Abstract

Background
Clostridium difficile infection (CDI) is associated with high mortality. Studies have shown an increased rate of venous thromboembolism (VTE) in patients with CDI. However, literature regarding the impact of CDI on outcomes of VTE-related hospitalizations is scarce. Our study aimed to assess the impact of CDI on in-hospital outcomes among VTE hospitalizations.

Methods
The 2016 National Inpatient Sample (NIS) was used to identify all adult hospitalizations in the United States with a primary discharge diagnosis of acute VTE. Hospitalizations with deep vein thrombosis (DVT) or pulmonary embolism (PE) were included under VTE. The sample was stratified based on the presence or absence of active CDI. Chi-square test and weighted Student’s t-test were used to analyze categorical and continuous variables, respectively. The adjusted odds ratio (OR) for clinical outcomes were calculated using multivariate logistic regression analysis. Subgroup analyses for DVT and PE hospitalizations were performed. All analyses were completed in SAS (SAS Institute Inc., Cary, NC), and a p-value of <0.05 was considered statistically significant.

Results
We identified 382,585 weighted hospitalizations for VTE. Among them, 0.8% had concomitant CDI. The presence of CDI was associated with a statistically significant increase in in-hospital mortality (6% vs. 3%), hospitalization cost ($147,356.5 vs. $55,193), and length of stay (13.7 vs. 5.4 days). There were more incidents of bleeding and acute respiratory failure requiring prolonged ventilation in patients with CDI. The odds of stroke were significantly higher in patients with CDI and DVT.

Conclusion
CDI independently increased in-hospital mortality in VTE. Preventing CDI in the VTE population may mitigate complications, improve in-hospital outcomes, and reduce treatment costs.

Introduction
Clostridium difficile infection (CDI) is a leading cause of nosocomial infection, resulting in a significant healthcare burden, morbidity, and mortality [1]. According to the literature, there was a two-fold increase in the incidence of CDI among hospitalized adults in the United States between 2001 and 2010, with more recent data suggesting approximately 365,000 CDI cases reported in the United States annually [2].

It is well-known that the pathogenesis of venous thromboembolism (VTE) involves the Virchow’s triad: stasis, endothelial injury, and hypercoagulability. Various studies have shown an increased rate of VTE in patients with CDI, likely secondary to the formation of a proinflammatory state [3,4]. However, data is scarce regarding the impact of CDI on outcomes of VTE hospitalizations. It is possible that CDI leads to poorer outcomes in these patients, whether due to a direct effect of CDI (prolonged hospital stay and

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associated complications), or due to the proposed effect of CDI on coagulability, which might be seen in terms of sequelae of clot extension, anticoagulation failure, embolic events, or bleeding complications. In this study, we sought to assess the impact of the presence or absence of CDI on outcomes of VTE hospitalizations.

Materials And Methods

Data were extracted from the 2016 Healthcare Cost and Utilization Project’s (HCUP) National Inpatient Sample (NIS). The NIS is the largest publicly available database in the United States and approximates a 20% stratified sample of discharges from US hospitals. In our analysis, all patients of ≥18 years of age who were identified with VTE-related hospitalizations (pulmonary embolism (PE) or deep vein thrombosis (DVT)) were included. Furthermore, VTE hospitalizations with and without CDI were identified, and their clinically relevant outcomes were compared. Given the publicly available nature of the dataset, the study was exempted from institutional review board (IRB) approval.

All statistical analyses followed the sample design elements (clusters, strata, and weights) provided by the NIS [5]. Continuous variables were reported as weighted means ±standard error (SE), and categorical variables were reported as weighted numbers and percentages. The standard errors of weighted means were estimated by using the Taylor linearization method that incorporates the sample design. Length of stay and total cost of hospitalization were normalized by log-transformation for all analyses, and antilog-transformed results from the multivariate linear regression models were then reported. The total costs of hospitalization were inflation-adjusted for 2018 using Consumer Price Index data provided by the US Department of Labor.

The differences in outcomes variables between hospitalizations with and without CDI were compared using weighted Student’s t-tests for continuous variables, and Rao-Scott modified chi-square tests for categorical variables. A multivariate logistic regression model was used to estimate the odds ratio (OR) of clinical outcomes after adjusting for patient demographics, hospital bed size, hospital location/teaching status, insurance type, household income, and relevant comorbidities, and incorporating hospital as a random effect. Subgroup analyses were conducted separately for hospitalizations with PE and DVT, again comparing in-hospital outcomes for those with and without CDI. Unadjusted and adjusted ORs and their corresponding 95% confidence intervals (CI) were reported. All statistical analyses were performed using the SAS Survey Procedures (SAS 9.4; SAS Institute Inc., Cary, NC). Statistical significance was defined by two-sided p-values of <0.05.

Results

We identified 382,585 admissions with VTE. Of those, 3,080 (0.8%) had a concomitant diagnosis of CDI. The VTE population with CDI had a higher mean age compared to the VTE population without CDI (66.2 vs. 63.1 years, respectively). No statistically significant difference was found in terms of gender, race, or mean household income between both populations (Table 1).

| Characteristics                  | VTE hospitalizations with Clostridium difficile infections | VTE hospitalizations without Clostridium difficile infections | P-value |
|---------------------------------|----------------------------------------------------------|-------------------------------------------------------------|---------|
| N (unweighted)                  | 616                                                      | 76,517                                                      |         |
| N (weighted)                    | 3,080                                                    | 382,585                                                     |         |
| Age, years                      | Mean 66.2, SE 0.6                                        | Mean 63.1, SE 0.1                                           | <.0001  |
| Length of stay, days            | 13.7, SE 0.6                                            | 5.4, SE 0.03                                               | <.0001  |
| Total cost of hospitalization, $ | 147,357, SE 12,734                                      | 55,193, SE 764                                             | <.0001  |
| Gender                          |                                                          |                                                             |         |
| Male                            | 1,405, 45.60%                                           | 182,305, 47.70%                                            | 0.32    |

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| Female       | 1,675 | 54.40% | 200,280 | 52.30% |
|-------------|-------|--------|---------|--------|
| Race/ethnicity |       |        |         |        |
| White       | 2,250 | 73.10% | 271,240 | 70.90% | 0.2  |
| Black       | 440   | 14.30% | 69,680  | 18.20% |
| Hispanic    | 235   | 7.60%  | 26,865  | 7%     |
| Asian or Pacific Islander | 45   | 1.50%  | 4,075   | 1.10%  |
| Native American | 15   | 0.50%  | 1,490   | 0.40%  |
| Other       | 95    | 3.10%  | 9,235   | 2.40%  |
| Insurance type |     |        |         |        |
| Medicare    | 2,010 | 65.30% | 202,675 | 53%    | < .0001 |
| Medicaid    | 365   | 11.90% | 48,995  | 12.80% |
| Private     | 570   | 18.50% | 103,955 | 27.20% |
| Self-pay    | 65    | 2.10%  | 14,240  | 3.70%  |
| Other       | 65    | 2.10%  | 11,170  | 2.90%  |
| Hospital region |     |        |         |        |
| Northeast   | 645   | 20.90% | 76,725  | 20.10% | 0.001 |
| Midwest     | 615   | 20%    | 85,945  | 22.50% |
| South       | 1,135 | 36.90% | 157,225 | 41.10% |
| West        | 685   | 22.20% | 62,690  | 16.40% |
| Hospital location/teaching status |     |        |         |        |
| Rural       | 125   | 4.10%  | 33,505  | 8.80%  | < .0001 |
| Urban non-teaching | 850 | 27.60% | 104,790 | 27.40% |
| Urban teaching | 2,105 | 68.30% | 244,290 | 63.90% |
| Hospital bed size |     |        |         |        |
| Small       | 440   | 14.30% | 71,310  | 18.60% | 0.026 |
| Medium      | 920   | 29.90% | 110,225 | 28.80% |
| Large       | 1,720 | 55.80% | 201,050 | 52.60% |
| Household income |     |        |         |        |
| Q1          | 800   | 26%    | 116,220 | 30.40% | 0.075 |
| Q2          | 895   | 29.10% | 97,850  | 25.60% |
| Q3          | 750   | 24.40% | 91,365  | 23.90% |
| Q4          | 635   | 20.60% | 77,150  | 20.20% |
| In-hospital mortality | 185 | 6%    | 11,385  | 3%    | 0.002 |
| Comorbidities |     |        |         |        |
| Renal failure | 635 | 20.60% | 50,745  | 13.30% | < .0001 |
| Deficiency anemia | 1,105 | 35.90% | 82,910  | 21.70% | < .0001 |
The VTE population with concomitant CDI was found to have higher prevalence of comorbidities compared to those without CDI, including renal failure (20.6% vs. 13.3%), congestive heart failure (35.9% vs. 21.7%), complicated diabetes (13.5% vs. 9.7%), metastatic cancer (13.3% vs. 7.5%), liver disease (6% vs. 3.6%), deficiency anemia (35.9% vs. 21.7%), coagulopathy (12% vs. 7.8%) and paralysis (7.1% vs. 3.2%). They were also more likely to present with sepsis (8.1% vs. 1.3%). However, the VTE population without CDI had a higher prevalence of hyperlipidemia (29.5% vs. 24.5%), obesity (21.2% vs. 13%), smoking (14.2% vs. 10.6%), and prior VTE (13.5% vs. 10.7%). VTE hospitalizations with CDI were found to have increased in-hospital mortality (6% vs. 3%, adjusted OR: 1.54, 95% CI: 1.09–2.17, p = 0.014), longer mean length of hospital stay (13.7 days vs. 5.4 days, adjusted OR: 2.10, 95% CI: 1.98–2.24, p < 0.001) and hospitalization cost ($147,356.5 vs. $55,193, adjusted OR: 2.01, 95% CI: 1.87–2.17, p < 0.001) (Table 2).

### TABLE 1: Baseline characteristics of the study population

| Variables                             | VTE patients                  | P-value |
|---------------------------------------|-------------------------------|---------|
|                                       | No Clostridium difficile infections | Clostridium difficile infections |         |
| In-hospital mortality                 |                               |         |
| Incidence, %                          | 3                             | 6       |
| Adjusted OR (95% CI)*                 | Ref                           | 1.54 (1.09–2.17) | 0.014   |

VTE: venous thromboembolism; SE: standard error
| Condition                        | Incidence, % | Adjusted OR (95% CI)* | Ref | Adjusted parameter estimate (95% CI)*† | Ref | Adjusted OR (95% CI)*† | Ref | Adjusted parameter estimate (95% CI)*† | Ref |
|---------------------------------|--------------|-----------------------|-----|----------------------------------------|-----|-----------------------|-----|----------------------------------------|-----|
| AKI                             | 9.9          | 2.32 (1.9–2.84)       | 2.32 (1.9–2.84) | < .0001                               |     | 2.32 (1.9–2.84)       | 2.32 (1.9–2.84) | < .0001                               |     |
| AKI-D                           | 0.3          | 1.6 (0.58–4.42)       | 1.6 (0.58–4.42) | 0.37                                  |     | 1.6 (0.58–4.42)       | 1.6 (0.58–4.42) | 0.37                                  |     |
| Shock state                     | 1.9          | 3.21 (2.35–4.39)      | 3.21 (2.35–4.39) | < .0001                               |     | 3.21 (2.35–4.39)      | 3.21 (2.35–4.39) | < .0001                               |     |
| Bleeding                        | 6.4          | 2.55 (2.05–3.17)      | 2.55 (2.05–3.17) | < .0001                               |     | 2.55 (2.05–3.17)      | 2.55 (2.05–3.17) | < .0001                               |     |
| DIC                             | 0.1          | 0.8 (0.11–6.01)       | 0.8 (0.11–6.01) | 0.83                                  |     | 0.8 (0.11–6.01)       | 0.8 (0.11–6.01) | 0.83                                  |     |
| Acute respiratory failure       | 7.4          | 2.22 (1.8–2.76)       | 2.22 (1.8–2.76) | < .0001                               |     | 2.22 (1.8–2.76)       | 2.22 (1.8–2.76) | < .0001                               |     |
| Stroke                          | 0.4          | 0.76 (0.24–2.39)      | 0.76 (0.24–2.39) | 0.64                                  |     | 0.76 (0.24–2.39)      | 0.76 (0.24–2.39) | 0.64                                  |     |
| Mechanical ventilation for >96 hours | 1.2      | 4.33 (3.05–6.16)      | 4.33 (3.05–6.16) | < .0001                               |     | 4.33 (3.05–6.16)      | 4.33 (3.05–6.16) | < .0001                               |     |
| Length of stay                  | 5.4 ±0.03    | 13.7 ±0.6             | 13.7 ±0.6        | < .0001                               |     | 13.7 ±0.6             | 13.7 ±0.6        | < .0001                               |     |
| Average hospital costs          | 55,193 ±764  | 147,356.5 ±12,734.1   | 147,356.5 ±12,734.1 | < .0001                               |     | 147,356.5 ±12,734.1   | 147,356.5 ±12,734.1 | < .0001                               |     |

**TABLE 2: In-hospital outcomes in VTE hospitalizations with and without Clostridium difficile infections**

*Adjusted for age, race, sex, insurance status, hospital characteristics, and all significant comorbidities listed in Table 1

†Parameter estimates represent the antilog of the b regression coefficients obtained from the log-transformed regression models

VTE: venous thromboembolism; OR: odds ratio; CI: confidence interval; AKI: acute kidney injury; AKI-D: acute kidney injury requiring dialysis; DIC: disseminated intravascular coagulation; SE: standard error
Notably, CDI in VTE hospitalizations was independently associated with increased risk of bleeding, acute kidney injury (AKI), shock state, acute respiratory failure requiring mechanical ventilation for >96 hours (p: <0.001 for all; adjusted for age, race, sex, insurance status, hospital characteristics, and all significant comorbidities listed in Table 1) (Figure 1). Figure 1: Adjusted odds ratio for in-hospital outcomes in VTE hospitalizations with Clostridium difficile infections

VTE: venous thromboembolism; OR: odds ratio; CI: confidence interval; AKI: acute kidney injury

Subgroup analyses of DVT vs. PE hospitalizations were also performed. For both groups, hospitalizations with concomitant CDI had an increased risk of AKI, bleeding, and acute respiratory failure needing mechanical ventilation for >96 hours (p: <0.001 for all, adjusted for age, race, sex, insurance status, hospital characteristics, and all significant comorbidities listed in Table 1) (Table 3).

| Variables          | PE hospitalizations  | DVT hospitalizations |
|--------------------|----------------------|----------------------|
|                    | No CDI infections    | CDI infections       | P-value | No CDI infections | CDI infections | P-value |
| In-hospital mortality | Incidence, %        |                      |         | Incidence, %      |                |         |
| Incidence, %        | 4.5                  | 7.9                  | 0.8     | 1.9              |                |         |
| Adjusted OR (95% CI)* | Ref                 | 1.39 (0.97–2.0)     | 0.072   | Ref              | 1.85 (0.57–5.96) | 0.31 |
| AKI                |                      |                      |         |                  |                |         |
| Incidence, %        | 11.7                 | 24.7                 | 7       | 23.7             |                |         |
| Adjusted OR (95% CI)* | Ref                 | 2.07 (1.63–2.62)    | < .0001 | Ref              | 2.97 (1.97–4.48) | < .0001 |
| AKI-D               |                      |                      |         |                  |                |         |
| Incidence, %        | 0.4                  | 0.2                  | 0.2     | 1.9              |                |         |
| Adjusted OR (95% CI)* | Ref                 | 0.48 (0.07–3.5)     | 0.47    | Ref              | 6.38 (1.83–22.15) | 0.0036 |
| Shock state         |                      |                      |         |                  |                |         |
| Incidence, %        | 3                    | 10.6                 | 0.3     | 1.3              |                |         |
| Adjusted OR (95% CI)* | Ref                 | 2.97 (2.15–4.11)    | < .0001 | Ref              | 2.51 (0.59–10.62) | 0.2122 |
| Bleeding            |                      |                      |         |                  |                |         |
| Incidence, %        | 7.4                  | 18.7                 | 5.3     | 14.1             |                |         |
### TABLE 3: In-hospital outcomes in DVT/PE hospitalizations with and without Clostridium difficile infections

*Adjusted for age, race, sex, insurance status, hospital characteristics, and all significant comorbidities listed in Table 1

†Parameter estimates represent the antilog of the b regression coefficients obtained from the log-transformed regression models

|                                | Adjusted OR (95% CI)* | Ref | 2.47 (1.92–3.17) | < .0001 | Ref | 2.69 (1.7–4.27) | < .0001 |
|--------------------------------|------------------------|-----|------------------|---------|-----|------------------|---------|
| **DIC**                        |                        |     |                  |         |     |                  |         |
| Incidence, %                   |                        | 0.2 | 0.2              | 0.0004  | 0   |                  | 0       |
| Adjusted OR (95% CI)*          | Ref                    |     | 0.91 (0.12–6.95) | 0.93    | Ref | NA               | NA      |
| Acute respiratory failure      |                        |     |                  |         |     |                  |         |
| Incidence, %                   | 11.2                   | 23.3 | 1.3              | 5.1     |     |                  |         |
| Adjusted OR (95% CI)*          | Ref                    |     | 1.99 (1.58–2.51) | < .0001 | Ref | 2.73 (1.24–5.99) | 0.0125  |
| **Stroke**                     |                        |     |                  |         |     |                  |         |
| Incidence, %                   | 0.6                    | 0.2  | 0.1              | 1.3     |     |                  |         |
| Adjusted OR (95% CI)*          | Ref                    |     | 0.24 (0.03–1.75) | 0.16    | Ref | 6.21 (1.34–28.73) | 0.0195  |
| Mechanical ventilation for >96 hours |                |     |                  |         |     |                  |         |
| Incidence, %                   | 1.8                    | 8.1  | 0.2              | 1.3     |     |                  |         |
| Adjusted OR (95% CI)*          | Ref                    |     | 3.93 (2.72–5.67) | < .0001 | Ref | 4.5 (1.02–19.8)  | 0.0484  |
| **Length of stay**             |                        |     |                  |         |     |                  |         |
| Mean ±SE                       | 5.9 ±0.05              | 14.5 ±0.8 | 5.0 ±0.04 | 12.5 ±1.2 |     |                  |         |
| Adjusted parameter estimate (95% CI)*† | Refer | | 2.05 (1.88–2.23) | < .0001 | Ref | 1.99 (1.76–2.24) | < .0001 |
| **Average hospital costs**     |                        |     |                  |         |     |                  |         |
| Mean ±SE                       | 60,903.1 ±985.7        | 166,302.7 ±17,358.8 | < .0001 | 47,306.4 ±655 | 108,513.9 ±12,478 | < .0001 |
| Adjusted parameter estimate (95% CI)*† | Refer | | 2.16 (2.00–2.33) | Ref | 1.84 (1.59–2.14) |         |

The odds of shock were greater in CDI and PE group (10.6% vs. 3%, adjusted OR: 2.97, 95% CI: 2.15–4.11, p: <0.001) (Figure 2), whereas the odds of stroke were higher in hospitalizations with CDI and DVT (1.5% vs. 0.1%, adjusted OR: 6.21, 95% CI: 1.5–25.71, p: <0.01) (Table 3) (Figure 3).
FIGURE 2: Adjusted odds ratio for in-hospital outcomes in PE hospitalizations with Clostridium difficile infections

PE: pulmonary embolism; AKI: acute kidney injury; OR: odds ratio; CI: confidence interval

FIGURE 3: Adjusted odds ratio for in-hospital outcomes in DVT hospitalizations with Clostridium difficile infections

DVT: deep vein thrombosis; AKI: acute kidney injury; AKI-D: acute kidney injury requiring dialysis; OR: odds ratio; CI: confidence interval

Discussion

CDIs pose a significant burden on healthcare systems, not just in the United States but across the world [6]. Past studies have demonstrated a two-fold increase in the incidence of CDI among hospitalized adults in the United States between 2001-2010 [2]. Data from 2012 showed that annual cost for management of CDI amounted to approximately $800 million in the United States and €3,000 million in Europe, barring the costs for secondary complications [7]. While the rate of healthcare-associated CDI decreased in the United States between 2011-2017 by an estimated 36%, the rate of community-associated CDI has not changed in that time and now accounts for nearly half of all infections [8]. CDI has also been shown to have an independent association with the development of VTE, and findings of associations between acute infections and increased risk of VTE support the hypothesis that CDI may be causing a proinflammatory, procoagulant state in the human body [9-11].

While the association between CDI and increased risk of VTE is known, data regarding the impact of CDI on outcomes of these cases remain scarce. Our study, to the best of our knowledge, is the first of its kind to assess the outcomes of VTE in the presence of CDI, and the data we present here suggest that the presence of CDI independently causes a substantial increase in healthcare costs. This can be seen directly in terms of increased raw cost of VTE hospitalizations, and also in terms of increased mean length of stay, AKI, bleeding complications, shock, and the need for mechanical ventilation.
Fully understanding the burden CDI places on healthcare is critical to ensure adequate allocation of resources to CDI treatment and prevention efforts. Also, understanding its impact in the setting of DVT and PE admissions, themselves sources of considerable morbidity and healthcare cost, would seem essential. This is of particular importance when considering the apparent success of infection control programs and reduced prescriptions of fluoroquinolones in reducing the rates of healthcare-associated CDI, suggesting that there are interventions whose widespread adoption could further reduce rates of CDI and its associated complications [12].

Many of the clinical outcomes presented here can be attributed to CDI, causing a systemic proinflammatory state, with hypovolemia secondary to gastrointestinal losses, and third spacing secondary to inflammation. This drives outcomes like shock, AKI, and the need for dialysis. CDI patients with VTE outcomes seem to have more underlying comorbidities in general, and these, in turn, may put them at a higher risk of prolonged hospital stay and poor clinical outcomes. However, the adverse outcomes mentioned here were found after adjusting for these comorbidities, suggesting that CDI is an independent cause of serious adverse events in VTE hospitalizations.

Both the DVT and PE subgroups showed an increased risk of the need for prolonged mechanical ventilation (>96 hours) for CDI hospitalizations, which is somewhat surprising. In PE patients, it might reflect a combination of both ventilation/perfusion (V/Q) mismatch from PE and systemic inflammatory state from CDI. However, the presence of the effect in DVT hospitalizations, with a comparable OR (3.93 in PE patients, 4.5 in DVT patients), suggests that the presence of thrombotic events marks greater disease severity in CDI. Though speculative, it prompts a need for further investigation, both in terms of research, and a higher index of suspicion for thrombotic events in CDI hospitalizations. The elevated risk of shock in hospitalizations with PE and CDI versus PE without CDI is less surprising and might be explained by the addition of obstructive elements to existing hypovolemic and distributive shock from CDI. Interestingly, the population with VTE but no CDI had a higher prevalence of hyperlipidemia, obesity, smoking, and prior VTE. All of these are independent risk factors for VTE, and their decreased prevalence in the VTE with CDI group further supports the theory that CDI is a separate cause of thrombotic disease burden. Further studies are warranted to determine the causality of these outcomes, which may impact how we approach treating patients with CDI while being cognizant of the possible complications caused by VTEs in this high-risk population. As for the marked increase in the incidence of stroke noted among CDI hospitalizations with DVT, which was absent among hospitalizations with CDI and PE, it is challenging to explain. While risk factors for arterial and venous thrombotic diseases are shared, the stroke itself being a notorious risk factor for the development of recurrent CDIs, and for VTE, the risks of developing PE and DVT after stroke are very similar [13]. This may be a fruitful area for further study.

Our study has a few limitations. Firstly, our analysis was retrospective in nature. Hence, it was difficult to ascertain the causal relationship between CDI and VTE. Secondly, given the observational nature of the study, we found it hard to identify and adjust for all possible confounders. Thirdly, as a database study, it was implausible to determine with certainty if a specific diagnosis had been made during the hospitalization of record or if a patient had carried a history of such a diagnosis. Lastly, one NIS entry is equivalent to one hospitalization. Hence, a single patient may account for multiple entries if hospitalized more than once within the study period. However, despite these limitations, we believe the results still highlight the significance of CDI infections in patients admitted for VTE.

Conclusions
Our study, to the best of our knowledge, is the first study of its kind to assess the outcomes of VTE in the presence of CDI. CDI remains a considerable burden in terms of increased length of hospital stay and healthcare costs, and it independently increases the risk of in-hospital mortality and various complications in VTE patients. Taking adequate steps to prevent CDI in the VTE population may avert unforeseen complications, improve in-hospital outcomes, and reduce healthcare costs.

Appendices

| Deep vein thrombosis | Pulmonary embolism | Clostridium difficile infections | Smoking | Alcohol abuse | Prior venous thromboembolism | Hyperlipidemia | Obesity | Congestive heart failure | Peripheral vascular disease | Diabetes, uncomplicated |
|----------------------|---------------------|---------------------------------|---------|--------------|-----------------------------|----------------|---------|------------------------|---------------------------|------------------------|
| A62401’              | A62592’             | A62401’                         | F172700’| F10101’      | Z86718’                     | E785’          | E6601’  | I099’                  | I700’                     | E100’                  |
| A62402’              | A62592’             | A62401’                         | F172700’| F10111’      | I62701’                     | E6601’         | I110    | I701’                  | E101’                     |
| A62403’              | A62599’             | A62407’                         | F172700’| F10120’      | I62702’                     | E6601’         | I130    | I70201’                | E109’                     |
| A62409’              | A62599’             | A62407’                         | F172700’| F101121’     | I62703’                     | E6601’         | I132    | I70202’                | E110’                     |

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| F17209' | F10129' | IB2709' | "E663' | I255 | I70203' | E111 |
| F17210' | F1014' | IB2711' | "E668' | I420 | I70208' | E119 |
| F17211' | F10150' | IB2712' | "E669' | I425 | I70209' | E120 |
| F17213' | F10151' | IB2713' | "Z6825' | I429 | I70211' | E121 |
| F17218' | F10159' | IB2719' | "Z6826' | I43 | I70212' | E129 |
| F17219' | F10180' | IB2721' | "Z6827' | P290 | I70213' | E130 |
| F17220' | F10181' | IB2722' | "Z6828' | I501' | I70218' | E131 |
| F17221' | F10182' | IB2723' | "Z6829' | I5020' | I70219' | E139 |
| F17223' | F10188' | IB2729' | "Z6830' | I5021' | I70221' | E140 |
| F17228' | F1019' | IB2501' | "Z6831' | I5022' | I70222' | E141 |
| F17229' | IB2502' | "Z6832' | I5023' | I70223' | E149 |
| F17290' | IB2503' | "Z6833' | I5030' | I70228' | E1100' |
| F17291' | IB2509' | "Z6834' | I5031' | I70229' | E1101' |
| F17290' | IB2511' | "Z6835' | I5032' | I70231' |
| F17298' | IB2512' | "Z6836' | I5033' | I70232' |
| F17299' | IB2513' | "Z6837' | I5040' | I70233' |
| IB2519' | "Z6838' | I5041' | I70234' |
| IB2521' | "Z6839' | I5042' | I70235' |
| IB2522' | "Z6841' | I5043' | I70238' |
| IB2523' | "Z6842' | I50810' | I70239' |
| IB2529' | "Z6843' | I50811' | I70241' |
| IB2531' | "Z6844' | I50812' | I70242' |
| IB2532' | "Z6845' | I50813' | I70243' |
| IB2533' | I50814' | I70244' |
| IB2539' | I5082' | I70245' |
| IB2541' | I5083' | I70248' |
| IB2542' | I5084' | I70249' |
| IB2543' | I5089' | I7025' |
| IB2549' | I509' | I70291' |
| IB2591' | I70292' |
| IB2592' | I70293' |
| IB2593' | I70298' |
| IB2599' | I70299' |
| IB25Y1' | I708' |
| IB25Y2' | I7090' |
| IB25Y3' | I7091' |
| IB25Y9' | I7092' |
| IB25Z1' | I7100' |
| I82622' | I825Z2' | I7101' |
|---------|---------|--------|
| I82623' | I825Z3' | I7102' |
| I82629' | I825Z9' | I7103' |
| I82A12' | I82701' | I711'  |
| I82A13' | I82702' | I712'  |
| I82A19' | I82703' | I713'  |
| I82C11' | I82709' | I714'  |
| I82C12' | I82711' | I715'  |
| I82C13' | I82712' | I716'  |
| I82B11' | I82713' | I718'  |
| I82B12' | I82719' | I719'  |
| I82B13' | I82721' | I731   |
| I82B19' | I82722' | I738   |
| I82C19' | I82723' | I739   |

**TABLE 4: ICD 10 codes**

ICD 10: International Classification of Diseases 10th Revision; DIC: disseminated intravascular coagulation

| Diabetes, complicated | Hypertension | Chronic kidney disease | Acute kidney injury | Surgery | Sepsis | Shock state | Acute kidney injury + dialysis | Bleeding | Paralysis | Acute respiratory failure | Stroke |
|-----------------------|--------------|------------------------|--------------------|---------|--------|-------------|-------------------------------|----------|-----------|--------------------------|--------|
| E1021'                | '10'         | N181                   | N178               | Y830'   | A4101' | R570'       | N186                          | D62'     | G8100'    | J9601'                  | I6300' |
| E1022'                | '110'        | N182                   | N170               | Y831'   | A4102' | R571'       | Z992                          | I6000'   | G8101'    | J9602'                  | I63011'|
| E1029'                | '119'        | N183                   | N171               | Y832'   | A411'  | R575'       | N178                          | I6001'   | G8102'    | J9600'                  | I63012'|
| E10311'               | '120'        | N184                   | N172               | Y833'   | A412'  | R579'       | N170                          | I6002'   | G8103'    | J9620'                  | I63013'|
| E10319'               | '129'        | N186                   | N179               | Y834'   | A413'  | R6521'      | N171                          | I6010'   | G8104'    | J9621'                  | I63019'|
| E10321'               | '130'        | N185                   | Y835'             | A414'   | T8110XA' | N172       | I6011'                      | G8110'   | J9622'    | I6302'                  |        |
| E10321' | 'I1310' | N189 | Y836' | A4150' | T8110X' | N179 | I6012' | GB111' | J9690' | I63031' |
| E103212' | 'I1311' | I1310' | Y838' | A4151' | T8110X' | I602' | GB112' | J9691' | I63032' |
| E103213' | 'I132' | Y839' | A4152' | T8111X' | I6020' | GB113' | J9692' | I63033' |
| E103219' | 'I150' | A4153' | T8111X' | I6021' | GB114' | R0603 | I63039' |
| E103229' | 'I151' | A4159' | T8111X' | I6022' | GB190' | J80 | I6309' |
| E103291' | 'I152' | A4181' | T8112X' | I6030' | GB191' | J810 | I6310' |
| E103292' | 'I158' | A4189' | T8112X' | I6031' | GB192' | J95821 | I63111' |
| E103293' | 'I159' | A419' | T8112X' | I6032' | GB193' | R092 | I63112' |
| E103299' | R6520' | T8119X' | I604' | GB194' | R0609 | I63113' |
| E10331' | T8119X' | I6050' | GB220' | R0689 | I63119' |
| E103311' | T8119X' | I6051' | GB221' | I6312' |
| E103312' | I6052' | GB222' | I63131' |
| E103313' | I606' | GB250' | I63132' |
| E103319' | I607' | GB251' | I63133' |
| E10339' | I608' | GB252' | I63139' |
| E103391' | I609' | GB253' | I6319' |
| E103392' | I610' | GB254' | I6320' |
| E103393' | I611' | GB30' | I63211' |
| E103399' | I612' | GB310' | I63212' |
| E10341' | I613' | GB311' | I63213' |
| E103411' | I614' | GB312' | I63219' |
| E103412' | I615' | GB313' | I6322' |
| E103413' | I616' | GB314' | I63231' |
| E103419' | I618' | GB320' | I63232' |
| E10349' | I619' | GB321' | I63233' |
| E103491' | I6200' | GB322' | I63239' |
| E103492' | I6201' | GB323' | I6329' |
| E103493' | I6202' | GB324' | I6330' |
| E103499' | I6203' | GB330' | I63311' |
| E10351' | I621' | GB331' | I63312' |
| E103511' | I629' | GB332' | I63313' |
| E103512' | H35731' | GB333' | I63319' |
| E103513' | H35732' | GB334' | I63321' |
| E103519' | H35733' | GB34' | I63322' |
| E103521' | H35739' | GB01' | I63323' |
| E103522' | H3560' | GB02' | I63329' |
| E103523' | H3561' | G041' | I63331' |
| E103529' | H3562' | GB00' | I63332' |
| Code   | Description | Code   | Description | Code   | Description |
|--------|-------------|--------|-------------|--------|-------------|
| E103531' | H3563'   | G114' | I63333'    |
| E103532' | H31301'   |        | I63339'    |
| E103533' | H31302'   |        | I63341'    |
| E103539' | H31303'   |        | I63342'    |
| E103541' | H31309'   |        | I63343'    |
| E103542' | H31311'   |        | I63349'    |
| E103543' | H31312'   |        | I6339'     |
| E103549' | H31313'   |        | I6340'     |
| E103551' | H31319'   |        | I63411'    |
| E103552' | H31411'   |        | I63412'    |
| E103553' | H31412'   |        | I63413'    |
| E103559' | H31413'   |        | I63419'    |
| E103569' | H31419'   |        | I63421'    |
| E103591' | H47021'   |        | I63422'    |
| E103592' | H47022'   |        | I63423'    |
| E103593' | H47023'   |        | I63429'    |
| E103599' | H47029'   |        | I63431'    |
| E1036'   | H4310'    |        | I63432'    |
| E1037X1' | H4311'    |        | I63433'    |
| E1037X2' | H4312'    |        | I63439'    |
| E1037X3' | H4313'    |        | I63441'    |
| E1037X9' | I621'     |        | I63442'    |
| E1039'   | I312       |        | I63443'    |
| E1040'   | S40011A'  |        | I63448'    |
| E1041'   | S40011D'  |        | I6349'     |
| E1042'   | S40011S'  |        | I6350'     |
| E1043'   | S40012A'  |        | I63511'    |
| E1044'   | S40012D'  |        | I63512'    |
| E1049'   | S40012S'  |        | I63513'    |
| E1051'   | S40019A'  |        | I63519'    |
| E1052'   | S40019D'  |        | I63521'    |
| E1059'   | S40019S'  |        | I63522'    |
| E10610'  | S40021A'  |        | I63523'    |
| E10618'  | S40021D'  |        | I63529'    |
| E10620'  | S40021S'  |        | I63531'    |
| E10621'  | S40022A'  |        | I63532'    |
| E10622'  | S40022D'  |        | I63533'    |
| E10628'  | S40022S'  |        | I63539'    |
| E10630' | S40029A' | I63541' |
| E10638' | S40029D' | I63542' |
| E10641' | S40029S' | I63543' |
| E10649' | M79A11' | I63549' |
| E1065' | M79A12' | I6359' |
| E1069' | M79A19' | I636' |
| E108' | M79A21' | I638' |
| E1121' | M79A22' | I6381' |
| E1122' | M79A26' | I6389' |
| E1129' | M79A3' | I639' |
| E11311' | M79A9' | I6601' |
| E11319' | I6602' |
| E11321' | I6603' |
| E113211' | I6609' |
| E113212' | I6611' |
| E113213' | I6612' |
| E113219' | I6613' |
| E11329' | I6619' |
| E113291' | I6621' |
| E113292' | I6622' |
| E113293' | I6623' |
| E113299' | I6629' |
| E11331' | I663' |
| E113311' | I668' |
| E113312' | I669' |
| E113313' | |
| E113319' | |
| E11339' | |
| E113391' | |
| E113392' | |
| E113393' | |
| E113399' | |
| E11341' | |
| E113411' | |
| E113412' | |
| E113413' | |
| E113419' | |
| E11349' | |
| E113491 |
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| E113492 |
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| E113499 |
| E11351  |
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| E113512 |
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| E11359  |
| E113591 |
| E113592 |
| E113593 |
| E113599 |
| E1136  |
| E1137X1 |
| E1137X2 |
| E1137X3 |
| E1137X9 |
| E1139  |
| E1140  |
| E1141  |
| E1142  |
| Code  | Description |
|-------|-------------|
| E133591' |  |
| E133592' |  |
| E133593' |  |
| E133599' |  |
| E1336' |  |
| E1337X1' |  |
| E1337X2' |  |
| E1337X3' |  |
| E1337X9' |  |
| E1339' |  |
| E1340' |  |
| E1341' |  |
| E1342' |  |
| E1343' |  |
| E1344' |  |
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| E1352' |  |
| E1359' |  |
| E13610' |  |
| E13618' |  |
| E13620' |  |
| E13621' |  |
| E13622' |  |
| E13628' |  |
| E13630' |  |
| E13638' |  |
| E13641' |  |
| E13649' |  |
| E1365' |  |
| E1369' |  |
| E138' |  |

**TABLE 5: ICD 10 codes continued**

ICD 10: International Classification of Diseases 10th Revision

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**Additional Information**

**Disclosures**
Human subjects: Consent was obtained by all participants in this study. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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