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BRIEF REPORT

A novel approach to managing COVID-19 patients; results of lopinavir plus doxycycline cohort

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Abstract

This manuscript aims to present a treatment algorithm we applied to manage COVID-19 patients admitted to our hospital. During the study period, 2043 patients with suspected COVID-19 were admitted to the emergency department. Molecular tests indicated that 475 of these patients tested positive for COVID-19. We administered hydroxychloroquine plus doxycycline to mild cases (isolated at home) for 3 days and lopinavir plus doxycycline to moderate and severe cases (hospitalized) for 5 days. The overall case fatality rate was 4.2% (20/475).

Keywords Doxycycline · Favipiravir · Lopinavir · Hydroxychloroquine · COVID-19

Introduction

Since the first report in December 2019 from Wuhan, Hubei Province, China, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread quickly worldwide [1]. Available data indicate that the clinical course and outcome of SARS-CoV-2 are much milder than those of SARS-CoV and MERS-CoV [2]. However, the socioeconomic consequences of the SARS-CoV-2 pandemic are enormous [3]. The false news regarding the clinical course and fatality rates triggered a global panic epidemic which has spread even faster than the virus. Social panic has the potential to accelerate the expected health burden of the disease [4].

Social panic causes excess inpatient capacity in hospitals as the number of individuals with mild nonspecific symptoms has been increasingly hospitalized. Controlling adverse outcomes of the disease and the panic among the public and healthcare staff depends on running an effective triage and management algorithm.

This manuscript aims to present a treatment algorithm we applied to manage COVID-19 patients admitted to our hospital and describe the characteristics of COVID-19 patients and the outcomes of the algorithm. This single-center, retrospective observational study was conducted in the Istanbul Medeniyet University Goztepe EA Hospital, a 600-bed affiliated hospital located in the Anatolian side of Istanbul. We

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obtained ethical approval from the Institute Ethics Committee, and signed informed consent was waived (2020/0193).

A case was defined as a patient with an epidemiologic risk factor who had body temperature of ≥ 38 °C and/or respiratory system symptoms which cannot be fully explained by any other condition or disease (based on WHO approach). A mild case was defined to have no signs of respiratory dysfunctions, while a moderate case had any sign of respiratory dysfunction, and a severe case had acute respiratory failure (ARF) and required ICU support either via invasive or noninvasive means. Noninvasive ventilation support was administered with high-flow masks. Respiratory dysfunction was assessed in a patient having any of the following: (a) shortness of breath, (b) respiration rate of > 23 breaths per minute, and (c) O_2 saturation < 94 in ambient air.

Hydroxychloroquine 200 mg, lopinavir 400 mg, and doxycycline 100 mg were all orally administered twice daily as recommended.

We managed COVID-19 patients with a 3-step treatment approach in our institute. First, mild cases were isolated at home and prescribed with hydroxychloroquine plus doxycycline for 3 days. Second, moderate to severe cases were hospitalized and prescribed with a regimen of lopinavir plus doxycycline plus ceftriaxone for 5 days. Third, we used a salvage therapy for patients who did not respond to or whose conditions worsened under the lopinavir treatment. This therapy involved the oral administration of favipiravir 1600 mg twice daily after two loading doses.

We performed all statistical analysis using the open-source R software (R Foundation for Statistical Computing, Vienna, Austria) [5–7].

Results and discussion

From March 22 to April 22, 2020, 2043 patients were admitted to our emergency department, presenting symptoms compatible with those stated in our case definition. PCR was positive for nasopharyngeal samples of 475 adult patients. We run a 3-step treatment algorithm, and our approach is displayed in Fig. 1. We hospitalized moderate to severe cases and administered lopinavir combined with doxycycline and ceftriaxone to 343 patients, among whom 161 had positive PCR test results (161/343, 46.9%). Unfortunately our lab ceased respiratory viral PCR panels and allocated all resources to SARS-CoV-2 PCR test during the study time. Therefore, we could not identify other causes and diagnosed COVID-19 PCR negative patients as viral respiratory tract infection of unknown etiology.

We followed 1700 mild cases under the treatment with hydroxychloroquine plus doxycycline at home. Besides, 314 patients isolated at home were found to have positive PCR test results (314/1700, 18.5%). PCR results were mostly available within 48 h, and patients with positive PCR test results were further followed by filiation teams of the Turkish Health Ministry. Filiation teams provided them with a 5-day course of hydroxychloroquine. Twenty-three of all patients treated at home were readmitted to the hospital because their initial symptoms worsened, and we administered lopinavir plus doxycycline. If these patients do not respond in 48 h, we instituted favipiravir treatment.

The overall case fatality rate was 4.2% (20/475). Two out of 268 patients aged < 50 years died (0.7%), one of whom was under treatment for acute lymphoblastic leukemia. The other patient had an unidentified muscle disease affecting the respiratory muscles [8]. There were three deaths among those aged 50–65 years (3/127, 2%) and 15 deaths among those aged > 65 years (15/80, 18.8%).

Figure 2 presents the daily incidence of PCR positive and negative patients. The burden of social panic is barely visible in this figure. Most patients had subjective symptoms yet inquired attention; therefore, time, effort, and care should be taken to relieve these patients. In other words, if not correctly managed, this panic had the potential to consume hospital resources reserved for severe patients.

Table 1 presents the baseline characteristics of PCR positive hospitalized patients. We administered our standard regimen, lopinavir plus doxycycline plus ceftriaxone, to these hospitalized patients. Among 161 cases, 31 required ICU support, and 20 deceased during ICU stay. However, 12 of these patients were severe at admittance. Of these nine patients immediately admitted to the ICU, five of whom died. Three other patients transferred to the ICU on the second day of admittance to the hospital also died.

Of the 161 hospitalized patients, 149 acquired lopinavir for at least 2 days before being admitted to the ICU. Only 12.7% (19/149) required ICU support with lopinavir treatment, two patients suddenly died, and 128 patients recovered from the disease.

Only 24% (38/158) of patients had a fever (≥ 38 °C). Deceased patients were older, had a higher prevalence of hypertension, and had a higher neutrophil counts than the others, while their lymphocyte counts, platelet counts, and levels of oxygen saturation in ambient air were lower. No difference was observed between two genders. Deceased patients had shorter elapsed time between the onset of symptoms and hospitalization.

This study presents a 3-step treatment protocol to manage COVID-19 patients. We administered hydroxychloroquine to mild cases isolated at home, lopinavir plus doxycycline to hospitalized moderate to severe cases, and favipiravir in the salvage treatment. We were able to run this approach smoothly.

To our best knowledge, this study is the very first to report data from Istanbul, Turkey. More importantly, our data present the results of a unique combination of lopinavir and doxycycline.

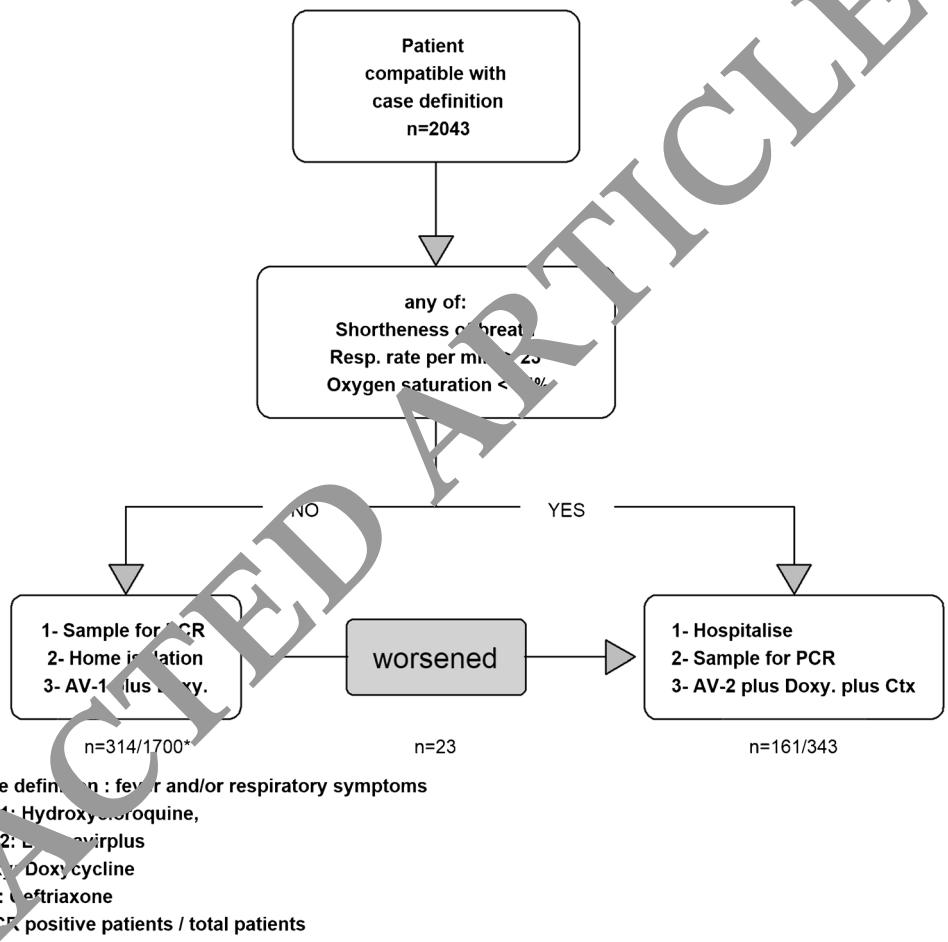

Fig. 1 The algorithm we applied in emergency department to manage outpatients with COVID-19

We, administered hydroxychloroquine to mild cases for only 3 days because of its potential side effects on cardiac functions [9]. The cardiac effects of hydroxychloroquine are demonstrated to depend on the accumulation of the drug and mostly start on the third day of the usage. These effects are more prominent among critically ill patients [10].

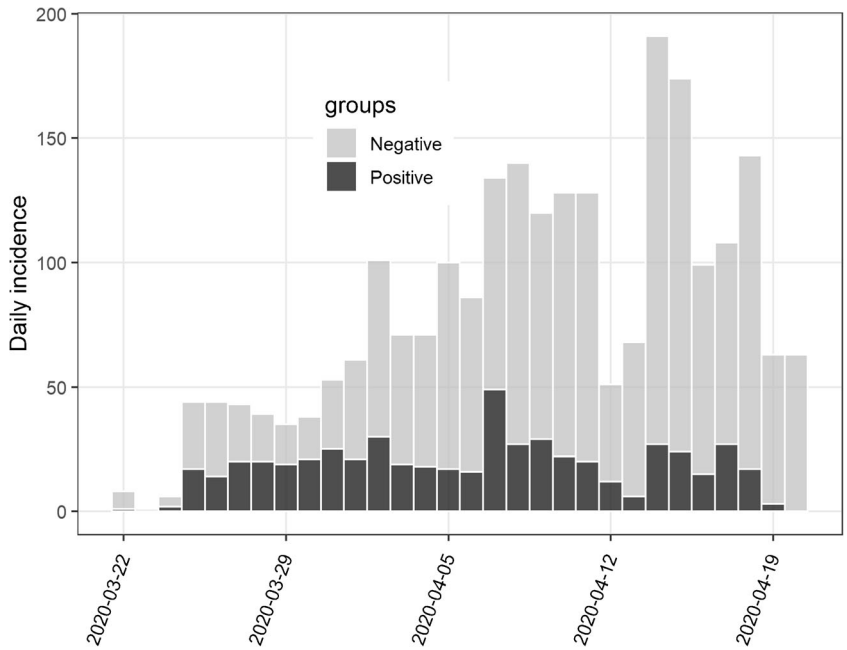

Fig. 2 The epidemic curve showing PCR negative and positive patients. It is noteworthy that the number of PCR positive patients decreases over time, but due to the ongoing fear in the population, the number of PCR negative patients do not decrease proportionally

Table 1 Baseline descriptive parameters of PCR positive hospitalized patients

Factors[1]	All *N= 161*	Survived *N= 141*	Died *N= 20*	*p*	N
Female gender	77 (47.8%)	67 (47.5%)	10 (50.0%)	1.000	161
Age (years)	61.0 [48.0;72.0]	59.0 [48.0;70.0]	74.5 [67.5;85.5]	< 0.001	161
Hypertension	57 (35.4%)	43 (30.5%)	14 (70.0%)	0.00	161
Diabetes	32 (20.6%)	26 (19.1%)	6 (31.6%)	0.230	155
ACEI: yes	32 (20.6%)	26 (19.1%)	6 (31.6%)	0.23	155
Elapsed time to ICU (days)	3.00 [0.00; 6.00]	3.00 [0.00; 6.00]	3.00 [0.50; 5.7]	0.984	31
Hospital stay (days)	2.00 [1.00; 5.00]	3.00 [1.00; 5.00]	1.50 [1.00; 9.25]	0.966	161
WBC ($\times 10^9$/L)	6.15 [4.80; 7.80]	6.10 [4.70; 7.65]	7.03 [5.40; 11.]	0.080	158
PLT ($\times 10^9$/L)	180 [138; 234]	181 [145; 236]	46 [1 ;]	0.104	158
EOS ($\times 10^9$/L)	0.01 [0.00; 0.03]	0.01 [0.00; 0.03]	0.0 [0.00; 0.03]	0.285	158
NEUT ($\times 10^9$/L)	4.44 [3.05; 5.67]	4.26 [2.89; 5.]	5.28 [4.43; 8.14]	0.007	158
LYM ($\times 10^9$/L)	1.20 [0.90; 1.60]	1.20 [1.00; 1.69]	0.90 [0.70; 1.30]	0.029	158
pH[2]	7.42 [7.38; 7.45]	7. [7. ; 7.44]	7.44 [7.41; 7.47]	0.061	138
pO_2	35.8 [25.8; 48.4]	34.9 [.4; 47.4]	38.2 [31.9; 56.2]	0.212	142
pCO_2	44.8 [40.0; 48.]	44.8 [40. ; 48.7]	43.0 [35.3; 47.8]	0.273	143
Temperature	37.0 [36.6; 37.9]	36.6; 37.7]	37.5 [36.9; 38.3]	0.085	158
High fever (≥ 38 °C)	38 (24.1%)	30 (21.4%)	8 (44.4%)	0.042	158
O_2 saturation	95.0 [.0; 96.0]	95.0 [93.0; 96.0]	88.0 [85.5; 94.0]	< 0.001	159
Respiration rate per min	1.0 [20.0; 25.0]	21.0 [20.0; 24.2]	22.0 [20.0; 26.0]	0.407	149
Elapsed time to hospitalization	5.0 [3.00; 7.00]	6.00 [3.00; 8.00]	4.00 [2.00;5.50]	0.015	152
Intubated	27 (16. %)	10 (7.09%)	17 (85.0%)	< 0.001	161

[1] ACE inhibitor, angiotensin converting enzyme inhibitor; elapsed time to ICU, time between hospitalization and ICU admission; O_2 saturation, saturation in ambient air; high fever, fever ≥ 38 °C; elapsed time to hosp., time between onset of symptoms and hospitalization

[2] Blood gases were mostly obtained during hospital stay not at admission

We administered lopinavir to moderate to severe cases for 5 days. Clinical trials demonstrated its effectiveness in the treatment of patients with SARS and MERS [11]. Molecular analysis indicates that lopinavir has a potential role in inhibiting SARS-CoV-2 protease, thereby blocking viral replication [12]. A recent study found a limited benefit of lopinavir compared with the standard of care treatment [13]. However, this study had substantial methodologic limitations, which raises questions about its conclusions.

We supplemented doxycycline to both lopinavir and hydroxychloroquine due to its immunomodulatory activity. Recent findings revealed the adverse effect of dysregulated immunity on the outcome of COVID-19 patients [14]. Doxycycline induces the suppressor of cytokine signaling (SOCS) proteins, a regulatory system on cytokine release [15]. Evidence accumulates that SOCS proteins, mainly SOCS-3 protein, prevent interleukin- and interferon-associated toxicity [16]. Notably, in the early stage of the disease, when there are enough healthy cells in the bronchi and alveoli, doxycycline might have some effect on preventing the upcoming cytokine storm. Doxycycline had been successfully used in dengue hemorrhagic fever due to its immunomodulatory activity [17]. However, we also consider covering other etiologies of community-acquired pneumonia. At admission, it is challenging to differentiate COVID-19 from other etiologies of pneumoniae, such as mycoplasma infections [18].

However, the study has several limitations which require to be addressed. The major limitation of this study lies in its retrospective and single-center nature which is a source of selection bias to evaluate the efficacy of a treatment. In our study, a considerable number of died patients were extremely severe at admittance and so directly allocated to ICU care.

A 3-step treatment algorithm ran smoothly in our hospital. We concluded that home isolation of mild cases is an effective means to manage the burden of disease, while lopinavir plus doxycycline is an alternative to current treatment regimens for COVID-19. However, in future epidemics, isolation of mild cases at new-settled fever clinics should be considered which might serve better to mitigate epidemics [19].

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethics approval The study protocol was approved by the Clinical Research Ethics Committee of Istanbul Medeniyet University Goztepe Training and Research Hospital, and signed informed consent was waived (2020/0193).

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