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Antiviral drug treatment profiles and clinical outcomes of COVID-19 patients at public hospitals in Erbil city.

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Abstract

Background & objectives: The World Health Organization has identified COVID-19 as a rapidly spreading global disease. Some antiviral drugs have shown promising efficacy in treating COVID-19. This study aims to identify the effects of antiviral drugs and compare them with other therapies in COVID-19 patients, while reviewing the clinical outcomes of these treatments.

Methods: This observational retrospective case study included 451 COVID-19 patients, comprising 57.0% males and 43% females, conducted in Rizgari, Erbil, at Central Emergency, Rozhawa Emergency, and Emirate Hospitals over one year from December 2020 to December 2021. COVID-19 cases were confirmed using reverse transcriptase polymerase-chain reaction (RT-PCR) assays, and treatment followed the WHO guidelines, involving antivirals (Remdesivir, Favipiravir), broad-spectrum antibiotics (levofloxacin, azithromycin, ceftriaxone, meropenem, imipenem), and supportive treatment with Becozym (Vitamins B1 + B2 + B3 + B5 + B6). Data were recorded in the statistical department of the hospitals.

Results: The total age range of the 451 patients was 95 (18-113) with a mean ± SD of 59.408 ± 18.26 years. The death rate was 22.39%. A majority of the survival patients were in the young age group (95.1%), while the death rate was higher in the old age group (more than 75 years). The death rate of patients treated with antiviral drug Remdesivir was 15.30%, while it was 37.93%, 73.45%, 15.25%, and 14.15% in patients on levofloxacin, ceftriaxone, meropenem, and Becozyme, espectively. Logistic regression analysis did not show any role of treatments in decreasing mortality.

Conclusions: Significant differences were observed in clinical outcomes; the majority of surviving patients were in the young age group, while older COVID-19 patients had worse illnesses and treatment outcomes. Diabetes and hypertension were significant predictors of COVID-19 mortality. Although Remdesivir treatment showed a statistically significant association between survival and death cohorts, it was not considered a predictor variable for survival. Antibiotics and supplement drugs like Becozyme were also not considered predictors of survival for COVID-19 patients.

Keywords: Antibiotic drugs, Antiviral drugs; Clinical outcomes, COVID-19, Supplement.

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Introduction

The Coronaviridae family encompasses coronaviruses (CoVs), which infect various hosts and manifest a range of clinical manifestations, ranging from severe, occasionally fatal respiratory infections to symptoms resembling the common cold. The current outbreak is caused by a novel virus initially named "2019-nCoV" or "SARS-CoV-2," which is believed to be closely related to the pathogen responsible for severe acute respiratory syndrome (SARS), known as SARS-CoV.[1] Both SARS-CoV-2 and SARS-CoV share 80% of the same RNA sequence, indicating a potential association. Advanced age and comorbidities, such as hypertension, diabetes, obesity, and smoking, increase the likelihood of severe disease presentation.[2] Most COVID-19 patients experience mild to moderate symptoms, resembling a bacterial infection, including fever, cough, fatigue, loss of taste and smell, difficulty breathing, or shortness of breath. Severe illness requiring ICU assistance was observed in only 6% of the infected individuals.[3] Due to the absence of a specific COVID-19 vaccination and antiviral treatment, medical practitioners commonly administer various antimicrobials to COVID-19 patients. Additionally, early-stage symptom evaluation poses challenges in differentiating COVID-19 from bacterial pneumonia.[4] Remdesivir, a nucleotide analog (adenosine), is considered a potential candidate drug for combating COVID-19 caused by SARS-CoV-2 infection. Although several clinical trials have evaluated its efficacy, the results have been conflicting. Nonetheless, the FDA has approved Remdesivir for treating COVID-19 in adults and children aged 12 and above, particularly for hospitalized patients. In comparison, Favipiravir, which also incorporates ATP and GTP into RNA-dependent RNA polymerase (RdRp), is less effective than Remdesivir. A study comparing Favipiravir and Ritonavir-Lopinavir treatments for SARS-CoV-2 showed that the Favipiravir group experienced a significantly shorter virus spread time, improved chest images, and fewer adverse reactions. Protease inhibitors used in HIV-1 therapy, such as Saquinavir, Amprenavir, Indinavir, Nelfnavir, Ritonavir, and Lopinavir, have also demonstrated efficacy against SARS-CoV.[5] The objective of this study was to describe the demographic features of COVID-19 patients, analyze the treatment profiles of antiviral drugs used, and assess clinical outcomes in terms of recovery or mortality.

Patients and methods

An observational retrospective case study was conducted in several designated COVID-19 hospitals (Rizgary, Erbil, Central Emergency, Rozhawa Emergency, Hospitals) in Erbil city. The study included 451 patients over one year, from December 2020 to December 2021, all confirmed to have COVID-19 through reverse transcriptase polymerase-chain reaction (RT-PCR) assays. The inclusion criteria were adults aged 18 and above with a positive COVID-19 test result. Pregnant patients and those with missing information in their records were excluded. COVID-19 patients received treatment according to the WHO guidelines, which included antivirals (Remdesivir, Favipiravir), broad-spectrum antibiotics (levofloxacin, azithromycin, Ceftriaxone, Meropenem, Imipenem), and supportive treatments (Becozyme) (Vitamins B1 + B2 + B3 + B5 + B6). Patients with SARS-CoV-2 infection were grouped into mild to moderate and severe to critical categories, based on the severity of illness as defined in the clinical spectrum of SARS-CoV-2 infection. Data were recorded in the statistical department of the hospitals while ensuring confidentiality and anonymity. The materials will not be reused in the future. For statistical analysis, the

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main tests used were the Chi-square test ($\chi 2$ test) to evaluate if there is a statistically significant discrepancy between the expected frequencies and the observed frequencies in one or more categories of a contingency table. Fisher's exact test was used if the expected count of > 20% of the cells was less than 5. Binary logistic regression models were utilized to examine the relationship between the clinical outcome (survival and death) as the dependent variable and a set of independent variables that demonstrated a significant correlation with the clinical outcome. The independent variables included demographic characteristics, hematological parameters, and treatments of COVID-19 patients. The selection of these independent variables was based on their observed significant correlations with the clinical outcome. A significance level of $p \leq 0.05$ and a 95% confidence interval (95% CI) were considered for the analysis. The statistical package for social sciences (SPSS, version 22) was employed for data analysis. The study protocol was approved by the Research Ethics Committee of the Kurdistan Higher Council of Medical Specialties (Protocol no. 1138, approval date: 7/6/2022).

Results

The age range of the total 451 patients was 95 (18-113) years, with a mean ± SD of (59.408 ± 18.26) years and a death rate of (22.39%). The survival rate was higher in young patients (94.1%) compared to patients aged more than 75 years (64.70%) (P<0.001), which was not significant among male and female cohorts (P=0.214). Most of the cured patients did not have chronic diseases in contrast to the deceased patients (83.70% vs. 33.13%) in hypertension (HT) and (80.18% vs. 31.07%) in diabetes mellitus (DM) (P<0.001). Additionally, the majority of patients had mild to moderate illness (81.2%), while the death rate among patients with severe to critical disease was (85.9%) (P<0.001), Table (1).

Table (1): Characteristics of patients, prevalence of chronic diseases, and severity of disease.

Characteristics	Alive**	Dead**	Total*	p-value***
	No. (%)	No. (%)	No. (%)	
Age				
18-44	95 (94.1)	6 (5.9)	101 (22.39)	<0.001
45-64	119 (77.27)	35 (22.73)	154 (34.14)	
65-74	70 (74.46)	24 (25.54)	94 (20.84)	
>75	66 (64.70)	36 (35.30)	102 (22.61)	
Sex				
Male	194 (75.50)	63 (24.50)	257 (57.0)	0.214
Female	156 (80.40)	38 (19.60)	194 (43.0)	
HT				
Yes	109 (66.87)	54 (33.13)	163 (36.1)	<0.001
No	241 (83.70)	47 (16.30)	288 (63.9)	
DM				
Yes	71 (68.93)	32 (31.07)	103 (22.8)	<0.001
No	279 (80.18)	69 (19.82)	348 (77.2)	
Severity of COVID-19				
Mild to moderate	338 (92.34)	28 (7.7)	366 (81.2)	<0.001
Severe to critical	12 (14.11)	73 (85.9)	85 (18.8)	
Total	350 (77.65)	101 (22.39)	451 (100)	

*Column % was calculated ** Row % was calculated, ***Chi square test χ^2, DM: diabetes mellitus, HT: hypertension.

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Hematological parameters comparison of study cohorts revealed that the death rate was (26.1%) vs (13.2%) in patients with a low and normal level of lymphocytes (p=0.03), and it was (26.85%) in cohorts with a high level of WBC more than (4.5 to 11.0 × 109/L). Additionally, the death rate was (25.74%) vs (7.32%) in patients with a high C-reactive protein (CRP) marker (p<0.001) Table (2).

Table (2): Hematological parameters and differences between recovered and dead patients

Hematological parameters			Alive 350 ** No (%)	Dead 101 ** No (%)	Total451 * No (%)	p-value***
Lymphocyte×10^9 /L,	Normal range 0.9–5.0 x109/L	Normal Low	112 (86.8) 238 (73.9)	17 (13.2) 84 (26.1)	129 (28.6) 322 (71.4)	0.03
WBC×10^9 /L	(4.5 to 11.0 × 109/L)	Normal High	102(93.07) 248 (72,51)	7 (6.42) 94 (26.85)	109 (22.40) 342 (77.60)	<0.001
CRP, mg/dl	0.0–1.0 mg/dl	Normal High	76 (92.68) 274 (74,26)	6 (7.32) 95 (25.74)	82 (18.2) 369 (81.8)	<0.001

*Column % was calculated, ** Row % was calculated, ***Chi square χ^2 test

The death rates of patients who received Remdesivir versus those who did not receive it were (15.30%) and (24.70%), respectively. The survival rate of the patients who received Remdesivir was (84.70%) (p=0.031). Additionally, (77.35%) of the alive patients did not receive Favipiravin.The death rates in patients who received antibiotics compared to those who did not receive them were as follows: levofloxacin (37.93% vs 21.32%, p=0.031, p=0.038), Ceftriaxone (73.45% vs 16.16%, p <0.001), Meropenem (15.25% vs 30.24%, p <0.001), and Becozyme (14.15% vs 25.15%, p=0.015). The survival rate of patients with Becozyme was (85.85%) Table (3).

Table (3): Death rate among patients with drugs treatments and clinical outcome

Drugs treatment		Alive 350 No %	Dead 101 No %	Total 451 No %	*p*-value
Antiviral drug Remdesivir 100mg amp,	No Yes	256 (75.30) 94 (84.70)	84 (24.70) 17 (15.30)	340 (75.4) 111 (24.6)	0.031(*)
Antiviral drug, Favipiravin200 Tablet	No Yes	338 (77.35) 12 (85.72)	99 (22.65) 2 (14.28)	437 (96.9) 14 (3.1)	0.745 (**)
Antibiotic levofloxacin 500 mg tablet,	No Yes	332 (78.68) 18 (62,07)	90 (21.32) 11 (37.93)	422 (93.6) 29 (6.4)	0.038 (*)
Antibiotic Azithromycin500mg tablet	No Yes	332 (78.48) 18 (64.28)	91 (21.52) 10 (35.72)	423 (93.8) 28 (6.2)	0.081(*)
Antibiotic, Ceftriaxone 500 mg vial	No Yes	337 (83.84) 13 (26.55)	65 (16.16) 36 (73.45)	402 (89.1) 49 (10.9)	<0.001(*)
Antibiotic, Meropenem500 mg vial	No Yes	150 (69.76) 200 (84.75)	65 (30.24) 36 (15.25)	215 (47.7) 236 (52.3)	<0.001 (*)
Antibiotic ,Imipenem 500mg iv vial	No Yes	343 (77.42) 7 (87.5)	100 (22.58) 1 (12.5)	443 (98.2) 8 (1.8)	0.960 (**)
Becozyme injection(Vitamins B1 + B2 + B3 + B5 + B6) IM / IV ampoule,	No Yes	253 (74.85) 97 (85.85)	85 (25,15) 16 (14.15)	338 (74.9) 113 (25.1)	0.015 (*)

*By Chi square χ^2 test, ** Fisher's Exact test

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Binary logistic regression was used to identify predictors of Covid-19 death. Old age more than 50 years (OR=6.157) and CRP (OR=6.767) were identified as predictor factors that increase the risk of mortality, along with antibiotic (ceftriaxone), DM, HT, and severe to critical spectrum of disease. On the other hand, a decrease in the probability of death was associated with a normal increase in WBC levels (OR=0.120). It should be noted that cases treated with Remdesivir and Becozyme were insignificant in the model, Table (4).

Table (4): Binary logistic regression analysis for factors associated with mortality.

		B	P-value	OR	95%CI
Age	> 50	1.818	0.001	6.157	2.043- 18.559
CRP		1.912	0.025	6.767	1.266- 36.166
lymphocyte		-0.887	0.074	0.412	0.156-1.090
WBC		-2.121	0.006	0.120	0.026- 0.543
Antiviral drug Remdesivir		0.083	0.850	1.087	0.459-2.571
Antibiotic Meropenem		-0.298	0.456	0.742	0.339-1.624
Antibiotic ceftriaxone		3.779	<0.001	43.776	7.96-240
Antibiotic levofloxacin		0.200	0.769	1.222	0.321-4.653
Becozym amp		-0.219	0.651	0.803	0.311-2.075
DM		1.721	0.001	5.590	2.066-15.126
HT		0.946	0.045	2.576	1.022-6.491
Severe COVID-19		4.349	<0.001	77.395	28.992-206.6
constant		-6.502	<0.001	0.001	

B: Regression coefficient, OR: Odds ratio, CI: Confidence Interval-value indicates the level of significance in the statistical analysis. " The "Constant" term is also included for statistical purposes but may not have a direct interpretation in the context of the study.

Discussion

This study focused principally on the treatment of 451 patients. Most of the surviving patients were in the young age group, while the death rate was high in the older age group, especially in those aged over 75. Age was identified as a significant factor increasing the risk of mortality in COVID-19 patients compared to other studies. The death rate of 4% among hospitalized COVID-19 patients was considered relatively low, which could be attributed to the Ministry of Health's policy of admitting all PCR-confirmed COVID-19 cases to the hospital, regardless of symptom severity.[9] Another study found an association between older age and high mortality in COVID-19 patients, reporting 304.9 deaths per 1000 cases in the US among patients aged 85 years or older.[10] Additionally, our research has revealed that diabetes and hypertension are significant predictors of COVID-19 mortality, consistent with findings from other investigations showing an increased death rate in patients with worsened COVID-19 infection.[11] Among pre-existing cardiovascular (CV) risk factors, diabetes mellitus and cardiopathy, in particular, appear to be significant predictors of the severity of COVID-19.[12] Lymphocytes are abnormally decreased in severe acute

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respiratory syndrome (SARS) and COVID-19.[13,14] Lymphocytopenia (lymphocyte count <1 × 10^9/L) although it was non-significant and a WBC which increased within normal range (4.5 to 11.0 × 109/L) was supposed to be significant predictors of alive. A clinical indicator of severity and prognosis could be considered the lymphocyte count, particularly CD4.[15] It had been found that most of the patients were with a normal range of WBC count. However, those with higher WBC lever patients were at a high risk of death, the death risk was associated with the WBC count at admission, although the index was at the normal range, those with higher WBC count patients were facing a much higher death possibility.[16] Nevertheless, accumulating evidence suggests that patients with severe COVID-19 might experience a cytokine storm syndrome.[17,18] Becozyme was not a predictor variable for the survival of COVID-19 patients in the present study could be to the young age group, which had milder to moderate illness and higher numbers. As obesity, hypertension, type 2 diabetes, kidney failure, cancer, and heart disease become more prevalent with age, these comorbidities can contribute to poor clinical outcomes in individuals infected with SARS-CoV-2. Younger populations have fewer of these comorbidities and, therefore, have a reduced likelihood of developing severe disease.[19] Elderly people have a weak immune response to infectious agents, making them more susceptible to severe infection.[20] Antibiotic treatments (Ceftriaxone) with high odds ratios were predictor factors for increased likelihood of mortality. Antibiotics do not directly affect SARS-CoV-2, but viral respiratory infections predispose to bacterial pneumonia. The high prescription of antibiotics occurred mainly during the first peak of the health emergency, with higher rates of ICU admission.[21,22] Additionally, older patients had more severe illnesses, necessitating the use of adjuvant medicines like corticosteroids and assisted ventilation more frequently in this patient population.[23,24] Antibiotics are not a treatment for COVID-19.[25,26] The high survival rate of alive patients with no antiviral treatment (Remdesivir), was not significant in the logistic regression model, is in agreement with other studies that reveal Remdesivir was not effective in improving clinical symptoms in patients.[27,28] Nevertheless, no randomized controlled experiment has yet demonstrated that Remdesivir significantly outperforms normal medical treatment in terms of lifesaving. Preliminary findings from the massive international study Solidarity trial, conducted by the World Health Organization, demonstrate that the medication has no appreciable effect on mortality, making Remdesivir an unlikely lifesaving medication.[29] The potency, pharmacokinetics, and viral kinetics of acute respiratory viruses must be understood to provide antiviral drugs in a dose-appropriate manner. In most cases, the so-called pro-inflammatory cytokine storm happens prior to the start of serious disease and a bad clinical prognosis. It is doubtful that any antiviral will be effective if a patient receives medication after developing a high viral load or after the cytokine storm begins.[30] Our study also showed no statistically significant association among patients with Favipiravir of survival and dead cohorts, which is in agreement with results from a study that revealed Favipiravir does not speed up the time to virological cure or clinical results and provides no indication of an antiviral benefit in treating early symptomatic COVID-19 infection.[31] The COVID-19 pandemic has highlighted our vulnerability to illnesses for which there are currently no effective treatments.[32] Currently, only inhaled interferon (IFN), small compounds, and monoclonal antibodies (mAbs) have been shown to be effective early in the course of infection.[33] The primary drawback of this study was that the

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majority of the participants were COVID-19 patients who had mild to severe illness. Risk factors, such as pre-existing comorbidities like hypertension and diabetes mellitus, and older age, were already identified. The older COVID-19 patients had substantially worse disease and responded to treatment worse than younger age groups. Additionally, COVID-19 is an immunological disease, and biologic therapy may provide patients with a favorable prognosis and improved outcomes.

Conclusion

Older COVID-19 patients experienced more severe illnesses and had lower treatment outcomes compared to younger patients. Old age, high CRP, low WBC, Antibiotic ceftriaxone, DM,HT, Severe COVID were significant predictors of death . Antiviral regimens were not predictive of survival in COVID-19 patients, and the results were similar when compared to antibiotic regimens. Nevertheless, the supplement Becozyme, which was prescribed for mild cases, was not a predictor variable for the survival of COVID-19 patients.

Recommendations

Finally, more extensive and carefully monitored research examining antiviral treatments is required to prove their effectiveness in treating COVID-19 patients.

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Conflicts of Interest:

None.

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