Original Research Article

Myocardial Infarction, Deep Venous Thrombosis and Pulmonary Embolism in COVID-19 Hospitalizations: Stats From the Nationwide Inpatient Sample 2020.

Abstract

Background

We studied the outcomes of SARS-CoV-2 (COVID) hospitalizations and their association with myocardial injury and thrombosis. We aimed to provide further insights into the impact of COVID on modern-day healthcare.

Methods

Retrospective analysis of the National Inpatient Sample 2020 database. We used the Internation Classification of Disease Code, Tenth Edition (ICD-10) to identify all hospitalizations with COVID. We then conducted a subgroup analysis of the population of interest: those who also developed myocardial infarction, pulmonary embolism, and deep venous thrombosis.

Results

We identified 335,799 hospitalizations with COVID. Of these, 1.6% (5,355) were diagnosed with non-ST-segment myocardial infarction (COVNSTEMI). The mean age of COVID hospitalizations was 71.7, with 60.50% males. The population prevalence included 53.10% Whites, 17.80% Blacks, 19.20% Hispanics, and 4.10% Asians. The average length of stay (LOS) was 10 days, and 37.60% of patients died during hospitalization. The average cost of hospitalization (TOTCHG) was $156,633. The COVSTEMI group comprised 1,364 cases, with a mean age of 67.4, in-hospital mortality of 47.4%, and the mean TOTCHG was $177,600. The DVTCOV group comprised 2,869 cases, while the PECOV group had 4,828 cases. Male predominance was observed in both groups, with mean ages of 66 years in the DVTCOV group and 64 years in the PECOV group. The DVTCOV group had a LOS of 16 days, with 24.71% mortality, while the PECOV group had a LOS of 11 days, with 19.20% mortality. The average TOTCHG in the DVTCOV group was $248,900, whereas it was $145,378 in the PECOV group.

Conclusion

Our study revealed significant mortality rates across different groups, including 38% in COVNSTEMI, 47% in COVSTEMI, 25% in DVTCOV, and 19% in PECOV. These findings

Comment [IG1]: Please revise. Look at comments in manuscript

highlight the severity of COVID-related complications and the substantial financial burden of hospitalization.

Keywords: SARS-CoV-2, COVID-19, Pulmonary embolism, PE, Deep venous thrombosis, DVT, Hospitalization.

Introduction

Coronavirus originates from the Latin word ‘corona,’ meaning ‘crown.’ It causes various respiratory illnesses varying from mild cold to severe respiratory distress syndrome. The novel coronavirus disease, also called severe acute respiratory syndrome (SARS)-CoV-2 and coronavirus disease 2019 (COVID-19), has become a global disease burden [1]. First discovered in Wuhan city of China, towards the end of December 2019, and was declared a global pandemic by the WHO in March 2020. There have been about 6,831,681 deaths worldwide and 110,364 deaths in the United States [2,3].

COVID-19 primarily affects the respiratory system, followed by the cardiovascular, hepatic, renal, gastrointestinal, and central nervous systems [4]. Symptoms, including breathlessness and respiratory failure, are the common clinical features seen [4]. According to previous reports, among all hospitalized patients with COVID-19, approximately 14-30% developed acute respiratory distress syndrome, with an associated mortality rate of 45-75% (5).

COVID-19 has several important cardiovascular sequelae [6-8]. Patients with prior cardiovascular disease are at higher risk for adverse events from COVID-19, while individuals without a history of cardiovascular disease are at risk for new-onset cardiovascular complications [8].

Thrombotic complications in patients diagnosed with COVID-19 have become major cardiovascular complications, leading to worsened outcomes (9,10). Pulmonary embolism (PE), deep vein thrombosis, ischemic stroke, and myocardial infarction are complications described in patients associated with COVID-19 infections [9,11].

The mechanisms by which COVID- 19 causes these thrombotic complications are not fully understood. Data on the prevalence and predictors of various cardiovascular complications (e.g., MI, stroke, or acute limb ischemia) remain limited [9,10]. Research postulates include possible excessive inflammation, hypoxia, immobilization, and diffuse intravascular coagulation in the

setting of COVID-19 infection as contributors to a hypercoagulable and prothrombotic state [12,13].

There need to be more studies detailing the outcome pattern of patients hospitalized with Covid 19. This study aims to describe the outcomes of covid 19 infections among hospitalized patients with a history of pulmonary embolism and deep venous thrombosis.

Materials & Methods

Database

We retrospectively analyzed the Nationwide Inpatient Sample (NIS) database of 2020. We objectively selected our sample using the International Classification of Disease Tenth Edition (ICD-10) code. The NIS is a publicly available deidentified database that contains over 90% of hospitalizations within the United States. It includes 48 states' hospitalization records, including Maryland. It records 20% of all hospital admissions weighted to reflect the real-world population. Since the NIS is deidentified and publicly available, it does not require Institutional Review Board (IRB) approval.

Comment [IG2]: This would suggest that the infection is type A sars cov 2.

Comment [IG3]: Please add. To strengthen the data, there should be a breakdown of how many hospitals are located in each of the 48 states..

Population of Interest

We identified hospitalization with a diagnosis of COVID-19. Using the ICD-10 code U071. Within this population, we looked for hospitalizations diagnosed with lower extremity deep venous thrombosis (DVTCOV) and pulmonary embolism (PECOV). Our outcomes of interest were the length of hospitalization (LOS), the average cost of hospitalization, and in-hospital mortality. We excluded the non-covid population from this study.

Analysis

Data from 2020 was implored for the analyses. We preferred the 2020 dataset because it captured the diagnosis of the novel COVID-19 more succinctly than the 2019 dataset. The 2020 NIS database was pooled from 48 states, including Maryland, representing 97% of the United States population, making the NIS the largest inpatient database. We applied a descriptive statistical method for demographics and baseline characteristics of patients, which are presented as percentages. We reported prevalence in percentages, LOS, and TOTCH in means.

Comment [IG4]: Please revise. Add acronym for TOTCH

Variables and significance

We included demographic and socioeconomic factors, such as age, sex, and ethnicity. Results with p values of <0.05 were adopted as statistically significant. All analyses were performed using Statistical Analysis System (SAS) software version 9.4 (SAS Institute Inc., Cary, NC).

Comment [IG5]: Please revise. Change to gender

Comment [IG6]: Please revise. Add the statistical analysis used for this study

Results

We identified 335,799 hospitalizations with COVID-19, of which 5850 (1.74%) and 9381 (2.79%) had a concurrent diagnosis of lower limb deep venous thrombosis (LDVT) and pulmonary embolism (PE) respectively, (p<0.0001). In the DVTCOV group, there were 2,869 (50.60%) Whites, 1,266 (22.33%) Blacks, 1,111 (19.59%) Hispanics, and 145 (2.56%) Asians (p<0.0001). While in the PECOV group, the Whites were 4828 (53.40%), 2,098 (23.20%) Blacks, 1,482 (16.40%) Hispanics, and 209 (2.31%) Asians (p<0.0001). There was a male predominance in both groups. The DVTCOV group had 61% males (See Figure *1* below), and the PECOV group had 59% males (p<0.0001). The mean age was 66 years (SD=14.7) in the DVTCOV group and 64 years (SD=15.6) in the PECOV group. Figure *1* depicts our findings.

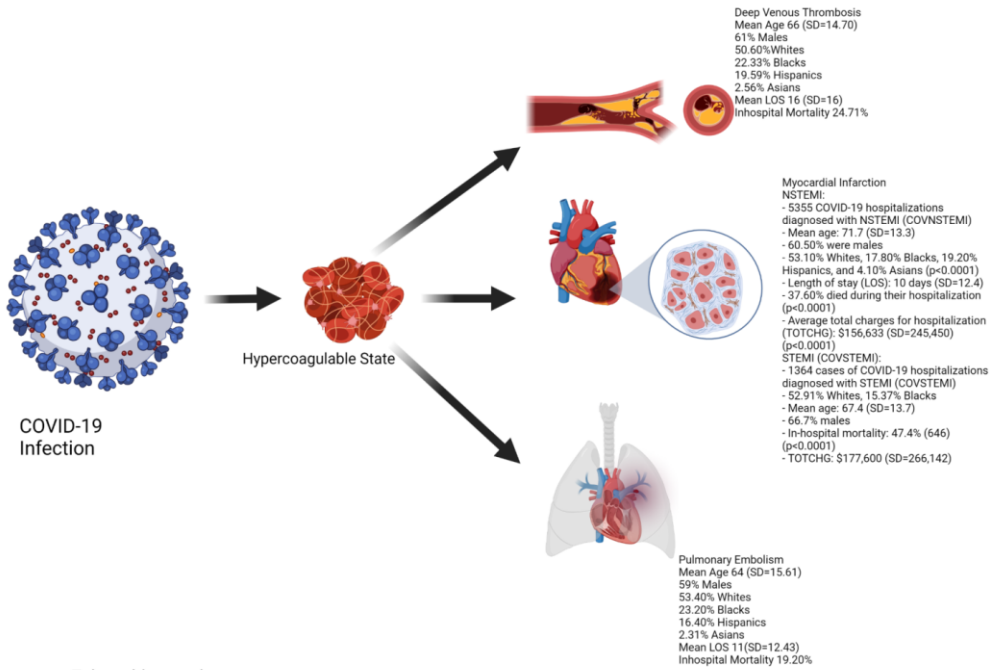
Regarding LOS and in-hospital mortality, the DVTCOV group had a mean LOS of 16 days (SD=16) and 1445 (24.71%) deaths (p<0.0001). The PECOV group had a mean LOS of 11 days (SD= 12.4) and 1799 (19.20%) deaths (p<0.0001). The average hospital charge in the DVTCOV group was $248,900 (SD= 399,860), while in the PECOV group, it was $145,378 (SD=289608) (p<0.0001). There were 5355 COVID-19 hospitalizations diagnosed with NSTEMI (COVNSTEMI), with a mean age of 71.7 (SD=13.3) and 60.50% were males, and population prevalence was 53.10% Whites, 17.80% Blacks, 19.20% Hispanics, and 4.10% Asians (p<0.0001). LOS 10 (SD=12.4), 2,012 (37.60%) died during their hospitalization (p<0.0001). TOTCHG $156,633 (SD=245,450) (p<0.0001). The COVSTEMI group had 1364 cases, 52.91% Whites, 15.37% Blacks, mean age 67.4 (SD=13.7), 66.7% males, and in-hospital mortality of 47.4% (646) (p<0.0001). The mean TOTCHG was $177600 (SD=266142). Figure *1* is an illustration of our findings.

Comment [IG7]: Must revise. The data in the result section should be presented in a table rather than in paragraph form. It was unclear whether the significant value represented a difference or a correlation between groups. I suppose these were comparisons or differences)

Comment [IG8]: Please revise. There could be misunderstanding in this sentence. Rephrase the sentence.

Comment [IG9]: Must revise. It was inconceivable for the mean to be only 145,378; the standard deviation was 28,9608, however.

Comment [IG10]: Please revise. This number should be revised.



Evbayekha et al.

Figure 1. Shows the prevalence of in-hospital mortality and ethnic distribution

Comment [IG11]: Please revise. The figure 1 from Evbayekha et al. was cited. This figure-described mechanism was not mentioned in the manuscript.

Discussion

This study revealed that PE and DVT are part of the spectrum of clinical manifestations of hospitalized COVID-19 patients. A high rate of thrombotic events has been reported in hospitalized COVID-19 patients [14]. Microvascular abnormalities in COVID-19 include endothelial inflammation, disruption of intercellular junctions, and microthrombi formation [15]. Studies have revealed a distinct COVID-19-associated coagulopathy, increased cytokines, and activation of platelets, endothelium, and complement in COVID-19. This pro-inflammatory condition results in immunothrombosis, as the host defense mechanism becomes dysregulated, leading to the excessive formation of immunologically mediated thrombi [15].

Comment [IG12]: Please consider adding. Since the data was obtained from 2020, type A COVID-19 is indicated. Compared to other types of COVID-19, there should be an explanation for concern regarding this infection.

We discovered that 3% of patients hospitalized for COVID-19 had PE, while 2% had lower limb deep venous thrombosis (LDVT). These findings of concurrent PE and DVT in hospitalized COVID-19 patients were lower compared to other studies. Erben et al. reported an incidence of 9% of hospitalized patients having DVT/PE [16], Ameri et al. found a PE rate of 7.5% in hospitalized COVID-19 patients [17], Fauvel et al. reported a PE rate of 8.3% [18]. However, Poissy et al. reported 20.6% of PE in hospitalized COVID-19 patients [19], Badr et al. noted an incidence of 32% of hospitalized COVID-19 with PE [20], Miró et al. identified 4.92% of

hospitalized COVID-19 patients having PE [21], while Benito et al., reported a PE incidence rate of 2.6% [22].

Baccellieri et al. reported 14.5% of hospitalized COVID-19 patients with lower limb DVT (DVTCOV) [14], and Franco-Moreno et al. noted an incidence of 7.7% of DVTCOV [23]. These varied incidences of DVTCOV and PECOV from multiple studies may result from the severity of the disease condition, coexisting morbidity, the age of patients, and the institution of thromboprophylaxis. Although several studies have reported a high incidence of PE in hospitalized COVID-19 patients [17-20], surprisingly, our findings revealed a low incidence of PE in hospitalized COVID-19. This may be due to the prompt initiation of thromboprophylaxis and the extent of severity of COVID-19 in patients. Studies have reported that DVTCOV mainly occurs in the infrapopliteal vein [24-25]. Cai et al. suggested that DVTCOV is associated with an increased risk of bilateral-sided DVT, especially in younger patients [24]. The study timing also has an impact on the incidence. The studies conducted before the widespread use of the COVID-19 vaccine may differ tremendously from studies after its implementation. This is supported by various data that suggest that the severity of COVID-19 infection is remarkably less in the vaccinated population [CDC].

Findings from our study revealed the mean age of patients in the DVTCOV group was 66 years, while that of the PECOV group was 64 years. This is consistent with other studies, which showed the mean age of hospitalized COVID-19 patients with DVT and/or PE was around 60 years [14-15,22]. Our findings were also consistent with those of Xu et al., which showed the mean age was 62 years for PECOV patients [26]. This may be due to other risk factors associated with this age group, including hypertension, diabetes mellitus, heart failure, smoking, obesity, dyslipidemia, malignancy, and chronic kidney disease (CKD), which are involved in ongoing inflammatory states. We discovered 50.60% of patients with lower limb DVT were whites, and 61% of patients in the DVTCOV group were males, while in the PECOV group, 53.40% were whites and 59% were male. This observation is lower when compared to other studies. Baccellieri et al. showed that 90% of hospitalized COVID-19 patients with DVT were Caucasians, while 76% of DVTCOV patients were males [14]. Ameri et al. showed that 78.8% of PECOV patients were males [17], collaborating with the Badr et al. study, which showed 78.4% of PECOV patients were males [20]. Similarly, Xu et al. also noted 73% of males in the PECOV group, but in contrast to our findings, whites made up 28% while blacks were 33% [26]. It has been shown that male gender is a non-modifiable risk factor for PE, especially in COVID-19 [18].

This study showed that the average length of stay was 16 days for hospitalized COVID-19 patients with DVT, while that for PE was 11 days. Studies have revealed that hospitalized COVID-19 with PE may require ICU care and invasive mechanical ventilation [22], which could account for the increased length of stay in the hospital. Baccellieri et al. showed that the median hospital stay for hospitalized COVID-19 patients with DVT was 24 days [14]. In comparison, Xu

et al. showed a mean length of stay of 13 days for hospitalized COVID-19 patients with PE [26], consistent with our findings for the PECOV group. Our study revealed that patients in the DVTCOV group had an increased length of hospitalization than those in the PECOV group. This may result from the sequelae that could arise in the DVTCOV group, with an increased risk of PE and the need to continuously evaluate patients using anticoagulants and regular deep vein imaging to determine its progression or resolution.

Regarding in-hospital mortality, our findings revealed that the DVTCOV group had 25% mortality while the PECOV group had 19%. Baccellieri et al. noted a mortality rate of 17% in hospitalized COVID-19 patients with DVT [14], while Pereira de Godoy et al. identified a mortality of 67% in hospitalized COVID-19 patients with DVT [27]. Fu et al. revealed in a meta-analysis that the mortality rate of COVID-19 patients with PE had significant mortality 21.9% compared to non-PE patients [28], Badr et al. revealed a mortality of 25.5% in PECOV patients [20], while Xu et al. noted a mortality rate of 20% in PECOV patients [26]. These high mortality rates in both the DVTCOV and PECOV groups may be synergistically related to other complications of COVID-19, which include myocarditis, shock, ARDS, arrhythmias, multiorgan dysfunction, etc., in conjunction with debilitating risk factors for comorbidities, immobility, older age, and ongoing systemic inflammation.

Our study showed the average hospital charge for the DVTCOV group to be $248,900, while that of the PECOV group was $145378. In comparison with patients with COVID-19 without DVT and PE, Ohsfeldt et al. showed the median cost for hospitalized COVID-19 patients to be $11,267 the cost per day was $1772. It gave an insight into the ICU cost of COVID-19 patients, with a median cost of $13,443, and the cost per day was $2902. However, patients requiring mechanical ventilation had hospital and ICU costs of $47,454 and $41,510 [29]. These findings reveal the enormous financial burden on patients in the DVTCOV and PECOV groups regarding hospital charges. The reasons for such costs could be due to various interventions undertaken during hospitalization, including invasive mechanical ventilators or extracorporeal membrane oxygenation (ECMO), length of hospital stay, ICU care, and presence of comorbidities.

Studies have shown that COVID-19 infection is involved in developing acute myocardial complications, including different forms of myocardial injury, such as myocardial infarction, myocarditis, and stress cardiomyopathy [30-31]. The suggested mechanisms include microvascular dysfunction, myocardial injury from hemodynamic instability or hypoxemia, thrombosis with coronary artery plaque destabilization due to inflammatory hypercoagulability, inflammatory myocarditis, and stress cardiomyopathy [32-34].

This study revealed 1.6% of COVNSTEMI patients' were hospitalized, while that of COVSTEMI was 0.4%. Our findings showed a smaller incidence of COVNSTEMI hospitalization compared to Majeed et al., which reported a 4.6% COVNSTEMI hospitalization [35]. In comparison, Case et al. showed an incidence of 5% COVNSTEMI hospitalization [36].

In the same vein, Rodriguez-Leor et al. observed an incidence of 9.0% of hospitalized COVSTEMI patients from all consecutive hospitalized STEMI patients [37]. In comparison, Choudry et al. reported an incidence of 33.9% of COVSTEMI patients from all consecutive hospitalized STEMI patients [38]. However, Saad et al. revealed an incidence of 0.7% COVSTEMI hospitalization in a multicenter study of out-of-hospital STEMI cases [39]; similarly, Case et al. noted an incidence of 0.7% COVSTEMI hospitalization [36]. We observed the mean age of COVNSTEMI hospitalization was 71.7 years, consistent with other studies showing that COVNSTEMI mainly occurred in older patients [35, 40]; however, the mean age of COVSTEMI was 67.4 years. These findings may be due to the prevalence of other cardiovascular risk factors (hypertension, hyperlipidemia, and smoking) that are predominant in this age group, with concurrent inflammatory comorbidities, including diabetes mellitus and chronic kidney disease. Moreover, the older age group has been known to be more susceptible to cardiovascular complications of COVID-19 [41], with this viral disease associated with endothelial dysfunction, extensive systemic inflammation, and cytokine storm, serving as an important risk factor for plaque rupture and thrombus formation [42,43].

Our study showed racial disparities in the incidence of COVNSTEMI and COVSTEMI hospitalizations, with whites accounting for 53% in both hospitalizations while blacks were 18% and 15%, respectively. This is consistent with Majeed et al., as they reported 51% of Caucasians with COVNSTEMI, with that of blacks being 18% [35]. Interestingly, Case et al. observed that black patients with acute myocardial infarction were more likely to be COVID-19 positive than whites [36]. Studies have reported that the African American population was the most hit during the COVID-19 pandemic [44-45].

The in-hospital mortality for the COVNSTEMI group was 37.60% compared with that of 47.4% in the COVSTEMI group. Majeed et al. discovered the mortality rate for the COVNSTEMI group was 37.30% [35], consistent with our findings. In comparison, Saad et al. revealed the rate of in-hospital mortality in the COVSTEMI group to be 78.5% [39], Bangalore et al. reported a mortality rate of 72% [45]; however, Hamadeh et al. reported a mortality of 12% [42-45]. It is known that patients having acute myocardial infarction with concomitant COVID-19 have a significantly increased risk of mortality compared to those without COVID-19 [36]. Multiple factors have been shown to be associated with this finding; they include the presence of high levels of inflammatory markers, older age, underlying comorbidities, need for ICU admission and mechanical ventilation, and some of these patients have coronary angiography and subsequent revascularization deferred due to their sicker clinical state [36, 39, 41]. The mean treatment cost for the COVNSTEMI group and that of the COVSTEMI group were $156,633 and $177600, respectively. Majeed et al. reported that COVNSTEMI patients' mean hospitalization cost was $149,121 [20, 35, 45]. These findings could be due to invasive cardiac interventions undertaken, including ICU admission and mechanical ventilation, length of hospitalization, treatment of comorbidities, and other complications.

Limitations of the study

The NIS database is helpful for research purposes. However, its design is an administrative tool for billing purposes and relies on the coders' accuracy, hence the possibility of overbilling, underbilling, and wrong coding. Some missing frequencies may impact analysis (although less likely) during the analyses. The NIS cannot differentiate between multiple hospitalizations for a single patient, hence can result in duplication. The NIS dataset cannot differentiate between hospitalizations vaccinated or not vaccinated against the COVID-19 virus. This made it impossible to estimate the prevalence of DVT and PE in these subgroups.

Conclusions

Our study demonstrates a significant association between myocardial infarction and thrombotic events (PE and DVT) and hospitalized COVID-19 patients. The distinct COVID-19-associated coagulopathy and microvascular abnormalities contribute to immunothrombosis and increased thrombotic risk. Racial and gender disparities are evident, with whites and males being more affected. COVID-19-related myocardial complications also contribute to higher mortality in COVSTEMI patients. Understanding these complexities is vital for optimizing patient management and healthcare planning. Further research is needed to explore tailored approaches and preventive strategies for these vulnerable patients.

Data Availability: The data used in this study was from publicly available data (NIS)

Regulatory Approval or Research Subject Protection Requirements: This manuscript does not require regulatory approval

Ethical approval: This Paper does not require ethical approval.

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Comment [IG13]: Please revise. How did the author determine that a relationship existed between groups? All data in the results section consisted of statistical comparisons.

Comment [IG14]: Please revise. Follow the template's reference guidelines. Many references lacked a publication year, displayed a double-year publication, or lacked a journal name.

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