



Role of Biomarker in COVID-19: A Study from Tertiary Care Center

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Abstract

Background: The COVID-19 infection affects all age groups and both genders. Recent studies have suggested that elder subjects are more prone to COVID-19 infection and its complications compared to young and middle-aged subjects. To investigate COVID-19 infection affecting patients with different age groups (young age, middle age and elder age) with biomarkers.

Methods: Data was collected retrospectively from Yashoda Hospital Hyderabad, and study period from April 2020 to October 2020.

Results: Out of 115 patients, men were 83 (72.3%) mean age was 55.7 ± 14.5 years (age range 18 to 89 years) mean duration of hospital stay was 10.9 ± 6.0 days (stay in hospital range 6 to 29 days). Hypertension was seen in 24 (20.8%), diabetes in 12 (10.4%), previous history of cardiovascular disease in 11 (9.5%) and previous history of cerebrovascular disease in 6 (5.2%). Mechanical ventilator support was required in 21 (18.2%), lung area affected on CT chest appearance was less than 25% in 50 (43%), 25% to 49% in 35 (30.4%), $\geq 50\%$ in 30 (26%). Mean C-Reactive Protein (CRP) value was 68.7 ± 18.6 mg/L, mean D-dimer 1471.8 ± 591.4 ng/ml, mean procalcitonin 1787.1 ± 550.8 ng/ml, mean interleukin-6 was 11.4 ± 3.8 pg/ml and mean serum ferritin was 428 ± 167.9 ng/ml. Among the age groups, 17.3% were young, 38.2% were middle aged and 44.3% were elderly and the overall mortality was 4.3%.

The elder age group was significantly associated with longer mean duration of hospital ($p=0.02$), higher mean CRP value ($p=0.006$), mean D-dimer value ($p<0.0001$), mean procalcitonin ($p<0.001$), mean interleukin-6 ($p=0.001$), mean serum ferritin ($p=0.001$) values compared to young and middle age patients.

Conclusion: Our study found elder age group constituted 44.3% of COVID-19 infected patients and inflammatory markers CRP, D-dimer, procalcitonin, interleukin-6 and serum ferritin levels were significantly higher in them.

Keywords: Elder age; CRP; Procalcitonin serum ferritin; D-dimer serum ferritin; COVID-19 infection

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Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a new type of coronavirus, which is infecting humans worldwide [1]. Declared a pandemic by the World Health Organization, mode of transmission is human to human [2]. It is unclear whether age or other risk factors influence risk of COVID-19 progression. Studies have reported COVID-19 in association with baseline comorbidities of hospitalized patients, but data on age-adjusted estimates of excess risk associated with comorbidities, especially from Indian subcontinent is scant [3]. The Center for Disease Control and Prevention (CDCP) reported that elder patients were more affected with COVID-19 infection [4]. Older adults with multiple risk factors and individuals with complex underlying health conditions have more severe COVID-19 infection [5].

Coronaviruses is a heterogeneous, cluster of large single-strand RNA viruses, widely distributed among mammals and birds and grouped in the family of *Coronaviridae* [6]. The genera of interest for humans are alpha and beta-coronavirus which compose the subfamily of *Coronavirinae*, along with gamma and delta coronavirus, not recognized as human pathogens [7]. The main routes of transmission of COVID-19 are by virus droplets and close contact with person to person transmission or through the fecal-oral route [6]. The empirical evidence on the association between

risk factors and severe or critical care outcomes of COVID-19, after accounting for age, among hospitalized patients with COVID-19 is limited [3]. The present study to investigated, the role of biomarkers in COVID-19 patients with different age groups.

Materials and Methods

We collected the data, prospectively, all COVID-19 cases admitted in Yashoda Hospital during the study period between March 2020 and October 2020. During the seven months, 150 patients were admitted with primary presumptive diagnosis of COVID-19. Out of the 150 patients, 28 patients had Reverse Transcription Polymerase Chain Reaction (RT-PCR) negative and 7 patients Left against Medical Advice (LAMA) within 2 days of admission. Remaining 115 patients were included in the study and their data was collected. Patients were trichotomized into young age: ≤ 45 years, middle age: 46 to 59 years and elder age: ≥ 60 years. The diagnosis of COVID-19 cases was based on the national recommendation of the New Coronavirus Pneumonia Prevention and Control Program (sixth edition) [8].

Laboratory Diagnosis of COVID-19

Diagnosis was confirmed in all using RT-PCR, detecting the COVID-19 RNA. Currently approved by World Health Organization (WHO) and Indian Council of Medical Research (ICMR), it is the gold standard [9].

Other Investigations

Patient's medical history and reports were collected at the time of admissions. All patients underwent detailed assessment with a set of laboratory investigations, including complete blood picture, liver function tests, urine analysis (including urine albumin), serum creatinine, blood urea, serum albumin, serum glucose, C-Reactive Protein (CRP), Interleukin-6 (IL-6) procalcitonin, D-dimer, serum ferritin. Computed Tomography (CT) scan chest was done in all patients. Based on the area of lung involved by COVID-19 infection, we divided into three categories. (<25%, 26% to 49% and >50% effected the chest). Risk factors assessment was done based on our previous studies [10]. This study was approved by the Institutional Scientific Committee.

Statistical Analysis

Statistical analysis was performed using SPSS Inc (Statistical Package for the Social Sciences) 17.0 software. Mean and Standard Deviation (SD) were calculated. The paired 't' test was applied for differences in continuous variables and chi square test was used to assess differences in the frequencies. All tests were two sided and p value <0.05 were considered statistically significant.

Results

Men were 83 (72.3%), mean age was 55.7 ± 14.5 years with age range from 18 to 89 years and duration of hospital stay was 10.9 ± 6.0 days (Table 1). Among all patients, 20 (17.3%) patients were young, 44 (38.2%) patients were middle aged and 51 (44.3%) were older patients. Hypertension was noted in 24 (20.8%), diabetes in 12 (10.4%), smokers were 12 (10.4%); alcoholics were 5 (4.3%). As per the chest CT scan, 50 (43.4%) had <25% area involvement, lung involvement of 26% to 49% was seen in 35 (30.4%) and more than 50% of lungs was affected in 30 (26%) patients. The mean CRP value was 68.7 ± 18.6 (mg/L), mean D-dimer value was 1471.8 ± 591.4 (ng/ml), mean procalcitonin was 1787.1 ± 550.8 (ng/ml), mean Interleukin-6 was 11.4 ± 3.8 (pg/ml) and mean serum ferritin was 428 ± 167.9 (ng/ml)

Table 1: Baseline characteristics.

Parameters	Number (n=115)
Men	83(72.3%)
Women	32(27.7%)
Mean age years	55.7 ± 14.5
Age range years	18-89
Young patients (<45 years)	20 (17.3%)
Middle age patients (46-59 years)	44 (38.2%)
Elder age patients (>60 years)	51 (44.3%)
Hospital stay duration range days	6-29
Hospital stay mean duration days	10.9 ± 6.0
Hypertension	24 (20.8%)
Diabetics	12 (10.4%)
Smoker	12 (10.4%)
Alcoholics	5 (4.3%)
Asthma	11 (9.5%)
Previous history of cardiovascular disease	11 (9.5%)
Previous history of cerebrovascular disease	6 (5.2%)
History of any cancer	4 (3.4%)
History of chronic kidney Disease	5 (4.3%)
Fever	115 (100%)
Dry cough	94 (81.7%)
Tiredness	82 (71.3%)
shortness of breath	51 (44.3%)
Mechanical ventilator	21 (18.2%)
Area of affected lung on Chest CT, n (%)	
<25%	50 (43.4%)
26-49%	35 (30.4%)
>50%	30 (26%)
Mean CRP value(mg/L)	68.7 ± 18.6
Mean D-dimer value	1471.8 ± 591.4
Mean Procalcitonin	1787.1 ± 550.8
Mean Interleukin -6	11.4 ± 3.8
Mean Serum Ferritin	428 ± 167.9
Hb	11.2 ± 1.8
Alanine aminotransferase (ALT)	72.1 ± 5.7
Aspartate aminotransferase (AST)	72.6±7.2
Gamma-glutamyl transferase (GGT)	63.8 ± 7.1
serum creatinine	1.1 ± 0.4
Mortality	5 (4.3%)

ml) (Table 1).

On comparison of the three age groups, mean duration of hospital was longer ($p=0.02$), hypertension was more prevalent ($p=0.04$), mean CRP value ($p=0.006$), mean D-dimer value ($p<0.0001$), mean procalcitonin ($p<0.0001$), mean Interleukin-6 ($p<0.0001$) and mean serum ferritin ($p=0.0001$) were significantly higher in elder patients (Table 2).

Discussion

The COVID-19 pandemic is impacting all age groups and seems

Table 2: Differences between the three age groups.

Parameters	Young age patients (n=20)	Middle age patients (n=44)	Elder age patients (n=51)	p value
Men	16 (80%)	33 (75%)	41 (80%)	0.4
Hospital stay duration range days	16-June	21-August	29-September	NA
Mean duration of hospital	8.1 ± 2.4	9.6 ± 4.7	17.3 ± 7.0	0.02
Fever	20 (100%)	44 (100%)	51 (100%)	0.9
Dry cough	10 (50%)	35 (79.5%)	49 (96%)	0.1
Tiredness	12 (60%)	36 (81%)	34 (66.6%)	0.3
shortness of breath	7 (35%)	16 (36.3%)	28 (54.9%)	0.4
Mortality	0	0	5 (9.8%)	0.1
Risk factors				
Hypertension	2 (10%)	5 (11.3%)	18 (35.2%)	0.04
Diabetes	0	3 (6.8%)	9 (17.6%)	0.08
Smokers	1 (5%)	2 (4.5%)	8 (15.6%)	0.1
Alcoholics	0	1 (2.2%)	4 (7.8%)	0.4
Asthma	1 (5%)	2 (4.5%)	5 (8.9%)	0.6
Previous history of coronary artery disease	0	2 (4.5%)	8 (15.6%)	
Previous history of cerebrovascular disease	0	1(2.2%)	5 (8.9%)	0.7
History of any cancer	0	0	2 (3.9%)	0.6
Chronic kidney Disease	0	2 (4.5%)	3 (5.8%)	0.6
Area of affected lung on Chest CT, (%)				
<25%	10 (50%)	20 (45.4%)	20 (39.2%)	0.2
26-49%	5 (25%)	14 (31.8%)	16 (31.3%)	0.1
>50%	5 (25%)	10 (22.7%)	15 (29.4%)	0.1
Mechanical ventilator	1 (5%)	5 (11.3%)	15 (29.4%)	0.6
Mean CRP value (mg/L)	45.2 ± 14.9	58.9 ± 19.4	64.3 ± 16.1	0.006
Mean D-dimer value (ng/ml)	745.5 ± 566.5	1292 ± 373.2	1820.4 ± 564.9	<0.0001
Mean Procalcitonin (ng/ml)	1210.1 ± 579.4	1641.7 ± 433.1	2120.6 ± 435.1	<0.0001
Mean Interleukin -6 (pg/ml)	8.7 ± 2.6	10.4 ± 3.7	15.1 ± 5.2	<0.0001
Mean Serum Ferritin (ng/ml)	239.1 ± 89.4	393.8 ± 147.9	510.4 ± 150.1	0.001
HB	12.9 ± 1.4	10.65 ± 1.7	9.9 ± 1.3	0.07
Mean serum creatinine	0.9 ± 0.3	1.0 ± 0.37	1.29 ± 0.5	0.4
Aspartate amino transferase (AST)	72.7 ± 7.1	71.7 ± 6.5	74.2 ± 7.4	0.09
Alanine amino transferase (ALT)	70.9 ± 6.7	72.1 ± 5.5	72.6 ± 5.4	0.08
Gamma-Glutamyl Transferase (GGT)	63.9 ± 7.1	64.3 ± 6.9	62.9 ± 7.4	0.06

to affect elderly people more. In the current study, among all patients with COVID-19, 17.3% belonged to young age, 38.2% were middle age and 44.3% belonged to elder age, our finding were supported by others [11]. Another study noted 6% were aged ≥ 85, 25% were aged 65 to 84 years, 18% each were aged 55 to 64 and 45 to 54 years, and 29% were aged 20 to 44 years [12]. Du et al. [13] found age more than 60 years had 3.7 times higher risk of COVID-19 infection [13].

Clinical Presentation

In our study, most common symptom was fever seen in 100% followed by cough in 81.7%, tiredness in 71.3%, shortness of breath and mechanical ventilator support requirement in 21 (18.2%) patients with COVID-19 infection, similar finding were observed by others [1,2,14,15]. In a study by Huang et al. [14], 98% patient had fever [14]. On the other hand Arentz et al. [15] a high prevalence of shortness of breath among 76% followed by fever in 52%, and dry cough in 48%

[15].

When we looked at the comorbidities and risk factors, 20.8% of all patients had hypertension, 10.4% were diabetic, 10.4% were smokers, 9.5% had chronic respiratory disease, 9.5% had history of cardiovascular disease, 5.2% had history of cerebrovascular disease while 3.4% had cancer, and similar findings were noted by others. Du et al. [16] identified that 37.6% of patients with COVID-19 had hypertension, 22.4% had diabetes, 11.8% coronary heart disease, 8.2% cerebrovascular disease and 2.4% had Chronic Obstructive Pulmonary Disease (COPD) [16]. Lesser prevalence of risk factors were noted in a Chinese study - cardiovascular disease was noted in 10.2%, diabetes in 7.3%, chronic respiratory disease in 6.3%, hypertension in 6% and cancer in 5.6% of COVID-19 infection patients [17].

Aging is an important risk factor and the elderly people are at risk of severe infections possibly because of the inefficient initial anti-

viral immune response. The presence of the chronic diseases marks declining immunity and biological aging, which is more important than the chronological age. Due to various factors, the clinical severity and outcomes including the mortality from COVID-19 in elderly patients is higher than that in young and middle-aged patients [18].

Older aged individuals are also likely to have various comorbidities like hypertension and are more likely to be on Angiotensin Converting Enzyme-2 Inhibitors (ACE-Is) and Angiotensin Receptor Blockers (ARBs). COVID-19 infection enters cells through the Angiotensin-Converting Enzyme-2 (ACE-2) receptor in the lungs gastrointestinal system, heart, endothelium and kidneys. Spike proteins presented on the outside of COVID-19 anchor to ACE-2 receptors on cells in the Lower Respiratory Tract (LRT) [19], and cause the respiratory infection. Patients on ARBs and ACE-Is may have up-regulated ACE-2 receptors and thus have an elevated risk of acquiring infection as well as experiencing a more severe course of COVID-19 infection [2].

Duration of Hospital Stay

In our study, we noted significantly higher duration of hospital stay in elder patients (17.3 ± 7.0 days) compared to young and middle age ($p=0.002$), these findings were advocated by Liu et al. [20].

Amongst the various lab parameters, we found no significant association between the three groups with mean hemoglobin, serum creatinine, serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Gamma-Glutamyl Transferase (GGT) levels, our findings were advocated by others [18].

CRP

CRP is an acute phase plasma protein used to diagnose inflammatory marker [10]. The CRP marker was found to be significantly increased in the initial phases of the infection for COVID-19 patient. In our study we found CRP levels were significantly higher in elder patients compared to younger and middle-aged patients ($p=0.006$), our results were supported by several studies [1,21].

The mean value of CRP level in elder patient in our study was 64.3 mg/L, this is in midst of values noted by others (43.1 to 111.3 mg/L) [1,21,22]. However few studies have showed no significant association between CRP positivity and age of patient [18].

D-dimer

D-Dimer is a specific bio-marker for patients with venous thromboembolism, and is also used as an inflammatory marker [23]. We found that the older patients had significantly higher levels, compared to the other two groups ($p<0.0001$), our findings were advocated by others [4], though few studies have shown no age correlation [1].

In our study, the mean value of D-dimer was 1820.4 ng/mL similar findings were noted by Jurado et al. [22]; a mean value of 1885.10 ng/mL was detected in their study [22]. As a prognostic marker, D-dimer should be considered in the management of hospitalized COVID-19 patients [24]. The elevated values among the older patients demonstrate their vulnerability to develop thrombotic complications. Although we found no difference in value among men and women, few studies have shown men to have higher values of D-dimer [25].

Procalcitonin

Procalcitonin is a 116 amino acid peptide that has an approximate

MW of 14.5 kDa and belongs to the Calcitonin (CT) super family of peptides. Calcitonin is a hormone released from C-cells of the thyroid gland with the function of regulating the body's calcium metabolism and during infection, procalcitonin levels are elevated [26]. Our data shows a significantly higher procalcitonin levels in elder patients when compared to young and middle-aged patients ($p<0.0001$), similar findings were noted by Guo et al. [1], Kim et al. [26].

However few studies were noted no significant age-related association of procalcitonin [18]. The levels may be secondary to more severe disease with longer ICU stay and thereby increased risk of secondary infections.

Interleukin-6

Interleukin-6 (IL-6) can be produced by almost all stromal cells and by immune system cells, such as B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes, mast cells and many non-lymphocytes, such as fibroblast and endothelial cells [27]. IL-6 plays a vital role in infectious diseases like influenza virus [28].

We found a significant high mean value of IL-6 - 15.1 pg/mL in elder patients compared to younger and middle-aged patients while another study showed IL-6 values to be higher in only males above 60 years of age [29]. Jurado et al. [22] noted in his study a higher mean IL-6 value of 113.7 pg/ml in elder patients [22]. Herold et al. [30] established in his study that IL-6 levels above 80 pg/mL was a strong predictor of severe COVID-19 infection [30]. However few studies have noted no significant elevated IL-6 with more than 60 years age group patients [31].

Ageing, multiple comorbidities can induce an inflammatory milieu and can predispose them to rise in IL-6 levels with infection, once again marking their tendency to have a more severe disease [32].

Serum Ferritin

Serum ferritin is a spherical protein structure, made-up of 24 H-and L-subunits that is expressed in several tissues and cell types and is also present in body fluids like blood plasma and serum [33]. Iron status can change with inflammation while ferritin levels are increased and can act as a marker [34]. During this pandemic time, studies have found that elevation of serum ferritin levels were associated with COVID-19 infection and mortality [35].

In our study we found higher mean serum ferritin values (510.4 ng/ml) in patients aged more than 60 years, compared to other two age groups, these findings supported by others [36]. Zhou et al. [31] detected in his study, an elevated mean serum ferritin of 1435.3 ng/ml in COVID-19 patients >60 years of age [31]. Another study in elder patients demonstrated a mean serum ferritin level of 1108.60 ng/mL [22]. High systemic ferritin may serve as an indicator of developing macrophage activation syndrome, rather than a factor driving COVID-19 pathogenesis [37].

Mortality

In our study we established an overall mortality of 4.3%, our findings have been advocated by others [1,38,39]. In the study by Ye et al. [38], the overall mortality rate was 4%. Wu et al. found an overall mortality rate of 2.3% [39]. Guo et al. [1], 2.9%; however few studies have shown higher mortality rate. The current study we demonstrated age as a risk factor for mortality-mortality rate of 9.8% in elder patient, our findings have been advocated by others [2,39], however some other studies have showed lesser mortality rate [1]. In our study

high mortality rate was seen in elderly patients having multiple risk factors like hypertension, CKD, diabetes and cardiovascular diseases, our finding supported by others [2,33].

Treatment Regime

In our study, all patients received Remdesivir for 5 days, vitamin C tablets and D injections, steroids along with Low Molecular Weight (LMW) heparin and other analgesic drugs. Antibiotics, tocilizumab and respiratory support were given as per requirement.

Limitations of the Study

Main limitation is our small sample size precluding multiple logistic regression analyses, lactate dehydrogenase and troponin were not assessed in all, the lab values were a single value at admission. As these values change with the disease course, repeated values and trends would have been more useful. However, these tests were not performed uniformly in all during hospital stay and at discharge and hence could not be analyzed. The study is hospital based and may not exactly represent the disease in the community.

Conclusion

In our study of hospitalized COVID-19 infected patients, 17.3% belonged to younger age group, 38.2% middle age and 44.3% to elder age group. In our study, longer mean hospital stay, elevated mean levels of CRP, D-dimer. Procalcitonin, IL-6 and serum ferritin were significantly associated with elder age patients. In our knowledge this is the first study from Indian sub-continent. Further large-scale studies are required to confirm these findings.

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