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Original Research

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Outcomes of Multiple Myeloma in Hospitalized Patients With Opioid Use Disorder: A Nationwide Analysis

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Abstract

Multiple myeloma is commonly associated with advanced age. This study aims to investigate how multiple myeloma outcomes are affected by opioid use disorder (OUD) among hospitalized patients. We analyzed the National Inpatient Sample (NIS) for 2019 and 2020 for our retrospective cohort study. International Classification of Diseases Clinical Modification codes (ICD-10-CM) were utilized to identify the population of interest. Primary and secondary outcomes were studied using a multivariate regression model. Among the 38,735 patients hospitalized with multiple myeloma, 350 patients had the concurrent diagnosis of opioid use disorder. OUD patients were found to be at increased risk for major depressive disorder a*OR*[1] 2.57 (95% CI 1.39–4.755), $p = 0.003$; delirium a*OR* 3.48 (95% CI 1.066–11.38); $p = 0.04$; insomnia a*OR* 2.77 (95% CI 1.31–5.87); $p = 0.008$; and hypercalcemia a*OR* 2.71 (95% CI 1.31–5.63) $p = 0.007$. Total hospitalization charges decreased in patients with OUD, and no significant difference between the two groups in the length of hospital stay or mortality was noted. Among patients admitted with OUD, the rates of delirium, major depressive disorder, insomnia, and hypercalcemia were higher than those without any OUD without any significant difference in mortality.

Keywords: *opioid use disorder; hypercalcemia; multiple myeloma and opioid use disorder; national inpatient sample and OUD; depression and opioid use disorder*

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[1] a*OR*: Adjusted Odds Ratio

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the appearance of abnormal clonal plasma cells in the bone marrow. These abnormal clonal plasma cells have the potential for uncontrolled growth, leading to destructive bone lesions, kidney injury, hypercalcemia, and anemia. Multiple myeloma is commonly associated with advanced age and affects an estimated 34,920 individuals in the United States and nearly 588,161 individuals worldwide each year (Cowan et al., 2022).

The opioid epidemic, along with opioid use disorder (OUD) in the United States, has led to a greater burden on healthcare professionals. With opioids remaining the mainstay of treatment in patients with severe cancer pain, such as hematologic malignancies like MM, they have been extensively employed in cancer treatments (Subramaniam et al., 2019). When these opioids are used for prolonged periods, they can result in debilitating dependence, which can heighten unnecessary consumption and cause adversities for both the general population and individuals undergoing cancer treatment.

Additionally, when opioids are used recreationally, they have the potential to cause significant harm and complications within populations that may already be especially vulnerable. The possible repercussions of such actions are significant and may result in serious health complications, resulting in extended hospitalization or fatalities (Preux et al., 2022).

Our study sought to investigate the correlation between opioid use and adverse hospital events, complications, and patient outcomes in patients hospitalized with multiple myeloma. While it is widely acknowledged that opioids can have detrimental effects on a patient's health, our study seeks to uncover nuanced information about how these drugs impact hospitalized individuals specifically.

Materials and Methods

Study Design

The National Inpatient Sample (NIS) is a complex and extensive administrative repository that operates under the purview of the Healthcare Cost and Utilization Project. The Agency for Healthcare Research and Quality sponsored the project. To achieve its goals, NIS utilizes a sophisticated survey methodology involving stratified sampling techniques to select approximately 20% of patients discharged from community hospitals across America. By implementing robust hospital weighing mechanisms, NIS facilitates generating comprehensive national projections with accuracy and precision. Overall, the remarkable depth of these data allows researchers to gain invaluable insights into various healthcare-related issues while providing medical professionals with accurate information regarding current trends in patient care practices throughout America's bustling network of hospitals.

Study Population

To identify a cohort of patients with multiple myeloma, the NIS data from 2019 and 2020 were utilized. To ensure accurate diagnosis, the International Classification of Diseases Clinical Modification codes (ICD-10-CM) from the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* were employed for coding purposes. The study sought patients over the age of 18 who were diagnosed with both multiple myeloma and opioid use disorders, as well as those who were solely diagnosed with multiple myeloma.

Study Outcomes

The primary outcome studied was inpatient mortality, which was assessed as a categorical variable indicating whether the patient remained alive or died during their hospital stay. Secondary outcomes included length of stay (LOS), total hospitalization charges, delirium, major depressive disorder, insomnia, hypercalcemia, venous thromboembolism, and acute respiratory failure.

Statistical Analysis

We conducted a thorough survey-weighted analysis that accounted for stratification and clustering in the National Input Survey (NIS) data. This analysis revealed important insights into predictors of mortality, LOS, cost of care, and other secondary outcomes. To fully explore these findings, we employed advanced statistical methods, such as chi-squared tests for categorical variables and *t*-tests for continuous variables when comparing baseline characteristics. To determine predictors of mortality and other secondary outcomes, the final multivariable regression model considered age, gender, race, and the number of hospital beds, along with several other key factors as confounding variables. Additionally, only those variables demonstrating significant differences during univariate analysis (with a *p*-value below 0.2) were incorporated. Furthermore, variables deemed crucial drivers for achieving the desired outcomes were integrated into our strategy irrespective of their statistical significance.

To assess the statistical significance of our findings, we utilized two-sided *p*-values. It was determined that any result with a *p*-value of less than or equal to 0.05 would be considered significant, indicating strong evidence for rejecting the null hypothesis. These analyses were conducted using Stata (Version 17.0) software from Stata Corporation in College Station, Texas, a widely respected and reliable tool within the field of data analysis and statistics.

Results

By utilizing ICD-10-CM coding, a total of 38,735 patients who were admitted to the hospital in the years 2019–2020 and diagnosed with multiple myeloma were identified from the NIS database. Of this population, it was discovered that 350 individuals had an additional diagnosis of opioid use disorder (OUD). In contrast, the remaining majority, consisting of approximately 38,385 patients, did not have any evidence of OUD.

Patients with OUD were comparatively younger (62.67 vs. 65.88), $p = 0.01$. A large proportion of patients with OUD were found to have a Charlson comorbidity index of > = 3 (75.71% vs. 63.4%), $p = 0.037$. Compared to patients without OUD, the majority of OUD patients had Medicare (59.09% vs. 54.64%), Medicaid (24.24% vs. 8.39%), or were uninsured (3.03% vs. 1.9%), $p < 0.001$. A higher percentage of patients without OUD had private insurance (35.07% vs. 13.64%). Patients with OUD were more likely to be discharged to skilled nursing facilities (3.7% vs. 2.77%) and to leave against medical advice (7.41% vs. 0.66%), $p < 0.001$. The Western region of the United States had the larger proportion of OUD vs. non-OUD patients (31.43% vs. 17.79%), and the Northeast and Midwest had the largest proportion of non-OUD patients as compared to OUD patients (21.95% vs. 15.71% and 22.1% vs. 14.29%, respectively), $p = 0.025$. The southern United States had an equal distribution of OUD and non-OUD patients (38.15% vs. 38.57%), $p = 0.025$. Table 1 summarizes the baseline characteristics of the patients in both categories.

Table 1. *Demographic Data and Comparison of Baseline Characteristics of Multiple Myeloma Patients With and Without OUD*

Baseline Participant Characteristics			
	Myeloma without OUD	Myeloma with OUD	*p*-value
Number of patients	38,385	350	
Patient characteristics			
Gender (%)			0.762
Male	21,549 (56.14)	190 (54.29)	
Female	16,836 (43.86)	160 (45.71)	
Age			
Mean age (SD)	65.88 (11.27)	62.67 (10.15)	0.011
Age distribution (%)			0.144
18–35	265 (0.69)	0 (0)	
36–45	1336 (3.48)	15 (4.29)	
46–64	15381 (40.07)	185 (52.86)	
>65	21403 (55.76)	150 (42.86)	
Race (%)			0.063
White	23730 (61.82)	170 (48.53)	
Black	9377 (24.43)	134 (38.24)	
Hispanic	3900 (10.16)	36 (10.29)	
Other	1378 (3.59)	10 (2.94)	
Median household income national quartile for patient zip code (%)			0.436
$1–$49,999	10,088 (26.28)	118 (33.82)	
$50,000–$64,999	9,109 (23.73)	82 (23.53)	
$65,000–$85,999	9,731 (25.35)	88 (25)	
>$86,000	9,462 (24.65)	62 (17.65)	
Charlson comorbidity index (%)			0.037
2	14,049 (36.6)	85 (24.29)	
3 or more	24,336 (63.4)	265 (75.71)	
Insurance provider (%)			<0.001
Medicare	20,974 (54.64)	207 (59.09)	
Medicaid	3,221 (8.39)	85 (24.24)	
Private	13,462 (35.07)	48 (13.64)	
Uninsured	729 (1.9)	11 (3.03)	

Comorbidities (%)			
Hypertension	13,815 (35.99)	110 (31.43)	0.459
Diabetes mellitus	6,748 (17.58)	75 (21.43)	0.389
Fluid and electrolyte disorders	21,311 (55.52)	190 (54.29)	0.836
Chronic kidney disease	11,059 (28.81)	100 (28.57)	0.965
Hyperlipidemia (HLD)	11,304 (29.45)	90 (25.71)	0.504
Discharge disposition (%)			<0.001
Home	27,150 (70.73)	240 (68.52)	
Home with home health	9,923 (25.85)	71 (20.37)	
Skilled nursing facility	1,063 (2.77)	13 (3.7)	
Against medical advice	253 (0.66)	26 (7.41)	
Hospital characteristics (%)			
Bed size of hospital (STRATA)			0.252
Small	5,359 (13.96)	40 (11.43)	
Medium	7,727 (20.13)	100 (28.57)	
Large	25,300 (65.91)	210 (60)	
Hospital location			0.192
Rural	1178 (3.07)	0 (0)	
Urban	37,207 (96.93)	350 (100)	
Hospital teaching status			0.942
Non-teaching hospital	4506 (11.74)	40 (11.43)	
Teaching hospital	33,879 (88.26)	310 (88.57)	
Region of hospital			0.025
Northeast	8,426 (21.95)	55 (15.71)	
Midwest	8,483 (22.1)	50 (14.29)	
South	14,644 (38.15)	135 (38.57)	
West	6829 (17.79)	110 (31.43)	

Among patients hospitalized with multiple myeloma, the primary outcome mortality rate was similar among both groups (non-OUD and OUD): a*OR* 0.68 (95% CI 0.16–2.88), $p = 0.605$. The primary outcome is summarized in Table 2.

Table 2. *Comparison of Primary and Secondary Outcomes in Multiple Myeloma Patients With and Without OUD*

Outcomes	Myeloma without OUD (%)	Myeloma with OUD (%)	Unadjusted *aOR* (95%CI)	*p*-value	a*OR* (95% CI)	*p*-value
Primary outcome						
In-hospital mortality	4.66	4.29	0.92 (0.29–.90)	0.881	0.68 (0 .16–.88)	0.605
Secondary outcomes						
Sepsis	5.86	1.43	0.23 (.03–1.69	0.150	0.23 (0.03–1.72)	0.152
ICU admission	5.65	5.71	1.01 (0.37–2.80)	0.983	1.01 (0.3–2.84	0.978
Intubation	3.91	4.29	1.10 (.34–3.52)	0.871	1.12 (0.35–3.62)	0.850
Acute respiratory failure	6.49	7.14	1.11 (0.38–3.23)	0.850	0.88 (0.31–.53)	0.813
Acute coronary syndrome	0.68	1.43	2.13 (.29–15.61)	0.459	2.19 (0.26–8.57)	0.471
Acute kidney injury	37.37	44.29	1.33 (.83–2.15)	0.239	1.47 (0.81–2.70)	0.206
Osteoporosis	3.79	2.86	0.75 (0.18–.08)	0.686	1.18 (0.27–5.12)	0.828
Delirium	2.21	5.71	2.68 (0.96–.49)	0.061	3.48 (1.066–11.38)	0.039
Major depressive disorder	10.93	24.29	2.61 (1.51–4.52)	0.001	2.57 (1.39–4.755)	0.003
Insomnia	7.58	14.29	2.03 (1.02–.04)	0.043	2.77 (1.31–5.87)	0.008
Constipation	21.26	22.86	1.10 (0.62–1.93)	0.749	1.12 (0.61–2.06)	0.723
Anemia	47.49	57.14	1.47 (0.91–2.38)	0.112	1.53 (0.91–2.57)	0.108
Malnutrition	17.83	20	1.15 (0.62–2.14)	0.655	1.23 (0.63–2.43)	0.543
GI bleed	3.31	1.43	0.42 (.06–3.08)	0.396	0.44 (0.06–3.25)	0.424
Red blood cells transfusion	17.53	7.14	0.36 (0.15–.90)	0.029	0.34 (0.13–0.88)	0.026
Hypercalcemia	21.4	32.86	1.80 (1.09–.98)	0.023	2.71 (1.31–5.63)	0.007
Acute venous thrombo-embolism	3.32	2.86	0.86 (0.21–.52)	0.830	0.90 (0.21–3.75)	0.880
Chemotherapy	0.81	1.43	1.78 (0.24–3.18)	0.572	2.36 (0.31–17.93)	0.408

a*OR*: Adjusted Odds Ratio; CI: 95% Confidence Interval; GI Bleed: Gastrointestinal Bleed; ICU: Intensive Care Unit; OUD: Opioid Use Disorder

After adjusting for confounding variables through multivariate regression analysis, no difference in the length of stay was appreciated between the two groups—without OUD, 9.38 days (95% CI 9.02–9.76); with OUD, 7.56 days (95% CI 5.03–10.09); $p = 0.154$ (see Table 3). However, total charges decreased in patients with

OUD as compared to those without OUD: USD 80,084 (95% CI 51,232–108,935) and 113,497 (95% CI 106,195–120,798), p = 0.023, respectively (see Table 3).

Table 3. *Comparison of Length of Stay and Total Hospitalization Charges in Multiple Myeloma Patients With and Without OUD.*

	Myeloma without OUD	Myeloma with OUD	p-value
LOS days (unadjusted)	11.38 (11.03–11.75)	9.41 (7.22–11.60)	0.079
LOS days (adjusted)	9.38 (9.02–9.76)	7.56 (5.03–10.09)	0.154
Total charges USD (unadjusted)	14,6233 (137,828–54,639)	11,6677 (88,041–145,312)	0.032
Total charges USD (adjusted)	11,3497 (10,6195–12,0798)	80,084 (51,232–108,935)	0.023

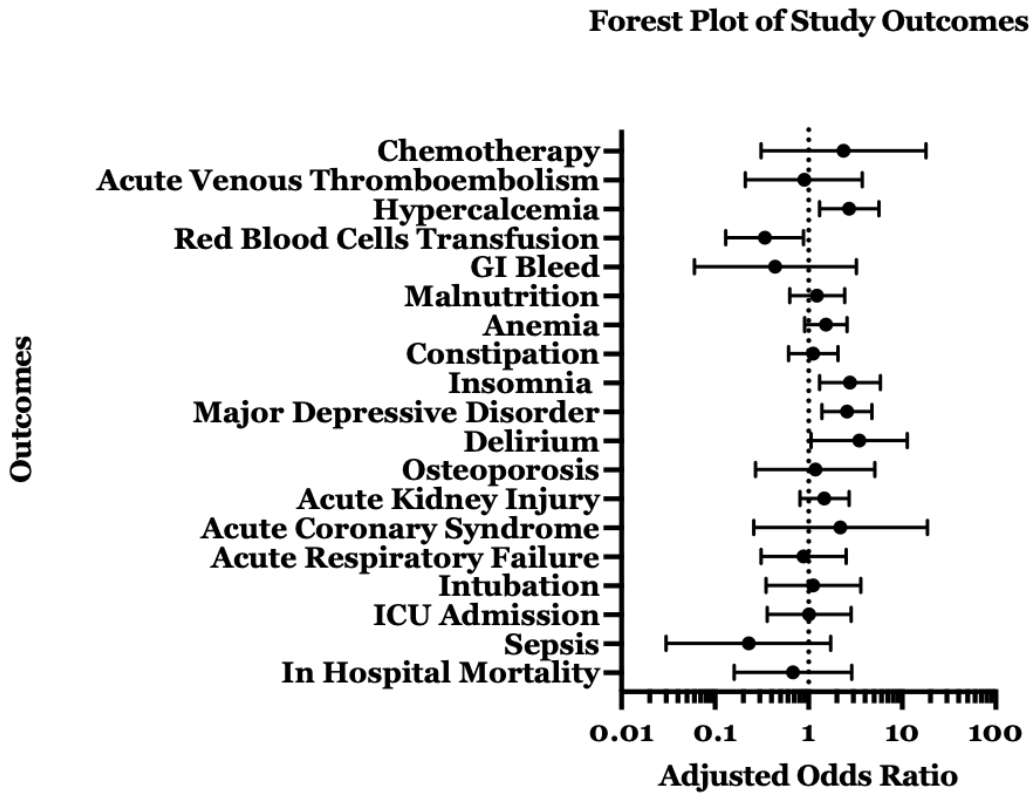
USD: United States Dollar; LOS: Length of Stay; OUD: Opioid Use Disorder

OUD was significantly associated with increased odds of delirium a*OR* 2.68 (95% CI 0.96–7.49), p = 0.061; major depressive disorder a*OR* 2.61 (95% CI 1.51–4.52), p = 0.001; and insomnia a*OR* 2.03 (95% CI 1.02–4.04), p = 0.043, as compared to patients with no OUD. Similarly, patients with OUD were more likely to have hypercalcemia (32.86% vs. 21.4%), a*OR* 2.71 (95% CI 1.31–5.63), p = 0.007 (see Table 2).

The odds of developing acute respiratory failure a*OR* 0.88 (95% CI 0.31–2.53), p = 0.813; acute coronary syndrome a*OR* 2.19(95% CI 0.26–18.57), p = 0.471; acute kidney injury a*OR* 1.47(95% CI 0.81–2.70), p = 0.206; osteoporosis a*OR* 1.18(95% CI 0.27–5.12), p = 0.828; and constipation a*OR* 1.12(95% CI 0.61–2.06), p = 0.723 were comparable between OUD and non-OUD patients.

There was no increased risk of anemia a*OR* 1.53(95% CI 0.91–2.57), p = 0.108; malnutrition a*OR* 1.23(95% CI 0.63–2.43), p =0.543; GI bleed a*OR* 0.44(95% CI 0.06–3.25) p = 0.424; red blood cells transfusion a*OR* 0.34(95% CI 0.13–0.88), p =0.026; acute venous thromboembolism a*OR* 0.90(95% CI 0.21–3.75), p = 0.880; sepsis a*OR* 0.23(95% CI 0.03–1.72), p = 0.152; and ICU admission a*OR* 1.01(95% CI 0.36–2.84), p = 0.978 between the two groups (see Figure 1).

Figure 1. *Forest Plot Demonstrating Adjusted Odds Ratios of Primary and Secondary Outcomes in Multiple Myeloma Patients With and Without Opioid Use Disorder.*



Discussion

A majority of individuals with MM experience pain related to their course of disease. The pain may likely be due to osteolytic bone lesions or a tumor compressing a nerve. The leading causes of chronic pain in MM patients are as follows: (1) pain from myeloma bone disease (MBD); (2) chemotherapy-induced peripheral neuropathy as a possible consequence of proteasome inhibitor therapy (i.e., bortezomib-induced); (3) post-herpetic neuralgia as a possible complication of varicella-zoster virus reactivation because of post-transplantation immunodepression; and (4) chronic pain in cancer survivors (Coluzzi et al., 2019).

In addition to the pain and physiological effects and impacts MM has on patients, MM also plays a role in psychological impairment. When surviving the disease, patients are often left with chronic pain, fatigue, insomnia, depression, cognitive dysfunction, cancer-related neuropathies, psychological impairment, and reduced quality of life (Shapiro, 2018).

Opioids have long been considered the primary mode of treatment for cancer patients—particularly those with MM (Boland et al., 2013). Nevertheless, it should be noted that prolonged use of opioids is associated with an elevated risk of dependence and addiction called opioid use disorder (OUD), which is becoming more prevalent in the United States and affects millions of Americans. OUD involves the misuse of opioids, which include prescription pain relievers, heroin, and fentanyl. However, opioid prescribing practices have come under scrutiny due to their association with addiction and overdose (Barnes et al., 2019).

While studies on the effects of opioids on chronic pain management have been conducted, little attention has been given to its effects amongst hospitalized cancer patients with OUD. One study analyzing opioid prescribing at a safety-net hospital investigated the prescription of opioids upon hospital discharge among opioid-naïve patients. Researchers found that receiving opioids for chronic pain was associated with future chronic opioid use (Calcaterra et al., 2015). OUD, as a consequence of prescription, highlights how physicians may inadvertently contribute to the complex issue of opioid dependence while searching for pain solutions.

Our comprehensive study aims to further explore the intricate relationship between opioid use disorder and patients hospitalized with MM, noting its potential complications and adverse hospital outcomes. Through rigorous analysis, we analyzed how this disorder affects hospitalized cancer patients and their treatment. We aimed to offer insights that can uncover a more nuanced understanding of this critical issue for medical professionals across disciplines and inform future modes of care delivery, shedding new light on an important topic in healthcare research.

After conducting an in-depth analysis, our study concluded that there was no statistically significant difference in mortality rates between the opioid use disorder (OUD) patient populations and those without. It should be noted, however, that earlier studies showed an increase in mortality among OUD patients—both within the general population and among cancer patients specifically (Chino et al., 2020). Nevertheless, these earlier investigations were not specific to any particular type of cancer and may have been limited by inadequate documentation of active versus palliative treatment for such individuals. As such, while this research offers important insight into the impact of OUD on overall health outcomes across diverse patient groups, further investigation with prospective studies is necessary to gain a more comprehensive understanding of its complex implications for different types of cancer, as well as varying stages and forms of treatment modalities.

Opioids were found to be intricately linked with a notable rise in depressive tendencies among individuals (Semenkovich et al., 2014). The outcomes yielded by our study align with the preexisting body of research, thereby attesting to the veracity and reliability of the correlation between opioid usage and an upsurge in depression levels. Likewise, it was observed that individuals suffering from MM exhibited a higher prevalence of insomnia with concomitant opioid use in comparison to those who did not consume opioids.

Patients diagnosed with malignancies are known to experience a heightened risk of depression, insomnia, and other psychological symptoms from their underlying malignancies (Valentino & Volkow, 2020). These debilitating conditions can exacerbate patients' already compromised quality of life, creating an unbearable situation for both the patient and the healthcare providers involved in their care. Unfortunately, concomitant opioid use only serves to amplify these risks by further increasing the likelihood of major depressive disorders and insomnia amongst this vulnerable population group, as proven by our study (Georges et al., 2020; Vekaria et al., 2021).

MM patients are undoubtedly confronted with an array of daunting hurdles on their path to recovery, one of which is the possibility of developing delirium (Wildes & Campagnaro, 2017). This debilitating condition can arise from several contributing factors, such as underlying malignancy, cancer treatment regimens that involve opioids, and recreational OUDs, amongst other causes (Shah & Huecker, 2019). Our study successfully highlighted the increased likelihood of developing this potentially devastating form of cognitive impairment, which is faced by MM patients with concurrent OUD.

Patients with MM often endure the challenging experience of hypercalcemia, which is considered a major metabolic complication resulting from excessive osteolysis and is considered a poor prognostic indicator of the disease (Zagouri et al., 2017). In our study, we found compelling evidence indicating that myeloma patients with concomitant OUD are at an even higher risk of hypercalcemia compared to those without OUD. This observation raises significant concerns regarding the negative clinical outcomes opioids may have on patients' overall health and course of the disease.

Although no statistically significant difference in the length of hospitalization was observed between the two populations, total charges were lower in patients with OUD. This fact can be explained by the increased number of patients leaving against medical advice. However, other clinical adverse events, such as sepsis, acute respiratory failure, acute kidney injury, ICU admission, acute coronary syndrome, GI bleeding, blood transfusions, venous thromboembolism, anemia, and mechanical ventilation, were similar between the two groups.

In our comprehensive study, we assessed the intricate and multifaceted effects of opioid usage in patients who were hospitalized with MM. Our research, however, went beyond just exploring the immediate implications of opioid administration. We also sought to shed light on their long-term consequences. Specifically, we analyzed how these medications can significantly contribute to physical and psychological outcomes and hospital resource utilization, causing a domino effect that leads to adverse outcomes. These outcomes could be detrimental for both patients and healthcare facilities. As such, physicians must re-evaluate their approach to pain management for this vulnerable patient population—one where opioids might not always be the most effective solution. Adopting alternative modes of treatment—or considering other forms of medication altogether (while also keeping patient safety a top priority)—will help improve overall clinical outcomes while simultaneously optimizing resource allocation.

The National Inpatient Sample (NIS) has emerged as a popular and useful resource for various types of research, although it is critical to recognize its limitations to ensure the precision and validity of the data from this database. One such limitation pertains to the dependence of the NIS on administrative data. This dependence may lead to erroneous coding in diagnoses and procedures (Mori et al., 2019).

Another crucial shortcoming of NIS pertains to the exclusion criteria, which involves patients who are not admitted or treated at hospitals, those who are not part of the Healthcare Cost and Utilization Project (HCUP), or who received outpatient care but were not accounted for by NIS.

Additionally, while the massive sample size offered by the NIS helps build robust statistical models, its extensive coverage might result in biased prevalence and incidence estimates due to a lack of representativeness with smaller populations or rare events. Lastly, apart from issues with patient population selection biasing outcomes, measures like re-admission rates can also be impacted since post-discharge follow-ups are not included in the data.

Conclusion

The impact of opioid use disorder (OUD) on individuals with MM cannot be overstated and can have a multitude of adverse implications, such as the development or exacerbation of major depressive disorder, delirium, insomnia, and hypercalcemia. The physical and psychological outcomes—in addition to hospital resource utilization—are shown to have negative long-term impacts for both hospitals and hospitalized patients with concomitant MM and OUD. While some studies suggested that OUD is associated with high mortality rates, our research did not establish any correlation between these two factors.

The alarming surge in opioid usage has emerged as a critical issue, eliciting concerns regarding negative outcomes in hospitals. These concerns emphasize the pressing need to explore innovative ways to tackle pain management efficiently, as well as alleviate suffering without subjecting patients to potentially harmful and highly addictive drugs. Our study supports reinforcement for action toward developing alternative approaches, integrative therapy, and an increasingly holistic approach aimed at mitigating the benefits and risks of opioid use in a manner that results in fewer comorbidities and negative clinical outcomes for patients receiving opioid therapy for cancer treatment.

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