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Original article

Role of measuring serum procalcitonin and receiving prophylactic antibiotic therapy in critical COVID-19 patients

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared as a pandemic in 2019-2020. Most cases are usually self- limited; however, it may unpredictably progress to severe form with high mortality rate. **Objectives:** To highlight the role of measuring serum procalcitonin (PCT) and receiving early prophylactic antibiotic therapy in terms of their relation to the mortality rate in hospitalized critical COVID-19 patients. **Methods:** this study analyzed sixty COVID-19 critical patients admitted to Tanta University Isolation Hospital from June to November, 2020. Respiratory tract and blood samples were collected **Results:** Our results showed that the mean serum PCT levels were significantly higher in deceased patients (15%) than in those who could survive corona-virus infection. Patients who received early prophylactic antibiotic therapy showed significant better survival rate than those who didn't. **Conclusion:** This study demonstrated that measuring PCT shows statically significant results with COVID-19 patients' outcome more than other commonly used laboratory markers such as CRP. Moreover, early administration of prophylactic antibiotic therapy in COVID-19 patients, especially critical ones, is crucial even in those with negative PCT values.

Introduction

Coronavirus disease-2019 (COVID-19) is an emerging infectious disease caused by the novel Coronavirus (SARS- COV2) [1]. The ongoing COVID-19 pandemic represents a huge challenge to the public health worldwide resulting in enormous burden on the healthcare systems with overwhelming medical, social and economic consequences globally [2]. By the end of 2020, the number of confirmed cases has exceeded 79 million reported cases and over 1.7 million deaths globally [3].

Although, the disease is mild (many patients are asymptomatic) and is usually self-limited in majority of cases with no need for hospitalization, it may rapidly and unpredictably progress to severe and devastating illness with high rate of morbidity and mortality [4]. This unpredicted rapid deterioration of certain cases surprised the medical community globally [5].

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One of the prominent aspects of COVID-19 is its systemic nature after primarily affecting the respiratory system especially in elderly and patients with underlying comorbidities who require hospitalization [6-8]. Among hospitalized patients, some develop severe viral pneumonia and multi-organ system failure with bad prognosis requiring ventilation and intensive care unit (ICU) admission [8]. Despite ICU care, high percentage of patients shows un-explained worsening of their condition that ends up with respiratory failure and rapid progression to death. [9-11].

The clinical researchers have thoroughly explored reliable biochemical indicators for COVID-19 severe conditions for the already overburdened medical infra-structure to achieve high risks and optimal allocation of resources [12]. Procalcitonin (PCT), C-reactive protein (CRP), ferritin (Fer), D-dimer, interleukin-6 (IL-6) and lactate dehydrogenase (LDH) have been linked to an increased risk of developing severe COVID-19 [13-15].

Procalcitonin is a glycoprotein calcitonin pro-hormone that is released by para-follicular thyroid cells. In physiological state, serum PCT level is significantly lower than 0.05 ng/ml. Moreover, in term of risk stratification timeframes PCT levels are considerably elevated after a microbial infection because it is released by all parenchymal tissue under the effect of endotoxins and pro-inflammatory cytokines. The cytokines released in COVID-19, notably interferon gamma (INF γ), have a negative impact on PCT levels [16]. Furthermore, in terms of risk stratification timescales, PCT has a rapid course, with inclining levels measured 2–6 hours after the stimulus, supporting its use as a prognostic tool [17].

The purpose of this study is to highlight the role of measuring serum PCT and receiving early prophylactic antibiotic therapy in terms of their relation to the mortality rate in hospitalized critical COVID-19 patients.

Methods

Study design and patient selection: This is a cross-sectional study that was carried on COVID-19 patients admitted to the ICU of Tanta University Isolation Hospital, Egypt between June and November 2020.

Inclusion criteria: Sixty critically ill patients were diagnosed to have COVID-19 based on real-time quantitative polymerase chain reaction (RT-PCR) tests applied on respiratory secretions obtained via naso-pharyngeal swabs. Patients over 18 years old with PCR confirmed COVID-19 were included in the study. Viral-bacterial coinfection was defined when PCR confirmed SARS-CoV2 patient had a positive culture for a bacterial pathogen obtained from lower respiratory tract collections (sputum, endotracheal aspirate, broncho-alveolar lavage fluid) within 48 hours of ICU admission. Isolation of bacterial pathogen at any other site than respiratory tract was not considered. Thus, sixty patients were included as illustrated in the study flow chart **(Figure 1)**. Informed consents were obtained from all participants in the study.

Data collection: Patient information, including demographic characteristics, history of comorbidity, symptoms, laboratory findings e.g. CRP, CT images and treatment were extracted from the original medical records.

Samples collection and assay: Clinical specimens for COVID-19 diagnostic testing were obtained according to the Centers for Disease Control and Prevention (CDC) guidelines [18, 19]. Management and laboratory investigation of cases were immediately initiated on admission.

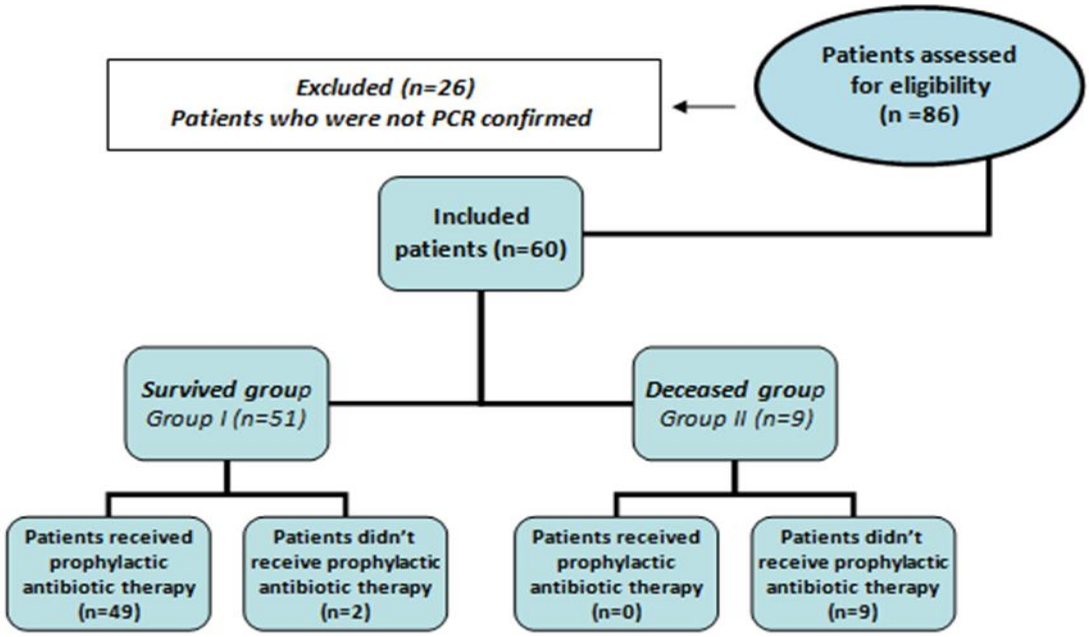
Blood samples: For PCT measurement, blood samples were collected within 24 hours after ICU admission in all patients. The serum was separated, stored at -20°C, and used subsequently for assaying serum PCT. The serum PCT was measured by (RayBio Human Procalcitonin ELISA Kit, USA) according to manual instructions. The detection limit of the kit was less than 30 pg/ml. The results were drawn and interpreted as standard curves.

Sputum samples: Patient sit at 45°C, inspired deeply and hold then coughed with expectoration in a clean container. Patients with dry cough were subjected to fiber-optic bronchoscopy and broncho-alveolar lavage under complete aseptic precautions where a sterile bronchoscope was introduced until peripheral bronchioles, 30-50 ml of sterile saline was injected throughout. Saline was aspirated and collected in a sterile plastic container with firmly fitted cover. These sputum samples were subjected to the standard microbiological culture and identification techniques.

Real-time PCR: Laboratory testing involved nasopharyngeal swabbing that was transported immediately to Tanta University Hospital laboratory and subjected to RT-PCR with RT-PCR Detection Kit System. The PCR conditions used followed those described by **Corman et al**. [20].

Statistics: Analysis was performed with T -test and Chi-square test. Statistical Package for Social Sciences (SPSS) version 23 was used for data analysis. Data were expressed in number (No.), percentage (%), mean (x), and standard deviation (SD). *p*-value < 0.05 was considered statistically significant.

Figure 1. The study flow chart.



Results

From June to November 2020, 60 critically ill patients were admitted to the ICU of Tanta University Isolation Hospital with RT-PCR confirmed severe SARS- CoV-2 infection; mortality rate was around 15% (9/60).

Demographic and clinical characteristics of the patients

The distribution of the patients' baseline characteristics according to age is shown in **table (1)** with no statistically significant difference between both groups as regards age.

Microbiological results

All patients were clinically and radiologically suspected COVID-19 that was confirmed by RT-PCR assay from a positive nasopharyngeal swab. The mean value of PCT was 1.133 ± 0.213 ng/ml (IQR 0.2) in the survived group and 6.722 ± 1.564 ng/ ml (IQR 2.5) in the deceased group with statistically significant difference between both groups as regards PCT value while no statistically significant difference was found between both groups as regards another laboratory marker (CRP) as shown in **table (1).**

Fourteen patients (23%) manifested bacterial co-infection upon ICU admission, indicated by the elevated PCT level and positive respiratory cultures of which 11 patients (78%) were not receiving prophylactic antibiotic therapy before admission. Out of these fourteen patients, nine patients (65%) couldn't survive **(deceased group)** with statistically significant difference between both groups as regards mortality rate as shown in **table (2)**. The relation between PCT values and receiving prophylactic antibiotic therapy showed statistically significant difference between both groups as regards PCT values as shown in **table (3).**

Table 1. Age, procalcitonin, C-reactive protein values in relation to survival rate.

	Group I (survived) (n=51)	**Group II (deceased) (n=9)**	**T**	***p*-value**
Age (years)	50.25 ± 15.915	60.89 ± 15.831	0.036	0.849
PCT (ng/ml)	1.133 ± 0.213	6.722 ± 1.564	26.240	**0.0001***
CRP	46.373 ± 50.4567	191.111 ± 53.9732	1.552	0.218

Table 2. Prophylactic antibiotic therapy in relation to survival rate.

Groups	Antibiotic therapy						Chi- square	
	Patients received prophylactic antibiotic therapy		Patients didn't receive prophylactic antibiotic therapy		TOTAL		X^2	*p* value
	N	%	N	%	N	%		
Group I (survived) (n=51)	49	96	2	4	51	85	**47.166**	**0.0008****
Group (deceased) (n=9)	0	0	9	100	9	15		
TOTAL	49	100	11	100	60	100		

Table 3. Relation between procalcitonin values and prophylactic antibiotic therapy.

Groups	Procalcitonin	T – test	
	Mean ± SD	T	*p*-value
Patients received prophylactic antibiotic therapy (n=49)	1.145 ± 0.209	65.266	**0.001***
Patients didn't receive prophylactic antibiotic therapy (n=11)	5.655 ± 2.757		

Discussion

The reason why certain COVID-19 patients become seriously ill, while others do not, remains an unsolved issue. Many variants like co-existing chronic medical conditions and the use of some immune-modulatory agents in some patients could influence patient's outcome. Therefore, some laboratory markers have been proposed as prognostic indicators and risk stratification markers [21-24].

Identifying whether patients are at danger of serious illness or death can help with decision-making, such as determining whether hospitalization, ICU referral, early artificial ventilatory intervention or immune-modulatory agents use are necessary [25]. This is especially important considering the pandemic's rapid progression, which has resulted in rationing of scarce resources such as mechanical ventilators and hospital available places [26].

In order to comprehend the potential of predicting the severity of disease and mortality outcomes, numerous hematological and biochemical (especially inflammatory) markers as well as symptoms were examined to this goal [6, 27].

Because of the distinct nature of PCT in bacterial versus viral infections, this biomarker may play an important role in COVID-19 prognosis. It is the peptide precursor of the hormone calcitonin is currently used as a marker of sepsis caused by bacterial infection that generally grades well with the degree of sepsis [28]. Its secretion is stimulated by the inflammatory cytokines and endotoxins while inhibited by interferon gamma, indicating specific relevance to bacterial infection [29].

Procalcitonin assays are widely used in clinical environments [30]. Recently, it has emerged as a potentially predictive biomarker in COVID-19 due to its unique properties, consistent kinetics, and the potential correlation of decreased levels with infection resolution [31].

In this study, we observed significant higher PCT values in deceased COVID-19 patients than survived ones. Our results are concomitant with a previous study which indicated that higher PCT value is associated with higher mortality rate in COVID-19 patients in general [31]. Our results are

also in-line with a more recent study which confirmed that PCT levels are predicted to quintuple in critically ill cases in specific [11,32,33] supporting the concept that any substantial increase in PCT baseline levels signposts the risk of developing severe clinical manifestations [34].

However, whereas PCT is widely recognized and used as a biomarker of bacterial infection [30], there is debate over its effectiveness as a COVID-19 prognostic tool suggesting that early triaged classification of patients and early application of protocol-based treatment results in good outcomes and low case fatality regardless the use of any prognostic markers [35,36].

In our study, fourteen patients (23%) manifested bacterial viral co-infection. Recent studies suggest that bacterial co-infection occurs in 14 and 28 % of critically ill COVID-19 patients [37-39]. Before this worldwide pandemic, antimicrobial stewardships and guidelines generally discouraged prescription of prophylactic antibiotics in viral infections especially if the patients' PCT values were less than 0.1 ng/ml while its use was highly recommended when PCT values exceeds 0.5 ng/ml [29].

Our results revealed better survival outcomes in COVID-19 patients who were on prophylactic antibiotic therapy (82%) than those who were not (12%) and even better survival rate in patients with bacterial-viral co-infection who were on prophylactic antibiotic therapy (22%) than those who didn't (78%). This comes in agreement with another recent study which suggested that withholding antibiotic use in critical COVID-19 patients when PCT levels were less than 0.1 ng/ml resulted in missing treatment of bacterial co-infection resulting in worse outcome and that the prophylactic administration of antibiotics in COVID-19 patients especially those with PCT more than 0.5 ng/ml resulted in successful management of majority of critical patients [33]. Although there is no role for antibiotics in the treatment of viral infections, the use of empiric antibiotics is now endorsed by the world health organization (WHO) to cover any bacterial super-infections [40].

In conclusion, this study demonstrated that measuring PCT shows statically significant results with COVID-19 patients' outcome more than other commonly used laboratory markers such as CRP. Moreover, early administration of prophylactic antibiotic therapy in COVID-19 patients, especially critical ones, is crucial even in those with negative PCT values.

Still there were some limitations of this study such as the relatively small sample size and being mono-centric which may limit the generalization of observed data. Larger scale studies, measurement of other significant laboratory markers and more conclusive data are needed to clarify the role of PCT in predicting the occurrence of bacterial co-infection in critically ill COVID -19 patients with subsequently better outcome.

Conflict of interest: No conflict of interest.

Authors' contribution: All authors contributed equally to this work.

Financial disclosure: This study was done as a part of the outbreak investigation conducted at Tanta University Hospitals, Egypt. Patients with laboratory-confirmed SARS-CoV-2 infection, who were admitted to Tanta University Isolation Hospital ICU between June and November, 2020 were included.

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