

1 **Original Research Article**
2 **Myocardial Infarction, Deep Venous Thrombosis and Pulmonary Embolism in COVID-19**
3 **Hospitalizations: Stats from the Nationwide Inpatient Sample 2020.**

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6
7 Abstract

8 Background

9 The outcomes of SARS-CoV-2 (COVID) hospitalizations and their association with myocardial
10 injury and thrombosis were studied. We aimed to provide further insights into the impact of
11 COVID-19 on modern-day healthcare.

12 Methods

13 Retrospective analysis of the National Inpatient Sample 2020 database. We used the
14 International Classification of Disease Code, Tenth Edition (ICD-10) to identify all
15 hospitalizations with COVID-19. We then conducted a subgroup analysis of the population of
16 interest: those who also developed myocardial infarction, pulmonary embolism, and deep venous
17 thrombosis.

18 Results

19 335,799 hospitalizations with COVID. Of these, 1.6% (5,355) were diagnosed with non-ST-
20 segment myocardial infarction (COVNSTEMI) were identified. The mean age of COVID-19
21 hospitalizations was 71.7, with 60.50% males. The population prevalence included 53.10%
22 Whites, 17.80% Blacks, 19.20% Hispanics, and 4.10% Asians. The average Length of stay
23 (LOS) was 10 days, and 37.60% of patients died during hospitalization. The average cost of
24 hospitalization (TOTCHG) was \$156,633. The COVSTEMI group comprised 1,364 cases, with a
25 mean age of 67.4, in-hospital mortality of 47.4%, and the mean TOTCHG was \$177,600. The
26 DVTCOV group comprised 2,869 cases, while the PECOV group had 4,828 cases. Male
27 predominance was observed in both groups, with mean ages of 66 years in the DVTCOV group
28 and 64 years in the PECOV group. The DVTCOV group had a LOS of 16 days, with 24.71%
29 mortality, while the PECOV group had a LOS of 11 days, with 19.20% mortality. The average
30 TOTCHG in the DVTCOV group was \$248,900, whereas it was \$145,378 in the PECOV group.

31 Conclusion

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

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

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

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40 Introduction

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

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

53 COVID-19 has several important cardiovascular sequelae [6-8]. Patients with prior
54 cardiovascular disease are at higher risk for adverse events from COVID-19, while individuals
55 without a history of cardiovascular disease are at risk for new-onset cardiovascular complications
56 [8].

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

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

65 setting of COVID-19 infection as contributors to a hypercoagulable and prothrombotic state
66 [12,13].

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

70 Materials & Methods

71 Database

72 This was a retrospective analysis of the Nationwide Inpatient Sample (NIS) database of 2020.
73 We objectively selected our sample using the International Classification of Disease Tenth
74 Edition (ICD-10) code. The NIS is a publicly available de-identified database that contains over
75 90% of hospitalizations within the United States. It includes 48 states' hospitalization records,
76 including Maryland. It records 20% of all hospital admissions weighted to reflect the real-world
77 population. Since the NIS is de-identified and publicly available, it does not require Institutional
78 Review Board (IRB) approval.

79 Population of Interest

80 Hospitalized patients with a diagnosis of COVID-19 were identified. Using the ICD-10 code
81 U071. Within this population, we looked for hospitalizations diagnosed with lower extremity
82 deep venous thrombosis (DVT/COV) and pulmonary embolism (PE/COV). Our outcomes of
83 interest were the Length of hospitalization (LOS), the average cost of hospitalization, and in-
84 hospital mortality. We excluded the non-covid population from this study.

85 Analysis

86 Data from 2020 was implored for the analyses. The analyses were conducted using data from the
87 year 2020. The preference for the 2020 dataset stemmed from its more concise capture of the
88 diagnosis of the novel COVID-19 compared to the 2019 dataset. The 2020 National Inpatient
89 Sample (NIS) database was aggregated from 48 states, including Maryland, and represented 97%
90 of the entire United States population, thus establishing the NIS as the largest inpatient database
91 available. A descriptive statistical method was applied to assess the demographics and baseline
92 characteristics of the patients. The results were presented in percentages, showcasing the
93 prevalence of specific factors. The mean values were also used to report the length of Length of
94 hospital stay (LOS), and total Hospital charges (TOTCH). in means.

95 Variables and significance

96 Demographic and socioeconomic factors, such as age, gender, and ethnicity, were included. The
97 data was analyzed using s multivariate logistic regression and chi-square. Results with p values
98 of <0.05 were adopted as statistically significant. All analyses were performed using Statistical
99 Analysis System (SAS) software version 9.4 (SAS Institute Inc., Cary, NC).

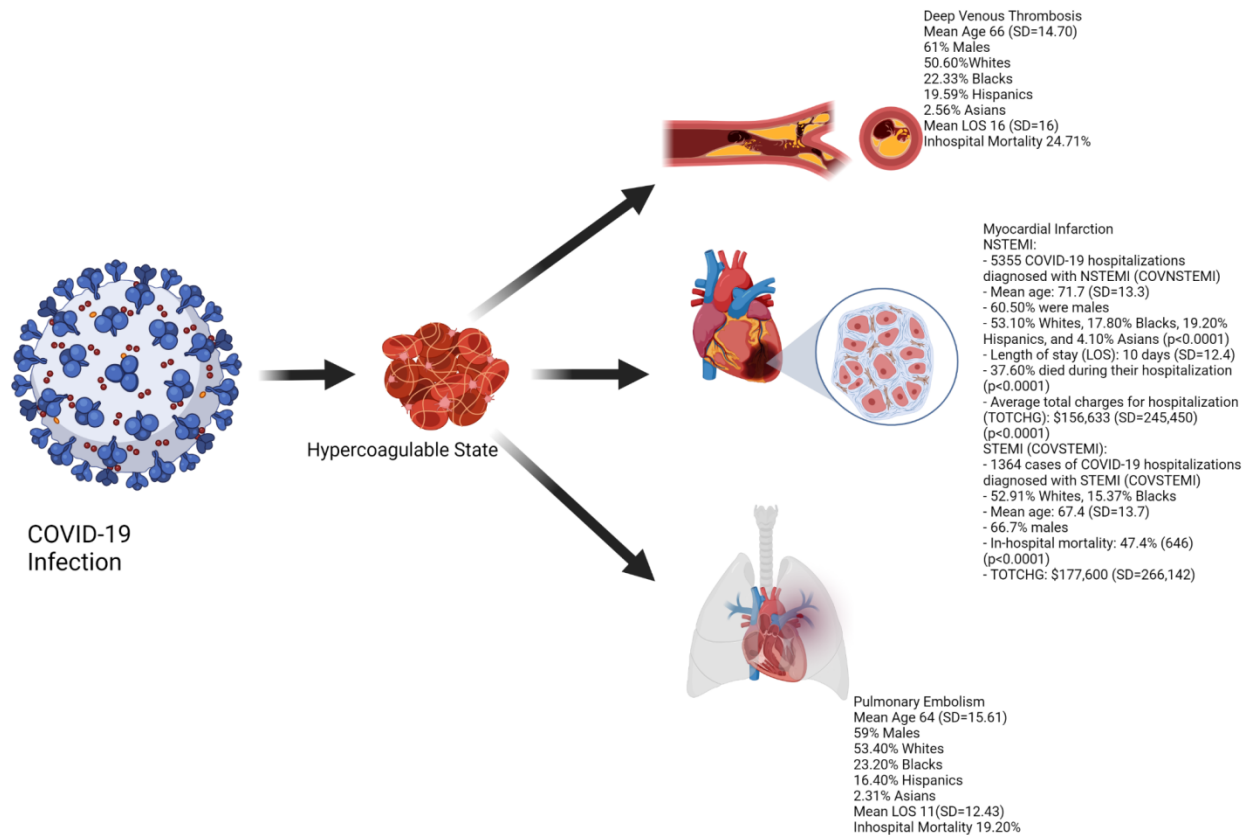
100 Results

101 A total of 335,799 hospitalizations attributed to COVID-19 were identified. Among these, 5850
102 cases (1.74%) were accompanied by a concurrent diagnosis of lower limb deep venous
103 thrombosis (LDVT), and 9381 cases (2.79%) had a simultaneous diagnosis of pulmonary
104 embolism (PE) (p<0.0001). In the DVTCOV group, there were 2,869 (50.60%) Whites, 1,266
105 (22.33%) Blacks, 1,111 (19.59%) Hispanics, and 145 (2.56%) Asians (p<0.0001). While in the
106 PECOV group, the Whites were 4828 (53.40%), 2,098 (23.20%) Blacks, 1,482 (16.40%)
107 Hispanics, and 209 (2.31%) Asians (p<0.0001). There was a male predominance in both groups.
108 The DVTCOV group had 61% males (See Figure 1 below), and the PECOV group had 59%
109 males (p<0.0001). The mean age was 66 years (SD=14.7) in the DVTCOV group and 64 years
110 (SD=15.6) in the PECOV group. Figure 1 depicts our findings.

111 Regarding LOS and in-hospital mortality, the DVTCOV group had a mean LOS of 16 days
112 (SD=16) and 1445 (24.71%) deaths (p<0.0001). The PECOV group had a mean LOS of 11 days
113 (SD= 12.4) and 1799 (19.20%) deaths (p<0.0001). The average hospital charge in the DVTCOV
114 group was \$248,900 (SD= 399,860), while in the PECOV group, it was \$145,378 (SD=289608)
115 (p<0.0001). There were 5355 COVID-19 hospitalizations diagnosed with NSTEMI
116 (COVNSTEMI), with a mean age of 71.7 (SD=13.3) and 60.50% were males, and population
117 prevalence was 53.10% Whites, 17.80% Blacks, 19.20% Hispanics, and 4.10% Asians
118 (p<0.0001). LOS 10 (SD=12.4), 2,012 (37.60%) died during their hospitalization (p<0.0001).
119 TOTCHG \$156,633 (SD=245,450) (p<0.0001). The COVSTEMI group had 1364 cases, 52.91%
120 Whites, 15.37% Blacks, mean age 67.4 (SD=13.7), 66.7% males, and in-hospital mortality of
121 47.4% (646) (p<0.0001). The mean TOTCHG was \$177600 (SD=266142). Figure 1 is an
122 illustration of our findings.

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124



125 Evbayekha et al.

126 Figure 1. The prevalence of in-hospital mortality and ethnic distribution

127 Discussion

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

136 The result showed that 3% of patients hospitalized for COVID-19 had PE, while 2% had lower
 137 limb deep venous thrombosis (LDVT). These findings of concurrent PE and DVT in hospitalized
 138 COVID-19 patients were lower compared to other studies. Erben et al. reported an incidence of
 139 9% of hospitalized patients having DVT/PE [14], Ameri et al. found a PE rate of 7.5% in
 140 hospitalized COVID-19 patients [17], Fauvel et al. reported a PE rate of 8.3% [18]. However,
 141 Poissy et al. reported 20.6% of PE in hospitalized COVID-19 patients [19], Badr et al. noted an
 142 incidence of 32% of hospitalized COVID-19 with PE [20], Miró et al. identified 4.92% of

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

145 Baccellieri et al. reported 14.5% of hospitalized COVID-19 patients with lower limb DVT
146 (DVTCOV) [14], and Franco-Moreno et al. noted an incidence of 7.7% of DVTCOV [23]. These
147 varied incidences of DVTCOV and PECOV from multiple studies may result from the severity
148 of the disease condition, coexisting morbidity, the age of patients, and the institution of
149 thromboprophylaxis. Although several studies have reported a high incidence of PE in
150 hospitalized COVID-19 patients [17-20], surprisingly, our findings revealed a low incidence of
151 PE in hospitalized COVID-19. This may be due to the prompt initiation of thromboprophylaxis
152 and the extent of severity of COVID-19 in patients. Studies have reported that DVTCOV mainly
153 occurs in the infrapopliteal vein [24-25]. Cai et al. suggested that DVTCOV is associated with an
154 increased risk of bilateral-sided DVT, especially in younger patients [24]. The study timing also
155 has an impact on the incidence. The studies conducted before the widespread use of the COVID-
156 19 vaccine may differ tremendously from studies after its implementation. This is supported by
157 various data that suggest that the severity of COVID-19 infection is remarkably less in the
158 vaccinated population [CDC].

159 Findings from our study revealed the mean age of patients in the DVTCOV group was 66 years,
160 while that of the PECOV group was 64 years. This is consistent with other studies, which
161 showed the mean age of hospitalized COVID-19 patients with DVT and/or PE was around 60
162 years [14-15,22]. Our findings were also consistent with those of Xu et al., which showed the
163 mean age was 62 years for PECOV patients [26]. This may be due to other risk factors associated
164 with this age group, including hypertension, diabetes mellitus, heart failure, smoking, obesity,
165 dyslipidemia, malignancy, and chronic kidney disease (CKD), which are involved in ongoing
166 inflammatory states. We discovered 50.60% of patients with lower limb DVT were whites, and
167 61% of patients in the DVTCOV group were males, while in the PECOV group, 53.40% were
168 whites and 59% were male. This observation is lower when compared to other studies.
169 Baccellieri et al. showed that 90% of hospitalized COVID-19 patients with DVT were
170 Caucasians, while 76% DVTCOV patients were males [14]. Ameri et al. showed that 78.8% of
171 PECOV patients were males [15], collaborating with the Badr et al. study, which showed 78.4%
172 of PECOV patients were males [20]. Similarly, Xu et al. also noted 73% of males in the PECOV
173 group, but in contrast to our findings, whites comprised 28% while blacks were 33% [26]. It has
174 been shown that male gender is a non-modifiable risk factor for PE, especially in COVID-19
175 [18].

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

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

187 Regarding in-hospital mortality, our findings revealed that the DVTCOV group had 25%
188 mortality while the PECOV group had 19%. Baccellieri et al. noted a mortality rate of 17% in
189 hospitalized COVID-19 patients with DVT [12], while Pereira de Godoy et al. identified a
190 mortality of 67% in hospitalized COVID-19 patients with DVT [27]. Fu et al. revealed in a meta-
191 analysis that the mortality rate of COVID-19 patients with PE had significant mortality of 21.9%
192 compared to non-PE patients [26]; Badr et al. revealed a mortality of 25.5% in PECOV patients
193 [18]. In comparison, Xu et al. noted a mortality rate of 20% in PECOV patients [26]. These high
194 mortality rates in both the DVTCOV and PECOV groups may be synergistically related to other
195 complications of COVID-19, which include myocarditis, shock, ARDS, arrhythmias, multiorgan
196 dysfunction, etc., in conjunction with debilitating risk factors for comorbidities, immobility,
197 older age, and ongoing systemic inflammation.

198 Our study showed the average hospital charge for the DVTCOV group to be \$248,900, while
199 that of the PECOV group was \$145,378. Compared to patients with COVID-19 without DVT and
200 PE, Ohsfeldt et al. showed the median cost for hospitalized COVID-19 patients to be \$11,267 per
201 day was, \$1,772. It gave an insight into the ICU cost of COVID-19 patients, with a median cost
202 of \$13,443, and the cost per day was \$2,902. However, patients requiring mechanical ventilation
203 had hospital and ICU costs of \$47,454 and \$41,510 [27]. These findings reveal the enormous
204 financial burden on patients in the DVTCOV and PECOV groups regarding hospital charges.
205 The reasons for such costs could be due to various interventions undertaken during
206 hospitalization, including invasive mechanical ventilators or extracorporeal membrane
207 oxygenation (ECMO), Length of hospital stay, ICU care, and presence of comorbidities.

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

214 This study revealed 1.6% of COVNSTEMI patients' were hospitalized, while that of
215 COVSTEMI was 0.4%. Our findings showed a more negligible incidence of COVNSTEMI
216 hospitalization compared to Majeed et al., which reported a 4.6% COVNSTEMI hospitalization
217 [32]. In comparison, Case et al. showed an incidence of 5% COVNSTEMI hospitalization [36].

218 In the same vein, Rodriguez-Leor et al. observed an incidence of 9.0% of hospitalized
219 COVSTEMI patients from all consecutive hospitalized STEMI patients [37]. In comparison,
220 Choudry et al. reported an incidence of 33.9% of COVSTEMI patients from all consecutive
221 hospitalized STEMI patients [38]. However, Saad et al. revealed an incidence of 0.7%
222 COVSTEMI hospitalization in a multicenter study of out-of-hospital STEMI cases [38];
223 similarly, Case et al. noted an incidence of 0.7% COVSTEMI hospitalization [33]. It was
224 observed that the mean age of COVNSTEMI hospitalization was 71.7 years, consistent with
225 other studies showing that COVNSTEMI mainly occurred in older patients [35, 40]; however,
226 the mean age of COVSTEMI was 67.4 years. These findings may be due to the prevalence of
227 other cardiovascular risk factors (hypertension, hyperlipidemia, and smoking) that are
228 predominant in this age group, with concurrent inflammatory comorbidities, including diabetes
229 mellitus and chronic kidney disease. Moreover, the older age group has been known to be more
230 susceptible to cardiovascular complications of COVID-19 [41], with this viral disease associated
231 with endothelial dysfunction, extensive systemic inflammation, and cytokine storm, serving as an
232 essential risk factor for plaque rupture and thrombus formation [42,43].

233 Our study showed racial disparities in the incidence of COVNSTEMI and COVSTEMI
234 hospitalizations, with whites accounting for 53% in both hospitalizations while blacks were 18%
235 and 15%, respectively. This is consistent with Majeed et al., as they reported 51% of Caucasians
236 with COVNSTEMI, with that of blacks being 18% [32]. Interestingly, Case et al. observed that
237 black patients with acute myocardial infarction were more likely to be COVID-19 positive than
238 whites [33]. Studies have reported that the African American population was the most hit during
239 the COVID-19 pandemic [44-45].

240 The in-hospital mortality for the COVNSTEMI group was 37.60% compared with that of 47.4%
241 in the COVSTEMI group. Majeed et al. discovered the mortality rate for the COVNSTEMI
242 group was 37.30% [32], consistent with our findings. In comparison, Saad et al. revealed the rate
243 of in-hospital mortality in the COVSTEMI group to be 78.5% [37], Bangalore et al. reported a
244 mortality rate of 72% [43]; however, Hamadeh et al. reported a mortality of 12% [42-45]. It is
245 known that patients having acute myocardial infarction with concomitant COVID-19 have a
246 significantly increased risk of mortality compared to those without COVID-19 [36]. Multiple
247 factors are associated with this finding; they include the presence of high levels of inflammatory
248 markers, older age, underlying comorbidities, need for ICU admission and mechanical
249 ventilation, and some of these patients have coronary angiography and subsequent
250 revascularization deferred due to their sicker clinical state [36, 39, 41]. The mean treatment cost
251 for the COVNSTEMI group and that of the COVSTEMI group were \$156,633 and \$177600,
252 respectively. Majeed et al. reported that COVNSTEMI patients' mean hospitalization cost was
253 \$149,121 [20, 35, 45]. These findings could be due to invasive cardiac interventions undertaken,
254 including ICU admission and mechanical ventilation, Length of hospitalization, treatment of
255 comorbidities, and other complications.

256 Limitations of the study

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

265 Conclusions

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

274 Data Availability: The data used in this study was from publicly available data (NIS)
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276 **Regulatory Approval or Research Subject Protection Requirements: This manuscript does**
277 **not require regulatory approval**

278 Ethical approval: This Paper does not require ethical approval.

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