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Original Article

Mortality Predictors and In-Hospital Outcomes in High Killip Class STEMI Patients: Insights from a Tertiary Cardiac Center

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Abstract

Objectives: Patients with ST elevation myocardial infarction (STEMI) presenting with high Killip class face an elevated risk of adverse outcomes. This study aimed to evaluate the in-hospital outcomes and identify predictors of mortality in such patients admitted to the intensive care unit (ICU) after primary percutaneous coronary intervention (PCI) at a tertiary cardiac center in a low-middle income country.

Methodology: A descriptive cross-sectional study was conducted in the ICU of a tertiary cardiac center in Pakistan. The study included adult patients (≥18 years) with high Killip class (≥III) at presentation, diagnosed with STEMI, and admitted to the ICU following primary PCI. Patients were monitored for adverse events, and mortality predictors were analyzed using binary logistic regression.

Results: A total of 125 patients were enrolled, with a predominance of males (62.4%) and a mean age of 61.7 ± 10.6 years. Most patients presented with Killip Class III (76%). The mean SOFA and APACHE II scores at ICU admission were 6 ± 2.9 and 13.1 ± 6.0, respectively. The in-hospital mortality rate was 28.0% (35/125). Multivariable analysis identified sub-optimal post-procedure TIMI flow (<III) and higher SOFA score as independent predictors of mortality, with adjusted odds ratios (ORs) of 11.08 [95% CI: 2.39-51.27] and 1.47 [95% CI: 1.11-1.94], respectively. Conversely, placement of an intra-aortic balloon pump was associated with a significantly reduced mortality risk (adjusted OR 0.07 [95% CI: 0.01-0.38]).

Conclusion: The study found a high in-hospital mortality rate among STEMI patients with high Killip class. Sub-optimal post-procedure TIMI flow and elevated SOFA scores were significant predictors of mortality, whereas intra-aortic balloon pump placement was associated with improved survival.

Keywords: ST elevation myocardial infarction (STEMI), Killip classification, intensive care unit (ICU), mortality, predictors

INTRODUCTION

Cardiovascular diseases (CVD) are a leading cause of global mortality, accounting for nearly one-third of all deaths. This alarming statistic is compounded by aging populations and demographic shifts, particularly in East and South Asia, where there has been a notable 12.5% increase in CVD-related deaths [1]. Ischemic heart diseases (IHD), including myocardial infarction and stroke, are primary contributors to this burden, underscoring the urgent need for effective management strategies [2].

Among the acute manifestations of IHD, ST-segment elevation myocardial infarction (STEMI) represents a significant cause of morbidity and mortality worldwide [3]. Recent advancements in evidence-based management, particularly primary percutaneous coronary intervention (PCI), have significantly improved outcomes for STEMI patients [4]. Timely administration of primary PCI, ideally within 12 hours of symptom onset, is now considered the gold standard for treating STEMI, offering substantial benefits in reducing mortality and improving patient outcomes [5,6].

Despite these advancements, a significant proportion of STEMI patients continue to experience adverse clinical outcomes, including vascular complications, bleeding events, renal impairments, and increased mortality [7]. Although mortality rates have declined, there has been a concurrent rise in post-infarction heart failure. The Killip Classification remains a vital tool in assessing risk, with higher Killip classes at admission being associated with a greater likelihood of adverse cardiovascular events and elevated mortality, regardless of the presence of obstructive coronary artery disease [8-10]. Consequently, timely reperfusion strategies, particularly primary PCI, are crucial in managing high-risk STEMI patients, offering benefits such as reduced infarct size and preserved left ventricular function [9-12].

Effective risk assessment and vigilant monitoring of hemodynamic parameters are essential in identifying high-risk patients, facilitating prompt interventions, and optimizing management strategies [13,14]. This study aims to evaluate the in-hospital outcomes and predictors of mortality among STEMI patients with high Killip class (≥ III) admitted to the intensive care unit (ICU) after primary PCI, focusing on a tertiary cardiac center in a low-middle income country to provide insights into improving patient care in similar settings.

METHODOLOGY

Study Design: This descriptive cross-sectional study was conducted to capture a comprehensive snapshot of adult patients presenting with ST-Elevation Myocardial Infarction (STEMI) in the intensive care unit (ICU) of the National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan. The study spanned from February 1, 2023, to June 30, 2023. This design provides a momentary view of patient characteristics, treatment responses, and outcomes within a specific timeframe, facilitating an in-depth analysis of the patient population during the study period.

Setting: The research was conducted in the ICU of NICVD, a leading institution in Karachi specializing in cardiovascular care. The setting was selected due to its high volume of acute cardiac cases and its adherence to standardized treatment protocols for STEMI patients.

Participants: The study focused on adult patients aged 18 years or older who presented with ST-Elevation Myocardial Infarction (STEMI) and were classified as Killip Class III or IV upon arrival at the emergency room. Killip Classes III and IV represent severe forms of myocardial infarction, indicating significant clinical implications and a higher risk of adverse outcomes. Exclusion criteria were carefully defined to ensure the study's relevance and reliability: patients classified as Killip Class I or II were excluded, as were those who refused to provide informed consent. These criteria helped narrow the focus to a specific subset of severe STEMI cases, enhancing the precision and applicability of the study findings.

Variables: The study examined several key variables to understand the impact of severe STEMI on patient outcomes. Primary variables included demographic details such as age, sex, and comorbid conditions. Clinical characteristics of interest encompassed Killip class, initial electrocardiogram (ECG) findings, and the treatment interventions administered. Outcome measures were comprehensive and included adverse

events (e.g., re-intubation, bleeding, arrhythmias), mortality, and the length of both hospital and ICU stays. Additionally, severity scores such as the APACHE II and SOFA scores were used to quantify disease severity and predict mortality risk, providing a quantitative assessment of patient condition.

Data Sources/Measurement: Diagnosis of STEMI was confirmed by experienced cardiologists based on presenting symptoms and initial 12-lead ECGs, following the fourth universal definition of myocardial infarction. Treatment adhered to institutional protocols, with the primary focus on fixing the infarct-related artery and planning elective PCI for multivessel disease. Data were systematically collected using a structured proforma, capturing demographic, clinical, and outcome data. Objective measures included APACHE II and SOFA scores to assess severity and risk.

Bias: To minimize bias, the study employed several strategies. Stringent inclusion and exclusion criteria were established to ensure a homogeneous study population, thereby reducing variability in the sample. A structured data collection form was utilized to standardize the acquisition of data, further enhancing the consistency of the information gathered. Additionally, adherence to institutional protocols for diagnosis and treatment helped reduce variability in patient care, contributing to the overall validity of the study's findings.

Study Size: The study included all eligible adult patients with STEMI classified as Killip Class III or IV who presented during the study period. The final sample size was determined by the number of patients meeting the inclusion criteria within the specified timeframe.

Quantitative Variables: Quantitative variables in the study included various measures of patient and clinical characteristics. Demographic data, such as age, were treated as continuous variables to allow for detailed statistical analysis. Clinical severity scores, specifically the APACHE II and SOFA scores, were also analyzed as continuous variables. Outcome measures, including the duration of hospital and ICU stays and the occurrence of specific clinical events (e.g., re-intubations and bleeding episodes), were recorded and analyzed to assess their impact and significance in the context of severe STEMI.

Ethics: The study was approved by the Institutional Review Board (IRB) of NICVD. Informed consent was obtained from all participants or their legal representatives, ensuring compliance with ethical standards and the protection of participants' rights and welfare throughout the study.

Statistical Methods: Data analysis was performed using Microsoft Excel 2013 and IBM SPSS software, version 21. Descriptive statistics, including frequencies, means, and standard deviations, were used to summarize the data. Comparative analyses were conducted using Chi-square tests and independent sample t-tests to identify significant differences between groups. Univariate and multivariable binary logistic regression analyses were employed to determine predictors of in-hospital mortality. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess the strength of associations. All analyses were conducted at a significance level of 0.05.

RESULTS

Participants: A total of 125 patients were enrolled in the study, of which 78 (62.4%) were male. The mean age of the participants was 61.7 ± 10.6 years. At presentation, 95 (76%) patients were classified as Killip Class III, while 30 (24%) were classified as Killip Class IV. Upon admission to the ICU, the mean SOFA score was 6 ± 2.9, and the mean APACHE II score was 13.1 ± 6.0.

Descriptive Data: Table 1 summarizes the clinical and demographic characteristics of the patients. The average age was similar between those who survived and those who did not, with no statistically significant difference (61.3 ± 10.4 years for survivors vs. 62.6 ± 11.1 years for non-survivors; p=0.567). Gender distribution showed no significant difference between survivors and non-survivors (p=0.633). The majority of patients (76%) were categorized as Killip Class III, with 24% in Killip Class IV. The mean SOFA score at admission was significantly higher in non-survivors compared to survivors (8.1 ± 2.7 vs. 5.2 ± 2.5; p<0.001), and similarly, the mean APACHE II score

was higher in non-survivors (16.6 ± 6.6 vs. 11.7 ± 5.2; p<0.001).

Outcome Data: Table 2 presents data on the hospital course and angiographic findings. The in-hospital mortality rate was 28.0% (35/125). Non-survivors had a significantly higher rate of cardiopulmonary resuscitation (CPR) compared to survivors (37.1% vs. 15.5%; p=0.008). Among patients who underwent CPR, those who died had a higher rate of failure to achieve target post-procedure TIMI III flow (40.0% vs. 6.7%; p<0.001) and a higher requirement for vasopressors/inotropic support (97.1% vs. 72.2%; p=0.002). Arrhythmias were more common in non-survivors (40.0% vs. 15.6%; p=0.003).

Table 3 details the results of the multivariable logistic regression analysis. Post-procedure TIMI flow < III and SOFA Score at admission were identified as independent predictors of in-hospital mortality, with adjusted odds ratios (ORs) of 11.08 [95% CI: 2.39 - 51.27] and 1.47 [95% CI: 1.11 - 1.94], respectively. In contrast, the use of an intra-aortic balloon pump (IABP) was associated with a significantly reduced mortality risk, with an adjusted OR of 0.07 [95% CI: 0.01 - 0.38].

Table 1: Clinical and demographic data for the STEMI patients with high Killip class (≥III) admitted to ICU after primary PCI

	Total	In-hospital Outcome		P-value
		Survived	Died	
Total (N)	**125**	**90 (72%)**	**35 (28%)**	-
Gender				
Male	78 (62.4%)	55 (61.1%)	23 (65.7%)	0.633
Female	47 (37.6%)	35 (38.9%)	12 (34.3%)	
Age (years)	61.7 ± 10.6	61.3 ± 10.4	62.6 ± 11.1	0.567
Killip class				
III	95 (76%)	72 (80%)	23 (65.7%)	0.093
IV	30 (24%)	18 (20%)	12 (34.3%)	
Intubation	123 (98.4%)	89 (98.9%)	34 (97.1%)	0.485
Catheterization laboratory	26 (20.8%)	20 (22.2%)	6 (17.1%)	
Intensive care unit	3 (2.4%)	1 (1.1%)	2 (5.7%)	0.388
Emergency department	94 (75.2%)	68 (75.6%)	26 (74.3%)	
Cardiopulmonary resuscitation (CPR)	27 (21.6%)	14 (15.6%)	13 (37.1%)	0.008
***Rhythm at the time of CRP**				
Asystole	2 (7.4%)	1 (7.1%)	1 (7.7%)	
Pulseless electrical activity	2 (7.4%)	0 (0%)	2 (15.4%)	
Ventricular tachycardia	14 (51.9%)	9 (64.3%)	5 (38.5%)	0.486
Ventricular fibrillation	3 (11.1%)	1 (7.1%)	2 (15.4%)	
Bradyarrest	6 (22.2%)	3 (21.4%)	3 (23.1%)	
***Duration of CRP**				
Less than 6 minutes	10 (37%)	7 (50%)	3 (23.1%)	
6 to 10 minutes	11 (40.7%)	6 (42.9%)	5 (38.5%)	0.172
10 to 14 minutes	3 (11.1%)	1 (7.1%)	2 (15.4%)	
More than 14 minutes	3 (11.1%)	0 (0%)	3 (23.1%)	
Type of MI				
Anterior wall MI	77 (61.6%)	57 (63.3%)	20 (57.1%)	
Anterolateral wall MI	3 (2.4%)	2 (2.2%)	1 (2.9%)	
Infero-posterior wall MI with RV infract	2 (1.6%)	1 (1.1%)	1 (2.9%)	
Inferior wall MI with RV infarct	11 (8.8%)	6 (6.7%)	5 (14.3%)	
Anterior wall MI with RBBB	13 (10.4%)	10 (11.1%)	3 (8.6%)	0.898
Infero-posterior wall MI	7 (5.6%)	5 (5.6%)	2 (5.7%)	
Inferior wall MI	9 (7.2%)	7 (7.8%)	2 (5.7%)	
Posterior wall MI	2 (1.6%)	1 (1.1%)	1 (2.9%)	
Lateral wall MI	1 (0.8%)	1 (1.1%)	0 (0%)	
At admission: SOFA Score	6 ± 2.9	5.2 ± 2.5	8.1 ± 2.7	<0.001
At admission: APACHE ll Score	13.1 ± 6	11.7 ± 5.2	16.6 ± 6.6	<0.001

MI = "myocardial infarction", RBBB = "right bundle branch block", RV = "right ventricular", SOFA = "sequential organ failure assessment", APACHE = "acute physiology and chronic health evaluation"
**based on patients with CPR*

Table 2: Angiographic data and hospital course for the STEMI patients with high Killip class (≥III) admitted to ICU after primary PCI

	Total	In-hospital Outcome		P-value
		Survived	Died	
Total (N)	**125**	**90 (72%)**	**35 (28%)**	-
Culprit vessel				
Left main	1 (0.8%)	0 (0%)	1 (2.9%)	0.089
Left anterior descending artery	92 (73.6%)	69 (76.7%)	23 (65.7%)	
Right coronary artery	17 (13.6%)	9 (10%)	8 (22.9%)	
Left circumflex	15 (12%)	12 (13.3%)	3 (8.6%)	
Number of vessels involved				
Single vessel disease	32 (25.6%)	23 (25.6%)	9 (25.7%)	0.818
Two vessel disease	37 (29.6%)	28 (31.1%)	9 (25.7%)	
Three vessel disease	56 (44.8%)	39 (43.3%)	17 (48.6%)	
Pre-procedure "thrombolysis in myocardial infarction" (TIMI) flow				
0	91 (72.8%)	62 (68.9%)	29 (82.9%)	0.297
I	21 (16.8%)	16 (17.8%)	5 (14.3%)	
II	9 (7.2%)	8 (8.9%)	1 (2.9%)	
III	4 (3.2%)	4 (4.4%)	0 (0%)	
Total ischemia time (hours)	11.3 ± 9.9	11.7 ± 9.9	10.4 ± 10	0.519
Post-procedure "thrombolysis in myocardial infarction" (TIMI) flow				
0	5 (4%)	3 (3.3%)	2 (5.7%)	<0.001
I	2 (1.6%)	1 (1.1%)	1 (2.9%)	
II	13 (10.4%)	2 (2.2%)	11 (31.4%)	
III	105 (84%)	84 (93.3%)	21 (60%)	
Need of re-intubation	7 (5.6%)	3 (3.3%)	4 (11.4%)	0.077
ICU stay (days)				
1	44 (35.2%)	23 (25.6%)	21 (60%)	0.008
2	48 (38.4%)	39 (43.3%)	9 (25.7%)	
3	25 (20%)	22 (24.4%)	3 (8.6%)	
4	5 (4%)	4 (4.4%)	1 (2.9%)	
5	3 (2.4%)	2 (2.2%)	1 (2.9%)	
Bleeding	8 (6.4%)	6 (6.7%)	2 (5.7%)	0.845
Need of renal replacement therapy	4 (3.2%)	3 (3.3%)	1 (2.9%)	0.892
Re-infarction	5 (4%)	2 (2.2%)	3 (8.6%)	0.104
Arrhythmias	28 (22.4%)	14 (15.6%)	14 (40%)	0.003
Asystole	0 (0%)	0 (0%)	0 (0%)	
Pulseless electrical activity	2 (7.1%)	0 (0%)	2 (14.3%)	0.142
Ventricular tachycardia	20 (71.4%)	12 (85.7%)	8 (57.1%)	0.094
Ventricular fibrillation	1 (3.6%)	0 (0%)	1 (7.1%)	0.309
Bradyarrest	5 (17.9%)	2 (14.3%)	3 (21.4%)	0.622
AV block	0 (0%)	0 (0%)	0 (0%)	
Vasopressors/Inotropic support	99 (79.2%)	65 (72.2%)	34 (97.1%)	0.002
Norepinephrine	93 (93.9%)	61 (93.8%)	32 (94.1%)	0.957
Dobutamine	12 (12.1%)	5 (7.7%)	7 (20.6%)	0.062
Levophed	4 (4%)	4 (6.2%)	0 (0%)	0.140
Epinephrine	3 (3%)	2 (3.1%)	1 (2.9%)	0.970
Inter-aortic balloon pump (IABP)	25 (20%)	21 (23.3%)	4 (11.4%)	0.135
Number of days on IABP	2 ± 0.8	2 ± 0.9	1.8 ± 0.5	0.612
Length of hospital stay (days)	2.2 ± 1.3	2.4 ± 1.2	1.8 ± 1.4	0.041

Main Results: The study revealed a notable in-hospital mortality rate of 28% among patients with severe STEMI classified as Killip Class III or IV. Key findings indicated that non-survivors had significantly higher SOFA and APACHE II scores at admission compared to survivors. Additionally, non-survivors experienced a higher rate of cardiopulmonary resuscitation (CPR) and a greater incidence of failure to achieve optimal post-procedure TIMI flow. Multivariable analysis highlighted that sub-optimal post-procedure TIMI flow and elevated SOFA scores were independent predictors of mortality. Conversely, the placement of an intra-aortic balloon pump (IABP) was associated with a reduced risk of mortality, suggesting its potential benefit in improving patient outcomes in this high-risk population.

Table 3: Univariate and multi-variable binary logistic regression analysis for in-hospital mortality among STEMI patients with high Killip class (≥III) admitted to ICU after primary PCI

	Univariate		Multivariable	
	OR [95% CI]	P-value	OR [95% CI]	P-value
Male (vs. female)	1.22 [0.54 - 2.76]	0.634	-	-
Age (years)	1.01 [0.97 - 1.05]	0.552	-	-
Killip class IV (vs. III)	2.09 [0.88 - 4.97]	0.097	1.52 [0.40 - 5.71]	0.539
Intubation	0.38 [0.02 - 6.28]	0.501	-	-
Cardiopulmonary resuscitation	3.21 [1.32 - 7.82]	0.010	1.01 [0.22 - 4.59]	0.987
Right ventricular infraction	2.45 [0.76 - 7.90]	0.133	0.46 [0.07 - 2.89]	0.411
Multi-vessel disease	0.99 [0.41 - 2.42]	0.985	-	-
Pre-procedure TIMI 0 flow	2.18 [0.81 - 5.85]	0.121	1.88 [0.48 - 7.32]	0.362
Total ischemia time (hours)	0.99 [0.94 - 1.03]	0.518	-	-
Post-procedure TIMI flow < III	9.33 [3.2 - 27.19]	<0.001	11.08 [2.39 - 51.27]	0.002
Re-intubation	3.74 [0.79 - 17.67]	0.096	3.09 [0.25 - 38.65]	0.381
Arrhythmias	3.62 [1.49 - 8.76]	0.004	1.70 [0.39 - 7.35]	0.476
Vasopressors/Inotropic support	13.08 [1.7 - 100.71]	0.014	9.91 [0.92 - 106.41]	0.058
Inter-aortic balloon pump placement	0.42 [0.13 - 1.34]	0.144	0.07 [0.01 - 0.38]	0.002
SOFA Score at admission	1.54 [1.28 - 1.85]	<0.001	1.47 [1.11 - 1.94]	0.006
APACHE ll Score at admission	1.15 [1.07 - 1.24]	<0.001	1.09 [0.97 - 1.23]	0.139

OR = "odds ratio", CI = "confidence interval", TIMI = "thrombolysis in myocardial infarction", SOFA = "sequential organ failure assessment", APACHE = "acute physiology and chronic health evaluation"

DISCUSSION

Our study provides valuable insights into the in-hospital outcomes and mortality predictors for STEMI patients presenting with high Killip class (≥III) who are admitted to the ICU following primary PCI in a low-middle-income country setting. The significant in-hospital mortality rate of 28% underscores the severity of STEMI in this high-risk group and highlights the urgent need for effective management strategies to enhance patient outcomes.

The high mortality rate observed in our study aligns with previous research indicating elevated mortality among STEMI patients with higher Killip classes [15]. For instance, Impellizzeri et al. demonstrated that a Killip class >1 was associated with a threefold increase in mortality among both STEMI patients with obstructive and non-obstructive coronary artery disease [16]. Similarly, Ramonfaur et al. found that a Killip class ≥2 was linked to a higher 30-day mortality rate, and Del Buono et al. identified Killip class III-IV at admission as an independent predictor of in-hospital mortality and major adverse cardiovascular events in anterior STEMI patients. These findings highlight that patients with higher Killip classes often present with more severe left ventricular dysfunction, extensive myocardial damage, and a higher burden of comorbidities, contributing to their elevated mortality risk.

Our analysis identified several factors associated with increased mortality in this cohort. Non-survivors had a significantly higher rate of cardiopulmonary resuscitation (CPR), indicating a more severe clinical course and a need for aggressive resuscitation. Previous studies, such as that by Chou et al. [17], have shown that survival rates post-CPR can vary widely, underscoring the critical prognostic implications of cardiac arrest following myocardial infarction. Elevated SOFA and APACHE II scores at ICU admission were also significantly associated with increased mortality, emphasizing the impact of systemic organ dysfunction on patient outcomes. Huang et al.[18] demonstrated that the SOFA score was a superior predictor of mortality compared to TIMI and GRACE scores, reinforcing its relevance in acute myocardial infarction (AMI) risk stratification. Despite the APACHE II score's predictive value, our study found that SOFA score was the more significant predictor of mortality in high Killip class STEMI patients [19,20].

Complications commonly associated with high Killip class STEMI, such as cardiogenic shock, pulmonary edema, and ventricular arrhythmias, further exacerbate the poor prognosis. Our study's findings are consistent with other research showing that sub-optimal post-procedure TIMI flow and elevated SOFA scores are independent mortality predictors [21-24]. Tsai et al. reported that Killip III patients had lower final blood flow restoration, a higher incidence of multi-vessel disease, and increased rates of advanced congestive heart failure, all contributing to worse

outcomes [23]. Similarly, De Luca et al. found that myocardial blush independently predicted one-year mortality in patients with advanced Killip class. Hatori et al. also identified factors such as age, TIMI thrombus grade, and systolic blood pressure as significant predictors of in-hospital mortality [24].

Interestingly, our study found that the placement of an intra-aortic balloon pump (IABP) was associated with reduced mortality risk, suggesting its potential benefit in high-risk STEMI patients with hemodynamic instability [25]. Although a meta-analysis reported an 11% reduction in mortality with IABP, the IABP-SHOCK-II trial did not find a significant mortality benefit, leading to downgraded recommendations in recent guidelines [26-29]. Despite this, our findings support the consideration of IABP in certain high-risk cases.

In addition to reperfusion therapy, aggressive medical management—including early administration of anticoagulants, antiplatelet agents, beta-blockers, ACE inhibitors, and statins—plays a crucial role in optimizing outcomes. These interventions are essential for reducing ischemic injury, preventing recurrent events, and improving long-term prognosis.

Limitations: This study has several limitations, including its single-center design and relatively small sample size, which may limit the generalizability of our findings. Future research should involve diverse patient populations from multiple centers to validate and extend our conclusions.

CONCLUSION

Our study found a substantial in-hospital mortality rate of 28.0% among STEMI patients with high Killip class (≥III). Non-survivors exhibited adverse prognostic factors, including higher rates of CPR, failure to achieve optimal post-procedure TIMI III flow, arrhythmias, and greater need for vasopressors or inotropic support. Elevated SOFA and APACHE II scores were associated with increased mortality risk, with multivariable analysis identifying sub-optimal post-procedure TIMI flow (<III) and elevated SOFA scores as independent predictors of mortality. Conversely, the use of an intra-aortic balloon pump (IABP) was linked to a significant reduction in mortality risk. These findings underscore the complex and high-risk nature of this patient group and highlight the need for vigilant monitoring, timely intervention, and tailored management strategies to improve outcomes and reduce mortality.

AUTHORS' CONTRIBUTION

SZ, GR, EUH, IH, PN, SK, and NUK: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. SZ, GR, EUH, IH, PN, SK, and NUK: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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