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CLINICO-RADIOLOGICAL PROFILE IN COVID-19 PATIENTS AND ITS CORRELATION TO PRIOR BCG VACCINATIONS STATUS

Shahid Majid[1], Mehvish Mushtaq[2], Inaamul Haq[3], Majid Jahangir[4], Naveed Nazir Shah[5], Khurshid Ahmad Dar[6*], Syed Suraiya Farooq[7], Tajamul Hussain Shah[8], Mohammad Yousef Dar[9]

[1]Senior Resident, Department of Respiratory Medicine, Government Medical College Srinagar, India
[2]Senior Resident, Department of Respiratory Medicine, Government Medical College Srinagar, India
[3]Assistant Professor, Department of Preventive and Social Medicine, Government Medical College Srinagar, India
[4]Professor and Principal, Government Medical College Baramulla, India
[5]Professor and Head, Department of Respiratory Medicine, Government Medical College Srinagar, India
[6*]Professor, Department of Respiratory Medicine, Government Medical College Srinagar, India
[7]Associate Professor, Department of Respiratory Medicine, Government Medical College Srinagar, India
[8]Assistant Professor, Department of Respiratory Medicine, Government Medical College Srinagar, India
[9]Assistant Professor, Department of Respiratory Medicine, Government Medical College Srinagar, India

***Corresponding Author:** Khurshid Ahmad Dar
*Professor, Department of Respiratory Medicine, Government Medical College Srinagar, India
Mail id: darkhurshid97@gmail.com

Abstract

Background: Given the impact of COVID-19 and the global scramble to find ways to combat its spread and mortality, there has been interest in whether existing vaccines like BCG could provide some protection against the virus.

Aim: This study aims to investigate the effectiveness of prior BCG vaccination in reducing COVID-19 infection and severity.

Methods: The study included adult patients, aged 18 years or older with laboratory confirmed COVID 19 either by Rapid antigen test(RAT) or RNA reverse transcriptase polymerase chain reaction (RT-PCR) assay from nasal, pharyngeal or lower respiratory tract sample, who were admitted for either quarantine or required hospitalization in view of moderate to severe COVID 19 disease. Radiological disease severity was assessed based on CT findings and severity score. These clinical, radiological and inflammatory parameters were compared between BCG vaccinated and non vaccinated patients.

Results: A total of 918 patients with laboratory confirmed COVID-19 infection of varying severity were included. Out of 918 included patients 604 (65.8%) were males and 314 (34.2%) were females

with male to female ratio of 1.8:1. Mean age of study population was 51.5±17.1 years with age ranging from 18 to 100 years. Total 472 patients (51.4%) had evidence of prior BCG vaccination whereas 446 patients (48.6 %) had no evidence of prior BCG vaccination. Majority of patients had severe COVID illness (434, 47.3%) followed by mild (286, 31.1%) and moderate illness (198, 21.6%). Most common comorbidity was diabetes (311, 33.9%) followed by hypertension (295, 32.1%).
Conclusion: We concluded that neonatal BCG vaccination limits the radiological severity of the COVID-19 pneumonia but does not give any mortality benefit to COVID-19 patients**.**

Keywords: COVID-19, BCG vaccination, mortality, severity, radiological profile.

Introduction

Severe acute respiratory distress syndrome caused by the SARS-CoV-2 virus is a highly infectious respiratory disease that was named as COVID -19 and was first identified in December 2019 in Wuhan, China.[1] The disease rapidly spread globally, leading World Health Organization (WHO) to declare it a pandemic in March 2020.[2] COVID-19 has impacted millions of people worldwide, with symptoms ranging from mild to severe respiratory illness, and has had profound effects on health systems, economies, and daily life globally.[3]

Number of factors have shown to be associated with either increased risk of worsening of COVID-19 infection or have a protective effect on COVID-19 infection. Factors associated with developing severe COVID-19 infection range from older age, presence of underlying comorbidities like hypertension, diabetes, COPD.[4] In contrast healthy diet, atopic conditions associated with lower ACE2 receptor expression have been associated with protective effect against COVID-19 infection.[5]

The observation that countries who continue to have BCG immunization program better contained COVID-19 lead to the hypothesis suggesting protective effect of BCG vaccine against COVID infection.[6] Isabel N. Kantor was the first to publicly explore whether BCG could have protective and preventive effects against COVID-19.[7] Following this, few trials were conducted which proposed that BCG might help reduce viremia after exposure to SARS-CoV-2 and could lessen the severity of COVID-19 and lead to quicker recovery.[8]

The Bacillus Calmette-Guérin (BCG) vaccine is primarily used against tuberculosis (TB).[9] The vaccine is made from a weakened strain of Mycobacterium bovis, a bacterium closely related to M. tuberculosis, which causes TB. BCG vaccination has been one of the oldest and most widely used vaccines worldwide, with a varying efficacy against TB ranging from 0% to 80%, reason for that being the prior exposure to nontuberculous mycobacterial antigens which hinder the BCG vaccination from offering protection.[10,11]

Given the impact of COVID-19 and the global scramble to find ways to combat its spread and mortality, there has been interest in whether existing vaccines like BCG could provide some protection against the virus. This hypothesis stems from observations that BCG might enhance the body's general immune responses, potentially making it more capable of fighting off infections beyond just TB. This concept, known as "trained immunity" implies that BCG could potentially boost the innate immune system and provide some degree of protection against severe forms of COVID-19.[12]

Considering the protective effect of BCG vaccination against COVID -19 infection, various trials studied the effect of revaccination with BCG on COVID -19. These trials failed to demonstrate the protective effect on SARS-CoV-2 infection, severe COVID-19, hospitalization.[13,14] During the time period of our study limited literature was available that evaluated the effect of BCG vaccination on COVID -19. This study aims to investigate the effectiveness of prior BCG vaccination in reducing COVID-19 infection and severity.

Material and methods

Study population and settings

This cross-sectional study was conducted at Government Chest Diseases Hospital, Srinagar, a tertiary facility affiliated with Government Medical College Srinagar which was deignated as one of the

quarantine and isolation facilities for management of COVID-19 patients in Kashmir valley. The study included adult patients, aged 18 years or older with laboratory confirmed COVID 19 either by Rapid antigen test(RAT) or RNA reverse transcriptase polymerase chain reaction (RT-PCR) assay from nasal, pharyngeal or lower respiratory tract sample, who were admitted for either quarantine or required hospitalisation in view of moderate to severe COVID 19 disease.

Data collection

Data regarding demographics, comorbid illness, BCG vaccination status, severity of COVID 19 infection, various laboratory and radiological parameters were recorded.

BCG vaccination status was inferred from the presence or absence of a scar in the left or right deltoid region. In national immunization program, BCG vaccination is done in the left deltoid region. To be sure of the vaccination we check for the vaccination scar in both left and right deltoid regions.

Radiological disease severity was assessed based on CT findings and severity score.[15,16] These clinical, radiological and inflammatory parameters were compared between BCG vaccinated and non vaccinated patients.

Severity scores

The clinical classification of COVID 19 infection was done by using a classification proposed by AIIMS/ICMR-COVID-19 National Task Force/Joint monitoring group[16] was used.

According to this classification, COVID-19 is classified into:

1. Mild disease: this group includes patients with upper respiratory tract symptoms and/or fever without shortness of breath or hypoxia.

2. Moderate disease: this group includes patients with any one of following • Respiratory rate ≥24/min, breathlessness. Spo2: 90% to 93% on room air.

3. Severe disease: this group includes patients with anyone of the following • Respiratory rate >30/min • Spo2 <90% on room air

Similarly for radiological classification, CT severity score proposed by Pan et al[15] was used. According to which , a score from 0 to 5 was assigned to each 5 lung lobes considering the extent of anatomical involvement as follows 0, no involvement; 1, < 5% involvement; 2, 5–25% involvement; 3, 26–50% involvement; 4, 5175% involvement; and 5, > 75% involvements. The resulting global CT score is the sum of each individual lobar score (0 to 25). The severity of the disease was assessed using CT severity score (total score out of 25) and categorized into mild (score < 7), moderate (score 7-18) and severe (score> 18). When present, related features such as fibrosis, subpleural lines, reversed “halo sign,” pleural effusion, and lymphadenopathy were also described.

Statistical analysis

Data was entered in a Microsoft Excel spreadsheet. Categorical variables were summarized as percentages. Normally distributed continuous variables without extreme values were summarized as mean and standard deviation. Continuous variables with extreme values or with a non-normal distribution, and ordinal scores were summarized as a five-number summary (Minimum, 1st Quartile, Median, 3rd Quartile, and Maximum); Minimum and maximum values, Median and Interquartile range were reported. Unpaired t-test was used to test the hypothesis of no difference between two means. For continuous variables with a non-normal distribution/ ordinal scores, the relationship of such variables with BCG scar was tested using the rank sum test, rank sum Variables test.

The relationship between two categorical variables was tested using Chi-square test. Two-sided p-values were reported and p value < 0.05 was considered significant.

Based on BCG vaccination status, patients were divided into those with prior BCG vaccination and those with no prior BCG vaccination. We then compared the demographic, clinical , laboratory and radiological parameters between the two groups.
Data was analyzed using stata version 15.

Ethical approval
The study was approved by the ethics committee of Government Medical College, Srinagar.

Results
There was no statistically significant difference in terms of age, gender and comorbid illness between the BCG vaccinated and non vaccinated group [Table 1].

Table 1: Demographic profile of study population

Characteristics at enrolment	**BCG vaccinated group,(n=472) 51.4%**	**BCG unvaccinated group,(n=446) 48.6%**	***p* value**
Age, years (mean + SD)	**51.5±17.1**	**50±15.2**	
Age (years), n(%)			
≤20	**15 (3.8)**	**4 (0.9)**	
21-40	**106 (22.4)**	**100 (22.4)**	
41-60	**188 (39.8)**	**175 (39.2)**	
61-80	**158 (33.5)**	**140 (31.4)**	
>80	**10 (2.1)**	**17 (3.8)**	
Female n(%)	**213 (45.1)**	**197 (44.2)**	**0.7**
Males n(%)	**259 (54.9)**	**249 (55.8)**	
Co -morbidity profiles			
Cardiovascular disease (CVD)	**45 (9.5)**	**37 (8.3)**	**0.51**
Chronic kidney disease (CKD)	**33 (7.0)**	**36 (8.1)**	**0.53**
Hypertension	**157 (33.3)**	**138 (8.5)**	**0.45**
Diabetes	**166 (35.2)**	**145 (32.5)**	**0.39**
History of TB	**22 (4.7)**	**34 (7.6)**	**0.60**

Among the 918 patients, 72.2% (663) had elevated CRP levels. 54% (496) had high ferritin levels, 72.1% (661) had high LDH levels. 64.1% (588) had high IL -6 levels. Furthermore 28.2% (259) had

high d-dimer levels. Serum CRP [16.45(8-61) vs 14 (7.7-28), p value= 0.003] and ferritin [390.5(220-640) vs 330(200-566.7), p value= 0.0067] were significantly higher in non vaccinated as compared to vaccinated group. Regarding clinical severity, there was no significant difference between the vaccinated and unvaccinated group However, radiological severity was significantly high in unvaccinated group [Table 2]. The most common type of opacity seen on CT was ground glass opacities which were seen in 89.0% patients followed by consolidation seen in 37.8% patients. The least common opacity seen was reverse halo sign seen in 0.1% of patients. 78.9% (725) patients had bilateral lung involvement and the most common lobe involved was left lower lobe (75.2%). Out of 918 patients, on the basis of CT severity scoring 9.1% (82) had mild disease, 87.4% (786) had moderate disease, 3.5% (31) had severe disease. Total 6.5% (60) patients had in hospital mortality. No significant difference was observed in terms of mortality between the two groups (7.9% vs 5.3%, p value=0.118) [Table 2].

Table 2: comparison of clinical and radiological parameters between BCG vaccinated and un vaccinated group.

Parameters	**BCG vaccination status**		***p* value**
	Absent	**Present**	
Clinical severity n(%)			**0.230**
	135(30.3)	**151(32)**	
Mild	**88(19.7)**	**110(23.3)**	**0.573**
Moderate	**223(50)**	**211(44.7)**	
Severe			**0.188**
			0.108
Inflammatory markers Median(IQR)			
CRP	**16.45(8-61)**	**14(7.7-28)**	
IL-6	**26(13-55)**	**22(15-45)**	**0.0032**
D DIMER	**0.4(0.2-0.6)**	**0.4(0.2-0.6)**	
FERRITIN	**390.5(220-640)**	**330(200-566.7)**	**0.0512**
			0.8673
			0.0067
Radiological severity n(%)			
			<0.0005
Mild	**5(1.2)**	**77(16.3)**	
Moderate	**403(94.3)**	**383(81.2)**	**0.00001**
Severe	**19(4.5)**	**12(2.5)**	
			0.00007
			0.1498
Outcome n(%)			**0.118**
Discharged	**411(92.1)**	**447(94.7)**	
Expired	**35(7.9)**	**25(5.3)**	

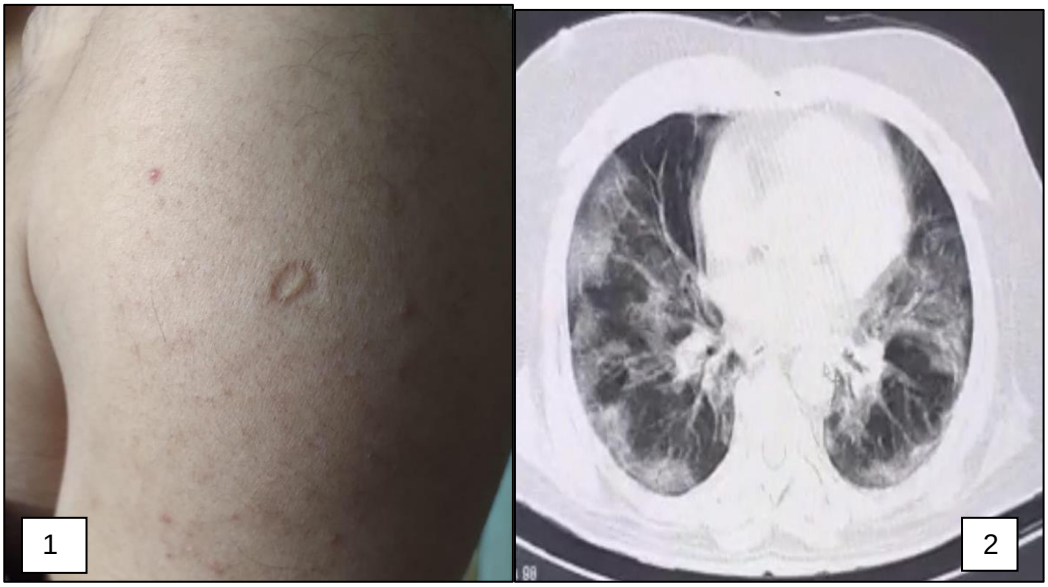

Figure 1: BCG vaccination scar on deltoid region of left arm.
Figure 2: CT chest showing bilateral peripheral ground glass opacities in COVID-19 patient.

Discussion

Our study demonstrated that BCG vaccination status had no effect on clinical severity and outcome of patients infected with COVID-19. However there was a trend towards raised inflammatory markers and radiological severity among unvaccinated patients. The Bacille Calmette-Guérin (BCG) vaccine, derived from an attenuated strain of M. bovis, is primarily known for its efficacy against childhood tuberculosis forms but its effectiveness in adults remains uncertain[17,18]. While randomized control trials demonstrate its efficacy against various bacterial and viral infections, including reducing neonatal and infant mortality rates, its role in mitigating COVID-19 severity is still under investigation.[19],[20] Some studies suggest a potential protective effect against acute lower respiratory tract infections and overall mortality in children under 5 years old in low-income countries.[21,22]

BCG vaccination appears to modulate immune responses to infections by inducing heterologous lymphocyte responses, enhancing macrophage activation, cytokine, and antibody production, potentially conferring protection against viral infections. However, conflicting findings exist regarding its impact on SARS-CoV-2 infection rates and severity.[23]

Our study aimed to elucidate the relationship between BCG vaccination
and COVID-19 severity and inflammatory markers. We found no significant association between prior BCG vaccination and clinical severity of COVID-19, consistent with some previous literature.[24] However, studies have reported varied results regarding BCG vaccination's impact on COVID-19 outcomes, with some indicating a potential decrease in seroprevalence and symptoms among vaccinated individuals.[25]

While analysing the inflammatory markers, we observed significant differences in CRP and ferritin levels between vaccinated and unvaccinated groups, suggesting a potential role of BCG vaccination in modulating inflammatory responses. Nevertheless, further research is needed to understand the mechanisms underlying these observations.

Additionally, our study explored chest CT findings in COVID-19 patients with respect to BCG vaccination status. We observed a significant association between BCG vaccination and CT severity scores, with vaccinated individuals showing milder disease manifestations compared to unvaccinated individuals. These findings align with existing literature highlighting the potential protective effect of BCG vaccination against severe COVID-19 pneumonia.[26,27,28]

However, despite these observations, our study did not find a correlation between BCG vaccination and mortality benefit in COVID-19 patients. This contrasts with some studies suggesting a potential reduction in COVID-19 mortality rates in countries with universal BCG vaccination policies.[29]

In conclusion, while our study adds to the growing body of evidence on the potential impact of BCG vaccination on COVID-19 outcomes, further research is needed to fully elucidate its effectiveness and mechanisms of action in combating the disease.

Conclusion

We concluded that neonatal BCG vaccination limits the radiological severity of the COVID-19 pneumonia but does not give any mortality benefit to COVID-19 patients**.**

Limitations

This study had a few limitations. First, the distribution of patients into two groups, BCG vaccinated and unvaccinated groups was done on the basis of presence or absence of BCG vaccination scar which could result in observation bias. Also, in some patients who would have been vaccinated but scar was not present due to inability of body to mount a reaction. Also, patients were not randomized according to age or comorbidities which would have affected the results.

Conflict of interest: Nil

Funding: Nil

References

1. World Health Organization . Geneva (Switzerland): World Health Organization; 2020. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020.
2. World Health Organization . Geneva (Switzerland): World Health Organization; 2020. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020.
3. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID- 19) implicate special control measures. J Med Virol. 2020 Mar 5
4. Fauci AS, Lane HC, Redfield RR. Covid-19—navigating the uncharted. N Engl J Med. 2020;382:1268–1269. doi: 10.1056/NEJMe2002387
5. Keswani A, Dhana K, Rosenthal JA, Moore D, Mahdavinia M. Atopy is predictive of a decreased need for hospitalization for coronavirus disease 2019. Ann Allergy Asthma Immunol. 2020;125:479–481. doi: 10.1016/j.anai.2020.07.012
6. Gursel M, Gursel I. Is global BCG vaccination-induced trained immunity relevant to the progression of SARS-CoV-2 pandemic? Allergy. (2020) 75:1815–9.
7. Kantor IN. BCG Versus COVID-19? Medicina (2020) 80:292–4.
8. Pereira, S.M., Barreto, F.R., de Souza, R.A. et al. Previous BCG vaccination is associated with less severe clinical progression of COVID-19. BMC Med 21, 145 (2023).
9. World Health Organization (February 2018). "BCG vaccines: WHO position paper – February 2018". Weekly Epidemiological Record. 93 (8): 73–96.
10. N.E. Aronson, M. Santosham, G.W. Comstock, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: a 60-year follow-up study.
11. Andersen P Doherty TMThe success and failure of BCG—implications for a novel tuberculosis vaccine, Nat Rev Microbiol, 2005, vol. 3 (pg. 656-62).
12. Netea, M.G., Quintin, J., van der Meer, J.W.M. (2011). Trained immunity: A memory for innate host defense. Cell Host & Microbe, 9(5), 355-361.
13. Upton CM, van Wijk RC, Mockeliunas L, Simonsson USH, McHarry K, van den Hoogen G, et al. Safety and Efficacy of BCG Re-Vaccination in Relation to COVID-19 Morbidity in Healthcare Workers: A Double-Blind, Randomised, Controlled, Phase 3 Trial. EClinicalMedicine (2022) 48:101414. doi: 10.1016/j.eclinm.2022.101414
14. Harris E. BCG Vaccine Not Effective Against COVID-19. JAMA. 2023;329(20):1730

15. Pan F, Ye T, Sun P et al (2020) Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. Radiology 200370. 10.1148/radiol.2020200370
16. Updated Detailed Clinical Management Protocol for COVID19 Adults. Ministry of Health and Family Welfare. India. https://www.mohfw.gov.in.
17. Mangtani P, Abubakar I, Ariti C, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials.
18. Ong CWM, Migliori GB, Raviglione M, et al. Epidemic and pandemic viral infections: impact on tuberculosis and the lung: a consensus by the World Association for Infectious Diseases and Immunological Disorders (WAidid), Global Tuberculosis Network (GTN), and members of the European Society of Clinical Microbiology and Infectious Diseases Study Group for Mycobacterial Infections (ESGMYC). Eur Respir J 2020;56:2001727.
19. Aaby P, Roth A, Ravn H, et al. Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period? J Infect Dis 2011; 204:245-52. 15
20. Biering-Sorensen S, Aaby P, Lund N, et al. Early BCGDenmark and neonatal mortality among infants weighing<2500 g: a randamoised controlled trial.
21. Hollm-Delgado MG, Stuart EA, Black RE. Acute lower respiratory infection among Bacille Calmette-Guerin (BCG)-vaccinated children. Pediatrics. 2014;133(1):e73-81.
22. Tavares Cruz C, Almeida B, Troster E, Oliveira C. Systematic Review of the Non-Specific Effects of Bacillus Calmette-Guérin Vaccine on Child Mortality. Journal of Infectious Diseases and Treatment. 2017;03(02)
23. Kleinnijenhuis, J., Quintin, J., Preijers, F., Benn, C. S., Joosten, L. A., Jacobs, C., ... & Netea, M. G. (2014). Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. Journal of Innate Immunity, 6(2), 152-158. https://doi.org/10.1159/000355628
24. Khanum I, Kumar L, Awan S, Jamil B. Severity of COVID-19 in bacillus Calmette-Guérin vaccinated population. Clin Exp Vaccine Res. 2021 Sep;10 (3):276-281. doi: 10.7774/cevr.2021.10.3.276. Epub 2021 Sep 30. PMID: 34703811; PMCID: PMC8511583
25. Richardson S, Hirsch JS, Narasimhan M, et al; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323 (20):2052-2059.
26. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, Diao K, Lin B, Zhu X, Li K, Li S, Shan H, Jacobi A, Chung M. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology. 2020 Jun;295(3):200463. doi:10.1148/radiol.2020200463. Epub 2020 Feb 20. PMID: 32077789; PMCID: PMC7233369
27. Bao C, Liu X, Zhang H, Li Y, Liu J. Coronavirus Disease 2019 (COVID-19) CT Findings: A Systematic Review and Meta-analysis. J Am Coll Radiol. 2020 Jun;17(6):701-709. doi: 10.1016/j.jacr.2020.03.006. Epub 2020 Mar 25. PMID: 32283052; PMCID: PMC7151282
28. Fu F, Lou J, Xi D, Bai Y, Ma G, Zhao B, Liu D, Bao G, Lei Z, Wang M. Chest computed tomography findings of coronavirus disease 2019 (COVID-19) pneumonia. Eur Radiol. 2020 Oct;30(10):5489-5498. doi: 10.1007/s00330-020-06920-8. Epub 2020 May 20. PMID: 32435925; PMCID: PMC7237879.
29. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv. 2020;(Jan).