Correlation Between Adult Tobacco Smoking Prevalence and Mortality of Coronavirus Disease-19 Across the World

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ABSTRAK

Latar belakang: *Coronavirus disease 2019 (COVID-19) merupakan sebuah pandemi global yang menyebar cepat ke seluruh dunia. Penelitian menunjukan perokok memiliki risiko lebih besar untuk mengalami manifestasi berat dan kematian akibat COVID-19 dibandingkan bukan perokok. Namun, studi yang tersedia saat ini masih terbatas. Penelitian ini bertujuan untuk menganalisis hubungan antara prevalensi perokok tembakau dewasa dengan mortalitas COVID-19 di seluruh dunia.* ***Metode:*** *studi ini merupakan studi korelasi, analisa regresi linier dilakukan untuk menganalisa korelasi antara data prevalensi merokok pada orang dewasa dengan Case Fatality Ratio (CFR) COVID-19 pada negara-negara yang memiliki 1000 kasus COVID-19 terkonfirmasi pada 3 Mei 2020.* ***Hasil:*** *tujuh puluh lima negara dilibatkan dalam penelitian ini dengan median CFR sebesar 3,66%. Tidak ada hubungan antara prevalensi perokok pria atau prevalensi perokok wanita dengan angka CFR COVID-19 di seluruh dunia. Analisis multivariat menunjukkan p-value = 0,823 untuk prevalensi perokok pria dan p-value 0,910 untuk prevalensi perokok wanita. Namun, pada negara berpendapatan menengah ke bawah, terdapat korelasi positif antara prevalensi pria dewasa yang merokok dengan tingkat kematian COVID-19. Didapatkan pada setiap peningkatan satu poin persentase prevalensi perokok pria dewasa mengakibatkan peningkatan CFR COVID-19 0,08% (95% CI 0,00% -0,15%, p = 0,041).* ***Kesimpulan:*** *ditemukan adanya hubungan antara prevalensi merokok pria dewasa dengan angka kematian COVID-19 di negara-negara berpenghasilan menengah ke bawah. Berdasarkan temuan tersebut, diperlukan penguatan kebijakan pengendalian tembakau yang lebih baik untuk menekan dampak pandemi COVID-19 khususnya pada negara dengan penghasilan menengah kebawah. Meskipun demikian, penelitian lebih lanjut masih diperlukan.*

Keywords: *COVID-19, tembakau, perilaku merokok, mortalitas, dunia.*

ABSTRACT

Background: *Coronavirus disease 2019 (COVID-19) is a global pandemic spreading worldwide. Limited studies showed that smokers were at higher risk of having severe complications and higher mortality. We aimed to analyze the possible correlation between adult tobacco smoking prevalence and COVID-19 mortality all over the world.* ***Methods:*** *this correlation study involved a linear regression to analyse the correlation between smoking prevalence data in adults and COVID-19 Case Fatality Ratio (CFR) in countries with 1000 confirmed COVID-19 cases on May 3, 2020.* ***Results:*** *seventy-five countries included with median CFR 3.66%. There was no relationship between adult male or female smoking prevalence and COVID-19 mortality in all over the countries. The multivariate analysis showed p-values of 0.823 and 0.910 for male and female smoking prevalence, respectively. However, in lower-middle-income countries (LMIC), there was a positive correlation between the prevalence of adult male smoking with the mortality of COVID-19. Each increment of one percentage of adult male smoking prevalence was associated with increase in COVID-19 CFR by 0.08% (95% CI 0.00%-0.15%,*

p=0.041). ***Conclusion:*** *there is correlation between the prevalence of adult male smoking and the CFR of COVID-19 in lower middle-income countries. Based on these findings, strengthening of tobacco control policies is essential to reduce the impact of the COVID-19 pandemic especially in LMIC. This still warrants further studies.*

Keywords: *COVID-19, tobacco, smoking, mortality, world.*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infection caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2).[1] COVID-19 has resulted in a public health emergency and an unprecedented economic crisis. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic. As of May 3rd, 2020 (the date of the latest data availability for this study) the disease has been infecting 3,349,786 people and causing 238,628 death.[2]

There is no clear light on when the COVID-19 pandemic will end. Studies show that it will take at least a decade to restore the social and economic conditions to their former state.[3] Policies that are effective, efficient, and have major effects on COVID-19 impact need to be considered. The measures include social restriction. Longer time spent indoors may increase the risk of harmful use of tobacco smoking.[4]

Smoking is main common risk factor of morbidity and mortality of various non-communicable diseases. We have also known that COVID-19 fatalities are higher among people with underlying comorbidities.[5] In a study predicting the 90-day mortality rate from viral pneumonia in hospitalized patients, smokers were twice as likely to die compared to those who did not smoke.[6] Recent studies show smoking increases the risk of developing severe symptoms and increases the risk of in-hospital mortality. A meta-analysis by Zhao et al.[7] suggested a significant relationship between smoking and the severity of COVID-19, OR 2.0 (95% CI 1.3-3.1). Studies by Zheng et al.[8] and Guo et al.[9] also showed similar finding, smoking increased the risk of severe symptoms and mortality by twofold compared to those who did not smoke.

By contrast, some researchers suggest a protective effect of smoking and COVID-19 based on epidemiologic data that were not controlled for age and comorbidities.[10] Preliminary meta-analysis based on Chinese patients suggest that active smoking does not apparently seem to be significantly associated with enhanced risk of progressing towards severe disease in COVID-19.[11] However, all studies included in this meta-analysis were limited in China.

In response to recent published possibility of smokers paradox, the centers for disease control and prevention and the World Health Organization recommend against smoking to reduce the risk of harm from the disease.[12] The link between tobacco smoking and COVID-19 needs further research. Here we described the correlation between adult tobacco smoking prevalence and the mortality of COVID-19 in many parts of the world.

METHODS

This correlation study utilized pooled data from all over the world. To investigate the correlation between adult smoking prevalence and COVID-19 mortality, only countries who had 1000 total confirmed cases by May 3rd, 2020 were included. A minimum confirmed case was required because extremely low case may reflect inadequate testing. Countries with no available data on adult smoking prevalence were excluded from this study.

Data Source

Mortality Data. Data of COVID-19 cases and death per country were obtained from the Coronavirus disease (COVID-2019) situation report-104 by WHO (May 3rd, 2020) available from https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200503-covid-19-sitrep-104.pdf?sfvrsn=53328f46_2.

Variables. We collected data prevalence of tobacco smoking in male and female adults across countries from WHO situation data in 2020 available from https://apps.who.int/gho/data/node.

main.65. The data of current health expenditure (% of Gross Domestic Product) was obtained from The World Bank data available from https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS. The Prevalence of population ages 65 and above also obtained from The World Bank data available from https://data.worldbank.org/indicator/SP.POP.65UP.TO.ZS. The Prevalence of Diabetes was based on International Diabetes Atlas year 2019.[13] The prevalence of hypertension and obesity were obtained from the latest WHO Global Health Observatory and Repository available from https://apps.who.int/gho/data/node.main.A867?lang=en. Countries' income was classified according to world bank data available at https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world- bank-country-and-lending-groups. All data were accessed on May 3rd, 2020.

Statistical Analysis

Case Fatality Ratio (CFR) for each country was measured by dividing total deaths to the total confirmed case in percent. Attack rate was measured by dividing total confirmed case/ 100,000 population. We performed spearman correlation analysis to analyze the correlation between adult tobacco smoking prevalence and mortality of COVID-19. Multivariate analysis was conducted by performing linear regression analysis to evaluate the relationship incorporating the studied variables (attack rate, health expenditure, prevalence of population above 65, and comorbidity). Many factors might influence the CFR of COVID-19 including a country's standard of medical care.[14] To account for that we performed sub-analysis according to country Gross National Income per capita in 2018. We divided countries into two categories: low and lower-middle-income countries (LMIC) with an income below 3.995 dollars and upper-middle (UMIC) to high-income countries (HIC) with an income above 3.995 dollars.

RESULTS

By May 3rd, 2020, 89 countries had more than 1000 total confirmed cases of COVID-19. However, only 75 countries whose data on adult tobacco smoking prevalence available. This study includes 15 (20%) LMIC, 22 (29.33%) UMIC, and 38 (50.67%) HIC (Appendix 1). By that, a total of 3,229,365 confirmed cases of COVID-19 with 235,524 death cases enrolled. Our study shows that the median of CFR per country in May 3rd 2020 was 3.66% (IQR: 3.89, min: 0.10 max: 19.10). The attack rate per 100,000 people was 65.78 (IQR: 153.28, min: 1.19, max: 614.94) and the median of adult male and female smoking prevalence was 30.3% (IQR: 20.2, min: 8 max: 82.7) and 12.6% (IQR: 17.7, min: 0.2 max: 39.3), respectively (**Table 1**).

From all countries included our study show significant negative correlation between the prevalence of adult male smoking and CFR of COVID-19. The Spearman's rank correlation

Table 1. Characteristic of country

	LMIC N=15 (20%)	UMIC and HIC N=60 (80%)	Total N=75 (100%)
Case Fatality Ratio (%) – median (IQR), (n=75)	3.08 (3.38)	3.97 (4.08)	3.66 (3.89)
Attack Rate/ 100,000 – median (IQR), (n=75)	7.13 (5.28)	93.55 (167.97)	65.78 (153.28)
Adult Tobacco Smoking Prevalence			
- Male – median (IQR), (n=75)	39 (27.3)	29.05 (19.8)	30.3 (20.2)
- Female – median (IQR), (n=75)	1.2 (5.0)	15.5 (15.5)	12.6 (17.7)
Health expenditure (%) – median (IQR), (n=75)	4.45 (3.15)	8.10 (3.49)	7.10 (3.89)
Prevalence of population > 65 (%) – median (IQR), (n=75)	5.28 (4.2)	16.17 (8.57)	14.67 (11.78)
Comorbidity			
- Prevalence of diabetes (%) – median (IQR), (n=74)	6.85 (2.7)	8.35 (4.85)	8.05 (4.2)
- Prevalence of obesity (%) – median (IQR), (n=73)	10.5 (13.2)	22.5 (5.8)	22 (6.2)
- Prevalence of hypertension (%)-median (IQR), (n=75)	22 (5.2)	25.0 (10.7)	23.5 (9.2)

coefficient was -0.2645 (p=0.022, **Figure 1A**). We also found there is significant positive correlation between the prevalence of adult female smoking and CFR of COVID-19. The Spearman's rank correlation coefficient was 0.3005 (p=0.009, **Figure 1B**).

Table 2 and **Table 3** shows linear regression analysis evaluating the relationship between adult male and adult female smoking prevalence with CFR of COVID-19 incorporating the studied variables. There are no significant relationship seen between adult male (p=0.823, **Table 2**) and female smoking prevalence (p=0.910, **Table 3**) with CFR of COVID-19 when including the confounding variable.

Correlation Between Adult Tobacco Smoking and CFR of COVID-19 in LMIC

In LMIC, we found a significant positive correlation between the prevalence of adult

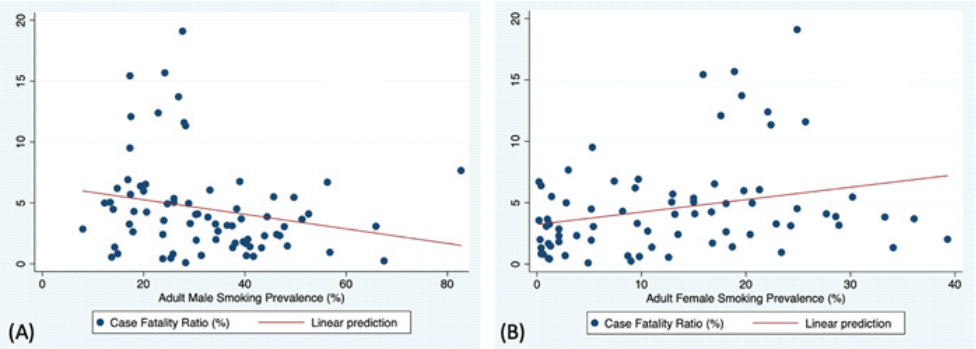

Figure 1. (A). Correlation of adult male smoking prevalence with COVID-19 case fatality ratio from all across countries (Spearman correlation r= -0.2645, p=0.022). (B). Correlation of adult female smoking prevalence with COVID-19 case fatality ratio from all across countries (Spearman correlation r=0.3005 p=0.009).

Table 2. Linear Regression Analyses of Male Smoking Prevalence and CFR of COVID-19.

	Total		LMIC		UMIC/HIC	
	β ± SE	p-value	β ± SE	p-value	β ± SE	p-value
Male Smoking Prevalence (%)	-0.01 ± 0.03	0.82	0.07 ± 0.03	0.04*	-0.06 ± 0.05	0.16
Health Expenditure (%)	0.23 ± 0.25	0.35	0.27 ± 0.37	0.50	0.25 ± 0.27	0.37
Prevalence of population > 65 (%)	0.17 ± 0.13	0.20	0.30 ± 0.21	0.21	0.21 ± 0.16	0.21
Prevalence of diabetes (%)	-0.28 ± 0.14	0.06	0.46 ± 0.19	0.05	-0.31 ± 0.17	0.07
Prevalence of obesity (%)	0.03 ± 0.06	0.69	-0.10 ± 0.02	0.25	0.06 ± 0.09	0.50
Prevalence of hypertension (%)	-0.06 ± 0.10	0.58	-0.44 ± 0.18	0.05	-0.02 ± 0.12	0.89
Attack Rate/ 100,000	0.01 ± 0.00	0.21	0.2 ± 0.40	0.40	0.01 ± 0.00	0.25

LMIC: Low Middle-Income Countries, UMIC: Upper middle-income countries, HIC: high income countries, SE: standard error, *) significant for p-value < 0.05.

Table 3. Linear Regression Analyses of Female Smoking Prevalence and CFR of COVID-19.

	Total		LMIC		UMIC/HIC	
	β ± SE	p-value	β ± SE	p-value	β ± SE	p-value
Female Smoking Prevalence (%)	0.01 ± 0.07	0.91	0.09 ± 0.32	0.80	-0.02 ± 0.08	0.85
Health Expenditure (%)	9.24 ± 0.25	0.33	0.02 ± 0.54	0.98	0.29 ± 0.27	0.30
Prevalence of population > 65 (%)	0.17 ± 0.14	0.24	0.11 ± 0.68	0.87	0.23 ± 0.19	0.20
Prevalence of diabetes (%)	-0.29 ± 0.14	0.05*	0.50 ± 0.28	0.13	-0.36 ± 0.17	0.03*
Prevalence of obesity (%)	0.03 ± 0.07	0.71	-0.05 ± 0.11	0.69	0.08 ± 0.09	0.37
Prevalence of hypertension (%)	-0.07 ± 0.11	0.54	-0.30 ± 0.42	0.50	-0.04 ± 0.13	0.73
Attack Rate/ 100,000	0.01 ± 0.00	0.19	0.02 ± 0.03	0.53	0.01 ± 0.00	0.12

LMIC: Low Middle-Income Countries, UMIC: Upper middle-income countries, HIC: high income countries, SE: standard error, *) significant for p-value < 0.05.

male smoking and CFR of COVID-19. The Spearman's rank correlation coefficient was 0.5214 (p=0.046). Each percentage point increase in adult male smoking prevalence caused a COVID-19 CFR increase of 0.08% (95% CI 0.00%-0.15%, p=0.041) in LMIC (**Table 2**). However, we do not find any correlation between the prevalence of adult female smoking and CFR of COVID-19. The Spearman's rank correlation coefficient was 0.2272 (p=0.415).

Correlation Between Adult Smoking and CFR of COVID-19 in UMIC and HIC

In UMIC and HIC, we found a significant negative correlation between the prevalence of adult male smoking and CFR of COVID-19. The Spearman's rank correlation coefficient was -0.4472 (p=0.000). We also found there is a significant positive correlation between the prevalence of adult female smoking prevalence and CFR of COVID-19. The Spearman's rank correlation coefficient was 0.2706 (p=0.037). However, there was no significant relationship between adult male and female smoking prevalence with CFR of COVID-19 in UMIC and HIC when including the confounding variable (**Table 2**).

DISCUSSION

To the best of our knowledge, this is the most comprehensive study to analyse the correlation of adult female and male smoking prevalence with the mortality of COVID-19 all over the world using pooled data from 75 countries. The global spread of tobacco use has been long known to have an impact on human health. However, only few studies were available explaining how tobacco impacts COVID-19 patients.

Our study showed there are no relationships between adult male or female smoking prevalence with COVID-19 mortality in all over the countries. The multivariate analysis showed p-values of 0.823 and 0.910 for male and female

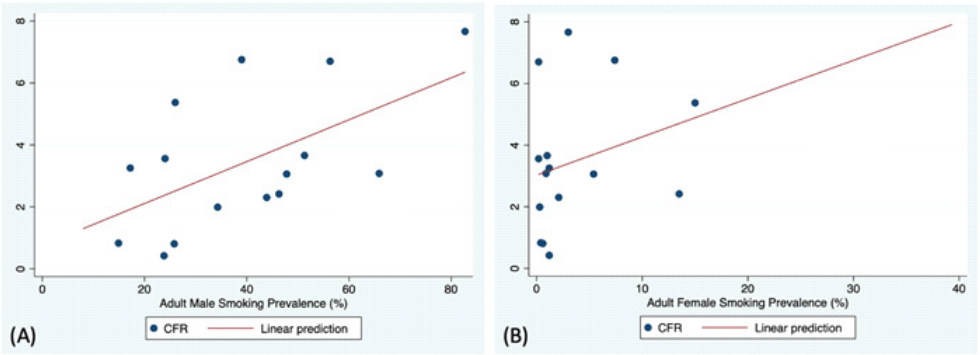

Figure 2. (A) Correlation of adult male smoking prevalence with COVID-19 case fatality ratio in Lower middle-income group (Spearman correlation r=0.5214, p=0.046). (B). Correlation of adult female smoking prevalence with COVID-19 case fatality ratio in Lower middle-income group (Spearman correlation r=0.2272, p=0.415).

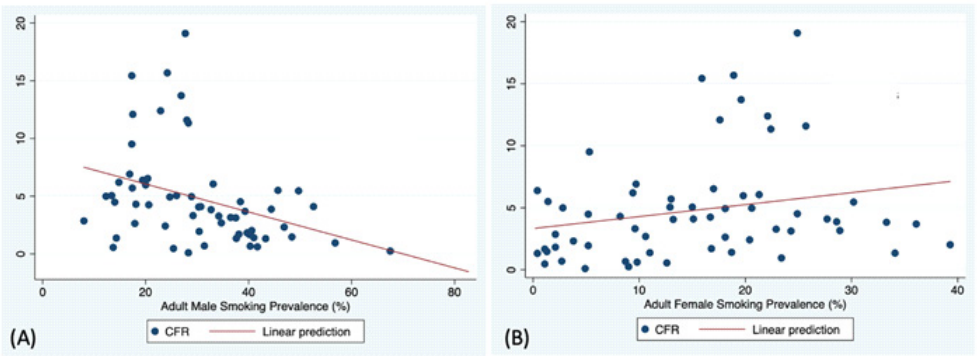

Figure 3. (A) Correlation of adult male smoking prevalence with COVID-19 case fatality ratio in upper and high-income countries group (Spearman correlation r=-0.4472, p=0.000). (B). Correlation of adult female smoking prevalence with COVID-19 case fatality ratio in upper and high-income countries group (Spearman correlation r=0.2706, p=0.037).

smoking prevalence respectively. However, in lower-middle-income countries (LMIC), there is a positive correlation between the prevalence of adult male smoking with the lethality of COVID-19. Each percentage point increase in adult male smoking prevalence caused a CFR of COVID-19 increase by 0.08% (95% CI 0.00%-0.15%, p=0.041).

Our study has some potential limitation to be discussed. First, we received the data of COVID-19 from situation reports by WHO, the number of deaths and cases might not always reflect the exact situation since there are differences in how different Governments across countries identifying infected cases. Second, we performed sub-analysis by categorizing countries according to their GNI per capita. However, there are still many factors that may influence the lethality of COVID-19 in which we do not control. Future studies may take into account prevalence of other related comorbidities such as chronic kidney disease, heart disease, stroke, respiratory disease, malignancy and autoimmune conditions. We also did not include weather parameters situation of each countries which may contribute to COVID-19 CFR.[15]

In bivariate analysis, we found a significant negative correlation between prevalence of adult male smoking and CFR of COVID-19 in all over the world also in sub-analysis UMIC and HIC groups. However, after adjusting for other variables there are no significant correlations found. Some studies reported active smokers are under represented among COVID-19 patients and there is also a study suggesting protective effect of smoking on COVID-19 mortality.[16,17] Those studies lead to widespread claim that smoking maybe protective against COVID-19.[17] However, knowing that early in pandemic there was a race to publish scientific articles, it might result in aberrant and non-standardized data collection and poor statistical analysis which can lead to erroneous conclusion. Both of the studies did not have quite variables to control smoking on COVID-19 are unfounded. There are no anyway the results of previous studies be an indicator to start or continue smoking.

In 2015, it was estimated that 80% of smokers all over the world live in the low- and low-middle-income-countries.[18] Our study showed that in there is a positive correlation between the prevalence of adult male smoking with COVID-19 mortality. The result was also significant after adjustment for other variables. Each percentage point increase in adult male smoking prevalence caused CFR of COVID-19 increase by 0.08% (95% CI 0.00%-0.15%, p=0.041).

The mechanisms on how smoking may be linked to COVID-19 outcomes include; smokers have increased gene expression of Angiotensin Enzyme 2 (ACE2), a known receptors of SARS CoV-2 than previous smokers and non-smokers.[19] It leads to an increase in vasoconstriction, vascular permeability, inflammation, and acute lung injury.[20] There is also evidence suggesting more circulating ACE2 in men which provides evidence for gender-based variations in disease severity.[21] Smoking increase the risk of lung damage by destroying ciliated epithelium and disrupts its function which protects the lungs through the production of mucus and rapid clearance of pathogens.[19,22] Smoking has been shown to up-regulate inflammation through activation of nuclear factor kappa-light-chain-enhancer of activated B cells, tumor necrosis factor-a, IL-1beta, and neutrophils. Smoking has been reported to down-regulate CXCL-10, which is an important chemokine for the recruitment of macrophages, neutrophils and natural killer cells, minimizing the capacity of the innate immune system to suppress viral replication.[23]

Due to the increasing population in LMIC, as well as the increasing youth population, growing incomes and prosperity, and relatively poor tobacco control, the prevalence of adult male smoking was higher compared to UMIC/HIC.[18] Other than that, the results might be influenced by several factors like limited testing of COVID-19 in the LMIC group. This can be proven from mean attack rate value which is only 7.13 at LMIC while at UMIC/HIC it can reach 93.55. Also, there is various capacity of each country in managing the disease that could influenced the outcome. In HIC the policy on tobacco control is well established.[18] The battle against tobacco use should continue, no other risk factors are as immediately modifiable as

smoking. Gas exchange, lung function, and blood circulation, improve quickly following smoking cessation.[19] We need to make effort in tobacco control policies and assisting smokers to successfully and permanently quit.

CONCLUSION

There is correlation between the prevalence of adult male smoking and the CFR of COVID-19 in LMIC. Based on these findings, strengthening of tobacco control policies and assistance related to smoking cessation are needed to reduce the impact of smoking on COVID-19 pandemic, especially in LMIC.

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