Evaluation of the Costs and Outcomes of COVID-19 Therapeutic Protocols in Critically Ill Patients in Alzahra Hospital, Isfahan, Iran

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Abstract

Background: During the COVID-19 pandemic, different drug protocols were used to treat and manage patients. Considering the diversity in these protocols and the high costs associated with the disease, we aimed to evaluate the costs and effects of the most common therapeutic protocols among critically ill COVID-19 patients.

Methods: In this retrospective cross-sectional study, a total of 235 critically ill COVID-19 patients were randomly selected from those hospitalized in the Intensive Care Units of Alzahra Hospital, Isfahan, Iran, between July and December 2020. The study assessed demographic data, outcomes (mortality rate), severity of the disease (SOFA score), and average direct costs of each therapeutic regimen. Statistical analysis included Cox-Regression analysis and Kaplan-Meier survival curve.

Results: We identified 21 therapeutic protocols based on prescribed medications, with six protocols being the most commonly used. The protocol containing dexamethasone + methylprednisolone showed the highest survival probability (0.79) with a median length of hospital stay of 17 days. Cost evaluation revealed that the dexamethasone protocol had the lowest average cost per patient, while the dexamethasone + methylprednisolone + remdesivir protocol had the highest. Hoteling costs accounted for 45% of the total costs, followed by medication costs (25%).

Conclusion: The dexamethasone + methylprednisolone therapeutic regimen demonstrated the highest effectiveness in terms of survival probability and was also associated with the lowest average cost per patient.

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Keywords: Covid-19, Cost Evaluation; Intensive Care Unit; Therapeutic Regimen

Introduction

Coronaviruses are a family of viruses that can cause illnesses ranging from the common cold to more severe diseases. The first coronavirus infection was reported in 1965, leading to mild respiratory symptoms. Among the five different types of coronaviruses, the most deadly was the Severe Acute Respiratory Syndrome (SARS), which infected approximately 8,000 people and had a mortality rate of around 10% (1). The most recent coronavirus outbreak, COVID-19, caused by the SARS-CoV-2 virus. It was first identified in Wuhan, China, on December 31, 2019, and quickly spread to 212 countries, prompting the World Health Organization (WHO) to declare it a pandemic on March 12, 2020 (2).

In Iran, the initial cases of COVID-19 were reported between February 19 and February 23, 2020, with 43

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confirmed cases and 8 deaths (2). Over the course of the pandemic, multiple waves of COVID-19 emerged, each characterized by varying symptoms and severity. Common symptoms included cough, shortness of breath, fever, fatigue, and loss of taste or smell. Abnormal chest radiographs were prevalent, with bilateral reticular nodular opacities and ground-glass opacities being the most common lung findings associated with the virus (3).

Research has significantly advanced our understanding of the pathophysiology of COVID-19, revealing that the virus activates immune cells and can lead to a hyper-inflammatory response known as a cytokine storm. This inflammatory cascade contributed to the severe respiratory distress observed in critically ill patients (4, 5).

The direct treatment costs for COVID-19 were significantly higher compared to other infectious diseases due to the increased likelihood of hospitalization and mortality. A substantial proportion of COVID-19 patients required intensive care services, leading to remarkable therapeutic costs (6). Various treatment options were proposed, including antiviral medications (such as interferon alpha, lopinavir-ritonavir, ribavirin, chloroquine phosphate, and Umifenovir), antibiotics (including azithromycin, moxifloxacin, tigecycline, and doxycycline), anticoagulants (such as heparin, enoxaparin, and rivaroxaban), and glucocorticoids for critically ill patients. Despite ongoing efforts to develop effective treatment guidelines, no universally approved treatment strategy with consistently promising effects has emerged (6-8).

Given the diversity in treatment protocols for hospitalized patients and the high costs associated with COVID-19, this retrospective cross-sectional study aimed to evaluate the costs and effects of the most common therapeutic protocols among critically ill patients. The study also assessed the impact of demographic and clinical factors on patient outcomes.

Methods

Setting

This retrospective cross-sectional study included critically ill COVID-19 patients who were admitted to the 3 Intensive Care Units (ICU), with 23 beds for each ICU, at Alzahra Hospital, a teaching hospital in Isfahan, Iran, from July 2020 to December 2020. During this period, the hospital was the primary referral center for COVID-19 patients, with a total of 1,032 hospitalized patients in the ICU. The study population comprised patients who were directly admitted to the ICU upon hospitalization and those who were transferred from other wards.

Sample Size Calculation

In the initial stage of the study, a comprehensive list of all COVID-19 patients hospitalized in the ICU was obtained from the hospital's information system. From this list, 235 patients were randomly selected using a systematic random sampling method. The sample size was calculated using the following formula:

$$n = \frac{\left(z_{1} - \frac{\alpha}{2}\right)^{2} p\,(1-p)}{d^{2}}$$

where:n: desired sample size, p: estimated mortality rate in the ICU (assumed maximum variance of 50%), d: desired sampling error (6%), α: level of confidence (95%)

Using a correction factor (n =n/(1+n/N)), where N is the total number of hospitalized patients, the estimated sample size was adjusted from 267 to 212. Taking into account a 10% allowance for potential missing data, the final sample size was determined to be 235 (9).

Patients

The selection of patients was based on recorded symptoms and diagnoses documented by specialist physicians in the patients' medical files. During the study period, routine Polymerase Chain Reaction (PCR) testing was not consistently performed; therefore, diagnosis was based on clinical criteria, including chest radiographs, CT scans, and clinical symptoms. The study included patients diagnosed with COVID-19 based on these criteria. Among the enrolled patients, the number diagnosed with positive PCR results, chest radiography, or clinical symptoms was documented.

Assessments

The study evaluated demographic information, clinical outcomes (mortality rate), disease severity (assessed using the Sequential Organ Failure Assessment [SOFA] score (10, 11) and direct medical costs from the payer's perspective. Direct medical costs included medications, medical equipment, hospitalization expenses, diagnostic and laboratory services, physician visits, and nursing services. Costs were valued using the latest edition of the health tariff book published by the Ministry of Health (tariffs for first-class governmental hospitals) and the Food and Drug Administration's website for medication costs. The cost calculations were restricted to the duration of ICU stay (until discharge from the ICU or death). If patients were transferred from other wards or the emergency department, only the costs incurred during the ICU stay were included, and costs from prior wards were not calculated.

The calculation of hospitalization costs included all expenses related to the ICU stay, such as daily bed charges, nursing care, and any necessary medical interventions.

Treatment Protocols

The primary medication categories used for patients were identified based on their pharmacological classifications and confirmed by clinical pharmacist experts at the hospital. These categories included:Antivirals (remdesivir or favipiravir), Anti-inflammatory and analgesic medications (non-steroidal anti-inflammatory drugs [NSAIDs] and corticosteroids), Anticoagulants (heparin and enoxaparin), Antibiotics and Other COVID-19-related medications (such as tocilizumab, vitamins, minerals, and famotidine).

The most common treatment protocols were identified based on patient records, considering all related medications administered during the ICU stay. Variations in dosage and duration of medication administration were not classified as separate protocols due to the potential low number of patients for each protocol. The definition of a treatment protocol included all medications administered to patients during their hospital stay, regardless of whether they were given simultaneously.

Data regarding the need for mechanical ventilation were also collected and included in the analysis. Comorbidities, which are known to play a significant role in COVID-19 mortality, were documented and analyzed in relation to patient outcomes.

Statistical Analysis

The extracted data were analyzed using Cox regression analysis and the Kaplan-Meier survival curve. The Cox regression method allowed for the exploration of the effect of one or more covariates on time-to-event analysis (12). The Kaplan-Meier estimate was used to evaluate the proportion of subjects surviving over time following treatment (13).

Descriptive statistics, including mean (± standard deviation) and frequency (percentage), were used to summarize the data. The normality of the data was assessed using the Shapiro-Wilk test. Analytical data were analyzed using SPSS version 20 software, with a p-value of less than 0.05 considered statistically significant.

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Results

The average age (±SD) of the 235 enrolled patients was 58.2 (±17.77) years, with men having an average age of 59 (±17.74) and women having an average age of 56 (±17.82) years. Table 1 presents the mortality rate and mean SOFA score of the study population based on age category and gender.

Table 1. Mortality rate and mean SOFA score of the study population, based on age and gender

Variables		N (%)	Mortality rate	SOFA score mean ± SD
Age	< 30	13 (5.5)	15%	2.5 ± 1.5
	30-39	29 (12.5)	27%	2.8 ±1.5
	40-49	38 (16)	36%	3.2 ±1.7
	50-59	33 (14)	58%	2.9 ±1.6
	60-69	51 (22)	65%	3.3 ±1.7
	70-79	45 (19)	67%	3.8 ±1.8
	≥ 80	26 (11)	85%	4.2 ±1.8
Gender	Male	153 (65)	59%	3.5 ±1.8
	Female	82 (35)	46%	2.9 ±1.8

Therapeutic Protocols

All patients were prescribed anticoagulants, NSAIDs, and antibiotics. Therefore, the protocols were categorized based on the use or nonuse of corticosteroids (dexamethasone and/or methylprednisolone), antivirals (remdesivir and/or favipiravir), interferons (Ziferon®; Interferon beta-1b or Recigen®; Interferon beta-1a), and tocilizumab. A total of 21 treatment protocols were identified based on the prescribed medications with 6 protocols being the most commonly used. Table 2 displays the most used protocols along with their associated mortality rate and severity based on the SOFA score.

Table 2. Frequency, Average length of hospitalization in ICU per patient, SOFA score, and mortality rate of each protocol

Protocol	Frequency N (%)	Length of ICU stay (mean ±SD) (days)	SOFA score (mean ±SD)	Mortality rate (%)
dexamethasone	62 (26.4)	13 ± 7.6	3.5 ±1.81	53%
dexamethasone + remdesivir	55 (23.4)	14.8 ± 7.5	3 ±1.73	49%
methylprednisolone	27 (11.5)	12.4 ± 9.7	3 ±1.80	52%
dexamethasone+ methylprednisolone + remdesivir	26 (11.1)	18.1 ± 1.3	2.5 ±1.76	43%
dexamethasone+ methylprednisolone	22 (9.4)	16.3 ± 7.3	4 ±1.76	50%
methylprednisolone+ remdesivir	11(4.7)	13.5 ± 5.4	2.5 ±1.79	73%

Table 3 shows the average total cost and patient share.

Table 3. Average cost per patient and patient share (IRR)

Cost type	Patient share (mean ±SD) range	Insurance share (mean ±SD) range	Total cost per patient (mean ±SD) range	Total cost per patient (%)
Medication	23.698.075± SD	29,261,414	52,959,489	25.44
Hoteling	16,000,847	79,482,649	94,483,496	45.39
Visits and nurse services	2,933,277	10,351,686	13,284,963	6.38
Diagnostic services	1,738,001	1,879,302	3,617,303	1.74
Laboratory services	3,488,975	10,433,268	13,922,243	6.69
Medical equipment	11,600,416	5,835,912	17,436,328	8.38
Other medical expenses	7,208,776	5,268,131	12,476,907	5.99
Total costs per patient	66,668,367	142,512,362	209,180,729	100

COX-regression, Kaplan-Meier and cost analyses of the treatment protocols

After incorporating age, therapeutic protocols, and a history of underlying diseases into the Cox regression model, the SOFA score emerged as the only significant covariate affecting the mortality rate. Consequently, this factor was controlled in the Kaplan-Meier survival analysis. The results of the Cox regression, Kaplan-Meier, and cost analyses of the treatment protocols are presented in Table 4 and Figure 1. The median length of hospital stay for all patients was estimated to be 22.5 days (95% CI: 16.7 – 21.3).

Table 4. Kaplan-Meier and cost analyses of the treatment protocols

Protocol	Survival probability (SOFA score adjusted)	Length of hospital stay median (95%CI) (days)	Costs per patient (mean± SD) (IRR)
Dexamethasone	0.58	15 (10.5 – 19.5)	159,179,444
Methylprednisolone	0.00	22 (14.4 – 29.6)	172,092,068
Dexamethasone + methylprednisolone	0.79	17 (7.9 - 26)	201,553,886
Dexamethasone + remdesivir	0.42	19 (15.2 – 22.7)	226,633,249
Methylprednisolone + remdesivir	0.00	18 (9.5 – 26.4)	218,739,998
Dexamethasone + methylprednisolone + remdesivir	0.29	24 (15.4 – 32.6)	267,837,319

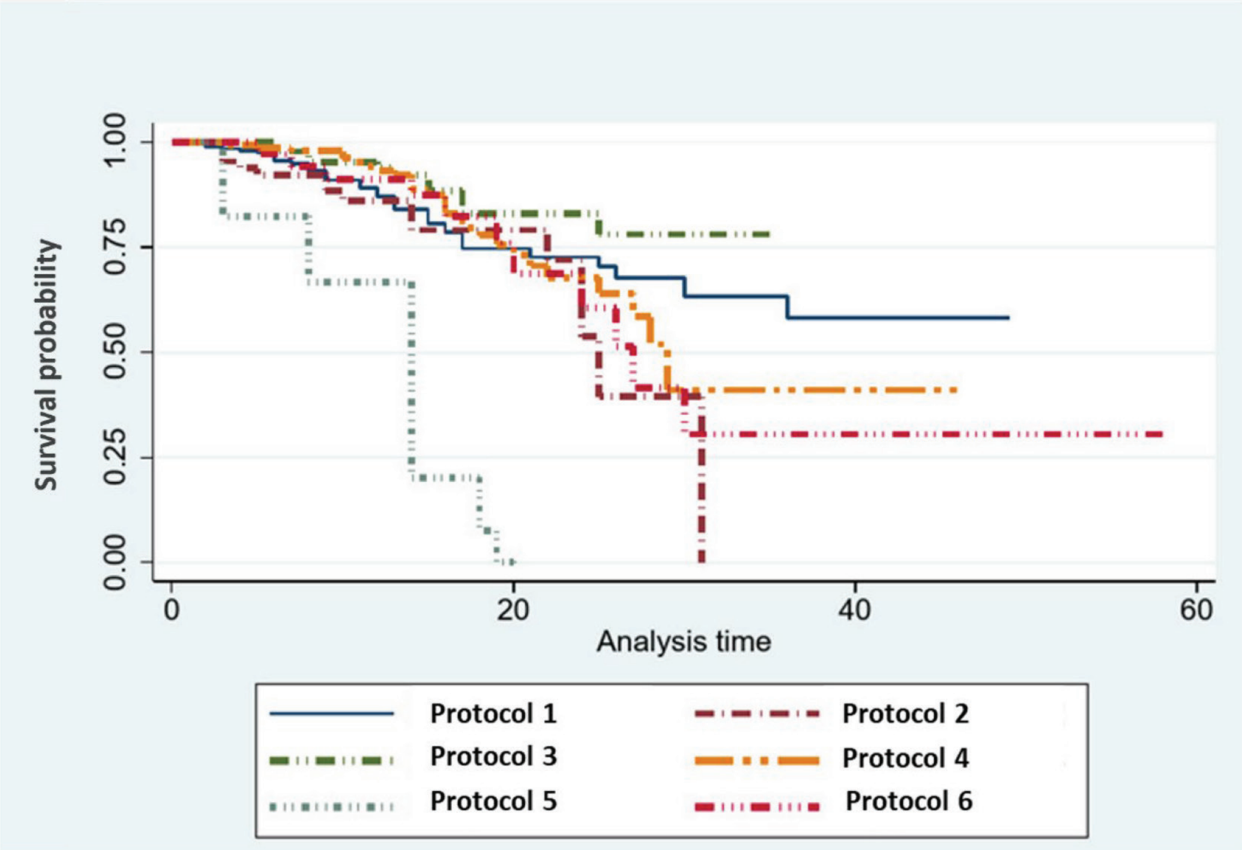

Figure 1: Kaplan-Meier survival curve adjusted for SOFA score

Protocol 1: dexamethasone, protocol 2: methylprednisolone, protocol 3: dexamethasone + methylprednisolone, protocol 4: dexamethasone + remdesivir, protocol 5: methylprednisolone + remdesivir, protocol 6: dexamethasone + methylprednisolone + remdesivir. Analysis time (Days)

Discussion

The findings of this study indicated that the mortality rate was higher among elderly patients, and male patients exhibited a higher severity of the disease compared to females. Our results align with previous literature. Clara Bonad et al. concluded that age significantly influences the mortality rate of Covid-19 patients (14). Mukherjee et al. in 2021 found that the severity of Covid-19 is often greater in men (15). Mohitosh Biswas et al. in 2021 explained that male Covid-19 patients face a higher risk of death compared to females. They also found that patients over 50 years old and those with underlying diseases such as kidney, cerebrovascular, cardiovascular or respiratory diseases, diabetes, high blood pressure, and cancer had a higher risk of death (16).

The primary driver of costs was hoteling, accounting for 45% of the total costs. Health insurance companies reimbursed an average of 84% of hoteling costs and 55% of medication costs. Similar results were obtained in a study conducted by Ghafari in Iran in 2020 (17). However, a study conducted in Shandong hospital, China, found that medication costs represented the largest share of total costs (18). This discrepancy may be attributed to differences in medication costs between countries.

Protocol No. 6 (dexamethasone + methylprednisolone + remdesivir) demonstrated the lowest mortality rate at 43%. However, when considering disease severity (SOFA score) at admission (shown in Table 4), Protocol No. 3 (dexamethasone + methylprednisolone) appeared to be the most effective protocol, with a survival probability of 0.79 and a median length of hospital stay of 17 days. Protocol No. 1 had a survival probability of 0.58 and a median length of hospital stay of 15 days.

The least costly protocol was the dexamethasone protocol (Protocol No. 1), with an average cost of 159,179,444 Rials per patient. The most expensive protocol was the dexamethasone + methylprednisolone + remdesivir protocol (Protocol No. 6), with an average cost of 267,837,319 Rials per patient. The addition of antivirals, particularly remdesivir, significantly increased costs.

Evaluation of the protocols revealed that the administration of injectable corticosteroids, including dexamethasone and methylprednisolone, slightly decreased the mortality rate. Although remdesivir demonstrated a beneficial effect on mortality rate when prescribed alongside a corticosteroid, its administration was not as effective as corticosteroids.

The only statistically significant factor for the mortality rate, according to the performed Cox-regression analysis, was SOFA, which served as a proxy for disease severity. In a retrospective study in Brazil, the survival and direct medical costs of 342 patients admitted in private hospitals with COVID-19 during the first wave were evaluated. In their study 143 (41.8%) patients were admitted to the ICU. The authors reported a mean cost of US$ 7,060,00 per patient (19). Due to the significant differences in medication and services tariffs between the countries, it is not feasible to compare these findings with each other.

In another study in Iran (Shiraz) costs and outcomes of 4 different medications (favipiravir, remdesivir, interferon-β, and Kaletra®) in patients with covid-19 during 2019-2020 were evaluated. The authors estimated drug regimen costs of less than 10 million Rials (333 $PPP) and 35–45 million Rials (1167–1500 $PPP) for 44.2% and 47.7% of the patients, respectively. According to this study, medication regimens had significant effects on the costs and outcomes of treatment. Those who had received Kaletra® (Lopinavir/ritonavir) had the lowest medication costs, while those receiving remdesivir had the highest. Also the patients receiving favipiravir had the shortest hospital stay and lowest mortality, while those receiving remdesivir had the highest mortality and longest hospital stay (6). As the medication regimens in this study included only one medication, it is not possible to straightforwardly compare our results with this study. Also the population of this study included both general and intensive cre units patients (only 9.4% of the patients were ICU-admitted) while our study included ICU patients only.

There are some limitations in this study. Due to the retrospective and cross-sectional nature of this study and the lack of access to patients, it was not possible to assess indirect costs, although according to the perspective of the study, there was no need to calculate indirect costs.

Conclusion

The results of this study indicated that the dexamethasone plus methylprednisolone protocol (protocol No. 3) was the most effective in terms of survival probability. Additionally, this treatment protocol has been found to have one of the lowest average costs per patient. These findings suggest that protocol No. 3 was a favorable option for patients in terms of both efficacy and cost-effectiveness. Considering the differences in the protocols and treatment of covid-19 disease among different hospitals, it is suggested that similar studies be done in other hospitals with a larger sample size for each protocol.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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