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ORIGINAL ARTICLE

Observational Study

Impact of depression on in-hospital outcomes for adults with type 2 myocardial infarction: A United States population-based analysis

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Abstract

BACKGROUND

Type 2 myocardial infarction (T2MI) is an ischemic myocardial injury in the context of oxygen supply/demand mismatch in the absence of a primary coronary event. However, though there is a rising prevalence of depression and its potential association with type 1 myocardial infarction (T1MI), data remains non-existent to evaluate the asso-ciation with T2MI.

AIM

To identify the prevalence and risk of T2MI in adults with depression and its impact on the in-hospital outcomes.

METHODS

We queried the National Inpatient Sample (2019) to identify T2MI hospitalizations using Internal Classification of Diseases-10 codes in hospitalized adults (≥ 18 years). In addition, we compared sociodemographic and comorbidities in the T2MI cohort with *vs* without comorbid depression. Finally, we used multivariate regression analysis to study the odds of T2MI hospitalizations with *vs* without depression and in-hospital outcomes (all-cause mortality, cardiogenic shock, cardiac arrest, and stroke), adjusting for confounders. Statistical significance was

achieved with a *P* value of < 0.05.

RESULTS

There were 331145 adult T2MI hospitalizations after excluding T1MI (median age: 73 years, 52.8% male, 69.9% white); 41405 (12.5%) had depression, the remainder; 289740 did not have depression. Multivariate analysis revealed lower odds of T2MI in patients with depression *vs* without [adjusted odds ratio (aOR) = 0.88, 95% confidence interval (CI): 0.86-0.90, *P* = 0.001]. There was the equal prevalence of prior MI with any revascularization and a similar prevalence of peripheral vascular disease in the cohorts with depression *vs* without depression. There is a greater prevalence of stroke in patients with depression (10.1%) *vs* those without (8.6%). There was a slightly higher prevalence of hyperlipidemia in patients with depression *vs* without depression (56.5% *vs* 48.9%), as well as obesity (21.3% *vs* 17.9%). There was generally equal prevalence of hypertension and type 2 diabetes mellitus in both cohorts. There was no significant difference in elective and non-elective admissions frequency between cohorts. Patients with depression *vs* without depression also showed a lower risk of all-cause mortality (aOR = 0.75, 95%CI: 0.67-0.83, *P* = 0.001), cardiogenic shock (aOR = 0.65, 95%CI: 0.56-0.76, *P* = 0.001), cardiac arrest (aOR = 0.77, 95%CI: 0.67-0.89, *P* = 0.001) as well as stroke (aOR = 0.79, 95%CI: 0.70-0.89, *P* = 0.001).

CONCLUSION

This study revealed a significantly lower risk of T2MI in patients with depression compared to patients without depression by decreasing adverse in-hospital outcomes such as all-cause mortality, cardiogenic shock, cardiac arrest, and stroke in patients with depression.

Key Words: Type 2 myocardial infarction; Depression; Major adverse cardiovascular events; Mortality; Stroke; Cardiac arrest; Outcomes

Core Tip: We studied the prevalence and risk of type 2 myocardial infarction (T2MI) in adults with depression and its impact on the in-hospital outcomes which revealed a significantly lower risk of T2MI in patients with depression compared to patients without depression by decreasing adverse in-hospital outcomes. Our study revealed decreased risks of all-cause mortality, cardiogenic shock, and cardiac arrest during T2MI hospitalization in patients with depression.

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INTRODUCTION

Coronary heart disease (CHD) and depression have become a global health problem[1,2]. In 2020, in the United States, CHD was the leading cause of morbidity and mortality (41.2%), with approximately 382800 deaths[3]. CHD is a syndrome characterized by myocardial cell death caused by ischemia resulting from the imbalance of supply and demand[4]. Myocardial infarction has been subclassified according to pathogenesis in 2007[4]. Type 1 myocardial infarction (T1MI) is a spontaneous episode occurring due to atherothrombosis or thrombus from an atherosclerotic plaque[4,5] or in the absence of acute atherothrombosis, known as T2MI[3,4]. Although disrupted atherosclerotic thrombus has remained the hallmark cause of acute MI, multiple other mechanisms are known to cause myocardial injury. However, definitive diagnostic and therapeutic strategies are yet to be defined[4,6].

Depression is one of the most common, debilitating illnesses, affecting around 26% of women and 18% of men in the United States[7]. Depression is more common in patients with acute MI, affecting approximately 20% of patients during the hospitalization with MI and over the first year after hospitalization[8], and has been classified as a significant risk factor for poor prognosis among patients with CHD[9]. Both mental illness and CHD have been imposing a significant economic and social burden due to their higher prevalence in high- and middle-income countries[10]. Several studies in recent years have reported growing evidence of links between depression and CHD[11,12], with a higher prevalence of depression among patients following acute myocardial infarction hospitalizations ranging from 15%-32%[13,14], which is also an independent predictor of increased mortality after acute MI[14,15]. Recently, a multicenter cohort observational study (TRIUMPH trial) done by Smolderen *et al*[8] showed that depression in patients with acute MI has been associated with long-term mortality but is mainly confined to untreated depression. A meta-analysis done by Barth *et al*[16] found that depression in MI is associated with a 2.5 times higher risk of mortality. Similarly, a meta-analysis done by van Melle *et al*[17] and Nicholson *et al*[11] found an increased risk of 2.0-2.5 times poor cardiac and mortality outcomes in 2 years after an MI in depression patients.

Although the majority of CHD trials were focused mainly on the role of biological risk factors, including smoking, hyperlipidemia, obesity, hypertension, diabetes mellitus, and lifestyle, more recently, stress, anxiety, and depression have been reported as the most significant risk factors for the coronary artery disease (CAD) even after controlling biological factors[18]. However, previous research studies have several limitations concerning causal interference. Despite the increasing occurrence of depression and its potential link to T1MI, there is a lack of data to assess this relationship with T2MI. Our objective is to determine the prevalence and risk of T2MI in adults with depression, as well as to examine its influence on in-hospital outcomes.

MATERIALS AND METHODS

Design and data source

In this retrospective observational study, we analyzed the National Inpatient Sample datasets for 2019, which are available through the Healthcare Cost and Utilization Project. The National Inpatient Sample is a large publicly available database representing 95% of hospitalizations in the United States, covering 48 states and the District of Columbia. We utilized the Internal Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) code I21.A1 to identify the principle of T2MI hospitalizations. This is an observational study looking at the prevalence and risk of T2MI in adults with depression and its impact on in-hospital outcomes. Comorbid depression was identified using these codes - F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2. Primary outcomes, including cardiovascular events, were identified using previously reported and validated ICD-10-CM codes or clinical classification software codes (The Clinical Classifications Software Refined groups ICD-10-CM/PCS codes into practical categories).

Study population and characteristics

Using the ICD-10 codes for 2019, we included hospitalized adult patients with a diagnosis of T2MI, excluding cases with T1MI.

Outcome measures

The primary outcome of this study is to assess the odds of T2MI and subsequent major adverse cardiovascular events (MACE: All-cause mortality, cardiogenic shock, cardiac arrest, and stroke) in T2MI patients with *vs* without comorbid depression. Secondary outcomes included health care utilization and length of hospitalization stay. We compared socio-demographic and comorbidities in the T2MI cohorts with *vs* without comorbid depression. Patient confounders were adjusted with multivariable regression analyses, which are known to have prognostic implications for our outcomes.

Statistical analysis

Patient characteristics and in-hospital outcomes were compared among patients with depression who were admitted with T2MI. Categorical data was displayed in percentages, and continuous data was represented using the median and interquartile range for non-normally distributed data. A P value below 0.05, determined through a two-tailed test, was deemed to show significance. National estimates were generated by leveraging the database's discharge weight and utilizing sample modules for analysis. Odds ratios (OR) and their 95% confidence intervals (CI) were obtained using multivariable logistic regression for in-hospital mortality and outcomes. The multivariable logistic regression was adjusted for covariates such as age, gender, race, zip code-based income quartile, primary payer, and a range of co-morbidities and prior conditions, including acquired immunodeficiency syndrome, alcohol and drug abuse, arthritis, hypertension (complicated and uncomplicated), diabetes (complicated and uncomplicated), hyperlipidemia, obesity, peripheral vascular disease, prior myocardial infarction with or without revascularization, tobacco use disorder, chronic lung disease, hypothyroidism, other thyroid disorders, previous MI or transient ischemic attack/stroke, and cancer. All reported P values are two-sided, with a value of < 0.05 considered significant. Statistical analyses were conducted using IBM SPSS Statistics 25.0 software (IBM Corp, Armonk, NY, United States).

RESULTS

Baseline characteristics

We identified 331145 adult T2MI hospitalizations after excluding T1MI cases. The median age was 73 years, 52.8% male and 69.9% white. Among these hospitalizations, 41405 (12.5%) had depression, leaving the remaining 289740 without depression. The T2MI+D+ cohort, in comparison with the T2MI-D- cohort, often consisted of younger (median age, 71 *vs* 73) females (59.9% *vs* 45.4%), with both cohorts predominantly including white (78.4, 68.7) (Table 1). T2MI-D+ had 4530 (11.2%), and T2MI-D- had 47880 (16.9%) black patients. The Hispanic population comprised 2490 (6.1%) in the T2MI+D+ cohort and 22790 (8.1%) in the T2MI+D- cohort. Both groups primarily had medicare-enrolled patients, 207830 (71.8%) in the T2MI-D- *vs* 30400 (73.5%) in T2MI+D+. Private insurance, including Health Maintenance Organization, was the next most common-36125 (12.5%) in T2MI+D- while medicaid was next most common in T2MI-D+ 4575 (11.1%).

Elective and non-elective admissions frequency did not differ significantly between cohorts. The prevalence of prior MI with any revascularization and peripheral vascular disease was comparable among cohorts with and without depression. However, patients with depression showed a higher prevalence of stroke at 10.1% compared to those without depression at 8.6%. Additionally, patients with depression exhibited a slightly higher prevalence of hyperlipidemia (56.5% *vs* 48.9%)

Table 1 Demographic characteristics and comorbidities in type 2 myocardial infarction-related hospitalizations with *vs* without depression

	Depression		Total T2MI, *n* = 331145	*P* value
	No, *n* = 289740	Yes, *n* = 41405		
Age at admission				
Median (IQR)	73 (62-83)	71 (61-81)	73 (62-82)	< 0.001
18-44 years	5.4%	5.0%	5.3%	
45-64 years	24.1%	27.6%	24.6%	
≥ 65 years	67.3%	70.1%	70.5%	
Sex				< 0.001
Male	54.6%	40.1%	52.8%	
Female	45.4%	59.9%	47.2%	
Race				< 0.001
White	68.7%	78.4%	69.9%	
Black	16.9%	11.2%	16.2%	
Hispanic	8.1%	6.1%	7.8%	
Asian or Pacific Islander	2.8%	1.4%	2.6%	
Native American	0.8%	0.9%	0.9%	
Others	2.8%	2.0%	2.7%	
Median household income quartile for patient zip code				< 0.001
0-25th	32.9%	31.2%	32.7%	
26-50th	26.5%	27.2%	26.6%	
51-75th	23.1%	23.6%	23.2%	
76-100th	17.5%	17.9%	17.5%	
Primary expected payer				< 0.001
Medicare	71.8%	73.5%	72.0%	
Medicaid	10.4%	11.1%	10.5%	
Private including HMO	12.5%	10.8%	12.3%	
Self-pay	2.9%	2.1%	2.8%	
No charges	0.2%	0.1%	0.2%	
Others	2.2%	2.4%	2.2%	
Type of admission				0.985
Non-elective	97.0%	97.0%	97.0%	
Elective	3.0%	3.0%	3.0%	
Location/teaching status of hospital				< 0.001
Rural	8.4%	9.0%	8.5%	
Urban non-teaching	15.6%	15.2%	15.5%	
Urban teaching	76.0%	75.8%	76.0%	
Region of hospital				< 0.001
Northeast	22.9%	21.7%	22.8%	
Midwest	23.1%	27.9%	23.7%	
South	35.0%	33.4%	34.8%	

West	19.0%	17.0%	18.7%	
Comorbidities				
Alcohol abuse	4.9%	0.6%	5.0%	< 0.001
Arthropathies	4.1%	5.8%	4.3%	< 0.001
Dementia	10.9%	15.8%	11.6%	< 0.001
Hypertension, complicated	49.9%	49.2%	49.8%	0.006
Hypertension, uncomplicated	19.9%	22.6%	20.2%	< 0.001
Diabetes with chronic complications	31.5%	32.4%	31.6%	< 0.001
Diabetes without chronic complications	9.0%	8.9%	9.0%	0.244
Hyperlipidemia	48.9%	56.5%	49.9%	< 0.001
Obesity	17.9%	21.3%	18.4%	< 0.001
Peripheral vascular disease	11.3%	11.6%	11.3%	0.095
Prior MI	12.2%	13.2%	12.3%	< 0.001
Prior TIA/stroke	8.6%	10.1%	8.8%	< 0.001
Drug abuse	5.0%	7.4%	5.3%	< 0.001
Tobacco use disorder	15.5%	19.4%	16.0%	< 0.001
Chronic pulmonary disease	31.4%	38.9%	32.3%	< 0.001
Hypothyroidism	15.0%	21.3%	15.8%	< 0.001
Other thyroid disorders	1.5%	1.9%	1.5%	< 0.001
Anxiety & fear related disorders	9.0%	39.3%	9.0%	< 0.001
Cancer	9.3%	7.7%	9.1%	< 0.001

$P < 0.05$ indicates statistical significance. IQR: Interquartile range; HMO: Health Maintenance Organization; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; TIA: Transient ischemic attack; T2MI: Type 2 myocardial infarction.

and obesity (21.3% *vs* 17.9%) compared to those without depression. Nonetheless, there was generally an equal prevalence of hypertension and type 2 diabetes mellitus in both cohorts.

Primary outcomes

Table 2 reveals significant differences in in-hospital outcomes for T2MI patients with versus without depression. Notably, patients with depression exhibited a lower all-cause mortality rate (5.8%) compared to those without depression (8.4%), alongside reduced incidences of cardiogenic shock, dysrhythmias, cardiac arrest, and stroke, with all differences being statistically significant ($P < 0.001$). After adjusting for potential confounders in a multivariable logistic regression analysis, the findings revealed that patients with depression had significantly lower odds of experiencing T2MI compared to those without depression [adjusted OR (aOR) = 0.88, 95%CI: 0.86-0.90, $P = 0.001$] (Table 3). Additionally, patients with depression were found to have lower risks of all-cause mortality (aOR = 0.75, 95%CI: 0.67-0.83, $P = 0.001$), cardiogenic shock (aOR = 0.65, 95%CI: 0.56-0.76, $P = 0.001$), cardiac arrest (aOR = 0.77, 95%CI: 0.67-0.89, $P = 0.001$), and stroke (aOR = 0.79, 95%CI: 0.70-0.89, $P = 0.001$) compared to patients without depression.

Secondary outcomes

For patients without depression, hospitalizations are associated with higher costs compared to patients with depression (median $53592 and $50156, respectively) without any change in length of stay with a median of 5 days. In contrast, patients with depression were most frequently transferred to skilled nursing facilities compared to patients without depression (32.7% *vs* 27.7%). This difference could reflect a need for more extended care or rehabilitation services in patients with depression (Table 2).

DISCUSSION

This study is one of the most extensive population-based outcome studies to explore the association between depression and the risks of T2MI, as well as its impact on incidence, demographics, and in-hospital outcomes. The study included a total of 331415 patients from the publicly available National Inpatient Sample 2019 database, of whom 41405 (12.5%) had depression. The clinical findings from this large observational study indicate that patients with depression showed an

Table 2 In-hospital outcomes in type 2 myocardial infarction hospitalizations in patients with *vs* without depression

	No depression (*n* = 289740)	Depression (*n* = 41405)	Total T2MI (*n* = 331145)	*P* value
All-cause mortality	8.4%	5.8%	8.1%	< 0.001
Cardiogenic shock	3.5%	2.2%	3.4%	< 0.001
Dysrrhythmia	43.8%	40.2%	43.3%	< 0.001
Cardiac arrest including ventricular fibrillation	3.4%	2.4%	3.3%	< 0.001
Stroke	5.3%	4.1%	5.2%	< 0.001
Disposition of patient				< 0.001
Routine	39.9%	36.4%	39.5%	
Transfers to short-term hospitalization	3.5%	2.9%	3.4%	
Transfer other includes: Skilled nursing facility, intermediate care facility, another type of facility	27.7%	32.7%	28.3%	
Home health care	19.0%	20.7%	19.2%	
Length of stay (days), median (IQR)	5 (3-9)	5 (3-8)	5 (3-9)	0.243
Total charges USD, median (IQR)	53592 (29003-105279)	50156 (28249-90301)	53139 (28872-103331)	< 0.001

P < 0.05 indicates statistical significance. IQR: Interquartile range; T2MI: Type 2 myocardial infarction.

Table 3 Multivariable odds ratios for type 2 myocardial infarction and subsequent major adverse cardiac outcomes associated with depression

Outcome	Predictor	Odds ratio	95% confidence interval	*P* value
T2MI	Depression	0.88	0.86-0.90	< 0.001
In T2MI patients				
In-hospital all-cause mortality	Depression	0.75	0.67-0.83	< 0.001
Cardiogenic-shock	Depression	0.65	0.56-0.76	< 0.001
Cardiac arrest including ventricular fibrillation	Depression	0.77	0.67-0.89	0.001
Stroke	Depression	0.79	0.70-0.89	< 0.001

The multivariable logistic regression analysis was adjusted for a comprehensive set of covariates, including age category, gender, race, income quartile based on zip code, primary payer, and a variety of comorbidities and prior conditions. These comorbidities encompassed acquired immunodeficiency syndrome, alcohol abuse, arthritis, both complex and uncomplicated hypertension, complex and uncomplicated diabetes, hyperlipidemia, obesity, peripheral vascular disease, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft, drug abuse, tobacco use disorder, chronic lung disease, hypothyroidism, other thyroid disorders, prior transient ischemic attack or stroke without neurologic deficit, and cancer. T2MI: Type 2 myocardial infarction.

inverse correlation with T2MI compared to patients without depression. It was observed that patients with depression had lower odds of all-cause mortality, cardiogenic shock, cardiac arrest, and stroke. Additionally, the study found that patients with depression had lower hospitalization costs with a similar mean length of stay compared to patients without depression. Previous studies have shown that depression is a significant risk factor for the development of CAD. Still, there is limited evidence for the impact of depression on T2MI.

This study also identified significant variations in the prevalence of depression among T2MI patients based on gender, with potential explanations including disparities in biological factors such as hormones, as well as psychosocial factors [19]. Another study indicated that female cohorts with CHD were at a 1.77-fold higher risk of experiencing depression compared to male cohorts[20]. Furthermore, we observed notable differences in the prevalence of depression in T2MI admissions based on race and region, with higher rates in white patients and increased prevalence in urban teaching hospitals, possibly reflecting variances in socioeconomic and sociocultural characteristics, as seen in other studies[21].

The presence of major depressive disorder has been associated with increased susceptibility to CAD, which raises the risk of illness and death despite advancements in medical and interventional treatments[3,9,14,15,18,22]. The precise mechanisms by which depression contributes to a heightened risk of CAD are not entirely understood[11,12]. However,

several potential causes of CAD in individuals with depression have been suggested, including heightened platelet aggregation[23,24], increased levels of inflammatory markers, elevated catecholamine levels, alterations in cortisol levels, heightened sympathetic tone, potential variability in heart rate, sedentary lifestyle, and non-adherence to prevention and treatment of risk factors. A meta-analysis by Barth *et al*[16] and Nicholson *et al*[11] disclosed an increased probability of CAD in people with depression, as well as a twofold rise in mortality over two years. However, our study discovered that the occurrence of depression among admissions for T2MI is roughly 12.5%. Additionally, we noted that patients with depression have a higher prevalence of obesity (21.3% *vs* 17.9%) and hyperlipidemia (56.5% *vs* 48.9%), likely due to changes in lifestyle and diet.

Patients with depression were at a two to fourfold increased risk of developing CAD at some point in their lifetime[25,26]. Several other epidemiological studies have emphasized the higher incidence of depression in patients with ischemic heart diseases, particularly within the first one to two years[27,28]. While there have been no studies in the literature examining the impact of depression on T2MI and outcomes, our study revealed decreased risks of all-cause mortality, cardiogenic shock, and cardiac arrest during T2MI hospitalization in patients with depression. This contrasts previous studies on T1MI and depression, as several meta-analyses have previously indicated a 10%-25% increased risk of all-cause mortality and cardiovascular mortality in patients with T1MI and depression[29,30]. The exact mechanism of how there is a protective effect with depression and T2MI is unknown. However, Serebruany *et al*[31] demonstrated that patients who are on anti-depressants have a favorable impact on the outcomes, possibly due to changes in serotonin activity, which we couldn't access in our study, which might impact the outcomes.

Several theories have been proposed in the literature regarding the potential link between depression, atherosclerosis, and stroke. One theory involves neuroendocrine dysfunction resulting from the dysregulation of the hypothalamic-pituitary-adrenocortical axis, platelet aggregation dysfunction[32], and immunological/inflammatory effects[33], which may elevate the risk of stroke. In recent years, studies have indicated that inflammatory cytokines, such as interleukins (IL-1, IL-2, IL-6), C-reactive protein, tumor necrosis factor α, IL-1β, and P-selectin, play a significant role in the development and rupture of atherosclerosis plaques, which are major contributors to CAD and stroke[34]. Our study has suggested a paradoxical lower risk of stroke in patients admitted with depression and T2MI. This could be attributed to variations in neurotransmitters or pathways in T2MI patients. Additionally, selective serotonin reuptake inhibitor medication may have protective effects against stroke, as indicated in previous research, beyond its antidepressant effects [35]. However, some other studies found a positive association between anti-depressants and stroke risk[36].

In this research, the unexpected discovery that depression may be linked to improved clinical outcomes in a cardiac context could be influenced by various factors. Patients with a depression diagnosis might receive careful monitoring and treatment due to perceived higher risks, leading to early identification and management of complications. Furthermore, the unique psychological traits of these individuals could affect their perception of pain and reporting, potentially influencing the nature and timing of the care they receive. Additionally, there is a possibility that certain antidepressant medications might unintentionally have beneficial effects on the heart, as suggested by studies exploring the cardiovascular impacts of psychiatric therapies. This surprising association emphasizes the complexity of mental health's influence on cardiovascular health outcomes. It underscores the need for further research to fully understand the underlying mechanisms and potential clinical implications for patients with depression or other mental health disorders in the context of T2MI.

Future directions

This study examining the link between depression and T2MI and associated subsequent MACE provided preliminary insights and paved the way for future prospective investigations. Its strength lies in analyzing a large dataset with more generalizable findings, minimized selection bias and controlled confounders in comprehensive multivariable analysis ensuring the reliability of its findings. Additionally, future longitudinal research could address limitations by exploring stages and severity of depression, medication adherence and social influences to enhance our knowledge of the link between depression and T2MI outcomes.

Limitations

Our study has several limitations. Firstly, we focused our analysis on T2MI hospitalizations using ICD-10 codes in adults aged 18 and above, which helped minimize selection bias by narrowing down the study population. We utilized the National Inpatient Sample for 2019 and identified cohorts admitted with T2MI using ICD-10 codes. However, this approach may introduce the possibility of misclassification, particularly regarding height and weight measurements. Nonetheless, this potential misclassification should be consistent among survivors and non-survivors, thus not significantly affecting the interpretation of the results. We did not consider different stages of depression, which could potentially impact the population in various ways. Furthermore, it is crucial to have access to more comprehensive data concerning the medication status, social determinants, and adherence of the cohorts. These variables have the potential to serve as confounding factors, especially about mortality within the demographic afflicted by depression. However, it is essential to note that the substantial sample size of our study enhances its statistical robustness, helping to mitigate the limitations above.

CONCLUSION

This study revealed a significantly lower risk of T2MI related admissions in patients with depression compared to patients without depression and lower odds of adverse in-hospital outcomes such as all-cause mortality, cardiogenic

shock, cardiac arrest, and stroke in T2MI patients with depression. It's important to consider potential confounding variables that could influence the study outcomes, such as medication usage, psychosocial factors, and the different stages of depression, all of which play a crucial role in the progression of the disease and the outcomes. Previous studies have not explored the impact of depression on T2MI outcomes, and further prospective studies are needed to evaluate the influence of depression on various in-hospital outcomes across different stages of depression. Additionally, it is essential to investigate the effects of medication, duration, and serotonin levels on T2MI.

FOOTNOTES

Author contributions: Neppala S and Desai R contributed to the resources of this manuscript; Neppala S, Chigurupati HD, Chinthapalli MT, and Desai R participated in the writing-original draft of this article; Neppala S, Chauhan S, and Desai R were involved in the visualization; Chigurupati HD, Chauhan S, Chinthapalli MT, and Desai R took part in the writing - review & editing; Chauhan S and Desai R contributed to the conceptualization and methodology of this manuscript; Chauhan S participated in the supervision of this study; Desai R contributed to the software and formal analysis of this manuscript. All authors have read and approved the final manuscript.

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