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Original Research

Assessment and management of the SARS-CoV-2 infection: A secondary center experience

Approach to COVID-19 infection

Ahmet Cem Yardımcı[1], Erdem Ergen[2], Elif Ergene[5], Yasemin Seckın Guner[3], Muzaffer Karnap[3], Hatice Ballı[1], Duygu Demırbas Keskın[4], Hulya Yuksel[4], Fusun Bocutoglu[5], Veysel Celal Akbel[2], Serkan Yıldız[6], Derya Kalyoncu[7]
[1] Department of Infectious Diseases and Clinical Microbiology
[2] Depatment of Ophthalmology
[3] Department of Internal Medicine
[4] Department of Otorhinolaryngology
[5] Department of Obstetrics and Gynecology
[6] Department of Urology
[7] Department of Pediatrics, Istinye State Hospital, Istanbul, Turkey

Abstract
Aim: The aim of the study was to evaluate the management and outcomes of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a secondary hospital.
Material and Methods: This study included 699 hospitalized patients who had positive rRT-PCR for SARS-CoV-2 and/or typical findings of COVID-19 on chest computed tomography (CT). Demographics, comorbidities, initial laboratory tests on admission, treatment modalities, complications and outcomes were evaluated retrospectively.
Results: The mean age was 57.0±15.6 (range:16-94 years), and male to female ratio was 1.24; 58.7% of the patients had at least one underlying comorbidity, the most common was hypertension; 18.1% of the patients had lymphopenia, 35.7% hyperferritinemia, 58.3% had increased lactate dehydrogenase, and 58.5% had increased D-dimer. Chest CT revealed moderate and severe stages in 57.9% of the patients. Hydroxychloroquine was given to 37.2% and favipiravir to 67.1% of the patients. No significant difference was observed between treatment groups in terms of mortality (P=0.487); 5.8% of the patients were transferred to the ICU, 75.6% of whom needed non-invasive and 36.5% invasive mechanical ventilation. The overall case-fatality rate was 0.9.
Discussion: Older age, male gender, low lymphocyte count, CT findings, including bilateral involvement and severe stage were significantly associated with poor prognosis and mortality.

Keywords
Adults, COVID-19, Outcome, SARS-CoV-2, Treatment

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Corresponding Author: Ahmet Cem Yardimcı, Istinye State Hospital, Istinye Street, No:98, 34465, Sariyer, Istanbul, Turkey.
E-mail: cemyardimci@gmail.com P: +90 212 323 44 44 / +90 506 336 98 71 F: +90 212 323 44 44
Corresponding Author ORCID ID: https://orcid.org/0000-0002-4727-3239

Introduction

The World Health Organization (WHO) designated coronavirus disease 2019 (COVID-19) in February 2020, declared it a pandemic on March 11, 2020. The clinical spectrum of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is wide-ranging from asymptomatic infection, mild upper respiratory tract illness, and pneumonia to life-threatening severe disease, even death [1-3].

To our knowledge, no previous studies have been conducted among patients with COVID-19 in secondary hospitals of our country. Here, we present clinical assessment, management and outcomes of the patients with SARS-CoV-2 infection in a secondary hospital.

Material and Methods

11,392 real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) tests were taken from the patients who admitted with suspicious symptoms or signs of COVID-19 to the emergency department of a secondary hospital in Istanbul between March 31 and May 30, 2020 and September 1 and December 31, 2020. 2448 of rRT-PCR tests were positive and 8670 were negative. A total of 699 patients who had positive rRT-PCR for SARS-CoV-2 and/or typical findings of COVID-19 at chest computed tomography (CT) were hospitalized and involved in this retrospective observational study. Three wards with 43 beds, and 6 beds in the intensive care unit (ICU) were reserved for COVID-19 patients.

Demographics, comorbidities, medications, triage vitals, symptoms and signs on admission, initial laboratory tests, PCR results, inpatient treatment, complications and outcomes were extracted retrospectively from electronic medical records.

Oropharyngeal and nasopharyngeal swab samples were taken from all of the patients at the emergency department before hospitalization and were transferred to a laboratory authorized by the Ministry of Health Public Health Office. rRT-PCR tests for SARS-CoV-2 were performed using Biospeedy COVID-19 RT-qPCR Detection Kits (Bioksen, Istanbul, Turkey).

All of the patients underwent routine blood examinations as complete blood count, biochemical tests, lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, D-dimer on admission. Cardiac enzymes, procalcitonin (PCT) and fibrinogen were tested if clinically indicated. Chest CT scan was also performed in every patient on admission.

The diagnosis of COVID 19 disease was based on the WHO guidance and the New Coronavirus Pneumonia Prevention and Control Program (fifth edition) published by the National Health Commission of China. Acccording to clinical features on admission, the patients were classified as mild, moderate, severe and critical cases. CT findings were classified as; 0: Normal, 1: Mild (ground-glass opacity and consolidation, lesions can be single or multiple and may de located in both lung lobes), 2: Moderate (large lesions in more than one lobe in both lungs, various sizes of consolidation and fibrosis), 3: Severe (lesions are diffuse in both lungs and in different density, white lung sign due to involvement of large areas of lung) [4]. Patients with oxygen saturation rate ≤ 93% were given oxygen support by nasal cannula or face masks. The standard treatment protocol recommended by the National Ministry of Health Public Health Office included oral oseltamivir (Tamiflu®) 2x75 mg/day due to the inability to rule out seasonal influenza, oral hydroxychloroquine (Plaquenil®) 2x400 mg loading dose and 2x200 mg/day maintenance dose and oral azithromycin 1x500 loading dose and 1x250 mg/day maintenance dose for 5 days during the first wave of the outbreak. Routine electrocardiography was performed before the initiation of treatment to rule out QT interval prolongation. If no improvement was observed, oral favipiravir or lopinavir 200 mg/ritonavir 50 mg (Kaletra®) 2x2 was initiated. Favipiravir (Favicovir®) was given at a loading dose of 2x1600 mg and 2x600 mg/day maintenance dose, and especially was preferred in the second wave. Additionally, vitamin C (1x3 gr) was used.

Later in the outbreak, low molecular weight heparin (LMWH), as Enoxaparin, was started according to body mass index (BMI< 40/kg/m2 1x40 mg/day, and BMI > 40/kg/m2 2x40 mg/day subcutaneously) to prevent venous thromboembolism. If creatinine clearance (CrCl)< 30 ml/min, standard dose of heparin (5000 U 2x1 or 3x1/day, subcutaneously) was recommended by National Ministry of Health guidelines. Methylprednisolone 40-80 mg/day intravenously was also added to the treatment protocol. If no response was observed with CS and signs of macrophage activation syndrome (MAS), including persistent fever, continuously increasing CRP, ferritin (> 700 µg/L), and D-dimer levels, lymphopenia, thrombocytopenia, neutrophilia and deterioration of liver function tests were detected, tocilizumab (Actemra®) 1x200-400 mg was administered.

Patients who clinically decompensated (tachypnea respiratory rate>30/min, dyspnea, refractory hypoxemia, hypotension) and had decreased oxygen saturation rate (<90%) despite treatment, oxygen support, and prone positioning were transferred to ICU.

The study protocol was approved by the local ethics committee (No:2/2021.K-08).

Statistical analysis

Statistical analysis was performed using SPSS 15.0 software (SPSS Inc, Chicago,IL,U.S.A.). Results were expressed as numbers and percentages for categorical variables and means ± SD, minimum and maximum for numerical variables. The analysis was conducted using the chi-square test. As the numerical variables did not meet the normal distribution, comparisons between two independent groups were made using the Mann-Whitney U test. P- values of <0.05 were considered statistically significant.

Results

The mean age of 699 patients was 57.0±15.6 (range:16-94 years), and male to female ratio was 1.24. The median duration of hospitalization was 6.4±4.8 days, significantly higher in patients with both diabetes mellitus (DM) and hypertension (HT) than in other patients (P=.003).

Overall, 58.7% of the patients had at least one underlying comorbidity. The most common comorbidity was HT, followed by DM, cardiovascular disease, asthma and chronic obstructive pulmonary disease (COPD). Clinical and demographic characteristics of the patients are shown in Table 1.

18.1% of the patients had lymphopenia, 35.7% hyperferritinemia, 58.3% increased LDH, 1.9% thrombocytopenia, 58.5% increased D-dimer, 45.5% increased PCT and 22.9% hyponatremia. The

laboratory findings of the patients are shown in Table 2.

When compared, no statistically significant differences were obtained in terms of complete blood count, biochemical parameters, and CT findings among patients according to age, sex, and underlying comorbidity except increased PCT levels in patients with DM and both DM and HT.

26.6% of the patients whose RT-PCR tests were negative, but had CT findings suggesting COVID-19 disease were accepted to be infected and given treatment. The combination of hydroxychloroquine, azithromycin and oseltamivir treatment was given to 20.2% of the patients in the first wave, and favipiravir monotherapy was given to all of the patients (n=426) in the second wave (Table 3). No significant difference was observed between treatment groups hydroxychloroquine and favipiravir in terms of mortality (2.3% vs 3.3%, P=.487).

1.49% of the patients who received favipiravir developed bradycardia responsive to atropine. Only 3 patients had rash due to drug side effects or the disease itself.

51.9% of the patients were treated with CS. Only two patients received pulse steroids. No significant difference was observed in mortality between patients who received CS, predominantly in the second wave, and those who did not (P=.487).

Tocilizumab was given to 5.7% (n=40) of the patients, all in the second wave; 60% of these patients were discharged and 37.5% (n=15) were transferred to our ICU; 33.3% (n=5) of our patients in ICU underwent invasive mechanical ventilation (IMV), 93.3% non-invasive ventilation (NIV) and 40% of them died; 80% of the patients treated with tocilizumab developed elevated liver enzymes up to five times upper normal limits, gradually returning to normal levels during follow-up. Convalescent plasma was given to 6 patients, 50% of whom died.

5.8% of the patients (n=41) were transferred to the ICU; 68.2% of these patients were male, and the mean age was 63.3±12.3. NIV was required in 75.6% of the patients in the ICU, whereas 36.5% of the patients underwent IMV. The patients in ICU had predominantly HT and DM (only HT in 4 patients, only DM in 2, and both HT and DM in 14). Only 7 patients had asthma and/or COPD; 34.1% of ICU patients had no underlying comorbidity. The overall mortality rate was 3.7 and 42.8% in our ICU. Respiratory failure was the most common complication, followed by cardiac arrest in the ICU. None of the patients survived among patients who underwent IMV. Older age, male sex, low lymphocyte count, CT findings including bilateral involvement and severe stage, and the need for IMVwere associated with poor prognosis and mortality (P=.047, P=.048, P=.029, P=.047, P<.001, and P<.001, respectively).

92.4% of our patients were discharged, only 1.5% (n=10) of them with an oxygen concentrator. During the study period, 2.4% of the patients, and 16.6% of the patients in ICU were transferred to other ICUs in the city due to lack of beds or more advanced care. Six patients with leukemoid reactions were referred to the hematology outpatient clinic, and one of them was diagnosed with chronic myeloid leukemia. Follow-up after discharge from the electronic health records, which includes all inpatient and outpatient visits of the patients, revealed that only 8 patients (5 in other hospitals and 3 at home) died. The rate of readmission within 30 days was 1.28.

Discussion

Previously reported studies among patients with COVID-19 have stated that older age, male gender and comorbidities were significantly associated with the severity of the disease and mortality [1-3,7-13]. Similarly, 55.5% of our patients were male and the median age was 57. It has been reported that 13-73.4% of the patients had comorbidities [8,9,13]; 58.7% of our patients had at least one accompanying comorbidity. The most common one was HT in our study, compatible with the

Table 1. The demographic and clinical characteristics of the patients on admission

Age (years; mean ± SD)	57.0 (15.6) (16-94)
Gender (male/female)	1.24 (388/311)
Duration of disease (days; mean ± SD)	6.4 (4.8)
Concomitant chronic diseases n, (%)	410 (58.7%)
Hypertension	301 (43.1%)
Diabetes mellitus	126 (18%)
Cardiovascular disease (ischemic heart disease, congestive heart disease)	65 (9.2%)
Asthma	62 (8.9%)
COPD	41 (5.9%)
Malignancy	8 (1.1%)
Chronic renal disease	16 (2.3%)
Cerebrovascular disease	12 (1.7%)
Infections (Hepatitis B, C)	3 (0.4%)
Others (Behcet disease, Celiac disease, ulcerative colitis,epilepsy, rhematoid arthritis)	14 (2%)
Signs and symptoms n, (%)	
Fever (temperature ≥37.3°C)	227 (32.5%)
Fatigue	149 (21.3%)
Sore throat	22 (3.1%)
Cough	348 (49.8%)
Dyspnea	224 (32%)
Nausea/vomiting	56 (8%)
Diarrhea	13 (1.9%)
Myalgia	74 (10.6%)
Headache	36 (5.2%)
Anosmia and ageusia	14 (2%)
Disease severity	
Mild	0
Moderate	587 (83.9%)
Severe	112 (16%)
Critical	0
Chest CT imaging n, (%)	
Normal	64 (9.2%)
Mild	230 (32.9%)
Moderate	294 (42.1%)
Severe	111 (15.9%)
Pleural effusion	2 (0.28%)
Pericardial effusion	1 (0.14%)
Lesion distribution n, (%)	
Unilateral	85 (12.2%)
Bilateral	550 (78.7%)
RT-PCR n, (%)	
Positive	509 (72.8%)
Negative	190 (27.1%)

COPD= Chronic obstructive pulmonary disease; RT-PCR= Reverse-transcription polymerase chain reaction;

Table 2. The laboratory findings of the patients on admission

Hemoglobin (110-160 g/L)	13.4 (1.7) (7.7-18.3)
White blood cell count (4-10 x103 µL)	7373.2 (3592.2) (580-36700)
Platelet count (100-300 x103 µL)	224.5 (90.0) (21-774)
Lymphocyte count (0.8-4.0 x103 µL)	1388.2 (695.4) (0-5670)
CRP (0-5 mg/L)	58.4 (69.1) (0-359.3)
LDH (135-225 IU/L)	268.0 (106.6) (20-956)
Ferritin (30-400 mcg/L)	400.0 (383.6) (10.9-2639)
D-dimer (0-500 µg/ml)	848.9 (1311.5) (0-21900)
Glucose (74-109 mg/dL)	139.7 (70.7) (25-856)
Urea (10-50 mg/dl)	36.1 (20.5) (8-195)
Creatinine (0.7-1.2 mg/dL)	1.03 (3.58) (0.01-2.91)
ALT (0-41 IU/L)	31.5 (29.5) (3-318)
AST (0-50 IU/L)	33.7 (30.3) (10-492)
Sodium (136-145 mmol/L)	139.7 (47.2) (121-163)
Potassium (3.5-5.5 mmol/L)	4.26 (0.49) (2.7-6.17)
Albumin (35-52 g/L)	31.7 (4.0) (18.4-44.7)
Fibrinogen (2-4 g/L)	5.38 (1.24) (2.28-7.59)
Procalcitonin (0-0.12 ng/ml)	0.31 (0.73) (0-5.11)
Troponin (0-0.014 ng/ml)	1.48 (7.26) (0-60.7)

ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; CRP= C-reactive protein; LDH= lactate dehydrogenase

Table 3. Treatments and clinical outcomes of the patients

Antiviral treatment n, (%)	
Oseltamivir	141 (20.2%)
Favipiravir	469 (67.1%)
Lopinavir/ritonavir	11 (1.6%)
Hydroxychloroquine n, (%)	260 (37.2%)
Azithromycin n, (%)	218 (31.2%)
Intravenous antibiotics n, (%)	293 (41.9%)
Systemic glucocorticoids n, (%)	363 (51.9%)
Anticoagulation (Enoxaparin) n, (%)	543 (77.7%)
Tocilizumab n, (%)	40 (5.7%)
Convalescent plasma n, (%)	6 (0.9%)
Oxygen therapy n, (%)	699 (100%)
Mechanical ventilation n, (%)	
Invasive	15 (2.1%)
Non-invasive	31 (4.4%)
Intensive care unit n, (%)	41 (5.8%)
Outcomes n, (%)	
Discharge	646 (92.4%)
Discharge from hospital with oxygen	10 (1.5%)
Concentrators	
Rehospitalization	9 (1.28%)
Death	26 (3.7%)

other studies [2,7,8,11,12,14] followed by DM [3,7,8,19,12], and cardiovascular diseases [3]. The incidence of COPD and asthma was lower in our patients (5.9% and 8.9%, respectively), as in the other studies [1-3,5,9,13].

Elevated CRP, ferritin, D-dimer, and PCT were indicators of poor prognosis [1-3,10,12]. Lymphopenia due to viral particle-induced cytoplasmic damage and apoptosis was also correlated with the severity of disease and mortality [1,2,10,11,14]. In our study, we observed that 18.1% of the patients had lymphopenia on admission, mostly associated with severe disease, and continue to decrease as the disease progressed, improved gradually in survivors, but remained low in non-survivors.

Mo et al. [8] reported that besides increased CRP and LDH levels, thrombocytopenia, low level of albumin, elevated neutrophil and AST were also correlated with poor prognosis, in contrast, we did not observe significant differences in these parameters among patients according to disease severity, treatment modality, and mortality. Increased levels of troponin [2,3,12] and progressive elevation of PCT [13], particularly in patients with critical disease were related with poor prognosis [2,3,12]. Significantly higher levels of PCT were observed in our patients with DM, and both DM and HT due to high inflammatory response rather than secondary bacterial infection, but this was not associated with mortality.

It has been stated that CT is more reliable than RT-PCR testing due to false-negative results [3,15]. Thus, CT was performed in all of our patients on admission. Mo et al. [8] and Feng et al. [12] reported that an increased incidence of bilateral pneumonia and pleural effusion was associated with severity of disease and poor prognosis. Chest CT revealed that 78.7% of our patients had bilateral lung involvement, and 57.9% of them had a moderate and severe stage, significantly in the second wave. Only two patients had pleural effusion, which regressed with treatment.

Currently, no effective proven antiviral treatment for patients with COVID-19 has been identified. Although Food and Drug Administration (FDA) cautions against the use of hydroxychloroquine due to arrhythmias, Satarker et al. [16] stated that hydroxychloroquine plus azithromycin can reduce viral load. Researchers who predominantly preferred hydroxychloroquine treatment [1,5,10] reported the rate of mortality as 21%, 2.8%, 20% and 21.2%, respectively. Although no statistically significant difference was observed in terms of mortality between treatment groups in this study, it was slightly higher in the group treated with favipiravir (3.3% vs 2.3%), which may be explained by the fact that the patients who had more severe disease were hospitalized in the second wave when compared with the first wave.

Many guidelines and reports stated that CS were contraindicated or not recommended due to complications, including prolonged viremia, hyperglycemia, avascular necrosis, bacterial superinfections, and psychosis [17,18]. Increased risk of disease progression, increased use of antibiotics, prolonged fever and length of hospital stay were also reported [19]. Some researchers proposed that the use of CS treatment was not significantly associated with mortality [17,18], while according to others, early CS might reduce inflammatory response, and prevent the progression of COVID-19 disease [19,20].

The Chinese Thoracic Society has developed an expert consensus statement on the use of corticosteroids in 2019-nCoV pneumonia, and stated that CS should be given low-to-moderate doses (≤0·5–1 mg/kg per day methylprednisolone or equivalent) for ≤7 days [21]. Li et al. [23] observed no difference between patients who were given low-dose (< 2 mg/kg) and high-dose (>2 mg/kg) CS; 51.9% of our patients, particularly in the second wave of the outbreak were given CS. No side effects were observed with CS treatment other than hyperglycemia in this study.

Tocilizumab was proposed to reduce the progression of the disease and the need for noninvasive or invasive mechanical

ventilation or death in hospitalized patients with COVID-19 pneumonia. Gupta et al. [22] reported that the risk of mortality was lower in critically ill patients treated with tocilizumab in the first 2 days of ICU admission compared with those who did not; 5.7 % of the patients received tocilizumab, of whom 37.5% were transferred to ICU, 60% were discharged and 40% died. In our opinion, tocilizumab reduces the progression of the disease, the need for ICU and IMV.

The rate of patients who needed intensive care has been reported to be 5-15.7% in different studies [1,9]. Mortality varies from 2.08% to 78% in patients with COVID-19 disease [5,7,12], and from 1.4% to 72% among ICU patients with COVID-19 [2,8,14]. In the studies conducted in our country, mortality rates between 2.08 and 10.5% [13,14] have been reported; 5.8% of our patients were transferred to the ICU and 36.5% of them underwent IMV. The mortality rate was 42.8% in our ICU. Approximately 50% of the patients in ICU had HT and DM. Strikingly, one-third of these patients had no underlying comorbidity.

Limitations of the study were being a single-center retrospective study, lack of smoking history, failure to record oxygen saturation rate on admission at the emergency department, inability to detect other common viruses (Influenza A and B, RSV, Adenovirus), inability to calculate BMI due to workload and the urgent start of the supportive treatment.

In conclusion, older age, male sex, low lymphocyte count, CT findings including bilateral involvement and severe stage were associated with a poor prognosis in this study. The voluntarism and cooperation of the doctors from various clinics and nursing staff were of great importance in the fact that hospitalization periods were short and the mortality rates were similar to those in higher-level tertiary hospitals.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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