ORIGINAL RESEARCH

Efficacy of Various Treatment Modalities on Patient-related Outcome in Hospitalized COVID-19 Patients – A Retrospective Study

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ABSTRACT

Background: The outbreak of coronavirus disease 2019 (COVID-19) caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in China, in December 2019, and was declared a pandemic by WHO on March 11, 2020. The treatment is evolving and is mostly supportive in nature. **Material and methods:** This was a single-center retrospective study that included confirmed COVID-19 cases treated at our institute (a tertiary care hospital in Jammu and Kashmir, India), between March 2020 and December 2020. Patients with age more than 18 years were included in the study. **Results:** On evaluating the effect of various drug therapies used in management of COVID-19 patients of all severity, use of remdesivir and famotidine was associated with significantly higher odds of survival. In subgroup of patients with severe disease, use of systemic steroids was associated with significantly higher odds of survival in addition to remdesivir and famotidine. In patients with severe COVID-19 illness, likelihood of survival was significantly higher in those who received combination of systemic steroids plus remdesivir compared to steroids and remdesivir alone. **Conclusion:** Steroids were effective in severe COVID-19 illness and the combination of steroids and remdesivir was more effective in severe illness. There is a need to undertake more large scale prospective randomized trials to determine the most effective drug therapies to treat the sick patients and prevent worsening of mild cases.

Keywords: Pandemic, COVID-19 illness, SARS-CoV-2, severe COVID-19

The outbreak of coronavirus disease 2019 (COVID-19) caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019 and was designated as a pandemic by the World Health Organization (WHO) on March 11, 2020.[1,2] The spectrum of COVID-19 ranges from asymptomatic infection to mild respiratory tract illness to severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure and death.[3] A number of clinical trials have evaluated different treatment modalities in the management of COVID-19 illness and many more are under way, primarily assessing the clinical outcome in terms of accelerating the viral clearance, reduction in duration of symptoms, progression of disease, need for mechanical ventilation and mortality.[4,5] Only few of these treatment interventions have shown significant clinical benefit. Corticosteroid use has been considered as the standard of care in management of COVID-19 patients with respiratory failure. Multiple observational and randomized controlled trials (RCTs) on corticosteroid use in hospitalized COVID-19 patients have shown reduction in mortality and decrease in progression of disease.[6,7] Based on trial results, remdesivir was approved for the management of hospitalized COVID-19 patients.[8] However, recent evidence suggested little or no benefit in reducing

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hospital stay, need for mechanical ventilation and reduction in mortality.[9] Results from initial RCTs that evaluated the use of tocilizumab (anti-interleukin [IL-6] receptor antibody) in COVID-19 produced conflicting results.[10-12] The results from two large RCTs reported reduction in mortality in a subset of COVID-19 patients with severe and critical illness.[12,13] A number of studies have compared the efficacy of various treatment modalities, either alone or in combination, in COVID-19 patients and reported beneficial effect of drugs like corticosteroids, tocilizumab and remdesivir on clinical outcome.[14] Our institute is the only tertiary care center in Jammu and Kashmir (J&K) that is involved in the management of severe to critical COVID-19 patients. To evaluate the effect of various treatment modalities on patient-related outcome (survival and mortality) in hospitalized COVID-19 patients, a retrospective study was planned.

MATERIAL AND METHODS

This was a single-center retrospective study that included confirmed COVID-19 cases treated at our institute (a tertiary care hospital in J&K UT) between March 2020 and December 2020. The study was approved by the Institutional Ethical Committee. Patients with positive nasopharyngeal swabs for reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 with age more than 18 years were included in the study. Patients with incomplete medical records, especially with no known outcome, those who died within 24 hours of admission and pregnant/lactating women were excluded.

Classification of Patients into Nonsevere and Severe Category

For the purpose of analysis, patients were divided into two groups, nonsevere and severe. Those with mild and moderate disease were grouped into nonsevere category, whereas those with severe and critical COVID-19-related illness were grouped into severe category. The classification of patients into various grades of severity was based on the definitions provided by Indian Council of Medical Research (ICMR).[15] Severity of illness was based on various clinical and radiological parameters. Mild group included those having upper respiratory tract symptoms and oxygen saturation ≥94% with normal radiology. Moderate group included those having lower respiratory disease during clinical assessment or imaging with SpO_2 ≤94% on room air. Severe group included patients with SpO_2 <90% on room air, a respiratory rate of >30 breaths/min, PaO_2/FiO_2 <300 mmHg or lung infiltrates >50% and critical group included patients having ARDS, septic shock or multiorgan dysfunction. Patients were managed in areas of hospital dedicated for COVID-19. Severe or critically ill patients were managed in high-dependency unit and dedicated COVID intensive care units (ICUs). All patients received treatment as per the institutional protocol that was based on the national and international available guidelines.

Outcome

Primary outcome studied was the effect of various drugs used in the management of COVID-19 illness on all-cause mortality and survival.

Data Extraction

Patient data was extracted from medical record files available in medical record keeping department. Data regarding patients' demographic profile, clinical presentation, severity of illness, laboratory parameters, treatment received and outcome in terms of mortality was recorded and entered on a preformed proforma. The data was then transferred and maintained on an excel spread sheet.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages, whereas continuous variables were described using mean, median and interquartile range (IQR) values. Difference in means of continuous variables was compared using independent 't' tests in case of normally distributed data and nonparametric test (Mann-Whitney test) was used in non-normally distributed data. Difference between categorical variables was assessed by using the χ^2 test or Fisher's exact test. A 'p' value of <0.05 was considered statistically significant. Multivariate logistic regression was done including medications that significantly affected the primary outcome on univariate analysis. All statistical analyses were performed using SPSS version 26.0 software.

RESULTS

A total of 1,000 RT-PCR COVID-19 positive patients were included in the study. The median age of the study population was 56 years (IQR 45-65), with majority of them being males, with nonsurvivor group having significantly higher median age (median age 62 [55-70] vs. 53 [40-65], p 0.001). Males outnumbered females (64.6% vs. 35.4%, p 0.67); however, no gender difference was observed between the two groups.

The most common comorbid illness observed was hypertension (50.9%), followed by diabetes mellitus (29.8%), chronic kidney disease (8.2%) and malignancy (8.1%). Among nonsurvivors, significantly higher proportion of patients had hypertension, chronic kidney disease, chronic lung disease and chronic liver disease (Table 1).

Patients in nonsurvivor group demonstrated increased median heart rate (100 [IQR 84.75-112], p 0.001), and increased respiratory rate (24 [IQR 20-30], p 0.001), compared to survivor group at the time of admission.

Majority of the patients (n = 658, 65.8%) had severe illness at the time of presentation. Likelihood of survival was significantly lower in patients belonging to severe category (88.9% vs. 56.7%, p 0.001).

Among various laboratory parameters, nonsurvivors had significantly lower hemoglobin, elevated total leukocyte count, higher creatinine, lower albumin, higher international normalized ratio (INR) and higher lactate dehydrogenase (LDH), creatinine phosphokinase (CPK), ferritin and IL-6 levels (Table 2).

Oxygen supplementation was provided to a total of 780 patients using nasal cannula (10.6%), face mask (22.3%), nonrebreathing mask (61.15%) and high flow nasal oxygen (5.8%). Mechanical ventilation was provided to 10.6% (n = 106) patients. Noninvasive ventilation was the most common mode of mechanical ventilation provided to 6.7% of patients while invasive mechanical ventilation was used in 3.9% of cases (Table 3).

On evaluating the effect of various drug therapies used in the management of COVID-19 patients of all severity, use of remdesivir and famotidine was associated with significantly higher odds of survival. In a subgroup of patients with severe disease, use of systemic steroids was associated with significantly higher odds of survival in addition to remdesivir and famotidine (Table 4).

In patients with severe COVID-19 illness, likelihood of survival was significantly higher in those who received combination of systemic steroids plus remdesivir compared to steroids and remdesivir alone (Table 5).

Table 1. Demographic and Clinical Profile of COVID-19 Patients

Patient characteristics	Total (n = 1,000)	Discharged (n = 695)	Died (n = 305)	P value
Age, median (IQR), years	56 (45-65)	53 (40-65)	62 (55-70)	0.001
Gender, no. (%)				
Male	646 (64.6)	446 (64.2)	200 (65.6)	0.670
Female	354 (35.4)	249 (35.8)	105 (34.4)	
Comorbid illnesses, no. (%)				
Hypertension	509 (50.9)	324 (46.6)	185 (60.7)	0.001
Diabetes mellitus	298 (29.8)	194 (27.9)	104 (34.1)	0.049
Chronic kidney disease	82 (8.2)	37 (5.3)	45 (14.8)	0.001
Malignancies	81 (8.1)	50 (7.2)	31 (10.2)	0.113
Chronic lung disease	52 (5.2)	28 (4)	24 (8)	0.012
Chronic liver disease	24 (2.4)	10 (1.4)	14 (4.6)	0.003
Cardiovascular disease	23 (2.3)	14 (2)	9 (3)	0.363
Cerebrovascular disease	21 (2.1)	14 (2)	7 (2.3)	0.776
Post-transplant	10 (1.0)	6 (0.9)	4 (1.3)	0.512
Vital signs				
Heart rate/min, median (IQR)	92 (82-106)	90 (80-104)	100 (84.75-112)	0.001
Systolic blood pressure (mmHg), median (IQR)	120 (110-130)	120 (110-130)	120 (107-132)	0.628
Respiratory rate/min, median (IQR)	21 (21-26)	20 (18-24)	24 (20-30)	0.001

Table 2. Laboratory Parameters of COVID-19 Patients

Laboratory parameters	Total (n = 1,000)	Discharged (n = 695)	Died (n = 305)	P value
Hb (g/dL), mean (SD)	11.9 (2.5)	12.19 (2.43)	11.12 (2.66)	0.001
TLC (x10^9/L), mean (SD)	8.35 (4.46)	7.69 (3.68)	10.21 (5.71)	0.001
NL ratio, median (IQR)	6.3 (2.8-12.6)	4.81 (2.29-9.22)	11.86 (6.22-22.63)	0.001
PLT (×10^9/L), mean (SD)	158.3 (85.95)	157.8 (80.95)	137.74 (83.91)	0.001
Creatinine (mg/dL), median (IQR)	1.03 (0.8-1.51)	0.72 (0.53-1.03)	1.44 (0.96-2.51)	0.001
Serum bilirubin (mg/dL), median (IQR)	0.63 (0.5-0.88)	0.61 (0.5-0.8)	0.96 (0.78-1.27)	0.001
Alanine transaminase (U/L), median (IQR)	36 (23-61)	38 (23-61)	33.5 (22-59.75)	0.291
Aspartate transaminase (U/L), median (IQR)	38.5 (23-51.75)	35 (22.5-48.5)	43 (37-60)	0.05
Alkaline phosphatase (U/L), median (IQR)	94 (74-123)	92 (72-118)	102 (77.5-141.5)	0.004
Serum albumin (g/dL), median (IQR)	3.2 (3.0-3.8)	3.4 (3.03-3.9)	3 (3-3)	0.001
Lactate dehydrogenase (U/L), median (IQR)	384 (267.75-525.25)	345 (262-482)	481 (393.25-694)	0.001
Creatinine phosphokinase (U/L), median (IQR)	96 (44.25-212)	90 (39-184)	151 (66-310)	0.002
Serum ferritin (ng/mL), median (IQR)	480 (289.5-933)	446 (259-885)	654 (388-1039)	0.011
Interleukin-6 levels (pg/mL), median (IQR)	34 (12.6-80.94)	26 (9-69)	61 (29-148)	0.001
INR, median (IQR)	1.14 (1.05-1.3)	1.13 (1.04-1.27)	1.19 (1.09-1.33)	0.001
APTT (seconds), median (IQR)	32.8 (30.5-36.8)	33 (30.5-37)	32 (30-37)	0.638
Prothrombin time (seconds), median (IQR)	15 (13.8-16.5)	15 (14-16)	15 (14-17.5)	0.003
Lactate dehydrogenase (U/L), median (IQR)	384 (267.75-525.25)	345 (262-482)	481 (393.25-694)	0.001
Creatinine phosphokinase (U/L), median (IQR)	96 (44.25-212)	90 (39-184)	151 (66-310)	0.002
D-dimer (ng/mL), median (IQR)	636 (239-1853)	584 (211-1455)	1053 (376-2451.5)	0.009

Hb = Hemoglobin; TLC = Total leukocyte count; SD = Standard deviation; IQR = Interquartile range; NL ratio = Neutrophil-to-lymphocyte ratio; PLT = Platelet; INR = International normalized ratio; APTT = Activated partial thromboplastin time.

Table 3. Effect of Various Treatment Modalities on Survival in COVID-19 Patients of All Severity

Treatment	Survivors (n = 695)	Nonsurvivors (n = 305)	OR* (95% CI)	P value
Oxygen supplementation	482 (69.3)	298 (97.7)	0.05 (0.02-0.11)	0.001
Remdesivir	305 (43.9)	108 (35.4)	1.42 (1.08-1.88)	0.012
Steroids	466 (67.1)	209 (68.5)	0.98 (0.69-1.24)	0.64
Antibiotics	613 (88.2)	266 (87.2)	1.09 (0.73-1.65)	0.65
Plasma therapy	57 (8.2)	31 (10.2)	0.79 (0.50-1.27)	0.31
Tocilizumab	15 (2.2)	11 (3.6)	0.59 (0.26-1.35)	0.18
Famotidine	528 (76)	183 (60)	2.10 (1.57-2.81)	0.001
Anticoagulants	410 (59)	224 (73.4)	0.52 (0.39-0.70)	0.001
Noninvasive ventilation	16 (2.3)	51 (16.7)	0.12 (0.07-0.21)	0.001
Invasive ventilation	3 (0.4)	36 (11.8)	0.03 (0.01-0.10)	0.001

*Odds ratio and 95% confidence interval for survival.

Table 4. Effect of Various Treatment Modalities on Survival in Severe COVID-19 Patients

Treatment	Survivors (n = 387)	Nonsurvivors (n = 271)	OR* (95% CI)	P value
Remdesivir	249 (64.3)	101 (37.3)	3.03 (2.20-4.17)	0.001
Steroids	344 (88.9)	191 (70.5)	3.35 (2.24-5.07)	0.001
Antibiotics	349 (90.2)	237 (87.5)	1.32 (0.81-2.13)	0.27
Plasma therapy	55 (14.2)	29 (10.7)	1.38 (0.85-2.24)	0.18
Tocilizumab	15 (3.9)	10 (3.7)	0.59 (0.26-1.35)	0.18
Famotidine	313 (80.9)	166 (61.3)	2.67 (1.88-3.77)	0.001
Anticoagulants	303 (78.3)	204 (75.3)	0.84 (0.58-1.22)	0.36
Noninvasive ventilation	14 (3.6)	41 (15.1)	0.21 (0.11-0.39)	0.001
Invasive ventilation	3 (0.7)	35 (13)	0.052 (0.01-0.15)	0.001

*Odds ratio and 95% confidence interval for survival.

Table 5. Treatment vs. Survival in Severe COVID-19

Treatment	Survivors (n = 387)	Nonsurvivors (n = 271)	OR (95% CI)	P value
Steroids only	121	109	0.67 (0.48-0.93)	0.017
Remdesivir only	26	19	0.95 (0.51-1.8)	0.88
Steroids plus remdesivir	223	82	3.13 (2.25-4.36)	0.001
None	17	60	0.16 (0.09-0.28)	0.001

Table 6. Multivariant Logistic Regression Analysis Adjusted for Age and Severity of Illness

Treatment	OR (95% CI)	P value
Remdesivir	2.69 (1.93-3.76)	0.000
Steroids	2.45 (1.57-3.82)	0.000
Famotidine	1.98 (1.35-2.90)	0.000

On multivariant regression analysis adjusted for age and severity of disease, use of remdesivir, systemic steroids and famotidine in management of COVID-19 illness was associated with significantly better survival (Table 6).

DISCUSSION

This retrospective study evaluated the effect of various medications used in the management of COVID-19 patients on survival. We observed that the use of remdesivir, steroids and famotidine significantly improved survival of hospitalized COVID-19 patients. Combination of remdesivir and steroids was better than remdesivir and steroids alone in improving survival.

Different modalities of treatment are under evaluation for different severities of COVID-19 illness. Symptomatic treatment is generally given for mild-to-moderate COVID-19 illness and inpatient supportive care plays an important role in moderate-to-severe illness. Many of the clinical trials have tried different treatment modalities for better management of COVID-19 patients and many more are under way for assessing the clinical outcome in terms of accelerating the viral clearance, reduction in duration of symptoms, halting the progression of disease, decreasing the need for mechanical ventilation and reducing mortality. The RCT by Wang et al failed to show any difference in time to clinical improvement with remdesivir compared to placebo (hazard ratio [HR] 1.23 [95% CI 0.87-1.75]), but this study was underpowered as only 237 patients were enrolled in the study.[16] A subsequent RCT - Adaptive COVID-19 Treatment Trial (ACTT-1) - concluded that the use of remdesivir in hospitalized patients shortens the time to clinical improvement with no mortality benefit.[17] One more RCT revealed that 5-day remdesivir along with standard treatment in patients with moderate COVID-19 had higher odds of a better clinical status vs. 10 days with standard care; however, there was no

mortality benefit.[18] But the largest trial for remdesivir, the SOLIDARITY trial, demonstrated little or no benefit on initiation of ventilation, length of hospital stay and overall survival with the use of this drug.[9] In our study, it was observed that the use of antiviral drug remdesivir in management of moderate-to-severe COVID-19 hospitalized patients was associated with significantly higher odds of survival. Our findings are supported by a Bayesian re-analysis of 4 clinical trials of remdesivir including 7,322 COVID-19 patients, demonstrating better survival in patients with oxygen but without requiring mechanical ventilation (probability of ≥1% absolute decrease in mortality 81%) than patients on oxygen with mechanical ventilation (probability of ≥1% absolute decrease in mortality 4%).[19]

Steroids have been the mainstay in the treatment of moderate-to-severe COVID illness. However, early use of corticosteroids in first week of viral pneumonia can lead to higher subsequent plasma viral load or prolonged SARS-CoV-2 virus shedding.[20,21] Use of steroids in COVID pneumonia in second week has been found to be effective in improving the clinical condition of those with high inflammatory markers and worsening oxygenation.[22] Earlier use of steroids in moderate-to-severe COVID-19 ARDS, as reported by Villar et al, demonstrated increase in ventilator-free days and reduction in overall mortality.[23] The RECOVERY trial demonstrated lower 28-day mortality in hospitalized COVID-19 patients on oxygen or on mechanical ventilation but this benefit was not seen in patients not receiving oxygen.[6] A systemic review and meta-analysis including 44 studies evaluated the efficacy and safety of steroids and reported them to have beneficial effect on short-term mortality and reduction in mechanical ventilation requirement.[7] In our study, it was observed that use of steroids in the subgroup of patients with severe COVID-19 illness was associated with significantly higher odds of survival. The combined effect of steroids and remdesivir on the outcome of COVID-19 patients has not been discussed much. A comparison study of remdesivir, with or without corticosteroids, by Garibaldi et al, has reported that concomitant use of these drugs does not reduce the time to death.[24]

Although remdesivir is associated with faster clinical improvement, in the SOLIDARITY trial, there was no evidence of effect modification of remdesivir for patients (approximately 50%) who also received corticosteroids.[9] However, the present study demonstrated better survival in patients receiving steroids along with remdesivir.

Famotidine is a histamine H_2-receptor antagonist that mainly suppresses gastric acid production. It has also been postulated that famotidine inhibits 3-chymotrypsin-like protease (3CLpro), an essential protein for viral replication.[25] Although literature regarding the use of famotidine in management of COVID-19 is sparse, results from few retrospective studies, including hospitalized patients, have demonstrated a reduced risk of in-hospital mortality and need for mechanical ventilation.[26-28] In our study, famotidine was found to be associated with high odds of survival in patients with all grades of severity and was an independent predictor for better survival.

Tocilizumab, an IL-6 receptor monoclonal antibody, inhibits soluble IL-6 receptor and membrane IL-6. Initially, many of the randomized clinical trials and meta-analyses had demonstrated reduced likelihood of progression to mechanical ventilation but the overall all-cause mortality was not affected. Initial trials results were conflicting; however, in RECOVERY trial, tocilizumab showed improved survival and chances of discharge from hospital by 28 days and reduced chances of mechanical ventilation.[10,11,13] The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) trial demonstrated that tocilizumab use in critically ill patients along with standard of care decreased time to clinical improvement and lowered mortality.[29] The effect of tocilizumab on survival outcome could not be well-determined in our study because of use in only 36 patients in total, either because of unavailability or unaffordability.

RELEVANCE

The COVID-19 pandemic is the biggest public health crisis the world is facing currently since the Spanish flu outbreak of 1918. The pace and the number of clinical trials undertaken to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence, even in the middle of a pandemic. Majority of drug therapies, except a few, have not shown desired therapeutic efficacy.

LIMITATIONS

This retrospective analysis has few limitations to note. First, large volume and rapid pace with which published literature on the treatment of COVID-19 comes routinely means that findings from these researches and recommendations are constantly evolving as new evidence arises. Second, the published treatment data to date derive exclusively from observational data or

small clinical trials introducing higher risks of bias or imprecision regarding the magnitude of treatment effect size. Third, our study included adult patients only and the data may not be applicable to pediatric populations.

CONCLUSIONS

The COVID-19 pandemic definitely represents the biggest global public health crisis of this century and, potentially, since the Spanish flu of 1918. There is a need to undertake more large scale prospective randomized trials to determine the most effective drug therapies to treat the sick patients and prevent worsening of mild cases.

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BA.2 Tied to Higher Susceptibility of Infection among Households Than BA.1

According to a study in Denmark, Omicron subvariant BA.2 was found to be tied to higher likelihood of infection among households, irrespective of vaccination status, compared to the original BA.1 variant. In comparison with BA.1, BA.2 was tied to more than double the odds of infection among unvaccinated people (OR 2.19), vaccinated individuals (OR 2.45), and those who had received a booster shot (OR 2.99), noted Frederik Plesner Lyngse of University of Copenhagen and colleagues. Additionally, unvaccinated primary cases in households with BA.2 infection were linked with over twofold higher odds of transmission (OR 2.62), in comparison with BA.1 households.

It was noted that the transmissibility was lower in both BA.1 and BA.2 households if the primary case was vaccinated, with or without a booster shot. The findings are posted as preprint on medRxiv… (*Medpage Today, February 1, 2022*)

Antibody Combination may Prevent COVID-19 Symptoms in Asymptomatic Individuals

According to a new study published in *JAMA*, giving a subcutaneous antibody combination of casirivimab and imdevimab to asymptomatic individuals who have tested positive for SARS-CoV-2 can significantly reduce the incidence of symptomatic COVID-19 over 28 days.

The study included 314 participants, of whom 310 (99.7%) completed the efficacy assessment period. Overall, 204 were asymptomatic and tested seronegative at baseline and were included in the primary efficacy analysis. The administration of subcutaneous combination of casirivimab and imdevimab 1200 mg (600 mg each) significantly prevented progression to symptomatic illness (29.0% vs. 42.3% with placebo).

The findings point to a new potential for monoclonal antibody treatment, which is currently being used for post exposure prophylaxis and treatment of symptomatic COVID-19 infection… (*Medscape, February 2, 2022*)

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