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Review Article

The Burden of Substance Use Disorders among Hospitalized Patients with Underlying Cardiovascular or Cerebrovascular Disease in the United States

Ahmed Brgdar[1*], Mohamed Taha[5], Ahmad Awan[2], Richard Ogunti[3], John Gharbin[1], Mayar Hamad[4], Prafulla Mehrotra[5]

[1]Department of Medicine, Howard University Hospital, Washington, USA;[2]Department of Cardiovascular Disease, Montefiore Medical Center, Bronx, NYC, USA;[3]Department of Medicine, University of Texas Health Science, Houston, Texas, USA;[4]Department of Science, University of Calgary, Calgary, Canada;[5]Department of Cardiovascular Disease, Howard University Hospital, Washington, USA

ABSTRACT

The COVID-19 pandemic has aggravated the already devastating prevalence of substance use and drug-related morbidity and mortality in the United States. Our objective in this literature review is to present an overview of the occurrence of substance use and its impact on in-hospital clinical outcomes and healthcare resource utilization among patients hospitalized with the primary diagnosis of Cardio Vascular Diseases (CVD) or Cerebro Vascular Diseases (CeVD) in the United States. Consistent with the worsening substance abuse problem in the United States, our findings indicate an increasing prevalence of all commonly abused substances among hospitalized CVD/CeVD patients. However, there were considerable differences in clinical outcomes and resource utilization depending on the substance. The current evidence does not indicate an increased risk of in-hospital mortality, complications, or resource utilization among tobacco users. In contrast, patients with underlying alcohol or opioid use disorders had an increased risk of mortality, in-hospital complications such as cardiorespiratory failure, and more resource utilization. Cannabis use was also associated with increased occurrence of in-hospital complications, resource utilization, and mortality risk among CeVD patients, especially those with ischemic stroke, but not among CVD patients. While stimulants, anxiolytics, sedatives, or hypnotics remain poorly studied, there are some indications that stimulant users may incur a higher cost of hospitalization with elevated in-hospital mortality risk. Together, the current evidence indicates that the coexistence of Substance Use Disorder (SUD) with CVD/CeVD complicates the management of both and is associated with poor in-hospital outcomes and healthcare resource utilization.

Keywords: Tobacco; Acohol; Opioids; Cannabis; Stimulants drugs; In-patient

INTRODUCTION

Substance abuse is a growing public health problem globally. In 2016, an estimated 844 people per 100,000 global populations had a Drug Use Disorder (DUD), and another 1,358 people per 100,000 populations were diagnosed with an Alcohol Use Disorder (AUD) [1]. The high prevalence is compounded by significant morbidity and mortality. In 2016 alone, 276 and 220 Disability-Adjusted Life Years (DALYs) were lost per 100,000 populations due to DUD and AUD, respectively [1]. Additionally, there were 1.14 billion tobacco smokers in 2019, with 2,580 DALYs attributed to tobacco smoking, the leading risk factor of death among men [2]. The COVID-19 pandemic has further exacerbated the already catastrophic substance use problem worldwide. In a recent systematic review, Roberts et al. highlighted an increase in problematic drinking behavior,

Correspondence to: Ahmed Brgdar, Department of Medicine, Howard University Hospital, Washington, USA; E-mail: ABrgdar@huhosp.org

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substance use, or drug-related emergency department admissions compared to pre-pandemic levels [3]. Some of the prominent factors associated with the worsening trends during the pandemic included mental health problems, fear about COVID-19, isolation, and boredom [3].

The adverse population health outcome of substance abuse has been particularly strong in the United States (US) [4,5]. The age-standardized drug-related death rate in the US has aggressively increased since 2000, while the death rate has stabilized or decreased in most other high-income countries [5]. The drug-related mortality rates account for about 15% of the difference in lower life expectancy in the US compared to other high-income countries among men and about 10% in women [5]. Among the working-age population, the drug-related mortality rate contributes to over a quarter of the difference in life expectancy [5]. Furthermore, a recent study of a population-level electronic health record from the US showed that patients with Substance Use Disorder (SUD) had a higher risk of COVID-19, especially those with Tobacco Use Disorder (TUD) and Opioid Use Disorder (OUD) and COVID-19 patients with SUD had significantly higher rates of hospitalization and mortality than COVID-19 patients without SUD [6].

A large proportion of the drug-related mortality in the US is attributed to an increase in overdose deaths. Fatal overdoses in working-age adults increased by 386.5%, from 6.7 deaths in 1999 to 32.5 deaths in 2017 per 100,000, with an even higher increase of 531.4% among young adults [4]. However, significant increases in organ system disease, including Cardio Vascular Diseases (CVD) and Cerebro Vascular Diseases (CeVD), have been noted with substances that carry a lower risk of fatal overdose or moderate users at low risk of overdose [4-6]. The evidence for increased risk of CVD, CeVD, or mortality with smoking and heavy alcohol use is robust and recent studies suggest that illicit drug use also poses a significant risk [7-16]. For instance, Gan et al. showed that individuals with any SUD had a 1.7 times higher risk of developing incident CVD than those without SUD after adjusting for covariates with the highest hazard ratio among those with OUD [2.08 (1.74-2.48)], followed by Stimulant Use Disorder [StUD; 1.78 (1.49-2.11)], AUD [1.75 (1.59-1.54)], and Cannabis Use Disorder [CUD; 1.31 (1.02-1.67)] [17]. Similarly, in the Swedish Drug Addict Treatment Evaluation study, opiate use (16.7%) was associated with the highest standardized mortality rate, followed by alcohol (13.1%), cannabis (9.2%), and stimulants (9.6%) [18]. Overall, about 13% of the cause of death was attributed to the circulatory system, including heart attacks and strokes [18].

Further, in a long-term follow-up study, patients previously hospitalized for SUD had a higher mortality rate than the general population, and CVD and CeVD, including cardiomyopathy and cerebral hemorrhage, were among the most common natural causes of death among substances users accounting for about 9% of all deaths [19]. In another long-term follow-up study, CVD accounted for 2.8 deaths per 1000 person-years among previous drug users, comparable to mortality rates associated with accidents (2.7 deaths per 1000 person-years) or tumors (2.3 deaths per 1000 person-years) and higher than for instance, liver cirrhosis (1.9 deaths per 1000 person-years) or suicide (1.9 deaths per 1000 person-years) [20]. Therefore, it is likely that organ system diseases such as CVD and CeVD associated with substance use adversely affect hospitalization rates, peri-procedural complications, and resource utilization. While drug overdose deaths have received considerable governmental, media, and scientific attention, there is no synthesis of the literature to date exploring the impact of SUD on in-hospital outcomes of patients with underlying CVD or CeVD [21-24].

Given that tobacco, alcohol, and cannabis are the three most widely used substances in the general US population, with a smaller number of stimulants or opioids users [25], the objective of this review is to present an overview of (1) the occurrence of TUD, AUD, CUD, OUD, or StUD; (2) the impact of substance use on in-hospital outcomes; and (3) the healthcare resource utilization indicated by cost and length of hospitalization among patients hospitalized with the primary diagnosis of CVD or CeVD in the US.

METHODOLOGY

Since the Healthcare Cost and Utilization Project's National Inpatient Sample (NIS) is the largest registry of hospitalization records in the US, we have relied largely on studies utilizing NIS datasets for this review. NIS provides nationally representative data, which include the principal diagnosis (primary discharge diagnosis), up to 29 secondary diagnoses, length of stay, up to 15 medical procedures performed during hospitalization, and total hospital costs.

Three databases (Pubmed, Web of Science, and Google Scholar) were searched for the relevant literature using a combination of three search terms as follows: (the name of the substance) and (in-patient or in-hopsital) and (heart disease or vascular disease or cardiovascular disease or cerebrovascular disease).

The inclusion criteria were articles published in English, publication date on or after 01 January 2000, and original analysis of data pertaining to SUD in hospitalized patients with underlying CVD or CeVD from the US. Protocols, reviews, commentaries, responses to authors, letters to the editor, and redacted articles were excluded from this review. In addition, given the paucity of related literature on hallucinogens, anxiolytics, sedatives, or hypnotics, we could not include these substances in the review.

PREVALENCE AND IMPACT OF SUBSTANCE ABUSE IN HOSPITALIZED PATIENTS WITH CVD/CEVD

Tobacco

Tobacco is the most widely used substance and is the leading cause of death globally [26]. Smoking is perhaps one of the best-studied CVD and CeVD risk factors and is the single most preventable cause of diseases associated with the circulatory system [26]. Smoking as a primary cause of hypertension, atherosclerosis, and athero thrombosis is well established with important implications for cardiovascular events, including but

not limited to Coronary Heart Disease (CHD), Heart Failure (HF), stroke, cardiac arrhythmia, aortic and peripheral artery disease, and cardiovascular mortality (Reviewed in detail elsewhere. See for recent reviews on the topic) [26,27]. The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines strongly emphasized the implication of promoting smoking cessation to reduce CVD-associated morbidity and mortality and recommended aggressive screening for tobacco use at clinical presentation in their 2019 guideline on the primary prevention of CVD [28]. As a well-established CVD risk factor with a global mandate and consensus on promoting cessation [26], the prevalence of TUD among hospitalized patients and its impact on in-hospital outcomes have been widely reported.

Among 3,631,507 Atrial Fibrillation (AF) hospitalizations between 2007 and 2015, 23.5% had concomitant TUD, which was substantially higher than the combined prevalence of SUD (5.1%), AUD (4.29%), or DUD (1.17%) among AF patients [29]. However, in-hospital outcomes of AF patients with TUD, such as incidence of stroke, in-hospital mortality, length of hospitalization, and the median cost of hospital stay, were comparable with AF patients with SUD, AUD, DUD, or without any substance use [29]. Similarly, among patients admitted with the primary diagnosis of Acute Myocardial Infarction (AMI) from 2005 to 2017, 32.7% reported tobacco use with increasing annual trends from 22% in 2005 to 45% in 3.7 in 2017 [30]. Moreover, tobacco users were more likely to undergo percutaneous coronary intervention (41% vs. 25%), coronary artery bypass surgery (6.9% vs. 4.9%), and incur a higher cost of hospitalization ($50,782 vs. $44,931) compared to non-users [30]. Increasing prevalence of tobacco use was also observed in patients hospitalized with acute ischemic stroke, from 27.9% in 2006 to 37.6% in 2017 [31]. However, the impact of smoking status on in-hospital outcomes was not reported in this study [31]. Even greater prevalence of smoking (52.8%) was noted among patients with AMI at index hospitalization between 2005 and 2015 [32].

In comparison, smoking is relatively less prevalent among hospitalized patients with HF than in patients with AF, acute ischemic stroke, or AMI. Among 989,080 patients hospitalized with a primary diagnosis of HF in 2014, TUD was noted in 12.1% compared to 6.2% and 3.5% of the patients with concomitant SUD and AUD, respectively [33]. Interestingly, while peripheral vascular disease, AMI, and ventricular tachycardia were more frequently encountered comorbidity among HF patients with TUD, the prevalence of hypertension and CHD was similar, and the prevalence of AF was lower compared to patients without any SUD [33]. Further, a relatively low smoking prevalence of 13.7% and 5.5% has been reported in patients hospitalized with peripartum cardiomyopathy with or without left ventricular thrombus, respectively, although smoking status was the strongest predictor of left ventricular thrombus among various comorbidities [34].

We could only identify two studies that assess the impact of smoking status on in-hospital outcomes of patients hospitalized with an underlying CVD. Using the 2011-2012 NIS data, Agarwal et al. showed that the prevalence of smoking among patients undergoing Transcatheter Aortic Valve Replacement (TAVR) was 24%, and despite higher cardiovascular comorbidities, smokers had lower in-hospital mortality (1.2% *vs.* 5.7%) and post-procedural hemorrhage (28.2% vs. 32.0%) compared to non-smokers although the risk of acute cerebrovascular events remained comparable between smokers and non-smokers [35]. Similarly, Dasenbrock et al. reported a smoking prevalence of 37.1% among patients admitted for endovascular or microsurgical repair of ruptured cerebral aneurysm during 2009–2011 and that current smokers did not have elevated risks of in-hospital mortality or post-procedural complications, and had lower risks of extended hospitalization, non-routine discharge, discharge to institutional care, or poor outcome measured by NIH-aneurysmal subarachnoid hemorrhage severity scale [36]. Although such paradoxical effects of smoking on CVD and CeVD patients have been previously attributed to younger patient age, lower comorbidities, or neuro protective effects of nicotine, the trends remained significant after adjusting for age and comorbidities [35,36]. This phenomenon is being increasingly recognized in the literature as the "smoking paradox" and is yet to be fully understood, warranting further investigations.

Alcohol

Several observational and prospective studies have demonstrated a J-shaped curve between alcohol consumption and cardiovascular mortality risk, with the lowest risk among light-moderate drinkers (5 to 25 g/day) and the highest risk among heavy drinkers compared to abstainers [14,37]. However, some researchers have questioned the cardioprotective effects of alcohol at any dose [38,39]. The acute detrimental effects of high doses of alcohol or chronic alcoholism have been well documented and include abnormal cardiac contractility and/or rhythm, arterial hypertension, sudden death, and chronic effects such as atrial or ventricular dysfunctions, arrhythmia, alcoholic cardiomyopathy, and heart failure have been recognized for decades [37].

Starkly different prevalence of AUD and associated clinical outcomes has been reported depending on the subpopulation of hospitalized patients. For example, only 0.4% of hospitalizations had troublesome alcohol history defined as discharge diagnoses of chronic alcohol syndrome and acute withdrawal when all hospitalizations recorded during 2009 and 2010 in the NIS were included in the analysis [40]. Interestingly, patients with troublesome alcohol history had a lower prevalence of cardiovascular comorbidities including HF, CHD, and chronic kidney disease or CVD risk factors such as diabetes, hyperlipidemia, or obesity than patients without troublesome alcohol history [40]. In addition, despite the higher prevalence of hypertension and tobacco use, patients with troublesome alcohol history had a lower risk of CHD, AMI, HF, or in-patient mortality [40]. However, in another analysis of the 2007-2014 NIS that specifically recruited elderly patients with prediabetes, 2.8% had concomitant AUD with a higher risk of all-cause mortality and stroke than patients without AUD [41]. Similarly, among patients admitted with the primary diagnosis of AMI from 2005 to 2017, 3.2% reported alcohol use with increasing annual trends from 2.4% in 2005 to 3.7% in 2017 and higher

cost of hospitalization ($56,440 vs. $46,729) compared to non-users despite lower cardiovascular comorbidities and risk factors [30].

Recently, the frequent co-occurrence of AF and alcohol use in in-patient settings has been observed. For example, out of the 1.5 million hospitalizations due to causes associated with alcohol withdrawal recorded in the NIS database between 2015 and 2018, about 10% had AF [42]. Although the prevalence of hypertension (~60%), CHF (~16%), cardiogenic shock (~0.8%), valvular heart disease (~2.7%), and prior MI (~4.8%) were similar in AUD patients with or without AF, arrhythmic patients with AUD had significantly higher rates of HF (8.40% vs. 4.58%) and in-hospital mortality (4.19% vs. 1.95%), a longer length of hospitalization (6 vs. 4 days), and total hospital charges (median: $12,615 vs. $7,860) [42].

Furthermore, we identified two studies that reported in-hospital outcomes for patients with alcoholic cardiomyopathy. A total of 365 alcoholic cardiomyopathy hospitalizations were recorded in the NIS database between 2002 and 2014, with a general declining trend, especially after 2010, while high variability in year-to-year mortality rate (range: 3.6%-5.3%) was noted without a clear trend [43]. However, an increasing prevalence of smoking, substance abuse, depression, hypertension, and liver disease among patients hospitalized with alcoholic cardiomyopathy was observed over the study period suggesting that the patients are increasing sicker at index hospitalization [43]. Also, the incidence of several in-hospital events, including cardiorespiratory failure (9% to 47.2%), deep vein thrombosis (0% to 1.6%), and pulmonary embolism (0.6% to 1.6%), showed substantial increases along with doubling of total hospital charges (from $30,753 to $62,619) between 2002 and 2014 [43]. However, the prevalence of in-hospital AF remained stable at around 30% in this population [43]. Similar rates of in-hospital occurrence of AF were reported in another study during 2007-2014, and although 48.2% of patients hospitalized with alcoholic cardiomyopathy had some form of cardiac arrhythmia, none of the arrhythmias with the exception of ventilation fibrillation was a predictor of in-hospital mortality [44].

Cannabis

With the legalization or decriminalization of cannabis in several states, the medicinal/recreational use of cannabis is being increasingly observed among hospitalized patients in the US. A total of 5,601,382 hospitalizations with either primary or secondary diagnosis of CUD were recorded in the NIS database between 1998 and 2014, with increasing annual frequency of hospitalization and a tripling of non-inflation adjusted median total hospital charges during the study period [45]. Importantly, there is a growing tendency of patients hospitalized with CUD being older, with more comorbidity, and a discharge diagnosis of psychiatric disorders than non-users [46]. Patients hospitalized with CUD were more likely to report concomitant alcohol and tobacco use, with a significantly higher incidence of co-occurring hypertension, obesity, HF, stroke, and sudden cardiac death than non-users [47]. The incidence of AF among cannabis users was numerically higher and approached statistical significance [47].

AF is the most common type of arrhythmia observed among cannabis users [48,49]. However, CUD is relatively less frequent among patients with AF, albeit with an increasing annual trend. In a recent study, only 0.6% of patients admitted with AF between 2008 and 2018 had concomitant CUD, but the proportion increased from 0.3% in 2008 to 1% in 2018 [50]. Similarly, low occurrence of CUD has been observed in Congestive Heart Failure (CHF), HF hospitalizations, or AMI. Among patients admitted with CHF between 2010 and 2014, only 0.5% of the patients had comorbid CUD [51]. Moreover, in-patient mortality, length of hospitalization, and hospital cost were lower among cannabis users with CHF than non-users [51]. A more recent report noted CUD in 0.8% of HF admissions with an increasing trend from 0.3% in 2008 to 1.3% in 2018 but with a lower risk of in-hospital mortality, shorter hospital stay, and comparable cost of hospitalization to patients without a concomitant diagnosis of substance abuse [52]. Low prevalence of cannabis use but with an increasing trend was also reported among patients admitted with the primary diagnosis of AMI from 0.3% in 2005 to 0.7% in 2017 [30].

In contrast, CUD is more frequently observed among patients hospitalized with AMI or ischemic stroke. For example, the prevalence of CUD among patients hospitalized with AMI was 2.7% in 2010 and increased to 3.9% in 2014, with increasing in-patient cost and mortality rate but with a shorter length of hospitalization [53]. Similarly, cannabis use was noted in 2.4% of acute ischemic stroke hospitalization from 2004 to 2011, marginally higher than the prevalence of cannabis use (2.1%) among all patients hospitalized during the study period [54].

Although CUD is becoming ever more common among hospitalized patients with CVD in recent years, and several underlying CVD such as coagulopathy, AMI, CHF, peripheral vascular disease, and coronary atherosclerosis are positively associated with in-hospital mortality among cannabis users [55], the evidence for exacerbated secondary complications or higher risk of incident CVD among cannabis users is less consistently reported. For instance, one study showed that cannabis users had lower odds of developing AF than a matched cohort of non-users with no increase in CVD incidence [56], while another indicated a higher risk of mortality among recreational cannabis users with arrhythmia [49]. Further, cannabis use was associated with an 8% increased risk of incident AMI but without additional mortality risk [57]. Similarly, among patients undergoing percutaneous coronary intervention, the risk of in-hospital mortality, bleeding, and stroke/transient ischemic attack among cannabis users was similar to non-users [58]. Moreover, cannabis users had significantly lower odds of in-hospital vascular complications [58]. Further, while CUD was increasingly prevalent among patients undergoing vascular surgery between 2006 and 2015, an increased risk of perioperative MI was noted among cannabis users compared to non-users, while the risk of sepsis was lower and that of stroke was similar compared to non-cannabis users [59].

However, studies consistently show exacerbated risk or incident CeVD, especially ischemic stroke, with adverse in-hospital outcomes. In patients aged 15-54-years, cannabis users had a 13% higher risk of acute ischemic stroke than non-users, with a

small but significantly higher risk of non-routine discharge, symptomatic cerebral vasospasm, and in-patient mortality [54]. The incidence of young-onset stroke increased by 14% between 2007 and 2014 among cannabis users, with a 16% increased risk of stroke compared to non-users [60]. While in-patient mortality among non-users admitted for stroke declined from 7.7% in 2007 to 5.9%; it increased from 3.7% to 4.3% among cannabis users during the study period with substantial increases in length of hospital stay and cost compared to non-users [60]. Furthermore, in patients with surgically or endovascularly treated ruptured intracranial aneurysms between 2009 and 2016, cannabis users were more likely to develop communicating hydrocephalous or obstructive hydrocephalous [61]. Additionally, endovascularly treated cannabis users had a higher risk of acute kidney injury, sepsis, and longer hospitalization length than non-users [61]. The risk of other endpoints such as stroke, respiratory or cardiac complications, or death was similar between cannabis users and non-users [61]. None of these clinical endpoints were different among cannabis users and non-users with surgically or endovascularly treated unruptured aneurism [61]. The null effect of cannabis use on in-hospital clinical endpoints, including mortality among patients with aneurysmal subarachnoid hemorrhage, was also demonstrated in an earlier study using the 2016 NIS dataset [62].

One of the challenges in interpreting these findings is the relatively high presence of comorbid substance use among cannabis users. For instance, the prevalence of tobacco use (64.4% vs. 31.5%), cocaine (26.7% vs. 3.1%), alcohol (23.7% vs. 7.5%), amphetamines (5.9% vs. 0.5%), opioids (4.8% vs 0.8%), or hallucinogens (2.1% vs 0.3%) were substantially higher among cannabis users admitted for acute ischemic stroke during 2004-2011 than non-users [54]. Similarly higher prevalence of comorbid substance use has also been reported among AMI patients [57]. In fact, alcohol and drug rehabilitation is the most common primary procedure among hospitalized recreational cannabis users [55]. We could only identify one study that assessed CVD risk and in-hospital outcomes among cannabis users without comorbid substance use. Desai et al. showed that the presence of arrhythmias (4.02% vs. 2.84%) was substantially higher among cannabis users aged 18-39 years without comorbid substance use in the 2007-2014 NIS dataset than non-users, with a small but statistically significant difference in the prevalence of AMI (0.23% vs. 0.14%), stroke (0.33% vs. 0.26%), and venous thromboembolism (0.53% vs. 0.84%) [63]. Strong increases in hospitalization rates for arrhythmias, AMI, stroke, and venous thromboembolism among cannabis users were observed between 2007 and 2014 [63]. Nevertheless, cannabis users had a significantly lower cost of hospitalization and in-hospital mortality than non-users, even though the length of hospitalization was longer [63]. This study suggests that even in the absence of comorbid substance use, cannabis may contribute significantly to the risk of incident CVD without worst in-hospital outcomes than cannabis-naïve patients.

Opioid

Opioid overdose accounts for over 60% of all overdose deaths [22], usually due to ventilatory depression [64]. In addition to the increasing risk of overdose death with opioids in the US over the past decade [22], the detrimental impact of opioids on the cardiovascular system has been recently highlighted by the American College of Cardiology [64,65]. Opioid use is known to adversely affect the cardiovascular system through direct action on its endogenous receptors, which suppresses heart rate and blood pressure while disrupting cardiac conduction, contractility, and repolarization or indirectly through traditional cardiovascular risk factors such as sleep apnea, obesity, and hyperglycemia [64].

The prevalence of prescription opioid overdose has outpaced non-prescription opioid overdose in the hospital setting. Of all the drug overdose-related hospitalization recorded in the NIS from 2000 to 2013, 16.4% were associated with prescription opioids and 2.3% with heroin, with over 3- and 2-fold increase in hospitalization rates respectively, during the study period [66]. Similarly, among 570,987 patients in the NIS database who were hospitalized with opioid overdose during 2010-2014, only 13.8% had an illicit opioid overdose, and most patients were hospitalized with prescription opioid overdose, although patients in both groups had a high risk of in-patient mortality compared to patients with non-opioid overdose [67]. Furthermore, patients with heroin overdose (3.8%) had a higher occurrence of cardiac arrest compared to those with a prescription opioid overdose (1.4%) or non-opioid overdose (0.6%), with increasing annual trends in both opioid overdose groups [66]. Similarly, in-hospital mortality was highest among patients with heroin overdose (4.4%) compared to those with a prescription opioid overdose (2.3%) or non-opioid overdose (1.2%) but without change in any of the subgroups with time [66].

In a more recent report, opioid abuse was noted in 3.1% of all cardiac arrest hospitalization from 2012 to 2018, increasing from 2.0% in 2012 to 3.9% in 2018 [68]. Although opioid abuse increased the risk of acute respiratory failure and mechanical ventilation, the risk of acute kidney injury leading to hemodialysis or sepsis was lower among patients admitted with opioid-related cardiac arrest [68]. Also, the length of stay and total hospital cost was significantly lower among opioid users with no change in risk of in-hospital mortality [68]. In contrast, a lower prevalence of OUD (0.6%) has been reported among patients admitted with a primary diagnosis of HF, but with an increasing trend between 2008 to 2018 from 0.2% to 1.1% and higher hospital costs than patients without substance abuse diagnosis [52]. However, HF patients with OUD had lower in-patient mortality and similar hospital stay length than non-OUD HF patients [52].

Increased occurrence of other cardiovascular events with opioid abuse has also been noted. Among patients hospitalized with opioid overdose between 2005 to 2015, 8.6% of the patients had at least one cardiovascular event, with arrhythmia being most reported (5.2%), followed by ischemic event (3.2%) and HF (0.7%) [69]. Further, patients with any cardiovascular event had a longer length of hospitalization, higher cost, and over 4.5 times higher odds of in-hospital mortality [69]. In another analysis of the NIS database, Acute Coronary Syndrome (ACS)-related hospitalizations in patients with a history of substance abuse increased from 168 per 100,000 admissions in 2012 to

315 per 100,000 admissions when overall ACS-related hospitalizations decreased nationwide during the study period [70]. Importantly, patients with a history of substance abuse presenting with ACS had higher in-patient mortality (9% vs. 7%) and increased length of hospitalization (6.9 days vs. 5.4 days), with opioid use as the main contributor [70].

Infective Endocarditis (IE) is frequently encountered among injection drug users, a common mode of administration of several opioids, including heroin, and can increase the risk of cardio embolic stroke. The number of stroke patients with concurrent IE and opioid use increased from 2.4% in 1993 to 18.8% in 2015 per 10 million US residents per year, parallel with the increase in opioid abuse in the US [71]. However, in an earlier analysis of the National Readmissions Database, patients with IE associated with injection opioid use had lower mortality and comparable readmission risk compared to IE patients without injectable drug use, although the reason for readmission for IE patients using injectable opioid was more likely to be due to endocarditis or septicemia indicating persistent substance abuse [72]. The lower mortality among injectable opioid users was attributed to younger age at index hospitalization and increased frequency of right-sided valve replacement in this subpopulation [72]. Together these studies suggest that opioid users are at increased risk of cardiovascular events, in-patient mortality, and, therefore, higher resource utilization, as also highlighted in a recent study [73].

Stimulants

There is a paucity of literature describing the prevalence or effect of stimulants on in-hospital outcomes of patients with underlying CVD. We identified two related articles, both published in the past two years, indicating the growing relevance of stimulant use on in-patient outcomes. The most recent of these studies utilized NIS data from 2006 to 2018 and showed that out of the 261.38 million total hospitalizations in the US, 0.9% had underlying cocaine abuse [74]. Although the prevalence of cocaine abuse initially decreased from 10,751 per million hospitalizations in 2006 to 7,451 per million hospitalizations in 2012, it subsequently increased to 11,891 per million hospitalizations in 2018, with a near doubling of total financial burden in terms of total hospital cost from $10.8 billion to $19 billion during the study period [74]. Also, increasing prevalence of MI (4.13% to 7.85%), hypertension (29.2% to 45.08%), arrhythmias (6.49% to 12.48%), cardiomyopathy (0.25% to 0.5%), heart failure (7.51% to 15.13%), peripheral vascular disease (0.8% to 3.68%), and CeVD (2.88% to 4.62%) was noted between 2006 and 2018 among cocaine users [74]. Further, the in-hospital mortality among cocaine users was 1.36% [74].

Another study described the trends in methamphetamine abuse. Among patients admitted with a primary diagnosis of HF, the proportions of patients misusing methamphetamine rose 12-fold from 547 hospitalizations in 2002 to 6,625 in 2014 [75]. For comparison, there was a 1.8- and 1.2-fold increase in HF patients hospitalized with concomitant cocaine and alcohol use disorder, respectively, during the study period [75]. However, a significantly lower proportion of methamphetamine-abusing patients with HF had CAD or AF, and a lower prevalence of traditional CVD risk factors such as diabetes, hypertension, and hyperlipidemia was observed compared to non-methamphetamine-using HF patients [75].

Although limited research is available on stimulants to draw a firm conclusion, cocaine and methamphetamine use are increasingly encountered among hospitalized patients, with some evidence to indicate a high prevalence of cardiovascular comorbidities and cost of hospitalization among cocaine users.

DISCUSSION

Consistent with the growing substance abuse problem in the US [76], the current evidence suggests an increasing prevalence of all commonly abused substances among CVD and CevD patients in the hospitalized setting. However, there are considerable differences in in-hospital outcomes and resource utilization depending on the substance. Tobacco use among hospitalized patients is well-documented, and the current evidence does not indicate an increased risk of in-hospital mortality, complications, or resource utilization among tobacco users. Cannabis use was associated with an increased risk of incident CVD in line with prior observation in population cohorts and randomized trials [77], but the current evidence does not indicate that cannabis use poses additional mortality risk or predicts higher resource utilization in CVD patients. However, cannabis use increases the occurrence of in-hospital complications, resource utilization, and mortality risk among CeVD patients. In contrast, patients with underlying AUD and OUD have an increased risk of mortality, in-hospital complications such as cardiorespiratory failure, and more resource utilization among both CVD and CeVD patients. Although only a few studies report on the impact of stimulants, there are some indications that stimulant users may incur a higher cost of hospitalization with elevated in-hospital mortality risk.

Together, these findings indicate that substance use has a significant impact on clinical outcomes of hospitalized patients with CVD and CeVD with a considerable additional burden of healthcare. Indeed, Peterson et al. showed that 10% of all hospitalized patients had a primary or secondary diagnosis of SUD and estimated the total annual cost of SUD-related hospitalization in the US at around $13 billion in 2017 [78]. AUD-related hospitalization alone accounted for 57.7% of the cost of hospitalization, followed by opioids (16.8%), stimulants (11.0%), cannabis (5.6%), and others (8.9%) [78]. Although relatively few studies report the impact of smoking status on length of stay and total hospital cost in patients with an underlying CVD, one study placed the total financial burden of adult tobacco use at around $225 billion during 2010-2014, or 11.7% of US annual healthcare spending, nearly half of which was covered by Medicare or Medicaid [79]. About 16.4% of this total cost was incurred in the in-patient setting [79].

The increased cost of hospitalization is particularly relevant in the US given that as many as 70% of patients can require in-patient readmission [80], drug-related mortalities are higher in economically distressed counties, and healthcare supply factors

have little effect on county-level mortality rates [81]. Moreover, an earlier study noted that drug-related hospitalization increases cyclically at the beginning of each month as economic aid such as supplemental security income is disbursed [82]. Therefore, the high cost of hospitalization is likely to further discourage economically disadvantaged substance users from seeking medical care driving the overall drug-related mortality trend upwards.

It is also crucial in the context of SUD to highlight that most patients tend to be polysubstance users [83]. In 2016, over half of the patients with drug-related hospitalization were diagnosed with two or more DUD, excluding tobacco and alcohol, even though tobacco is the most common secondary drug for all DUD subgroups when included in the analysis [84]. The divergent physiological effects of different substances [85,86] pose a challenge to interpreting the effects and pinning the implications of individual substance use in the real-world clinical setting. However, studies investigating the effects of polysubstance use or SUD as a whole are rare. In our recent study, we showed that 20% of young adults hospitalized in the US in 2019 with a cardiac event had a concomitant diagnosis of SUD (excluding tobacco but including alcohol), and SUD was a predictor of cardiac arrest, HF, AF, and AMI despite a lower prevalence of cardiovascular comorbidities in SUD patients compared to patients without SUD [85]. Moreover, SUD was associated with higher in-patient mortality [85]. Similarly, earlier studies in the patients with AMI plus concurrent SUD (excluding tobacco but including alcohol) or peripheral arterial disease plus concurrent SUD (excluding tobacco and alcohol) report higher risks of in-hospital mortality compared to drug-naïve patients [87].

Similarly, little information is available on the impact of Anxiolytic, Sedative, or Hypnotic (ASH) drug use in hospitalized CVD patients. However, a recent study showed that hospitalization rates of ASH patients increased over 3-fold from 96 to 299 per 100,000 NIS hospitalizations between 1998 and 2014, with higher in-patient mortality and healthcare resource utilization [88]. Given the increase in in-hospital encounters with ASH, there is an urgent need to investigate its impact on the clinical outcome of CVD patients.

CONCLUSION

In conclusion, substance use is being increasingly encountered among hospitalized patients with underlying CVD and CeVD in the US. The coexistence of SUD with CVD/CeVD complicates the management of both and is associated with a higher occurrence of cardiovascular events and healthcare resource utilization. The impact of some substances such as stimulants, anxiolytics, sedatives, or hypnotics on clinical outcomes of hospitalized patient's remains poorly studied and, given their increasing prevalence in this subpopulation, warrants further investigations.

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