Clinical Characterization of 162 COVID-19 patients in Israel: Preliminary Report from a Large Tertiary Center

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ABSTRACT **Background:** In February 2020, the World Health Organisation designated the name COVID-19 for a clinical condition caused by a virus identified as a cause for a cluster of pneumonia cases in Wuhan, China. The virus subsequently spread worldwide, causing havoc to medical systems and paralyzing global economies. The first COVID-19 patient in Israel was diagnosed on 27 February 2020.

Objectives: To present our findings and experiences as the first and largest center for COVID-19 patients in Israel.

Methods: The current analysis included all COVID-19 patients treated in Sheba Medical Center from February 2020 to April 2020. Clinical, laboratory, and epidemiological data gathered during their hospitalization are presented.

Results: Our 162 patient cohort included mostly adult (mean age of 52 ± 20 years) males (65%). Patients classified as severe COVID-19 were significantly older and had higher prevalence of arterial hypertension and diabetes. They also had significantly higher white blood cell counts, absolute neutrophil counts, and lactate dehydrogenase. Low folic acid blood levels were more common among severe patients (18.2 vs. 12.9 vs. 9.8, $P = 0.014$). The rate of immune compromised patients (12%) in our cohort was also higher than in the general population. The rate of deterioration from moderate to severe disease was high: 9% necessitated non-invasive oxygenation and 15% were intubated and mechanically ventilated. The mortality rate was 3.1%.

Conclusions: COVID-19 patients present a challenge for healthcare professionals and the whole medical system. We hope our findings will assist other providers and institutions in their care for these patients.

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In February 2020, the World Health Organization designated the name Coronavirus disease-2019 (COVID-19) to a clinical condition caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. The virus was initially identified in December of 2019 as a cause for a cluster of pneumonia cases in several provinces in China. Its clinical features range from asymptomatic carriage, flu-like symptoms including cough, fever, general weakness, myalgia, and respiratory failure requiring mechanical ventilation. There are several reports of the virus having non-respiratory clinical manifestations such as diarrhea, myocarditis and even hemorrhagic necrotizing encephalopathy [2-4]. The disease is highly infectious with a reproductive number (R0) ranging from 2.2–3.5 [5], which explains its rapid spread throughout the world. As of April 2020, the worldwide patient population was 1,617,576 with 96,939 deaths. These numbers continued to dramatically increase. Accumulating evidence suggests that in contrast to the initial, mild disease caused by viral replication, more severe manifestations of disease are immune-mediated with a cytokine storm characteristic of its advanced, lethal stages [6].

Israel's first experience with the virus was atypical, comprising a mission to bring home the 11 Israeli citizens onboard the Diamond Princess cruise ship and who had not yet tested positive for the virus. On the night of 11 February 2020, those patients were flown to Israel via a private jet and immediately transferred to the quarantine facility at Sheba Medical Center, Tel Hashomer. Of that group, two patients later tested positive for the virus. The quarantine center, later converted into Department of Internal Medicine: Corona Care Unit, was the first internal ward department in Israel, designated to treat COVID-19 patients. The first COVID-19 case diagnosed in Israel, a 40-year-old male who returned from Italy, was diagnosed on 20 February 2020, and was hospitalized as an inaugural patient. From that moment on and up to the present time, the department continues to admit patients and treats the

Table 1. Patient characteristics according to disease severity

	Overall	Mild	Moderate	Severe	*P* value*
N	162	92	44	26	
Age, mean ± standard deviation	52 ± 20	47 ± 22	57 ± 15	61 ± 14	**0.001**
Male, n (%)	105 (64.8)	48 (52.2)	36 (81.8)	21 (80.8)	**0.001**
Body mass index, kg/m^2	27.3 (23.9–31.2)	27.1 (23.6–30.9)	29.0 (24.3–33.4)	26.9 (25.5–31.0)	0.394
Obesity, mean ± standard deviation	31 ± 19.1	14 ± 15.2	13 ± 29.5	4 ± 15.4	0.121
Ischemic heart disease, n (%)	12 (7.4)	5 (5.4)	3 (6.8)	4 (15.4)	0.228
Hypertension, n (%)	49 (30.2)	18 (19.6)	18 (40.9)	13 (50.0)	**0.002**
Chronic renal failure, n (%)	2 (1.2)	0(0)	1 (2.3)	1 (3.8)	0.224
Diabetes, n (%)	30 (18.5)	11 (12.0)	11 (25.0)	8 (30.8)	**0.040**
Chronic obstructive pulmonary disease, n (%)	2 (1.2)	1 (1.1)	0(0)	1 (3.8)	0.364
Epilepsy, n (%)	1 (0.6)	0(0)	1 (2.3)	0 (0)	0.259
Smoking, n (%)	11 (8.9)	6 (9.4)	2 (5.3)	3 (13.6)	0.535

All data are presented in the form of median (interquartile range) unless otherwise specified
*Bold indicates significance

largest patient cohort in Israel, alongside other designated departments and intensive care units throughout Israel. As of 12 April 2020, the number of COVID-19 patients in Israel was 10,095 with 92 deaths [7].

PATIENTS AND METHODS

STUDY POPULATION

This analysis includes all patients who are admitted for COVID-19 in department of internal medicine: corona care unit and intensive care unit at the Sheba Medical Center from February 2020 to 10 April 2020. Clinical data including chronic illnesses, chronic medications, and laboratory workups were extracted from the medical registry. All-cause mortality was available for all patients.

AIM

The main goal of our study was to describe the population presenting with COVID-19 infection, including demographic characteristics, clinical characteristics, and short-term outcomes.

ETHICS

The study was approved by the local institutional ethics committee.

STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation when normally distributed or median with interquartile range (IQR) if skewed. Categorical variables were presented as frequency (%). Continuous data were compared with the Student *t*-test and categorical data were compared with the use of the Chi-square test or the Fisher exact test. A *P* value of < 0.05 was considered statistically significant. Statistical analyses were performed with R, R Core Team (2013).

RESULTS

We treated a total of 162 patients, with a mean age of 52 ± 20, of whom 65% were male. The median body mass index (BMI) was 27 kg/m^2, IQR 24–31; and 19% were obese (BMI > 30 kg/m^2). Our cohort included 9% smokers. The prevalence of background medical conditions was 7% for ischemic heart disease, 30% for hypertension, and 19% for diabetes. Disease severity tended to be higher older individuals (mean age 47 vs. 57 vs. 61, $P = 0.001$) and patients were more likely to be male (80% vs. 84% vs. 52%). They were more likely to present with hypertension (50% vs. 41% vs. 20%, $P = 0.002$) and diabetes (31% vs. 25% vs. 12% $P = 0.001$).

Table 1 details patient characteristics according to the severity of disease. There are several methods for severity classification. We chose a simplified version to classify symptoms: mild disease included flu-like without clinical and imaging signs of pneumonia; moderate included pneumonia and hypoxemia; and severe included requiring intensive help for proper oxygenation (either high-flow oxygen delivery device or artificial ventilation, either non-invasive or invasive).

When observing the entire cohort population, we note that their differential blood counts were mostly unremarkable: white blood cells (WBC) 6.2 K/ml, absolute neutrophil count (ANC) 4.5 K/ml. The absolute lymphocyte count was lower than the normal reference range 0.9 K/ml. Platelets median was 189 K. Chemistry results were also within the normal reference range: sodium 136 mg/Dl, potassium 4.2 mg/dl, creatinine 0.9 mg/dl, and urea 32 mg/dl. Alanine aminotransferase (ALT) median was normal 27 IU/L and ALT was slightly elevated 43 IU/L. Temperature (37°C), room air 0_2 saturation 96%, and systolic blood pressure (127 mmHg) on presentation were also within normal ranges.

Severe patients, compared to the mild and moderate disease patients, differed in higher ANC (7.8 vs. 4.2 vs. 4.21 $P = 0.012$). A trend toward higher WBC (8.2 vs. 5.5 vs. 6.1, $P = 0.057$) and

Table 2. Patient vital signs and laboratory results according to disease severity*

	Overall	Mild	Moderate	Severe	*P* value**
N	162	92	44	26	
White blood count	6.2 (4.7–9.0)	6.1 (4.7–7.6)	5.5 (4.3–8.6)	8.2 (4.6–13.4)	0.057
Platelets	189.0 (139.0–239.2)	188.0 (154.5–231.5)	163.5 (104.5–213.5)	213.0 (144.0–299.0)	0.074
Absolute neutrophil count	4.5 (3.3–6.9)	4.2 (3.4–5.8)	4.2 (3.2–6.3)	7.3 (3.9–10.1)	**0.022**
Absolute lymphocyte count	0.9 (0.6–1.3)	1.0 (0.7–1.4)	0.7 (0.5–1.2)	0.8 (0.6–1.2)	0.118
Potassium	4.2 (3.9–4.5)	4.1 (3.8–4.4)	4.2 (3.9–4.4)	4.4 (3.9–4.6)	0.184
Sodium	136.0 (132.0–139.0)	138.0 (134.5–140.0)	135.5 (132.0–137.0)	134.0 (130.0–138.0)	**0.011**
Creatine phosphokinase	123.0 (81.5–300.8)	95.0 (68.0–128.8)	116.0 (70.0–234.5)	238.0 (118.0–828.0)	**0.012**
Aspartate transaminase	43.0 (31.0–60.0)	36.0 (27.0–48.5)	39.0 (29.5–54.2)	62.0 (42.0–83.0)	**0.001**
Alanine transaminase	27.0 (20.0–41.0)	25.0 (18.5–40.5)	26.0 (20.0–39.8)	31.0 (23.0–49.0)	0.392
C-reactive protein	95.3 (42.8–159.2)	68.1 (41.6–107.6)	98.5 (40.2–153.7)	132.4 (88.3–245.8)	**0.003**
Lactate dehydrogenase	372.0 (285.5–475.5)	298.0 (230.5–392.0)	367.5 (297.0–431.5)	538.0 (405.0–676.0)	**< 0.001**
Creatinine	0.9 (0.7–1.0)	0.8 (0.6–0.9)	1.0 (0.7–1.1)	0.9 (0.8–1.1)	**0.020**
Urea	32.0 (24.2–39.8)	26.0 (21.5–36.5)	31.5 (28.0–38.0)	38.0 (34.0–48.0)	**0.005**
Folic acid	12.4 (9.6–20.4)	18.2 (11.3–22.0)	12.9 (9.7–16.4)	9.6 (6.5–12.3)	**0.005**
Vitamin B12	517.5 (310.5–888.0)	393.5 (305.0–657.0)	470.5 (194.5–865.5)	797.0 (538.5–1375.5)	**0.039**
Ferritin	473.5 (198.3–843.1)	263.6 (80.2–473.6)	769.2 (321.6–1026.0)	579.8 (260.2–1005.1)	**0.030**
Transferrin	199.0 (141.0–239.0)	232.0 (207.0–266.0)	177.5 (137.5–211.8)	148.5 (135.8–193.2)	**0.003**
First temperature	37.1 (36.5–37.6)	36.9 (36.3–37.3)	37.5 (37.1–38.0)	37.2 (36.6–37.8)	**< 0.001**
Initial SPO_2 in room air	96.0 (94.0–98.0)	97.0 (96.0–98.0)	95.0 (93.0–96.0)	92.0 (89.0–97.0)	**< 0.001**
Initial SPO_2 with oxygen	95.0 (92.0–97.0)	96.0 (94.0–97.0)	94.0 (92.0–96.2)	95.0 (92.0–97.0)	0.616
Initial systolic blood pressure	127.0 (115.0–145.0)	129.0 (115.0–146.0)	129.5 (117.0–142.8)	116.5 (109.2–131.0)	0.053
Minimal SPO_2 in room air	94.0 (90.8–96.0)	95.0 (94.0–97.0)	92.0 (85.8–94.8)	84.0 (75.5–91.0)	**< 0.001**
Minimal saturation with oxygen	90.5 (82.0–92.8)	92.0 (91.0–95.0)	91.0 (85.8–92.5)	82.0 (68.0–90.0)	**< 0.001**
Minimal systolic blood pressure	107.0 (99.0–118.5)	109.0 (104.0–120.0)	107.5 (100.2–119.0)	85.5 (80.2–104.0)	**< 0.001**
Maximal systolic blood pressure	148.0 (136.0–163.5)	145.0 (131.0–159.0)	149.5 (143.8–161.2)	168.0 (150.0–180.0)	**< 0.001**
Maximal temperature	37.9 (37.2–38.6)	37.4 (36.9–38.0)	38.2 (37.8–38.9)	38.6 (38.3–39.1)	**< 0.001**

All data are presented in the form of median (interquartile range) unless otherwise specified
*Odds ratio (95% confidence interval)
**Bold indicates significance
SPO_2 = peripheral capillary oxygen saturation

higher platelet count (213 vs. 163 vs. 188, $P = 0.074$). Aspartate aminotransferase (AST) levels were higher (62 vs. 39 vs. 36, $P = 0.001$). Folic acid levels were significantly lower in severe patients (18.2 vs. 12.9 vs. 9.6, $P = 0.005$). They had higher lactate dehydrogenase levels (538 vs. 368 vs. 298, $P < 0.001$), higher C-reactive protein (CRP) levels (146 vs. 99 vs. 68, $P = 0.002$). Room air 02 saturation on arrival was lower (92 vs. 95 vs. 97, $P < 0.001$) and there was no significant difference in systolic blood pressure on presentation (116 vs. 130 vs. 129, $P = 0.53$). Table 2 details the differences in laboratory parameters by severity level in our patient cohort.

Of our patient cohort, 71% of patients were discharged either home or to other quarantine modalities. Death toll of patients treated by our department was 3.1% (5 patients). Median department length of stay was 6 days, IQR 3–10.

All deaths were in the severe disease subgroup. They account for 19.2% of the group total. Only two patients from the severe disease group were discharged.

Table 3 details the different treatment modalities and short-term clinical outcomes in our cohort. During their stay, aside from medical treatment, patients were encouraged to self-acquire prone position. This position resulted with significant improvements in their oxygenation values.

DISCUSSION

At the time of this publication, the COVID-19 pandemic was still in its early phase, with no foreseeable decline on a global or local level. We recorded new information about these patients daily and adapted our management strategy accordingly. Sheba Medical Center was the first to admit patients who were suspected to have been infected with SARS-CoV-2 and we continued to admit COVID-19 patients, with more departments opening, almost on a weekly basis.

In our department we began practicing restrictive medicine: entering the quarantine compound only as needed, usually for

Table 3. Treatments and short-term outcomes according to disease severity

	Overall	Mild	Moderate	Severe	*P value***
N	162	92	44	26	
Discharged, n (%)	115 (71.0)	84 (91.3)	29 (65.9)	2 (7.7)	**< 0.001**
Department length of stay*	6.0 (3.0–10.0)	4.0 (2.0–10.2)	6.0 (4.0–9.0)	8.0 (3.2–12.5)	0.176
Intensive care unit admission, n (%)	24 (14.8)	0 (0)	3 (6.8)	21 (80.8)	**< 0.001**
Mortality, n (%)	5 (3.1)	0 (0)	0 (0)	5 (19.2)	**< 0.001**
Levofloxacine, n (%)	59 (36.4)	20 (21.7)	27 (61.4)	12 (46.2)	**< 0.001**
Plaquenil, n (%)	44 (27.2)	6 (6.5)	19 (43.2)	19 (73.1)	**< 0.001**

All data are presented in the form of median (interquartile range) unless otherwise specified
*Odds ratio (95% confidence interval)
**Bold indicates significance

emergent medical treatment or to perform a list of pre-planned aggregated tasks. This reduced team exposure and the risk of infection. We were able to achieve this by combining telemedicine tools and expert clinical reasoning. The former allowed us to see our patients, talk to them, obtain vital signs, and perform basic physical examinations such as auscultation of the heart and lungs. The latter allowed us to direct evidence-based treatment that was incorporated into decades of clinical experience and apply medicine that is restrictive in physical contact with patients but not inferior in quality.

We considered the patients in the COVID-19 ward as first and foremost internal medicine patients with COVID-19 infection. The fact that they concurrently presented with a COVID-19 infection did not alter the complexity of their background diseases. Our clinical experience showed that young and healthy patients would emerge from the disease unscathed as was demonstrated by our data showing that the severe patients were older and are more likely to present with atherosclerosis-associated illnesses. The fact that more of them had diabetes supported our assumption that chronic medical conditions worsen prognosis even when not directly related to disease pathogenesis. As a result, the two most important anamnestic features for patient classification were age and previous medical history.

The data showed that major renal impairments related to acute disease were uncommon and that elevated blood pressure on presentation did not seem to have a major clinical impact. An interesting and possibly actionable finding was the significantly low levels of serum folic acid among severe patients.

With regard to clinical symptoms, we noticed that the most common presenting complaint was severe general weakness, which was disproportionate to objective findings. As a result, there was also a tendency for anorexia and dehydration. The myalgia was predominantly in the lower back and did not present as diffuse myalgia, without sensitivity on muscle palpation. The respiratory distress was at times overwhelming: isolated desaturation up to hypoxemic respiratory insufficiency with no or mild CO_2 retention. We found no wheezing or other clinical evidence for bronchoconstriction. Usage of high-flow oxygenation (Vapotherm, USA) was generally beneficial. Nevertheless, patients experiencing profound hypoxemia tended to deteriorate up to endotracheal intubation with no obvious means of stopping this sequence. With regard to hypoxemia, some patients were silently hypoxemic. Clinical trials to incorporate all of our patients should be initiated.

CONCLUSIONS

Management of COVID-19 patients presents a novel challenge for caregivers and medical systems alike. At such times when new information was being generated on a daily basis and the scientific community as a whole was gathered in the struggle to halt this pandemic before it took countless more lives, we presented our findings and thoughts to assist other providers and institutions in their care for patients.

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