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Quantifying the Impact of Treatments on the Recovery of COVID-19 Patients in Twin Cities of Rawalpindi and Islamabad, Pakistan

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus-2. It emerged in Wuhan, China and spread all over the world. Therapeutic effectiveness of different drugs and vaccines used to control the disease has been tested globally. Physicians in Pakistan have also used readily available drugs and antibiotics to combat COVID-19 infection. This study aims to examine the association between the various states of patients (recovered or dead) and different variables including age, gender, and the treatment provided. Lastly, it assesses the odds of recovery of patients corresponding to various treatment groups. The study was conducted retrospectively on patients admitted to major hospitals in the twin cities of Islamabad and Rawalpindi, Pakistan from February 2020 to August 2020. The patients were categorized based on the treatment provided and the medicines prescribed. The sensitivity analysis of the data revealed that the outliers were distorting the results. Therefore, further evaluations were made using non-parametric tests to handle the outliers. Pearson's chi-square test was employed to find the association between the state of patients' recovery corresponding to their age and sex. The results showed no association between the gender of patients and their state of recovery, while the age of patients was found to be related to their state of recovery. Also, a significant association was found between the state of recovery of patients and their prescribed treatment.

Keywords: age, antibiotics, COVID-19, gender, treatment

1. INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic started in late 2019 and it was caused by a newly discovered virus [1, 2]. This virus was named "Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2)" by the International Committee on Taxonomy of Viruses

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(ICTV) on February 11, 2020 [3]. The infection originated from a zoonotic source in Wuhan, China [4]. On January 30, 2020, the World Health Organization (WHO) proclaimed COVID-19 an international public health emergency and on March 11, 2020, it declared SARS-CoV-2 a global pandemic [4, 5]. On February 5, 2021, WHO reported 105.74 million cases of COVID-19 worldwide, including 2.3 million deaths [6, 7].

SARS-CoV-2 is a novel, encapsulated, non-segmented, single-stranded positive-sense RNA (+ssRNA) virus that belongs to the family Coronaviridae [8–10]. It is transmitted through the aerosols and droplets coming out of the respiratory tract of the infected person [11]. This condition is characterized by various symptoms, from minor flu-like symptoms to pneumonia or Acute Respiratory Distress Syndrome (ARDS), Severe Acute Respiratory Syndrome (SARS), and mortality [2, 12]. The previous coronavirus epidemics, such as Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS), caused 813 and 858 deaths, respectively; COVID-19, on the other hand, has had a high mortality rate [13, 14].

Since the emergence of SARS-CoV-2, scientists have tested different drugs, developed vaccines, and conducted studies to determine the efficacy of therapies in controlling the pandemic and lowering the fatality rate [15]. In this regard, several antimicrobials have been investigated [16]. Antiviral, antibiotic, antiparasitic, and anti-inflammatory drugs have been employed, while other therapeutics include convalescent plasma therapy, interferon therapy, oligonucleotide-based therapies, mesenchymal stem cell therapy, hyper immunoglobulin and RNA interference [17, 18]. International clinical trials have been conducted to evaluate the effect of drugs, including certain antibiotics [19]. Antibiotics such as azithromycin, rapamycin, quercetin, and doxycycline have been proposed for treating COVID-19 [20]. In COVID-19 therapy, however, the combination of azithromycin and hydroxychloroquine appears to be significantly more effective [16, 21]. Replication of other viruses, including Zika and Ebola, have also been inhibited by azithromycin [20, 22]. Antibiotics such as azithromycin, rapamycin, and doxycycline suppress viral replication and protein synthesis [20]. Inhibiting virus production should aid in reducing virus transmission to other patients [23]. Even though antibiotics and other therapies have been used against COVID-19, their effectiveness in treating the disease is debatable [24]. At the same time, the alarming speed with which antibiotics have been used can eventually result in antibiotic resistance in human population [24, 25]. These antibiotics are commonly used to treat pneumonia, upper respiratory tract infections, and other diseases caused by opportunistic microorganisms. Since azithromycin is a broad-spectrum antibiotic, it is commonly used to treat chest infections, such as pneumonia, which is also a symptom of COVID-19 infection [26].

2. MATERIAL AND METHODS

The current retrospective study was conducted in selected hospitals (Pakistan Air Force Hospital, Pakistan Institute of Medical Sciences, Holy Family Hospital, and Benazir Bhutto Shaheed Hospital) of the twin cities of Islamabad and Rawalpindi, Pakistan from February 2020 to August 2020. Clinical data of 1,812 patients diagnosed with the first variant of COVID-19 (confirmed case using PCR test on nasal and oropharyngeal swab sample) were collected with the approval of the

National Institute of Health, Pakistan. The data were collected systematically using a standardized data collection form including detailed medical information about the patient's age (varying between 5 months and 97 years), sex, date of admission and discharge (or death), medical history, presenting signs and symptoms, initial categorization of COVID-19 (mild, moderate, severe, and critical), and types of therapeutic agents (including but not limited to the use of antibiotics, antimalarial, antivirals, antiparasitics, anticoagulants, and corticosteroids) used for the treatment and management of the disease during their hospital stay. According to the recorded data, among 1,812 patients, 1,343 patients in total recovered from COVID-19.

The methodology of the current study was designed to examine the association between patients' state of recovery and their age and sex. It was also designed to determine the association between treatment groups and the patients' state of recovery. Additionally, the odds of the recovery of patients corresponding to various treatment groups were assessed. Pearson's Chi-Square test was used to analyze the association between the variables mentioned above. In order to compare age with the state of patients, groups of patients were created with an interval of 10 years, such as 20-29 years, 30-39 years, 40-49 years, 50-59 years, ≥60 years. The only exception was the first age group composed with an interval of 20 years. The reason was the small number of infected individuals in the age group 0-9 in comparison to other age groups.

The medicines administered to the patients included cough syrup, Panadol, antibiotics, corticosteroids, and anticoagulants. The antibiotics prescribed were azithromycin, ceftriaxone, tienam, tanzo, moxifloxacin, cefixime, levofloxacin, vancomycin, clarithromycin, and meranun. The corticosteroids used were solocartif, depo-medrol, and dexa injection. The anticoagulants used included methylprednisolone, clexane, and heparin. The patients were categorized based on the type of treatment they received during their stay in the hospital. The following treatment groups were formed for further investigation: 1. Cough syrup with Panadol, 2. Antibiotics, 3. Steroids, 4. Cough syrup with Panadol and antibiotics, 5. Cough syrup with Panadol, antibiotics, and steroids, 6. Cough Syrup with Panadol and steroids, and 7. Antibiotics and steroids.

It was found that the distribution of patients among these groups, based on dosage or treatment given, was not uniform. There were as low as four patients and as high as more than a thousand patients in a single group. Furthermore, using the Kolmogorov Smirnov test, it was found that the data were not normally distributed for all groups, rather some were not heavily skewed. Further examination revealed that the data contained outliers, negatively affecting the results. A sensitivity analysis test was performed in this regard and it was found that the outliers distorted the results. Pearson's chi-square test was used to test the association between the variables. All the analysis was carried out using the IBM SPSS Version 25. The significance level was taken as 0.05 for all the tests.

3. RESULTS

3.1. Association between Age Groups and the State of Recovery

The recovery time of patients was analyzed as corresponding to their age. It was found that the two variables are (slightly to moderately) positively correlated with the Pearson's correlation

coefficient of 0.236. Furthermore, the state of patients (recovered or dead) was analyzed as corresponding to different age groups. Visual representation of different age groups among the recovered and dead states of patients is shown in Figure 1. It can be observed that the count of dead patients aged 60 or more is far higher than the other age groups, while the number of recovered patients is higher in the age group 30-39. A significant association was found between these two variables which shows that the variable age does affect the recovery or death of the patients.

3.2. Association between Sex and the State of Recovery

The state of patients (recovered or dead) was analyzed corresponding to the sex of patients (male and female). It was found that no strong association exists between these two variables. However, according to the data, the number of recovered male patients was higher than that of female patients (Figure 2).

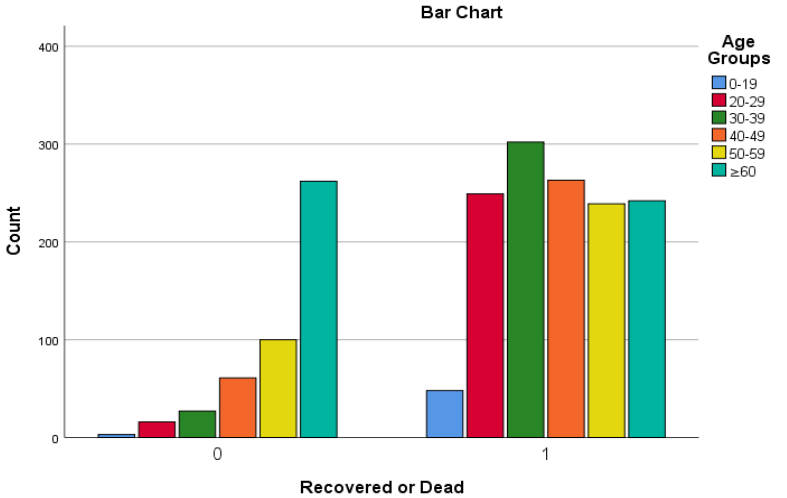

Figure 1. Number of the Dead (Represented by 0) and Recovered (Represented by 1) patients Corresponding to Different Age Groups

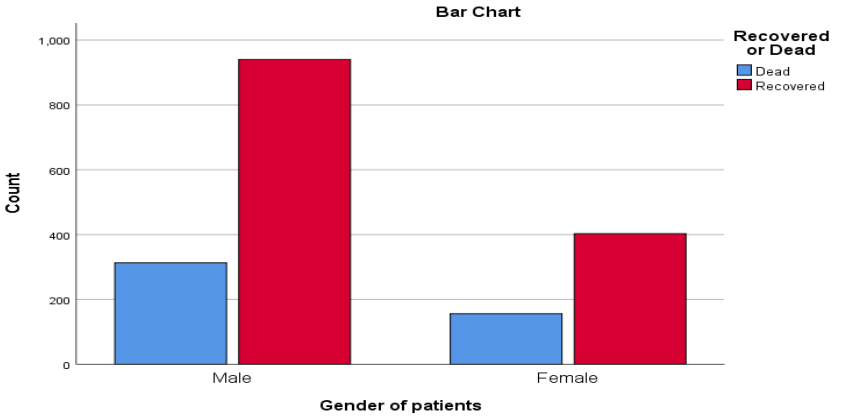

Figure 2. Division of Recovered and dead Patients Based on their Gender

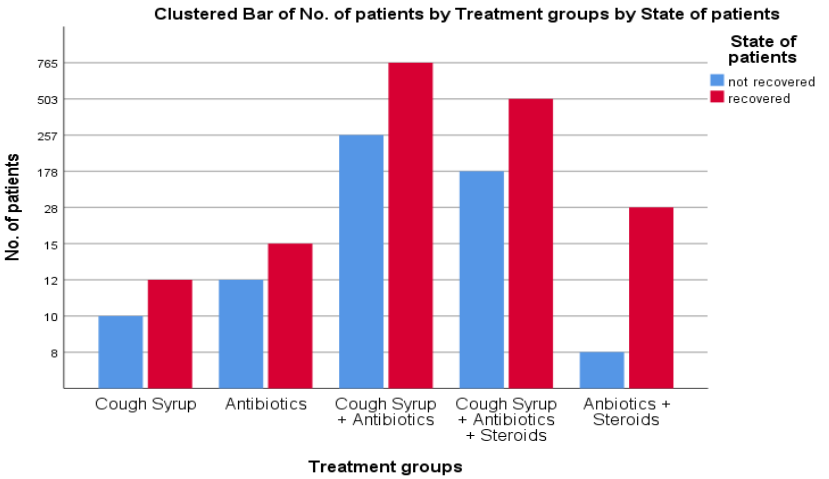

Figure 3. Number of Recovered and Dead Patients in Different Treatment Groups

3.3. Association between Treatment Groups and the State of Recovery

The state of recovery of patients was analyzed corresponding to the different treatment groups given to the patients. Due to the small (less than 5) number of patients in treatment groups 2 and 3, these were excluded from further analysis. It was found that a significant association exists between the state of recovery (recovered or dead) and treatment groups (Figure 3), although because of the *p*-value 0.045 the strength of this association cannot be considered robust.

3.4. Odds Ratio for Treatment Groups

Odds ratios were calculated for the treatment groups corresponding to the state of recovery of patients (recovered or dead). Treatment group 1 was found to have 41.4% odds of recovery (cough syrup with Panadol) against the corresponding untreated group, while treatment group 4 was found to have 43% odds of recovery

(cough syrup with Panadol and antibiotics) against the corresponding untreated group. Furthermore, it was determined that there were no significant odds of recovery for the treatment groups 5 (cough syrup with Panadol, antibiotics, and steroids), 6 (cough syrup with Panadol and steroids), and 7 (antibiotics with steroids) against the corresponding untreated groups.

4. DISCUSSION

COVID-19 was declared a pandemic in early 2020 after its emergence in Wuhan, China [1]. Since then, it has spread and infected all age groups irrespective of gender. At the time of its emergence, there was no treatment available for this new virus (SARS-CoV2), so different available treatments were tested. Pakistan is also on the list of the countries affected by COVID-19. This study reports the data collected during the first wave of COVID-19 (in the year 2020) from different hospitals situated in the twin cities of Rawalpindi and Islamabad, Pakistan. Different parameters were utilized including different treatment groups, age, sex, and the recovery state of patients to analyze the data. Furthermore, it was observed that the count of dead patients in the age group 60 or more was far higher than the other age groups. While, the number of recovered patients was higher in the age group 30-39.

Scientists have performed several comparable experiments to determine the association between patient age and recovery duration. In a study conducted in India by Manash Pratim on 221 patients with COVID-19, it was observed that the average recovery time of 60-year-old patients is 25 days, while for patients below 60 years of age it is 21 days [27]. Seyed Ahmad and colleagues carried out another cross-sectional study on a total of 478 COVID-19 patients in Tehran [28]. A bivariate analysis was performed between demographic and clinical findings and the prolonged recovery period. The results showed that 49% of patients aged less than or equal to 50 years recovered in less than 14 days, while 37.1% took more than 15 days to recover. For patients over 50 years of age, the results showed that 51.0% recovered in less than or equal to 14 days and 62.9% recovered in more than or equal to 15 days. The above findings demonstrate a substantial relationship between the age of patients and the time it takes for them to recover. Also, the findings of prior studies corroborate the current findings, implying a link between age and recovery time.

Another important demographic factor that was tested to find its co-relevance with patients' recovery time was the sex of patients. The results showed no significant difference between the groups of male and female patients. However, when the total number of recovered patients was compared, it was found that male patients outnumbered the female ones. Several studies assessing the effect of multiple factors on recovery time have been carried out by different scientists on COVID-19 patients. Reaz Mahmud carried out a cohort study in a tertiary care hospital in Bangladesh on 355 patients [29]. The results showed that female sex is one of the critical factors in developing the post-COVID-19 syndrome. Another study analyzing the effects of age and sex on recovery from COVID-19 was conducted on a dataset of 5,769 recovered Israeli patients [30]. The results showed that male and female patients aged >30 years had significantly more extended recovery periods than younger patients. This suggested that younger individuals recover faster regardless of their sex.

The results of the current study suggest that the state of patients is not robustly

related with the treatment they are provided. Although, statistics show that the groups treated with cough syrup and antibiotics had more recovered patients in this study than any other group. Similar studies have been carried out to test the effects of different antibiotics, antivirals, and steroids on COVID-19 patients. Maria Ines Mitrani and colleagues carried out a study that tested the administration of amniotic fluid-derived nanoparticles in three severely ill COVID-19 patients. They administered Zofin to the patients. Zofin is an acellular biologic therapeutic derived from perinatal sources. The results showed improvements in Intensive Care Unit (ICU), clinical status, and respiratory systems after the administration of Zofin. Shio-Shin Jean and colleagues reviewed the different treatment options for COVID-19 patients. They concluded that a combination of hydroxychloroquine and azithromycin showed excellent cynical efficacy in Chinese patients. Another study conducted by Mukkaram Jamat Ali and colleagues also reviewed the different treatment options for COVID-19. They found different antimicrobial agents to be more effective in treating the disease. The tested treatment showed that remdesivir, lopinavir/ritonavir, favipiravir, ribavirin, immunoglobulin, and corticosteroids are associated with a shorter recovery time [31].

Statistically, the odds ratio quantifies the strength of the association between any two events. Chi-Square test was applied to the data, followed by risk estimation to evaluate the odds ratio. Treatment 1 consisted of the administration of cough syrup along with Panadol. Treatment 1 was given to 22 people, of which 12 recovered and 10 showed none or a very insignificant recovery rate. On the other hand, Treatment 1 was not given to 1,790 patients, of which 1331 recovered and 456 died. The odds ratio was calculated for treatment group one, corresponding to the state of recovery of patients (recovered or not recovered). After risk estimation, treatment group 1 was found to have a 41.4% chance of recovery as an untreated group. Treatment 2 involved the administration of cough syrup with Panadol and antibiotics to the patients. Treatment 2 was administered to 27 patients, of which 15 recovered and 12 did not recover or showed no response to the administered medicine. Meanwhile, 1,785 patients were not given Treatment 2, of which 1,328 recovered. The odds ratio was calculated for treatment group two, corresponding to the state of recovery of patients (recovered or not recovered). It was calculated that there were 43% odds of recovery against the corresponding untreated group. Treatment 3 included administering cough syrup with Panadol, antibiotics, and steroids to the patients. This treatment was administered to 1,022 patients, of which 765 recovered and 527 did not show any recovery. This treatment was not given to 790 patients, of which 578 recovered and 212 showed no recovery. The odds ratio was calculated for treatment group three, corresponding to the state of recovery of patients (recovered or not recovered). No significant odds of recovery were determined against the corresponding untreated group. Treatment 4 included cough syrup with Panadol and steroids, given to 681 patients in total, of which 503 patients recovered and 178 showed no recovery. This treatment was not given to 1131 patients, of which 840 recovered and 291 showed no recovery. Risk estimations to calculate the odds ratio showed no significant odds of recovery against the corresponding untreated group. Treatment 5 included antibiotics with steroids. This treatment was administered to 36 patients, of which 28 recovered and 8 showed no

recovery. On the other hand, 1,776 patients were not given this treatment, of which 1,315 recovered and 461 showed no recovery. Risk estimation with 95% confidence interval was used to calculate the odds ratio for treatment group 5, corresponding to the state of recovery of patients. Significant odds of recovery were determined against the corresponding untreated group.

4.1. Conclusion

The COVID-19 patient data was analyzed to check the efficacy of different variables such as age, sex, treatment groups, and the state of patients (recovered or dead). The current study implies that the older age groups have a lower tendency to recover from infection caused by COVID-19, neglecting the factor of sex because no significance association was noted between the recovery rates of different sexes, though a higher number of male patients recovered than female patients, considering the fact that male infected individuals outnumbered female individuals. Cough syrup, Panadol, and antibiotics proved their effectiveness in comparison with other treatment groups under study. However, there is a need to investigate antibiotics accompanied by randomized clinical trials to provide the most reliable evidence on the effectiveness of these pharmaceutical products.

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