Original Research

Estimating COVID-19 recovery time in a cohort of Italian healthcare workers who underwent surveillance swab testing

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ABSTRACT

Objectives: The COVID-19 pandemic is putting a huge strain on the provision and continuity of care. The length of sickness absence of the healthcare workers as a result of SARS-CoV-2 infection plays a pivotal role in hospital staff management. Therefore, the aim of this study was to explore the timing of COVID-19 recovery and viral clearance, and its predictive factors, in a large sample of healthcare workers.

Study design: This is a retrospective cohort study.

Methods: The analysis was conducted on data collected during the hospital health surveillance programme for healthcare staff at the University Hospital of Verona; healthcare workers were tested for SARS-CoV-2 through RT-PCR with oronasopharyngeal swab samples. The health surveillance programme targeted healthcare workers who either had close contact with SARS-CoV-2–infected patients or were tested as part of the screening-based strategy implemented according to national and regional requirements. Recovery time was estimated from the first positive swab to two consecutive negative swabs, collected 24 h apart, using survival analysis for both right-censored and interval-censored data. Cox proportional hazard was used for multivariate analysis.

Results: During the health surveillance programme, 6455 healthcare workers were tested for SARS-CoV-2 and 248 (3.8%, 95% confidence interval [CI]: 3.4–4.3) reported positive results; among those who tested positive, 49% were asymptomatic, with a median age of 39.8 years, which is significantly younger than symptomatic healthcare workers (48.2 years, $P < 0.001$). Screening tests as part of the health surveillance programme identified 31 (12.5%) of the positive cases. Median recovery time was 24 days (95% CI: 23–26) and 21.5 days (95% CI: 15.5–30.5) in right- and interval-censoring analysis, respectively, with no association with age, sex or presence of symptoms. Overall, 63% of participants required >20 days to test negative on two consecutive swabs. Hospitalised healthcare workers (4.8%) were older and had a significantly longer recovery time compared with non-hospitalised healthcare workers in both analyses (33.5 vs 24 days, $P = 0.005$).

Conclusions: Recovery from COVID-19 and viral clearance may take a long time, especially in individuals who are hospitalised. To detect asymptomatic cases, screening programmes for healthcare workers is recommended.

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Introduction

SARS-CoV-2 is a new single-stranded RNA coronavirus, first identified in Wuhan, China, in December 2019, and it is responsible for the onset of coronavirus disease 2019 (COVID-19) in humans.[1,2] The most common clinical presentation of severe COVID-19 is acute respiratory distress syndrome, while many people report mild symptoms, such as fever, cough and coryza. Some cases of COVID-19 are fully asymptomatic;[3] however, the exact percentage of asymptomatic cases remains uncertain.[4]

Italy is among the countries that has been worst hit by the coronavirus pandemic, with 3,920,945 total cases and 118,357 deaths (data last updated 22 April 2021).[5] Veneto, where the University Hospital of Verona is located, has the second most numerous cases among the Italian regions (405,031 total cases and 11,183 deaths).[5]

The COVID-19 pandemic has proved to be a challenge for healthcare systems around the world and, although many ongoing studies are making a valuable contribution in understanding this new infection, many issues remain unresolved. Criteria to safely readmit SARS-CoV-2–infected individuals into the community are still debated.[6,7] Healthcare workers (HCWs) are a particular subset of the general population that may acquire SARS-CoV-2 as an occupational infection. Special attention should be paid to plan their re-integration into the workplace, as they may transmit the infection to patients, other HCWs or visitors.[8] One of the main problems with SARS-CoV-2–infected HCWs is finding the right balance between the necessity to isolate until viral clearance and returning to work to ensure the continuity of care for patients.[9]

Up to October 2020, in Italy, a SARS-CoV-2 patient was considered to have recovered and to no longer be infectious following two negative tests, together with the complete resolution of the signs and symptoms of COVID-19.[10,11] Whereas, a 14-day self-quarantine was recommended for untested individuals who had close contact with a SARS-CoV-2–infected case. However, it is still unclear what actual timespan is required for an individual to reach viral clearance and to no longer be considered infectious. The aim of this study was to explore the timing of COVID-19 recovery and viral clearance, and its predictive factors, in a large sample of HCWs.

Methods

A retrospective study was conducted using data from the health surveillance programme (HSP) of the University Hospital of Verona (UHV) located in the Veneto Region (Italy).

Health surveillance programme

The HSP was established at a national level[12] to ascertain the SARS-CoV-2 virological status of all employees in healthcare settings, to protect the health of healthcare staff and their patients, and to ensure the continuity of care. Specific procedures aimed at implementing the HSP at the local level were developed by the Veneto region[13] as described below.

Setting and population. The HSP was conducted at the UHV, which is one of the main hospitals in the Veneto region, with 1215 beds and 124 day-hospital beds. As a high-level facility, it serves an area of 922,000 inhabitants, as well as patients from other Italian regions. The programme was organised and conducted by a specially appointed taskforce, comprising of staff from the Hospital Medical Management, Occupational Medicine and Microbiology Units, as well as residents of the postgraduate Schools of Hygiene and Occupational Medicine. The HSP included all UHV employees, staff temporarily operating at UHV structures (e.g. contractors, PhD students, internship holders) and University of Verona staff operating at UHV facilities. Employees on parental or sick leave and staff not currently working at the UHV were excluded from the HSP. All HCWs involved in the HSP between 29 February 2020, the date of the first swab collected in the UHV, and 18 May 2020, were included in this retrospective analysis.

HSP pathways for symptomatic and asymptomatic cases. The HSP had two different pathways for symptomatic and asymptomatic HCWs who had close contact with a SARS-CoV-2–infected individual (see Supplementary file). Close contact was defined as either contact with a SARS-CoV-2–infected individual within two metres, for more than 15 min and without any personal protective equipment, or an unprotected direct contact with the secretions of a SARS-CoV-2–infected individual. Asymptomatic close contacts were offered an oronasopharyngeal swab as soon as possible. Specific ambulatories were assigned to the HSP and the booking was managed by the staff of the task forces. HCWs who tested negative after close contact were exempt from quarantine, but they were monitored with swab repetition at days 7 and 14, starting from the date of close contact. For symptomatic (e.g. cough, rhino conjunctivitis, fever, ageusia, anosmia, sore throat) individuals who had come into close contact with a SARS-CoV-2 individual, a test was performed as quickly as possible in dedicated spaces of the emergency room to avoid contact with asymptomatic HCWs. If the test result was negative, they were required to stay home until resolution of symptoms and then to follow the HSP asymptomatic pathway.

If an individual had a positive test result to any of the swabs, home self-isolation was recommended for 14 days. At the end of this period, two swabs were performed, 24 h apart. Only if both swabs were negative the HCW was considered 'recovered' and allowed to go back to work. In cases where one of the two swabs tested positive, both swab tests had to be repeated after 7 days.

Prior to swab sample collection, a short epidemiological questionnaire was completed for every HCW (both symptomatic and asymptomatic), to ascertain the actual date of close contact, the presence of any symptoms, the nature of the contact (whether in the workplace or outside), and HCW age, working ward and personal contact details. Trained medical personnel, assisted by a professional nurse, collected oronasopharyngeal (both nostrils) swabs, in accordance with national and international guidelines.[14,15] Samples were tested for SARS-CoV-2 infection by a commercial real-time PCR method, Seegene AllplexTM2019-nCoV Assay (Seegene, Seoul, South Korea), which identifies the virus by a multiplex real-time PCR targeting three viral genes (E, RdRP and N gene). Samples were considered positive with a cycle threshold (Ct) value of ≤40 for at least one of the three target genes. Validation of the results was done with the National Reference Laboratory of National Health Institute.[16] Limit of detection of the AllplexTM2019-nCoV Assay was 4.8 copies/mL.

HSP screening. In addition to providing oronasopharyngeal swabs for individuals who were identified as having been in close contact with a SARS-CoV-2 patient, the HSP also provided testing to all HCWs, hence adopting a mass testing strategy.[17] Repeated screening swabs were carried out with different timings based on ward risk, in accordance with the protocols of the Veneto region.[13] Individuals working in high-risk wards were tested every 10 days, employees in the other clinical and surgical wards every 20 days, whereas the staff in the administrative sector were tested every 30 days. In the UHV, intensive care units, infectious and respiratory diseases wards and COVID units were considered as high-risk wards.

Ethics

In accordance with Decree-Law N.14 of 9 March 2020, personal data were collected to guarantee public health and to ensure the diagnosis and care of infected individuals in the context of the

COVID-19 emergency.[18] All the data were collected exclusively for the purpose of the HSP; they were anonymised and presented in an aggregated format to ensure privacy of the participants. The research was performed following the ethical standards of the 1964 Declaration of Helsinki and was launched and approved by the Institutional Board of the Veneto Regional Health Authority.[19]

Statistical analyses

A descriptive analysis was first conducted; frequency rates and percentages were used for categorical variables and medians for continuous variables. Cumulative incidence of COVID-19−positive HCWs was obtained through the Clopper Pearson method with an established 95% confidence interval (CI). Continuous variables were compared via the Mann-Whitney-U non-parametric test. Proportions for categorical variables were compared using the Chi-squared and Fisher's exact test. The median time to viral clearance (i.e. two consecutive negative tests, 24 h apart) was examined by Kaplan−Meier estimates. The association between clinical and demographic characteristics was investigated via Cox proportional hazard regression. Survival analysis was applied when considering either right- or interval-censored data.[20] With right-censoring analysis, the date of the second negative test was taken to be the exact recovery time. On the other hand, interval-censoring analysis considered the first positive swab as starting time point (t_0), the last positive swab before two consecutive negative swabs as left limit of the interval (t_l) and the second negative swab as right limit of the interval (t_r). A P-value <0.05 was considered significant. All analyses were performed using R software (version 3.5.2).

Results

Characterisation of COVID-19-positive HCWs

In the study period, 6455 HCWs underwent at least one oronasopharyngeal swab and 248 (3.8%; 95% CI: 3.4−4.3) tested positive for SARS-CoV-2 (Table 1). No significant differences emerged between the group of SARS-CoV-2−positive HCWs and non-infected HCWs with respect to age-, sex- or ward-related risk (Table 1). COVID-19-positive HCWs were identified either after referral to the HSP following close contact with a SARS-CoV-2−infected case (n = 217; 87.5%) or following the screening provided by the HSP (n = 31; 12.5%).

Of the 248 COVID-19-positive HCWs, 127 (51%) experienced at least mild symptoms (e.g. cough, rhino conjunctivitis, fever,

ageusia, anosmia, sore throat). Symptomatic HCWs had a median age of 48.2 years and were significantly older than the asymptomatic HCWs (39.8 years, P < 0.001). Seven of the symptomatic subjects (5.5%) were identified through the screening provided by the HSP. For the 109 (85.8%) HCWs with a known date of symptom onset, the median time between this date and the first positive swab was 3 days (95% CI: 2−4). In 16 (14.7%) of the symptomatic HCWs, symptoms appeared after the first positive swab (with a median time-lag of 3.5 days).

During the study period, 95% (n = 236) of COVID-19-positive HCWs were back at work after two consecutive negative swab tests for SARS-CoV-2.

Recovery time estimation

The median time of recovery, starting from the first positive swab test result and taking the second negative swab as the last day of infection, was 24 days (95% CI: 23−26) (Fig. 1). At the end of the study, 156 (63%) HCWs needed more than 20 days to achieve two consecutive negative swabs. HCWs who were tested after having been in close contact with a SARS-CoV-2−infected case had a median recovery time of 25 days (95% CI: 23−28); however, the median recovery time was 21 days (95% CI: 16−24) for those who were tested as part of the HSP (Tables 2 and 3).

HCWs who required hospitalisation for SARS-CoV-2 infection showed statistically longer times for recovery than COVID-19-positive HCWs who were not hospitalised (33.5 days vs 24 days; P = 0.005) (Fig. 2).

The HSP scheduled tests at fixed time points. Data structure was therefore considered with an analysis for median recovery time in the presence of interval-censored data.[21] Results obtained with interval-censoring method showed a slight difference in the estimate of median time to recovery compared with right-censoring analysis. For interval-censoring data analysis, the median recovery time estimate was 21.5 days (95% CI: 15.5−30.5) (Fig. 1); having been in close contact with a SARS-CoV-2−infected case and hospitalisation were still found to be associated with a longer recovery time (Tables 2 and 3).

Discussion

To date, only a few studies have investigated the virological status of HCWs, even though SARS-CoV-2 is known to be a nosocomial agent[22] with important outbreaks occurring in hospitals and

Table 1
Healthcare workers characteristics distinguishing by swab, symptoms and hospitalisation.

Characteristic	Positive swab in HCWs			Symptoms in positive HCWs				Hospitalisation of positive HCWs		
	Yes (n = 248)	No (n = 6207)	p-Value[a]	Yes (n = 127)	No (n = 118)	Unknown (n = 3)	p-Value[b]	Yes (n = 12)	No (n = 236)	p-Value[b]
Sex [n (%)]			0.985				0.319			0.210
Male	80 (32%)	1906 (31%)		46 (36%)	33 (28%)	1 (33%)		6 (50%)	74 (31%)	
Female	168 (68%)	4301 (69%)		81 (64%)	85 (72%)	2 (67%)		6 (50%)	162 (69%)	
Age in years [Median (IQR)]			0.432				<0.001			0.007
	45.1	45.7		48.2	39.8	46.2[c]		56.2	44.7	
	(31.1−53.9)	(32.3−54.1)		(33.8−54.9)	(29.9−52.3)			(45.3−60.9)	(30.9−53.2)	
Ward [n (%)]			0.591							
High-risk[d]	24 (10%)	542 (9%)								
Low-risk	244 (90%)	5665 (91%)								

IQR, interquartile range.
[a] p-values were computed using Chi-squared test and Mann-Whitney-U non-parametric test.
[b] p-values were computed using Fisher's exact test and Mann-Whitney-U non-parametric test.
[c] IQR not reported because of the low number of subjects.
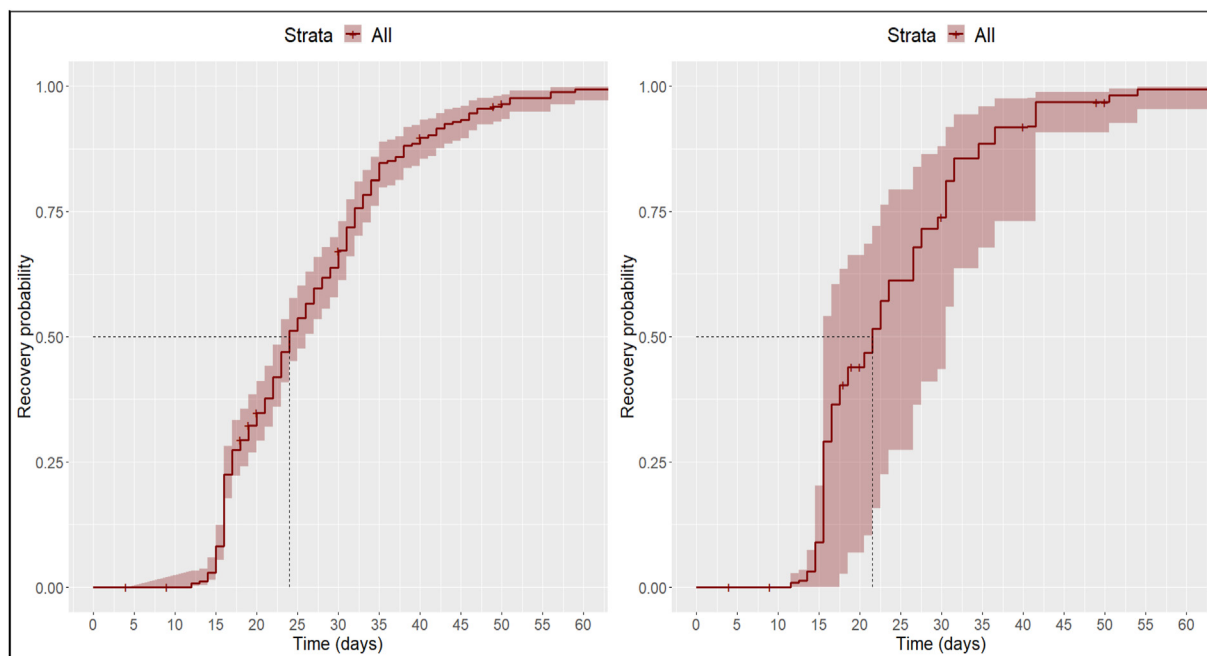[d] Infectious disease and respiratory disease ward, intensive care unit, COVID unit.

Fig. 1. Kaplan–Meier curves for recovery probability analysis with right-censoring data analysis (left panel) and interval-censoring data analysis (right panel). The left figure shows the Kaplan–Meier plot of time to COVID-19 recovery from the first positive swab to the last of the two negative swabs (performed with a time distance of 24 h) used to confirm viral clearance in healthcare workers. The right figure shows the Kaplan–Meier plot of COVID-19 recovery time in healthcare workers with interval-censoring data, considering the first positive swab as starting time point (t0), the last positive swab before two consecutive negative swabs as left limit of the interval (tl) and the second negative swab as right limit of the interval (tr). The median recovery time is the length of time corresponding to the probability of 0.5 (24 and 21.5 days, respectively, in the left and right figures).

in nursing homes.[23,24] Because asymptomatic individuals are thought to be contagious,[25–27] it is important to extend testing to all HCWs. Indeed, in the present study sample, almost half of the COVID-19-positive cases showed no symptoms at the time of testing. While no difference in age, sex or working ward was detected between negative and positive subjects, as shown in other studies,[24] the symptomatic cases were significantly older. Older people are known to be more severely affected by SARS-CoV-2.[28] A minority (14.7%) of the individuals who tested positive developed symptoms after the initial swab test. As infectiousness begins in the preclinical stage,[29] the HSP strategy was effective in identifying

cases at disease onset, thus reducing the potential spread of the infection. HCWs who showed symptoms were not permitted to return to work and were rapidly tested.

In the study sample, 95% of COVID-19-positive HCWs had recovered at the time of data collection. The median time from the first positive swab to the second consecutive negative test was 24 days, which is similar to findings reported by Carmo et al.,[30] who found a median recovery time of 24 ± 9 days. Recovery times between 9.5[31] and 21 days[9,32,33] have been reported in other studies.[34,35] These differences may be due to different diagnostic strategies or to the timing of the first positive swab. Indeed, in our

Table 2
Kaplan–Meier estimation of recovery time considering right- and interval-censoring analysis.

Stratification variables	Right-censoring analysis			Interval-censoring analysis		
	n	Median recovery (days)	95% CI	n	Median recovery (days)	95% CI
Total	236	24.0	23–26	236	**21.5**	15.5–30.5
Sex						
Male	78	25.5	22–30	78	22.5	15.5–34.5
Female	158	24	23–26	158	20.5	15.5–30.5
Age group (years)						
25–29	32	20	17–23	32	16.5	15.5–31.5
30–39	61	25	23–31	61	23.5	15.5–39.5
40–49	42	27	22–30	42	22.5	17.5–31.5
50–59	81	23	20–26	81	20.5	15.5–30.5
60–66	20	29.5	23–24	20	25.5	21.5–30.5
Symptoms						
Yes	123	26	23–29	123	22.5	15.5–31.5
No	111	23	21–26	111	20.5	15.5–30.5
Close contact						
Yes	210	25	23–28	210	22.5	15.5–30.5
No	26	21	16–24	26	16.5	15.5–23.5
Hospitalisation						
No	224	24	22–26	224	21.5	15.5–30.5
Yes	12	33.5	27–56	12	29.5	26.5-NA[a]

CI, confidence interval.
[a] A 95% upper confidence limit of NA (infinity) is common in survival analysis due to the fact that the data is skewed.

Table 3
Recovery hazard ratios (HRs) estimated in the multivariate Cox proportional hazard model considering right- and interval-censoring analysis.

Characteristic	Right-censoring analysis			Interval-censoring analysis		
	HR	95% CI	P-Value	HR	95% CI	P-Value
Sex	0.93	0.70—1.23	P = 0.614	0.90	0.67—1.21	P = 0.488
Age	1.00	0.99—1.01	P = 0.762	1.00	0.99—1.01	P = 0.780
Symptoms	0.91	0.69—1.19	P = 0.489	0.95	0.69—1.30	P = 0.766
Close contact	0.44	0.28—0.69	P < 0.001[a]	0.48	0.32—0.71	P < 0.001[b]
Hospitalisation	0.42	0.23—0.77	P = 0.005[a]	0.46	0.22—0.96	P = 0.039[b]

CI, confidence interval.
[a] Recovery probability is 54% significantly lower in subjects who had a close contact compared to those who did not and 58% significantly lower in hospitalised subjects compared to non-hospitalised ones.
[b] Recovery probability is 52% significantly lower in subjects who had a close contact compared to those who did not and 54% significantly lower in hospitalised subjects compared to non-hospitalised ones.

study, there is a significant difference between those who were tested in the shortest time possible (i.e. because of being in close contact with an infected individual) and those who tested positive at the regular HSP testing. Individuals who tested positive as part of the HSP showed a shorter median recovery time (21 days), which is consistent with the aforementioned studies. Moreover, when we conducted a censoring-interval survival analysis to take into account the surveillance timing structure, the recovery time resulted in a median recovery time of 21.5 days, in line with literature data.[32,33]

Considering the two types of analysis (Fig. 1), recovery time estimated through a right-censored analysis describes the time needed to confirm (as per HSP criteria) the recovery of HCWs and thus to allow them back to work. This result plays a crucial role for the organisation and staff management. To adequately plan the level of safe staffing and to provide the continuity of care, a recovery time of at least 20 days should be considered. On the other hand, interval-censored analysis shows a better estimation of the

time of viral clearance since it takes into account the interval between the last positive and the two negative swabs, when clearance is likely to have occurred.

In our study, the multivariate Cox proportional hazard model showed no significant differences in the time to recovery related to sex, which is consistent with the literature.[30,34,35] Age was also not related to a longer recovery time in our sample;[35] however, other studies, have found a significant association between older age and prolonged time to viral clearance.[34,36,37]

COVID-19-positive HCWs who required hospitalisation had a significantly longer recovery time, when all other covariates in the model were fixed. This result, confirmed in the censoring-interval analysis, highlights how the severity of the disease is an independent risk factor for a longer time of recovery and viral clearence.[34—36]

The main limitation of the present study is the retrospective study design. The analysis was based on data collected primarily for the HSP. Elderly people, who are most severely affected by COVID-19, are not represented in the HSP sample, which consisted of young and middle-aged HCWs. In addition, only a few HCWs in this investigation were hospitalised; thus, further studies are needed to confirm the associations suggested by the current results. These issues might limit the generalisability of the results, although the current findings have important implications for surveillance programmes and public health policies.

In Italy, the current guidelines,[11] based on the WHO strategy,[38] recommend testing after 10 days from the first positive swab in the case of asymptomatic individuals and testing after 10 days from the onset of symptoms (with at least 3 days without symptoms) in the case of symptomatic individuals. In accordance with the results of the present research, the time needed to achieve viral clearance is much longer and therefore such a close swab timing, while beneficial for a rapid re-integration into social life and into the workplace, might lead to repeated tests, thus becoming unnecessarily expensive. A longer time interval before testing to confirm
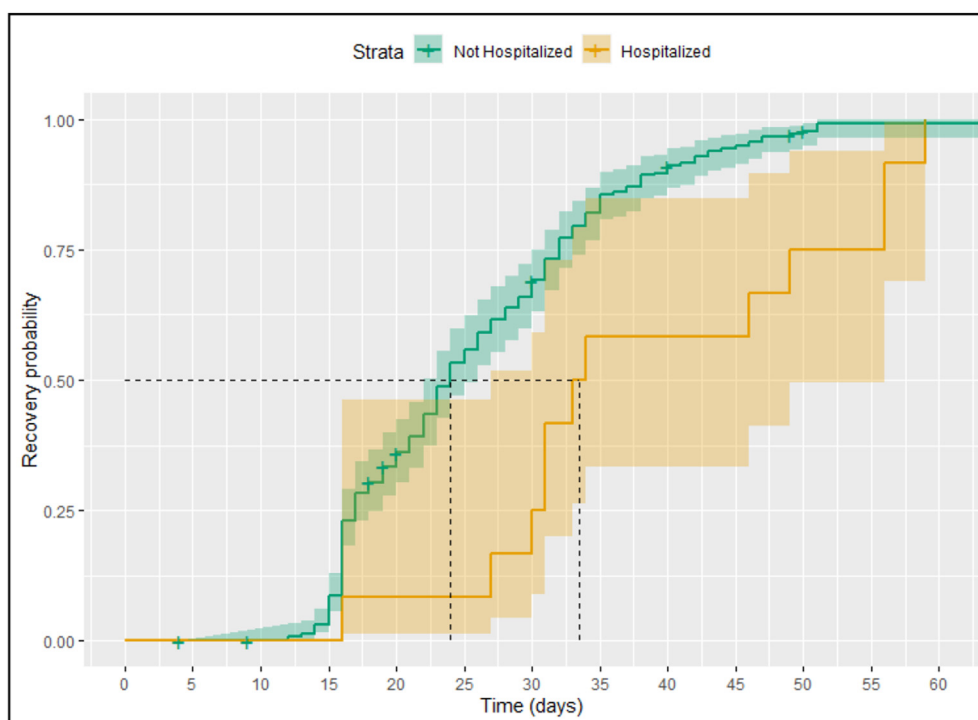

Fig. 2. Kaplan—Meier curves for recovery probability of hospitalised and non-hospitalised healthcare workers. The Kaplan—Meier plot was built without considering interval-censored data. Median recovery time was significantly different in the two groups of subjects (33.5 days in hospitalised and 24 days in non-hospitalised healthcare workers).

SARS-CoV-2 clearance in infected individuals might be advisable, especially in resource-limited countries.[30]

Conclusions

The viral clearance of SARS-CoV-2 and, consequently, the recovery assessment through a negative RT-PCR test takes a long time, especially in hospitalised individuals and in infected HCWs who had been in close contact with a SARS-CoV-2—infected case. This represents a serious burden for the health system and for personnel management. HCWs, hospital management and stakeholders should consider a recovery time of at least 20 days to optimise hospital resources.

A large proportion of infected individuals are asymptomatic at the time of testing[39,40] and it is known that infectiousness is already increasing from the preclinical and subclinical stage.[29] Therefore, it is important to test regardless of clinical presentation, especially in healthcare settings. Implementation of screening programmes in healthcare settings will allow testing of all personnel, including the HCWs, who may not report symptoms or may underestimate them.

Author statements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2021.05.014.

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