: B.D., E.T., E.G.U.C., D.T., F.E.G., H.Ç., Writing: B.D., E.T., B.Z.Y., D.D., H.Ç., E.Ç.

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References

1. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205:18-47. [Crossref]
2. Luppi F, Cerri S, Taddei S, Ferrara G, Cottin V. Acute exacerbation of idiopathic pulmonary fibrosis: a clinical review. Intern Emerg Med. 2015;10:401-411. [Crossref]
3. Sim JK, Oh JY, Lee EJ, Hur GY, Lee SH, Lee SY, et al. Serum procalsitonin for differential diagnosis of acute exacerbation and bacterial pneumonia in patients with interstitial lung disease. Am J Med Sci. 2016;351:499-505. [Crossref]
4. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalsitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375:463-474. [Crossref]
5. Erenler AK, Yapar D, Terzi Ö. Comparison of Procalcitonin and C-reactive Protein in Differential Diagnosis of Sepsis and Severe Sepsis in Emergency Department. Dicle Medical Journal. 2017;44:175-182. [Crossref]
6. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198:44-68. [Crossref]
7. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med. 2016;194:265-275. [Crossref]
8. Ding J, Chen Z, Feng K. Procalcitonin-guided antibiotic use in acute exacerbations of idiopathic pulmonary fibrosis. Int J Med Sci. 2013;10:903-907. [Crossref]
9. Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab. 2004;89:1512-1525. [Crossref]
10. Han X, Zhong H, Hong D, Li C, Su H, Xu K. Elevated procalcitonin levels in primary hepatic neuroendocrine carcinoma: Case report and literature review. Medicine (Baltimore) 2020;99:e21210. [Crossref]
11. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. Crit Care Med. 2008;36:941-952. [Crossref]
12. Irwin AD, Carrol ED. Procalcitonin. Arch Dis Child Educ Pract Ed. 2011;96:228-233. [Crossref]
13. Christ-Crain M, Müller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. Eur Respir J. 2007;30:556-573. [Crossref]
14. Reinhart K, Karzai W, Meisner M. Procalcitonin as a marker of the systemic inflammatory response to infection. Intensive Care Med. 2000;26:1193-1200. [Crossref]
15. Shaddock EJ. How and when to use common biomarkers in community-acquired pneumonia. Pneumonia (Nathan). 2016;8:17. [Crossref]
16. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788-824. [Crossref]
17. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. J Infect Dis. 2000;181:176-180. [Crossref]
18. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004;39:206-217. [Crossref]
19. Jiang R, Han B, Dou C, Zhou F, Cao B, Li X. Analysis of antibiotic usage for viral community-acquired pneumonia in adults. Front Med. 2021;15:139-143. [Crossref]
20. Antoniou KM, Cottin V. The challenge of acute exacerbation of pulmonary fibrosis. Respiration. 2012;83:13-16. [Crossref]
21. Juarez MM, Chan AL, Norris AG, Morrissey BM, Albertson TE. Acute exacerbation of idiopathic pulmonary fibrosis-a review of current and novel pharmacotherapies. J Thorac Dis. 2015;7:499-519. [Crossref]
22. Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CCH, Doi Y, et al. Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection. N Engl J Med. 2018;379:236-249. [Crossref]
23. Alyacoubi S, Abuowda Y, Albarqouni L, Böttcher B, Elessi K. Inpatient management of community-acquired pneumonia at the European Gaza Hospital: a clinical audit. Lancet. 2018;391(Suppl 2):40. [Crossref]
24. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med. 2004;164:637-644. [Crossref]
25. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, et al. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. BMC Health Serv Res. 2007;7:102. [Crossref]
26. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415-427. [Crossref]
27. Moisa E, Dutu M, Corneci D, Grintescu IM, Negoita S. Hematological Parameters and Procalcitonin as Discriminants between Bacterial Pneumonia-Induced Sepsis and Viral Sepsis Secondary to COVID-19: A Retrospective Single-Center Analysis. Int J Mol Sci. 2023;24:5146. [Crossref]
28. Zhao Z, Li X, Zhao Y, Wang D, Li Y, Liu L, et al. Role of C-reactive protein and procalcitonin in discriminating between infectious fever and tumor fever in non-neutropenic lung cancer patients. Medicine (Baltimore). 2018;97:e11930. [Crossref]
29. Wang Z, Huo B, Wu Q, Dong L, Fu H, Wang S, et al. The role of procalcitonin in differential diagnosis between acute radiation pneumonitis and bacterial pneumonia in lung cancer patients receiving thoracic radiotherapy. Sci Rep. 2020;10:2941. [Crossref]
30. Ito A, Ishida T, Tachibana H, Arita M, Yamazaki A, Washio Y. Utility of procalcitonin for differentiating cryptogenic organising pneumonia from community-acquired pneumonia. Clin Chem Lab Med. 2019;57:1632-1637. [Crossref]
31. Hassan J, Khan S, Zahra R, Razaq A, Zain A, Razaq L, et al. Role of Procalcitonin and C-reactive Protein as Predictors of Sepsis and in Managing Sepsis in Postoperative Patients: A Systematic Review. Cureus. 2022;14:e31067. [Crossref]
32. Kärkkäinen M, Nurmi H, Kettunen HP, Selander T, Purokivi M, Kaarteenaho R. Underlying and immediate causes of death in patients with idiopathic pulmonary fibrosis. BMC Pulm Med. 2018;18:69. [Crossref]