Journal of Community Hospital Internal Medicine Perspectives

Volume 14 | Issue 1 Article 2

COVID-19 Infection and Clinical Outcomes in Hospitalized Patients with Rheumatoid Arthritis: Insights from the National Inpatient Sample

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Abstract

Background: **Coronavirus-19, primarily a respiratory virus, affects multiple organs and can lead to exacerbation of autoimmune or systemic conditions. Patients with autoimmune diseases, rheumatoid arthritis particularly, are susceptible to infection and complications from COVID-19. RA has become well-associated with COVID-19 infections, but large-scale studies evaluating outcomes among this vulnerable group are limited.**

Methods: **For the retrospective analysis, we used the National Inpatient Sample database to compare COVID-19 patients with and without RA. A total of 1,050,040 adult hospitalizations were included in the study between January 1 to December 31, 2020: COVID-19 with RA ($n = 21,545$; 2.1%) and COVID-19 without RA ($n = 1,028,495$; 97.9%). The primary outcome was in-hospital mortality. Secondary outcomes included mechanical ventilation requirement, vasopressor use, cardiac arrest, cardiogenic shock, acute kidney injury, acute kidney injury requiring hemodialysis, gastrostomy, tracheostomy, length of stay, health care utilization costs, and disposition. A secondary analysis evaluating in-hospital mortality and mechanical ventilation with respect to age was conducted.**

Results: **COVID-19 patients with RA had significantly increased in-hospital mortality compared to COVID-19 patients without RA (12.9% vs 11.1%, adjusted OR [aOR]: 1.2 [95% CI 1.1−1.3], $p < 0.001$). This cohort also had significantly increased rates of mechanical ventilation, pressor use, and cardiogenic shock.**

Conclusions: **Given limited large evidence regarding COVID-19 with respect to RA, future research should be focused on this topic to improve outcomes for this subset of patients.**

Keywords: COVID-19, Rheumatoid arthritis, Mortality, Age, Complications, United States, National inpatient sample

1. Introduction

Rheumatoid arthritis (RA) is a chronic and progressive, systemic, inflammatory, and autoimmune disease that typically involves synovial joints symmetrically and leads to bone destruction.[1,2] Early use of disease-modifying antirheumatic drugs (DMARDs) and biologics has been shown to improve outcomes; however, these agents require close monitoring.[1] Its etiology is unclear but involves a combination of genetic and environmental factors, with the genetic component contributing to disease severity.[1,3,4]

Viral infections, such as influenza, have been shown to increase mortality in RA patients, highlighting the importance of studying the impact of COVID-19 on this patient population.[5] The association of RA with COVID-19 infection has been well-established by numerous studies since the onset of the pandemic.[6,7] It has been suggested that RA

Received 24 August 2023; accepted 20 October 2023.
Available online 12 January 2024

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https://doi.org/10.55729/2000-9666.1288

patients may have an increased risk of severe COVID-19 infection due to dysregulated immune responses.[6,7] Furthermore, the use of immunomodulatory medications such as DMARDs and biologics in RA patients may complicate the management of COVID-19 infection.[8] Therefore, evaluating the outcomes of COVID-19 patients with RA is of utmost importance. In this study, we utilized the National Inpatient Sample (NIS) to compare the outcomes of COVID-19 patients with and without RA.

2. Materials and methods

The NIS is the largest all-payer database of hospital inpatient stays in the United States. It contains discharge data from a 20% stratified sample of community hospitals in the United States and is a part of the Healthcare Quality and Utilization Project (HCUP).[9] It is sponsored by the Agency for Healthcare Research and Quality. Each discharge information includes de-identified elements such as patient demographics, payment source, hospital characteristics, principal diagnosis, secondary diagnoses, comorbidity measures, and procedural diagnoses. 40 discharge diagnoses and 25 procedures are recorded for each patient by using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM).

Using the HCUP-NIS data from 2020, we identified a retrospective cohort study of admissions with the principal discharge diagnosis of COVID-19 (ICD-10-CM codes U07.1) in patients 18 years or older.[9] We identified two cohorts. The first cohort had a principal diagnosis of COVID-19 and a coexisting secondary diagnosis of RA (identified using ICD-10-CM codes M05xx, M060xx, M062xx, M063xx, M064xx, M068xx, M069xx). The second cohort had a principal diagnosis of COVID-19 without a coexisting secondary diagnosis of RA.

For each hospitalization, baseline demographic characteristics, hospital characteristics, and clinically relevant comorbidities were identified. Clinical comorbidities were identified using Elixhauser comorbidities[10] and ICD-10-CM codes. Descriptive statistics were used to summarize the continuous and categorical variables. The mean and standard error were used for the continuous variables and the categorical variables were expressed as percentages. The Rao-Scott Chi-square test was used for univariate analyses between group comparisons for categorical variables and weighted simple linear regression for continuous variables. Weighted logistic and linear regression was performed to determine the association between RA and various clinical outcomes in primary COVID-19 hospitalizations. The output of the logistic regression was reported as odds ratio (OR) with a 95% confidence interval (CI). The logistic regression and linear model were adjusted for age, sex, race, comorbidities listed in Table 1, and hospital characteristics.

Hospital total charges were converted to cost estimates using hospital-specific cost-to-charge ratios provided by HCUP. All statistical analyses were performed using Stata 16.1 (StataCorp, College Station, TX).[11] Our analyses considered survey design complexity by incorporating sampling weights, primary sampling units, and strata. This allowed us to estimate population proportions, means, and regression coefficients using svy commands. Standard errors were computed using Taylor series linearization. The p-value of <0.05 was considered statistically significant.

3. Results

3.1. Demographics and baseline comorbidities

A total of 1,050,040 hospitalized COVID-19 adult patients, with 21,545 (2.1%) patients diagnosed with COVID-19 infection and RA between January 1 to December 31, 2020, were our first cohort. Our second cohort included 1,028,495 COVID-19 patients without RA during this study period. Hospitalizations with COVID-19 infection and RA had significantly more females (72.9% vs 46.7%, $p < 0.001$), Whites (64.0% vs 52.4%, $p < 0.001$), and had a higher mean age (68.8 years vs 64.7 years, $p < 0.001$) compared to those without RA (Table 1).

Patients with COVID-19 and RA exhibited a higher prevalence of several conditions compared to those without RA: chronic pulmonary disease (35.3% vs 23.2%, $p < 0.001$), hypertension (74.3% vs 67.5%, $p < 0.001$), congestive heart failure (20.2% vs 16.7%, $p < 0.001$), among others. Those with RA had a higher smoking history (30.6% vs 26.9%, $p < 0.001$) and drug abuse (2.3% vs 1.8%, $p = 0.034$) but a lesser prevalence of diabetes mellitus (35.3% vs 40.9%, $p < 0.001$) and alcohol abuse (0.9% vs 1.9%, $p < 0.001$). No significant variations were found between the two groups in conditions like obesity and renal failure. As per the Elixhauser Comorbidity Index, RA patients with COVID-19 presented significantly higher scores, and most were treated at urban teaching hospitals. A larger percentage of the RA cohort used Medicare (67.8% vs 52.0%, $p < 0.001$).

3.2. In-hospital mortality

In-hospital mortality was significantly higher among patients with COVID-19 and RA

Table 1. Baseline characteristics of hospitalized COVID-19 patients without RA and with RA.

Variables	No RA (Weighted n = 1028495)	RA (Weighted n = 21545)	Total (Weighted n = 1050040)	p value
Age (mean [S.E.]) years	64.66 (0.08)	68.75 (0.20)	64.74 (0.08)	<0.001
Female	46.66	72.92	47.2	<0.001
Race				<0.001
White	52.42	63.97	52.66	
Black	18.49	17.23	18.47	
Hispanics	20.68	13.26	20.53	
Others	8.41	5.54	8.35	
Comorbidities				
Chronic pulmonary disease	23.24	35.28	23.48	<0.001
Atrial fibrillation	11.52	13.16	11.55	0.001
Diabetes mellitus	40.88	35.34	40.76	<0.001
Hypertension	67.54	74.33	67.68	<0.001
Congestive heart failure	16.69	20.17	16.76	<0.001
Obesity	27.37	27.13	27.37	0.729
Peripheral vascular disease	4.51	5.5	4.53	0.003
Renal failure	20.12	21.28	20.15	0.067
Liver disease	4.52	4.29	4.52	0.473
Neurological disorders	14.23	14.3	14.23	0.898
Deficiency Anemias	3.41	4.46	3.43	<0.001
Hypothyroidism	13.77	22.77	13.95	<0.001
Valvular disease	3.84	5.59	3.88	<0.001
Smoking	26.91	30.61	26.99	<0.001
Alcohol abuse	1.9	0.91	1.88	<0.001
Drug abuse	1.82	2.25	1.83	0.034
Carotid artery disease	0.48	0.84	0.49	0.001
Dyslipidemia	42.27	46.69	42.36	<0.001
Ischemic heart disease	22.15	26.48	22.24	<0.001
Prior Cerebrovascular disease	8.37	9.96	8.4	<0.001
Prior PPM or ICD	3.55	3.71	3.56	0.575
Hospital Location				<0.001
Rural	11.7	13.88	11.74	
Urban non-teaching	19.29	19.84	19.3	
Urban teaching	69.01	66.28	68.95	
Bed Size of the hospital				0.159
Small	25.73	24.23	25.7	
Medium	28.9	29.68	28.91	
Large	45.37	46.09	45.39	
Region				<0.001
Northeast	17.71	15.9	17.68	
Midwest	23.21	26.99	23.29	
South	41.84	41.84	41.84	
West	17.23	15.27	17.19	
Primary Expected Payer				<0.001
Medicare	52.02	67.83	52.34	
Medicaid	11.72	6.47	11.61	
Private insurance	27.84	21.84	27.72	
Self-pay, no charge, or other	8.42	3.85	8.33	
Elixhauser Comorbidity Index				<0.001
0–4	68.83	43.19	68.3	
5–8	29.33	51.06	29.78	
≥9	1.84	5.76	1.92	

Abbreviations: COVID-19, coronavirus-19; RA, rheumatoid arthritis; n, number; S.E., standard error; PPM, permanent pacemaker; ICD, implantable cardioverter-defibrillator.

compared to those without RA (12.9% vs 11.1%, adjusted OR [aOR]: 1.2 [95% CI 1.1–1.3], $p < 0.001$) (Table 2).

Mortality was further divided, evaluating age. Mortality for COVID-19 patients with RA was significantly higher among patients aged 18–44 years (5.2% vs 2.5%, aOR: 2.9 [95% CI 1.5–5.6], $p = 0.002$) and 65–79 years (15.0% vs 13.6%, aOR: 1.2 [95% CI 1.1–1.4], $p = 0.006$) (Table 3) compared to COVID-19 patients without RA.

Table 2. In-hospital complications, mortality, and quality measures and disposition for hospitalized COVID-19 patients without RA and with RA.

Variables	No RA (Weighted $n = 1028495$)	RA (Weighted $n = 21545$)	Total (Weighted $n = 1050040$)	Adjusted OR	95% CI Lower	95% CI Upper	p value
Pressors use	1.76	2	1.77	1.40	1.12	1.75	0.004
Invasive mechanical ventilation	9.86	10.16	9.86	1.21	1.08	1.35	0.001
Cardiogenic shock	0.38	0.51	0.38	1.64	1.06	2.54	0.026
Disposition to SNF, ICF, or other facility	19.73	21.69	19.77	0.89	0.81	0.97	0.011
AKI	25.29	24.67	25.27	0.99	0.92	1.07	0.832
AKI requiring dialysis	1.75	1.14	1.74	0.85	0.63	1.15	0.298
Gastrostomy	1.26	1.32	1.26	1.23	0.92	1.65	0.155
Tracheostomy	0.87	0.53	0.87	0.70	0.33	1.49	0.351
Cardiac arrest	2.78	2.53	2.77	1.05	0.86	1.28	0.634
In-hospital mortality	11.14	12.88	11.17	1.21	1.09	1.34	<0.001
LOS (mean [S.E.]) days	7.48 (0.03)	7.52 (0.12)	7.48 (0.03)	0.17	−0.06	0.41	0.148
Cost, US $ (mean [S.E])	19089.89 (218.62)	18902.88 (512.93)	19086.05 (217.02)	1029.48	259.46	1799.49	0.009

Abbreviations: COVID-19, coronavirus-19; RA, rheumatoid arthritis; OR, odds ratio; CI, confidence interval; n, number; SNF, skilled nursing facility; ICF; intermediate care facilities; AKI, acute kidney injury; LOS, length of stay; S.E., standard error; US, United States; $, dollars; PPM, permanent pacemaker; ICD, implantable cardioverter-defibrillator.

3.3. In-hospital complications

The COVID-19 and RA cohort required more invasive mechanical ventilation (10.2% vs 9.9%, aOR: 1.2 [95% CI 1.1–1.4], $p = 0.001$) and pressor use (2.0% vs 1.8%, aOR: 1.4 [95% CI 1.1–1.8], $p = 0.004$), and had higher cardiogenic shock (0.5% vs 0.4%, aOR: 1.6 [95% CI 1.1–2.5], $p = 0.026$) compared to patients with COVID-19 without RA. There was no significant difference in Acute Kidney Injury (AKI), AKI requiring hemodialysis, cardiac arrest, or the requirement of gastrostomy and tracheostomy between both cohorts (Table 2).

Invasive mechanical ventilation use was further divided, evaluating age. Patients aged 18–44 years within the COVID-19 and RA cohort had significantly higher mechanical ventilation requirement (10.4% vs 6.6%, aOR: 1.9 [95% CI 1.2–3.1], $p = 0.009$) compared to COVID-19 patients without RA (Table 3).

3.4. In- hospital quality measures and disposition

Of those who survived, patients with COVID-19 and RA had significantly more discharges to facilities (skilled nursing facilities (SNF), intermediate care facilities (ICF), or other facilities) (21.7% vs 19.7%, aOR: 0.9 [95% CI 0.8–1.0], $p = 0.011$) compared to those with COVID-19 without RA. Patients with COVID-19 without RA had significantly higher hospitalization costs (adjusted mean difference 1029.5 [95% CI 259.5–1799.5], $p = 0.009$) than COVID-19 patients with RA. There was no

Table 3. Sub-analysis of age on invasive mechanical ventilation and in-hospital mortality of hospitalized COVID-19 patients without RA and with RA.

Variables	No RA	RA	Total	Adjusted OR	95% CI Lower	95% CI Upper	p value
Age 18–44	$n = 125365$	$n = 960$	$n = 126325$				
Invasive mechanical ventilation	6.61	10.42	6.64	1.90	1.18	3.08	0.009
In-hospital mortality	2.49	5.21	2.51	2.90	1.49	5.63	0.002
Age 45–64	$n = 352870$	$n = 6660$	$n = 359530$				
Invasive mechanical ventilation	10.47	9.91	10.46	1.01	0.83	1.24	0.888
In-hospital mortality	6.51	7.06	6.52	1.19	0.94	1.50	0.148
Age 65–79	$n = 342545$	$n = 9135$	$n = 351680$				
Invasive mechanical ventilation	12.53	12.42	12.53	1.12	0.96	1.30	0.163
In-hospital mortality	13.58	15	13.62	1.23	1.06	1.43	0.006
Age 80+	$n = 207005$	$n = 4785$	$n = 211790$				
Invasive mechanical ventilation	6.36	6.17	6.36	1.12	0.86	1.45	0.41
In-hospital mortality	20.22	18.5	20.19	1.05	0.88	1.25	0.615

Abbreviations: COVID-19, coronavirus-19; RA, rheumatoid arthritis; OR, odds ratio; CI, confidence interval; n, number.

difference with respect to the mean length of stay between the two cohorts (Table 2).

4. Discussion

From January 1 to December 31, 2020, our study revealed that 2.1% (21,545) of 1,050,040 hospitalized COVID-19 adults also had RA. Key findings include: (1) Higher in-hospital mortality in COVID-19 patients with RA. (2) Increased cardiogenic shock, mechanical ventilation, and pressor use in the RA group. (3) Both younger (18–44) and older (65–79) COVID-19 patients with RA had increased mortality, with younger ones requiring more mechanical ventilation. (4) Patients with both conditions had higher Elixhauser Comorbidity Index scores.

RA patients have a 50% increased risk of infection hospitalization (19.6 vs. 12.9 per 100 person-years) compared to non-RA individuals.[5] The literature reports a 0.2% hospitalization rate for severe COVID-19 in RA patients, lower than our 2.1%.[12] The larger scale of our study might explain this discrepancy. Existing literature indicates 69% of RA patients affected by COVID-19 are females, similar to the 73.1% in viral illnesses.[5,7] Our data also shows women as the most affected. While men generally face greater COVID-19 risk,[7,13,14] women with RA are more vulnerable. A susceptibility to RA in women, at a ratio of 3:1 to men, is partially due to low androgen levels.[15,16] Hormonal differences, such as androgen deficiency and excess estrogen, may predispose individuals to the development of RA, and these hormones may also stimulate inflammatory cytokines that are instrumental in the inflammatory response associated with both RA and COVID-19 (e.g. interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]).[15,17]

In our analysis, the most predominant demographic group affected by both RA and COVID-19 were Whites. This finding aligns with previous studies wherein a large percentage of the population studied with both COVID-19 and rheumatic diseases were Whites.[18,19] Despite the higher incidence in Whites as per Gianfrancesco et al., there was an increase in hospitalizations and requirements for ventilatory support among minority groups such as African Americans, Latinx, and Asians. However, there was no discernible difference in mortality rates among these groups.[18] Our research did not investigate race as a potential mortality risk factor. Typically, minority groups bear a heavier disease burden when it comes to COVID-19 and rheumatic diseases compared to Whites.[18,20] However, it's challenging to draw definitive conclusions from the racial data as the reported differences aren't substantial, and hospitalization rates may merely reflect the distribution of the US population. Future studies should place a greater emphasis on understanding the racial disparities within this patient subset.

As for age, our research found that individuals of advanced age (60s and beyond, average age 68.8 years) with both COVID-19 and RA were more susceptible to the disease. This aligns with the existing literature reporting an average age of 63 years.[7,21,22] Older patients, particularly those with comorbid conditions and a weakened immune system, are at the greatest risk of disease contraction and subsequent mortality.[23] Our study found that patients with both COVID-19 and RA had multiple comorbidities like chronic pulmonary disease, hypertension, and more. Similar findings were reported by Abualfadl et al., including conditions like renal failure.[6,14,24] Doran et al. suggest such comorbidities heighten infection risk in RA patients.[5] Our data supports this, as RA patients with COVID-19 had higher Elixhauser Comorbidity Index scores, indicating increased mortality risks. Proper management of these conditions, alongside RA and COVID-19 treatments, is crucial.

Our study found a 12.9% in-hospital mortality rate in patients with both COVID-19 and RA, higher than the 2.9%–8.6% found in other studies.[7,25,26] While Jung et al., D'Silva et al., and Mahdavi et al. didn't associate RA with increased mortality,[7,25,26] our higher rate might be due to early-pandemic challenges, differing demographics, and a larger sample size. A deeper look revealed higher mortality among those aged 18–44 and 65–79 with RA and COVID-19. Existing research notes higher mortality in the elderly from COVID-19 due to factors like weakened immunity and living conditions.[27] Older RA patients face exacerbated rheumatologic issues, while younger ones experience intense immune responses causing severe disease.[28,29]

Our COVID-19 patients with RA showed higher needs for mechanical ventilation, pressor use, and had increased cardiogenic shock rates. This mirrors D'Silva et al.'s findings of greater ICU and ventilation needs for those with COVID-19 and rheumatic disease.[7] Yet, it differs from Raiker et al., who found no significant complications.[19] The reasons behind these divergent results remain unclear but may be attributed to the higher prevalence of cardiovascular-related comorbidities and chronic pulmonary disease in this population, coupled with potential antirheumatic drug-induced lung injury, especially with methotrexate.[7,30] Upon sub-analyzing the requirement for mechanical ventilation to evaluate

age, it was observed that younger patients (18–44 years) required more mechanical ventilation compared to older patients, in line with previous studies showing a more intense immune response in younger COVID-19 patients leading to severe respiratory distress syndrome.[29]

The COVID-19 pandemic presents a significant concern for patients with rheumatic conditions due to the prevailing immune dysfunction within this population and their concurrent immunosuppressive treatments.[8] Broadly, COVID-19 patients receive treatments comprising steroids, antivirals (e.g., remdesivir), and palliative medications that have demonstrated benefits.[31] Patients with RA are managed with DMARDs and biologics, with possible steroid administration contingent on disease burden and flare-ups.[8] These medications necessitate careful monitoring owing to potential adverse effects, particularly during an acute illness.

Several rheumatologic agents, including IL-1 and IL-6 inhibitors (e.g., tocilizumab), antimalarials, IVIG, and JAK inhibitors, have been tested for COVID-19 treatment with varied success in trials.[8] Corticosteroids, while useful in early treatment, can lead to amplified immunosuppression if initiated late, potentially causing severe infections.[23] Despite the high risk of rheumatoid flare during COVID-19, health bodies recommend maintaining RA regimens with dosage tweaks.[32] Vaccination is essential for RA patients, yet there are concerns that drugs like rituximab or methotrexate could reduce vaccine efficacy.[15,33] Even so, most health organizations advocate for vaccination in rheumatic patients, advising medication adjustments during the vaccine period.[33]

Concerns have arisen about the onset of rheumatoid arthritis after COVID-19 infection or vaccination, causing vaccine hesitancy.[34] Isolated reports have noted anti-citrullinated protein antibodies post-infection, and some mention RA flare-ups post-vaccination.[34,35] Due to the nature of these studies (mainly case reports), a direct link between RA and COVID-19 or vaccines isn't confirmed. Importantly, our study did not assess 'long COVID' or role of vaccination status; therefore, our findings cannot be extrapolated to address these issues. Large, prospective studies would provide invaluable clarification.

5. Limitations

This study, despite offering significant insights, does carry inherent limitations. NIS database from 2020 primarily incorporates data from non-vaccinated patients. This is due to the fact that the U.S. FDA only granted the first Emergency Use Authorization for COVID-19 vaccines in December 2020, towards the very end of our study period. Consequently, we were unable to analyze the impact of COVID-19 vaccination and long COVID on patients with RA, given the unavailability of this data in our source. The limitation of reliance on ICD codes in the NIS database also merits acknowledgement as it might introduce reporting bias. The findings of our study are inherently dependent on the accuracy and consistency of coding practices across different medical institutions, which could vary and hence, affect the true prevalence of certain conditions. Specific variables, including the effect of individual immunosuppressive therapies used by RA patients on COVID-19 severity, were not explored in this study as the NIS database does not provide laboratory data or treatment used. Finally, the scope of our retrospective study design is inherently limited. Although it can identify and report associations, it is unable to conclusively establish causal relationships.

Future research opportunities from this study are vast. Firstly, we need studies on the impact of COVID-19 vaccines on RA patients, as our data primarily covers non-vaccinated individuals. Such studies should assess vaccine efficacy, safety, and effects on disease severity in this group. Long-term effects of COVID-19 in RA patients, or 'long COVID', also need exploration. Research should probe potential links between long COVID and RA progression. The study of new-onset RA after COVID-19 infection or vaccination could illuminate their immunological relationship. Additionally, the influence of specific RA therapies on COVID-19 severity deserves attention. Finally, comprehensive studies, like randomized trials, can establish clear causal links between RA, COVID-19, and vaccines, ultimately benefiting patient management.

6. Conclusion

Our study not only enhanced our understanding of rheumatic disease in the context of COVID-19 but also set a critical foundation for future inquiries. We observed a significant elevation in in-hospital mortality rates, alongside an increased utilization of mechanical ventilation, pressor use, and occurrences of cardiogenic shock among COVID-19 patients with RA. These significant statistics underscore the need for vigilant monitoring and specialized management of rheumatic patients who are grappling with severe COVID-19 disease and its subsequent complications. In light of these implications, it becomes increasingly clear that strategic

measures to optimize the management of these patients are imperative to mitigate the observed increased morbidity and mortality.

Disclaimers

We have ensured that our manuscript adheres to the journal's guidelines and formatting requirements. We have conducted a thorough review of the literature to ensure that our work is original and does not infringe on any copyrights. The manuscript has not been submitted to any other journal and is not under consideration for publication elsewhere, nor has it been presented at a conference or meeting. No funding was used in the conduct of this research, and all authors declare no conflict of interest.

Sources of support

Not applicable

Funding

This research received no external funding.

Institutional review board statement

Not applicable

Informed consent statement

Not applicable

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

Restrictions apply to the availability of these data. Data were obtained from the National Inpatient Sample database, US.

Author contributions

Conceptualization: AA, ABS.
Methodology: AA.
Software: AA.
Validation: EE.
Formal Analysis: AA.
Data curation: SA, HS.
Resources: ABS, EE.
Writing original draft: MGD.
Writing reviewing and editing: ABS, AA, EE.
Visualization: MGD, HS, SA.
Supervision: ABS, EE.

All authors have read and agreed to the published version of the manuscript.

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