COMPARATIVE ANALYSIS OF C-REACTIVE PROTEIN /ALBUMIN RATIO AND RANSON CRITERIA FOR EVALUATING THE SEVERITY OF ACUTE PANCREATITIS.

SIDRA ANEES

(06-117222-002)

BAHRIA UNIVERSITY ISLAMABAD

PAKISTAN

COMPARATIVE ANALYSIS OF C-REACTIVE PROTEIN /ALBUMIN RATIO AND RANSON CRITERIA FOR EVALUATING THE SEVERITY OF ACUTE PANCREATITIS.

SIDRA ANEES

(06-117222-002)

A thesis submitted in fulfillment of the

Requirements for the award of the degree of

Master of Philosophy (Physiology)

DEPARTMENT OF PHYSIOLOGY

BAHRIA UNIVERSITY HEALTH SCIENCES CAMPUS

NOVEMBER 2024

APPROVAL FOR EXAMINATION

Student Name: Sidra Anees Registration No. 80425

Program of study: MPhil Physiology

Thesis Title: "**Comparative analysis of C - reactive protein /albumin ratio and Ranson criteria for evaluating the severityof acute pancreatitis.**"

It is to certify that above mentioned student thesis has been completed to my satisfaction and to my belief. Its standard is appropriate for submission and evaluation. I have also conducted a plagiarism test of this thesis using HEC prescribed software and found similarity index 16 % that is within the permissible limit set by HEC for the MPhil degree thesis. I have also found the thesis in format recognized by the Bahria University for MPhil thesis.

Principle Supervisor's Seal and Signature: _____

Prof Dr Shazia Shakoor
MBBS(DUHS), MPhil (JPMC PhD(KU)
Professor of Physiology
FU Health Sciences
achi

THESIS COMPLETION CERTIFICATE

Student Name: Sidra Anees Registration No. 80425

Program of study: MPhil Physiology

Thesis Title: "**Comparative analysis of C - reactive protein /albumin ratio and Ranson criteria for evaluating the severityof acute pancreatitis.**"

It is to certify that above mentioned student thesis has been completed to my satisfaction and to my belief. Its standard is appropriate for submission and evaluation. I have also conducted a plagiarism test of this thesis using HEC prescribed software and found similarity index 16 % that is within the permissible limit set by HEC for the MPhil degree thesis. I have also found the thesis in format recognized by the Bahria University for MPhil thesis.

Principle Co-Supervisor's Seal and Signature: _____

Date:

Name: Dr. Zahid Ali Memon

AUTHOR'S DECLARATION

I, Sidra Anees, hereby state that my MPhil thesis title "**Comparative analysis of C - reactive protein /albumin ratio and Ranson criteria for evaluating the severityof acute pancreatitis.**" is my own work and has not been submitted previously by me for taking any degree from this university, Bahria University Health Science Campus Karachi, or anywhere else in the country/world.

At any time if my statement is found to be incorrect even after my graduation, the university has the right to withdraw/cancel my MPhil degree.

Name of student: Sidra Anees

Date:

PLAGIARISM UNDERTAKING

I, solemnly declare that research work presented in the thesis titled "**Comparative analysis of C - reactive protein /albumin ratio and Ranson criteria for evaluating the severityof acute pancreatitis.**" is solely my research work with no significant contribution from any other person. Small contribution/help wherever taken has been duly acknowledged and that complete thesis has been written by me.

I understand the zero-tolerance policy of the HEC and Bahria University towards plagiarism. Therefore, I as Author of the above-mentioned thesis declare that no portion of my thesis has been plagiarized and any material used as reference is properly referred/cited.

I undertake that if I am found guilty of formal plagiarism in the above title thesis even after ward of MPhil degree, the university reserves the right to withdraw/ revoke my MPhil degree and that HEC and the University has the right to publish my name on the HEC/University website on which names of scholar are placed who submitted plagiarized thesis.

Scholar/ Author's Sign: _____

Name of Scholar: Sidra Anees

TO MY BELOVED FAMILY

MEMEBERS, TEACHERS AND ABOVE

ALL “ALLAH” WHO CREATED US

ACKNOWLEDGEMENTS

In the name of Allah, the Most Gracious, the Most Merciful, I begin with profound gratitude and humility. Alhamdulillah, all praise is due to Allah for granting me the strength, patience, and perseverance to complete this MPhil thesis. His boundless mercy and guidance have been my constant companion, illuminating my path and sustaining me through the challenges of this academic journey.

I extend my deepest gratitude to my parents, whose unwavering support, boundless love, and unending prayers have been the cornerstone of my success. Their sacrifices, encouragement, and belief in my abilities have provided the strength and motivation necessary to overcome every obstacle. Words cannot adequately express my appreciation for their enduring faith and support. To my siblings, I offer heartfelt thanks for their unwavering encouragement and companionship.Their understanding, humor, and shared moments of joy have provided a much-needed balance to the demands of academic life. Their achievements and endeavors have been a constant sourceof inspiration, pushing me to strive for excellence.

I am profoundly grateful to my supervisor Prof Dr.Shazia Shakoor, whose wisdom, guidance, andunwavering support have been instrumental in the completion of this thesis. Their insightful feedback, constructive criticism, and encouragement have significantly enriched my research, helping me to navigate the complexities of my work with confidence and clarity.

To my teachers, I extend my sincere appreciation for their dedication, knowledge, and mentorship.Their passion for teaching and commitment to my academic growth have been a guiding light throughout my studies. I am particularly indebted to those who have gone above and beyond to support and inspire me.

My heartfelt thanks also go to my seniors, whose advice, experience, and encouragement have been invaluable. Their willingness to share their knowledge and insights has greatly facilitated my academic journey, providing me with the guidance and reassurance needed to pursue my goals.

I am equally grateful to my class fellows, whose camaraderie, collaboration, and friendship have made this journey both memorable and enjoyable. Their support, discussions, and shared experiences have enriched my academic and personal life, creating a sense of community and belonging. The bonds forged during this period are cherished, and their contributions to my journey are deeply appreciated.

Sidra Anees

ABSTRACT

Acute pancreatitis is a sudden inflammation of the pancreas, which is characterized by the activation of pancreatic enzymes and auto digestion of the gland itself. It is becoming a prevalent disease in western as well as Asian population including Pakistan. High rates of gallstones and alcohol consumption are the contributing factors to this prevalence The exact prevalence of acute pancreatitis in Pakistan is not well-documented, but estimates indicate that the incidence ranges from 5 to 80 cases per 100,000 people annually, depending on the region and population studied. Acute pancreatitis can clinically be manifested as severe abdominal pain, nausea, vomiting and fever. A few of its common etiologies include gallstones, alcohol, certain medications, and metabolic disorders. It has a wide range in severity from mild, self-limiting episodes to severe, life-threatening complications. The diagnosis of acute pancreatitis is typically confirmed through clinical evaluation, laboratory tests, and imaging studies. Various scoring systems are used to analyze it severity such as Ranson's criteria, BISAP and APACHE score. In this study a new parameter CRP/Albumin ratio is assessed in comparison of the traditional Ranson's criteria. After FRC and IRB approval, 105 patients were included age group 18-60 years with a diagnosis of acute pancreatitis. Patients with co-morbidities such as Chronic Liver Disease, Chronic Kidney Disease, or chronic inflammatory were excluded from the study. Age, Gender, Ranson criteria. CRP/Albumin ratio were the parameters of the study. ELISA test was performed for this study. Data was analyzed using SPSS version 25. Quantitative variables such as age, WBC, LDH, AST, serum amylase, serum lipase, CRP, serum albumin, creatinine, serum bilirubin, urea, hematocrit, duration of symptoms, SBP, DBP, heart rate, respiratory rate, SpO2, CRP / Albumin ratio and Ranson score was reported as mean and SD or median (IQR). While qualitative variables such as gender, residence, diabetes, hypertension, smoking and severity of acute pancreatitis was reported as frequency and percentage. Chi- square test and Fisher test were also applied. P value was less than 0.05 and it's statistically significant. In our study male were greater in number

than female. More people were from rural areas than urban areas. Most of the patients were smokers, they had diabetes, hypertension and multi organ failure. Our study specified that the CRP/albumin ratio (CAR) has significant advantages over the old Ranson criteria for assessing acute pancreatitis. Unlike the Ranson criteria, which require numerous parameters and a 48-hour assessment time, the CRP/Albumin ratio is a simple, easily accessible blood test that can be evaluated at admission, offering rapid insight into the patient's inflammatory and nutritional status. This enables quicker risk categorization and decision-making. Furthermore, the CAR integrates the dynamic markers of CRP and albumin, indicating both acute inflammation and general health state, whereas the Ranson criteria require a more complex and time-consuming combination of clinical and laboratory measurements. The CRP/Albumin's simplicity and immediacy make it a more practical and potentially more effective tool for early AP control.

Keywords: CRP/albumin ratio, acute pancreatitis, Lactate dehydrogenase, Diabetes mellitus, hypertension, Blood urea nitrogen, Ranson criteria.

TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AP	Acute pancreatitis
MAP	Mild Acute pancreatitis
MSAP	Moderately severe Acute pancreatitis
SAP	Severe acute pancreatitis
CRP	C-reactive Protein
CAP	Complicated acute pancreatitis
CAR	C-reactive protein (CRP)-albumin ratio
ALB	Albumin
BISAP	Bedside Index of Severity in Acute Pancreatitis

SIRS	Systemic inflammatory response syndrome
MODS	Multiple organ dysfunction syndrome
PLR	Platelet-lymphocyte ratio
NLR	Neutrophil-lymphocyte ratio
RDW	Red-cell distribution width
IL-6	Interleukin 6
ABP	Acute biliary pancreatitis
PaO2	Partial pressure of arterial oxygen
ATP	Adenosine triphosphate
MPTP	Mitochondrial permeability transition pores
ROS	Reactive oxygen species
ATG	Autophagy-related gene
LAMP	Lysosomal associated membrane protein

PAAF	Pancreatitis-associated ascitic fluid
ELISA	Enzyme-Linked Immunosorbent Assay
RR	Respiratory rate
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
WBC	White blood cell
Hb	Haemoglobin
HCT	Haematocrit
PLT	Platelet
AMY	Amylase
LPS	Lipase
BIL	Bilirubin
AST	Aspartate aminotransferase
LDH	Lactate dehydrogenase

BUN	Blood urea nitrogen
Cr	Serum creatinine
NPV	Negative predictive value
PPV	Positive predictive value
Ca2+	Serum calcium
MCTSI	Modified CT severity index
APACHE II	Acute physiology and chronic health evaluation II
M	Median
SD	Standard deviation
ER	Endoplasmic reticulum
FFAs	Free fatty acids
UPR	Unfolded protein response

LIST OF ANNEXURES

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Acute pancreatitis is due to the immediate inflammation of pancreas and it is one of the serious diseases. There is a wide range of severity, complications, and outcomes foracute pancreatitis. There is not much information available on the epidemiology of this disease, but according to international statistics, there are 56 cases of acute pancreatitis per100,000 people annually in the UK. Over 220,000 hospital admissions for the condition each year in the US (Han, S., Ye, et al. 2019) An epidemiologic analysis that included data from the UK and Europe showed the incidence of this has been increased from all thecauses Additionally, it has been observed that the risk of acute pancreatitis rises with age(He, S. et al. 2022).

The incidence of acute pancreatitis in males is 10% to 30% higher than in females. Among patients admitted to the hospital, 20% to 30% experience severe cases. Acute pancreatitis has a severe course, with 25% of patients facing serious and potentially fatal outcomes. While the general mortality rate for acute pancreatitis is estimated at 5%, it can rise to 30% in cases of severe acute pancreatitis. The most common causes of acute pancreatitis are gallstones and alcohol consumption, which together account for nearly half of all cases in the UK. Currently, 25% of acute pancreatitis cases are not treatable with medication, leading to a focus on supportive care. Recommended approaches include early urgent cholecystectomy, targeted antibiotics, and endoscopic retrograde cholangiopancreatography (ERCP). Supportive treatments such as enteral feeding and intravenous hydration are also important, alongside an assessment of the severity of the condition to ensure that patients receive the appropriate care for their needs. A variety of diagnostic procedures and scoring systems are available for diagnosing acute pancreatitis.

It has been examined in relation to various inflammatory markers, including CRP (C-reactive protein), procalcitonin, lactate dehydrogenase, and albumin. Because CRP is more accessible and affordable than many other inflammatory indicators, it is frequently used as a marker of inflammation. The levels of C-reactive protein increase in response to infections, various cardiovascular conditions, and inflammatory diseases such as rheumatoid arthritis (Ong, Y., & Shelat, V. G., 2021). In the presence of inflammatory disorders, there is typically a minimum variation of 25% in plasma levels of this acute-phase protein, CRP.

When inflammatory disorders occur, there is at least a 25% variation in the plasma levels of the acute-phase protein CRP (Toouli et al., 2002). The serum has the highest concentrations of CRP, and certain bacterial infections can increase these levels by up to 1,000-fold (Venkatesh et al., 2020). However, once the stimulation is removed, CRP levels decline exponentially over a period of 18 to 20 hours, which corresponds to the half-life of CRP (Wang et al., 2020). Acute tissue injury resulting from trauma or advanced cancer can cause CRP plasma levels to rise from approximately 1 g/mL to over 500 g/mL within 24 to 72 hours (Mohammad et al., 2018).

Acute pancreatitis is a significant reason for hospitalization and is becoming increasingly common among children, pregnant women, and the elderly. Moderately severe acute pancreatitis, characterized by fluid and/or necrotic collections, can lead to considerable morbidity. In contrast, severe cases that involve ongoing organ failure can result in high mortality rates. The diagnosis of acute pancreatitis is made when 2 of the following 3 criteria are present: abdominal pain consistent with Acute pancreatitis (severe upper abdominal or left upper quadrant burning pain radiating to the back, nausea, and vomiting that is worse with eating), serum lipase or amylase level at least 3 times above the upper limit of normal, and characteristic features of Acute Pancreatitis on cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]

Recommended tests include measuring serum triglycerides, a complete blood count, liver and kidney function tests, as well as transabdominal ultrasound and chest imaging. Various scoring systems are present to assess the severity and depict the prognosis of acute pancreatitis such as ranson’s criteria, crp/albumin ratio, BISAP, APACHE-II. Ranson criteria uses 11 parameters which are age, white blood cell count (WBC), blood glucose, serum

aspartate transaminase (AST), serum lactate dehydrogenase (LDH), serum calcium, fall in hematocrit, arterial oxygen (PaO2), blood urea nitrogen (BUN), base deficit, and sequestration of fluids. Its limitation is that the score and severity of acute pancreatitis cannot be determined until 48 hours have passed since admission.

BISAP (Bedside Index for Severity in Acute Pancreatitis) score is a clinical tool which predicts the severity and mortality risk in patients with acute pancreatitis. It's a quick and straightforward scoring system based on five criteria that can be assessed within the first 24 hours of hospitalization. The BISAP score includes five criteria, with one point assigned for each:

BUN > 25 mg/dL (Blood Urea Nitrogen level, which indicates kidney function)

Impaired Mental Status (GCS < 15)

SIRS (Systemic Inflammatory Response Syndrome) criteria (≥2 criteria met)

Age > 60 years

Pleural Effusion detected on imaging

A BISAP score of ≥3 is associated with a higher risk of complications and mortality in acute pancreatitis. BISAP is useful in the early phase of pancreatitis but may not account for changes in the patient's condition after the first 24 hours.

APACHE II stands for Acute Physiology and Chronic Health Evaluation II and is a tool to assess the severity and prognosis of critically ill patients, especially in intensive care units (ICUs). Acute Physiology Score (APS): Based on 12 physiological variables, such as temperature, blood pressure, heart rate, respiratory rate, oxygenation, pH, sodium, potassium, creatinine, hematocrit, white blood cell count, and Glasgow Coma Scale.

C-reactive protein (CRP) to albumin ratio is an emerging biomarker used in the assessment and prognosis of acute pancreatitis. Research is focusing on three primary aspects of the condition's pathogenesis: inflammatory responses, intracellular calcium overload in the pancreas, and mitochondrial dysfunction. Immediate priorities in management should include enteral nutrition, intravenous fluid resuscitation, pain relief, and, if needed, critical care and organ support.

Other treatments that may have negative consequences include parenteral nutrition, antibiotics, and pancreatic exocrine and endocrine replacement therapy (Szatmary P, et al., 2022). Acute pancreatitis (AP) is characterized by inflammation of the pancreas, resulting in intense stomach pain and elevated serum levels of pancreatin. Complications from AP can include pancreatic autodigestion, edema, bleeding, necrosis, and even failure of distant organs. Approximately 20% of patients with AP progress to severe acute pancreatitis (SAP) or moderate-to-severe acute pancreatitis (MSAP), conditions known for their rapid progression, poor prognosis, and a high mortality rate of 30%. In contrast, most cases of AP are mild and have a favorable prognosis. However, it is essential to recognize the seriousness and poor outlook associated with AP, particularly because SAP can lead to extended hospital stays and significant financial burdens. Early assessment of prognostic factors and prompt recognition of the disease's severity can facilitate timely treatment, ultimately improving prognosis and survival rates.

Acute pancreatitis (AP) is one of the most common gastrointestinal conditions, characterized by a rapidly developing inflammation of the pancreas. Its severity and clinical presentation can vary widely. Globally, the incidence of AP ranges from 4.9 to 73.4 cases per 100,000 people. While most patients experience a mild form of the condition and have a relatively good prognosis, 15% to 20% of cases progress to severe acute pancreatitis (SAP), which is associated with higher rates of morbidity and mortality.

Patients with SAP typically face two critical periods of increased mortality. The first peak occurs within the first two weeks due to the release of various cytokines, leading to a systemic inflammatory response syndrome (SIRS) that can result in multiple organ dysfunction syndrome (MODS) and early death. The second peak occurs about two weeks later, when complications such as infections, peripancreatic necrosis, and secondary MODS contribute to roughly half of the fatalities.

Early identification of patients at risk for developing SAP is crucial for timely treatment and optimal care. Several scoring systems have been developed and validated to assess the severity of acute pancreatitis. The most commonly used in clinical practice are the Bedside Index for Severity in Acute Pancreatitis (BISAP) score, Ranson criteria, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) system.

While the APACHE II scoring system is comprehensive, using it can be challenging, as it requires baseline values of 12 physiological parameters. The Ranson criteria can only be assessed after 48 hours of hospitalization. Although the BISAP score is comparable to the APACHE II in predicting severity, organ failure, and mortality in AP, it is noted to have lower sensitivity for mortality and SAP.

Unfortunately, due to the numerous characteristics involved, limited sensitivity, and the complexities associated with rapid evaluation, there are currently no widely accepted standards. Therefore, there is a need for new and simpler predictors to support scoring systems.

The development of quick biomarkers for accurate prognosis prediction in acute pancreatitis (AP) has garnered significant interest. Several common, easily accessible, and cost-effective laboratory tests, such as the platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and red cell distribution width (RDW), serve as the foundation for various direct or combined indicators of systemic inflammation.

Research has shown a strong correlation between elevated NLR values within the first 48 hours of admission and severe acute pancreatitis (SAP). NLR serves as an independent negative prognostic factor in AP. In cases of AP caused by hypertriglyceridemia, NLR is a low-cost and accessible test that shows promise in predicting disease severity. Additionally, previous studies have indicated that both NLR and PLR can predict the severity of gallstone-related AP. Red cell distribution width (RDW), which reflects the diversity in circulating erythrocyte size, has also been positively correlated with the severity of AP, suggesting it could be a valuable predictor. However, prior research regarding the efficacy of these indicators in forecasting the prognosis of individuals with AP has produced conflicting results (Zhou et al., 2019).

Acute pancreatitis (AP) is an inflammatory condition that can affect multiple organs and presents with a wide range of clinical symptoms and severity levels. While 65–85% of AP cases are self-limiting and do not require specific treatment or result in lasting effects,

some patients may experience severe episodes that can lead to systemic inflammatory response syndrome (SIRS), which has a high morbidity and mortality rate.

To prevent complications such as pancreatic necrosis and organ failure, it is crucial to use risk stratification to assess the severity of the disease early on, particularly on the day of admission. This approach allows for timely interventions in patients identified as high-risk.

Several multi-factorial scoring systems and imaging tools have been developed to help in the early identification of severe AP. These include the C-reactive protein (CRP) and procalcitonin biochemical markers, the Bedside Index for Severity in AP (BISAP), the modified Marshall score, the Sequential Organ Failure Assessment (SOFA) score, and the Computed Tomography Severity Index (CTSI).

In addition to assessing severity, there is increasing interest in the use of specific laboratory indicators and rapid biomarkers for accurately predicting the prognosis of AP.The inflammatory state and severity of disease in patients with AP have also been suggested to be shown by a number of direct or combined markers of systemic inflammation as easily accessible laboratory test, sush as platelet- lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), mean platelet volume (MPV), and CRP (Duru H.2023).

The cause of acute pancreatitis (AP) is the aberrant activation of pancreatic enzymes, which leads to the auto-digestion of the pancreas itself. This process triggers both systemic and localized inflammatory responses. Pro-inflammatory cytokines and anti-inflammatory mediators are released, increasing permeability and causing injury to the pancreatic microcirculation. About 80–90% of patients experience a self-limiting cascade of inflammation. However, a small percentage of patients experience a significant release of inflammatory mediators into the bloodstream, which can lead to multiple organ dysfunction syndrome and, in rare cases, even death.

The diagnosis of AP is confirmed through patient history, clinical symptoms, and elevated levels of pancreatic enzymes in plasma. Specifically, an increase in amylase or lipase that is more than three times the normal level confirms the diagnosis. Contrast-enhanced computed tomography (CECT) is the best imaging modality for assessing the

pancreas, especially when investigating complications such as pancreatic necrosis, pancreatic pseudocysts, pancreatic-pleural fistulas, and vascular complications. Some of these complications may require surgical intervention.

In cases of infected pancreatic necrosis, image-guided aspiration or necrosectomy may be employed. If percutaneous catheter drainage and antibiotics fail to treat pancreatic abscesses, surgical debridement and drainage may become necessary. Rarely, pseudocysts require drainage, which can be performed using laparoscopic and endoscopic techniques (Chauhan, R. et al., 2022).

Acute pancreatitis (AP) is a severe condition characterized by a sudden onset of intense abdominal pain. It poses significant local and systemic complications, leading to high rates of morbidity and mortality. AP is not only a major cause of gastrointestinal hospitalizations but also entails substantial financial burdens. Recent studies indicate that the incidence of AP is rising, likely due to several risk factors, including obesity and gallstone disease. Patients suffering from the severe form of this condition face a higher risk of death, with mortality rates ranging from 36% to 50%. The general mortality rate of acute pancreatitis ranges from 3% to 10%. Its etiology is complex and uncertain, with the two most common causes being alcohol consumption and gallstones (Samanta J., et al., 2019).

The causes of acute pancreatitis are diverse and are characterized by inflammation of the pancreatic tissue. Key factors contributing to this condition include alcohol consumption and gallstones. The Bedside Index of Severity in Acute Pancreatitis (BISAP) score has become one of the most widely used systems for assessing severity. Various characteristics and scoring systems can be utilized to evaluate acute pancreatitis. Numerous studies have compared different scoring systems, including BISAP and the Ranson score, to determine the severity of the illness. One such study found that the specificity values were 69.2% for the BISAP score and 97.4% for the Ranson score (Karabuga, B, et al. 2022).

Acute biliary pancreatitis (ABP) is a common emergency in the gastroenterology department, primarily caused by several factors: self-digestion of pancreatic tissue, overflow of pancreatic fluid, a weak pancreatic mucosal barrier, and blockage of the pancreatic duct due to gallstones and inflammation.

The main clinical symptoms of ABP include jaundice, abdominal distension, and abdominal pain (Pirouz, A., et al., 2021).

Acute pancreatitis has a variety of global causes. Currently, the most commonly noted reasons in most research are gallstones (40–70%) and alcohol intake (25–35%). Recent studies indicate that the prevalence of acute pancreatitis is rising across Asia (Zhou et al., 2024).

In fact, the causes of acute pancreatitis can be easily identified in 75–85% of cases. In affluent nations, the most prevalent causes are alcohol consumption (36%) and stones obstructing the common bile duct (38%) (Spanier et al., 2008).

Gallstone migration obstructs the duct, which results in pancreatitis triggered by gallstones. The pancreatic duct, the bile duct, or both may be specifically affected. Pancreatitis is encouraged by duct obstruction because it raises duct pressure and causes the uncontrollably high activation of digesting enzymes (Diehl, A. K., et.al 1997).

Pancreatitis may arise with endoscopic retrograde cholangiopancreatography(ERCP). 35%–70% of patients experience asymptomatic hyperamylasaemia following the operation. When ERCP used to address dysfunction of the Oddi sphincter rather than to remove gallstones from the bile duct, there is a greater chance that acute pancreatitis would result. A few other risk factors for post-ERCP pancreatitis are female sex, young age, the number of cannulation attempts made on the papilla, and inadequate pancreatic duct emptying following opacification. In high-risk individuals, implantation of a temporary pancreatic stent may prevent post-ERCP pancreatitis (Cheng, C. L., et.al 2006).

Another uncommon and erratic cause of acute pancreatitis is hypercalcemia. Given individuals with persistent hypercalcemia have a low prevalence of pancreatitis, more variables are most likely required to trigger pancreatitis. Acute pancreatitis is not often drug-induced. There have been documented cases of drug-induced pancreatitis (Lankisch, P, et.al 1995).

While numerous infectious factors are associated with acute pancreatitis, no specific microbe has been identified within the pancreas. However, there is a noted connection between parasite infestations, as well as bacterial and viral infections, and acute pancreatitis (Parenti DM et al., 1996).

Some researchers have hypothesized that certain genetic abnormalities may be linked to recurrent acute pancreatitis that occurs without an obvious cause; however, there is currently no solid evidence to support this theory (Dzieniszewski, 2004).

Acute pancreatitis can also be caused by an intraductal papillary mucinous tumor. This type of tumor can obstruct the main pancreatic duct and its side branches, leading to an accumulation of mucus. As a result, the blockage can cause pancreatic hyperstimulation and increased pressure within the pancreatic duct. Therefore, the same mechanisms that lead to acute biliary pancreatitis can also trigger acute pancreatitis in cases involving these tumors (Wang et al., 2009).

Organ failure is defined as a significant functional impairment of an organ system that is essential for sustaining life. The severity of organ malfunction can be quantified using specific metrics that reflect an organ's primary function. For example, serum creatinine is used to assess renal function, while the partial pressure of arterial oxygen (PaO2) measures pulmonary function.

In the context of acute pancreatitis (AP), the respiratory, renal, and cardiovascular systems are considered the most critical, as they are the most frequently affected. While the Sequential Organ Failure Assessment (SOFA) score is commonly used in cases of sepsis, the modified Marshall grading system is preferred for assessing the severity of organ dysfunction in AP.

Severe acute pancreatitis (SAP) is characterized by any organ dysfunction of grade 2 or higher that persists for more than 48 hours. In cases of moderate acute pancreatitis, transient organ failure that lasts less than 48 hours is deemed necessary (Hamada, S., et al., 2014).

The percentage of patients with acute pancreatitis who develop organ failure varies across different studies and is largely influenced by the context in which the research is conducted. Research conducted in tertiary care hospitals has shown a significantly higher frequency of organ failure, while data from population-based cohort studies indicate a smaller proportion of individuals experiencing this complication.

In population studies, the percentage of patients developing organ failure (severe acute pancreatitis) ranges from 8% to 20%. However, in large cohorts from tertiary care facilities, the percentage can be as high as 40% (Garg, P. K., et al., 2019). The severity of acute pancreatitis also shows considerable variation; some individuals may experience moderate, self-limited episodes, while others may go through severe, debilitating, and potentially fatal attacks. The exact etiological factors that trigger these episodes remain unclear.

Acinar cells are believed to be the starting point for the events that lead to acute pancreatitis. In the early stages of this condition, damage to the acinar cells initiates a local inflammatory response. If this reaction is severe, it can develop into a systemic inflammatory response syndrome (SIRS). An overactive SIRS can result in multiple organ dysfunction syndrome (MODS) and damage to distant organs. These complications are major contributors to the morbidity and mortality associated with acute pancreatitis in cases of MODS (Bhatia, M., et al., 2005).

SAP progresses through two stages. The first stage, which lasts one to two weeks, involves a pro-inflammatory response that can lead to systemic inflammatory response syndrome (SIRS). This response is a sterile reaction, meaning that sepsis or infection is unlikely to occur. If SIRS becomes severe, pro-inflammatory mediators can cause early multiple organ failure, affecting the respiratory, cardiovascular, renal, and hepatic systems.

Pancreatic necrosis often occurs within the first four days after the onset of symptoms. However, if the disease progresses over the first two weeks, the extent of pancreatic necrosis can vary and may increase. Most patients experiencing severe early organ failure will have visible pancreatic necrosis on a computed tomography (CT) scan.

It's important to note that systemic inflammatory response syndrome (SIRS) can occur in the early stages of severe pancreatitis even in the absence of significant pancreatic necrosis.

Fluid collections around the pancreas that develop during this time are referred to as acute fluid collections if they persist for less than four weeks. After four weeks, these are classified as pancreatic pseudocysts (PPCs) (Buter, A., et al., 2002).

The most common causes of acute pancreatitis include alcohol consumption, hypercalcemia, gallstones, hypertriglyceridemia, and idiopathic factors. It is crucial to determine the severity of the condition within the first 24 to 48 hours, as the patient's prognosis largely depends on this initial assessment. An early diagnosis can reduce mortality rates to as low as 5%, significantly improving outcomes. Conversely, a delayed or incorrect diagnosis can increase the risk of death to as much as 30%.

Acute pancreatitis can be diagnosed through various methods, including imaging scans, blood tests, and clinical evaluations. Blood tests can measure levels of pancreatic enzymes and other markers of inflammation. Imaging techniques, such as magnetic resonance imaging and computed tomography (CT) scans, can visualize the pancreas and identify any abnormalities. Additionally, clinical evaluations help assess the severity and prognosis of the disease.

Timely and accurate identification of acute pancreatitis is essential for effective treatment and management of this potentially fatal condition. It is worth noting that the use of the C-reactive protein (CAR) may facilitate the quick and precise determination of the severity of acute pancreatitis, especially in low-income countries. This could lead to better patient outcomes and a reduction in surgical mortality rates (Ghaffar et al., 2024).

There are reports indicating yearly incidence rates of acute pancreatitis (AP) ranging from 13 to 45 cases per 100,000 individuals. The updated Atlanta classification system categorizes AP into three degrees of severity: moderately severe acute pancreatitis (MSAP), severe acute pancreatitis (SAP), and mild acute pancreatitis (MAP). The classification is based on the presence of systemic or local complications. When there are no systemic or local issues, acute pancreatitis is classified as mild (MAP).

MAP includes patients with acute fluid collections, necrotic collections, pseudocyst formation, or walled-off necrosis, as well as those who experience transient organ failure lasting less than 48 hours. In contrast, individuals classified as SAP have experienced organ failure for more than 48 hours. Due to the significant morbidity and mortality associated with these conditions, the main focus in managing AP is preventing the progression from mild to more severe forms.

Occasionally, SAP and MSAP are grouped together as complicated acute pancreatitis (CAP), which carries its own implications for treatment. Alarmingly, patients with CAP have a documented mortality rate of 30% to 40%. Given this high risk, there has been considerable interest in developing and validating multifactorial scoring systems and single predictors to identify patients more likely to develop CAP.

While scoring systems like Ranson, Glasgow, and APACHE II have been widely used in the past, they each have their limitations. This has led to an interest in identifying individual biochemical markers as predictors for CAP. One such predictor is C-reactive protein (CRP) (Ahmad, R., et al., 2021).

Acute pancreatitis (AP) is a severe condition characterized by significant local and systemic problems, leading to high morbidity and mortality rates. It typically presents with sudden, intense abdominal pain. AP poses a considerable financial burden and is the most common gastrointestinal reason for hospitalization. Numerous studies have shown an increasing incidence of AP, likely due to a combination of risk factors such as obesity and gallstone disease. Patients with severe acute pancreatitis face a higher risk of death, with mortality rates ranging from 36% to 50%. In general, the mortality rate for acute pancreatitis is between 3% and 10%.

The causes of this condition are complex and not fully understood, but the two most common triggers are alcohol consumption and gallstones (Samanta J et al., 2019).

Enzyme activation plays a crucial role in local pancreatic injury, leading to systemic involvement and peripancreatic tissue damage in acute pancreatitis (AP), an inflammatory condition with a complex pathophysiology. The incidence of AP ranges from 4.6 to 100 cases per 100,000 people in Europe. The primary causes of AP are alcohol abuse and gallstones, with gallstones being particularly prevalent in Mediterranean countries and southern nations such as Portugal. The ratio of cases due to gallstones compared to those caused by alcohol is often greater than 5:1 and can sometimes reach as high as 10:1.

The mortality rate from AP typically ranges from 2% to 5%, but in severe cases, it can rise to between 30% and 50%. Numerous studies emphasize the importance of identifying patients at risk of complications or mortality within the first 48 hours after symptoms onset. It is essential to develop an appropriate strategy that includes fluid resuscitation, pain management, and nutritional support during this critical period.

As a result, close monitoring or immediate admission to an intensive care unit is vital, along with identifying patients who may need to be transferred to specialized facilities (Silva-Vaz et al., 2020).

Currently, several metrics are used to assess the prognosis of acute pancreatitis (AP), including the Bedside Index of Severity in Acute Pancreatitis (BISAP), the modified computed tomography severity index (MCTSI), and Ranson scores. However, the complexity of these multiple criteria and algorithms limits their practical application in clinical settings. Therefore, there is an urgent need for a simpler, faster, and more real-time method to predict disease prognosis. Research has shown that serum markers such as albumin (ALB) and C-reactive protein (CRP) are associated with better outcomes in AP (Zhao Y, 2023).

In 1974, severity scoring methods were developed to predict the severity of acute pancreatitis (AP) in adults (Ridker PM et al., 2003). The Glasgow-Imrie Criteria for assessing the severity of AP is also known as the modified Glasgow Pancreas Score (GPS) (Ciubotaru I et al., 2005).

The scoring system, which involves monitoring biochemical markers within 48 hours of admission, is still commonly used today and has proven effective in both gallstone and non-gallstone acute pancreatitis cases (Mounzer, R., et al. 2012).

Ranson et al. began assessing the severity of this illness in 1974. Since then, several multifactorial scoring systems using standard clinical and biochemical criteria have been developed to forecast severity (Ranson, J. H., et al. 1976).

The most widely used scoring system for assessing acute pancreatitis is the Ranson criteria. This system takes into account the patient's age at admission, alongside various biochemical measurements such as hematocrit, BUN, glucose, LDH, AST, and WBC count. Additionally, it considers results for calcium levels, PaO2, base deficit, and fluid deficit at 48 hours.

While the Ranson criteria and its modified version, the Imrie (Glasgow) score, can be useful in the early stages of acute pancreatitis, their predictive power diminishes after 48 hours. Another limitation of these criteria is that they are not consistently reproducible while the illness is active (Basit, H., 2022).

Although classification systems such as Ranson's criteria are still widely employed, organ failures caused by acute pancreatitis (AP), certain laboratory values, and patient anthropometric factors have been demonstrated to influence disease prognosis. These Indicators are increasingly being used to determine the prognosis of illness (İspiroğlu, M. 2020).

In SAP, laboratory results typically show metabolic abnormalities and organ failure. Serum lipase and amylase levels more than three times the upper normal range are thought to be indicative of pancreatitis, which is used to diagnose AP. Due to the pancreatic acinar cells' leaking into the interstitial space and subsequent absorption into the circulation, several enzymes are increased in AP (Vissers, et.al 1999).

Endoscopic ultrasonography (EUS) is a useful diagnostic tool for individuals with acute pancreatitis (AP). It can help identify those who require therapeutic endoscopic retrograde cholangiopancreatography (ERCP), effectively reducing the potential risks associated with diagnostic ERCP when assessing choledocholithiasis. However, there are some limitations to EUS, including the risk of adverse effects in critically ill patients, the inconsistent availability of qualified endosonographers with both endoscopic and imaging expertise, and the tendency to overestimate the necrotic debris content in pancreatic fluid collections (Zerem E., 2014).

Magnetic resonance imaging (MRI) serves as an effective alternative to computed tomography (CT) for identifying parenchymal necrosis. Additionally, in the evaluation of the pancreatic duct (PD), magnetic resonance cholangiopancreatography (MRCP) can be a substitute for endoscopic retrograde cholangiopancreatography (ERCP) (Morgan D. E., 2008).

MRI plays a crucial role in guiding further management due to its ability to accurately characterize pancreatic and peripancreatic fluid collections or abscesses, indicating whether they are partially or fully fluid. It is non-invasive and does not involve radiation, and MRCP can effectively detect bile duct stones. Additionally, MRI can reveal the presence of disconnected pancreatic ducts.

However, there are some drawbacks to MRI and MRCP. These include extended acquisition times, difficulties in applying the technique to critically ill patients, the risk of gadolinium toxicity in individuals with renal insufficiency, and incompatibility with pacemakers and other metal implants (Wada, K. et al., 2010).

The National Institutes of Health defines a biomarker as "a characteristic that can be measured and assessed objectively as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention." (Strimbu, k, et.al 2010).

The three main functions of biomarkers are prognosis, therapeutic individualization, and diagnosis. It is important to identify the severity of AP as soon as possible, on the day of admission especially, since this is when therapies to prevent organ failure and pancreatic necrosis are thought to be best defined. However, none of the biochemical indicators or clinical scoring systems in use today are reliably accurate, have a broad applicability, or play a decisive role. As a result, it is still very difficult to detect severe AP in its early stages. (Kaplan, M., et.al 2017).

Biomarkers that can accurately and promptly predict the severity of acute pancreatitis (AP) are essential. Clinicians would benefit from markers that assist in the early diagnosis of high-risk patients. Although several scoring systems and inflammation markers have been developed for this purpose, including procalcitonin, interleukin-6, the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), the red blood cell distribution width to platelet ratio, as well as the PANC3, Ranson, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and the Atlanta criteria, there is still a need for more effective tools (Park, J. et al., 2015).

With the exception of parenteral intravenous fluids, analgesics, and supportive care, 65% to 85% of cases of acute pancreatitis (AP) are self-limited and do not require special treatment. However, the remaining cases may experience severe episodes, leading to increased rates of morbidity and mortality. To reduce the risk of death, it is important to identify this subgroup of patients early in the course of the illness and treat them aggressively. Correctly identifying those with mild conditions is crucial, as it helps prevent unnecessary overtreatment, which can have costly consequences (Leppäniemi, A., et al., 2019).

Since AP is an inflammatory pancreatic disease that can affect nearby tissue and distant organ systems, biomarkers have remained crucial (Bedel, C, et.al 2021).

C-reactive protein (CRP) is considered one of the most useful molecular markers available. It is widely accessible and accurate, with peak levels typically occurring no sooner than 72 hours after the onset of symptoms. Many experts and guidelines suggest that a CRP level of ≥150 mg/l at 48 hours after the onset of symptoms indicates a poor prognosis (Pavlidis et al., 2023).

Although C-reactive protein (CRP) is a straightforward biochemical marker that is readily available in clinical settings, numerous studies have indicated that its clinical relevance in the early stages of acute pancreatitis (AP) is limited. CRP may not effectively identify severe cases of AP at an early stage (Cardoso et al., 2013). Furthermore, new guidelines from the American Pancreatic Association and the International Association of Pancreatology advise against routinely triaging patients to an intensive care unit based solely on one marker, such as CRP, hematocrit, blood urea nitrogen, or procalcitonin (Almeida et al., 2015).

The most valuable single biochemical measure remains C-reactive protein (CRP). It is accurate and generally accessible, although it increases slowly, typically peaking no sooner than 72 hours after the onset of symptoms. A high CRP concentration of greater than 150 mg/L serves as a significant prognostic indicator, showing 85% sensitivity within the first 72 hours of symptom onset. This suggests that acute pancreatitis has a complex progression. Elevated CRP levels can be a sensitive indicator of severe acute pancreatitis (Khanna, A. K., et al., 2013).

Interleukin 6 (IL-6), Tumor Necrosis Factor Alpha (TNFα), and Interleukin 1 Beta (IL-1β) are inflammatory mediators that stimulate the liver to produce a pentraxin known as C-reactive protein (CRP). This acute-phase protein is elevated in the serum as a result of infections, inflammatory diseases, trauma, and cancer. Previous studies have confirmed that CRP is a reliable indicator of outcomes in critically ill patients.

Serum albumin is another acute-phase protein that is utilized in the critical care context as a prognostic indicator. Inflammatory signals cause this protein to be downregulated, and low levels of it have been linked to both an elevated risk of short-term death and a severe inflammatory response (Piñerúa-Gonsálvez, J. et.al 2023).

C-reactive protein (CRP) is valuable for assessing the severity of infectious and inflammatory diseases. However, the exact CRP cut-off values for these conditions are not yet established. Research indicates that CRP levels exceeding 210 mg/L in acute pancreatitis can differentiate between mild and severe cases,

achieving 83% sensitivity and 85% specificity. Additionally, albumin levels, which are abundant in plasma, may decrease in cases of sepsis and other serious conditions. This reduction can occur due to diminished production, increased degradation, and heightened vascular permeability, resulting in the leakage of this protein. The lower albumin levels are associated with a higher risk of organ failure and mortality in acute pancreatitis (Tarar, M. Y., et al., 2022).

Numerous distinct biochemical values have been recognized as putative indicators of the intensity of a pancreatitis episode and are factored into several scoring schemes. Leucocyte count is frequently included in scoring schemes including APACHE II, MGC, and Ranson criteria. Neutrophil-lymphocyte ratio (NLR) applications in several critical and cardiac diseases have been documented (Jones, er.al 2017).

Low serum albumin levels and high C-reactive protein (CRP) levels are specifically associated with severe disease activity. These markers indicate a higher risk and reduced sensitivity to corticosteroid and anti-tumor necrosis factor-alpha (anti-TNF) therapies. Recent research has shown that the CRP to albumin ratio (CAR) is a predictive marker for various cancer types, sepsis, and acute pancreatitis. Elevated CAR values are associated with poor prognosis, a higher inflammatory burden, and increased mortality (Sayar et al., 2019).

The typical levels of the CRP/albumin ratio are still debated, but it has recently been identified as a new predictive score related to mortality and inflammation levels. Most earlier studies that sought to link the CRP/albumin ratio to acute pancreatitis severity and mortality produced encouraging findings. However, there is currently no meta-analysis that compiles the results of all these investigations (Mariadi, I. K., et al., 2023).

In Figure 1.1, there is a notable shift from a pro-inflammatory response to an anti-inflammatory one that occurs during the first one to two weeks. During this "second or late phase," the patient becomes susceptible to the translocation of intestinal flora due to the failure of the intestinal barrier. This issue can lead to the development of a secondary infection in the necrotic tissue and fluid collections surrounding the pancreas.

There are two peaks in mortality associated with this condition. Early mortality is primarily caused by severe systemic inflammatory from the accumulation of peri-pancreatic fluid and infections related to pancreatic necrosis. (Besselink M.G et al 2009)

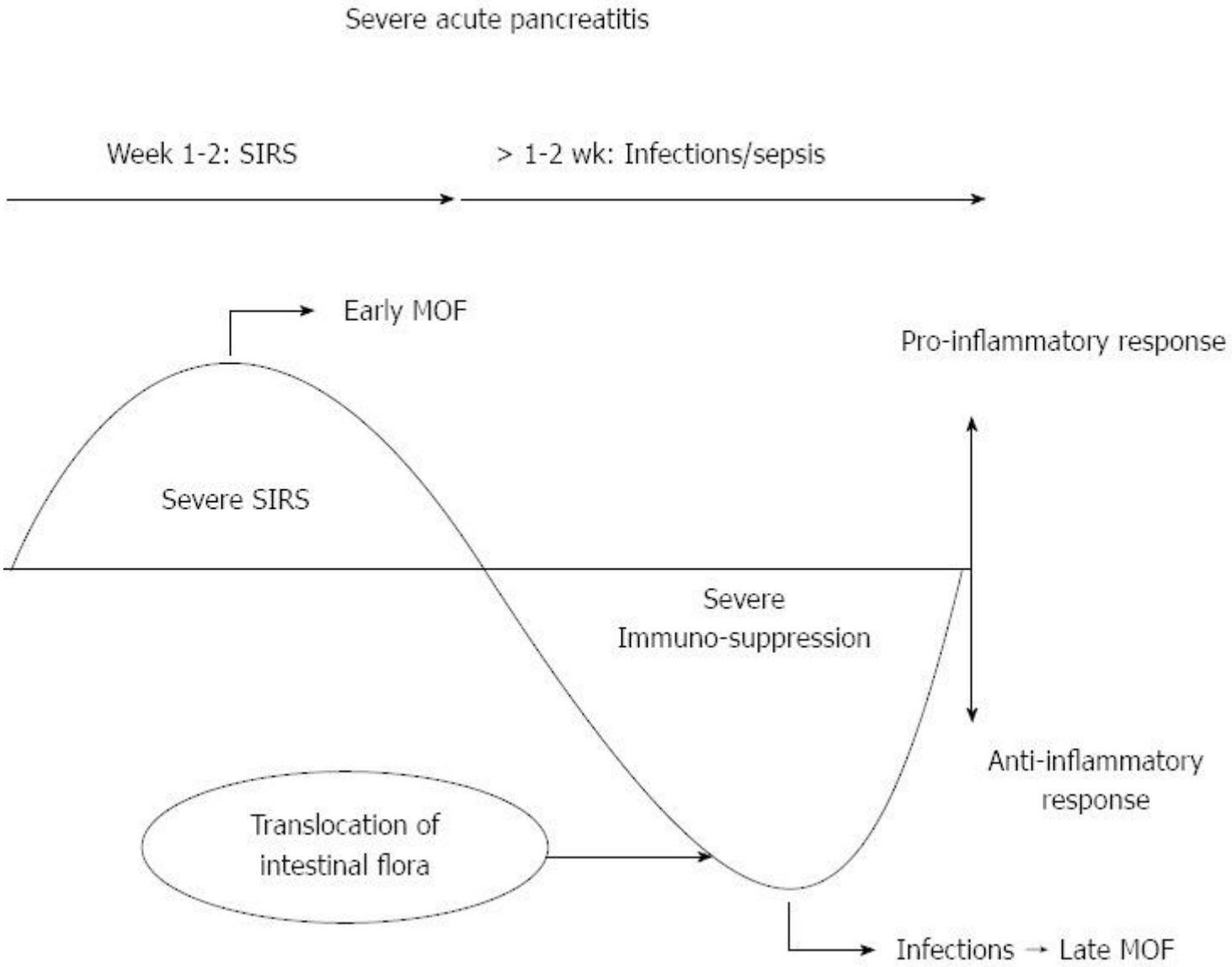


Figure 1.1 shift from a pro-inflammatory to an anti-inflammatory response (Besselink, M. G., et.al 2009)

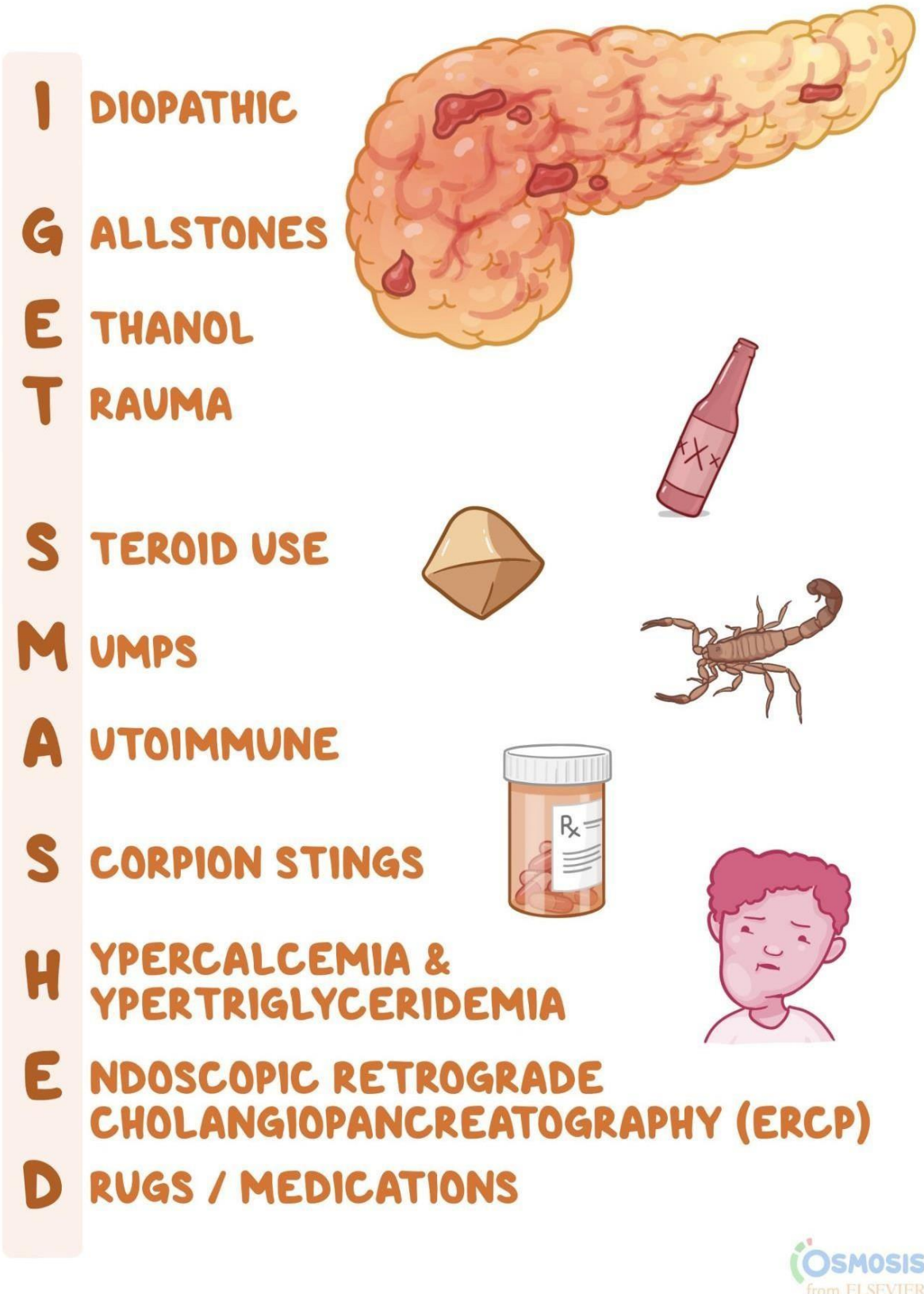


Figure 1.2 Causes of Acute pancreatitis (Georgina Tiarks, 2024)

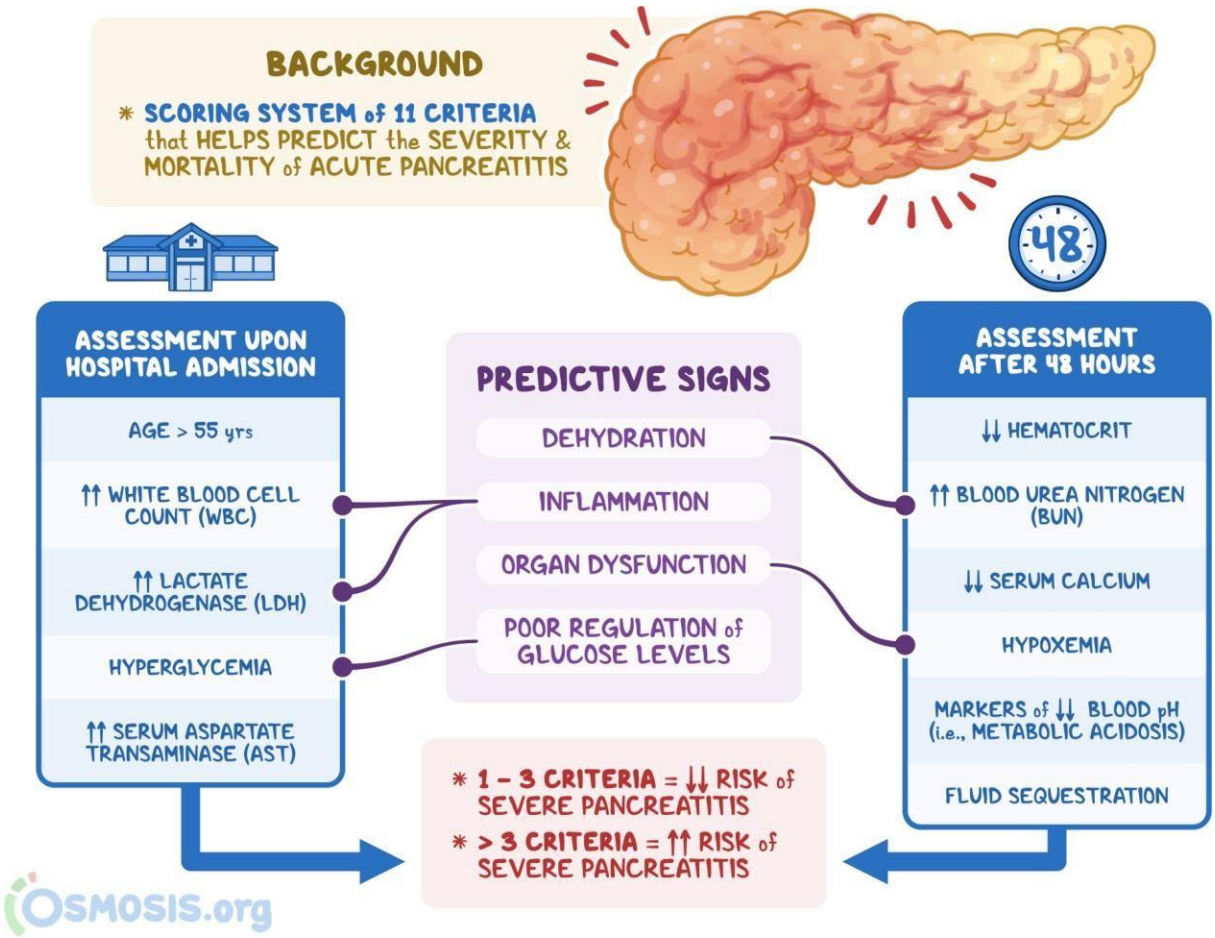


Figure 1.3 Ranson Criteria Scoring System (Anna Hernández, MD, 2021)

RATIONALE OF STUDY /RESEARCH GAP

This study has been conducted to compare the usefulness of detecting severity of acute pancreatitis by measuring CRP/Albumin ratio, as compared to Ranson's criteria.

1.2.1 Theoretical Gap

There is limited research on the utility of the albumin-to-CRP ratio in predicting the severity of acute pancreatitis. By addressing this theoretical gap through a comprehensive examination, we can determine the clinical significance and reliability of the CRP/albumin ratio as a predictor of acute pancreatitis severity. Clinicians can benefit from understanding how the CRP/albumin ratio relates to Ranson's criteria and its ability to predict clinical outcomes, such as complications and hospital length of stay. This knowledge can aid in risk stratification and inform treatment decisions.

1.2.2 Contextual Gap / Analysis

The CRP/albumin ratio should be assessed in relation to other established markers of acute pancreatitis severity. To bridge this contextual gap, measures such as the APACHE II score and the Bedside Index for Severity in Acute Pancreatitis (BISAP) are utilized. Understanding the effectiveness of the CRP/albumin ratio in predicting the severity of the condition requires evaluating its performance alongside these recognized indicators.

1.2.3 Methodological gap/Analysis

The CRP/albumin ratio in acute pancreatitis has several methodological flaws. To achieve a more reliable and precise prediction of severity, it is essential to use standardized techniques, make direct comparisons with Ranson's criteria, and consider temporal and dynamic variations. To address these gaps and ensure the accuracy and applicability of the albumin/CRP ratio in predicting the severity of acute pancreatitis, well-

designed prospective trials are necessary. These trials should employ standardized methods, include direct comparisons, and evaluate clinical outcomes.

1.3 PROBLEM STATEMENT

The main issue is evaluating the effectiveness of albumin and CRP in predicting the severity of acute pancreatitis compared to Ranson's criteria. The lack of consensus among current methods limits clinical decision-making and patient care. Studies that compare these two approaches should focus on ensuring consistency, comparability, and severity assessment. To determine their clinical usefulness across different patient populations, more research is needed.

1.4 RESEARCH QUESTION/ HYPOTHESIS OF THE STUDY

A) Null Hypothesis (H0): There is no difference in efficacy of the CRP/Albumin ratio and Ranson Criteria for assessing the severity of acute pancreatitis.

B) Alternative Hypothesis (HA): There is a difference in efficacy of the CRP/Albumin ratioand Ranson Criteria for assessing the severity of acute pancreatitis

1.5 RESEARCH OBJECTIVE

To determine the efficacy of the CRP/Albumin ratio in comparison to Ranson Criteriafor assessing the severity of acute pancreatitis.

1.6 SIGNIFICANCE OF THE STUDY

The CRP/albumin ratio has the potential to serve as a more accurate and timely predictor of disease severity. While the Ranson criteria are well-established and comprehensive, they require a longer observation period, which can delay necessary early interventions. In contrast, the CRP/albumin ratio is a simple and inexpensive biomarker that can be measured quickly. It reflects both the inflammatory response and nutritional status of the patient. Therefore, the CRP/albumin ratio is more effective for assessing the severity of acute pancreatitis in its early stages, enabling prompt and targeted treatment.

CHAPTER 2

LITERATURE REVIEW

The biliary etiology was the focus of much of the early research on acute pancreatitis. However, studies have shown that alcohol consumption is a significant etiological factor, especially in males. There are regional differences in the etiological components; most current European studies suggest that biliary etiology is predominant, while Asian studies indicate that alcohol is the more critical factor.

The gold standard for diagnosing acute pancreatitis is the evaluation of serological lipase and amylase levels. Although various comprehensive and complex scoring systems have been developed, Ranson's scoring method remains the most straightforward and widely used.

Currently, the best approach to treating acute pancreatitis is considered to be conservative management. Surgery is typically only necessary for cases involving biliary pancreatitis, infected pancreatic necrosis, or abscess formation. Overall mortality rates have decreased since the introduction of effective conservative treatments and early diagnostic techniques.

The recurrence and progression of acute pancreatitis are well-documented, with several potential complications such as ascites, pseudocysts, necrosis, abscesses, venous thrombosis, and aneurysms possibly requiring surgical intervention (Greenberg, 2015).

Acute pancreatitis is a significant cause of severe abdominal pain. The clinical manifestations of this condition have been well-documented. Most individuals who recover experience no lasting effects. However, some patients may face serious complications, such as pancreatic ascites and necrosis, which are associated with higher rates of morbidity and mortality.

Although the majority of cases are benign and resolve on their own, a small percentage of patients may experience a rapidly progressing inflammatory process that requires extended hospitalization, resulting in considerable morbidity and potential fatality rates of up to 50%.

The underlying mechanism involves the auto-digestion of the pancreas due to the activation of the zymogens produced by the pancreas, which triggers a strong inflammatory response mediated by the immune system. This inflammatory response can be localized to the pancreas or develop into a systemic inflammatory response syndrome (SIRS) (Lee, 2019). The majority of subsequent damage is attributed to the immune response, which is independent of the initial trigger.

To manage severe pancreatitis, which carries a high risk of morbidity and mortality, a comprehensive understanding of the pathogenic pathways is essential. However, there are currently no reliable methods for predicting which specific cases will lead to a severe form of acute pancreatitis. Various imaging, biochemical, and clinical criteria have been proposed as indicators of the severity of acute pancreatitis. Notably, pancreatic enzymes such as amylase and lipase have proven ineffective as diagnostic markers or prognostic indicators.

Researchers are investigating biomarkers like pro-calcitonin and C-reactive protein (CRP) as potential prognostic indicators. Measuring CRP levels is cost-effective and straightforward, aiming to assess whether an early single measurement of CRP is a reliable indicator of mortality and morbidity in acute pancreatitis (Deherkar, 2019).

Severe pancreatitis is associated with higher rates of morbidity and mortality. While most cases are benign and resolve on their own, a small percentage of patients may experience a rapidly progressing inflammatory process that requires extended hospitalization. This can lead to considerable morbidity and potentially fatality rates of up to 50%.

The underlying mechanism involves the auto-digestion of the pancreas caused by the activation of zymogens produced by the pancreas itself, which triggers a strong inflammatory response from the immune system. This response may be localized to the pancreas or could develop into a systemic inflammatory response syndrome (SIRS) (Lee, 2019). Most of the subsequent damage is attributed to the immune response, which occurs independently of the initial trigger.

Severe pancreatitis is an inflammatory disease that affects the pancreas. It is characterized by intense abdominal pain and elevated serum pancreatic levels, and it can also lead to dysfunction in distant organs and pancreatic autodigestion. Approximately 20% of patients with acute pancreatitis (AP) may progress to moderate or severe acute pancreatitis (SAP or MSAP), which is marked by rapid development and a poor prognosis, with a mortality rate of about 30%. Most cases of AP are mild and have a favorable outlook. However, it is important to recognize the serious prognosis and severity associated with AP, particularly due to prolonged hospital stays and the significant financial burdens caused by SAP.

Early diagnosis of disease severity and assessment of prognostic indicators can be crucial for timely intervention, potentially improving prognosis and survival rates. Currently, several metrics, including Ranson's criteria, the Bedside Index of Severity in Acute Pancreatitis (BISAP), and the Modified Computed Tomography Severity Index (MCTSI), are used to evaluate the prognosis of AP. However, their application in clinical practice is limited by the complexity of their calculations, which require numerous parameters and intricate algorithms (Mederos, 2021). Therefore, there is an urgent need for a quicker and simpler real-time method for forecasting disease prognosis.

Studies have linked serum markers such as albumin and C-reactive protein (CRP) to the prognosis of AP. However, their predictive value is often inadequate when used in isolation. Research has shown that the albumin to CRP (ALB/CRP) ratio can be an effective indicator of the progression of inflammatory response-related disorders. In cases of AP, patients undergoing debridement often present with significantly higher CRP/albumin ratios upon admission (Zhao et al., 2020).

The prognosis of acute pancreatitis (AP) may be associated with the CRP/Albumin ratio. According to Kaplan et al., the CRP/Albumin ratio can help predict the likelihood of death in AP patients. However, the relationship between the severity of AP and the Albumin/CRP ratio—particularly regarding organ failure, severe acute pancreatitis (SAP), and pancreatic necrosis—remains unclear. To enhance survival, it is crucial to assess the severity of AP in a simple, non-invasive manner. The CRP/Albumin ratio was compared with the MCTSI score, Ranson score, and BISAP score to evaluate its effectiveness in predicting the intensity and prognosis of patients diagnosed with AP (Kaplan, 2017).

A high death rate is associated with debridement during the treatment of acute pancreatitis (AP) in patients who experience failure of conservative therapy, severe infection, per pancreatic necrosis, and minimally invasive methods such as percutaneous catheter drainage. Although these patients have undergone surgical treatment, the mortality rates range from 11% to 39%, with reoperation rates between 60% and 70%, and complication rates from 34% to 95%. These variations are due to the wide range of inflammation and the necessity for surgical debridement, as well as the risk of developing major infections (Prasanth, 2022).

It is crucial to evaluate and predict the potential surgical hazards before proceeding, as debridement related to acute pancreatitis carries considerable risks for morbidity and mortality, with poor prognoses. Currently, the severity of acute pancreatitis is assessed using various methods, including the Acute Physiology and Chronic Health Evaluation II Score (APACHE II) and Ranson's Criteria. However, the complexity and multiple characteristics required to calculate these scores limit their clinical usability. Therefore, there is an urgent need for a simpler, quicker, and real-time technique to assess disease severity and the effectiveness of debridement (Karabuğa, 2022).

Prior research has shown a connection between the intensity and prognosis of acute pancreatitis (AP) and serum levels of creatinine, albumin, and C-reactive protein (CRP). While each of these markers has limited predictive value individually, using them together significantly improves prediction sensitivity. Typically, CRP and creatinine levels are elevated in AP, whereas albumin levels are often low, affecting overall prognostic accuracy.

Combining CRP or creatinine with albumin could enhance the sensitivity of the test, as albumin levels tend to decrease in AP while CRP and creatinine levels remain higher. Existing studies have already explored the CRP-to-albumin ratio in AP patients, finding that those with higher CRP/albumin ratios had mortality rates 19.3 times greater at a cut-off value of 16.28, underscoring the predictive power of this combination.

Creatinine is also a valuable marker for AP. However, no research has yet examined the ratio of creatinine to albumin. This study aims to compare the predictive value of the creatinine/albumin ratio with that of the CRP/albumin ratio to assess the effectiveness of creatinine/albumin in predicting surgical outcomes in AP patients.

Acute pancreatitis is one of the most common conditions associated with high morbidity and mortality rates. The severity of AP is evaluated using various scoring systems, which help calculate the likelihood of complications and death (Gori, 2020).

Given the increasing use of the acute-phase reactant protein C-reactive protein (CRP) and the abundant circulating protein in plasma, albumin, the CRP-to-albumin ratio can be useful in assessing the severity of acute pancreatitis. Studies have shown that the CRP/albumin ratio upon admission is positively correlated with the future incidence of severe acute pancreatitis, longer hospital stays, and higher mortality rates.

Over the years, various grading systems have been developed to help clinicians determine the severity of acute pancreatitis and accurately estimate the fatality rate. Some well-known grading systems include the Glasgow score, Ranson score, acute physiological assessment, Atlanta classification, the APACHE score (Acute Physiology and Chronic Health Evaluation), and the BISAP score (Bedside Index for Severity in Acute Pancreatitis).

To accurately assess the severity of the condition, it is essential to consider these rating systems, along with multiple blood test results and physical assessments, some of which are measured at different intervals specifically at admission and again after 48 hours (Haider Kazmi, S. J., et al., 2022).

C-reactive protein (CRP) has recently been used as a marker to assess the severity of viral infections and inflammatory disorders. Although the specific CRP cut-off values for various scenarios are still largely unknown, levels exceeding 210 mg/L in acute pancreatitis have been shown to differentiate between moderate and severe cases with 85% specificity and 83% sensitivity (Gao, 2022).

Albumin, a common protein found in plasma, may decrease during sepsis and severe illnesses due to reduced production, increased breakdown, and heightened vascular permeability, which leads to the leakage of this protein. This decline in albumin levels is a significant factor to consider, as it is associated with increased mortality and the progression of acute pancreatitis cases and organ failure (Tarar, 2022).

Acute pancreatitis (AP) has become increasingly common worldwide in recent years, with an estimated 34 cases per 100,000 people annually (Petrov MS et al., 2018). The most prevalent causes of AP are gallstones and alcohol consumption; however, other notable causes of local and systemic inflammation include hypertriglyceridemia, endoscopic retrograde cholangiopancreatography (ERCP), trauma, obesity, diabetes, certain medications, and infections (Roberts SE et al., 2017). The approach to treating AP has changed significantly in recent years, focusing more on minimally invasive therapies as a key element of multidisciplinary care and a step-up approach (Boxhoorn L et al., 2021).

Over time, minimally invasive surgery has increasingly replaced open surgery. This approach primarily includes endoscopy, small incision surgery, percutaneous drainage (PCD), and video-assisted surgery (Trikudanathan et al., 2019). In open surgery, necropsies are conducted in the abdomen and/or retroperitoneum (RN).

Acute pancreatitis (AP) is no longer treated with a single method due to the complexity and variety of its symptoms. Instead, a range of therapies has been integrated, considering the extent and severity of necrosis. This strategy is referred to as the "step-up approach." A multidisciplinary team is assembled to provide comprehensive care, focusing on critical care medicine, as well as endoscopic, surgical, and radiological procedures.

To improve cure rates and reduce complications, individualized treatment plans should be developed for each patient, tailored to their unique conditions. Furthermore, the step-up approach should be more widely applied to the treatment of AP to enhance patients' quality of life and long-term prognosis (Van Brunschot et al., 2013).

Over the past ten years, there has been a decline in the population death and morbidity of AP due to prompt and correct diagnosis and treatment (Machicado JD, et.al 2017); nonetheless, the severity of AP's sequelae has not diminished (Shah AP et.al 2018). After an episode of AP, 20% of patients have impaired pancreatic endocrine and/or exocrine function as a result of extensive necrosis of pancreatic parenchymal cells (Hollemans RA, et. al 2018).

Additionally, 10% of patients develop chronic pancreatitis (CP) after their first episode of acute pancreatitis (AP), and approximately one-third of patients who experience recurrent AP eventually develop CP. Those who abuse alcohol and men are particularly at risk for this progression (Sankaran SJ et al., 2015).

Moreover, following an initial episode of AP, 37% of patients go on to develop prediabetes or diabetes mellitus. Overall, patients have a two-fold increased risk of developing diabetes within five years after an episode of AP compared to the general population (Das SL et al., 2013).

Significant progress has been made in the last ten years in our understanding of the pathophysiology of acute pancreatitis (AP). This includes insights into the mechanisms of calcium (Ca^{2+}) overload, trypsinogen activation, impaired autophagy, and endoplasmic reticulum (ER) stress. Understanding these mechanisms is crucial for grasping both the occurrence and progression of AP.

Recently, exosomes, which serve as vehicles for storing and transporting proteins, nucleic acids, and lipids, have been found to play a significant role in the pathophysiological processes of various diseases. They may also have a regulatory function in the evolution of AP (Guo XY et al., 2019).

Researchers are increasingly focusing on the role of exosomes in the pathogenesis of acute pancreatitis (AP) because this field is relatively new, and the mechanisms behind the condition remain unclear. Consequently, exosomes may potentially serve as novel biomarkers or targets for the identification and management of AP. To discover innovative therapeutic targets, it is essential to gain a deeper understanding of the pathophysiology of pancreatitis, especially since there are currently no effective guidelines for treating AP. Therefore, we aim to review recent advancements in our understanding of the pathophysiology, diagnosis, and treatment of AP to better guide future treatment options.

To adjust the 2012 Atlanta Classification for more accurate and reliable identification of acute pancreatitis (AP), at least two of the following three diagnostic criteria must be met (Banks PA et al., 2013):

1. A threefold increase in serum lipase and/or amylase levels above the upper limit of normal.

2. Chronic and severe abdominal pain that frequently radiates to the back.

3. Typical imaging signs indicating acute pancreatitis.

Elevated levels of amylase and lipase can occur due to conditions such as acute cholecystitis, gastrointestinal perforation, and intestinal obstruction. However, their diagnostic value is limited in cases of hyperlipidemic pancreatitis and alcoholic pancreatitis. Therefore, imaging is often necessary to confirm a diagnosis of acute pancreatitis.

The best method for diagnosing acute pancreatitis (AP) and pancreatic necrosis is an enhanced computed tomography (CT) scan. Common findings on cross-sectional imaging include fluid collections, pancreatic edema, uneven density, peripancreatic fat stranding, and pancreatic hypertrophy. If multiple "soapy" density-reducing patches of different sizes appear in an enlarged pancreas, necrotizing pancreatitis should be considered. It's important to note that these characteristics are not usually visible in the early stages of AP, as pancreatic necrosis typically manifests 72 hours after the onset of clinical symptoms (Taydas O et al., 2018).

Consequently, imaging may not be necessary within the first 72 hours after admission for patients showing typical clinical signs of acute pancreatitis (AP) supported by laboratory tests (Crockett SD et al., 2018). However, if necrotizing pancreatitis is suspected, an enhanced CT scan or CT perfusion should be performed. This will facilitate urgent monitoring and management of adverse outcomes, helping to prevent irreversible pancreatic necrosis and reducing the risk of death. Several scoring systems, including the Acute Physiology and Chronic Health Examination II score, the Harmless Acute Pancreatitis Score, the Ranson score, and the CT Severity Index (CTSI), can be utilized to evaluate the severity of AP (Tenner S et al., 2014).

A score of less than three indicates a better prognosis, and the Contrast-Enhanced Computed Tomography Severity Index (CTSI) has good prognostic value in these cases (Brand M et al., 2014). There are three types of acute pancreatitis (AP): moderately severe acute pancreatitis (MSAP), severe acute pancreatitis (SAP), and mild acute pancreatitis (MAP) (Pieńkowska J et al., 2016).

Interstitial edematous pancreatitis, characterized by the absence of organ failure and systemic or local complications, is a key feature of Mild Acute Pancreatitis (MAP). In contrast, the primary cause of Moderate to Severe Acute Pancreatitis (MSAP) and Severe Acute Pancreatitis (SAP) is necrotizing inflammation. A common outcome of MSAP is transient organ failure lasting less than 48 hours, which may or may not be accompanied by localized or systemic complications. The most frequent local complications include sterile or infected pancreatic necrosis (IPN), fluid accumulation around the pancreas, and the formation of pancreatic pseudocysts (Braha J et al., 2018).

Intermittent organ failure and a decline in disease status are features of systemic complications, which occur in 20% of acute pancreatitis (AP) cases (Xiao B et al., 2019). In contrast, severe acute pancreatitis (SAP) is characterized by chronic organ failure lasting longer than 48 hours. This condition is associated with a poor prognosis, and approximately 30% of cases can result in death (Garg PK et al., 2019).

The pathophysiology of acute pancreatitis (AP), a common digestive system disorder, is complex and involves several factors, including exosomes, endoplasmic reticulum (ER) stress, trypsinogen activation, excess calcium (Ca^{2+}), and defective autophagy. Among these, the activation of trypsinogen and calcium overload represent two equally significant intracellular pathways involved in the development of AP. Additionally, there are other factors that have a limited impact on the onset of this condition.

One common way the body experiences cell damage is through an excess of Ca^{2+} signaling and malfunction in the mitochondria. Under normal physiological conditions, the ryanodine receptor and inositol trisphosphate (InsP3) receptor pathways work together, with the ryanodine receptor playing a key role. This allows cholecystokinin to activate the endoplasmic reticulum (ER), leading to the release of stored Ca^{2+} (Feng et al., 2018).

In response to the resulting Ca^{2+} influx, adenosine triphosphate (ATP) is produced by the mitochondria. Simultaneously, proteases are released from the activated secretory granules at the apex of acinar cells (Voronina et al., 2015).

Key stages in the formation of SAP, triggered by acinar cell dysfunction, include an excess of intracellular Ca2+ and mitochondrial dysfunction. These changes are induced by factors such as cholecystokinin, alcohol consumption, and bile acids (Biczo G et al., 2018).

Extracellular calcium ions (Ca2+) are facilitated in entering the cell through Ca2+ release-activated Ca2+ channel protein 1 (ORAI1), which exacerbates Ca2+ overload (Lur G et al., 2011). Persistent overload of intracellular cytosolic Ca2+ can damage the mitochondrial membrane, increasing the permeability of the mitochondrial permeability transition pores (MPTP). This alteration affects the membrane potential and regulates the sensitivity of cyclophilin D, leading to a decrease in ATP production (Maléth J et al., 2016).

When ATP is depleted, the ATP-dependent smooth endoplasmic reticulum Ca2+ channels (SERCA), which transport Ca2+ from the cytoplasm to the endoplasmic reticulum, and the ATP-dependent plasma membrane Ca2+ pumps (PMCA), which transport Ca2+ from the intracellular space to the extracellular space, are inhibited. This blockage ultimately causes damage to acinar cells (Criddle DN et al., 2007).

This process disrupts the Ca^{2+}-Na^{+} pump on the cell membrane, as well as the Ca^{2+} pump and ATP-dependent channels on the endoplasmic reticulum. This disruption exacerbates the excess of intracellular calcium. Ultimately, the increased calcium activates both intracellular and pericellular enzymes, leading to pancreatic self-digestion (Peng S et al., 2016).

Mitochondrial failure impairs cell autophagy, leading to an increase in reactive oxygen species (ROS) and cytokines, which worsen damage to pancreatic cells. Damaged pancreatic cells release chemicals such as tissue factor, DNA, and heat shock proteins. These substances activate inflammatory signaling pathways, including NF-κB, MAPK, STAT3, and PI3K, resulting in both local and systemic inflammation (Li Z et al. 2020).

Mitochondrial injury worsens endoplasmic reticulum (ER) stress and lysosomal damage. It also triggers the release and activation of cathepsinogen and trypsinogen, leading to cytoplasmic protein breakdown and cell necrosis (Figure 2.1) (Mukherjee R et al., 2016). Research into the mechanisms of calcium (Ca2+) overload suggests that inhibiting Ca2+ channels to prevent acute pancreatitis from progressing to necrotizing pancreatitis warrants further investigation. ORAI1 channel inhibitors can prevent external Ca2+ ions from entering acinar cells while effectively alleviating intracellular Ca2+ overloads.

ORAI1 channel inhibitors have been shown in studies to effectively prevent necrosis in acute pancreatitis (AP) in animal models and human acinar cells, while also significantly reducing local and systemic inflammation (Wen L, et al 2015).

MPTP inhibitors may become a promising target for treating acute pancreatitis (AP) because they can effectively prevent a reduction in ATP production. These inhibitors help maintain intracellular calcium ion transport through ATP-dependent SERCA and PMCA channel proteins, thereby reducing the risk of calcium overload within cells. One such MPTP inhibitor, documented in TRO40303, has shown the ability to preserve cell membrane potential and prevent necrosis in both animal models of alcoholic pancreatitis and human acinar cells (Javed MA et al., 2018).

By preventing external Ca^{2+} ions from entering acinar cells, ORAI1 channel inhibitors can effectively reduce intracellular Ca^{2+} overload. Research has shown that these inhibitors can significantly decrease both local and systemic inflammation and successfully prevent necrosis in acute pancreatitis (AP) in human acinar cells and animal models (Wen L, et al. 2015).

Additionally, MPTP inhibitors may present a viable target for AP therapy, as they can successfully halt the decline in ATP synthesis. This preservation allows ATP-dependent SERCA and PMCA channel proteins to continue transporting intracellular Ca^{2+} ions, thus reducing the risk of Ca^{2+} overload. In animal models of alcoholic pancreatitis and human acinar cells, TRO40303 acts as an MPTP inhibitor, effectively maintaining cell membrane potential and preventing necrosis (Atar D, et al. 2015).

In addition to being effective and well tolerated for treating hepatitis and acute myocardial infarction, TRO40303 may also serve as a useful treatment for acute pancreatitis (AP) (Schaller S et al., 2015). The effectiveness of high-calorie parenteral nutrition (PN) in maintaining adequate ATP consumption during AP is currently being evaluated in a multicenter clinical trial (Márta K et al., 2017).

Figure 2.1 shows Cholecystokinin, alcohol, and bile acids activate the ER to release stored Ca^{2+} via the InsP3 receptor pathway. ORAI1 promotes Ca^{2+} to enter the cell from the extracellular space, further increasing the Ca+ overload. Sustained Ca+ overload increases the permeability of MPTP, which determines the sensitivity of cyclophilin D and Change in the membrane potential, leading to ATP depletion and cell necrosis. While ATP depletion damages acinar cells by blocking SERCA and PMCA, which aggravates the intracellular Ca+ overload. and Ca+ overloadcan activate trypsinogen and inflammatory signaling.

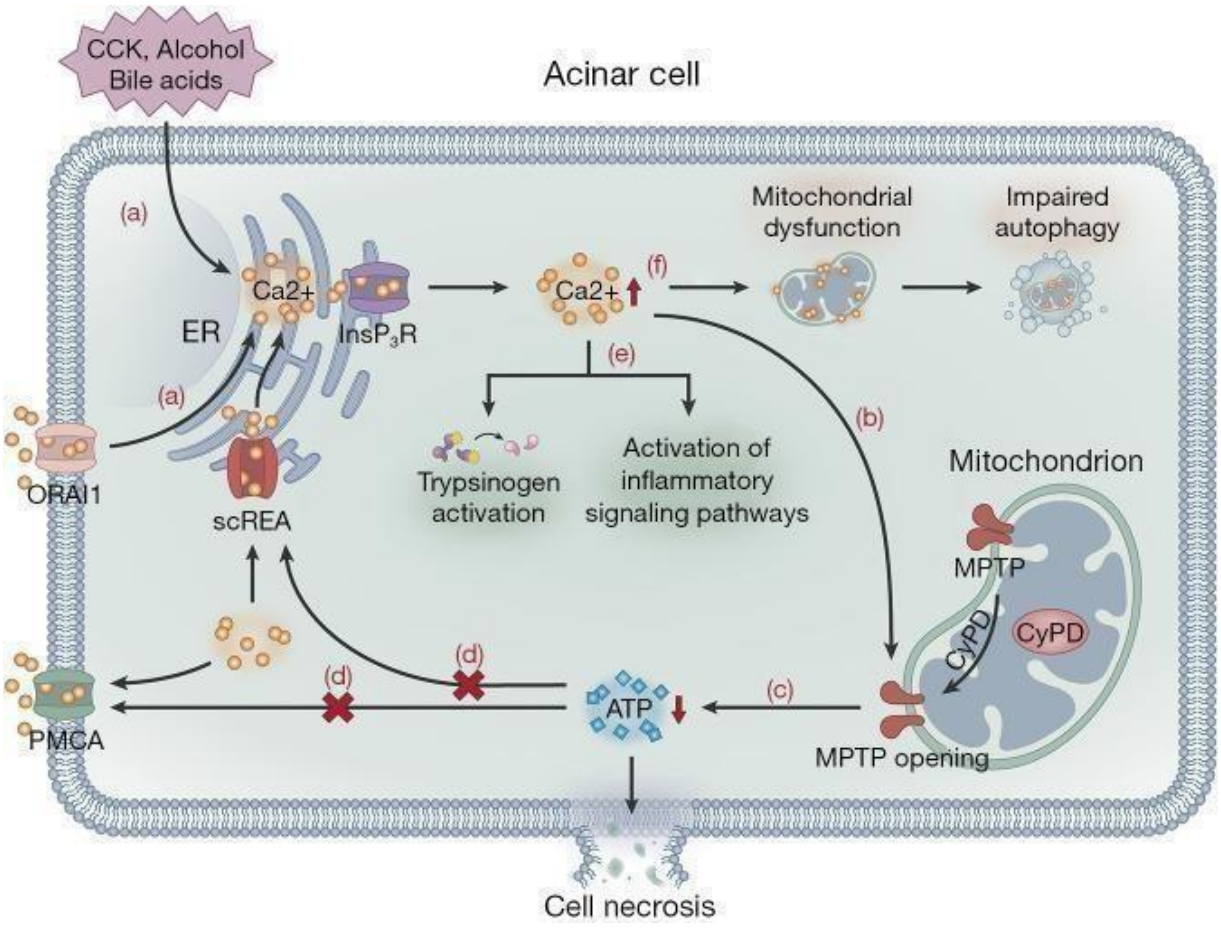


Figure 2.1 Cholecystokinin, alcohol, and bile acids activate the ER to release stored Ca^{2+} (Zheng, et.al 2021)

Trypsinogen activation is another important, widely studied pathogenetic pathway of AP. Trypsinogen cannot be activated due to the presence of trypsin inhibitors and zymogen granule exocytosis at the apex of acinar cells (Dawra R, et.al 2011); hence, it cannot trigger AP. Alcohol consumption, bile acids, and pancreatic toxic substances stimulate acinar cells, resulting in the increased synthesis of lysosomal and digestive enzymes in these cells. Furthermore, pancreatic toxic substances inhibit the release of zymogen granules from the apex of acinar cells, leading to an increase in thecontent of lysosomal and zymogen granules in acinar cells. The lysosome andzymogen granules subsequently fuse with one another, a process known as colocalization (Chvanov M, et.al 2018). Cathepsin B in lysosomes activates trypsinogen, causing the release of cathepsin B and trypsin intothe cytoplasm following lysosomal membrane rupture (Talukdar R, et.al 2016).

Cathepsin B in lysosomes also acts on the RIP3-RIP1-MLKL signalingpathway to promote the formation of the RIP3-RIP1 necrosis complex, whichthen acts downstream on MLKL protein molecules, resulting in the phosphorylation and oligomerization of MLKL protein to translocate to the plasma membrane, ultimately leading to acinar cell necroptosis (Han J, et.al 2011). Blocking the RIP1-RIP3 signaling pathway by genetic modification or RIP1-specific necrosis inhibitors can alleviate the severity of acinar cell damage. Nec-1 has been used to examine the contribution of RIP1 to inflammation in disease models (Liu Y, et.al 2019) and can prevent heart disease and inhibit ROS production in a mouse model via downregulation of the RIP1/RIP3/MLKL signaling pathway (Zhang L, et.al 2018).

GSK2982772, a novel RIP1 inhibitor, actively blocks necroptosis andinflammation (Harris PA, et.al 2017). Animal studies have shown that RIPA-56 is a target for RIP1, reducing TNF α-mediated cell death and organ injury associated with the systemic inflammatory response syndrome (SIRS) (Ren Y, et.al 2017) and may thus be a potential target for AP treatment (Louhimo J,et.al 2016). On the other hand, trypsin causes self-digestion of acinar cells, with the rupture of the lysosomal membrane leading to the release of cytochrome-c from the mitochondria, which activates caspase-3 and mediatescell apoptosis (Figure 2) (He S, et,al 2009). Currently, trypsinogen activationin acinar cells remains the central pathway considered to cause AP (Zhan X, et.al 2019). However, some studies have reported that trypsinogen activationalso occurs in macrophages (Sendler M. et.al 2018); thus, the complete pathogenetic mechanism of AP needs to be further investigated.

Figure 2.2 shows Alcohol, bile acids, and pancreatic toxins stimulate acinar cells, increasing lysosomesynthesis. Pancreatic toxins inhibit the release of zymogen granules from the apex ofacinar cells, which leads to an increase in the content of zymogen granules. The lysosome and zymogen granules become fused, a process known as colocalization and Cathepsin B causes trypsinogen activation, resulting in the release of cathepsin B and trypsin into the cytoplasm. The released cathepsin B acts on the RIP3-RIP1-MLKL signaling pathwayto promote RIP3-RIP1 necrosis complex formation. The RIP3- RIP1 complex acts on the MLKL, causing MLKL phosphorylation and oligomerization,which then translocates to the plasma membrane, ultimately leading to acinar cells necroptosis. The cathepsin B released after lysosomal membrane rupture leads to the release of cytochrome-c from the mitochondria, which activates caspase-3 and mediatescell apoptosis.

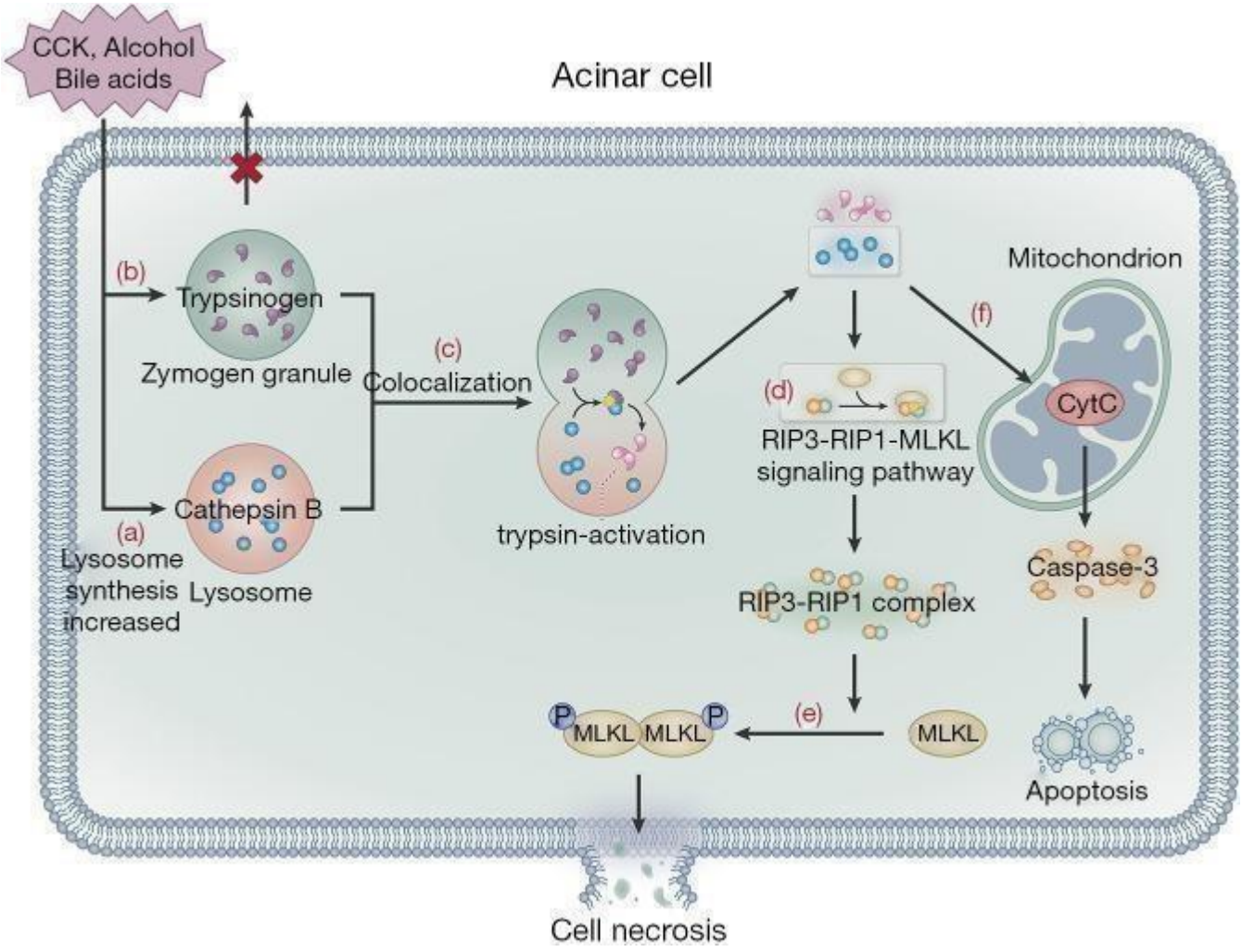


Figure 2.2 Alcohol, bile acids, and pancreatic toxins stimulate acinar cells (Zheng, et.al 2021)

Impaired autophagyis a central mechanism for cell protection, allowing cells toremove damaged, aged, and nonfunctional organelles as well as denatured protein macromolecules to provide energy for cellular regeneration and recycling (Antonucci L, et.al 2015). The process of autophagy includes four main steps (Gukovskaya AS, et.al 2017). The first step is autophagy induction, in which cells stimulated by autophagy signals form an autophagy precursor,an open circular double membrane comprised of ER, Golgi apparatus, and plasma membrane. In the second step, mediated by the autophagy-related gene(ATG), the autophagy precursors gradually elongate and enclose damaged, aged organelles and part of the cytoplasm to form vesicle-like structures, which develop into autophagosomes. In the third step, mediated by the lysosomal associated membrane protein (LAMP), the autophagosomes transfer their encapsulated contents to the lysosome cavity where they fuse with cathepsin B to form autolysosomes. Finally, in the fourth step, after the autophagosomes are fused, they are degraded by lysosome hydrolase and thedegradation products are recycled into the cell (Figure 2.3).

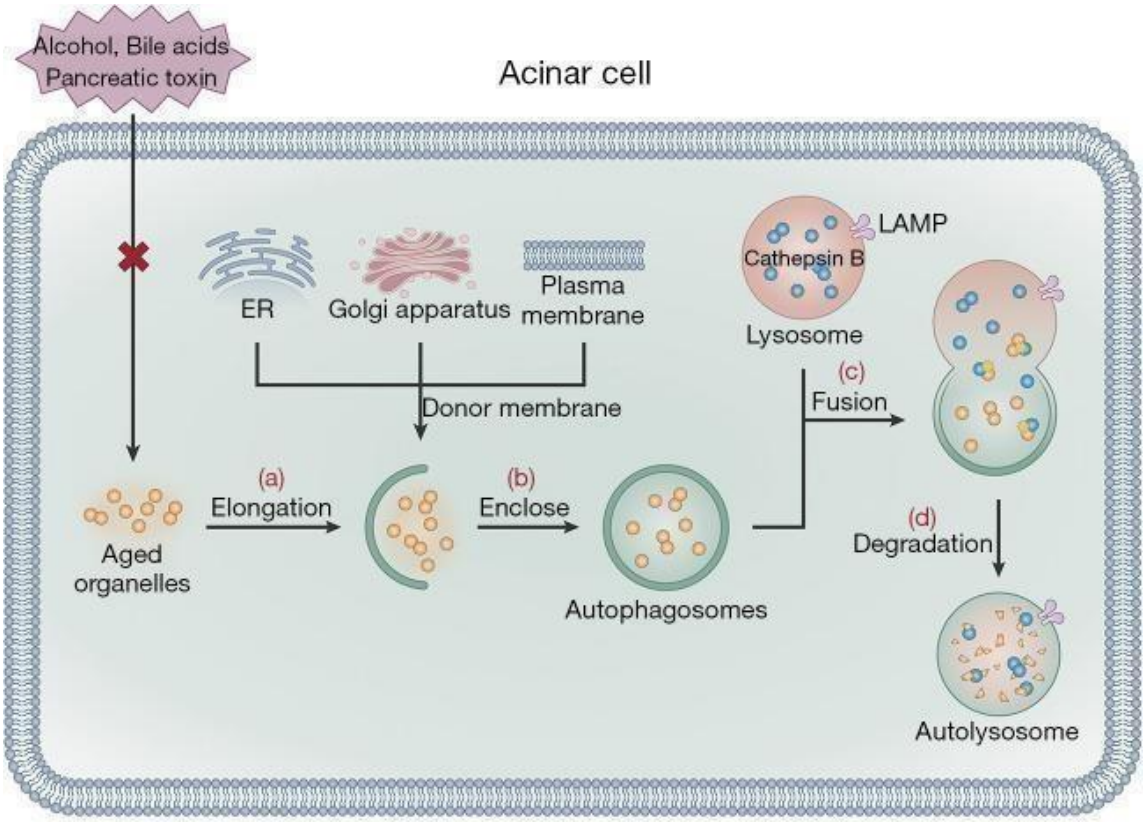


Figure 2.3 Autophagy precursor (Zheng, et.al 2021)

There are two purposes for Autophagy (Gukovskaya AS, et.al 2019), in response to different metabolic stressors physiological autophagy either can eliminate undesirable or ageing organelles, or it can act as a protective mechanism to preserve homeostasis. Overdosing on autophagy can result in autophagy stress or malfunctioning autophagy, which exacerbates damage to organelles and ultimately kills cells. Research has demonstrated that the pathological process of AP is not initiated by physiological autophagy (Mizushima N, et.al 2004). Nevertheless, once pancreatic toxins activate acinar cells.

Alcohol or bile acid ingestion impairs the autophagy process, causing inflammation and cell death. Impaired autophagy has been identified as a significant pathogenic event in AP, which is related with aberrant pancreatic enzyme activation (Mareninova OA. Et.al 2009). A few studies have indicated that the extent of autophagy vacuoles generated in acinar cells and trypsinogen activation are dramatically diminished in AP mice models with knock-out ATG5, reducing the severity of AP. One such study demonstratesthat autophagy in the early stages of AP stimulates trypsinogen, which accelerates disease development (Diakopoulos KN, et.al 2015).

As a result, understanding the process of defective autophagy early in AP may provide a new target for clinical development of novel AP medicines. Oxidative stress is also elevated as a result of bacterial translocation, which exacerbates AP-associated lung injury; this process may be linked to reduced autophagy (Wang H, et.al 2020). The AP models of IL-22 transgenic mice and IL-22 recombinant adenovirus animals triggered by caerulein confirmed that IL-22 can inhibit autophagosome formation via the Beclin-1 pathway, lowering the severity of AP (Feng D, et.al 2012). Furthermore, defective autophagy causes trypsinogen activation, ER stress, and mitochondrial malfunction, which eventually results in acinar cell damage and death.

As a result, understanding how AP might restore acinar cell autophagy is an important future study area. Furthermore, earlier research has shown that trehalose can lessen the degree of pancreatic injury in AP animal models, which may be linked to higher autophagy levels; however, the particular protective mechanism remains unknown (Lee HJ, et.al 2018).

Hypoxia, alcohol use, Ca2+ excess, and oxidative stress can all induce ER stress, which causes poor post-translational modification and increased protein synthesis (Hetz C, et.al 2015). Because pancreatic acinar cells have a high concentration of ER, the pancreas is particularly sensitive to ER stress (Wu JS, et.al 2016). Basic cell biology researchhas revealed that ER over-activation may be a key mechanism that causes and exacerbates pancreatic damage (Zhao Q, et.al 2018).

ER stress is induced by an increase in unfolded or misfolded proteins in the ER. The stress signal is delivered to the nucleus via the ER membrane, which causes a series of particular target transcription and protein translation levels to be downregulated, allowing the cell to survive, a process known as the unfolded protein response (UPR). In the early stages of ER stress in acinar cells, the UPR is activated to restore ER homeostasis and allow cell survival (Barrera K, et.al 2018). UPR is regulated by three ER transmembrane proteins: IRE1α, PERK, and ATF6 (Walter P, et.al 2011). When unfolded proteins accumulate in the ER, BiP/GRP78 dissociates from three transmembrane proteins and binds to unfolded proteins, initiating UPR signaling pathways (Ron D, et.al 2007)

Self-dimerization and phosphorylation of the cytoplasmic domain can activate PERK and stimulate the phosphorylation of eukaryotic translation initiation factor-2α (eIF2α). This process can decrease the pressure on the ER to fold freshly synthesised proteins, halt or stop protein synthesis, and quickly decrease the beginning of mRNA translation. This is significant because increased transcription of factor C/EBP homologous protein (CHOP), which triggers cell death, can result from ATF4 overexpression. By reducing the amount of protein folding required in the ER and limiting the buildup of misfolded proteins, PERK-mediated phosphorylation of eIF2α may stop mRNA translation and prevent CHOP-induced cell death (Aoi K, et.al 2019).

ATF6 is transported to the Golgi apparatus and cleaved at site-1 (S1P). Site 2 (S2P) proteases. The N-terminal transcription activation domain is released and transported to the nucleus as a transcription factor, promoting the production of the ER molecular chaperones XBP1 and CHOP (Ghosh R, et.al 2014). ATF6 increases the ER's Protein folding ability.

When the IRE1 signaling pathway is engaged, IRE1 excises a 26-nucleotide intron of unsliced X- box binding protein 1 (XBP-1) mRNA, It generates spliced XBP-1 mRNA (XBP1s). The protein encoded by XBP1 is rapidly degraded, reducing ER stress (Lugea A, et,al 2017). (Figure 2.4)

Unfolded protein response (UPR) is a sophisticated signaling network that can activate the PERK, ATF6, and IRE1 signaling pathways, hence inhibiting protein translation and synthesis. Meanwhile, the UPR pathway can promote protein folding and misfolded protein degradation, both of whichreduce ER stress (Figure 2.4). When the ER disorder exceeds the cell's regulatory capability, ER homeostasis cannot be restored, and the resulting prolonging of ER stress produces inflammation and cell death (apoptosis). The incidence and progression of AP are strongly linked to ER stress (Kapuy O, et.al 2020). UPR promotes the NF-κB inflammatory pathway through three signaling routes, exacerbating acinar cell inflammation and necrosis.

The approach eventually results in AP aggravation. NF-κB inhibitors (IL-10 and cAMP) can prevent ER stress, reduce pro-inflammatory molecules like TNF-α, IL-1, and IL-6, and slow inflammation. Several investigations have shown that PPAR-γ ligands, pyrolidine dithiocarbamate (PDTC), proteasome inhibitors, and calpain I inhibitors can decrease NF-κB activation in experimental AP (Jin HZ, et.al 2019). Another study found that 4-phenylbutyric acid (4-PBA) can prevent the activation of trypsinogen and UPR, easing the pro-apoptotic pathways associated with ER stress and lowering systemic inflammation and cell apoptosis (Malo A, et.al 2013).

An observational study indicated that HMG-CoA reductase inhibitors induce UPR, while long-term statin treatment reduces the severity of AP. Therefore, HMG-CoA reductase inhibitors help reduce the recurrence of AP (Lee PJ, et.al 2018).

Figure 2.4 shows ER stress can be triggered by alcohol, bile acids, pancreatic toxins, and increased protein synthesis. UPR is caused by an increase of misfolded or unfolded proteins in the ER. ATF6 is transferred to the Golgi apparatus and is cleaved by S1P and S2P.

The N-terminal transcription activation domain is released and transferred to the nucleus as a transcription factor to promote transcription of the target gene. PERK-mediated phosphorylation of eIF2αshuts off mRNA translation, decreasing the protein folding load and preventing misfolded proteins from being accumulated. ATF4 upregulation can result in CHOP expression, inducing cell apoptosis

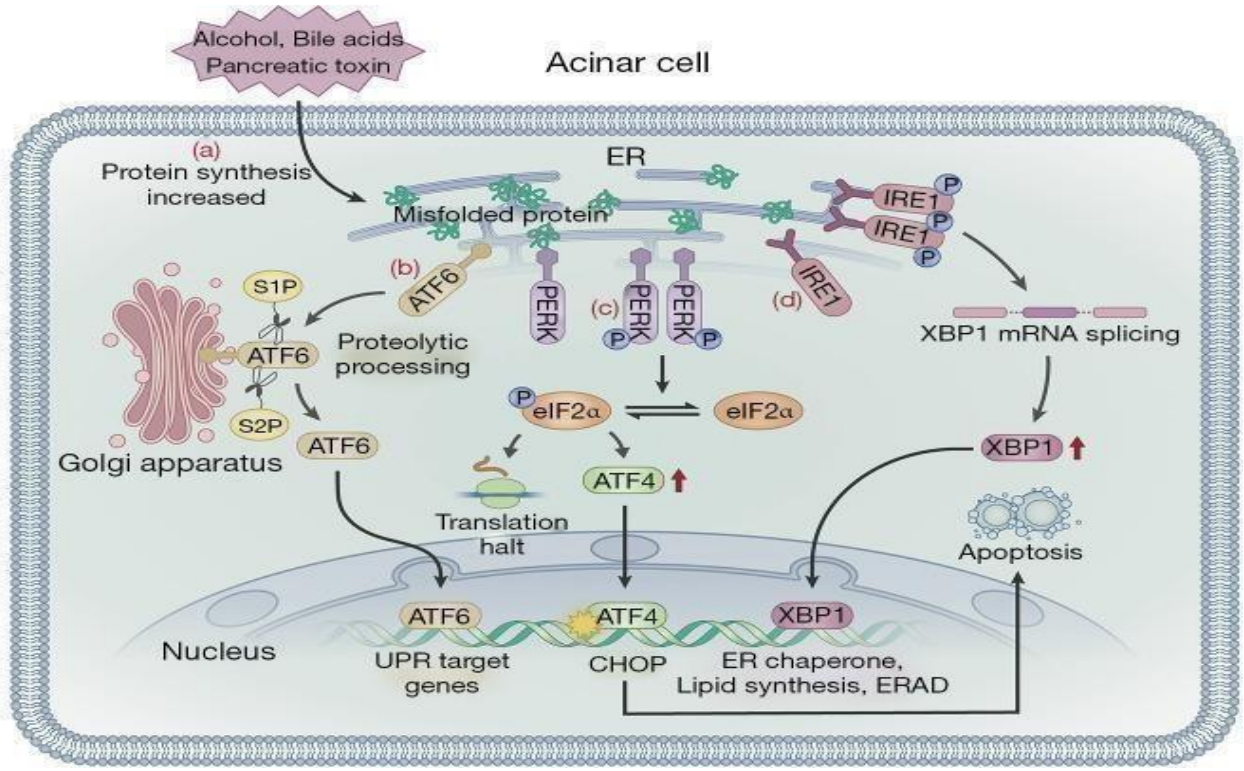


Figure 2.4 ER stress (Zheng, et.al 2021)

Exosomes are vesicles produced by numerous live cells that contain RNA and proteins (30-100 nm in size). Given the large increase in exosomes in the peripheral blood of AP patients, exosomes may play an important regulatory function in the course of pancreatitis, which has recently been a major research issue. In the rat AP model, the pancreas' release of exosomes into the peripheral circulation was considerably increased. Some of the exosome contents can immediately enter the liver through the portal system and be kept in the liver tissue, while the remaining contents of the exosomes can be destroyed by the high hydrolytic activity of pancreatitis-associated ascitic fluid (PAAF) and then transported to the hepatic tissue. As an outcome, the liver may produce and release additional exosomes. When fluorescently labelled exosomes were studied, it was discovered that exosomes from the circulatory system could successfully reach and be absorbed by alveolar macrophages. Exosomes from the AP model's circulatory system can activate alveolar macrophage cells by switching their phenotype from M2 to M1, exacerbating the severity of lung injury produced by AP (Bonjoch L, et.al 2016). Another study discovered that plasma-derived exosomes can activate NOD-like receptor protein 3 (NLRP3) inflammasomes to cause pyrolysis of alveolar macrophages, resulting in AP-related lung damage.

In contrast, inhibitors that block exosome release or uptake can reduce alveolar macrophage pyroptosis, lowering the degree of AP-induced lung injury (Wu XB, et.al 2020) (Figure 2.5).

Abundant exosomes in acinar cells' culture media during AP may activate macrophages. Analysis of microRNA (miRNA) and target genes in exosomes indicated that acinar cells activate macrophages primarily via the MAPK pathway in AP, which contributes to acinar cell damage through apoptosis, necrosis, and autophagy (Yang Y, et.al 2020). These findings are extremely important in advancing research on exosome-miRNA interactions in AP.

Exosomes can trigger the CaN/NFAT signaling pathway via miRNA-23a, which causes the transcription of a variety of chemical factors and ATGs.

This causes trypsinogen to be released abundantly in interstitial tissues, resulting in local inflammation that can spreadto the systemic level (Hudson MB, et.al 2014).

Exosome-miRNA can also be transported toother organs via the circulatory system, including the lungs, kidneys, and digestive tract. Exosomes-miRNA activates these organs, causing them to produce additional exosomes, inducing cell death and organ damage (Wang T, et.al 2018). However, exosomes from various cells may play distinct roles in the pathophysiology of AP. Exosomes produced frombone marrow mesenchymal stem cells (MSCs) have been shown to repair AP (Munir F, et.al2019).

Furthermore, exosomes-miR-223-3p from MSCs might reduce cerebral damage by suppressing the M1 polarization-mediated pro-inflammatory response, which may be linked to a negative effect on exosomes-miR-223-3p for CysLT2R (Zhao Y et.al 2020). As a result, more research is needed into the similarity and specificity of exosomes in different cells, tissues, and organs, as well as the exosome targeting mechanism and target organ gene regulatory mechanism. Exosomes, which can shield RNA or protein from destruction, could be a potential therapeutic in the future. As a result, pharmacological trials concentrating on exosome-related targets may improve the success rate of AP therapy.

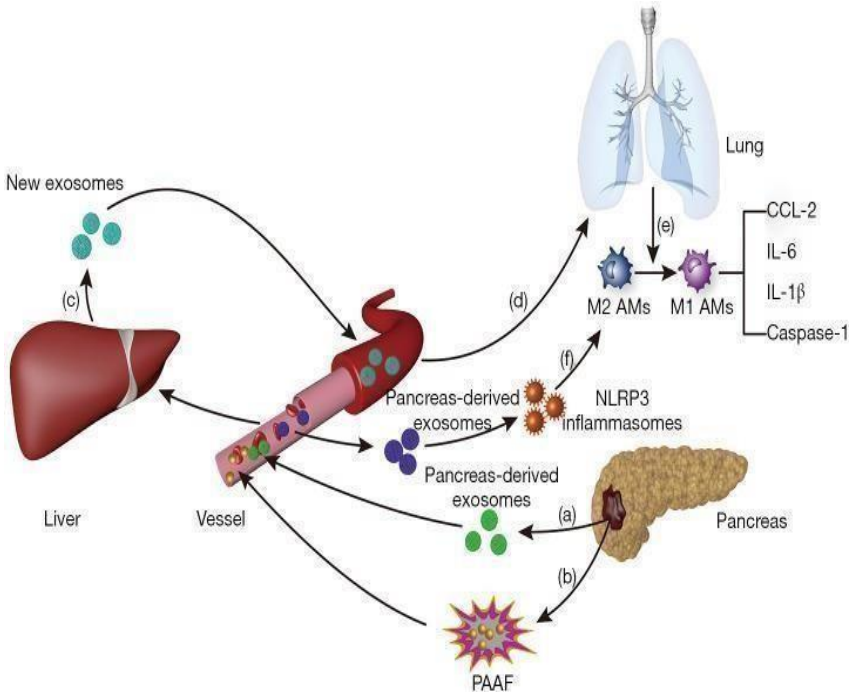


Figure 2.5 Plasma derived exosomes (Zheng, et.al 2021)

OPERATIONAL DEFINITIONS

1. ACUTE PANCREATITIS:

Acute pancreatitis is an abrupt inflammation of the pancreas that can vary in severity from a minor, self-limiting condition to a serious, potentially fatal condition. Abdominal pain, increased pancreatic enzymes, and different levels of tissue injury to the pancreas and peri pancreas are its defining characteristics. In this study, the term "acute pancreatitis" refersto a clinically or radiologically confirmed inflammatory disease of the pancreas, with or without indications of organ dysfunction.

2. C-REACTIVE PROTEIN (CRP):

A biomarker for acute pancreatitis disease severity assessment, CRP is an acute-phase reactant generated by the liver in response to inflammation.

3. ALBUMIN:

Albumin is a protein produced by the liver is frequently coupled with CRP as a measure of inflammation and nutritional status.

4. RANSON CRITERIA:

A series of clinical and laboratory measures known as the Ranson criteria are used to evaluate the degree and prognosis of acute pancreatitis. The criteria were first created in 1974 by John Ranson and others, and they have since undergone modifications and validation in order to be used in clinical settings. Serum glucose, serum calcium, hematocrit, blood urea nitrogen, arterial oxygen tension, and clinical findings (pleural effusion, serum LDH, serum AST, and changes in white blood cell count over 48 hours) are among the eleven measure

that make up the criteria. The number of criteria that are met by the patient both upon admission and 48 hours later determines their score. Patients are categorised as having a low, moderate, or high risk of death and complications using the Ranson score.

5. C-REACTIVE PROTEIN (CRP)/ ALBUMIN RATIO:

A biological marker called the C-reactive protein (CRP)/albumin ratio is computed by dividing the blood CRP level by the serum albumin level. Whereas albumin is a sign of inflammation and nutritional status, CRP is an acute-phase reactant that the liver produces in response to inflammation. The CRP/albumin ratio has been suggested as a predictor of acute pancreatitis disease severity because it shows the equilibrium between pro- and anti-inflammatory activities. In this context, the CRP/albumin ratio refers to the precise measurement of these two indicators in individuals diagnosed with acute pancreatitis.

6. SEVERITY OF ACUTE PANCREATITIS:

Based on clinical, biochemical, and radiological characteristics, the degree of pancreatic and systemic involvement is categorized as mild, moderate, or severe.

6.1 MILD ACUTE PANCREATITIS:

Associated with limited pancreatic necrosis and temporary organ dysfunction, this condition carries a low risk of mortality and sequelae.

6.2 MODERATE ACUTE PANCREATITIS:

This condition has a moderate risk of complications and death, substantial pancreatic inflammation, and ongoing organ dysfunction.

6.3 SEVERE ACUTE PANCREATITIS:

Distinguished by severe pancreatic necrosis, ongoing organ failure, and systemic consequences, this condition carries a high risk of death if prompt medical attention is not received.

7 TRUE POSITIVE (TP):

A test result that correctly indicates the presence of a condition or characteristic.

8 FALSE POSITIVE (FP):

A test result that correctly indicates the absence of a condition or characteristic.

9 TRUE NEGATIVE (TN):

A test result which wrongly indicates that a particular condition or attribute is present.

10 FALSE NEGATIVE (FN):

A test result which wrongly indicates that a particular condition or attribute is absent

11 SENSITIVITY:

It refers to the probability of a positive test, conditioned on truly being positive. It is calculated as TP/TP+FN.

12 SPECIFICITY:

It refers to the probability of a negative test, conditioned on truly being negative. It is calculated as TN/TN+FP.

13 DIAGNOSTIC ACCURACY:

Diagnostic accuracy is the proportion of correct diagnosis found by adiagnostic test. It is calculated as TP+TN/TN+FP+FN+T

SECTION 3

RESEARCH METHODOLOGY

3.1 METHODOLOGY

3.1. Study Design

It is a Cross-sectional study.

One kind of observational research technique that is frequently employed in the social sciences and epidemiology is the cross-sectional study design. With this design, information is gathered at a given moment from a population or representative subset. Analyzing the frequency and correlations between relevant characteristics in that population is the goal.

A 'snapshot' of the population at one particular moment is provided by the study. Cross-sectional studies do not monitor changes over time, in contrast to longitudinal studies, which follow people over an extended period of time.

When compared to longitudinal research, data gathering is usually speedier and less expensive.

Prevalence data are excellent for determining the prevalence of a particular trait within a community or the impact of a health issue.

It is able to assist in the generation of hypotheses for additional study.

3.2 Subjects

105 patients (Males and females) with the disease acute pancreatitis were recruited from the civil hospital, Karachi. These patients were fulfilling the inclusion criteria.

3.3 Place of sample collection

The study was conducted at Dr.Ruth KmPfau Civil Hospital, Karachi.

3.4 Inclusion Criteria

Patients within the age group 18-60 years with a diagnosis of acute pancreatitis were included in this study (Patients with raised amylase levels)

3.5 Exclusion Criteria

Patients with co-morbidities such as

Chronic Liver Disease,

Chronic Kidney Disease,

Or chronic inflammatory were excluded from the study.

3.6 Duration of Study

3.6.1 Individual study period: 72 hours.

3.6.2 Total study period: Total duration of study was 6 months after approval from Bahria University Health Sciences Campus and Institutional Review Board (IRB) BUHS-IRB # 042/ 24, 08-01-2024 and Faculty Review Committee (FRC) FRC-BUHS 06/2024, , 08-01-2024)

3.7 Sample Size Estimation

A 105 patients were estimated using the OpenEpi, with a confidence range of 95% and a margin of error of 5%.

Sample Size(n) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	105
80%	77
90%	94
97%	110
99%	118
99.9%	127
99.99%	132

3.7.1 Sample Size

105 Patients (Male and Female) were included in the study.

3.8 Sampling Technique

Non Probability Convenient sampling method.

In non-probability convenience sampling, participants are chosen for a study not by chance but rather according to their accessibility and availability. This kind of sampling does not seek to create a sample that is representative of the total population; rather, it is typically employed when rapid and low-cost data collecting is required.

The researcher selects participants based on how easily they can be reached. This frequently includes people who are willing or able to contribute right away. Because the researcher chooses easily accessible individuals, data may be acquired quickly.

This method frequently makes use of individuals who are easily accessible, it is generally less expensive.

It assists in producing preliminary understanding, insights, and ideas about events that can be investigated in greater detail in subsequent, more thorough investigations.

3.9 Subject Evaluation Form

Attached as annexures

3.9.1 Subject consent form (English & Urdu)

Attached as annexures

3.9.2 Research Lab / Commercial Lab Facility to be used

NA

3.10 Material

3.10.1 Culture Media

N/A

3.10.2 Drugs

N/A

3.10.3 Equipment

EDTA tubes, Eppendorf tubes 5cc syringes, tourniquet,Enzyme linked immunosorbent Assay machine, ELIZA washer.

3.10.3.1 EDTA tubes

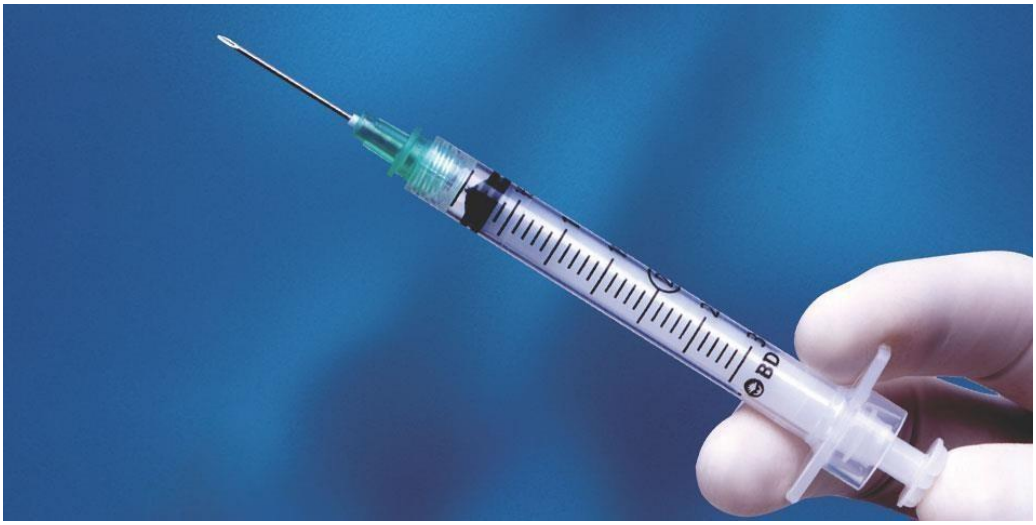
One kind of blood collection tube used in medical and lab settings is the EDTA tube. They include ethylenediaminetetraacetic acid, or EDTA, an anticoagulant that binds to calcium ions to stop blood clotting.

3.10.3.2 Eppendorf tubes

Eppendorf tubes provide a practical and dependable way to handle small volumes of liquids, making them essential instruments in contemporary labs. They are appropriate for a range of uses, from sample storage to intricate molecular biology research, thanks to their design and material qualities.

3.10.3.3 Syringes:

Medical devices called syringes are used to inject or remove fluid from the body. They are made up of a hollow cylindrical barrel with a plunger that may be pulled or pushed to inject or remove fluid, and a needle attached to it.



3.10.3.4 Tourniquet:

A tourniquet is a medical device that limits blood flow by applying pressure to a limb or extremity. In order to reduce significant bleeding, this is frequently done during blood draws, intravenous injections, surgeries, and emergency situations.

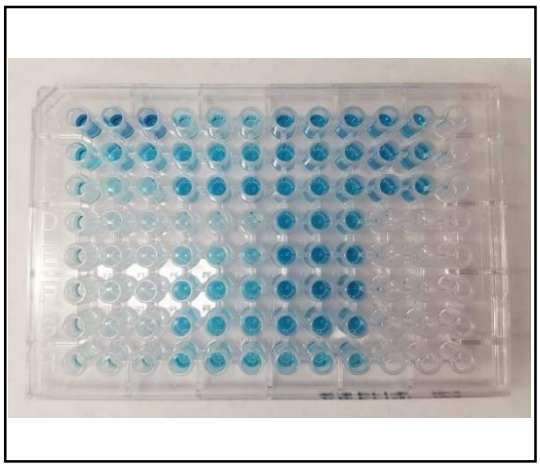
3.10.3.5 ELISA:

An extensively used laboratory method for identifying and measuring materials like proteins, peptides, antibodies, and hormones is called enzyme-linked immunosorbent assay, or ELISA. Because of its extreme sensitivity and specificity, ELISA is a vital tool in many domains, such as industry quality control, research, and medical diagnostics.

3.10.3.6 ELISA WASHER:

A microplate washer, sometimes referred to as an ELISA washer, is a type of lab equipment used in ELISA (Enzyme-Linked Immunosorbent Assay) protocols that is intended to automate the washing procedures. In order to provide accurate and trustworthy results, washing is an essential step in the ELISA process since it eliminates unbound reagents and lowers background noise. The effectiveness and consistency of this process are greatly improved by the ELISA washer.

(a)



(b)

(c)

(d)

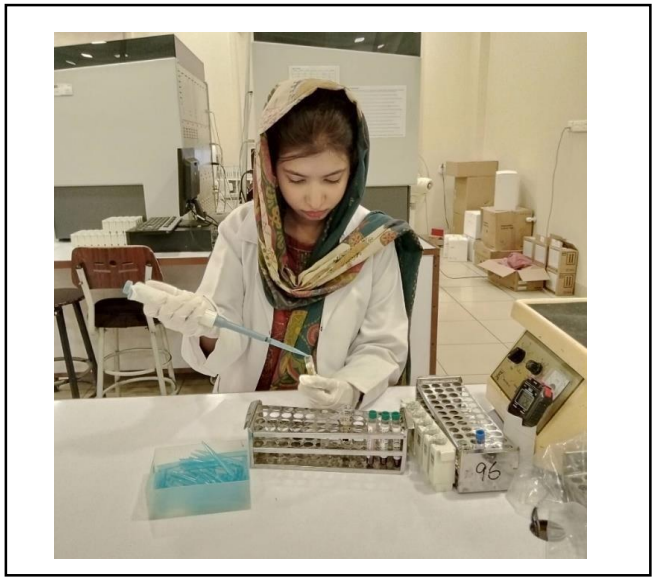
(e)

Figure 3.1 a to e Equipment

(a)

(b)

Figure 3.2 Kits



(a)

(b)

(c)

Figure 3.3 Sample collection, processing and preparation

3.11 Parameters of Study

The parameters of the study are:

Age,

Gender,

Ranson Criteria

CRP/Albumin ratio.

3.12 Protocol / Procedure of Study

1. After taking approval from institute, 105 patients at the Civil Hospital were selected.
2. The selection of participants was made on the basis of subject evaluation form, which was be filled out by the researcher, after taking consent from participant.
3. Blood sample was taken of the participants
4. The blood samples of patients, already diagnosed with acute pancreatitis by serum amylase/lipase, or by imaging, was taken for serum albumin and CRP, by venipuncture at the Civil hospital by their trained laboratory staff following all SOPs.
5. The blood sample was stored and CRP and serum albumin was evaluated by using the ELISA kit in lab of civil hospital Karachi. Labs used for calculating ranson score were already sent by doctors.
6. Once the samples were collected and evaluated, data was ready for interpretation
7. Entry of data was done in the SPSS software
8. After data entry, data was analyzed and documented.
9. The formulated Informed Proforma was structured as follows: the initial segment encompassed demographic particulars, including optionally provided names, age in years, gender, and relevant clinical data (abdominal and physical examination findings), as well as biochemical characteristics (serum amylase and lipase) sourced from patients' medical records.
10. The subsequent section was dedicated to determining serum albumin and CRP levels, establishing correlations with disease severity upon admission, and subsequently

comparing these findings with the established Ranson criteria.

11. The data collection process involved the assessment of CRP and albumin samples obtained from patients enrolled at the time of admission, facilitating a comprehensive analysis.

Human Albumin (ALB) ELISA Kit:

Catalog Number EHALB (96 tests), EHALBX10 (10 x 96 tests) Rev. 7

The solid-phase sandwich Enzyme-Linked Immunosorbent Assay (ELISA) kit for human albumin (ALB) was used, which is intended to identify and measure the amount of human albumin present in serum, plasma, and cell culture medium. It's working contents are as follows.

Prepare 1X Wash Buffer:

1. Wash Buffer was permitted after concentrating, (20X) to room temperature, stirred to dissolve any salts that may have precipitated.
2. Wash Buffer (20 mL) was diluted, and concentrate is added to 380 millilitres of distilled or deionized water. 1X Wash Buffer was signed up.
3. Concentrate and the 1X Wash Buffer was kept chilled. The diluted buffer was used within a month.

Prepare diluent:

Before use, Assay Diluent B was needed to be diluted five times with deionized or distilled water.

Preparation of biotin conjugate:

1. Before using, biotin conjugate was quickly spin down.
2. Biotin conjugate concentration was created in the vial by adding 100 µL of 1X Assay Diluent B.
3.Pipette was used to gently mix the concentrate (which keeps for five days at 4°C)

4. To use the biotin conjugate concentrate in step 2 of the ELISA protocol, it was diluted, 80 times with 1X Assay Diluent B.

Sample preparation guidelines:

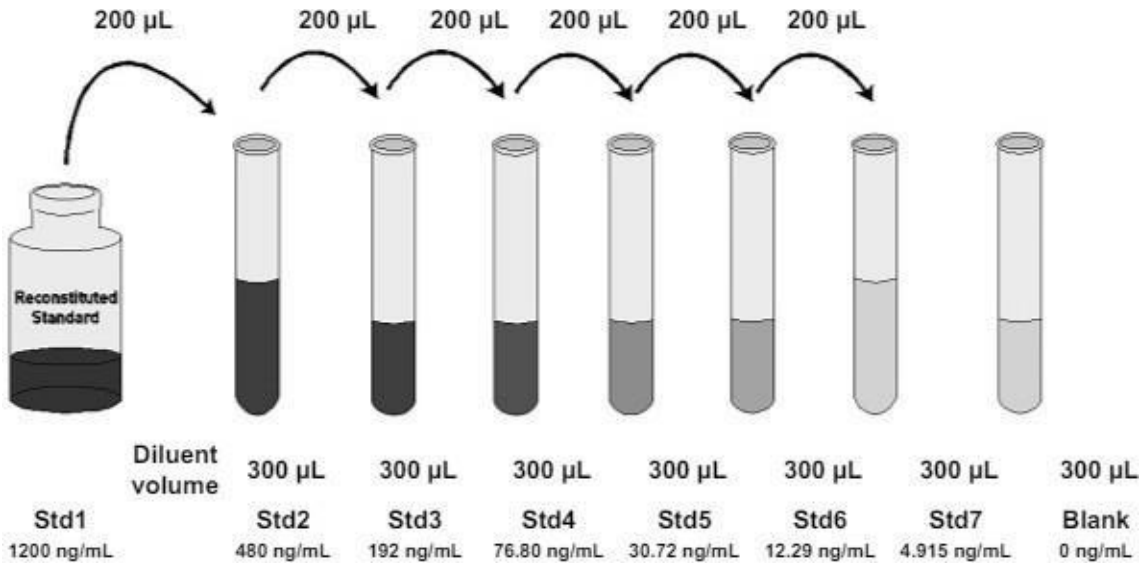
1. Samples were gathered in tubes devoid of endotoxins and pyrogens.
2. If samples were not going to be examined right away, they were frozen after collection.
3. Before doing an analysis, samples were fully defrost and thoroughly mixed (not swirlled), refrained from using lipemic or hemolyzed sera
4. Before doing an analysis, the sample was filtered or centrifuged if it contained a lot of particle debris.

Pre-dilute samples:

1. Test Assay Samples of serum, plasma, and cell culture supernatant were diluted using diluent C.
2.Thin serum and plasma by a factor of 500,000.

Dilute standards

1. A vial of lyophilized standard was spun for a short while.
2.1200 ng/mL standard solution was made, by adding 600 µL of Assay Diluent C to the lyophilized standard vial.
3. Each tube was pipetted with 300 µL of Assay Diluent C.
4. A series of dilutions was created by using the 1200 ng/mL standard solution (shown below). Before the next transfer, each tube was properly combined.
5. The zero standard was Assay Diluent C (0 ng/mL).



Prepare 1X Streptavidin-HRP solution:

Note that the Streptavidin-HRP was prepared within 15 minutes of use.

1. Before using, the Streptavidin-HRP was gently mixed with a pipette by spinning it briefly, as precipitates may form during storage.
2. 1X Assay Diluent B was diluted 2,000 times with streptavidin-HRP.

ELISA:

Before using, all of the reagents were allowed to come to room temperature and were combined. For each experiment, a standard curve was created. To use, the strips were placed inside the frames.

a.100 µL of standards were poured into the relevant wells for the standard curve. To begin with, each well was filled with 100 µL of diluted samples.

b. A lid was placed on the wells and were gently shook for 2.5 hours at room temperature.

c. The solution was thrown away and 1X Wash Buffer was used to wash four times. It was Washed by using an auto washer or multichannel pipette to fill each well with 300 µL of Wash Buffer. For optimal performance, all liquids were completely removed at every stage.Use. The plate was turned over and was pat dry with fresh paper towels.

d. 100 µL of the ready-made biotin conjugate was added to each well.

e. It was gently shaken and incubated at room temperature for one hour.

f. The remedy was thrown away and Washed again as in step 3.

First, 100 µL of the prepared Streptavidin-HRP solution was added (according to the recipe below) to each.

g. It was gently shaken and incubated at room temperature for 45 minutes.

i. Each well was filled with 100 µL of TMB substrate. It started to become blue on the substrate.

j. The mixture was gently shaken and was allowed sit at room temperature for half an hour in the dark.

k. The stop solution was incorporated and each well was filled with 50 µL of Stop Solution. The well's solution turned from blue to yellow.

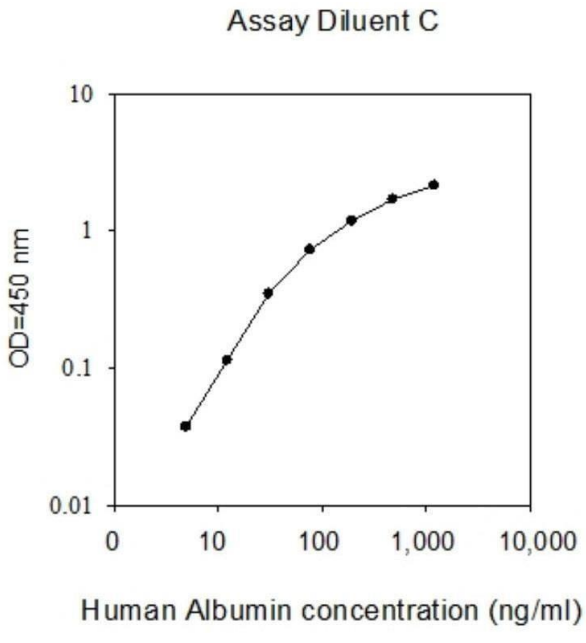
Standard curve:

1.450 nm absorbance reading was taken. After adding the Stop Solution, the plate was read after thirty minutes.

2. The standard curve was created, using software for curve fitting.

The best standard curve fit was provided by a four parameter technique.

3. Using the standard curve as a guide, the concentrations were determined for samples that are unknown. Multiple values were produced for the sample(s) by using the suitable factor to account for the dilution of the sample.

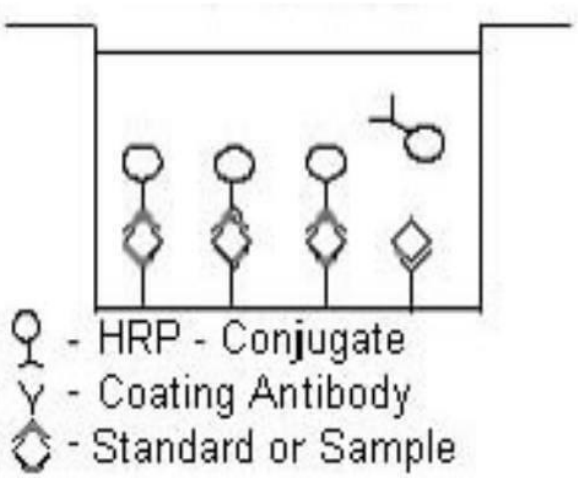


Human CRP Instant ELISA Kit:

Catalog Number BMS288INST

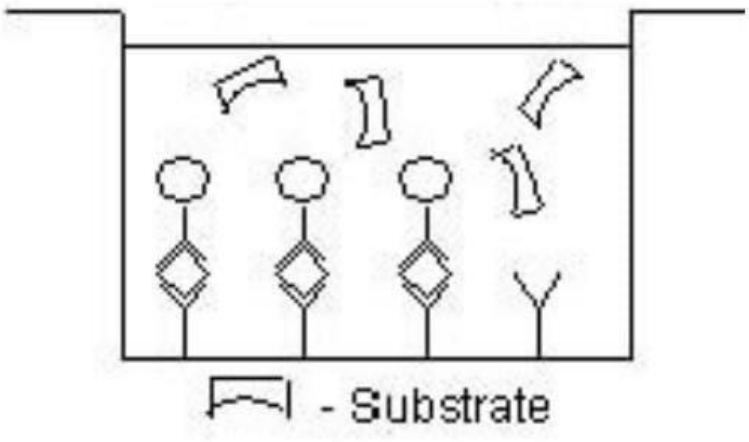
Principles of the test:

Microwells were coated with an anti-human C-reactive protein polyclonal antibody. Antibodies adsorbed to the microwells were bound by human C-reactive protein, which was either present in the sample or standard; a Human C-reactive protein that had been bound by the first antibody is bound by the HRP-conjugated monoclonal anti-human C-reactive protein antibody.



FIRST INCUBATION

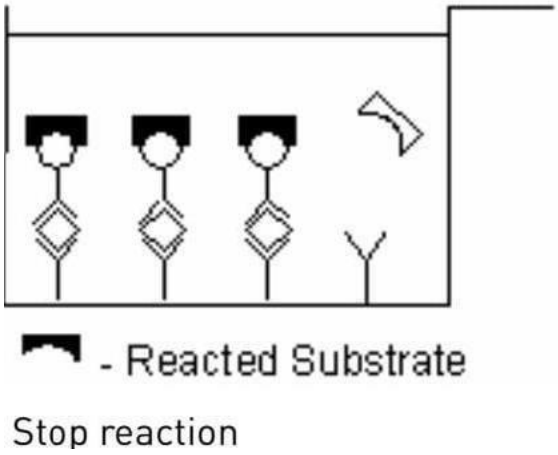
Following incubation unbound enzyme conjugated anti-human C-reactive protein is removed during a wash step and substrate solution reactive with HRP is added to the wells.



SECOND INCUBATION

Depending on how much soluble human C-reactive protein was in the sample, a colored product was formed. Acid was added to stop the reaction, and absorbance was gauged at 450 nm.

Seven human C-reactive protein standard dilutions were used to create a standard curve, and the concentration of the human C-reactive protein sample was ascertained.



Storage:

The whole kit or the ELISA plate was kept at -20°C.

Preparation of reagents and samples:

1. Before beginning the test method, the buffer concentration was needed to be diluted and brought to room temperature.

2. Gently reheated the buffer concentrate if crystals were formed in it. Until all of the

crystals were dissolved.

Wash buffer (1x)

1. A clean 500 mL graduated cylinder was filled to the brim with the full contents (25 mL) of the Wash Buffer Concentrate (20x). The volume was raised to its highest level. 500 millilitres of deionized or glass-distilled water.

2. It was placed in a sanitized washing basket and kept between 2° and 25°C. Note that Wash Buffer (1x) has a 30-day stability period.

Assay buffer (1x)

1. The whole contents of the Assay Buffer (5 mL) were poured. Concentrated 20 times into a sterile, graded 100 mL cylinder.
2. The last volume of 100 millilitres of purified water was reached while gently stiring.

Test protocol:

1. After removing the plate from -20°C, it was used right away. Samples were applied before the pellets have completely dissolved because this initiated the binding reaction in the standard strips. As soon as water is added.

2. In order to eliminate any pellet residues that attach to the well rim, the wells were filled completely or used at least 400 µL of washing buffer as directed in the handbook when performing the washing phase. and produced a wide range of results.

3.The washing buffer settled in the wells for a short while before allowing for aspiration.

4. The standard strip covers were removed, so that all of the lyophilized pellets stay in the wells. Assay Buffer was used to dilute serum or plasma samples 1:500 in accordance with the following dilution scheme:

1. 490 µL of Assay Buffer plus 10 µL of Sample
2. 450 µL of Assay Buffer plus 50 µL of prediluted sample
3. The number of microwell Strips required to test the desired number of samples plus microwell Strips for blanks and standards (colored) were determined. Each sample, standard,blank, and optional control sample was assayed in duplicate.
4. Extra microwell Strips from holder were removed and stored in foil bag with the

desiccantprovided at -20°C sealed tightly. Microwell strips containing the standard curve were placed,in position A1/A2 to H1/H2

5. As directed on the label of the standard strips (A1, A2 to H1, H2), distilled water was addedto each standard and blank well.
   The sample wells were filled with 50 µL of distilled water.
6. The indicated wells were filled with 100 µL of each prediluted Sample at a ratio of 1:500, in duplicate, and the contents were stirred.
7. Plate cover was placed over it and use a microplate shaker set to 400 rpm to incubate it for two hours at room temperature (18 to 25 degrees Celsius).
8. The microwell strips were washed three times, aspirating the contents of each well thoroughly in between washes, using about 400 µL of Wash Buffer per well.
9. To get rid of extra Wash Buffer after the last wash, microwell strips were tapped on anabsorbent pad or paper towel. After washing, the microwell strips were used right away.
10. 100 µL of TMB Substrate Solution was added to every well even the ones that are blank.
11. For approximately ten minutes, the microwell strips were incubated at ambient temperature(18° to 25°C).

The color development on the plate was watched and the substrate reaction was stopped. Each experiment required a unique determination of the optimal time frame for color development. Once the dark blue color was developed on the highest quality, the stop solution was added. The ELISA reader tracked the colour development at 620 nm. As soon as Standard 1's OD reaches between 0.9 and 0.95, the substrate reaction was terminated.

100 µL of Stop Solution was piped into every well—including the blank wells—to halt the enzyme process. It was imperative that the Stop Solution be applied promptly and evenly.

Throughout the microwells in order to render the enzyme entirely inactive.

After adding the Stop Solution, results were read right away, or within an hour if the microwell strips are kept in the dark at 2 to 8°C.

Using 450 nm as the primary wave length (620 nm as the reference wave length is optional; 610 nm to 650 nm is acceptable), the absorbance of each microwell was determined using a spectrophotometer.

The color development on the plate was watched and the substrate reaction was stopped. Each experiment required a unique determination of the optimal time frame for color development. Once the dark blue color was developed on the highest quality, the stop solution was added. The ELISA reader tracked the colour development at 620 nm. As soon as Standard 1's OD reaches between 0.9 and 0.95, the substrate reaction was terminated.

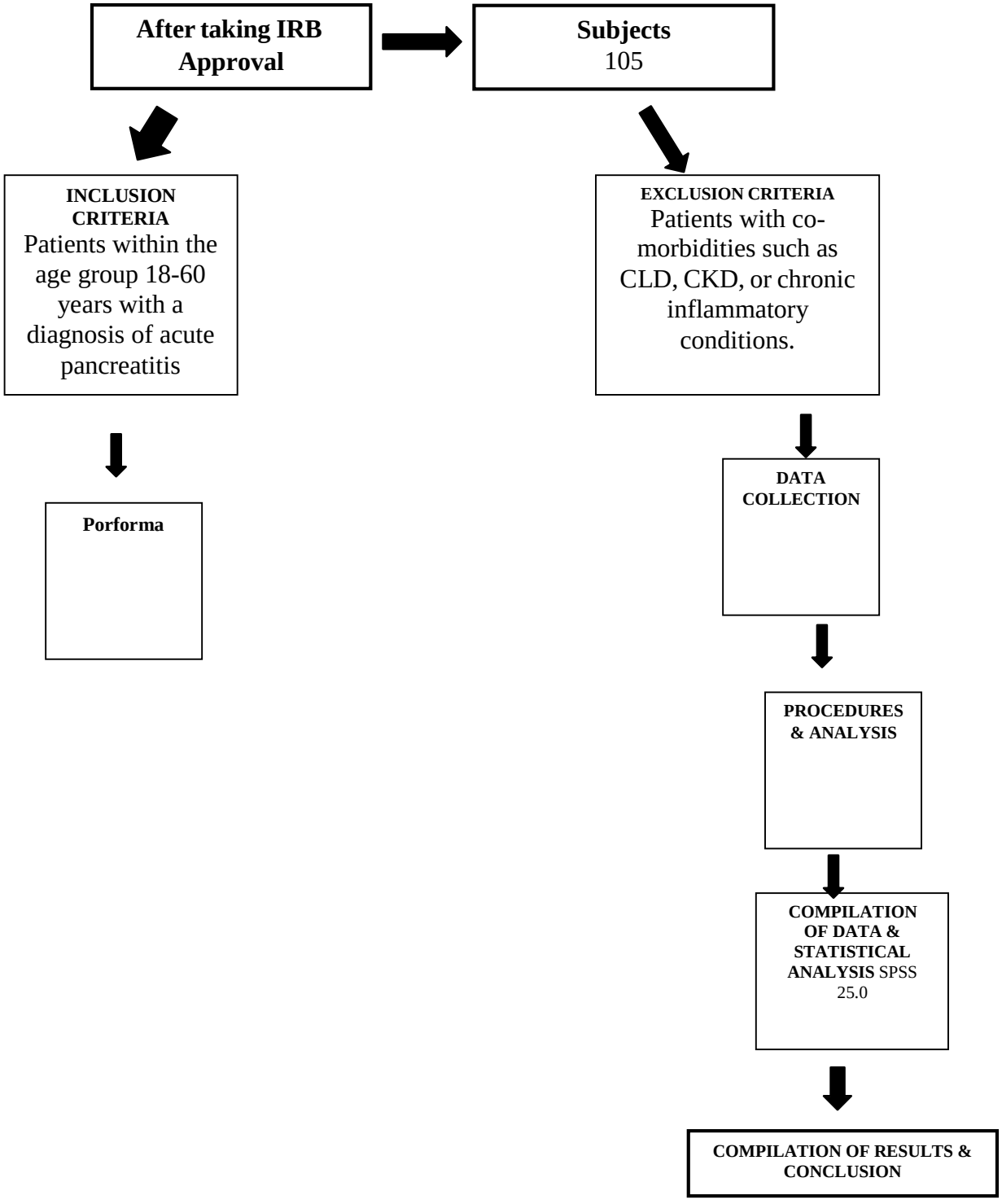
100 µL of Stop Solution was piped into every well—including the blank wells—to halt the enzyme process. It was imperative that the Stop Solution be applied promptly and evenly.

Throughout the microwells in order to render the enzyme entirely inactive.

After adding the Stop Solution, results were read right away, or within an hour if the microwell strips are kept in the dark at 2 to 8°C.

Using 450 nm as the primary wave length (620 nm as the reference wave length is optional; 610 nm to 650 nm is acceptable), the absorbance of each microwell was determined using a spectrophotometer.

3.13 Flow Chart/ Algorithm of the Study



3.14 STATISTICAL ANALYSIS

Data was analyzed using SPSS version 25. Quantitative variables such as age, WBC, LDH, AST, serum amylase, serum lipase, CRP, serum albumin, creatinine, serum bilirubin, urea, hematocrit, duration of symptoms, SBP, DBP, heart rate, respiratory rate, SpO2, CRP / Albumin ratio and Ranson score was reported as mean and SD or median (IQR). While qualitative variables such as gender, residence, diabetes, hypertension, smoking and severity of acute pancreatitis was reported as frequency and percentage. Chi- square test and Fisher test were also applied. P value was less than 0.05 and it's statistically significant.

RESULTS

4.1 Demographic profile

The study comprised 105 patients in total, of which 36.2% were female and 63.8% were male. Patients ranged in age from 18 to 60 years old, with a mean age of 42.20±13.60 years. Of the patients, 21.9% were under 30 years old, 48.6% were between the ages of 31 and 50, and 29.5% were beyond 50. 51.4% of the patients were from rural areas and 48.6% were from urban areas. Tables 4.1 and 4.3 (Figure 4.1 and Figure 4.3) provide comprehensive descriptive statistics pertaining to gender, age, and place of residence

Table 4.1: Frequency distribution of gender (n=105)

	Frequency	**Percent**
Male	67	63.8
Female	38	36.2
TOTAL	**105**	**100**

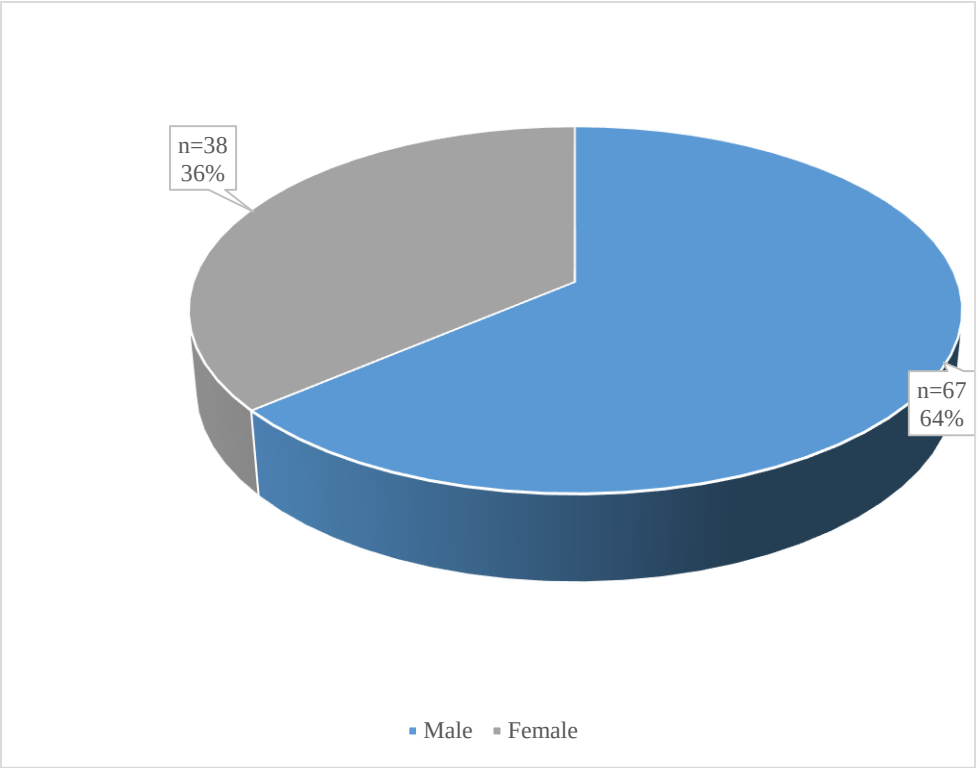


Figure 4.1: Pie chart presenting gender distribution

Table 4.2: Descriptive statistics of age (years) (n=105)

	Mean	**Std. Deviation**	**Min**	**Max**	**Range**
Age(years)	42.20	13.60	18	60	42

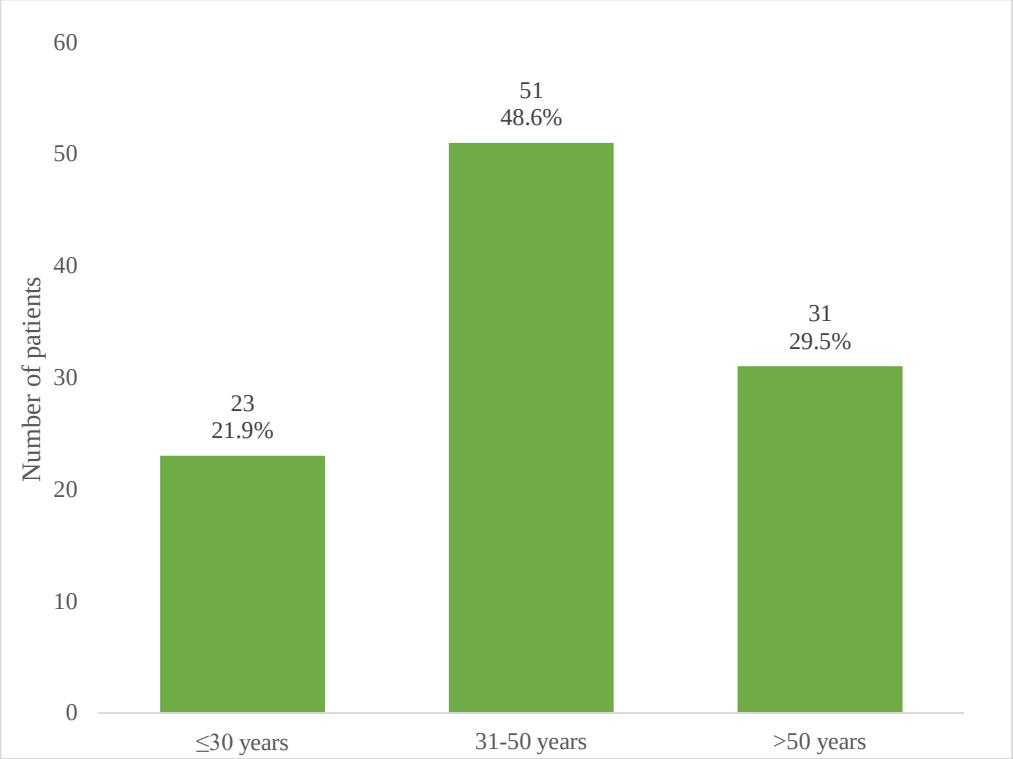


Figure 4.2: Bar chart presenting age groups

Table 4.3: Frequency distribution of residence (n=105)

	Frequency	**Percent**
Urban	51	48.6
Rural	54	51.4
TOTAL	**105**	**100**

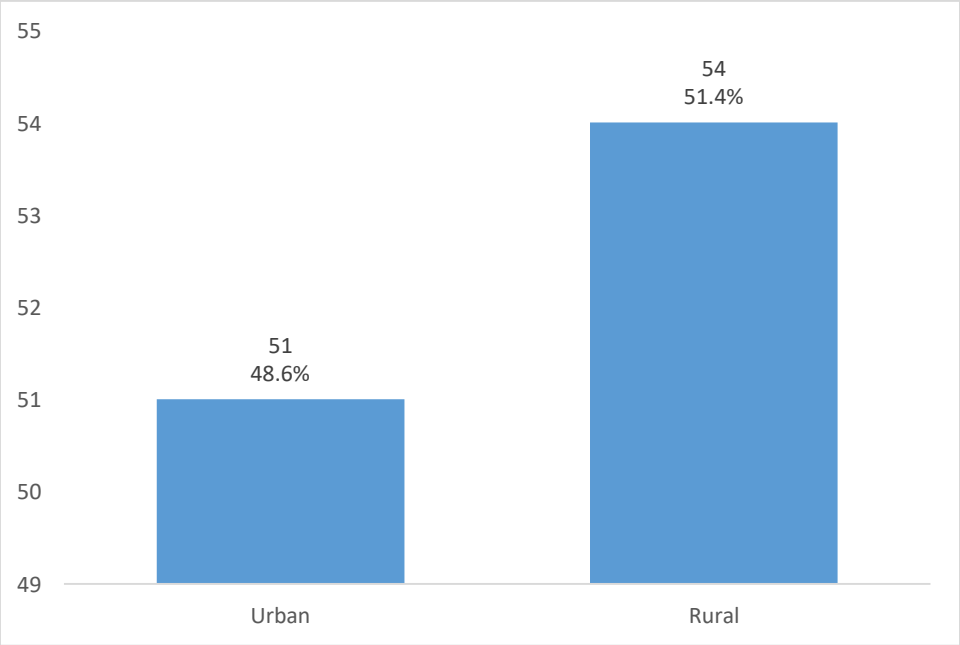


Figure 4.3: Bar chart presenting distribution of residence

4.2 Co morbids

Table 4.4 to Table 4.7 (Figure 4.4 to Figure 4.6) show that out of 105 patients, 50.5% were smokers and 49.5% were non-smokers. Additionally, 46.7% of patients had diabetes mellitus, 49.5% had hypertension, and 66.7% had multi-system organ failure.

Table 4.4: Frequency distribution of smoking status (n=105)

	Frequency	**Percent**
Smokers	53	50.5
Non-Smokers	52	49.5
TOTAL	**105**	**100**

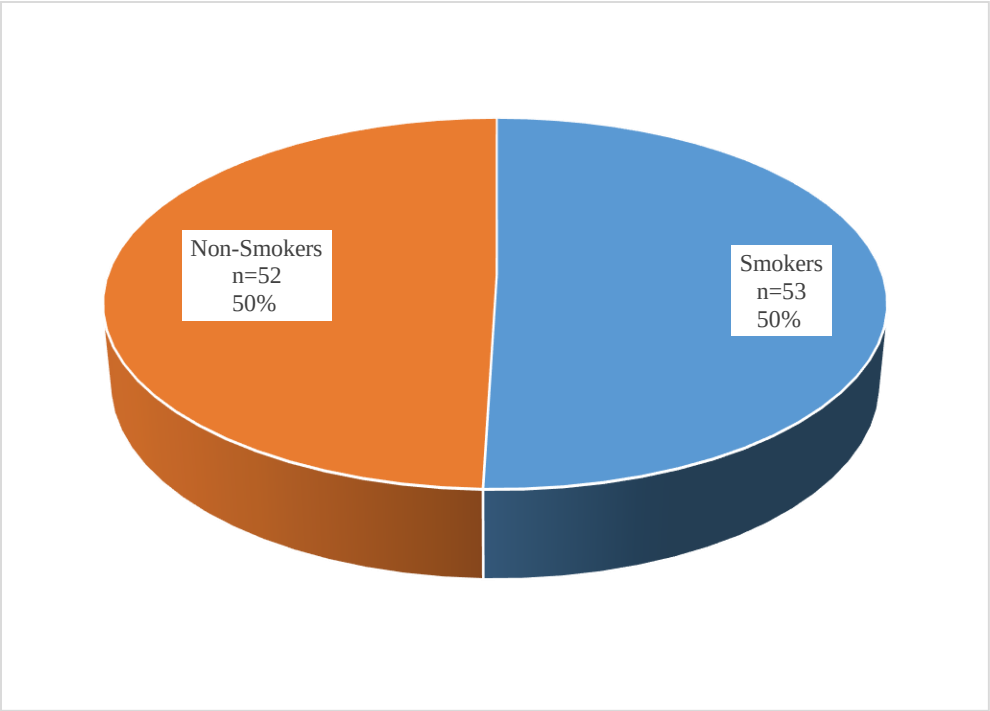


Figure 4.4: Pie chart presenting distribution of smokers and non-smokers

Table 4.5: Frequency distribution of diabetes mellitus (n=105)

	Frequency	**Percent**
Yes	49	46.7
No	56	53.3
TOTAL	**105**	**100**

Table 4.6: Frequency distribution of hypertension (n=105)

	Frequency	**Percent**
Yes	52	49.5
No	53	50.5
TOTAL	**105**	**100**

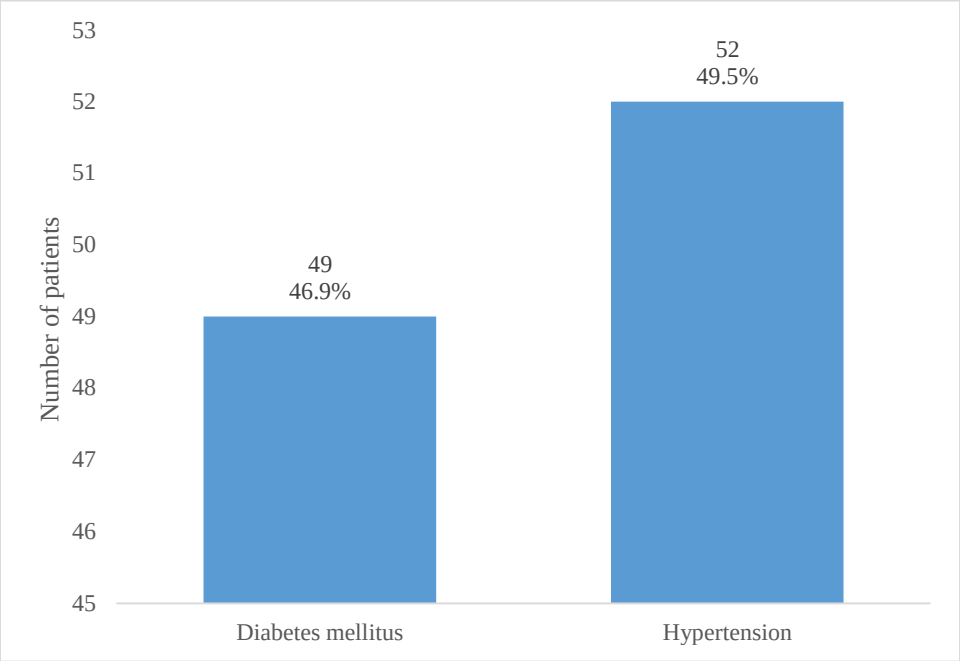


Figure 4.5: Bar chart presenting distribution of diabetes mellitus and hypertension

Table 4.7: Frequency distribution of multi-system organ failure (n=105)

	Frequency	**Percent**
Yes	70	66.7
No	35	33.3
TOTAL	**105**	**100**

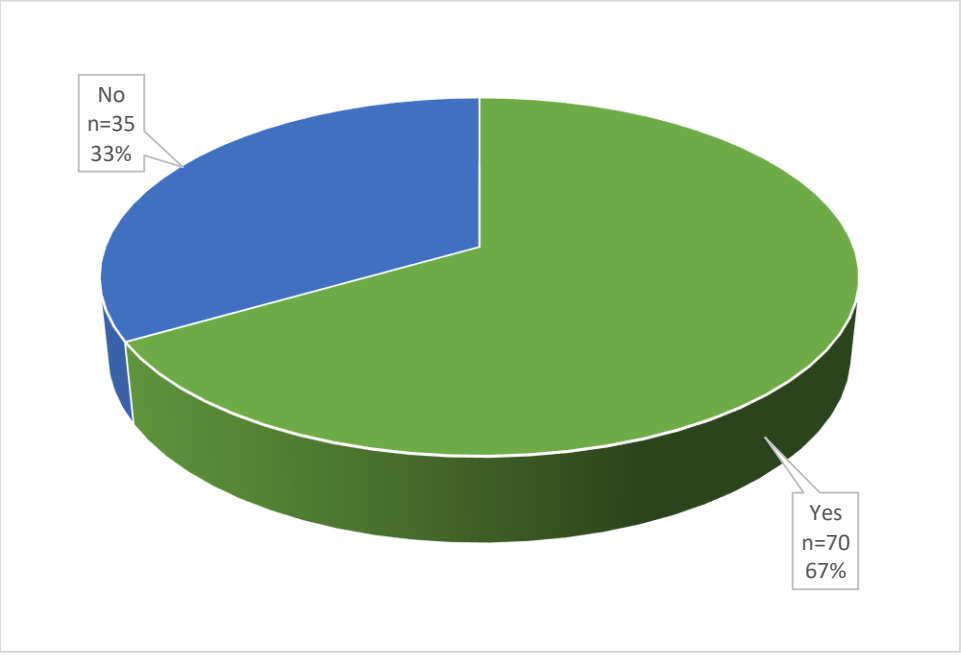


Figure 4.6: Pie chart presenting distribution of multi-system organ failure

4.3 Cardiovascular Profile

The average heart rate, diastolic blood pressure, and systolic blood pressure were 133.000±17.384 beats per minute, 64.619±7.835 mmHg, and 74.619±10.040 mmHg, respectively. Table 4.8 and Figure 4.7 presents comprehensive descriptive information of the cardiovascular profile.

Table 4.8: Descriptive statistics of cardiovascular profile (n=105)

	Mean	**Std. Deviation**	**Min**	**Max**	**Range**
Systolic blood pressure (mmHg)	74.619	10.04	50	90	40
Diastolic blood pressure (mmHg)	64.619	7.83	50	90	40
Heart rate (beats/min)	133.000	17.38	100	175	75

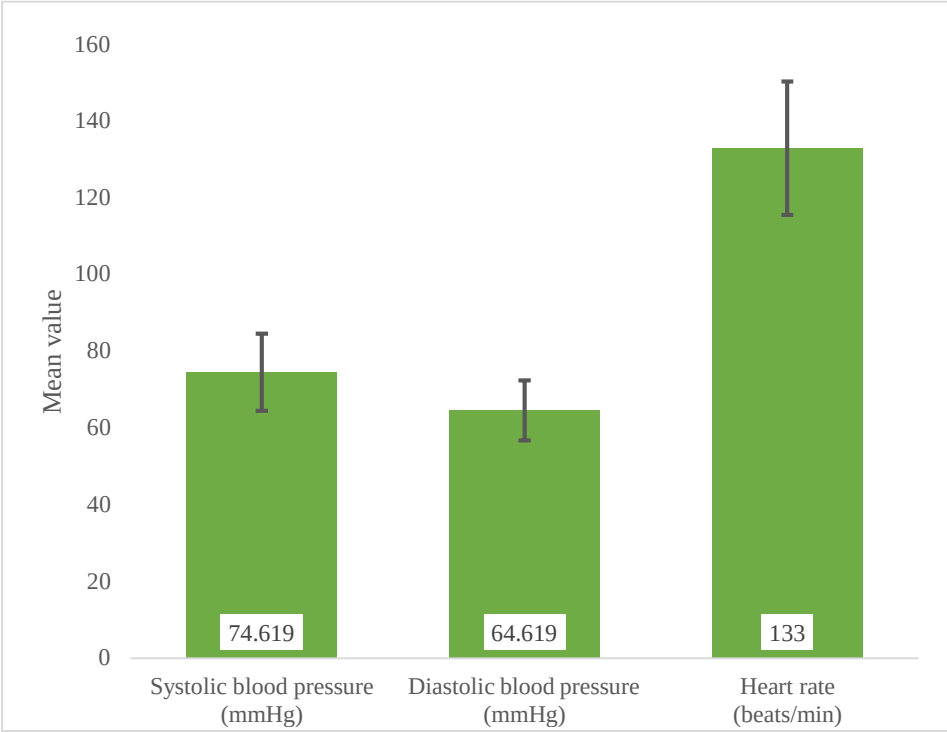


Figure 4.7: Mean heart rate, systolic and diastolic blood pressure

4.4 Renal and liver function profile

The mean values of the creatinine, blood urea nitrogen and renal function test were 2.247±0.278 mg/dL, 9.276±4.617 mg/dL, and 5.480±3.745 mg/dL, respectively. Table 4.9 (Figure 4.8) provides comprehensive descriptive information for the creatinine, blood urea nitrogen, and renal function test.

The mean values for LDH, AST, bilirubin, and liver function test were 359.828±8.231 U/L, 258.495±7.819 U/L, 1.735±0.448 mg/dL, and 2.648±0.636, respectively. Table 4.10 presents the detailed descriptive data for these tests (figures 4.9 and 4.10).

Table 4.9: Descriptive statistics of renal function profile (n=105)

	Mean	Std. Deviation	Min	Max	Range
Creatinine (mg/dL)	2.247	0.27	1.8	2.9	1.1
Blood Urea Nitrogen (mg/dL)	9.276	4.61	5	25	20
Renal Function Test	5.480	3.74	0.15	13.6	13.45

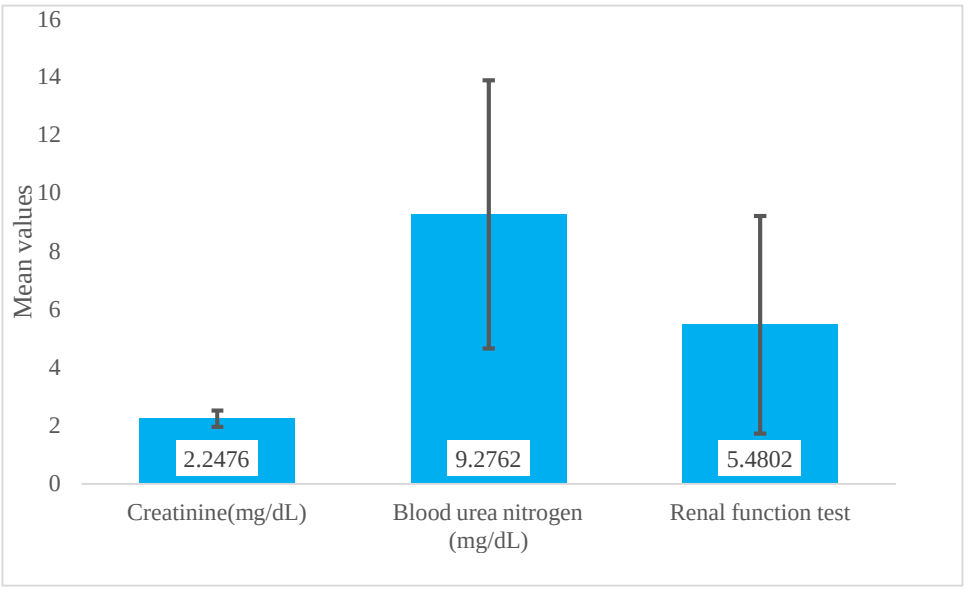


Figure 4.8: Mean creatinine, blood urea nitrogen and renal function test

Table 4.10: Descriptive statistics of liver function profile (n=105)

	Mean	Std. Deviation	Min	Max	Range
LDH (U/L)	359.828	8.23	350	380	30
AST(U/L)	258.495	7.81	245	276	31
Bilirubin (mg/dL)	1.735	0.44	1.2	2.8	1.6
Liver Function Test	2.648	0.63	1.1	4.24	3.14

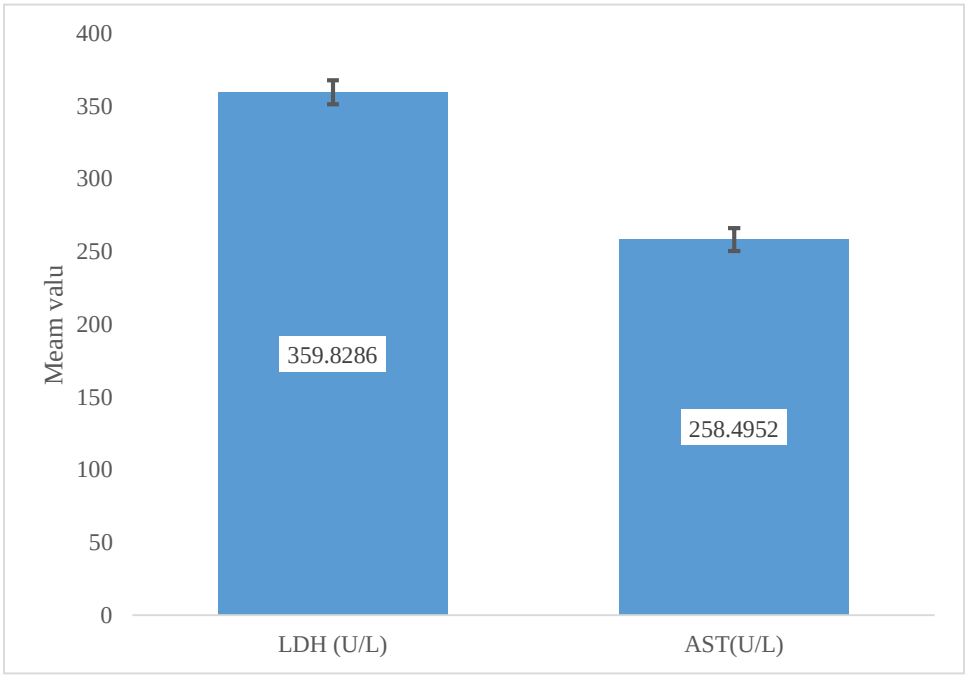


Figure 4.9: Mean LDH and AST among study population

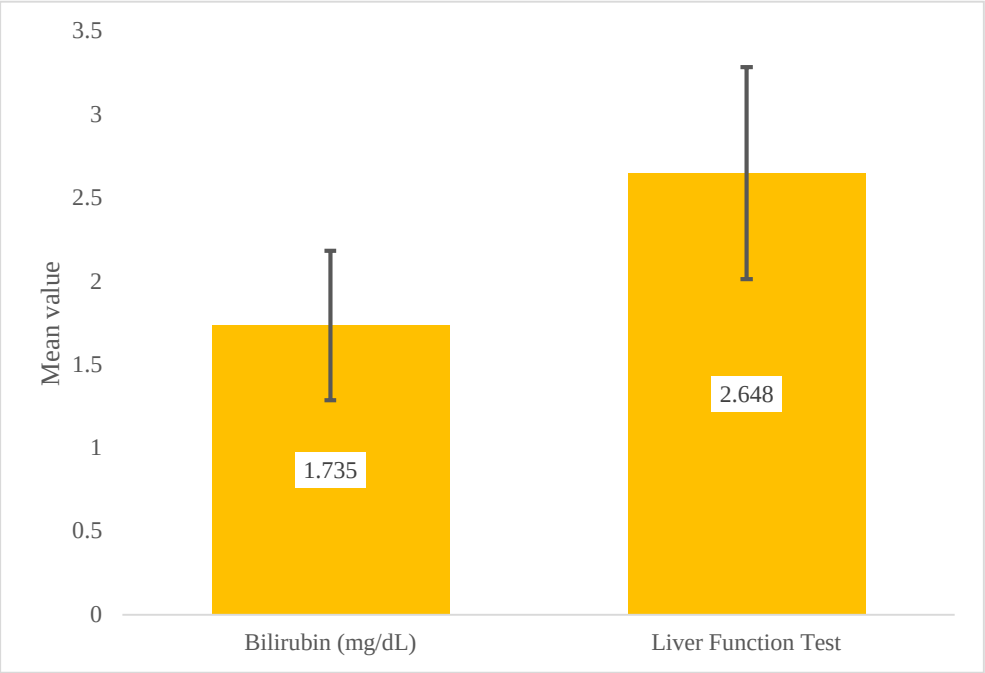


Figure 4.10: Mean bilirubin and liver function test among study population

4.5 Respiratory, immune response hematological, and digestive functions profile

As shown in Table 4.11 (figure 4.11), the mean respiratory rate was 27.361 breaths/minute and the mean oxygen saturation was 52.190±6.790%.

According to Tables 4.12 and 4.13 (figures 4.12 and 4.13), the mean white blood cell count was 18114.285±1436.571/cmm, and the mean neutrocytosis was 13.585±9.049 x109 /L. The mean values for hemoglobin, amylase, and lipase were, respectively, 8.228±6.340%, 327.666±17.916 U/L, and 513.961±51.613 U/L.

Table 4.11: Descriptive statistics of respiratory profile (n=105)

	Mean	**Std. Deviation**	**Min**	**Max**	**Range**
Respiratory Rate (Breaths/min)	27.361	4.60	20	38	18
SPO2 (%)	52.190	6.79	40	65	25

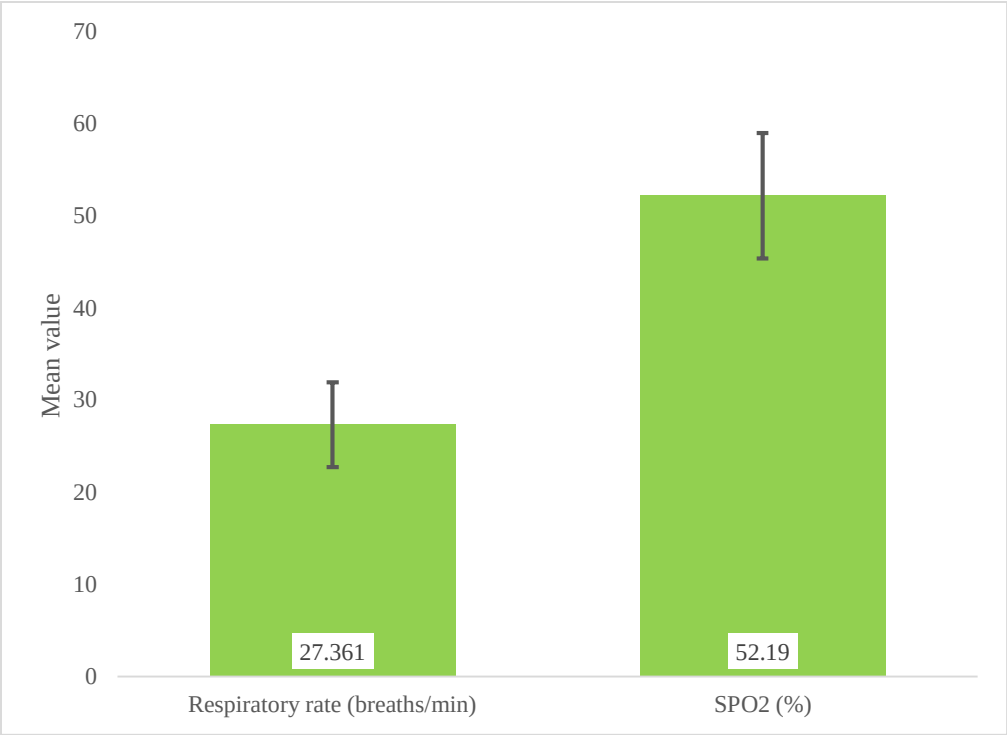


Figure 4.11: Mean respiratory rate and oxygen saturation among study population

Table 4.12: Descriptive statistics of inflammation or immune response profile (n=105)

	Mean	**Std. Deviation**	**Min**	**Max**	**Range**
White blood cells (/cmm)	18114.285	1436.57	15000	21000	6000
Neutrocytosis ($x10^9$ /L)	13.585	9.049	0.4	36	35.6

Table 4.13: Descriptive statistics of hematological and digestive functions profile (n=105)

	Mean	Std. Deviation	Min	Max	Range
Hematocrit (%)	8.228	6.34	2	32	30
Amylase (U/L)	327.666	17.916	300	350	50
Lipase (U/L)	513.961	51.613	480	890	410

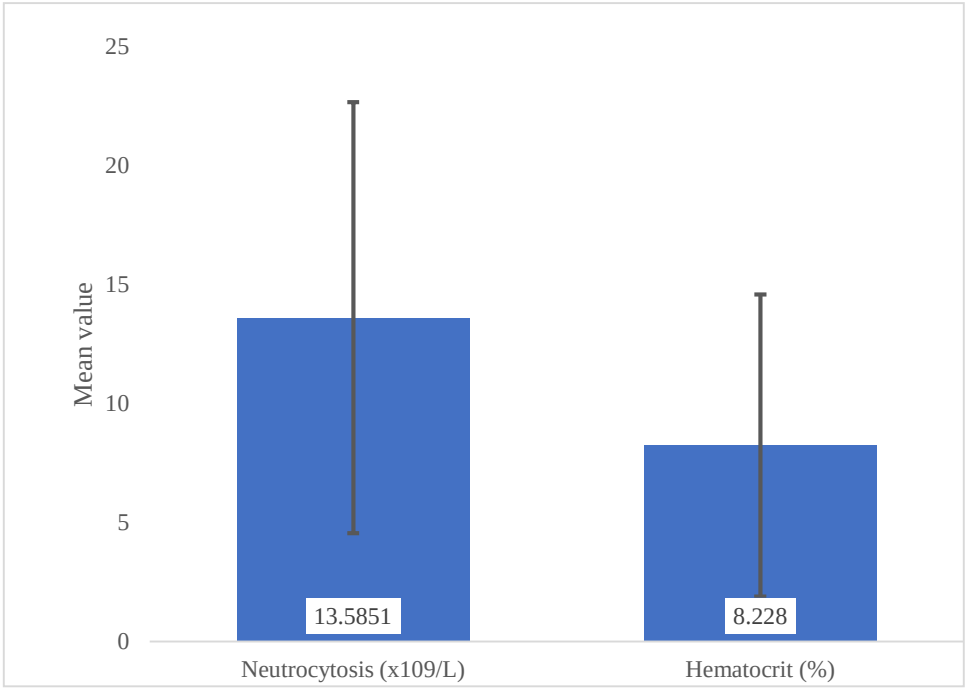


Figure 4.12: Mean neutrocytosis and hematocrit among study population

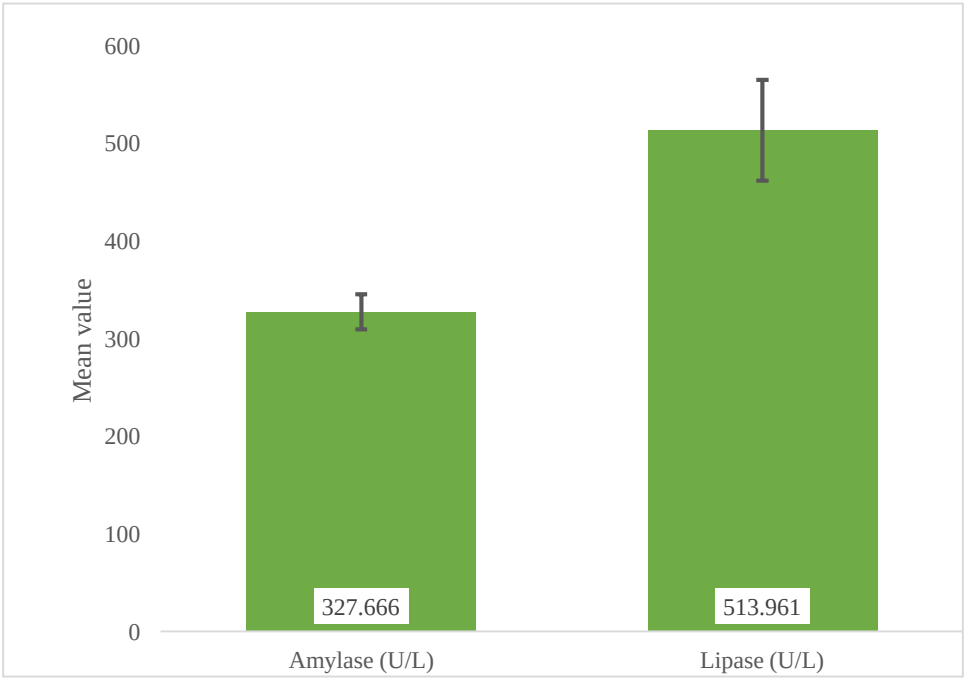


Figure 4.13: Mean amylase, lipase among study population

4.6 Severity of acute pancreatitis

Tables 4.14 and 4.15 (figure 4.14) show that the mean Ranson score was 6.485±2.144, with 5 (4.8%) patients having mild acute pancreatitis, 63 (60%) having moderate acute pancreatitis, and 37 (35.2%) having severe acute pancreatitis.

Mean CRP, albumin, and CRP-albumin ratio were 2.385±0.690 mg/dL, 5.357±4.122 mg/dL, and 12.980±9.870 mg/dL respectively. There were 51 patients (48.6%) who had a CRP-albumin ratio <4.35, while 54 patients (51.4%) had a CRP-albumin ratio ≥4.35. Extensive descriptive statistics, as shown in Figures 4.15 and 4.16 of Tables 4.16 and 4.17

Table 4.14: Descriptive statistics of Ranson score (n=105)

	Mean	**Std. Deviation**	**Min**	**Max**	**Range**
Ranson Score	6.485	2.144	2	10	8

Table 4.15: Frequency distribution of acute pancreatitis severity by Ranson score (n=105)

	Frequency	**Percent**
Mild (0-2)	5	4.8
Moderate (3-6)	63	60
Severe (7-10)	37	35.2
TOTAL	**105**	**100**

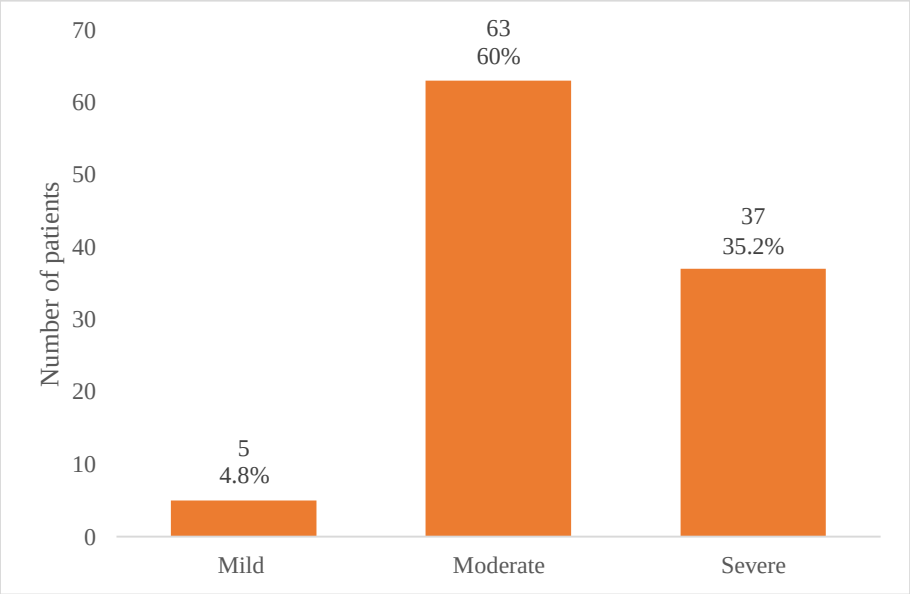


Figure 4.14: Severity of acute pancreatitis by Ranson score

Table 4.16: Descriptive statistics of CRP, albumin and CRP-albumin ratio (n=105)

	Mean	Std. Deviation	Min	Max	Range
CRP (mg/dL)	12.980	9.870	1.24	36.00	34.76
Albumin (g/dL)	2.485	0.690	0.80	4.24	3.44
CRP-Albumin ratio	5.357	4.122	0.35	13.60	13.25

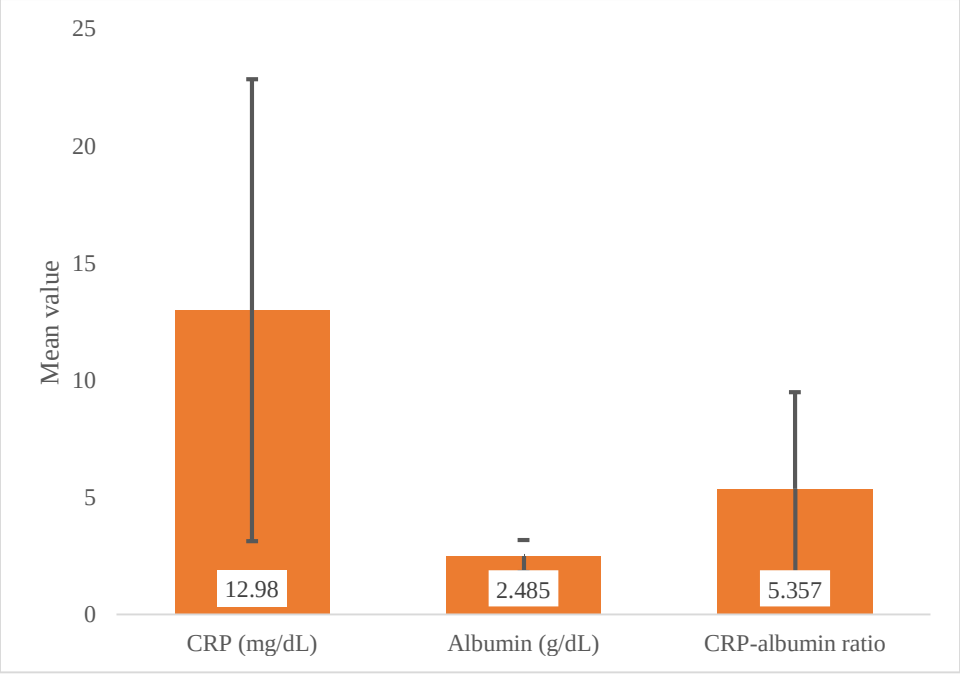


Figure 4.15: Mean CRP, albumin and CRP albumin ratio

Table 4.17: Frequency distribution of CRP-Albumin ratio (n=105)

	Frequency	**Percent**
<4.35	51	48.6
≥4.35	54	51.4
TOTAL	**105**	**100**

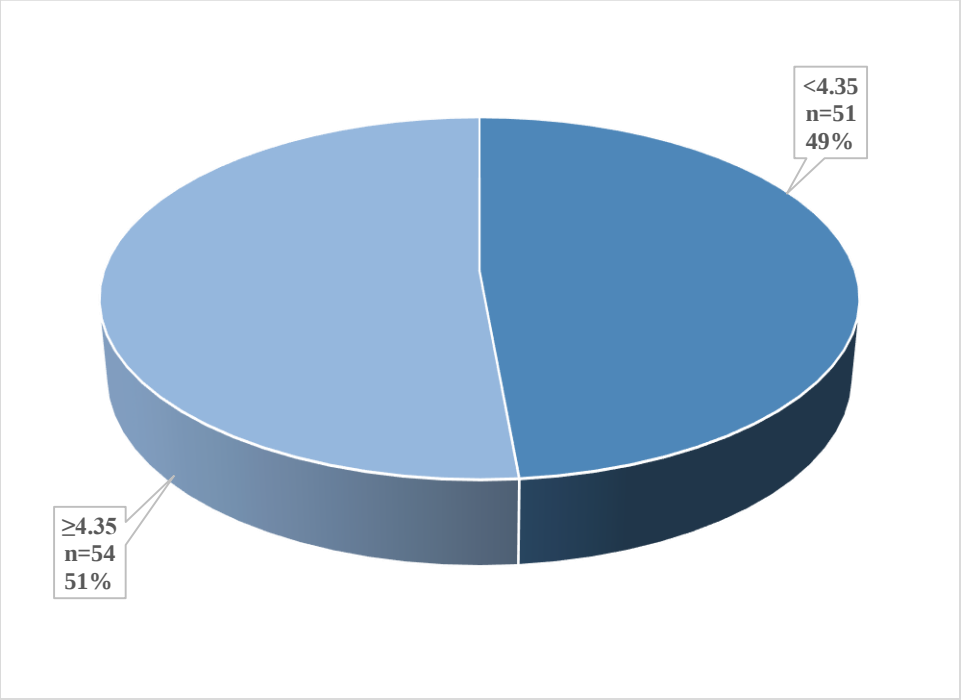


Figure 4.16: Distribution of CRP-Albumin ratio

4.7 Diagnostic accuracy of CRP-albumin ratio in comparison of Ranson score

The CRP-albumin ratio's sensitivity, specificity, predictive values, and diagnostic accuracy were determined using the Ranson score as the gold standard for the diagnosis of severe acute pancreatitis. According to the CRP albumin ratio, 34 patients had a true positive diagnosis of severe acute pancreatitis, and 51 patients had a true negative diagnosis, both of which were accurate. As shown in Table 4.18, the corresponding values for sensitivity, specificity, PPV, NPV, and accuracy were 91.9%, 75%, 66.7%, 94.4%, and 80.95%.

The sensitivity, specificity, PPV, NPV, and accuracy for male patients were 95.5%, 80%, 95.5%, 80%, and 85.07% whereas Sensitivity, specificity, PPV, NPV, and accuracy were 86.7%, 65.2%, 61.9%, 88.2%, and 73.7% among female patients, respectively.

The sensitivity, specificity, PPV, NPV, and accuracy among patients aged 30 years or older were 81.8%, 91.7%, 90%, 84.6%, and 86.95%.

The comparable values for sensitivity, specificity, PPV, NPV, and accuracy among patients between the ages of 31 and 50 were 94.7%, 62.5%, 60%, 95.2%, and 74.50% and sensitivity, specificity, PPV, NPV, and accuracy was 63.6%, 83.3%, and 87.09% among patients older than 50.

The stratification according to gender, age, residence, smoking status, diabetes mellitus, hypertension and multi-system organ failure was done and sensitivity, specificity, and diagnostic accuracy were also calculated. Detailed results are presented from Table 4.19 to Table 4.33 respectively.

Table 4.18: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard (n=105)

CRP albumin ratio	Severe Acute pancreatitis by Ranson score			P-VALUE
	Yes	**No**	**Total**	
<4.35	34	17	**51**	**0.00***
≥4.35	3	51	**54**	
Total	**37**	**68**	**105**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
91.9%	**75%**	**66.7%**	**94.4%**	**80.95%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.19: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for male patients (n=67)

CRP albumin ratio	Severe Acute pancreatitis by Ranson score			P-VALUE
	Yes	No	Total	
<4.35	21	9	**30**	**0.00***
≥4.35	1	36	**37**	
Total	**22**	**45**	**67**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
95.5%	**80%**	**95.5%**	**80%**	**85.07%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.20: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for female patients (n=38)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	13	8	**21**	**0.00***
≥4.35	2	15	**17**	
Total	**15**	**23**	**38**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
86.7%	**65.2%**	**61.9%**	**88.2%**	**73.7%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.21: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for patients with age≤30 years (n=23)

CRP albumin ratio	Severe Acute pancreatitis by Ranson score			P-VALUE
	Yes	No	Total	
<4.35	9	1	10	0.00*
≥4.35	2	11	13	
Total	11	12	23	
Sensitivity	Specificity	PPV	NPV	Accuracy
81.8%	91.7%	90%	84.6%	86.95%

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.22: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for patients with age 31-50 years (n=51)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	18	12	**30**	**0.00***
≥4.35	1	20	**21**	
Total	**19**	**32**	**51**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
94.7%	**62.5%**	**60%**	**95.2%**	**74.50%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.23: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for patients with age >50 years (n=31)

CRP albumin ratio	Severe Acute pancreatitis by Ranson score			P-VALUE
	Yes	No	Total	
<4.35	7	4	**11**	**0.00***
≥4.35	0	20	**20**	
Total	**7**	**24**	**31**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
100%	**83.3%**	**63.6%**	**83.3%**	**87.09%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.24: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for patients from urban areas (n=51)

CRP albumin ratio	Severe Acute pancreatitis By Ranson score			P-VALUE
	Yes	No	Total	
<4.35	15	8	**23**	**0.00***
≥4.35	1	27	**28**	
Total	**16**	**35**	**51**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
93.8%	**77.1%**	**65.2%**	**96.4%**	**82.35%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.25: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for patients from rural areas (n=54)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	19	9	**28**	**0.00***
≥4.35	2	24	**26**	
Total	**21**	**33**	**54**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
90.5%	**72.7%**	**67.9%**	**92.3%**	**79.62%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.26: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for smokers (n=53)

CRP albumin ratio	Severe Acute pancreatitis by Ranson score			P-VALUE
	Yes	No	Total	
<4.35	17	7	**24**	**0.00***
≥4.35	1	28	**29**	
Total	**18**	**35**	**53**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
94.4%	**80%**	**70.8%**	**96.6%**	**84.9%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.27: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for non-smokers (n=52)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	17	10	**27**	**0.00***
≥4.35	2	23	**25**	
Total	**19**	**33**	**52**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
89.5%	**69.7%**	**63%**	**92%**	**76.92%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.28: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for diabetic patients (n=49)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	18	8	**26**	**0.00***
≥4.35	1	22	**23**	
Total	**19**	**30**	**49**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
94.7%	**73.3%**	**69.2%**	**95.7%**	**81.63%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.29: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for non-diabetic patients (n=56)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	16	9	**25**	**0.00***
≥4.35	2	29	**31**	
Total	**18**	**38**	**56**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
88.9%	**76.3%**	**64%**	**93.5%**	**80.35%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.30: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for hypertensive patients (n=52)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	16	11	**27**	**0.00***
≥4.35	1	24	**25**	
Total	**17**	**35**	**52**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
94.1%	**68.6%**	**59.3%**	**96%**	**76.92%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.31: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for non-hypertensive patients (n=53)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	18	6	**24**	**0.00***
≥4.35	2	27	**29**	
Total	**20**	**33**	**53**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
90%	**81.8%**	**75%**	**93.1%**	**84.90%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.32: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for patients with multi-system organ failure (n=70)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	32	12	**44**	**0.00***
≥4.35	1	25	**26**	
Total	**33**	**37**	**70**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
97%	**67.6%**	**72.7%**	**96.2%**	**81.42%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

* Significant at 0.05 level.

Table 4.33: Diagnostic accuracy of CRP-Albumin ratio in detection of severe acute pancreatitis with Ranson score as gold standard for patients with no multi-system organ failure (n=35)

CRP albumin ratio	**Severe Acute pancreatitis by Ranson score**			**P-VALUE**
	Yes	**No**	**Total**	
<4.35	2	5	**7**	**0.111****
≥4.35	2	26	**28**	
Total	**4**	**31**	**35**	
Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy**
50%	**83.9%**	**28.6%**	**92.9%**	**80%**

Chi square/Fisher exact test was applied.
P-Value ≤0.05 considered as significant.

**Not Significant at 0.05 level.

CHAPTER 5

DISCUSSION

Acute pancreatitis is a relatively common condition worldwide and is characterized by acute and severe upper abdominal pain. AP is an inflammatory condition of the pancreas and may have a variable severity. Most of the patients have mild disease with minimal morbidity, and the rest of the patients have 10%-20% of mortality in Severe acute pancreatitis (Banks PA. et.al 2016)

Accurate and timely identification of the severity and prognostic factors of AP patients is critical. Currently, Ranson Score, BISAP, and MCTSI were frequently used for early identification of the severity of AP (Silva-Vaz P, et.al 2020).

A simple, repeatable, and non-invasive laboratory procedure, is needed to predict the severity and prognostic factors of AP patients. In a study by Mustafa K, the researcher used the CRP/ALB ratio to predict SAP, death, pancreatic necrosis, and organ failure among AP patients. CRP/ALB ratio on day 1 was related to SAP and pancreatic necrosis, nevertheless, CRP/ALB ratio on day 1 was not related to death and organ failure. The findings demonstrated the predictive value of the CRP/ALB ratio for the determination of theseverity and prognosis of AP. However, CRP/ALB ratio may not superior to the Ranson, MCTSI, and BISAP scores. The predictive value of the CRP/ALB ratio may be helpful to the assessment of SAP and prognosis in AP patients. Previous studies have shown CRP/albumin ratio as an important prognostic marker in acute pancreatitis. Mustafa K. et al.,in 2017, concluded in his study that the CRP/albumin ratio is a novel but promising, easy-to-measure, repeatable, non-invasive inflammation-based prognostic score in acute pancreatitis(Kaplan M , et.al 2017)

A high CRP typically indicates an acute inflammatory or infectious process, but a low albumin level is typically linked to chronic illness, which is frequently caused by a nutritional deficit. These studies are easily accessible, typically in a matter of minutes, are frequently carried out automatically as a component of an admission profile in cases of acute admission (Blatchford O, et.al 2000).

Yilmaz et al. also looked at the connection between severe acute pancreatitis and the CRP/albumin ratio along with Red blood cell distribution width. Using Ranson scoring, they discovered that if the ratio was more than 8.51, they could predict severity with 66% sensitivity and 90% specificity. While in this study we also checked the connection between CRP/albumin ratio and Ranson Criteria. We discovered that if the ratio will be less than 4.35 then the sensitivity is 91% and specificity is 75% (Yılmaz, E. et.al 2018).

The accuracy of CRP in assessing the likelihood of organ failure was 83.3%, (Shanshan Han,et.al 2023), In this study 66.7% patients had multi-system organ failure.

Prior research demonstrated the clear significance of CRP, Cr, and Albumin for illnesses associated with systemic inflammatory response, such acute pancreatitis; nevertheless, their prognostic value in isolation is inadequate. Consequently, some research integrated such factors for a stronger predictive impact (Azab, B, et.al 2011).

In comparison to a single marker, the CRP/ALB ratio, which combines the index of ALB and CRP levels, is known to be more consistently associated with prognosis and accurately reflects the extent of inflammation or nutritional inadequacy (Oh, T. et.al 2018).

Numerous research has looked at the CRP/ALB ratio's predictive significance in a range of illnesses. The current investigation shown that the CRP/ALB ratio on days two and three might predict the SAP and prognosis outcome of AP. High CRP and low ALB levels were linked to in-hospital mortality in SAP patient when AP patients underwent debridement, the admission CRP/ALB ratio was noticeably increased (Kim, M. H., et.al 2015).

Our research showed no discernible relationship between prognostic status and blood cell counts, NLR or PLR. Similarly, previous research likewise found no statistically significant changes in platelet counts at the time of admission between patients with AP and healthy groups (Yarkaç, A, et.al 2019).

Additionally, according to (Siregar GA et.al 2019) the kind of organ failure was used to stratify the patients. Seven of the 24 patients (29.1%) with severe AP had multiple organ failure that persisted for more than 48 hours, while 17 of the patients only had single organ failure. The majority of individuals experiencing chronic single organ failure had an acute renal damage, as evidenced by their elevated serum creatinine level. In this study 66.7% patients had multi-system organ failure. And the elevated creatinine levels were 2.24. It could be because of pancreatic necrosis, hypovolemia or renal insufficiency.

The levels of mean respiratory rate and mean oxygen saturation were elevated in a study by (Jı X, et,al 2022) 27 was the value of RR and the mean of SpO2 was 64. While in this study the value of mean respiratory rate was 27.361 and the mean of SPO2 was 52.19. It could be because of Hypoxia.

In a study by Li, et 2017 there were only 7 patients who had diabetes mellitus out of 359 while in this study 49 patients had Diabetes mellitus out of 105.It could be because of hypoglycemia. Because the pancreas was inflamed and damaged.

In a study by Zhao Y et, al 2023, AST was slightly elevated which was 38.50 but, In this study the levels of AST were 258.495. In the same study the levels of LDH were 309.00 whereas in this study LDH levels were 359.828. Which is also elevated. It could be because of organ failure. And the value of BUN in this study was 5.00 which is less than the normal range. But, in this study the value of BUN was 9.276 which is normal.

In this study the value of BUN was 9.276 while in the study by Sun, et.al 2021 the value of BUN was 4.6. It could be due to hypovolemia or hypercatabolism. In this study the value of creatinine was 2.247 while in the comparative study the value of creatinine was 62. It could be due to pancreatic necrosis or hypovolemia.

In a study the value of WBCs was 13221.47 but, in this study the WBCs levels were 18114.285. Both values are elevated due to inflammation or infection in our patients' body. In the same study the value of BUN was 34.34 which is elevated it could be because of Hypovolemia or Hypercatabolism but, in this study the value of BUN was 9.276 which is normal. In the same study the sensitivity of CRP was 84.86, specificity was 30.95, accuracy was 46.06, PPV was 32.37 and NPV was 84.00. While in this study the Sensitivity was 91.9%, specificity was 91.9%, PPV was 66.7%, NPV was 94.4%, and accuracy was 80.95% (Kim. Et.al 2015).

In a study the ratio of male patients was 62 while 42 female patients were included. In this study the ratio of males is greater than female like in this study. It could be because of lifestyle or smoking. In the same study 16 patients were smokers and 88 were non-smokers. While in this study 53 were smokers and 52 were non-smokers. Individuals who smoke are more likely to get gallstones (DuruH. 2023).

In a study the number of patients who had diabetes are 22 out of 155. While in this study 49 patients had diabetes out of 105. It could be because of hypoglycemia and 15 % patients had multiple organ failure whilein this study 66.7 % patients had multiple organ failure (Sayar, et.al 2018)

In this study the ratio of male was greater than female while in a study by Zhou, et.al 2019 the ratio of male as compared to female were also more. It could be because of smoking or lifestyle. And the number of diabetic patients were 51 while in this study the number of diabetic patients were 49. It could be due to gallstone. In this study the value of BUN was 9.276 which is a normal value. But, in the study by Zhou et.al the value of BUN was contradicted that is 5.67 which is less than the normal value.

In this study the value of LDH was 359.828 while the value of LDH in a similar study by Deherkar, et.al 2019 was 284.54. These both values are elevated. It could be due to Tissue damage. In this study the value of AST was 258.495 which is extremely elevated while in the similar study the value of AST was 59.71. It could be because of organ failure. The higher levels of AST or LDH shows bad prognosis. In this study the ratio of male was greater than female while in this study the ratio of male was also greater than female. It could be because

of smoking. In this study the value of WBCs was 18114.285 but, the value of WBCs is contradicted to this current study which was 13559.00. It could be due to any inflammation or infection in the body.

In this study 67 out of 105 patients were male and 38 were female. But, according to Trivikraman et al., 2016 study, 86 of the 100 participants were male and 14 were female. The majority of the patients were in the age range of 30-40 years.

In this study the ratio of male was greater than female while in the coinciding study by Liang, et.al 2019 the ratio of male is greater than female. It could be due to lifestyle or smoking. In this study 49 patients were diabetic while 56 were non diabetic. In the comparative article the results of diabetes are similar to our study, the number of diabetic patients were 22 and the number of non- diabetic patients were 82. It could be due to hypoglycemia.

In this study the number of smokers were 53 while the number of non-smokers were 42. But, in the comparative study by Liang, et.al 2019 the number of smokers were 44 and number of non-smokers were 60. It could be due to the damage of pancreatic tissues or gallstone. In my current study the value of BUN was 9.276 but, the similar study the value of BUN was 13.64. It could be due to Hypovolemia or Hypercatabolism

In this study the number of smoker were 53 and non-smokers were 42 while in a study by Piñerúa-Gonsálvez, et.al 2023 the number of smokers were 116 and non-smokers were 606. It could be due to gallstone. In this study the number of diabetic patients were 49 and Non diabetic were 56 while inthe comparative study the number of diabetic patients were 118 and non-diabetic were 604. It could be due to hypoglycemia.

In this study the number of hypertensive patients were 52 and non-hypertensive patients were 53 while in the comparative study the number of hypertensive patients were 385 and non-hypertensive patients were 337. It could be due to any pain and stress. (Pavlidis, et.al 2023)

In this study the ratio of male was greater than female while in the study by Behera, et.al 2023 the ratio of male was also greater than female. It could be due to lifestyle or smoking. In this study the value of creatinine was 2.247 which is elevated. It could be due

to pancreatic necrosis or hypovolemia while in the comparative study the value of creatinine was 1.6 which is normal. In this study the value of bilirubin was 1.735 while in the comparative study the value of bilirubin was 2.58 these both values are elevated. It could be due to abnormal LFTs.

In this study the value of AST was 258.495 which is extremely elevated while in the comparative study the value of AST was 75.25 which is also elevated. It could be due to organ failure. In this study the value of Albumin was 2.485 it could be due to any infection. While in the comparative study the value of Albumin was 3.52. In this study the value of CRP was 12.980 while in the comparative study the value of CRP was 12.05. It could be due to inflammation. In a study the value of CRP/ Albumin ratio was 5.357 while in the comparative study the value of CRP/Albumin was 3.54 (Triester, et.al 2010)

In this study the CRP/Albumin ratio for moderate acute pancreatitis according to Ranson criteria was 34 and the CRP/Albumin ratio for severe acute pancreatitis according to Ranson criteria was 17. Severe pancreatitis resulted in a statistically significant ($p = 0.000$) while in the comparative study by Kiyak, et.al 2022 the Ranson criterion showed a mean CAR value of 2.4±1.9 for moderate pancreatitis and 5.5±2.6 for severe pancreatitis. Severe pancreatitis resulted in a statistically significant ($p<0.001$). Ranson Criteria is a criteria that divided patients into mild, moderate and severe. In this study the number of diabetic patients were 49 while in the comparative study the number of diabetic patients were
36.It could be due to hypoglycemia. In a study the number of hypertensive patients were 52 while in the comparative study the number of hypertensive patients were 66. It could be due to any stress and pain.

In this study the CRP/Albumin ratio for patients with organ failure with cut off value of 4.35 97% sensitivity, 67.6% specificity, 72.7% PPV, 96.2% NPV, 81.42% Accuracy.

While in a study by M, Y., Nagda, et.al 2023 The CRP/albumin ratio performed well in predicting persistent organ failure with a cut-off of 0.25: 85% sensitivity, 80% specificity, 68% positive predictive value, 90% negative predictive value, and 82% overall accuracy. The predictive value of the ratio is: 72.7 % PPV and 96.2 % NPV.

In a study by Fu, Y., et.al 2019 CRP/Albumin, a combined pattern of CRP and albumin, may reveal the outcome of diseases in a better way than either one would individually. CRP/Albumin has been implicated in several diseases, including various cancers, and has a better prognostic value than other peripheral blood cell count-based indicators.

According to Shannon et al. 2021, individuals with low Albumin levels often have a poor prognosis. Serum Albumin levels are typically low in critically ill patients with a variety of diseases. This decrease may be attributed to the role of Albumin in increasing the production of several anti-inflammatory substances (such as lipoxins, hemolysins, and protective proteins) during oxidative stress to facilitate recovery from the disease.

According to Wang, et.al 2024 CRP/Albumin takes CRP and Albumin levels into account and reflects a combination of renal function and nutritional status. In AP, elevated CRP levels may reflect renal dysfunction or systemic metabolic changes, while decreased Albumin levels may indicate deterioration in nutritional status. Therefore, CRP/Albumin, as a comprehensive indicator, can more comprehensively reflect the metabolism and nutritional status of patients, and is more closely related to the pathological and physiological characteristics of acute pancreatitis.

In this study the number of diabetic patients were 49 and non-diabetic patients were 56 while in the study by Ni, T., et.al 2022 the number of diabetic patients were 40 and non-diabetic patients were 76. It could be due to hypoglycemia. In this study the number of hypertensive patients were 52 and non-hypertensive patients were 53 while in the study the number of hypertensive patients were 56 and non- hypertensive patients were 60. It could be due to any stress or pain.

In this study the Pancreatitis severity was divided into mild, moderate and severe. The patients who had mild acute pancreatitis were 4.8%, the patients who had Moderate acute pancreatitis were 60%, and the patients who had severe acute pancreatitis were 35.2 %. Moderate acute pancreatitis patients were greater than in number. While in the contradicted study by J. Uludağ, et.al 2022 the patients who had mild acute pancreatitis were 80.6 %, the patients who had moderate acute pancreatitis were 18.5 % and, the patients who had severe acute pancreatitis were 0.9 %. Mild acute pancreatitis patients were greater in number. Ranson Criteria is the criteria which is used to divide the patients into mild, moderate or severe.

In this study the Pancreatitis severity was divided into mild, moderate and severe. The patients who had mild acute pancreatitis were 4.8%, the patients who had Moderate acute pancreatitis were 60%, and the patients who had severe acute pancreatitis were 35.2 %. Moderate acute pancreatitis patients were greater than in number. While in the contradicted study by He, F, et.al 2021 the patients who had mild acute pancreatitis were 68.18%, the patients who had moderate acute pancreatitis were 20.20%, the patients who had severe acute pancreatitis were 11.62 %. The patients who had mild acute pancreatitis were greater in number. Ranson Criteria is the criteria which is used to divide the patients into mild, moderate or severe.

In a study by Somasekar, et.al 2011 early detection of blood oxygen partial pressure in elderly AP patients was crucial for timely diagnosis and treatment. Elderly people often have various co-morbidities that might negatively impact organ performance.

In this study the mean of Ranson score was 6.485 while in the comparative study by Eachempati, et.al 2002 the Ranson score was 3.4. There are 11 parameters in Ranson Criteria. Each parameter has one point. If there are more than 3 points, then there are more chances that patients have severe acute pancreatitis.

In this study 67 patients were male and 38 patients were female while in a contradicted study by Ahlawat ,et.al 2018 15 were male and 35 were female. It could be due to smoking, gallstone or lifestyle. In this study thenumber of smokers were 53 and non-smokers were 42. While in the comparative study 12 patients were smokers and 38 patients were non-smokers.

This could be due to gallstone. In this study the patients who had mild acute pancreatitis were 4.8 and the patients who had severe acute pancreatitis were 53.2%. while in the comparative 82% of cases had mild AP, with only 18% having severe AP. Ranson Criteria is the criteria which is used to divide the patients into mild, moderate or severe.

In this study the ratio of male was greater than female which 67 patients were male out of 105 and 38 patients were female. While in a comparative study by Zhou, et.al 2015 the ratio of male was greater than female which 316 patients were male out of 367 and51 patients were female. It could be due to smoking or lifestyle. In this study the number of patients who were smokers are 53 and non-smokers were 42. While in the comparative study the number of smokers were 302 and non-smokers were 65. It could be due to gallstone.

In this study the ratio of male was greater than female. 67 patients were male and 38 patients were female. While in a study by Shuanglian, et.al 2023 the ratio of male is greater than female. 181 were Male patients and 43 were female patients. It is due to smoking or lifestyle. In my current study 49 patients were diabetic and 56 patients were non-diabetic. While in the comparative study 92 patients were diabetic and 132 patients were non-diabetic. It could be due to hypoglycemia. In a current study the value of amylase was 327.666 while in the comparative study the value of amylase was 238.200. This could be due to any infection or obstruction of pancreatic duct. In this study the value of AST was 258.495 which is extremely elevated. It could be due to organ failure. While in the contradicted study the value of studywas 28.050 which is normal. In my current study the value of LDH was 359.828. While in the comparative study the value of LDH was 248.350. It could be due to Tissue damage. The value of AST or LDH are much elevated it is due to the bad prognosis such as organ failure or tissue damage. In my current study the value of BUN was 9.276. While in the comparative study the value of Bun was 4.575. It could be due to liver damage or malnutrition.

In this study the ratio of male was greater than female. 67 patients were male and 38 patients were female. While in the comparative study by Lin, et.al 2022 the ratio of male was greater than female. 247 were male and 124 were female. It could be due to smoking or lifestyle. In this study 49 patients had diabetesand 56 patients were non-diabetic. While in the comparative study the number of patients who had diabetes were 115 and non-diabetic patients were 256. It could be due to hypoglycemia. In this study the number of patients who had blood pressure were 52 and non-hypertensive were 53, while in thecomparative study the number of hypertensive patients were 62 and non-hypertensive were 309. It could be due to any stress or pain. In this study the patients who had mild acute pancreatitis were 4.8%, the patients who had Moderate acute pancreatitis were 60%, and the patients who had severe acute pancreatitiswere 35.2 %. Moderate acute pancreatitis patients were greater than in number. While in thecomparative study he patients who had mild acute pancreatitis were 63, the patients who hadModerate acute pancreatitis were 208, and the patients who had severe acute pancreatitis were 100. Moderate acute pancreatitis patients were greater than in number. Ranson criteria is the criteria which is used to divide the patients into mild, moderate or severe.

5.2 IMPLICATIONS:

The CRP to albumin ratio (CAR) is increasingly recognized as a useful metric in the treatment of acute pancreatitis (AP). It combines the acute phase protein CRP, which rises in lresponse to inflammation, with albumin, a negative acute phase reactant that declines during infection and inflammation.

5.2.1 THEORITICAL IMPLICATIONS:

The CRP-to-albumin ratio (CAR) is a comprehensive indicator of the inflammatory response and nutritional status in acute pancreatitis. Elevated CRP values indicate a robust inflammatory reaction, but low albumin levels indicate a severe systemic response and poor nutritional status. The CAR thus functions as a composite indication of illness severity, providing crucial insights into the underlying pathophysiology of AP. In theory, the CAR can be used to predict patient outcomes, as greater ratios are frequently associated with increased morbidity and mortality. This predictive value can help us better understand how the disease progresses and develop more accurate prognostic models.

5.2.2 PRACTICAL IMPLICATIONS:

In clinical practice, assessing the CAR can help identify high-risk AP patients who need more thorough monitoring and treatment. This early risk categorization can help patients avoid problems and enhance their outcomes. Furthermore, hospitals can use CAR to better allocate resources, focusing more attention and care on patients with high ratios. The CAR can also influence therapeutic changes, such as commencing early nutritional support or intensive anti-inflammatory medication for people with high ratios. Furthermore, the CAR can help with patient counselling by providing clear information regarding illness severity and predicted treatment courses, thereby improving compliance and setting realistic expectations.

Finally, the CAR can be a useful endpoint in clinical trials, helping to assess the efficacy of new medications or interventions in AP and guiding for the future research.

5.2.3 POLICY IMPLICATIONS:

Incorporating the CAR into clinical recommendations for AP management may standardize risk classification and decision-making processes. This inclusion would ensure that all patients are evaluated using a consistent and potentially useful prognostic sign. Policies might also require routine CAR measurement in patients admitted with AP, assuring widespread and consistent use of this marker. Furthermore, health insurance policies might recognize the value of CAR by paying the expenses of associated diagnostics, removing financial barriers and encouraging its usage in clinical practice. These regulatory reforms could result in more consistent and effective AP management across various healthcare settings.

5.3 LIMITATIONS AND STRENGTHS OF THE STUDY:

A. LIMITATIONS:

1. Non-specificity: Elevated CRP levels can be detected in a variety of inflammatory illnesses, reducing the specificity of this ratio for determining the severity of acute pancreatitis. This can make it difficult to distinguish pancreatitis from other inflammatory illnesses.

2. Less Historical Validation: In contrast to more established methods such as the Ranson criteria, the CRP/Albumin ratio has less historical data and clinical validation in the setting of acute pancreatitis. This may limit its acceptability and usein clinical practice.

B. STRENGTHS:

1. Simplicity and Speed: The CRP/Albumin ratio can be promptly derived from regular blood tests, providing valuable information about the patient's status without the need for sophisticated procedures.

2. Non-invasive: The test requires only a simple blood draw, which is minimally invasive and generally available, making it convenient for both patients and healthcare providers.

3. Dynamic indicator: CRP is an acute-phase reactant, making it a sensitive indicator of inflammation and enabling for early detection of changes in the patient's condition. This dynamic response is especially important for tracking illness development or response to treatment.

4. Accessibility: Because CRP and albumin levels are frequently assessed in clinical settings, the ratio can be calculated and applied without the need for extra specialized tests.

5.4 RECOMMADATIONS:

1. Incorporate as a Complementary Tool: Use the CRP/Albumin ratio in conjunction with recognized severity assessment methods such as the Ranson criteria, APACHE II, and BISAP score. This combination method can improve the overall assessment and provide a more complete picture of the patient's condition.
2. Evaluate Dynamically: Use the CRP/Albumin ratio to continuously evaluate the patient's inflammatory response and nutritional state over time. Regular measurements can help track illness development and the patient's reaction to treatment.
3. Interpret with Cautions: Caution should be exercised when interpreting the CRP/Albumin ratio in isolation, particularly in the presence of other inflammatory diseases that may cause CRP levels to rise. To make educated decisions, consider the patient's general clinical situation as well as any additional diagnostic findings.
4. Educate Healthcare Providers: Educate healthcare providers on the CRP/Albumin ratio's strengths and limitations, emphasizing its importance as part of a multifaceted strategy to diagnosing acute pancreatitis severity. Ensure that they understand how to analyze and

incorporate the ratio into other clinical data.

5. Research and Validation: Encourage additional research and clinical studies to validate the CRP/Albumin ratio in acute pancreatitis. Larger investigations and clinical trials can assist demonstrate its usability, dependability, and predictive value when compared to established severity grading methods.

6. Develop standardized techniques for measuring and interpreting the CRP/Albumin ratio in the setting of acute pancreatitis. Consistency in testing and reporting can increase their usefulness and dependability in clinical practice.

7. Patient-Specific Considerations: When interpreting the CRP/Albumin ratio, consider age, comorbidities, and baseline nutritional status. Personalizing the assessment can result in more accurate prognosis and individualized treatment recommendations.

5.5 CONCLUSION:

The CRP/albumin ratio (CAR) has significant advantages over the old Ranson criteria for assessing acute pancreatitis. Unlike the Ranson criteria, which require numerous parameters and a 48-hour assessment time, the CAR is a simple, easily accessible blood test that can be evaluated at admission, offering rapid insight into the patient's inflammatory and nutritional status. This enables quicker risk categorization and decision-making according to severity of disease in patients already diagnosed with acute pancreatitis, by tradition amylase, lipase or imaging. Furthermore, the CAR integrates the dynamic markers of CRP and albumin, indicating bothacute inflammation and general health state, whereas the Ranson criteria require a more complex and time-consuming combination of clinical and laboratory measurements. The CAR's simplicity and immediacy make it a more practical and potentially more effective toolfor early AP control.

REFERENCES

Aoi, Nishio, A., Okazaki, T., Masahiro Takeo, Masuda, M., Fukui, T., Uchida, K., & Okazaki, K. (2019). Inhibition of the dephosphorylation of eukaryotic initiation factor 2α ameliorates murine experimental pancreatitis. Pancreatology, 19(4), 548–556. https://doi.org/10.1016/j.pan.2019.04.005

Ahlawat, V., & Godara, R. (2018). Clinical Study of Demographic Profile, Etiology, Severity and Outcome of Acute Pancreatitis in a Tertiary Care Teaching Hospital in Northern India. Journal of Gastrointestinal & Digestive System, 08(05). https://doi.org/10.4172/2161-069x.1000575

Ahmad, R., Bhatti, K. M., Ahmed, M., Malik, K. A., Rehman, S., Abdulgader, A., Kausar, A., & Canelo, R. (2021). C-Reactive Protein as a Predictor of Complicated Acute Pancreatitis: Reality or a Myth? Cureus. https://doi.org/10.7759/cureus.19265

Almeida, N., Fernandes, A., & Casela, A. (2015). Predictors of Severity and In-Hospital Mortality for Acute Pancreatitis: Is There Any Role for C-Reactive Protein Determination in the First 24 Hours?

Antonucci, L., Fagman, J. B., Kim, J. Y., Todoric, J., Gukovsky, I., Mackey, M., Ellisman, M. H., & Karin, M. (2015). Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress. Proceedings of the National Academy of Sciences of the United States of America, 112(45), E6166-6174. https://doi.org/10.1073/pnas.1519384112

Atar, D., Arheden, H., Berdeaux, A., Bonnet, J.-L. ., Carlsson, M., Clemmensen, P., Cuvier, V., Danchin, N., Dubois-Rande, J.-L. ., Engblom, H., Erlinge, D., Firat, H.,

Halvorsen, S., Hansen, H. S., Hauke, W., Heiberg, E., Koul, S., Larsen, A.-I. ., Le Corvoisier, P., & Nordrehaug, J. E. (2014). Effect of intravenous TRO40303 as an adjunct to primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: MITOCARE study results. European Heart Journal, 36(2), 112–119. https://doi.org/10.1093/eurheartj/ehu331

Azab, B., Jaglall, N., Atallah, J. P., Lamet, A., Raja-Surya, V., Farah, B., Lesser, M., & Widmann, W. D. (2011). Neutrophil-Lymphocyte Ratio as a Predictor of Adverse outcomes of Acute Pancreatitis. Pancreatology, 11(4), 445–452. https://doi.org/10.1159/000331494

Banks, P. A. (2016). Acute Pancreatitis. Pancreas, 45(5), 633–640. https://doi.org/10.1097/mpa.0000000000000632

Banks, P. A., Bollen, T. L., Dervenis, C., Gooszen, H. G., Johnson, C. D., Sarr, M. G., Tsiotos, G. G., & Vege, S. S. (2012). Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut, 62(1), 102–111. https://doi.org/10.1136/gutjnl-2012-302779

Barrera K, & Stanek A, Okochi K. (2018). Acinar cell injury induced by inadequate unfolded protein response in acute pancreatitis. World J Gastrointest Pathophysiol .

Basit, H., Ruan, G. J., & Mukherjee, S. (2022). Ranson Criteria. In StatPearls. StatPearls Publishing. (n.d.).

Bedel, C., Korkut, M., & Selvi, F. (2021). New markers in predicting the severity of acute pancreatitis in the emergency department: Immature granulocyte count and percentage. Journal of Postgraduate Medicine, 67(1), 7–11. https://doi.org/10.4103/jpgm.JPGM_784_20

Behera, M., Mishra, D., Sahu, M., Nittala, R., Singh, A., Pati, G., Agarwal, S., & Narayan, J. (2022). C-reactive protein/albumin and ferritin as predictive markers for severity and mortality in patients with acute pancreatitis. Gastroenterology Review. https://doi.org/10.5114/pg.2022.115609

Besselink, M. G., van Santvoort, H. C., Boermeester, M. A., Nieuwenhuijs, V. B., van Goor, H., Dejong, C. H. C., Schaapherder, A. F., & Gooszen, H. G. (2009). Timing and impact of infections in acute pancreatitis. British Journal of Surgery, 96(3), 267–273. https://doi.org/10.1002/bjs.6447

Bhatia, M., Wong, F. L., Cao, Y., Lau, H. Y., Huang, J., Puneet, P., & Chevali, L. (2005). Pathophysiology of acute pancreatitis. Pancreatology, 5(2-3), 132–144. https://doi.org/10.1159/000085265

Biczo, G., Vegh, E. T., Shalbueva, N., Mareninova, O. A., Elperin, J., Lotshaw, E., Gretler, S., Lugea, A., Malla, S. R., Dawson, D., Ruchala, P., Whitelegge, J., French, S. W., Wen, L., Husain, S. Z., Gorelick, F. S., Hegyi, P., Rakonczay, Z., Gukovsky, I., & Gukovskaya, A. S. (2018). Mitochondrial Dysfunction, Through Impaired Autophagy, Leads to Endoplasmic Reticulum Stress, Deregulated Lipid Metabolism, and Pancreatitis in Animal Models. Gastroenterology, 154(3), 689–703. https://doi.org/10.1053/j.gastro.2017.10.012

Blatchford, O., Murray, W. R., & Blatchford, M. (2000). A risk score to predict need for treatment for uppergastrointestinal haemorrhage. The Lancet, 356(9238), 1318–1321. https://doi.org/10.1016/s0140-6736(00)02816-6

Bonjoch, L., Casas, V., Carrascal, M., & Closa, D. (2016). Involvement of exosomes in lung inflammation associated with experimental acute pancreatitis. The Journal of

Pathology, 240(2), 235–245. https://doi.org/10.1002/path.4771

Boxhoorn, L., van Dijk, S. M., van Grinsven, J., Verdonk, R. C., Boermeester, M. A., Bollen, T. L., Bouwense, S. A. W., Bruno, M. J., Cappendijk, V. C., Dejong, C. H. C., van Duijvendijk, P., van Eijck, C. H. J., Fockens, P., Francken, M. F. G., van Goor, H., Hadithi, M., Hallensleben, N. D. L., Haveman, J. W., Jacobs, M. A. J. M., & Jansen, J. M. (2021). Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. New England Journal of Medicine, 385(15), 1372–1381. https://doi.org/10.1056/nejmoa2100826

Braha, J., & Tenner, S. (2018). Fluid Collections and Pseudocysts as a Complication of Acute Pancreatitis. Gastrointestinal Endoscopy Clinics of North America, 28(2), 123–130. https://doi.org/10.1016/j.giec.2017.11.001

Brand, M., Götz, A., Zeman, F., Behrens, G., Leitzmann, M., Brünnler, T., Hamer, O. W., Stroszczynski, C., & Heiss, P. (2014). Acute Necrotizing Pancreatitis: Laboratory, Clinical, and Imaging Findings as Predictors of Patient Outcome. American Journal of Roentgenology, 202(6), 1215–1231. https://doi.org/10.2214/ajr.13.10936

Buter, A., Imrie, C. W., Carter, C. R., Evans, S., & McKay, C. J. (2002). Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. The British Journal of Surgery, 89(3), 298–302. https://doi.org/10.1046/j.0007-1323.2001.02025.x

Cardoso, F. S., Ricardo, L. B., Oliveira, A. M., Canena, J. M., Horta, D. V., Papoila, A. L., & Deus, J. R. (2013). C-reactive protein prognostic accuracy in acute pancreatitis. European Journal of Gastroenterology & Hepatology, 25(7), 784–789. https://doi.org/10.1097/meg.0b013e32835fd3f0

Chauhan, R., Saxena, N., Kapur, N., & Kardam, D. (2022). Comparison of modified Glasgow-Imrie, Ranson, and Apache II scoring systems in predicting the severity of acute pancreatitis. Polish Journal of Surgery, 95(1), 1–8. https://doi.org/10.5604/01.3001.0015.8384

Cheng, C.-L., Sherman, S., Watkins, J. L., Barnett, J., Freeman, M., Geenen, J., Ryan, M., Parker, H., Frakes, J. T., Fogel, E. L., Silverman, W. B., Dua, K. S., Aliperti, G., Yakshe, P., Uzer, M., Jones, W., Goff, J., Lazzell-Pannell, L., Rashdan, A., & Temkit, M. (2006). Risk Factors for Post-ERCP Pancreatitis: A Prospective Multicenter Study. The American Journal of Gastroenterology, 101(1), 139–147. https://doi.org/10.1111/j.1572-0241.2006.00380.x

Chvanov, M., De Faveri, F., Moore, D., Sherwood, M. W., Awais, M., Voronina, S., Sutton, R., Criddle, D. N., Haynes, L., & Tepikin, A. V. (2018). Intracellular rupture, exocytosis and actin interaction of endocytic vacuoles in pancreatic acinar cells: initiating events in acute pancreatitis. The Journal of Physiology, 596(13), 2547–2564. https://doi.org/10.1113/jp275879

Ciubotaru, I., Potempa, L. A., & Wander, R. C. (2005). Production of Modified C-Reactive Protein in U937-Derived Macrophages. Experimental Biology and Medicine, 230(10), 762–770. https://doi.org/10.1177/153537020523001010

Criddle, D., Mclaughlin, E., Murphy, J., Petersen, O., Sutton, R., & Group, M. (2007). Fax +41 61 306 12 34 E-Mail karger@karger.ch. Pancreatology, 7, 436–446. https://doi.org/10.1159/000108960

Das, S. L. M., Singh, P. P., Phillips, A. R. J., Murphy, R., Windsor, J. A., & Petrov, M. S. (2013). Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic

review and meta-analysis. Gut, 63(5), 818–831. https://doi.org/10.1136/gutjnl-2013-305062

Dawra, R., Sah, R. P., Dudeja, V., Rishi, L., Talukdar, R., Garg, P., & Saluja, A. K. (2011). Intra-acinar Trypsinogen Activation Mediates Early Stages of Pancreatic Injury but Not Inflammation in Mice with Acute Pancreatitis. Gastroenterology, 141(6), 2210-2217.e2. https://doi.org/10.1053/j.gastro.2011.08.033

Deherkar, J. A., Pandey, A., & Deshmukh, S. (2019). C-reactive protein levels in acute pancreatitis and its clinical significance. International Surgery Journal, 6(9), 3328-3334. (n.d.).

Diakopoulos, K. N., Lesina, M., Wörmann, S., Song, L., Aichler, M., Schild, L., Artati, A., Römisch-Margl, W., Wartmann, T., Fischer, R., Kabiri, Y., Zischka, H., Halangk, W., Ihsan Ekin Demir, Pilsak, C., Walch, A., Mantzoros, C. S., Steiner, J. M., Erkan, M., & Schmid, R. M. (2015). Impaired Autophagy Induces Chronic Atrophic Pancreatitis in Mice via Sex- and Nutrition-Dependent Processes. Gastroenterology, 148(3), 626-638.e17. https://doi.org/10.1053/j.gastro.2014.12.003

Diehl, A. K. (1997). Gallstone Size and Risk of Pancreatitis. Archives of Internal Medicine, 157(15), 1674. https://doi.org/10.1001/archinte.1997.00440360088009

Duru, H. (2023). Utility of Ranson score, computed tomography severity index and CRP criteria in risk stratification on the day of hospital admission in patients with acute pancreatitis: A cross-sectional analysis. Turkish Journal of Trauma and Emergency Surgery. https://doi.org/10.14744/tjtes.2022.33332

Dzieniszewski, J., & Gabryelewicz, A. (2004). Pancreas; Pancreatitis-Polish accomplishments. Journal of physiology and pharmacology, 54, 155-166. (n.d.).

Eachempati, S. R., Hydo, L. J., & Barie, P. S. (2002). Severity Scoring for Prognostication in Patients with Severe Acute Pancreatitis. Archives of Surgery, 137(6). https://doi.org/10.1001/archsurg.137.6.730

Feng, D., Park, O., Radaeva, S., Wang, H., Yin, S., Kong, X., Zheng, M., Zakhari, S., Kolls, J. K., & Gao, B. (2012). Interleukin-22 ameliorates cerulein-induced pancreatitis in mice by inhibiting the autophagic pathway. International Journal of Biological Sciences, 8(2), 249–257. https://doi.org/10.7150/ijbs.3967

Feng, S., Wei, Q., Hu, Q., Huang, X., Zhou, X., Luo, G., Deng, M., & Lü, M. (2018). Research Progress on the Relationship Between Acute Pancreatitis and Calcium Overload in Acinar Cells. Digestive Diseases and Sciences, 64(1), 25–38. https://doi.org/10.1007/s10620-018-5297-8

Fu, Y. J., Li, K. Z., Bai, J. H., & Liang, Z. Q. (2019). C-reactive protein/albumin ratio is a prognostic indicator in Asians with pancreatic cancers: a meta-analysis. Medicine, 98(48), e18219. (n.d.).

Gao, L., Chong, E., Pendharkar, S., Hong, J., Windsor, J. A., Ke, L., Li, W., & Phillips, A. (2022). The Effects of NLRP3 Inflammasome Inhibition in Experimental Acute Pancreatitis. Pancreas, 51(1), 13–24. https://doi.org/10.1097/mpa.0000000000001971

Garg, P. K., & Singh, V. P. (2019). Organ Failure Due to Systemic Injury in Acute Pancreatitis. Gastroenterology, 156(7), 2008–2023. https://doi.org/10.1053/j.gastro.2018.12.041

Ghaffar, S., Shahnoor, S., Khan, A. M., Asif, A., Fida, M., Oduoye, M. O., & Nafula, W. P. (2024). CRP Albumin Ratio: A novel noninvasive and cost-effective method for

assessing the severity of acute pancreatitis. Health Science Reports, 7(1). https://doi.org/10.1002/hsr2.1801

Ghosh, R., Wang, L., Wang, Eric S., Perera, B. Gayani K., Igbaria, A., Morita, S., Prado, K., Thamsen, M., Caswell, D., Macias, H., Weiberth, Kurt F., Gliedt, Micah J., Alavi, Marcel V., Hari, Sanjay B., Mitra, Arinjay K., Bhhatarai, B., Schürer, Stephan C., Snapp, Erik L., Gould, Douglas B., & German, Michael S. (2014). Allosteric Inhibition of the IRE1α RNase Preserves Cell Viability and Function during Endoplasmic Reticulum Stress. Cell, 158(3), 534–548. https://doi.org/10.1016/j.cell.2014.07.002

Gori E, Pierini A, Lippi I, Ceccherini G, Perondi F, Marchetti V. Evaluation of C- reactive protein/albumin ratio and its relationship with survival in dogs with acute pancreatitis. New Zealand veterinary journal. 2020;68(6):345-8. (n.d.).

Greenberg, J. A., Hsu, J., Bawazeer, M., Marshall, J., Friedrich, J. O., Nathens, A., Coburn, N., Huang, H., & McLeod, R. S. (2015). Compliance with Evidence-Based Guidelines in Acute Pancreatitis: an Audit of Practices in University of Toronto Hospitals. Journal of Gastrointestinal Surgery, 20(2), 392–400. https://doi.org/10.1007/s11605-015-3023-9

Gukovskaya, A. S., Gorelick, F. S., Groblewski, G. E., Mareninova, O. A., Lugea, A., Antonucci, L., Waldron, R. T., Habtezion, A., Karin, M., Pandol, S. J., & Gukovsky, I. (2019). Recent Insights into the Pathogenic Mechanism of Pancreatitis: Role of Acinar Cell Organelle Disorders. Pancreas, 48(4), 459–470. https://doi.org/10.1097/MPA.0000000000001298

Gukovskaya, A. S., Gukovsky, I., Algül, H., & Habtezion, A. (2017). Autophagy,

Inflammation, and Immune Dysfunction in the Pathogenesis of Pancreatitis. Gastroenterology, 153(5), 1212–1226. https://doi.org/10.1053/j.gastro.2017.08.071

Guo, X.-Y., Xiao, F., Li, J., Zhou, Y.-N., Zhang, W.-J., Sun, B., & Wang, G. (2019). Exosomes and pancreatic diseases: status, challenges, and hopes. International Journal of Biological Sciences, 15(9), 1846–1860. https://doi.org/10.7150/ijbs.35823

Haider Kazmi, S. J., Zafar, M. T., Zia, B. F., Khalid, S. R., Kumar, V., Tabassum, S., Ali, A., Aziz, N., Khan, N. A., Kumari, K., Saleem, K., & Asghar, M. S. (2022). Role of serum C-reactive protein (CRP)/Albumin ratio in predicting the severity of acute pancreatitis: A retrospective cohort. Annals of Medicine & Surgery, 82. https://doi.org/10.1016/j.amsu.2022.104715

Hamada, S., Masamune, A., Kikuta, K., Hirota, M., Tsuji, I., & Shimosegawa, T. (2014). Nationwide Epidemiological Survey of Acute Pancreatitis in Japan. Pancreas, 43(8), 1244–1248. https://doi.org/10.1097/mpa.0000000000000200

Han, J., Zhong, C.-Q., & Zhang, D.-W. (2011). Programmed necrosis: backup to and competitor with apoptosis in the immune system. Nature Immunology, 12(12), 1143–1149. https://doi.org/10.1038/ni.2159

Han, S., Ye, J., Liu, R., Chen, W., & Feng, Z. (2019). The role of CRP or albumin with ranson scale in predicting severe acute pancreatitis mortality risk. Int J Clin Exp Med, 12(8), 10531–10536.

He, F., Zhu, H. M., Li, B. Y., Li, X. C., Yang, S., Wang, Z., & Zhang, M. (2021). Factors predicting the severity of acute pancreatitis in elderly patients. Aging clinical and experimental research, 33(1), 183–192. (n.d.).

He, S., Wang, L., Miao, L., Wang, T., Du, F., Zhao, L., & Wang, X. (2009). Receptor

Interacting Protein Kinase-3 Determines Cellular Necrotic Response to TNF-α. Cell, 137(6), 1100–1111. https://doi.org/10.1016/j.cell.2009.05.021

He, S.-S., Li, D., He, Q.-Y., Chen, X.-P., Lin, Y.-X., Yu, Y.-W., Chen, F.-L., & Ding, J. (2022). Establishment of Early Multi-Indicator Prediction Models of Moderately Severe Acute Pancreatitis and Severe Acute Pancreatitis. Gastroenterology Research and Practice, 2022, 1–10. https://doi.org/10.1155/2022/5142473

Hetz, C., Chevet, E., & Oakes, S. A. (2015). Proteostasis control by the unfolded protein response. Nature cell biology, 17(7), 829-838. (n.d.).

Hollemans, R. A., Hallensleben, N. D. L., Mager, D. J., Kelder, J. C., Besselink, M. G., Bruno, M. J., Verdonk, R. C., & van Santvoort, H. C. (2018). Pancreatic exocrine insufficiency following acute pancreatitis: Systematic review and study level meta-analysis. Pancreatology, 18(3), 253–262. https://doi.org/10.1016/j.pan.2018.02.009

Hudson, M. B., Woodworth-Hobbs, M. E., Zheng, B., Rahnert, J. A., Blount, M. A., Gooch, J., Searles, C., & S. Russ Price. (2014). miR-23a is decreased during muscle atrophy by a mechanism that includes calcineurin signaling and exosome-mediated export. American Journal of Physiology-Cell Physiology, 306(6), C551–C558. https://doi.org/10.1152/ajpcell.00266.2013

İspiroğlu, M. (2020). Comparison between prognostic indicators in organ insufficiency with acute pancreatitis. Turkish Journal of Trauma and Emergency Surgery. https://doi.org/10.14744/tjtes.2020.18552

J. Dzieniszewski, & A Gabryelewicz. (2003). Pancreas; pancreatitis--Polish accomplishments. Journal of Physiology and Pharmacology, 54 Suppl 3, 155–166.

Javed, M. A., Wen, L., Awais, M., Latawiec, D., Huang, W., Chvanov, M., Schaller, S.,

Bordet, T., Michaud, M., Pruss, R., Tepikin, A., Criddle, D., & Sutton, R. (2018). TRO40303 Ameliorates Alcohol-Induced Pancreatitis Through Reduction of Fatty Acid Ethyl Ester–Induced Mitochondrial Injury and Necrotic Cell Death. Pancreas, 47(1), 18–24. https://doi.org/10.1097/mpa.0000000000000953

Jı X, Zhou J, Wu W, Tang Y, Xu T.(2022) Application of high-flow oxygen therapy in acute pancreatitis complicated with acute respiratory dysfunction. Turk J Med Sci. Jun;52(3):707-714. (n.d.).

Jin, H., Yang, X., Zhao, K., Mei, F., Zhou, Y., You, Y., & Wang, W. (2019). Apocynin alleviates lung injury by suppressing NLRP3 inflammasome activation and NF-κB signaling in acute pancreatitis. International Immunopharmacology, 75, 105821–105821. https://doi.org/10.1016/j.intimp.2019.105821

Jones, M. J., Neal, C. P., Ngu, W. S., Dennison, A. R., & Garcea, G. (2017). Early warning score independently predicts adverse outcome and mortality in patients with acute pancreatitis. Langenbeck's Archives of Surgery, 402(5), 811–819. https://doi.org/10.1007/s00423-017-1581-x

Kaplan, M., Ates, I., Akpinar, M. Y., Yuksel, M., Kuzu, U. B., Kacar, S., Coskun, O., & Kayacetin, E. (2017). Predictive value of C-reactive protein/albumin ratio in acute pancreatitis. Hepatobiliary & Pancreatic Diseases International, 16(4), 424–430. https://doi.org/10.1016/s1499-3872(17)60007-9

Kapuy, O., Márton, M., Bánhegyi, G., & Vinod, P. K. (2019). Multiple system-level feedback loops control life-and-death decisions in endoplasmic reticulum stress. FEBS Letters. https://doi.org/10.1002/1873-3468.13689

Karabuga, B., Gemcioglu, E., Konca Karabuga, E., Baser, S., & Ersoy, O. (2022).

Comparison of the predictive values of CRP, CRP/albumin, RDW, neutrophil/lymphocyte, and platelet/lymphocyte levels in

determining the severity of acute pancreatitis in patients with acute pancreatitis according to the BISAP score. Bratislava Medical Journal, 123(02), 129–135. https://doi.org/10.4149/bll_2022_020

Khanna, A. K., Meher, S., Prakash, S., Tiwary, S. K., Singh, U., Srivastava, A., & Dixit, V. K. (2013). Comparison of Ranson, Glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and Procalcitonin in Predicting Severity, Organ Failure, Pancreatic Necrosis, and Mortality in Acute Pancreatitis. HPB Surgery, 2013, 1–10. https://doi.org/10.1155/2013/367581

Kim, M. H., Ahn, J. Y., Song, J. E., Choi, H., Ann, H. W., Kim, J. K., Kim, J. H., Jeon, Y. D., Kim, S. B., Jeong, S. J., Ku, N. S., Han, S. H., Song, Y. G., Choi, J. Y., Kim, Y. S., & Kim, J. M. (2015). The C-Reactive Protein/Albumin Ratio as an Independent Predictor of Mortality in Patients with Severe Sepsis or Septic Shock Treated with Early Goal-Directed Therapy. PloS one, 10(7), e0132109. (n.d.).

Kiyak, M., & Tanoglu, A. (2022). Comparison of the Efficacy of Balthazar Score and C-Reactive Protein-Albumin Ratio for Determination of Acute Pancreatitis Severity. Current health sciences journal, 48(1), 81–87. (n.d.).

Lankisch, P. G., Droge, M., & Gottesleben, F. (1995). Drug induced acute pancreatitis: incidence and severity. Gut, 37(4), 565–567. https://doi.org/10.1136/gut.37.4.565

Lee HJ, Yoon YS, Lee SJ.(2018) Mechanism of neuroprotection by trehalose: controversy surrounding autophagy induction. Cell Death Dis;9:712. 10.1038/s41419- 018-0749-9 . (n.d.).

Lee PJ, Ma Fe Muñoz-Moreno, Agustín Mayo-Iscar, María Antonia Udaondo-Cascante, & Reyes Busta Nistal. (2019). Statin intake can decrease acute pancreatitis severit. Pancreatology, 19(6), 807–812. https://doi.org/10.1016/j.pan.2019.07.004

Leppäniemi, A., Tolonen, M., Tarasconi, A., Segovia-Lohse, H., Gamberini, E., Kirkpatrick, A. W., Ball, C. G., Parry, N., Sartelli, M., Wolbrink, D., van Goor, H., Baiocchi, G., Ansaloni, L., Biffl, W., Coccolini, F., Di Saverio, S., Kluger, Y., Moore, E., & Catena, F. (2019). 2019 WSES guidelines for the management of severe acute pancreatitis. World Journal of Emergency Surgery, 14(1). https://doi.org/10.1186/s13017-019-0247-0

Li, Y., Zhao, Y., Feng, L., & Guo, R. (2017). Comparison of the prognostic values of inflammation markers in patients with acute pancreatitis: a retrospective cohort study. BMJ Open, 7(3), e013206. https://doi.org/10.1136/bmjopen-2016-013206

Li, Z., Xu, C., Tao, Y., Liang, Y., Liang, Q., Li, J., Li, R., & Ye, H. (2020). Anisodamine alleviates lipopolysaccharide-induced pancreatic acinar cell injury through NLRP3 inflammasome and NF-κB signaling pathway. Journal of Receptors and Signal Transduction, 40(1), 58–66. https://doi.org/10.1080/10799893.2020.1713808

Liang, Y., Zhao, X., & Meng, F. (2019). Procalcitonin, C-Reactive Protein, and Neutrophil Ratio Contribute to the Diagnosis and Prognosis of Severe Acute Pancreatitis. Iranian journal of public health, 48(12), 2177–2186. (n.d.).

Liu, Y., Liu, T., Lei, T., Zhang, D., Du, S., Girani, L., Qi, D., Lin, C., Tong, R., & Wang, Y. (2019). RIP1/RIP3-regulated necroptosis as a target for multifaceted disease therapy (Review). International Journal of Molecular Medicine. https://doi.org/10.3892/ijmm.2019.4244

Louhimo, J. M., Steer, M. L., & Perides, G. (2016). Necroptosis Is an Important Severity Determinant and Potential Therapeutic Target in Experimental Severe Pancreatitis. Cellular and Molecular Gastroenterology and Hepatology, 2(4), 519–535. https://doi.org/10.1016/j.jcmgh.2016.04.002

Lugea, A., Gerloff, A., Su, H.-Y., Xu, Z., Go, A., Hu, C., French, S. W., Wilson, J. S., Apte, M. V., Waldron, R. T., & Pandol, S. J. (2017). The Combination of Alcohol and Cigarette Smoke Induces Endoplasmic Reticulum Stress and Cell Death in Pancreatic Acinar Cells. Gastroenterology, 153(6), 1674–1686. https://doi.org/10.1053/j.gastro.2017.08.036

Lur, G., Sherwood, Mark W., Ebisui, E., Haynes, L., Feske, S., Sutton, R., Burgoyne, Robert D., Mikoshiba, K., Petersen, Ole H., & Tepikin, Alexei V. (2011). InsP3 receptors and Orai channels in pancreatic acinar cells: co-localization and its consequences. Biochemical Journal, 436(2), 231–239. https://doi.org/10.1042/bj20110083

Machicado, J. D., Gougol, A., Stello, K., Tang, G., Park, Y., Slivka, A., Whitcomb, D. C., Yadav, D., & Papachristou, G. I. (2017). Acute Pancreatitis Has a Long-term Deleterious Effect on Physical Health Related Quality of Life. Clinical Gastroenterology and Hepatology, 15(9), 1435-1443.e2. https://doi.org/10.1016/j.cgh.2017.05.037

Maléth, J., & Hegyi, P. (2016). Ca^{2+}toxicity and mitochondrial damage in acute pancreatitis: translational overview. Philosophical Transactions of the Royal Society B: Biological Sciences, 371(1700), 20150425. https://doi.org/10.1098/rstb.2015.0425

Malo, A., Krüger, B., Göke, B., & Kubisch, C. H. (2013). 4-Phenylbutyric Acid Reduces

Endoplasmic Reticulum Stress, Trypsin Activation, and Acinar Cell Apoptosis While Increasing Secretion in Rat Pancreatic Acini. Pancreas, 42(1), 92–101. https://doi.org/10.1097/mpa.0b013e318259f6ca

Mareninova, O. A., Hermann, K., French, S. W., O'Konski, M. S., Pandol, S. J., Webster, P., Erickson, A. H., Katunuma, N., Gorelick, F. S., Gukovsky, I., & Gukovskaya, A. S. (2009). Impaired autophagic flux mediates acinar cell vacuole formation and trypsinogen activation in rodent models of acute pancreatitis. Journal of Clinical Investigation. https://doi.org/10.1172/jci38674

Mariadi, I., Somayana, G., Shalim, C., Sindhughosa, D., Daniella, D., & Purwanta, A. (2023). Prognostic value of C-reactive protein-to-albumin ratio in acute pancreatitis: a systematic review and meta-analysis [version 2; peer review: 2 approved].

Márta, K., Szabó, A. N., Pécsi, D., Varjú, P., Bajor, J., Gódi, S., Sarlós, P., Mikó, A., Szemes, K., Papp, M., Tornai, T., Vincze, Á., Márton, Z., Vincze, P. A., Lankó, E., Szentesi, A., Molnár, T., Hágendorn, R., Faluhelyi, N., & Battyáni, I. (2017). High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): protocol of a multicentre randomised double-blind clinical trial. BMJ Open, 7(9), e015874. https://doi.org/10.1136/bmjopen-2017-015874

Mederos, M. A., Reber, H. A., & Girgis, M. D. (2021). Acute Pancreatitis. JAMA, 325(4), 382–390. https://doi.org/10.1001/jama.2020.20317

Mizushima, N., Yamamoto, A., Matsui, M., Yoshimori, T., & Ohsumi, Y. (2004). In Vivo Analysis of Autophagy in Response to Nutrient Starvation Using Transgenic Mice Expressing a Fluorescent Autophagosome Marker. Molecular Biology of the Cell, 15(3), 1101–1111. https://doi.org/10.1091/mbc.e03-09-0704

Mohammad, E. J., Abbas, K. M., Hassan, A. F., & Abdulrazaq, A. A. (2018). Serum c-reactive protein as a predictive factor for spontaneous stone passage in patients with 4 to 8 mm distal ureteral stones. International Surgery Journal, 5(4), 1195. https://doi.org/10.18203/2349-2902.isj20181034

Morgan, D. E. (2008). Imaging of Acute Pancreatitis and Its Complications. Clinical Gastroenterology and Hepatology, 6(10), 1077–1085. https://doi.org/10.1016/j.cgh.2008.07.012

Mounzer, R., Langmead, C. J., Wu, B. U., Evans, A. C., Bishehsari, F., Muddana, V., Singh, V. K., Slivka, A., Whitcomb, D. C., Yadav, D., Banks, P. A., & Papachristou, G. I. (2012). Comparison of Existing Clinical Scoring Systems to Predict Persistent Organ Failure in Patients With Acute Pancreatitis. Gastroenterology, 142(7), 1476–1482. https://doi.org/10.1053/j.gastro.2012.03.005

Mukherjee, R., Mareninova, O., Odinokova, I., Huang, W., Murphy, J., Chvanov, M., Javed, M., Wen, L., Booth, D., Cane, M., Awais, M., Gavillet, B., Pruss, R., Schaller, S., Molkentin, J., Tepikin, A., Petersen, O., Pandol, S., Gukovsky, I., & Criddle, D. (2016). Mechanism of mitochondrial permeability transition pore induction and damage in the pancreas: inhibition prevents acute pancreatitis by protecting production of ATP.

Munir, F., Jamshed, M. B., Shahid, N., Muhammad, S. A., Ghanem, N. B., & Zhang Qiyu. (2019). Current status of diagnosis and Mesenchymal stem cells therapy for acute pancreatitis. Physiological Reports, 7(21). https://doi.org/10.14814/phy2.14170

M,Y, Nagda, J., Gandhi, R., Patel, R. H., & Dhruvam Babaria. (2023). Exploring the Prognostic Significance of the C-reactive Protein/Albumin Ratio in Assessing the

Severity of Acute Pancreatitis: A Prospective Observational Study in the Indian Population. Cureus. https://doi.org/10.7759/cureus.51170

Ni, T., Wen, Y., Wang, Y., Jiang, W., Sheng, H., Chen, E., Mao, E., Lan, Z., Huang, Y., & Zhou, Y. (2022). Association between albumin or prealbumin levels at different stages and prognosis in severe acute pancreatitis: a 5-year retrospective study. 12(1). https://doi.org/10.1038/s41598-022-21278-1

Oh, T., Ji, E., Na, H., Min, B., Jeon, Y.-T., Do, S.-H., Song, I.-A., Park, H.-P., & Hwang, J.-W. (2018). C-Reactive Protein to Albumin Ratio Predicts 30-Day and 1-Year Mortality in Postoperative Patients after Admission to the Intensive Care Unit. Journal of Clinical Medicine, 7(3), 39. https://doi.org/10.3390/jcm7030039

Ong, Y., & Shelat, V. G. (2021). Ranson score to stratify severity in Acute Pancreatitis remains valid – Old is gold. Expert Review of Gastroenterology & Hepatology, 15(8), 865–877. https://doi.org/10.1080/17474124.2021.1924058

Parenti, D. M., Steinberg, W., & Kang, P. (1996). Infectious Causes of Acute Pancreatitis. Pancreas, 13(4), 356–371. https://doi.org/10.1097/00006676-199611000-00005

Park, J., Chang, J. H., Park, S. H., Lee, H. J., Lim, Y. S., Kim, T. H., Kim, C. W., & Han, S. W. (2015). Interleukin-6 is associated with obesity, central fat distribution, and disease severity in patients with acute pancreatitis. Pancreatology, 15(1), 59–63. https://doi.org/10.1016/j.pan.2014.11.001

Pavlidis, E. T., & Pavlidis, T. E. (2023). Management of infected acute necrotizing pancreatitis. World Journal of Clinical Cases, 11(2), 482–486. https://doi.org/10.12998/wjcc.v11.i2.482

Pavlidis, T. E., Psarras, K., Symeonidis, N. G., Pavlidis, E. T., & Sakantamis, A. K. (2011).

Current surgical management of pancreatic endocrine tumor liver metastases. Hepatobiliary & Pancreatic Diseases International, 10(3), 243–247. https://doi.org/10.1016/s1499-3872(11)60040-4

Peng, S., Gerasimenko, J. V., Tsugorka, T., Gryshchenko, O., Samarasinghe, S., Petersen, O. H., & Gerasimenko, O. V. (2016). Calcium and adenosine triphosphate control of cellular pathology: asparaginase-induced pancreatitis elicited via protease-activated receptor 2. Philosophical Transactions of the Royal Society B: Biological Sciences, 371(1700), 20150423. https://doi.org/10.1098/rstb.2015.0423

Petrov, M. S., & Yadav, D. (2018). Global epidemiology and holistic prevention of pancreatitis. Nature Reviews Gastroenterology & Hepatology, 16(3), 175–184. https://doi.org/10.1038/s41575-018-0087-5

Pieńkowska, J., Gwoździewicz, K., Skrobisz-Balandowska, K., Marek, I., Kostro, J., Szurowska, E., & Studniarek, M. (2016). Perfusion-CT - Can We Predict Acute Pancreatitis Outcome within the First 24 Hours from the Onset of Symptoms? PLOS ONE, 11(1), e0146965. https://doi.org/10.1371/journal.pone.0146965

Piñerúa-Gonsálvez, J., María, L., Ruiz-Rebollo, Del, R., Zambrano-Infantino, C., Rizzo-Rodríguez, A.-L., & Fernández-Salazar, L. (2023). Value of CRP/albumin ratio as a prognostic marker of acute pancreatitis: a retrospective study TRABAJO ORIGINAL. REV ESP ENFERM DIG, 115(12), 707–712. https://doi.org/10.17235/reed.2023.9345/2022

Pirouz, A., Sadeghian, E., Jafari, M., Eslamian, R., Elyasinia, F., Mohammadi-Vajari, M. A., Ghorbani Abdehgah, A., & Soroush, A. (2021). Investigating the Factors Affecting the Development of Biliary Pancreatitis and Their Relationship with the

Type and Severity of Complications. Middle East Journal of Digestive Diseases, 13(1), 43–48. https://doi.org/10.34172/mejdd.2021.202

Prasanth, J., Prasad, M., Mahapatra, S. J., Krishna, A., Prakash, O., Garg, P. K., & Bansal, V. K. (2022). Early Versus Delayed Cholecystectomy for Acute Biliary Pancreatitis: A Systematic Review and Meta-Analysis. World Journal of Surgery, 46(6), 1359–1375. https://doi.org/10.1007/s00268-022-06501-4

Ranson, & J. H., Rifkind, K. M., & Turner, J. W. (1977). Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. Journal of the American College of Emergency Physicians, 6(5), 228. https://doi.org/10.1016/s0361-1124(77)80518-2

Ren, Y., Su, Y., Sun, L., He, S., Meng, L., Liao, D., Liu, X., Ma, Y., Liu, C., Li, S., Ruan, H., Lei, X., Wang, X., & Zhang, Z. (2017). Discovery of a Highly Potent, Selective, and Metabolically Stable Inhibitor of Receptor-Interacting Protein 1 (RIP1) for the Treatment of Systemic Inflammatory Response Syndrome. Journal of Medicinal Chemistry, 60(3), 972–986. https://doi.org/10.1021/acs.jmedchem.6b01196

Ron, D., & Walter, P. (2007). Signal integration in the endoplasmic reticulum unfolded protein response. Nature Reviews Molecular Cell Biology, 8(7), 519–529. https://doi.org/10.1038/nrm2199

Samanta, J., Dhaka, N., Gupta, P., Singh, A. K., Yadav, T. D., Gupta, V., Sinha, S. K., & Kochhar, R. (2019). Comparative study of the outcome between alcohol and gallstone pancreatitis in a high-volume tertiary care center. JGH Open, 3(4), 338–343. https://doi.org/10.1002/jgh3.12169

Sankaran, S. J., Xiao, A. Y., Wu, L. M., Windsor, J. A., Forsmark, C. E., & Petrov, M. S. (2015). Frequency of Progression From Acute to Chronic Pancreatitis and Risk

Factors: A Meta-analysis. Gastroenterology, 149(6), 1490-1500.e1. https://doi.org/10.1053/j.gastro.2015.07.066

Sayar, S. (2018). A Practical Marker to Determining Acute Severe Ulcerative Colitis: CRP / Albumin Ratio. Northern Clinics of Istanbul. https://doi.org/10.14744/nci.2018.78800

Sayar, S., Kurbuz, K., Kahraman, R., Caliskan, Z., Atalay, R., Ozturk, O., Doganay, H. L., & Ozdil, K. (2019). A practical marker to determining acute severe ulcerative colitis: CRP/albumin ratio. Northern Clinics of Istanbul, 7(1), 49–55. https://doi.org/10.14744/nci.2018.78800

Schaller, S., Michaud, M., Latyszenok, V., Robert, F., Hocine, M., Arnoux, T., Gabriac, M., Codoul, H., Bourhane, A., de Bellefois, I. C., Afxantidis, J., & Pruss, R. M. (2015). TRO40303, a mitochondrial-targeted cytoprotective compound, provides protection in hepatitis models. Pharmacology Research & Perspectives, 3(3). https://doi.org/10.1002/prp2.144

Sendler, M., Weiss, F.-U., Golchert, J., Homuth, G., van den Brandt, C., Mahajan, U. M., Partecke, L.-I., Döring, P., Gukovsky, I., Gukovskaya, A. S., Wagh, P. R., Lerch, M. M., & Mayerle, J. (2018). Cathepsin B-Mediated Activation of Trypsinogen in Endocytosing Macrophages Increases Severity of Pancreatitis in Mice. Gastroenterology, 154(3), 704-718.e10. https://doi.org/10.1053/j.gastro.2017.10.018

Server Sezgin Uludağ, Nazim Güreş, Sabri Şirolu, Ahmet Aşkar, Ahmet Necati Şanlı, Abdullah Kağan Zengin, & Mehmet Faik Özçelik. (2022). Investigating the Correlation between Severe Acute Pancreatitis and Pancreatic Necrosis with Some Serum Parameters. Turkish Journal of Trauma and Emergency Surgery.

https://doi.org/10.14744/tjtes.2021.96782

Shannon, C. M., Ballew, S. H., Daya, N., Zhou, L., Chang, A. R., Sang, Y., Coresh, J., Selvin, E., & Coresh, J. (2021). Serum albumin and risks of hospitalization and death: Findings from the Atherosclerosis Risk in Communities study. Journal of the American Geriatrics Society, 69(10), 2865–2876. https://doi.org/10.1111/jgs.17313

Shanshan Han1 , Jun Ye2 , Rui Liu2 , Weiwei Chen2 , Zhiqiang Feng1 feb 19, (2023) The role of CRP or albumin with ranson scale in predicting severe acute pancreatitis mortality risk. (n.d.).

Shuanglian, Y., Zeng Huiling, Xunting, L., Deng Yifang, Yufen, L., Xie Shanshan, Si Lijuan, & Liu Yunpeng. (2023). Establishment and validation of early prediction model for hypertriglyceridemic severe acute pancreatitis. Lipids in Health and Disease, 22(1). https://doi.org/10.1186/s12944-023-01984-z

Silva-Vaz, P., Abrantes, A. M., Morgado-Nunes, S., Castelo-Branco, M., Gouveia, A., Botelho, M. F., & Tralhão, J. G. (2020). Evaluation of Prognostic Factors of Severity in Acute Biliary Pancreatitis. International Journal of Molecular Sciences, 21(12), 4300. https://doi.org/10.3390/ijms21124300

Siregar, G. A., & Siregar, G. P. (2019). Management of Severe Acute Pancreatitis. Open Access Macedonian Journal of Medical Sciences, 7(19). https://doi.org/10.3889/oamjms.2019.720

Somasekar, K., Foulkes, R., Morris-Stiff, G., & Hassn, A. (2011). Acute pancreatitis in the elderly - Can we perform better? The Surgeon, 9(6), 305–308. https://doi.org/10.1016/j.surge.2010.11.001

Spanier, B. W. M., Dijkgraaf, M. G. W., & Bruno, M. J. (2008). Epidemiology, aetiology

and outcome of acute and chronic pancreatitis: An update. Best Practice & Research Clinical Gastroenterology, 22(1), 45–63. https://doi.org/10.1016/j.bpg.2007.10.007

Stirling, A. D., Moran, N. R., Kelly, M. E., Ridgway, P. F., & Conlon, K. C. (2017). The predictive value of C-reactive protein (CRP) in acute pancreatitis – is interval change in CRP an additional indicator of severity? HPB, 19(10), 874–880. https://doi.org/10.1016/j.hpb.2017.06.001

Strimbu, K., & Tavel, J. A. (2010). What are biomarkers? Current Opinion in HIV and AIDS, 5(6), 463–466. https://doi.org/10.1097/coh.0b013e32833ed177

Sun, H.-W., Lu, J.-Y., Weng, Y.-X., Chen, H., He, Q.-Y., Liu, R., Li, H.-P., Pan, J.-Y., & Shi, K.-Q. (2021). Accurate prediction of acute pancreatitis severity with integrative blood molecular measurements. Aging, 13(6), 8817–8834. https://doi.org/10.18632/aging.202689

Szatmary, P., Grammatikopoulos, T., Cai, W., Huang, W., Mukherjee, R., Halloran, C., Beyer, G., & Sutton, R. (2022). Acute Pancreatitis: Diagnosis and Treatment. Drugs, 82(12), 1251–1276. https://doi.org/10.1007/s40265-022-01766-4

Talukdar, R., Sareen, A., Zhu, H., Yuan, Z., Dixit, A., Cheema, H., George, J., Barlass, U., Sah, R., Garg, S. K., Banerjee, S., Garg, P., Dudeja, V., Dawra, R., & Saluja, A. K. (2016). Release of Cathepsin B in Cytosol Causes Cell Death in Acute Pancreatitis. Gastroenterology, 151(4), 747-758.e5. https://doi.org/10.1053/j.gastro.2016.06.042

Tarar, M. Y., Khalid, A., Choo, X. Y., Khurshid, S., Tumeh, H., & Muhammad, K. (2022). Use of the C-Reactive Protein (CRP)/Albumin Ratio as a Severity Tool in Acute Pancreatitis: Systematic Review. Cureus. https://doi.org/10.7759/cureus.29243

Taydas, O., Unal, E., Karaosmanoglu, A. D., Onur, M. R., & Akpinar, E. (2017). Accuracy

of early CT findings for predicting disease course in patients with acute pancreatitis. Japanese Journal of Radiology, 36(2), 151–158. https://doi.org/10.1007/s11604-017-0709-9

Tenner, S., Baillie, J., DeWitt, J., & Vege, S. S. (2013). American College of Gastroenterology Guideline: Management of Acute Pancreatitis. American Journal of Gastroenterology, 108(9), 1400–1415. https://doi.org/10.1038/ajg.2013.218

Toouli, j., brooke-smith, m., bassi, c., carr-locke, d., telford, j., freeny, p., imrie, c., & tandon, r. (2002). Guidelines for the management of acute pancreatitis. Journal of gastroenterology and Hepatology, 17, S15–S39. https://doi.org/10.1046/j.1440-1746.17.s1.2.x

Triester, S., & Kowdley, K. (2010). Clinical Reviews Pancreatic and Biliary Disease Prognostic Factors in Acute Pancreatitis.

Trikudanathan, G., Wolbrink, D. R. J., van Santvoort, H. C., Mallery, S., Freeman, M., & Besselink, M. G. (2019). Current Concepts in Severe Acute and Necrotizing Pancreatitis: An Evidence-Based Approach. Gastroenterology, 156(7), 1994-2007.e3. https://doi.org/10.1053/j.gastro.2019.01.269

Trivikraman, R., Chayampurath, R., & Malieckal, J. (2016). Validity of bedside index of severity in acute pancreatitis score in comparison with C reactive protein in assessing the severity of acute pancreatitis. International Journal of Research in Medical Sciences, 5248–5251. https://doi.org/10.18203/2320-6012.ijrms20164188

Van Brunschot, S., Van Grinsven, J., Voermans, R., Bakker, O., Gh Besselink, M., Boermeester, M., Bollen, T., Bosscha, K., Bouwense, S., Bruno, M., Cappendijk, V., Consten, E., Dijkgraaf, M., Van Eijck, C., Willemien Erkelens, G., Van Goor, H.,

Hadithi, M., Haveman, J.-W., Jansen, J., & Laméris, J. (2013). Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial [ISRCTN09186711].

Venkatesh, N. R., Vijayakumar, C., Balasubramaniyan, G., Chinnakkulam Kandhasamy, S., Sundaramurthi, S., G. S., S., & Srinivasan, K. (2020). Comparison of Different Scoring Systems in Predicting the Severity of Acute Pancreatitis: A Prospective Observational Study. Cureus. https://doi.org/10.7759/cureus.6943

Vissers, R. J., Abu-Laban, R. B., & McHugh, D. F. (1999). Amylase and lipase in the emergency department evaluation of acute pancreatitis. The Journal of Emergency Medicine, 17(6), 1027–1037. https://doi.org/10.1016/s0736-4679(99)00136-5

Voronina, S., Collier, D., Chvanov, M., Middlehurst, B., Beckett, Alison J., Prior, Ian A., Criddle, David N., Begg, M., Mikoshiba, K., Sutton, R., & Tepikin, Alexei V.(2015). The role of Ca2+ influx in endocytic vacuole formation in pancreatic acinarcells. Biochemical Journal, 465(3), 405–412. https://doi.org/10.1042/bj20140398

Wada, K., Takada, T., Hirata, K., Mayumi, T., Yoshida, M., Yokoe, M., Kiriyama, S., Hirota, M., Kimura, Y., Takeda, K., Arata, S., Hirota, M., Sekimoto, M., Isaji, S., Takeyama, Y., Gabata, T., Kitamura, N., & Amano, H. (2009). Treatment strategy for acute pancreatitis. Journal of Hepato-Biliary-Pancreatic Sciences, 17(1), 79–86. https://doi.org/10.1007/s00534-009-0218-z

Walker, H., Melling, J., Jones, M., & Melling, C. V. (2021). C-reactive protein accurately predicts severity of acute pancreatitis in children. Journal of Pediatric Surgery. https://doi.org/10.1016/j.jpedsurg.2021.08.007

Wang, G.-J., Gao, C.-F., Wei, D., Wang, C., & Ding, S.-Q. (2009). Acute pancreatitis: Etiology and common pathogenesis. World Journal of Gastroenterology, 15(12), 1427. https://doi.org/10.3748/wjg.15.1427

Wang, H., Li, C., Jiang, Y., Li, H., & Zhang, D. (2020). Effects of Bacterial Translocation and Autophagy on Acute Lung Injury Induced by Severe Acute Pancreatitis. Gastroenterology Research and Practice, 2020, 1–8. https://doi.org/10.1155/2020/8953453

Wang, J., Li, H., Luo, H., Shi, R., Chen, S., Hu, J., Luo, H., Yang, P., Cai, X., Wang, Y., Zeng, X., & Wang, D. (2024). Association between serum creatinine to albumin ratio and short- and long-term all-cause mortality in patients with acute pancreatitis admitted to the intensive care unit: a retrospective analysis based on the MIMIC-IV database. Frontiers in Immunology, 15. https://doi.org/10.3389/fimmu.2024.1373371

Wang, T., Jiang, L., Wei, X., Liu, B., Zhao, J., Xie, P., Yang, B., & Wang, L. (2018). RETRACTED: MiR-21-3p aggravates injury in rats with acute hemorrhagic necrotizing pancreatitis by activating TRP signaling pathway. Biomedicine & Pharmacotherapy, 107, 1744–1753. https://doi.org/10.1016/j.biopha.2018.08.164

Wen, L., Voronina, S., Javed, M. A., Awais, M., Szatmary, P., Latawiec, D., Chvanov, M., Collier, D., Huang, W., Barrett, J., Begg, M., Stauderman, K., Roos, J., Grigoryev, S., Ramos, S., Rogers, E., Whitten, J., Velicelebi, G., Dunn, M., & Tepikin, A. V. (2015). Inhibitors of ORAI1 Prevent Cytosolic Calcium-Associated Injury of Human Pancreatic Acinar Cells and Acute Pancreatitis in 3 Mouse Models. Gastroenterology, 149(2), 481-492.e7. https://doi.org/10.1053/j.gastro.2015.04.015

Wu, X.-B., Sun, H.-Y., Luo, Z.-L., Cheng, L., Duan, X.-M., & Ren, J.-D. (2020). Plasma-derived exosomes contribute to pancreatitis-associated lung injury by triggering NLRP3-dependent pyroptosis in alveolar macrophages. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1866(5), 165685–165685. https://doi.org/10.1016/j.bbadis.2020.165685

Xiao, B., Xu, H.-B., Jiang, Z.-Q., Zhang, J., & Zhang, X.-M. (2019). Current concepts for the diagnosis of acute pancreatitis by multiparametric magnetic resonance imaging. Quantitative Imaging in Medicine and Surgery, 9(12), 1973–1985. https://doi.org/10.21037/qims.2019.11.10

Yang, L., Liu, J., Xing, Y., Du, L., Chen, J., Liu, X., & Hao, J. (2016). Comparison of BISAP, Ranson, MCTSI, and APACHE II in Predicting Severity and Prognoses of Hyperlipidemic Acute Pancreatitis in Chinese Patients. Gastroenterology Research and Practice, 2016, 1–7. https://doi.org/10.1155/2016/1834256

Yang, Y., Huang, Q., Luo, C., Wen, Y., Liu, R., Sun, H., & Tang, L. (2020). MicroRNAs in acute pancreatitis: From pathogenesis to novel diagnosis and therapy. Journal of Cellular Physiology, 235(3), 1948–1961. https://doi.org/10.1002/jcp.29212

Yarkaç, A., Kose, A., Bozkurt Babuş, S., Ates, F., Orekici Temel, G., & Ölmez, A. (2019). The value of hematological parameters in acute pancreatitis. Ulusal Travma ve Acil Cerrahi Dergisi = Turkish Journal of Trauma & Emergency Surgery: TJTES, 25(5), 453–460. https://doi.org/10.5505/tjtes.2018.69857

Yılmaz E M, & Altay Kandemir. (2018). Significance of Red Blood Cell Distribution Width and CRP/Albumin Levels in Predicting Prognosis of Acute Pancreatitis. Ulusal Travma ve Acil Cerrahi Dergisi. https://doi.org/10.5505/tjtes.2018.98583

Zerem, E. (2014). REVIEW. World J Gastroenterol, 20(38), 13879–13892. https://doi.org/10.3748/wjg

Zhang, L., Feng, Q., & Wang, T. (2018). Necrostatin-1 Protects Against Paraquat-Induced Cardiac Contractile Dysfunction via RIP1-RIP3-MLKL-Dependent Necroptosis Pathway. Cardiovascular Toxicology, 18(4), 346–355. https://doi.org/10.1007/s12012-017-9441-z

Zhao, Q., Tang, X., Huang, J., Li, J., Chen, Q., Sun, Y., & Wu, J. (2018). Melatonin Attenuates Endoplasmic Reticulum Stress in Acute Pancreatitis. Pancreas, 47(7), 884–891. https://doi.org/10.1097/mpa.0000000000001082

Zhao, Y., Gan, Y., Xu, G., Hua, K., & Liu, D. (2020). Exosomes from MSCs overexpressing microRNA-223-3p attenuate cerebral ischemia through inhibiting microglial M1 polarization mediated inflammation. Life Sciences, 260, 118403. https://doi.org/10.1016/j.lfs.2020.118403

Zhao, Y., Xia, W., Lu, Y., Chen, W., Zhao, Y., & Zhuang, Y. (2023). Predictive value of the C-reactive protein/albumin ratio in severity and prognosis of acute pancreatitis. Frontiers in Surgery, 9. https://doi.org/10.3389/fsurg.2022.1026604

Zhou, H., Mei, X., He, X., Lan, T., & Guo, S. (2019). Severity stratification and prognostic prediction of patients with acute pancreatitis at early phase. Medicine, 98(16), e15275. https://doi.org/10.1097/md.0000000000015275

Zhou, T., Zhan, J., Hong, S., Hu, Z., Fang, W., Qin, T., Ma, Y., Yang, Y., He, X., Zhao, Y., Huang, Y., Zhao, H., & Zhang, L. (2015). Ratio of C-Reactive Protein/Albumin is An Inflammatory Prognostic Score for Predicting Overall Survival of Patients with Small-cell Lung Cancer. Scientific Reports, 5(1). https://doi.org/10.1038/srep10481

Zhou, W., Liu, Q., Wang, Z., Yao, L., Chen, J., & Yang, X. (2024). Analysis of the clinical profile and treatment efficiency of hyperlipidemic acute pancreatitis. Lipids in Health and Disease, 23(1). https://doi.org/10.1186/s12944-024-02057-5

FACULTY RESEARCH COMMITTEE
FACULTY OF HEALTH SCIENCES
(FRC-FoHS)

LETTER OF APPROVAL

Date: 08-01-2024

To,
Dr. Sidra Anees
MPhil – Student
Department of Physiology
BUHSCK

Subject: **Faculty Research Committee**
FRC-BUHSCK Approval of Research Study

Title of Study: Comparative analysis of c-creative protein/albumin ratio and ranson criteria for evaluating the severity of acute pancreatitis.

Name of Student: **Dr. Sidra Anees**
Reference No: **FRC-BUHS 06/2024**

Dear Dr. Sidra Anees

Thank you for submitting research proposal to FRC-BUHSCK. The committee has approved your project.
Regards

PROF. DR. Shehla M. Baqai HI (M)
Maj. Gen (R)
Chairperson FRC-BUHSCK

Cc:
Registrar
Director PGP
Director QA
Director DRC
Dean HS
Secretary FRC
HOD Concerned
Student Concerned

Bahria University
Health Sciences Campus, Karachi

IRB

No one left behind for research.

Institutional Review Board

BUHS-IRB # R-042/24
Date:08- 01-24
Name of PI: Sidra Anees
Affiliation & Department: MPhil Candidate: Physiology
Address-BUHS,C Sailor Street, DHA Phase 2, Karachi

Subject: **APPROVAL OF YOUR RESEARCH PROPOSAL:**

Title of the research

"Comparative analysis of CRP/ Albumin Ratio and Ranson Criteria for evaluating the severity of Acute pancreatitis."

Dear Sidra Anees,

I am writing this letter at your request to confirm that we support the research project "Comparative Analysis of CRP/ Albumin Ratio and Ranson Criteria for evaluating the severity of Acute Pancreatitis.
The research will determine the efficacy of the CRP/Albumin Ratio with Ranson's criteria for assessing the severity of Acute pancreatitis. The IRB is committed to supporting the project for a duration of six months, as outlined in the proposed guidelines in the IRB application. This should provide you with a clear timeline and a sense of security in your research endeavor.

Suppose any unanticipated problems or adverse advents occur. In that case, it is up to Ms. Sidra Anees to report these events to the IRB as promptly as possible. The research will contribute to predicting Acute Pancreatitis with scientific rigor. We will be happy to support this endeavor.

Sincerely,

Thaver

Prof Dr. Inayat H. Thaver
CHS (Community Medicine); PhD (Public Healt
Chairperson, Institutional Review Board (IRE
Bahria University Health Sciences Campu
Karachi

Prof. Dr. Inayat H. Thaver
Chair, Institutional Review Board.

INFORMED CONSENT FORM

Title of Study: Comparative analysis for C-reactive protein (CRP)/Albumin ratio and Ranson Criteria in evaluating the severity of Acute Pancreatitis

Name of Research Scholar: Sidra Anees Rajput

You are giving your consent to participate voluntarily and at your own will in this research clinical trial project that aims to analyze "Rationalize Level of Serum C-Reactive Protein (CRP)/Albumin ratio Versus Ranson's Criteria in predicting the severity of Acute Pancreatitis"

You have been explained in detail the nature and significance of participating in the project and you understand the provided explanation.

You have been told that findings of your disease and your data will be kept strictly confidential and will be used only for the benefit of community, publications and paper presentations.

You have been explained that laboratory investigations will be conducted for the diagnosis of disease. For this purpose, you fully agree to give your blood samples at the beginning and end of study.

You also agree to give all relevant information needed, in full and to the best of your knowledge to the researcher. It is clarified to you that no incentive will be provided to you for participating in the study except the cost of lab investigations and drugs, whereas you do have the right to withdraw from the study at any time.

You are advised to contact Sidra Anees on mobile number: 0315 8562036 in case of any query/ emergency related to your disease.

Name of Patient:

S/D/ W/o:

Signature / Thumb impression of patient:

Name of Researcher:

Signature of Researcher:

باخبر رضامندی کا فارم

مطالعہ کا عنوان: شدید لبلبے کی سوزش کی شدت کی پیش گوئی کرنے میں سیرم سی-ری ایکٹیو پروٹین البومن/(CRP)

تناسب بمقابلہ رینسن کے معیار کی سطح

ریسرچ اسکالر کا نام: سدرہ انیس راجپوت

آپ اس تحقیقی کلینیکل ٹرائل پروجیکٹ میں رضاکارانہ طور پر اور اپنی مرضی سے حصہ لینے کے لیے اپنی

البومن تناسب بمقابلہ رینسن کے /(CRP) سیرم سی-ری ایکٹیو پروٹین;quot&رضامندی دے رہے ہیں جس کا مقصد معیار کا

-;quot&تجزیہ کرنا ہے

آپ کو پروجیکٹ میں حصہ لینے کی نوعیت اور اہمیت کے بارے میں تفصیل سے بتایا گیا ہے اور آپ فراہم کردہ

وضاحت کو سمجھتے ہیں

،آپ کو بتایا گیا ہے کہ آپ کی بیماری کے نتائج اور آپ کے ڈیٹا کو سختی سے خفیہ رکھا جائے گا اور صرف کمیونٹی

اشاعتوں اور کاغذی پیشکشوں کے فائدے کے لیے استعمال کیا جائے گا

آپ کو سمجھایا گیا ہے کہ بیماری کی تشخیص کے لیے لیبارٹری تحقیقات کی جائیں گی۔ اس مقصد کے لیے، آپ مطالعہ

کے آغاز اور اختتام پر اپنے خون کے نمونے دینے پر مکمل اتفاق کرتے ہیں

آپ تمام متعلقہ معلومات کو مکمل طور پر اور اپنی بہترین معلومات کے مطابق محقق کو دینے سے بھی اتفاق کرتے ہیں

آپ کے لیے واضح کیا جاتا ہے کہ آپ کو مطالعہ میں حصہ لینے کے لیے کوئی ترغیب نہیں دی جائے گی سوائے لیب کی تحقیقات اور ادویات کے اخراجات کے، جب کہ آپ کو کسی بھی وقت مطالعہ سے دستبردار ہونے کا حق حاصل ہے

آپ کو مشورہ دیا جاتا ہے کہ اپنی بیماری سے متعلق کسی بھی سوال/ایمرجنسی کی صورت میں سدرہ انیس سے موبائل

نمبر: 0315 8562036 پر رابطہ کریں

:مریض کا نام

S/D/ W/o:

:مریض کے دستخط/ انگوٹھے کا نشان

PROFORMA

Demographic data:-

Name:- Age:-__ in years Gender:- Male /Female

Diagnosis of Pancreatitis on C.T scan abdomen: Yes/No

Biochemical markers

-Amylase (>140 U/L): (Raised/ not raised)

-Lipase (>140 U/L): (Raised/ not raised)

Any co-morbidities present:-

- Obesity (BMI>30 kg/m^2)
- Diabetes mellitus (past Medical history and current HbA1c>6.5%)
- Chronic kidney disease (past Medical history and current creatinine level of >1.3 mg/dL)
- Hypertension (past Medical history)
- Others, please specify:-_____
- Ranson's Criteria:

Acute pancreatitis not secondary to gallstones	**Acute pancreatitis secondary to gallstones**

○ **At admission:** Blood glucose > 11.11 mmol/L (> 200 mg/dL) Age > 55 years Serum LDH > 350 IU/L Serum AST > 250 IU/L WBC count > 16000 cells/mm3 ○ **Within 48 hours:** Serum calcium < 2.0 mmol/L (< 8.0 mg/dL) Hematocrit decreased by > 10% Oxygen (hypoxemia with PaO2 < 60 mmHg) BUN increased by 1.8 or more mmol/L (5 or more mg/dL) after IV fluid hydration Base deficit (negative base excess) > 4 mEq/L Sequestration of fluids > 6 L	○ **At admission:** Glucose > 220 mg/dl Age > 70 years LDH > 400 IU/L AST > 250 IU/ 100 ml WBC count > 18000 cells/mm3 ○ **Within 48 hours:** Serum calcium < 8 mg/dL Hematocrit decreased by > 10% Base deficit > 4 mEq/L BUN increased by > 2 mg/dL Sequestered fluid > 6L

- Biochemical markers (on admission):

CRP:	Albumin:

thesis plagiarism file final copy.docx

ORIGINALITY REPORT

16%	8%	13%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	2%
2	Zhi Zheng, Yi-Xuan Ding, Yuan-Xu Qu, Feng Cao, Fei Li. "A narrative review of acute pancreatitis and its diagnosis, pathogenetic mechanism, and management", Annals of Translational Medicine, 2021 Publication	2%
3	www.researchgate.net Internet Source	1%