

Inflammatory Representation of COVID-19 at the Time of Hospitalization: An Insight into the Mild, Moderate, Severe and Critical COVID-19 Disease

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Introduction

- The ongoing state of the COVID-19 pandemic necessitates the characterization of the biological basis of disease severity.

Objective

- Our objective was to correlate the clinical severity of illness upon hospitalization with inflammatory sero-biomarker levels.

Methods

- A single-center prospective cohort study was conducted at a 776-bed tertiary care urban academic medical center in Detroit, Michigan. The study was approved by the Institutional Review Board.

- Adults with confirmed reverse-transcriptase-polymerase-chain-reaction assay for COVID-19 were recruited in equal numbers into four disease severity categories, as defined by the WHO, upon hospital admission from Jan. 8th, 2021, to Sept. 1st, 2021.

- Electronic medical charts were reviewed. In addition to clinical markers, cytokines and chemokines such as CCL2, IL-18, CXCL-10 (IP-10), TNF- α , IL-1ra, IL-10, Granzyme B, IL-6, and IL-8 were assessed at hospital presentation to gain detailed understanding of COVID-19 pathology.

Results

- We included 200 patients with 50 patients each in each group: mild, moderate, severe and critical illness.
- The mean age of the cohort was 58.6 \pm 15.9 years, 104 (52%) were male, and 135 (67.5%) were black/African American.
- The common comorbidities were hypertension (67.5%), chronic lung diseases (26.5%), and heart failure (15.5%).
- At the time of admission, oxygen therapy was needed in 49.5% but intubation was needed in only 0.5%.

Table 1. Study Demographics

		COVID-19 severity				
		Mild (N=50)	Moderate (N=50)	Severe (N=50)	Critical (N=50)	Total (N=200)
Sex	Male	31 (62%)	20 (40%)	28 (56%)	25 (50%)	104 (52%)
	Female	19 (38%)	30 (60%)	22 (44%)	25 (50%)	96 (48%)
Demographic	White	14 (28%)	16 (32%)	20 (40%)	11 (22%)	61 (30.5%)
	Black/A.A.	34 (68%)	33 (66%)	30 (60%)	38 (76%)	135 (67.5%)
	Other	2 (4%)	1 (2%)	0	1 (2%)	4 (2%)

Table 2. Symptoms and treatment at the presentation

	COVID-19 severity				
	Mild (N=50)	Moderate (N=50)	Severe (N=50)	Critical (N=50)	Total (N=200)
Myocardial Infarction	7 (14%)	3 (6%)	8 (16%)	5 (10%)	23 (11.5%)
Heart Failure	9 (18%)	4 (8%)	9 (18%)	9 (18%)	31 (15.5%)
Peripheral Vascular Disease	2 (4%)	3 (6%)	1 (2%)	4 (8%)	10 (5%)
Cerebrovascular Disease	2 (4%)	5 (10%)	4 (8%)	6 (12%)	17 (8.5%)
Dementia	1 (2%)	1 (2%)	1 (2%)	0 (0%)	3 (1.5%)
Chronic Pulmonary Disease	10 (20%)	17 (34%)	15 (30%)	11 (22%)	53 (26.5%)
Rheumatic Disease	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (0.5%)
Peptic Ulcer Disease	2 (4%)	2 (4%)	0 (0%)	1 (2%)	5 (2.5%)
Diabetes without Complication	3 (6%)	4 (8%)	3 (6%)	6 (12%)	16 (8%)
Hemiplegia/Paraplegia	0 (0%)	1 (2%)	1 (2%)	1 (2%)	3 (1.5%)
Renal Disease	9 (18%)	5 (10%)	7 (14%)	6 (12%)	27 (13.5%)
Peritoneal Dialysis	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (0.5%)
Hemodialysis	0 (0%)	2 (4%)	3 (6%)	1 (2%)	6 (3%)
History of Malignancy	4 (8%)	10 (20%)	2 (4%)	7 (14%)	23 (11.5%)
Mild Liver Diseases	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1 (0.5%)
Moderate to Severe Liver Disease	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (0.5%)
History of Transplant	0 (0%)	1 (2%)	0 (0%)	3 (6%)	4 (2%)
Hypertension	32 (64%)	33 (66%)	35 (70%)	35 (70%)	135 (67.5%)

Table 3. Concurrent alcohol, tobacco, and drug use prior to COVID-19 infection

	COVID-19 severity				
	Mild (N=50)	Moderate (N=50)	Severe (N=50)	Critical (N=50)	Total (N=200)
Smoking	16 (32%)	4 (8%)	4 (8%)	8 (16%)	32 (16%)
Alcohol use	14 (28%)	9 (18%)	6 (12%)	6 (12%)	35 (17.5%)
Drug use	7 (14%)	2 (4%)	1 (2%)	2 (4%)	12 (6%)
Intravenous Drug use	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)

Table 4. Inflammation markers at hospital presentation. (Mean \pm Standard Deviation)

	COVID-19 severity			
	Mild (N=50)	Moderate (N=50)	Severe (N=50)	Critical (N=50)
CRP	34.99 \pm 41.35	72.37 \pm 7.76	90.31 \pm 73.06	82.83 \pm 84.11
LDH	228.77 \pm 60.83	341 \pm 109.52	440.22 \pm 188.31	616.75 \pm 548.77
PT	14.91 \pm 2.37	16.83 \pm 7.31	15.10 \pm 3.55	14.99 \pm 1.98
D-Dimer	1561.49 \pm 3215.059	1584.26 \pm 1713.199	2350 \pm 3920.196	3728.89 \pm 5612.500
Ferritin	629.68 \pm 1015.235	752.26 \pm 1054.079	1414.23 \pm 2990.297	643.09 \pm 633.093
Procalcitonin	0.2569 \pm 0.23048	0.1565 \pm 0.29252	0.4333 \pm 0.66137	1.3210 \pm 3.97355
Troponin	0.0308 \pm 0.00487	0.0311 \pm 0.00577	0.0659 \pm 0.09887	0.0750 \pm 0.12588
CPK	236.44 \pm 236.44	162.31 \pm 151.217	260.05 \pm 296.275	1265.14 \pm 1826.734

Table 5. Inflammation cytokines and chemokines at the hospital presentation (Mean \pm Standard Deviation)

	COVID-19 severity			
	Mild (N=50)	Moderate (N=50)	Severe (N=50)	Critical (N=50)
CCL-2	692.23 \pm 463.63	767.27 \pm 730.67	930.17 \pm 743.04	798.40 \pm 455.45
IL-18	412.91 \pm 252.75	498.49 \pm 209.91	486.71 \pm 245.52	454.79 \pm 265.81
CXCL-10	1424.50 \pm 1373.34	2036.63 \pm 1024.94	2772.88 \pm 1877.98	2518.33 \pm 2379.95
TNF	16.56 \pm 7.09	16.94 \pm 7.69	16.80 \pm 6.36	23.68 \pm 13.47
IL-1ra	2619.89 \pm 3023.94	4171.34 \pm 10138.52	8715.00 \pm 21829.35	6766.0 \pm 14066.29
IL-10	17.55 \pm 45.64	16.56 \pm 14.34	25.09 \pm 41.90	18.27 \pm 14.59
Granzyme B	82.91 \pm 107.9	85.59 \pm 78.17	68.39 \pm 39.58	102.59 \pm 124.58
IL-6	36.25 \pm 34.68	101.15 \pm 143.6	95.55 \pm 84.44	125.55 \pm 185.95
IL-8	49.27 \pm 44.94	66.87 \pm 121.54	53 \pm 39.16	557.42 \pm 3141.68

Table 6. Symptoms and treatment at presentation

	COVID-19 severity					
	Mild (N=50)	Moderate (N=50)	Severe (N=50)	Critical (N=50)	Total (N=200)	
Shock requiring pressors	1 (2%)	2 (4%)	7 (14%)	9 (18%)	19 (9.5%)	
ARDS	2 (4%)	1 (2%)	11 (22%)	7 (14%)	21 (10.5%)	
AKI	16 (32%)	9 (18%)	19 (38%)	33 (66%)	77 (38.5%)	
New venous thrombosis	1 (2%)	1 (2%)	3 (6%)	10 (20%)	15 (7.5%)	
Steroids	16 (32%)	41 (83.7%)	50 (100%)	31 (62%)	138 (69.3%)	
Remdesivir	8 (16%)	16 (32%)	35 (70%)	17 (34%)	76 (38%)	
Convalescent Plasma	3 (6%)	1 (2%)	5 (10%)	1 (2%)	10 (5%)	
Other experimental drugs	2 (4%)	1 (2%)	4 (8%)	4 (8%)	11 (5.5%)	
Anticoagulant and antiplatelets	45 (90%)	39 (78%)	35 (70%)	36 (72%)	155 (77.5%)	
Indication of using Anti-coagulant	Therapeutic	17 (38.6%)	13 (34.5%)	15 (42.9%)	17 (48.6%)	62 (40.8%)
	Preventive	27 (61.4%)	25 (65.8%)	20 (57.1%)	18 (51.4%)	90 (59.2%)
Oxygen Supplement Required on Admission	No	38 (76%)	25 (50%)	6 (12%)	32 (64%)	101 (50.5%)
	Yes	12 (24%)	25 (50%)	44 (88%)	18 (36%)	99 (49.5%)
	Nasal Cannula	11	21	32	8	72
	High Flow	0	3	3	5	11
	NRB	1	1	3	0	5
	biPAP	0	0	6	4	10
MV	0	0	0	1	1	

Table 7. Final Disposition

	COVID-19 severity					
	Mild (N=50)	Moderate (N=50)	Severe (N=50)	Critical (N=50)	Total (N=200)	
Final Disposition	Died	2 (4%)	2 (4%)	12 (24%)	10 (20%)	26 (13%)
	Survived	48 (96%)	48 (96%)	38 (76%)	40 (80%)	174 (87%)

List of Abbreviations

Abbreviation	Definition	Abbreviation	Definition
COVID-19	Coronavirus Disease 2019	CXCL-10	C-X-C motif chemokine ligand 10
WHO	World Health Organization	TNF	Tumor Necrosis Factor
CDC	Center of Disease Control	IL-1ra	Interleukin 1 Receptor Antagonist
CXR	Chest X-Ray	IL-10	Interleukin-10
DVT	Deep Vein Thrombosis	IL-6	Interleukin-6
CRP	C-Reactive Protein	IL-8	Interleukin-8
LDH	Lactate Dehydrogenase	ARDS	Acute Respiratory Distress Syndrome
PT	Prothrombin Time	AKI	Acute Kidney Injury
CPK	Creatine Phosphokinase	NRB	Non-Rebreather Mask
CCL-2	CC-chemokine Ligand 2	biPAP	Bilevel Positive Airway Pressure
IL-18	Interleukin-18	MV	Minute Ventilation

The authors have no conflict of interest.

Discussion

- Our study population included a substantial number of black/African American individuals from the Detroit metropolitan area.
- Interestingly, smoking, alcohol and drug use were inversely correlated with the COVID-19 severity for admitted patients.
- Hypertension, chronic lung diseases and heart failure were the most prevalent comorbidity across all the cohorts. However, there were no clear trend in correlating these comorbidities with COVID-19 severity.
- We observed elevated levels of AKI, venous thrombosis, and elevated oxygen supplement requirement with respect to COVID-19 severity.
- We noted COVID-19 severity dependent increase in CRP, LDH, D-Dimer, Ferritin, and CPK levels in conjunction with CXCL-10, IL-1ra, IL-10, IL-6, IL-8, and CCL-2 levels. The correlative increase was prominent among mild, moderate and severe COVID-19 disease at hospital presentation.

Conclusion

- COVID-19 severity dependent increase in AKI along with inflammatory marker suggests underlying role of vascular inflammation affecting the functioning of kidney.
- Clinical inflammatory markers in conjunction with chemokine and cytokines suggests COVID-19 severity dependent immunological regulation for mild, moderate and severe disease. Further, they also suggest critical COVID-19 may not be immunologically regulated at hospital presentation.
- Inverse correlation of smoking, alcohol and drug use with COVID-19 severity on presentation requires further observation and investigation.

References

- Bhargava A et al, Predictors for Severe COVID-19 Infection. Clin Infect Dis. 2020 Nov 5;71(8):1962-1968. doi: 10.1093/cid/ciaa674. PMID: 32472676; PMCID: PMC7314166.
- Akagi EF et al, Clinical features and risk factors for community-onset bloodstream infections among coronavirus disease 2019 (COVID-19) patients. Infect Control Hosp Epidemiol. 2021 Jul;42(7):899-901. doi: 10.1017/ice.2021.88. Epub 2021 Mar 12. PMID: 33706821; PMCID: PMC7985891.