

Is Viral Load a Prognostic Indicator for Outcome of Covid-19 Patients? A Prospective Cohort Study in Iran

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Research

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Abstract

Background: Covid-19 has different clinical symptoms and severity. Predicting its progress and results is clinically important. Hence, in this study, we investigated the relationship between virus load and the outcomes in Golestan Province.

Methodology: We conducted a retrospective cohort study of COVID-19 diagnosed with RT-PCR testing from May 2020 to December 2020. According to the severity of the disease, the study groups were divided into three groups: outpatient, inpatient, and inpatient with death. SARS-CoV-2 viral load was assessed using cycle threshold (Ct) values from a reverse transcription-polymerase chain reaction assay applied to nasopharyngeal swab samples. Demographic properties, Clinical characteristics, and CT values of the studied patients were compared. Data were analyzed using STATA Version 16.0 software.

Results: Of 1318 included subjects, 599 were outpatient, and 719 were hospitalized. Of the hospitalized patients, 487 were recovered and 232 died. The mean age (year) of patients was 48.81 ± 18.40 and 51.9% were female. There were significant differences between the age and the severity of the disease, the mean age of patients who died was higher than other patients ($p < 0.001$). The mean CT value of all patients was 26.80 ± 4.43 , which was higher in outpatients than inpatients' cases ($p < 0.001$). We did not find any significant differences for the Ct values between recovered and dead cases ($p = 0.66$). CT value levels were not significantly different between age and sex groups.

Conclusions: According to the results of the study, CT value can be used only as a factor to determine the severity of the disease at the time of admission, but the load of the virus is not a factor to predict the outcome.

Introduction

COVID-19, which is the biggest pandemic in the world, has caused a lot of human and economic losses and has killed millions of people so far, and the number of infected people is increasing day by day [1, 2]. As of June 10, 2020, SARS-CoV-2 had infected more than 111 million people and killed more than 2,468,314 people throughout the world. The various studies indicated that the fatality rate from 2 to 10 percent [3]. Although the majority of patients who develop COVID19 have mild presentations [4], 18–33% of patients who are hospitalized require mechanical ventilation and up to 20% of hospitalized patients die [5, 6]. Its incubation period is 2 to 14 days and it has a high transmission rate and asymptomatic carriers can spread it. The virus is mainly transmitted through the respiratory system and its clinical symptoms are nonspecific in the early stages and indistinguishable from common cold symptoms [6–9]. Some classic respiratory symptoms such as fever, cough, shortness of breath, and myalgia are the main indicators for screening of patients. Furthermore, some symptoms, such as olfactory and taste disorders, have unexpectedly manifested in this disease [3].

The current standard test to diagnose COVID-19 is to collect nose, throat, and lower respiratory tract secretions and use a reverse transcription-polymerase chain reaction (RT-PCR) assay to detect SARS-CoV-

2 RNA [10]. These RT-PCR assays only report to clinicians whether SARS-CoV-2 is detected or not detected. The main method due to the ease and efficiency is sampling from the nasopharynx and nose [11–13]. In the PCR test in detecting COVID-19 the nucleic acid virus can be found in salivary and nasal secretions. These assays also contain quantitative information on cycle threshold (CT) values that are inversely correlated with viral load and are not reported clinically. The CT value is used as the number of amplification cycles to identify nucleic acids. The CT value is inversely related to the virus load and indirectly indicates the degree of virus replication [14]. In the case of SARS-CoV-1, the severity of the disease and fatality increased with increasing virus load in the nasopharynx [15, 16]. In contrast, except for two studies that had conflicting results [17, 18], the impact of SARS-CoV-2 viral load on clinical outcomes in hospitalized patients has not been thoroughly investigated. Given the importance of estimating the prognosis of the disease and its consequences, this aimed to determining the role of CT value in the prognosis of the disease and highlighting outcomes in patients with COVID-19 in Golestan province in Iran.

Methods

This study was performed as a retrospective cohort study on patients with Covid-19 in the period from May to December 2020 in Golestan province in Iran on the southern shore of the Caspian Sea. In this study, patients with suspected symptoms of Covid-19 were screened by the health care system and their Covid infection was confirmed by PCR. The final diagnosis was made by nasopharyngeal sampling with two swabs, one through the nose and the other through the throat. After sampling by trained experts under the standard conditions of sample transfer, all tests were transferred to the laboratory of the virology department of Golestan University of Medical Sciences and the tests were performed under the supervision of faculty members. After confirmation of Covid-19 in patients, based on the severity of symptoms, patients with mild to moderate symptoms were treated on an outpatient basis, but patients with severe-critical symptoms were admitted to 5-Azar Hospital in Gorgan, which was one of the two referral hospitals for Covid-19 patients in the province. The following criteria were considered for hospitalization: poor general condition, respiratory distress, suspicion of organ failure, comorbidities, the respiratory rate more than 32 times per minute, and arterial oxygen saturation less than 90 percent. Patients who did not have the above indicators were examined on an outpatient basis and the necessary recommendations were given to control the disease. CT value was used to determine the virus load in Covid-19 patients. To determine the CT value of the RT-PCR test in the SARS-CoV-2 samples, less than 35 replication cycles are considered as a criterion for diagnosis. So that the lower the CT rate, the higher the viral load in patients. Data from this study were extracted from the hospital database. These data included the variables of age, sex, the time interval from admission to recovery, time interval from admission to death, and final status of patients (recovery/death). Patients with clinical signs of COVID19 whose PCR test was negative were excluded from the study. To assess the prognosis of the disease, the time interval between admission to recovery or death was calculated for all hospitalized patients. Accordingly, the shorter the duration of hospitalization of recovered patients, the better the patient's prognosis and if it was longer, it was considered as a worse prognosis. In the case of dead patients, the

shorter the duration of hospitalization to death, the more severe the prognosis, and the longer the interval, the better the prognosis.

Continuous variables were represented with mean and standard deviation and categorical variables were represented as proportion. We examined the severity of the disease in different age and sex groups in the outpatient, recovered inpatient, and dead inpatient using the Chi-square test. One-way ANOVA was used to compare the mean CT values and time intervals in severity patients and age groups. We used Spearman's correlation to assess the relationship between the month of admission and age. Analyses were conducted using STATA version 16.0 (StataCorp, College Station, TX). A p-value less than 0.05 was judged statistically significant.

Results

A total of 1318 cases of COVID-19 were included in this study. Among these patients, 599 were outpatients and 719 were hospitalized. Of the hospitalized patients, 487 recovered and 232 died. The mean age of patients was 48.81 ± 18.40 years and 51.90% of patients were female. Comparison of the mean age of patients according to the type of patients included in the study showed a significant difference ($p < 0.001$). So that in the study of the PostHoc test the mean age of hospitalized patients was significantly higher than the mean age of outpatients ($P < 0.001$). Also, the mean age of patients who died was significantly higher than outpatients ($p < 0.001$). Also, the comparison between the mean age of recovered hospitalized patients and dead hospitalized patients showed that the mean age of dead patients was significantly higher ($p < 0.001$). Comparison of patients' status with their gender shows that there is no significant difference between them ($p = 0.95$) (Table 1).

The time interval between admission to recovery and admission to death of patients was evaluated and it showed that the mean time interval between admission and recovery was 8.98 ± 6.74 days. Also, the mean time interval from admission to death was 11.51 ± 10.90 days. Overall, the meantime from admission to recovery and the meantime from admission to death in the age and sex groups of COVID-19 patients were compared, it shows that the mean of these variables is not significantly different in age and sex groups (Table 2).

This study showed the mean CT values were 26.80 ± 4.43 . The mean of CT values was significantly different in conditions groups ($P < 0.001$). So that when the mean CT values in outpatients are compared with inpatients, this factor is significantly higher in outpatients ($p < 0.001$). Also, the mean CT values in outpatients were significantly higher than in patients who died ($p < 0.001$), which indicates a high viral load in hospitalized patients (recovered and died) compared to outpatients. However, there was no significant difference in terms of mean CT values in the groups of recovered and dead patients ($p = 0.66$) (Table 1). Also, no significant difference was observed when the mean CT values were compared between age and sex groups (Table 2).

To show the severity of the disease in recovered hospitalized patients and died hospitalized patients, the duration of hospitalization was divided into three groups: hospitalization less than one week,

hospitalization one to two weeks, and hospitalization more than two weeks. According to this classification, hospitalization for more than three weeks in recovered hospitalized patients was considered as high disease severity and hospitalization of dead patients was considered as high disease severity. Based on this classification, this study showed that among the hospitalized patients who recovered, 254 (52.16%) were hospitalized for less than one week, 170 (34.91%) were hospitalized for one to two weeks, and 63 (12.94 %) were hospitalized for more than two weeks. Also, among the hospitalized patients who died, 103 (44.98%) were hospitalized for less than one week, 64 (27.95%) were hospitalized for one to two weeks, and 62 (27.07%) were hospitalized for more than two weeks. Comparison of the mean CT values based on this classification showed that there was no significant difference between them (Table 3).

The last admission of the subjects in this study was on November 29, 2020. When we examined the age of patients at different admission dates, the data show that over time the age of patients slightly decreased ($r = -0.003$) which is not significant. ($p = 0.94$).

The findings also showed that changes in the month of admission of patients were not correlated with age. ($p = 0.47$) (Fig. 1). Also, the status of CT values in different months of admission shows that there is no significant change for both hospitalized and dead patients (Fig. 2). Examination of the sex distribution of dead patients shows that before July, in most months, the frequency of admission was higher in women, but after July, the frequency of admission was always higher in men. This ratio is almost the same for recovered patients (Fig. 3).

Table 1

Distribution and comparison of age and sex of Covid-19 patients according to disease severity

Variable	N (%)	Outpatient	Inpatient with recovery	Inpatient with death	P-value
Total	1318 (100)	599 (45.45)	487 (36.95)	232 (17.60)	-
Age, (Mean \pm SD)	48.81 \pm 18.40	38.27 \pm 13.62	53.36 \pm 15.58	66.49 \pm 17.14	< 0.001
Age group (year)	< 20	55 (4.17)	43 (7.18)	8 (1.64)	< 0.001
	20–40	433 (32.85)	318 (53.09)	97 (19.92)	
	40–60	475 (36.04)	199 (33.22)	220 (45.17)	
	\geq60	355 (26.93)	39 (6.51)	162 (33.26)	
Sex	Male	634 (48.10)	286 (47.75)	237 (48.67)	0.95
	Female	684 (51.90)	313 (52.25)	250 (51.33)	
Cycle threshold (Ct) values	26.80 \pm 4.43	27.45 \pm 4.55	26.37 \pm 4.41	26.05 \pm 3.93	< 0.001

Table 2

Comparison of the time interval between hospitalization to recovery and time interval between hospitalization and death, CT values in age and sex groups of Covid-19 patients

	Variable	The interval between hospitalization and discharge	P-value	The interval between hospitalization and death	P-value	Cycle threshold (CT) values	P-value
Total		8.98 ± 6.74		11.51 ± 10.90		26.80 ± 4.43	
Age group (year)	< 20	10 ± 8.61	0.48	8.25 ± 9.84	0.46	27.36 ± 5.04	0.14
	20–40	8.72 ± 6.83		16.55 ± 16.35		27.03 ± 4.50	
	40–60	8.88 ± 7.30		11.76 ± 11.80		26.86 ± 4.47	
	≥60	9.22 ± 5.77		10.91 ± 9.67		26.38 ± 4.16	
Sex	Male	9.56 ± 7.74	0.18	10.71 ± 9.97	0.48	26.92 ± 4.37	0.36
	Female	8.43 ± 5.58		12.25 ± 11.67		26.70 ± 4.49	

Table 3

Comparison of the interval between hospitalization, recovery, and death with Cycle threshold (Ct) values

Variable		N (%)	Cycle threshold (CT) values	P-value
The interval between hospitalization and recovery	Lower one week	254 (52.16)	26.09 ± 4.44	0.13
	1–2 weeks	170 (34.91)	26.92 ± 4.34	
	More than 2 weeks	63 (12.94)	26.04 ± 4.36	
The interval between hospitalization and death	Lower one week	103 (44.98)	26.11 ± 3.99	0.97
	1–2 weeks	64 (27.95)	25.98 ± 3.70	
	More than 2 weeks	62 (27.07)	26.14 ± 4.13	

Discussion

In our study, 1318 patients who had a definitive diagnosis of Covid-19 by RT PCR were evaluated. 599 of them had mild to moderate disease and were treated on an outpatient basis and followed up. 719 cases had the severe or critical illness and were hospitalized.

In our study, the mean age was 48.81 ± 18.4 years and 51.9% were female. In the study of Mohsen Rokni et al., which was performed on 233 hospitalized patients, the mean age was 49.8 years and 64% of them were male [19]. Also, in the study of Soare Fucio Klingler et al., who performed on 875 hospitalized patients, the median age was 48 years (range, 2–97 years) and 50.9% of patients were female [20]. In the study of A Derviro et al., which was performed on hospitalized patients, the mean age was the median age of 72 (IQR 62.5–83.5) years and 64.4% of patients were male and the mortality rate was 28.7% [21]. In the study of Victor M et al., which was performed on 2511 hospitalized patients, the mean age was 62.7 ± 19 years and 50.9% were male and 8.6% were hospitalized in ICU and 11.6% died [22]. In the study of Barrett et al., which was performed on 1123 hospitalized patients, the mean age was 62 ± 16 years [23]. Comparing the results of these studies, the difference can be in the samples. In our study, we included both inpatients and outpatients, while in the mentioned studies, only inpatients were examined. There was no significant difference between men and women in previous reports and this shows the similarity of age and sex of patients in different studies.

In our study, the mean age of patients with mild to moderate severity, hospitalized patients who recovered, and hospitalized patients who died were 38.27 ± 13.62 , 53.36 ± 15.58 , and 66.49 ± 17.14 years, respectively. That is, the severity of the disease increased with age. A study by Ghweil et al. found that severe illness was more common in the elderly and mild cases occurred at a younger age. The mean age of patients was 62.6 ± 0.1 years in severe cases and 55.5 ± 10.1 years in mild cases [24]. Similar results were reported in the study by Liu et al. That is, the risk of severe disease in older age is higher than younger ages [25]. In the study of Mohase et al. and Yang Ell et al., the severity of the disease was also reported in the elderly [26, 27]. In a study by Javanian et al., older age was reported to be effective in mortality [28]. Also, in the study of Wang et al., old age was expressed as a worse prognosis in patients with Covid-19 [29]. The reason why the severity of the disease increases in old age may be due to decreased cell-mediated immune function and decreased humoral immune function. Also, in old age, the duration of the inflammatory process is longer and leaves more serious complications [30]. The prevalence of underlying diseases is also higher in old age [31], so the more severe disease in old age can be justified by these reasons.

Mortality in patients in our study was also assessed in terms of gender, which was not significantly different. Some studies have found gender to be effective in the mortality of Covid patients and have reported higher mortality in men than women [3], which is inconsistent with the results of our study.

In our study, the CT value in all patients was 26.8 ± 4.43 and in patients with mild to moderate severity who were treated on an outpatient basis was 27.45 ± 4.55 and in cases of severe and critical disease who recovered or died were 26.37 ± 4.41 and 26.05 ± 3.93 , respectively. As the numbers show, it is inferred that the load of the virus in outpatients is lower than in the other two groups. Although there was a difference

in hospitalized patients, this difference was not significant. In the study of Zeng et al., the viral load was reported to be higher in patients with severe infection [32]. In the study of Magleby et al., the viral load was higher in elderly patients [33]. In the study of Liu et al., the CT value was reported higher in patients with a severe infection than patients with milder infection [18]. In the study of Zhou et al., the median CT value in the incubation period was reported higher than the time of hospitalization [34]. In the study of Faico-Filho et al., The Faico-Filho et al. reported a U shape pattern for CT value. That is, in patients with mild disease severity and in severe cases of disease, the viral load was higher than in cases with moderate severity. In the same study, the CT value in different age groups was not significantly different [20]. In the study of He et al., the amount of viral load in patients with different intensities was not different [35]. Based on the results of our study and some reports, it seems that a decrease in CT value as an indicator of virus load was more associated with an increase in disease severity. In our study, no correlation was found between CT value and age, and sex of patients. In the study of Taziki et al., the CT value of the age groups did not differ significantly [36].

In our study, the relationship between CT value and mortality of hospitalized patients, ie cases with the severe and critical disease, was investigated, but no significant difference was observed. In the study of Magleby et al., the viral load at the time of admission was reported independent of the probability of death [33]. The study by Yagci et al. and Faico-Filho et al. reported a similar result [12, 20]. In contrast, other articles have reported different results. In the study of Faico-Filho et al., a lower CT value was reported along with increased mortality risk [20]. A study by Magleby et al. had shown a similar conclusion [33]. The difference in these results may be due to the different design of the study or the prevalence of some underlying factors in the severity of the disease that had affected the mortality. In our study, there was no significant difference between the CT values of hospitalized or dead patients and the length of hospitalization time. In the study of Magleby et al., the amount of viral load at the time of admission was reported independent of the possibility of intubation [33]. In the study by Faico-Filho et al., survivors had higher CT values than those who died (27 vs. 21) [20], which is inconsistent with our study results. The difference in these results may be due to other factors influencing the outcome of the disease.

There are several reports about the relationship between HIV, Ebola, and Influenza viral load as a predictor of disease severity and progression of infection or its outcome [37–39]. Of course, some results were not conclusive [40]. However, SARS-Co-2 decreases the absolute amount of lymphocytes and increases inflammatory markers such as CRP and IL6, which is associated with worsening of the disease [41]. This finding has also been reported by Zhou et al. [30]. Also, the CT value can be affected by the sampling location, the experience of the person taking the sample, because usually samples taken from sputum have a higher viral load than samples taken from the throat [42]. Viral infections have been reported to cause an increase in acute phase reactants and can induce severe systemic inflammatory reactions that are known as cytokine storms [43]. These reactions are higher in patients with the severe disease than in mild or moderate cases and have been reported to be associated with disease severity [44].

In our study, the mean age of patients with severe disease who recovered slightly decreased from the onset of the pandemic to the time of this study, but the mean age of patients who died during this period did not change. Also, the sex distribution of patients showed that in the number of dead hospitalized patients before July, the frequency of women was more than men, but after this date, the frequency of men was always higher than women, and this ratio was still present for recovered hospitalized patients. The mean CT value did not change significantly during this period. Although these changes have not been significant, in many other cases the behavior of the virus in terms of severity, prevalence, and clinical symptoms have changes that can be influenced by environmental or genetic factors of the virus and need further study. Some limitations of this study in generalizing the results should be considered. In both groups of outpatients and inpatients, PCR test was performed only once and at the time of referral and it was not possible to repeat the test during hospitalization or a specific period.

Conclusion

Regarding the predictive role of CT value in predicting the deterioration of Covid-19 patients, the results of this study show that the amount of CT value at the time of admission is important only in predicting the severity of the disease this time and is an indicator of higher viral load; but regarding the course and outcome of the disease, the mean CT value of the admission time is not useful. However, even in mild cases of the disease or low viral load, due to the possibility of transmission to others and to prevent, the patient isolation should be considered.

Declarations

Ethical approval and consent to participate

The study was under the Declaration of Helsinki 1964 and its successive amendments. Moreover, the study protocol was approved by the Regional Ethical Committee at Golestan University of Medical Sciences, Gorgan, Iran (IR.GOUMS.REC.1399.031).

Consent to publish

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

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None.

Authors' contributions

MHT and SMH performed the study. AR and MM analyzed the data and wrote the manuscript. AT and MHT provided clinical data. AR, MM, MHT, and SMH helped edit the paper. MHT and SMH supervised the study and applied for grants. All authors read and approved the final manuscript.

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Figures

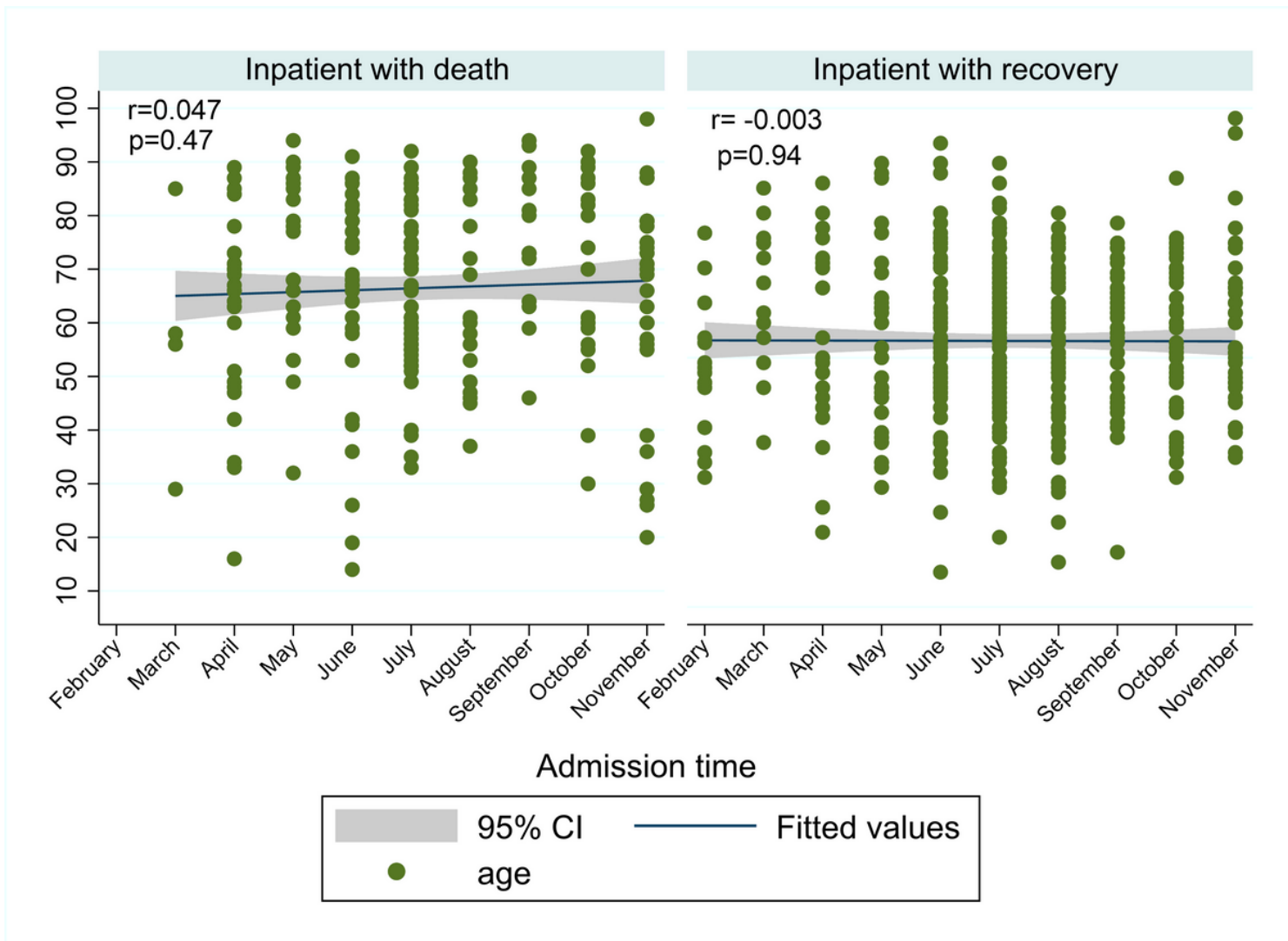


Figure 1

The trend of age changes in Covid-19 patients with the date of admission

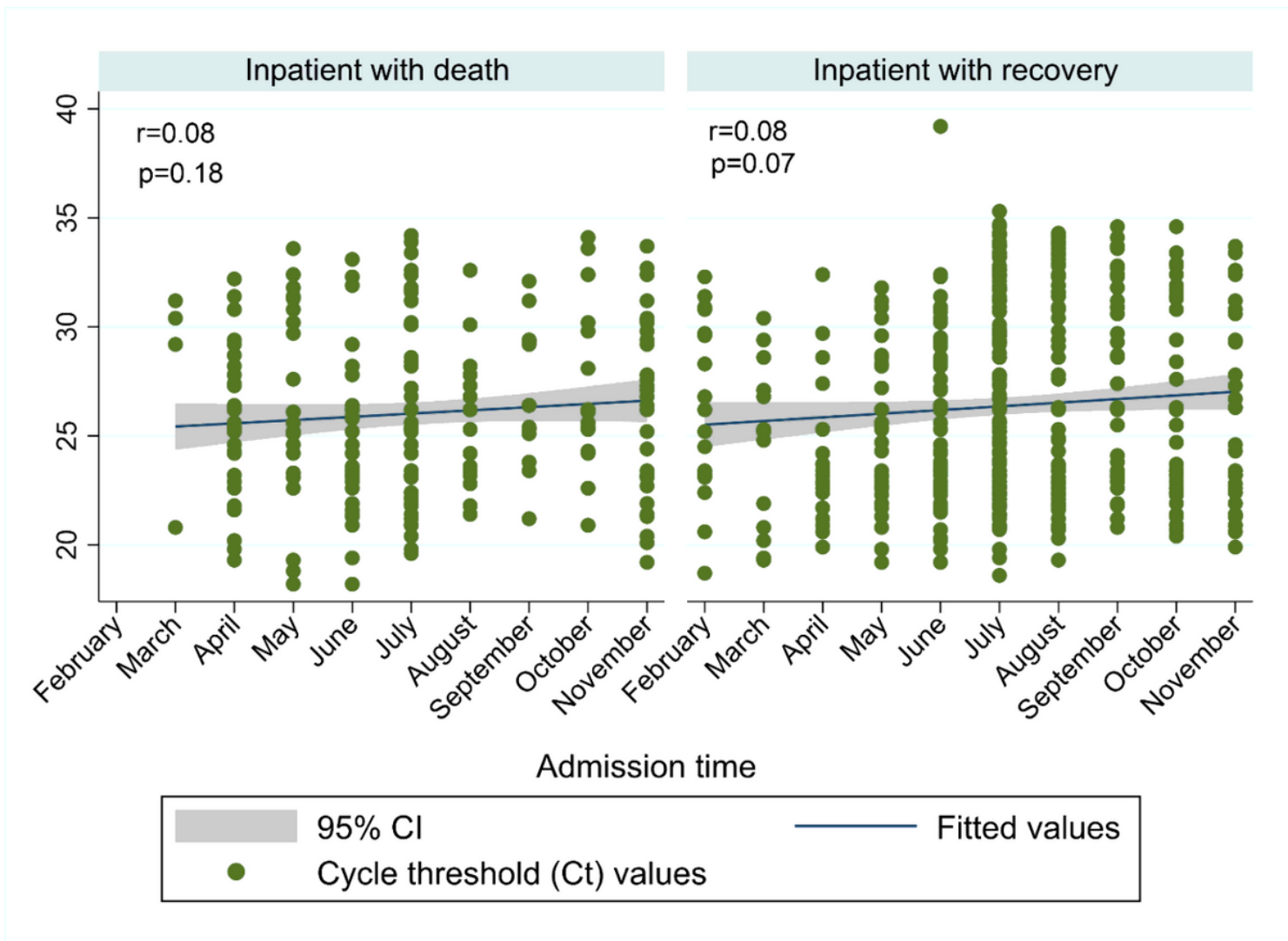


Figure 2

The trend of CT values changes in Covid-19 patients with the date of admission

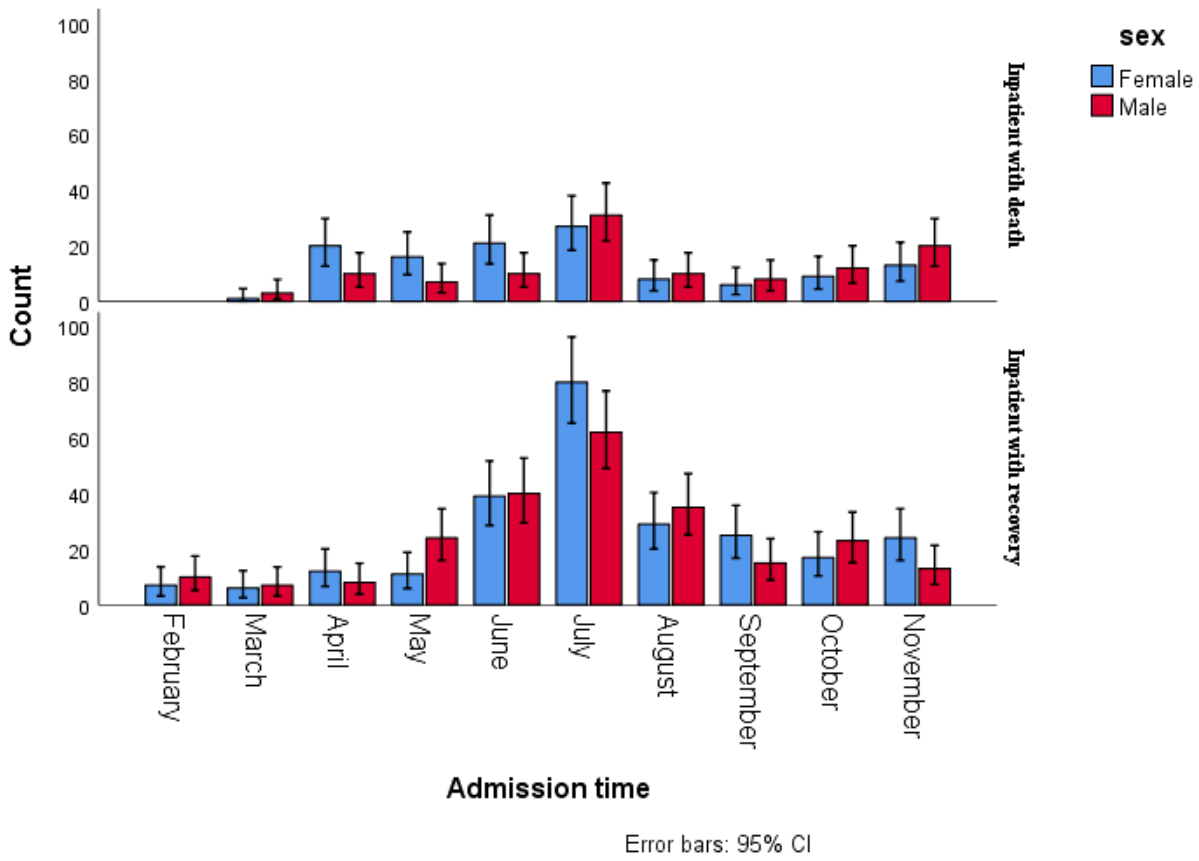


Figure 3

Distribution of sex for admission of Covid-19 patients at different times according to the type of patients