Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Do we know when to end isolation of persons affected with COVID-19?

1. Introduction

The pathogen responsible for coronavirus disease 2019 (COVID-19) is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This novel coronavirus was first detected in Wuhan, China in late December 2019 [1]. Since initial detection of the virus, more than 1,800,000 cases of COVID-19 have been confirmed worldwide, and over 400,000 persons have recovered. The first case in Israel was reported on February 27, 2020. To date, over 13,500 have been diagnosed and more than 4,000 have recovered [2].

Initially, during the outbreak of COVID-19 in Israel, all persons who tested positive were admitted to hospitals. Nowadays all those with mild disease are isolated in designated *hotels,* whereas those with moderate and severe disease are admitted to designated internal medicine or intensive care unit departments within hospitals. The criterion for discharge from isolation is two consecutive negative tests of (SARS-CoV-2) RNA detection. One difficulty faced by clinicians, as well as by patients, is the unknown time-frame of hospitalization until discharge of symptomatic patients.

The aims of our report are to offer a time-frame for ending the isolation of patients affected by COVID-19, and to describe the time to recovery according to demographic characteristics, sex differences and coexisting conditions. We describe the dynamics of the disease that paralleled changes in the viral load, based on SARS-CoV-2 RNA detection during February and March 2020.

2. Methods

We followed the 20 patients with laboratory-confirmed COVID-19 infection who were treated following a diagnosis of COVID-19, and who recovered from the infection during March 2020. All the diagnoses were by semi-quantitative RT-PCR on nasopharyngeal swabs.

We assessed patterns of clinical disease and viral load from nasopharyngeal samples that were obtained once daily for the first 3 days following hospital admission, and once every 2 or 3 days until discharge. Clinical specimens for COVID-19 diagnostic testing were obtained in accordance with US Centers for Disease Control and Prevention (CDC) guidelines. Nasopharyngeal samples were tested with the assay developed by the CDC [3], and based on the World Health Organization standard. All the samples were refrigerated and shipped to Rabin Medical Center, where RNA extraction, RT-PCR, and the virus isolation and titration procedures were performed. Envelope protein gene (E), RNA-dependent RNA polymerase gene (RdRP), and nucleocapsid (N) gene were measured by the RT-PCR (AllplexTM 2019-nCoV) [4,5]. If one target was detected, the assay was reported as positive. Recovery was defined as two negative measurements for all three genes. Here we describe the days to recovery from the first day of appearance of symptoms. Local ethical board approval and informed consent for analyzing routine procedures during the outbreak was waved at the time by the Director-General of the Israel Ministry of Health.

3. Statistical analysis

Descriptive statistics were used to summarize the data. The results are reported as means and standard deviations, or ranges. Categorical variables were summarized as counts and percentages. We used Chi Square and Fisher's Exact test to study differences between men and women, between persons older and younger than the median age, and between those with and without elevated body temperature ($\geq 38^{\circ}$) during hospitalization. We calculated a morbidity score for each patient according to the number of chronic diseases at the time of admission. According to this score, we examined the association between morbidity and time to recovery. The Kruskal-Wallis test was used to compare those with and without comorbidities upon admission. No imputation was made for missing data. All the analyses were performed with IBM SPSS statistics.

4. Results

The population consisted of 8 women and 12 men. The mean age was 49.0 (17•1) years (range 18–75 years) yet women were older (60•2 vs. 41•4, $p = 0.012$). Thirteen (65%) had a body temperature above 38 °C at admission, 6 (30%) had hypertension, 3 (15%) type 2 diabetes, 9 (45%) dyslipidemia, and three were current smokers. Only one patient was treated by chloroquine, zinc, and azithromycin during hospitalization. The mean time to discharge was 17 days, the range was 13–21 days. The mean length of hospital stay was longer for patients who presented with a body temperature above 38°C during hospitalization (n = 13) than for those who did not have an elevated body temperature (17•5 vs. 16•7 days $p = 0.6$). Accordingly, the number of days to negative detection of each gene was longer among those with an elevated body temperature than among those without (gene E, 15•5 vs. 15•3; gene N, 17•5 vs. 16•7; and gene RdRp, 15•8 vs. 15•6 $p > 0.05$ for all). Stratifying our population by median age (above and below 44 years), the time to full recovery was shorter for the younger than the older patients: 17•0 vs. 17•3 days. The time to negative detection of each gene was also shorter among the younger than the older patients, for example 14•4 vs 16•7 days, $p = 0.08$, for gene E. Elevated body temperature presented in 78% (7/9) of the older patients, and 54% (6/11) of the younger patients.

Fig. 1a describes the time (in days) until a complete negative result (negative detection of all three genes), according to patient sex. Although older, the women exhibited a shorter time to recovery than did the men (16•7 vs. 17•5 days $p = 0.6$). We further examined the time from admission until negative detection of each gene. Fig. 1b shows the time to recovery in all three detected genes by hospitalization day, from the first day of symptoms. All genes E, RdRp and N correlated with the sum of days leading to discharge; the strongest correlation was for gene

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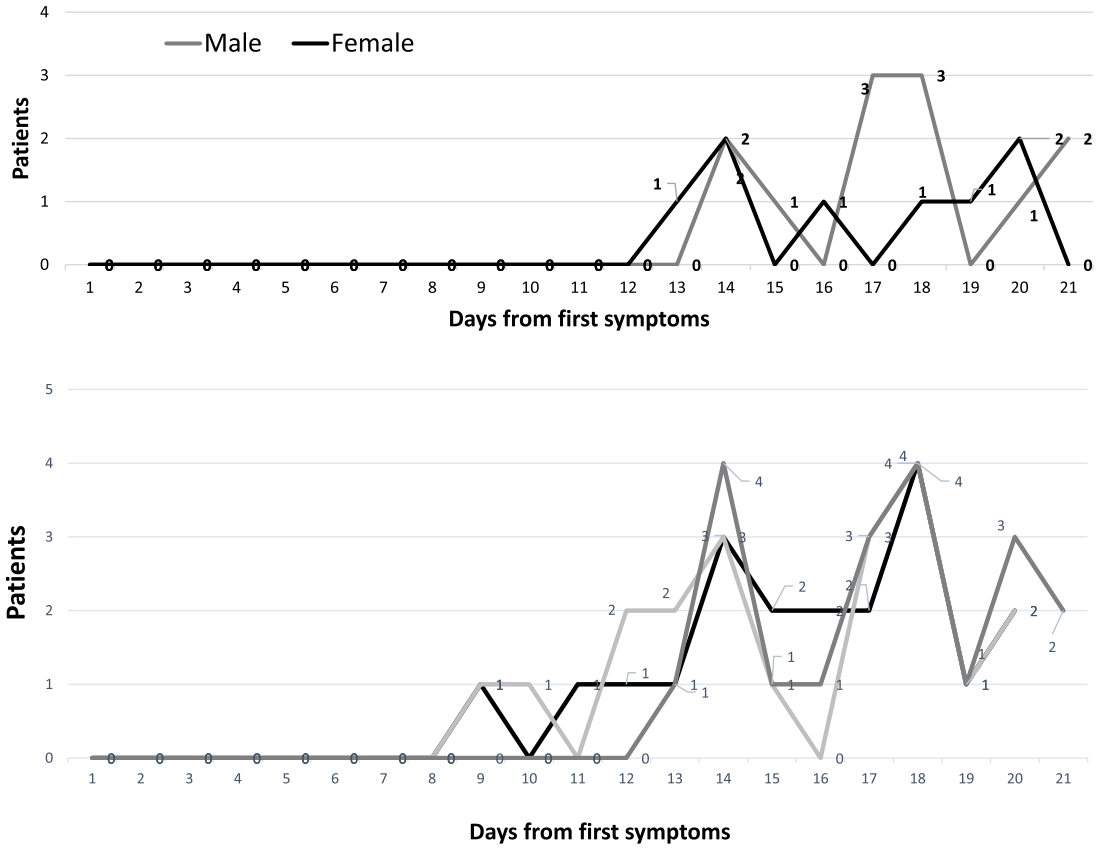

Fig. 1. (a). Days until a negative COVID-19 result, according to patient sex. (b). The first negative result for all genes by hospitalization day
Light grey line: Envelope protein (E) gene; Black line: RNA-dependent RNA polymerase gene (RdRP); Dark grey line: Nucleocapsid (N) gene

N (r = 0.78, r = 0.82. r = 1.0, respectively, $p < 0.001$ for all). The time to recovery was longer for patients with hypertension or lung disease. Compared to those without hypertension, for those with hypertension (n = 6), the number of days to recovery was 18•5 vs. 16•6, $p = 0.13$; and for each of the genes E, RdRp, and N: 17•8 vs. 14•4, $p = 0.03$; 17•7 vs. 14•9, $p = 0.05$; and 18•5 vs. 16•6, $p = 0.13$, respectively. In patients with no chronic illnesses at the time of admission (n = 11), negative detections of gene E and RdRP were after 14•5 and 14•9 days, respectively. This contrasts to 16•4 and 16•7 days, respectively, for those with comorbidities upon admission. Full recovery was determined in those without comorbidities after 17•0 days, when gene N was also not detected, and for those with comorbidities after 17•4 days.

5. Discussion

The time to discharge after the onset of COVID-19 symptoms is two weeks minimum. Recovery was longer for patients with comorbidities, especially hypertension, or those with elevated body temperature during hospitalization. Women seem to recover faster than men.

Some studies have reported sex-differences in patients with COVID-19 [6], suggesting that men might be affected at a higher rate and more severely than women. In Italy, 82% of 1591 patients were men [7]. Moreover, among critically ill patients in China, 67% were men [8]. Although the reasons for a possibly lower rate of infection among women are not fully understood, we suggest that women, once affected, might recover more quickly.

In our cohort, patients with comorbidities, and specifically those with hypertension, were more likely to present a longer recovery. Whether patients with hypertension are at increased risk for COVID-19 infection has been recently debated [9]. Among 1043 patients in Italy, 49% had hypertension [7].

Of the three genes measured by the RT-PCR, gene N was most correlated with full recovery from COVID-19. In a recent study of 9 patients [10], seroconversion occurred after 7 days in 50% of the patients and in 14 days in all of them, but was not followed by a rapid decline in viral load. This emphasizes the need for a method that correlates between serological and RT-PCR tests.

To our knowledge this is the first report to offer a time-frame for recovery from COVID-19 and the end of isolation, depending on baseline and hospitalization conditions of the patients.

All authors have no conflict of interest.

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