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Smoking status related to Covid-19 mortality and disease severity in a veteran population[☆]

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ABSTRACT

Introduction: Cigarette smoking is associated with development of significant comorbidities. Patients with underlying comorbidities have been found to have worse outcomes associated with Coronavirus Disease 2019 (Covid-19). This study evaluated 30-day mortality in Covid-19 positive patients based on smoking status.

Methods: This retrospective study of veterans nationwide examined Covid-19 positive inpatients between March 2020 and January 2021. Bivariate analysis compared patients based on smoking history. Propensity score matching adjusted for age, gender, race, ethnicity, Charlson comorbidity index (0–5 and 6–19) and dexamethasone use was performed. A multivariable logistic regression with backwards elimination and Cox Proportional Hazards Ratio was utilized to determine odds of 30-day mortality.

Results: The study cohort consisted of 25,958 unique Covid-19 positive inpatients. There was a total of 2,995 current smokers, 12,169 former smokers, and 8,392 non-smokers. Death was experienced by 13.5% (n = 3503) of the cohort within 30 days. Former smokers (OR 1.15; 95% CI, 1.05–1.27) (HR 1.13; 95% CI, 1.03–1.23) had higher risk of 30-day mortality compared with non-smokers. Former smokers had a higher risk of death compared to current smokers (HR 1.16 95% CI 1.02–1.33). The odds of death for current vs. non-smokers did not significantly differ.

Conclusion: Compared to veteran non-smokers with Covid-19, former, but not current smokers with Covid-19 had a significantly higher risk of 30-day mortality.

1. Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for coronavirus disease 2019 (Covid-19) [1]. This disease has affected millions of individuals globally and has led to severe health outcomes and economic burden. Patients with Covid-19 can present with a wide variety of symptoms ranging from mild to severe disease requiring hospitalization. Though, whether smoking increases risk of death is conflicting in the literature [2,3].

Cigarette smoking is the primary cause of preventable death in the

United States (U.S.) resulting in an excess of 480,000 deaths per year [4]. Patients who smoke cigarettes are more likely to develop cardiovascular and respiratory disease [4]. Furthermore, smoke from cigarettes also decreases immune function and can lead to increased concentrations of pro-inflammatory markers [5]. Active smoking, in earlier studies, was not significantly associated with Covid-19 disease severity [6,7]. Larger meta analyses however, found that smoking increased mortality associated with Covid-19 [8–10].

In the veteran population, smoking constitutes a significant problem. Approximately 3 in 10 U.S. military veterans reported using some form

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of tobacco product from 2010 to 2015. The majority of veterans also have additional risk factors associated with severe Covid-19 infection including male gender, older age, obesity, and coexisting cardiovascular diseases [11]. Thus, the purpose of this study is to evaluate the association between smoking status and 30-day all-cause mortality from Covid-19.

2. Methods

2.1. Patient selection and informatics approach

Data was retrospectively extracted through the Corporate Data Warehouse (CDW) and analyzed in the VA Informatics and Computing Infrastructure (VINCI) [12]. The Covid-19 Shared Data Resource was utilized to identify Covid-19 cases, comorbidities, smoking status and outcomes of inpatients from March 3, 2020 through January 20, 2021 [13]. Covid-19 positive cases were defined by the first documented positive result. Patients hospitalized in 125 healthcare systems nationwide were included. The primary outcome was 30-day all-cause mortality following the first positive Covid-19 result. This study was deemed exempt by the Institutional Review and Board and was approved by the Research and Development committee of VA Western New York.

Comorbidities were defined in the Covid-19 Shared Data Resource using a combination of ICD-10 codes and Natural Language Processing. Comorbidities were defined within 2 years of positive Covid-19 test. Patients were grouped based on their smoking status and defined as nonsmokers, former smokers, and current smokers. Smoking categorizations were based on self-reported smoking data from Million Veteran Program (MVP) Baseline and Lifestyle survey responses within the two years prior to admission. A previous study examined the validity of VA structured data to determine accurate smoking status and found that between current and never/former smokers the kappa statistic was 0.80 and the total agreement was 90.2% [14].

2.2. Statistics

Bivariate analysis was used to compare patients based on smoking history using Chi-squared tests for categorical data and Student's t-test for continuous data. Smoking status was unknown in 2,405 veterans and they were excluded from the analysis. The rate of missing variables was less than 10% thus imputation was not utilized. Demographic and clinical data were retrospectively obtained and matched using propensity score matching algorithm. Groups were propensity score matched to adjust for the following covariates: age, gender, race, ethnicity, Charlson comorbidity index (0–5 and 6–19) and use of dexamethasone. Dexamethasone was included because it has been shown to decrease mortality in hospitalized patients with Covid-19 receiving oxygen without invasive mechanical ventilation [15]. Age and body mass index were both continuous variables. The optimal matching method was used for all comparisons. We utilized the optimal matching method using the *optmatch* package via MatchIt, in R Studio. The optimal matching method matches samples with the lowest propensity score difference compared with the more common nearest neighbor method where it matches samples with the first sample that is below a set caliber. A 3:1 match was used when comparing current smokers to former smokers and current smokers to non-smokers. A 1:1 match was performed between former smokers to non-smokers.

To determine predictors of 30-day mortality in the propensity matched groups, a multivariable logistic regression with backwards stepwise elimination was performed to determine factors which impacted likelihood of death at 30-days. The wrapper method for feature selection was chosen due to the mortality complexities in Covid-19 patients. The feature selection identifies the smallest set of features which results in reducing the complexity of a model, building a robust model while minimizing overfitting by selecting the right set of features. Cox proportional hazards ratio and Kaplan Meier curves were generated

to determine factors which impacted death at 30-days. Variables with a p-value <0.05 were included in the analysis and eliminated based on non-significance. Multicollinearity was tested using the variance inflation factor. Odds ratios with 95% Confidence Intervals (CI) were produced to determine the odds of death at 30 days. Medians were presented with an interquartile range (IQR). Balance of the propensity score matching algorithm was assessed by the distribution of propensity scores presented in the supplemental appendix via jitter plot and table of standardized mean difference (SMD). Standardized mean difference (SMD) range was 0.027–0.34 (Supplement 1). Imbalance was found if SMDs were greater than 0.25. All variables were below 0.25 with the exception of age in current vs. former smoker. All variables with significant differences were included as a factor in the multivariable logistic regression analysis.

To determine risk of 30-day mortality in the propensity matched groups, a Cox proportional hazards model was used. Results were presented as a Hazards Ratio (HR) with 95% Confidence Interval (CI). Kaplan Meier survival curves were generated for each smoking status pair as was the log-rank test. Propensity score matching, Cox proportional hazards model and survival curves were performed in R version 3.4.1 and the remaining statistical analyses were performed on JMP Pro version 12.

3. Results

The study cohort consisted of 25,958 inpatients of which 95% were men and 63% were Caucasian. In the overall cohort, there was a total of 2,995 current smokers, 12,169 former smokers, and 8,392 veterans who reported to have never smoked (non-smokers). Balance after propensity score matching improved for most of the baseline characteristics between the two groups. Balance of the other baseline characteristics remained similar after matching. The SMD after propensity score matching ranged from 0.027 to 0.34. From a graphical standpoint, balance was achieved based on the similarities in the matched sections of the jitter plot (Supplement). The median age was 71 years old (IQR 62–77). The median length of stay was 6 days (IQR 3–12 days). Overall, 29% (7,578/25,958) of patients were admitted to the ICU and the median length of stay in the ICU was 5 days (IQR 2–10 days). There were 3.2% (n = 834) deaths in 7 days, 7.7% (n = 1994) in 14 days, and 5% (n = 3503) in 30 days.

3.1. Current smokers vs. non-smokers

A total of 8,391 current smokers were matched with 2,994 non-smokers in a 3:1 ratio. Mortality of current smokers was 11.5% and 9.2% in non-smokers; $p = 0.0005$ (Table 1). In the multivariable logistic regression current smokers had a higher odds of 30-day mortality compared with non-smokers (OR 1.03; 95% CI, 0.89–1.2), although the results were not significant (Table 2). At 30 days, the Kaplan-Meier survival curves between current smokers and non-smokers were statistically different by the log-rank test ($p = 0.00084$). In the multivariate Cox proportional hazards model, risk of 30-day mortality between current smokers and non-smokers did not significantly differ (HR 0.98, 95% CI, 0.85–1.13) (Table 3). Other variables that increased the risk of 30-day mortality were age, male gender, and history of congestive heart failure (CHF) and diabetes. Patients of non-Hispanic ethnicity were found to have a decreased risk for death at 30 days compared to those of Hispanic ethnicity.

3.2. Former smokers vs. non-smokers

Former smokers (n = 8,391) and non-smokers (n = 8,391) were propensity matched in a 1:1 ratio. Death in 30 days from Covid-19 diagnosis was experienced by 13.5% of former smokers and 11.5% of non-smokers; $p < 0.0001$ (Table 1). In a multivariable analysis, former smokers had 1.15 times higher odds of death (95% CI 1.05–1.27)

Table 1
Characteristics of the Covid-19 positive cohort based on smoking status.

	Current Smoker N = 8391	Non-Smoker N = 2994	P-Value	Former Smoker N = 8391	Non-Smoker N = 8391	P-Value	Former Smoker N = 8982	Current Smoker N = 2994	P-Value
Age	64.6 ± 12.9	67 ± 14.4	<0.0001	68.7 ± 12.5	67 ± 14.4	<0.0001	68.9 ± 11.7	64.6 ± 12.9	<0.0001
Gender			<0.0001			<0.0001			0.003
Male	7707 (91.9%)	2876 (96.1%)		8003 (95.4%)	7707 (91.9%)		8727 (97.2%)	2876 (96.1%)	
Female	684 (8.2%)	118 (3.9%)		388 (4.6%)	684 (8.2%)		255 (2.8%)	118 (3.9%)	
Race			0.002			0.07			0.004
White	4879 (58.2%)	1837 (61.4%)		4990 (59.5%)	4879 (58.2%)		5702 (63.5%)	1837 (61.4%)	
Black	2771 (33.0%)	941 (31.4%)		2632 (31.4%)	2771 (33.0%)		2550 (28.4%)	941 (31.4%)	
Other	741 (8.8%)	216 (7.2%)		769 (9.2%)	741 (8.8%)		730 (8.1%)	216 (7.2%)	
Ethnicity			<0.0001			0.03			<0.0001
Hispanic or Latino	827 (9.9%)	180 (6.0%)		738 (8.8%)	827 (9.9%)		796 (8.9%)	180 (6.0%)	
Not Hispanic or Latino	7333 (87.4%)	2735 (91.4%)		7447 (88.8%)	7333 (87.4%)		7983 (88.9%)	2735 (91.4%)	
Other	231 (2.8%)	79 (2.6%)		206 (2.5%)	231 (2.8%)		203 (2.3%)	79 (2.6%)	
BMI	28 ± 6.8	30.8 ± 7.1	<0.0001	30.4 ± 7.1	30.8 ± 7.1	0.0006	28.6 ± 6.2	28 ± 6.8	<0.0001
Comorbidities									
Asthma	718 (8.6%)	158 (5.3%)	<0.0001	582 (6.9%)	718 (8.6%)	<0.0001	602 (6.7%)	158 (5.3%)	0.006
Cerebrovascular Disease	319 (3.8%)	150 (5.0%)	0.004	391 (4.7%)	319 (3.8%)	0.006	489 (5.4%)	150 (5.0%)	0.36
CHF	1328 (15.8%)	571 (19.1%)	<0.0001	1516 (18.1%)	1328 (15.8%)	0.0001	1700 (18.9%)	571 (19.1%)	0.86
Cirrhosis	242 (2.9%)	214 (7.2%)	<0.0001	404 (4.8%)	242 (2.9%)	<0.0001	482 (5.4%)	214 (7.2%)	0.0003
CKD	2250 (26.8%)	686 (22.9%)	<0.0001	2294 (27.3%)	2250 (26.8%)	0.44	2588 (28.8%)	686 (22.9%)	<0.0001
COPD	1458 (17.4%)	1169 (39.0%)	<0.0001	2465 (29.4%)	1458 (17.4%)	<0.0001	2823 (31.4%)	1169 (39.0%)	<0.0001
CVD	4023 (47.9%)	1654 (55.2%)	<0.0001	4644 (55.4%)	4023 (47.9%)	<0.0001	5116 (57.0%)	1654 (55.2%)	<0.10
Diabetes	4230 (50.4%)	1282 (42.8%)	<0.0001	4397 (52.4%)	4230 (50.4%)	0.01	4594 (51.2%)	1282 (42.8%)	<0.0001
HIV	100 (1.2%)	51 (1.7%)	0.04	81 (1.0%)	100 (1.2%)	0.16	103 (1.2%)	51 (1.7%)	0.02
HTN	6438 (76.7%)	2247 (75.1%)	0.06	6691 (79.7%)	6438 (76.7%)	<0.0001	7169 (79.8%)	2247 (75.1%)	<0.0001
Mortality < 30 days	966 (11.5%)	276 (9.2%)	0.0005	1132 (13.5%)	966 (11.5%)	0.0001	1171 (13.0%)	276 (9.2%)	<0.0001

Key: BMI: body mass index, CHF: congestive heart failure, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, HIV: human immunodeficiency virus, HTN: hypertension.

Table 2
Risk of 30-day mortality via multivariate logistic regression.

Variable	Current vs. Non-Smokers			Former vs. Non-Smokers			Former vs. Current		
	Odds Ratio	95% Confidence Interval	p-value	Odds Ratio	95% Confidence Interval	p-value	Odds Ratio	95% Confidence Interval	p-value
Smoking Status	1.03	0.89–1.2	0.68	1.15	1.05–1.27	0.0037	1.18	1.02–1.36	0.023
Age	1.07	1.06–1.07	<0.0001	1.06	1.06–1.07	<0.0001	1.06	1.05–1.07	<0.0001
Gender									
Male vs. Female	1.96	1.36–2.95	0.0002	1.60	1.22–2.16	0.0006	1.69	1.01–3.05	0.044
Comorbidities									
CHF	1.26	1.07–1.49	0.0060	1.14	1.01–1.28	0.028	–	–	–
Cirrhosis	–	–	–	1.33	1.05–1.66	0.017	–	–	–
CKD	1.18	1.03–1.36	0.017	–	–	–	1.27	1.13–1.44	<0.0001
CVD	0.86	0.75–0.99	0.04	–	–	–	–	–	–
Diabetes	1.23	1.09–1.40	0.0013	1.15	1.05–1.27	0.0039	1.24	1.11–1.40	0.0002

Key: CHF: congestive heart failure, CKD: chronic kidney disease, CVD: cardiovascular disease.

compared to non-smokers (Table 2). Significant comorbidities for increased odds of 30-day mortality included: increasing age, male gender, a history of diabetes, CHF, and cirrhosis (Table 2). In the Cox Proportional Hazards Model Former Smokers had an increased risk of death (HR 1.13 95% CI 1.03–1.23). Other factors that increased the risk of death included age, male sex, Hispanic or Latino ethnicity and cirrhosis (Table 3).

3.3. Former smokers vs. current smokers

A total of 8,982 former smokers were matched with 2,994 current smokers in a 3:1 ratio. Thirty-day mortality was 13% in former smokers and 9.2% in current smokers; $p < 0.0001$ (Table 1). In the multivariable logistic regression analysis, patients with diabetes, chronic kidney disease (CKD), and male gender had an increased 30-day mortality associated with Covid-19 infection. Current smokers had a 15% lower risk of mortality when compared with former smokers (OR 0.85; 95% CI, 0.74–0.98) (Table 2). In the Cox Proportional Hazards model, former smokers had an increased risk of death (HR 1.16 95% CI 1.02–1.33).

Other factors which increased the likelihood of death included age, African American race, Hispanic or Latino ethnicity, CKD and diabetes. (Table 3).

4. Discussion

Compared to veteran non-smokers with Covid-19, former, but not current, smokers with Covid-19 had a significantly higher risk of 30-day mortality. By contrast, no significant differences were observed between current smokers and non-smokers. Earlier studies found that active smoking was not significantly associated with Covid-19 disease severity [6,7]. Larger meta analyses with diverse patient populations found that smoking overall increased mortality associated with Covid-19 [8–10].

Goblet cells are the main source of mucous production and an increase could provide a greater barrier against respiratory pathogens. In smokers, there is an increase in pro-inflammatory cytokines leading to endothelial damage and immune system disturbances which may also contribute to worsened outcomes. An opposing hypothesis is that cigarette smoke produces ACE2 allelic variants which inhibit binding

Table 3
Risk of 30-day mortality via multivariate Cox-proportional hazards model.

Variable	Current vs. Non-Smokers		Former vs. Non-Smokers		Former vs. Current	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Smoking Status	0.98	0.85–1.13	1.13	1.03–1.23	1.16	1.02–1.33
Age	1.06	1.05–1.07	1.06	1.05–1.06	1.06	1.05–1.06
Gender						
Male vs. Female	1.85	1.28–2.69	1.60	1.21–2.11	1.69	0.99–2.87
Race						
Caucasian vs. African Americans	0.96	0.84–1.09	0.86	0.78–0.95	0.84	0.74–0.94
Other vs. African Americans	1.07	0.84–1.36	1.10	0.92–1.31	1.24	1.01–1.54
Ethnicity						
Not Hispanic or Latino vs. Hispanic or Latino	0.82	0.67–0.99	0.78	0.67–0.90	0.82	0.69–0.99
BMI	1.00	0.99–1.01	1.01	0.99–1.01	0.99	0.98–1.01
Comorbidities						
Asthma	0.93	0.73–1.19	0.96	0.80–1.16	0.98	0.78–1.24
Cerebrovascular Disease	0.94	0.72–1.23	0.98	0.81–1.19	1.01	0.82–1.24
CHF	1.21	1.03–1.41	1.02	0.90–1.15	1.10	0.96–1.26
Cirrhosis	1.11	0.84–1.46	1.27	1.02–1.55	1.20	0.97–1.50
CKD	1.05	0.92–1.20	1.10	0.99–1.21	1.19	1.05–1.34
COPD	1.04	0.91–1.19	1.08	0.97–1.19	1.03	0.92–1.15
CVD	0.88	0.77–1.01	1.07	0.97–1.19	0.99	0.87–1.12
Diabetes	1.18	1.05–1.33	1.09	0.99–1.19	1.20	1.07–1.34
HIV	1.40	0.83–2.34	0.66	0.36–1.19	0.83	0.49–1.40
HTN	1.01	0.86–1.19	0.99	0.87–1.12	0.97	0.84–1.12

Key: CHF: congestive heart failure, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, CVD: cardiovascular disease, HIV: human immunodeficiency virus, HTN: hypertension.

between SARS-CoV-2 and structurally different ACE2 receptors. Additionally, nicotine interferes with the renin-angiotensin system increasing the expression and/or activity of renin and downregulating the expression and/or activity of ACE2 which would favor positive outcomes in Covid-19 positive patients [16].

A large study of over 17 million people using the OpenSAFELY platform examined associations with Covid-19 related mortality. A Post-hoc analysis in a model adjusted for age and sex found that current and former smoking was associated with an increased risk of mortality, however in a model which was fully adjusted, these groups had a lower risk of death (hazards ratio (HR) 0.89 (0.82–0.97)). The reasoning for these disparate results was due to chronic respiratory disease that likely arbitrate the effect of smoking. When their model was adjusted for only demographic factors, there was a non-significant positive hazard ratio for current smoking (HR 1.07 (0.98–1.18)). This is similar to our study which found that current smokers and non-smokers had similar mortality (OR 1.03 95%CI(0.89–1.2)) [2,3].

A study of over 400,000 patients found age related differences in mortality due to Covid-19 in smokers. In patients age 69 and over, mortality was twice as high as non-smokers, whereas in patients under the age of 69 there was no difference in death between those who smoked and those who didn't [2,3]. These results are consistent with our findings. The average age of our population ranged from 64 to 69 years of age and similarly found no difference in Covid-19 mortality between current and non-smokers.

Smokers are at increased risk for cardiovascular and respiratory diseases, diabetes and certain types of cancer [4]. These comorbidities have been found to have increased risk of Covid-19 mortality [17]. In our study, we found that patients with CHF, CKD, cirrhosis and diabetes had an increased odds of mortality. Though comorbidities were comprehensive, it is possible that some conditions were omitted which may drive the resultant mortality risks.

A study evaluated the association of cumulative pack-year exposure with Covid-19 outcomes and found a dose-response association between pack-years and adverse outcomes [18]. Smokers with a 30 pack year history were more likely to die from Covid-19 compared with non-smokers. Our study was unable to determine the pack-year history

of our patients. Former smokers may have a longer history of smoking compared to current smokers with greater respiratory damage or respiratory diseases accounting for the mortality trends seen in our study.

Our study was limited by its retrospective design and inability to determine duration of smoking prior to Covid-19. Although propensity score matching was utilized to reduce the risk of information and selection bias, the study was unable to eliminate all the risk given the retrospective nature of the study. These results are generalizable to a veteran population which is predominately older males. Future studies in patients over the age of 75–80 years of age that consider markers of disease severity are needed, age was matched as a continuous variable. There was a significant difference in terms of age in that former smokers were on average 2–4 years older in age than current or never smokers, which may be accounted for in future analyses by dichotomizing the age variable. It is unknown whether these results are duplicated with the use of vaping products. This study was also unable to adjust for clinical indicators of Covid-19 severity and/or multi-organ involvement which could lead to significant residual confounding. Strengths of this study include the large number of veterans evaluated, the ability to adjust for bias associated with nonrandom allocation with the use of propensity score matching, and availability of additional information regarding comorbid conditions.

5. Conclusion

Compared to veteran non-smokers with Covid-19, former, but not current, smokers with Covid-19 had a significantly higher risk of 30-day mortality. By contrast, no significant differences were observed between current smokers and non-smokers. Age and comorbidities also impact mortality in patients with Covid-19.

CRediT authorship contribution statement

Laura A. Wilkinson: Conceptualization, Methodology, Writing – original draft. **Kari A. Mergenhagen:** Conceptualization, Methodology, Data curation, Formal analysis, Supervision, Writing – review & editing. **Michael T. Carter:** Conceptualization, Data curation, Methodology,

Writing – review & editing. **Hubert Chua:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Collin Clark:** Methodology, Writing – review & editing. **Bethany A. Wattengel:** Conceptualization, Writing – review & editing. **John A. Sellick:** Conceptualization, Writing – review & editing. **Ali A. El-Solh:** Conceptualization, Methodology, Writing – review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2021.106668>.

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