International Journal of Community Medicine and Public Health
Samiullah S et al. Int J Community Med Public Health. 2024 Feb;11(2):1011-1015
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20240298

Review Article

Unveiling the role of procalcitonin in COVID-19: a literature review

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Received: 19 November 2023
Revised: 12 January 2024
Accepted: 16 January 2024

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ABSTRACT

Procalcitonin (PCT), a key hormone regulating calcium homeostasis, has previously shown the potential to differentiate between bacterial and viral infections. However, when we move further into the field of COVID-19 pandemic, an unprecedented question was raised: Can PCT levels increase without bacterial co-infection in SARS-CoV-2 infection? This review systematically searched PubMed, Scopus, and Google Scholar for articles on procalcitonin (PCT) in the context of COVID-19 published from 2019 to 2023. Inclusion criteria focused on relevant articles, excluding non-English publications. Increasing PCT levels were observed in COVID-19 patients, especially in severe cases, often interpreted as evidence of bacterial co-infection. However, the role of PCT in the immune response to SARS-CoV-2 remains unclear. The proposed mechanisms suggest that SARS-CoV-2 can stimulate the production of PCT even in the absence of bacterial co-infection by modulating the interferon (IFN) pathway and reducing the regulation of monocyte function. Furthermore, PCT has implications in antibiotic management, with guidelines recommended to avoid antibiotics in patients with low serum PCT levels. Increased PCT values show associations with the severity of disease, including increased mortality, which further underlines the need for a detailed understanding of the dynamics of the PCT in COVID-19. This review emphasizes the evolving significance of PCT in COVID-19, with elevated PCT levels emerging as a valuable prognostic indicator, aiding in disease severity assessment and management. However, the intricate dynamics of PCT in COVID-19 demand further investigation, particularly in distinguishing viral infection from bacterial co-infection.

Keywords: COVID-19, SARS-CoV-2, Pro-Calcitonin, PCT, Biomarker

INTRODUCTION

Procalcitonin (PCT) is the predecessor of a vital hormone regulating calcium homeostasis, calcitonin. This polypeptide hormone is produced by thyroid C-cells and other cells, including monocytes.[1] PCT has previously demonstrated the potential to differentiate between bacterial and viral infections, specifically those affecting the lower respiratory tract.[2,3] Additionally, it has been investigated as a marker for bacterial infections in individuals suspected of having sepsis.[4,5,6] Research shows that PCT may reliably distinguish culture-negative and culture-positive sepsis from non-infectious illnesses, establishing it as a biomarker for bacterial sepsis diagnosis.[1,5] It is stimulated by several essential signaling molecules like IL-6, TNF, and several cytokines associated with bacterial infection.[7] Increased PCT synthesis is observed in the presence of cytokines, generated by bacterial infection, as well as lipopolysaccharides (LPS). It is not boosted by sterile inflammation or viral infection.[8]

The role of C-reactive protein (CRP) in infection diagnosis

C-reactive protein (CRP) and PCT are critical in diagnosing and treating infectious illnesses. Tang M. et al.'s study discovered that individuals with co-infection were substantially more likely to have higher PCT levels

than those with mono-infection, indicating that co-infected patients had more severe inflammatory reactions.[9]

Evidence of elevated PCT in COVID-19 patients

Three of the four patients with secondary infection in Huang et al.'s study had procalcitonin levels greater than 0.5 ng/ml, which could indicate bacterial infections.[10] However, the clinical utility of procalcitonin alone in the differential diagnosis of bacteria and SARS-CoV-2 infection was concluded with requiring further validation.[11] An increase in the levels of PCT in COVID-19 patients is linked to severe illness and death across many studies.[12,13] Elevated PCT levels in COVID-19 patients, particularly in severe instances, would be interpreted as evidence of bacterial co-infection.[1] This has always been a common notion. However, when venturing further into the field of the COVID-19 pandemic and trying to glean adequate knowledge, an unprecedented question was eventually raised - Can a rise in PCT level occur without bacterial co-infection in SARS-CoV-2 infection? Could PCT be part of the human immune response to SARS-CoV-2, especially in severe COVID-19 cases? Several studies regarding procalcitonin as an inflammatory marker wanted to keep an open mind and not restrict their knowledge based on prior information.

METHODS

In this literature review, we conducted a comprehensive study of peer-reviewed articles and research documents on the role of PCT in COVID-19. The aim was to clarify the possible correlation between elevated PCT levels and severe COVID-19 results, and to investigate the mechanisms underlying the increase of PCT in the absence of bacterial co-infection.

Literature search

We performed a systematic search of scientific databases, including PubMed, Scopus, and Google Scholar, using keywords such as 'COVID-19,' 'SARS-CoV-2,' 'procalcitonin,' 'PCT,' and 'biomarker.' The search was limited to articles published between 2019 and 2023.

Inclusion and exclusion criteria

Papers were considered if they offered pertinent data on PCT in the context of COVID-19, including its diagnostic, prognostic, or therapeutic implications. Studies not related to PCT and COVID-19, review articles, and publications not in English were excluded.

Data collection

The insights from the chosen articles were integrated to offer a consistent narrative about the role of PCT in COVID-19. We organized the information into sections discussing the diagnostic potential of PCT, its correlation with disease severity, potential causes of PCT increase, and its function in antibiotic stewardship and prognosis evaluation in COVID-19.

Data synthesis

The findings from the selected articles were synthesized to provide a coherent narrative regarding the role of PCT in COVID-19. We categorized the information into sections discussing the diagnostic potential of PCT, its association with disease severity, potential mechanisms of PCT elevation, and its role in antibiotic stewardship and prognosis assessment in COVID-19.

Critical appraisal

The quality and relevance of each selected article were critically appraised to ensure the inclusion of reliable and scientifically sound research.

MECHANISMS OF PCT ELEVATIONS IN COVID-19

Hypotheses on PCT increase in COVID-19

No such study assesses the direct association between PCT and bacterial co-infection in COVID-19 patients so far. The probable immunological mechanisms through which SARS-CoV-2 might raise PCT levels in the absence of bacterial co-infection are discussed in this article.

Seeing as SARS and COVID-19 are both coronaviruses, it is hypothesised that the human immune system would respond similarly and that PCT levels would not rise in COVID-19 until bacterial co-infection occurs.[12,13]

Role of interferons (IFNS) and stat proteins

In most viral infections, IFN levels are elevated, which inhibits PCT synthesis.[14] However, SARS-CoV-2 proteins suppress IFN function and enhance STAT3 signaling in monocytes, resulting in enhanced PCT synthesis. In human cells infected with SARS-CoV-2, STAT1 and IFNs are inhibited, whereas STAT3 is activated.[15]

Numerous SARS-CoV-2 proteins stimulate STAT3-dependent transcriptional pathways, most notably in monocytes, resulting in enhanced PCT production. After LPS stimulation of monocytes, the miR-125b decreased, whereas STAT3 and phosphorylated STAT3 rose, increasing PCT expression.[16] More SARS-CoV-2-infected cells and more PCT are produced when STAT3a isoform is expressed. SARS-CoV-2 suppresses STAT1 phosphorylation, resulting in increased IFN-stimulated gene transcription in monocyte-derived dendritic cells and macrophages.[17] Structural defects in STAT1 caused by ORF6 or NSP1 trigger compensatory mechanisms that lead to STAT3-dependent transcriptional pathways. Additionally, it has been demonstrated that STAT3 suppresses the STAT1-mediated IFN-1 response. This alternate STAT3 transcriptional pathway is thought to be

responsible for most of the pathology observed in severe COVID-19 patients, including enhanced coagulopathy/thrombosis, proinflammatory state, and T cell lymphopenia.[15]

Monocyte dysfunction and dysregulated secretion

Furthermore, it was found that monocyte activity was reduced in COVID-19 due to increased viral proliferation induced by non-neutralising immunoglobulin M (IgM), IgG, complement, hypoxia, macrophages losing their antiviral role owing to lymphopenia, and hyperactivation of immature monocytes. COVID-19's enhanced PCT production was due to monocyte dysfunction and dysregulated secretory production.[18]

CLINICAL IMPLICATIONS OF PCT LEVELS IN COVID-19

Recent research in Pakistan revealed no statistically relevant variation in procalcitonin levels in COVID-19 patients with bacterial infection compared to those without bacterial infection (p=0.883).[19] Another such study conducted by May et al presented that procalcitonin levels were higher in patients with community-associated infections (CAI). The research ensured that its tests were repeated every 72 hours, which accounted for its liability and no misleading errors. The study also found that other inflammatory markers like ferritin and erythrocyte sedimentation rate (ESR) did not significantly change between their cohort groups. Whereas considering IL-6 as a procalcitonin stimulator, it comes as no surprise that their levels were remarkably high in CAI patients. Mean CRP was also found to be increased, suggesting that inflammation has been taking place.[20]

As revealed by Liu et al PCT levels greater than 0.07 ng/ml with an area under the curve (AUC) of 0.812 and sensitivity and specificity of 73.15% and 84.85%, respectively, for the prediction of morbidity can be considered in routine clinical practice in conjunction with other biochemical markers and clinical picture.[21]

PCT in antibiotic stewardship

Sheffield Teaching Hospitals NHS Foundation Trust recommends against the usage of antibiotics in COVID-19 patients with low serum PCT, which generally ranges under 0.25 ng/ml unless advised by a senior physician. To test the credibility of this guideline, E. J. Williams et al conducted a retrospective cohort study from March to April 2020.

Results demonstrated reduced antibiotic use in patients with PCT 0.25 ng/ml with no increase in mortality, coupled with reducing future carbapenem prescriptions during hospitalisation.[22]

Zheng et al's study shows that a local guideline advocating against antibiotic usage for proven COVID-19 patients with PCT 0.25 ng/ml lowered antibiotic utilisation compared to national figures, with no notable distinction on the 28-day outcome, which is in accordance with the data published by the International Severe Acute Respiratory and Emerging Infection Consortium, the UK's largest COVID-19 patient registry.[23]

Correlation between PCT levels and disease severity

Bacterial co-infection aggravates systemic inflammation, exacerbating the illness and deteriorating the prognosis.[24] Patients with severe and catastrophic COVID-19 sickness had more significant PCT levels than those with milder disease.[12,25]

The increased mortality seen in individuals with PCT values more than 0.25 ng/ml corroborates other authors' findings, establishing a correlation between elevated PCT values and severe illness or death.[26,27] Greater PCT is likely to represent bacterial superinfection and resultant deterioration in many situations. The prospect of improving antimicrobial stewardship by using a higher PCT threshold or other criteria is also conceivable in severe COVID-19 patients, where PCT levels can be possibly elevated independent of bacterial infection.[22]

PCT'S ROLE IN DETECTING CONCURRENT INFECTIONS

A study performed in the USA revealed that procalcitonin was a poor indicator of CAI among adult patients with COVID-19. Although procalcitonin was substantially increased in patients with CAI than healthy participants, it showed poor sensitivity and specificity for detecting community-associated bacteremia, bacterial pneumonia, and bacteriuria, using a threshold of 0.25 or 0.5 ng/ml.[20]

May et al explain that increased procalcitonin levels in COVID-19 are mainly caused by disease-induced inflammation rather than bacterial co-infection. According to their findings, procalcitonin does not seem to be a reliable predictor of antibiotic initiation in patients with COVID-19.[20] They also found that the chances of carbapenem prescription tripled in patients with high PCT. This is critical given the rising global prevalence of carbapenemase-producing enterobacteriaceae.

While the study established a link between PCT and antimicrobial use, it was not feasible to ascertain if the PCT result alone influenced clinical practice regarding antimicrobial delivery. Both the clinical picture and additional infection indicators might have had a role in the decision-making process.

Lastly, it is unclear if the elevation in procalcitonin levels is attributable to concurrent bacterial infection, general systemic inflammation linked to immunological dysregulation or acute respiratory distress syndrome.[28] The potential of a procalcitonin-guided antibiotic treatment strategy in patients with pneumonia and bacteremia has

been established in clinical studies conducted on infected individuals.[29,30]

The COVID-19 pandemic threatens to increase antimicrobial resistance through expanding empirical antimicrobial treatment.

Although its relevance in detecting concurrent infections in patients with COVID-19 is not yet established, procalcitonin is one technique that might be used to minimise the usage of antibiotics.[28] Some studies have shown that PCT levels stay normal in severe COVID-19; whether they rise in bacterial infections has not been documented, indicating the necessity for sizeable comparative research to investigate this link.[25]

PCT as a prognostic biomarker in COVID-19

PCT seems to appear as a promising prognostic biomarker in COVID-19. Initially elevated PCT levels may be used as a prompt prognosticator of criticalness, deteriorating clinical picture, and even mortality in COVID-19.

The biomarker can also serve as a risk stratification tool for intensive resource allocation and aggressive therapeutics in conjunction with clinical details and other biomarkers, in an already over occupied medical centers globally amidst the crisis.[31]

UNCERTAINTY AND FUTURE RESEARCH

Factors influencing the PCT level in COVID-19

Although several studies have highlighted the correlation between high PCT levels and severe cases of COVID-19, further research is needed to explain the complicated mechanisms of the PCT elevation when there is no bacterial co-infection. Future research should consider the role of other cytokines, immune responses, and viral factors that could contribute to the synthesis of PCT in COVID-19.

Addressing the challenges of antibiotic resistance

As our review suggests, PCT-based antibiotic management protocols can reduce the unnecessary use of antibiotics in COVID-19 patients. However, further investigations are needed to determine the influence of PCT-based antibiotic decisions on antimicrobial resistance patterns. This important research area can help to shape antimicrobial guidelines in and out of the pandemic.

CONCLUSION

We believe that this condensed form sheds some insight on how PCT's journey from a calcium-regulated hormone precursor to a potential COVID-19 biomarker is symbolic of the dynamic nature of science. As we move towards this unprecedented global health crisis, ongoing research into the multifaceted role of PCT offers hope and the potential to shape our response to future pandemics.

ACKNOWLEDGEMENTS

We'd like to thank RAK Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates, for their encouragement and support. COVID-19 research is a fastest emerging topic, and the authors would like to thank any prospective authors whose work was not included in the current review.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Samiullah S, Ahmad A, Patni MA. Unveiling the role of procalcitonin in COVID-19: a literature review. Int J Community Med Public Health 2024;11:1011-5.