Original Article

Severity Index and Outcome of Hospitalized COVID-19 Patients in Capital Hospital, CDA, Islamabad

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Abstract

Introduction: The global covid epidemic claims significant mortality and healthcare burden. The current study was conducted to assess clinical characteristics, predictors of severity, and outcome in terms of mortality of patients with Covid-19 infection.

Materials and Methods: This descriptive cross-sectional study was conducted at the Department of Medicine, Capital Hospital Islamabad (Feb. 01, 2021, to April 25, 2021). The study included 221 adult patients of both genders, who presented with features suggestive of Covid-19. Detailed clinical evaluation, Covid PCR, radiological investigations, blood complete picture, and inflammatory markers (ferritin, D dimers, LDH, C-reactive protein, interleukin-6 levels were performed). Based on the severity Index, patients were labelled as mild, moderate, or severe Covid. Patients were managed and followed till discharge or death. The association of covid severity was studied with the inflammatory markers, white cell counts, and outcome (i.e., death or recovery). Data analyzed by SPSS version 42, Chi-square applied as a test of significance and significant $p< 0.05$.

Results: As per the severity index, 86(38.9%) cases had mild, 91(41.2%) had moderate and 44(19.9%) had severe Covid-19. Lymphopenia was observed in 154(69.7%), positive CRP 178(80.5%), raised serum ferritin 114(51.5%), raised D-dimers 139(66.9%), lactic dehydrogenase 167(75.5%) having a significant association with disease severity. Serum interleukin (performed in moderate and severe cases) had a mean value of 54.1+105.94pg/ml. Diabetes mellitus was found to be significantly associated with mortality ($p=0.007$) as well as hypertension ($p<0.0001$). 207 cases recovered and discharged; 14(6.33%) expired.

Conclusion: Covid-19 is a disease with variable presentations. The severity of Covid-19 infection is directly related to lymphopenia as well as elevated inflammatory markers. IL-6 levels, raised in more severe cases, that signify an immune response to Covid-19. The disease is more severe in patients with co-morbids.

Keywords: Covid-19, Coronavirus-disease, Pandemic, Covid Severity Index, mortality.

Introduction

The pandemic of Coronavirus disease (COVID-19) is far from being over. What started as an outbreak in Wuhan in November 2019 was eventually declared a global health concern by the World health organization (WHO) on March 11, 2020.[1]

Since the first reports of Coronavirus cases from Wuhan, at the end of 2019, more than six million confirmed cases of COVID-19 have been reported globally, in all continents except for Antarctica.[2] Updated case counts in English can be found on the World Health Organization and European Centre for Disease Prevention and Control websites.

Coronavirus disease is caused by SARS-C0V-2, which shares both structural and ancestral origin to SARS-C0V-1 and MERS. The incubation period ranges from a minimum of 4 days to a maximum of 14 days with a mean value of 5.1 days.[3,4]

Currently, the main transmission routes are via respiratory droplets and direct human-to-human contact in which virus is released in the respiratory secretions when an infected person coughs, sneezes, or talks. The infectivity of an affected individual is 2.5-2.9. Hence general hygiene precautions, maintaining a safe distance, and wearing a facemask minimizes the risk of virus spread to a great degree.

The spectrum of Covid symptoms ranges from common such as fever, dry cough, shortness of breath to less reported including gastrointestinal such as diarrhea and taste or olfactory issues. However, it can develop into severe pneumonia, ARDS, and even multi-organ failure.

The disease process starts when the virus via its spike protein gets attached to the host cell and invades.[5] Once the virus gets inside a human body, it binds to the ACE-2 receptor expressed on alveoli and other cells and starts replicating. This results in damage to type-2 pneumocytes releasing specific inflammatory mediators which attract macrophages. Macrophages engulf the virus. IL-1, IL-6, TNF-alpha, and Interferon are released; this is called a cytokine storm.

The standard method for diagnosing Covid-19 infection is performing RT-PCR on nasopharyngeal or oropharyngeal swabs and a high-resolution CT scan of the chest.[6] According to one study conducted in China, CT sensitivity was 97.2%, whereas the sensitivity of initial real time-PCR was 83.3%.

The supportive hematological labs[7,8] indicative of Covid-19 are lymphopenia and raised inflammatory markers such as serum ferritin, C-Reactive Protein, D-dimers, Lactate dehydrogenase, troponin levels.

There is no cure for Covid-19 disease and treatment is supportive aiming to alleviate symptoms and hasten recovery. Remdesivir, Tocilizumab, Corticosteroids, and Anticoagulants are among the main treatment modalities.[9] Supportive therapy includes Vitamin-D, Zinc, and Vitamin C supplementation.

The Covid-19 infection has been observed to be of variable severity. In this study of 221 patients, clinical symptoms, progress and various factors affecting disease severity and outcome of patients have been analyzed. The result from this duty will provide regional data of severity index in relation to demography, hematological parameters, inflammatory markers, and predictors of mortality. This may be helpful in the evaluation and management plan of Covid cases based on severity index and risk factors for better outcome and prognosis.

Materials and Methods

This was a hospital-based descriptive cross-sectional study. Patients included in the study were admitted to the COVID isolation ward and COVID wards A and B of the Medical Department at Capital Hospital, Islamabad from February 1st, 2021 to April 25th, 2021. The patients with the mild covid disease who were discharged from the emergency COVID room were not included in the study. The study was conducted after approval from the hospital ethical committee. The purpose and benefits of the study were explained to all patients and verbal consent was obtained

The sample size was 221 cases. The sampling technique was non-probability consecutive sampling. Patients were of either gender and age 18 years and above. Detailed history and clinical examination were performed. Total 221 patients with clinical suspicion of Covid-19 infection were included in this study. Patients both Covid Real-time polymerase chain reaction (RT-PCR) positive and negative were included. In RT—PCR negative patients, inflammatory markers and radiological examination were used to detect the Covid-19 infection. Patients, less than 18 years of age and Covid PCR negative patients with normal inflammatory markers were excluded from this study.

Blood Complete Picture (CP), serum ferritin, lactate dehydrogenase (LDH), C-reactive Protein (CRP), D-Dimers, and Interleukin-6 (IL-6) were noted. Reference normal range for Blood CP: WBC count of 4.5-10 per microliter, lymphocyte count 20-45%, LDH <480 U/I, CRP <10 mg/dl, IL-6 was <7pg/ml, D-dimers <500ng/ml and S. Ferritin <250ng/ml were

considered normal. We categorized the study group into mild, moderate, and severe groups. Chest x-ray and High-resolution computed tomography (where technically feasible) were performed too.

Disease Severity: The confirmed Covid cases were clinically classified as mild, moderate, and severe/ critical disease according to the National Institute of Health (NIH) Pakistan guidelines published in 2020 and defined as below;

1. **Mild Disease:**
   - Presence of symptoms consistent with COVID without any hemodynamic compromise needs for oxygen or chest x-ray findings.
   - Oxygen saturation >94%.
2. **Moderate Disease:**
   - Hypoxia (Oxygen saturation <94% but >90%)
   - Chest x-ray with infiltrates involving <50% of lung fields.
   - No complications and manifestations related to severe condition.
3. **Severe/ critical Disease:**
   - In adults, clinical signs of pneumonia (fever, cough + any of the following)
   - Respiratory rate > 30/min
   - Severe respiratory distress
   - SPO2 <90% on room air
   - Chest X-ray involving >50% of lung fields
   - Multiple organ failure

The data about the age, gender, disease level, presenting complaints, and inflammatory markers were entered into a proforma for collection and analysis. Data were analyzed using SPSS version 42. Mean value +/- S.D was determined for quantitative data (i.e., age, C-reactive protein, ferritin, d-dimers, LDH), and frequencies (%) were determined for qualitative data (i.e., gender, PCR status, Covid severity, presence or absence of lymphopenia, treatment received).

Chi-square test applied as a test of significance to study the association of disease severity with PCR status, gender, lymphopenia, derangement of inflammatory markers, treatment received, and outcome in terms of mortality. P-value<0.05 taken as statistically significant. Data is presented in the form of tables, bar graphs, and pie charts.

Results

Amongst 221 proven cases of Covid, there were 125(56.6%) males and 96(43.4%) females. The mean age was 57.20±13.17 years with a range of 18-90 years. Total 155(70%) cases were Covid PCR +ve and the rest of 66(30%) cases were diagnosed based on contact history, inflammatory markers, and CT scan findings. As per the disease severity index, 86(38.9%) cases had mild covid, 91(41.2%) has moderate and 44(19.9%) had severe Covid.

Lymphopenia (lymphocytes<20%) was observed in 154(69.7%) cases and was found to be significantly associated with disease severity ***(Table 1, p=0.003)***. C-reactive protein (as per laboratory cutoff value was positive in 178(80.5%) cases. There was a significant association of CRP with disease severity (***p=0.001***). Serum ferritin means the value was 367.9±464 ng/ml. As per the cut-off value of 250 ng/ml, it was raised in 114(51.5%) cases having a significant association with disease severity (***p<0.0001***).

The mean D-dimers were found to be 962±1853 ng/ml. D-dimers were raised in 139(66.9%) Covid cases having significant association with disease severity (p=0.001). Serum LDH was raised in 167(75.5%) cases and was significantly associated with disease severity (***Table 1, p=0.025***). Serum interleukin was performed only in certain cases according to the criteria for the performance of this costly investigation. Out of 103 cases in which interleukin-6 was performed the mean value observed was 54.1 ± 105.94 pg/ml (maximum value observed was 590 pg/ml)

Various co-morbid conditions were also studied in the study group. Diabetes was observed in 28(12.7%) cases out of 221. The expiry was observed in 05(17.9%) of diabetics as compared to 09(4.7%) of non-diabetics. Diabetes was significantly associated with mortality ***(p=0.007)***. Hypertension was observed in 21(9.5%) out of 221 cases. The expiry was observed in 06(28.6%) of hypertensives as compared to 08(4%) of non-hypertensives. Hypertension was significantly associated with mortality ***(p<0.0001)***. Other co-morbid conditions observed were COPD in 4(1.8%), asthma 2(0.9%), ischemic heart disease 4(1.8%), pulmonary tuberculosis 03(1.3%), CKD 2(0.9%), one case of hypothyroidism and lymphoma.

There were 176(79.6%) cases out of 221 above 50 years of age. 27(15.3%) cases of ≥50 years age as compared to 01(2.2%) less than 50 years of age. Diabetes was significantly associated with age ≥ 50 in admitted Covid cases (***p=0.018***). Hypertension was seen in 20(11.4%) of patients > 50 years of age and wasn't significantly associated with age ≥ 50 in admitted covid cases (***p=0.062***).

Regarding the outcome in terms of mortality, 207 cases were managed and discharged and 14 cases expired. The mortality observed was 6.33%. Mortality was not found to be associated with gender or PCR status.

However, there was a significant association of mortality with disease severity, 25% of cases with severe disease expired Vs. <2.2% cases of mild to moderate disease (***p<0.001***).

Mortality was also studied in relation to the treatment received, the 23.5% of the cases receiving both remedesvir and tocilizumab expired Vs. <5.6% expiry of the patients receiving remedesvir or none of these therapies (***Table 2, Figure 2, p=0.008***).

Table 1: presenting the outcome of COVID cases in terms of mortality and association with gender, age, disease severity, PCR status, and anti-viral therapy (n=221)

Variable	*Among all n(%)*	*Mild n=86*	*Moderate n=91*	*Severe n=44*	*P-value*
PCR status					
• PCR+	155(70.1%)	50(32.3%)	67(43.2%)	38(24.5%)	***0.003***
• PCR-	66(29.9%)	36(54.5%)	24(36.4%)	06(9.1%)	
Lymphocyte count					
• Lymphopenia (<20%)	154(69.7%)	55(35.7%)	60(39%)	39(25.3%)	***0.009***
• No lymphopenia (≥20%)	67(30.3%)	31(46.3%)	31(46.3%)	05(7.5%)	
C-reactive protein					
• Negative	43(19.5%)	59(68.6%)	12(13.2%)	04(9.1%)	***0.001***
• Positive	178(80.5%)	27(31.4%)	79(86.8%)	40(90.9%)	
Ferritin					
• Raised	114(51.5%)	0(0%)	52(45.6%)	32(28%)	**<0.0001**
• Normal	108(48.8%)	56(59%)	39(36%)	12(11%)	
(mean+SD)	367.9+464.0 (6-3990)	217.5+234.0	381.1+500.6	667.1+588.9	
D Dimers					
• Raised	139(66.9%)	40(28.8%)	66(47.5%)	32(23%)	***0.001***
• Normal	83(33.1%)	46(55.4%)	25(30%)	12(14.5%)	
(mean+SD)	962+1853	356+359	826+1386	2426+3214	
LDH					
• Raised	167(75.5%)	0(0%)	59(35.3%)	39(23.4%)	***0.025***
• Normal	55(24.8%)	1(1.8%)	27(49.1%)	05(9.1%)	
(mean+SD)	589+450	442+307	565+404	929+589	
Treatment Received					
• *Remedesvir*	*142(64.3%)*	*50(58.1%)*	*65(71.4%)*	*27(61.4%)*	***<0.0001***
• *Remedesvir & tociluzumab*	*17(7.7%)*	*0(0%)*	*05(5.5%)*	*12(27.3%)*	
• *None of these*	*62(28.1%)*	*36(41.9%)*	*21(23.1%)*	*05(11.4%)*	

(Test of significance Chi-square test; significant p<0.05)

Table 2: presenting the outcome of COVID cases in terms of mortality and association with gender, age, disease severity, PCR status, and anti-viral therapy (n=221)

Variable	*Among all n(%)*	*Expired n=14*	*Discharged n=207*	*P-value*
Gender				
• Males	125(56.6%)	08(6.4%	90(93.8%)	**0.964**
• females	96(43.4%)	06(6.2%)	117(93.6%)	
Age (mean ± SD)	57.20±13.17 (18-90 years)	64.71+12.26 (42-85)	56.87+12.57 (18-90)	***0.006***
Severity of disease				
• Mild	86(38.9%)	01(1.2%)	85(98.8%)	***<0.0001***

• Moderate	91(41.2%)	02(2.2%)	89(97.8%)	
• Severe	44(19.9%)	11(25%)	33(75%)	
PCR status				
• PCR+	155(70.1%)	11(7.1%)	144(92.9%)	**0.476**
• PCR-	66(29.9%)	03(4.5%)	63(95.5%)	
Anti-viral therapy				
• No-antiviral	62(28.1%)	02(3.2%)	60(96.8%)	***0.008***
• Remedesivir Only	142(64.3%)	08(5.6%)	134(94.4%)	
• Both remedesivir & Toclizumab	17(7.7%)	04(23.5%)	13(76.5%)	

(Test of significance Chi-square test; significant p<0.05)

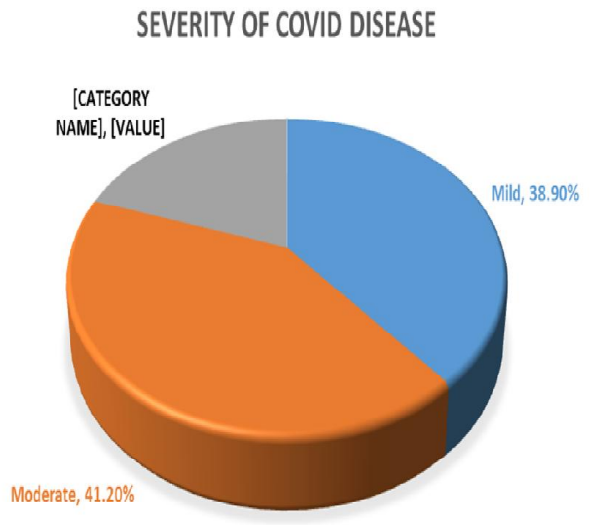

Figure 1: Severity of Covid-19 disease observed (n=221)

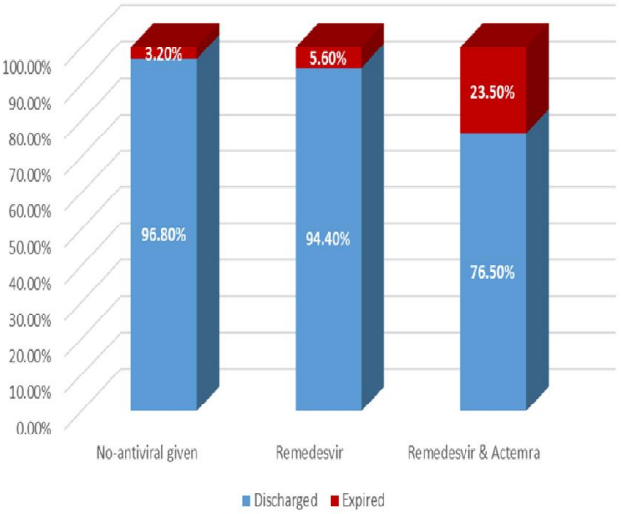

Figure 2: Comparison of treatment modalities and outcome (n=221)

Discussion

The study aimed to measure the severity of Covid-19 infection in the patients treated by the Department of Medicine in The Capital Hospital. It also evaluated the factors attributed to disease mortality.

The analysis demonstrated that the most common symptoms of COVID-19 infected patients were fever (89%), body aches (86%), and dry cough (71%). Other symptoms were fatigue, shortness of breath, diarrhea, and vomiting. About 4% of the patient presented with a sole history of altered taste sensation. Few patients were asymptomatic. A study in Wuhan, China also has demonstrated various presenting symptoms of COVID patients.[10]

The Republic of Korea developed a disease severity classification system for COVID 19-disease. Severity was measured by recording pulse rate, temperature, blood pressure, respiratory rates, and level of consciousness.[11] In our study COVID 19 infection was also classified as mild, moderate, and severe. The disease was mild (38.9%) vs moderate (41.2%) vs severe (19.9%) in the hospitalized patients keeping in view that the majority of mild cases presenting in our hospital were not admitted and were discharged from the emergency Covid room on home treatment.

Studies have shown that Pro-inflammatory cytokines play a pivotal role in the pathophysiology of tissue damage in COVID-19. There is a damaging immune reaction sustained by cytokines. Macrophages and monocytes infiltrate the alveoli. Uncontrolled inflammatory response results in cytokine storm and multi-organ failure.[12] High CRP and IL-6 levels are associated with respiratory failure, mechanical ventilation, and mortality in COVID-19 patients.[13] In our study we tested mostly IL-6 levels in severe Covid cases to look for the cytokine release syndrome. Although CRP was positive in the majority of cases in our study there was no statistical significance while evaluating the severity of the disease because in many

cases we had qualitative values of CRP only. As a result, we were not able to compare its value in the severity index.

In Covid infection, there is leucopenia and lymphopenia. Lymphocytes express the coronavirus receptor ACE-2 and may be a direct target of the virus.[14] Blood lymphopenia indicates the severity of COVID-19 patients.[15] As a result, it also measures prognosis. In our study lymphopenia correlates well with the severity of disease (p=<0.003).

The role of ferritin as a marker of inflammation is well known. Recently serum ferritin has been cited as one of the indicators of mortality.[16] In our study serum ferritin was raised in severe COVID infection leading to increased mortality.

The D-dimer level is used to measure and assess clot formation. In a cohort study, a significantly higher D-dimer level (median 1.8 microgram/ml vs 0.5 microgram/ml, p-value 0.001) was found in severe cases than in mild cases.[17] Our study sowed D. dimer correlates well with the severity of disease (p=0.001)

A pooled analysis has revealed that elevated LDH was associated with a 6-fold increased odds of severe COVID disease. It was associated with a more than 16-fold increase in odds of mortality.[18] In our study LDH level also increased with severity of disease (p<0.0001).

Large scale data demonstrates that there is no gender difference in the proportion of people infected with COVID-19 infection but males are at a significantly higher risk of severe disease and death than females.[19] In our study mortality rate was slightly higher in males as compared to females.

A study has shown that the mortality rate may rise and mild COVID disease may become severe especially in the elderly or the ones with comorbids.[20] Our study shows that the mean age is 64.71 in the patient who expired vs 56.87 in a discharged patient. In our study mortality was also high in patients with co-morbids i.e., Hypertension and Diabetes mellitus.

A population-based cohort study of Denmark`s population has demonstrated that among in-patient COVID PCR positive patients, 21% (356 of 1657) died within 30 days which was a 3 to 3.1 fold increased 30 days mortality rate when compared with COVID PCR negative in-patients (all P<0.001).[21] In our study mortality was not associated with COVID PCR positive or negative status (p=0.476).

According to WHO the only drug proven to increase COVID-19 survival rate is dexamethasone and steroids are recommended in severe disease. A trial in the USA National Institute of Health has shown that remdesivir has cut the time to recover from COVID19 infection from 15 to 11 days. A recent trial has shown that remdesivir was superior to placebo in shortening time to recovery in hospitalized COVID-19 infected adults.[22] We gave remdesivir alone to 142(64.3%) admitted patients who were more symptomatic and were either having fluctuating oxygen saturation levels or impaired inflammatory markers, while no antiviral treatment was given to 62(28.1) stable patients. Out of remdesivir treated 134 (94, 4%) patients were discharged vs 8(5.6%) and only 8(5.6%) expired.

A study reported tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death in hospitalized covid pneumonia patients, but it did not improve survival.[23] In our study Tocilizumab and remdesivir combined were given to 17(7.7%) patients with impending CRS. 13(76.5%) patients improved and discharged vs 4(23.5%) patients expired (p=0.008).

There have been ongoing regional and international studies regarding the Covid. In view of the novelty and unpredictable course of illness, extensive research is required. The need of the time is to look for effective, efficient, sensitive, specific, and health care system-friendly diagnostic and therapeutic options. This study has real-time valuable data of 221 cases that were extensively investigated and managed despite epidemic burden and financial constraints. Certain limitations of the study that need to be mentioned are sampling technique, inability to perform interleukin-6 in all cases due to financial constraints or recommendations, and the follow-up for long-term outcome in these cases. Despite these limitations, this study provides a valuable comparison of inflammatory markers and demography in relation to disease severity and mortality that can be an asset for regional and international referencing and guidelines.

Conclusion

Our study has shown that the severity of the Covid-19 infection is directly related to a rise in inflammatory markers and COVID infection is more severe in elderly patients due to associated co-morbids resulting in impairment of the immune system. There is no mortality difference in Covid positive or negative patients. We suggest measurement of inflammatory markers and radiological examination to assess the severity of the disease in Covid-19 PCR negative patients. More comparative studies are needed to evaluate the role of antiviral treatment. Identifying

risk factors for early progression towards severe disease and mortality is fundamental in the management of COVID-19 patients.

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