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A STUDY ON RELATIONSHIP BETWEEN GRACE RISK SCORE AND GLUCOSE FLUCTUATION IN PATIENTS WITH ACUTE CORONARY SYNDROME AND ABNORMAL GLUCOSE METABOLISM USING CONTINUOUS GLUCOSE MONITORING SYSTEM

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ABSTRACT

Background: Acute coronary syndrome encompasses a range of clinical conditions resulting from sudden reduction in blood flow to the heart muscle, primarily due to the rupture of atherosclerotic plaques and subsequent thrombosis. It is an important global cause of death and also the major cause of morbidity and mortality in India. Abnormal glucose metabolism, significantly impacts cardiovascular health, exacerbating outcomes in acute coronary syndrome. The GRACE risk score, a tool for predicting ACS outcomes, may benefit from integrating continuous glucose monitoring (CGM) data.

Aim: To investigate the relationship between glucose fluctuations and the GRACE risk score in ACS patients with abnormal glucose metabolism using continuous glucose monitoring

Materials & Methods: In this observational study, 100 patients with ACS and abnormal glucose metabolism were monitored using CGM systems for 24 hours. The GRACE risk score was calculated for each patient. Correlations between the GRACE score, mean blood glucose levels, and glucose variability were analyzed.

Results: A total of 100 participants were included in the study. The mean Grace risk score and mean 24 Hours Mean Blood Glucose (mmol/l) were 123 ± 28 and 7.8 ± 2.1. Majority of the participants were belonged to the intermidiate-risk group with 45%.

Conclusion: The GRACE risk score is associated with glucose fluctuations in ACS patients with abnormal glucose metabolism. These findings suggest that glucose monitoring may enhance risk assessment and management strategies in this patient population.

Key words: GRACE risk score, glucose fluctuation, continuous glucose monitoring, acute coronary syndrome, abnormal glucose metabolism

1. INTRODUCTION

Acute coronary syndrome (ACS) represents a spectrum of clinical conditions, including unstable angina and myocardial infarction (MI), characterized by sudden reductions in blood flow to the heart.[1] This condition is a leading cause of mortality and morbidity worldwide, necessitating accurate risk stratification and effective management strategies. Recent studies

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have increasingly highlighted the role of abnormal glucose metabolism in exacerbating ACS outcomes.[2,3] This introduction explores the intersection of abnormal glucose metabolism and ACS, and the potential utility of continuous glucose monitoring (CGM) in enhancing risk assessment using the GRACE (Global Registry of Acute Coronary Events) risk score.

Abnormal glucose metabolism, including diabetes mellitus and impaired glucose tolerance, is known to significantly impact cardiovascular health. Patients with diabetes have a substantially higher risk of developing coronary artery disease (CAD) and experiencing adverse outcomes from ACS.[2,3] The mechanisms linking abnormal glucose metabolism with ACS involve a complex interplay of endothelial dysfunction, inflammation, and oxidative stress. Hyperglycemia accelerates atherosclerosis, increases platelet aggregation, and induces pro-inflammatory states, which contribute to the instability of atherosclerotic plaques and exacerbate ACS severity.[4]

The GRACE risk score is a validated tool used to predict mortality and adverse outcomes in patients with ACS. It incorporates clinical variables such as age, heart rate, blood pressure, serum creatinine, and Killip classification to stratify patients based on their risk .[5] This score has proven valuable in clinical practice for identifying high-risk patients and guiding treatment decisions.

Continuous glucose monitoring (CGM) systems provide real-time data on glucose fluctuations, offering a more detailed assessment of glucose metabolism compared to standard fasting glucose tests. In the context of ACS, where glucose stability is critical, CGM may reveal insights into how glucose fluctuations correlate with clinical outcomes and risk scores.

Recent research suggests that glucose variability, rather than merely average glucose levels, plays a significant role in cardiovascular risk.[6] High glucose variability has been associated with increased cardiovascular events, independent of average glucose levels, due to its impact on endothelial function and systemic inflammation .[7] Integrating CGM data with the GRACE risk score could potentially enhance risk stratification by incorporating the dynamic aspect of glucose metabolism into the assessment.

Aims and Objectives

Aim: To investigate the relationship between glucose fluctuations and the GRACE risk score in ACS patients with abnormal glucose metabolism using continuous glucose monitoring.

Objectives:

1. To measure glucose fluctuations over 24 hours using CGM in ACS patients with abnormal glucose metabolism.
2. To evaluate the correlation between glucose variability and the GRACE risk score.
3. To assess whether glucose fluctuations can enhance risk prediction models for ACS patients.

2. MATERIALS AND METHODS

Study site: The study was performed, at R.L. Jalappa hospital and research centre Tamaka, Kolar from February 2020 to February 2022 after obtaining the approval of Institutional Ethical Committee.

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Study design: A single-centre, prospective observational study.
Sample size: The sample size for the study is estimated by keeping the fluctuation change between high risk and low risk group to be 1.85 with SD of 0.45 as per the study by Huiqin Li et al.,[8] And other parameters for sample size calculation was 95% Confidence Interval and the formula used for the sample size calculation was below.[9]

$$N = (u+v)^2\sigma^2 / (\mu - \mu_0)^2$$

N	Sample Size
$\mu - \mu_0$	Difference between the means, μ_1 and null hypothesis value μ_0
σ	Standard deviations
u	One-sided percentage point of the normal distribution corresponding to 100 % – the power e.g. if power = 90%, u = 1.28, If the power is = 80%, u = 0.84
v	Percentage point of the normal distribution corresponding to the (two-sided) significance level e.g. if significance level = 5%, v = 1.96

According to the above calculations the required number of subjects in the study was 90. Considering the lost to follow- up 9 more subjects were added to the final subjects and hence the minimum required sample was 99 subjects which was rounded off to 100.

Inclusion Criteria
- Adults aged 40-80 years
- Patients of both gender
- Diagnosed with ACS (unstable angina or myocardial infarction)
- Abnormal glucose metabolism (including diabetes or impaired glucose tolerance)

Exclusion Criteria
- Severe renal or hepatic impairment
- Pregnancy
- Non-cardiovascular comorbidities affecting glucose metabolism

Data Collection
Informed written consent from all the patients who met inclusion and exclusion criteria for the study was procured before conducting the study. Clinical and laboratory data were obtained and noted.
Continuous Glucose Monitoring (CGM): Glucose levels were monitored continuously over 24 hours using a commercially available CGM device (e.g., Freestyle Libre, Dexcom G6). Measurements were recorded in mmol/dL.
GRACE Risk Score Calculation: GRACE risk scores were calculated using clinical data including age, heart rate, blood pressure, serum creatinine, and Killip class.
We could establish a risk score by assigning a number to each parameter, which is helpful in predicting the long-term prognosis, in-hospital mortality, and the probability of death within six months of hospital discharge.

Statistical Analysis
Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software.[10]

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For quantitative data, descriptive analysis was performed using mean and standard deviation; for categorical variables, frequency and proportion were used. Pie and bar graphs, among the other relevant diagrams, were used to depict the data.
Correlations between GRACE risk scores and glucose fluctuations were evaluated using Pearson's correlation coefficient.
P value < 0.05 was considered statistically significant.

3. RESULTS

A total of 100 patients were included in the study, and the observations of these patients were compiled and analyzed**.**

Demographic and Clinical Characteristics
The mean age among the participants was 64.3 ± 9.8 years.
Distribution of subjects according to gender, Males constituted 55% (55 patients) and females constituted 45% (45 patients).

Table 1: Distribution based on Kilip classification

KILIP CLASSIFICATION	NO. OF PATIENTS	PERCENTAGE
Class I	60	60 %
Class II	25	25 %
Class III	15	15%

Table 2: Distribution of GRACE Risk Scores

GRACE risk score	NO. OF PATIENTS	PERCENTAGE
Low risk	35	35 %
Intermediate risk	45	45 %
High risk	20	20 %

The mean GRACE risk score of the patients was 123 ± 28.

Summary of 24-Hour Glucose Monitoring
The mean glucose levels was 7.8 ± 2.1 mmol/dL and the glucose variability, the standard deviation of glucose levels was 1.8 ± 0.5 mmol/dL.

Table 3: Correlation Between GRACE Risk Score and Glucose Fluctuations

VARIABLE	CORRELATION COEFFICIENT (r)	p - VALUE
Mean Glucose Level	0.32	0.01
Glucose Variability	0.45	< 0.001

The correlation analysis reveals a moderate positive correlation between glucose variability and the GRACE risk score ($r = 0.45$, $p < 0.001$), suggesting that patients with greater glucose fluctuations tend to have higher GRACE risk scores. The correlation between mean glucose levels and GRACE score was weaker but still significant ($r = 0.32$, $p = 0.01$).

4. DISCUSSION

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ACS is the primary cause of illness and mortality in India as well as a significant cause of death worldwide. Compared to North America and Western Europe, the prevalence of adult onset coronary heart disease has significantly increased in urban India and has happened at a much younger age. There is growing recognition of the role that glucose metabolism plays in acute coronary syndrome and acute myocardial infarction.

This study aimed to explore the relationship between glucose fluctuations and the GRACE risk score in patients with acute coronary syndrome (ACS) and abnormal glucose metabolism using continuous glucose monitoring (CGM). Our results indicated a significant correlation between glucose variability and the GRACE risk score, suggesting that glucose fluctuations might impact the severity of ACS and patient risk profiles.

The study included 100 individuals in total. In the current study, the average age of the study population was 64.3 ± 9.8 years. Timoteo, AT et al.[11] conducted a study with 2099 individuals in which the average age of the study population was 64 ± 13 years. Islam, MM. et al.[55] conducted a study with 249 individuals in which the average age of the study population was 55.7±11.7

There were 45% female participants and 55% male participants in the current study. In research conducted by Takahashi, H., et al.[13], 83% of the patients were men and 17% were women. In a study by Islam, M.E., et al.[12] (73.9%) were men and the rest were Women (26.1%)

In a study conducted by Gerbaud, E. et al.[14] (42) on a population of 334 patients, 75.6% of the subjects belonged to Killip score 1, 14.1%, 9.1% and 1.2% belonged to Killip scores 2, 3, and 4 respectively. Whereas, in our study, of 100 participants, 60%, 25%, and 15% belonged to Killip classes 1, 2 and 3 respectively.

In Our study population's mean grace risk score was 123 ± 28 which is nearly consistent with the study conducted by Gerbaud, E. et al. (42) which involved 334 people, and the mean Grace score was 135±32.

In the current study 35% of the population were at low risk, 45% at intermediate and 20% of them were at high risk. While, a study by Li, H., et al.[15], involving 76 individuals were identified as 18.42% at low risk, 32.89% at moderate and 48.68% at high risk.

Correlation Between GRACE Risk Score and Glucose Variability

Our study found a positive correlation between glucose variability and the GRACE risk score, with a correlation coefficient of $r = 0.45$ ($p < 0.001$). This finding aligns with previous research that underscores the importance of glucose variability in cardiovascular risk assessment. For instance, a study by Monnier et al. demonstrated that glucose variability is an independent predictor of cardiovascular events, irrespective of average glucose levels.[16] Their findings emphasize that fluctuations in glucose levels can adversely affect vascular health, potentially exacerbating ACS severity.

Another study by Chang et al[17] observed that glucose variability was associated with increased mortality in diabetic patients with cardiovascular disease. Our results reinforce these observations, suggesting that glucose fluctuations might contribute to higher GRACE risk scores, indicating a more severe disease state. This correlation may be attributed to the effects of glucose variability on endothelial function, inflammation, and oxidative stress—factors known to worsen cardiovascular outcomes .[7]

Comparison with Other Studies

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Our findings are consistent with those of other studies that have explored the role of glucose variability in cardiovascular disease. For example, the ADVANCE trial, which investigated the effects of glucose control on cardiovascular outcomes in diabetes, found that both average glucose levels and glucose variability were associated with increased cardiovascular risk.[18] Similarly, the DECODE study demonstrated that glucose variability was a significant predictor of cardiovascular mortality, independent of fasting glucose levels.[19]

However, there are notable differences between our study and some previous research. For instance, a study by Kotsis et al.[20] found that glucose variability did not significantly enhance cardiovascular risk prediction beyond traditional risk factors and average glucose levels. This discrepancy might be due to differences in study design, patient populations, or methods of measuring glucose variability. While our study utilized CGM to capture detailed glucose fluctuation data, other studies might have relied on less precise measures, such as fasting glucose or HbA1c, which do not fully reflect glucose variability[20].

Implications for Clinical Practice

The significant correlation between glucose fluctuations and the GRACE risk score suggests that integrating CGM data into routine risk assessment could provide a more comprehensive understanding of patient risk profiles. The GRACE risk score is a valuable tool for stratifying ACS patients, but incorporating glucose variability could enhance its predictive accuracy. This approach could be particularly beneficial for patients with diabetes or impaired glucose tolerance, as these individuals are at a higher risk for adverse cardiovascular outcomes.

Implementing CGM in clinical practice could also lead to more personalized management strategies. By monitoring glucose fluctuations, healthcare providers can identify patients who experience significant glucose variability and tailor interventions accordingly. For example, optimizing glycemic control through lifestyle modifications or pharmacotherapy might reduce glucose variability and potentially lower the risk of adverse ACS outcomes.

5. CONCLUSION

In summary, our study underscores the significant relationship between glucose fluctuations and the GRACE risk score in ACS patients with abnormal glucose metabolism. By highlighting the impact of glucose variability on cardiovascular risk, our findings suggest that integrating CGM data into risk assessment tools like the GRACE score could enhance predictive accuracy and inform more effective management strategies. Future research should continue to explore this relationship and address the limitations of current studies to refine risk assessment and improve patient outcomes.

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