TO STUDY THE ASSOCIATION BETWEEN GLYCEMIC GAP AND ADVERSE OUTCOMES IN DIABETIC PATIENTS ADMITTED TO ICU–A ONE YEAR LONGITUDINAL STUDY IN KLE'S DR.PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI.

BY

REG NO: BG0120012

Dissertation

Submitted to

KAHER, Belagavi, Karnataka

In partial fulfilment

of the requirements for the degree of

M.D.

IN

GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE

J. N. MEDICAL COLLEGE
BELAGAVI - 590010. KARNATAKA

JUNE/JULY-2023

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI

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ABSTRACT

Background: Stress-induced hyperglycemia has been independently associated with an increased risk of mortality in critically ill patients with Diabetes Mellitus. Glycemic gap is a marker of stress induced glycemic excursion in patients with diabetes, that can be used to predict adverse outcomes in patients with diabetes admitted to the ICU. Objective of this study was to correlate glycemic gap and adverse outcomes in patients with type 2 diabetes mellitus (DM) admitted to the ICU.

Study design: A one-year longitudinal observational study in a tertiary care Hospital.

Materials and Methods: Patients with Type 2 Diabetes Mellitus admitted in Medical ICU at our Tertiary Care Centre, fulfilling the inclusion criteria, from January to December 2021, were included in the study. Data including clinical, laboratory data with calculation of glycemic gap, and follow up records of the patients were collected and compared between improved and deteriorated group of patients, with study of adverse events in deteriorated group. Correlation between glycemic gap and outcome of patients were studied.

Statistical analysis: Data was collected and analysed in Microsoft Excel. The student t-test (http://vassarstats.net/tu.html) was used for the evaluation of continuous data and the chi-square test (http://vassarstats.net/newcs.html) for categorical variables. A correlation matrix was evaluated from excel data analysis (Excel 2019), to correlate glycemic gap with outcomes of patients.

Results: The study considered patients aged between 21-98 years, with the mean age being 61.42 years. Descriptive analysis of the glycemic panel revealed the mean HbA1C of the study subjects as 9.11±4.08%. The corresponding mean admission RBS, A1C Derived Average Glucose (ADAG), and Glycemic Gap reported were

208.3±70.03 mg/dl, 214.87±116.97 mg/dl, and 4.28±0.77 mg/dl. Analysis of glycemic panel parameters analysis revealed a significant statistical difference in HbA1C, admission RBS, ADAG, and glycemic gap between the improved and worsened groups (0.09, <.0001, 0.09, <.0001 respectively). In addition, the glycemic gap was found to be significantly more in the worsened group when compared to the improved group. The mean length of ICU stay noted was 4.94±2.80 days, and increased length of ICU stay, MODS and AKI showed significant positive correlation with mortality rate. The study has noted multiple organ dysfunction syndrome (MODS) as the common adverse event (14.84%), followed by acute kidney injury (11.72%), acute respiratory distress syndrome (10.16%) and shock (2.35%). A positive correlation was noted between the glycemic gap and worsened outcomes, whereas a negative correlation was noted between the glycemic gap and improved outcomes.

Conclusion: The present study showed that higher glycemic gap is a simple marker for predicting adverse outcome in diabetic patients. The glycemic gap may serve as an effective tool to evaluate the severity and prognosis of patients with Type 2 Diabetes Mellitus, who have been admitted with critical illness. The present study could aid in reducing ICU mortality, by early detection and treatment of the stress induced hyperglycemia, in critically ill diabetic patients.

LIST OF ABBREVIATIONS

ACCORD:	Action to Control Cardiovascular Risk in Diabetes
ADA:	American Diabetes Association
ADAG:	A1C-derived average glucose
AHF:	Acute Heart Failure
AKI:	Acute kidney injury
APACHE II:	Acute Physiology and Chronic Health Evaluation II
ARDS:	Acute respiratory distress syndrome
ARF:	Acute respiratory failure
AUROC:	Area under the receiver operating characteristic
BMI:	Body mass index
CAP:	Community-acquired pneumonia
CGM:	Continuous glucose monitoring
CVD:	Cardiovascular disease
DALY:	Disability adjusted life years
DFUs:	Diabetic foot ulcers
DKA:	Diabetic Ketoacidosis
DM:	Diabetes Mellitus
DN:	Diabetic nephropathy
DPP-4:	Dipeptidyl peptidase IV
FFA:	Free fatty acids

GAD:	Glutamic acid decarboxylase
GDM:	Gestational diabetes mellitus
GFR:	Glomerular filtration rate
GG:	Glycemic gap
GV :	Glycemic variability
HbA1c:	Glycosylated haemoglobin
HG:	Hyperglycaemia
HHS:	Hyperosmolar hyperglycemic syndrome
IAA:	Insulin autoantibodies
IAAP:	Islet amyloid polypeptides
ICU:	Intensive Care Unit
IDDM:	Insulin-dependent diabetes mellitus
IFG:	impaired fasting blood glucose
IGT:	Impaired glucose tolerance
IL:	Interleukin
IR:	Insulin Resistance
MACE:	Major adverse cardiac event
MAGE:	Mean amplitude of glycemic excursion
MODS:	Multiorgan dysfunction syndrome
MODY:	Maturity-onset diabetes of the young
MI:	Myocardial infarction

Neuro D1:	Neurogenic differentiation 1
NIDDM:	Non-insulin dependent diabetes mellitus
NF:	Necrotizing fasciitis
NNMS:	National Noncommunicable Disease Monitoring Survey
OGIT:	Oral glucose tolerance test
PAD:	Peripheral artery disease
PAX6:	Paired box gene 6
PDX-1:	Pancreatic and duodenal homeobox-1
PKC:	Protein Kinase C
RBC:	Red blood cell
RBS:	Random blood sugar
ROS:	Reactive oxygen species
SGLT-2:	Sodium-glucose transporter-2
SIH:	Sress-induced hyperglycemia
T1DM:	Type 1 diabetes mellitus
T2DM:	Type 2 diabetes mellitus
TNF:	Tumour necrosis factor
UGI:	Upper gastrointestinal
URP:	Unfolded protein response
WBC:	White blood cell
WHO:	World Health Organization

TABLE OF CONTENTS

Sl. NO.	TITLE	PAGE NO.
1	INTRODUCTION	1-3
2	OBJECTIVES	4
3	REVIEW OF LITERATURE	5-35
4	METHODOLOGY	36-38
5	RESULTS	39-60
6	DISCUSSION	61-64
7	CONCLUSION	65
8	SUMMARY	66-67
9	BIBLIOGRAPHY	68-80
10	ANNEXURES	81-89
	ANNEXURE I – CONSENT FORM	81-85
	ANNEXURE II – PROFORMA	86-88
	ANNEXURE III – MASTER CHART	

LIST OF TABLES

Sl. No.	TITLE	PAGE No.
1	Classification of diabetes	**7**
2	Monogenic diabetes	**7-8**
3	Stages and diagnostic criteria for type 1 diabetes	**26**
4	Criteria for the diagnosis of type 2 diabetes mellitus	**27**
5	Descriptive analysis of age and gender in the study population	**39**
6	Descriptive analysis of the Glycemic Panel in the study population (n=128)	**40**
7	Descriptive analysis of the complete Hemogram in the study population (n=128)	**44**
8	Descriptive analysis of the Renal profile distribution graph in the study population (n=128)	**45**
9	Descriptive analysis of the Serum Electrolytes in the study population (n=128)	**46**
10	Descriptive analysis of the Liver Profile in the study population (n=128)	**48**
11	Adverse Outcome in the study population(n=128)	**49**
12	Mortality and ICU stay in the study population(n=128)	**50**
13	Descriptive analysis of demographic parameters between improved and worsened group	**51**
14	Comparison of Glycemic Panel parameters between improved and worsened group	**52**

15	Comparison of Hemogram parameters between improved and worsened group	**55**
16	Comparison of renal profile between improved and worsened group	**56**
17	Comparison of Serum Electrolyte parameters between improved and worsened group	**57**
18	Comparison of Liver Profile parameters between improved and worsened group	**58**
19	Correlation between glycemic gap and outcomes in the study population(n=128)	**60**

LIST OF FIGURES

Sl. No.	TITLE	PAGE No.
1	Signalling pathways involved in insulin secretion in β-cells in physiological conditions (A) and mechanisms leading to dysfunction (B)	**17**
2	Clinical stages of diabetic retinopathy	**20**
3	Types of diabetic neuropathy	**22**
4	Glomerulonephropathy in diabetes	**25**
5	Glucose-lowering medication in type 2 diabetes	**29**
6	Demographic characteristics of the study population	**39**
7	Glycemic Panel distribution in the study population (n=128)	**40**
8	Complete Hemogram distribution in the study population	**43**
9	Renal profile distribution graph in the study population	**45**
10	Serum Electrolytes distribution graph in the study population	**46**
11	Liver Profile distribution in the study population(n=128)	**47**
12	Bar plot for mortality in the study population(n=128)	**49**
13	Comparison of demographic parameters between improved and worsened group	**50**
14	Boxplot graph comparing Glycemic Panel parameters in improved and worsened group	**51**
15	Boxplot graph comparing Hemogram distribution between the improved and worsened group	**54**

16	Box plot graph comparing the renal profile between improved and worsened group	**56**
17	Box plot graph comparing the Serum Electrolyte parameters between improved and worsened group	**57**
18	Boxplot graph comparing Liver profile parameters in improved and worsened group	**59**

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder which is characterized by hyperglycemia and glucose intolerance. It is associated with impaired insulin secretion and impaired peripheral sensitivity to insulin, as well as eventual β-cell dysfunction. Persistent hyperglycemia is a hallmark of this chronic metabolic condition, which may result from decreased insulin production, elevated peripheral insulin resistance, or a combination of the two. In addition to other metabolic abnormalities in diabetes mellitus patients, this persistent hyperglycemia damages multiple organ systems and causes the emergence of both life-threatening and severe health consequences. The complications include microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications leading to a 4-fold increased risk of cardiovascular diseases. Diabetes has become one of the most significant and difficult health problems facing the world's population today due to its rising prevalence on a global scale.[1]

The prevalence of diabetes has been increasing in the majority of the world's regions as a result of urbanisation and the adoption of modern lifestyle patterns at a rate that is proportional to their rapid economic development. The prevalence of diabetes is high, and concentrated in emerging nations. Globally and in developing nations like India, the burden of diabetes is large and rising, primarily due to increasing rates of overweight/obesity and unhealthy lifestyles. In India, there are currently 77 million diabetics, and by 2045, there are expected to be over 134 million. Similar to India, this trend is mostly being driven by an increase in unhealthy lifestyles and overweight/obesity. In India, there are currently an estimated 77 million diabetics, and by 2045, there are expected to be over 134 million.[2]

Patients in life-threatening conditions, such as sepsis with multiple organ dysfunction, major operations, and acute myocardial infarction, exhibit stress-induced hyperglycemia excursions. Stress-induced hyperglycemia causes an increase in gluconeogenesis and a decrease in glycogenolysis because it is caused by an increase in the amounts of hormones that regulate blood sugar, including cortisol, catecholamines, glucagon, and growth hormone.[3]

Patient outcomes are correlated with both the glucose at the time of admission and the mean glucose level over the course of the hospital stay. Patients hospitalized to the ICU frequently experience stress-related hyperglycemia. Evidence suggests that maintaining euglycemia lowers the risk of infection. The presence of hyperglycemia is linked to an increased risk of infectious complications in patients.[4,5]

A potential risk factor for diabetes complications has been discovered as glycemic variability (GV), which is defined as a crucial aspect of glucose homoeostasis. It is widely accepted that oxidative stress is the mechanism through which GV causes diabetic complications. Due to the increased risk of diabetic macrovascular and microvascular problems, hypoglycemia, mortality rates, and other negative clinical outcomes, it is becoming increasingly necessary to take into account when evaluating glycemic management in clinical practice.[6,7] Patients being admitted to the intensive care unit (ICU) frequently experience glycemic excursions, which are linked to adverse outcomes.[8] Therefore, monitoring glycemic excursions can be a key factor in predicting unfavourable outcomes in diabetic patients.

Numerous studies have discovered a strong positive connection between mean plasma glucose levels during the previous three months and glycosylated haemoglobin (HbA1c), A1C-derived average glucose (ADAG), which is calculated

by the following formula**, ADAG = ([28.7 x HbA1c]-46.7)**. It has been hypothesized that the glycemic gap, which is calculated by deducting the A1C-derived average glucose (ADAG) from the admission level of glucose, i.e., **Glycemic gap= Admission Blood Glucose- ADAG**, eliminates the influence of long standing hyperglycemia on the disease severity assessment in patients with diabetes. The glycemic gap, maybe a strong indicator of outcomes than the average glucose determined by HbA1C.[3]

In diabetic patients who have been admitted to the Intensive Care Unit (ICU), the glycemic gap is a marker of glycemic excursions that can be used to foretell adverse outcomes and used in the evaluation of severity and prognosis of diabetic individuals who are critically ill.[8]

The aim of the study is to determine the association between glycemic gap and adverse outcomes in Type 2 Diabetes Mellitus patients, admitted to ICU.

OBJECTIVES

To study the association between Glycemic Gap and adverse outcomes in Type 2 Diabetes Mellitus patients admitted to Medical ICU.

REVIEW OF LITERATURE

1.1 History

Ancient Egyptians documented clinical traits that are similar to those of diabetic Mellitus more than three thousand years ago. The first records of diabetes are believed to have been found in an Egyptian papyrus from around 1550 BC, which describes a rare ailment that causes its sufferers to lose weight quickly and urinate a lot. Araetus of Cappodocia originally used the name "diabetes" (81-133AD).[9,10] Famous Indian surgeon Sushruta used the term "madhumeha" (honey-like urine) to describe diabetes in his book Samhita about the fifth century BC. He noted that in addition to the urine's sweet flavor and sticky feel to the touch, diabetes is also characterised by its propensity to attract ants.[11] Following the discovery of the sweetness of patient urine and blood, Thomas Willis (Britain) coined the phrase Mellitus (honey sweet) in 1675. [9] In the 1770-1800 era Matthew Dobson recognizes that people with diabetes' pee have a sweet taste because there is too much sugar in both their blood and urine. Moreover, he notes that while some people with diabetes pass away within five weeks, others live much longer, indicating the initial sign of both type 1 and type 2 diabetes. Claude Bernard first uses the term "glycogen" in the 1800s after learning that a chemical produced by the liver is identical to the sugar that diabetics' urine contains, which was the first time that diabetes, glycogen, and metabolism have been linked. aul Langerhans explains in 1869 that the pancreas has two types of cells, one of which secretes tiny cell islands. The purpose of these cells, which later came to be known as the "Islets of Langerhans,". In 1889, Joseph von Mering and Oskar Minkowski removed the pancreas from dogs and found that the animals soon started to exhibit diabetic symptoms.[10] Frederick Banting and John

MacLeod received the Nobel Prize in Medicine in 1923 for the discovery of insulin.[11] Sir Harold Percival published research in 1936 that categorises patients' levels of insulin sensitivity as type 1 or type 2 diabetes whereas the life expectancy of a diabetic is rising by 1945 as insulin therapies continue to advance. In 1955 Carbutamide, the first oral medication is created to help reduce blood sugar levels.[10]

1.2 Classification of diabetes mellitus (DM)

DM can be classified into a number of different subtypes, including Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, gestational diabetes, maturity-onset diabetes of the young (MODY), neonatal diabetes, and secondary causes of Diabetes brought on by endocrinopathies, steroid use, etc. The two primary forms of Diabetes Mellitus are - Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), both of which are typically brought on by defective secretion of insulin (Type 1 Diabetes Mellitus) or defective action (T2DM). T1DM often affects kids or teenagers, nonetheless, T2DM is more likely to impact older and middle-aged people who have persistent hyperglycemia as a result of poor dietary and lifestyle choices. [12]

Table 1: Classification of diabetes [13]

Types	Secondary causes
1] Insulin-dependent diabetes mellitus (IDDM, Type 1) 2] non-insulin-dependent diabetes mellitus (NIDDM, Type 2) a] Nonobese NIDDM (Type 1 in evolution) b) Obese NIDDM c) Maturity onset diabetes of the young (MODY)	1] Pancreatic disease e.g.- chronic pancreatitis in alcoholics. 2] Hormonal abnormalities. pheochromocytoma, Cushing's syndrome. 3] Drug or chemical induced. 4] Insulin receptor abnormalities. 5] Genetic syndromes e.g., lipodystrophies. 6] Others include poorly or ill-defined types that do not fit into any of the above.

Only 5% of people with diabetes have monogenic abnormalities that result in b-cell malfunction, such as neonatal diabetes and MODY.

Table 2: Monogenic diabetes [13]

	Gene	Inheritance	Clinical features
MODY	GCK	AD	GCK-MODY: stable, nonprogressive elevated fasting blood glucose; typically does not require treatment; microvascular complications are rare; small rise in 2-h PG level on OGTT (<54 mg/dL [mmol/L])
	HNF1A	AD	HNF1A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; lowered renal threshold for glucosuria; large rise in 2- h PG level on OGTT (>90 mg/dL [5 mmol/L]); sensitive to sulfonylureas
	HNF4A	AD	HNF4A-MODY: progressive insulin secretory defect with presentation in adolescence or early adulthood; may have large birth weight and transient neonatal hypoglycemia; sensitive to sulfonylureas

	HNF1B	AD	HNF1B-MODY: developmental renal disease (typically cystic); genitourinary abnormalities; atrophy of the pancreas; hyperuricemia; gout
Neonatal diabetes	INS ABCC8	AD AD	Permanent: IUGR; insulin requiring Transient or permanent: IUGR; rarely developmental delay; responsive to sulfonylureas

MODY: Maturity onset diabetes of the young, OGTT : Oral glucose tolerance test

Type 1 diabetes mellitus

Type 1 diabetes , an immune-mediated type of diabetes reporting 5-10% diabetes, was embraced earlier as insulin-dependent diabetes or juvenile-onset diabetes which can occur due to pancreatic β--cells destruction by an autoimmune disease that is cellular in nature.[14] It is characterized by a lack of insulin and the ensuing hyperglycemia.[15] "The hallmark of type 1 diabetes is the presence of autoantibodies against the pancreatic islet cells, which also includes autoantibodies to insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), protein tyrosine phosphatase (IA2 and IA2), and zinc transporter protein (ZnT8A). These pancreatic autoantibodies could be found in the serum of these patients months or years before the onset of the disease."[16,17] Strong HLA connections exist for autoimmune type 1 diabetes, with links to the DR and DQ genes that may be either protective or predisposing.[18] The pace of -cell apoptosis in this kind of diabetes varies greatly, being swift in some people, primarily in infants and children, and sluggish in others, primarily adults. Ketoacidosis may be the first sign of the illness in certain individuals, especially children and adolescents, whereas mild fasting hyperglycemia in others can quickly progress to severe hyperglycemia and/or ketoacidosis in the context of infection or other stress. Others, especially adults, might still have some -

cell function, which would keep them from going into ketosis for a long time. However, over time, they would need insulin to survive, which would put them at danger of going into ketosis.[14] Patients rarely have obesity when they first develop this type of diabetes, but it is not a diagnostic obstacle. Additionally, these patients have a higher risk of developing other autoimmune diseases like Graves' disease, Hashimoto's thyroiditis, Addison's disease, vitiligo, celiac sprue, autoimmune hepatitis, myasthenia gravis, and pernicious anaemia. There are some types of type 1 diabetes whose causes are unknown. Some of these patients lack autoimmune signs yet have persistent insulinopenia and a propensity for ketoacidosis. Although there is no scientific proof of -cell autoimmunity and this form of diabetes is not HLA related, it is highly inherited.[14]

Type 2 diabetes mellitus

One of the most prevalent metabolic diseases in the world, Type 2 Diabetes Mellitus (T2DM), is predominantly brought due to a confluence of two key factors: insufficiency of insulin secreted by pancreatic beta-cells with failure of insulin-responsive tissues to react to the hormone. The World Health Organization (WHO) describes diabetes mellitus as a chronic metabolic condition marked by high blood glucose levels that, over time, cause damage to the heart, blood vessels, eyes, kidneys, and nerves. T2DM, which is characterised by insufficient insulin secretion by pancreatic islet cells, tissue insulin resistance (IR), and an insufficient compensatory insulin secretory response, accounts for more than 90% of cases of diabetes mellitus. As the illness worsens, insulin secretion becomes unable to keep glucose levels in balance, leading to hyperglycemia. The key traits of T2DM patients are obesity or developing higher fat percentage in the body, especially in the

abdominal region. Adipose tissue in this scenario promotes insulin resistance through a number of inflammatory pathways, including higher release of free fatty acids (FFA) and dysregulated adipokines. The incidence and prevalence of T2DM have increased by four times as a result of population aging, sedentary lifestyles, high-calorie diets, and the global rise in obesity. The pancreas (-cells and -cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue are among the organs involved in the development of T2DM. According to developing research, key pathophysiological factors include defects in adipokine regulation, inflammation, defects in intestinal microbiota, immunological dysregulation, and inflammation. Genetics and environmental factors both have an impact on T2DM epidemiology. Genetic factors become influenced after being exposed to an environment that promotes sedentary behaviour and increased calorie intake. Genome-wide association studies have discovered common glycemic genetic variations for T2DM, although they only account for 10% of the variance in all traits, indicating that uncommon variants are significant. People with diverse phenotypes may be more predisposed to certain clusters of cardiovascular disease risk factors, such as hypertension, insulin resistance, and dyslipidemia.[19] A meta-analysis study by emerging Risk Factors Collaboration et al reported that Diabetes Mellitus is associated with an increased risk of mortality from vascular diseases such as coronary heart disease, ischemic stroke, and others. Independent of other traditional risk factors, diabetes increases the risk of developing a wide spectrum of vascular disorders by around a factor of two. Fasting blood glucose concentration is slightly and non-linearly linked with the risk of vascular diseases in adults without diabetes.[20]

Gestational diabetes mellitus

It is known as gestational diabetes mellitus (GDM) when the first signs of glucose intolerance appear or are first noticed during pregnancy. "Whether or not insulin or only diet modification is used for treatment, and whether or not the condition lasts after delivery, the definition is still applicable. It does not rule out the possibility that undiagnosed glucose intolerance existed before or started at the same time as the pregnancy. The risks to the fetus increase in a continuous fashion with increasing maternal glycemia. The diagnosis of gestational diabetes is based on the results of an oral glucose-tolerance test, except in women with severe hyperglycemia, who should be considered to have type 1 or type 2 diabetes and treated accordingly. Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually. The prevalence may range from 1 to 14% of all pregnancies, depending on the population studied and the diagnostic tests employed.[21]"2

1.3 Prevalence and burden of Diabetes mellitus

Global scenario

According to World Health Organization (WHO)The bulk of the approximately 422 million individuals with diabetes globally reside in low- and middle-income nations, and diabetes is directly responsible for 1.5 million fatalities annually. Over the past few decades, there has been a consistent rise in both the incidence and prevalence of diabetes.[22] The anticipated prevalence of diabetes worldwide in 2019 is 9.3% (463 million people), and it is expected to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. Urban areas (10.8%) and high-income countries (10.4%) have greater prevalence rates than rural areas (7.2%) and low-income countries (4.0%), respectively. One in two (50.1%) diabetics

are unaware that they have the disease. Impairment in glucose tolerance is predicted to affect 7.5% (374 million) people worldwide in 2019 and 8.0% (454 million) people by 2030 and 8.6% (548 million) people by 2045.[23] A total of 1.5 million deaths were directly related to diabetes in 2019, and 48% of these deaths occurred in those under the age of 70.[22] Over 90% of diabetics worldwide have type 2 diabetes. About 537 million persons between the ages of 20 and 79 will have diabetes in 2021.According to projections, there would be 643 million diabetics worldwide by 2030 and 783 million by 2045.[24] 240 million adults with diabetes, or 44.7% of the total, are undiagnosed. 81% of these individuals reside in low- and middle-income nations. In 2021, diabetes was projected to be the cause of $966 billion in worldwide health expenditures. Over the last 15 years, this indicates an increase of 316%. In 2021, it is projected that 6.7 million adults will have died from diabetes or its complications, excluding the mortality risks linked to COVID-19. That equates to 12.2% of all deaths worldwide, or more than one in 10. Impaired glucose tolerance (IGT) affects 541 million adults, or 10.6% of all adults globally, and puts them at a significant risk of becoming type 2 diabetes.[25] Lin et al reported in a study that, between 1990 and 2017, the global burden of diabetes disease grew significantly. The number of diabetes-related deaths worldwide grew by 125.5%, from 0.61 million (0.59–0.62) in 1990 to 1.37 million (1.34–1.40) in 2017. Age-standardized mortality rose to 17.5 from 15.7 (15.3-16.1) (17.1–17.9). Global Disability-Adjusted-Life-Years (DALYs) grew by 116.7% from 31.3 million (26.1-37.8) in 1990 to 67.9 (55.4-82.6) in 2017. DALY rates that are age-standardized increased from 717.7 (599.2-863.6) to 839.0. (685.1–1,020.1). As for type 2 diabetes age-standardized rates of type 2 diabetes increased from 1990 to 2017, incidence increased from 228.5 (213.7-244.3) to 279.1 (256.6-304.3), prevalence increased from 4,576.7 (4,238.6-4,941.9) to 5,722.1 (5,238.2-

6,291.0), death rates increased from 10.0 (9.5-10.6) to 13.2 (12.7-13.7), and DALYs increased from 553.6 (435.1-696.5) to 709.6 (557.2-888.3).[26]

Indian scenario

According to ICMR recommendations, diabetes cases in India have increased by 150%.[27] In India, there are currently estimated to be 77 million diabetics, and by 2045, there are expected to be over 134 million. About 57% of these people are still undiagnosed.[2] The prevalence of diabetes in India is 8.3% with 774,194,700.[28] According to the Health of the Nation 2022 study, the southern and eastern regions of India had higher prevalence rates of diabetes mellitus than the national average of 6.96%. Compared to rural areas, which had a prevalence of 6.70%, urban areas had a higher prevalence of 7.01%. The study also found that obesity in women over 35 increased the risk of heart disease and other problems as well as poor diabetes control. With a 0.5 increase in HbA1c diabetes marker levels, data also showed poor diabetes control in women with high cholesterol.[29] According to the National Noncommunicable Disease Monitoring Survey (NNMS) reported In India, the prevalence of diabetes mellitus and impaired fasting blood glucose (IFG) was 9.3% and 24.5%, respectively. 45.8% of those with DM were aware, 36.1% were receiving treatment, and 15.7% had it under control. Older persons had a higher chance of developing diabetes (OR 8.89, 95% CI 6.66-11.87) and were 16 times more aware of the condition.[30] Diabetes prevalence in India increased from 7.1% in 2009 to 8.9% in 2019. With 77 million diabetics, India comes in second place behind China in the world's diabetes epidemic. There are 12.1 million of them who are over 65, and 27.5 million are anticipated by the year 2045. Approximately 43.9 million persons, or close to 57% of the total number of adults with diabetes in India, are believed to be

undiagnosed.[2] According to the authors of the India State-Level Disease Burden Initiative Diabetes study, the prevalence and number of diabetics in India rose from 5.5% and 26.0 million in 1990 to 7.7% and 65.0 million in 2016. The highest frequency was recorded in Tamil Nadu in 2016, followed by Kerala, Delhi, Punjab, Goa, and Karnataka. The age-standardised DALY rate for diabetes rose the most among the major non-communicable diseases in India from 1990 to 2016 by 39.6% (32–46.7).[31] The biggest disease burden or DALY rate increase from 1990 to 2016 was seen for diabetes, at 80%. Diabetes is one of the most prevalent non-communicable diseases. In 2016, there was a 4-fold variation in the disease burden or DALY rate across Indian states for diabetes.[32]

1.4 Pathophysiology

Due to broken feedback loops between insulin action and insulin production, the pathogenesis of diabetes is characterised by unusually high blood glucose levels. When -cell dysfunction happens, the body's capacity to maintain physiological glucose levels is limited because less insulin is produced. However, decreased glucose uptake in adipose tissue, muscle, and the liver, as well as increased glucose synthesis in the liver, are both related to insulin resistance (IR). Even though both of these events occur early in the pathophysiology and help to cause the disease, -cell dysfunction typically manifests as a more severe condition than IR. The development of T2DM, however, is accelerated by hyperglycemia when both IR and β -cell dysfunction are present. [33,34]

A. Physiology of β-Cell

The development of both type 1 and type 2 diabetes is heavily influenced by pancreatic β -cell dysfunction. Insulin is a crucial metabolic regulator that is made in

β -cells. Proinsulin is produced after preproinsulin has been created. After being transformed into insulin and C-peptide, proinsulin is subsequently kept in secretary granules and released when needed. Both the transcriptional level and the translational level control the synthesis of insulin. While the stability of preproinsulin mRNA and its untranslated regions regulate protein translation, the cis-acting sequences in the 5' flanking region and trans-activators like paired box gene 6 (PAX6), pancreatic and duodenal homeobox-1 (PDX-1), MafA, and -2/Neurogenic differentiation 1 (NeuroD1) regulate insulin transcription. The process of producing insulin in cells results in the fusion of secretory granules with the plasma membrane. While other foods like free fatty acids and amino acids can increase glucose-induced insulin release, glucose is the primary trigger for insulin production. Additional hormones that control insulin secretion include melatonin, oestrogen, leptin, growth hormone, and glucagon-like peptide-1. As a result, the -cell functions as the body's metabolic hub, linking the endocrine system and nutrition metabolism. Although the main signal for insulin secretion is an increase in intracellular [Ca2+], cAMP signaling-dependent pathways are also crucial for controlling insulin production.[35] Due to their strategic placements inside the cell and their capacity to mediate Ca2+ induced Ca2+ release, RY receptors (RYR) can amplify Ca2+ signals and may play significant roles in stimulus- insulin secretion coupling. Involved in the stimulation of insulin secretion, RYR increases Ca2+ signals when the channel is sensitised by messenger molecules produced by food metabolism or ligand-binding.[36] Other cell signals may also help or improve β-cells' ability to produce insulin. Among them, cAMP may be the most significant messenger enhancing the release of insulin. According to growing evidence, cAMP mobilises secretory vesicles that carry insulin by reducing intracellular Ca2+ reservoirs and raising intracellular Ca2+ concentrations.

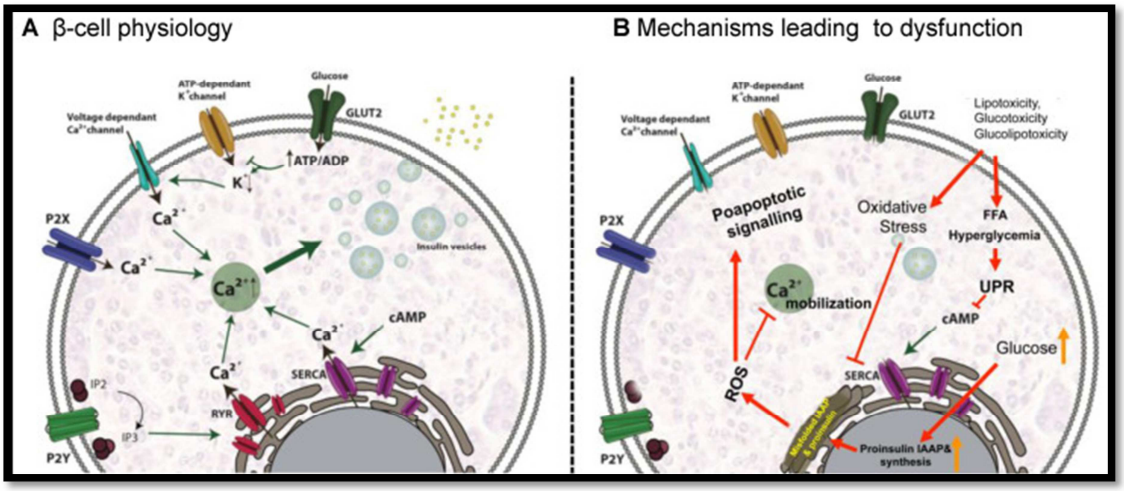
Additionally, there is strong evidence that extracellular ATP is a key regulator of -cell function. It is generally known that when glucose is stimulated, -cells release ATP by exocytosing insulin granules. Independent of glucose, purinergic signalling through P2Y and P2X purinergic receptors promotes Ca2+ mobilisation and controls insulin exocytosis. It has been suggested that the release of insulin from P2Y receptors may be mediated by intracellular Ca2+ mobilisation in response to inositol-1,4,5-trisphosphate (IP3) production, which causes the release of Ca2+ from ER storage and increases the Ca2+ signal that causes exocytosis.[26]

B. β-Cell Dysfunction mechanism

Hyperglycemia and hyperlipidemia are frequently present in an excessive dietary state, similar to that found in obesity, encouraging IR and chronic inflammation. Due to variations in their genetic vulnerability, in these conditions, β-cells are vulnerable to toxic stresses such as inflammation, inflammatory stress, ER stress, metabolic/oxidative stress, and amyloid stress, which have the potential to ultimately result in the loss of islet integrity.[37] Obesity-related lipotoxicity, glucotoxicity, and glucolipotoxicity cause metabolic and oxidative stress, which harms beta cells. A surplus of FFAs and hyperglycemia cause ER stress by activating the apoptotic unfolded protein response (UPR) pathways, which in turn causes -cell malfunction. By inhibiting the sarco/endoplasmic reticulum Ca2+ ATPase (SERCA), which is responsible for ER Ca2+ mobilisation, activating IP3 receptors, or directly impairing ER homeostasis, stress resulting from high levels of saturated free fatty acids (FFAs) can activate the UPR pathway. Additionally, proinsulin biosynthesis and islet amyloid polypeptides (IAAP) are increased in -cells by prolonged high glucose levels, which causes an accumulation of misfolded insulin and IAAP as well as an

increase in the production of oxidative protein folding-mediated reactive oxygen species (ROS). These actions change physiological ER Ca2+ mobilisation, favour proapoptotic signals, promote the degradation of proinsulin mRNA, and trigger the release of interleukin (IL)-1, which draws in macrophages and intensifies local islet inflammation.[38,38] Inaccuracies in the production of any insulin precursors or of insulin itself, In addition to causing the secretion pathway to malfunction, this can result in insulin secretory dysfunction, which is the main cause of -cell degeneration and the basis of T2DM. As an illustration, decreased expression of the GLUT2 glucose transporter would impact the downstream signalling pathway, while failure in the folding of proinsulin is another observation that is frequently connected to inadequate insulin synthesis and diabetes.[39,40]

Figure 1: Signalling pathways involved in insulin secretion in β-cells in physiological conditions (A) and mechanisms leading to dysfunction (B)[26]



(**A**) Insulin release is primarily triggered by a response to high glucose concentrations and glucose in mainly internalized mainly through GLUT2 transporter. Glucose catabolism increases ATP/ADP ratio, ATP-dependant potassium channels are closed leading to membrane depolarization and opening of the voltage dependant Ca^{2+}

channels. The latter enables Ca^{2+} influx triggering insulin exocytosis. Additional Ca^{2+} channels as P2X, P2Y, SERCA and RYR contribute to Ca^{2+} mobilization and insulin secretion. (**B**) hyperglycemia and hyperlipidemia promote oxidative stress leading to ROS generation that inhibits Ca^{2+} mobilization and activates proapoptotic signals. Additionally, an excess of FFAs and hyperglycemia lead to the activation of the apoptotic unfolded protein response (UPR) pathways and generation of ER stress. Sustained high glucose levels increase proinsulin and IAAP biosynthesis, which generate ROS. GLUT2: glucose transporter 2, P2X: purinergic receptor X; P2Y: purinergic receptor Y; IP2: inositol 1,3-bisphosphate; IP3: inositol 1,4,5-trisphosphate; RYR: ryanodine receptor channel; SERCA: sarco-endoplasmic reticulum Ca^{2+}-ATPase; FFA: free fatty acid, ROS: reactive oxygen species; UPR: unfolded protein response.

1.5 Complications

The acute complications of diabetes mellitus include diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome**,** hypoglycemia, and diabetic coma.

Diabetic ketoacidosis: Diabetic ketoacidosis (DKA) is a dangerous and sometimes fatal diabetes complication. People with type 1 diabetes are more likely to experience DKA. DKA can also occur in people with type 2 diabetes. DKA occurs when the body lacks enough insulin to allow blood sugar to enter cells for use as fuel. Instead, the liver converts fat into ketone-producing acids, which it uses as fuel. Ketones can accumulate in the body to harmful amounts if they are created in excess or too quickly. DKA results from a drop in blood pH caused by increased quantities of ketone bodies.[41,42]

Hyperosmolar hyperglycemic syndrome (HHS): Diabetes mellitus has a complication known as hyperosmolar hyperglycemic syndrome (HHS), which is a cli nical disease. Patients that are obese are the ones who typically experience it. There is resistance of the peripheral tissue to the action of insulin as a result of obesity and hig h body mass index (BMI). Type 2 diabetes can cause HHS, a dangerous and sometime s fatal consequence. HHS fatality rates can reach 20%.[43]

Hypoglycemia: A major side effect of glucose-lowering treatment in people with diabetes mellitus is hypoglycemia. The term "hypoglycemia" is frequently used to describe a plasma glucose level below 70 mg/dL. Individuals with severe hypoglycemia have been linked to a six-fold rise in diabetes-related fatalities compared to patients who don't have severe hypoglycemia.[44, 45]

Diabetic coma: A diabetic coma is a medical emergency in which a person with diabetes mellitus is unconscious as a result of one of the acute complications of diabetes, such as severe diabetic hypoglycemia, advanced diabetic ketoacidosis, or hyperosmolar nonketotic coma, in which severe hyperglycemia and dehydration alone are sufficient to cause unconsciousness.[46]

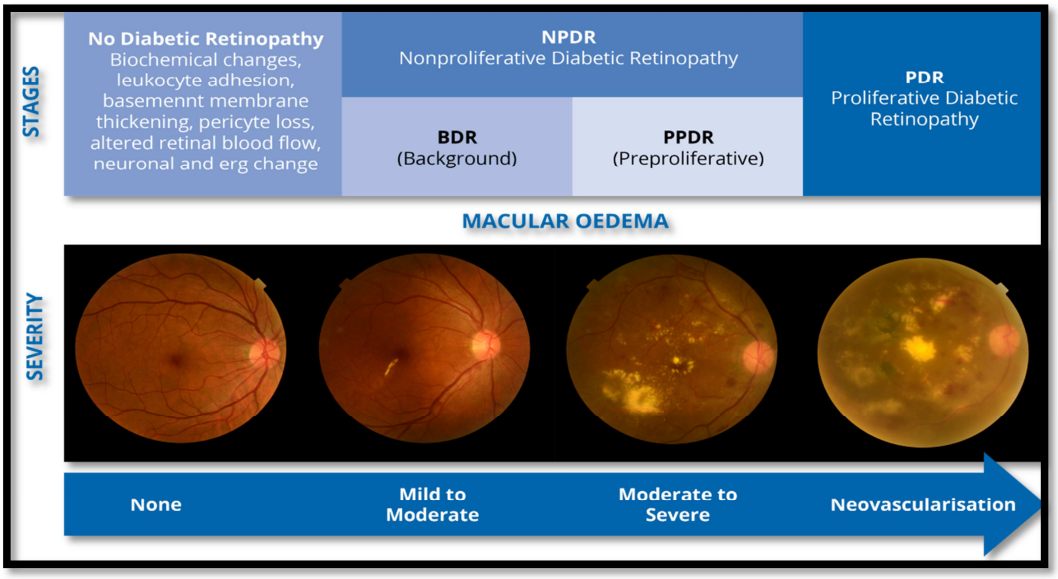
The **chronic complications** of diabetes mainly include microvascular diseases and macrovascular diseases.

Microvascular diseases: Microvascular consequences include injury to the eyes(retinopathy), the neurological system (nephropathy), and the kidneys (nephropathy).

Diabetic retinopathy: Long-term incidence of retinopathy, which in most individuals is typically found to have been present for decades and increases the risk of vision

loss over time, is linked to an increased risk of blindness in diabetic people. Through activation of Protein Kinase-C (PKC), hyperglycaemia (HG) can cause diabetic retinopathy. Numerous metabolic pathways may be elevated, cell growth and apoptosis may be stimulated, and cellular permeability may rise as a result of PKC activation. Changes in these processes are linked to the development of many diabetes-related vascular problems, such as cardiomyopathy, atherosclerosis, neuropathy, nephropathy, and retinopathy. Certain apoptotic development factors are stimulated by HG and states of oxidative stress connected to diabetic retinopathy, and these factors may help diabetic cataracts form. Additionally, diabetics may have an increased chance of developing retinopathy and the related condition of blindness due to the raised glucose level in their retinal cells. Additionally, elevated ROS levels brought on by oxidative stress can result in an increase in lipid peroxidation and a concurrent weakening of the antioxidant protection system, both of which cause DNA damage in the retina of diabetic patients.[47]

Figure 2: Clinical stages of diabetic retinopathy[48]



Diabetic neuropathy

Over time, at least 50% of people with diabetes develop diabetic neuropathy, which is defined by a loss of sensory function that starts distantly in the lower extremities and is both painful and associated with significant morbidity.[49]

1. Peripheral neuropathy

A type of nerve injury known as peripheral neuropathy normally affects the feet and legs but can also affect the hands and arms. Peripheral neuropathy is a fairly frequent form of neuropathy; between one-third and fifty percent of diabetics experience it.[50] One of the biggest issues impacting individuals with DM is diabetic peripheral neuropathy. This may result in either diabetes complications or both. In some circumstances, uncontrolled diabetes patients with sensory or sensorimotor neuropathies have an increased risk of foot ulceration and amputation. Chronically high blood sugar levels are linked to diminished protective nitric oxide generation and malfunction of the Na^+/K^+ -ATPase as well as an active polyol pathway with reduced blood flow to endoneurial tissues. In addition, because insulin-like growth factor is inhibited, brain cell regeneration is significantly diminished. Increased polyol pathway activation reduces the amount of NADPH needed to activate glutathione reductase, aldose reductase, and endothelial nitric oxide synthase. Increased polyol pathway activation reduces the amount of NADPH needed to activate glutathione reductase, aldose reductase, and endothelial nitric oxide synthase. All of this causes oxidative stress to intensify and speeds up neurodegeneration. Additionally, an increase in intraneural sorbitol can cause the necrosis of nerve cells, which leads to cellular deterioration. Patients with diabetes mellitus (DM) have glycation of proteins

within their nerves, which destabilises the cytoskeleton, slows axonal transport and nerve impulses while increasing neuron degeneration.

Figure 3: Types of diabetic neuropathy[51]

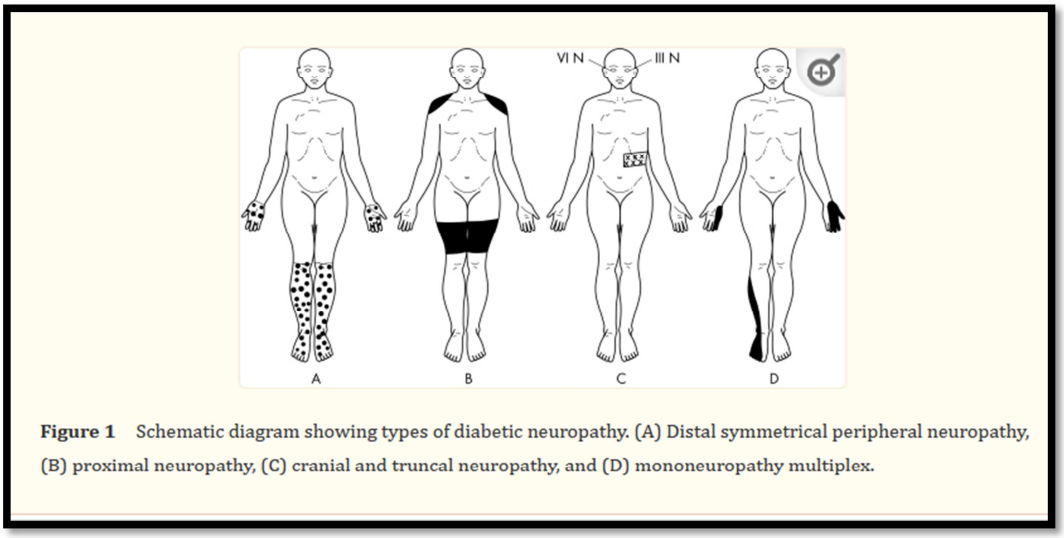


Figure 1 Schematic diagram showing types of diabetic neuropathy. (A) Distal symmetrical peripheral neuropathy, (B) proximal neuropathy, (C) cranial and truncal neuropathy, and (D) mononeuropathy multiplex.

2. Autonomic neuropathy

a. Diabetes and gastrointestinal dysfunction

Digestive system dysfunction could result from autonomic neuropathy. Patients with diabetes who also have autonomic neuropathy may have early satiety, bloating, nausea, vomiting, abdominal discomfort, and heartburn. Usually, diabetic individuals with protracted HG are found to have gastroparesis or slowed stomach emptying. In addition to causing acid reflux illness, delayed bowel movements, constipation, and diarrhoea, diabetic enteropathy also increases the risk of bacterial, viral, and fungal gastrointestinal tract infections. Due to a decrease in the production and release of amylase, a crucial digestive enzyme involved in the digestion of carbohydrates, diabetes-induced HG is also linked to salivary and exocrine pancreatic insufficiencies.[52, 53]

b. Diabetes and erectile dysfunction

The primary cause of erectile dysfunction, a common consequence of diabetes mellitus, is either impaired neural activation or reduced blood circulation in the penile tissue. There are other factors implicated in erectile dysfunction in diabetic patients in addition to the vascular and neuronal disturbance, such as hormonal changes, chronic illnesses, malnutrition, penile tissue infection, and psychological impacts. Men with diabetes are much more likely than men without diabetes to experience DM-related impotence. Increased levels of free radicals, such malondialdehyde, are thought to interfere with the neuronal and vascular processes regulating penile erection.[54-57]

c. Diabetic Foot

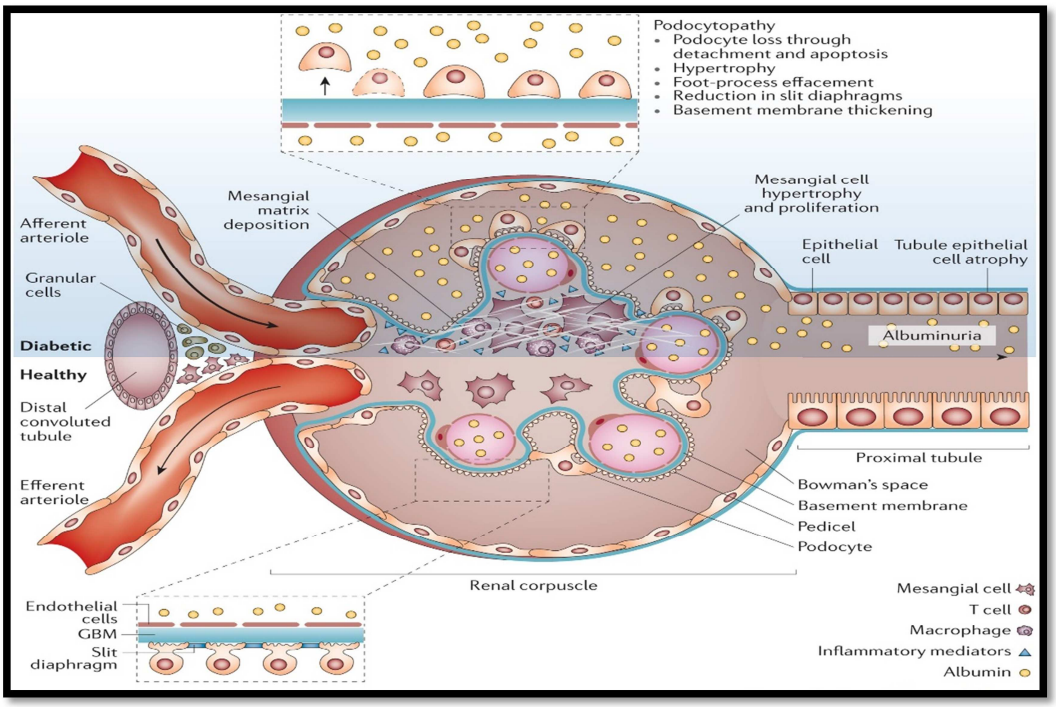
Diabetes-related foot develops as a result of the interaction between aberrant blood vessel and nerve structure and function, which causes diminished angiogenesis, loss of sensation, untreated secondary wound infections, ulceration, and ultimately foot amputation. The combination of ischemia and neuropathy that results in diabetic foot ulcers is the main cause. Due to a reduction in proprioception caused by diabetes, foot damage is more common. In the wounded areas, the underlying ischemia prevents wound healing, and the added infections cause ulceration.[58-60]

15% of diabetics experience diabetic foot ulcers (DFUs), a major factor in amputations. Reduced peripheral blood flow and local angiogenesis are the results of a number of mechanisms, including reduced cell and growth factor responsiveness, and all of these factors may be responsible for DFU patients' inability to heal.[61]

Diabetic nephropathy

A phenomenon known as diabetic nephropathy (DN), also known as diabetic kidney disease, is characterised by the reduction of glomerular filtration rate (GFR) in diabetics as well as the presence of abnormal amounts of urine albumin excretion. Globally, diabetic nephropathy is a major contributor to end-stage renal failure and chronic kidney disease.[62] High blood pressure and chronic hyperglycemia are the main risk factors for developing DN.[63] The glomerular basement membrane and glomerular endothelial cell barrier exhibit morphological deterioration in diabetic nephropathy. In turn, this causes a rise in the amount of protein filtering out of the urine, which indicates that the patient has disrupted protein decomposition. Renal function impairment can result from the advancement of oxidative stress in diabetes mellitus (DM). Patients with diabetic nephropathy may be genetically predisposed to the condition, but it can also be brought on by certain environmental irritants. A third of people with uncontrolled diabetes may develop diabetic nephropathy, which will require kidney dialysis. This may be as a result of the aforementioned genetic predisposition or as a result of the interaction between cytokines and advanced glycation end products or reactive oxygen species.[64]

Figure 4: Glomerulonephropathy in diabetes[65]



Macrovascular diseases: Cardiovascular disease, stroke, and peripheral vascular disease are examples of macrovascular consequences.

Cardiovascular disease (CVD)

In patients with types 1 or 2 diabetes mellitus, cardiovascular disease continues to be the predominant cause of morbidity and mortality. Patients with type 2 diabetes mellitus are disproportionately affected by cardiovascular disease and have a significantly increased risk of cardiovascular morbidity and mortality compared to people without diabetes. The majority of this additional risk is linked to these individuals' increased prevalence of well-known risk factors like hypertension, dyslipidemia, and obesity.[66, 67] In addition, those with diabetes have a 5-fold higher chance of experiencing their first myocardial infarction (MI) and a 2-fold higher risk of experiencing a subsequent MI compared to those who have never had diabetes.[68]

Stroke

The risk of stroke is generally known to be increased by diabetes. Various blood arteries may experience pathologic alterations, and if cerebral vessels are directly impacted, it may result in stroke. Furthermore, people with uncontrolled glucose levels who have had a stroke had worse post-stroke outcomes and increased mortality. A third of stroke patients have diabetes, which puts patients with diabetes at around double the risk of having a stroke as opposed to people without the disease.[69, 70]

Peripheral artery disease

Peripheral artery disease (PAD) is the atherosclerosis of the arteries that supply the lower extremities and is linked to atherothrombosis in other vascular beds, such as the cardiovascular and cerebral circulation systems. Diabetes mellitus makes people more likely to develop PAD and speeds up the disease's progression, rendering them more vulnerable to ischemia events and functional impairment than people without the disease.[71]

1.6 Diagnosis

Table 3: Stages and diagnostic criteria for type 1 diabetes [72]

	Stage 1	**Stage 2**	**Stage 3**
Stage	Autoimmunity Normoglycemia Presymptomatic	Autoimmunity Dysglycemia Presymptomatic	New-onset hyperglycemia Symptomatic
Diagnostic criteria	Multiple autoantibodies No IGT or IFG	Multiple autoantibodies Dysglycemia: IFG and/or IGT FPG 100–125 mg/dL (5.6–6.9 mmol/L) 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) A1C 5.7– 6.4% (39–47 mmol/mol)	Clinical symptoms Diabetes by standard criteria

(IGT)-Impaired glucose tolerance. (IFG)- impaired fasting glucose.

Table 4: Criteria for the diagnosis of type 2 diabetes mellitus

FPG >126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h
OR
2-h PG>200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water
OR
A1C > 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay
OR
In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose > 200 mg/dL (11.1 mmol/L).

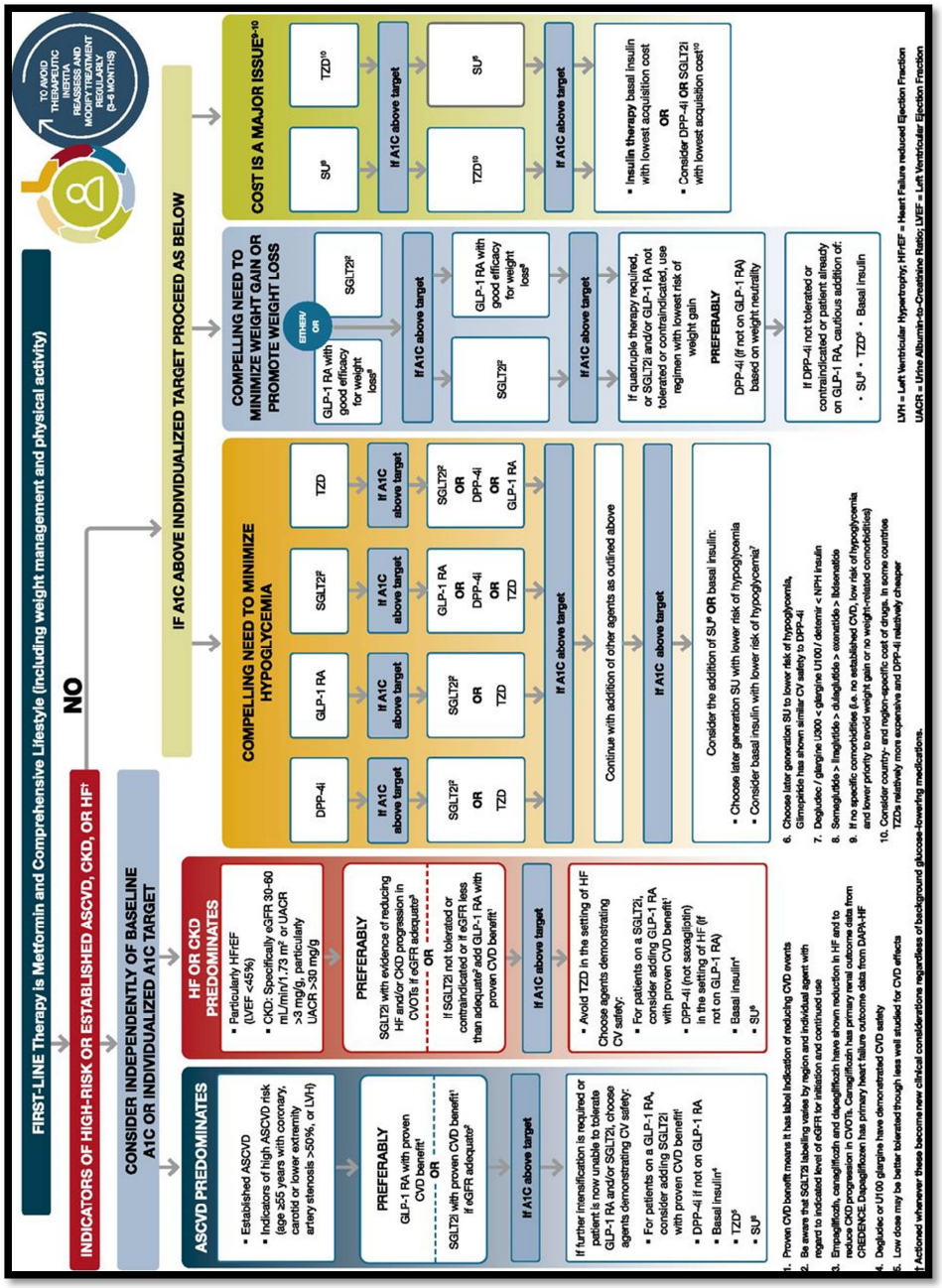
1.7 Management

Diabetes has a complicated physiology and treatment plan that necessitate numerous interventions for effective disease control. The management of diabetes depends on patient involvement and diabetic education.[72] "Ideally, HbA1c should be less than 7% and glucose levels must be maintained between 90 and 130 mg/dL. Although keeping blood glucose levels under control is crucial, overly aggressive treatment may cause hypoglycemia, which can have negative or fatal effects.[73] Lifestyle management, which includes nutrition treatment, physical exercise, smoking cessation advice, psychosocial care, and diabetes self-management education and support, is a key component of diabetes care. In order to improve diabetes care, patients and caregivers should work together to identify ways to improve lifestyle starting with the initial comprehensive medical evaluation, continuing through all subsequent evaluations and follow-up, and while assessing complications and managing co-occurring conditions.[74] Since a lack of insulin is the main contributing

factor to T1DM, the majority of treatments involve giving patients insulin via daily injections or an insulin pump. However, diet and exercise alone may be sufficient for the management of T2DM, especially at first. Other treatments could aid in improving insulin sensitivity or raising the hormone's production by the pancreas. Biguanides (Metformin), sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagonlike peptide-1 agonist, selective dipeptidyl peptidase IV inhibitors (DPP-4), amylinomimetics, and sodium-glucose transporter-2 are a few of the specific pharmacological types (SGLT-2) Metformin, which decreases basal and postprandial plasma glucose levels, is one of the first-line diabetes medications. Patients with T2DM may also need insulin therapy, particularly if they are at the end of the disease's course and have trouble controlling their blood sugar levels. Patients who are extremely obese may benefit from bariatric surgery to lower their glucose levels. It is suggested for patients with significant co-morbidities who have not improved with conventional therapies.1 Regular testing is necessary since microvascular issues are a concern with diabetes. Trained medical practitioners can examine for diabetic retinopathy by performing routine diabetic retinal exams. A clinical neurologic evaluation and nerve conduction testing can help identify patients with neuropathy who could need an amputation. Patients may also be advised by doctors to routinely check their feet for lesions that neuropathy may mask. Low-dose TCAs, duloxetine, anticonvulsants, topical capsaicin, and opioids can be used to treat diabetic neuropathic pain. In patients with albuminuria - greater than 30 mg/g creatinine, testing microalbumin in urine can identify the estimated GFR as well as the early renal consequences of diabetes. Due to their antiproteinuric properties, ACE inhibitors and ARBs are the preferred medications for patients with Type 1 or Type 2 diabetes mellitus to avoid the progression from microalbuminuria to

macroalbuminuria. The American Diabetes Association (ADA) additionally advises that diabetics undergo routine blood pressure checks, with the ideal readings include130 mmHg systolic and 85 mmHg diastolic. The overall approach for glucose-lowering medication in type 2 diabetes is listed in below figure 5.

Figure 5: Glucose-lowering medication in type 2 diabetes[75]



2. Stress-induced hyperglycemia

Stress hyperglycemia is typically characterised by increased whole-body glucose uptake, which is mostly brought on by non-insulin-mediated glucose transfer via GLUT-1 transporters to body tissues and is described as hyperglycemia resolving spontaneously following dissipation of acute sickness. Critically sick patients with previously normal glucose tolerance might develop stress-induced hyperglycemia; this hyperglycemia resolves as the patient recovers. Stress hyperglycemia is defined by ADA (American Diabetes Association) as an elevation of fasting glucose ≥ 7 mmol/L(>126 mg/dl), or 2-hour postprandial glucose ≥ 11 mmol/L(>200 mg/dl) [101], and is known to be a marker of illness severity, with the magnitude of hyperglycemia strongly associated with short-term mortality, in patients with Diabetes Mellitus. The pathophysiology of stress-induced hyperglycemia is hypothesised to entail transient insulin resistance in conjunction with relative insulin shortage, as seen by the inadequacy of plasma insulin concentrations to counteract hyperglycemia.[76] Even when glucose homeostasis had previously been healthy, stress-induced hyperglycemia is a typical issue in patients admitted to the intensive care unit. The presence of excessive amounts of glucagon, growth hormone, catecholamine, and glucocorticoid, either endogenous or exogenous, as well as high levels of cytokines in the blood or tissues, especially tumour necrosis factor-[TNF] and interleukin-1, are the main causes of stress hyperglycemia. Despite hyperglycemia, this metabolic environment prevents insulin from suppressing hepatic gluconeogenesis.[77] A study of 1,000 sequentially admitted patients by Bellomo et al reported that, up to 50% of patients experienced critical illness-associated hyperglycemia, and diabetes affected 27.5% of the sample. The degree of hyperglycemia caused by stress is highly linked to short-term mortality, especially in patients without a history of diabetes, and is known to be

a measure of the severity of the illness.[78] it is also found that following stroke, both diabetes and non-diabetic patients with Stress hyperglycemia have higher mortality and worse recovery rates.[79] Plummer et al, reported that Stress-induced hyperglycemia appears to roughly double the risk of incident diabetes in people who survive critical illness, and acute hyperglycemia during critical illness identifies people at significantly higher risk of incident diabetes after being discharged from the hospital.[80] In ST-elevation myocardial infarction patients with or without diabetes, stress-induced hyperglycemia was independently linked to an increase in severe unfavourable cardiovascular and cerebrovascular outcomes.[81]

3. Glycemic excursions and glycemic gap

The association between glycemic excursions and the frequency of micro- and macrovascular problems and risk of hypoglycemia from diabetes provides more evidence for the significance of glycemic excursions in diabetic individuals.[82] Large glycemic excursions may be more closely associated with endothelial dysfunction and cardiovascular events than hyperglycemia. Measuring the magnitude of changes in blood glucose levels is frequently done using the mean amplitude of glycemic excursion (MAGE). In patients with diabetes mellitus, MAGE significantly contributes to vascular endothelial dysfunction and cardiovascular events.[83] Continuous glucose monitoring (CGM) is used clinically to evaluate glycemic excursion.[84] Studies have reported that Increased Glycemic variability was linked to a higher rate of mortality among hospitalised patients.[85] It is also associated with longer, earlier and emergency hospitalization. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial found that the HbA1c fluctuation was a significant predictor of death from any cause.[86] Patients who were admitted to the intensive care

unit (ICU) frequently experienced glycemic excursions, which were linked to unfavourable outcomes.[87,88]

In diabetic individuals, the glycemic gap is a marker of this excursion. It can be used to foretell unfavourable outcomes in diabetic patients hospitalised to the intensive care unit. It is determined by deducting the plasma glucose at admission from the A1C-derived average glucose (ADAG), **Glycemic Gap = ADAG – Admission RBS**.[89] "

Several studies have studied association of HbA1C with average glucose levels in an effort to demonstrate the marker's usefulness as a measure of glycemic management, with mixed results. The International HbA1c-derived Average Glucose (ADAG) trial was carried out by Nathan et al. in 2008, establishing a linear dependence between HbA1c and averaged plasma glucose levels. This trial also introduced a straightforward mathematical equation for calculating the estimated average glucose level using the HbA1c level. The relationship between A1C and ADAG is described by the formula **ADAG = 28.7 x A1C - 46.7.**

The glycemic gap could be used to assess the prognosis of diabetic patients who are critically ill. The usefulness of the APACHE-II score to predict ICU mortality was greatly enhanced by the addition of the glycemic gap.[3] Compared to admission glucose levels, glycemic gap (GG) is a better predictor of the homeostatic response of the glucose level to physical stress.[90] Glycemic gap may be thought of as a valuable measure for predicting the illness severity and prognosis of patients with diabetes hospitalised for acute heart failure (AHF), according to a study in which 425 diabetic patients were admitted due to AHF.[3] A study by Chen et al has reported that, in patients with diabetic necrotizing fasciitis(NF), a higher glycemic gap was significantly and independently related with adverse outcomes. The laboratory risk

indicator for NF scores, APACHE II scores, and CRP levels strongly correlated with the glycemic gap. The best cutoff point for using the ROC curve to predict unfavourable outcomes was a glycemic gap of 146 mg/dL. Patients with hyperglycemia gaps >146 mg/dL had higher APACHE II ratings and incidence rates of adverse outcomes, particularly bacteremia and acute renal damage, compared to patients with glycemic gaps ≤146 mg/dL.[91] A study by Ghanem et al, of 100 diabetic patients with acute coronary syndrome monitored throughout their hospitalisation reported that Glycemic gap is a better indicator in diabetic patients presenting with ACS than admission blood glucose alone. Patients with diabetes who experienced a major adverse cardiac event (MACE) had a considerably greater glycemic gap than those who did not experience a MACE.[92] A study by Mcdonnell et al reported that, in addition to previously recognised risk variables for poor outcomes, including as age, Hispanic ethnicity, and BMI, we discovered that Glycemic Gap is a stronger predictor of in-hospital mortality than blood glucose alone in patients with diabetes or hyperglycemia admitted for COVID-19.[93] The glycemic gap is a straightforward way to evaluate glucose variability, and studies have shown that it can predict the advancement of diabetic retinopathy. In hyperglycemic emergencies of type 2 diabetes, particularly in hyperosmolar hyperglycemic condition, elevated glycemic gap indicating stress-induced hyperglycemia (SIH) occurs.[94] Chen et al reported in a study of 203 diabetic community-acquired pneumonia (CAP) patients reported that Glycemic gaps were linked to worse outcomes for diabetic patients with community-acquired pneumonia. In comparison to acute hyperglycemia and long-term glycemic controls, patients with glycemic gaps ≥40 mg/dL exhibited higher AUROC values for the emergence of unfavourable events. The odds ratio for the incidence of all bad events was 3.84 for patients with high glycemic gaps. While the glycemic gap was

considered when calculating the pneumonia severity index, CURB-65, or SMART-COP scores, the ability to forecast the emergence of negative consequences improved.[95]

4. Adverse outcomes in diabetes patients

Adverse outcomes typically signify substantial negative events that occurred as a patient's diabetes progressed; they can have a severe impact on quality of life and significantly increase the financial burden on the healthcare system and it is crucial for health system planning to be able to anticipate negative outcomes from diabetic complications.[96]The adverse outcomes such as Multiorgan dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), shock, upper gastrointestinal (UGI) bleed, acute kidney injury (AKI), and acute respiratory failure (ARF)can be seen in admitted patients with Diabetes mellitus in the ICUs.[89]

5. Association between the glycemic gap and adverse outcomes in diabetic patients admitted to ICU

A study by Liao et al reported that the severity and prognosis of critically ill diabetic patients can be evaluated using glycemic gap. The study examined the clinical outcomes and Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores of 518 patients, of whom 87 (17.0%) passed away while receiving ICU care. No survivors had considerably higher APACHE-II scores and glycemic gaps than survivors (P 0.001), however. Diabetes-related critically sick patients with a glycemic gap ≥80mg/dL had significantly higher ICU mortality and worse outcomes compared to patients with <80mg/dL. The area under the ROC curve improved from 0.755-0.794 (NRI = 13.6%, P = 0.0013) when the glycemic gap was added to the APACHE-II score, improving the discriminative performance for predicting ICU

mortality.[3] Another study comprising of 200 type 2 diabetes mellitus patients admitted to the ICU observed that MODS (P < 0.01), ARDS (P = 0.026), shock (P = 0.043), UGI bleed (P = 0.013), AKI (P = 0.01), and ARF (P 0.01) were all linked to a higher glycemic gap. Glycemic gap cutoffs of 43.31, 45.26, and 39.12 were discovered to be discriminating for predicting ICU mortality (area under the receiver operating characteristic [AUROC]=0.631, P = 0.05), MODS (AUROC = 0.725, P 0.001), and ARF (AUROC = 0.714, P 0.001).[89] Fawzy et al, reported in a cross sectional study of the 240 severely ill patients admitted to the ICU, the glycemic gap can be used to gauge the severity and prognosis of critically ill patients, and its inclusion in the APACHE II score has improved its effectiveness as a predictor of mortality. Elevated glycemic gap was substantially associated with increased ICU mortality.[97] Issarawattana et al reported in a study of 528 subjects admitted to the medical ICU, Significant glycemic variability measures were higher in nonsurvivors than in survivors, and glycemic variability was independently related with intensive care unit death.[98] Sanaa et al reported in a study of 150 subjects with type 2 diabetes admitted to the intensive care unit that, the risk of multiorgan dysfunction syndrome, acute respiratory distress syndrome, shock, upper gastrointestinal bleeding, acute kidney injury, acute respiratory failure, and ICU mortality were all significantly increased by higher glycemic gap levels. The best cutoff value for predicting unfavourable outcomes in critically ill diabetic patients was 64.25 with a sensitivity of 62.5% and a specificity of 60%. Significantly a greater glycemic gap was observed in nonsurvivor cases compared to survivors.[99] A retrospective study of 431 patients by Lou et al reported that, 28-day mortality of critically sick diabetic patients was independently correlated with glycemic GAP between mean blood glucose levels within 5 days of ICU admission.[100]

METHODOLOGY

Study design

A one-year longitudinal observational study in a tertiary care Hospital.

Period of study

1st January 2021 to 31st December 2021.

Source of the data

Patients admitted to the ICU of Medicine with a diagnosis of Type 2 Diabetes Mellitus at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, a tertiary care hospital in Karnataka, India, fulfilling the inclusion criteria during the study.

The inclusion and exclusion criteria considered are briefed below:

Inclusion criteria

- Age>18 years,
- Consecutive Type 2 diabetes mellitus patients admitted to Medical ICU.

Exclusion criteria

- Acute complications of Type 2 Diabetes mellitus at the time of presentation to the hospital:
    1. Hypoglycemia (blood glucose < 70 mg/dL)
    2. Diabetic Ketoacidosis.
    3. Hyperosmolar Non Ketotic Hyperglycemia.

- Type 1 Diabetes Mellitus.
- Patients on prior treatment with corticosteroids.
- Severe Anemia.

Ethical consideration

The study was approved by the institutional human ethics committee. Informed written consent was obtained from all the study participants and only those participants who signed the informed consent were included in the study.

Sample size: 132

The sample size was calculated with a statistician for a longitudinal study considering similar studies in the area with the same disease.

$n=9.5\times(100-9.5)\times(1.96)252$

$n=132.11\approx132$

Data collection tool

All the relevant parameters were documented in a structured study proforma.

Material and methods

Venous blood was collected from each patient after an overnight fast and used for biochemical analysis.

Plasma glucose at admission and HbA1C was analysed by HPLC technique, through which ADAG (HbA1C Derived Average Glucose) and Glycemic gap were further calculated.

- To convert HbA1c levels to chronic average blood glucose levels, the below equation was used

  ADAG = [(28.7 x HbA1c) -- 46.7].

- The glycemic gap will be calculated from the glucose level on admission, as follows:

Glycemic Gap = [Admission RBS -- ADAG].

Investigations included HbA1C, plasma Glucose at admission, RBS, CBC, LFT, Serum Creatinine, Blood Urea Nitrogen, and Serum Electrolytes.

Statistical analysis

Data will be collected and stored in Microsoft Excel. Data will be analysed using Microsoft Excel. Continuous variables will be given in mean± sd/median (range). The student t-test (http://vassarstats.net/tu.html) was used for the evaluation of continuous data and the chi-square test (http://vassarstats.net/newcs.html) for categorical variables. A correlation matrix was evaluated from excel data analysis (Excel 2019). Graphs were plotted using Python (version: 3.10.0) in the Jupyter Notebook (version: 6.2.0).

RESULTS

The study included a total of 128 out of 132 subjects (4 excluded on the basis of exclusion criteria).

Figure 6: Demographic characteristics of the study population

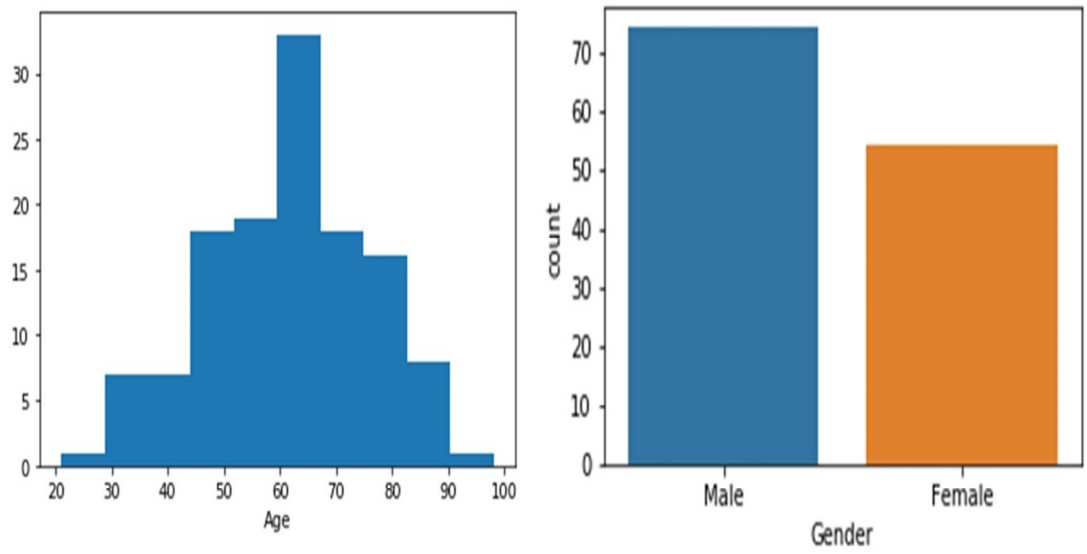


Table 5: Descriptive analysis of age and gender in the study population

Demography	
Variables	**Mean±SD (Range)**
Age (years)	61.42±14.66 (21 - 98)
Gender (M(F))	74 (54)

Among the 128 study subjects, the mean age of distribution was 61.42, with a standard deviation of 14.66. The minimum age was 21 years and the maximum age was 98 years.

The corresponding number of male and female subjects enrolled were 74 (57.81%) and 54 (42.19%) (Figure 6, Table 5).

Figure 7: Glycemic Panel distribution in the study population (n=128)

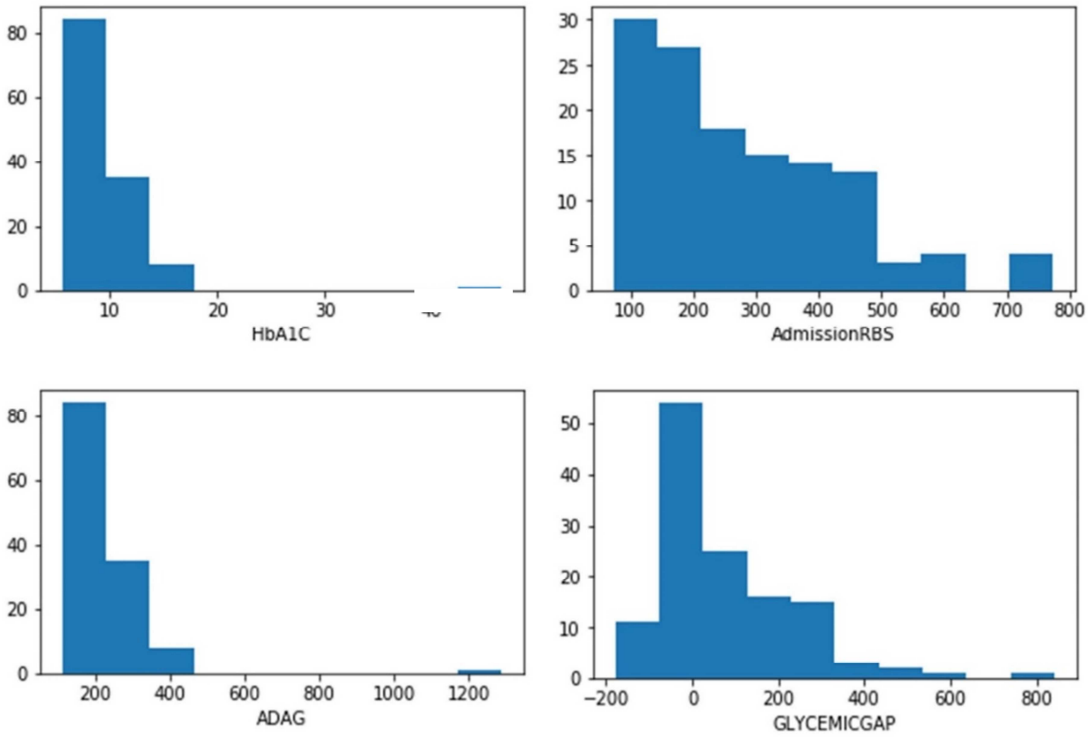
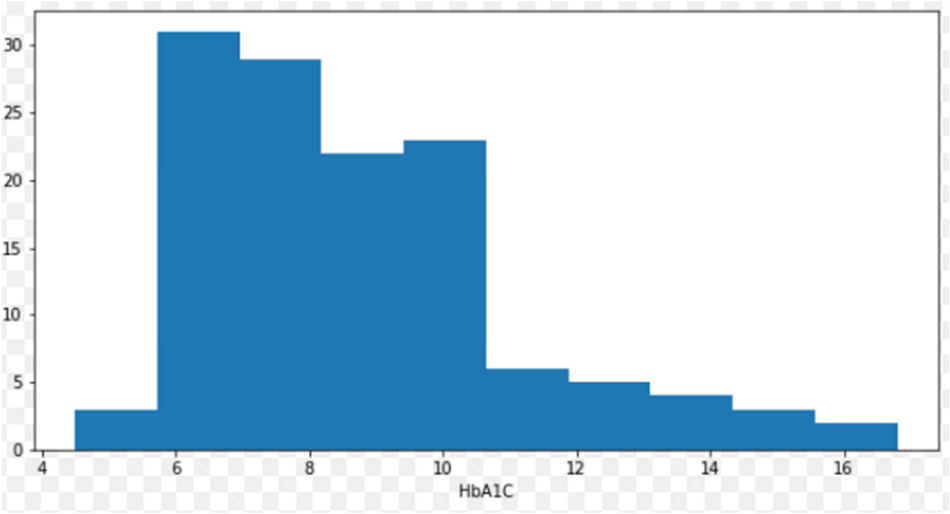


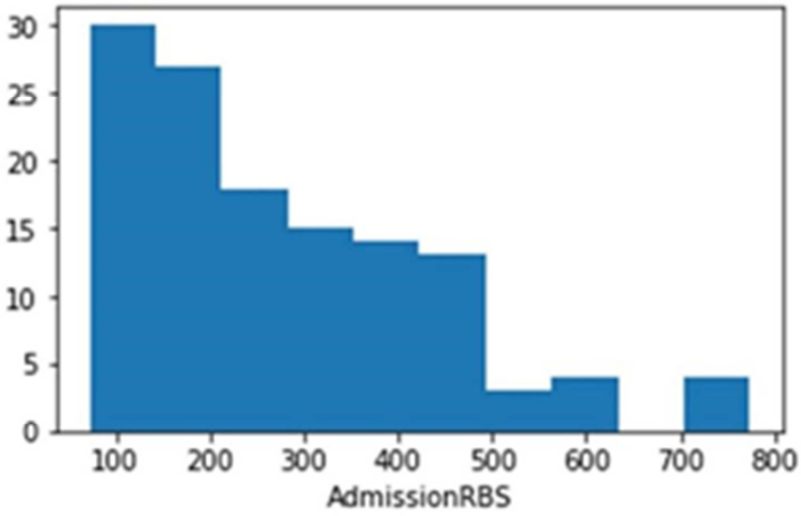
Table 6: Descriptive analysis of the Glycemic Panel in the study population (n=128)

Glycemic Panel	
Variables	**Mean±SD (Range)**
HbA1C %	9.11±4.08 (5.5 – 16.8)
Admission RBS mg/dl	208.3±70.03 (72 - 774)
ADAG mg/dl	214.87±116.97 (111.15 - 1287.85)
Glycemic GAP mg/dl	4.28±0.77 (-88.08 - 842.85)

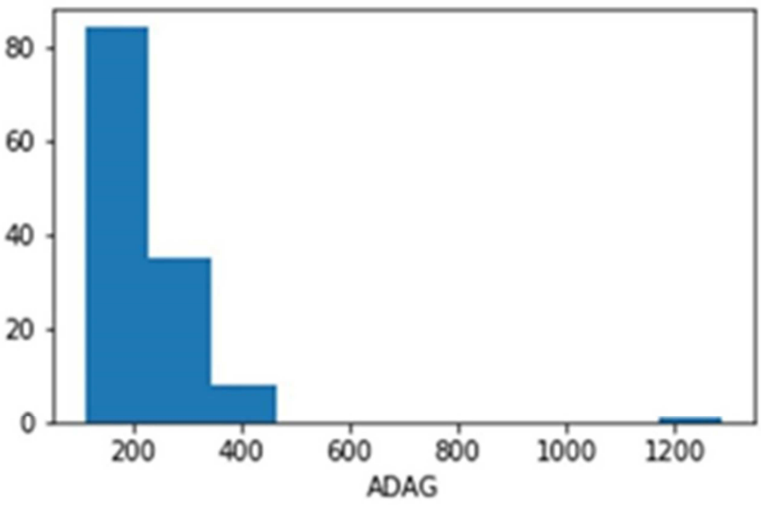
RBS: random blood glucose, ADAG: A1C-derived average glucose



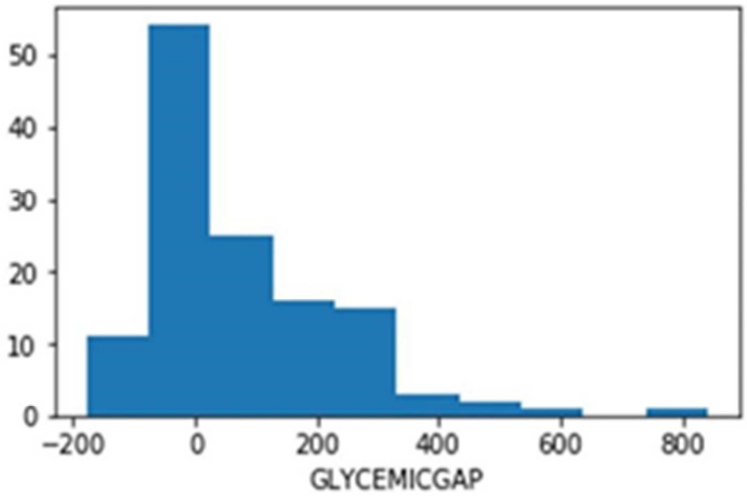
The statistical analysis of the Glycemic parameters revealed the following. Among the 128 subjects, the mean **HbA1C** noted was 9.11, with a standard deviation of 4.08**%**. The minimum HbA1C noted was 5.5, and the maximum was 16.8. (Figure 7, Table 6).



The mean **admission RBS** noted among the subjects was 208.3 with a standard deviation of 70.03 mg/dl. The minimum vale of Admission RBS noted was 72 and the maximum was 774 mg/dl (Figure 7, Table 6).



The mean **ADAG (A1C derived Average Glucose)** noted among the subjects was 214.87 with a standard deviation of 116.97 mg/dl.The minimum value of **A1C derived Average Glucose** noted was 111.15 and the maximum was 1287.85 774 mg/dl (Figure 7, Table 6).



The mean **Glycemic Gap** noted among the subjects was 4.28 with a standard deviation of 0.77 mg/dl. The minimum value of **Glycemic Gap** noted was 88.08 and the maximum was 842.85 mg/dl (Figure 7, Table 6).

Figure 8: Complete Hemogram distribution in the study population

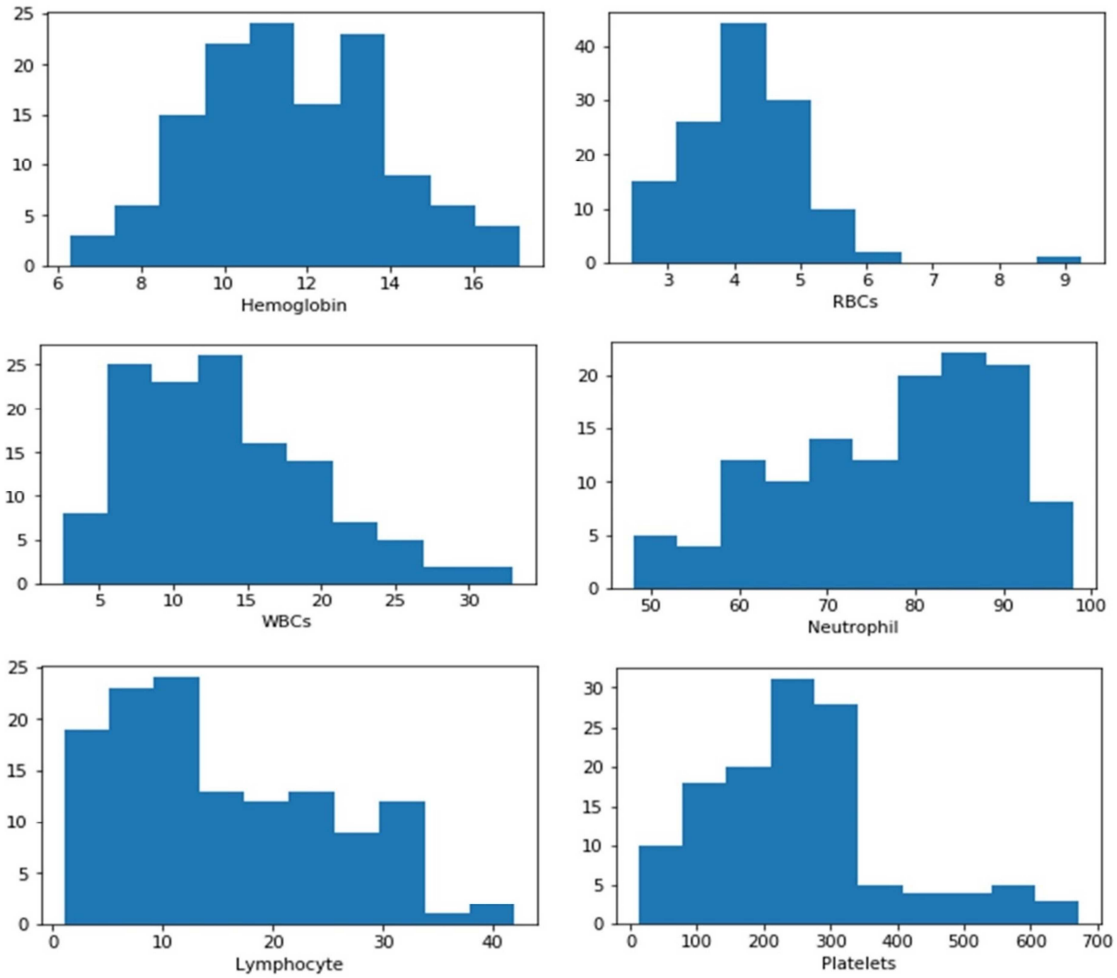


Table 7: Descriptive analysis of the complete Hemogram in the study population (n=128)

Complete Hemogram	
Variables	**Mean±SD (Range)**
Haemoglobin (g/dl)	11.62±2.26 (6.3 - 17.1)
RBCs (x 10^6 cells /µL)	4.2±0.89 (2.44 - 9.25)
WBCs (x 10^3 cells /µL)	13.40±6.21 (2.5 - 33)
Neutrophil (%)	76.9±12.23 (48 - 98)
Lymphocyte (%)	15.51±9.58 (1 - 42)
Platelet Count (x 10^3 cells /µL)	254.59±138.37 (12 - 673)

Descriptive analysis of the complete Hemogram distribution of the study subjects revealed a mean Haemoglobin of 11.62 g/dl with a standard deviation of 2.26 g/dl, the minimum Haemoglobin noted was 6.3 g/dl and the maximum was 17.1 g/dl.

Among the study subjects, the mean RBCs noted were 4.2 x 10^6cells/µl with a standard deviation of 0.89 x 10^6cells/µl, the minimum RBCs noted were 2.44 x 10^6cells/µl and the maximum were 9.25 x 10^6cells/µl.

Among the study subjects, the mean WBCs noted were 13.40 x10^6cells/µl with a standard deviation of 6.21x 10^6cells/µl, the minimum WBCs noted were 2.5 x 10^6cells/µl and the maximum were 33 x 10^6cells/µl.

The distribution of Neutrophils was in the range of 48 – 98 %, with a mean of 76.9 and a standard deviation of 12.23 **%.**

The distribution of Lymphocyte was in the range of 1- 42 %, with a mean of 15.51 and a standard deviation of 9.58 **%.**

The study noted a mean Platelet Count of 254.59 with a standard deviation of 138.37 x 10^3cells/µl, with a minimum platelet count of 12 and a maximum platelet count of 673 respectively (Figure 8, Table 7).

Figure 9: Renal profile distribution graph in the study population

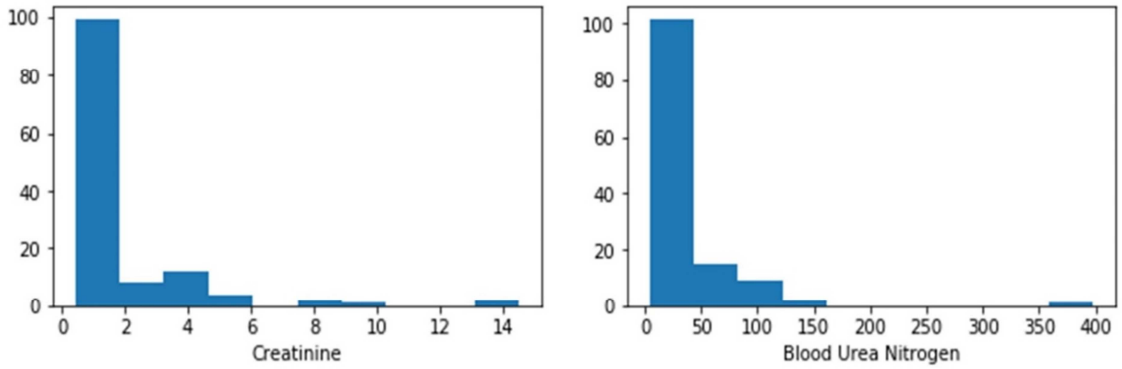


Table 8: Descriptive analysis of the Renal profile distribution graph in the study population (n=128)

Renal profile	
Variables	**Mean±SD (Range)**
Creatinine (mg/dl)	1.92±2.22 (0.42 - 14.53)
Blood Urea Nitrogen (mg/dl)	30.82±43.89 (4.26 - 398.25)

The mean Creatinine noted among study subjects was 1.92 with a standard deviation of 2.22 mg/dl, and the mean Blood Urea Nitrogen level was 30.82 with a standard deviation of 43.89 mg/dl (Figure 9, Table 8).

Figure 10: Serum Electrolytes distribution graph in the study population

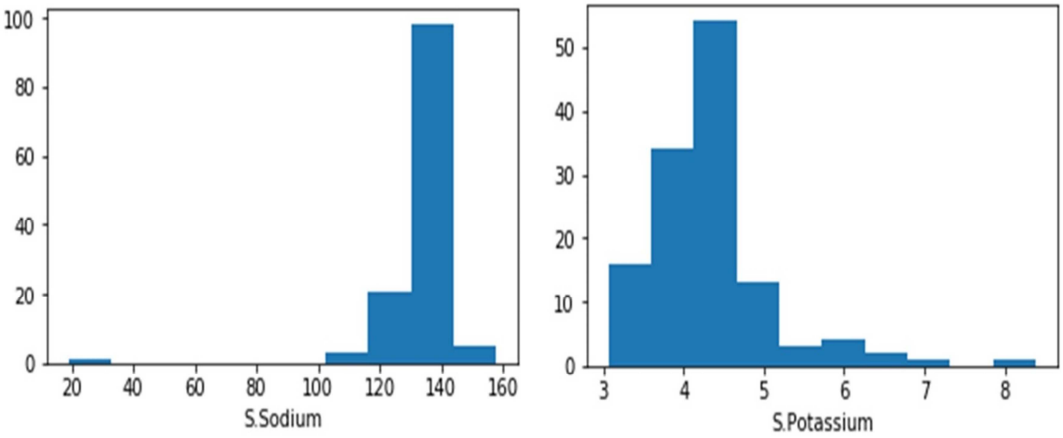


Table 9: Descriptive analysis of the Serum Electrolytes in the study population (n=128)

Serum Electrolytes	
Variables	**Mean±SD (Range)**
Serum Sodium mEq/L	137.03±26.14 (19 - 393)
Serum Potassium mEq/L	4.28±0.77 (3.06 - 8.39)

Descriptive analysis of the serum electrolytes revealed a mean Serum Sodium of 137.03 with a standard deviation of 26.14 mEq/L and Serum Potassium of 4.28 with a standard deviation of 0.77 mEq/L(Figure 10, Table 9).

Figure 11: Liver Profile distribution in the study population(n=128)

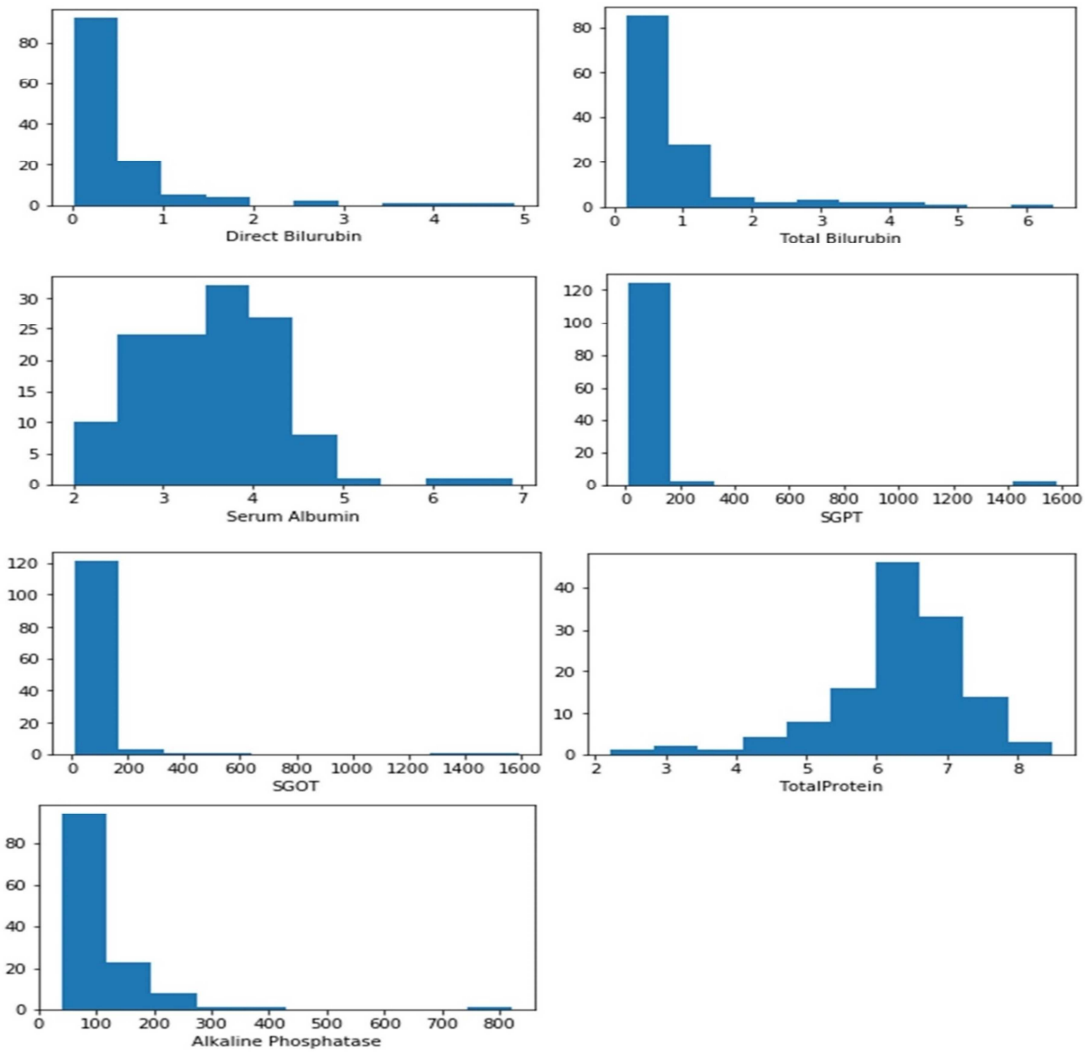


Table 10: Descriptive analysis of the Liver Profile in the study population (n=128)

Liver Profile	
Variables	**Mean±SD (Range)**
Total Bilirubin mg/dl	0.88±0.97 (0.17 - 6.39)
Direct Bilirubin mg/dl	0.52±0.75 (0.01 - 4.9)
SGOT U/L	64.77±189.50 (10 - 1592)
SGPT U/L	52.57±195.23 (9 - 1577)
Serum Albumin gm/dl	3.54±0.80 (2 - 6.9)
Total Protein gm/dl	6.34±0.96 (2.2 - 8.5)
Alkaline Phosphatase U/L	115.98±82.53 (39 - 822)

SGOT: serum glutamic-oxalacetic transaminase, SGPT: serum glutamic-pyruvic transaminase

Among the study subjects, the mean total bilirubin and direct bilirubin noted among the study subjects were 0.88 with a standard deviation of 0.97 and 0.52 with a standard deviation of 0.75 mg/dl. The mean SGOT 64.77 with a standard deviation of 189.50 U/L, the mean SGPT was 52.57 with a standard deviation of 195.23 U/L, the mean serum albumin was 3.54 with a standard deviation of 0.80 gm/dl, the mean total protein was 6.34 with a standard deviation of 0.96 gm/dl, and alkaline phosphatase reported was 115.98 with a standard deviation of 82.53 U/L(Figure 11, Table 10).

Table 11: Adverse Outcome in the study population(n=128)

Adverse Outcome	
Improved	81 (63.28%)
Multi organ dis function syndrome	19 (14.84%)
Acute Kidney Injury	15 (11.72%)
Acute Respiratory Distress Syndrome	13 (10.16%)
Shock	3 (2.35%)
No Adverse Events	92 (71.88%)

Figure 12: Bar plot for mortality in the study population (n=128)

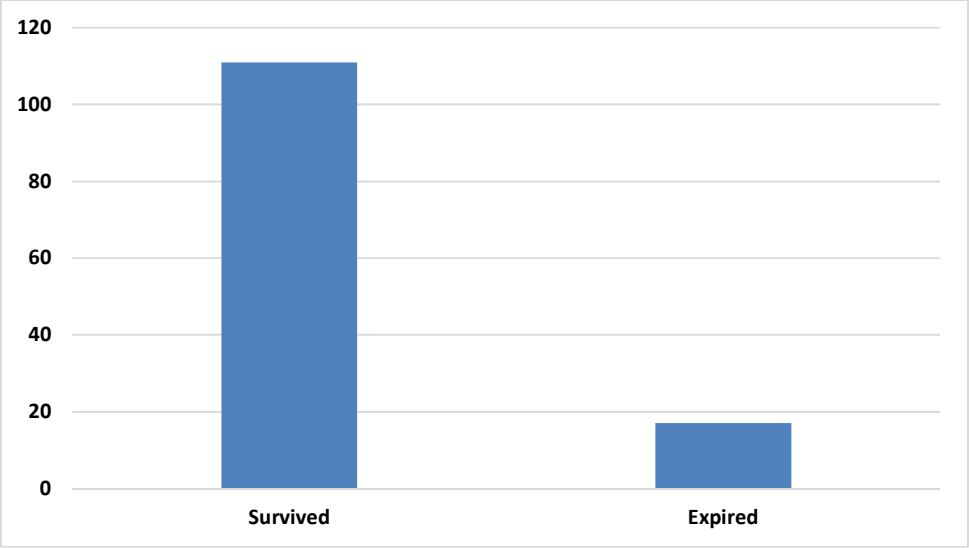


Table 12: Mortality and ICU stay in the study population(n=128)

Mortality & ICU stay	
Survived	111 (86.72%)
Expired	17 (13.28%)
Length of ICU stay in days	4.94±2.80 (1-12)

The total patients (128) were further divided into improved and worsened groups. 81 patients who were shifted from ICU to the general ward were allocated to the improved group and 47 patients who continued their stay in ICU were allocated to the worsened group.

Figure 13: Comparison of demographic parameters between improved and worsened group

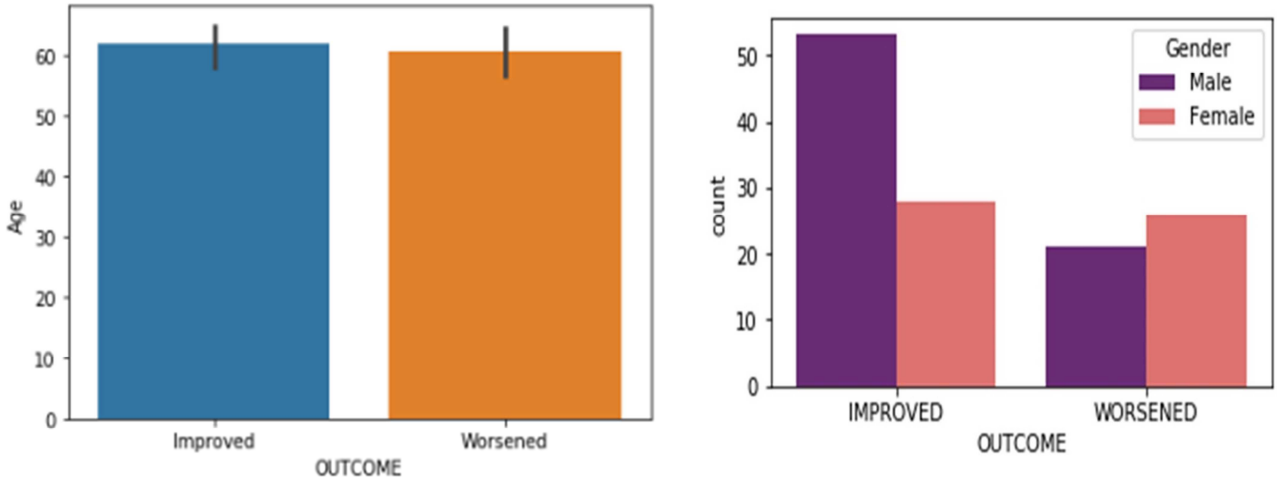


Table 13: Descriptive analysis of demographic parameters between improved and worsened group

Demography			
	Improved (N=81)	**Worsened (N=47)**	**p-value**
Age	61.86±15.03	60.66±14.12	0.33#
Gender(Male/Female)	53/28	21/26	0.04*

A significant statistically significant difference was noted for gender between the improved and worsened groups (P 0.04), whereas age did not show any significant difference between the two groups (P 0.33) (Figure 13, Table 13).

Figure 14: Boxplot graph comparing Glycemic Panel parameters in improved and worsened group

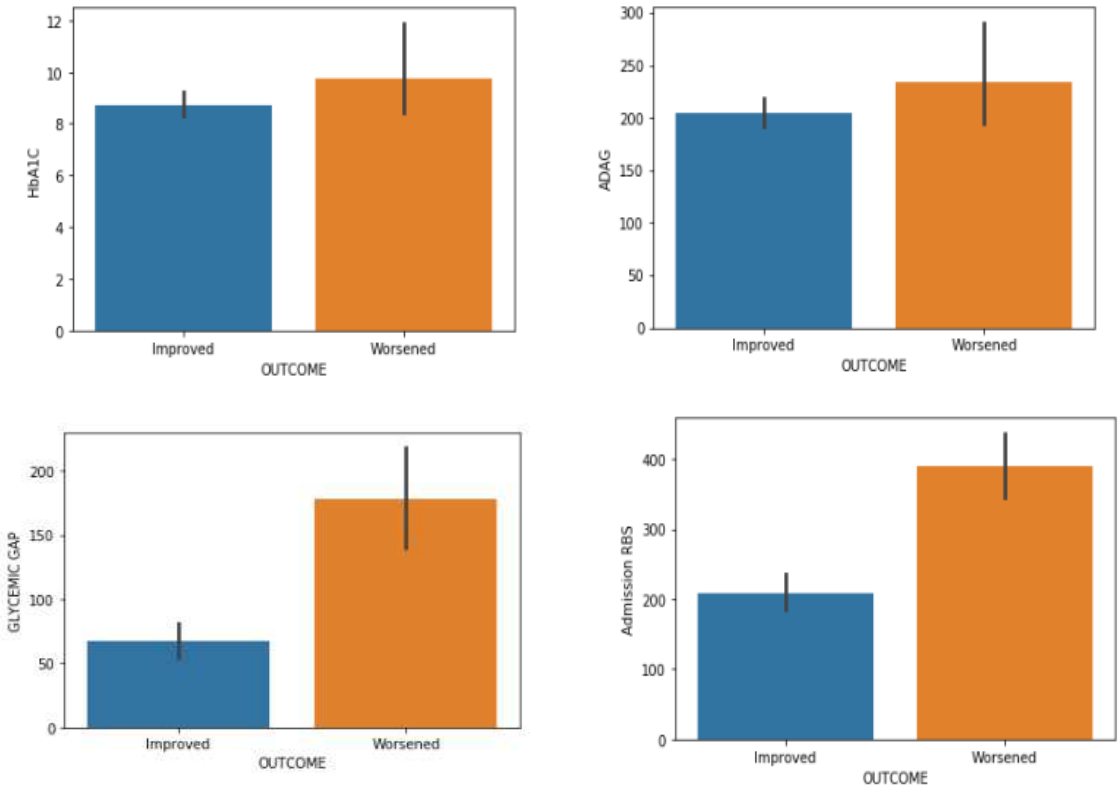


Table 14: Comparison of Glycemic Panel parameters between improved and worsened group

Glycemic Panel			
	Improved (N=81)	**Worsened (N=47)**	**p-value**
HbA1C%	8.74±2.3	9.76±6.0	0.09[#]
Admission RBS mg/dl	208.65±113.81	390.11±164.71	<.0001[#]
ADAG mg/dl	204.16±66.0	233.34±172.19	0.09[#]
Glycemic GAP mg/dl	4.5±89.95	192.63±185.91	<.0001[#]

RBS: random blood glucose, ADAG: A1C-derived average glucose

Glycemic Panel parameters analysis revealed a significant statistical difference in HbA1C, and admission RBS, ADAG, and Glycemic gap between the improved and worsened groups. A significantly greater glycemic gap was found in the worsened group of patients compared to the improved group (Figure 14, Table 14).

Analysis of glycemic panel parameters analysis revealed a significant statistical difference in HbA1C between the 2 groups (P 0.09, Figure 14, Table 14). HbA1C is considered as the gold standard for optimal diabetes management and its restoration to normal levels helps to reduce/prevent diabetic complications. Admission RBS was also found to be significantly different between the improved and worsened groups (P <.0001, Figure 14, Table 14). Stress hyperglycemia is defined by ADA (American Diabetes Association) as an elevation of fasting glucose ≥ 7 mmol/L(>126 mg/dl), or 2-hour postprandial glucose ≥ 11 mmol/L(>200 mg/dl) [101], and is known to be a marker of illness severity, with the magnitude of hyperglycemia strongly associated with short-term mortality, in patients with Diabetes Mellitus.

ADAG and glycemic gap were found to be significantly different between the improved and worsened groups (0.09 and <.0001 respectively, Figure 14, Table 14). In addition, the glycemic gap was found to be significantly more in the worsened group when compared to the improved group (Figure14). Glycemic gap may serve as an excellent tool to estimate the severity and prognosis of critically ill patients with type 2 diabetes. Previous studies have noted the significant association of higher glycemic gap levels with acute kidney injury, multiorgan dysfunction syndrome, acute respiratory distress syndrome, shock, upper gastrointestinal bleeding and ICU mortality.

Figure 15: Boxplot graph comparing Hemogram distribution between the improved and worsened group.

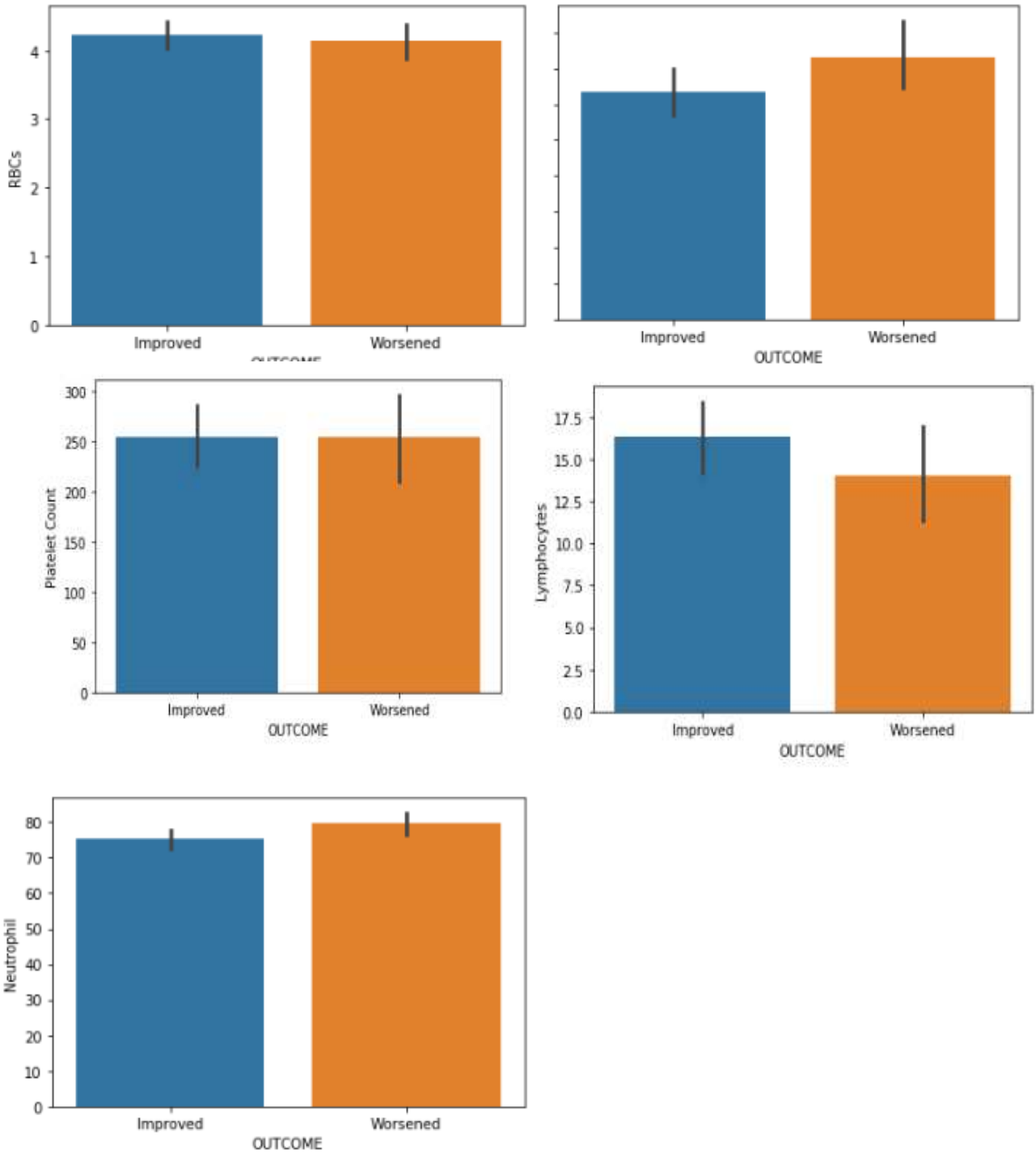


Table 15: Comparison of Hemogram parameters between improved and worsened group.

Complete Hemogram			
	Improved (N=81)	**Worsened (N=47)**	**p-value**
Hemoglobin g/dl	11.52±2.22	11.79±2.34	0.25#
RBCs x 10^3cells /µL	4.23±0.90	4.14±0.88	0.29#
WBCs x10^3cells /µL	12.7±5.93	14.61±6.56	0.05#
Neutrophil %	75.36±12.79	79.55±10.80	0.03#
Lymphocyte %	16.37±9.67	14.02±9.33	0.09#
Platelet Count x10^3 cells/µL	254.8±135.37	254.23±144.87	0.49#

RBC: red blood cell, WBC: white blood cell

There was a significant statistical difference in WBCs, neutrophils, and lymphocyte count found between the improved and worsened groups. There was a non-statistical difference in Haemoglobin level and platelet count between the two groups(Figure 15, Table 15).

Figure 16: Box plot graph comparing the renal profile between improved and worsened group

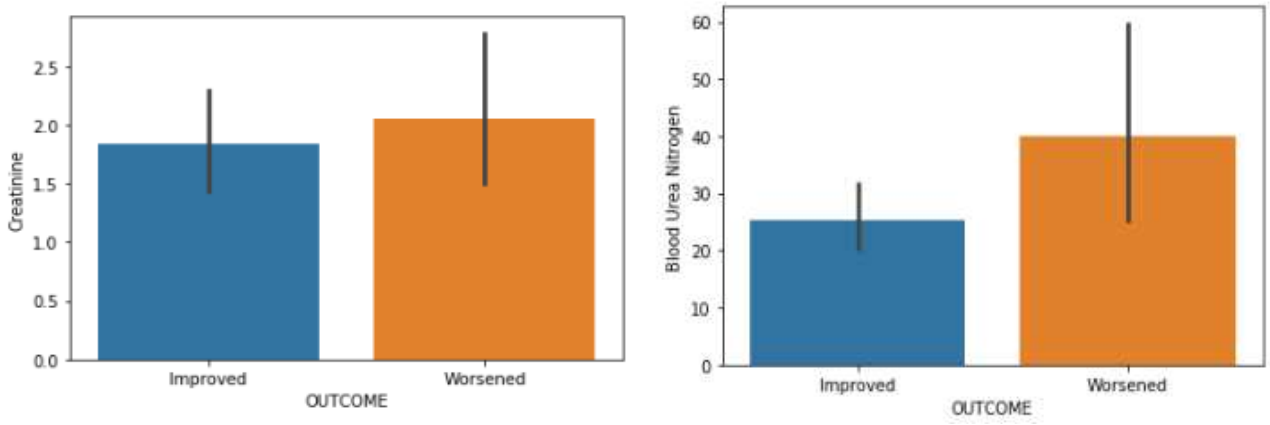


Table 16: Comparison of renal profile between improved and worsened group

Renal profile			
	Improved (N=81)	**Worsened (N=47)**	**p-value**
Creatinine mg/dl	1.85±2.14	2.05±2.35	0.31#
Blood Urea Nitrogen mg/dl	25.43±25.93	40.1±63.33	0.03#

A significant statistical difference was found in the blood urea nitrogen level between the improved and worsened groups whereas there was a non-significant statistical difference found for Creatinine between the two groups(Figure16, Table 16).

Figure 17: Box plot graph comparing the Serum Electrolyte parameters between improved and worsened group

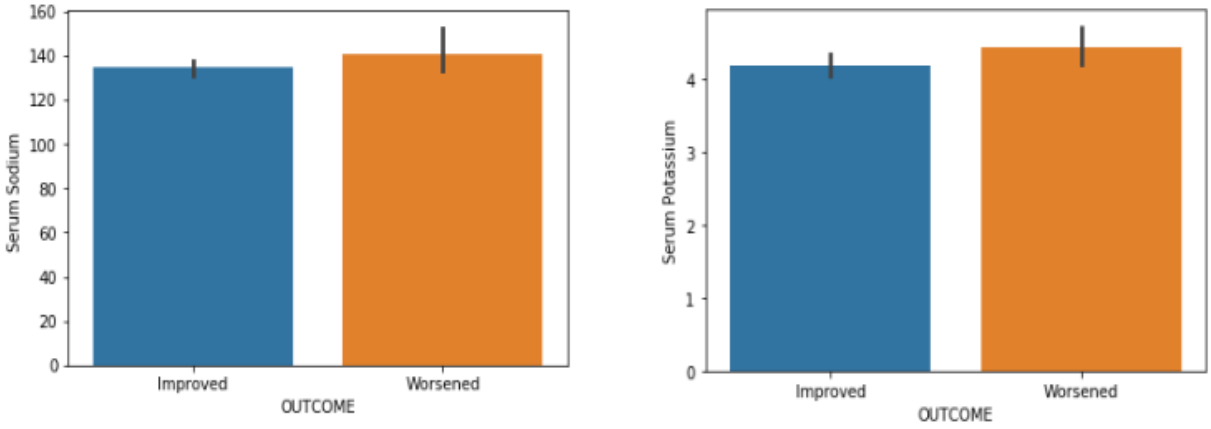


Table 17: Comparison of Serum Electrolyte parameters between improved and worsened group

Serum Electrolytes			
	Improved (N=81)	**Worsened (N=47)**	**p-value**
Serum Sodium mEq/L	134.93±14.68	140.66±38.6	0.12#
Serum Potassium mEq/L	4.19±0.63	4.44±0.94	0.04#

A significant statistical difference in serum potassium level was found between the improved and worsened group. Whereas there was a non-significant statistical difference in serum sodium levels between the group (Figure 17, Table 17).

Table 18: Comparison of Liver Profile parameters between improved and worsened group

Liver Profile			
	Improved (N=81)	**Worsened (N=47)**	**p-value**
Total Bilirubin mg/dl	0.86±0.84	0.91±1.16	0.41#
Direct Bilirubin mg/dl	0.54±0.74	0.5±0.78	0.39#
SGOT U/L	52.04±152.49	86.7±240.68	0.16#
SGPT U/L	42.9±171.94	69.23±231.02	0.23#
Serum Albumin gm/dl	3.63±0.87	3.39±0.64	0.05#
Total Protein gm/dl	6.33±1.05	6.35±0.77	0.45#
Alkaline Phosphatase U/L	111.58±57.64	123.55±113.72	0.22#

SGOT: serum glutamic-oxalacetic transaminase, SGPT: serum glutamic-pyruvic transaminase

A significant statistical difference in serum albumin levels was found between the improved and worsened group. Whereas total bilirubin, direct bilirubin, SGOT, SGPT, serum albumin, total protein, and alkaline phosphatase did not show any significant statistical difference between the two groups (Figure18, Table 18).

Figure 18: Boxplot graph comparing Liver profile parameters in improved and worsened group

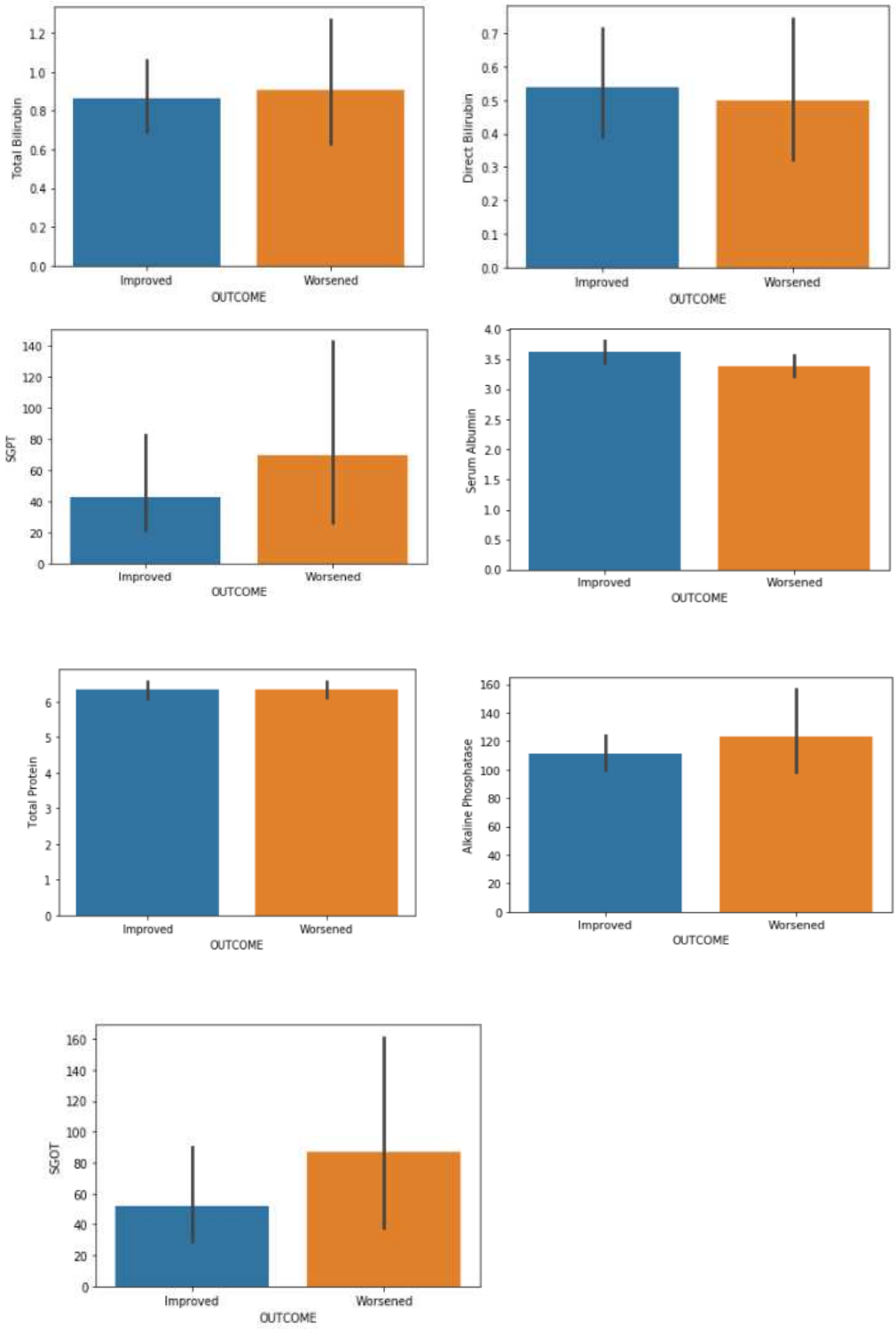


Table 19: Correlation between glycemic gap and outcomes in the study population(n=128)

	Multi organ disfunction syndrome	Acute Kidney Injury	Acute Respiratory Distress Syndrome	Shock	No Adverse Events	Survived	Expired	ICU STAY	HbA1C	Admission RBS	ADAG	GLYCEMIC GAP
Multi organ disfunction syndrome	1											
Acute Kidney Injury	0.74	1										
Acute Respiratory Distress Syndrome	-0.14	-0.04	1									
Shock	-0.06	-0.06	-0.05	1								
No Adverse Events	-0.67	-0.58	-0.54	-0.25	1							
Survived	-0.48	-0.36	-0.33	-0.09	0.63	1						
Expired	0.48	0.36	0.33	0.09	-0.63	-1.00	1					
ICU STAY	0.64	0.57	0.37	0.17	-0.84	-0.55	0.55	1				
HbA1C	0.21	0.04	-0.02	-0.05	-0.13	-0.04	0.04	0.01	1			
Admission RBS	0.34	0.22	0.31	0.01	-0.46	-0.45	0.45	0.33	0.31	1		
ADAG	0.21	0.04	-0.02	-0.05	-0.13	-0.04	0.04	0.01	1.00	0.31	1	
GLYCEMIC GAP	0.38	0.16	0.30	0.04	-0.49	-0.39	0.39	0.35	0.34	0.86	0.34	1

A positive correlation was found between the glycemic gap and worsened outcomes whereas a negative correlation was noted between the glycemic gap and improved outcomes (Table 19).

DISCUSSION

The longitudinal observational study was conducted at KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre in Belagavi, Karnataka. The study included 128 patients (4 were excluded on the basis of exclusion criteria), with type 2 diabetes mellitus admitted to Medical ICU and followed up for one year, i.e. from 1st January 2021 to 31st December 2021. The key objective of the study was to evaluate the association between glycemic gap and adverse outcomes in Type 2 Diabetes Mellitus patients admitted to ICU.

Patients included in the study were aged between 21-98 years, with the mean age being 61.42 years. The mean age reported in a study by Donagaon et al, was 62.01 years.[89] The corresponding mean age noted by Liao et al, for surviving and non-surviving patients were 72.6 and 76.4 years.[3] Whereas the respective ages noted by Gazareen et al, were 61.5 and 49.0 years.[99]

The mean hemoglobin level reported in the present study was 11.62 g/dl. The mean hemoglobin levels reported by Jen-Chun et al, in diabetic survivors and non-survivors were 11.3 g/dl and 11.0 respectively.[3] The respective mean hemoglobin levels reported by EL Eslam et al, were 10.33 g/dl and 11.2 g/dl.[99] Fawzy et al, noted hemoglobin levels of 12.52 and 12.35 in in improved and expired diabetes patients.[97]

Among the other parameters studied, the study noted a statistically significant difference in Hemogram parameters i.e, WBCs, neutrophils, and lymphocyte count between the improved and deteriorated groups. The mean WBCs noted in the study was 13.40 x10^6cells/µl, the distribution of Neutrophils was in the range of 48 – 98 %, with a mean of 76.9, and the distribution of Lymphocyte was in the range of 1- 42

%, with a mean of 15.51 and a standard deviation of 9.58 **%,** with a higher value of WBCs, neutrophils, and lymphocytes in the deteriorated group.

The study noted a statistically significant difference in Blood Urea Nitrogen between the improved and worsened groups, and the mean Blood Urea Nitrogen level was 30.82.

There was a statistically significant difference in the serum albumin between the improved and deteriorated group of patients, with mean serum albumin of 3.54.

The mean HbA1C was 9.11 in the present study. A mean HbA1c of 9.09 was reported in a study by Donagaon et al.[89] The mean HbA1cs observed in survived and non-survived patients by Wei-Chou et al, were 7.2 and 7.0.[3] The corresponding values noted by Zewain et al, for non-survivors and survivors were 13.25 and 8.6.[99] Saad et al, reported HbA1c of 6.98 and 6.49 in improved and expired patients respectively.[97]

The mean ADAG (A1C Derived Average Glucose) reported in the present study was 214.87. A mean ADAG of 200.12 was reported in a study by Dharmalingam et al.[89] mean ADAGs of 333.57 and 200.2 were reported for non-survivors and survivors by Zewain et al.[99]

The mean glycemic gap reported in the present study was 4.28 mg/dl. The corresponding mean glycemic gaps reported by Chi-Ming et al, in surviving and non-surviving patients were 57.1 and 131.2 [3] The mean glycemic gaps of 87.81 and 57.59 were reported for nonsurvivors and survivors by Eslam et al.[99] Saad et al, reported HbA1cs of 70.4 and 107.83 in improved and expired patients respectively.[97]

Given that it takes into account both the patient's plasma glucose at admission and their pre-existing glycemic condition, the glycemic gap may be a better predictor

of outcome in critically ill diabetic patients.[99] In the present study, the glycemic panel indicators including HbA1C, ADAG, RBS and glycemic gap were significantly higher in worsened group of patients compared to improved group.

The study also noted significantly higher glycemic gap in the worsened group of patients who continued their stay in ICU compared to the improved group who were shifted from ICU to the general ward. Saad et al, reported that a poor prognosis and higher ICU mortality are linked to higher glycemic gaps.[97] The study also found that the glycemic gap of worsened group of patients (192.63±185.91) was significantly higher than that improved patients (4.5±89.95) (P<.0001). According to a study by Shih-Hung et al, the glycemic gap can be used to assess the severity and prognosis of critically ill diabetic patients. Patients who had a glycemic gap of more than 80 mg/dL had significantly higher ICU mortality and worser outcomes than those with a glycemic gap of less than 80 mg/dL.[3] Dharmalingam et al, noted that higher values of glycemic gap were strongly linked to higher likelihood of ICU death, leading researchers to draw the conclusion that glycemic gap can be used to gauge a patient's prognosis when they are admitted with a critical illness and are Diabetic.[89] Eslam et al, noted that higher glycemic gap was linked to increased risk for shock, upper gastrointestinal bleed, acute renal injury, acute respiratory distress syndrome, and multiorgan dysfunction syndrome. ICU mortality was also significantly increased by higher glycemic gap levels. Using the glycemic gap, one can assess the severity of and outlook for type 2 diabetic patients who have been admitted with critical illness.[99]

The mean length of ICU stay noted in the current study was 4.94±2.80 days, and increased length of ICU stay, MODS and AKI showed significant positive correlation with mortality rate.

The present study has noted multiple organ dysfunction syndrome (MODS) as the common adverse events (14.84%), followed by acute kidney injury (11.72%), acute respiratory distress syndrome (10.16%) and shock (2.35%). Donagaon and Dharmalingam reported that glycemic gap levels were related to a higher risk of MODS, acute respiratory distress syndrome, shock, upper gastrointestinal haemorrhage, acute renal injury, and acute respiratory failure, which is consistent with the findings of the current study.[89] Zewain et al, also observed similar association and concluded on the use of glycemic gap, which can be used to evaluate and estimate the prognosis of patients with type 2 diabetes admitted under critical care.[99]

CONCLUSION

The present study showed that higher glycemic gap is a simple marker for predicting adverse outcome in diabetic patients. The glycemic gap may serve as an effective tool to evaluate the severity of the disease and prognosis of patients with Type 2 Diabetes Mellitus, who have been admitted with critical illness. The present study could aid in reducing ICU mortality, by early detection and treatment of stress induced hyperglycemia with early initiation of insulin therapy, in critically ill diabetic patients.

SUMMARY

Stress-induced hyperglycemia has been associated with an increased risk of mortality in critically ill patients with Type 2 diabetes. Glycemic gap is a marker of stress induced glycemic excursion in patients with diabetes, that can be used to predict adverse outcomes in patients with diabetes admitted to the ICU. It is determined by deducting the plasma glucose at admission from the A1C-derived average glucose (ADAG), **Glycemic Gap = ADAG – Admission RBS**.

In this one year longitudinal observational study, which recruited 128 patients with Type 2 Diabetes Mellitus admitted to the ICU of KLE's Dr. Prabhakar Kore Hospital, Glycemic gap was calculated for all patients, and its correlation with outcome was studied. Analysis of the glycemic panel revealed a mean HbA1C of the study subjects as 9.11±4.08%. The corresponding mean admission RBS, A1C Derived Average Glucose(ADAG), and Glycemic Gap reported were 208.3±70.03 mg/dl, 214.87±116.97 mg/dl, and 4.28±0.77 mg/dl. Analysis of glycemic panel parameters analysis revealed a significant statistical difference in HbA1C, admission RBS, ADAG, and glycemic gap between the improved and worsened groups (0.09, <.0001, 0.09, <.0001 respectively). In addition, the glycemic gap was found to be significantly more in the worsened group when compared to the improved group. A positive correlation was noted between the glycemic gap and worsened outcomes, whereas a negative correlation was noted between the glycemic gap and improved outcomes.

In the deteriorated group, the study noted multiple organ dysfunction syndrome (MODS) as the common adverse event (14.84%), followed by acute kidney injury (11.72%), acute respiratory distress syndrome (10.16%) and shock (2.35%).

Hence, the study showed that higher glycemic gap is a simple marker for predicting adverse outcome in diabetes patients. The glycemic gap may serve as an effective tool to evaluate the severity and prognosis of patients with Type 2 Diabetes Mellitus, who have been admitted with critical illness.

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ANNEXURE I

INFORMED CONSENT FORM

Dear Mr./Mrs./Dr. _____, you are kindly requested to enroll yourself in a research study tilted-TO STUDY THE ASSOCIATION BETWEEN GLYCEMIC GAP AND ADVERSE OUTCOMES IN DIABETIC PATIENTS ADMITTED TO ICU – **A ONE YEAR LONGITUDINAL STUDY IN KLE'S DR.PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI,** being conducted by Dr. _____, a post graduate student in M.D. General Medicine and the study will be carried out under the direct supervision and guidance of Dr. _____, Professor, Department of General Medicine, Jawaharlal Nehru Medical College, Belgaum.

You have been requested to participate in this as you fit into the laid out criteria for a study 'subject'/ participant.

Your participation in study is voluntary. During the study you will be asked some questions and you are supposed to answer to the best of your knowledge. Your decision whether or not to participate in the study will not affect your treatment in any form. If you decide not to participate you are free to withdraw at any time.

TITLE OF THE STUDY: To study the association between glycaemic gap and adverse outcomes in diabetic patients admitted to ICU – A one year longitudinal study in KLE's Dr.Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

PURPOSE OF THE STUDY: To assess the prognostic value of Glycaemic Gap in determining adverse outcomes, in Type 2 Diabetes Mellitus patients admitted to ICU.

PROCEDURES INVOLVED: If you agree to enroll yourself in my study, you will be interviewed regarding your present, past and family history then you will be clinically examined in detail and investigated accordingly.

Then you will be subjected to a few investigations namely

1. HbA1C.
2. Plasma Glucose at admission (RBS)
3. CBC
4. LFT
5. Serum Creatinine
6. Blood Urea Nitrogen
7. Serum Electrolytes

RISKS AND BENEFITS: There are no potential risks involved in this study.

Benefits of taking part in this research: By taking part in this study, prognostic value of Glycemic Gap in determining adverse outcomes, in Type 2 Diabetes Mellitus patients admitted to ICU can be known.

VOLUNTARY PARTICIPATION / WITHDRAWAL FROM THE STUDY: Taking part in the study is voluntary. You may choose not to enroll yourself in this study and may choose to leave the study anytime in between.

ALTERNATIVES: Your decision regarding participation in study will not change present or future health care services offered to you at KLES

Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You would simply be excluded from the study if you wish to, and all your details shall be kept confidential and you will get the routine line of management.

PRIVACY AND CONFIDENTIALITY: All data collected or disclosed by you during the course of participation of study, will be kept fully confidential. If however during the course it becomes necessary for the progress of the course to disclose the identity, it would be done so only after your informed & written consent.

The only people to know that you are a research subject are members of the research team. No information about you will be disclosed to other without your written permission except:

- In emergency to protect your rights AND welfare.
- If required by law.

AUTHORIZATION TO PUBLISH RESULT: The results of the study may be used to publish an article. When the results of research published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential.

FINANCIAL INCENTIVES FOR PARTICIPATION: No additional costs shall be incurred upon you for the purpose of this study. It is purely being done with the idea of research and all the cost of study will be borne by the investigator.

COMPENSATION: In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, or you will be given information about where to receive medical care. However, no reimbursement, compensation or free medical care will be given.

QUESTIONS/CONTACT DETAILS: You shall be free to contact the below mentioned name & addresses anytime during the study period for any clarification or help as you may desire for.

In case of the queries during study or in future you may contact following persons,

1**. Dr. Harsha Hegde**,
Chairperson, JNMC, IEC
& Scientist D, ICMR,
National Institute of Traditional Medicine, Belgaum
Ph No- 9480422500

CONSENT FORM

I, voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has been read to me, this consent form and have had all the questions answered.

……..…… …..……

Name of the Participant Signature of the participant

or Left-Hand Thumb impression

…… ……

Name of Investigator Signature of investigator

or Left-Hand Thumb impression

……. ……..

Name of Witness Signature of Witness

or Left-Hand Thumb impression

Date:

Place:

ANNEXURE II

PROFORMA

CASE NO:

NAME:

AGE/SEX:

IP NO.:

ADDRESS:

OCCUPATION

DATE OF ADMISSION:

COMPLAINTS AT PRESENTATION:

Past history:

Family history

Personal history

Treatment history

PHYSICAL EXAMINATION:

GENERAL CONDITION:

PALLOR- YES/NO

ICTERUS-YES/NO

LYMPHADENOPATHY-YES/NO

CYANOSIS- YES/NO

CLUBBING-YES/NO

EDEMA-YES/NO

VITALS:

TEMPERATURE

PULSE RATE

RESPIRATORY RATE

BLOOD PRESSURE

SYSTEMIC EXAMINATION:

R. S. :

C.V.S.:

C.N.S :

P.A. :

INVESTIGATIONS

- HbA1C.
- Plasma Glucose at admission (RBS)
- CBC
- LFT
- Serum Creatinine
- Blood Urea Nitrogen
- Serum Electrolytes

To convert HbA1c levels to chronic average blood glucose

levels, we used the following equation:

ADAG=[(28.7 x HbA1c) -- 46.7].

The glycemic gap was calculated from the glucose level on admission, as follows:

Glycemic Gap=[Plasma Glucose on admission(RBS) -- ADAG].

Association between glycemic gap and outcome of patient will be studied**.**

OUTCOME OF THE PATIENT- AT THE END OF HOSPITAL STAY WILL BE FOLLOWED UP.

- **PARAMETERS OF PROGNOSIS IN TERMS OF ADVERSE EFFECTS INCLUDE-**

1. **MULTIORGAN DYSFUNCTION SYNDROME (MODS).**
2. **ACUTE RESPIRATORY DISTRESS SYNDROME.**
3. **SHOCK.**
4. **UPPER GASTROINTESTINAL BLEED.**
5. **ACUTE RESPIRATORY FAILURE.**

ANNEXURE -IV - MASTER CHART

				Complete Hemogl						Renal profile		Serum Electrolytes		Liver Profile							Glycemic Panel										
Sl. No	IP No.	Age	Sex	Hemoglobin	RBCs	WBCs	N	L	Platelet Count	Creatinine	BUN	S. Sodium	S. Potassium	TB	DB	SGOT	SGPT	S. Albumin	Total Protein	Alkaline Phosphatase	HbA1C	Admission RBS	ADAG	**ADAG**	GLYCEMIC GAP	**GLYCEMIC GAP**	Admission RBS	OUTCOME		ADVERSE OUTCOME	ICU STAY	MORTALITY
1	1108618	49	M	8.9	3.08	11.2	88	9	252	7.91	50.9	142	4.78	0.20	0.10	20	17	2.4	5.2	139	6.3%	72 mg/dl	134	134.11	62	-62.11	72	IMPROVED			3	
2	1108391	66	M							1.20	25.69	133	4.26	0.45	0.19	31	13	3	8.4	190	10.3%	178 mg/dl	248.9	248.91	7.9	-70.91	178	IMPROVED			2	
3	1047475	71	M							2.37	41.58	129	4.81	3.36	2.87	52	32	2.4	5	97	8.0%	214 mg/dl	182	182.9	31	31.1	214	IMPROVED			4	
4	1108190	78	M	11.6	4.17	5.7	70	20	123	0.94	9.34	19	3.48	1.13	0.52	25	66	3.6	6.7	100	8.0%	126 mg/dl	182.9	182.9	56.9	-56.9	126	IMPROVED			5	
5	1054447	59	M	14	5.01	18.2	80	10	523	5.37	75.2	131	5.25	0.9	0.7	22	25	3.5	5.4	112	9.7%	326 mg/dl	231.6	231.69	94.3	94.31	326	IMPROVED			2	
6	1107458	77	M	10.7	3.79	12.6	81	15	194	1.60	14.48	133	4.95	0.56	0.09	21	17	3.5	6.2	61	8.2%	295 mg/dl	188.6	188.64	106.3	106.36	295	IMPROVED			1	
7	1107356	52	M	10.5	4.34	5.8	70	19	95	0.64	15.41	136	3.56	0.75	0.38	21	14	2.5	7.2	115	7.6%	119 mg/dl	171.4	171.42	52.4	-52.42	119	IMPROVED			4	
8	1106849	70	M	14.6	4.94	11.1	85	7	112	0.73	8.41	138	4.2	1.17	0.41	34	30	4.5	6.8	117	6.5%	150 mg/dl	139.8	139.85	10.1	10.15	150	IMPROVED			3	
9	1106003	56	F	9.1	3.95	21	83	12	220	2.64	28.95	134	3.8	0.28	0.13	12	10	3.1	7.4	112	11.6%	182 mg/dl	286.2	286.22	104.2	-104.22	182	IMPROVED			2	
10	1108248	53	M	10.5	3.69	20.5	92	4	53	4.00	69.12	126	4.33	0.82	0.68	17	14	2.1	4.6	117	9.9%	243 mg/dl	237.4	237.43	5.5	5.57	243	IMPROVED			4	
11	1107201	62	M	11.4	4.02	18.2	82	10	450	3.40	104.61	127	5.98	1.28	1.12	49	44	2.5	7.5	232	9.1%	516 mg/dl	214.47	214.47	301.5	301.53	516	WORSENED		MODS, AKI	7	
12	1108189	61	M	12	4.16	19.9	95	1	180	2.68	105.08	147	4.18	0.51	0.31	21	17	2.8	5.7	66	10.9%	462 mg/dl	266.13	266.13	195.8	195.87	462	WORSENED		MODS, AKI	12	EXPIRED
13	1108607	90	M	11	3.92	25.7	79	10	318	3.18	36.43	135	4.5	0.56	0.35	37	44	2.3	5.3	203	5.5%	90 mg/dl	111.1	111.15	38.1	-21.15	90	IMPROVED			5	
14	1108571	56	M	12.8	4.73	17.8	95	4	178	1.28	23.82	133	4.42	0.59	0.27	15	15	3.7	6.6	92	9.2%	294 mg/dl	217.3	217.34	76.6	76.66	294	IMPROVED			3	
15	1108089	76	F	12.1	4.07	12.9	86	6	309	0.84	11.21	142	3.53	0.45	0.10	169	62	2.6	7	139	8.1%	182 mg/dl	185.7	185.77	3.7	-3.77	182	IMPROVED			4	
16	1105798	56	M	14.4	5.32	9.7	74	22	285	0.78	11.68	136	4.2	0.35	0.12	10	12	3.9	7.5	178	12.8%	380 mg/dl	320.6	320.66	59.3	59.34	380	IMPROVED			5	
17	1104449	60	M	13.7	4.88	12.7	89	8	276	0.65	11.21	134	3.86	0.47	0.15	59	19	4.4	7.2	143	7.7%	188 mg/dl	174.2	174.29	13.7	13.71	188	IMPROVED			2	
18	1107970	49	F	12.4	4.74	13	61	33	307	0.94	16.81	144	4.2	0.39	0.13	15	23	4.3	7.9	150	14.7%	271 mg/dl	375.19	375.19	104.19	-104.19	271	IMPROVED			1	
19	1108120	67	M	10.1	3.47	4.5	49	40	160	1.36	8.87	144	3.89	0.68	0.28	16	16	2.8	5.6	49	7.5%	97 mg/dl	168.5	168.55	71.5	-71.55	97	IMPROVED			3	
20	1108842	83	M	11.6	4.91	10.8	76	17	238	1.09	18.21	143	4.6	0.6	0.14	29	14	2.9	6.8	55	6.9%	223 mg/dl	151.3	151.33	71.6	71.67	223	IMPROVED			4	
21	1018662	82	M	13.1	4.58	11.8	86	13	217	1.17	18.22	136	5.22	0.54	0.32	28	16	2.9	5.7	62	9.7%	311 mg/dl	231.6	231.69	79.3	79.31	311	WORSENED		ARDS	9	EXPIRED
22	1049665	40	F	13.5	5.07	8.9	59	31	91	0.45	10.74	132	4.17	0.38	0.12	70	96	3.4	6.6	217	6.9%	248 mg/dl	151.3	151.33	96.6	96.67	248	IMPROVED			3	
23	1045223	54	M	11.5	3.9	21.7	88	10	123	0.81	13.08	129	4.28	0.23	0.09	14	11	3.1	6	129	14.1%	427 mg/dl	357.9	357.97	69.03	69.03	427	WORSENED			4	
24	1043386	98	F	10.7	3.7	22.5	51	2	646	4.40	51.86	143	4.15	0.29	0.16	29	11	3.6	6.9	416	7.0%	94 mg/dl	154.2	154.2	60.2	-60.2	94	IMPROVED			5	
25	1039356	68	M	12.9	4.28	6.6	64	22	168	0.79	8.65	135	4.18	0.29	0.15	13	21	4.2	6.8	82	8.4%	190 mg/dl	194.3	194.38	4.3	-4.38	190	IMPROVED			1	
26	1024898	62	M	11.3	4.26	20.6	87	5	219	1.64	21.9	144	3.29	3.93	2.64	79	42	3.4	6.4	78	6.2%	113 mg/dl	131.2	131.24	18.2	-18.24	113	IMPROVED			3	
27	1024715	67	M	10.4	3.36	8.2	64	25	263	9.35	50	139	6.43	0.56	0.32	11	10	3.4	3.2	82	6.8%	126 mg/dl	148.46	148.46	22.4	-22.46	126	IMPROVED			2	
28	1041268	70	M	11.8	4.19	8.9	89	6	313	1.00	8.64	134	4.2	0.28	0.14	22	12	3.5	6.3	80	6.7%	96 mg/dl	145.5	145.59	49.5	-49.59	96	IMPROVED			5	
29	1039564	75	M	14.3	4.86	5.6	80	16	147	1.14	10.45	134	4.54	0.51	0.19	20	15	4.3	7.5	96	6.5%	100 mg/dl	139.8	139.85	39.8	-39.85	100	IMPROVED			4	
30	1047260	85	M	9.7	4.05	21.6	83	6	290	0.70	6.54	134	3.35	0.62	0.42	14	10	2.3	4.5	86	7.1%	75 mg/dl	157.07	157.07	82.07	-82.07	75	IMPROVED			6	
31	1022535	62	M	13.3	5.05	12.3	73	17	303	1.01	8.24	130	3.86	0.64	0.23	66	14	4.1	7.7	64	10.1%	394 mg/dl	234.17	243.17	100.83	150.83	394	WORSENED		ARDS	8	
32	1026087	70	F	9.9	3.8	9.8	87	10	107	1.48	50.46	128	7.12	0.44	0.1	115	51	2.6	8.5	144	7.7%	195 mg/dl	174.2	174.29	20.8	20.71	195	IMPROVED			5	
33	999358	72	F	10.1	4.49	10.1	73	13	40	1.05	8.22	144	3.35	0.52	0.26	20	18	4.5	7	68	6.5%	426 mg/dl	139.85	139.85	286.15	286.15	426	WORSENED		ARDS	10	EXPIRED
34	1043829	45	M	13.6	4.8	9.8	75	19	257	1.26	12.14	138	4.42	1.08	0.42	18	24	4.7	6.7	66	7.8%	147 mg/dl	177.16	177.16	30.16	-30.16	147	IMPROVED			6	
35	1020454	54	M	14.6	5.56	4.5	64	28	150	0.77	8.87	127	3.98	0.72	0.32	20	41	4.6	7	94	7.8%	155mg/dl	177.16	177.16	22.16	-22.16	155	IMPROVED			2	
36	1018666	68	M	13.4	5.13	17.7	75	18	369	0.78	10.74	140	4.02	0.38	0.26	18	16	4.1	7.2	67	7.6%	105 mg/dl	171.4	171.42	66.4	-66.42	105	IMPROVED			1	
37	1024394	67	F	9.6	3.11	3.7	54	29	62	0.86	6.22	138	4.61	0.96	0.72	26	25	4.2	6.4	62	6.6%	158 mg/dl	142.7	142.72	15.28	15.28	158	IMPROVED			4	
38	1025815	65	F	11.5	3.96	23.4	85	5	137	4.46	85.04	121	5.75	0.47	0.23	24	10	2.7	6.9	217	7.5%	302 mg/dl	168.5	168.55	133.45	133.45	302	WORSENED		MODS,AKI	11	EXPIRED
39	1043537	70	F	7.7	2.64	25.1	78	7	488	7.84	73.83	126	6.18	0.21	0.16	19	10	2.9	6.4	226	6.5%	774 mg/dl	139.85	139.85	634.15	634.15	774	WORSENED			4	
40	1038416	82	F	10.5	4.05	18.9	89	6	190	3.49	76.63	110	3.98	0.33	0.11	25	15	2	5.1	97	10.4%	72 mg/dl	251.7	251.78	179.7	-179.78	72	IMPROVED			5	
41	1033104	60	M	11.2	5.1	24	92	8	378	14.53	159.34	112	8.39	2.2	1.89	30	55	3.2	6.5	822	6.8%	386 mg/dl	271.8	148.46	114.2	237.54	386	WORSENED		MODS, AKI	9	
42	1026337	78	F	11.8	4.06	14.5	89	6	280	2.41	35.98	134	4.51	0.22	0.13	10	12	3.1	7	154	10.2%	451 mg/dl	246.04	246.04	204.96	204.96	451	WORSENED			5	
43	1031885	65	F	7.8	4.12	14.6	78	16	673	0.67	8.87	138	4.71	0.22	0.1	13	9	3.8	6.4	110	7.5%	131 mg/dl	168.5	168.55	37.5	-37.55	131	IMPROVED			3	
44	1034384	60	F	14.8	5.46	9.9	85	11	29	0.67	5.24	118	5.8	0.39	0.11	46	50	2.5	5.1	195	8.3%	432 mg/dl	191.5	191.51	240.4	240.49	432	WORSENED		ARDS	6	
45	1034451	45	M	13.6	4.08	9.8	62	17	311	1.09	8.22	144	4.98	0.62	0.48	21	12	4.2	6.4	112	8.2%	165 mg/dl	188.6	188.64	23.4	-23.64	165	IMPROVED			2	
46	1023401	50	M	9.2	4.2	14.4	88	12	549	5.73	84.11	120	4.05	4.35	4	37	47	2.6	5.5	159	10.2%	254 mg/dl	246.04	246.04	7.96	7.96	254	IMPROVED			1	
47	1022480	30	F	12.5	4.66	16.5	85	6	324	4.04	30.37	108	3.16	0.52	0.16	10	11	3.3	6.8	95	6.6%	542 mg/dl	142.7	142.72	399.2	399.28	542	WORSENED		MODS, AKI	8	EXPIRED
48	1030307	40	M	9.5	5.03	15.6	70	15	230	1.34	32.3	126	4.86	4.9	1.36	1592	1577	3.8	6.1	101	6.5%	423 mg/dl	139.8	139.85	283.1	283.15	423	WORSENED		MODS, AKI	12	EXPIRED
49	1026447	51	F	12.7	5.18	17.3	83	12	309	0.74	8.64	143	4.10	0.90	0.41	15.00	11.00	3.60	7.80	181	6.5%	287 mg/dl	139.8	139.85	147.1	147.15	287	WORSENED		MODS	11	
50	1116166	59	M	8.9	4.4	16.5	97	2	356	1.00	6.22	141	3.54	0.63	0.22	37	21	3.6	7.6	115	6.5%	176 mg/dl	139.8	139.85	36.15	36.15	176	IMPROVED			2	
51	1041066	65	F	13.1	4.86	13	68	26	341	0.52	10.61	134	4.2	0.63	0.1	14	11	4.3	7.4	112	9.7%	195 mg/dl	231.69	231.69	36.6	-36.69	195	IMPROVED			2	
52	1031022	58	M	9.3	2.84	9.4	58	26	146	0.96	9.24	142	4.2	6.39	4.9	91	17	2.2	6.6	112	6.5%	398 mg/dl	139.8	139.85	258.15	258.15	398	WORSENED		SHOCK	7	
53	1024495	56	F	9.4	4.01	27.4	81	18	575	1.10	9.28	135	4.37	0.57	0.47	10	11	2.4	6.7	249	8.1%	144 mg/dl	185.7	185.77	41.7	-41.77	144	IMPROVED			4	
54	1036974	65	F	9.3	3.91	11.6	78	15	653	0.83	7.64	145	4.21	0.86	0.62	21	12	3.8	6.4	102	14.2%	626 mg/dl	375.19	360.84	250.81	265.16	626	WORSENED		ARDS	8	EXPIRED
55	1041066	65	F	13.1	4.86	13	68	26	341	0.52	9.32	138	4.2	0.63	0.1	34	11	4.3	7.4	108	9.7%	432 mg/dl	231.6	231.69	200.3	200.31	432	WORSENED		SHOCK	5	
56	1048058	60	F	16	6.1	17.6	86	4	280	0.48	4.26	141	4.3	0.42	0.23	17	9	3.8	7.3	112	10.2%	286 mg/dl	263.2	246.04	22.7	39.96	286	WORSENED		MODS	9	EXPIRED
57	1025183	57	F	9	3.56	15.5	89	7	254	1.25	34.7	139	3.66	0.25	0.1	128	70	3.3	6.3	149	7.1%	386 mg/dl	157.07	157.07	228.9	228.93	386	WORSENED		MODS	8	
58	1017665	88	F	10.1	2.92	25.9	75	3	169	1.59	12.24	141	4.28	2.9	0.69	28	10	3.6	6.8	102	8.4%	158 mg/dl	194.3	194.38	36.3	-36.38	158	IMPROVED			2	
59	1023266	51	M	12.1	4.31	19.7	82	4	111	3.61	31.77	141	4.2	0.73	0.41	40	16	2.9	5.9	125.00	13.80%	614 mg/dl	349.3	349.36	264.7	264.64	614	WORSENED		MODS, AKI	6	EXPIRED
60	1048814	64	F	12.2	4.61	13.4	76	14	160	0.70	14.2	129	4.47	0.38	0.08	15	13	3.3	5.8	109	9.2%	413 mg/dl	217.3	217.34	195.6	195.66	413	IMPROVED			3	
61	1043639	73	F	11.2	3.77	13.1	82	3	323	0.42	11.68	131	4.31	1.34	0.47	24	16	4.4	6.7	91	7.2%	482 mg/dl	159.9	159.94	322.06	322.06	482	WORSENED		MODS	9	EXPIRED
62	1042841	38	F	12.9	4.29	7.2	48	42	84	0.60	12.48	139	3.87	0.3	0.25	363	275	3.5	5.9	157	6.4%	384 mg/dl	136.9	136.98	247.02	247.02	384	WORSENED		ARDS	8	
63	1022669	85	F	9.5	3.48	12.5	61	33	328	1.48	29.28	141	4.2	0.29	0.22	14	12	2.9	6.3	89	6.50%	86 mg/dl	139.8	139.85	53.8	-53.85	86	IMPROVED			4	
64	1030237	62	F	9.2	2.44	8.5	69	30	100	0.65	14.2	141	3.8	0.39	0.2	26	11	3.7	6.2	39	6.4%	486 mg/dl	136.9	136.98	349.02	349.02	486	WORSENED			5	
65	1029502	58	M	11.7	4.2	12.4	83	12	253	0.98	9.1	140	4.2	0.22	0.1	40	29	3	6.2	55	8.5%	324 mg/dl	197.2	197.25	126.7	126.75	324	IMPROVED			4	
66	1026542	68	M	8.4	2.51	6.7	78	18	163	1.05	22.1	141	4.2	1.63	0.81	39	19	3.2	6.2	128	6.4%	581 mg/dl	139.8	136.98	441.15	444.02	581	WORSENED		ARDS	7	
67	1026456	80	M	12.5	4.77	8.1	65	25	327	0.69	24.2	135	4.2	0.74	0.24	34	26	3.4	6	51	7.1%	428 mg/dl	157.07	157.07	270.9	270.93	428	WORSENED		ARDS	8	EXPIRED
68	1026236	66	M	9.3	2.69	15.6	87	6	44	2.72	40.8	133	4.17	1.17	3.85	54	36	2.3	5.2	89	6.8%	81 mg/dl	148.4	148.46	67.46	-67.46	81	IMPROVED			3	
69	1040524	61	F	8.2	3.03	20.7	82	13	234	0.80	30.2	140	4	0.84	0.5	29	35	3	5.8	94	7.9%	396 mg/dl	180.03	180.03	215.97	215.97	396	IMPROVED			2	
70	1006173	68	M	13.2	4.45	22.6	90	4	171	0.54	22.1	135	3.06	1.37	0.4	16	13	4.3	6.6	76	6.8%	382 mg/dl	148.46	148.46	233.54	233.54	382	**IMPROVED**			1	

71	1038755	50	F	11.1	3.03	5900	67	29	227	1.69	20.2	142	3.8	0.28	0.15	35	22	3.8	6.4	65	7.1%	107 mg/dl	157.07	157.07	50.07	-50.07	107	WORSENED		AKI	9	
72	1046949	64	M	7.8	2.63	15.4	85	12	252	1.20	20.4	141	4.2	0.3	0.15	19	32	2.8	5.8	148	9.6%	626 mg/dl	228.8	228.82	397.18	397.18	626	WORSENED		MODS	10	EXPIRED
73	1037317	70	F							1.02	32.8	141	4.2	1.83	0.94	41	20	2.6	5.8	68	6.8%	388 mg/dl	148.46	148.46	239.54	239.54	388	IMPROVED			4	
74	1032553	58	M	13.8	4.6	22.6	59	16	141	1.72	36.9	138	4.8	1.52	1.4	25	13	3.2	6.6	202	14.5%	216 mg/dl	369.4	369.45	153.45	-153.45	216	IMPROVED			5	
75	1032444	38	F	11.6	5.17	12.8	65	25	512	0.85	20.8	131	4.9	0.3	0.14	24	20	3.5	6.1	113	9.4%	135 mg/dl	223.08	223.08	88.08	-88.08	135	WORSENED		ARDS	9	
76	1051572	77	F	10.5	3.76	16	80	11	230	2.40	398.25	137	3.31	0.23	0.14	21	14	4.4	7.3	77	10.5%	256 mg/dl	254.5	254.65	1.45	1.35	256	WORSENED		MODS,AKI	8	
77	1046836	74	F	12.4	4.6	13.4	84	10	206	1.83	36.9	139	4.41	0.41	0.13	15	10	3.6	6.1	77	16.6%	727	429.72	429.72	297.28	297.28	727	WORSENED		MODS, AKI	10	EXPIRED
																														4	
79	1032488	82	M	8.3	2.86	9.3	64	27	445	5.27	79.43	125	5.5	0.56	0.47	1367	1562	3.4	6.3	90	8.8%	432 mg/dl	205.86	205.86	226.14	226.14	432	IMPROVED			6	
80	1041939	70	M	9.7	3.53	5.3	55	35	129	0.92	10.2	125	3.9	0.82	0.13	40	15	3.3	6.2	90	6.5%	155 mg/dl	139.85	139.85	15.15	15.15	155	IMPROVED			5	
81	1007581	52	F	10.5	3.59	18.1	89	9	86	1.59	34.5	136	4.27	0.82	0.68	22	15	4.2	6.8	70	8.7%	272 mg/dl	202.9	202.99	69.01	69.01	272	IMPROVED			4	
82	977378	60	F	11.3	3.6	14.4	71	21	561	1.10	10.9	130	3.5	0.9	0.68	28	16	4.1	6.3	72	7.0%	142 mg/dl	154.2	154.2	12.2	-12.2	142	IMPROVED			6	
83	912299	46	F	9.8	4.12	6.9	59	32	303	0.84	11.2	140	4.2	0.80	0.72	20	16	4.8	6.4	78	7.2%	107 mg/dl	159.94	159.94	52.94	-52.94	107	IMPROVED			7	
84	1013541	51	F	11	4.82	18.1	62	30	513	0.78	10.2	136	4.01	0.68	0.32	42	36	4.2	6.8	88	6.5%	116 mg/dl	139.85	139.85	23.85	-23.85	116	WORSENED		SHOCK	12	
85	1045480	68	F	12.2	4.24	11.8	76	16	292	1.28	11.8	138	4.83	0.4	0.17	38	27	2.5	6	88	5.7%	95 mg/dl	116.89	116.89	21.89	-21.89	95	WORSENED			4	
86	1051610	46	F	15.8	5.29	15	94	4	240	0.81	10.3	151	4.16	0.48	0.28	22	24	4.2	7	66	8.8%	266 mg/dl	205.86	205.86	60.14	60.14	266	IMPROVED			5	
87	1030177	65	F	10.1	3.77	15.6	71	23	558	1.29	14.2	135	4.2	0.17	0.05	16	15	2.3	6	144	10.3%	209 mg/dl	248.9	248.91	39.9	-39.91	209	WORSENED		MODS,AKI	8	
88	1032020	82	F	10.9	3.77	15.8	82	3	288	0.91	11.2	127	3.4	0.56	0.28	18	11	3.9	6.6	48	8.7%	341 mg/dl	202.9	202.99	138.01	138.01	341	WORSENED			4	
89	1035357	88	M	13.4	6.4	20.3	92	3	240	1.00	11.2	138	4.2	3.57	0.84	23	11	3.4	7.7	78	6.8%	120 mg/dl	148.4	148.46	28.46	-28.46	120	IMPROVED			3	
90	953423	40	F	10.7	4.25	7.35	81	15	301	1.20	10.2	135	4.2	0.22	0.13	21	16	4.7	7.2	72	9.3%	307 mg/dl	220.21	220.21	86.79	86.79	307	IMPROVED			2	
91	1013574	65	M	13	4.4	14.2	98	11	313	1.00	14.1	136	4.2	0.71	0.01	54	15	3.4	6.8	78	8.9%	376 mg/dl	208.7	208.73	167.2	167.27	376	IMPROVED			5	
92	1024663	58	M	13.4	4.72	29.2	95	3	313	0.99	10.2	130	4.56	1.28	0.46	23	12	2.9	5.4	84	10.3%	348 mg/dl	248.9	248.91	99.09	99.09	348	WORSENED		SHOCK	5	EXPIRED
93	1011922	85	F	10.6	3.87	33	96	3	266	3.29	48.2	121	6.5	0.58	0.26	35	26	3.5	5.8	88	9.1%	464 mg/dl	223.08	214.47	240.92	249.53	464	WORSENED			3	
94	1024773	21	M	6.7	2.59	7.7	86	9	256	14.23	134.11	158	3.53	0.24	0.07	22	16	2.6	4.9	78	6.7%	176 mg/dl	145.5	145.59	30.48	30.41	176	IMPROVED			2	
95	1022162	76	M	11.1	4.12	6.9	70	20	250	1.16	12.2	131	4.2	0.39	0.21	22	16	3.9	6.9	84	10.6%	130 mg/dl	257.5	257.52	127.5	-127.52	130	IMPROVED			1	
96	1023642	30	M	16.5	5.35	2.5	86	12	70	1.91	10.8	138	4.1	3.16	1.78	502	254	2.8	4.9	49	16.5%	445 mg/dl	426.8	1287.85	18.15	842.85	445	WORSENED		MODS	6	
97	1037562	55	M	10.7	3.97	10.5	77	12	324	0.67	8.6	141	3.35	0.23	0.19	16	9	2.9	5.8	84	6.9%	161 mg/dl	151	151.33	10	9.67	161	IMPROVED			3	
98	1041058	49	F	8.5	3.48	11.3	82	8	369	1.10	10.2	138	4.2	2.13	1.61	45	21	2.7	6.1	108	8.4%	84 mg/dl	194.3	194.38	110.3	-110.38	84	IMPROVED			4	
99	1044022	50	F	7.2	3.34	12.6	77	18	317	1.20	86.2	140	3.5	0.66	0.49	10	10	2.8	6.6	86	16.8%	713 mg/dl	435.4	435.46	277.5	277.54	713	IMPROVED			5	
100	1008761	50	F	9.6	3.65	9.7	88	9	66	1.00	8.8	136	4.8	0.84	0.68	22	16	4.2	6.8	72	9.4%	714 mg/dl	223.08	223.08	204.9	490.92	714	WORSENED		ARDS	6	EXPIRED
101	1011841	67	M	9.8	3.43	6.4	60	20	189	3.34	40.2	138	4.6	0.37	0.15	19	11	4.2	7.5	70	7.0%	91 mg/dl	154.2	154.2	63.2	-63.2	91	IMPROVED			3	
102	1020812	65	M	16	5.36	10.1	62	22	237	0.77	8.8	127	4.5	0.63	0.26	20	19	4	6.9	84	11.4%	160 mg/dl	280.4	280.48	120.48	-120.48	160	IMPROVED			2	
103	1012446	51	M	9.6	3.98	24	62	30	554	1.20	8.6	136	4.8	0.32	0.1	15	15	3.6	7.6	88	7.1%	101 mg/dl	157.07	157.07	56.07	-56.07	101	IMPROVED			4	
104	5638030	60	M	13.2	4.81	13	86	9	205	0.93	8.6	141	3.8	1.05	0.63	235	92	3.7	6.3	78	6.5%	151 mg/dl	139.8	139.85	11.15	11.15	151	IMPROVED			3	
105	1047791	60	F	11.6	4.08	6.2	67	26	219	1.20	48.3	141	4.2	0.42	0.14	26	24	4.3	7	86	13.2%	420 mg/dl	332.14	332.14	87.86	87.86	420	IMPROVED			3	
106	1047475	71	M	9.2	3.34	16.1	83	5	203	2.37	84.2	142	3.8	3.36	2.87	52	32	2.4	5	84	8.0%	230 mg/dl	182.9	182.9	47.1	47.1	230	IMPROVED			2	
107	1054447	59	M	10.6	3.8	19.7	89	6	111	5.45	88.2	141	3.8	2.8	1.8	42	38	4.2	6.2	88	9.7%	224 mg/dl	231.6	231.69	7.69	-7.69	224	IMPROVED			2	
108	1131746	72	M	8.7	2.89	14.3	89	8	171	4.19	108.2	141	3.8	0.48	0.26	171	138	3.2	5.8	108	10.0%	395 mg/dl	240.3	240.3	154.7	154.7	395	WORSENED		MODS, AKI	12	
109	1129999	44	M	17.1	5.68	30.2	90	4	314	1.20	8.6	144	4.8	0.61	0.21	42	40	4.1	7.1	88	7.0%	99 mg/dl	154.2	154.2	55.2	-55.2	99	WORSENED		MODS, AKI	11	EXPIRED
110	986137	63	M	9.6	3.65	7.7	71	21	219	3.33	11.8	141	3.8	0.55	0.2	16	10	3.3	6.5	88	10.6%	249 mg/dl	257.5	257.52	8.5	-8.52	249	WORSENED			2	
111	1066783	68	M	11.6	4.61	7.7	50	33	216	1.10	8.2	133	3.7	0.61	0.24	12	12	4.2	6.3	84	10.1%	271 mg/dl	243.17	243.17	27.8	27.83	271	IMPROVED			3	
112	977197	65	F	12.1	9.25	12.9	89	7	329	1.10	8.6	145	5	0.54	0.21	22	20	3.9	6.5	82	7.9%	195 mg/dl	180.03	180.03	14.97	14.97	195	IMPROVED			3	
113	1066750	77	M	10.9	3.98	9.6	70	22	264	1.43	8.8	126	4.6	0.42	0.09	17	11	2.7	6.8	84	14.4%	520 mg/dl	366.5	366.58	153.4	153.42	520	IMPROVED			4	
114	1067073	78	M	11.2	4.36	8.2	90	8	170	1.65	22.1	141	3.8	1.44	1.18	39	31	6.9	3.4	98	8.8%	193 mg/dl	265.8	205.86	12.8	-12.86	193	IMPROVED			5	
115	1067090	64	M	14.2	5.12	10.6	57	33	220	1.10	20.2	141	4.8	0.34	0.15	15	17	4.1	6.5	98	12.5%	291 mg/dl	312.05	312.05	21.05	-21.05	291	IMPROVED			6	
116	1067377	31	M	13.8	4.2	14.6	72	16	148	0.88	8.2	142	3.8	0.98	0.42	31	33	5	8	88	12.8%	352 mg/dl	320.6	320.66	31.3	31.34	352	WORSENED			3	
117	1067461	75	F	12.9	4.69	10.8	63	28	246	1.20	20.8	142	4.2	0.42	0.16	42	36	3.4	6.8	88	6.6%	135 mg/dl	142.7	142.72	7.7	-7.72	135	WORSENED			3	
118	1067634	64	M	11.82	4.1	8.8	72	30	216	1.82	16.2	132	3.4	1.82	1.1	164	105	3.6	6.2	305	11.5%	149 mg/dl	283.3	283.35	134.3	-134.35	149	IMPROVED			4	
119	1067599	51	M	13.3	4.58	14	51	31	326	1.28	4.8	144	3.8	0.34	0.15	15	10	4.2	6.9	106	10.9%	132 mg/dl	266.13	266.13	134.13	-134.13	132	IMPROVED			4	
120	1067708	32	F	6.3	3.98	6.9	83	13	77	0.87	6.2	127	3.6	0.96	0.76	93	31	4.8	2.2	93	6.7%	143 mg/dl	145.5	145.59	2.59	-2.59	143	IMPROVED			5	
121	1061578	57	M	11.3	3.92	8.5	85	9	216	4.20	88.3	138	142	0.3	0.1	25	19	2.5	4.6	88	9.1%	367 mg/dl	214.4	214.47	152.5	152.53	367	WORSENED		ARDS	9	
122	1074387	73	M	10.6	3.66	5.2	63	24	232	0.70	8.2	139	3.69	0.51	0.25	95	27	3.8	7	88	10.0%	207 mg/dl	240.3	240.3	33.3	-33.3	207	IMPROVED			3	
123	1136900	34	M	14.4	4.12	5.4	80	12	144	1.12	7.78	134	3.8	0.9	0.7	42	32	6.4	3.8	248	9.0%	248 mg/dl	211.6	211.6	36.4	36.4	248	IMPROVED			4	
124	1132742	66	M	15.6	3.7	8.2	76	22	137	1.80	10.9	140	4.3	0.8	0.9	62	33	4.5	6.8	160	9.6%	195 mg/dl	228.8	228.82	33.82	-33.82	195	IMPROVED			4	
125	1136944	84	F	13.2	4.4	7.7	56	12	243	0.80	12.2	133	4.2	0.7	0.6	20	12	3.5	6.4	108	7.1%	250mg/dl	142.8	157.07	107.13	92.93	250	IMPROVED			3	
126	1136933	38	F	12.2	5.4	3.6	59	30	345	0.60	10.2	138	4.5	0.4	0.3	22	14	3.8	5.5	170	12.1%	350mg/dl	276.3	300.57	73.6	49.43	350	IMPROVED			2	
127	1136327	30	M	15.5	3.6	7.8	70	22	440	0.80	17.2	134	3.6	0.78	0.3	56	34	4.4	6.2	130	11.6%	266mg/dl	263	286.22	3	-20.22	266	IMPROVED			2	
128	1135856	46	M	16.3	4.4	8.9	90	22	120	1.30	40.2	136	3.9	1.1	0.9	79	69	3.2	5.6	106	8.1%	377 mg/dl	169.5	185.77	207.4	191.23	377	WORSENED		ARDS	7	EXPIRED
129	1133831	75	M	16.6	3.4	6.3	80	21	440	1.80	56.3	144	4.5	0.8	0.6	56	42	3.4	6.4	106	10.4%	312 mg/dl	230.9	251.78	81	60.22	312	WORSENED		ARDS, AKI	9	
130	1132376	72	F	14.2	2.8	15.3	95	10	12	1.70	50.6	143	3.9	0.9	0.8	42	34	3.5	4.7	120	10.0%	230 mg/dl	220.3	240.3	9.7	-10.3	230	WORSENED		MODS, AKI	8	
131	1136714	48	M	15.6	4.4	16.5	78	22	130	1.40	45.2	137	3.6	0.6	0.3	43	22	3.6	6.4	130	12.0%	240 mg/dl	237.7	297.7	3.3	-57.7	240	IMPROVED			5	
132	1136311	36	F	13.4	4.5	18.5	90	12	78	1.80	56.7	140	3.6	0.8	0.6	22	12	3.8	6.5	120	7.0%	200mg/dl	140.2	154.2	59.8	45.8	200	IMPROVED			4	