Time to a Negative SARS-CoV-2 PCR Predicts Delayed Return to Work After Medical Leave in COVID-19 Infected Health Care Workers

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Objective: To investigate whether HCWs return to work (RTW) after COVID-19 was associated with time to a negative viral detection test. **Methods:** To evaluate the association of RTW with an undetectable RT-PCR adjusting for different factors. **Results:** Three hundred seventy-five HCWs who required medical leave for COVID-19 at a hospital in Madrid. Multivariable analyses confirmed the association of delayed RTW with interval to negative PCR (OR_{adj} 1.12, 95% CI 1.08, 1.17) as well as age, sex, and nursing staff and clinical support services compared to physicians. A predictive model based on those variables is proposed, which had an area under the receiver operating curve of 0.82. **Conclusions:** Delayed RTW was associated with longer interval to a negative RT-PCR after symptom onset, adjusting for occupational category, age, and sex.

Keywords: COVID-19, health care workers, occupational infections, occupational injury, occupational lung disease, return to work

The pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has overwhelmed the entire world. The resulting disease, labeled ''coronavirus disease 2019'' (COVID-19), is known to have affected more than 140 million persons and caused more than 3,000,000 deaths worldwide as of April 17, 2021.[1] As many features of the infection that were labeled as ''unprecedented,'' the occupational risks of infection were in fact both precedented and known[2,3] for a variety of occupations, including health care workers (HCWs) charged with caring for individuals infected with contagious diseases. Although early investigations from the United States were distracted with the association of ethnicity and race differences on infection rates,[4] more detailed analyses have uncovered differential occupational exposures to infectious agents and diseases in general,[5] and to the SARS-CoV-2 virus in particular[6] as key underlying risk factors in pandemics such as COVID-19. Specifically with regards to HCWs compared to the general population, a Chinese study estimated at 3-fold the increased incidence rate.[7] A subsequent large epidemiological study from the United States and the United Kingdom[8] estimated again at 3-fold the increased risk of COVID-19 infection compared to the general community, after adjusting for testing frequency and other factors. A recent systematic review[9] has summarized the evidence of the increased occupational risk of coronavirus infections including SARS-CoV-2 among HCWs.

With more than 3.4 million cases and close to 77,000 deaths thus far, Spain is among the 10 most affected countries in the world.[1] Unlike previous viral epidemics, COVID-19 is recognized as an occupational disease or injury for different types of workers in Spain and other countries,[10] and it is reasonable to expect a similar trend in the rest of the world. As such, and with concerns about protracted neuropsychological,[11] respiratory,[12,13] cardiovascular,[14] and other potentially disabling effects in those recovering from the infection,[15] it is important to investigate factors predicting return to work (RTW) after related medical leaves[10] among workers at increased occupational risk for COVID-19. The aim of our study was to determine whether prolonged RTW after COVID-19 was associated with the interval since symptom onset for an initially positive viral RNA detection test to become negative in HCWs at a tertiary level care hospital in Madrid, Spain.

METHODS

We conducted a prospective study of health care workers (HCW)s in the Employee Health Service (EHS) at the Fundación Jiménez Díaz University Hospital (FJDUH) in Madrid, a tertiary care 659-bed hospital in Madrid, Spain. The EHS was responsible for screening, diagnosing, and following HCWs for COVID-19. The observation period was from 4-March-2020 until 6-June-2020. This study was approved by the FJDUH Research Ethics Committee.

Worker evaluation and data acquisition

HCWs were evaluated preferably within the first 48 hours at the EHS if symptomatic, based on the presence of fever (temperature $\geq$99.9°F), dyspnea, recent onset of persistent cough, chest pain and other respiratory and constitutional symptoms, ageusia and/or anosmia, diarrhea, etc. An initial reverse transcriptase polymerase chain reaction for the SARS-CoV-2 virus (RT-PCR) test (VIASURE SARS-CoV-2 Real Time PCR Detection Kit, CerTest Biotec, S.L., Zaragoza, Spain) was performed, and a positive result led to a medical leave. The workers were followed up clinically and by telephone, and subsequent RT-PCR and testing for IgM and IgG antibodies determined the return to work per published protocol.[16] If the infected worker had not required hospital admission and had been asymptomatic for 3 days, a diagnostic RT-PCR was requested within 10 days of symptom onset:

- -if this test result was negative, isolation ended and the worker returned to work.
- -if the RT-PCR was positive, IRT-PRC would be performed at 48 hours:
  - if this test turned out to be negative, isolation was lifted and the worker could return to work.
  - if positive, the clinical and microbiological situation was revaluated at 14 days for clinical management and return to work.

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Clinical significance: Health care workers are occupationally at risk of acquiring COVID-19. In this study, prolonged medical leave duration after COVID-19 was associated with a longer interval for direct viral detection test to become negative, but also with occupational factors. We also derived a predictive model for our outcome of interest.

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The clinical follow-up of the employees was jointly performed by EHS at the FJDUH, and the workers' primary care clinicians, while the latter were ultimately responsible for the administrative process of the medical leaves.

Our dichotomous outcome was RTW from medical leave after an interval equal to or exceeding 30 days. Our main predictor was the interval in days for an initially positive SARS-CoV-2 RT-PCR test to become negative. Our covariates were (1) age at diagnosis; (2) sex; (3) body mass index, both as a continuous variable, or categorized as obese ($BMI > 30\,kg/m^2$) or not; (4) disease severity, classified as critical if it required mechanical ventilation, severe if hypoxemia and/or tachypnea developed, and mild if neither did; (5) medical comorbidities, described with the Charlson comorbidity index,[17,18] and categorized as 0 or ≥ 1. Additionally, *a priori* infection risk categories were established for HCWs and for service areas in the hospital. The former were classified into physician, nursing staff (nurses and nurse assistants), and clinical support services (including technicians, administrative support, security guards and orderlies, and other). In the clinical support services group, only the security guards and orderlies had direct contact with patients. The service areas were grouped by high, intermediate, and lower infection risk. Higher exposure risk was deemed to occur in the Intensive Care Units (including the converted Operating Rooms), Respiratory Intermediate Care Unit, and Emergency Room. Intermediate exposure risk was deemed to occur in the medical wards, and lower risk in areas such as administrative offices, and other clinical areas.

Statistical analyses

Descriptive data are presented as counts and percentages, mean and SD, or median and IQR, as appropriate. Simple and multivariable logistic regression analyses were then performed to examine the association of a prolonged medical leave (>30 days) and interval (in days) for the SARS-CoV-2 RT-PCR to become negative after symptom onset, and adjusting for the above-mentioned covariates. We also sought to develop a predictive model and used the leave-one-out cross-validation method[19] to evaluate its classification performance, which was summarized by the receiver operating curve (ROC) and the area under it. Given the potential associations of some of the covariates, we evaluated multicollinearity using the variance inflation factor. Interaction terms were explored by comparing models with and without interaction term, using the likelihood ratio test. Statistical significance allowed an α error of 0.05, and odds ratios with 95% confidence intervals are presented.

RESULTS

The first COVID-19 patient was admitted to FJDUH on 26-February-2020, and the first infected HCW was diagnosed on 4-March-2020. By 6-June-2020, we had a total of 395 HCWs with confirmed COVID-19 (9.8% of the working population of the hospital), of whom 376 requested medical leave. For one of those workers, we were unable to establish the date of symptom onset, and 19 pauci- or asymptomatic workers were administratively assigned to work from home, and were not officially on medical leave, so the final study population consisted of 375 HCWs, of whom 346 HCWs (90.9%) had returned to work. No death has been recorded. We summarized the characteristics of the 346 HCWs in Table 1. Female sex and nursing staff occupations predominated. The workers were generally healthy, with only 8.8% being obese, and 12.8% having one or more chronic medical diseases. The frequency of an interval from symptom onset to RTW ≥ 30 days for the study group was 126 (33.6%), suggesting a substantial proportion of prolonged disease duration.[25] The workers of the study had a median of 3 RT-PCR tests (IQR 2 to 3, range 1 to 7).

Table 2 shows the results of unadjusted analyses. All the 34 workers who had not returned to work at the end of the study observation period were included in the group with >30 days until RTW. Delayed RTW was associated with interval to negative SARS-CoV-2 RT-PCR result exceeding 30 days (OR 1.12, 95% CI 1.08, 1.16), as well as age, obesity, nursing staff and non-direct patient contact occupational groups, and disease classified as clinically critical or severe. This finding translates into a 12% increase in the odds of RTW > 30 days for each day to a negative RT-PCR test result.

Adjusted multivariable analyses (Table 2) confirmed the association of delayed RTW with interval to negative RT-PCR (OR_{adj} 1.12, 95% CI 1.08, 1.17), as well as those of age, and nursing staff and non-direct patient contact occupational group (compared to physicians), but not of obesity, or severity of clinical presentation. Occupational group and hospital risk area were associated (Chi-Square *P*-value < 0.001), and phi coefficient $= 0.4$. But the final model includes only one of these two variables, specifically occupational group. We did not find an association between clinical severity and occupational group or hospital service area. Male sex, on the other hand, was associated with adjusted decreased odds of delayed RTW. A proposed predictive model including the five significant variables (see Table 3) showed an area under the receiving operating curve of 0.82 (Fig. 1). The variance inflation factor values were between 1 and 1.5, indicating the absence of a multicollinearity problem in the model. We did not found interactions between predictors.

The Kaplan–Meier survival curve (Fig. 2) shows that there were patients with prolonged symptom persistence (33 subjects with 60 days with symptoms).

TABLE 1. Characteristics of Study Population of 375 Health Care Workers With COVID-19, Who Had Requested Medical Leave and Their Work Status Had Been Assessed By 6-June-2020

Variable	N (%) or mean ± SD or median (Q1–Q3)
Return to work (RTW)	341 (90.9%)
Interval (d)	25 (20–32)
Interval > 30 d	126 (33.6%)
Interval to negative PCR (d)	15 (12–19.5)
Age (yrs)	41.0 ± 11.4
Female sex	263 (70.1%)
Body mass index (BMI, kg/m^2)	24.3 ± 3.96
BMI > 30 kg/m^2 (n, %)	33 (8.8%)
Charlson index ≥ 1	48 (12.8%)
Occupational group	
Physician	122 (32.5%)
Nursing staff	188 (50.2%)
Nurses	112 (29.9%)
Nurse assistant	76 (20.3%)
Clinical support services	65 (19.1%)
Technician	17 (4.5%)
Security guard/orderlies	18 (4.8%)
Administrative support	18 (4.8%)
Other	12 (3.2%)
Clinical severity	
Mild	363 (96.8%)
Severe	10 (2.7%)
Critical	2 (0.5%)
Hospital service areas	
Higher exposure risk	
Intensive care units	46 (12.3%)
Emergency room	36 (9.6%)
Intermediate exposure risk	
Inpatient wards	218 (58.1%)
Lower exposure risk	
Other clinical areas	50 (13.3%)
Administrative offices	25 (6.7%)

RTW, return to work; SD, standard deviation.

TABLE 2. Unadjusted and Adjusted Analyses of RTW, with >30-day Interval to Negativization of the RT-PCR as Main Predictor in 346 HCWs at FJDUH, in Madrid, Spain

	Time to Return to Work		Unadjusted Analyses		Adjusted Analyses	
Variable	**≤30 days**	**>30 days**	**OR (95% CI)**	***P***	**OR_{adj} (95% CI)**	***P***
Days to negative PCR	14 (12–17)	20 (14–26)	1.12 (1.08, 1.16)	<0.001	1.12 (1.08, 1.17)	<0.001
Age (yrs)	38.0 ± 10.8	46.8 ± 10.5	1.08 (1.05, 1.10)	<0.001	1.07 (1.04, 1.10)	<0.001
BMI (kg/m^2)	23.8 ± 3.77	25.2 ± 4.17	1.09 (1.04, 1.15)	0.001	1.05 (0.98, 1.12)	0.206
Sex						
Female	169 (67.9%)	94 (74.6%)	ref	ref	ref	ref
Male	80 (32.1%)	32 (25.4%)	0.72 (0.44, 1.16)	0.179	0.32 (0.15, 0.66)	0.002
BMI						
≤30	233 (93.6%)	109 (86.5%)	ref	ref		
>30	16 (6.4%)	17 (13.5%)	2.27 (1.10, 4.70)	0.025		
Charlson index						
0	223 (89.6%)	104 (82.5%)	ref	ref	ref	ref
≥1	26 (10.4%)	22 (17.5%)	1.81 (0.98, 3.35)	0.057	0.60 (0.27, 1.32)	0.206
Occupational group						
Physician	100 (40.2%)	22 (17.5%)	ref	ref	ref	ref
Nursing staff	119 (47.8%)	69 (54.8%)	2.64 (1.56, 4.64)	0.001	1.99 (1.02, 4.02)	0.048
Clinical support services	30 (12.0%)	35 (27.8%)	5.30 (2.74, 10.5)	<0.001	7.71 (3.23, 19.4)	<0.001
Clinical severity						
Mild	247 (99.2%)	116 (92.1%)	ref	ref	ref	ref
Critical/severe	2 (0.8%)	10 (7.9%)	10.6 (2.75, 70.0)	0.003	4.71 (0.91, 37.4)	0.089
Hospital service areas						
Higher exposure risk	61 (24.5%)	21 (16.7%)	ref	ref	ref	ref
Intermediate exposure risk	142 (57.0%)	76 (60.3%)	1.55 (0.89, 2.79)	0.128	1.33 (0.67, 2.69)	0.422
Lower exposure risk	46 (18.5%)	29 (23.0%)	1.83 (0.93, 3.65)	0.081	0.50 (0.19, 1.27)	0.151

FJDUH, Fundación Jiménez Díaz University Hospital; HCWs, health care workers; RT-PCR, reverse transcriptase polymerase chain reaction; RTW, return to work.

DISCUSSION

We demonstrated in this study of HCWs that prolonged (>30 days) medical leave after COVID-19 was associated with the interval for the initially positive SARS-CoV-2 RT-PCR test to become negative. Other reports have described prolonged COVID-19 sick leaves in HCWs.[20,21] Age, female sex, and non-patient care health care occupational groups were also associated with delayed RTW, and we internally validated a predictive model for our outcome of interest.

HCWs were among the first reported affected occupational groups by the COVID-19 pandemic.[22,23] The Centers for Disease Control and Prevention in the United States reported that HCWs accounted for 19% of COVID-19 cases among those with occupational information. Similarly, 24.1% of cases in Spain until May 11, 2020, worked in healthcare settings.[24] In those reports, it was notable the predominance of female sex and, despite some deaths, the relatively better outcomes compared to what had been reported for the general population. Most subjects affected by COVID-19 survive, and there is a need to investigate non-lethal adverse outcomes, as concerns about post-infectious prolonged symptom persistence[25] begin to emerge. Accordingly, our study demonstrated that substantial proportions of our HCWs met disease duration criteria for ongoing or even prolonged COVID-19 infection.

Our study confirms the previously identified[22,26–28] association of age with adverse clinical outcome (in this case prolonged medical leave as measured by delayed RTW), exemplifies how properly conducted studies are necessary to identify risk factors to avoid misguided approaches to disease prevention in health care organizations.[29] Obesity and chronic disease comorbidity have also widely reported as adverse outcome predictors,[27,28] but their low prevalence in our study population plus confounding from other factors probably explain why we did not identify an independent effect in our models. We identified strongly associated occupational factors, in that groups with less direct and/or prolonged patient contact had worse odds compared to nursing staff, and the latter in turn compared to physicians. Direct patient contact and procedures usually performed by physicians (like intubations, invasive procedures, etc) have been identified as an occupational risk factor in systematic reviews.[9] Our finding of increased risk among non-direct patient contact HCW does not necessarily contradict that, and calls

TABLE 3. Proposed Predictive Model of Time to Return to Work Exceeding 30 days in Health Care Workers With COVID-19 Medical Leave, Following Stepwise Procedure and Including Only the Predictive Risk Factors

Variable	**Coefficient**	**OR_{adj}**	**(95% CI)**	***P***
Age	0.065	1.07	(1.04, 1.09)	<0.001
Male sex	−0.701	0.50	(0.26, 0.92)	0.029
Days to negative PCR	0.115	1.12	(1.08, 1.17)	<0.001
Nursing staff	0.743	2.10	(1.11, 4.10)	0.025
Clinical support services	1.594	4.92	(2.30, 10.9)	<0.001
Constant	−5.928	–	–	–

COVID-19, coronavirus disease 2019.

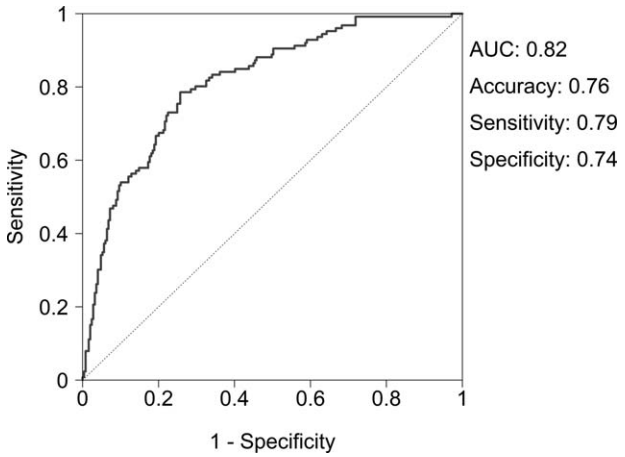

FIGURE 1. Evaluation of the classification performance of the predictive model presented in Table 3, summarized by area under the receiver operating curve (ROC).

attention to workers with relatively incidental unprotected infectious exposures, as observed by Lai et al.[30] This is not surprising, considering the increasing evidence for predominantly airborne aerosol transmission of SARS-CoV-2,[31] and the wide range of occupations that have that type of exposure in the general population,[5] often without the level of infection control training and exposure protection afforded to HCWs, and particularly to physicians. Physicians had less risk than nursing staff, and that may have been due to unmeasured and/or time-varying factors such as availability of PPE, adherence to infection control practices, or shorter contact with infected patients. Other factors like environmental contamination will need to be considered in ongoing and future studies. Most importantly, and despite the lack of additional information, our study suggests that occupational exposure factors confound the association of the widely accepted risk factors identified in general population COVID-19 studies. Future studies are needed to confirm and further investigate these associations, including an evaluation of our suggested predictive model.

Our study had several strengths including the availability of a well-structured RTW protocol,[15] and of SARS-CoV-2 RT-PCR and serology testing at our institution since very early into the pandemic. On the other hand, the majority of our infected HCWs had mild disease severity (96.8%), and substantially lower chronic disease

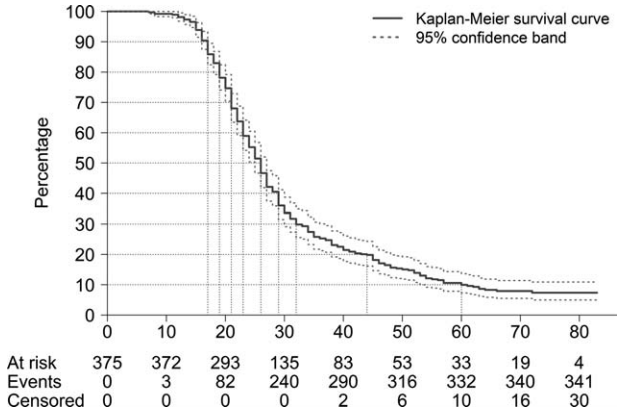

FIGURE 2. Kaplan–Meier survival curve with the 95% confidence band of interval to return to work (in days, on the abcissa) in 346 HCWs. HCWs, health care workers.

comorbidity[32] and obesity[8] than reported in other studies, which may have limited our ability to detect the adverse effect of those risk factors. That is particularly more so for clinical severity. We also lacked data on differential PPE availability and utilization, and adherence to infection control protocols among our different occupational groups and hospital service areas. We also lacked, in the context of a severe pandemic, more detailed investigation of family or community versus occupational transmission in our HCWs, but their increased COVID-19 risk identified in larger population-based studies[7,8] addresses any question in that regard.

In conclusion, we identified prolonged interval for an initially positive SARS-CoV-2 RT-PCR test to become negative as a significant predictor of delayed RTW after COVID-19 in HCWs. We developed and internally validated a predictive model and will seek to externally validate it in the near future.

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