EDITORIAL

Procalcitonin (in COVID-19): The Incessant Quest

Raymond D Savio

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Department of Critical Care Medicine, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India

Corresponding Author: Raymond D Savio, Department of Critical Care Medicine, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India, Phone: +91 918056051847, e-mail: raymonddominicsavio@yahoo.com

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Since the discovery of procalcitonin (PCT) in 1975, our quest to expand its horizon has been quite incessant and undeterred. Whether this is nugatory is often disputed! Nonetheless, its journey from chicken[1] to humans and from carcinoma[2] to sepsis[3] as a biomarker today has been quite inspiriting. Despite the fact that the origin and purpose of its synthesis remains elusive and speculative, the clinical utility of PCT has been entrenched in the last two decades, either as a scientific practice or a habit. Our endeavor to lodge PCT in the diagnostic, therapeutic, and prognostic arena is evident from the 1,020,000 search results on Google and 6,312 results on PubMed as on date.

As we continue to argue and negate the role of PCT as a diagnostic tool and for initiation of antibiotics, its application in antimicrobial stewardship by facilitating a discontinuation decision is underpinned by reasonable research.[4,5] Into the bargain, there is emerging data to suggest a possible prognostic role for PCT in various settings including sepsis and beyond.[6] It is not surprising and matter of factly quite befitting that PCT also seeks to find a role in the present coronavirus disease-2019 (COVID-19) pandemic as a promising prognostic biomarker.

The current pandemic has perhaps seen one of the biggest outbursts in big data, research, and literature contributing to a wealth of hypotheses, if not answers, and in this flurry of finds, PCT appears to have ratified its role in foretelling the severity of patients with COVID-19. The general observation has been a relatively normal PCT value among patients with COVID-19. This is likely attributed to higher levels of interferon γ (IFN-γ) in viral illness, which naturally suppresses the production of PCT. A rising trend or an absolute high PCT value on the other hand was more often noted to be a harbinger of severe disease. This was conceived to be from a bacterial co/secondary infection with elevated levels of interleukins (IL-1β, IL-6) and tumor necrosis factor (TNF-α), which stimulate production of PCT from multiple extrathyroidal sites. A concise meta-analysis by Lippi et al. in March 2020, possibly the first, sought to study this relation.[7] The analysis that included a total of four studies showed that elevated PCT values were accompanied by a fivefold higher risk of developing a severe disease (OR 4.76; 95% CI, 2.74–8.29). The pathogenetic mechanism for this cause-effect however remains to be proved. The rest of the year continued to witness a surge of scrutiny to this relation culminating in guidelines and recommendations. The recently published position paper by ISCCM concerning management of patients with COVID-19 recommended measuring PCT upon hospitalization for risk assessment and prioritization.[8]

The systematic review published in this issue by Dr Sibtain Ahmed et al. is yet another attempt to evince the prognostic value of PCT in patients with COVID-19.[9] This narrative review has included 52 original studies with a total of 15,296 patients. Literature retrieval was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool and the authors reported an excellent inter-investigator agreement for inclusion of articles (κ statistic = 0.90). Considering that trials were included from January to June 2020, 77% of them were of the Chinese origin. The only Indian trial included was by Dr Bhandari et al., a prospective cohort of 21 patients from a single center in Jaipur, wherein the elevated PCT level was observed in all patients with severe disease.[10] Eighty five percent of the studies reported a significant association of elevated PCT level with severity of COVID-19. The optimal cut-off for PCT level used in 35% of the studies was >0.05 ng/mL to identify severe disease.

There are several limitations to the above observation based on confounders pertaining to PCT, ethnic representation, heterogeneity of the included studies, publication bias, nature of statistical analysis, etc. Moreover, crucial clinical information that could totally drift our thinking can never be sought from the available studies. Howbeit the authors have made an earnest attempt to defend some of these gaps. It should also be understood that this systematic review is an appraisal of gathered evidence and not a statistical summary. Nonetheless, this opens up another avenue for the role of PCT in prognostication and hopefully resource optimization.

It would be fascinating to envisage a randomized trial with PCT-guided triage in patients with COVID-19 or the development of a novel biomarker scoring tool incorporating such elements as PCT, CRP, D-dimer, ferritin, LDH, and the like, to aid in more objective decision making. This could optimistically mitigate a situation of resource constraint or assist in referral decisions. In case there is still a lurking soul seeking a mortality benefit from the use of PCT values for clinical decisions, there may never come a scientific pledge.

Will I use PCT to risk stratify patients with COVID-19? Seems like a "yes" in synchrony with best science. Will I monitor serial PCT? Again scores a "yes" in the event of clinical deterioration on a background of normal PCT or for antimicrobial stewardship, starting with a raised PCT. Is this a Grade 1A? No way, hang on…! The quest is incessant.

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