ASSOCIATION OF VARIOUS INFLAMMATORY MARKERS AND CT SEVERITY INDICES IN CLINICAL OUTCOME AND PROGNOSIS OF ACUTE PANCREATITIS

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfilment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(GENERAL MEDICINE)

JULY 2020 **DR. ISHA STUTEE**

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DECLARATION

I hereby declare that the thesis titled "**ASSOCIATION OF VARIOUS INFLAMMATORY MARKERS AND CT SEVERITY INDICES IN CLINICAL OUTCOME AND PROGNOSIS OF ACUTE PANCREATITIS**" embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled **"ASSOCIATION OF VARIOUS INFLAMMATORY MARKERS AND CT SEVERITY INDICES IN CLINICAL OUTCOME AND PROGNOSIS OF ACUTE PANCREATITIS"** is the Bonafide work of Dr Isha Stutee carried out under our guidance and supervision, in the Department of General Medicine, All India Institute of Medical Sciences, Jodhpur.

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"*After all, the ultimate goal of all research is not objectivity, but truth.*"

- Helene Deutsch

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Last but by far not the least, I express thanks to all my patients without whom this milestone was not possible.

Dedicated to my family and friends

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ABBREVATIONS

AIP	Acute Interstitial Pancreatitis
ALI	Acute Lung Injury
ANA	Antinuclear Antibody
ANC	Acute Necrotizing Collection
ANP	Acute Necrotic Pancreatitis
AP	Acute pancreatitis
APBDU	Anomalous Pancreaticobiliary Ductal Union
APFC	Acute peripancreatic fluid collection
ARDS	Acute Respiratory Distress Syndrome
BISAP	Bedside Index for Severity in Acute Pancreatitis
BUN	Blood Urea Nitrogen
CARS	Compensatory Anti-Inflammatory Response Syndrome
CASR	Calcium-Sensing Receptor Gene
CECT	Contrast Enhanced CT
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CMV	Cytomegalovirus
CP	Chronic Pancreatitis
CRP	C- Reactive Protein
CTSI	CT Severity Index
ESR	Erythrocyte Sedimentation Rate
ERCP	Endoscopic Retrograde Cholangiopancreatography
IL	Interleukin
KFT	Kidney Function Test
LDH	Lactate dehydrogenase

LFT	Liver Function Test
LMR	Lymphocyte Monocyte Ratio
MAP	Mild Acute Pancreatitis
MCTSI	Modified CT Severity Index
MOF	Multiple Organ Failure
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
MSAP	Moderately Severe Acute Pancreatitis
NLR	Neutrophil Lymphocyte Ratio
PLR	Platelet Lymphocyte Ratio
PNI	Prognostic Nutritional Index
PTH	Parathyroid Hormone
PPV	Positive Predictive Value
RAC	Revised Atlanta classification
RAP	Recurrent Acute Pancreatitis
RDW	Red-Cell Distribution Width
RyR	Ryanodine Receptor
SAP	Severe Acute Pancreatitis
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
TNF-α	Tumor Necrosis Factor-A
TTP	Thrombotic Thrombocytopenic Purpura
WON	Walled-off Necrosis

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SUMMARY OF THE PROJECT

Background: There has been lot of interest in the development of rapid biomarkers that can accurately predict a patient's prognosis for acute pancreatitis. Numerous direct or combined indicators of systemic inflammation, such as the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), red-cell distribution width (RDW), CRP, LDH, and IL-6, have been thoroughly investigated to evaluate the severity and prognosis of acute pancreatitis.

Aims and objectives: To assess the prognostic value various inflammation markers like NLR, LMR, RDW, CRP, IL 6 and LDH in acute pancreatitis. To find association between various inflammatory markers with BISAP and APACHE II; and the CT Severity Index in prognosis of acute pancreatitis and to observe the common causes and clinical outcomes of acute pancreatitis in the patients admitted in AIIMS Jodhpur.

Methods: In this study we prospectively studied Acute Pancreatitis patients of more than 18 years, from 1st Jan 2021 to July 2022 at All India Institute of Medical Sciences (AIIMS), Jodhpur. 80 patients of acute pancreatitis were enrolled after taking informed written consent. Laboratory investigations were done on presentation and day 7 of illness. BISAP was calculated on presentation. CECT abdomen was done on day 5 to 7 of illness. Age and gender wise distribution of AP was calculated. Mean values and standard deviation was calculated for all laboratory investigations. Appropriate statistical tests were applied to calculate association of age, inflammatory markers, urea, clinical severity indices like BISAP and CT severity indices like CTSI and MCTSI were compared with severity of acute pancreatitis, development of local complications and duration of hospital stay. Inflammatory markers were also compared with BISAP, CTSI and MCTSI. ROC curve was plot for independent predictors of severity and local complications and R^2 was calculated.

Results: The most common cause of AP in our study population was alcohol (around 51% cases) followed by gallstones (around 24% of cases).

In our study, significant correlation of LDH was seen with duration of hospitral stay (p value <0.0001). LDH was significantly different in patients having BISAP score less than 2 and score of 2 or more. Mean LDH was 351 in patients BISAP or less than 2 and 897 in patients with score of 2 or more (p value <0.0001). Higher LDH was seen in patients with higher BISAP, CTSI and MCTSI. Serum LDH of >435.00 has 100% sensitivity and 66.8 % specificity to predict severity of acute pancreatitis, (Area under the curve- 0.898 (0.810 – 0.987), p value- <0.0001). Serum LDH of >274 has 76.2% sensitivity and 70.6% specificity to predict complication in a case of acute pancreatitis, (Area under the curve- 0.802 (0.700 – 0.904), p value- <0.0001).

In our study, significant correlation of duration of hospitral stay was seen with CRP (p value 0.024). Mean value of CRP was significantly different the groups with or without local complications. Mean CRP was 85 in patients without any complications and 136 in patients with complications (p value 0.022). However, there CRP did not vary significantly between severe and non-severe pancreatitis.

ESR was significantly different between patients having MCTSI score less than 6 and score of 6 or more. Mean ESR was 34 in patients with MCTSI score less than 6 and 48 in patients with score of 6 or more (p value 0.037). However, ESR did not significantly vary with severity, complications, duration of hospital stay, BISAP or CTSI. And hence could not be used to predict severity or local complications in pancreatitis.

Mean value IL-6 was significantly different in patients having BISAP score less than 2 and score of 2 or more. Mean IL-6 was 109 in patients BISAP or less than 2 and 348 in patients with score of 2 or more (p value 0.025). However, IL-6 did not significantly vary with severity, complications, duration of hospital stay, MCTSI or CTSI. And hence could not be used to predict severity or local complications in pancreatitis.

NLR, LMR and PLR were not significantly different in severe and non-severe pancreatitis, or between patients with or without local complication and could not be used to predict severity or local complications in pancreatitis. NLR. PLR and PLR had no significant correlation with duration of hospital stay. None amongst NLR, LMR and PLR significantly vary with CTSI, MCTSI or BISAP score.

Conclusion: There is need of better and cheaper biomarkers for prediction of outcome and prognosis. In this study we used newer biomarkers like NLR, PLR, LMR, RDW, IL-6 along with LDH, ESR, CRP and blood urea. Overall, Serum LDH was seen as single best prognostic marker in Acute Pancreatitis. Serum LDH could reliably predict severity of Acute Pancreatitis and local complication in patients in AP. LDH also correlates well with duration of Hospital stay. Significant correlation of CRP and RDW was seen with duration of hospital stay. However, neither RDW nor CRP could predict severity of acute pancreatitis. In contrast to all previous studies NLR, PLR, LMR and IL-6 could not predict severity, local complications in pancreatitis or duration of hospital stay.

INTRODUCTION

Acute pancreatitis is an acute inflammatory process involving the pancreas with varying degrees of involvement of other regional tissue or remote organ systems.

Pancreatitis has been categorized into three categories: acute pancreatitis (AP), recurrent acute pancreatitis (RAP), and chronic pancreatitis (CP).

According to studies, AP can develop into RAP and ultimately CP in a continuous disease trajectory. But not all AP cases proceed to RAP, and not all RAP cases progress to CP. This trajectory is influenced by multiple extrinsic and intrinsic risk factors, including extrinsic factors such as alcohol use and smoking, and intrinsic factors such as hereditary mutations and autoimmune diseases (1).

Incidence of acute pancreatitis varies from 35 to 80 cases per 1 lakh individuals worldwide, affecting a greater number of males than females (2). Gall stones and alcohol consumption together account for 70% of cases of Acute Pancreatitis. The risk of developing AP in patients with gallstones is seen to be greater in men, but more women develop gallstone related AP since gallstones occur with increased frequency in women (3). It has been seen that 10% of instances of AP are due to hypertriglyceridemia, with pregnancy increasing the risk. About 20% of cases of AP are related to abdominal trauma, however there is no link between the force of the trauma and the degree of pancreatic injury (4). Hereditary risk factors can put a patient at an increased risk of developing AP when combined with additional risk factors like alcohol consumption, smoking, and hypertriglyceridemia (4).

According to 2012 revised Atlanta classification, based on the presence or lack of necrosis, acute pancreatitis is currently classified into two distinct subtypes: necrotizing pancreatitis and interstitial pancreatitis. (5). Interstitial pancreatitis is defined as acute inflammation involving the pancreatic parenchyma and peripancreatic tissues, but without any recognizable tissue necrosis. CECT criteria of interstitial pancreatitis include pancreatic parenchyma enhancement after giving intravenous contrast agent with no findings of peripancreatic necrosis. Necrotizing pancreatitis is defined as pancreatic inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis. CECT criteria of necrotizing pancreatitis include lack of pancreatic parenchymal enhancement after giving intravenous contrast agent and/or presence of findings of peripancreatic necrosis such as acute necrotic collection and walled off necrosis (5,6). About10–20% of cases of AP develop Acute necrotizing pancreatitis (ANP) and is linked to greater death and morbidity rates (7–10).

The dynamic disease process of AP comprises two overlapping periods with early and late death peaks (11–13). The second later phase, which can range from weeks to months, follows the early phase, which normally lasts for the first week. Systemic abnormalities develop during the early stage as a result of the host's reaction to the local pancreatic insult. The pancreatic inflammation results in activation of cytokine cascades that results in clinical manifestation of systemic inflammatory response syndrome (SIRS) (14,15). The likelihood that pancreatitis will be worsened by organ failure increases when SIRS is present and persistent, so such patients should be managed as though they have severe acute pancreatitis

(16,17). The late phase is characterized by the presence of local complications or by persistence of systemic signs of inflammation, so the late phase is seen only in patients with moderately severe or severe acute pancreatitis. The compensatory anti-inflammatory response syndrome (CARS), which can increase the risk of infection, may follow the SIRS of the early phase, but these events are complicated and little understood (6,18).

Although the condition is modest in the majority of patients and has a decent prognosis, 20–30% of people go on to have a serious clinical course with greater morbidities and mortality (19). In SAP, the mortality rate typically ranges between 2% and 10% (20). In SAP patients, two mortality peaks have been identified and reported. Early deaths typically occur within the first two weeks as a result of systemic inflammatory response syndrome (SIRS) brought on by the production of different cytokines, whereas the other half die after two weeks as a result of peripancreatic necrosis, infection, and secondary MODS (21).

The progression of the disease may be related with the genetic polymorphism involving cellular regulatory mechanisms, such as the regulation of apoptosis and oxidative stress or propensity to create proinflammatory cytokines. It was shown that polymorphisms involving the promoter regions of the interleukin genes including IL-1, IL-6, IL-8, and IL-10 affected transcriptional activity and were thus thought to be possible risk factors for the severity of AP. (22–25). A meta-analysis conducted in 2013 by Yin et al. found that other IL-1, IL-6, or IL-10 polymorphisms did not raise the risk of AP, but the IL-8 -251T-A polymorphism did (26).

Acute Pancreatitis is classified as Mild Acute Pancreatitis (MAP) if there is no local complication or organ failure, Moderately Severe Acute Pancreatitis if there is transient organ failure (less than 48 hours) or there is local or systemic complication in absence of persistent organ failure and Severe Acute Pancreatitis (SAP) if organ failure persists for more than 48 hours(27). Organ failure is defined by modified marshal criteria (14), which includes assessment of three organ systems: kidney, respiratory system or cardiovascular system. Organ failure is defined as a score of ≥2 using the modified Marshall scoring system after evaluating the three organ systems namely cardiovascular, renal and respiratory systems. Local complications include pancreatic necrosis, peripancreatic fluid collections, pancreatic ascites, walled of necrosis, pancreatic pseudocyst, disruption of the primary pancreatic duct or its secondary branches, involvement of adjacent organs by necrotizing pancreatitis, obstructive jaundice, pancreatic enteric fistula, splanchnic blood vessels thrombosis (like splenic vein thrombosis and portal vein thrombosis), and bowel infarction (28).

Although local complications may indeed be discovered in the early stages, it is usually not advised to perform imaging to document local complications within the first week of the disease for the reasons listed below. First, imaging may not be able to adequately detect the existence and quantify the degree of pancreatic and peripancreatic necrosis during the first few days of the disease (29). If necessary, a CECT Abdomen performed between the fifth and seventh day following admission is more accurate in detecting the presence and severity of pancreatic necrosis. Second, the degree of morphologic changes and necrosis is not always directly proportional to the severity of organ failure (30,31). Last but not least,

even if scanning performed within the initial week reveals pancreatic necrosis or peripancreatic fluid collections,, in most cases no therapy needs to be administered for these conditions during this period (30).

Systemic complications can involve pulmonary, cardiovascular, hematological, gastrointestinal, renal or central nervous system and may include metabolic complications. Common cardiovascular manifestations of AP include abnormalities in cardiac contractility, rhythm, and the vasomotor tone of peripheral vessels. Hypovolemia and metabolic derangements are the key pathogenetic factors of cardiac manifestations of AP (32). Around 50% acute pancreatitis patients have electrocardiographic changes, most common of which are flattening of T-wave and depression of the ST-segment (33,34). Pulmonary complication includes pleural effusion, atelectasis, pneumonitis, ARDS and mediastinal fluid (35).

Organ failure may be transient (less than 48 hours) as in moderately severe acute pancreatitis (MSAP) or may be persistent (more than 48 hours) as in severe acute pancreatitis (SAP). Persistent organ failure may involve a single organ or may include multiple organ failure. Multiple organ failure (MOF) is defined as organ failure affects more than one organ system. A mortality rate of up to 36–50% has been observed for patients who experience persistent organ failure in the first few days of the illness (14,15).

There has been lot of interest in the development of rapid biomarkers that can accurately predict a patient's prognosis for acute pancreatitis. Numerous direct or combined indicators of systemic inflammation, such as the neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), red-cell distribution width (RDW), CRP, LDH, and IL-6, have been thoroughly investigated to evaluate the severity and prognosis of acute pancreatitis (40). Out of these, NLR within the first 48 hours of hospitalization is strongly associated with severe acute pancreatitis and serves as an independent poor prognostic factor for AP (41). NLR is a low-cost, easily available test and has a promising role in predicting the severity of hypertriglyceridemia-induced acute pancreatitis. The RDW indicates the variation in erythrocyte size in circulation. Previous research has shown that RDW is a useful predictor of acute pancreatitis severity and that it is positively correlated with the severity of the condition. (42). The discriminatory power of earlier research to predict the outcome of patients with acute pancreatitis, however, is inconsistent.

The purpose of current work is focused on assessing the prognostic value of various inflammation markers and various radiological and clinical severity indices in acute pancreatitis. We also aimed to find a simple, rapid, and inexpensive biomarker for reliable prognosis prediction of acute pancreatitis that correlates well with the CT Severity Indices and clinical outcome of the patient. We also planned to observe the common causes of acute pancreatitis in the given population and the common complications that occur in acute pancreatitis.

REVIEW OF LITERATURE

The term "pancreatitis" refers to an acute or chronic inflammation of the pancreas that is characterized by premature activation of digestive enzymes within the pancreatic acinar cells and resulting in pancreatic auto-digestion (43).

Acute pancreatitis is an acute inflammatory process of the pancreas with varying degree involvement of other regional tissue or remote organ system. Diagnosis of acute pancreatitis is made if patients have any two of the aforementioned: symptoms such as abdominal pain that is consistent with AP, serum amylase or lipase greater than three times the upper limit of normal or radiological imaging including abdominal ultrasound, CT or MRI showing changes consistent with AP. If CT/MRI/ERCP indications of chronic pancreatitis are present, pancreatitis is defined as chronic, and each episode of pancreatitis is thought to be an aggravation of inflammation superimposed on chronic pancreatitis. Pancreatitis is diagnosed as acute until there is evidence of such chronic changes.

Incidence of AP varies from 35 to 80 cases per 100,000 individuals worldwide, affecting a greater number of males than females (2).

The spectrum of AP ranges from mild and self-limited interstitial pancreatitis to necrotizing pancreatitis. Acute inflammation involving the pancreatic parenchyma and peripancreatic tissues without any apparent tissue necrosis is termed as acute interstitial pancreatitis (AIP). When a contrast agent is injected intravenously, the pancreatic parenchyma is enhanced, and pancreatic necrosis also isn't seen on the CT scan in acute interstitial pancreatitis. Pancreatic inflammation associated with necrosis of pancreatic parenchyma and/or peripancreatic tissue is termed as acute necrotizing pancreatitis (ANP), as per revised Atlanta classification which on CT is seen as lack of enhancement of pancreatic parenchyma following injection of IV contrast agent and/or observations that are congruent with peripancreatic necrosis such as acute necrotizing collection (ANC) and walled-off necrosis (WON) (5).

Development and recurrence of acute and chronic pancreatitis are influenced by a number of genetic, environmental, and metabolic variables (44). The two major cause of acute pancreatitis remains alcohol consumption and gallstones. (4) Other common

causes include hypertriglyceridemia, drugs (like azathioprine, 6-mercaptopurine, sulfonamides, and valproic acid), trauma, ERCP and abdominal and nonabdominal operations.

Uncommon causes of AP include hypercalcemia, vasculitis, ischemic hypoperfusion, connective tissue disorders like lupus erythematosus, thrombotic thrombocytopenic purpura (TTP), pancreatic cancers like intraduct papillary mucinous tumor, cystic fibrosis, renal failure, infections (including viral infections like mumps, CMV, coxsackievirus and parasitic infections like ascaris, Cryptosporidium, Clonorchis and Microsporidia), structural or congenital abnormalities and autoimmune pancreatitis (45–48).

Genetic, structural or congenital abnormalities are now being seen as the major risk factors for recurrent acute (RAP) and chronic pancreatitis (CP) in the pediatric population (49).

The pancreaticobiliary system's developmental abnormalities, such as the pancreas divisum, choledochal cyst, annular pancreas, anomalous pancreaticobiliary ductal union (APBDU), ectopic pancreatic tissue sources, and enteric duplication cysts, are the most commonly observed congenital causes of AP. These abnormalities may present with acute pancreatitis in childhood but more frequently do so in adulthood (50). Individuals with choledochal cysts linked to APBDU are considerably more likely to have pathologically verified inflammation and signs of hepatitis, cholangitis, or pancreatitis than patients without such conditions. (51).

Many genes have been recently studied for their role in pathogenesis of AP. The cationic trypsinogen gene (PRSS1), the pancreatic secretory trypsin inhibitor gene (SPINK1), and the cystic fibrosis transmembrane conductance regulator (CFTR) gene are the three most frequently mutated genes found to be associate with increased risk of development of acute pancreatitis (52). Gain-of-function mutations in the gene encoding PRSS1 and loss-of-function mutations in genes that encode SPINK1 and CFTR have been associated with recurrent (RAP) and chronic pancreatitis (CP) (44). Other mutations related to hereditary pancreatitis include mutations in the chymotrypsin C (caldecrin) gene (CTRC) and the calcium-sensing receptor gene (CASR), though the associated risk of RAP and CP seems to be smaller with these mutations (44).

S. no	Etiology of Acute Pancreatitis
1.	Gallstone
2.	Alcohol consumption
3.	Hypertriglyceridemia
4.	Abdominal Trauma
5.	Post-ERCP
6.	Abdominal and nonabdominal operations
7.	Hypercalcemia
8.	Hyperparathyroidism
9.	Autoimmune Pancreatitis
10.	Congenital anomalies: Pancreatic divisum, choledochal cyst, anomalous pancreaticobiliary ductal union (APBDU), annular pancreas,
11.	Viral infections: Mumps, CMV, coxsackievirus
12.	Parasitic infections: Ascaris lumbricoides, Clonorchis sinensis, Cryptosporidium, Microsporidia
13.	Drugs: Azathioprine, 6-mercaptopurine, sulfonamides, and valproic acid
14.	Connective Tissue Disorders: Systemic Lupus Erythematosus
15.	Vasculitis: Polyarteritis Nodosa
16.	Hereditary Pancreatitis Cystic Fibrosis

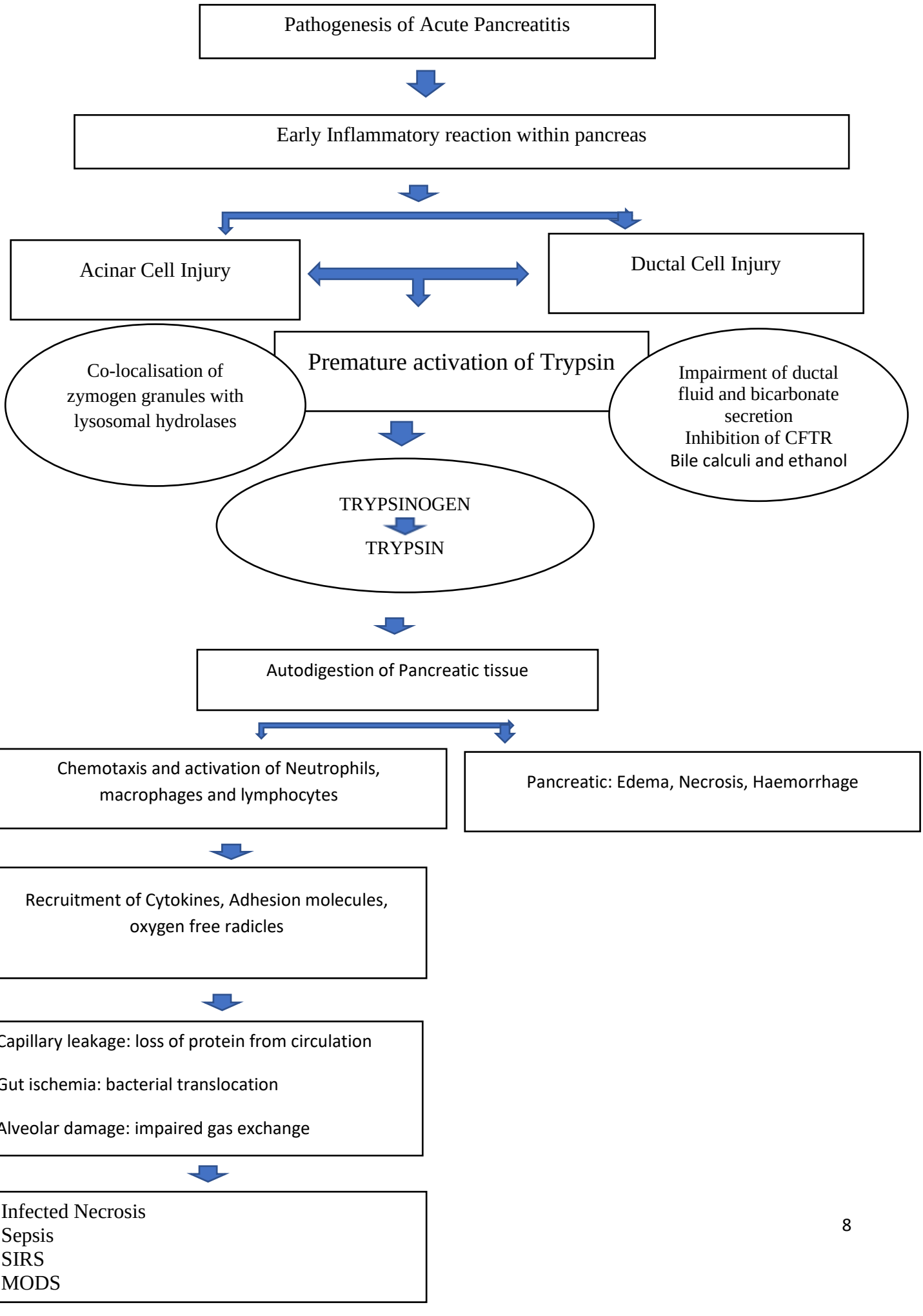
17.	Toxins: Scorpion bites, organophosphate poisoning
18.	Idiopathic

The commonly proposed theories about the pathogenesis of acute pancreatitis include theory of common bile-pancreatic duct pathway, theory regarding autodigestion of pancreatic parenchyma, theory of gallstone migration, theory of enzyme activation, theory of activation of kinin and complement system, theory of microcirculation disturbance, theory of excessive leukocyte activation, theory of pancreatic acinar cell apoptosis and necrosis, however the part each of these theories play in pathogenesis of AP is not completely unraveled (53–56).

Zymogens, which are released pancreatic proenzymes, are often activated in the intestinal lumen. Contrarily, the pathogenesis of acute pancreatitis is crucially influenced by the premature activation of zymogens, especially proteases, inside the pancreatic acinar cell (43). This theory is supported by many observations. First, SAP manifests as morphological alterations that closely resemble that seen in digestive necrosis. Second, rise in pancreatic and serum levels of activated proteases precede any morphological evidence of acinar cell injury (57). Third, pretreatment with serine protease inhibitors block trypsinogen activation and pancreatitis (58,59). Fourth, gain of function mutations in the cationic trypsinogen gene can increase the risk of hereditary pancreatitis (60). An aberrant rise in intracellular Calcium ion (Ca^{2+}) plays an important role in this pathological protease activation (61). Release from cytosolic Ca2+ pools is primarily responsible for the initial increase in Ca2+ that occurs following stimulation of acinar cells by the secretagogue. It has been demonstrated that premature protease activation is caused by Ca2+ ion released by the ryanodine receptor (RyR), which is an intracellular Ca2+ channel. (62).

Atrophic acinar cells stimulate various inflammatory cells, such as macrophages and polymorphonuclear cells, which release a number of pro-inflammatory cytokines, including tumour necrosis factor (TNF)- α, IL-1, IL-6, IL-8, IL-18 and IL-33, and, during pancreatic injury. Pancreatic stellate cells (PSCs) are activated by these pro-inflammatory cytokines to promote chronic pancreatitis (55,63).

Fig: Pathogenesis of Acute Pancreatitis



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According to Atlanta severity scoring acute Pancreatitis is classified as Mild Acute Pancreatitis (MAP) if there is no local complication or organ failure, Moderately Severe Acute Pancreatitis if there is transient organ failure (less than 48 hours) or there is local or systemic complication in absence of persistent organ failure and Severe Acute Pancreatitis (SAP) if organ failure persists for more than 48 hours (16).

Local complications include pancreatic necrosis, peripancreatic fluid collections, pancreatic ascites, walled of necrosis, pancreatic pseudocyst, disruption of the primary pancreatic duct or its secondary branches, involvement of adjacent organs by necrotizing pancreatitis, obstructive jaundice, pancreatic enteric fistula, splanchnic blood vessels thrombosis (like splenic vein thrombosis and portal vein thrombosis), and bowel infarction (28).

Fluid collections more often develop in the early stages of pancreatitis. Acute peripancreatic fluid collection (APFC) is the accumulation of peripancreatic fluid in interstitial pancreatitis without peripancreatic necrosis. This nomenclature only refers to peripancreatic fluid pockets that are detectable within the first four weeks following the development of interstitial pancreatitis. On an abdominal CECT scan, it appears as a homogenous fluid-density collection adjacent to the pancreas, constrained by normal peripancreatic fascial planes with no discernible wall enclosing the collection and no intrapancreatic extension.

A pancreatic pseudocyst is a fluid accumulation that is encapsulated and usually seen outside of the pancreas with little to no necrosis and a clearly delineated inflammatory wall. This condition typically develops more than 4 weeks after the interstitial pancreatitis first manifests. It appears on the CECT abdomen as a completely encapsulated, well-circumscribed, typically round or oval homogenous fluid density mass without any non-liquid component and a well-defined wall.

Acute necrotic collection (ANC) is a collection, associated with necrotizing pancreatitis, consisting in varying degrees of fluid and necrosis involving either the pancreatic parenchyma and/or the peripancreatic tissues. It appears as a heterogeneous mass on the CECT abdomen, with non-liquid density that varies in intensity at different regions and

no discernible wall enclosing the collection. It may be intrapancreatic, extrapancreatic, or both.

APFC and ANC are difficult to differentiate an on ultrasound or CECT abdomen, within the first week of AP. During this period, both types of collections may appear as areas with fluid density. After the first week, it is easier to distinguish between these two significant types of collections, making it possible to refer to a peripancreatic collection associated with pancreatic parenchymal necrosis as an ANC and not an APFC.

The term "walled-off necrosis" (WON) refers to a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis which has formed a distinct inflammatory wall. WON typically manifests >4 weeks following the onset of necrotizing pancreatitis. On CECT, it presents as a heterogeneous mass having both fluid and non-liquid density, variable degrees of loculations, and a clearly defined wall. It may be intrapancreatic, extra-pancreatic, or both.

Acute necrotizing pancreatitis can develop an infection that spreads from the pancreas to the peripancreatic tissues, the retroperitoneum, and, less frequently, the peritoneal cavity. This condition is known as infected pancreatic necrosis. gram-negative bacteria of enteric origin are the most commonly isolated microorganisms in cases of acute bacterial pancreatitis. However, there has been a recent trend toward a rise in the incidence of gram-positive cocci isolation. The single most isolated species in infected necrosis is Enterococcus. The patient's clinical course or the results of a CECT abdominal test can raise suspicions about the possibility of infection of an ANC or of a WON. Clinical suspicion of infected necrosis is aroused when a patient with acute necrotizing pancreatitis experiences a profound and sudden deterioration of their clinical status that results in septic shock or multiple organ dysfunction syndrome. On CECT abdomen, presence of gas can be observed within the necrotic collection. Depending on the quantity of liquid content present at the time of the scan, the extraluminal air, located in regions of necrosis, may or may not form an air/fluid level. Whenever in doubt, the necrotic collection may be used for fine needle aspiration for culture.

Pancreatic ascites is an uncommon clinical entity caused due to continuous pancreatic secretion leakage into the peritoneum as a result of pancreatic duct injury and formation of pancreato-peritoneal fistula. The presence of a pseudocyst or walled-off necrosis increases the odds of developing pancreatic ascites in a patient of acute pancreatitis.

Systemic complications can involve pulmonary, cardiovascular, hematological, gastrointestinal, renal, central nervous system and metabolic complications.

The ability of the pancreatic gland to create a number of powerful vasoactive peptides, enzymes, and hormones is reflected in the multisystem involvement in AP. (36). The pathogenesis of hypocalcemia in pancreatitis is multifactorial. Recently described but nevertheless questioned theories include the imbalance between parathormone and calcitonin, the interaction of glucagon, gastrin, and other pancreatic hormones with Parathyroid hormone and calcitonin, the binding of serum calcium with albumin facilitated by free fatty acids, and the remobilization of calcium ions in muscles and liver. (37–39). Theory of calcium-soap formation is also a widely accepted theory. Coagulation abnormalities were also found to be initiated by the activated trypsin, and the resultant microvascular coagulation was found to have a role in major organ dysfunction. Adult respiratory distress syndrome (ARDS) in AP may be the result of digestion of pulmonary surfactant by the active enzymes and/or microvascular thrombosis (35). Myocardial depressive factor or vasoactive peptides like bradykinin were thought to be the causes of the depression of heart function and shock. Rennin angiotensin alterations and other renal complications like acute renal failure have also been seen in pancreatitis. Moderate visual disturbances, or even blindness, as a result of retinal vessel thrombosis in a patient with AP has been seen (32).

Common cardiovascular manifestations of AP include abnormalities in cardiac contractility, rhythm, and the vasomotor tone of peripheral vessels. Hypovolemia and metabolic derangements are the key pathogenetic factors of cardiac manifestations of AP (32). Around 50% acute pancreatitis patients have electrocardiographic changes, most common of which are flattening of T-wave and depression of the ST-segment (33,34).

Pulmonary complication includes pleural effusion, atelectasis, pneumonitis, Acute lung injury (ALI), ARDS and mediastinal fluid (35). Pancreatic proteolytic enzymes and proinflammatory cytokines generated as a result of pancreatic injury are the primary mediators of the pulmonary consequences of AP. Involvement of pulmonary vasculature can lead to pulmonary thromboembolism. One of the most significant organ dysfunctions experienced by AP patients is ALI. Among patients with AP, ALI is one of the most frequent causes of prehospitalization mortality. Three stages of ALI have been described traditionally. Patients in the initial stage exhibit arterial hypoxia with no obvious radiological abnormalities. The second stage is defined by modest radiological abnormalities. The patient develops ARDS in the third stage, which is marked by bilateral diffuse coalescent opacities, having increased density posteriorly, that don't

clear completely with the use of diuretics. ARDS often manifests two to seven days after the start of pancreatic inflammation.

The incidence of pleural effusion previously reported in acute pancreatitis was about 3–17%, but recent reports have shown an incidence of up to 50% patients on CT imaging. There are several mechanisms that have been described in context of pleural effusion in patients of pancreatitis. The transdiaphragmatic lymphatic obstruction is one of the mechanisms. Another theory is that the pancreatic duct disruption leads to formation of a pancreatico-pleural fistula with resultant leakage of pancreatic enzymes. Yet another explanation is, exudation of fluid, from the subpleural diaphragmatic vessels, into the pleural cavity leads to pleural effusion in AP.

Organ failure may be transient (less than 48 hours) as in moderately severe acute pancreatitis (MSUP) or may be persistent (more than 48 hours) as in severe acute pancreatitis (SAP). Persistent organ failure may involve single or multiple organs. Multiple organ failure (MOF) is term used when the organ failure affects more than one organ system. A mortality rate of up to 36–50% has been observed for patients who experience persistent organ failure in the first few days of the illness (14,15). Modified marshal criteria is used define organ failure (14), which includes assessment of three organ systems: kidney, respiratory system and cardiovascular system. Organ failure is indicated by a score of 2 for one of these three organ systems in the modified Marshall scoring system.

Treatment of Acute pancreatitis mainly comprise of early aggressive intravenous hydration. Early, aggressive intravenous fluid resuscitation supports the micro- and macrocirculation and avoids major side effects such pancreatic necrosis. In numerous clinical investigations, lactated Ringer's solution appeared to be more useful than normal (0.9%) saline for resuscitation as fewer patients developed SIRS with lactated Ringer's solution. Analgesics are given for control of pain.

In cases of severe acute pancreatitis, routine prophylactic antibiotic usage is not recommended. Additionally, in order to avoid the development of infected necrosis in situations of sterile necrosis, antibiotics should not be administered. For infections other than pancreatic infections, such as bacteremia, cholangitis, pneumonia, urinary tract infections, and Bacteremia, antibiotics should be used. Patients with pancreatic and extra-pancreatic necrosis who worsen or do not improve after 7 to 10 days of hospital admission should be suspected of having infected necrosis. In such a case, either a fine needle aspiration with

microscopic examination and culture guided by CT should be done to determine the most appropriate antibiotic to administer, or empiric antibiotics must be started after obtaining samples of the infectious agents to be cultured and tested for sensitivity. Antibiotics which have been documented to penetrate pancreatic necrosis, such as carbapenems, quinolones, and metronidazole, should be given in patients with infected necrosis in order to postpone or completely avoid procedures. In cases of acute pancreatitis, routine antifungal usage in addition to antibiotics is not advised.

ERCP is not needed early in most patients of gallstone related AP in absence of clinical or laboratory evidence of ongoing biliary obstruction. In absence of cholangitis and/or jaundice MRCP and EUS are preferred over ERCP for screening of choledocholithiasis. However, patients of AP with concurrent acute cholangitis should undergo ERCP within 24 hours of hospital admission. In patients who are high risk for developing severe post-ERCP pancreatitis, pancreatic duct stenting or rectal NSAID suppository can be used.

Feeding can be started immediately in patients of mild acute pancreatitis after resolution of nausea, vomiting and pain abdomen. Low fat containing solid meals are as safe as clear liquid diet in mild acute pancreatitis. In severe acute pancreatitis, enteral nutrition is recommended in preventing infectious complications. Parenteral nutrition should be avoided as far as possible, unless enteral feeding is not available, not tolerated or is not meeting caloric requirement. Nasogastric and nasojejunal feeding are equally effective and safe forms of enteral feeding.

Cholecystectomy should be performed before discharge in patients of mild gallstone acute pancreatitis to prevent recurrence of AP. However, in necrotizing biliary pancreatitis, cholecystectomy should be deferred till resolution of inflammation and resolution or stabilization of fluid collection, in order to prevent infection.

Asymptomatic pseudocyst and necrotic collection do not need surgical, radiological or endoscopic drainage irrespective of its size, location and extension. Patients of infected necrosis who are clinically stable, drainage should be delayed at least by 4 weeks to allow liquefaction of the content and formation of a fibrous wall around the necrosis. In patients of symptomatic infected necrosis, minimally invasive methods of necrosectomy should be preferred over open necrosectomy.

Several drugs, such as antisecretory agents, immunomodulators, protease inhibitors, antioxidants, and anti-inflammatory agents, have been studied as potential therapies in acute pancreatitis. Preclinical studies have shown potential benefit of using somatostatin and its analogues in acute pancreatitis.

The role of steroids in acute pancreatitis has been controversial. The efficiency of steroid medication was shown to depend on the severity of the disease in one experimental research of caerulein-induced acute pancreatitis in rats, with dexamethasone being much more beneficial in pancreatitis with severe inflammation. However, several studies have linked high-dose hydrocortisone with increased mortality and complication rates, including sepsis or infection. Steroids have also been linked to the development of acute pancreatitis.

Studies have suggested the role of indomethacin in cases of post-ERCP pancreatitis, however similar benefits have not been seen in non-ERCP related pancreatitis.

Interleukin-10 (IL-10) can reduce the severity of caerulein-induced AP in rat model if administered before or after the disease is established, according to animal research. Studies have indicated that lexipafant therapy of mouse pancreatitis produced by taurodeoxycholate and caerulein lowers the severity of pancreatitis-related problems. Lexipafant alone is not effective in treating severe acute pancreatitis, according to a randomised clinical trial, which found no significant decrease in organ failure or local consequences in AP patients.

According to numerous preclinical studies, anti-oxidant medications may be able to target the cellular injury brought on by reactive oxygen species in acute pancreatitis, that has now been studied in numerous clinical trials. Numerous randomised clinical trials that evaluated the effects of acetylcysteine, selenium, vitamin A, and vitamin c in the treatment of AP found that these anti-oxidants increased plasma antioxidants levels and reduced markers of oxidative stress, but did not improve organ dysfunction in the patients taking them. A meta-analysis of randomised controlled studies using glutamine revealed a mortality reduction (RR = 0.3, 95%CI: 0.15-0.6) and decreased infectious complications (RR = 0.58, 95%CI: 0.39-0.87) in patients receiving glutathione, but no change in the length of hospitalization. But only those getting whole parenteral feeding were found to benefit from glutathione. As a result, more research on the function of antioxidants in AP is required.

Due to laboratory findings showing FFP had an inhibitory effect on the proteolytic activity in the serum of patients with acute pancreatitis, fresh frozen plasma (FFP) has also been

investigated as a potential treatment for acute pancreatitis. A large multi-center controlled clinical trial revealed no difference between the groups treated with colloids and FFP in terms of their treatment outcomes.

The U.S. Food and Drug Administration granted Panoquell-CA1 a conditional approval for the management of clinical symptoms associated with acute canine pancreatitis on November 15, 2022. Panoquell-CA1 is an injectable drug with fuzapladib sodium as the active ingredient that targets the cell adhesion molecules.

It is of vital importance to recognize patients at risk of developing severe acute pancreatitis at an early phase to initiate timely treatment and optimize therapy.

In acute pancreatitis, hemoconcentration may predict more severe disease (i.e. pancreatic necrosis) and azotemia is a risk factor for mortality (64).

Blood urea nitrogen (BUN) was examined to determine whether early variations in BUN could predict mortality in AP and Wu et al. discovered that throughout the first 48 hours of hospitalisation, BUN levels were consistently higher in non-survivors than in survivors ($P < 0.0001$) (65).

Koutroumpakis et al. investigated admission hematocrit, rise in blood urea nitrogen at 24 hours, and other laboratory parameters for predicting pancreatic necrosis and persistent organ failure in AP. They discovered that among the currently used laboratory parameters and scoring systems, admission hematocrit 44% and rise in BUN at 24 hours may be the best predictive tools for predicting pancreatic necrosis and persistent organ failure in AP. (66).

Bedside index of severity in acute pancreatitis (BISAP) score is calculated by the following criteria BUN >25 mg/dL (8.9 mmol/L), abnormal mental status with a Glasgow coma score <15, evidence of SIRS (systemic inflammatory response syndrome), patient age >60 years old and imaging study revealing pleural effusion. Each criterion is given one point each and the final BISAP score is calculated by adding points of each criterion, 0 to 2 points indicate lower mortality (<2%) and 3 to 5 indicate higher mortality (>15%).

The patient's age and 12 common physiological measurements, such as PaO2 (depending on FiO2), body temperature, mean arterial pressure, blood pH, heart rate,

respiratory rate, serum sodium, serum potassium, serum creatinine, hematocrit, WBC count, and Glasgow Coma Scale, are used to calculate the patient's "APACHE II" score. These are assessed within the first day of admission.(65)

Kumar et al. compared APACHE II, Ranson's score, BISAP, and MCTSI in predicting the severity of AP based on the revised Atlanta Classification (2012) demonstrated that APACHE II can be a helpful prognostic scoring system for predicting the severity of AP and can play role of a vital tool for identifying the patient population which would need early resuscitation and prompt referral because of having high likelihood of requirement of tertiary care during the course of their illness, especially in developing countries with scarce resources (67).

Wan et al. did a large hospital-based retrospective study, in which they studied whether serum creatinine and APACHE-II score within 24 hours of admission can effectively predict persistent organ failure in AP, and demonstrated that an APACHE-II score of ≥ 8 and a serum creatinine level ≥ 1.8 mg/dl within 24 hours of admission can positively predict persistent organ failure in AP. (43)

Pando et al. in their study tried to see, could early changes in BUN predict mortality in AP in which they compared BISAP Score, APACHE-II, and other laboratory markers demonstrated that rise in BUN at 24 hours can predict mortality and persistent multiorgan failure, comparable to the most widely used scores, like APACHE-II and BISAP. Rise in BUN at 24 hours is a risk factor for outcomes such death, multiorgan failure, and severe AP. While in predicting severe AP, the BISAP score performed better than both the APACHE-II and the rise in BUN at 24 hours. (68).

Transabdominal ultrasound should be performed in all patients of acute pancreatitis. CECT and MRI abdomen should be reserved for the patients in whom diagnosis in not confirmed on transabdominal ultrasound or who fail to improve after 48 to 72 hours of hospital admission or to evaluate for complications.

However, during the first few days of onset of AP, imaging may not be able to accurately characterize the presence and extent of pancreatic and peripancreatic necrosis (29). CECT Abdomen should be done, 5–7 days after admission, as during this time it is more reliable in establishing the presence and extent of pancreatic necrosis and other local complications.

CECT abdomen in the assessment of AP is useful not only for diagnosis but also for detecting local pancreatic and peripancreatic complications and provides important information for planning further interventional procedures. Several radiological prognostic indices have been developed in the past. CT Severity Index (CTSI) and modified CT severity index (Modified CTSI) are two of them. The CT severity index (CTSI), that evaluates the severity of acute pancreatitis, is based on results from a CT scan with intravenous contrast. It has been discovered that the severity of computed tomography findings and clinical severity indices correspond well. The CTSI combines two scores: a) the Balthazar score, which rates the severity of pancreatitis (A-E), and b) the grade of pancreatic necrosis. The same author expanded upon the conventional Balthazar score in 1990 by introducing the necrosis scoring system. Further modifications that were made to the CTSI, resulted in the development of Modified CTSI (MCTSI) in the year 2004The MCTSI simplifies examination of the degree of peripancreatic inflammation (presence or absence of peripancreatic fluid) and pancreatic parenchymal necrosis (as none, 30%, or > 30%) in comparison to the CTSI. It also incorporates extra-pancreatic consequences in the assessment.The maximum score that can be obtained is 10 in both the scores.

Many studies have been done in past to compare CTSI and MCTSI in predicting severity of Acute Pancreatitis.

Comparison of CT Severity Index (CTSI) and Modified CTSI (MCTSI)

Characteristics	CTSI (0–10)	MCTSI (0–10)
Pancreatic inflammation		
Normal pancreas	0	0
Focal or diffuse enlargement of pancreas	1	2
Peripancreatic inflammation	2	2
Single acute fluid collection	3	4
Two or more acute fluid collections	4	4
Pancreatic parenchymal necrosis		
None	0	0
Less than 30%	2	2

Between 30% and 50%	4	4
More than 50%	6	4
Extrapancreatic complication	-	2

Bollen et al. evaluated the MCTSI and CTSI for grading the severity of AP, and they concluded that there were no appreciable differences between the two. Both CT indexes are superior to APACHE II in their ability to diagnose clinically severe illness and their ability to predict the pancreatic infection and need for any intervention. (69).

Sahu et al. found that both CTSI and MCTSI showed strong correlation with clinical outcome parameters and had good concordance with the revised Atlanta classification grading of severity in their study on severity assessment of AP using CTSI and MCTSI and their correlation with the clinical outcomes and severity. When segregating mild from moderate/severe AP, MCTSI performed better than CTSI in terms of sensitivity but not specificity. For diagnosing moderate to severe disease, the sensitivity, specificity, positive predictive value (PPV), and accuracy of the CTSI were 97.1%, 100%, 100%, and 98.3% respectively, while for the MCTSI, they were 100%, 92.3%, 94.4%, and 96.7% respectively. (70).

According to a study by Zhou et al. on the severity stratification and prognostic prediction of AP patients in the early stages, the NLR, PLR, RDW, glucose, and BUN levels of the severe acute pancreatitis (SAP) group were significantly higher than those of the mild acute pancreatitis (MAP) group at the time of admission. Their research revealed that the severity and mortality of AP were associated with NLR, PLR, RDW, BUN, SOFA, BISAP, Ranson, and APACHE II. BISAP was the most accurate predictor for SAP, whereas SOFA was better at predicting patient mortality in AP. RDW outperformed other laboratory predictors in terms of both predicting SAP and AP mortality. Combining SOFA with RDW or BISAP with RDW may enhance the performance of a single SOFA, BISAP, or RDW in terms of prediction. RDW exhibited the highest discriminatory ability of the laboratory measures investigated, and it is a practical, affordable, and reliable marker for both SAP and mortality. (71).

Li et al. investigated many inflammatory indicators in acute pancreatitis, including the Neutrophil-Lymphocyte Ratio (NLR), Lymphocyte-Monocyte Ratio (LMR), Prognostic Nutrition Index (PNI), and Red Cell Distribution width (RDW), and evaluated their prognostic significance in mortality and severity (AP). They found that, non-survivors have higher RDW, higher NPR, lower LMR and lower PNI at baseline compared with survivors of AP. CRP RDW and PNI were independently associated with occurrence of SAP. According to this study NLR was the most powerful marker of overall survival (40).

M.Yalçın, et al. in his study on 'Acute pancreatitis and RDW suggested that RDW can effectively distinguish acute necrotic pancreatitis (ANP) from acute interstitial pancreatitis (AEP)', and be used to evaluate the prognosis of AP. It is an easy-to-use, affordable, and reproducible biomarker. RDW values between patients with AEP and ANP were statistically different ($p = 0.011$). 16.4 was the RDW cutoff value, with a sensitivity of 29.2% and a specificity of 89.83%. (72).

Vengadakrishnan et al, studied clinical profile of acute pancreatitis and its correlation with severity indices, and discovered that laboratory indicators such elevated lipase, CRP, and LDH values correlated well with mortality and morbidity, and that CRP and LDH at admission might be utilised as prognostic markers in prediction of morbidity and death in AP. (73).

Various recent studies have found role of IL-6 in acute pancreatitis. Interleukin-6 is an important pro-inflammatory cytokine strongly linked to acute pancreatitis, chronic pancreatitis and pancreatic cancer (74). The JAK/STAT signaling pathway is activated by IL-6, which does so by way of the gp130 protein. (74). According to studies, people with pancreatitis have greater serum levels of IL-6 than individuals who are otherwise healthy have. (75,76). The severity of acute pancreatitis is decreased on IL-6 neutralization by anti-IL-6 antibody therapy, that leads to reduction of STAT-3 activation in pancreatic acinar cells (77). Thus IL-6 can serve as a reliable early marker for pancreatitis.

Sathyanarayan et al. studied 108 patients of acute pancreatitis out of which 30 presented within 72 hours of onset. He discovered that the level of IL-6 was considerably greater on day 3 in patients with severe pancreatitis compared to those with moderate pancreatitis ($P = 0.04$) and in patients who experienced organ failure versus those who

did not (P = 0.004). IL-6 had a sensitivity and specificity of 81.8% and 77.7% respectively, to predict severe pancreatitis, at a cut-off value of 122 pg/mL on day 3 (78).

Rao et al evaluated Interleukin (IL)-6, IL-8, IL-10, and C-reactive protein (CRP) for predicting outcomes of acute pancreatitis, which was measured within 24 hours of admission in 40 patients of clinically predicted SAP. They discovered that IL-6 28.90 pg/mL, evaluated within 48 hours of the onset of AP, performed better than the other studied biomarkers for predicting the development of severe pancreatitis. IL-6 28.90 pg/mL exhibited a positive predictive value (PPV) of 95.65% in predicting the progression to severe pancreatitis, with a sensitivity of 62.86% and specificity of 80% (79).

Our work was focused on assessment of the prognostic value various inflammation markers like NLR, LMR, RDW, CRP, IL 6 and LDH in predicting severity and clinical outcome in acute pancreatitis.

OBJECTIVES

To assess the prognostic value various inflammation markers like NLR, LMR, RDW, CRP, IL 6 sand LDH in acute pancreatitis.

SECONDARY OBJECTIVES

1. To find association between various inflammatory markers with BISAP and the CT Severity Index in prognosis of acute pancreatitis
2. To observe the common causes and clinical outcomes of acute pancreatitis in the patients admitted in AIIMS Jodhpur.

MATERIAL AND METHODS

STUDY SETTINGS:

This was a prospective observational study. We screened all patients presenting to emergency and outpatient services of departments of General Medicine, General surgery and Gastro-surgery of All India Institute of Medical Sciences, Jodhpur, Rajasthan with pain abdomen and/or vomiting between 1st Jan 2021 to July 2022 and 80 patients were enrolled in the study after excluding patients with other causes of abdominal pain, chronic pancreatitis, pancreatic carcinoma, and the patients who refused to give consent.

STUDY PARTICIPANTS:

INCLUSION CRITERIA:

1. All patients with diagnosis of acute pancreatitis, where diagnosis was made when a patient had any two of the following:
    1. Symptoms such as abdominal pain, consistent with the disease
    2. Serum Amylase or Lipase greater than 3 times the upper limit of normal
    3. Radiological imaging consistent with the diagnosis usually using Abdominal Ultrasound / CT/ MRI
2. Patients with Age >18 years

EXCLUSION CRITERIA

1. All patients of known case of chronic pancreatitis presented as acute exacerbation
2. All patients of known case of pancreatic carcinoma
3. Patient not willing to give written informed consent

DATA COLLECTION

80 patients were enrolled for the study, their socio-demographic data, like name, age and gender were taken after taking informed consent. Detailed clinical evaluation consisting of detailed clinical history (including presenting complaints, history of present illness, history, personal history and socioeconomic history) followed by detailed clinical examination was done for all the patients. All patients underwent baseline hematological and biochemical assessment as per routine clinical care including complete blood count, serum electrolytes, blood glucose, c reactive protein, erythrocyte sedimentation rate, liver function test, kidney function test on admission and 7 days after onset of symptoms. Serum amylase and lipase was done for diagnosis of acute pancreatitis. We also did lipid profile, LDH, interleukin 6, serum Calcium, chest x-ray, and ultrasound whole abdomen on admission. BISAP was calculated for all patients on presentation. Serum LDH, interleukin 6 and serum calcium were repeated 7 days after the onset of symptoms. Between day 5 to 7 of illness, CT (computed tomography) abdomen with contrast was done in all patients with normal renal function and non-contrast imaging in patients with impaired renal function to look for local complication. MRI (magnetic resonance imaging) and MRCP (magnetic resonance cholangiopancreatography) was done only when it was thought essential for evaluation, by the treating physician.

SAMPLING AND SAMPLE SIZE:

We enrolled 80 patients of acute pancreatitis after taking written informed consent. Laboratory investigations were done on presentation and day 7 of illness. BISAP was calculated on presentation. CECT abdomen was done on day 5 to 7 of illness, to look for local complications and classify AP into Acute Interstitial Pancreatitis and Acute Necrotizing Pancreatitis. After collecting all data, the data was analyzed with the help of SPSS. Age and gender wise distribution of AP was calculated. Mean values and standard deviation were calculated for all laboratory investigations. Appropriate statistical tests were applied to calculate association of age, inflammatory markers, urea, clinical severity indices like BISAP and CT severity indices like CTSI and MCTSI were compared with severity of acute pancreatitis, development of local complications and duration of hospital stay. Inflammatory markers were also compared with BISAP, CTSI and MCTSI. Mean values of inflammatory markers were compared with severity and development of local complication using independent student t test. Gender, BISAP, CTSI and MCTSI were compared with severity and development of local complication using chi-square test and odd ratio was calculated. A correlation study was done to look for relation of inflammatory markers with duration of hospital stay and Pearson coefficient was calculated. Multivariate analysis was done for all inflammatory markers that had statistically significant association with severity and development of local complications. ROC curve was plot for independent predictors of severity and local complications and R^2 was calculated.

METHODOLOGY: FLOW CHART

All patients of Acute Pancreatitis were enrolled from Outpatient, Inpatient and Emergency department of AIIMS, Jodhpur during Jan 2021-July 2022

All patients were underwent baseline testing and other required tests as per clinician's decision

CBC, CRP, ESR, IL 6, LDH, LFT, KFT, Lipid profile, Serum Calcium were done

Imaging including Ultrasound Whole Abdomen and Chest X-Ray were done on presentation

Clinical Severity Indices like BISAP were calculated

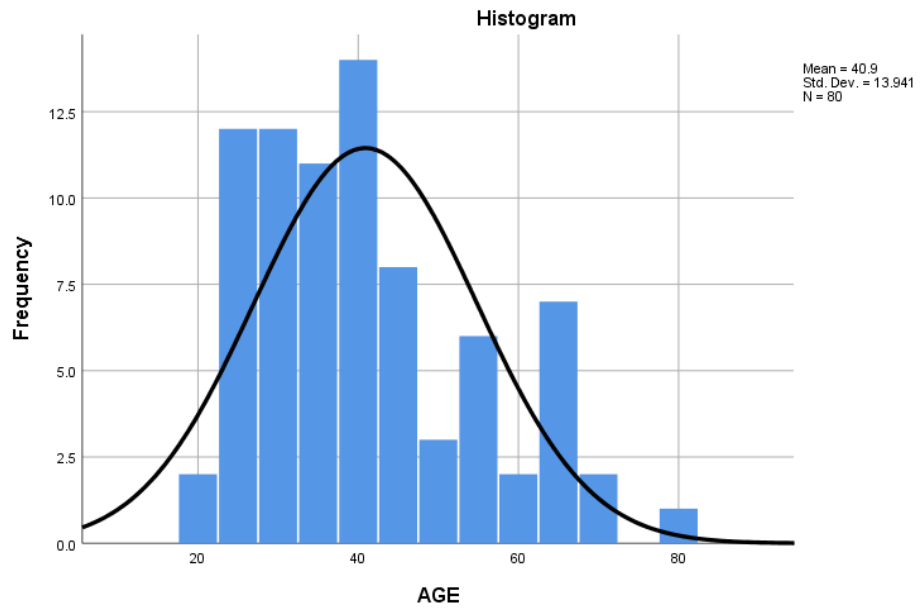
CECT ABDOMEN : CTSI at day 7 after onset of symptom

All routine blood investigations, CRP, ESR, IL 6, LDH, Serum Calcium were repeated on day 7 after onset of symptom

Results were analysed

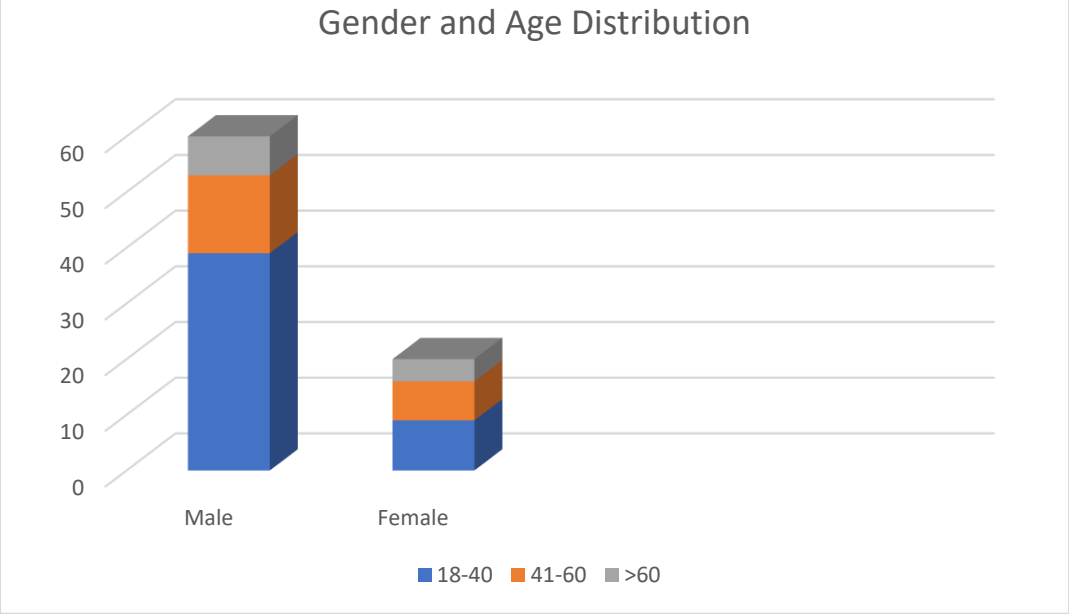
RESULTS

Fig 1: Age Distribution of patients of Acute Pancreatitis, (N=80)



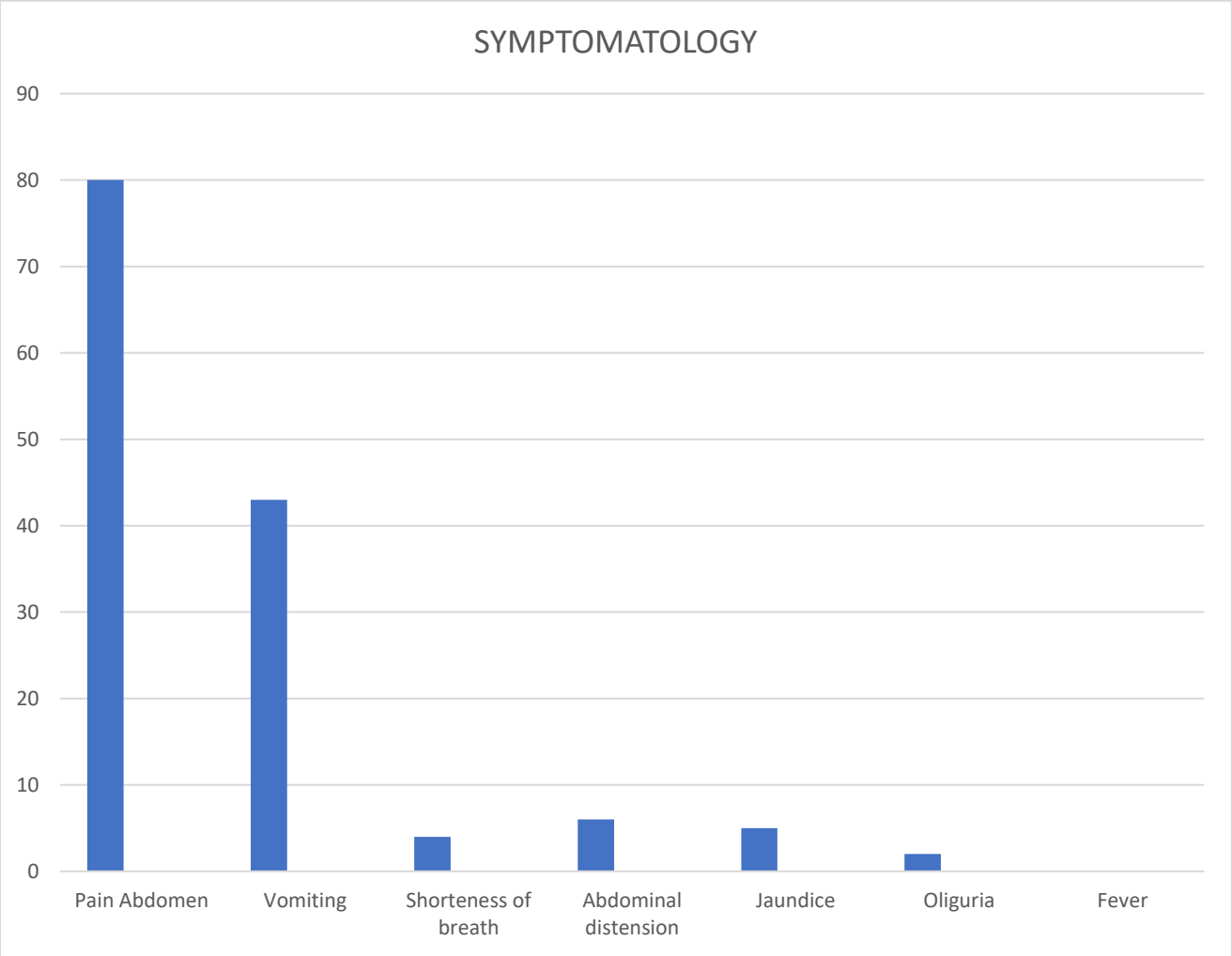
Incidence of Acute Pancreatitis was seen distributed from age of 20 years to 80 years in our study population with the mean age of presentation being 40.9 years with standard deviation of 13.94.

Fig 2: Gender and gender wise Age Distribution of patients of Acute Pancreatitis (N=80)



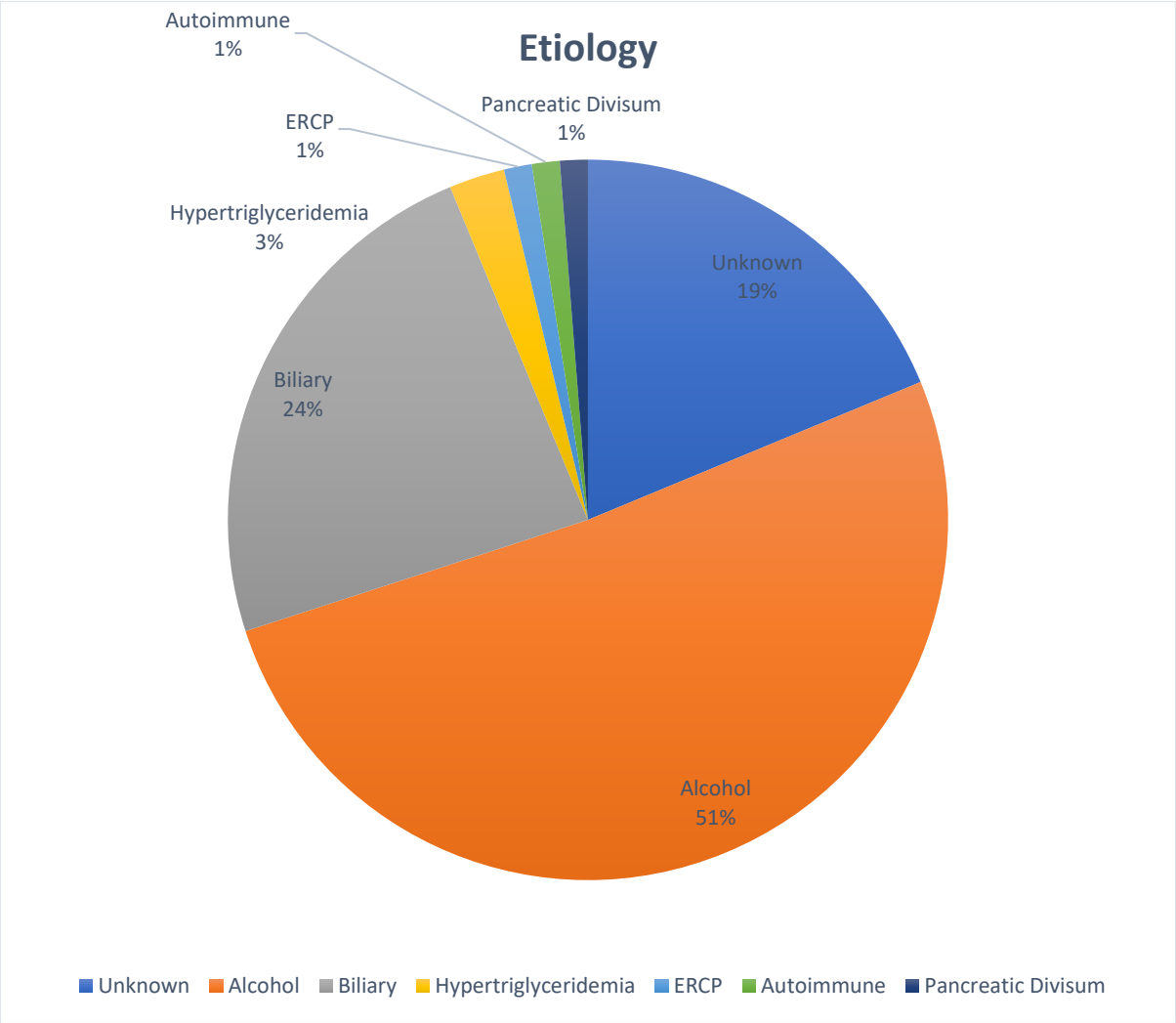
Acute pancreatitis was more commonly seen in males in comparison to females, with male: female ratio of 3:1 in the study population and young males more commonly affected than elderly males. Out of the 60 male patients of AP, 39(65%) were below the age of 40.

Fig 3: Symptoms at presentation in Acute Pancreatitis



The most common presenting symptom of Acute Pancreatitis was abdominal pain followed by vomiting and abdominal distension. Other symptoms included shortness of breath, jaundice and decreased urine output.

Fig 4: Etiology of Acute Pancreatitis (N=80)

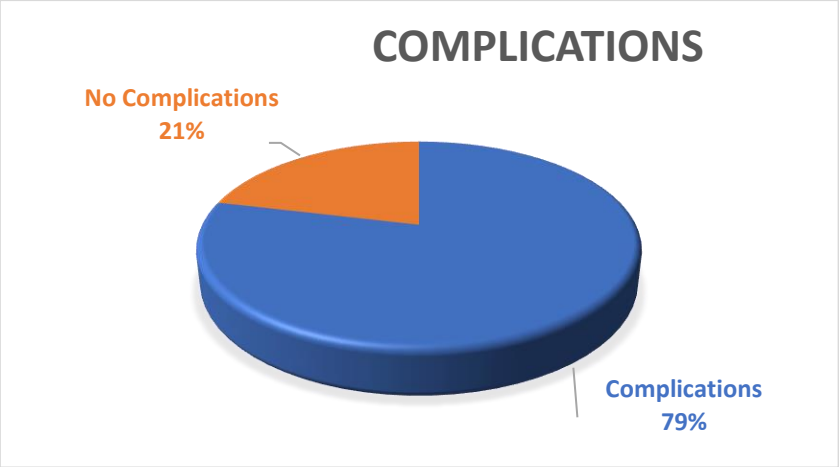


The most common cause of AP in the study population was Alcohol (around 51% cases) followed by Gallstones (around 24% of cases). Other causes seen in the study population were hypertriglyceridemia, ERCP, Autoimmune pancreatitis and anatomical abnormalities like pancreatic divisum. In about 19% of cases, the cause could not be found even after extensive workup.

Table 1: Outcome of patients admitted with AP

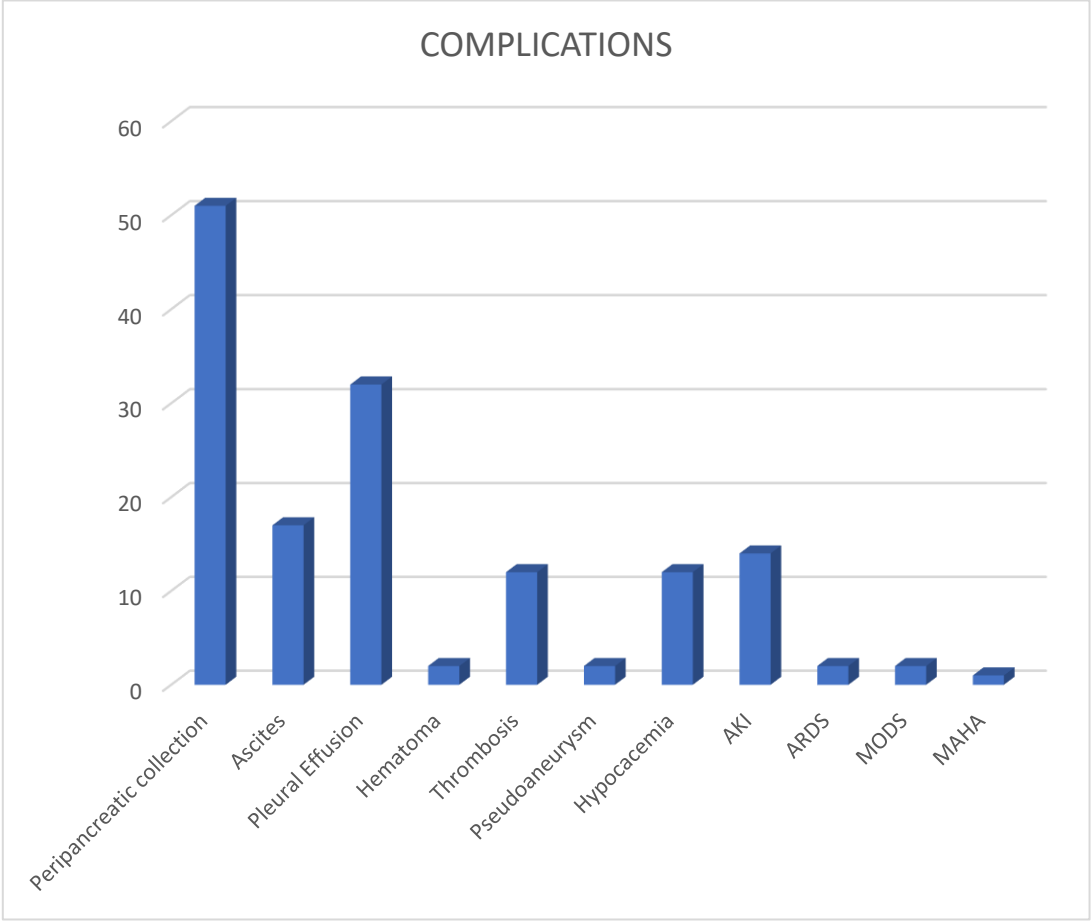
	No. of Patients	MEAN AGE
Survival	77	40.68
Death	3	46.67

Fig 5: Percentage of patient having local or systemic complications in AP (N=80)



About 79% of patients of acute pancreatitis either had local or systemic complications and only 21% patients had no complications.

Fig 6: Local and systemic complications with their frequencies seen in patients of Acute Pancreatitis



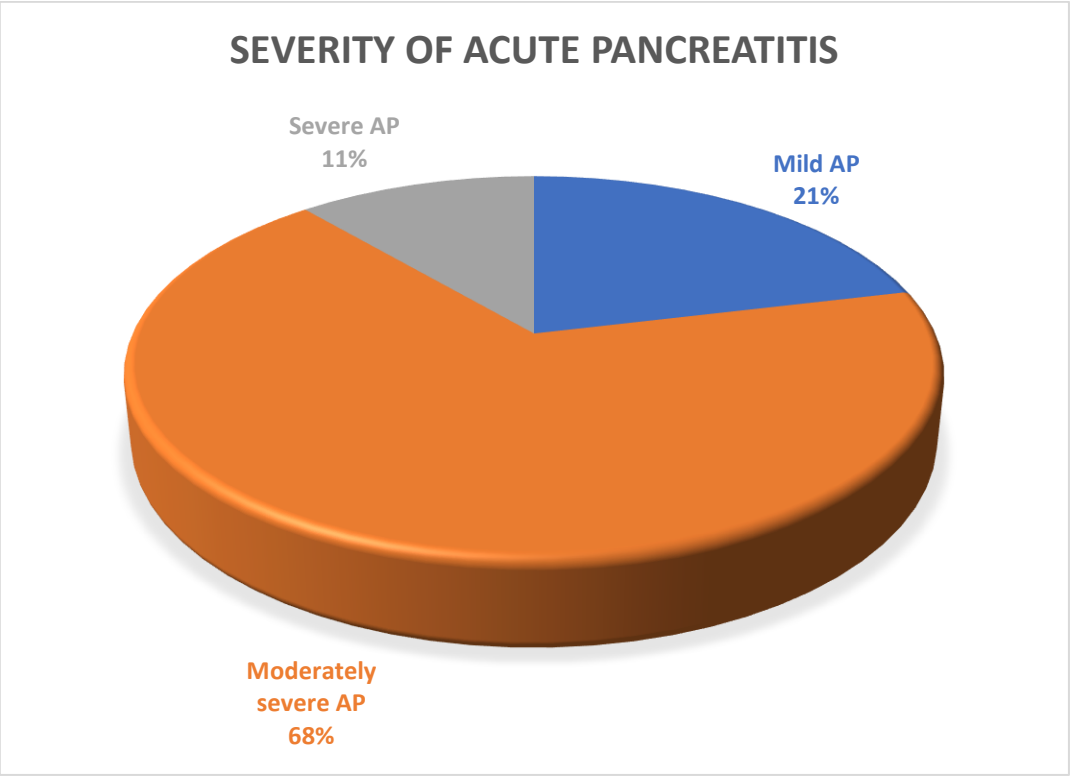
Overall local complications were seen more commonly than systemic complications. The most common local complication seen in acute pancreatitis was peripancreatic collection followed by pleural effusion and ascites. Splanchnic vein thrombosis is also a common complication of AP. Most common organ failure seen in AP was renal followed by pulmonary.

Table 2: Frequency and Percentage distribution of Acute interstitial pancreatitis and Acute Necrotising Pancreatitis.

	No. of Patients	Percentage
Acute Interstitial Pancreatitis	38	47.5
Acute Necrotising Pancreatitis	40	50.0
Normal Imaging	2	2.5

Almost equal number of patients had interstitial and necrotising pancreatitis on imaging. 2 patients had normal imaging although they had symptoms suggestive of pancreatitis and elevated Serum amylase and lipase.

Fig 7: Severity of Acute Pancreatitis (N=80)



Most patients (up to 68%) had moderately severe pancreatitis, having local complications and/or transient organ failure, followed by mild acute pancreatitis (21%), with no complications or organ failure. Minority had severe acute pancreatitis (11%) characterized by persistent organ failure.

Table 3: Laboratory Investigation at baseline and Day 7 (N=80)

	Baseline		**Day 7**	
	Mean	Std. Deviation	**Mean**	Std. Deviation
Hb **(**gm/dl)	12.87	3.219	11.12	2.55
TLC (/uL)	14247.25	5436.812	12856.55	6895.25
PLATELET (10^6/uL)	2.59	1.32	3.34	1.86
AMYLASE (u/L)	1129.44	1475.109	-	-
LIPASE (u/L)	1716.76	2360.457	-	-
UREA (mg/dL)	39.48	42.670	33.68	45.29
CREATININE (mg/dL)	1.47	1.691	1.13	1.34
ALT (IU/L)	79.16	90.213	47.76	56.04
AST (IU/L)	83.96	99.864	53.39	49.38
BILIRUBIN (mg/dl)	4.06	12.6	1.8	4.1
SODIUM (Meq/l)	132.95	15.498	134.98	4.98
POTTASIUM (Meq/l)	4.03	0.900	3.89	0.67
CALCIUM (mg/dL)	8.37	0.74	8.34	.64
TRIGLYCERIDE (mg/dl)	178.2	249.7	162.68	102.69

TLC was higher on presentation with mean TLC 14,247 on presentation and 12856 on day 7. There was no significant difference in other investigations at baseline and day 7.

Table 4: Inflammatory Markers at baseline (N=80)

	Minimum	Maximum	Mean	Std. Deviation
CRP **(**mg/L**)**	0.49	410	125.72	82.91
ESR **(**mm/hr**)**	4	155	40.93	29.31
NLR	0.84	37.8	11.77	8.26
PLR	25.89	817.9	234.09	167.06
LMR	0.48	7.10	1.74	1.19
RDW (%)	12.7	19.7	14.47	1.34
IL6 (pg/ml)	0	3007	160.70	391.413
LDH (IU/L)	92	2427	467.86	403.133
UREA **(**mg/dL**)**	5	293	39.48	42.670

Table 5: Inflammatory Markers at Day 7 (N=80)

	Minimum	Maximum	Mean	Std. Deviation
CRP **(**mg/L**)**	0.55	279	113.61	68.23
ESR **(**mm/hr**)**	2	170	44.86	32.36
NLR	0.61	34.17	7.98	5.94
PLR	19.67	170.0	262.98	214.91
IL6 (pg/ml)	0.02	1700	139.57	277.02
LDH (IU/L)	68	1288	33.68	227.71
UREA **(**mg/dL**)**	4	281	33.68	45.29

Mean CRP, NLR, IL6, LDH, Urea was higher on baseline than day 7 while mean ESR and LDH were lower on baseline than day 7.

Fig 8: Pie chart showing distribution of MCTSI Score in the study population (N=80)

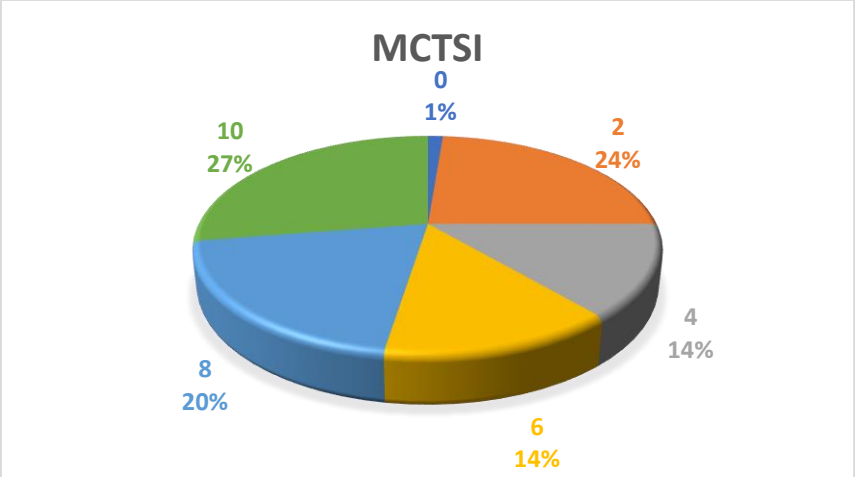


Table 6: showing distribution of MCTSI Score in the study population (N=80)

MCTSI Score	Number of Patients
0	1
2	19
4	11
6	11
8	16
10	22

Almost equal number of patients had MCTSI 6 and below and score more than 6, with 38 (47%) patients having score of more than 6 and 42 (53%) patients had score of 6 or less.

Fig 9: Pie chart showing distribution of CTSI Score in the study population (N=80)

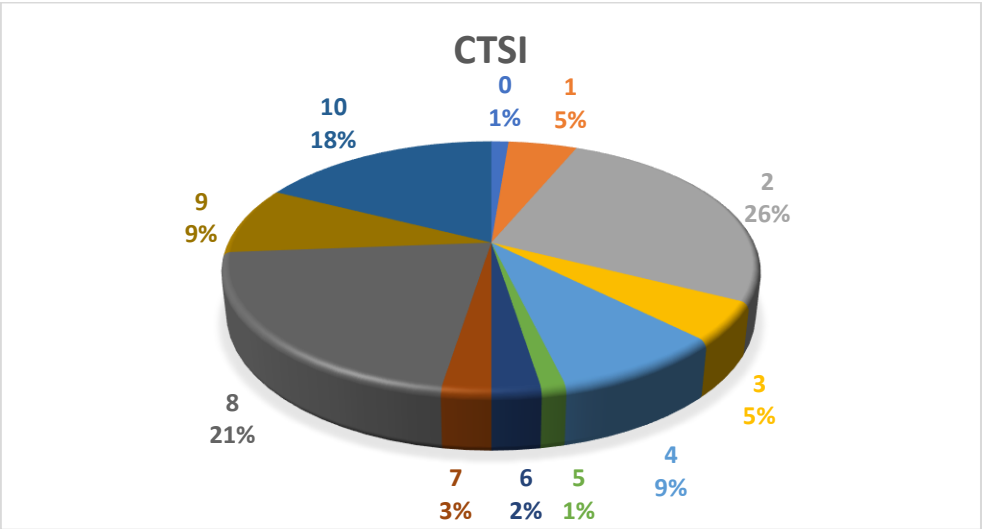


Table 7: distribution of CTSI Score in the study population (N=80)

CTSI Score	Number of Patients
0	1
1	4
2	21
3	4
4	7
5	1
6	2
7	2
8	17
9	7
10	14

Almost equal number of patients had CTSI 6 or more and score less than 6, with 38 (47%) patients having score of more than 6 and 42 (53%) patients had score of 6 or less.

Fig 10: Pie chart showing distribution of BISAP Score in the study population (N=80)

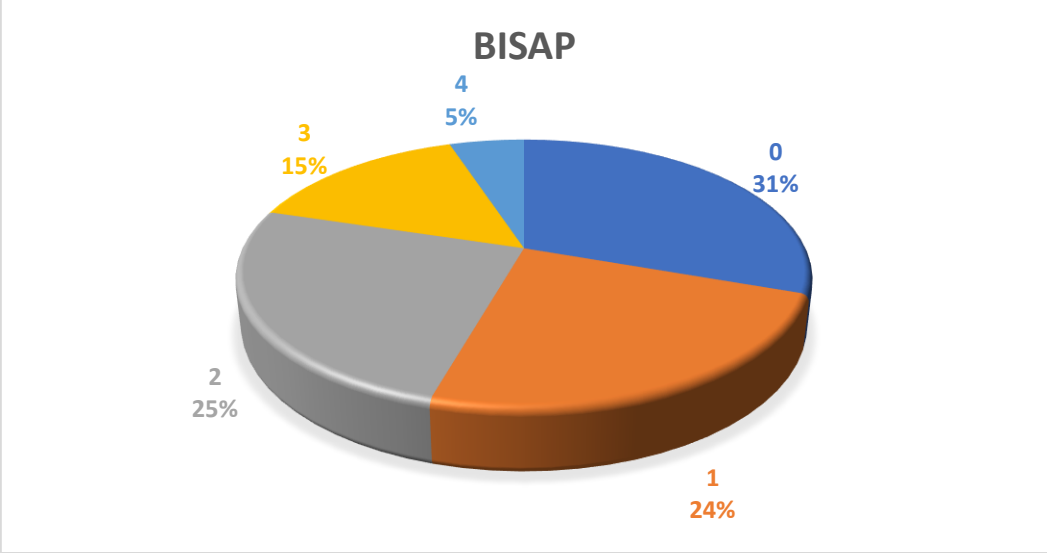


Table 8: Distribution of BISAP score in the study population

BISAP Score	Frequency
0	25
1	19
2	20
3	12
4	4

Table 9: Association of Inflammatory markers and Severity of Acute Pancreatitis (N=80)

MARKERS	p value	Non-Severe (Mean)	Severe (Mean)	Difference of mean With 95% confidence interval
Age	0.746	40.72	42.32	1.61 (-8.2 – 12.49)
NLR	0.481	11.54	13.59	2.09 (-3.79 – 7.89)
PLR	0.284	241	177	-0.63 (-181.2 – 53)
LMR	0.345	1.78	1.38	-0.40 (-1.24 – 0.43)
RDW	0.899	14.4	14.5	0.06 (-0.89 – 1.01)
Amylase	0.375	1076	1543	466.3 (-574 – 1506)
Lipase	0.03	1513	3317	1803 (180 – 3426)
CRP	0.103	120.3	168.2	47.93 (-9.84 – 105)
ESR	0.762	41	38	-3.17 (-23.9 – 17.59)
IL6	0.649	153	217	63.54 (-213.5 – 340)
LDH	**<0.0001**	**381**	**1152**	**771 (544 – 998)**
Urea	**<0.0001**	**29.8**	**115.5**	**85.7 (62 – 108)**

Mean values of age and inflammatory markers were compared between severe and non-severe pancreatitis using Student T test and it was found that LDH and blood urea were significantly different the two comparison groups. Mean LDH was 381 in non- severe pancreatitis and 1152 in the severe pancreatitis group (p value <0.0001). Mean blood urea in the non-severe pancreatitis was 28.8 whereas, it was 115.5 in the severe pancreatitis group (p value <0.0001).

Table 10: Association of clinical severity index and CT severity indices with Severity of AP

	p value	Odds Ratio With 95% Confidence Interval
Gender	0.307	0.342 (0.04-2.920)
BISAP	**<0.0001**	**10.909 (2.368- 50.266)**
CTSI	**0.025**	**8.299 (0.978- 69.26)**
MCTSI	**0.008**	**10.93 (1.297- 92.143)**

Gender, BISAP, CTSI and MCTSI score were compared between patients with severe and non-severe pancreatitis using Chi-square, and it was found the BISAP, CTSI and MTCI score were significantly associated with severity of pancreatitis.

Table 11: Association of Inflammatory markers with Complications (N=80)

MARKERS	p value	No complications (Mean)	complication (Mean)	Difference of mean With 95% confidence interval
Age	0.746	40.72	42.33	1.61 (-8.26 – 11.49)
NLR	0.60	10.8	12.02	1.19 (3.32 – 5.7)
PLR	0.133	288	219	-68 (-158 – 21)
LMR	0.695	1.84	1.71	0.128 (-0.78 – 0.52)
RDW	**0.029**	**13.8**	**14.6**	**0.128 (0.08 – 1.5)**
Amylase	0.971	1117	1132	14.9 (-792 – 822)
Lipase	0.95	1747	1708	-38 (-1331 – 1253)
CRP	**0.022**	**85**	**136**	**51.7 (7.8 – 95.5)**
ESR	0.283	34.1	42.7	8.64 (-7.28 – 24.5)
IL6	0.193	50.54	190.43	139 (-72 – 351)
LDH	**0.011**	**248**	**527**	**278 (66 – 490)**
Urea	0.091	23.94	43.67	19.7 (-3.2 – 42.6)

Mean values of age and inflammatory markers were compared between patients having local complication or not having any complications using Student T test and it was found that RDW, CRP and LDH were significantly different the two comparison groups. Mean RDW was 13.8 in patients without any complications and 14.6 in patients with complications (p value 0.029). Mean CRP was 85 in patients without any complications and 136 in patients with complications (p value 0.022). Mean LDH was 248 in patients without any complications and 527 in patients with complications (p value 0.011).

Table 12: Association of clinical severity index and CT severity indices with complications (N=80)

	p value	**Odds Ratio With 95% Confidence Interval**
Gender	0.636	0.750 (0.227 - 2.474)
BISAP	0.16	1.37 (1.179 - 1.591)
CTSI	**<0.0001**	**26 (3.238 - 208.803)**
MCTSI	**<0.0001**	**2.520 (1.859 - 3.417)**

Gender, BISAP, CTSI and MCTSI score were compared between patients with or without complications using Chi-square, and it was found the CTSI and MTCI score were significantly associated with development of local complications in AP.

Table 13: Correlation of Inflammatory markers with duration of hospital stay (N=80)

MARKERS	Pearson Coeff	p value
Age	-0.009	0.940
NLR	0.068	0.547
PLR	-0.057	0.613
LMR	-0.168	0.135
RDW	**0.253**	**0.024**
Amylase	0.111	0.328
Lipase	0.178	0.113
CRP	**0.255**	**0.024**
ESR	0.088	0.439
IL6	0.067	0.558
LDH	**0.434**	**<0.0001**
Urea	**0.232**	**0.039**

Correlation of age and inflammatory markers with duration of hospital stay was evaluated and pearson coefficient was calculated and significant correlation of duration of hospitral stay was seen with RDW (p value 0.0024), CRP (p value 0.024), LDH (p value <0.0001) and urea (p value 0.039).

Table 14: Association of Inflammatory markers with BISAP (N=80)

MARKERS	p value	BISAP≤ 2 (Mean)	BISAP >2 (Mean)	Difference of mean With 95% confidence interval
Age	0.564	40.43	42.65	2.21 (-5.39 – 9.83)
NLR	0.091	10.95	14.7	3.82 (-0.62 – 8.26)
PLR	0.749	230	245	14.75 (-82.39 – 111.9)
LMR	0.376	1.80	1.51	- 0.29 (-0.93 – 0.35)
RDW	0.987	14.47	14.48	0.006 (-7.324 – 0.744)
Amylase	0.424	1060	1385	324 (-479 – 1129.0)
Lipase	0.313	1577	2232	655 (-628 -1939)
CRP	**0.014**	**114**	**169**	**55 (11.4 – 98.7)**
ESR	0.430	39.57	45.94	6.37 (-9.61 – 22.3)
IL6	**0.025**	**109**	**348**	**238 (31.2 – 446.1)**
LDH	**<0.0001**	**351**	**897**	**545 (362 – 729)**
Urea	**0.001**	**31**	**68**	**37 (15.4 – 59.0)**

Mean values of age and inflammatory markers were compared between patients having BISAP score less than 2 and score of 2 or more using Student T test and it was found that CRP, IL-6, LDH and urea were significantly different the two comparison groups. Mean CRP was 114 in patients BISAP or less than 2 and 169 in patients with score of 2 or more (p value 0.014). Mean IL-6 was 109 in patients BISAP or less than 2 and 348 in patients with score of 2 or more (p value 0.025). Mean LDH was 351 in patients BISAP or less than 2 and 897 in patients with score of 2 or more (p value <0.0001). Mean urea was 31 in patients BISAP or less than 2 and 68 in patients with score of 2 or more (p value 0.001).

Table 15: Association of Inflammatory markers with MCTSI (N=80)

MARKERS	p value	MCTSI <6 (Mean)	MCTSI ≥6 (Mean)	Difference of mean With 95% confidence interval
Age	0.064	43.6	37.8	-5.77 (-11.89 – 0.34)
NLR	0.794	12.0	11.5	-0.48 (-4.19 – 3.2)
PLR	0.678	241	225	-15.6 (-90.5 – 59.1)
LMR	0.625	1.68	1.81	0.13 (-0.40 – 0.66)
RDW	0.484	14.3	14.5	0.30 (-0.38- 0.81)
Amylase	0.111	1379	852	-527 (-1178 – 123)
Lipase	0.547	1869	1548	-320 (-1377 – 735)
CRP	0.403	118	133	15.6 (-21.3 – 52.6)
ESR	**0.037**	**34**	**48**	**13.6 (0.841 – 26.412)**
IL6	0.148	100	227	127 (-46 – 300)
LDH	**<0.0001**	**320**	**630**	**310 (143- 477)**
Urea	0.051	30.6	49.2	18.5 (-0.82 – 37.27)

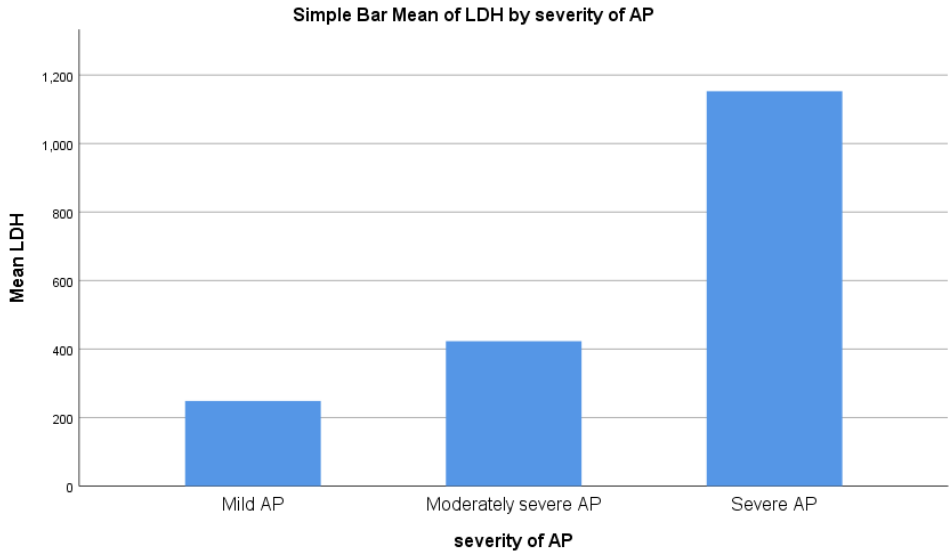
Mean values of age and inflammatory markers were compared between patients having MCTSI score less than 6 and score of 6 or more using Student T test and it was found that ESR and LDH were significantly different the two comparison groups. Mean ESR was 34 in patients with MCTSI score less than 6 and 48 in patients with score of 6 or more (p value 0.037). Mean LDH was 320 in patients with MCTSI score less than 6 and 630 in patients with score of 6 or more (p value <0.0001).

Table 16: Association of Inflammatory markers with CTSI (N=80)

MARKERS	p value	CTSI <4 (Mean)	CTSI ≥4 (Mean)	Difference of mean With 95% confidence interval
Age	0.160	43.27	38.86	-4.41 (-10.59 - 1.77)
NLR	0.822	11.54	11.96	0.421 (-3.39 – 4.13)
PLR	0.679	242	226	-15.6 (-90.5 – 59.3
LMR	0.825	1.77	1.71	-0.059 (-0.594 – 0.475)
RDW	0.471	37	43	0.21 (-0.38 – 0.82)
Amylase	0.151	1385	909	-475 (-1129 – 178)
Lipase	0.327	1997	1475	-522 (-1576 – 531)
CRP	0.209	113	136	23.45 (-13.42 – 60.32)
ESR	0.086	34.8	46.1	11.27 (-1.64 – 24.19)
IL6	0.089	80	229	149 (- 23 – 322)
LDH	**<0.0001**	**298**	**613**	**315 (149 – 482)**
Urea	0.095	30.89	46.8	15.96 (-2.86 – 34)

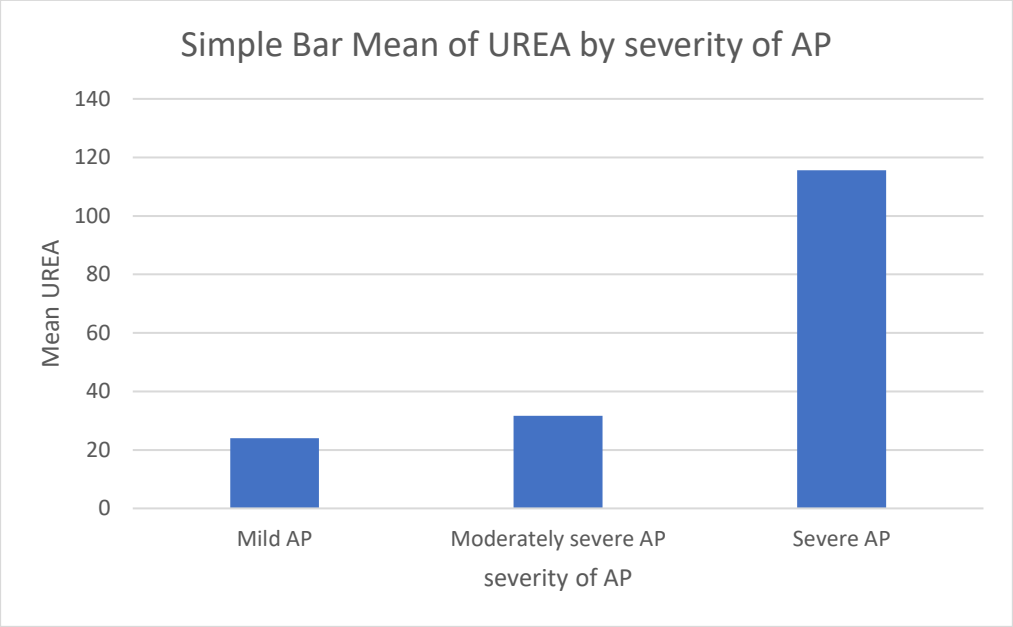
Mean values of age and inflammatory markers were compared between patients having CTSI score less than 4 and score of 4 or more using Student T test and it was found that LDH was significantly different the two comparison groups. Mean LDH was 298 in patients with CTSI score less than 4 and 613 in patients with score of 4 or more (p value <0.0001).

Fig 11: Bar graph showing association between LDH and severity of pancreatitis



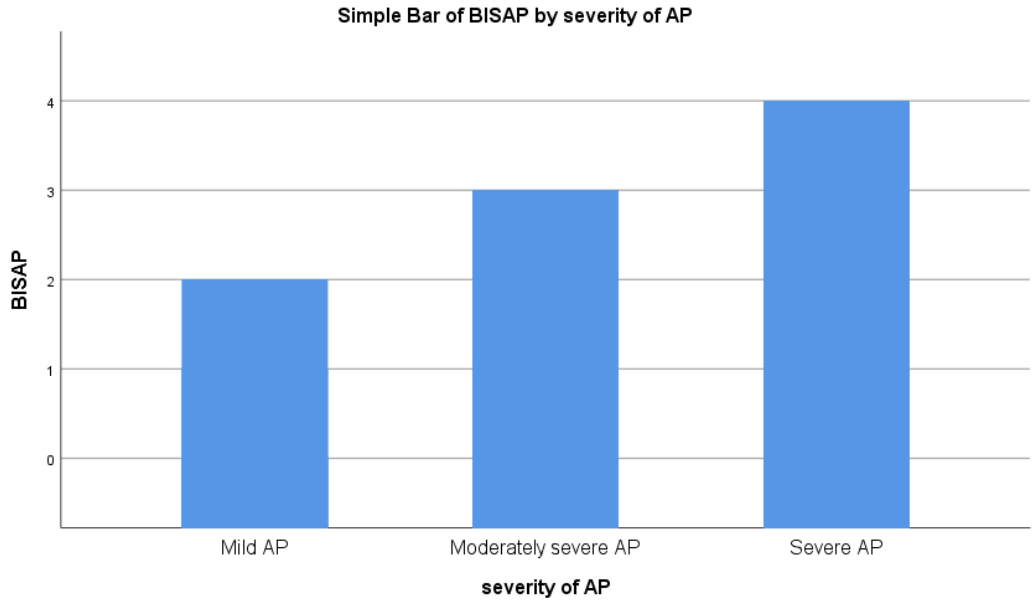
Higher Serum LDH was seen with increasing severity of pancreatitis.

Fig 12: Bar graph showing association between LDH and severity of pancreatitis



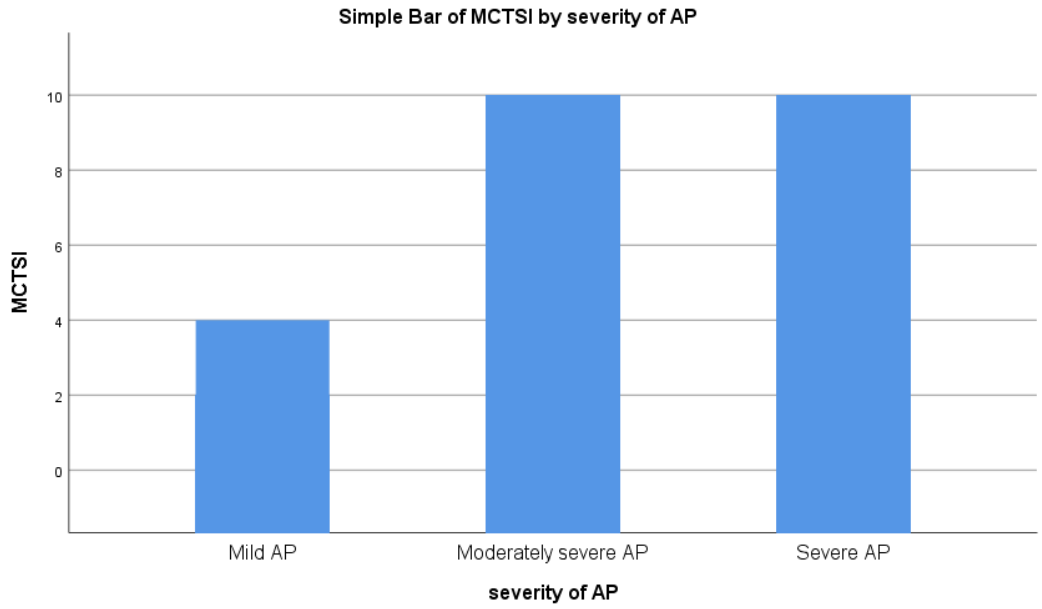
Higher Serum LDH was seen with increasing severity of pancreatitis.

Fig 13: Bar graph showing association between LDH and severity of pancreatitis



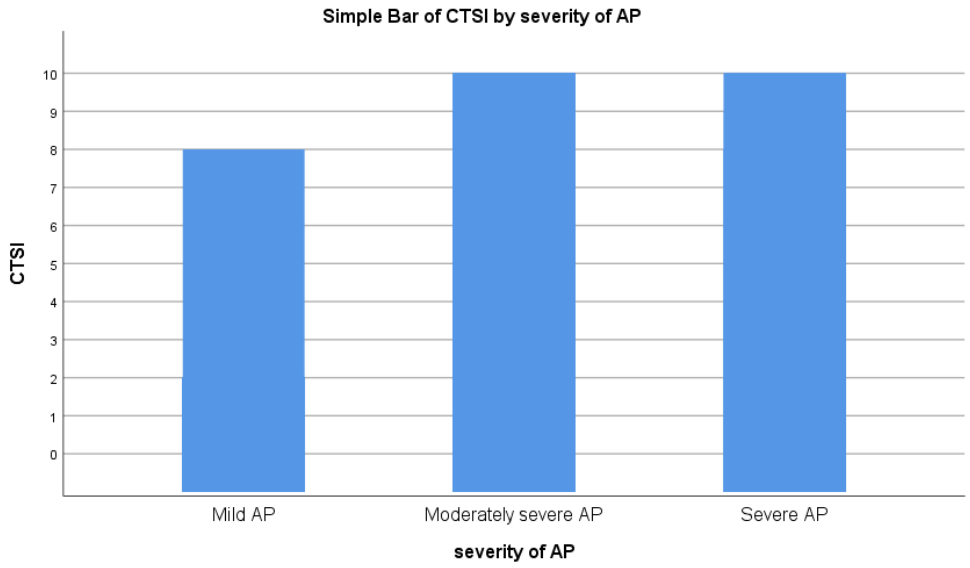
Higher BISAP score is seen with increasing severity of pancreatitis.

Fig 14: Bar graph showing association between MCTSI and severity of pancreatitis



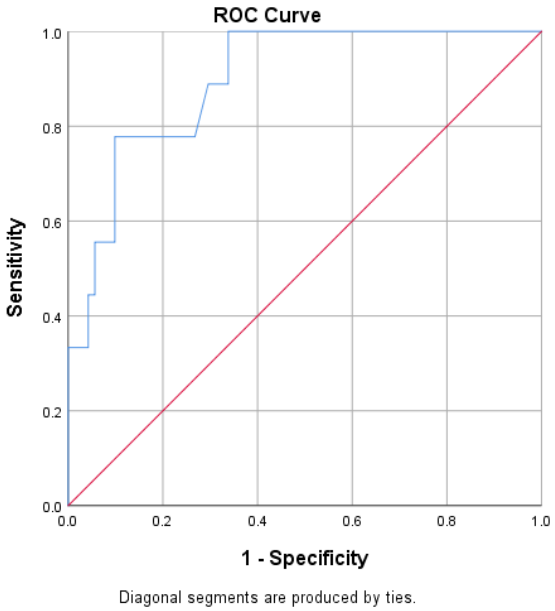
Higher MCTSI score is seen with increasing severity of pancreatitis.

Fig 15: Bar graph showing association between CTSI and severity of pancreatitis



Higher MCTSI score is seen with increasing severity of pancreatitis.

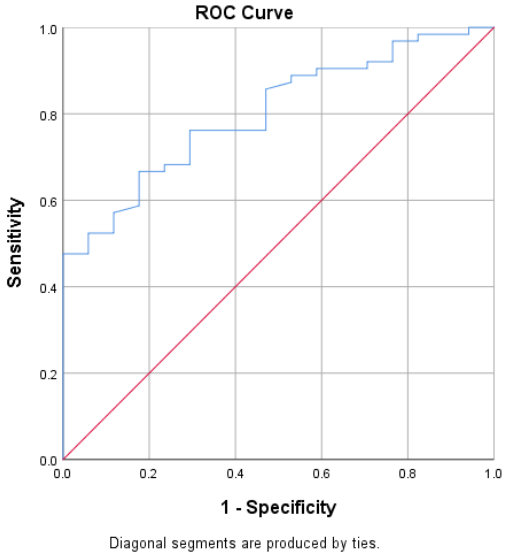
Fig 16: ROC curve of LDH vs severity of acute pancreatitis



Area under curve with 95% Confidence Interval	P value
0.898 (0.810 – 0.987)	<0.0001

ROC curve of LDH was plot against severity of acute pancreatitis and it was found that LDH can significantly predict severity of pancreatitis. Serum LDH of >435.00 has 100% sensitivity and 66.8 % specificity to predict severity of acute pancreatitis.

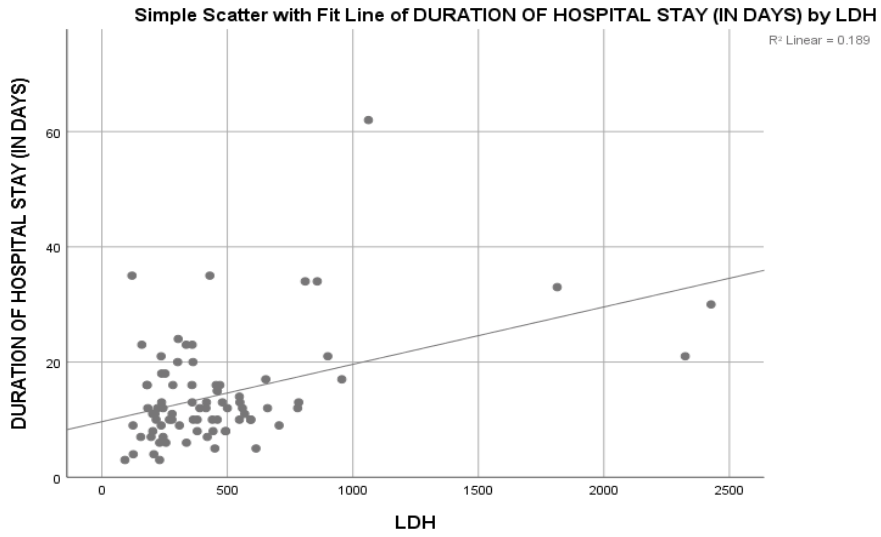
Fig 17: ROC curve of LDH vs complications in acute pancreatitis



Area under curve with 95% Confidence Interval	P value
0.802 (0.700 – 0.904)	<0.0001

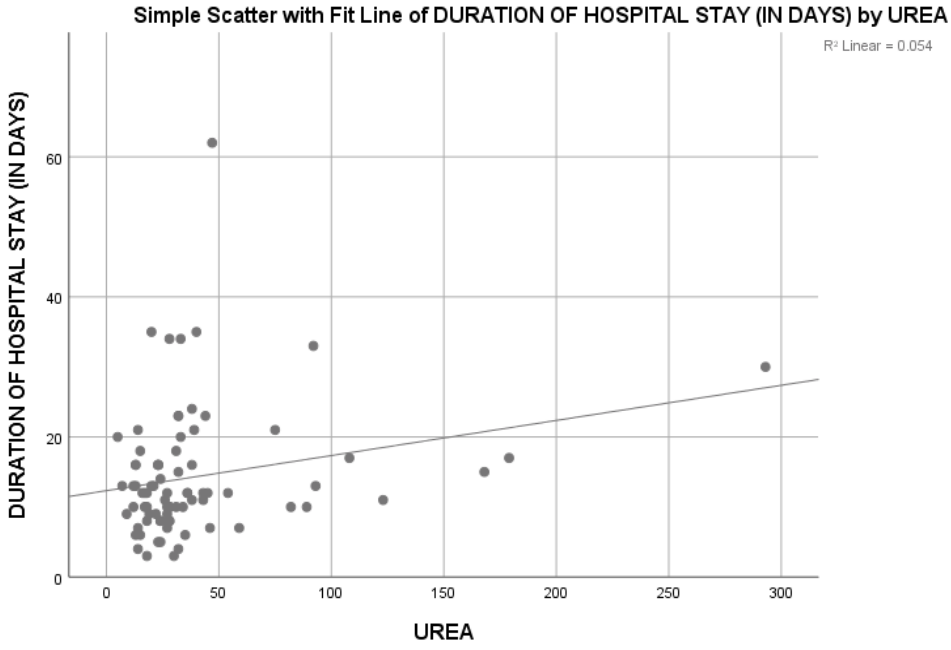
ROC curve of LDH was plot against severity of acute pancreatitis and it was found that LDH can significantly predict severity of pancreatitis. Serum LDH of >274 has 76.2% sensitivity and 70.6% specificity to predict complication in a case of acute pancreatitis.

Fig 18: Scatter plot of LDH with duration of hospital stay in acute pancreatitis



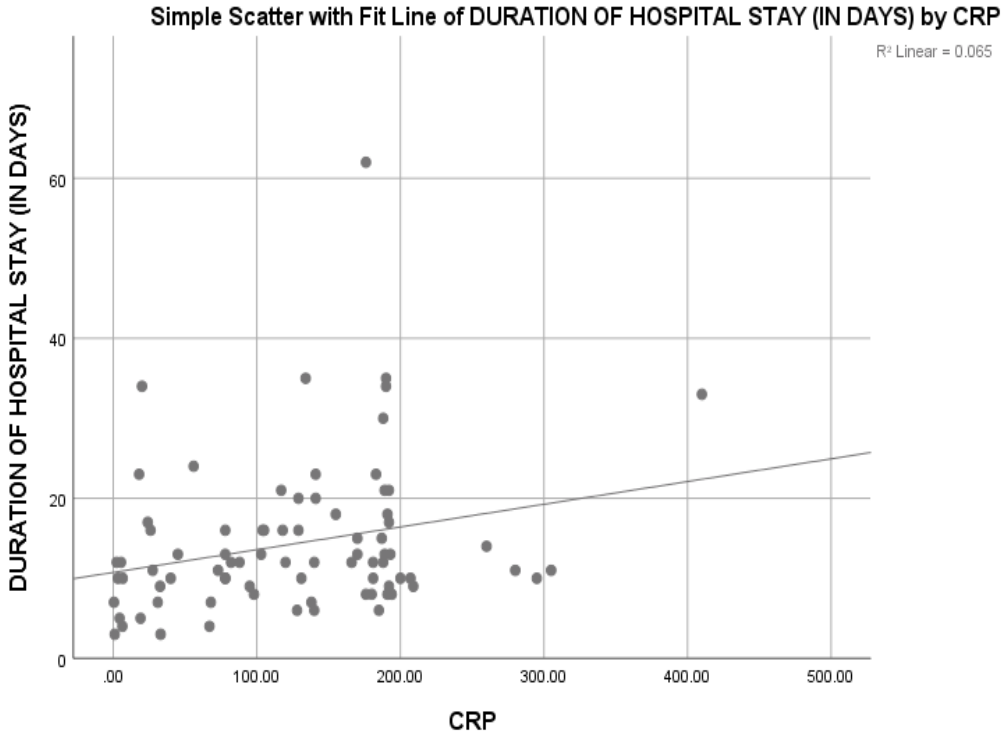
Scatter plot of LDH with duration of hospital stay showed relation of LDH with duration of hospital stay with R^2 of 0.189.

Fig 19: Scatter plot of Urea with duration of hospital stay in acute pancreatitis



Scatter plot of LDH with duration of hospital stay showed some relation of blood urea with duration of hospital stay with R^2 of 0.054.

Fig 20: Scatter plot of CRP with duration of hospital stay in acute pancreatitis



Scatter plot of CRP with duration of hospital stay did not show strong relation of blood urea with duration of hospital stay with R^2 of 0.054.

DISCUSSION

The term "pancreatitis" refers to an acute or chronic inflammation of the pancreas that is characterized by premature activation of digestive enzymes within the pancreatic acinar cells and resulting in pancreatic auto-digestion (43).

Epidemiology

We enrolled 80 patients of acute pancreatitis after taking written informed consent. Mean age of the patients of the study population was 40.9 years, with minimum age of 20 years and maximum age of 80 years. Males were more commonly seen to be affected by acute pancreatitis in comparison to females, with male: female ratio of 3:1 in the study population and young males more commonly affected than elderly males.

The most common presenting symptoms of acute pancreatitis in our study population was pain abdomen followed by vomiting and abdominal distension. Other symptoms included shortness of breath, jaundice and decreased urine output.

Etiology

The most common cause of acute pancreatitis in our study population was alcohol (around 51% cases) followed by gallstones (around 24% of cases). Together alcohol and gallstones comprised of 75% of cases of acute pancreatitis in our study population. This observation was similar to that made by Weiss et al., as he found 70% of cases of acute pancreatitis was together caused by alcohol and gallstones (4). Other causes seen in the study population were hypertriglyceridemia, ERCP, Autoimmune pancreatitis and anatomical abnormalities like pancreatic divisum. In about 19% of cases, cause could not be found even after extensive workup.

The most common cause of acute pancreatitis in males was alcohol while the most common cause in females was gallstones. This observation was similar to previous studies done by authors like Lankisch et al and Weiss et al (3,4).

Disease spectrum and severity

The spectrum of AP ranges from interstitial pancreatitis to necrotizing pancreatitis. In our study population 47.5% patients has acute interstitial pancreatitis and around 50% had acute necrotizing pancreatitis.

About 21% patients in our study population had mild acute pancreatitis, with no complications or organ failure, and around 68% had moderately severe pancreatitis, having local complications and/or transient organ failure. Severe acute pancreatitis characterized by persistent organ failure was seen in only 11% of patients.

Investigations

Investigation including inflammatory markers were done at presentation and 7^{th} day of illness. It was noted that TLC was higher on presentation in comparison to day 7 of illness,

with mean TLC 14,247 on presentation and 12856 on day 7. Mean CRP, NLR, IL6, LDH, Urea was higher on baseline than day 7 while mean ESR and LDH were lower on baseline than day 7.

BISAP score was calculated in all patients at presentation, out of 80 patients, 64 (80%) had score of 0 or 1 and 16 (20%) had score of 2 or more. It has been seen that BISAP score, 0 to 2 points indicate lower mortality (<2%) and 3 to 5 indicate higher mortality (>15%).

Zhou et al. in his study on severity stratification and prognostic prediction of patients with acute pancreatitis at early phase suggested that BISAP was the single most valuable predictor for SAP(71).

Similar to previous studies, in our study also, BISAP score predicted severity of pancreatitis in our study group. Odds ratio of BISAP for having severe pancreatitis was 10.909 (95% CI- 2.368- 50.266) (p value <0.0001). BISAP could not predict local complication in our acute pancreatitis patients.

Both CTSI (CT Severity Index) and MCTSI (Modified CT severity Index) were calculated in all patients undergoing CECT Abdomen. Out of 80 patients,38 (47%) patients had a CTSI score of more than 6 and 42 (53%) patients had score of 6 or less. Out of 80 patients, 38 (47%) patients had a MCTSI score of more than 6 and 42 (53%) patients had score of 6 or less.

Fig: Pseudocyst of Pancreas

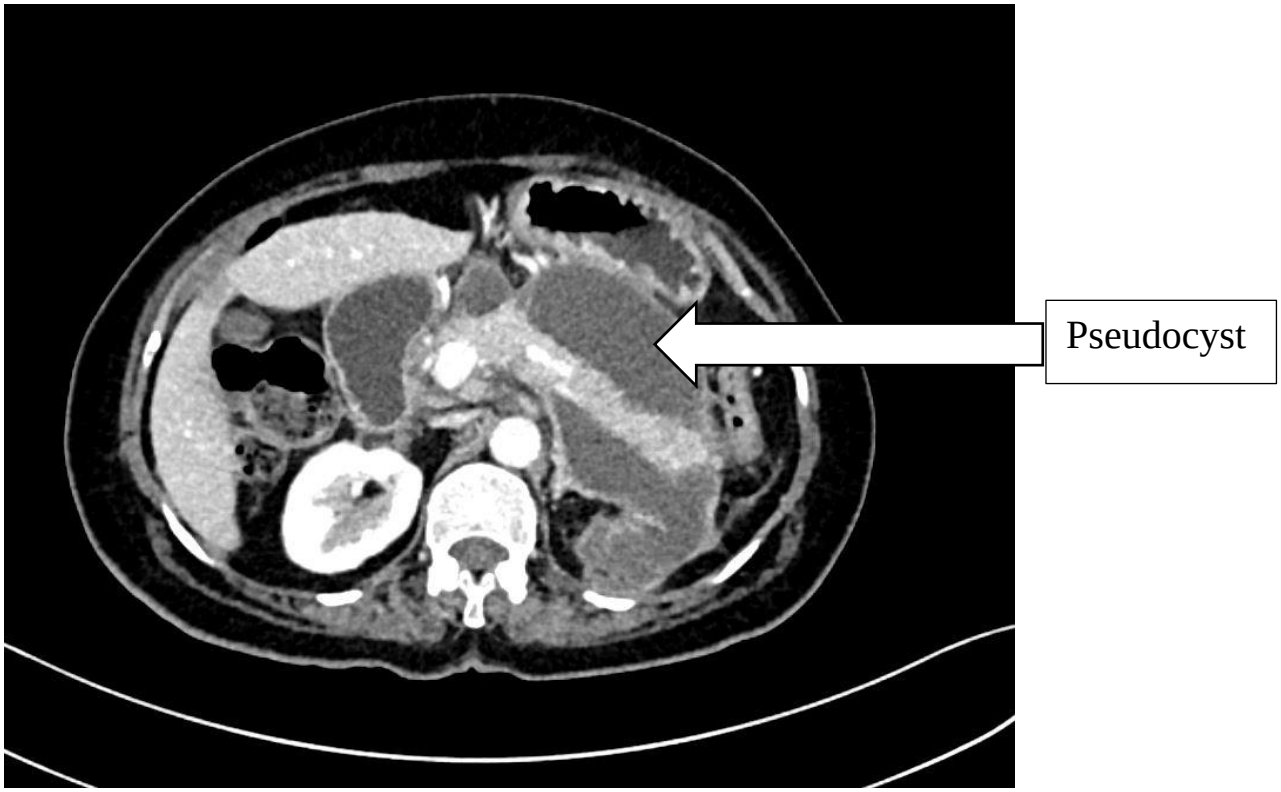


Fig: Walled off Necrosis (WON)

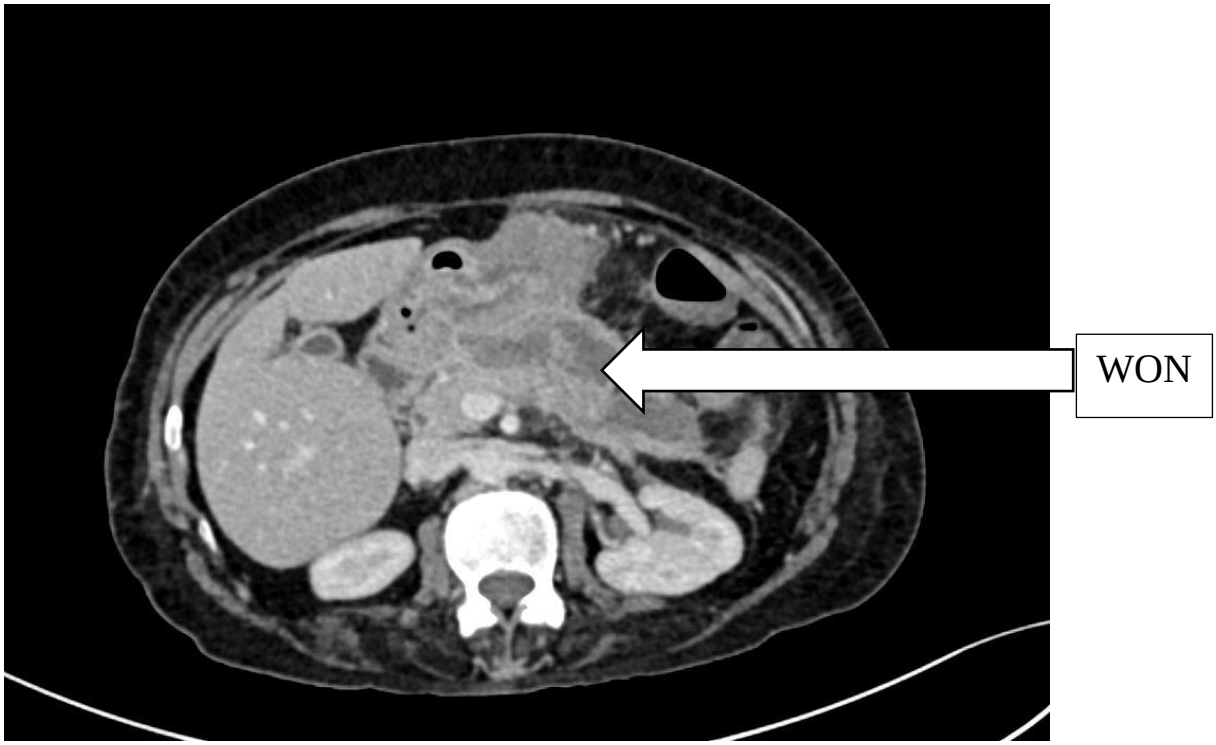
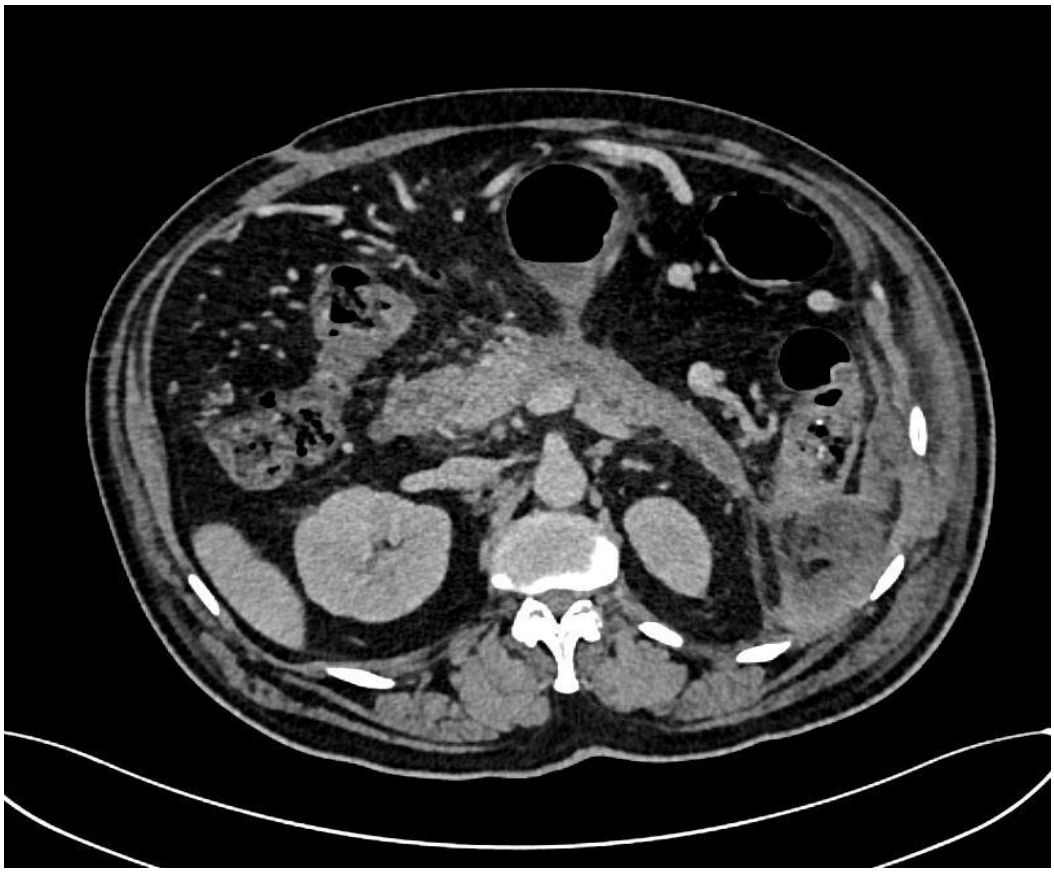


Fig: Splenic Vein Thrombosis



Sahu et al. in their study on severity assessment of AP using CTSI and MCTSI and their correlation with the clinical outcomes and severity as per the revised Atlanta classification found that both CTSI and MCTSI showed significant correlation with clinical outcome parameters, and had good concordance with the revised Atlanta classification grading of severity.

Bollen et al. had evaluated MCTSI and CTSI for assessing severity of AP, and found that there were no significant differences between the CTSI and the MCTSI in evaluating the severity of AP.

Similar to previous studies, in our study also, CTSI and MTCI score were both significantly associated with severity of pancreatitis and development of complication. Odds ratio of CTSI for having severe pancreatitis was 8.299 (95% CI- 0.978- 69.26) (p value 0.025). Odds ratio of MCTSI for having severe pancreatitis was 10.93 (95% CI- 1.29- 92.143) (p value 0.008). Odds ratio of CTSI for development of local complications was 1.37 (95% CI- 1.179 - 1.591) (p value 0.16). Odds ratio of MCTSI for development of local complications was 1.37 (95% CI- 1.179 - 1.591) (p value 0.16).

Mean values of inflammatory markers were compared with severity of pancreatitis, occurrence of local complications, duration of hospital stay, clinical severity index like BISAP, CT severity indices like CTSI and MCTSI.

LDH is one of the 11 criteria of the Ranson score and has been studied independently in patients with AP. Chen et al. found that serum LDH activity was significantly higher in severe than in mild AP in 42 patients with acute pancreatitis in their study.

Vengadakrishnan et al, studied clinical profile of acute pancreatitis and its correlation with severity indices, and found that lab markers like high values of lipase, CRP and LDH correlated well with the mortality and morbidity and CRP and LDH at admission could be used as prognostic markers for predicting morbidity and mortality in AP (80).

Similar to previous observation, in our study, mean values of LDH was significantly different severe and non-severe pancreatitis group. Mean LDH was 381 in non- severe pancreatitis and 1152 in the severe pancreatitis group (p value <0.0001). LDH was also significantly different the groups with or without local complications. Mean LDH was 248 in patients without any complications and 527 in patients with complications (p value 0.011).

In our study, significant correlation of LDH was seen with duration of hospitral stay (p value <0.0001).

LDH was significantly different in patients having BISAP score less than 2 and score of 2 or more. Mean LDH was 351 in patients BISAP or less than 2 and 897 in patients with score of 2 or more (p value <0.0001).

LDH was significantly different between patients having MCTSI score less than 6 and score of 6 or more. Mean LDH was 320 in patients with MCTSI score less than 6 and 630 in patients with score of 6 or more (p value <0.0001).

LDH was significantly different between patients having CTSI score less than 4 and score of 4 or more. Mean LDH was 298 in patients with CTSI score less than 4 and 613 in patients with score of 4 or more (p value <0.0001).

So, it was LDH was significantly increased in patients with severe pancreatitis and patients with local complications. Higher LDH was seen in patients with higher BISAP, CTSI and MCTSI.

Serum LDH of >435.00 has 100% sensitivity and 66.8 % specificity to predict severity of acute pancreatitis, (Area under the curve- 0.898 (0.810 – 0.987), p value- <0.0001).

Serum LDH of >274 has 76.2% sensitivity and 70.6% specificity to predict complication in a case of acute pancreatitis, (Area under the curve- 0.802 (0.700 – 0.904), p value- <0.0001).

Wu et al. had studied blood urea nitrogen to see if early changes in BUN could predict mortality in AP found that BUN levels were persistently higher among non-survivors than survivors during the first 48 hours of hospitalization (P < .0001) (65).

Koutroumpakis et al. had studied admission hematocrit and rise in blood urea nitrogen at 24 hours and other laboratory markers for predicting persistent organ failure and pancreatic necrosis in AP and found that admission hematocrit ≥44% and rise in BUN at 24 hours may be the optimal predictive tools predicting persistent organ failure and pancreatic necrosis in AP among existing laboratory parameters and scoring systems (66).

Pando et al. demonstrated that rise in BUN at 24 hours predicts mortality and persistent multiorgan failure, comparable to the most widely used scores, like APACHE-II and BISAP. Rise in BUN at 24 hours is a risk factor for outcomes such death, multiorgan failure, and severe AP.

In our study, mean values of blood urea were significantly different severe and non-severe pancreatitis group. Mean blood urea in the non-severe pancreatitis was 28.8 whereas, it was 115.5 in the severe pancreatitis group (p value <0.0001).

In our study, significant correlation of duration of hospitral stay was seen with urea (p value 0.039).

Mean value of urea was significantly different in patients having BISAP score less than 2 and score of 2 or more. Mean urea was 31 in patients BISAP or less than 2 and 68 in patients with score of 2 or more (p value 0.001).

However, blood urea did not significantly vary between group with or without local complications.

Li et al had compared prognostic values of inflammation markers in patient with AP and found that compared with survivors of AP, non-survivors have higher RDW, higher NPR, lower LMR and lower PNI at baseline. CRP RDW and PNI were independently associated with occurrence of SAP. NLR was the most powerful marker of overall survival (40).

Zhou et al. had suggested that NLR, PLR, RDW, BUN, SOFA, BISAP, Ranson, and APACHE II were associated with severity and mortality of AP. RDW was superior to other laboratory predictors in prediction of not only SAP, but also mortality of AP. Among the laboratory parameters studied, RDW had the highest discriminatory capacity, and it is a convenient, economic and reliable marker for both SAP and mortality.

In our study, mean values RDW was significantly different the groups with or without local complications. Mean RDW was 13.8 in patients without any complications and 14.6 in patients with complications (p value 0.029).

In our study, significant correlation of duration of hospitral stay was seen with RDW (p value 0.0024).

However, there was no significant difference in RDW between severe and non-severe pancreatitis.

In contrast to all previous studies NLR, PLR and LMR were not significantly different in severe and non-severe pancreatitis, or between patients with or without local complication and could not be used to predict severity or local complications in pancreatitis.

NLR. PLR and LMR had no significant correlation with duration of hospital stay.

None amongst NLR, PLR and LMR significantly vary with CTSI, MCTSI or BISAP score.

In our study, mean value of CRP was significantly different the groups with or without local complications. Mean CRP was 85 in patients without any complications and 136 in patients with complications (p value 0.022).

In our study, significant correlation of duration of hospitral stay was seen with CRP (p value 0.024).

Mean values of CRP was significantly different in patients having BISAP score less than 2 and score of 2 or more. Mean CRP was 114 in patients BISAP or less than 2 and 169 in patients with score of 2 or more (p value 0.014).

However, there CRP did not vary significantly between severe and non-severe pancreatitis.

In our study, ESR was significantly different between patients having MCTSI score less than 6 and score of 6 or more. Mean ESR was 34 in patients with MCTSI score less than 6 and 48 in patients with score of 6 or more (p value 0.037). However, ESR did not significantly vary with severity, complications, duration of hospital stay, BISAP or CTSI. And hence could not be used to predict severity or local complications in pancreatitis.

Sathyanarayan et al. studied 108 patients of acute pancreatitis out of which 30 presented within 72 hours of onset. The level of IL-6 on day 3 was significantly higher in severe pancreatitis than in mild pancreatitis (P = 0.04) and was significantly higher in patients who developed organ failure compared with those who did not (P = 0.004). IL-6 had a sensitivity

and specificity of 81.8% and 77.7% respectively, to predict severe pancreatitis, at a cut-off value of 122 pg/mL on day 3 (78).

In our study, mean value IL-6 was significantly different in patients having BISAP score less than 2 and score of 2 or more. Mean IL-6 was 109 in patients BISAP or less than 2 and 348 in patients with score of 2 or more (p value 0.025). However, IL-6 did not significantly vary with severity, complications, duration of hospital stay, MCTSI or CTSI. And hence could not be used to predict severity or local complications in pancreatitis.

Treatment

All patients were treated with aggressive intravenous fluid, expect the patients with pre-existing cardiovascular comorbidities, analgesics, antiemetics and other symptomatic management. Enteral feeding was started as soon as possible when vomiting improved and patient was capable to accept oral feeding. Nasogastric feeding was used only when the patient could not take feed orally due to altered sensorium or was unable to maintain the prescribed daily calory intake by mouth.

Antibiotics were given only to patients with proven infected necrosis or patients of acute necrotizing pancreatitis with severe sepsis after ruling out all other sources of infection. In patients with infected necrosis, antibiotics was given as per the culture and sensitivity report. Carbapenem antibiotics were most commonly used empirical antibiotic.

ERCP (Endoscopic Retrograde Cholangiopancreatography) was not used in the routine diagnostic evaluation but was used as a therapeutic intervention in patients for treatment of choledocholithiasis or structural abnormalities in the pancreas or its duct, when considered necessary by the treating physician.

EUS (Endoscopic Ultrasound) guided or Ultrasound guided drainage of peripancreatic collection was done only in symptomatic patients with peripancreatic collection, like patients with infected peripancreatic necrosis, not improving with antibiotics and other conservative management.

Outcome

3 out of 80 patients died during hospital stay in our study population, with mortality rate of 3.75% in our study population. The average mortality rate in Severe Acute Pancreatitis as noted previously is around 2%–10% (20). However, our data may represent slightly lower mortality than actual mortality as patients admitted directly in intensive care unit were not enrolled in our study.

CONCLUSION

Acute pancreatitis has significant morbidity and mortality. The most common cause of acute pancreatitis is alcohol consumption and gallstones. There is a need of better and cheaper biomarkers for prediction of outcome and prognosis. In this study we used newer biomarkers like NLR, PLR, LMR, RDW, IL-6 along with LDH, ESR, CRP and blood urea. Overall, Serum LDH was seen as single best prognostic marker in Acute Pancreatitis. Serum LDH could reliably predict severity of Acute Pancreatitis and local complication in patients in AP. LDH also correlates well with duration of Hospital stay. Significant correlation of CRP and RDW was seen with duration of hospital stay. However, neither RDW nor CRP could predict severity of acute pancreatitis.

In contrast to all previous studies NLR, PLR, LMR and IL-6 could not predict severity, local complications in pancreatitis or duration of hospital stay.

Higher serum CRP, IL-6, LDH and urea was associated with higher BISAP score, ESR and LDH was associated with MCTSI and LDH alone was associated with CTSI.

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Institutional Ethics Committee

No. AIIMS/IEC/2021/3506 Date: 12/03/2021

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3341**

Project title: **"Association of various inflammatory markers and CT severity indices in clinical outcome and prognosis of acute pancreatitis"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Isha Stutee**
Guide:	**Dr. M.K.Garg**
Co-Guide:	**Dr. Naresh Midha, Dr. Mithu Banergee, Dr. Subhash Chandra Soni & Dr. Pawan Garg**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

APPENDIX-1

All India Institute of Medical Sciences

Jodhpur, Rajasthan

Informed Consent Form

Title of Thesis/Dissertation: **TO STUDY THE ASSOCIATION OF VARIOUS INFLAMMATORY MARKERS AND CT SEVERITY INDICES IN CLINICAL OUTCOME AND PROGNOSIS OF ACUTE PANCREATITIS"**
Name of PG Student: Dr. Isha Stutee, Contact No. - 8292705940
Patient/Volunteer Identification No.: _____

I,_____S/o or D/o_____

R/o_____give my full, free, voluntary consent to be a part of the study **"**TO STUDY THE ASSOCIATION OF VARIOUS INFLAMMATORY MARKERS AND CT SEVERITY INDICES IN CLINICAL OUTCOME AND PROGNOSIS OF ACUTE PANCREATITIS", the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.
I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from _____(Company Name) or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of PG Student

Witness 1
Signature
Name: _____
Address: _____

Witness 2
Signature
Name: _____
Address: _____

APPENDIX-2

अखिलभारतीयआयुर्विज्ञानसंस्थान
जोधपुर, राजस्थान

<u>सूचितसहमतिपत्र</u>

थीसिस का शीर्षक "तीव्र अग्नाशयशोथ के विभिन्न सूजन मार्करों की भूमिका की मूल्यांकन तथा सीटी गंभीरता सूचकांक से संबंध"

पीजीछात्रकानाम: ईशास्तुति ,दूरभाष।संख्या : 8292705940
रोगी / स्वयंसेवी पहचान संख्या.: _____
मैं,_____पुत्र /पुत्री_____
निवासी_____निम्नलिखितअध्ययनकाहिस्साबननेकेलि एमेरीपूर्ण, नि: शुल्क, स्वैच्छिकसहमतिदेताहूँ
"तीव्र अग्नाशयशोथ (Pancreatitis) के विभिन्न सूजन मार्करों की भूमिका का मूल्यांकन तथा सीटी गंभीरता सूचकांक से संबंध" , जिसकी प्रक्रिया और प्रकृति मेरी पूरी संतुष्टि के लिए मेरी अपनी भाषा में मुझे समझायी गयी है। मैं पुष्टि करता हूं कि मेरे पास प्रश्न पूछने का अवसर था।

मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और किसी भी कारण के बिना, किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं | मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्र की गई जानकारी एम्स जोधपुर से या नियामक प्राधिकरणों से जिम्मेदार व्यक्ति द्वारा देखी जा सकती है।मैं इन व्यक्तियों के लिए अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं|

दिनांक: _____ _____
स्थान : _____ हस्ताक्षर/बाएं अंगूठे की छाप

यहप्रमाणितकरनेकेलिएकिउपर्युक्तसहमतिमेरीउपस्थितिमेंप्राप्तकीगईहै।

तारीख :_____ _____
स्थान: _____ हस्ताक्षर पीजी छात्र

साक्षी1 साक्षी2
हस्ताक्षर _____ हस्ताक्षर _____

नाम: _____ नाम: _____
स्थान : _____ स्थान : _____

APPENDIX-3

PATIENT INFORMATION SHEET

Name of the patient: **Patient ID.:**

1. **Aim of the study**: TO STUDY THE ASSOCIATION OF VARIOUS INFLAMMATORY MARKERS AND CT SEVERITY INDICES IN CLINICAL OUTCOME AND PROGNOSIS OF ACUTE PANCREATITIS
2. **Study site:** Out Patient, in-patient and emergency services of Department of General Medicine and Gastrosurgery, All India Institute of Medical Sciences, Jodhpur, Rajasthan.
3. **Study procedure:** All the above-mentioned variables will be assessed by detailed history, clinical examination and laboratory investigations. All patients will be subjected to baseline laboratory investigations, serum amylase, lipase, LDH, IL 6, Ultrasound Whole Abdomen, Chest X-Ray and CECT Abdomen.
4. **Likely benefit:** The study will suggest a reliable and inexpensive biomarker for risk stratification for development of acute pancreatitis
5. **Confidentiality:** All the data collected from each study participant will be kept highly confidential.
6. **Risk:** Enrollment in above study poses no substantial risk to any of the study participant and if any point of time participant want to withdraw himself/ herself, he/ she can do so voluntarily at any point of time during the study.

For further information / questions, the following personnel can be contacted:

Dr, Isha Stutee

Junior Resident, Department of Internal Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan. Ph: 8292705940

परिशिष्ट -3

रोगीसूचनापत्र

रोगीकानाम:

रोगीआईडी .:

"तीव्र अग्नाशयशोथ के विभिन्न सूजन मार्करों की भूमिका की मूल्यांकन तथा सीटी गंभीरता सूचकांक से संबंध"

"तीव्र अग्नाशयशोथ के विभिन्न सूजन मार्करों की भूमिका की मूल्यांकन तथा सीटी गंभीरता सूचकांक से संबंध" लिए एक अध्ययन में भाग ले रहे हैं।
तीव्र अग्नाशय शोथ न्युट्रोफिल लिम्फोसाइट अनुपात, लिम्फोसाइट मोनोकाइट अनुपात, लाल कोशिका विकर्षण चौड़ाई, इंटरल्यूकिन 6, एलडीएच तथा सीआरपी, की भूमिका की मूल्यांकन अध्ययन स्थल: मेडिसिन चिकित्सा विभाग तथा गैस्ट्रोसर्जरी विभाग अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान के आउटपेशेंट, आईपीडी और आपातकालीन सेवाएं।

1. **हम आपकी आयु, लिंग, आपकी बीमारी और आपके द्वारा प्राप्त किए गए उपचार के बारे में जानकारी एकत्र करेंगे।**
2. **हम पूर्ण रक्त गणना,इंटरल्यूकिन 6, एलडीएच तथा सीआरपी परीक्षण करेंगे।**
3. **हम छाती का एक्सरे, पेट का अल्ट्रासाउंड और सीटी करेंगे**
4. **गोपनीयता: आपके द्वारा एकत्र किए गए सभी डेटा को अत्यधिक गोपनीय रखा जाएगा।**
5. **जोखिम: उपर्युक्त अध्ययन में नामांकन आपके लिए कोई बड़ा जोखिम नहीं है।आप बिना किसी परिणाम के अध्ययन के किसी भी समय अध्ययन से वापस ले सकते हैं।**

अधिकजानकारी / प्रश्नों के लिए, निम्नलिखित कर्मियों से संपर्क किया जा सकता है:
डॉ ईशा स्तुति ,आंतरिक चिकित्सा विभाग, ऑल इंडिया इंस्टीट्यूट ऑफ मेडिकल साइंसेज, जोधपुर, राजस्थान। फोननंबर : **8292705940**

APPENDIX-4

SOCIO-DEMOGRAPHIC AND CLINICAL PROFORMA

PATIENT ID:

NAME OF PATIENT

AGE/GENDER:

ADDRESS:

CONTACT NUMBER:

CHIEF COMPLAINTS:

BRIEF HOPI:

PAST HISTORY:

TREATMENT HISTORY:

FAMILY HISTORY:

PERSONAL HISTORY:

VITALS:

TEMP:

PULSE:

RR:

BP:

RBS:

GENERAL PHYSICAL EXAMINATION:

SYSTEMIC EXAMINATION:

INVESTIGATIONS:

	DAY 1	DAY 7
CBC **Hb** **TLC** **DLC** **PLT**		
CRP		
ESR		
LFT		
KFT		
ELECTROLYTES		
LDH		
IL-6		

CHEST XRAY	

FINAL DIAGNOSIS:

TREATMENT GIVEN:

TOTAL DURATION OF ILLNESS:

DURATION OF HOSPITAL STAY:

BISAP:

APACHE:

CTSI:

MODIFIED CTSI:

ANY COMPLICATIONS DURING HOSPITAL STAY: