Recovery of Olfactory and Gustatory Dysfunctions in COVID-19 Patients in Iran: a Prospective Cohort Study

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Abstract

Background: Olfactory and gustatory dysfunctions (OD and GD) manifested unpredictably in COVID-19 patients. Considering the high prevalence of OD and GD and the importance of the sense of smell and taste in the quality of life, this study aimed to determine the association of some demographic and clinical factors with OD and GD recovery in COVID-19 patients in Iran.

Methods: This prospective cohort study was performed on COVID-19 patients with OD and GD during the first and second peak of pandemic in Golestan province, Iran. We used a local health care registry system for data collection. All cases had positive RT-PCR test for SARS-CoV-19 in nose and nasopharynx swab samples. Variables included age, sex, ethnicity, geographical location, time of onset of symptoms, severity of OD and GD (complete or partial). The follow-up time for recovery from OD and GD was six months. Time to recovery for OD and GD was estimated by Kaplan-Meier considering complete recovery as an endpoint. Differences among groups were evaluated using log-rank test and Cox proportional-hazard models as appropriate in SPSS version 16.

Results: A total of 242 patients completed the study. The mean age of patients was 39.12 ± 11.89 years. There were 127 (52%) females. After six months, 239 (98.8%) patients had complete OD recovery and 80.9% and 83.56% of patients recovered within the first 30 days following the onset of OD or GD, respectively. The mean time of OD recovery was significantly higher (35.07 ± 4.25 days) in cases infected in the first peak of pandemic than in the second peak (21.65 ± 2.05 days) ($p=0.004$). This finding also was observed for the recovery time of GD ($p=0.005$). The mean recovery time of GD was significantly higher in women than men (35.55 ± 4.33 vs. 23.20 ± 2.46 days) ($p=0.04$). The age (less than 20 years), second peak of epidemic, and partial dysfunction were identified as significant predictors for recovery.

Conclusions: COVID-19–related OD and GD had high rate of recovery in the first month from onset of symptoms. Age of patients, severity of OD/GD and infecting in second peak of epidemic might be related to the recovery of OD or GD in patients with COVID-19.

Introduction

Coronaviruses can cause a wide range of disorders from mild acute upper respiratory tract infections to severe life treating diseases including SARS, MERS and COVID 19 (1-3). The coronavirus pandemic is developed by severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 virus. The clinical manifestations of COVID 19 are diverse and include olfactory and gustatory dysfunctions (OD and GD) (4-7). However, the OD or GD in COVID 19 has unique properties and differs from OD or GD in other viral disease. They are very common and are known as a principal manifestation of disease and in most cases are independent to nasal congestion or rhinitis (8). The incidence of OD has been reported in various studies from a minimum of 0.5% to 0.65%, to a maximum of 0.86% to 0.88% (9, 10). The virus has a strong tendency to infect the olfactory system (11). The virus can also enter the brain through the olfactory bulb (12, 13). It is strongly recommended that in COVID 19 pandemic all patients with the OD

should be isolated (14). OD may lead to disruption of daily activities, mood disorders, decreased appetite, and decreased quality of life (15). Since the sense of smell contributes to the sense of taste, patients with hyposmia or anosmia also have difficulty in taste sensation and may have impairments in appetite and enjoyment of food (16). There are still many questions for otolaryngologists and neurologists about the prognosis of OD and GD (17). There are several studies about the short-term outcome of OD and GD in COVID 19 and most of them report good recovery in most cases. However, there are limited reports regarding the long-term outcome of OD recovery and its prognosis; especially in a minority of patients that suffering from OD for more prolong time (17-20). Considering the high prevalence of OD and GD in COVID 19 and the importance of the sense of smell and taste in the quality of life, this study aimed to determine the association of some demographic and clinical factors with OD and GD recovery during the coronavirus pandemic in Golestan province.

Methods

This clinical-based prospective cohort study was undertaken between March 25th and October 24th, 2020 in Golestan province, in northeastern Iran. The study was approved by the Ethics Committee of Golestan University of Medical Sciences (No. IR.GOUMS.REC.1399.031). Patients received clear oral information. Their oral consent was obtained through telephone interviews.

The patients were identified from a local health registry system. It was a computerized database of electronic health records. All patients diagnosed as having COVID-19 by reverse transcriptase PCR (RT-PCR) test for SARS-CoV-2 from nasopharyngeal swabs. Among them, outpatient cases with OD were included in the study. The OD and GD were assessed as a self-report. The exclusion criteria were as follows: patients with a history of cognitive disorders, and patients with OD and/or GD known before the epidemic.

Demographic data including sex, age, and general symptoms were collected from the electronic health records. Information about OD and/or GD of each patient, including the duration of the symptoms and the time to recovery were obtained by telephone interview. Patients were followed by dedicated online surveys from March 25th and October 24th 2020. The grade of OD and GD was defined as “partial” or “complete” to avoid subjective interpretations. All patients were then contacted by telephone up to four times to complete the study. The study follow-up was stopped on October 24, 2020.

A descriptive analysis was performed. Categorical variables were described as frequency rates and percentages, and continuous variables were described using mean, median, and standard deviation (SD). Time to recovery for OD and GD was estimated by Kaplan-Meier curves considering complete recovery as an endpoint. Differences among groups were evaluated using log-rank test and Cox proportional-hazard models as appropriate. Variables analyzed were age, gender, ethnicity, morbidity in two epidemic waves (February to April, and May to July), onset of OD, grade of OD, gastrointestinal dysfunction, and timing of presentation of OD and GD. Multivariable analysis was performed with Cox proportional hazards models including all variables. Statistical Package for the Social Sciences for Windows (SPSS version 26, 0; IBM

Corp, Armonk, NY, USA) was used to perform the statistical analyses. A level of $p < 0.05$ was used to determine statistical significance.

Results

A total of 242 patients completed the study. The mean age of patients was 39.12 ± 11.89 years (range 9–75). There were 127 (52%) females and 115 (48%) males. The following ethnicities composed the cohort: Fars (49.6%), Turkmen (45%), and Sistani (5.4%). 117 cases were from the first wave (February to April) and 125 cases were from the second wave (May to July) of COVID-19 epidemic in Iran. (Table 1).

Table 1

With respect to the onset of general symptoms in COVID-19 patients (e.g. the start of fever, cough, dyspnea, fatigue, diarrhea, abdominal pain, anorexia, nausea or vomiting), the incidence of OD in 27 (11.2%), 15 (6.2%) and 200 (82.6%) cases were occurred before, after and simultaneous with onset of general symptoms respectively. The mean time between OD and general symptoms was 5.03 ± 2.32 and 10 ± 10.51 days in the case of before and after onset respectively. The incidence of complete and partial forms of OD was 77.7% and 22.3%, respectively. The incidences of complete and partial GD and the gastrointestinal dysfunction were 70.2%, 20.2% and 38.8% respectively. OD recovery status in 242 cases showed that after six months, 239 (98.8%) patients had complete recovery, one (0.4%) had partial recovery and two (0.8%) had no recovery. Also, from 219 cases with GD disorder, all cases had complete recovery after six months (Table 1). The recovery times of the OD and GD was shown in Figure 1. 80.9% and 83.56% of patients recovered from OD and GD within the first 30 days following the onset of OD or GD, respectively (Figure 1).

Mean and median time to recovery of OD and GD were presented in Table 2. The mean time of OD recovery in cases infected in the first peak of pandemic was significantly higher (35.07 ± 4.25) than in cases infected in the second peak (21.65 ± 2.05) ($p=0.004$). Also, this difference was similar for recovery time of GD ($p=0.005$). The mean recovery time of GD was significantly higher in women (35.55 ± 4.33) than men (23.20 ± 2.46) ($p=0.04$).

The final multivariable Cox-regression analysis model identified that age less than 20 years vs age >60-year, second wave epidemic, and partial olfactory dysfunction were identified as significant predictors of OD recovery. The hazard of OD recovery among patients with age less than 20 years was 3.96 times (Adjusted Hazard Ratio (aHR): 3.96, 95% CI: 1.25-12.52) higher than patients age >60-year. The hazard of OD recovery among cases that infected in the second peak of epidemic was increased by 54% (aHR: 1.54; 95% CI: 1.09-2.18) as compared to first peak. Furthermore, the hazard of OD recovery among individuals who had partial OD was 2.97 times (aHR: 2.97; 95% CI: 1.21-7.29) higher as compared to those who had complete OD (Table 3, figures 2, 3 and 4). Also, age less than 20 years and second peak of epidemic were significantly associated with increased aHRs for gustatory dysfunction (GD) (Table 4, figures 5 and 6).

Discussion

This study was designed to investigate the recovery process of OD and GD over time in patients with COVID-19. This study showed that approximately 81% of OD and 84% of GD recovered in the first 30 days of their onsets and with a mean recovery time of 35.93 ± 27.71 days and 37.75 ± 29.52 days for OD and GD respectively. In addition, age less than 20 years, incidence at the time of the second peak of pandemic and partial grade of OD are among the factors affecting the recovery from OD. Among these factors, age and incidence in the second pandemic peak were also factors affecting the recovery from GD.

In the present study 52.5% of cases were female. This higher incidence of OD in COVID-19 women patients was similar with other reports. In the study of Romero-Gameros, C.A. et al. the incidence of OD in women was 63.5% (21). In addition, the study by Chary et al. and Gorzkowski et al. reported higher incidence of OD in women than in men (22, 23). The study by Lechien et al. showed that 59.1% of 252 patients with COVID-19-induced OD were female (24). The results of these studies are consistent with the results of our study. However, a study by Meini et al. On 100 hospitalized patients with COVID-19 showed that men had a 2: 1 ratio of olfactory and taste disorder compared to women (25). This difference may be due to the inpatient setting of this study.

Our study showed that the mean age of patients was 39.12 ± 11.89 years and most patients were in the age group of 20 to 40 years. Other studies have shown almost the same findings as our study, including the study of Gorzkowski et al. that reported a mean age of 39.7 ± 13.7 years (23) and the study of Romero-Gameros et al. that reported a mean age of patients of 41 ± 13 years (21). In the study of Lechien et al., the mean age of patients was 36.9 ± 11.4 years (24) and in the study of Amer et al. the mean age of patients was 34.26 ± 11.91 years (26); but in the study of Meini et al., that conducted on hospitalized patients, the mean age was 65 ± 15 years, this difference may be due to the difference in the studied population (25).

Based on the results of our study, in 82.6% of cases the onset of OD and general symptoms in COVID-19 patients was at the same time or simultaneous, in 11.2% of cases OD start before general symptoms, and in 6.2% of cases the onset of OD was after the general symptoms. This observation was similar to other reports. Lv et al. showed that in more than 87% of cases, the onset of OD and GD coincided with the onset of general symptoms of COVID-19 (27). Ramasamy et al. found that 15.9% of patients reported onset of OD or GD before the onset of general symptoms, 34.1% after, and 36.4% with the onset of general symptoms of COVID-19 (28). Therefore, the most common time of onset of OD coincides with the onset of general symptoms, which is consistent with the findings of our study. In addition, our study showed that in COVID-19 patients who did not develop OD at the onset of the general symptoms, the mean of time window was 5.03 ± 2.32 days before and 10 ± 10.51 days after the general symptoms. Ramasamy et al. reported that in most COVID-19 patients in their study the median duration of OD and also the complete recovery time from it was 7 days (28). In addition, the study by Chary et al., showed that OD occurred from 3 days before to 7 days after general symptoms of COVID-19 (22).

The recovery rate of OD in this study was 80.99% at the end of the first 30 days, this rate reaches 81.82% by 90 days and 98% of patients recover by 6 months. This trend was also observed for GD and in our study all cases of GD had complete recovery within 6 months of follow-up. Gorzkowski et al., showed that 95.71% of OD recovered within 26 days after the onset of OD, and 51.43% of patients achieved complete recovery (23). Meini et al. reported 82% improvement for OD during the 4-week follow-up (25). Lv et al., showed that during 4 weeks 89.7% of COVID-19 patients had GD and OD recovery (27). Paderno et al., reported 87% and 82% recovery rates for OD and GD during one month respectively (29). Hopkins et al., reported a 79% recovery rate over the course of a month (30). Amer et al., reported complete and partial OD recovery rate of 96 patients with COVID-19; this rate was 33% and 41% for complete and partial recovery respectively within 11 days, while 25% did not achieve any recovery during one month (26). In a study by Vaira et al., 7.3% of patients still had severe disorders during the two-month follow-up (31). Cho et al. also reported an OD recovery rate of 71.8% (32). In general, the results of these studies are consistent with our findings and the comparison of the results of the above studies shows that a significant percentage of patients achieve OD and GD recovery in a short time and the difference in the percentages of recovery rates may be attributed to the assessment method of OD or GD, the duration of follow-up or genetic susceptibility to the disease.

In the present study, the mean and median of recovery time were 28.05 ± 2.33 and 14 ± 0.56 days for OD, and 29.52 ± 2.55 and 14 ± 0.60 days for GD. In study of Chary et al., the recovery time for OD and GD was 15 days (22). The OD recovery time in the study of Meini et al., was 18 days (25). In the study by Cho et al., the mean time for OD recovery was 10.3 ± 8.3 days (30). Gorzkowski et al., and Romero-Gameros, C.A. et al., reported 11.6 and 10 days, respectively as the mean recovery time from onset of OD (21, 23). In the study by Cho et al., mean time for GD recovery was 9.5 ± 6.8 days and the complete recovery rate of GD was 83.3% (32).

The present study did not show a significant difference for the median recovery time in patients with OD in terms of gender, age groups and ethnicity. So that the findings of the study of Chary et al. and the study of Lv et al. are in line with the results of our study (22, 27). However, our study showed that the median recovery time was higher in people infected with the first peak of the epidemic than in those infected in the second peak of the epidemic, which may be due to the fact that OD and GD was known in the first peak, therefore there was more knowledge about the management of OD or GD cases in the second peak and this may be the reason of the reduction of the recovery time. It may also be related to changes in the pathogenicity of SARS-Cov-2 virus. Gorzkowski et al., studied 229 patients with COVID-19 and reported higher incidence of OD in cases that were infected before March 20, 2020 and lower incidence in cases that were infected later (70.3% vs. 53.9%) (23).

Our study showed that the probability of recovery for OD and GD over time in the under 20 years' age group is about 4 times higher than in the over 60 years' age group. The study by Paderno et al. also showed that the patients with the partial OD were more likely to recover than patients with complete OD. However, this study did not show a significant difference for recovery of OD or GD among age groups (29). Lv et al., also showed that age and gender had no effect on the improvement of OD or GD (27).

We studied the recovery of OD and GD in COVID-19 patients over a long period of time, e.g., 6 months and our result showed that 98% of patients had been recovered during this time. However, it is necessary to point out the limitations of this study. The evaluation of OD and GD in COVID-19 patients was done by means of a self-reported method and there was no objective assessment. In addition, no quantitative scale was used to classify the severity of OD or GD. The status of smoking and other co-morbidities' or diseases with potential effect on the OD or GD recovery process were not investigated. These limitations can be applied in future studies.

Conclusions: COVID-19–related OD and GD had high rate of recovery in the first month from onset of symptoms. Age of patients, severity of OD/GD and infecting in second peak of epidemic might be related to the recovery of OD or GD in patients with COVID-19. In the treatment plan of these patients it is advisable to reassure the patients about the good prognosis and recovery of OD and GD.

Declarations

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Authors' contributions

MHT and SMH performed the study. AR and MM analyzed the data and wrote the manuscript. AT and MHT provided clinical data. MAV helped the statistical analysis. 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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Availability of data and materials

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

Ethical approval and consent to participate

The study was approved by the Ethics Committee of Golestan University of Medical Sciences (No. IR.GOUMS.REC.1399.031). Patients received clear oral information. Their oral consent was obtained through telephone interviews.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Tables

Table 1: Characteristics of COVID-19 Patients Presenting with Olfactory/Gustatory Dysfunction

Variable	Frequency
Age, mean (SD), years	39.12±11.89
Age, n (%), year	
<20	4 (1.7)
20-40	133 (55)
40-60	91 (37.6)
=>60	14 (5.8)
Sex, n (%)	
Female	127 (52.5)
Male	115 (47.5)
Ethnicity	
Fars	120 (49.6)
Turkmen	109 (45)
Sistani Persian	13 (5.4)
Waves of epidemic	
First wave	117 (48.3)
Second wave	125 (51.7)
Onset of olfactory dysfunction, n (%)	
At the same time as general symptoms of COVID-19	200 (82.6)
Before general symptoms of COVID-19	27 (11.2)
After general symptoms of COVID-19	15 (6.2)
Severity olfactory dysfunction, n (%)	
Complete olfactory dysfunction	188 (77.7)
Partial olfactory dysfunction	54 (22.3)
Gustatory dysfunction, n (%)	
Complete gustatory dysfunction	170 (70.2)
Partial gustatory dysfunction	49 (20.2)
Non gustatory dysfunction	23 (9.5)
Gastrointestinal dysfunction, n (%)	

Yes	94 (38.8)
No	148 (61.2)
Outcome of olfactory symptoms after 6 Month, n (%)	
Recovery	239 (98.8)
Partial recovery	1 (0.4)
Nonrecovery	2 (0.8)
Outcome of Gustatory symptoms after 6 Month, n (%)	
Recovery	219 (100)

Table 2. Distribution of mean and median time of OD and GD recovery by patients' characteristics

Variable	Olfactory dysfunction		Gustatory dysfunction	
	Mean time of OD recovery	Median time of OD recovery	Mean time of GD recovery	Median time of GD recovery
	Mean±SE	Median±SE	Mean±SE	Median±SE
Total	28.05±2.33	14±0.56	29.52±2.55	14±0.60
Sex				
Female	32.75±3.82	14±0.76	35.55±4.33	14±1.05
Male	22.82±2.39	0.14±0.56	23.20±2.46	14±0.71
	0.06*		0.04	
Age group				
<20	8±1.41	8±2	8±2	10±0
20-40	29.13±3.29	14±0.78	31.18±3.70	14±0.94
40-60	26.58±3.62	14±0.78	27.09±3.78	14±0.91
60<	33.14±9.42	14±3.70	34.92±9.99	14±8.98
	0.07		0.13	
Ethnicity				
Fars	34.05±4.08	14±0.95	36.03±4.34	15±0.98
Turkmen	22.83±2.46	12±0.86	23.06±2.61	12±0.86
Sistani Persian	17.92±4.26	14±3.59	19.20±5.53	7±4.34
	0.06		0.04	
Waves				
First wave	35.07±4.25	15±1.56	36.36±4.27	15±1.68
Second wave	21.65±2.05	12±0.64	21.66±2.22	12±0.65
	0.004		0.005	
Onset of olfactory dysfunction				
At the same time as general symptoms of COVID-19	27.27±2.48	14±0.59	29.12±2.76	14±0.63
Before general symptoms of COVID-19	31.25±7.59	12±2.59	29.92±7.88	12±3.33
After general symptoms of COVID-19	32.53±11.93	14±2.65	32.53±11.93	14±2.65

	0.91		0.98	
Severity olfactory dysfunction				
Complete olfactory dysfunction	29.76±2.69	14±0.66	30.80±2.92	15±0.96
Partial olfactory dysfunction	22.22±4.51	11±1.63	25.40±5.22	12±1.34
	0.07		0.16	
Gastrointestinal dysfunction				
No	29.93±3.23	14±0.69	30.91±3.55	14±0.75
Yes	25.05±3.14	12±0.68	27.32±3.44	12±1.41
	0.15		0.28	

*Log Rank (Mantel-Cox) test

Table 3. Crude and adjusted hazard ratios for recovery of olfactory dysfunction (OD)

Variables	Crude HR, (95% CI)	P value	Adjusted HR, 95% CI	P value
Sex				
Female	Ref		Ref	
Male	1.26 (0.97-1.63)	0.08	1.26 (0.96-1.64)	0.09
Age group				
<20	3.50 (1.13-10.81)	0.02	3.96 (1.25-12.52)	0.01
20-40	1.07 (0.61-1.86)	0.81	1.09 (0.62-1.92)	0.75
40-60	1.07 (0.60-1.88)	0.81	1.03 (0.58-1.83)	0.91
60<	Ref		Ref	
Ethnicity				
Fars	Ref		Ref	
Turkmen	1.31 (1.00-1.72)	0.04	1.09 (0.79-1.51)	0.56
Sistani Persian	1.50 (0.84-2.69)	0.16	1.22 (0.63-2.34)	0.54
Waves				
First wave	Ref		Ref	
Second wave	1.43 (1.09-1.87)	0.008	1.54 (1.09-2.18)	0.01
Onset of olfactory dysfunction				
At the same time as general symptoms of COVID-19	Ref		Ref	
Before general symptoms of COVID-19	0.92 (0.61-1.38)	0.69	0.94 (0.60-1.48)	0.80
After general symptoms of COVID-19	0.93 (0.97-1.65)	0.93	1.16 (0.66-2.04)	0.59
Severity olfactory dysfunction				
Complete olfactory dysfunction	Ref		Ref	

Partial olfactory dysfunction	1.30 (0.96-1.76)	0.09	2.97(1.21-7.29)	0.01
Gastrointestinal dysfunction				
No	Ref		Ref	
Yes	1.19 (0.91-1.55)	0.18	1.08 (0.80-1.44)	0.60
Gustatory dysfunction				
Complete gustatory dysfunction	0.71 (0.46-1.11)	0.13	0.86 (0.54-1.39)	0.55
Partial gustatory dysfunction	0.89 (0.54-1.48)	0.67	0.42 (0.15-1.19)	0.10
Non gustatory dysfunction	Ref		Ref	

Abbreviations: HR, hazard ratio; CI, confidence interval. *Adjusted for all covariates

Table 4. Crude and adjusted hazard ratios for recovery of Gustatory dysfunction (GD)

Variables	Crude HR, (95% CI)	P value	Adjusted* HR, 95% CI	P value
Sex				
Female	Ref		Ref	
Male	1.31 (0.99-1.72)	0.05	1.27 (0.96-1.68)	0.09
Age group				
<20	3.62 (1.01-12.90)	0.04	4.40 (1.20-16.09)	0.02
20-40	1.06 (0.60-1.89)	0.82	1.14 (0.64-2.05)	0.64
40-60	1.09 (0.60-1.96)	0.77	1.05 (0.57-1.90)	0.87
60<	Ref		Ref	
Ethnicity				
Fars	Ref		Ref	
Turkmen	1.36 (1.03-1.81)	0.03	1.12 (0.80-1.58)	0.49
Sistani Persian	1.56 (0.81-3.01)	0.17	1.21 (0.57-2.57)	0.60
Waves				
First wave	Ref		Ref	
Second wave	1.45 (1.10-1.92)	0.009	1.58 (1.11-2.26)	0.01
Onset of olfactory dysfunction				
At the same time as general symptoms of COVID-19	Ref		Ref	
Before general symptoms of COVID-19	1.00 (0.66-1.52)	0.98	1.00 (0.62-1.60)	0.99
After general symptoms of COVID-19	1.03 (0.61-1.76)	0.88	1.23 (0.70-2.16)	0.46
Severity olfactory dysfunction				
Complete olfactory dysfunction	Ref		Ref	
Partial olfactory dysfunction	1.23 (0.90-1.68)	0.19	1.00 (0.33-2.97)	0.99

Gastrointestinal dysfunction				
No	Ref		Ref	
Yes	1.15 (0.87-1.51)	0.31	1.02 (0.75-1.38)	0.88
Gustatory dysfunction				
Complete gustatory dysfunction	Ref		Ref	
Partial gustatory dysfunction	1.27 (0.92-1.75)	0.13	1.45 (0.47-4.46)	0.50

Abbreviations: HR, hazard ratio; CI, confidence interval. *Adjusted for all covariates

Figures

Figure 1

Pattern of recovery time for patients with olfactory and gustatory dysfunction

Figure 2

The cumulative hazard of recovery of OD over age group from February to July 2020

Figure 3

The cumulative hazard of recovery of OD over epidemic wave from February to July 2020

Figure 4

The cumulative hazard of recovery of OD over severity of OD from February to July 2020

Figure 5

The cumulative hazard of recovery of GD over age group from February to July 2020

Figure 6

The cumulative hazard of recovery of GD over epidemic wave from February to July 2020