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Original article:

PREVALENCE AND IMPACT OF TOBACCO USE DISORDER ON IN-HOSPITAL MORTALITY IN PATIENTS HOSPITALIZED WITH NON-GROUP 1 PULMONARY HYPERTENSION: A NATIONWIDE PROPENSITY SCORE-MATCHED ANALYSIS, 2019

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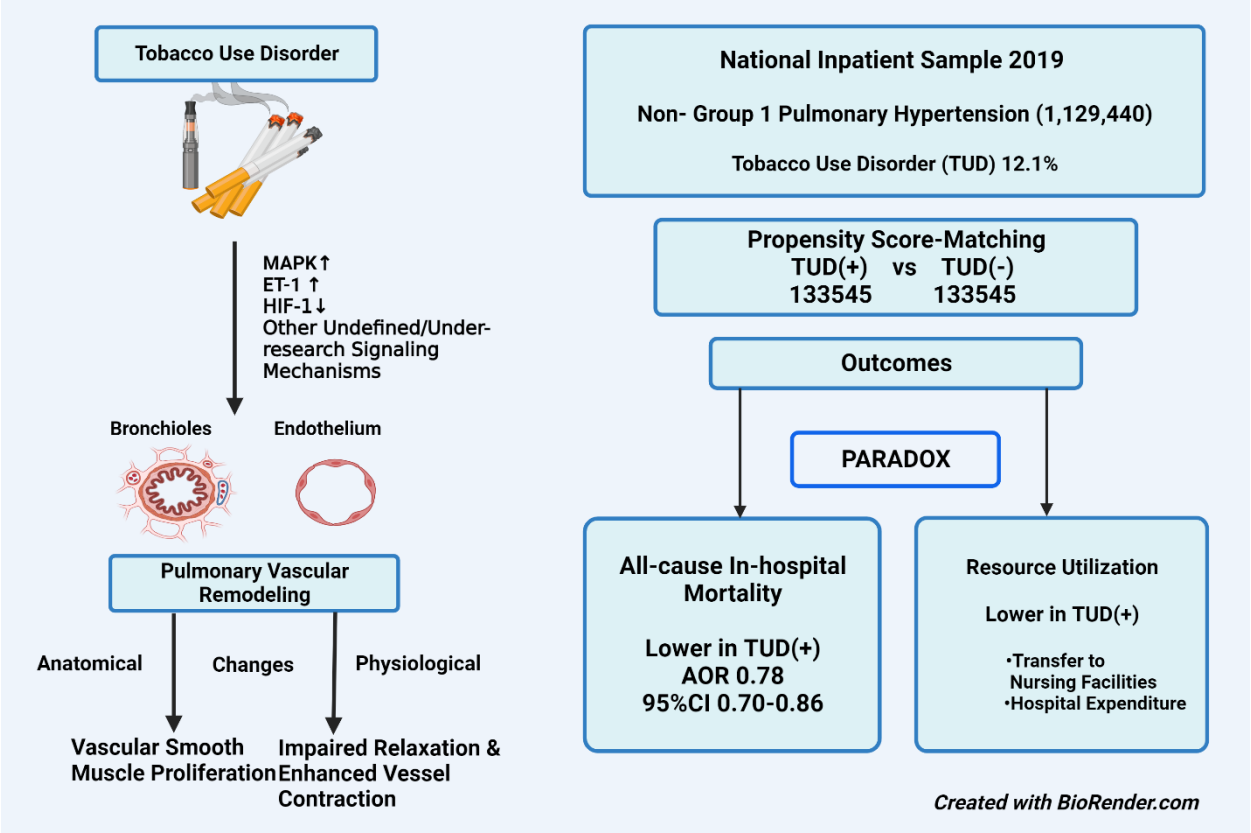

Figure 1: Graphical abstract

ABSTRACT

Numerous studies indicated that patients with tobacco use disorder (TUD) are inversely associated with mortality in what is known as the smoker's paradox. However, limited studies have been conducted on the impact of TUD on the in-hospital mortality rates of patients with secondary pulmonary hypertension (PH, Non-Group 1 PH). Using the 2019 National Inpatient Sample, we identified PH and divided it into TUD and non-TUD to compare the comorbidities and in-hospital mortality between the two after 1:1 propensity-score matching. Of 1,129,440 PH hospitalizations, 12.1 % had TUD. After matching (n=133545, each group), TUD had lower median age (62 vs. 63), higher females (49 vs. 46.6 %), blacks (25.9 vs. 25.3 %), lower household income (40.8 vs. 32.7 %), Medicaid (22.4 vs. 14.8 %), non-elective (93.5 vs. 89.8 %), rural (9.3 vs. 6.7 %), urban non-teaching (17.2 vs 15.8 %) admissions. All CV comorbidities and other substance use were higher in TUD except CHF and valvular heart disease, TUD+ cohort and lower mortality (3.3 vs. 4.2 %, OR 0.78, p<0.001), higher routine discharges (53.8 vs. 51.3 %, p<0.001) and lower total charges ($47155 vs. 51909, p<0.001) than non-TUD. Although PH patients with TUD had a higher comorbidity burden, they had lower in-hospital mortality rates along with lower total charges of hospitalization, mandating real-world data to validate these results.

Keywords: Pulmonary arterial hypertension, tobacco use disorder, smoker's paradox

INTRODUCTION

Tobacco use disorder is a mental health condition characterized by nicotine dependence or tobacco addiction and uncontrollable use of these substances to avoid withdrawal via vaporizer pen, nicotine pen, and tobacco products. Several studies explored the association between tobacco use disorder (TUD)/ smoking and cardiovascular and pulmonary vascular diseases. Earlier studies have demonstrated that cigarette smoke, through multiple pathways, may induce activation of mitogen-activated protein kinase (MAPK) signal pathway and subsequent up-

regulation of ET-1 and its receptors which then can cause receptor-mediated contraction, proliferation of pulmonary vascular smooth muscle cells, pulmonary vascular remodeling, and elevated pulmonary arterial pressure (Zhang and Xu, 2020). As a result of altered blood arteries, pulmonary arterioles exhibit increased resistance, which is a hallmark of pulmonary arterial hypertension (PAH) (Emmons-Bell et al., 2022). Smoking is a well-known risk factor for COPD, and research has revealed that chronic hypoxia causes systemic loss of the protein Hypoxia-inducible factor-1 (HIF-1), which has been proven to reduce pulmonary hypertension (Ball et al., 2014).

Tobacco use has also been implicated in the proliferation of pulmonary vascular smooth muscle through elevated nitric oxide and endothelin dysfunction (Seimetz et al., 2011; Wright et al., 2004) Reactions between nitric oxide and oxidants have been shown to increase pulmonary artery pressure, inherently leading to PAH. While tobacco use is implicated in the development of PAH (Kaneko et al., 1998), limited data exist on the impact of TUD on the in-hospital outcomes of patients admitted with non-Group 1 Pulmonary hypertension/secondary pulmonary hypertension [non-group 1 PH].

MATERIALS AND METHODS

Using the weighted National Inpatient Sample dataset (AHRQ, 2019) and previously validated ICD-10 codes, we identified admissions in patients with non-group 1 PH and divided it into TUD and non-TUD cohorts. In the United States, the NIS is a publicly accessible all-payer dataset that is part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ) (HCUP Database 2016-2017). Weighted NIS data is made up of about 35 million yearly in-hospital encounters from over 1000 non-federal acute care hospital centers in 45 states (excluding long-term acute care and rehabilitation centers). The weighted data is representative of over 95 % of community hospitalizations in the United States. The Institutional Review Board (IRB) approval was not mandatory as the NIS is public and does not reveal patients' identifiers.

Propensity score matching (1:1) was performed, adjusting for age, sex, and race and 0.01 caliper width without replacement to obtain matched TUD+ vs. TUD- cohorts. We compared the two matched cohorts' baseline patient-level characteristics and preexisting comorbidities. The primary endpoint was the all-cause in-hospital mortality, and the secondary endpoint was healthcare resource utilization, including disposition of patients, hospital stay, and charges. Complex sample modules with IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) and weighted data were used for all analyses. We used Pearson chi-square test for categorical measures and the Mann-Whitney U test for continuous variables. Multivariable regression analyses were performed controlling potential sociodemographic characteristics and pre-existing comorbid conditions. A two-tailed p-value of <0.05 was the threshold for statistical significance (Figure 2).

RESULTS

We identified 1,129,440 adult hospitalizations with non-group 1 PH in 2019; of those, 12.1 % had TUD. After matching (n=133545, each group), the TUD+ cohort consisted of younger (62 vs. 63), females (49 % vs. 46.6 %), blacks (25.9 % vs. 25.3 %), patients from lower household income (40.8 % vs. 32.7 %), Medicaid enrollees (22.4 % vs. 14.8 %) who were more often admitted non-electively (93.5 vs. 89.8 %) (Figure 3). Furthermore, we observed that the TUD+ cohort had more frequent admissions in rural (9.3 % vs. 6.7 %) and urban non-teaching (17.2 % vs 15.8 %) centers. The TUD+ cohort exhibited higher rates of comorbidities such as alcohol use (11.1 % vs. 3.9 %), depression (17.0 % vs. 14.35 %), AIDS (1.3 % vs. 1.0 %), peripheral vascular disease (13.4 % vs. 10.1 %), prior myocardial infarction (12.6 % vs. 10.5 %), prior coronary artery bypass grafting (8.7 % vs. 8.1 %), prior transient ischemic attack/stroke (8.6 % vs. 7.9 %), valvular

disease (14.3 % vs. 14.2 %), liver disease (9.5 % vs. 8.4 %), drug abuse (13.1 % vs. 4.1 %), Cannabis use disorder (4.2 % vs. 1.3 %), chronic obstructive pulmonary disease (COPD) (62.4 % vs. 39.3 %), and Cancer (5.8 % vs. 6.8), in comparison to the TUD-cohort (Table 1).

However, The TUD- Cohort population demonstrated a greater prevalence of major cardiovascular comorbidities, including hypertension (62.5 % vs. 61.7 %), diabetes mellitus (44.8 % vs. 35.8 %), hyperlipidemia (47.0 % vs. 44.8 %), obesity (35.8 % vs. 26.6 %), as well as other comorbidities such as arthropathies (6.8 % vs. 4.3 %), prior venous thromboembolism (10 % vs. 8.5 %), chronic kidney disease (45.5 % vs. 33.3 %), and congestive heart failure (34.7 % vs. 34.5 %), hypothyroidism (15.9 % vs 11.8 %) (Figure 4) . (p:<0.001 for all, age, sex, race, median household income, insurance status, and all significant comorbidities except CHF and valvular disease and other thyroid disorders listed in Table 1).

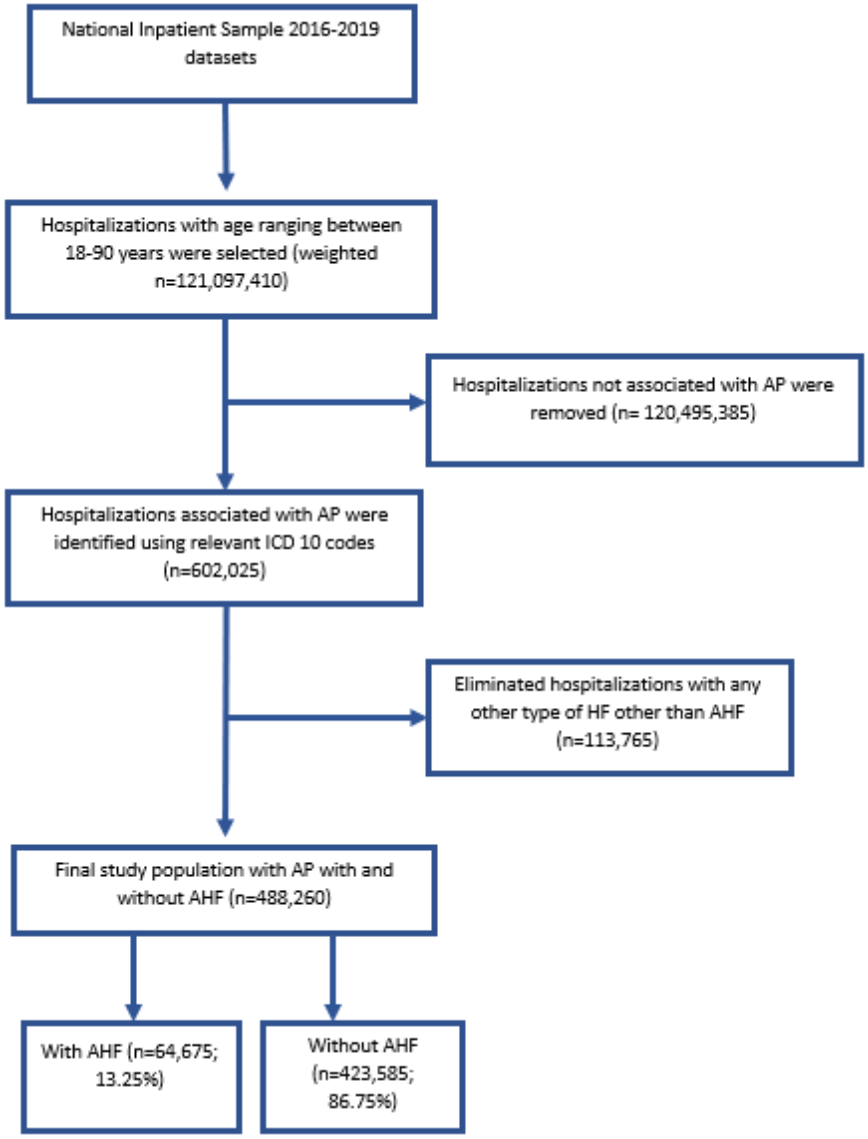

Figure 2: Study design and algorithm of patient selection
ICD 10: International Classification of Diseases, Tenth Revision; AP: Aspiration Pneumonia; AHF: Acute Heart Failure

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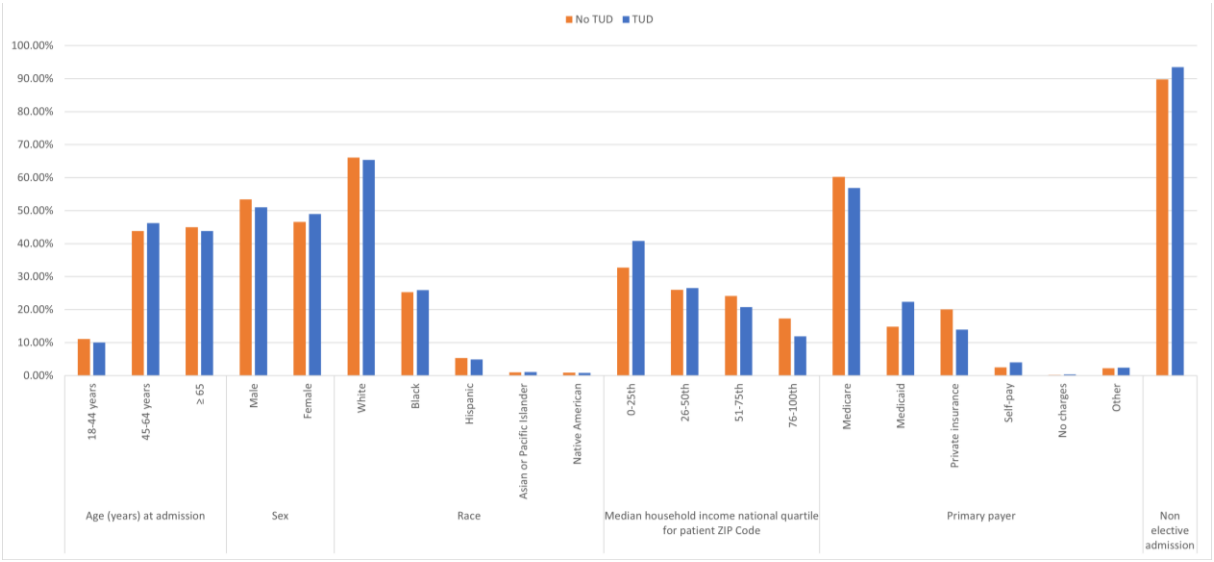

Figure 3: Differences in demographics of non-group 1 PH with vs without TUD

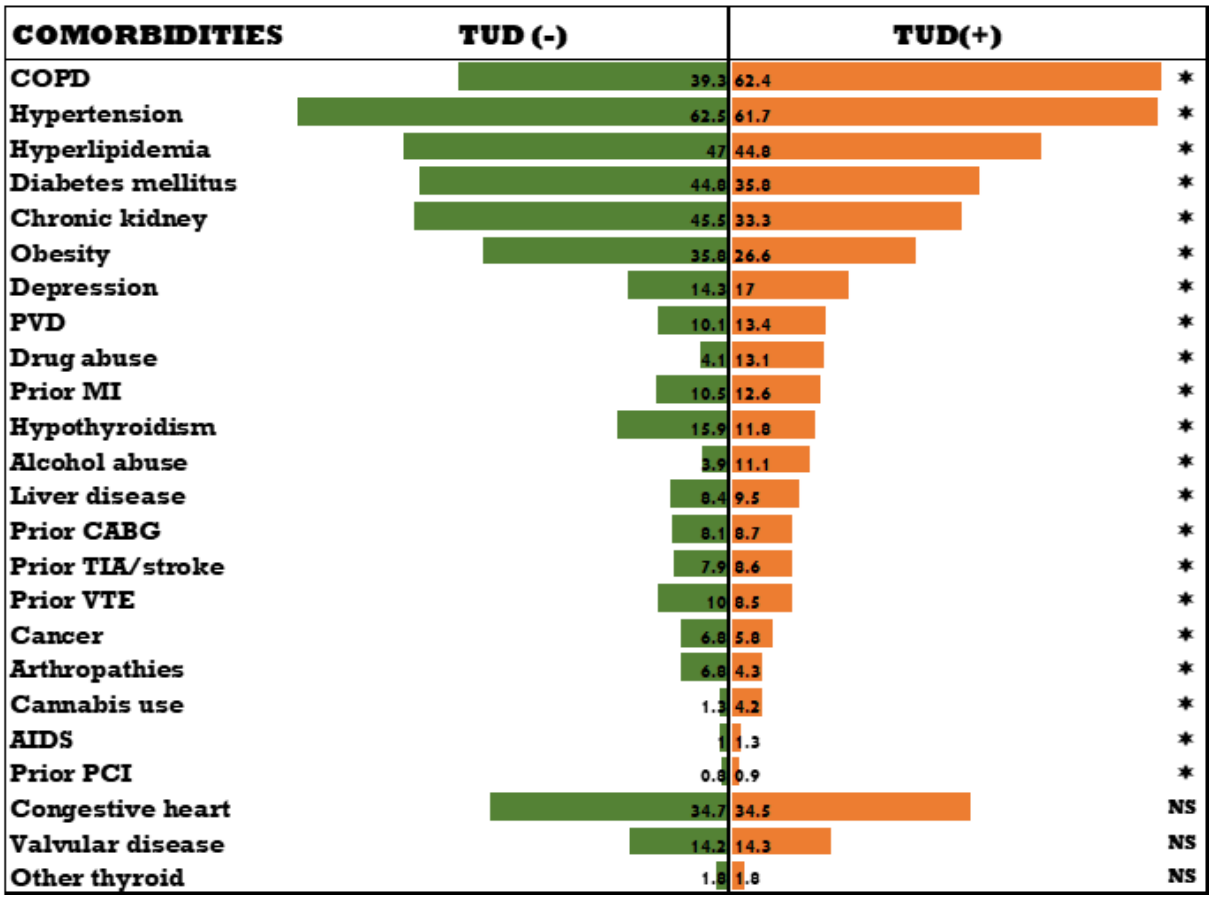

Figure 4: Differences in comorbidities of non-group 1 PH with vs without TUD
COPD= chronic obstructive pulmonary disease; PVD= peripheral vascular disease; MI= myocardial infarction; CABG= coronary artery bypass grafting; TIA= transient ischemic attack; VTE= venous thromboembolism; AIDS= acquired immunodeficiency syndrome; PCI= percutaneous coronary intervention
*: Significant; All values in the figure are in %.

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Table 1: Adults hospitalized with secondary pulmonary hypertension [non-group- 1 PH] with vs. without tobacco use disorder (2019)

Variable		Tobacco Use Disorder			P value
		NO (n=133545)	YES (n=133545)	Total Non-Group 1 PH (n=267090)	
Age (years) at admission	Median [IQR]	63 (54-72)	62 (55-71)	63 (54-71)	
	18-44 years	11.1 %	10.0 %	10.6 %	<0.001
	45-64 years	43.8 %	46.2 %	45.0 %	<0.001
	≥ 65	45.0 %	43.8 %	44.4 %	<0.001
Sex	Male	53.4 %	51.0 %	52.2 %	<0.001
	Female	46.6 %	49.0 %	47.8 %	<0.001
Race	White	66.1 %	65.4 %	65.8 %	<0.001
	Black	25.3 %	25.9 %	25.6 %	<0.001
	Hispanic	5.3 %	4.9 %	5.1 %	<0.001
	Asian or Pacific Islander	1.0 %	1.1 %	1.1 %	<0.001
	Native American	0.9 %	0.8 %	0.9 %	<0.001
Median household income national quartile for patient ZIP Code	0-25th	32.7 %	40.8 %	36.7 %	<0.001
	26-50th	26.0 %	26.5 %	26.2 %	<0.001
	51-75th	24.1 %	20.8 %	22.4 %	<0.001
	76-100th	17.3 %	11.9 %	14.6 %	<0.001
Primary payer	Medicare	60.2 %	56.9 %	58.6 %	<0.001
	Medicaid	14.8 %	22.4 %	18.6 %	<0.001
	Private insurance	20.1 %	13.9 %	17.0 %	<0.001
	Self-pay	2.5 %	4.0 %	3.3 %	<0.001
	No charges	0.2 %	0.4 %	0.3 %	<0.001
	Other	2.2 %	2.4 %	2.3 %	<0.001
Non elective admission		89.8 %	93.5 %	91.6 %	<0.001

Table 1 (cont.): Adults hospitalized with secondary pulmonary hypertension [non-group- 1 PH] with vs. without tobacco use disorder (2019)

COMORBIDITIES				
AIDS	1.0 %	1.3 %	1.2 %	<0.001
Alcohol abuse	3.9 %	11.1 %	7.5 %	<0.001
Arthropathies	6.8 %	4.3 %	5.5 %	<0.001
Depression	14.3 %	17.0 %	15.7 %	<0.001
Hypertension	62.5 %	61.7 %	62.1 %	<0.001
Diabetes mellitus	44.8 %	35.8 %	40.3 %	<0.001
Hyperlipidemia	47.0 %	44.8 %	45.9 %	<0.001
Obesity	35.8 %	26.6 %	31.2 %	<0.001
Peripheral vascular disease	10.1 %	13.4 %	11.8 %	<0.001
Prior MI	10.5 %	12.6 %	11.6 %	<0.001
Prior PCI	0.8 %	0.9 %	0.8 %	<0.001
Prior CABG	8.1 %	8.7 %	8.4 %	<0.001
Prior TIA/stroke	7.9 %	8.6 %	8.3 %	<0.001
Prior venous thromboembolism	10.0 %	8.5 %	9.3 %	<0.001
Chronic kidney disease	45.5 %	33.3 %	39.4 %	<0.001
Congestive heart failure	34.7 %	34.5 %	34.6 %	0.44
Valvular disease	14.2 %	14.3 %	14.3 %	0.45
Liver disease	8.4 %	9.5 %	8.9 %	<0.001
Drug abuse	4.1 %	13.1 %	8.6 %	<0.001
Cannabis use disorder	1.3 %	4.2 %	2.7 %	<0.001
COPD	39.3 %	62.4 %	50.8 %	<0.001
Hypothyroidism	15.9 %	11.8 %	13.8 %	<0.001
Other thyroid disorders	1.8 %	1.8 %	1.8 %	0.77
Cancer	6.8 %	5.8 %	6.3 %	<0.001

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Table 1 (cont.): Adults hospitalized with secondary pulmonary hypertension [non-group- 1 PH] with vs. without tobacco use disorder (2019)

Outcomes					
All-cause mortality		4.2 %	3.3 %	3.8 %	<0.001
		OR	**95 % CI LL**	**95 % CI UL**	**p**
Unadjusted		0.78	0.71	0.86	<0.001
Adjusted		0.78	0.70	0.86	<0.001
Disposition of patient	Routine	51.3 %	53.8 %	52.5 %	<0.001
	Other transfers, SNF ICF	18.7 %	16.9 %	17.8 %	<0.001
	Home healthcare	21.2 %	19.6 %	20.4 %	<0.001
Length of stay (days)	Median [IQR]	5 (3-9)	5 (3-8)	5 (3-8)	
Total charges (USD)	Median [IQR]	51909 (27755-104463)	47155 (26297-89379)	49451 (26982-96875)	

P<0.05 indicates statistical significance.
MI= myocardial infarction; PCI= percutaneous coronary intervention; CABG= coronary artery bypass grafting; TIA= transient ischemic attack; IQR= interquartile range; OR= odds ratio; CI= confidence interval; LL= lower level; UL= upper level; SNF= skilled nursing facility; ICF= Intermediate care facility
Multivariable regression models were adjusted for age, sex, race, median household income quartile, payer status, type of admission, hospital bed size, location/teaching status and region, comorbidities including AIDS, arthropathies, hypertension, diabetes, hyperlipidemia, obesity, peripheral vascular disease, prior history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, drug abuse, alcohol abuse, cannabis use disorder, opioid use disorder, COPD, chronic kidney disease and cancer

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The TUD+ cohort had a lower rate and odds of mortality (3.3 % vs. 4.2 %, adjusted OR 0.78, p<0.001) vs. the TUD- cohort when adjusted for potential confounders. Furthermore, the TUD+ cohort often had routine discharges (53.8 % vs. 51.3 %, p<0.001), lower rate of transfers (16.9 % vs. 18.7 %, p<0.001), and less requirement of home healthcare (19.6 % vs. 21.2 %, p<0.001), which might have translated into lower total charges ($ 47155 vs. 51909, p<0.001) than TUD- cohort.

DISCUSSION

Smoking is a known major risk factor for cardiovascular diseases such as myocardial infarction (MI), peripheral vascular disease (PVD), and cerebrovascular diseases. Smoking remains a leading avoidable cause of death (Kondo et al., 2019). We hypothesized the role of smoking on outcomes of pulmonary hypertension (non-group 1) hospitalization and mortality. The evidence supporting pathophysiology remains undetermined, like our study factors such as younger age and perhaps lower comorbidities were attributed to the findings (Aune et al., 2011). Our study divided the non-group 1 PH cohort into TUD+ and TUD- groups. Our significant findings were TUD+ cohort was younger compared to TUD- cohort. Minor gender difference was noted in both groups. However, Keusch et al. showed gender disparity in smoking-related PH even when the active male and female smokers were similar. However, females had significantly higher secondhand smoke exposure contributing to the development of PH (Keusch et al., 2014).

Studies showed that metabolic syndrome is associated with a higher risk of all-cause mortality, cardiovascular risk, and CVD mortality (Guembe et al., 2020). In our study, severe comorbidities such as prior MI, prior PCI, prior coronary artery bypass graft (CABG), chronic obstructive pulmonary disease (COPD), and prior transient ischemic attack (TIA)/Strok

e were prevalent in the TUD+ cohort compared to TUD- cohort. But TUD- cohort had a higher prevalence of metabolic syndrome comorbidities such as HTN, DM, hyperlipidemia, and obesity. Studies so far have shown cardiovascular disease burden is directly correlated to the inflammatory status with increased vascular remodeling, which is noted in PH as well in the setting of tobacco use (Brassington et al., 2019), the higher prevalence of cardiovascular risk, older age population in TUD- group could be the reason for higher all-cause mortality that supports smoker's paradox.

COPD is the main cause of pulmonary hypertension, which promotes the remodeling of pulmonary arterioles, and hypoxic vasoconstriction results in increased pulmonary blood pressure (Ball et al., 2014; Chaouat et al., 2005; Lam et al., 2009). The TUD+ group has a higher prevalence of COPD (62.4 % vs 39.3 %). However, the impact of COPD on all-cause mortality compared to other morbidities in non-group 1 PH needs further investigation to validate the results. It stimulates the necessity for additional investigation, both in the context of research and a higher index in the non-group 1 PH cohort, to determine the outcome of this study.

We discovered that the group TUD+ has lower all-cause mortality compared to TUD- cohort. Additionally, the length of stay was shorter in the TUD+ group, which reflected lower hospitalization costs than in the TUD- group which could be because the population is younger with overall less severe comorbidities. TUD + group had a higher rate of routine patient disposition (53.8 % vs. 51.3 %). The smoker's paradox of lower all-cause mortality, length of stay, and cost of hospitalization in the TUD+ group is not known in non-group 1 PH thus far. The only previous studies that have demonstrated smoker's paradox is in cardiovascular disease in the 1980s and then in 2011, with data supporting decreased in-hospital mortality for acute coronary syndrome in hospitalized patients (Aune et al., 2011; Kelly et al., 1985). Based on the results of our investigation, the smoker's paradox may be caused by differences in comorbidities and population ages, our study raises an

important concern to understand the overall impact of smoking on outcomes of non-group 1 PH patients which is paradoxical to evidence thus far.

Like any study, ours has limitations. Inherent limitations of retrospective analysis including unable to control all confounders remains. NIS database has fundamental biases due to coding errors, administrative errors, or billing errors. Our two main groups of TUD+ and TUD- are based on patient's reporting which also creates a bias in the dataset, we were also unable to quantify smoking exposure, number of pack years. We were unable to differentiate between the types of non-group 1 PH due to NIS database billing and availability of sample size in each group. Given the retrospective observational analysis, only association can be concluded and the results of the smoker's paradox in the non-group 1 PH cohort need to be validated by additional prospective randomized data analysis, and further longitudinal studies are needed to determine which comorbidities are primarily responsible for the worse short-term outcome in the TUD group to form causative inferences.

CONCLUSION

Conclusively, non-group 1 PH patients with TUD+, despite having a higher comorbidity burden, however, they had lower in-hospital mortality rates along with lower healthcare resource utilization and lower hospital charges mandating prospective randomized data to validate these results of the "smoker's paradox" in better short-term outcomes in patients with non-group 1 PH and concomitant TUD.

Acknowledgments

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