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Research Article

The Risk of Infective Endocarditis among COVID-19 Patients with Non-Medical Opioid Use

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ABSTRACT

Patients with opioid use disorder are more likely to get coronavirus disease 2019 (COVID-19). Cardiovascular diseases frequently present in COVID-19 patients and can increase their susceptibility to invasive infectious diseases, such as infective endocarditis (IE). This study examines the difference in IE incidence following COVID-19 diagnosis between individuals with and without non-medical opioid use. De-identified electronic medical records data were retrieved from TriNetX, a web-based database. Patients in the U.S., aged 18-60 years, with a diagnosis of COVID-19 during January 2020 - January 2021 were included in this study. Development of IE was determined within three months after COVID-19 diagnosis. Logistic regression was conducted to estimate the risk of developing IE between COVID-19 patients with and without opioid use after propensity score matching. COVID-19 patients with non-medical opioid use had 6.8 times the risk of developing IE compared with COVID-19 patients without opioid use (95% CI: 5.44, 8.56; p<0.0001) after propensity score matching. Findings suggest a significant risk of IE among COVID-19 patients with a history of non-medical opioid use. It provides objective evidence to account for baseline opioid use in the risk assessment of IE among COVID-19 patients.

Introduction

I Opioid Use and COVID-19

The opioid epidemic has become a worldwide public health problem that has many dimensions. It is estimated that about 11.8 million U.S. citizens (4.4% of the population) have non-medical opioid use [1, 2]. This includes prescription opioids and non-medical opioids, such as heroin. In 2015, the economic and social costs of the national opioid crisis were estimated to be $504 billion [3]. A nationwide retrospective case-control study of over 73 million patients showed that patients with opioid use disorder were ten times as likely to get coronavirus disease 2019 (COVID-19) compared with patients without opioid use disorder and had significantly higher prevalence of comorbidities [4]. Among the

COVID-19 patients, compared with patients without substance use disorder, those with the disorder had significantly poorer outcomes related to hospitalization and death [4]. Opioid use may increase vulnerability to infections through inhibition of immune functions [5-7]. Cardiovascular diseases frequently present themselves in COVID-19 patients and COVID-19 has diverse cardiovascular manifestations [8]. The pharmacological effects of non-medical use of drugs may facilitate COVID-19 and its poor prognosis [4].

II Opioid Use and Infective Endocarditis (IE)

Among the debilitating consequences of intravenous opioid use are invasive infectious diseases. A large cohort study found approximately three-quarters of the hospitalizations for intravenous drug use (IDU)-associated infections were linked with injecting opioids [9]. Injecting

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heroin is common among those who use non-medical prescription opioids [10]. Among these infections, the annual hospitalization of patients with drug use-associated IE has increased up to twelve-fold between 2008 and 2017, and two-thirds of the IE hospitalizations were associated with opioids [11].

IE occurs as a result of the endothelium of the heart becoming infected and developing a lesion of a fibrin/platelet clot sheltering the infectious agents [12]. *Staphylococcus aureus* has been found to be the most prevalent causative bacteria in IE patients, followed by the viridians group streptococci and other streptococci [13, 14]. While IE is still relatively uncommon, with researchers reporting the incidence of 21.8 cases per 100,000 adults in 2016, IDU-associated IE cases have risen rapidly [15, 16]. The incidence of IE in individuals who use intravenous drugs is 50 to 100 times higher than individuals who do not use intravenous drugs [17]. There has been a massive rise in IDU-associated IE hospitalizations, growing three-folds between 2003 and 2016 [15]. Persons with IDU-associated IE hospitalization have significant morbidity, mortality, and cost. They often have long hospital stays, cardiac surgeries, recurrences, and poor long-term survivals [16-18]. The 30-day mortality from IDU-associated IE is estimated at 30% at 30 days [13]. There is a substantial financial burden on the patient as well as on the overall healthcare system. In the U.S., the costs associated with hospitalization due to IE increased from $1.58 billion in 2003 to $2.34 billion in 2016 and were significantly higher for IDU-associated IE patients when compared with non-drug use-associated IE ($291,037 vs $132,140; p<.001) [15, 18].

III COVID-19 and IE

COVID-19 is known to cause a severe inflammatory response resulting in a wide variety of cardiovascular manifestations, coagulopathy-associated complications, and damage to many organ systems [19-21]. Secondary bacterial infections have also been associated with COVID-19 in hospitalized, critically ill patients with COVID-19 [22]. The cardiovascular effects and coagulation anomalies associated with COVID-19 can increase the susceptibility to IE, even though there is limited evidence of COVID-19 concomitant with IE [19, 21]. While no population-based studies exist, a few case reports have been published documenting the incidence of IE subsequent to COVID-19 diagnosis [19, 21-25].

Some of the risk factors that contribute to IE in COVID-19 include severe inflammatory response and endothelial damage and dysfunction. The severe degree of widespread inflammation induced by this viral infection may result in damage to the endocardium, thus creating an environment where microorganisms can adhere and colonize [20]. In addition, immunosuppressive medications used in treating COVID-19 can result in an increased risk of developing infections that have the potential to spread to the endocardium via a hematogenous route [20]. These contributing factors could ultimately lead to the development of IE. However, it should be noted that researchers from Denmark reported no significant difference in overall IE incidence during the first six months of the 2020 COVID-19 pandemic [26]. The association between COVID-19, IE, and opioid use remains an unanswered question. It is important to assess the incidence of IE among COVID-19 patients and the differences by opioid use, so that management guidelines can be developed among this special sub-population group. The purpose of this research is to examine the difference in IE incidence following COVID-

19 diagnosis between individuals with and without non-medical opioid use.

Methods

I Data Source

Data were retrieved for this research from TriNetX, a web-based database and retrospective research tool that provides data on de-identified electronic medical records, including demographics, diagnoses, procedures, medications, and measurements. The data are de-identified based on the standards defined in the Health Insurance Portability and Accountability Act (HIPAA). The TriNetX database comprises real-time data from a network of over 22 healthcare organizations that include primary care and specialist providers [27].

II Sample and Variables

The sample for this study included patients in the U.S., ages 18 to 60 years, who had a diagnosis of COVID-19 between January 20, 2020, and January 20, 2021. The variable, COVID-19, was determined with the following International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes: U07.1; B34.2; B97.29; J12.81;94534-5; 94505-5; 94506-3; 94543-5; 94507-1; 94506-3; 94507-1; 94533-7; 94534-5; 94508-9; 94507-1; 94316-794500-6; 94309-2; and 9088. The code, B97.89, other viral agents as the cause of diseases classified elsewhere, was excluded. The independent variable, non-medical opioid use, was self-reported in the medical records and identified with ICD-10-CM codes F11 (opioid related disorders), F11.1 (opioid abuse), F11.2 (opioid dependence), and F11.9 (opioid use, unspecified), and their subcategories. COVID-19 patients were then categorized as those with and without non-medical opioid use. The outcome, IE, was required to have been identified at least one day after the risk factor (non-medical opioid use).

The outcome variable, IE, was identified with ICD-10-CM codes: I33 (acute and subacute endocarditis), I33.0 (acute and subacute IE), I38 (endocarditis, valve unspecified), and I39 (endocarditis and heart valve disorders in diseases classified elsewhere). This study included patients who were diagnosed with IE within 90 days of contracting COVID-19. Also included in the study were self-reported demographic variables (sex, race), socioeconomic status identified with ICD-10-CM code Z55-Z65 (based on the question whether the person had potential health hazards related to socioeconomic and psychosocial circumstances), nicotine dependence (F-17), body mass index (measured), diabetes (Z-68), and chronic lower respiratory diseases (J40-47) which are either established or potential risk factors for COVID-19 [28, 29].

III Statistical Analysis

TriNetX internal software with its custom request platform from Java 1.8.0_171, R 3.44 (R core Team, Vienna, Austria), and Python 3.6.5 provides data analysis for frequency determinations and comparisons [30]. The system provides a propensity score matching (PSM) option with recommendations based on signals or graphical representation when matching is suggested. PSM provides a sample that approximates randomization when matched and yields two balanced groups for comparative analyses. Two cohorts of patients were created by TriNetX user interface, based on specified inclusion and exclusion criteria and

matched for confounding variables using the built-in PSM capability. For this research, the matched variables included in the PSM model are sex, race, nicotine dependence, socioeconomic status, body mass index, diabetes, and chronic lower respiratory disease.

Two logistic regression models were used to examine the association between COVID-19 patients with and without opioid use and IE. The first regression analysis was based on the unadjusted model, and the second model examined the association after PSM. The risk ratio of IE for three months following COVID-19 diagnosis was determined comparing patients with and without non-medical opioid use in each of the two models.

Results

The sample included 1,631,515 individuals with COVID-19. Of this sample, 32,388 (2.9%) were diagnosed with non-medical opioid use. Compared with COVID-19 patients who did not have opioid use, patients with non-medical opioid use were significantly older (mean age 41.6 vs. 38.6 years), White (71.4% vs. 61.8%); had chronic lower respiratory tract disease (34.7% vs. 12.3%); and had nicotine dependence (58.6% vs. 8.7%). Among COVID-19 patients, 1.8% patients with non-medical opioid use and 0.09% patients with no opioid use developed IE within 90 days of contracting COVID-19 (Table 1).

Table 1: Sample characteristics of infective endocarditis among COVID-19 patients with/without non-medical opioid use.

	Before Propensity Score Matching			After Propensity Score Matching		
	Opioid Use	**No Use**	**p-value**	**Opioid Use**	**No Use**	**p-value**
	n =32,388	n=1,599,127		n =32,388	n =32,388	
	n (%)	**n (%)**		**n (%)**	**n (%)**	
Female	16,643(51.4%)	931,797 (58.3%)	<.0001	16,643 (51.4%)	16,788 (51.8%)	0.2543
White	23,129 (71.4%)	988,395 (61.8%)	<.0001	233,129 (74.1%)	23,036(71.1%)	0.4194
Black	5,980 (18.5%)	265,907 (16.6%)	<.0001	5,980 (18.5%)	6,161(19.0%)	0.0684
Chronic lower RD[1]	11,254 (34.7%)	196,455 (12.3%)	<.0001	11,254 (34.7%)	11,332 (35.0%)	0.5202
Diabetes	5,719 (17.7%)	108,270 (6.8%)	<.0001	5,719 (17.7%)	5,743 (17.7%)	0.8048
BMI	7,973 (24.6%)	177,554 (11.1%)	<.0001	7,973 (24.6%)	8,052 (24.9%)	0.4719
Nicotine dependence	18,970 (58.6%)	139,324 (8.7%)	<.0001	18,970 (58.6%)	18,977 (58.6%)	0.9555
SES[1]	7,844 (24.2%)	51,559 (3.2%)	<.0001	7,844 (24.2%)	7,835(24.2%)	0.9342
Incident IE	580 (1.8%)	1,503 (0.09%)		580 (1.8%)	85 (0.2%)	
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
Age (years)	41.6 ± 10.9	38.6 ± 12.4	<.0001	41.6 ± 10.9	41.7 ± 10.9	0.6832

[1]Note acronyms: CI: confidence Interval; IE: infective endocarditis; n: number; s: standard deviation; RD: respiratory diseases; BMI: body mass index in kg/m^2; SES: socioeconomic status, this variable included person's potential health hazards related to socioeconomic and psychosocial circumstances. The study includes data reported between 27 January 2020 and 20 January 2021.

Factors matched were sex, race, body mass index, nicotine dependence, age, chronic respiratory diseases, and socioeconomic status.

Using PSM, the sample of individuals with non-medical opioid use (n=32,388) was matched with a sample of similar characteristics and size (n=32,388), but with no opioid use (Table 1). After PSM, 580 cases of IE developed among COVID-19 patients with non-medical opioid use and 85 IE cases developed among COVID-19 patients with no opioid use within 90 days of COVID-19 diagnosis. In the unmatched sample before PSM, the risk ratio for IE within 90 days of contracting COVID-19 was 19.01 (95% CI: 17.32, 20.96; p<.0001) for participants, ages 18-60 years, who had non-medical opioid use compared with participants who did not have opioid use. In the matched sample, the risk ratio continued to be significant at 6.82 (95% CI: 5.44, 8.56; p<.0001) (Table 2).

Table 2: Risk Ratio of infective endocarditis among COVID-19 patients with/without non-medical opioid use.

	Before Propensity Score Matching (Unadjusted) Risk Ratio [95% CI]	After Propensity Score Matching Risk Ratio [95% CI]
Opioid use	19.01 (17.32, 20.96)	6.82 (5.44, 8.56)
No opioid use	Reference	Reference

Analysis for before propensity score matching based on opioid use = 32,388 and no use = 1,599, 127; and analysis after propensity score matching based on opioid use and no use = 32,388. Factors matched were sex, race, body mass index, nicotine dependence, age, chronic respiratory diseases, and socioeconomic status.

Discussion

To our knowledge, this is the first study to examine the difference in IE incidence between individuals with and without non-medical opioid use in a large cohort of COVID-19 patients. Our study showed that the risk of developing IE among COVID-19 patients with non-medical opioid use was almost seven-folds compared with COVID-19 patients without opioid use. In the data extracted from TriNetX facilities within the timeframe of January 20, 2020, to January 20, 2021, 1.8% of the sample of COVID-19 patients with opioid use developed IE within 90 days post COVID-19; and 0.09% of the sample of COVID-19 patients without opioid use developed IE within 90 days post COVID-19. By comparison, in 2016, the U.S. national incidence rate of IE was 21.80 (95% CI, 21.60-21.97) per 100,000 population adults) [15].

Researchers have found that the individuals who have been afflicted by the opioid crisis are at greater risk of a plethora of subsequent infections and health conditions, such as HIV, septic arthritis, *Staphylococcus aureus* bacteremia, thrombophlebitis, myositis, fungemia, osteomyelitis/discitis, abscesses, and IE [31]. Among these serious diseases and conditions, IE is rapidly increasing in prevalence, especially among individuals with substance use. IDU-associated hospitalizations for IE have tripled in the U.S., increasing from 4.8% in 2003 to 15.1% in 2016 [15]. The opioid crisis in the U.S. has steeply escalated IE, particularly among people who inject opioids due to reuse of needles, washers, filters, and water [5, 32].

There is scarce literature on opioid use and COVID-19 as the disease is so novel. Researchers have reported co-infection at COVID-19 diagnosis to be uncommon in the general public [33, 34]. Of the 989 consecutive patients in Spain, 7.2% had co-infections and only 1.5% of the veteran administration patients who tested positive for COVID-19 had co-infections [33, 34]. In a prospective cohort study of 277 survivors, half had post-acute COVID-19 syndrome at 10-14 weeks after disease onset [35]. Researchers for this study examined the risk of developing one infection, IE, as a sequela of COVID-19 and opioid use and found a significantly higher risk of IE among this group of COVID-19 patients with non-medical opioid use.

Strengths and Limitations

This paper has several strengths. We were able to statistically control for some of the major potential confounders. Patients diagnosed with COVID-19 may present with concomitant comorbidities and clinical conditions. Patients with comorbidities, such as respiratory diseases, hypertension, and diabetes, are more likely to have poorer health than patients without comorbidities [36]. They are also more likely to have poor prognosis and clinical outcomes [36]. In our study, COVID-19 patients with non-medical opioid use had significantly higher proportion of comorbidities. Stratification of data by opioid use clearly presents the distribution of comorbidities between the two groups.

This study has several limitations. Firstly, it is restricted to patients who were tested for COVID-19 and whose data exist in the electronic medical record of the healthcare organizations within the network. Therefore, undiagnosed COVID-19 patients could not be included in this study; although patients with IE are likely to have sought medical care. Secondly, there are several common symptoms and clinical manifestations of COVID-19 and IE, posing challenges to identify differences between a cardiac and a respiratory etiology [37]. Therefore, it is possible that symptoms related to IE might have been incorrectly attributed to a diagnosis of COVID-19 [38]. The diagnosis of IE requires transthoracic echocardiography and/or transesophageal echocardiography [38]. However, because echocardiography has a high risk of contamination from COVID-19 among healthcare personnel, it is likely that the diagnostic procedures were underperformed and, hence, IE cases were underdiagnosed during the pandemic [23, 24, 38]. Thirdly, some comorbidities were self-reported in the medical records. It is likely that opioid use was underreported. Fourthly, during the pandemic, management of IE and surgery was severely restricted at many health centers [23].

Lastly, many hospitals and healthcare centers could not perform serological testing to identify microorganisms causing IE due to the same high risk of spread of Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [23]. Although IE has heterogeneous manifestations, a clinician may be suspicious of IE when a patient presents with symptoms and has a history of IDU [13].

Conclusion

This study demonstrates significantly higher IE incidence rates among a large sample of COVID-19 patients with non-medical opioid use compared with patients without non-medical opioid use. It provides objective evidence to account for baseline opioid use in the risk assessment of IE among COVID-19 patients. Future studies should try to investigate the complex interplay between COVID-19, opioid use, and IE, especially the biological mechanism increasing the vulnerability of COVID-19 patients and causing a rise in these life-threatening infections.

Highlights

i. This is the first study to examine the difference in infective endocarditis incidence following COVID-19 diagnosis between individuals with and without non-medical opioid use.
ii. Findings demonstrate significantly higher incidence risk of infective endocarditis among a large sample of COVID-19 patients with non-medical opioid use compared with patients without non-medical opioid use.
iii. It provides objective evidence to account for baseline opioid use in the risk assessment of infective endocarditis among COVID-19 patients.

Data Availability

Data were available to WVU researchers by requesting TriNetX account through West Virginia Clinical and Translational Science Institute.

Ethics Statement

This research was acknowledged as non-human subject research by the West Virginia University Institutional Review Board (IRB), number 2010154420.

Author Contributions

Wiener RC: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision; Waters C: Study conception and design, drafting of manuscript, critical revision; Bambrick C: Drafting of manuscript, critical revision; Bhandari R: Study conception and design, interpretation of data, drafting of manuscript, critical revision.

Disclosures

Authors have no financial, economic or professional interest to disclose.

Conflicts of Interest

None.

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