The 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 is an important global cause of death and also the major cause of morbidity and mortality in India. The importance of glucose metabolism in patients with "acute coronary syndrome" has been increasingly recognized. **Aims**: To determine the association between grace risk score and glucose fluctuation in patients with acute coronary syndrome and abnormal glucose metabolism using Continuous Glucose Monitoring System. **Materials & Methods**: Prospective Cohort Study conducted for a period of 18 months from January 2019 to June 2020 **Results**: A total of 77 participants were included in the study. The mean age of the participants was identified as 52.31 ± 7.9. Majority of the participants were belonged to killip class II with 58.44%. Elevated Cardiac Enzymes and ST Deviation were identified in 55.84% and 44.16% of participants. The mean Grace risk score and mean 24 Hours Mean Blood Glucose (mmol/l) were 129.35 ± 31.15 and 9.67 ± 3.28. Majority of the participants were belonged to the high-risk group with 35.06%. The median 24 hours mean blood glucose (mmol/l) in low risk, moderate and high risk were 6.32 (IQR 6.03 to 8.5), 9.08 (IQR 7.983 to 9.93) and 11.3 (IQR 10.16 to 13.8) respectively. **Conclusion**: High prevalence of abnormal glucose metabolism was found in ACS patients. Higher blood glucose fluctuation is associated with moderate and high GRACE risk scores in patients with ACS and abnormal glucose metabolism.

Keywords: Grace Risk Score, Fluctuation, Acute Coronary Syndrome, Abnormal Glucose Metabolism

INTRODUCTION:

The presence of acute coronary syndrome in individuals with CVD can enhance the risk of abnormal glucose metabolism as compared to the normal population (25.2%).[1] The guidelines for the management of non-ST-elevation acute coronary syndrome prefer the utilization of scoring systems such as GRACE score to calculate risk and guide management decisions.[2] The GRACE score is considered as a validated and established score for the risk stratification in ACS.[3] In Urban India, coronary heart disease (CHD) prevalence in adult has increased considerably and occurred at a much younger age as compared to North America and Western Europe. CHD global fatality was estimated to be 17.5 million/year, 31% of deaths - 75% in low- and middle-income countries; the prevalence of CHD in rural India was estimated to be 3%–4% and 8%–10% in urban areas.[4] Early recognition of the glycemic status of ACS

patients at a time of admission to the coronary care unit can determine the future cardiovascular events and increased risk of death.[5] The GRACE risk score has been developed from a registry data and accounts with newer prognostic variables to estimate the risk of death or a consequent myocardial infarction MI in patients following an initial ACS. It is important to provide the correct treatment based on the risk score of the patient. The current study is an attempt at understanding "the relationship between blood glucose fluctuation and GRACE risk score in ACS patients and how blood glucose fluctuation in patients with abnormal glucose metabolism affect GRACE score using Continuous Glucose Monitoring System".

MATERIALS & METHODS:

This prospective cohort study was conducted in the department of General Medicine at RL JALAPPA HOSPITAL and NH HOSPITAL for a period of 18 months from January 2019 to June 2020. "Patients with Acute Coronary Syndrome and abnormal glucose metabolism were considered as study population". Based on the GRACE risk score, they were divided into low risk, moderate risk and high risk. The sample size 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.,[6] And other parameters for sample size calculation was 95% Confidence Interval and the formula used for the sample size calculation was below.[7]

$$ N = \frac{(u+v)^2 \sigma^2}{(\mu - \mu_0)^2} $$

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

v   Percentage point of the normal distribution corresponding to the (two-sided) significance level

According to the above calculations the required number of subjects in to the stud was 70. Considering the 10% lost to follow- up 7 more subjects were added to the final subjects and hence the minimum required sample was 77 subjects.

Inclusion Criteria includes the patients who had unstable angina pectoris, ST elevated MI, non-ST elevated MI, diabetes history, newly diagnosed diabetic patients and patients with impaired glucose tolerance. Whereas, patients who had a history of mental illness and those not suitable for using CGMS were excluded. Study was approved by the institutional human ethics committee. Informed written consent was obtained from all the participants. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. Confidentiality of the study participants was maintained. All the relevant parameters were documented in a structured study proforma.

METHODOLOGY:

A continuous glucose monitoring system (CGMS) was used to real-time monitor blood glucose for 72 hrs after the patient was admitted into CCU. Using CGMS 24 hours of mean blood glucose was measured. "The GRACE risk score was the sum of eight quantified parameters including age, heart rate, systolic blood pressure, creatinine level, heart failure (Killip class), elevated cardiac enzymes, ST-segment elevation, and cardiac arrest at admission". "By giving a score based on each of the parameters, we can make a risk score which was useful for making predictions on in-hospital mortality and risk of death within 6 months after discharge from the hospital, the long-term prognosis".

Statistical Methods:

A 24 hours mean blood glucose (mmol/l) was considered as the primary outcome variable. Grace risk score group was considered as Primary Explanatory Variables. Age, gender, pulse (per minute) etc., were considered as Other explanatory variables. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram & pie diagrams. All the quantitative parameters will be checking the normal distribution within each category. A shapiro- wilk's test (p>0.05) and a visual inspection of their histograms, normal Q-Q plots and box plots showed that the 24 hours mean blood glucose (mmol/l) parameter were non-normally distributed. The comparison between and 24 hours mean blood glucose (mmol/l) and Grace risk score grouping was assessed by comparing the median values. Kruskal Wallis test was used to assess statistical significance. Association between quantitative

explanatory and outcome variables was assessed by calculating the Spearman correlation coefficient, and the data was represented in a scatter diagram. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.[8]

RESULTS:
A total of 77 subjects were included in the final analysis.

Table 1 Summary of baseline parameters (N=77)

Baseline parameters	summary
Age (mean ± SD) (in years)	52.31 ± 7.9 (41, 76)
Male	57 (74%)
Female	20 (26%)
Pulse (Per Minute)	89.29 ± 16.83 (68, 150)
Systolic Blood Pressure (In Mm)	125.06 ± 12.85 (100, 160)
Serum Creatinine (In Mg/Dl)	1.35 ± 0.82 (0.20, 5.00)
Killip Class 1	28 (36.36%)
Killip Class 2	45 (58.44%)
Killip Class 3	4 (5.19%)
Elevated Cardiac Enzymes	43 (55.84%)
ST Deviation	34 (44.16%)
Grace Risk Score	129.35 ± 31.15 (84, 211)
24 Hours Mean Blood Glucose (Mmol/L)	9.67 ± 3.28 (5.11, 21)
Hypertension	59 (76.62%)
Smoking	53 (68.83%)
Alcohol	39 (50.65%)
Dyspnoea	70 (90.91%)
Chest Pain	74 (96.10%)
Body Mass Index	22.22 ± 1.36 (19, 26)
Blood Urea (mg/dL)	37.4 ± 12.59 (19, 92)
Hba1C (mmol/mol)	7.82 ± 1.99 (5.10, 14.90)
Hemoglobin (g/L)	11.58 ± 1.69 (8, 15)
Total Leucocyte Count (mm3)	15.5 ± 2.57 (11.20, 22)
Creatinine Kinase MB (IU/L)	6.55 ± 3.05 (2, 11.52)
TROPONIN I (ng/mL)	1.49 ± 3.62 (0.12, 21.02)
Uric Acid (mg/dL)	3.82 ± 0.91 (0.30, 6)
Triglycerides (mg/dL)	261.62 ± 57.53 (140, 450)
Cholesterol (mg/dL)	220.81 ± 33.65 (152, 292)
High Density Cholesterol (mg/dL)	43.7 ± 7.21 (25, 72)
Low Density Cholesterol (mg/dL)	111.4 ± 53.76 (36, 222)
Grace Risk Score Grouping	
Low Risk	26 (33.77%)
Moderate Risk	24 (31.17%)
High Risk	27 (35.06%)

The mean age of the participants was 52.31 ± 7.9. Around, 57 (74%) were male and 20 (26%) were female. The mean of pulse (per minute) and Systolic Blood Pressure (in mm) were 89.29 ± 16.83 and 125.06 ± 12.85 respectively. The mean Serum Creatinine (In mg/dl) was 1.35 ± 0.82. Around 28 (36.36%) were in Class 1, 45 (58.44%) were in Class 2 and 4 (5.19%) were in class 3. Majority 43 (55.84%) were in Elevated Cardiac Enzymes and 34 (44.16%) were in ST Deviation. The mean Grace risk score was 129.35 ± 31.15. Around, 26 (33.77%) were at low risk, 24 (31.17%) were at moderate risk and 27 (35.06%) were at high risk. The mean 24 Hours Mean Blood Glucose (mmol/l) was 9.67 ± 3.28. Around, 59 (76.62%) had hypertension, 53 (68.83%) were smokers and 39 (50.65%) consumed alcohol, 70 (90.91%) had Dyspnoea, 74 (96.10%) had chest pain. The mean Body Mass Index was 22.22 ± 1.36 whereas, the mean Blood Urea (mg/dL) was 37.4 ± 12.59 and the mean Hba1C was 7.82 ± 1.99. The mean Hemoglobin (mmol/mol) was 11.58 ± 1.69. The mean of

Total Leucocyte Count (mm3, Creatinine Kinase MB (IU/L), TROPONIN I (ng/mL), Uric acid (mg/dL) were identified with 15.5 ± 2.57, 6.55 ± 3.05, 1.49 ± 3.62 and 3.82 ± 0.91 respectively. Whereas, the mean of Triglycerides (mg/dL), Cholesterol (mg/dL), High-Density Cholesterol (mg/dL) and the Low-Density Cholesterol (mg/dL) were noted with 261.62 ± 57.53, 220.81 ± 33.65, 43.7 ± 7.21 and 111.4 ± 53.76 respectively. (Table 1)

Table 2 Association between Grace risk score and 24 hours mean blood glucose (mmol/l) (N=77)

parameters	24 hours mean blood glucose (mmol/l) Median (IQR)	P value
Low risk (N=26)	6.32 (6.03 to 8.5)	<0.001
Moderate risk (N=24)	9.08 (7.983 to 9.93)	
High risk (N=27)	11.3 (10.16 to 13.8)	
Low vs Moderate risk		<0.001
Moderate vs high risk		<0.001
Low vs moderate risk		<0.001
Grace risk score vs. 24 hours mean blood glucose (mmol/l)	0.698	<0.001

The difference in Grace risk score groups and 24 hours mean blood glucose (mmol/l) was statistically significant. (P value<0.001). There was a moderate positive correlation between Grace risk score and 24 hours mean blood glucose (rs value: 0.068, P value: <0.001). (Table 2)

Table 3: Association Between Grace Risk Score System and Baseline Parameters (N=77)

Parameters	Low Risk (N=26)	Moderate Risk (N=24)	High Risk (N= 27)
Age groups (in years)			
<50	23 (88.5%)	6 (25%)	4 (14.8%)
50-60	3 (11.5%)	16 (66.7%)	12 (44.4%)
61-70	0	2 (8.3%)	8 (29.6%)
>70	0	0	3 (11.1%)
Pulse rate groups (in minutes)			
<70	2 (7.7%)	0	0
70-80	13 (50%)	9 (37.5%)	0
81-90	10 (38.5%)	8 (33.3%)	3 (11.1%)
91-100	1 (3.8%)	7 (29.2%)	8 (29.6%)
101-110	0	0	7 (25.9%)
111-120	0	0	6 (22.2%)
121-130	0	0	2 (7.4%)
131-140	0	0	0
>140	0	0	1 (3.7%)
Systolic Blood Pressure (in mm)			
<110	5 (19.2%)	6 (25%)	10 (37%)
110-120	2 (7.7%)	2(8.3%)	5 (18.5%)
121-130	12 (46.2%)	10 (41.7%)	9 (33.3%)
131-140	5 (19.2%)	5 (20.8%)	2 (7.4%)
141-150	2 (7.7%)	0	1 (3.7%)
>150	0	1 (4.2%)	0
Serum Creatinine (mg/dl)			
<1	17 (65.4%)	10 (41.7%)	3 (11.1%)
1-1.99	8 (30.8%)	14 (58.3%)	18 (66.7%)
2-2.99	0	0	4 (14.8%)
3-3.99	0	0	1 (3.7%)
>3.99	1 (3.8%)	0	1 (3.7%)
Killip class			
I	18 (69.2%)	10 (41.7%)	0

II	8 (30.8%)	14 (58.3%)	23 (85.2%)
III	0	0	4 (14.8%)
IV	0	0	0
Other Risk Factors			
Elevated Cardiac Enzymes	24 (92.3%)	14(58.3%)	5(18.5%)
ST Deviation	2 (7.7%)	10 (41.7%)	22 (81.5%)

Among the low risk group, 23 (88.5%) were aged <50 years, 13 (50%) had pulse rate (in minutes), 12 (46.2%) had Systolic Blood Pressure (in mm), 17 (65.4%) had serum creatinine (mg/dl) <1, 18 (69.2%) were in Killip Class I and 24 (92.3) had Elevated Cardiac Enzymes in Other Risk Factors. Among the moderate risk group, 16 (66.7%) were aged between 50-60 years, 9 (37.5%) had pulse rate (in minutes) , 10 (41.7%) had Systolic Blood Pressure (in mm) , 14 (58.3%) had serum creatinine (mg/dl), 14 (58.3%) were in Killip Class II and 14 (58.3) had Elevated Cardiac Enzymes in Other Risk Factors. Similarly, in high-risk population, 12 (44.4%) were aged between 50-60 years, 8 (29.6%) had pulse rate (in minutes) , 10 (37%) had Systolic Blood Pressure (in mm) <110, 18 (66.7%) had serum creatinine (mg/dl) , 23 (85.2%) were in Killip Class II and 22 (81.5) had ST Deviation in Other Risk Factors. (Table 3)

DISCUSSION:

ACS is an important global cause of death and also the major cause of morbidity and mortality in India. In Urban India, coronary heart disease prevalence in adult has increased considerably and occurred at a much younger age as compared to North America and Western Europe. The importance of glucose metabolism in acute coronary syndrome and acute myocardial infarction has been increasingly recognized. The present study was conducted to determine the association between grace risk score and glucose fluctuation in acute coronary syndrome and abnormal glucose metabolism. A total of 77 subjects were enrolled in the study.

In the present study, 52.31± 7.9 was the mean age of the participants. In a population of 2099 participants. Timoteo, AT et al[9], performed a study in which 64 ± 13 years was the mean of age which is higher to our results. The proportion of males and females in the study population were 74% and 26%. Takahashi, H., et al[10], performed a study in which 83% of the patients were males and 17% females which resembles to our study. In the current study, participants in the Killip class 1, 2 and 3 were identified with 36.36%, 58.44% and 5.19% respectively. Gerbaud, E. et al[11], conducted a study in 334 patients in which 75.6% of participants were belonged to Killip score 1 whereas 14.1%, 9.1% and 1.2% were belonged to Killip score 2, 3 and 4 respectively which is an increased rate to our study results.

In the current study, 129.35 ± 31.15 was the mean grace risk score. Gerbaud, E et al[11], showed a mean Grace score of 135±32 as compared to our study.

In the present study, low risk, moderate risk and high-risk groups were identified with 33.77%, 31.17% and 35.06% respectively. Li, H., et al[12], conducted a study in 76 participants in which 18.42% were identified in the low-risk group while moderate and high risk were identified with 32.89% and 48.68% respectively. In the

current study, 9.67 ± 3.28 was the 24 hours mean blood glucose level identified in the study population. In the present study, dyspnoea and chest pain were observed in 90.91% and 96.10% of participants. In 4087, participants Tscherry K., et al[13] study identified chest pain in 66% of population. In the current study, 22.22 ± 1.36 was the body mass index noticed in the participants. Gerbaud, E et al[11], showed 28.5±4.7 as the mean BMI of the study population.

In the present study the mean of blood urea, HbA1C, Hb, TLC, creatinine kinase MB, troponin I, uric acid, triglycerides, cholesterol, HDL and LDL were identified with 22.22±1.36, 7.82±1.99, 11.58±1.69, 15.5±2.57, 6.55±3.05, 1.49±3.62, 3.82±0.91, 261.62±57.53, 220.81±33.65, 43.7±7.21 and 111.4±53.76 respectively. Gerbaud, E et al[11] study showed the mean of HBA1c, troponin I, triglycerides, cholesterol, high-density cholesterol and low-density cholesterol with 7.55±1.44, 22.6±56.8, 4.56±3.96, 4.55±1.40, 1.06±0.51 and 2.72±1.19 respectively.

Among study population, the median 24 hours mean blood glucose (mmol/l) in low risk, moderate and high risk were 6.32 (IQR 6.03 to 8.5), 9.08 (IQR 7.983 to 9.93) and 11.3 (IQR 10.16 to 13.8) respectively. Li, H. et al (6) performed a study in 76 patients in which 15.38% of participants with abnormal glucose metabolism belonged to low-risk group whereas, 36.53% and 48.08% to moderate and high-risk group. Also, 25% of patients with normal glucose metabolism were belonged to low risk while 25% and 50% to the moderate and high-risk group, respectively.

There was a moderate positive correlation between Grace risk score and 24 hours mean blood glucose. In the current study majority of the participants in the low-risk group were aged < 50 years, 50% had pulse rate (in minutes) in the range 70-80, 46.2% had Systolic Blood Pressure (in mm) in the range 121-130, 65.4% had serum creatinine (mg/dl) <1, 69.2% were in Killip Class

I and 92.3% had Elevated Cardiac Enzymes in Other Risk Factors.

In the study population, 66.7% of the participants in the moderate risk group were aged between 50-60 years, 37.5% had pulse rate (in minutes) in the range 70-80, 41.7% had Systolic Blood Pressure (in mm) in the range 121-130, 58.3% had serum creatinine (mg/dl) in the range 1-1.99, 58.3% were in Killip Class II, and 58.3% had Elevated Cardiac Enzymes in Other Risk Factors. Whereas among the high-risk, 44.4% were aged between 50-60 years, 29.6% had pulse rate (in minutes) in the range 91-100, 37% had Systolic Blood Pressure (in mm) <110, 66.7% had serum creatinine (mg/dl) in the range 1-1.99, 85.2% were in Killip Class II, and 81.5% had ST Deviation in Other Risk Factors.

Limiting factors include single-center study with small sample size. We only used SD as a parameter of blood glucose variabilities more parameters such as MAGE and MODD can be used more convincedly. Follow up was not performed in the study population. The study can be conducted in a large sample size for a long duration of time. Management and follow up can also be performed in future studies.

CONCLUSION:

In conclusion, the prevalence of abnormal glucose metabolism was identified high in patients with acute coronary syndrome. Also, the higher blood glucose fluctuation is associated with moderate and high GRACE risk scores in patients with ACS and abnormal glucose metabolism.

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