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Profiling of inflammatory biomarkers in mild to critically ill severe acute respiratory syndrome corona virus-19 (SARS Covid-19) patients from Karachi, Pakistan

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Abstract: SARS-Covid-19 infection got spread in many countries and WHO declared it as a serious global Pandemic. Pro-inflammatory cytokines storm generated by Covid-19 infection hyper-activates inflammatory response in host body, resulting in elevated release of inflammatory biomarkers. Present article describes the characteristic profile of these inflammatory and related biomarkers in a total of 48 critically ill Covid-19 patients, (Male = 38, F = 10), with mildly ill to severe, critically ill status and thus grouped accordingly. Inflammatory Biomarkers, Ferritin, ProCalcitonin, C-Reactive Protein, coagulation marker-D-Dimer, chemical analytes, Protein, Albumin, BUN, Bilirubin, Creatinine, and enzymes, Lactate Dehydrogenase, γ-Glutamyl transpeptidases, Alkaline phosphatase were routine analyzed by standard methods described earlier. D-dimer, Ferritin, CRP and Procalcitonin exhibited variable alterations ($P<0.05$ to $P<0.001$), more markedly in critically ill patients than in the mild and severe. Biochemical analytes and enzymatic parameters showed elevated levels ($P<0.05$ to $P<0.01$) mostly in critically ill category of patients when compared with mild or severe, except total protein and albumin, which remained non-significant. It is concluded that cytokine, chemokines and pro-inflammatory markers, which released in abnormally high concentrations in Covid-19 patients of variable syndrome intensity, are significant indicators of disease severity, progression and success of treatments. As the pharmacological options may vary with the different stages of the disease therefore identifying the correct stage of the disease may be very useful in selecting the best option.

Keywords: Biomarkers, Covid-19, syndrome intensity.

INTRODUCTION

In Dec 2019, world came to know about a deadly virus, later named Severe Acute Respiratory Syndrome Corona Virus-19 or SARS-Covid-19. Covid-19 infection got spread in many countries and WHO declared it as a serious global Pandemic. It seriously affects respiratory system via air droplets or direct contact resulting in pneumonia like condition which in about 15% cases caused acute respiratory distress syndrome (ARDS). Mortality, which stood at 6.4% occurring as a result of ARDS complication, was linked to accelerated cytokine storm (also known as hypercytokinemia), leading to abnormally elevated production of pro-inflammatory cytokines which cause extensive tissue damages, multi-organ failure and death. In addition to ARDS, respiratory failure, acute renal injury, neurological distress was also noted in Covid-19 patients (WHO, 2020, Zeng *et al*., 2020). These pro-inflammatory cytokines storm generated by Covid-19 infection hyper-activates inflammatory response in host body, resulting in elevated release of inflammatory biomarkers, such as C-reactive protein, D-Dimer, procalcitonin, Ferritin and enzymes such as lactate dehydrogenase, phosphatases and /or transpeptidases. Alterations in the chemicals such as bilirubin, creatinine, blood urea nitrogen (BUN), albumin and hematological analytes such as Hb, Complete Blood Counts were also noted in critically ill patients (Gong *et al*. 2020; Guan *et al*. 2020). These biomarkers are now used as screening and diagnostic tests to assess Covid-19 disease progression, aggression or recovery. Present article describes the characteristic profile of inflammatory and related biomarkers, ferritin, lactate dehydrogenase (LDH), D-Dimer, CRP and procalcitonin in critically ill Covid patients. Classification of disease stages on the basis of these biomarkers is vital for optimal treatment and therapeutic options (Caruso, 2020). Since hyperinflammtion is one of marked manifestation of Covid 19, pharmaceutical interventions became utmost importance for clinicians and infectious disease experts (Siddiqui and Mehra 2020).

MATERIALS AND METHODS

Study setting and patients group

A total of 48 patients, (Male = 38, F = 10), all SARS Covid-19 positive patients with mildly ill to severe, critically ill status were selected and thus grouped

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accordingly (Liu *et al*., 2020). Patients were grouped as having mild clinical manifestation that exhibited 1) milder symptoms, 2) mild or no pulmonary lesions, whereas patients were grouped in severe category manifesting 1) Shortness of breath, with respiratory rate ≥ 30 beats/min, 2) Oxygen saturation ≤ 93-95% at rest, 3) arterial partial pressure of oxygen ≤ 300 mmHg and 4) pulmonary images showing lesions with size < 50 % within 48 hr, but doesn't required ventilation. Critically ill patients were grouped that exhibited all symptoms and signs similar to severe group but with oxygen saturation ≤ 90%, lesion size ≥ 50% and essentially requiring ICU admission and ventilation assistance.

All consented to participate and provided information. Study was approved by research committee and completed at the Chemical Pathology and Clinical Biochemistry lab Services, Liaquat National Hospital and Lyari General Hospital, Karachi. Demographic, in addition to age, signs and symptoms at the time of assessment and admission to hospital were also noted. Clinical outcome was also noted and registered.

Analytical methods for biomarkers, chemical analytes and enzymes

Inflammatory Biomarkers, Ferritin, ProCalcitonin (PCT), C-Reactive Protein (CRP), coagulation marker-D-Dimer, chemical analytes, Protein, Albumin, BUN, Bilirubin, Creatinine, and enzymes, Lactate Dehydrogenase (LDH), γ-Glutamyl transpeptidases (gGT), Alkaline phosphatase (ALP) were routine analyzed by standard methods described earlier (Alam and Ali, 2020; Alam *et al*., 2020; Matinuddin *et al*., 2018; Alam and Sultana, 2015; Tietz, 1995).

STATISTICAL ANALYSIS

Patients' groups were compared with each other as per mild, severe and critically ill status and reported. Data considered significant, markedly significant and highly significant when P considered as $P<0.05$ or $P<0.01$ or $P< 0.001$, respectively by applying student's t-test using SPSS version 25. All other data were either presented as percentage or mean ±SD.

RESULTS

Results are summarized in tables 1 & 2. There were a total of 48 patients, with males =38 (79.16%), and females =10 (20.83%), all SARS Covid-19 positive. Their symptoms and signs were assessed and noted to be categorized into mildly ill (n =22, 45.83%), severely ill (n =15, 31.25%) but not critical (means non fatal) and critically ill (n = 11, 22.91%) (means requiring extensive life support, with possible fatal outcome) status. They were grouped accordingly with demographic status in addition to age (59.20±14.30 yrs) and possible clinical outcome, remained in hospital, treated, discharged or died. Major signs and symptoms were fever n = 47 (97.91%), cough n = 41 (85.41%), shortness of breath n = 22 (45.83%), muscle ache n = 25 (52.08%), chest distress n =18 (37.50%), most importantly more than 1 sign or symptom n=38 (79.16%), in addition to nausea, vomiting, headache etc. As mentioned earlier, patients were categorized into mildly (M), severely (S) and critically ill (CI) and thus their inflammatory biomarkers and Coagulation function marker were tabulated accordingly and compared**.** D-dimer (<0.5μg/mL) showed variable elevation 1.5±0.55 in M, 3.95±1.35 in S and markedly elevated in CI 7.80±2.65 such that D-Dimer in CI is significant ($P<0.05$) as compared to M and markedly significant S vs CI ($P<0.001$). Similarly inflammatory markers and storage protein Ferritin, CRP and Procalcitonin exhibited variable alterations such that PCT (<0.5ng/mL) in S is significant vs M ($P<0.05$) and highly significant in S vs CI, CRP (<0.5 mg/L) highly significant in M vs S ($P<0.001$) and in S vs CI ($P<0.001$), and ferritin (15-400 ng/mL) which was noted to be highly significant in M vs Sand M vs CI (table 2). Biochemical analytes and enzymatic parameters showed elevated levels ($P<0.05$ to $P <0.01$) mostly in critically ill category of patients when compared with mild or severe, except total protein and albumin, which remained non-significant.

DISCUSSION

Data gathered in the last 8 months regarding Covid-19 pandemic, showed that individuals who were Covid-19 positive, recovered and those who got expired, were 352,296, 321,563 and 7,092 respectively (WHO, Ministry of Pakistan, 2020). Total cases in the world stood at 53.3 million, deaths 1.3 million, and 34.4 million got recovered (WHO, 2020). Male predominance has been noted in Covid-19 patients, probably due to wider exposure time, and age group mostly older than 18 yrs (Huang *et al*., 2020), however children and infant were also found to be positive with variable range of clinical symptoms and signs (Velavan *et al*., 2020). Mortality rate stood at around 2.0% of those infected and suffered serious clinical manifestations (Velavan and Meyers, 2020). Unfortunately, individuals and patients with pre-disposition of cardiac, pulmonary, and endocrine disorders or under treatments, medication of metabolic or systemic diseases were the most vulnerable and suffered serious complications whenever became positive from Covid-19 infections (Guan *et al*., 2020; Mehta *et al*., 2020). What's more intriguing and dangerous about Covid-19 infections is that many patients remained asymptomatic, thus making them a hazardous source of infection spread. However, not necessarily remaining asymptomatic means no disease spread or clinical implications, like those with symptomatic positive cases, some gets respiratory distress, pneumonia, cardiac problems, needing ventilator assistance and ICU admissions (Zeng *et al*., 2020).

Table 1: The demographic and clinical characteristics of 48 patients with SARS-CoV-2 infection (Characteristics as per methodology Wang *et al.* 2020)

Patients	*n* = 48
Age (mean ± SD), years	59.20 ± 14.30
Sex	
Male	38 (79.16%)
Female	10 (20.83%)
Signs and symptoms at the time of assessment and admission	
Fever	47 (97.91%)
Cough	41 (85.41%)
Shortness of breath	22 (45.83%)
Muscle ache	25 (52.08%)
Chest distress	18 (37.50%)
Diarrhea	09 (18.75%)
Headache	10 (20.83%)
Confusion	6 (12.5%)
Nausea and vomiting	8 (16.6%)
Chest pain	7 (14.58%)
More than 1 sign or symptom	38 (79.16%)
Severity grouping	
Mild	22 (45.83%)
Severe	15 (31.25%)
Critically ill	11 (22.91%)
Clinical outcome	
Remained in hospital and discharged	43 (89.58%)
Died	4 (8.33%)

Data are presented as numbers (%). SARS-CoV-2, severe acute respiratory syndrome Covid-19

Table 2: Characteristic pattern of biomarkers in SARS-COVID-19 patients of different severity and critical levels

	Mild (*n* = 22)	Severe (*n* = 15)	Critically ill (*n* = 11)
Age, years	50.10 ± 10.40	62.20 ± 11.55	65.45 ± 12.65
Blood biochemistry markers			
Total protein (6.3-7.9g/dl)	6.2± 2.50NS	6.1± 2.40NS	6.0± 1.85NS
Albumin (3.0-5.0 g/dl)	3.1± 1.10 NS	3.05± 1.25 NS	3.0± 1.50NS
Total bilirubin (< 1.2 mg/dl)	7.65± 3.50	8.90± 2.85A***	14.10± 7.55A**
γ-Glutamyl transpeptidase (< 60 U/L)	61.5± 18.15	72.45± 24.50	84.10± 25.65A**
Alkaline phosphatase (30-130 U/L)	84.10± 22.10	88.65± 28.55	91.50± 36.40A**
Lactate dehydrogenase (135-225 U/L)	311.5± 75.40A*	480.35± 100.35	562.60± 145.35B**
Blood urea nitrogen (7-20 mg/dl)	21.10± 6.50	24.35± 9.35	32.45± 10.20B**
Serum creatinine (0.84-1.21 mg/dl)	1.41± 0.95	1.95± 0.85	2.45± 1.10A**
Coagulation function marker			
D-dimer (< 0.5 µg/mL)	1.5± 0.55	3.95± 1.35A**	7.80± 2.65C***
Infection/Inflammatory biomarkers			
Procalcitonin (< 0.5 ng/mL)	0.35± 0.10	0.48± 0.06A**	0.95± 0.20C***
C-reactive protein (< 0.5 mg/L)	3.5± 1.15	9.10± 1.10C*	10.30± 2.65C***
Serum ferritin (15-400 ng/mL)	560.10± 95.35	1201.4±110.45C*	1450± 120.50C**

Data are *n* (%), mean (± SD). M, mild; S, severe; CI, Critically ill. *M vs. S or **M vs. CI has statistical difference. ***S vs. CI has statistical difference. *A*< 0.05; *B*<0.01; *C*<0.001. NS= non significant

Most deaths occurred due to complications from ARDS and consequently hyper active-inflammatory response, resulting in release of cytokine, chemokines and pro-inflammatory markers in abnormally high concentrations, causing multi organ dysfunction and deteriorations.

Our current data presented here showed characteristic summary of inflammatory and related biomarkers such as ferritin, lactate dehydrogenase (LDH), D-Dimer, CRP and procalcitonin in mildly disease, serious and critically ill Covid-19 patients admitted in local hospitals of Karachi,

Pakistan. As expected, critically ill patients exhibited the highest level of elevation in all coagulating and inflammatory marker inclusive of storage iron protein ferritin and analytes such as total bilirubin, BUN, creatinine, enzymes LDH, ALP and gGT. This trait in patients that needed hospitalization was also reported from China (Liu *et al*., 2020; Zeng *et al*., 2020), USA (Al Samkari *et al*., 2020; Smith *et al*., 2020), Vietnam (Velavan and Meyers, 2020), France (Hadjadj *et al*., 2020; Toubiana *et al*., 2020), UK (Shiripanthong *et al*., 2020). As stated earlier elevation of these markers were activated or instigated by a cytokine storm which causes hyperactivity of host immune system (Chang *et al*., 2020; Gong *et al*.., 2020; Mo *et al*., 2020). Consequently, this frenzied release of pro-inflammatory components results in marked pulmonary distress, cardiac dysfunctions, and renal insufficiency and thus critical outcome and untoward prognosis (Fox *et al*., 2020; Chen *et al*., 2020; Gong *et al*., 2020; Mo *et al*., 2020; Zeng *et al*., 2020). Several studies of past year 2020 have already shown release of biomarkers, pro-inflammatory in nature, such as CRP, PCT, IL6, D-Dimer, Ferritin and ESR, due to physiological and biochemical alteration, resulting in cytokine storm and resultant severity of Covid-19 disease (Metha *et al*., 2020; Zeng *et al*., 2020). What scientists, clinicians, infectious diseases experts revealed that since this cytokine storm is life-threatening, most of the patients with markedly elevated inflammatory markers needed hospitalization and some required ICU and ventilator assistance. Systemic inflammation, homeostasis flux, uncontrolled immune response, multi organ dysfunctional status attributes as a consequential inference of this overly activated inciting outcome, making this SARS Covid-19, a dangerous clinical syndrome (Chen *et al*., 2020; Fox *et al*., 2020; Gong *et al*., 2020; Mo *et al*., 2020; Zeng *et al*., 2020). However, studies related to, suggested and tested, inflammatory biomarkers of Covid-19 noted strong correlation of their concentration with intensity of the disease, thus additionally making them monitoring tools as well (Goa *et al*., 2020; Wang *et al*., 2020). Pharmaceutical studies and medication practices carried out in 2020 showed hopeful outcome when patients were given tocilizumab and dexamethasone, resulting in reducing the severity of the disease and decreasing mortality rate (Metha *et al*., 2020). Addition of lopinavir/ritonavir and in some cases hydroxycholorquine, prednisolone as adjunctive therapy also reported to assist in easing hyper-inflammatory response, as assessed with the aid of biomarkers (Mehta *et al*., 2020; Guaraldi *et al*., 2020). Thus it may be suggested that staging of the disease severity with the help of biomarkers and proper treatment as per the severity of the disease could be a significant factor in reducing the mortality and as suggested by Ribas (2020) toxicity of the treatment could be increased instead of clinical benefits if a treatment is prescribed in the inappropriate phase.

CONCLUSION

Inflammatory markers were markedly elevated in critically ill patients than in mild and severe. Biochemical analytes and enzymatic parameters showed elevated levels ($P<0.05$ to $P<0.01$) mostly in critically ill category of patients when compared with mild or severe, except total protein and albumin, which remained non-significant. It is concluded that cytokine, chemokines and pro-inflammatory markers, which are released in abnormally high concentrations in Covid-19 patients of variable syndrome intensity, are significant indicators of disease severity and progression and can play a vital role in the success of treatment.

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