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## Pneumonia in healthcare workers during a COVID-19 outbreak at a cardiovascular hospitals



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### ABSTRACT

**Objectives:** During the coronavirus disease 2019 (COVID-19) pandemic, healthcare workers (HCWs) have been at high risk of infection. This study investigated clinical and treatment characteristics of infected HCWs at a cardiovascular hospital.

**Methods:** This retrospective study was conducted at a tertiary cardiovascular hospital and included HCWs with confirmed COVID-19. Subjects completed a questionnaire on health status, symptoms, admission to hospital and treatment. Vaccination status against tuberculosis, hepatitis B and seasonal influenza was assessed. Pneumonia was defined as ground glass opacifications (GGOs) and consolidations on computed tomography (CT).

**Results:** This study included 107 HCWs with confirmed COVID-19, representing 15% of all HCWs ( $n = 726$ ) at the study hospital. Most of the confirmed cases worked in the cardiac surgery department, the anaesthesiology and intensive care medicine department, and the postoperative ward [74/107 (69%)]. A substantial number of infected HCWs were asymptomatic [31 (28.9%)], and 38 (35.5%) were admitted to hospital. The mean  $\pm$  standard deviation length of hospital stay was  $8.1 \pm 5.6$  days. Seventy-five of 107 (70.1%) confirmed cases had been vaccinated against seasonal influenza. Pneumonia with GGOs and consolidations on CT occurred in 25 of 107 (23.4%) HCWs, with 14 (13.1%) cases of bilateral involvement. On multivariate logistic regression analysis including characteristics known to be associated with poorer outcomes in COVID-19 (i.e. obesity, diabetes mellitus, coronary artery disease, cerebrovascular disease, current smoking, heart failure, seasonal influenza immunization), only seasonal influenza immunization remained an independent predictor of the occurrence of bilateral pneumonia (odds ratio 0.207, 95% confidence interval 0.050–0.847;  $P = 0.029$ ).

**Conclusions:** The association found between seasonal influenza immunization and less-aggressive COVID-19 pneumonia may support the implementation of preventive measures to reduce the global burden of COVID-19.

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### Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Patients with confirmed COVID-19 can be completely asymptomatic, or can present with life-threatening forms of acute respiratory distress syndrome and multi-organ failure (Guan et al., 2020). COVID-19 was first reported as an unusual form of pneumonia in Wuhan,

Hubei Province, China in December 2019 (Huang et al., 2020). Multislice computed tomography (CT) has been used extensively for early identification of COVID-19 pneumonia; typical features include peripheral – often bilateral – ground glass opacifications (GGOs) with multifocal distribution, and linear consolidations. These consolidations tend to progress rapidly towards organized pneumonia patterns on follow-up examination (Hani et al., 2020; Huang et al., 2020; Lomoro et al., 2020). The distinctive features of COVID-19 on CT can be useful to differentiate it from other common causes of pneumonia, such as bacterial infection.

The COVID-19 pandemic has placed healthcare workers (HCWs) at high risk of infection. In China, more than 3300 HCWs have been infected (2–20% of all cases of COVID-19), resulting in many deaths.

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In Italy, approximately 20% of all HCWs have been infected by SARS-CoV-2 (Anonymou, 2020; Heymann and Shindo, 2020).

In Serbia, the rate of COVID-19 has been relatively low, with 12,310 cases and 254 deaths (1409 infected cases per 1 million inhabitants) (COVID-19 coronavirus pandemic, 2020). HCWs in Serbia have also been affected, but the total number is not known, and reports from medical institutions with COVID-19 outbreaks are scarce. Therefore, this study investigated the demographic, clinical, diagnostic and treatment characteristics of HCWs with COVID-19 at a large tertiary cardiovascular hospital in Serbia.

## Methods

This retrospective study was conducted at a single, high-volume university cardiovascular hospital providing 24-h cardiac surgery and interventional cardiology services. The study population comprised HCWs working at the cardiovascular hospital who were infected with SARS-CoV-2 and had a confirmed diagnosis of COVID-19 based on polymerase chain reaction (PCR) results. The HCWs gave their consent to participate in this study and completed a predefined questionnaire. The study was conducted in accordance with the Declaration of Helsinki.

### Study population

The questionnaire asked about previous medical conditions, ongoing diseases, prescribed medications, symptoms related to COVID-19, dates of hospital admission, and diagnostic procedures and therapies received. The use of supplemental oxygen, mechanical ventilation and antibiotics in hospitalized HCWs was explored. Medical records were collected from treating institutions. After study completion, the vital status of participants was assessed via telephone interview with one of the investigators.

A diagnosis of COVID-19 was made following a positive reverse transcription polymerase chain reaction (RT-PCR) result from throat and nose swabs. A real-time fluorescent RT-PCR kit (BGI Genomics, Wuhan, China) was used to detect 2019-nCoV. The tests were repeated after 7 and 14 days.

### Data collection

Data collected from HCWs included: age; gender; work position; health status prior to infection with SARS-CoV-2; presence of chronic disease; and prescribed medications. Diseases known to influence the severity of COVID-19 are: active or previous cancer; hypertension; diabetes mellitus; coronary artery disease (defined as previous myocardial infarction, percutaneous or surgical revascularization or known severe coronary artery disease not amenable to treatment); cerebrovascular disease (defined as previous cerebrovascular accident or known severe carotid artery disease and/or treated with surgery or stent implantation); heart failure (defined as left ventricular ejection fraction <35%); chronic renal failure (defined as glomerular filtration rate <60 ml/min/m<sup>2</sup>);

chronic obstructive pulmonary disease; bronchial asthma; obesity (defined as body mass index >30 kg/m<sup>2</sup>); and smoking status (current or former). The following COVID-19 symptoms were also assessed: sore throat; cough; rhinitis; fever; myalgia; loss of sense of smell or taste; diarrhoea; headache; shortness of breath; and tiredness. Finally, vaccination status was assessed, focusing on immunization against tuberculosis, hepatitis B and seasonal influenza.

Pneumonia was defined as GGOs with consolidations typical for COVID-19 pneumonia on CT, together with the presence of symptoms. Pneumonia was classified as unilateral or bilateral based on the distribution of CT findings (Hani et al., 2020; Huang et al., 2020; Lomoro et al., 2020).

The medical records of hospitalized HCWs were used to collect data on the duration of hospitalization; use of supplemental oxygen; need for non-invasive or invasive mechanical ventilation; intensive care unit (ICU) admission; and use of antibiotics, the antimalarial drug chloroquine or immunomodulatory medications.

### Statistical analysis

Continuous data are presented as mean ± standard deviation, and categorical data as presented as count and percentage. Continuous variables were compared using *t*-test and Mann–Whitney *U*-test for normally and non-normally distributed variables, respectively. Chi-squared test and Fisher's exact test were used to test categorical variables. The effects of patient characteristics on confirmed bilateral pneumonia were explored using multivariate logistic regression, and expressed as odds ratio (OR) with 95% confidence interval (CI). Forward stepwise regression was used to determine independent predictors of bilateral pneumonia in a multivariate analysis model. Stepwise selection iteratively selected the most significant variable with a multivariate *P*-value <0.25 to start the model. At each step, another significant variable was added and, after running the model, a check was performed to remove any variables with a multivariate *P*-value >0.10. This was repeated with the complete set of variables until no more variables could be added and no variables could be removed. A *P*-value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using PASW-Statistics 18.0 (SPSS Inc, Chicago, IL, USA).

## Results

This study included 107 confirmed cases of COVID-19 among 726 (15%) HCWs in active service at the time of diagnosis. The cases were recorded between 20 March and 22 April 2020 at the Institute for Cardiovascular Diseases Dedinje, Belgrade, Serbia. Among the confirmed cases, 28 (26.1%) were doctors, 64 (59.8%) were nurses, five (4.6%) were radiology technicians, four (3.8%) were physical therapists, two (1.9%) were cardiovascular perfusionists, and four (3.8%) worked in the hospital's non-medical services. The majority

**Table 1**  
Distribution of infected medical professionals by department.

Department	Infected staff	Total staff in department	%
Cardiac surgery, <i>n</i> (%)	13	109	11.9
Anaesthesiology and intensive care medicine, <i>n</i> (%)	36	151	23.8
Postoperative ward, <i>n</i> (%)	25	196	12.7
Cardiology, <i>n</i> (%)	15	122	12.3
Radiology, <i>n</i> (%)	8	56	14.3
Physical therapy, <i>n</i> (%)	6	20	30.0
Non-medical service, <i>n</i> (%)	4	72	5.6
Total	107	726	15.0

**Table 2**  
Clinical characteristics of all patients: hospitalized vs non-hospitalized.

Variable	Total (n = 107)	H (n = 38)	NH (n = 69)	P-value
Age (years)	39.1 ± 11.4	38.1 ± 9.8	39.9 ± 12.4	0.471
No previous disease, n (%)	71 (66.3)	21 (55.3)	50 (72.2)	0.043
Malignancy, n (%)	2 (1.9)	1 (2.6)	1 (1.5)	0.587
Hypertension, n (%)	10 (9.3)	5 (13.1)	5 (7.2)	0.736
Coronary artery disease, n (%)	4 (3.8)	1 (2.8)	3 (4.3)	0.640
Heart failure, n (%)	1 (0.9)	0 (0.0)	1 (1.5)	0.587
Diabetes mellitus, n (%)	3 (2.8)	1 (2.8)	2 (2.9)	1.000
Bronchial asthma, n (%)	1 (0.9)	0 (0.0)	1 (1.5)	0.587
COPD, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Chronic renal failure, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Previous CVD, n (%)	2 (1.9)	0 (0.0)	2 (2.9)	0.510
Thyroid disease, n (%)	8 (7.5)	7 (18.4)	1 (1.5)	0.007
Arrhythmia, n (%)	4 (3.8)	2 (5.2)	2 (2.9)	0.567
BMI >30 kg/m <sup>2</sup> , n (%)	5 (4.7)	3 (7.9)	2 (2.9)	0.337
Current smoker, n (%)	32 (29.9)	11 (28.9)	21 (30.4)	0.378

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; H, hospitalized; NH, non-hospitalized.

of infected HCWs worked in the cardiac surgery department, the anaesthesiology and intensive care medicine department, and the postoperative ward (74/107, 69.1%), while there were fewer cases of COVID-19 among HCWs working in the cardiology department and services that spanned the entire hospital (e.g. radiology, physical rehabilitation) (Table 1). The average age of infected HCWs was <40 years, and almost 30% were current smokers. Clinical data are shown in Table 2.

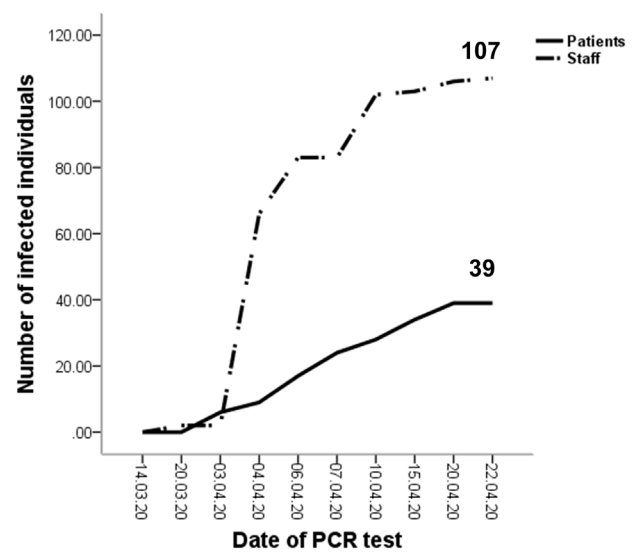
The epidemic started on 20 March 2020, when two cases of COVID-19 were recorded in HCWs. On 4 April 2020, there was a sharp increase in the number of infected HCWs, and this peaked on 22 April 2020. Over the same time frame, the number of infected patients hospitalized in the cardiac surgery department also increased (Figure 1).

Regarding manifestations of COVID-19, a substantial number of infected HCWs were asymptomatic [31 (28.9%)]. Symptomatic individuals predominantly complained of sore throat, general weakness and fever (Table 3).

In total, 38 HCWs (35.5%) were admitted to hospital for treatment, and the mean length of hospital stay was 8.1 ± 5.6 days. The majority of HCWs who did not require hospital treatment quarantined at home [41/107 (38.3%)] or at a facility for collective quarantining [28/107 (26.2%)]. Fewer non-hospitalized HCWs had previous medical conditions or thyroid disorders compared with hospitalized HCWs (Table 2). In hospital, most HCWs received chloroquine [21/38 (55.2%)] and underwent treatment with various intravenous antibiotics (Table 4). Three HCWs [3/38 (7.9%)] were admitted to intensive care units (ICUs) because of prolonged hypoxia, and one was intubated and treated with positive pressure ventilation for 6 days. HCWs admitted to ICU received the interleukin 6 inhibitor tocilizumab. No deaths occurred among the entire cohort.

Vaccination status was assessed in all HCWs with COVID-19. The vaccination rate for Bacillus Calmette–Guérin (BCG) vaccine was 100%, as this is mandatory for all newborns in Serbia. Seventy-three (68.2%) and 75 (70.1%) HCWs had been immunized against hepatitis B and seasonal influenza, respectively. No differences in immunization status were found between hospitalized and non-hospitalized HCWs [influenza: hospitalized 28/38 (71.1%) vs non-hospitalized 47/69 (68.1%), *P* = 0.414; hepatitis B: hospitalized 28/38 (73.7%) vs non-hospitalized 45/69 (65.2%), *P* = 0.457].

Pneumonia with GGOs and consolidations on CT occurred in 25 (23.4%) HCWs with COVID-19, and 14 (13.1%) cases had bilateral involvement. Bilateral pneumonia was less common in HCWs who had been vaccinated against seasonal influenza [vaccinated 6/75 (8.0%) vs unvaccinated 8/32 (25%); *P* = 0.07]. On multivariate



**Figure 1.** Cases of coronavirus disease-2019 among patients and healthcare workers (HCWs). The diagram depicts temporal trends in the cumulative infection of HCWs and cardiac surgery patients. PCR, polymerase chain reaction.

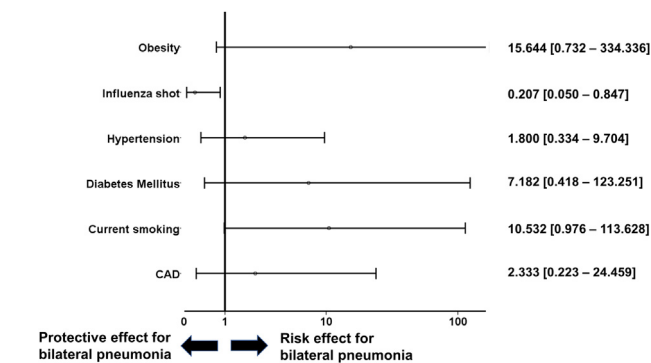
**Table 3**  
Complaints of symptomatic patients with coronavirus disease 2019.

Symptom	n = 76
Sore throat, n (%)	38 (50.0)
Rhinorrhoea, n (%)	23 (30.2)
Fever, n (%)	43 (56.6)
Fever <37.3 °C, n (%)	10 (13.2)
Fever 37.3–38.0 °C, n (%)	23 (30.2)
Fever 38.1–39 °C, n (%)	10 (13.2)
Fever >39.0 °C, n (%)	0 (0.0)
Cough, n (%)	31 (40.8)
General weakness, n (%)	37 (48.7)
Headache, n (%)	20 (26.3)
Diarrhoea, n (%)	21 (27.6)
Myalgia, n (%)	22 (28.9)
Breathlessness, n (%)	13 (17.1)
Loss of smell or taste, n (%)	20 (26.3)

logistic regression analysis that included patient characteristics known to be associated with poorer outcomes in COVID-19 (i.e. obesity, diabetes mellitus, coronary artery disease, cerebrovascular disease, current smoker, heart failure, seasonal influenza

**Table 4**  
Antibiotics administered to hospitalized patients with coronavirus disease 2019.

Antibiotic	n = 38
Azithromycin, n (%)	19 (50.0)
Ceftriaxone, n (%)	16 (42.1)
Levofloxacin, n (%)	3 (7.9)
Ciprofloxacin, n (%)	1 (2.6)
Cefixime, n (%)	1 (2.6)
Vancomycin, n (%)	2 (5.2)
Amoxicillin, n (%)	1 (2.6)
Metronidazole, n (%)	1 (2.6)



**Figure 2.** Forest plot of risk factors for bilateral pneumonia. The diagram displays the impact of patient characteristics on multivariable regression of the occurrence of bilateral pneumonia. The odds ratio (OR) and 95% confidence interval (CI) are given for each characteristic. CAD, coronary artery disease.

immunization), only seasonal influenza immunization remained an independent predictor for the occurrence of CT-confirmed bilateral pneumonia (OR=0.207; 95% CI 0.050–0.847;  $P = 0.029$ ) (Table 5, Figure 2) (Hajifathalian et al., 2020; Shi et al., 2020; Wang et al., 2020).

**Discussion**

The COVID-19 pandemic has affected healthcare systems worldwide, partly due to rapid spread in the population and partly because a substantial number of infected cases require medical attention and hospitalization. As COVID-19 causes profound hypoxia in many infected individuals, leading to the need for supplemental oxygen and mechanical ventilation, the burden on hospitals, particularly ICUs and their staff, is very high (COVID-19 coronavirus pandemic, 2020; Guan et al., 2020). The highly pathogenic and infectious nature of SARS-CoV-2, and the high number of patients admitted to hospitals, has resulted in infection outbreaks among HCWs, further hampering the function of healthcare systems (Otter et al., 2016; Wang et al., 2020).

**Table 5**  
Univariate and multivariate predictors of bilateral pneumonia on computed tomography.

	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Diabetes mellitus	7.182 (0.418–123.251)	0.174	2.9E (0.000)	1.000
Hypertension	1.800 (0.334–9.704)	0.494	–	–
Coronary artery disease	2.333 (0.223–24.459)	0.480	–	–
Seasonal influenza immunization	0.297 (0.082–1.074)	0.064	0.207 (0.050–0.847)	0.029
Obesity	5.133 (0.763–34.549)	0.093	15.644 (0.732–334.336)	0.078
Current smoker	3.000 (0.615–14.626)	0.174	10.532 (0.976–113.628)	0.052
Heart failure	0.000 (0.000)	1.000	–	–

CT, computerized tomography; OR, odds ratio; CI, confidence interval.

This study investigated an outbreak of COVID-19 at a tertiary cardiovascular hospital. COVID-19 was diagnosed in two HCWs on 20 March 2020, followed by a rapid spread of infection and a sharp increase in the number of infected HCWs at the beginning of April 2020, corresponding with the incubation period of SARS-CoV-2 (Guan et al., 2020; Huang et al., 2020). The source of infection could have been a female patient admitted to the hospital on 8 March 2020, presenting with ST elevation myocardial infarction with normal coronary angiogram and a history of fever. The patient was resuscitated but died on the day of admission. Alternatively, one of the first cases from the cardiac surgery department had recently travelled to Austria, where he could have contracted the virus. Following the identification of COVID-19 among HCWs, PCR tests were performed for all hospitalized patients in the cardiac surgery department, including those admitted and awaiting surgery, and all HCWs who had been in contact with infected patients. On 5 April 2020, nine patients in the cardiac surgery department tested positive, including five patients on the pre-operative ward who were completely asymptomatic (Figure 1). This resulted in complete shutdown of the cardiac surgery department, the anaesthesiology and intensive care medicine department, and the postoperative ward.

The highest percentages of infected HCWs were recorded in the anaesthesiology and intensive care medicine department and the physical therapy department. This can be explained by close contact of HCWs with patients and coworkers in these departments. Airway management, central venous line placement and thoracic drainage are associated with increased risk of viral dissemination (Cook et al., 2020), and physical therapy of cardiovascular patients carries an increased risk of infection for HCWs performing treatments. Additionally, physical therapists work in various departments, increasing the number of contacts with patients and other employees, further increasing the possibility of infection (Felten-Barentsz et al., 2020).

Most infected HCWs were young, and more than half did not have any previous medical conditions. Interestingly, almost 30% were completely asymptomatic, which is not uncommon among young, previously healthy individuals (Bai et al., 2020; Hu et al., 2020). The reported rates of asymptomatic individuals vary substantially between studies, from as low as 1% in a large cohort of Chinese patients to >50% in a study from the cruise ship *Diamond Princess*. The need to treat an asymptomatic carrier of SARS-CoV-2 has been a matter of debate (Gao et al., 2020; Mizumoto et al., 2020). In the present study, asymptomatic HCWs were not treated with antiviral agents, antibiotics or chloroquine, and their disease course was uneventful. The significance of asymptomatic cases as a source of infection depends on their distribution in the population, and the amount and duration of virus dispensation from the upper respiratory tract (Gao et al., 2020). In the study population, viral dissemination among close contacts, as estimated by the infected HCWs, was very low in the whole group ( $0.18 \pm 0.61$  individuals), but it should be noted that

this self-estimate was not explored further with systematic testing of families and close contacts. The low rate of viral dissemination could also be attributed to the fact that these cases were medically educated, and followed self-isolation and hygiene measures from the moment of COVID-19 diagnosis.

Fewer non-hospitalized HCWs had previous medical conditions and thyroid disorders compared with hospitalized HCWs (Table 2). Hospitalized HCWs had a higher incidence of hypertension and obesity which, although not significant, could be associated with higher incidence of hospital admission for COVID-19 (Driggin et al., 2020; Zhou et al., 2020). The higher incidence of thyroid disease among hospitalized HCWs could be due to the susceptibility of the immune system to SARS-CoV-2, and an excessive and disproportionate response to viral infection. An association between an autoimmune response to viral particles and thyroid disease (Hashimoto thyroiditis) has been reported previously. An increased immune response to SARS-CoV-2 in an individual with autoimmune thyroid disorder could lead to more severe clinical manifestations and increased risk of hospital admission (Desail- loud and Hober, 2009; Gasparyan et al., 2020; Shukla et al., 2018).

The low rates of death and acute respiratory distress syndrome among the study population could be attributed to their overall profile (i.e. young, relatively healthy individuals). The only HCW requiring mechanical ventilation was a 63-year-old radiology technician who was obese, a current smoker, and had multiple comorbidities (hypertension, diabetes mellitus and coronary artery disease). These characteristics complied with the risk profile for ICU admission and poor outcome in COVID-19 (Driggin et al., 2020).

The main finding of this study was a lower incidence of CT-confirmed bilateral pneumonia in patients who had been immunized against seasonal influenza. To the authors' knowledge, no studies to date have suggested cross-reactivity to SARS-CoV-2 in individuals immunized against influenza. This idea is based on the premise that individuals vaccinated against a viral disease produce antibodies that can cross-react against the proteins of various viral species, and thus prevent other viral infections or cause individuals to have a mild form of the illness. This hypothesis has been used to explain the lower rates of COVID-19 in children in countries where vaccination against measles and rubella is mandatory (Gasparyan et al., 2020; Salman and Salem, 2020). The basis for this could be the similar ontogenesis of various viral species. Coronaviridae (including SARS-CoV-2) and Orthomyxoviridae (including influenza virus), both RNA viral species, express similarity in the structure of haemagglutinin esterases, which seems to be a consequence of lateral gene transfer that occurred 8000 years ago. The process of lateral gene transfer supposedly occurred from Influenza C virus to one of the Coronavirus (member of Coronaviridae family). The genetic information was transferred from Influenza virus C to Coronavirus leading to similarity in certain proteins named haemagglutinin esterases (Wang et al., 2008; Zeng et al., 2008). The seasonal influenza vaccine for 2019/2020 contained three or four strains of influenza A and B viruses, which may exhibit cross-reactivity with some of the proteins in SARS-CoV-2.

Another possible mechanism is the so-called 'trained' immunity phenomenon, meaning that influenza vaccination could modulate and improve the immune response to another virus. This mechanism has been attributed to mandatory vaccination against tuberculosis. It has been hypothesized that in countries where individuals have been immunized with multiple doses of BCG vaccine, they have acquired an improved immune response to other pathogens, including SARS-CoV-2, leading to lower rates of infection and severe complications such as acute respiratory distress syndrome and death (Gasparyan et al., 2020).

This study has several limitations. The study group was relatively small and the incidence of bilateral pneumonia was low. This may

limit the validity of conclusions that can be drawn regarding the positive effects of seasonal influenza immunization as an adjunctive measure to fight the global burden of COVID-19. However, this association between previous immunization status and susceptibility to SARS-CoV-2 infection should be explored further.

## Conclusions

The COVID-19 pandemic poses an immense risk for HCWs in hospitals where cardiovascular surgery and interventions are performed. The association found between seasonal influenza immunization and less-aggressive COVID-19 pneumonia may support the implementation of preventive measures to reduce the global burden of COVID-19.

## Conflict of interest statement

None declared.

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None.

## Ethical approval

This study was approved by the institutional ethics committee.

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