Characteristics and Recovery Prognosis Factors Among COVID-2019 Infected Cases: A Tunisian Nationwide Analysis

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Research article

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Abstract

Background: The outbreak of coronavirus disease (COVID-19) continues to constitute a public health of international concern. Few data are available on the duration and prognosis factors for recovery. We aimed to study the recovery time among a Tunisian cohort of COVID-19 confirmed patients and identify its prognosis factors.

Methods: A retrospective and national study was conducted from March 2 to May 8, 2020, recruiting all patients who were diagnosed with COVID-19, by RT-PCR methods, in Tunisia. Data were collected via phone call interview. Kaplan-Meir Methods and Cox proportional hazards regression models were, respectively, used to study the recovery time and estimate its prognosis factors.

Results: 1030 patients with COVID-19 (aged 43.2 ± 18.2 years, 526 female (51.1%)) were enrolled. Among them 174 (16.9%) were healthcare professionals. Out of 173 patients (17.8%) admitted to the hospital, 47 were admitted in an intensive care unit. Among those who didn't require specialized care, 55.5% were self-isolated at home, while the rest were in specialized centers. Almost ¾ of the patients were symptomatic. A total of 634 (61.6 %) patients have recovered and 45 (4.4 %) patients died. The median duration of illness was estimated to be 31 days (95% CI: [29 - 32]). Older age (HR=0.66, CI:[ 0.46-0.96], P=0.031) and symptoms (HR=0.61, CI:[ 0.43-0.81], P=0.021) were independently associated with a delay in recovery time. Being a healthcare professional (HR=1.52, CI :[1.10-2.08], P=0.011) and patients in home isolation compared to isolation centers (HR=2.99, CI :[1.85-4.83], P<10⁻³) were independently associated with faster recovery time.

Conclusion: The duration of illness was estimated to be one month. However, this long estimated duration of illness may not equate to infectiousness. A particular attention must to be paid to elderly and symptomatic patients with closer monitoring.

Background

Coronavirus disease 2019 (COVID-19), an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first reported in December 2019, in Wuhan, Hubei Province in China. Since then, the number of cases increased rapidly in China and soared dramatically across the world with human-to-human transmission to become one of the most challenging global health problems. On 30 January 2020, the World health organization considered COVID-19 as a public health emergency of international concern and announced the pandemic threat in March 11,2020 (1, 2). On May 15, 2020, 4 553 394 confirmed cases of covid-19 were identified, worldwide, with death rate of 6.7% and 37.7% of recovery(3).

In Tunisia, the first confirmed case of COVID-19 was reported on March 2, 2020. Since then, several measures have been taken to brake the spread of the epidemic among the population, including successively screening at point of entry, 14 days isolation of travelers returning from risk areas, closure of school and university facilities, ban of sports and cultural events, borders closure, curfew and finally, a
national lockdown was announced on March 22, 2020. On May 8, 2020, the total number of confirmed cases of COVID-19 was 1030 (4).

Several studies have addressed clinical, radiological and biological issues in COVID-19 patients. The clinical spectrum is large and ranges from asymptomatic or mild forms, accounting for about 80%, to cases of acute respiratory distress syndrome that may lead to intensive care or death(5).

However, we note a scarcity of data on prognosis factors associated with a better outcome and recovery. Since an early recovery reduces the shedding and spread of the virus, identifying recovery prognosis factors may improve our understanding of the dynamics of transmission and foster the control of the epidemic (6).

The present study aims to estimate recovery time and identify related prognosis factors among Tunisian infected people with COVID-19.

**Methods**

**Study design**

Our study includes all confirmed COVID 19 cases listed among the database of the national observatory of new and emerging diseases (ONMNE), which is the national center for disease control and surveillance.

**Case definition**

A confirmed COVID-19 case is defined as any person, whether symptomatic or not, with laboratory confirmation of SARS-CoV-2 infection using real-time reverse transcriptase–polymerase chain reaction (RT-PCR).

**Laboratory confirmation of SARS-CoV-2 infection**

The laboratory testing for SARS by RT/PCR was the laboratory method of reference to confirm cases. Charles Nicolle hospital laboratory which is the national influenza WHO collaborating laboratory was the reference laboratory at national level. It received all the specimens during the first period of outbreak investigation. Later on, other laboratories performing SARS specific PCR tests were involved.

SARS-CoV-2 infection was confirmed in all patients by testing nasopharyngeal swab samples with a real-time reverse transcription– polymerase chain reaction assay

**Recovery monitoring and criteria**

From March 2, 2020, when the first case was reported, all confirmed cases are consistently and timely reported by the laboratory to the national observatory for new and emerging diseases (ONMNE) where a team of trained physicians was responsible to ensure the follow-up of all confirmed cases by phone calls.
All positive cases are assigned to keep a 14 days quarantine until to get two negative laboratory testing. Epidemiological, demographic, isolation setting and conditions, symptoms, treatment and outcome data were collected from positive cases during the quarantine. COVID-19 patients were isolated at home or in dedicated covid-19 centers. Hospitalization was only indicated for the serious cases requiring a respiratory assistance or special care. The recovery statement is based on laboratory data. For asymptomatic patients, the first recovery testing is scheduled for the last day of the quarantine. For symptomatic patients, the first recovery testing is done three days after the symptoms disappearance and at least seven days after onset symptoms. In both situation, the second recovery testing is done 24 to 48 h after the first negative sample. If the first recovery test is still positive, then the second recovery test is done 7 days later. The formal recovery criteria is defined by two successive negative RT-PCR control specimen and recovery time is defined as the period from the date of symptoms onset to the date of second negative RT-PCR test result (when patients got positive RT-PCR result following false negative result, it was considered as non-effective negative result in our study). After recovery statement, a mandatory 14 days home auto-isolation is indicated.

**Statistical analysis**

Statistical analysis were performed using SPSS version 17.0 software. Data were expressed as frequencies and percentages for categorical variables and as means and standard deviations (SD) or medians and interquartile ranges (IQR) as appropriate for continuous variables. The median time to recovery was estimated by Kaplan-Meir Methods. Cox proportional hazards regression models were used to estimate factors influencing the recovery time, with the hazards ratio (HR) and its 95% confidence interval (95%CI). Statistical significance was determined at $P<0.05$.

**Results**

**Clinical profile of patients**

A total of 1030 patients tested positive for COVID 19 disease were collected between March 2 and Mai 8, 2020. The mean age was 43.2 years ± 18.2, and 526 (51.1%) were female. Almost all patients are Tunisians (Table 1) and quarter of infections were imported, mainly from France or Turkey. One hundred seventy three patients (17.8%) were admitted to the hospital, most of them in a non-intensive care department and only 47 in an intensive care unit (ICU). Sixty six patients (38%) received an hydroxychloroquine treatment. Half of the cases received such treatment in a hospital setting and the others received it either from a private doctor or as self-medication. Patients who do not require care have been self-isolated at home (55.5%) or in dedicated centers for positive cases (44.5%). One hundred forty one patients were healthcare professionals who were infected in half of the cases in a healthcare setting.
Table 1
Demographic and clinical characteristics of patients with COVID-19 in Tunisia.

| Characteristics               | N (%) |
|-------------------------------|-------|
| **Age groups (years)**        |       |
| < 15                          | 63 (6.3) |
| 15–34                         | 287 (28.9) |
| 35–54                         | 369 (37.2) |
| 55–74                         | 232 (23.4) |
| ≥ 75                          | 42 (4.2) |
| **Gender**                    |       |
| Male                          | 504 (48.9) |
| Female                        | 526 (51.1) |
| **Nationality**               |       |
| Tunisian                      | 999 (97) |
| Non Tunisian                  | 31 (3)  |
| **Medical staff**             |       |
| Yes                           | 141 (14.8) |
| No                            | 809 (85.2) |
| **Contamination mode**        |       |
| Imported contamination        | 246 (23.9) |
| Local contamination           | 783 (76.1) |
| **Hospitalization**           |       |
| Yes                           | 173 (17.8) |
| No                            | 800 (82.2) |
| **Admission to ICU**          |       |
| Yes                           | 47 (4.8) |
| No                            | 926 (95.2) |
| **Isolation mode**            |       |

ICU: intensive care unit
Almost 75% of patients had symptoms. The most common symptoms were fatigue, cough and fever, which occurred respectively in 51.6%, 51.3% and 48.3% of symptomatic patients. Symptoms such as headache, anosmia and digestive signs were also common in those patients (Table 2).

Table 2  Distribution of clinical signs among symptomatic patients with COVID-19 in Tunisia.

| Symptoms       | N = 602 |
|----------------|---------|
| Cough          | 311 (51.6) |
| Fatigue        | 309 (51.3) |
| Fever          | 291 (48.3) |
| Headache       | 210 (34.8) |
| Anosmia        | 195 (32.4) |
| Digestive signs| 188 (31.2) |
| Loss of taste  | 165 (27.4) |
| Dyspnea        | 140 (23.3) |
| Others signs   | 129 (21.4) |

As of May 8, 2020, a total of 634 (61.6%) patients were recovered, 45 (4.4%) patients were dead and 351 (34%) were still being followed.

**Recovery prognosis factors**
Survival analysis was used to analyze the prognosis factors for recovery in patients with COVID-19. It showed that the median duration of illness was estimated to be 31 days (95% Confidence Interval [CI]: [29–32]) (Fig. 1). In univariate analysis, older age (Fig. 2), imported transmission of the infection and being symptomatic (Fig. 3) were associated with a longer duration of illness. Whereas, being a healthcare worker (Fig. 4) and patients in home isolation (Fig. 5) were associated with a shorter duration of illness. Using Cox regression, older age (HR = 0.66, CI: [0.46–0.96], P = 0.031) and having symptoms (HR = 0.61, CI: [0.43–0.81], P = 0.021) were independently associated with a delay in recovery time. Being a healthcare professional (HR = 1.52, CI: [1.10–2.08], P = 0.011) and patients in home isolation compared to isolation centers (HR = 2.99, CI: [1.85–4.83], P < 10⁻³) were independently associated with faster recovery time (Table 3).

### Table 3
Factors associated with recovery time among patients with COVID-19 in Tunisia.

|                                | Univariate Cox regression | Multivariate Cox regression |
|--------------------------------|----------------------------|-----------------------------|
|                                | HR | 95% CI      | P value     | HR | 95% CI      | P value     |
| Male                           | 0.93 | 0.79–1.09 | 0.405 | 0.93 | 0.57–1.50 | 0.754 |
| Age > 60 years                 | 0.68 | 0.55–0.85 | 0.001 | 0.66 | 0.46–0.96 | 0.031 |
| Tunisian Nationality           | 0.93 | 0.57–1.50 | 0.754 | 0.66 | 0.46–0.96 | 0.031 |
| Healthcare worker              | 1.86 | 1.52–2.27 | < 10⁻³ | 1.52 | 1.10–2.08 | 0.011 |
| Imported infection             | 0.83 | 0.69–0.99 | 0.038 | 0.83 | 0.69–0.99 | 0.038 |
| Home isolation                 | 1.69 | 1.4–2.06  | < 10⁻³ | 2.99 | 1.85–4.83 | < 10⁻³ |
| Hospitalization                | 0.95 | 0.76–1.18 | 0.635 | 0.95 | 0.76–1.18 | 0.635 |
| Admission in ICU               | 0.95 | 0.71–1.28 | 0.73  | 0.95 | 0.71–1.28 | 0.73  |
| Symptoms                       | 0.56 | 0.46–0.68 | < 10⁻³ | 0.61 | 0.43–0.81 | 0.001 |
| Chloroquine treatment          | 1.09 | 0.82–1.46 | 0.55  | 1.09 | 0.82–1.46 | 0.55  |

**Discussion**

Several studies have described the epidemiological, clinical, and radiological profile of patients with confirmed COVID-19 infection (7, 8) but few studies have focused on the course including the recovery issue and how much time that needs of the disease.

We described the demographic and clinical characteristics of confirmed COVID-19 Tunisians patients, estimated the median disease duration using the survival analysis and investigated the factors affecting the recovery time for COVID-19.
The main result of our study is the long duration of the disease. The patient is announced cured 31 days from the first day of the onset of symptoms for symptomatic patients and from the laboratory confirmation date for the asymptomatic patients.

Our national cohort reached 1,030 COVID-19 infected patients. It is a relatively young population with almost patients under 55 years of age. In the literature, a mean age between 48 and 55 years was reported (7, 9–12). For the gender, there was no predominance of men or women. The number of imported cases was higher than the number of local contaminations until 03/18/2020. The trend reversal (local contamination vs imported cases) was evident from 03/21/2020 announcing the installation of horizontal transmission (13).

Most of cases were mild as evidenced by relatively low ICU admissions and a high number of asymptomatic patients or with mild symptoms that do not require treatment in a hospital structure. In fact, the proportion of mild and asymptomatic cases versus severe and fatal cases for COVID-19 infection is currently still unknown. According to a Chinese report publishing all confirmed, suspected, and asymptomatic cases in China, 80% of infections were mild and can recover at home (14). Concerning clinical presentation of COVID-19 disease, the common symptoms reported by symptomatic patients were cough, fatigue and fever in nearly half of cases and headache in 35% of cases, which was consistent with general symptoms of viral infection. Similar symptoms were described in several case series (7, 10, 15). One out of three symptomatic patients reported loss of smell and/or taste. This type of disturbance was widely reported in the literature specially among patients with mild and moderate forms of coronavirus disease (16, 17). A multicenter European study showed that 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions (18).

The median duration of illness was estimated to be 31 days counting from the day of onset symptoms for symptomatic patients and from confirmation date for asymptomatic patients. This estimation for illness duration was long. In a recent Singapore study, similar results were recorded. It indicate that by day 15 from onset of illness, only 30% of all COVID-19 patients are PCR-negative by nasopharyngeal swab, this rises to 95% by day 33 (19). According to these results, the duration of viral shedding by PCR may extend to a month and sometimes longer for a small group of patients. Current guideline suggested two consecutive negative RT-PCR test results is one of the criteria for hospital discharge or discontinuation of quarantine. However, a high false negative rate of viral test was reported(20) and some patients experienced a "turn positive" of nucleic acid detection by RT-PCR test for SARS-CoV-2 after two consecutive negative results, which may be related to the false negative of RT-PCR test and prolonged nucleic acid conversion (21). The Singapore study indicates also that viable virus was not found after the second week of illness despite the persistence of PCR detection of RNA(19). It is, then, important to note that traces of virus detected by RT-PCR were not necessarily correlated with the ability of transmission.

In addition, a recent Canadian study demonstrate that infectivity as defined by growth cell culture were most likely between days one and five (22). These data indicate that even viral RNA detection may persist
in some patients, such persistent RNA detection represent non-viable virus and such patients are non-infectious(19). These findings are consistent with the new WHO recommendations for discontinue transmission-based precautions (including isolation) and release from the COVID-19 care pathway (23) with 10 days after symptom onset, plus at least 3 days without symptoms for symptomatic patients and 10 days after test positive for asymptomatic patients. These new recommendations should be taken in a count to adapt strategy to discontinue isolation of COVID-19 patients in our country.

Cox regression model showed that younger patients recover faster compared to elderly patients. Similar findings were reported (24, 25). In fact, many studies found a high proportion of severe cases and fatality rate among elderly patients with COVID-19 (11, 26–29).

Based on the result of this study, being a healthcare worker was showed to be significantly associated to a lower median time to viral clearance after onset of symptoms. This finding could be explained by the fact that the healthcare workers’ monitoring and control protocol is different from that of other COVID-19 patients. Indeed, the COVID-19 monitoring and control protocol adopted by the Tunisian health authorities was inspired from the recovery criteria of the European center for disease prevention and control (ECDC) documents (30). This protocol consists in carrying out a control sample for asymptomatic patients after 14 days from the date of confirmation. For symptomatic ones, if the fever or any other signs persist beyond 14 days, the control sample will be postponed for 3 days after the disappearance of the last sign. These deadlines are not respected for healthcare staff involved in the clinical management of COVID-19 patients. Healthcare workers infected with COVID-19 follow a closer control protocol, which may explain the faster time to viral clearance among them.

Results showed that the place of isolation is playing a significant role in survival time to recovery from COVID-19 infection. According to the output of the cox model, COVID-19 patients in self-isolation at home are almost three times more likely to recover faster than those in dedicated COVID-19 centers. In fact, the Tunisian strategy was based in the first phase of the epidemic on the isolation of confirmed COVID-19 cases in their place of residence and to hospitalize only the serious cases requiring a respiratory assistance or special care. Afterwards, given the registration of an increasing number of secondary cases among the close contacts of confirmed patients, the health authorities decided to create specialized centers to isolate COVID-19 patients in order to limit community transmission. The delay in recovery for COVID-19 patients isolated in COVID-19 centers compared to those in self-isolation at home could be explained by the fact that patients do not respect self-isolation inside these centers leading sometimes to mass gatherings. This promiscuity inside the dedicated centers for infected people may thus promote the maintenance of viral load.

Symptomatic patients seem also to have slower recovery duration.

This study has some limitations. There was a lack in some clinical information such as comorbidities and vital signs (heart rate, respiration rate, blood pressure….). In addition, since we used phone interview information concerning, biological and radiological data were not available for patients who have been hospitalized.
Conclusions

The study findings showed that the estimated duration of illness was excessively long, which influenced Tunisian jurisdictions to guide policies of firm isolation and discharge. This partly explains the success in controlling the epidemic in Tunisia. However, with current science data, which proves that viral detection by PCR does not equate to infectiousness, we strongly recommend to lighten our quarantine strategy in accordance with the new WHO recommendations.

We also found that older age and symptoms were independently associated with slower recovery time, whereas healthcare professional and patients in self-isolation at home were independently associated with faster recovery time. These results reinforce guidance that additional control measures must be undertaken to avoid mass gatherings inside isolation centers. Elderly and symptomatic patients need particular attention and closer monitoring.

Abbreviations

COVID-19: Coronavirus disease, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, WHO: World Health Organization, ONMNE: The National Observatory of New and Emerging Diseases, RT-PCR: Real-time reverse transcriptase–polymerase chain reaction, SARS: Severe acute respiratory syndrome, ECDC: The European center for disease prevention and control.

Declarations

Ethics approval and consent to participate

The follow-up data of individual patients were collected via National Observatory of New and Emerging Diseases of Tunis, Tunisia. Data were anonymized for this study. Neither ethical approval nor individual consent was not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data supporting our findings are contained within this article

Competing interests

None declared.

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**Authors’ contributions**

CH interpreted the data and drafted the manuscript. IC, NN, MO, RM, OB, YA and IB collected the data and performed the literature research. AH, MS and HL provided helpful information. MKC and NBB designed the study, provided guidance and approved the final manuscript. All authors discussed the results, critically read and revised the manuscript and gave final approval for publication.

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**Figures**
Figure 1

Survival curve showing survival time to recovery from COVID-19 infection
Figure 2

Cumulative proportion of patients with detectable SARS-CoV-2 RNA by day after illness onset between patients aged 60 years and over and patients under 60 years.
Figure 3

Cumulative proportion of patients with detectable SARS-CoV-2 RNA by day after illness onset between symptomatic and asymptomatic patients.
Figure 4

Cumulative proportion of patients with detectable SARS-CoV-2 RNA by day after illness onset between healthcare worker and other patients.
Figure 5

Cumulative proportion of patients with detectable SARS-CoV-2 RNA by day after illness onset between patients in home isolation and patient in dedicated centers for positive cases.