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REPORT

Varying pattern of blood gases, ferritin, procalcitonin, C - Reactive protein, interleukin 6 and lactate dehydrogenase in Covid-19 patients suffering from diverse Co-Morbid, suspected cytokine storm and periodic effects of antiviral and steroidal treatments

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Abstract: This study depicted varying pattern of inflammatory markers and blood gases of selected SARS Covid-19 patients with triggered cytokine storm, during their stay in ICUs, HDUs, on ventilators for 21 days. All were treated with Antiviral (remdesivir), steroid (dexamethason) and antipyretic (paracetamol) medications. Procalcitonin, PCT, C-reactive protein CRP, Interleukin 6 (IL6) and Lactate dehydrogenase (LDH**)** blood gases pressure (pO2, pCO2), coagulation (D-Dimer DD) and Iron storage proteins (Ferritin Ft) were analyzed by fully automated analyzers. All biomarkers of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th days and reported as significant where $p<0.05$, to assess progression, worsening or recovery status. IL6 ($P<0.0224$, $P< 0.0228$) and CRP ($P<0.0277$) exhibited none or mild statistical significance difference, with the exception of Ferritin ($P<0.0185$; $P<0.0088$) and D Dimer ($P<0.0086$), demonstrating slow recovery, revealing stronger cytokine storming assault. LDH, pCO2 and pO2 exhibited variable significance difference when data of earlier days were compared with recovery phase, thus advocating blended treatment or progressing of disease. Analysis confirms overwhelming pathogenesis of SARS Covid-19 distinctive cytokine storm, which needed to be cautiously monitored as infection progressed using pro-inflammatory biomarkers as indicators of recovery or worsening of the disease.

Keywords: Covid-19, cytokine storm, inflammatory markers.

INTRODUCTION

Covid-19 pandemic started from a localized city of China, Wuhan, in 2019 and spread all around the world by March 2020, with estimated 18 million confirmed cases by August, 2020 and 688,000 fatalities (Caricchio *et al*., 2021). Named Severe Acute Respiratory Syndrome (SARS)-Covid-19, it is characterized by hyperimmune response, clinical known as cytokine storm (Caricchio *et al*., 2021; Henderson *et al*., 2020; Petrosillo *et al*., 2020; Zachariah *et al*., 2020). Unrestrained and difficult to manage, this cytokine storm is dysfunctional set of immunological reactions, mostly immuno-pathogenic in nature and as SARS-Covid-19 progressed, causes extensive release of cytokines, including Tissue-necrotic factor-a (TNF-a), Interleukin-6, 12 and 8 (IL-6, IL12, IL-8) (Caricchio *et al*., 2021; Henderson *et al*., 2020; Petrosillo *et al*., 2020; Zachariah *et al*., 2020). Once in circulation, these cytokines induces severe respiratory distress, inflammatory diffusions, renal, cardiac and muscular damages, hemophagocytic lymphohistiocytosis and in marked disease progression and worsening cases, death. It was reported that not only clinical symptoms and signs, determining inflammatory and tissue damage markers (Procalcitonin, PCT, C-reactive protein CRP, IL6 and LDH, blood gases pressure (pO2, pCO2), coagulation D-Dimer and Iron storage proteins (Ferritin Ft) is of utmost significance, specially in cases of worsening clinical condition that requires Intensive care (ICUs), high dependency unit (HDU) admissions (Caricchio *et al*., 2021; Chen *et al*., 2020; Henderson *et al*., 2020; Li *et al*., 2020; Moore and June, 2020; Petrosillo *et al*., 2020; Zachariah *et al*., 2020). Moreover, patients with co-morbid such as diabetes, hypertension, renal or cardiac problems are more prone to develop complications and thus required major medical and medication interventions, in addition to management of Cytokine storm (Adhikari *et al*., 2020; Caricchio *et al*., 2021; Zhou *et al*., 2020). Recent studies published for Pakistani population suffering from Covid-19 infections described clinical and diagnostic abnormalities (Ahsan *et al*., 2021, Asghar *et*

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al., 2020), however in-depth analysis of changes in blood gases, alterations in major inflammatory markers, in relation to Cytokine storm, is too little and thus required multi tier investigations and analyses. Present study described varying pattern of inflammatory markers and blood gases of selected SARS Covid-19 patients (with diagnosed co-morbid), with triggered cytokine storm, during the course of their stay in ICUs, HDUs, on ventilators and their treatments with anti-viral, steroidal and anti-pyretic agents.

MATERIALS AND METHODS

Patient's selection, Study Setting and design

Presented study was carried out at the Department of Clinical Biochemistry & Chemical Pathology, Liaquat National Hospital and Department of Pathology, Lyari General Hospital, Karachi. Study period was from 16th October 2020 till 30th January 2021 and approved by the institutional research ethical committee (RC-LNH-Biochem-052021/43). Patients' selection was done as per methodology and criteria described earlier (Brouquia *et al*., 2021; Chen *et al*., 2020; Liu *et al*., 2020). Selected patients were a small group of six individual (males = 5, female =1), RT-PCR confirmed cases of SARS-Covid-19, with variable clinical and management status, chosen carefully as per set standards (Brouquia *et al*., 2021; Chen *et al*., Liu *et al*., 2020), to asses varying pattern of inflammatory markers (ferritin, LDH, PCT, IL6, CRP) and pressure of blood gases during the course of their stay in hospital till their recovery or adverse outcome (as in one case where one patients, on ventilator, passed away on 20th day of stay).

Patients clinical status and management regiment were, one each of 3 patients were in ICU, HDU and on vent and remaining three were having underlying co-morbid of severally asthmatic, cardiac and renal problems and admitted in specialized Covid ward, however doesn't require critical care or ventilator assistance. Their inflammatory, iron protein, enzyme, and coagulation markers with arterial pressure of blood gases were assessed for 21 days (day of discharge was either 21st day or 23rd day), which were the actual days of admitted stay at hospital and presented as individual parametric values per day (see table 1 to 8), inclusive of elevation (progression of disease) or decline (recession of adverse condition/improvement). Treatment regiments were antiviral (e.g Remdesivir [Bemsivir-Lyophilized-Searle-Pak] , 100mg/iv per day, goes upto 200mg/iv per day), steroidal (Dexamethasone, 6 mg/iv [D-Cort injection-Brookes Pharma]) and anti-pyretic (Paracetamol/ Panadol-GSK-500 mg, twice per day) agents.

Analytical parameters and protocols

Blood was collected from each patient for analyses of PCT, CRP, IL6, LDH, blood gases pressure (pO2, pCO2), D-Dimer and Iron storage proteins, Ferritin according to standard principles and methodologies (Becker *et al*., 2004; Pagana *et al*., 2019; Scheller *et al*., 2011; Schumann *et al*., 2002; Tietz, 1995). Determination was done using fully automated analyzers, Cobas 6000 dry chemistry c501 and iECL immunology e411 (Roche Diagnsotics, Basil), Beckman Coulter Access 2 hybrid (Beckman Coulter, USA), and Nova-PHOX, arterial blood gases analyzer (Nova Biomedical, Massachusetts, USA) with standard protocols and analytical plans described earlier (Alam and Ali, 2020; Alam and Sultana, 2015; Alam *et al*., 2020; Matinuddin *et al*., 2018;). Reference ranges of each parameter are given in table 1 to 8.

STATISTICAL ANALYSIS

Parametric component data (e.g Ferritin, PCT, IL6 etc) of each patient category was statistically compared through Student's t-test (SPSS, version 22 (IBM, SPSS USA), with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where $p<0.05$. If p value came out significant meant elevation or alteration in the inflammatory markers were still marked as compared to the start of the disease, and recovery was slow, suggesting a stronger Covid-19 cytokine storm assault and poor prognostic response to the treatments, even after 10th or 14th or 17th day of stay.

RESULTS

Results are summarized in table 1 to 8. Six selected patients were a small group (n = 6, males = 5, female = 1) of confirmed SARS-Covid-19 individuals, with varying clinical and management status. Their pattern of inflammatory markers (ferritin, LDH, IL6, CRP, PCT) and pressure of blood gases were analyzed for 21 days till their recovery or morbid outcome (one patient, on ventilator, passed away on 20th day of stay). Three patients were in ICU, HDU and on vent, and remaining three were with co-morbid of severally asthmatic, cardiac and renal patients, admitted in specialized Covid ward, not requiring critical care or ventilator assistance. All were treated with Antiviral (remdesivir), steroid (dexamethason) and antipyretic (paracetamol) medications with unstable outcomes. Patents' in ICU, HDU and on Ventilator showed slow recovery even after increase in doses of remdesivir and dexamethasone, noticeable by elevated levels of PCT, IL6, CRP, ferritin and altered levels of pCO2 and pO2 even beyond 14th and 17th day (table 1, 2, 4, 6-8). One Patient on ventilator passed away on 20th day due to multiple complications.

IL6 ($P<0.0224$, $P<0.0228$) and CRP ($P<0.0277$) exhibited none or mild statistical significance difference, with the exception of Ferritin ($P<0.0185$; $P<0.0088$) and D-Dimer ($P<0.0086$), when levels of 1st to 7th days were compared with 10th to 17th days in all patients, signifying slow recovery, manifested by continuing higher levels of pro-

Table 1: Ferritin (ng/ml). Parametric component data of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where p<0.05

Patients (n = 6)	Gender	Days							
		1	4	7	10	14	17	21	P < 0.05
ICU (n = 1)	M	470	540	860	1560	1134	1021	990	0.0088*
HDU (n = 1)	M	500	600	890	1325	1036	800	600	0.5567
Ventilator (n = 1)	M	600	800	1342	1578	1600	1610	--	0.0185*
Asthmatic (n = 1)	M	350	580	600	750	700	589	500	0.0625
Cardiac (n = 1)	M	412	542	610	700	680	550	452	0.0692
Renal (n = 1)	F	430	500	700	810	659	601	500	0.1107

Ferritin Ranges between; Males 30-400 ng/ml; females: 15-150 ng/ml *Significant

Table 2: Lactate dehydrogenase (U/L). Parametric component data of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where p<0.05

Patients (n = 6)	Gender	Days							
		1	4	7	10	14	17	21	P<0.05
ICU (n = 1)	M	236	300	390	398	460	432	376	0.0373*
HDU (n = 1)	M	250	334	340	500	432	370	310	0.1209
Ventilator (n = 1)	M	245	356	450	580	590	520	--	0.0139*
Asthmatic (n = 1)	M	220	321	390	438	490	410	350	0.0340*
Cardiac (n = 1)	M	260	350	400	510	500	490	430	0.0084**
Renal (n = 1)	F	180	210	230	300	390	335	300	0.0053**

Normal ranges; males: 135-225 U/L; females: 135-214 U/L, *Mild Significant, **Highly significant

Table 3: D-Dimer (mg/ml). Parametric component data (e.g Ferritin, PCT, IL6 etc) of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where p<0.05

Patients (n = 6)	Gender	Days							
		1	4	7	10	14	17	21	P<0.05
ICU (n =1)	M	1.4	2.1	2.5	3.4	2.1	1.6	1.1	0.2945
HDU (n = 1)	M	1.8	2.3	2.9	3.2	2.4	2.0	1.4	0.3476
Ventilator (n =1)	M	2.0	3.4	4.2	5.6	7.9	8.0	--	0.0086**
Asthmatic (n = 1)	M	1.2	1.9	2.1	2.3	1.5	1.2	0.9	0.4417
Cardiac (n = 1)	M	1.1	1.1	1.3	1.7	1.2	1.0	0.5	0.2874
Renal (n = 1)	F	0.9	1.0	1.4	1.2	1.0	0.9	0.5	0.3623

Normal Range: D-Dimer < 0.5 mg/ml ; **Highly significant

Table 4: Pro Calcitonin (ng/ml). Parametric component data of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where p<0.05

Patients (n = 6)	Gender	Days							
		1	4	7	10	14	17	21	P<0.05
ICU (n =1)	M	0.50	0.78	0.95	1.3	2.3	2.6	2.1	0.0165*
HDU (n =1)	M	0.67	1.2	1.70	2.1	2.6	2.1	2.0	0.0171*
Ventilator (n =1)	M	1.2	1.6	2.1	2.5	3.0	2.6	--	0.0120*
Asthmatic (n =1)	M	1.1	1.3	1.2	1.1	0.8	0.6	0.5	0.0394*
Cardiac (n =1)	M	0.78	0.99	1.2	1.3	1.1	0.7	0.5	0.4271
Renal (n =1)	F	0.43	0.56	0.98	0.76	0.6	0.5	0.3	0.4252

Normal range: Pro-calcitonin (PCT) < 0.5 ng/ml; *Mild Significant

inflammatory markers till 17th day, revealing stronger cytokine storming assault. LDH, pCO2 and pO2 exhibited none, mild and marked significance difference when data of earlier days were compared with the recovery phase advocating blended treatment on disease outcomes. Expectedly, in case of patient on Ventilator, except IL6, all pro-inflammatory markers exhibited milder significance difference between levels of 1st 7th days vs 10th-17th days, acknowledging offensively marked immunology response that lead to multi-organ dysfunction and finally mortality. Medication treatments with antiviral, steroidal and antipyretic drugs did cause

Table 5: C - reactive protein (mg/L). Parametric component data of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where p<0.05

Patients (n = 6)	Gender	Days							
		1	4	7	10	14	17	21	P<0.05
ICU (n =1)	M	3.2	4.5	6.5	7.4	6.1	4.8	3.2	0.1623
HDU (n=1)	M	3.5	4.6	7.6	6.7	5.4	4.0	3.0	0.4656
Ventilator (n =1)	M	4.6	5.7	8.9	10.1	9.8	9.7	--	0.0277*
Asthmatic (n =1)	M	3.2	4.6	4.9	5.7	6.8	3.4	2.1	0.1992
Cardiac (n =1)	M	2.6	2.8	4.0	3.4	3.2	2.3	1.8	0.3890
Renal (n =1)	F	1.9	2.4	3.4	2.4	1.7	1.2	0.7	0.1137

Normal range: <0.50 mg/L; *Mild Significant

Table 6: Interleukin 6 (pg/ml). Parametric component data of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where p<0.05

Patients (n = 6)	Gender	Days							
		1	4	7	10	14	17	21	P<0.05
ICU (n =1)	M	10	15	18	22	22	20	17	0.0224*
HDU (n =1)	M	17	23	40	45	40	38	30	0.0582
Ventilator (n =1)	M	20	33	49	56	47	43	--	0.0935
Asthmatic (n =1)	M	10	12	15	17	13	14	12	0.1418
Cardiac (n =1)	M	9	12	13	13	12	10	10	0.4170
Renal (n =1)	F	12	14	15	12	10	9	8	0.0278*

Normal range: < 7.0 pg/ml; *Mild Significant

Table 7: PCO2 (mmHg). Parametric component data of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where p<0.05

Patients (n = 6)	Gender	Days							
		1	4	7	10	14	17	21	P<0.05
ICU (n =1)	M	39	42	55	50	40	39	36	0.3594
HDU (n =1)	M	40	41	44	49	45	40	39	0.1772
Ventilator (n =1)	M	42	43	45	50	55	50	--	0.0055**
Asthmatic (n =1)	M	32	41	44	51	44	40	35	0.1410
Cardiac (n =1)	M	41	44	52	40	39	36	36	0.0519
Renal (n =1)	F	37	39	41	48	50	44	38	0.0089**

PCO2 ranges between 35 to 45 mmHg; **Marked Significant

Table 8: PO2 (mmHg). Parametric component data of each patient category was statistically compared with days 1st, 4th, 7th versus 10th, 14th and 17th day and reported as significant where p<0.05

Patients (n = 6)	Gender	Days							
		1	4	7	10	14	17	21	P<0.05
ICU (n =1)	M	88	81	80	75	88	90	90	0.4074
HDU (n =1)	M	84	80	79	74	88	90	91	0.2994
Ventilator (n =1)	M	64	75	73	80	84	88	--	0.0156*
Asthmatic (n =1)	M	74	74	79	83	88	90	90	0.0065**
Cardiac (n =1)	M	78	84	85	89	89	90	90	0.0387*
Renal (n =1)	F	84	88	88	90	91	89	88	0.0417*

PO2 ranges >79 mmHg; *Mild Significant, **Marked Significant

decline in pro-inflammatory markers and normalization of pCO2 and pO2, however, balancing towards non-diseased state was slow and irregular, confirming high viral load, stronger cytokine storm and variable resistance to multi-level management.

DISCUSSION

Recently reported studies regarding SARS Covid-19 and its clinical manifestations, inclusive of cytokine storm revealed that accelerated elevation and sustained high

levels of pro-inflammatory markers, such as IL6, D-Dimer, CRP, LDH, Ferritin and underlying hypoxic state are directly linked with adverse morbidity and likely mortality, if treatments fails (Brouquia *et al*., 2021; Liu *et al*., 2020, Sun *et al*., 2020, Wang *et al*., 2020; Yan *et al*., 2020). Our study exhibited similarities with earlier and recent reports and thus confirming SARS Covid-19 infection intensity and mortality characteristics, significant varying clinical pattern of biomarkers and dissolved gases that were resulted from diversified morbidities, marked cytokine storm and adverse immunological response. One of the most noteworthy and illustrious manifestation of Covid-19 infection is shortness of breath, hypoxic state or hypocapnia, which was very recently reported to show poor outcome (Brouquia *et al*., 2021), mostly preceded by ICU admission and ventilator assistance (Tobin *et al*., 2020; Lv *et al*., 2020). It was suggested that respiratory centers became prone to viral intrigues and creates dyspnea, which sometime remain silent and unnoticeable, but as disease progresses, it intensifies and generate poor prognosis even after high doses of antiviral or steroidal treatments (Carsana *et al*., 2020; Klok *et al*., 2020; Ottesad *et al*., 2020).

Our study highlighted the intriguing feature of SARS Covid-19, the perilous cytokine storm, manifested by actively accelerating pro-inflammatory markers, from coagulation marker D-Dimer to enzyme LDH, chemokine IL6 to infectious protein CRP, from iron storage protein Ferritin to respiratory status indicators viz pressure of dissolved gases CO2 and O2. Most of the markers remained above normal levels, even after extended hospital stay and all possible treatments and care for 21 days. These elevation profoundly depicted hyperimmune system, triggered by abnormally increased secretion of cytokines, causing mass systemic cellular hyperactivity, tissue damages, and multi-organ dysfunctions. Moreover, such hyperactive inflammatory condition also illustrates supra-influencing reactionary innate immune mechanism, confirmed by slow recovery, poor prognosis, even after multi-level therapy of antiviral, steroidal such as remdesivir and dexamethasone and in some cases higher than usual doses. It has been reported that hospitalized patients of Covid-19 that were on ventilation or on oxygen given dexamethasone showed lower 28-day mortality (Horby *et al*., 2021). Deficient or tamed T cell response, lethargic and mute purging of immuno-reactive cells such as monocytes and macrophages, removal or complete extermination viral infected cells, which are some of the characteristic milestones of Cytokine-storm, are best explained reasoning for poor prognosis and besieging SARS Covid-19 pathogenesis (Caricchio *et al*., 2021; Lucas *et al*., 2020, Vardhana *et al*., 2020). Tissue and cellular damages, coagulation disorders, irregularity in B cell synthesis and acute phase protein production, osteoclastic cells dysfunctions, liver dysfunction, both storage and synthetic and pulmonary hypertensions are some of the pathogenic clinical manifestations or diverse morbidity seen in our study of SARS Covid-19 infected patients (Al-Samkari *et al*., 2020; Caricchio *et al*., 2021; Hasan *et al*., 2020, Lv *et al*., 2020; Parry *et al*., 2020). Furthermore, it was also noted that underlying co-morbid, diabetes, renal insufficiency and pulmonary dysfunction further enhances progressing and stealthily spreading viral infections, resulting in poor outcome (Brouquia *et al*., 2021; Caricchio *et al*., 2021; Liu *et al*., 2020; Rao *et al*., 2020).

CONCLUSION

Present study described varying levels of pro-inflammatory markers and blood gases status in SARS Covid-19 patients (n=6), admitted in ICU, HDU, on ventilator and some with underlying co-morbidities. Analyzed data clearly indicated ramification of a strong cytokine storm which is major characteristic of SARS Covid-19 infections, inducing multi organ dysfunctions, tissue damages and progressing pathology. Treatments with antiviral and steroidal agents does prompted slow but reasonable recovery, exhibited by declining pro-inflammatory markers and normalization of blood gases status.

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