Original Article

Assessment of Mortality of Admitted Patients having Nicotine Dependence in a Tertiary Care Hospital and its Relationship with Other Clinical Variables

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Background : Presence of co-morbidities with COVID-19 is a poor prognostic factor for survival. The Nicotine dependence may enhance the risk of death during any immuno-compromised state. This cross sectional study aims to find out the correlation between mortality due to COVID and its relationship with Nicotine dependence.

Materials & Methods : 136 patients admitted in COVID hospital in a Tertiary Care Hospital have been recruited in this study. The Nicotine dependence (FTND Scale), Stress (PSS) and outcome (alive or dead) have been analyzed by appropriate statistical methods.

Results: Demographic variables like residence has emerged as statistically significant (p=0.003) variable. Clinical variables like length of stay in hospital, presence of co-morbidity, vaccination status, outcome (all p value=0.000) and SpO_2 during admission (p=0.002) have been found statistically highly significant. The linear regression analysis with cause of death as dependent variable and other predictors like nicotine dependence, vaccination status, co-morbidity, other substance dependence, stress, length of stay at hospital, SpO_2 during admission; has found the adjusted R square value 0.678. Paired T test has found all above predictors except perceived stress scale total are significant. Paired samples t test has found all paired variables are significant except vaccination status and cause of death (p=0.362) and vaccination status and PSS total score (p=0.142). However, survival analysis and hazard function of outcome when plotted in Kaplan Meier curve, the length of stay, Nicotine dependence and survival have not found statistically significant (p=0.304).

Conclusion : Nicotine dependence has not been found directly attributed for death due to COVID-19. When compared with parametric tests the causality appears to be directly related. However, when logistic regression, survival analysis and Omnibus Tests of Model Coefficients have been carried out which nullifies the impact of confounding variables; the tobacco dependence has not been found to be directly attributed to mortality in this study.

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Key words **: Nicotine Dependence, COVID-19 Mortality, Co-morbidities, Perceived Stress, Survival Factor.**

The presence of Co-morbidities in COVID-19 is a poor prognostic factor. The mortality rate of COVID patients in a COVID hospital where moderate and severe cases are being admitted is expected to be higher if Nicotine dependence is present. There has not been any systematic study to find direct causal association and mortality due to COVID. There could be confirming variables attributed to death due to COVID and this study aims to find out the direct or indirect evidence of nicotine dependence, which could be an important prognostic variable of outcome of the admitted COVID patients. A multicentric study in Malaysia has found that smokers have higher risk of Acute Respiratory Distress Syndrome (ARDS) [OR, Odds ratio] 1.69; renal injury (OR 1.55) and acute liver injury (OR 1.33) than non-smokers in COVID-19 positive patients[1]. Similar study done in Bangladesh has also suggested that smoking is directly attributed to the COVID risk and course of illness. Smokers are at higher risk on having mild (OR=1.35), severe (OR=1.3) and critical (OR=2.45) cases than non-smokers[2]. In a group of 622 patients has been found smoking as an

Editor's Comment :

- The outcome of in patients who're admitted in COVID depends on multiple factors.
- The direct causal relationship between nicotine dependence and mortality due to COVID is difficult to ascertain due to confounding variables.
- In this present study, on 136 patients admitted in a Tertiary Care Government Medical Colege & Hospital in Eastern India, the direct causal relationship has not been found between mortality due to COVID and nicotine dependence.

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independent variable was statistical significant while comparing non survivors *versus* survivors in patients with COVID-19 even after adjustment of other variables like age, gender and underline diseases Hazard Ratio (HR) 1.897, P=0.007[3]. Another study group from Middle East has found that both mortality and morbidity due to COVID-19 are significantly higher among smokers than non-smokers[4].

Materials and Methods

The hypothesis of the present study is that Nicotine dependence increases the mortality in patients diagnosed of COVID-19. The primary objective of the present study is to find out the association between Nicotine dependency and mortality in COVID-19. The secondary objectives of the present study are to analyze survival function, hazard ratio and length of stay as outcome measures and their association with Nicotine dependence. The study design is a cross sectional in person interview maintaining COVID protocol. The age group selected was 15-60 years of both genders with desired sample size for the study applying the formula is N=4pq where p=prevalence, q= (100-p) and permissible error is 15%. N = 4X 2X98X.15=118 in round figure. The recovered patient and the close family members of patients who died due to COVID have been included in this study. The study has been done by household survey from records available in Chief Medical Officer of Health (CMOH) office in Murshidabad district for 18 weeks as per the list available. From the database of register of COVID patients admitted in COVID hospital, 152 patients or the survivors of individual who died due to COVID have been included in the study on the basis of computerized random number generation. A written informed consent has been taken from the patients or their survivors. The subjects from whom voluntary informed consent couldn't be taken and those who are physically and mentally unable to respond in this interview have been excluded from the study. In this group, 16 patients or their survivors have refused to participate in the study. So, finally 136 subjects have been recruited in the present study. The following instruments have been used in the present study (i) Clinical data profile sheet for demographic variables, (ii) Fagerstorm Test for Nicotine Dependence (FTND) to assess the level and pattern of dependence[5]. There are six questions in FTND. Scoring in this instrument has been done as follows (a) less than 4 = Low Dependence, (ii) 4 to 6 = Moderate Dependence. And (iii) Above 6 = High Dependence. Fagerstorm Test for Nicotine dependence is a validated standard instrument which provides ordinal measures of Nicotine dependence. The validated scale has been used by various researchers in local vernacular as well[6-8].

Perceived Stress Scale (PSS) to assess the stress of deceased family members and COVID survivors[9]. There are 10 questions in PSS. Scoring has been done as follows (a) Scores ranging from 0-13 is considered as Low stress, (ii) Scores ranging from 14-26 is considered as Moderate stress and (iii) Scores ranging from 27-40 is considered as High perceive stress. The patients were interviewed by Trained Doctors (Public Health Specialist and Psychiatrist) and Psychologist/ Counselor by the house to house visit. The clinical psychologist National Tuberculosis Control programme (NTCP) has been instructed to collect the data by the communication of the area related Health worker like- Accredited Social Health Activist (ASHA), Auxiliary Nurse Midwife (ANM), Senior Treatment Supervisors (STS), Community Health Officer (CHO), Health Supervisor etc, and related Block Medical Officer of Health (BMOH). In this purpose the incidental cost and mobility support will be spent from the fund of NTCP, Murshidabad. The data has been tabulated and analyzed is Statistical Package of Social Sciences (SPSS) Version 18.0, IBM Corp[10].

Results

In this study, majority were male subjects (89.0%) and most of patients are from rural sector (52.2%), most of patients are educated up to primary standard (Class 4), majority of them are self employed or business man (23.5%) most of the study population are Hindu by religion (70.6%) and having lower family income (INR<10,000/month). Among the demographic variables only residence has been found to be statistically significant in one-way ANOVA test (p = 0.003) (Table 1).

Among the clinical variables, the length of stay has been found to be statistically significant. The majority of the study subjects have been admitted in COVID Hospital for more than seven days. (n=79, 58.1%, p = 0.000). The majority of patients stayed in COVID Hospital (n = 79, 58.1%, p = 0.000) for more than 7 days which suggests the chronicity and severity of illness among the study population. The SpO_2 during admission has emerged a statistically important clinical variable in the study population. During admission around one fourth of the study population had SpO_2 ranging from 81-94% (n = 33, 24.2%, p = 0.002) and around one in tenth admission cases had SpO_2 <80% during admission (n = 13, 9.6%, p = 0.002). The majority of admitted patients had COPD,

Table 1 — *Demographic Variables & Frequencies of Study Population*

Age	Frequency (n%)	F	Significance (p)
Below 18 years	14 (10.3)	0.077	0.781
18-30 years	23 (16.9)		
31-45 years	48 (35.3)		
46-60 years	51 (37.5)		
Gender :			
Male	121 (89.0)	1.699	0.154
Female	15 (11.0)		
Residence :			
Urban	42 (30.9)	4.222	0.003**
Semi Urban	23 (16.9)		
Rural	71 (52.2)		
Education :			
Illiterate	17 (12.5)	8.166	0.347
Primary (up to 4th standard)	36 (26.5)		
Secondary (5th-10th standard)	30 (22.1)		
Higher Secondary (11th and 12th standards)	17 (12.5)		
Graduate	31 (22.8)		
Postgraduate/Master's degree	5 (3.7)		
Occupation :			
Unemployed/Students	25 (18.4)	3.552	0.110
Manual Workers	25 (18.4)		
Semi Skilled worker	5 (3.7)		
Skilled worker	5 (3.7)		
Private Job	3 (2.2)		
Government Job	19 (14.0)		
Business	32 (23.5)		
Retired	22 (16.2)		
Family Income (per month) :			
<10,000	61 (44.9)	0.333	0.172
10,001 - 20,000	35 (25.7)		
20,001 - 30,000	20 (14.7)		
30,001 - 40,000	9 (6.6)		
40,001 - 50,000	5 (3.7)		
> 50,000	6 (4.4)		
Religion :			
Hindu	96 (70.6)	0.052	0.585
Muslim	40 (29.4)		
Christian	0 (0.0)		
Others	0 (0.0)		
Migratory labour :			
Yes	2 (1.5)	0.309	0.289
No	134 (98.5)		
Tobacco Dependence :			
Yes	77 (56.6)	0.246	0.637
No	59 (43.4)		

*Significance p<0.05; **Significance p<0.01

followed by Hypertension and Type 2 Diabetes Mellitus as co-morbidity, which has been found to be statistically significant (p = 0.000). During the study period both doses of COVID vaccine have been received by around half of the study population (n = 67, 49.3%, p = 0.000) and single dose of COVID vaccine has been received by around one eighth of study population (n = 18, 13.2%, p = 0.000) (Table 2). While analyzing the tabulated data by linear regression statistics with cause of death as dependent variable and other predictors (Fagerstorm's test for Nicotine dependence, vaccination status, co-morbidities, any dependence other than tobacco, Perceived Stress Scale (PSS), length of stay at COVID hospital, SpO_2 during admission), it has been found that the cause of death as a significant predictor with the above variables (adjusted R square = 0.678, F = 36.480, p = 0.000)(Table 3). By analyzing Paired 't' test it dependent variables as cause of death the variables like Tobacco dependence (p = 0.022), any dependence other than tobacco (p = 0.005), Length of stay at COVID Hospital (p = 0.000), SpO_2 during Admission (p = 0.000), Co-morbidity (p = 0.014), Vaccination status (p = 0.002) and Fagerstorm's Questionnaire (FQ) score total (p = 0.016) have been found to be statistically significant. However, Perceived Stress Scale (PSS) total score has not been found to have co-relation with cause of

Table 2 — *Clinical Variables of Study Population*

Length of Stay in COVID Hospital	Frequency (n%)	F	Significance (p)
1-3 days	32 (23.5)	25.056	0.000**
4-7 days	25 (18.4)		
7 days and above	79 (58.1)		
SpO_2 during admission :			
> 95%	90 (66.2)	4.363	0.002**
81% - 94%	33 (24.2)		
Below 80%	13 (9.6)		
Presence of Co-morbidity :			
Hypertension	27 (19.9)	8.012	0.000**
Diabetes Mellitus	21 (15.4)		
HIV-AIDS	3 (2.2)		
Cancer	3 (2.2)		
Coronary Artery Decease (CAD)	4 (2.9)		
COPD	78 (57.4)		
Vaccination status :			
1 Dose of vaccine	18 (13.2)	6.410	0.000**
Both doses of vaccine	67 (49.3)		
Vaccine not taken	51 (37.5)		
Outcome :			
Alive	78 (57.4)	33.513	0.000**
Dead	58 (42.6)		

*Significance p<0.05 **Significance p<0.01

Table 3 — *Linear regression analysis of Dependent variable cause of death with other variables*

Model	Sum of Squares	df	Mean Square	F	Significance (p value)
Regression	229.154	8	28.644	36.480	0.000**
Residual	99.721	127	0.785		
Total	328.875	135			

Model	R	R square	Adjusted R square	Standard error of the Estimate
1	0.835[a]	0.697	0.678	0.836

a. Dependant Variable: Cause of Death
b. Predictors: (Constant), FQTOT, Whether Vaccinated, Co-Morbidity, Any dependence other than Tobacco, PSSTOT, Length of stay at COVID Hospital, SpO_2 during admission, Tobacco Dependence (any)

death (p = 0.231)(Table 4). The Paired samples statistics like (i) PSS (total score) and FQ (total score), (ii) Cause of death and co-morbidity, (iii) PSS total and Co-morbidity, (iv) FQ total and Cause of Death, (v) Tobacco Dependence and Cause of Death, (vi) Tobacco Dependence and Co-morbidity; all have been found to be highly significant statistically (p = 0.000), have been found to be statistically significant. However, (vii) Vaccination Status and Cause of Death (p = 0.362) and (viii) Vaccination status and PSS total (p = 0.142) have not been found to be significant statistically (Table 5). The Kaplan Meier survival table analysis has been done with respect to actual length of staying in hospital (dependant variable) with outcome (alive or dead) and level of Tobacco dependence. The computation has been done with respect to cumulative proportion surviving at the time (estimate and standard error) and number of cumulative events (Table 6). The link between length of stay in Hospital,Tobaco dependence and survival outcome plotted in Survival function (Fig 1) and Hazard function (Fig 2).

The length of stay in the hospital, tobacco dependence and survival (outcome alive and dead) has been analyzed by Kaplan Meier survival analysis (Fig 1). Time frame analyzed was 'actual number of days spent in COVID Hospital' and status factor analyzed was survival in binary variable as outcome (Alive & Dead). The factor & strata analyzed was whether there is history of Tobacco dependence or not. The Cox regression model and omnibus test of model coefficient has been analyzed to find out the likelihood based on chi square test whether there is any correlation between mortality due to COVID and Tobacco dependence with respect to length of stay in the hospital which again didn't show any significance (p=0.350) (Table 7).

Discussion

Some researchers have found that smoking may have negative correlation with the disease progression of COVID-19 and adverse outcome which has been challenged explaining multiple mechanisms like influence of Renin-angiotensin System (RAS), affinity of Angiotensin Converting Enzyme II (ACE-2) to small airway epithelia of smokers, expression of nicotinergic acetylcholine receptors (α7 subunit of nAChR) in bronchial epithelial cells, type II alveolar epithelial cells and interstitial lung fibroblasts[12]. Significantly, higher CHRNA7 expression has been found in current smokers especially in obese individual affected with COVID[13].

The majority of study subjects represent male, hindu subjects with rural background, educated upto primary level and monthly income is less than 10,000 per month. As expected all the clinical variables like length of stay in hospital, SpO_2 during admission,

Table 4 — *Paired 't' Test*

Dependant variable: Cause of Death	Unstandardized Coefficients		Standardized Coefficients	't' Statistics	Significance (p value)
Tobacco Dependence (any)	-1.156	0.498	-0.369	-2.323	0.022*
Any dependence other than tobacco	-0.770	0.271	-0.144	-2.840	0.005**
Length of stay at COVID hospital	-1.079	0.098	-0.579	-10.987	0.000**
SpO2 during admission	0.616	0.127	0.262	4.862	0.000**
Co-Morbidity	-0.094	0.038	-0.131	-2.484	0.014*
Whether Vaccinated	0.377	0.117	0.162	3.208	0.002**
PSSTOT	-0.015	0.012	-0.064	-1.204	0.231
FQTOT	0.117	0.048	0.390	2.449	0.016*

*Significance p<0.05; **Significance p<0.01

Table 5 — *Paired Samples Test*

		Paired Differences				Significance (p value)
		Mean	STD. Deviation (SD)	t Statistics	df	
Pair 1	PSSTOT - FQTOT	-13.29412	8.86200	-17.494	135	0.000**
Pair 2	Cause of Death - Co-morbidity	-2.125	3.054	-8.115	135	0.000**
Pair 3	PSSTOT - Co-morbidity	-1.14706	6.77745	-1.974	135	0.050*
Pair 4	FQTOT - Cause of Death	14.27206	5.38787	30.892	135	0.000**
Pair 5	Whether Vaccinated - Cause of Death	0.118	1.501	0.914	135	0.362
Pair 6	Whether Vaccinated - PSSTOT	-0.86029	6.79670	-1.476	135	0.142
Pair 7	Tobacco Dependence (any)-Cause of Death	-0.691	1.662	-4.849	135	0.000**
Pair 8	Tobacco Dependence (any)-Co-morbidity	-2.816	2.255	-14.565	135	0.000**

*Significance p<0.05; **Significance p<0.01

Table 6 — *The Kaplan Meier survival analysis with length of stay in hospital versus Nicotine dependance and survival*

Tobacco Dependence (any)	Mean[a]				Chi square (χ^2)	df	Significance (P)
			95% Confidence Interval				
	Estimate	STD. Error	Lower Bound	Upper Bound			
Present	2.782	0.063	2.658	2.906	1.059	1	0.304
Absent	2.817	0.061	2.696	2.937			
Overall	2.797	0.044	2.710	2.884			

*Significance p<0.05; **Significance p<0.01; df =degree of freedom

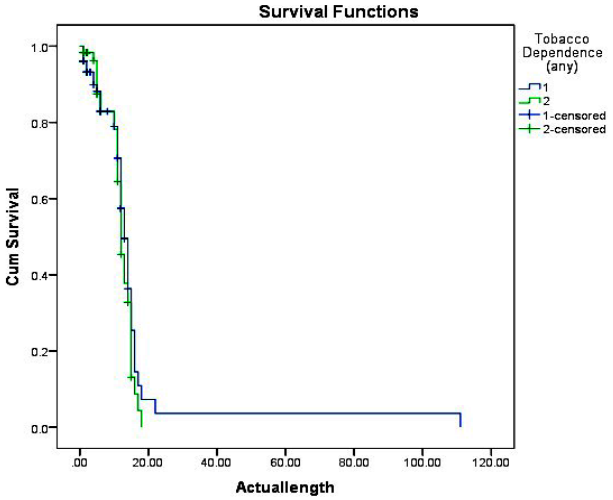

Fig 1 — Survival functions of outcome

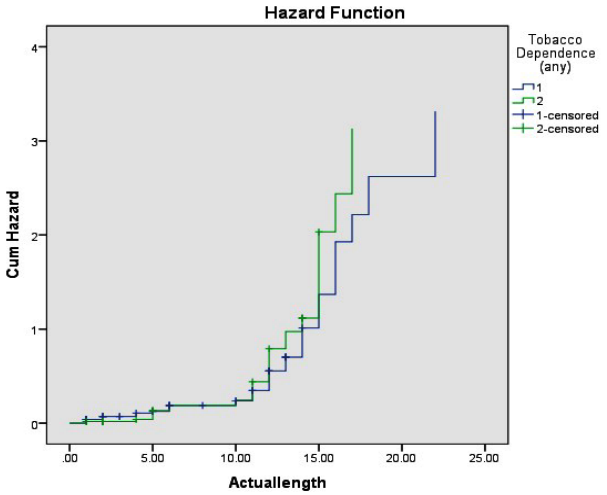

Fig 2 — Hazard functions of outcome

Table 7 — *Cox Regression Model with Length of Stay (dependant variable), survival and Tobacco dependence*

Omnibus Tests of Model Coefficients									
-2 Log	Overall (score)			Change From Previous Step			Change From Previous Block		
Likelihood	Chi-square	df	Significance	Chi-square	df	Significance	Chi-square	df	Significance
581.963	0.877	1	0.349	0.873	1	0.350	0.873	1	0.350
Tobacco	Mean	B	SE	Wald	df	Significance	Exp(B)		
Dependency	1.434	0.216	0.231	0.8745	1	0.350	1.241		

df = degree of freedom, SE = Standard Error, Wald = Wald statistic of logistic regression, B = unstandardized regression weight

presence of Co-morbidities and outcome have been found to be statistically significant and Perceived Stress Scale (PSS) score has also been found to be statistically significant with the clinical variables.[11] Linear regression analysis with cause of death as dependant, criterion variable and other variables as predictor variable or regressor has been analyzed. The coefficient of determination (adjusted R square) value shows 0.678 which means 67.8% of the observed variation can be explained by this model. Tobacco dependence can be attributed for higher risk of contamination of COVID for using hand, touching lips, sharing tobacco products etc. Smoking has direct relationship with faster disease progression both in ever and current smokers in meta-analysis[14]. Patient with any history of smoking has been found to have poor outcome in meta-analysis of 47 studies but many of them have smaller sample size or methodological issues. This study attempts to eliminate those confounding variables, selection and response biases[15]. In other Preferred Reporting Items for Systemic Reviews and Meta-analysis (PRISMA) analysis 207 studies with 49 variables have analyzed including Co-morbidities and smoking history but again direct causal ratio couldn't be extracted[16]. In UK, using Open SAFELY software which examined the database of 10,926 COVID related death but again direct causal relationship in between Nicotine dependence and COVID death couldn't be ascertained[17]. In fact, in one meta-analysis has found current smokers have reduced risk, former smokers have higher risk of hospitalization and never smokers fall in between[18]. Even cumulative exposure with duration of use with mortality due to COVID have been compared in one cohort study which showed Odds Ratio (OR) 2.25 for hospitalization and OR 1.89 for death with smokers compared to non-smokers[19].

Conclusion

The cause of the relationship between COVID death and degree with pattern of Nicotine dependence could be an important epidemiological variable to formulate public health strategy as well as early formulation strategy for appropriate COVID management. The direct causal relationship can't be attributed between Nicotine dependence and mortality in COVID in this present study by regression, survival and hazard analysis. However, Nicotine dependence can be attributed as a significant risk of mortality due to COVID, synergistic adverse prognostic factor with Co-morbidity, perceived stress, length of stay, SpO_2 during admission and vaccination status of COVID infected admitted indoor patients having Moderate and Severe COVID illness. There is limitation of the present study.

A longitudinal study with larger sample across multiple centers could have larger effect size and strong statistical association. Despite the above shortcomings, the present study has explored the direct causal relationship between Nicotine dependence and mortality due to COVID controlling confounding variables. The above findings need to be extrapolated with different Race, Ethnicity, Culture and Socio-economic status across nations and continents to sum up and make a final conclusion.

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Conflicts of Interest : None.

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References

1 Ismail N, Hassan N, Abd Hamid MHN, Yusoff UN, Khamal NR, Omar MA, *et al* — Association of smoking and severity of COVID 19 infection among 5,889 patients in Malaysia: A multi-center observational study. *Int J Infect Dis* 2022; **116:** 189-96. doi: 10.1016/j.ijid.2022.01.011. Epub 2022 Jan 10. PMID: 35021062; PMCID: PMC8743378.

2 Mohsin FM, Tonmon TT, Nahrin R, Tithy SA, Ame FA, Ara I, *et al* — Association Between Smoking and COVID-19 Severity: Evidence from Bangladesh. *J Multidiscip Healthc* 2021; **14:** 1923-33. doi: 10.2147/JMDH.S317603. PMID: 34326643; PMCID: PMC8315768.

3 Peng F, Lei S, Zhang Q, Zhong Y, Wu S — Smoking Is Correlated With the Prognosis of Coronavirus Disease 2019 (COVID-19) Patients: An Observational Study. *Front Physiol* 2021; **12:** 634842. doi: 10.3389/fphys.2021.634842. PMID: 33762967; PMCID: PMC7982916.

4 Heydari G, Arfaeinia H — COVID-19 and smoking: More severity and death - An experience from Iran. *Lung India* 2021; **38(Supplement):** S27-S30. doi: 10.4103/lungindia.lungindia_757_20. PMID: 33686976; PMCID: PMC8104333.

5 Meneses-Gaya IC, Zuardi AW, Loureiro SR, Crippa JA — Psychometric properties of the Fagerström Test for Nicotine Dependence. *J Bras Pneumol* 2009; **35(1):** 73-82. English, Portuguese. doi: 10.1590/s1806-37132009000100011. PMID: 19219334.

6 Bhattacharyya R, Sanyal D, Bhattacharyya S, Chakraborty K, Neogi R, Banerjee BB — Depression, Sexual Dysfunction, and Medical Comorbidities in Young Adults Having Nicotine Dependence. *Indian J Community Med* 2020; **45(3):** 295-298. doi: 10.4103/ijcm.IJCM_153_19. Epub 2020 Sep 1. PMID: 33354005; PMCID: PMC7745808.

7 Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO — The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 1991; **86:** 1119-27.

8 Pomerleau C S, Majchrezak MI, Pomerleau OF — Nicotine dependence and the Fagerstrom Tolerance Questionnaire: a brief review. *J Substance Abuse* 1989; **1:** 471-7.

9 Simon PD — The 10-item Perceived Stress Scale as a valid measure of stress perception. *Asia Pac Psychiatry* 2021; **13(2):** e12420. doi: 10.1111/appy.12420. Epub 2020 Sep 1. PMID: 32869503.

10 IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. (Released 2016)

11 Russo P, Bonassi S, Giacconi R, Malavolta M, Tomino C, Maggi F — COVID-19 and smoking: is nicotine the hidden link? *Eur Respir J* 2020; **55(6):** 2001116. doi: 10.1183/13993003.01116-2020. PMID: 32341101; PMCID: PMC7236819.

12 Leung JM, Yang CX, Sin DD — COVID-19 and nicotine as a mediator of ACE-2. *Eur Respir J* 2020; **55(6):** 2001261. doi: 10.1183/13993003.01261-2020. PMID: 32350104; PMCID: PMC7191112.

13 Chatterjee SS, Bhattacharyya R, Bhattacharyya S, Gupta S, Das S, Banerjee BB — Attitude, practice, behavior, and mental health impact of COVID-19 on doctors. *Indian J Psychiatry* 2020; **62(3):** 257-65. doi: 10.4103/psychiatry. Indian J Psychiatry_333_20. Epub 2020 May 15. PMID: 32773868; PMCID: PMC7368446

14 Patanavanich R, Glantz SA — Smoking is associated with worse outcomes of COVID-19 particularly among younger adults: a systematic review and meta-analysis. *BMC Public Health* 2021; **21:** 1554.

15 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. *J Med Virol* 2021; **93(2):** 1045-56. doi: 10.1002/jmv.26389. Epub 2020 Aug 13. PMID: 32749705; PMCID: PMC7436545.

16 Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, *et al* — Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLoS One* 2020; **15(11):** e0241955. doi: 10.1371/journal.pone.0241955. PMID: 33201896; PMCID: PMC7671522.

17 Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, *et al* — Factors associated with COVID-19-related death using Open SAFELY. *Nature* 2020; **584(7821):** 430-6. doi: 10.1038/s41586-020-2521-4. Epub 2020 Jul 8. PMID: 32640463; PMCID: PMC7611074.

18 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. doi: 10.1111/add.15276. Epub 2020 Nov 17. PMID: 33007104; PMCID: PMC7590402.

19 Lowe KE, Zein J, Hatipoglu U, Attaway A — Association of Smoking and Cumulative Pack-Year Exposure With COVID-19 Outcomes in the Cleveland Clinic COVID-19 Registry. *JAMA Intern Med* 2021; **181(5):** 709-11. doi: 10.1001/jamainternmed.2020.8360. Erratum in: JAMA Intern Med. 2021 May 1;181(5):727. PMID: 33492361; PMCID: PMC7835916.