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ORIGINAL ARTICLE

Association of Serum Anion Gap and Angiographic Severity of Coronary Artery Disease by Gensini Score in Patients with Acute Coronary Syndrome

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Abstract

Background: The serum anion gap (AG) has been reported to have an association with the severity of coronary artery diseases (CAD). This association is not yet well studied in Bangladesh. Gensini Score (GS) gives insight into the severity of CAD. Acute Coronary Syndrome is a severe type of coronary artery disease. The study of severity of CAD by GS in relation to AG following acute coronary syndrome (ACS) remains limited in Bangladesh.

Methods: This cross-sectional analytical study was conducted at the department of Cardiology, Sir Salimullah Medical College Mitford Hospital, Dhaka, for a duration of 12-months following ethical approval. A total of 90 patients with Acute Coronary Syndrome (ACS) who underwent coronary angiography were included after getting written informed consent. 45 patients were included in group A (anion gap 8 mEq/L to 16 mEq/L) and 45 patients were in group B (anion gap >16 mEq/L). Data were collected on pre designed data collection sheet separated case-record form and analyzed by SPSS-26.

Results: Mean age of the patients in Group A and Group B was 59.5±11.9 years and 64.9±9.1 years accordingly. Age was significantly higher in Group B than Group A. Among all, 53.3% of the patients had Gensini score ≥50, 46.7% had Gensini score <50. Mean Gensini score in Group A and Group B was 43.9±6.3 and 54.8±1.4 accordingly. Mean Gensini score was significantly higher among the patients with anion gap above 16mEq/L. A cut off value Anion gap>16 mEq/L (AUC=0.899, 95% CI=0.831-0.967, p<0.001) in the prediction of severe CAD (Gensini score ≥50) showed 81.25% sensitivity, 80.95% Specificity, 82.98% PPV, 79.07% NPV and 81.11% accuracy.

Conclusion: This study investigated the association of serum anion gap and the severity of coronary artery disease as measured by Gensini Score (GS) in patients with acute coronary syndrome (ACS). A higher anion gap levels (>16 mEq/L) were associated with increased severity of CAD by Gensini scores in patients with ACS.

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Introduction:

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the present world (Al-shorbagy et al., 2018)[1]. Cardiovascular diseases account for more than 17 million deaths globally each year thus contributing 30% of all deaths. This is expected to grow to 23.6 million by the year 2030. CAD alone caused 7 million deaths worldwide in 2010 and it is an increase of 35% since 1990 (Wong, 2014)[2].

Acute coronary syndrome (ACS) encompasses a spectrum of conditions that include patients presenting with recent changes in clinical symptoms or signs, with or without changes on 12-lead electrocardiogram

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(ECG) and with or without acute elevations in cardiac troponin (cTn) concentrations (Byrne et al., 2023)[3]. Patients presenting with suspected ACS may eventually receive a diagnosis of acute myocardial infarction (AMI) or unstable angina (UA). The diagnosis of myocardial infarction (STEMI & NSTMI) is associated with cTn release and is made based on the fourth universal definition of myocardial infarction[(4)]. UA is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis. It is characterized by specific clinical findings of prolonged (>20 min) angina at rest; new onset of severe angina; angina that is increasing in frequency, longer in duration, or lower in threshold; or angina that occurs after a recent episode of MI (Byrne et al., 2023)[3]. ACS are associated with a broad range of clinical presentations, from patients who are symptom free at presentation to patients with ongoing chest discomfort/symptoms and patients with cardiac arrest, electrical/haemodynamic instability, or cardiogenic shock (CS). Patients presenting with suspected ACS are typically classified (based on ECG at presentation) as STEMI & NSTEMI. After this, patients can be further classified (based on the presence or absence of cardiac troponin elevation) as STEMI, NSTEMI & UA. These features (ECG changes and cardiac troponin elevation) are important in the initial triage and diagnosis of patients with ACS (Byrne et al., 2023)[3].

The serum anion gap (AG) is a mathematically derived parameter that has been in use for more than 50 years (Kraut and Madias, 2007)[5]. Its widest application in the diagnosis of various forms of metabolic acidosis. It is calculated from the electrolytes measured in the chemical laboratory. The serum anion gap (AG) is the sum of serum chloride and bicarbonate concentrations subtracted from the serum sodium and potassium concentration where the concentration is examined as mEq/L. That is, AG = [Na+ (mEq/L) + K+ (mEq/L)] - [Cl- (mEq/L) + HCO3- (mEq/L)]. Methods for the measurement of the anion gap consist of colorimetry for [$HCO^{"}_3$] and [$Cl^{"}$] as well as flame photometry for [Na^+] and [K^+]. The normal reference values ranged from 8 mEq/L to 16 mEq/L (Kraut and Madias, 2007)[5]. The anion gap can be classified as low, normal, or high. Low values most commonly indicate laboratory error or hypoalbuminemia but can denote the presence of a paraproteinemia or intoxication with lithium, bromide, or iodide, monoclonal and polyclonal gammopathy (Kraut and Madias, 2007)[(5)]. In patients with a normal anion gap, the drop in $HCO-_3$ is the primary pathology. The lost $HCO-_3$ is replaced by a chloride anion, and thus there is a normal anion gap. Normal anion gap may occur due to gastrointestinal loss of $HCO-_3$ concentration (i.e., diarrhea), kidney loss of $HCO-_3$ (i.e., proximal renal tubular acidosis (RTA) also known as type 2 RTA), kidney dysfunction (i.e., distal renal tubular acidosis also known as type 1 RTA), renal hypo aldosterone (i.e., renal tubular acidosis also known as type IV RTA), mineralocorticoid deficiency (Addison's disease), ingestions of ammonium chloride and acetazolamide and total parenteral nutrition.

A high anion gap indicates increased concentration of unmeasured anions like lactate, beta-hydroxybutyrate, acetoacetate, phosphate, and sulfate, which occurs with disease or intoxication, causes loss of $HCO-_3$ due to bicarbonate's activity as a buffer. Thus, finding a high anion gap should result in a search for conditions that lead to excesses of the unmeasured anions. Causes of high anion gap metabolic acidosis include lactic acidosis, ketoacidosis (diabetic ketoacidosis, hazardous alcohol use), toxins (methanol, ethylene glycol, propylene glycol, lactic acid, uremia, aspirin, iron, isoniazid, cyanide) and kidney failure. High anion gap acidosis may be caused by decreased acid excretion and decreased $HCO-_3$ reabsorption as well. Despite many limitations, calculation of the serum anion gap remains an inexpensive and effective tool that aids detection of various acid-base disorders, hematologic malignancies, and intoxications (Yang et al., 2017)[(6)]. The association of serum anion gap (AG) and coronary artery disease (CAD) in patients with acute coronary syndrome (ACS) was previously not clear. In a large study in 2017, it is found that a total of 24.9% participants who had severe CAD had their AG levels greater than 16 mEq/L (Yang et al., 2017)[6].

A coronary angiography is a minimally invasive procedure to access the coronary circulation of the heart using a catheter. It is performed for both diagnostic and interventional (treatment) purposes. Coronary angiography is still the gold standard for diagnosing CAD and offers visual information on the degree of coronary atherosclerosis and certain characteristics of the plaque (Adam et al., 2019)[7]. Cardiovascular events and death rates are strongly correlated with the angiographic features of patients

with ACS (Pan et al., 2023)[8]. More stenotic coronary lesions have increased chances of developing occlusion and myocardial infarction (Sen et al., 2017)[9].

A few coronary angiography-based scoring systems have been developed to evaluate lesion severity and offer some prognostic data for patients with CAD. These include Gensini, SYNTAX, Vessel score (Friesinger score, Sullivan stenosis score), CASS-50, CASS-70, Duke CAD Severity Index, Duke jeopardy score, Jenkins score. While these scoring systems offer quantitative assessment, there is insufficient specific information obtained by most of these scoring systems. Based on angiographic data, the Gensini scoring system is an objective way to assess the severity of CAD (Yildirim et al., 2017)[10].

It may be a useful tool for quantitative determination of atherosclerosis. There exists a considerable correlation between atherosclerotic plaque burden and angiogram rating systems. Scoring methods therefore seem to be a reliable indicator of the burden of CAD plaque (Charach et al., 2021)[(11)]. The Gensini score have some more advantages over other score, such as coronary plaques with less than 50% narrowing are not evaluated in the SYNTAX scoring system, but these lesions are included in the Gensini scoring system. Gensini score (GS) has been found to be correlated with the severity of coronary lesions, especially with multivessel disease, coronary artery bypass grafting (CABG) and implanted left internal mammary artery (LIMA) or drug eluting stent. GS reflecting severity of atherosclerosis is related to several cardiovascular risk factors, such as age, high density lipoprotein, hypertension, and diabetes. GS can provide valuable information about the severity and prognosis of CAD.

This study aimed to evaluate the association of serum anion gap and angiographic severity of coronary artery disease by Gensini Score in patients with acute coronary syndrome.

Rationale of the Study:

Acute coronary syndrome (ACS) is a fatal condition creating a severe global health threat. Previously we think Acute coronary syndrome (ACS) as an urban disease but at present it extends to rural areas also. Coronary artery disease (CAD) is a chronic condition usually occurring after the sixth decade of life. In the last few decades, different studies have shown an increased incidence of CAD in very young (≤40-year-old) people (Pablo et al. 2022). So, Identifying the severity of coronary artery disease can guiding the treatment of this population.

The serum anion gap (AG) emerges as a simple, easily accessible biomarker with potential value to evaluate the severity of coronary artery disease. We can easily calculate serum anion gap (AG) by measuring serum electrolytes which is comparatively less costly, easily calculated and less time consuming (Yang et al. 2017). Furthermore, serum electrolytes routinely done in CCU at the time of admission of the ACS patient. So, there will be no extra cost or burden for the patient. Moreover serum electrolytes is available in upazila level.

Coronary angiography is still the gold standard for diagnosing CAD and offers visual information on the degree of coronary atherosclerosis (Adam et al. 2019). Gensini score (GS) may be a useful tool for quantitatively determining atherosclerosis. There exists a considerable correlation between atherosclerotic plaque burden and angiogram rating systems. Gensini score (GS) were correlated to the severity of coronary lesions, especially with multivessel disease. But, coronary angiogram is still not available at rural areas, even at the district level also. Therefore, after ACS we can calculate serum anion gap (AG) by using serum electrolytes to assess disease severity and can take necessary steps which can save the life of the patient. However, the role of AG in assessing CAD severity is largely unexplored. In abroad there is a large study in 2017 which found that a total of 24.9% patients who had severe CAD had their AG levels greater than 16 mEq/L (Yang et al. 2017). There is some data about AG associated with poor outcomes and is an independent risk factor for short-term mortality in patients with AMI but the role of AG in assessing CAD severity is not yet well studied in Bangladesh. This study aimed to investigate the association of serum AG and coronary angiographic severity of coronary artery disease by Gensini score in patient with ACS, and if we can predict the disease severity from AG, then easily an appropriate medical management with special attention to an interventional strategy can be planned which will help to reduce the mortality and morbidity of these ACS patients.

Research Question:

High serum anion gap (AG) is associated with angiographic severity of coronary artery disease (CAD) by Gensini Score (GS) in patients with acute coronary syndrome (ACS)

Objectives of the Study:

General objective:

To evaluate the association of serum anion gap with angiographic severity of coronary artery disease by Gensini score in patients with acute coronary syndrome

Specific objectives:

To measure serum electrolytes and calculate the serum anion gap (AG) in patients with acute coronary syndrome

To calculate the angiographic severity of ACS patients by Gensini score following coronary angiogram

To find out the association between serum anion gap and the gensini score among the ACS patients

Materials and method:

Study design: Cross sectional analytical study.

Study place: Department of Cardiology, Sir Salimullah Medical College Mitford Hospital, Dhaka

Study period: March 2023 – February 2024

Study population: Patients with Acute Coronary Syndrome who underwent coronary angiography were included in the study

Sampling method: The sample was collected by purposive sampling method.

Sample size calculation: For this study, sample size calculation was done by following statistical formula.

Formula of calculating sample size is,

$n = [(Z_\alpha + Z_\beta)^2 \times \{(p1 (1-p1) + (p2 (1-p2))\}]/ (p1 - p2)^2$

$n = [(1.96 + 1.64)^2 \times \{(0.60 (1-0.60) + (0.249 (1-0.249))\}]/ (0.60 – 0.249)^2$

n = 13 x 0.427/ 0.123

n = 45

where,

n = sample size required in each group,

p1 = proportion of normal anion gap = 0.60,

p2 = proportion of high anion gap = 0.249,

Z_α: This depends on level of significance, for 5% this is 1.96

Z_β: This depends on power, for 95% this is 1.64

Based on above formula the sample size required per group is 45.

Hence, total sample size required is 90.

Selection Criteria:

Inclusion criteria:

Patients admitted in CCU with ACS who underwent coronary angiography

Age ≥18 years

Gender – Male & Female

Exclusion criteria:

Acute heart failure with cardiogenic shock

Patients with congenital heart disease, or valvular heart disease, or cardiomyopathy, or myocarditis, or pericarditis

Patients with Acute & Chronic kidney disease (eGFR<45/min)

Patient taking alcohol regularly

Patient with known endocrine disease

Addison's disease, Adrenal insufficiency, Cushing's syndrome, Grave's disease, Hyperthyroidism, Hypothyroidism, Acromegaly

Patient taking following drugs-

Diuretics, Biguanide, Salicylates, Bicarbonate, CA inhibitors (e.g. acetazolamide), Anti-viral/HIV drugs (e.g. lamivudine), Valproic acids (VPAs)

Study variables:

Personal and Demographic variables -

Age

Gender

Clinical variables -

Co-morbidities (hypertension, diabetes mellitus, hypercholesterolemia)

Risk factors (smoking history, prior MI)

Laboratory variables:

Serum electrolytes (Na, K, CL, HCO3)

ECG

Echocardiography

Coronary Angiogram

Serum creatinine

Fasting lipid profile

Troponin-I

Outcome variables:

Serum anion gap

Gensini score

Data collection Procedure:

The study was conducted at the Inpatient Department of Cardiology in CCU at Sir Salimullah Medical College Mitford Hospital, Dhaka. Recruitment into the study began after informed consent was obtained from eligible patients. Patients were thoroughly informed about the aims, objectives, and detailed procedures of the study before examination and were encouraged for voluntary participation with the freedom to withdraw at any time. Patients fulfilling the inclusion and exclusion criteria were enrolled. Detailed clinical history and relevant investigational data were collected in a semi-structured pretested case record form for each patient by the investigator.

At first patient was evaluated by a 12-lead surface ECG (Advanced ECG-6 plus) with a 25 mm/s paper speed and a 1mV of (10 mm) obtained in a supine position within 10 minutes of arrival in CCU. hs-Troponin-I (Auto Immuno-chemistry Analyzer (Access-2), BACMAN COULTAR, USA) was measured within the first hour of hospital admission. After admission in CCU, serum electrolytes (EASYLYTE PLUS) were sent with other routine investigations and done by ISE methods. Serum Anion gap was calculated using the equation, AG = [Na+ (mEq/L) + K+ (mEq/L)] - [Cl- (mEq/L) + HCO3- (mEq/L)]. According to the result of AG, patients were divided into two groups, Group-A (AG=8 mEq/L to 16 mEq/L) & Group -B (AG= >16 mEq/L). Echocardiography (Philips Affinity 70C) was done within 24 hours of hospital admission, and ejection fraction was recorded using the Simpson method.

Then, eligible patients underwent invasive evaluation by coronary angiography in index hospitalization. Diagnostic coronary angiography was performed via the trans-femoral or trans-radial approach by an expert interventional cardiologist using SHIMADZU BRANSIST ALEXA. Coronary angiograms were recorded to digital media for quantitative analysis and calculation of Gensini score. Coronary angiograms were obtained for each coronary vessel in ≥2 projections. Analysis of all coronary angiograms was performed visually by same two experienced cardiologists. The coronary artery narrowing was expressed as a percentage of luminal diameter stenosis. Lesions with ≥70% narrowing in a major epicardial artery or with ≥50% narrowing in the left main coronary artery were considered significant angiographic stenosis. Gensini score was calculated for every patient to assess the angiographic severity.

During calculation of gensini score, points were given to every lesion according to the percentage of stenosis multiplied by the importance of the diseased artery. Accordingly, 1 was given for 25% stenosis, 2 for 50%, 4 for 75%, 8 for 90%, 16 for 99%, and 32 for total occlusion. Each lesion score was multiplied by a factor that took into account the importance of the lesion's position in the coronary circulation. Final Gensini score was calculated by summation of the individual coronary segment scores. A Gensini score of 36 points was regarded as the cut-off value for CAD severity (Gensini score < 36 points – absent or mild coronary atherosclerosis, Gensini score ≥36 points –moderate to severe coronary atherosclerosis) (Roy et al., 2018).

All collected information was stored in separate data record forms. After checking, all the data were analyzed using SPSS-26.

Data Collection Tools:

- A checklist was prepared for each patient.
- Informed written consent form in Bangla
- Informed written consent form in English
- Tools for physical examination
- Laboratory investigation reports
- A semi-structured questionnaire

Data processing and analysis:

After collection of all the required data, these were checked, verified for consistency and tabulated using the SPSS version 26 (IBM Corp., Armonk, NY).

Frequencies and percentages were calculated as summary measures for the qualitative variables.

Arithmetic mean and standard deviation were used to describe the quantitative variables.

The unpaired t-test was used to compare symmetrically distributed continuous variables.

Chi-square test was used to compare categorical variables.

Receiver Operating Characteristic (ROC) curve was constructed by SPSS to determine the cut-off values of Anion gap to predict severe CAD (Gensini score ≥50).

STEP 1 Calculation of the severity score for each lesion ≥ 25% and adjustment for total occlusions or 99% obstructive lesions receiving collaterals			
Degree of stenosis (%)	Receiving collaterals	Adjustment for collaterals	Severity Score
1-25	-	0	1
26-50	-	0	2
51-75	-	0	4
76-90	-	0	8
91-99	no	0	16
99	yes	-8	8
100	no	0	32
100	yes, and normal source vessel	-16	32-16=16
100	yes, and 25% stenosis source vessel	-12	32-12=20
100	yes, and 50% stenosis source vessel	-8	32-8=24
100	yes, and 75% stenosis source vessel	-4	32-4=28
100	yes, and 90% stenosis source vessel	-2	32-2=30
100	yes, and 99% stenosis source vessel	-1	32-1=31

STEP 2 A multiplying factor is applied to each lesion score based upon its location in the coronary tree		
Segment	Right Dominance	Left Dominance
RCA proximal	1	1
RCA mid	1	1
RCA distal	1	1
PDA	1	1
PLB	0.5	0.5
Left Main	5	5
LAD proximal	2.5	2.5
LAD mid	1.5	1.5
LAD apical	1	1
1st Diagonal	1	1
2nd Diagonal	0.5	0.5
LCx proximal	2.5	3.5
LCx mid	1	2
LCx distal	1	2
Obtuse Marginal	1	1
STEP 3 Sum of all the lesion severity scores		

Diagnostic accuracy was measured by calculating sensitivity, specificity, positive predictive value, negative predictive value and accuracy.

A 'p' value < 0.05 was considered as statistically significant.

After completion, the data were presented in the form of tables, figures and graphs as necessary.

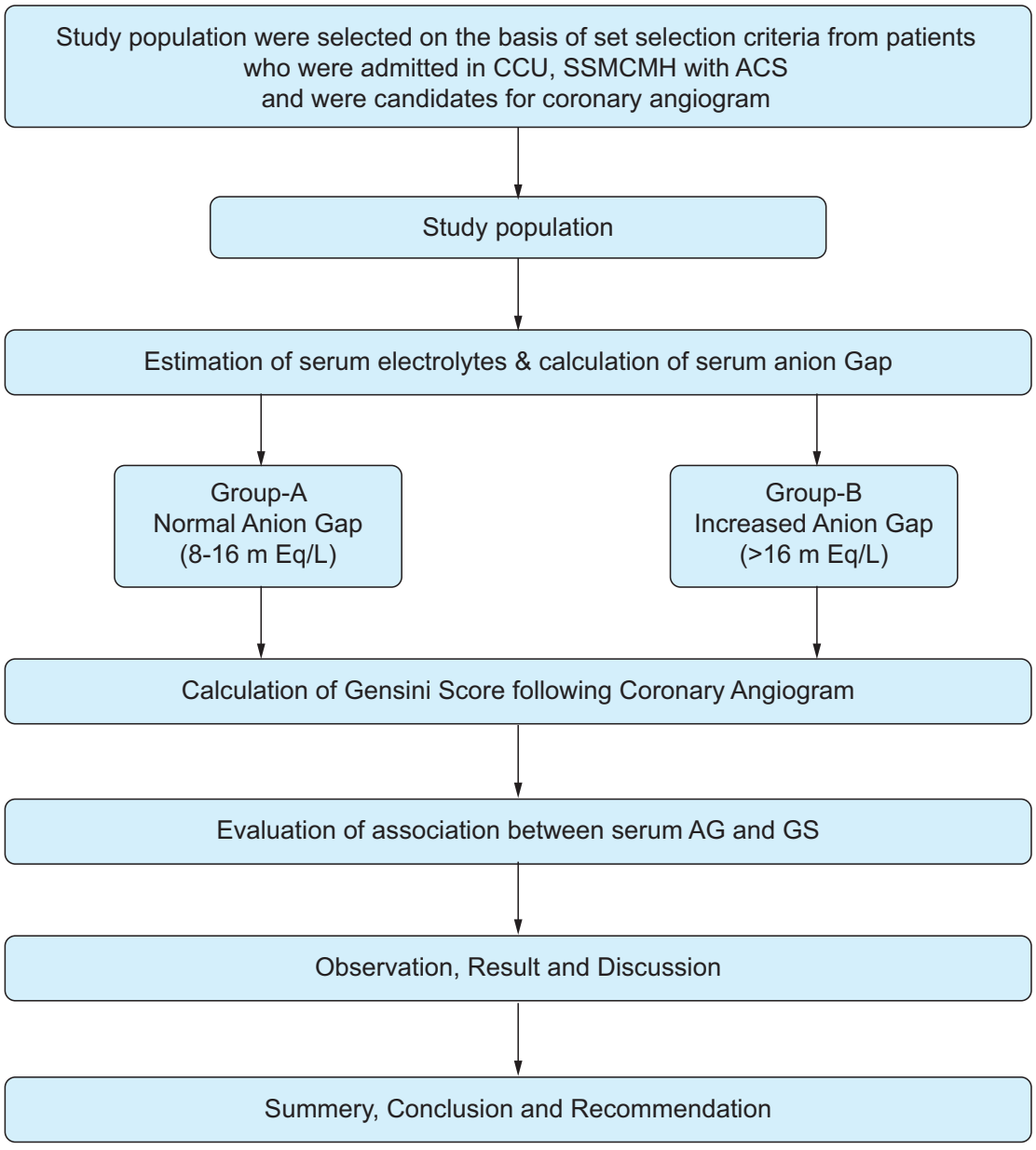
Ethical consideration:

Before starting the study, the research protocol was approved by the IEC (Institutional Ethics Committee)

of Sir Salimullah Medical College, Dhaka. Precaution were taken to protect confidentiality of the participants. Informed written consent were obtained from the study subject without any influences. The contents of the consent requirements included explanation of the nature and purpose of the study, explanation of the procedure of the study, all information regarding benefits and hazard to all participants, explanation that they have the right to refuse and withdraw or accept to participate in the study & full understanding of the results of this research and their probable welfare implications.

It was also mention that the subject will not gain financial benefit from this study, and the study will not involve collection of any body organ or tissue. Subjects were assured that data obtained from the study will be used only for the research purpose. Through this research, patient would not be confronted with any physical, psychological or social risks. Participant's basic human rights would not be violated in any way. If the participants have any question or any other problems, they were requested to contact with the investigator.

Study Flow Chart:



Operational Definitions:

Acute coronary syndrome: Acute coronary syndromes (ACS) encompass a spectrum of conditions that include patients presenting with recent changes in clinical symptoms or signs, with or without changes on 12-lead electrocardiogram (ECG) and with or without acute elevations in cardiac troponin (cTn) concentrations. Patients presenting with suspected ACS may eventually receive a diagnosis of acute myocardial infarction (AMI) or unstable angina (Byrne et al. 2023).

Myocardial Infarction: The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/ or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

Symptoms of myocardial ischemia;

New ischemic ECG changes;

Development of pathological Q waves;

Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;

Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs) (Thygesen et al. 2019).

ST-Elevation Myocardial Infarction: Electrocardiographic manifestations suggestive of acute myocardial ischemia (in the absence of left ventricular hypertrophy and bundle branch block):

New ST-elevation at the J-point in two contiguous leads with the cut-point: ≥1 mm in all leads other than leads V2–V3 where the following cut-points apply: ≥2mm in men ≥40 years; ≥2.5 mm in men < 40 years, or ≥1.5 mm in women regardless of age Thygesen et al., 2019).

NSTE Myocardial Infarction: These patients may exhibit other ECG alterations, including transient ST-segment elevation, persistent or transient ST-segment depression, and T wave abnormalities, including hyperacute T waves, T wave inversion, biphasic T waves, flat T waves, and pseudonormalization of T waves. Alternatively, the ECG may be normal. The majority of patients in this category who subsequently display a typical rise and fall in cardiac troponin levels (i.e. fulfilling MI criteria as per the fourth universal definition of MI) will receive a final diagnosis of non-ST-elevation MI (NSTEMI) (Byrne et al. 2023).

Unstable Angina UA is defined as myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury/necrosis. It is characterized by specific clinical findings of prolonged (>20 min) angina at rest; new onset of severe angina; angina that is increasing in frequency, longer in duration, or lower in threshold; or angina that occurs after a recent episode of MI (Byrne et al. 2023).

Hypertension: According to 2017 ACC/ AHA/ AAPA/ ABC/ ACPM/ AGS/ APhA/ ASH/ ASPC/ NMA/ PCNA Guideline:

Normotensive: Normotensive will be defined as individuals had no history of hypertension and did not take any medication for hypertension.

Control of Hypertension: According to the 2018 ESC/ ESH Clinical Practice Guidelines for the Management of Arterial Hypertension; control of hypertension will be considered if BP less than SBP<130 & DBP<80 mmHg.

Normal: Blood pressure less than 120/80 mm Hg

Elevated: Systolic between 120-129 and diastolic less than 80; (Whelton et al. 2018).

Diabetes Mellitus (American Diabetes Association 2023): American Diabetic Association (ADA) criteria for diagnosis of diabetes:

Fasting plasma glucose ≥126 mg/dl (7.0 mmol/l) or

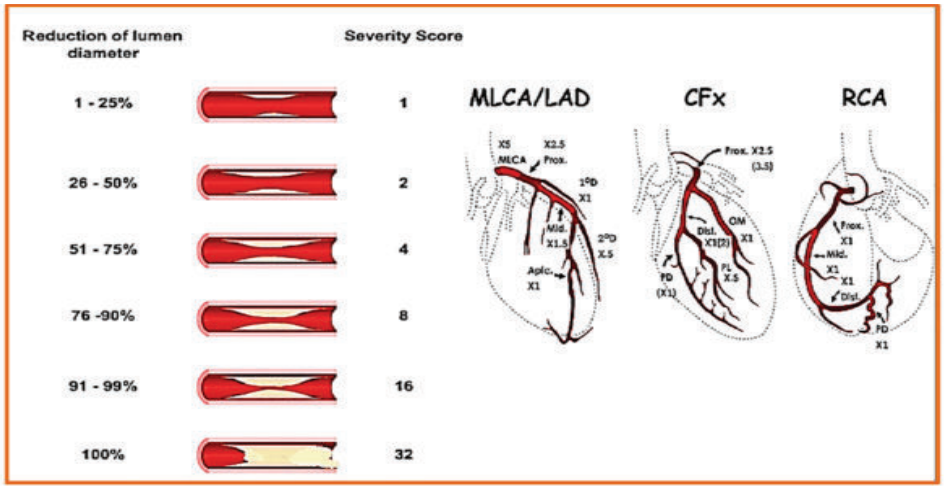
2-hr plasma glucose ≥200 mg/dl (11.1 mmol/l) or

HbA1c ≥6.5% or

Patients with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l)

Gensini score (Gensini 1983; Rampidis et al. 2019): The severity of CAD was assessed by using the Gensini score, which grades narrowing of the lumens of the coronary arteries as 1 for 1–25% narrowing, 2 for 26–50% narrowing, 4 for 51–75% narrowing, 8 for 76–90% narrowing, 16 for 91–99% narrowing, and 32 for total occlusion. This score is then multiplied by a factor that takes into account the importance of the lesion's position in the coronary arterial tree, for example, 5 for the left main coronary artery, 2.5 for the proximal left anterior descending coronary artery and proximal left circumflex coronary artery (3.5 if left

circumflex coronary artery is dominant), 1.5 for the mid-region of the left anterior descending coronary artery, 1 for the distal left anterior descending coronary artery, the first diagonal, the proximal, mid- and distal-region of the right coronary artery, the postero-descending, the mid- and distal-region of the left circumflex coronary artery (2 for both of them if left circumflex coronary artery is dominant) and the optus margin, and 0.5 for the second diagonal and the postero-lateral branch. The Gensini score was expressed as the sum of the scores for the all coronary arteries.



STEP 1 Calculation of the severity score for each lesion ≥ 25% and adjustment for total occlusions or 99% obstructive lesions receiving collaterals

Degree of stenosis (%)	Receiving collaterals	Adjustment for collaterals	Severity Score
1-25	-	0	1
26-50	-	0	2
51-75	-	0	4
76-90	-	0	8
91-99	no	0	16
99	yes	-8	8
100	no	0	32
100	yes, and normal source vessel	-16	32-16=16
100	yes, and 25% stenosis source vessel	-12	32-12=20
100	yes, and 50% stenosis source vessel	-8	32-8=24
100	yes, and 75% stenosis source vessel	-4	32-4=28
100	yes, and 90% stenosis source vessel	-2	32-2=30
100	yes, and 99% stenosis source vessel	-1	32-1=31

STEP 2 A multiplying factor is applied to each lesion score based upon its location in the coronary tree

Segment	Right Dominance	Left Dominance
RCA proximal	1	1
RCA mid	1	1
RCA distal	1	1
PDA	1	1
PLB	0.5	0.5
Left Main	5	5
LAD proximal	2.5	2.5
LAD mid	1.5	1.5
LAD apical	1	1
1st Diagonal	1	1
2nd Diagonal	0.5	0.5
LCx proximal	2.5	3.5
LCx mid	1	2
LCx distal	1	2
Obtuse Marginal	1	1

STEP 3 Sum of all the lesion severity scores

Results:

This cross-sectional analytical study was conducted in the department of Cardiology, Sir Salimullah Medical College Mitford Hospital, Dhaka. A total of 90 patients with Acute Coronary Syndrome who underwent coronary angiography was enrolled in the study by purposive sampling. Depending on anion gap, 45 patients were in group A (AG: 8 mEq/L to 16 mEq/L) and 45 were in group B (AG: >16 mEq/L).

Table-I

Age distribution of the study subjects (N=90)

Age group (years)	Group A (n=45) Number (%)	Group B (n=45) Number (%)	p-value
<50	14 (31.1)	4 (8.9)	
50 to 70	23 (51.1)	28 (62.2)	0.013*
>70	8 (17.8)	13 (28.9)	0.017**
Mean±SD	59.5±11.9	64.9±9.1	

p-value was determined by Ch-square test and **Independent sample t test. Data was presented with frequency (%), mean±SD and within parenthesis percentage over column in total.

Group A= Anion Gap 8 mEq/L to 16 mEq/L

Group B= Anion Gap >16 mEq/L

Majority of study subjects in both groups belonged to the age group 50-70 years. Age difference of both groups was significant.

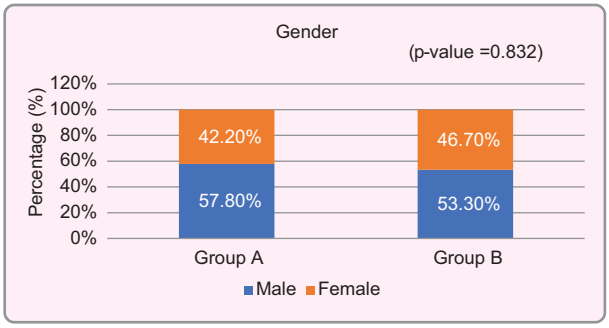


Figure-1: *Gender distribution of the study subjects (N=90)*

p-value was determined by Ch-square test (p=0.832).

Group A= Anion Gap 8 mEq/L to 16 mEq/L

Group B= Anion Gap >16 mEq/L

No significant difference regarding gender was found between the groups.

Table-II

Distribution of the study subjects according to risk factors (N=90)

Risk factors	Group A (n=45)	Group B (n=45)	p-value
Hypertension	20 (44.4)	31 (68.9)	0.001*
Diabetes mellitus	22 (48.9)	18 (40)	0.525*
Family History	2 (4.4)	4 (8.9)	0.677**
Obesity	6 (13.3)	3 (6.7)	0.485**
Smoking habit	8 (17.8)	3 (6.7)	0.197**

p-value was determined by *Ch-square test and **Fisher Exact test. Data was presented with frequency (%) and within parenthesis percentage over column in total.

Group A= Anion Gap 8 mEq/L to 16 mEq/L

Group B= Anion Gap >16 mEq/L

Hypertension was found significantly higher in Group B.

Table- III

Distribution of the study subjects according to severity of CAD by Gensini score (N=90)

Gensini score	Group A (n=45)	Group B (n=45)	p-value
High Gensini score (≥50)	9 (20)	39 (86.7)	<0.001*
Low Gensini score (<50)	36 (80)	6 (13.3)	
Mean±SD	43.9±6.3	54.8±1.4	<0.001**

p-value was determined by *Ch-square test and **Independent sample t test. Data was presented with frequency (%) and within parenthesis percentage over column in total.

In Group A, 36 study subjects (80%) had low Gensini Score and in Group B, 39 (86.7%) had high Gensini Score.

Mean Gensini score in Group A and Group B was 43.9±6.3 and

54.8±1.4 accordingly.

Gensini Score was found significantly higher in Group B.

A cut off value Anion gap>16 mEq/L (AUC=0.899, 95% CI=0.831-0.967, p<0.001) in the prediction of severe CAD (Gensini score ≥50) showed 81.25% sensitivity, 80.95% Specificity, 82.98% PPV, 79.07% NPV and 81.11% accuracy.

Cut off value	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
>16 mEq/L	0.899	81.25%	80.95%	82.98%	79.07%	81.11%

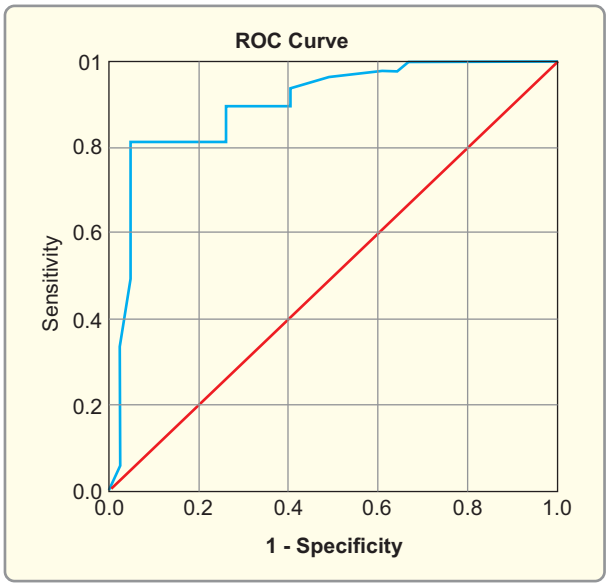


Figure-2: *ROC curve analysis of anion gap in the prediction of coronary artery disease severity (Gensini score ≥50) (N=90)*

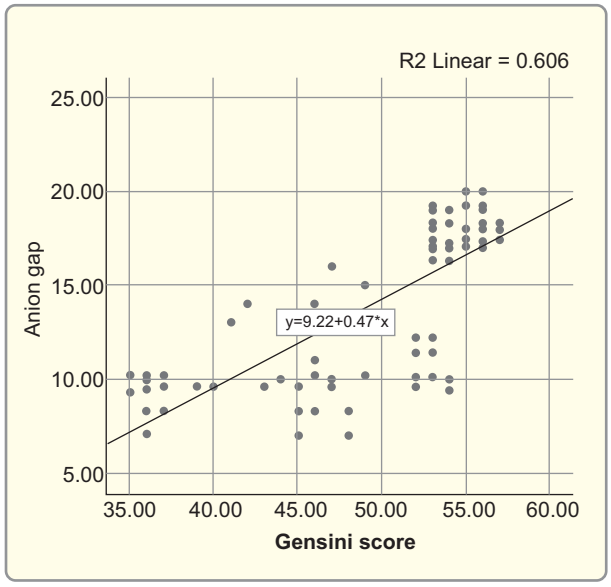


Figure 3: *Scattered plot showing correlation of anion gap with Gensini score*

Table-IV

Diagnostic accuracy test of Anion gap in the prediction of severe CAD (Gensini score ≥50) (n=90)

Anion Gap	Gensini score ≥50	Gensini score <50	Total
≥16	TP39	FN8	TP+FN47
<16	FP9	TN34	FP+TN43
Total	TP+FP48	FN+TN42	90

A cut off value of anion gap ≥16 mEq/L in the prediction of Gensini score ≥50 could truly detect 39 cases and anion gap <16 mEq/L in the prediction of Gensini score below 50 could truly detect 34 cases.

Table-V

Risk factors analysis for severity of CAD by multivariate logistic regression

	Odds ratio	95% CI	p-value*
Age	1.030	0.971-1.093	0.318
Hypertension	0.374	0.107-1.308	0.124
Anion gap	11.762	2.126-65.062	0.005

p-value was determined by Multivariate logistic regression.

Anion gap showed positive association with GS (r=0.779, p<0.001)

Multivariate logistic regression analysis showed that anion gap was significantly associated with severity of CAD.

Discussion:

Anion gap is one instrument that can be used to evaluate and provide a prediction based on the unique characteristics of each patient, offering some degree of efficacy in therapy and management alternatives. Current study was aimed to find out the association of serum anion gap and angiographic severity of coronary artery disease by Gensini score in patients with acute coronary syndrome. The study was conducted at the Inpatient Department of Cardiology from March 2023 to February 2024 in CCU at Sir Salimullah Medical College Mitford Hospital, Dhaka. Among 90 enrolled patients with ACS, 45 patients had anion gap 8 mEq/L to 16 mEq/L (Group A) and 45 patients had anion gap >16 mEq/L (Group B).

In both Group A and Group B, majority of the patients were aged between 50 to 70 years (51.1% vs 62.2%). Mean age of the patients in Group A and Group B was 59.5±11.9 years and 64.9±9.1 years accordingly. Age

was found significantly higher in Group B than Group A. Previous study also observed that participants with the highest group of serum anion gap (mEq/L) (serum AG ≥16 mmol /L) showed higher values for age (Ji and Peng, 2023)[16]. In the study of Cheng et al. also observed that increasing age was significantly associated with increased anion gap (Cheng et al. 2020)[(17)]. Neeland et also observed that mean age of the patients with CAD was above 60 years ranged from 55 to 71 years (Neeland et al. 2012)[18]. Although acute coronary syndrome mainly occurs in patients >50 years, younger patients can be affected as well (Ricci et al. 2017)[19].

In both Group A and Group B male predominant was observed (57.8% vs 53.3%). No significant difference was found between groups. Previous study by Yang et al. also revealed that male patients was higher among ACS in comparison to female and no significant difference was found between the gender and different group of anion gap (Yang et al. 2017)[6]. Neeland et al. found 66% of the patients with CAD was male (Neeland et al. 2012)[18]. Previous other study also observed male predominant among the patients with ACS (Cheng et al. 2020; Ji et al. 2022)[17,16].

Hypertension and diabetes mellitus was found more common among the study subjects. Besides, in Group A 4.4% had Prior MI. and in Group B, 8.9% had Prior MI. Besides, 6.7% had obesity and 6.7% had smoking habit. Comorbidity was found higher among increased anion gap group but only hypertension showed statistically significant. Previous study also observed that participants with the highest group of serum anion gap (serum AG ≥16 mmol /L) showed higher number of hypertension than the lower group (Ji and Peng 2023)[(16)]. Sharma et al. unveiled that hypertension was associated with ACS and increased the anion gap (Sharma et al. 2020)[20]. Another study also revealed that hypertension was significantly associated with increased anion gap (Taylor et al. 2007)[21].

When diagnosing and treating coronary artery disease, the conventional anion gap method is very helpful in clinical practice. Besides, Gensini score (GS) provides valuable information on severity and prognosis of coronary artery disease (CAD) (Charach et al. 2021)[11]. According to current study, Gensini score was used to measure the severity of ACS whereas 53.3% of the patients had Gensini score ≥50, 46.7% had Gensini score <50. Mean Gensini score in low anion gap group and high anion group was 43.9±6.3mEq/L and 54.8±1.4mEq/L accordingly. Mean Gensini score was significantly higher among the patients with anion gap above 16mEq/L. A cut off value Anion gap>16 mEq/L (AUC=0.899, 95% CI=0.831-0.967, p<0.001) in the prediction of severe CAD (Gensini score ≥50) showed 81.25% sensitivity, 80.95% Specificity, 82.98% PPV, 79.07% NPV and 81.11% accuracy. A prior study found a positive correlation between serum anion gap levels and severity of disease, with higher serum anion gap levels associated with higher patient mortality (Ji and Peng 2023)[16]. Another study also revealed that increased risk of cardiac morbidity or mortality was linked to larger serum anion gap level and also indicated that if the serum anion gap levels are discovered to be high, this suggests a worse prognosis (Sharma et al. 2020)[20].

Limitations:

- Single centre study
- Randomization was not done

Conclusion:

This study investigated the association of serum anion gap and the severity of coronary artery disease as measured by Gensini Score (GS) in patients with acute coronary syndrome (ACS). A higher anion gap levels (>16 mEq/L) were associated with increased severity of CAD by Gensini scores in patients with ACS.

Recommendations:

- Further randomized multicenter studies and longer follow-up are recommended.
- Anion gap assessment could be incorporated into routine evaluations to predict angiographic severity in patients with acute coronary syndrome (ACS), facilitating adoption of timely management strategies.

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