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Examine The Risks Of And Potential Protective Effects Against Covid-19 In Relation To Smoking Status

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Abstract:

The relationship between smoking and the incidence of COVID-19 remains ambiguous. Several epidemiological studies have reported a low prevalence of smokers among hospitalized COVID-19 patients, raising a hypothesis that smoking has a potential protective effect against the disease. **Aims:** This study aims to examine the risks of and potential protective effect against COVID-19 in relation to smoking status. **Methods: Setting:** The study was carried out in three different Public Cafe in Lattakia city, Syria. **Subjects:** The study subjects comprised 60 persons who confirmed they did not have the laboratory-confirmed covid-19 disease. They were divided into two equal groups. The cases group: smokers. The controls group: nonsmokers. **Tools:** Two tools were used for data collection: the socio-demographic and clinical data structured interview schedule, and the self- reported COVID-19 and serology test. **Results:** The self- reported COVID-19 was significantly higher among smokers than nonsmokers (56.67% vs 26.67%,), and a significantly higher proportion of smokers tested positive for COVID-19 than the nonsmokers (80.0% vs 40.0%). **Conclusion:** The smoking increases both the likelihood of contracting COVID-19 and symptomatic disease. **Recommendations:** Smoking cessation should be considered as an essential element in strategies to blunt the COVID-19 pandemic.

Keywords: COVID-19 Incidence, Smoking, Tobacco, Infection.

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تقييم المخاطر والتأثير الوقائي المحتمل ضد كوفيد- 19 فيما يتعلق بحالة التدخين

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الملخص:

لا تزال العلاقة بين التدخين وحدوث مرض كوفيد- 19 غامضة. أفادت العديد من الدراسات الوبائية عن انخفاض معدل انتشار المدخنين بين مرضى كوفيد- 19 المستشفيات ، مما أثار فرضية أن التدخين له تأثير وقائي محتمل ضد المرض. **الهدف:** تهدف هذه الدراسة إلى تقييم المخاطر والتأثير الوقائي المحتمل ضد كوفيد- 19 فيما يتعلق بحالة التدخين. **الطرق:** المكان: أجريت الدراسة في ثلاثة مقاهي عامة مختلفة في مدينة اللاذقية ، سوريا. العينة: شملت عينة الدراسة 60 شخصًا أكدوا عدم إصابتهم بمرض كوفيد -19 المؤكد مختبريًا. تم تقسيمهم إلى مجموعتين متساويتين. مجموعة الحالة: المدخنون. مجموعة الضابطة: غير المدخنين. الأدوات: تم استخدام أداتين لجمع بيانات الدراسة: استمارة المقابلة المنظمة للمعلومات الديموغرافية والسريرية، واختبار كوفيد- 19 واختبار الأمصال المبلغ عنه ذاتيًا. النتائج: كان كوفيد- 19 المبلغ عنه ذاتيًا أعلى بشكل ملحوظ بين المدخنين من غير المدخنين (56.67٪ مقابل 26.67٪)، وكانت نسبة الاختبار الايجابي لكوفيد- 19 أعلى بكثير عند المدخنين مقارنة بغير المدخنين (80.0٪ مقابل 40.0٪).

الخلاصة: يزيد التدخين من احتمالية الإصابة بكوفيد- 19 وكون الاصابة مترافقة بأعراض.

التوصيات: يجب اعتبار الإقلاع عن التدخين عنصرًا أساسيًا في استراتيجيات مكافحة جائحة كوفيد- 19.

الكلمات المفتاحية : الإصابة بكوفيد- 19، التدخين، التبغ، العدوى.

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Introduction:

Since its outbreak in late 2019, coronavirus disease (COVID-19) has become an ongoing health problem accompanied by a profound effect on the economy and health worldwide (Lai CC, et al. 2020). COVID-19 is primarily a viral respiratory disease evoked by the newly discovered breed of coronavirus, that is termed Severe Acute Respiratory Syndrome related Corona-Virus 2 (SARS-CoV-2) (Lamers MM, et al. 2022). Owing to its high virulence rate, transmissibility and mortality, the World Health Organization (WHO) declared it a pandemic in January, 2020. As of 2 September 2022, there were a total of 600,555,262 confirmed cases, of whom 6,472,914 fatalities globally (World Health Organization. 2022).

To fight COVID-19 effectively, several risk factor associated with the disease susceptibility and severity have been identified, among them smoking have attracted a keen interest. Smoking is a well-established risk factor for infectious respiratory illness, with smokers five times more likely to contract influenza and three times more likely to develop pneumococcal pneumonia than nonsmokers (Lawrence H, et al. 2019). There are multiple proposed mechanisms that link smoking to increasing the susceptibility to the disease. Principally, smoke exposure results in damage to the lung epithelium, decreasing mucociliary clearance, disturbs the epithelial barrier, increases mucosal inflammation, and impairs pulmonary immune function, causing smokers to become more vulnerable to infectious pathogens (Shastri MD et al, 2021).

More specifically, in the context of the COVID-19, recent studies revealed that smoke exposure triggers an upregulation of angiotensin-converting enzyme 2 (ACE2) receptors, a known receptors of SARS CoV-2 in the lung, thus facilitating viral dissemination and infection. Also, it was found that smoking exacerbates the disease severity by blocking the immune system singling pathways, especially interferon which plays a pivotal role in the host early immune response, thereby blunting the capacity of the immune system to suppress viral replication and restrain infection. Putting together, it has been postulated that smokers are particularly at a higher quantum of risk of both acquiring and worsening of COVID-19 (Leung JM, et al. 2021, V'kovski P, et al. 2021).

Notwithstanding smoking effects, several epidemiological studies reported a low prevalence of smokers among hospitalized COVID-19 patients, raising a hypothesis that it has a potential protective effect against the disease (Berlin I, et al. 2020, Guan WJ, et al 2020, Rossato M, et al. 2020). Furthermore, numerous studies have focused on smoking impact on COVID-19, and their results were contradictory and inconclusive. Some studies found no significant association between smoking and increased the disease severity, hospitalization and mortality (Lippi G, et al. 2020, Simons D, et al. 2021). In contrast, other studies indicated that smoking had a negative impact on COVID-19 progression and higher risks of disease -related death (Patanavanich R, et al. 2020, Clift AK, et al. 2022, Baker J, et al. 2022).

Consequently, despite a plethora of studies conducted, there is a great controversy in the literature over whether smoking is considered a predisposing factor for COVID-19 infectivity. This may be partially explained by the majority of studies relied heavily on hospitalized cases, while a significant proportion of infected patients will present as asymptomatic or mild infections and would not require hospitalization. Thus, extrapolation from this subgroup to population risk might not be appropriate. Additionally, limited information is available on a community because of scarce population based studies (Clift AK, et al, 2022, Pradhan M, et al. 2022).

To overcome these limitations, community based study using serology testing is a valuable research instrument and highly recommended. Serology testing (also called antibody testing) is laboratory based test aimed to detect the presence of plasma antibodies (Immunoglobulin (IgA, IgG, IgM) against SARS-CoV-2, which produced as part of the host's immune response to viral infection. In comparison with other antibody, IgG persists in the body for an extended period post infection, hence considered a powerful indicator for seroconversion mainly for prior infection. By virtue of their ability to detect previously infected individuals, this test may provide an actual estimation of infected population and allow investigating a given association precisely (Liu G, et al. 2021).

Against this backdrop, the relationship between smoking and the incidence of COVID- 19 remains

ambiguous. Additionally, better understanding the risk factors associated with the disease particularly modifiable host factors such as smoking, may be of importance in confronting the contagions and lessening the disease severity. Toward this end, this study aimed to examine the risks of and potential protective effects against COVID-19 in relation to smoking status.

Materials And Method:

Materials:

Design: A case- control design.

Setting: The study was carried out in three different public cafe in Lattakia city, Syria.

Subjects : the study subjects amounted to 60 persons of both genders. They were chosen from the previous settings using the convenience sampling technique.

The inclusion criteria were: adults who confirmed that they did not have the laboratory-confirmed covid-19, attended the above mentioned settings, and accept to participate in the study.

Tools: two tools were used to collect the study data.

Tool I: Socio-demographic and clinical data structured interview schedule:

It was developed by the researcher and included two parts:

1: Data about the persons': Socio demographic characteristics of the elders such as age, sex, social status, level of education, monthly income, and area of residence.

2: Health history: Presence of chronic disease, medication used, smoking, alcohol intake, exercise history, and Anthropometric measurements as weight, height, and body mass index.

Tool II: Self-reported COVID-19 and serology test: It was developed by the researcher after through review of literature and included two parts:

1: Self-reported COVID-19: Participants were told about the key symptoms of COVID-19 namely: fever, fatigue, myalgia and continuous cough. Then, they were asked if they had such symptoms in the last three month. Those who responded "yes" were labelled as having a self-reported COVID-19.

2: Serology testing: is laboratory based test used to detect the presence of plasma anti-SARS-CoV-2 IgG antibodies, as objective evidence of a previous illness, using Enzyme-linked immunosorbent assay (ELISA).

Method

1. Official approvals from the competent authorities to carry out the study were obtained.
2. The researcher visited the above mentioned settings at different days and times. A survey to all customers in the three cafe was done in order to identify those fulfilling the study criteria and he selects 60 persons by using the convenience sample technique
3. The (60 persons) who consented to participate in the study was divided into two equal groups, 30 participants in each group. The cases group: was current smokers. The controls group: was nonsmokers. It was planned to recruit cases and controls in a 1:1 ratio and match them for age, sex, area of residence and body mass index.

. After obtained informed consent, each subject was interviewed individually to obtain the necessary data (the interview was conducted at a private place in each cafe). Anthropometric measurement was taken (weight, height, BMI) and a blood sample was obtained from each participant.

. All blood samples were anonymized, and were transported immediately to a private laboratory. The enzyme-linked immunosorbent assay (ELISA) test was used for qualitative detection of IgG antibody to SARS-CoV-2, using the EUROIMMUN Anti-SARS-CoV-2 ELISA. According to the manufacturer's recommendations, samples were considered positive for IgG above Nova Tec units (NTU) 1.1. The reported clinical sensitivities/specificities for IgG by the manufacturer was 100% /99,6% (ELISA test systems from EUROIMMUN. 2022).

Data collection started from the first of August 2020 to the middle of October 2020.

Ethical considerations:

- Privacy and confidentiality of the collected data was assured. Each person was informed about his right to withdraw from the study without penalties.
- Approval from the faculty of medicine ethical committee was obtained. A written informed consent was obtained from each participant of both groups after explanation of the aim of the study.

Statistical analysis:

- All analyses were completed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corporation).
- Descriptive statistics using means (standard deviations) for continuous data and frequencies (%) for categorical data were calculated.
- The chi-square and Fisher's exact tests were used to compare percentages between groups.
- Monte Carlo correction: correction for chi-square when more than 20% of the cells have expected to count less than 5
- The t test was used to compare differences between continuous variables.
- P-values ≤ 0.05 was considered to be significant.

Results:

Table (1) shows the socio-demographic characteristics of the persons. No significant difference was found between the smoker and nonsmoker groups with respect to socio-demographic characteristics. The age of the persons ranged from 18 to 62 years. The mean age of the smoker and nonsmoker groups was 38.3±10.6 years and 38.7±11.8 years respectively. More than half (56.67%) of smoker and nearly two third (66.67%) of nonsmoker were single. As regards educational level (73.0%) had higher education. Two fifth (40.0%) of smoker and more than half (56.67%) of nonsmoker had a monthly income ranged from 40000 to 80000 Syrian Lira.

Table (2) shows the health profile of the persons. No significant difference was found between the smoker and nonsmoker groups with respect to their health profile. It appears from the table that (70.0%) of the persons in the both groups reported having no chronic diseases. The majority (76.6% of smoker and 86.67% of nonsmoker) did not consume alcohol. Half of the person in the both groups had a habit of exercising regularly. The mean body mass index BMI of the smoker and nonsmoker groups was 64.3±15 and 63.5±11.6 respectively.

Table (3) shows the relation between the self-reported COVID-19 and the serology testing of the both groups. As regards the self- reported COVID-19, the seek healthcare, and the serology testing the differences between the smoker and nonsmoker groups are statistically significant (P=0.018, P=0.038, and P=0.002) respectively.

Discussion:

The COVID-19 pandemic represents a grave threat to global health and imposes an immense strain on health care systems, societies, and economies worldwide (Levin AT, et al. 2022). On the basis of the knowledge that COVID-19 preferentially affects the respiratory system, smoking is hypothesized to be a highly likely susceptibility factor for increased infectivity and poor disease outcomes. Yet, current evidence on the role of smoking in COVID-19 is still unclear or inconsistent (Benowitz NL, et al. 2022). Here we present the results of a case-control study investigating the risks of and potential protective effects against COVID-19 in relation to smoking status.

The present study revealed that a significantly higher proportion of smokers had a tested positive for SARS-CoV-2 than nonsmokers. This may indicate that smoking not only cannot provide protection against COVID-19, but smoking also may increase the risk of infection. A wealth of reasons can explain this result including; smoking induces substantial structural and mechanical changes in the respiratory tract, attenuates immune system response to infectious pathogens, and facilitates viral entry into the host cells and replication (Benowitz NL, et al. 2022, Purkayastha A, et al. 2020).

In agreement with these findings, **Chimsimbe *et al.*,** who investigated the risk factors associated with contracting COVID-19, concluded that smoking is an independent risk factor for COVID-19 occurrence (Chimsimbe M, et al. 2022). Also, this result was echoed in the study of **Thomas *et al*** (Thomas DRh, et al. 2022). Furthermore, **Rosoff *et al.,*** provide strong genetic based evidence of the negative impact of smoking on COVID-19, and endorse the conclusion that smoking increases individual-level susceptibility from COVID-19 (Rosoff DB, et al. 2021). Finally, **Maraqa *et al.,*** demonstrated that SARS-CoV-2 antibodies positivity was were significantly associated with sex, smoking, and COVID-19 contact history (Maraqa B, et al. 2021).

Nevertheless, these present study findings disagree with the findings of **Arasteh *et al.,*** and **Tsigaris *et al.,*** who found an inverse correlation between smoking prevalence and COVID-19 occurrence.

However, both authors clarify that the association does not confirm that smoking has a therapeutic or prophylactic role in COVID-19 (Arasteh A, et al. 2022, Tsigaris P, et. 2020). In short, the discrepancies between these studies findings and the current study results may be attributed to differences in the research methodology. Specifically, the criteria used to define the cases and smoking status were questionable. While the former used only self-reported COVID-19 as a proxy of infection, the latter depended on electronic health records that may contain incomplete histories. Besides, in both studies the smoking history encompasses current, former, and never smokers and this may have led to misclassification of smoking status. Consequently, these might affect the examined association.

Additionally, the current study demonstrated that a significantly higher proportion of smokers had a self-reported COVID-19 than nonsmokers, suggesting that smoking was associated with a noticeably increased the risk of symptomatic disease. Similar to our results, **Hopkinson *et al.*,** point out that smokers were more likely to suffer from symptoms suggesting a diagnosis of COVID-19 (Hopkinson NS, et al. 2020). Also, a representative population survey in England reported that odds of self-reported COVID-19 were significantly higher among smokers in comparison with nonsmokers (Tattan_Birch H, et al. 2021). In contrast, **Saurabh *et al.*,** observed that tobacco smoking was associated with reduce the likelihood of developing symptoms suggestive of COVID-19, and assign this finding to residual confounding owing to unknown factors (Saurabh S, et al. 2021).

One of the most intriguing finding emerged from the current study was that a high percentage of both smokers and nonsmokers had had either asymptomatic or mild disease. As evidenced by a small proportion of both studied groups sought a medical care to remediate their symptoms once they had COVID-19 like features. From this result two important points, at least, can be inference. First and foremost, with regard smoker particularly, continues cough is a key feature, as well as the disease is primarily transmitted through respiratory droplets and aerosols spilled by infected people. Taken together, in addition to have higher susceptibility to developing COVID-19, smokers might also be a potential source for disease transmission.

Secondly, both smokers and nonsmokers did not develop sever disease. This finding, mainly for smoker, is in contrast with the conclusion of many studies that smoking is a predisposing factor for sever disease progression (He Y, et al. 2022, Reddy RK, Charles WN, et al 2022). Possible explanations for this finding. Firstly; the current study did not recruit individual with laboratory-confirmed covid-19, namely the reverse-transcription Polymerase Chain Reaction (RT-PCR) test which considered a golden standard test for confirming the COVID-19 diagnosis, and in Syria, like the majority of low income centuries, this test is expensive and restricted to sever clinical cases (Maraqa B, et al. 2021, Makoah NA, et al. 2022). So, individual with laboratory-confirmed covid-19 may differ significantly from individual with non-laboratory-confirmed covid-19. Secondly, the participants in our study were somewhat younger (mean age was nearly 38 years), and did not have a smoking related disease that considered the mean mechanism by which smoking linked to disease progression. Thirdly; as **De Santi *et al.*,** stated that smoking responsible of only one third of probability of disease development, underscoring that there are other factors implicated in disease progression (De Santi M, et al. 2021).

The strengths of the present study were rooted in the study's participants who draw directly from the community as well as the incidence of the COVID-19 was measured subjectively and objectively, while its limitations were imbedded in its retrospective nature. In addition, the sample size was small due to the cost of serology testing. Therefore, our findings need to be further verified in large prospective population-based studies.

Conclusion:

It can be concluded from the study that smoking increases both the likelihood of contracting COVID-19 and symptomatic disease.

Recommendations:

- Smoking cessation should be considered as an essential element in strategies to blunt the COVID-19 pandemic.

- Public health efforts should include raising community awareness of these risks, emphasizing smoking cessation advice, and promoting smokers to seek care early in their illness.

Table (1): Distribution of persons in the smoker and nonsmoker groups according to their sociodemographic characteristics.

Sociodemographic Characteristics	Smoker group		Nonsmoker group		Significant
	NO. n=30	% 100	NO. n=30	% 100	
- Age (in years):					P=0.09
• 20 –	8	26.67	8	26.67	
• 30 –	7	23.33	11	36.67	
• 40 –	12	40.0	4	13.33	
• 50 –	3	10.0	7	23.33	
Mean ± SD	38.3 ± 10.6		38.7 ± 11.8		
- Sex:					P=0.796
• Female	14	46.67	15	50.0	
• Male	16	53.33	15	50.0	
- Marital status:					P=0.789
• Single	17	56.67	20	66.67	
• Married	12	40.0	9	30.0	
• Widowed	1	3.33	1	3.33	
- Educational Level:					P=1
• Up to preparatory	3	10.0	2	6.67	
• Secondary	5	16.67	6	20.0	
• Higher education	22	73.33	22	73.33	
- Monthly income:					P=0.302
• 0	7	23.33	6	20	
• 40000 –	12	40.0	17	56.67	
• 80000 –	8	26.67	7	23.33	
• > 100000	3	10.0	0	0.0	
- Area of residence					P=1
• Rural	11	36.67	11	36.67	
• City	19	63.33	19	63.33	

* Significant $P \leq 0.05$

Table (2): Distribution of persons in the smoker and nonsmoker groups according to their health profile.

Health Profile	Smoker group		Nonsmoker group		Significant
	NO. n=30	% 100	NO. n=30	% 100	
- Comorbidity:					
• None	21	70.0	21	70.0	P=0.771
• One disease	9	30.0	7	23.33	
• Two disease	0	0.0	1	3.33	
• More than two disease	0	0.0	1	3.33	
- Wight (Kg):	64.3 ± 15		63.5 ± 11.6		P=0.8326
- Length (Cm)	168.5 ± 9.7		168 ± 10.5		P=0.849
- BMI	22.7 ± 3.6		22.8 ± 2.6		P=0.9228
- Smoking:					
• No	0	0.0	30	100.0	
• Yes	27	90.0	0	0.0	
• Sometimes	3	10.0	0	0.0	
- Alcohol intake:					
• No	23	76.67	26	86.67	P=0.317
• Yes	7	23.33	4	13.33	
- Exercise:					
• No	8	26.67	7	23.33	
• Sometimes	6	20.0	8	26.67	P=0.825
• Yes	16	53.33	15	50.0	

* Significant P ≤ 0.05

Table (3): Self-reported COVID-19 and serology testing of the smoker and nonsmoker groups.

Items	Smoker group		Nonsmoker group		Significant
	NO. n=30	% 100	NO. n=30	% 100	
- Self-reported COVID-19:					
• No	13	43.33	22	73.33	P=0.018*
• Yes	17	56.67	8	26.67	
- Seek healthcare:					
• No	22	73.33	28	93.33	P=0.038*
• Yes	8	26.67	2	6.67	
- Serology testing:					
• Negative	6	20.0	18	60.0	P=0.002*
• Positive	24	80.0	12	40.0	

* Significant P ≤ 0.05 IgG immunoglobulin G

References:

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020; 55(3). https://doi.org/10.1016/j.ijantimicag.2020.105924.
2. Lamers MM, Haagmans BL. SARS-CoV-2 pathogenesis. Nature Reviews Microbiology. 2022; 20(5):270-84. https://doi.org/10.1038/s41579-022-00713-0.
3. World Health Organization. WHO coronavirus (COVID-19) dashboard. Available at: (https://www.who.int/emergencies/diseases/novel-coronavirus-2019, accessed on 2/9/2022).
4. Lawrence H, Hunter A, Murray R, Lim WS, McKeever T. Cigarette smoking and the occurrence of influenza–Systematic review. Journal of Infection. 2019; 79(5):401-6. https://doi.org/10.1016/j.jinf.2019.08.014.
5. Shastri MD, Shukla SD, Chong WC, Rajendra KC, Dua K, Patel RP, et al. Smoking and COVID-19: What we know so far. Respiratory medicine. 2021; 176(2021). https://doi.org/10.1016/j.rmed.2020.106237.
6. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. European Respiratory Journal. 2020; 55(5). DOI: 10.1183/13993003.00688-2020.
7. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nature Reviews Microbiology. 2021; 19(3):155-70. https://doi.org/10.1038/s41579-020-00468-6.
8. Berlin I, Thomas D, Le Faou AL, Cornuz J. COVID-19 and smoking. Nicotine Tob Res. 2020; 22(9):1650-52. https://doi.org/10.1093/ntr/ntaa059.
9. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. New Engl J Med. 2020; 382:1708-20. DOI: 10.1056/NEJMoa2002032.
10. Rossato M, Russo L, Mazzocut S, Di Vincenzo A, Fioretto P, Vettor R, et al. Current smoking is not associated with COVID-19. Eur Respir J. 2020; 55. DOI: 10.1183/13993003.01290-2020.
11. Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). Eur J Internal Med. 2020; 75:107-08. https://doi.org/10.1016/j.ejim.2020.03.014.
12. Simons D, Shahab L, Brown J, Perski O. The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7). Addiction. 2021; 116(6):1319-68. https://doi.org/10.1111/add.15276.
13. Patanavanich R, Glantz SA. Smoking is associated with COVID-19 progression: a meta-analysis. Nicotine and tobacco research. 2020; 22(9):1653-6. https://doi.org/10.1093/ntr/ntaa082.
14. Clift AK, von Ende A, San Tan P, Sallis HM, Lindson N, Coupland CA, et al. Smoking and COVID-19 outcomes: an observational and Mendelian randomisation study using the UK Biobank cohort. Thorax. 2022; 1:77(1):65-73. http://dx.doi.org/10.1136/thoraxjnl-2021-217080.
15. Baker J, Krishnan N, Abroms LC, Berg CJ. The Impact of Tobacco Use on COVID-19 Outcomes: A Systematic Review. Journal of Smoking Cessation. 2022; 2022:1-11. https://doi.org/10.1155/2022/5474397.
16. Pradhan M, Shah K, Alexander A, Ajazuddin, Minz S, Singh MR, et al. COVID-19: clinical presentation and detection methods. Journal of Immunoassay and Immunochemistry. 2022; 43(1). https://doi.org/10.1080/15321819.2021.1951291.
17. Liu G, Rusling JF. COVID-19 antibody tests and their limitations. ACS sensors. 2021 5; 6(3):593-612. https://doi.org/10.1021/acssensors.0c02621.
18. ELISA test systems from EUROIMMUN. (https://www.coronavirus-diagnostics.com/antibody-detection-tests-for-covid-19.html, accessed on 5/4/2022).

19. Levin AT, Owusu-Boaitey N, Pugh S, Fosdick BK, Zwi AB, Malani A, et al. Assessing the burden of COVID-19 in developing countries: systematic review, meta-analysis and public policy implications. BMJ global health. 2022; 7(5). http://dx.doi.org/10.1136/bmjgh-2022-008477.
20. Benowitz NL, Goniewicz ML, Halpern-Felsher B, Krishnan-Sarin S, Ling PM, O'Connor RJ, et al. Tobacco product use and the risks of SARS-CoV-2 infection and COVID-19: current understanding and recommendations for future research. The Lancet Respiratory Medicine. 2022; 10(9):900-15. https://doi.org/10.1016/S2213-2600(22)00182-5.
21. Purkayastha A, Sen C, Garcia Jr G, Langerman J, Shia DW, Meneses LK, et al. Direct exposure to SARS-CoV-2 and cigarette smoke increases infection severity and alters the stem cell-derived airway repair response. Cell stem cell. 2020 3; 27(6):869-75. https://doi.org/10.1016/j.stem.2020.11.010.
22. Chimsimbe M, Mucheto P, Gombe T, Govha E, Juru P, Omondi M, et al. Factors associated with contracting Severe Acute Respiratory Syndrome Corona Virus type-2 in Norton Town, Zimbabwe, 2021: a case-control study. Journal of Interventional Epidemiology and Public Health. 2022; 5 (9). DOI: 10.11604/JIEPH.supp.2022.5.1.1224.
23. Thomas DRh, Fina LH, Adamson JP, Sawyer C, Jones A, Nnoaham K, et al. Social, demographic and behavioural determinants of SARS-CoV-2 infection: A case-control study carried out during mass community testing of asymptomatic individuals in South Wales, December 2020. Epidemiology & Infection. 2022; 150: 1-12. https://doi.org/10.1017/S0950268822000620.
24. Rosoff DB, Yoo J, Lohoff FW. Smoking is significantly associated with increased risk of COVID-19 and other respiratory infections. Commun Biol. 2021; 4(1):1–11. https:// doi. org/ 10. 1038/s42003- 021- 02685-y.
25. Maraqa B, Basha W, Khayyat R, Abdul- Hadi A-R, Jabareen J, Al-Shakhra K, et al. Prevalence of SARS-CoV-2 antibodies in the Palestinian population: A primary health center-based cross-sectional study. Plos one. 2021; 16(10). https://doi.org/10.1371/journal.pone.0258255.
26. Arasteh A, Mostafavi S, Mirza-Aghazadeh-Attari M, Alizadeh M, Mostafavi Montazeri SM, et al. Associations between Wearing Masks, Hand Washing, and the Risk of COVID-19 Contraction: A Case-Control Study in the Northwest of Iran. J Occup Health Epidemiol. 2022; 11(1):23-31. DOI: 10.52547/johe.11.1.23.
27. Tsigaris P, Teixeira da Silva JA. Smoking prevalence and COVID-19 in Europe. Nicotine and Tobacco Research. 2020; 22(9):1646-9. https://doi.org/10.1093/ntr/ntaa121.
28. Hopkinson NS, Rossi N, Moustafa JS, Laverty AA, Quint JK, Freidin MB, et al. Current tobacco smoking and risk from COVID-19: results from a population symptom app in over 2.4 million people. Medrxiv. 2020; 1. Doi: https://doi.org/10.1101/2020.05.18.20105288.
29. Tattan-Birch H, Perski O, Jackson S, Shahab L, West R, Brown J. COVID-19, smoking, vaping and quitting: a representative population survey in England. Addiction. 2021; 116(5):1186-95. https://doi.org/10.1111/add.15251.
30. Saurabh S, Verma MK, Gautam V, Kumar N, Jain V, Goel AD, et al. Tobacco, alcohol use and other risk factors for developing symptomatic COVID-19 vs asymptomatic SARS-CoV-2 infection: a case–control study from western Rajasthan, India. Trans R Soc Trop Med Hyg. 2021; 115(7): 820-31. https://doi.org/10.1093/trstmh/traa172.
31. He Y, He Y, Hu Q, Yang S, Li J, Liu Y, et al. Association between smoking and COVID-19 severity: A multicentre retrospective observational study. Medicine. 2022; 7:101(29). http://dx.doi.org/10.1097/MD.0000000000029438.
32. Reddy RK, Charles WN, Sklavounos A, Dutt A, Seed PT, Khajuria A. The effect of smoking on COVID-19 severity: A systematic review and meta-analysis. Journal of medical virology. 2022; 93(2):1045-56. https://doi.org/10.1002/jmv.26389.

33. Makoah NA, Tipih T, Litabe MM, Brink M, Sempa JB, Goedhals D, et al. A systematic review and meta-analysis of the sensitivity of antibody tests for the laboratory confirmation of COVID-19. Future virology. 2022; 17(2):119-39. https://doi.org/10.2217/fvl-2021-0211.
34. De Santi M, Diotallevi A, Brandi G. Seroprevalence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in an Italian cohort in Marche Region, Italy. Acta Bio-Medica : Atenei Parmensis 2021: 92(1). https:// doi. org/ 10. 23750/abm. v92i1. 10847.