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ORIGINAL ARTICLE

Correlation between Antiviral and Steroid Therapies, COVID-19 Severity, and patient Outcomes: A Cross-Sectional Study

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ABSTRACT

Aim: To investigate the relationship between the severity of COVID-19 and the impact of antiviral medications, specifically Remdesivir, and steroid treatments on disease outcomes.
Study design and setting: A cross-sectional study involving 103 COVID-19 patients was conducted at Ziauddin University's outpatient departments (OPDs), inpatient facilities and intensive care units (ICUs) during the years 2021 and 2022.
Methodology: Patients who tested positive for COVID-19 through PCR testing were included in the study. SARS-CoV-2 RNA was detected through qualitative RT-PCR, and data were retrieved from medical records, encompassing demographic, clinical, and laboratory details. The impact of antiviral and steroid treatments on disease severity and outcomes was analyzed using SPSS for statistical analysis. Ethical considerations were paramount, with measures including obtaining informed consent and securing approval from the Ethical Review Committee (ERC).
Results: Remdesivir use correlated with lower severity and higher discharge rates ($p < 0.001$); steroids were associated with improved discharge rates ($p = 0.037$). Younger age (≤50 years) related to milder cases ($p = 0.003$), and dyspnea indicated increased severity ($p = 0.001$). Comorbidities were associated with a higher likelihood of severe outcomes ($p = 0.009$). Fever and cough, common symptoms, were not significant predictors. Various lab markers showed no significant associations with COVID-19 severity.
Conclusion: Antiviral and steroid therapies, especially Remdesivir, show promise in mitigating COVID-19 severity and improving outcomes. Larger prospective studies are needed for validation in this ongoing global health emergency.
Keywords: Antiviral, Remdesivir, RT-PCR, SARS-CoV-2, Steroid.

INTRODUCTION

In December 2019, the city of Wuhan, located in the Hubei province of China, became the epicenter for a novel health crisis as it reported a concerning cluster of patients presenting with primary pneumonia. This pneumonia was attributed to a newly identified coronavirus, later termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. Upon genetic analysis, it was revealed that this virus shared a substantial 79.5% genetic identity with the previously known SARS-CoV, responsible for the severe acute respiratory syndrome outbreak in 2003[2].

The rapid global dissemination of SARS-CoV-2 led to the manifestation of a spectrum of clinical conditions collectively termed coronavirus disease 2019 (COVID-19)[3]. This disease showcased a wide range of clinical presentations, encompassing asymptomatic cases to severe forms characterized by conditions like acute respiratory distress syndrome (ARDS), septic shock, and multiple organ dysfunction syndrome (MODS)[4]. The variability in symptom severity underscored the complex nature of the disease and posed significant challenges to healthcare systems worldwide.

By March 23, 2020, the impact of COVID-19 on mainland China became pronounced, with a reported total of 81,601 confirmed cases. The general mortality rate associated with these cases was documented at 4.0%, reflecting the severity and potential lethality of the disease.[5] Notably, critically ill patients faced a mortality rate comparable to that observed in cases of the Middle East respiratory syndrome (MERS), which is caused by yet another coronavirus. The progression of this infection can cause increased immune responses and inflammatory reactions .[6]Therefore, a variety of therapeutic approaches have been used to treat the disease at various stages, including methods utilizing antiviral drugs, antiretrovirals, antimalarial medications, anti-inflammatory agents, corticosteroids, immunomodulators, and immunoglobulin therapies.[7] The primary approach to managing COVID-19 involves supportive therapies such as fluid management, oxygen therapy, and mechanical ventilation.

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Various classes of drugs have undergone testing for the treatment of moderate to severe COVID-19 infections, including antiviral agents such as remdesivir (RDV), originally developed for Ebola virus treatment in 2017. In July 2020, the European Medicines Agency granted conditional marketing authorization for RDV in COVID-19. Clinical trials, including NIAID ACTT-1, ACTT-2, and ACTT-3, assessed RDV's efficacy and safety, revealing its notable benefits for patients receiving oxygen but not on invasive mechanical ventilation at Day 1. Additionally, immunomodulatory drugs like corticosteroids have been explored to manage the hyperinflammatory response in COVID-19. Corticosteroids, known for their anti-inflammatory effects, have shown promise in reducing the risk of 28-day mortality, particularly in patients undergoing mechanical ventilation, based on some studies[8].

The majority of the research on COVID-19 pharmacological treatments has relied on findings from observational studies. However, many of these studies are influenced by biases caused by differences in demographics, patient and disease characteristics, discrepancies in institutional practices and standards, and disparities in healthcare infrastructure and financial support.[9]As a result of the considerable differences identified in these investigations, obtaining an agreement on effective COVID-19 therapies have proven to be rather difficult. Among the prospective therapeutic choices, antiviral drugs such as remdesivir show promise in reducing virus progression and illness severity[10]. Although certain studies using randomized controlled designs gave detailed insights into the outcomes related with COVID-19 antiviral medications, the number of relevant trials in these investigations was restricted, frequently due to their early publication during the pandemic's start. This study will analyze the patient population receiving antiviral treatments and corticosteroid therapy to discern the intricate correlation between COVID-19 severity and its subsequent treatment outcomes.

MATERIAL AND METHODS

Participant Selection and Ethical Considerations: Participants in this study were individuals who had tested positive for COVID-19 through PCR testing and sought medical care at Ziauddin

University's outpatient departments (OPDs) or received inpatient care in the ward and intensive care unit (ICU) during the years 2021 and 2022. The study placed a strong emphasis on ethical guidelines, ensuring informed consent from all participants and obtaining approval from the Ethical Review Committee (ERC) *Reference Code:5540622 UTMM* to ensure the highest standards of ethical conduct.

Detection of SARS-CoV-2 RNA: The determination of SARS-CoV-2 RNA positivity was carried out using qualitative RT-PCR with in vitro diagnostic kits. The methods closely followed the manufacturer's recommendations, ensuring the accuracy and reliability of the test results. Patients were stratified based on their SARS-CoV-2 status, wherein positive individuals were substantiated through the presence of at least one affirmative RT-PCR test outcome, while negative cases were exclusively ascertained by negative RT-PCR findings.

Data Collection and Analysis: The pertinent information was taken from medical records, including demographic details, clinical traits, and antiviral reactions. Disease severity was categorized into various strata, and a rigorous statistical analysis was conducted to investigate the intricate relationship between antiviral steroid therapies responses and the severity of COVID-19 within the study's participants.

Statistical Analysis: The statistical analysis was carried out using SPSS version 21. Qualitative variables were assessed using ratios and percentages, whereas quantitative variables were described using means and standard deviations. The relationship between severity and outcome in relation to clinicopathological factors and antiviral treatment was examined using the chi-square test, with a significance criterion set at a p-value of 0.05.

RESULTS

Clinical and demographic features of the patients: The study included a patient group with varied severity levels: 4.9% were asymptomatic, 21.5% had light symptoms, 26.2% had moderate symptoms, 34% had severe symptoms, and 13.6% were in critical condition. Remdesivir was administered to about 35% of patients, while 65% were not. 44.7% of patients received steroids, compared to 55.3% who did not. Patients tended to be older (74.8%), with an almost equal gender distribution of 52.8% men and 47.6% women. Common initial symptoms included fever (62.1%), cough (65%), and dyspnea (66%). Elevated inflammatory markers were common, with the majority of patients having increased levels: TLC (88.3%), Ferritin (65%), LDH (88.3%), Procalcitonin (99%), D-Dimer (79.6%), CRP (89.3%), and Pro.BNP (89.3%). In terms of outcomes, 68% were discharged, 30.1% unfortunately passed away and 1.9% requested discharge (Table 1).

Association of Demographic and clinical characteristics of Patients With severity: The study identified significant factors associated with COVID-19 severity. Notably, patients treated with Remdesivir had a lower likelihood of severe illness ($p < 0.001$) and the use of steroids, which was linked to improved discharge rates ($p = 0.037$). While younger individuals (aged <50) were less prone to severe cases ($p = 0.003$). Conversely, the presence of dyspnea was strongly linked to increased severity ($p = 0.001$). However, gender, fever, cough, and co-morbidities showed no significant associations with disease severity. Additionally, various laboratory markers, including TLC, De-Dimer, Ferritin, LDH, CRP, Procalcitonin and Pro-BNP, were not significantly associated with COVID-19 severity in our patient cohort. These findings provide valuable insights for understanding the predictors of COVID-19 severity (Table 2).

Table 1: Demographic and clinical characteristics of patients.

Characteristic	Frequency (%)
Severity	
Asymptomatic	5 (4.9%)
Mild	22 (21.5%)
Moderate	27 (26.2%)
Severe	35 (34%)
Critical	14 (13.6%)
Antiviral (Remdesivir)	
Yes	36(35.0%)
No	67(65.0%)
Steroid	
Yes	46(44.7%)
No	57(55.3%)
Age (Years)	
<=50	26 (25.2%)
>50	77 (74.8%)
Gender	
Male	54 (52.8%)
Female	49 (47.6%)
Presentation	
Fever	64 (62.1)
Cough	67 (65%)
Dyspnea	68 (66%)
Raised Inflammatory Markers	
TLC	91 (88.3%)
Ferritin	67 (65%)
LDH	91 (88.3%)
Procalcitonin	102 (99%)
De-Dimer	82 (79.6%)
CRP	92 (89.3%)
Pro.BNP	92 (89.3%)
Outcome	
Discharged	70 (68%)
Deaths	31 (30.1%)
DOR	2 (1.9%)

Association of demographic and clinical characteristics with the Outcome of the diseases: In this study, significant factors impacting COVID-19 outcomes included the use of Remdesivir (associated with higher discharge rates, $p<0.001$), steroid treatment (linked to improved discharge rates, $p = 0.037$), and the presence of comorbidities (associated with lower discharge rates, $p=0.009$). Younger age (≤50 years) was also significant for better outcomes ($p = 0.021$), while symptoms like cough were significant for higher discharge rates ($p=0.014$). Gender, fever, dyspnea, and various laboratory markers did not exhibit significant associations with COVID-19 outcomes in this patient cohort (Table 3).

Table 2: Association of Demographic and clinical characteristics of Patients With severity:

Characteristics	n=103	Severity					p value*
		Asymptomatic 5 (4.9%)	Mild 22 (21.4%)	Moderate 27 (26.2%)	Severe 35 (34%)	Critical 14 (13.6%)	
Antiviral (Remdesivir)							
Yes	36 (35.0%)	0 (0.0%)	4 (18.2)	10 (37.0%)	16 (45.7%)	13 (12.6%)	0.000*[a]
No	67 (65.0%)	13 (12.6%)	18 (81.8%)	17 (63.0%)	19(54.3%)	10 (71.4%)	
Steroid							
Yes	46(44.7%)	0(0.0%)	5(22.7%)	11(40.7%)	22(62.9%)	8(57.1%)	0.037
No	57(55.3%)	5(100.0%)	17(77.3%)	16(59.3%)	1337.1%)	6(42.9%)	
Age (Years)							
<=50	26 (25.2%)	9 (8.7)	9 (8.7)	6 (5.8%)	7 (6.8%)	4 (3.9%)	0.003*[a]
>50	77 (74.8%)	13 (12.6%)	13 (12.6%)	21 (20.4%)	28 (27.2%)	1 (1%)	
Gender							
Male	54 (52.8%)	6 (5.8%)	9 (8.7)	13 (12.6%)	17 (16.5%)	9 (8.7)	0.478*
Female	49 (47.6%)	4 (3.9%)	13 (12.6%)	14 (13.6%)	18 (17.5%)	5 (4.9%)	

Co-morbid							
Yes	52(50.5%)	1(20.0%)	12(54.5%)	15(55.6%)	14(40.0%)	10(71.4%)	0.009*[a]
No	14(13.6%)	1(20.0%)	6(27.3%)	5(18.5%)	2(5.7%)	0(0.0%)	
NA	37(35.9%)	3(60.0%)	4(18.2%)	7(25.9%)	19(54.3%)	4(28.6%)	
Fever							
Yes	64 (62.1%)	2 (1.9%)	10 (9.7%)	17 (16.5%)	23 (22.3%)	12 (11.7%)	0.128*
No	39 (37.9%)	3 (2.9%)	12 (11.7%)	10 (9.7%)	12 (11.7%)	2 (1.9%)	
Cough							
Yes	67 (65%)	3 (2.9%)	11 (10.7%)	21 (20.4%)	28 (27.2%)	13 (12.6%)	0.399*
No	36 (35%)	2 (1.9%)	11 (10.7%)	6 (5.8%)	7 (6.8%)	1 (1%)	
Dyspnea							
Yes	68 (66%)	0 (0%)	6 (5.8%)	20 (14%)	38 (26.6%)	26 (18.2%)	0.001*[a]
No	35 (34%)	5 (4.9%)	16 (15.5%)	15 (10.5%)	7 (4.9%)	6 (4.2%)	
TLC							
Normal	48 (46.6%)	0 (0%)	14 (13.6%)	14 (13.6%)	15 (14.6%)	5 (4.9%)	0.088
Raised	55 (53.4%)	5 (4.9%)	8 (7.8%)	13 (12.6%)	20 (14%)	9 (8.7)	
De-Dimer							
Normal	21 (20.4%)	0 (0%)	8 (7.8%)	7 (6.8%)	4 (3.9%)	2 (1.9%)	0.121*
Raised	82 (79.6%)	5 (4.9%)	14 (13.6%)	20 (19.4%)	31 (30.1%)	12 (11.7%)	
Ferritin							
Normal	36 (35%)	1 (1%)	10 (9.7%)	7 (6.8%)	15 (14.6%)	3 (2.9%)	0.329*
Raised	67 (65%)	4 (3.9%)	12 (11.7%)	20 (19.4%)	20 (19.4%)	11 (10.7%)	
LDH							
Normal	12 (11.7%)	2 (1.9%)	2 (1.9%)	3 (2.9%)	5 (4.9%)	0 (0%)	0.189*
Raised	91 (88.3%)	3 (2.9%)	20 (19.4%)	24 (23.3%)	30 (29.1%)	14 (13.6%)	
CRP							
Normal	12 (11.7%)	0 (0%)	3 (2.9%)	5 (4.9%)	4 (3.9%)	0 (0%)	0.430*
Raised	91 (88.3%)	5 (4.9%)	19 (18.4%)	22 (21.4%)	31 (30.1%)	14 (13.6%)	
Pro-calcitonin							
Normal	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0.446
Raised	102 (99%)	5 (4.9%)	21 (20.4%)	27 (26.2%)	35 (34%)	14 (13.6%)	
Pro-BNP							
Normal	11 (10.7%)	0 (0%)	0 (0%)	6 (5.8%)	4 (3.9%)	1 (1%)	0.126
Raised	92 (89.3%)	5 (4.9%)	22 (21.4%)	21 (20.4%)	31 (30.1%)	13 (12.6%)	

[a]significant p value (P < 0.05), *Chi square test

Table 3: Association of demographic and clinical characteristics with the Outcome of the diseases

Parameters	**n=103**	**Outcome**			p value*
		Discharge 70 (68.0%)	**Death 31 (30.1%)**	**DOR 2 (1.9%)**	
Antiviral (Remdesivir)					
Yes	36 (35.0%)	32 (31.1%)	2 (1.9%)	0 (0.0%)	0.000
No	67 (65.0%)	38 (36.9%)	29 (28.2%)	2 (1.9%)	
Steroid					
Yes	46(44.7%)	37(35.9%)	9 (8.7%)	0 (0.0%)	0.037
No	57(55.3%)	33(32.0%)	22 (21.4%)	2 (1.9%)	
Age (Years)					
<=50	26 (25.2%)	14 (13.6%)	10 (9.7%)	0 (0.0%)	0.021
>50	77 (74.8%)	56 (54.4%)	21 (20.4%)	2 (1.9%)	
Gender					
Male	49 (47.6%)	31 (30.1%)	16 (15.5%)	0 (0.0%)	0.258
Female	54 (52.8%)	39 (37.9%)	15 (14.6%)	2 (1.9%)	
Co-morbid					
Yes	52(50.5%)	37(35.9%)	15(14.6%)	0 (0.0%)	
No	14(13.6%)	14(13.6%)	0(0.0%)	0(0.0%)	0.009
NA	37(35.9%)	19(18.4%)	16(15.5%)	2(1.9%)	
Fever					
Yes	64 (62.1%)	41 (39.8%)	21 (20.4%)	0 (0.0%)	0.366
No	39 (37.9%)	29 (28.2%)	10 (9.7%)	2 (1.9%)	
Cough					
Yes	67 (65%)	39 (37.9%)	26 (25.2%)	0 (0.0%)	0.014
No	36 (35%)	31 (30.1%)	5 (4.9%)	2 (1.9%)	
Dyspnea					
Yes	68 (66%)	45 (43.7%)	21 (20.4%)	0 (0.0%)	0.559
No	35 (34%)	25 (24.3%)	10 (9.7%)	2 (1.9%)	
TLC					
Normal	48 (46.6%)	32 (31.1%)	14 (13.6%)	0 (0.0%)	0.310
Raised	55 (53.4%)	38 (36.9%)	17 (16.5%)	2 (1.9%)	
De-Dimer					
Normal	21 (20.4%)	18 (17.5%)	3 (2.9%)	0 (0.0%)	0.140
Raised	82 (79.6%)	52 (50.5%)	28 (27.2%)	2 (1.9%)	
Ferritin					
Normal	36 (35%)	31 (30.1%)	5 (4.9%)	0 (0.0%)	0.014
Raised	67 (65%)	39 (37.9%)	26 (25.2%)	2 (1.9%)	
LDH					
Normal	12 (11.7%)	12 (11.7%)	0 (0.0%)	0 (0.0%)	0.041
Raised	91 (88.3%)	58 (56.3%)	31 (30.1%)	2 (1.9%)	

CRP					
Normal	12 (11.7%)	1110.7%)	1 (1.0%)	0 (0.0%)	0.172
Raised	91 (88.3%)	59 (57.3%)	30 (29.1%)	2 (1.9%)	
Pro-calcitonin					
Normal	1 (1%)	1 (1%)	0 (0.0%)	0 (0.0%)	0.788
Raised	102 (99%)	69 (67.0%)	31 (30.1%)	2 (1.9%)	
Pro-BNP					
Normal	11 (10.7%)	9 (8.7%)	2 (1.9%)	0 (0.0%)	0.558
Raised	92 (89.3%)	61 (59.2%)	29 (28.2%)	2 (1.9%)	

DISCUSSION

In the quest to confront the unprecedented global challenge posed by COVID-19, understanding the correlation between antiviral treatments and the severity of the disease has emerged as a critical area of investigation[11,12,13]. The novel coronavirus, SARS-CoV-2, has disrupted lives and healthcare systems worldwide, prompting an urgent need for effective therapeutic interventions. As we delve into the intricate landscape of antiviral treatment options, it becomes evident that this journey is marked by complexity and contradictions[14]. Efforts to standardize COVID-19 treatment have not yielded a consistently effective antiviral drug against SARS-CoV-2[15].

In this cross-sectional study of 103 patients, we investigated the correlation between the use of antiviral and steroid treatments and their impact on COVID-19 severity and patient outcomes. Our study delved into various aspects, including the relationship between inflammatory markers and disease severity and outcome. Intriguingly, we found that patients with more severe illness were more likely to have elevated levels of inflammatory markers. Moreover, we explored how the use of antiviral and steroid treatments influenced these inflammatory markers and ultimately impacted patient outcomes.

Our findings show consensus with previous studies like, In the context of their study encompassing 280 COVID-19 cases, the research conducted by J. Wu et.al delved into the critical factors that influence the severity and prognosis of this disease. Their findings illuminated a compelling relationship between age and comorbidities with the risk of experiencing severe outcomes. Importantly, they underscored the pivotal role of early antiviral treatment in enhancing the prospects of recovery from severe COVID-19[10].

Similarly, another study conducted by Nicoleta Negrut et al, involving 105 COVID-19 patients treated with antiviral therapy, it was observed that patients who received lopinavir/ritonavir (LPV/r) in the K group tended to have shorter hospitalization durations compared to those in the darunavir/ritonavir (DRV/r) group (D group). This suggests that LPV/r treatment may be associated with shorter hospital stays for COVID-19 patients[16]. The study conducted by Trinh Cong Dien et al examined the effects of antiviral and steroid treatments on COVID-19 severity and outcomes. According to the study, hospital stays were cut down for individuals who received antiviral therapy as opposed to those who did not. In addition, patients with COVID-19 who used steroids had a lower probability of experiencing severe consequences.[17]In a study directed by Mohammad E. M. Mahfouz and his team, they evaluated antiviral therapies for severe COVID-19 cases.

According to their research, 20.7% of patients who were in critical condition survived. Higher mortality was correlated with older age and concomitant conditions including diabetes and hypertension. Notably, remdesivir use, either alone or in combination with favipiravir, increased survival rates, indicating their effectiveness[18]. Furthermore, Ryo Nagasawa et al, evaluated the safety and effectiveness of a three-drug combination therapy for COVID-19 patients who were hospitalized, which included high-dose steroids, remdesivir (REM), and baricitinib (BAR). According to their findings, those who received this combination therapy for their conditions significantly improved. With just a small percentage of serious side events—mostly hyperglycemia—the medication was well tolerated. These findings point to the potential advantages of combining antiviral and steroid therapies to improve outcomes in people with mild to moderate hepatitis COVID-19[19] Umeh CA and colleagues methodically studied the impact of antiviral medicines, steroids, and angiotensin-converting enzyme inhibitors (ACEI) on mortality in COVID-19 patients with increased troponin levels in their study. The study, which included 1788 COVID-19 participants, yielded notable results. Conventional medications typically used to treat viral myocarditis, such as remdesivir, dexamethasone, and ACEI, were found to have no meaningful effect on mortality in this specific patient population. These findings shed light on the complex interaction of antiviral medicines and steroids in the context of COVID-19 severity and patient outcomes[20].

This cross-sectional study has contributed valuable insights to the ongoing research on COVID-19 treatment. As the world confronts the formidable challenge of the pandemic, understanding the intricate relationship between antiviral and steroid therapies, COVID-19 severity, and patient outcomes remains of paramount importance. Nevertheless, it is crucial to acknowledge certain limitations within our study. Our relatively modest sample size of 103 patients may not fully represent the diverse spectrum of COVID-19 cases. Future studies with larger and more diverse cohorts are warranted to validate our findings. Additionally, the retrospective nature of our study might introduce some inherent biases, emphasizing the need for prospective studies to provide more robust evidence.

CONCLUSION

Statistical analysis revealed compelling evidence that the administration of antiviral medication exhibited a salient correlation with a mitigated severity profile among COVID-19 patients. Simultaneously, the utilization of steroid therapy exhibited a noteworthy association with enhanced clinical outcomes. These findings underscore the pivotal role of tailored therapeutic interventions in ameliorating the spectrum of COVID-19 severity, presenting an intricate landscape for optimizing patient care strategies.

Authorship and contribution declaration: Each author of this article fulfilled following Criteria of Authorship:

1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

All authors agree to be responsible for all aspects of their research work.

Ethics Approval: Ethical approval for the study was granted by the Institutional Ethical Review Committee under reference code 5540622UTMM on August24th, 2022.

Conflict of Interest: The authors assert that there are no conflicts of interest related to the study.

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