The Prognostic significance of Red cell distribution width (RDW) and Neutrophil–Lymphocyte Ratio (NLR) in Acute Pancreatitis: Identification of an Optimal values

DISSERTATION SUBMITTED FOR

MD DEGREE (BRANCH 1) GENERAL MEDICINE

MAY 2018

THE TAMILNADU
DR.M.G.R MEDICAL UNIVERSITY

CHENNAI – TAMILNADU

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled "**The Prognostic significance of Red cell distribution width (RDW) and Neutrophil–Lymphocyte Ratio (NLR) in Acute Pancreatitis: Identification of an Optimal values**" is the bonafide work of **Dr.R.PON RAJ**, in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in May 2018.

Dr.D.MARUTHU PANDIYAN ***M.S, FICS, FRCS***

THE DEAN,

Madurai Medical College

Madurai.

CERTIFICATE FROM THE HOD

This is to certify that this dissertation entitled **"The Prognostic significance of Red cell distribution width (RDW) and Neutrophil–Lymphocyte Ratio (NLR) in Acute Pancreatitis: Identification of an Optimal values"** is the bonafide work of **Dr.R.PON RAJ**, in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in May 2018.

Prof. Dr. V.T. PREMKUMAR M.D.,
Professor and HOD,
Department Of Medicine,
Government Rajaji Hospital,
Madurai Medical College, Madurai.

CERTIFICATE FROM THE GUIDE

This is to certify that this dissertation entitled **"The Prognostic significance of Red cell distribution width (RDW) and Neutrophil–Lymphocyte Ratio (NLR) in Acute Pancreatitis: Identification of an Optimal values"** is the bonafide work of **Dr.R.PON RAJ**, in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in May 2018.

Dr. J.SANGUMANI M.D, D.diab
Professor of Medicine
Chief, Vth Medical Unit
Madurai Medical College &
Govt. Rajaji Hospital Madurai.

DECLARATION

I, **Dr.R.PON RAJ,** solemnly declare that this dissertation titled "**The Prognostic significance of Red cell distribution width (RDW) and Neutrophil–Lymphocyte Ratio (NLR) in Acute Pancreatitis: Identification of an Optimal values**" is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.J.SANGUMANI M.D, D.diab,** Professor, Department of General Medicine, Madurai Medical college , Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of M.D Degree General Medicine Branch-I examination to be held in May 2018.

Place: Madurai **Dr.R.PON RAJ**

Date:

ACKNOWLEDGEMENT

Above all I thank the Lord Almighty for His grace and guidance.

My sincere thanks to our **Dr.MARUTHUPANDIYAN** M.S Dean, Madurai Medical College and Government Rajaji Hospital, for permitting me to utilize the clinical materials from this hospital to conduct the study.

My respect and sincere gratitude to my beloved HOD **Prof. Dr.V.T.PREMKUMAR, M.D.,** Head of the Department of Medicine, Government Rajaji Hospital, Madurai Medical College for his valuable Guidance and encouragement during the study and also throughout my course period.

I extend my gratitude and sincere thanks to my beloved teacher, my guide and my Unit Chief Prof**. Dr.J.SANGUMANI M.D, D.diab** for his valuable suggestions, patience, guidance and support throughout the study and also throughout my course period.

I Am greatly indebted to my Beloved Professors **Dr. R. BALAJINATHAN, Dr.M.NATARAJAN, M.D., Dr. G BAGIALAKSHMI M.D., Dr.C.DHARMARAJ, M.D., Dr.R.PRABHAKARAN M.D.,** for their valuable suggestions throughout the Course of the study.

I am extremely thankful to the Assistant Professors of Medicine of my Unit, **Dr.R.SUNDARAM M.D, Dr.K.S.RAGHAVAN M.D, D.diab** for their valid guidance, encouragement and suggestions.

I extend my sincere thanks to **Prof. Dr. M.KANNAN M.D, D.M,** HOD Department of Medical gastroenterology, Government Rajaji Hospital and Madurai Medical College for his unstinted support and valuable guidance throughout the study period.

I am extremely thankful to **Prof. Dr. MOHANKUMARESAN, MD.,** Head of the Department of Bio-chemistry for their constant support, guidance, cooperation and to complete this study.

My special thanks and love for my wife **Dr.PRIYADHARSHINI**, **M.B.B.S.,** my son **AARAV SRIRAM** my colleagues **Dr.INAN LOLLEN, Dr. RAM PRASANTH** for their support throughout the study.

Finally, I thank all the patients, the most integral part of the work, who were always kind and cooperative. I pray for their speedy recovery, comfort and strength.

CONTENTS

INTRODUCTION

"Acute pancreatitis" is usually a self-limiting disease; however, severe form of the disease developed in 25 % of patients & it is associated with a mortality of up to 50 %. Available Scoring system's aim is to stratify the severity of the AP, and this in turn guides the management with improving outcomes.

Currently available gold standard scoring system for assessment of 'Acute pancreatitis' is the "Acute Physiology and Chronic Health Evaluation" (APACHE II), is labor intensive and is not widely adopted for patients with acute pancreatitis outside of the intensive care setting. Other scoring systems such as the "Sequential Organ Failure Assessment" (SOFA) have been developed but are still suitable only in the intensive care setting and not for routine use in all patients presenting with acute pancreatitis.

As such, they are not suitable for stratifying patients at the time of admission or shortly thereafter Simplified tests using serum markers such as procalcitonin, interleukin-6, and interleukin-8 have been said to be able to predict the severity of AP, but these are expensive, non-validated in the clinical arena, and not readily available.

Red cell distribution width is an independent prognostic marker, it has been used in many pathological conditions, such as CVS diseases, respiratory diseases, RA and progressive inflammatory status, and even in malignancy

The white blood cell count (WBC count) is a routinely performed, easily available haematological test that is already added in many of the current scoring systems. Components of the total WBC count include 'neutrophils' & 'lymphocytes' both can be used individually as markers of inflammation. Poor outcome is due to an uncontrolled systemic inflammatory response syndrome (SIRS), it leads to progression of acute pancreatitis to multi-organ dysfunction syndrome (MODS).

Indeed, the WBC count is one of the criteria in scoring of the SIRS. Neutrophils increased in SIRS and lymphocyte depletion occurs in severe sepsis, both are associated with a poor outcome of acute pancreatitis. The neutrophil–lymphocyte ratio (NLR) is a measure of the divergence of these two WBC components, and may be more accurate than the total WBC count or individual neutrophil/lymphocyte counts in predicting poor outcome in benign and malignant surgical conditions.

AIMS AND OBJECTIVES

The aim of the current study is to investigate the validity of RDW and NLR in predicting outcome, and to determine an optimal cut-off value that would allow division of patients in to mild (MAP) and severe acute pancreatitis (SAP) groups based on NLRs & RDW within the first 48 h of hospitalization.

REVIEW OF LITERATURE

PHYSIOLOGY OF PANCREATIC EXOCRINE SECRETION

The pancreas secrete 20 different enzymes along with 1500-3000 mL of isosmotic alkaline fluid per day that pH of the fluid is >8. These enzymes and bicarbonate needed for major digestive activity of the GIT and provide an optimal alkaline environment for the function of these enzymes.

REGULATION OF PANCREATIC SECRETION

Intimate interaction of hormonal and neural systems are crucial for exocrine pancreas function. Gastric acid is the stimulus for the release of secretin from the duodenal mucosa (S cells) which in turn stimulates pancreatic ductal cells and enhance the secretion of water and electrolytes.

Long-chain fatty acids, essential amino acids (tryptophan, phenylalanine, valine, and methionine) & gastric acid itself stimulates release of cholecystokinin (CCK) from the duodenal and proximal jejunal mucosa (Ito cells). Further CCK evokes an enzyme-rich secretion from
acinar cells in the pancreas.

Through the vagus nerve, the parasympathetic nervous system exerts significant control over pancreatic secretion. Secretion evoked by secretin and

CCK depends on permissive roles of vagal afferent and efferent pathways. Neuronal control plays important role in enzyme secretion, whereas water and bicarbonate secretions are heavi1y dependent on the hormonal effects of secretin and to a lesser extent CCK. Also vagal stimulation affects the release of a secretin agonist, vasoactive intestinal peptide (VIP).

Pancreatic exocrine secretion is also influenced by inhibitory neuropeptides (somatostatin, pancreatic polypeptide, peptide YY, neuropeptide Y, enkephalin, pancreastatin, calcitonin gene-related peptides, glucagon & galanin). Although pancreatic polypeptide and peptide YY may act primarily on nerves outside the pancreas, somatostatin acts at multiple sites. Nitric oxide (NO) is also an important neurotransmitter.

ENZYME SECRETlON

Highly compartmentalized acinar cells are concerned with the secretion of pancreatic enzymes. Proteins synthesized by the rough endoplasmic reticulum are processed in the Golgi apparatus and then targeted to the appropriate site like zymogen granules, lysosomes or other cell compartments.

The zymogen granules migrate to the apical region of the acinar cell awaiting the appropriate neural or hormonal stimulatory response. The pancreas secretes amylolytic, lipolytic and proteolytic enzymes into the duct

lumen. Amylolytic enzymes (amylase) hydrolyze starch to oligosaccharides and to the disaccharide maltose.

The lipolytic enzymes (lipase, phospholipase A_2, cholesterol esterase). Actually bile salts inhibit lipase, but if colipase binds with lipase that prevents disinhibition. Bile salts also activate phospholipase A and

cholesterol esterase.

Exopeptidases (carboxypeptidases, aminopeptidases) which act on the free carboxyl-and amino-terminal ends of peptides whereas Endopeptidases (trypsin, chymotrypsin) are proteolytic enzymes which act on internal peptide bonds of proteins and polypeptides. Both are known as "the proteolytic enzymes" they are secreted as inactive zymogen precursors.

Ribonucleases (deoxy ribonucleases ribonuclease) are also secreted. Enterokinase are found in the duodenal mucosa known as that forms the trypsin from cleaves the lysine-isoleucine bond of trypsinogen. Then Trypsin through a "cascade phenomenon" activates the other proteolytic zymogens and phospholipaseA_2. All pancreatic enzymes have pH optima in the alkaline range.

The nervous system initiates pancreatic enzyme secretion. The neurologic stimulation is cholinergic involving extrinsic innervation by the vagus nerve and subsequent innervation by intrapancreatic cholinergic nerves.

Acetylcholine and gastrin-releasing peptides are the stimulatory neurotransmitters.

These are activate calcium-dependent secondary messenger systems, resulting in the release of zymogens into the pancreas duct. VIP is present in intrapancreatic nerves and potentiates the effect of acetylcholine.

AUTO PROTECTION OF THE PANCREAS

Auto digestion of the pancreas is prevented by

1. Pancreatic proteases stored as proenzyme
2. Intracellular calcium homeostasis (destruction of spontaneously activated trypsin if low intracellular calcium is present in the cytosol of the acinar cell)
3. acid-base balance
4. The synthesis of protective protease inhibitors (20% of intracellular trypsin activity is inhibited by pancreatic secretory trypsin inhibitor [PSTI] or SPINK1) Chymotrypsin C can also lyse and inactivate trypsin.

These protease inhibitors are found in the acinar cell, the pancreatic secretions and the α1-and α2 -globulin fractions of plasma.

If any of these four protective mechanisms lost that can leads to premature enzyme activation, auto digestion and acute pancreatitis.

ENTEROPANCREATIC AXIS AND FEEDBACK INHIBITION

Control of Pancreatic enzyme secretion achieved by a negative feedback mechanism that again induced by the presence of active serine proteases in the duodenum. To illustrate perfusion of the duodenal lumen with phenylalanine that stimulates early digestion leads to prompt increase in plasma CCK levels & increased secretion of chymotrypsin and other pancreatic enzymes. But simultaneous perfusion with trypsin that also stimulates late digestion, blunts both responses. Conversely protease inhibitors perfusion to the duodenal lumen leads to enzyme hypersecretion. The duodenum contains a peptide called “CCK-releasing factor” (CCK-RF) that is involved in stimulating CCK release. It appears that serine proteases inhibit pancreatic secretion by inactivating a CCK-releasing peptide in the lumen of the small intestine.

“Thus the integrative result of both bicarbonate and enzyme secretion depends on a feedback process for both bicarbonate and pancreatic enzymes. Acidification of the duodenum releases secretin which stimulates vagal and other neural pathways to activate pancreatic duct cells which secrete bicarbonate. This bicarbonate then neutralizes the duodenal acid and the feedback loop is completed. Dietary proteins bind proteases thereby leading to an increase in free CCK-RF. CCK is then released into the blood in

physiologic concentrations acting primarily through the neural pathways (vagal-vagal). This leads to acetylcholine mediated pancreatic enzyme secretion. Proteases continue to be secreted from the pancreas until the protein within the duodenum is digested. At this point pancreatic protease secretion is reduced to basic levels thus completing this step in the feedback process"

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable involvement of other regional tissues or remote organ systems. **Mild acute pancreatitis** consists of minimal or no organ dysfunction and an uneventful recovery.

Severe pancreatitis manifests as organ failure and/or local complications such as necrosis, abscess, or pseudocyst.

Overall, about 20% of patients with acute pancreatitis have a severe course, and 10% to 30% of those with severe acute pancreatitis die.

CAUSES OF ACUTE PANCREATITIS

Common Causes

- Gallstones
- Biliary sludge and microlithiasis
- Alcohol

- Mechanical obstruction of ampulla
- Hypertriglyceridemia
- Trauma
- Post ERCP
- Pregnancy
- Post-operative
- Ischemia
- Drugs : Pentamidine, didanosine, salicylates, sulindac, frusemide, thiazides Sulphasalazine, mesalamine, L-asparaginase, azathioprine, valproic acid & ACE-inhibitors

Uncommon Causes

- Vascular causes and vasculitis (ischemic-hypo perfusion states after cardiac surgery)
- Connective tissue disorders and thrombotic thrombocytopenic purpura (TTP)
- Cancer of the pancreas
- Hypercalcemia
- Periampullary diverticulum

- Pancreas divisum
- Hereditary pancreatitis
- Cystic fibrosis
- Renal failure
- Infections (mumps, coxsackievirus, cytomegalovirus echovirus, parasites)
- Autoimmune (e.g. type 1 and type 2)

Causes to Consider in Patients with Recurrent Bouts of Acute pancreatitis Without an Obvious Etiology

- Occult disease of the biliary tree or pancreatic ducts, especially microlithiasis
- biliary sludge
- Drugs
- Alcohol abuse

- Metabolic: Hypertriglyceridemia, hypercalcemia
- Anatomic: Pancreas divisum Pancreatic cancer
- Intraductal papillary mucinous neoplasm (IPMN)
- Hereditary pancreatitis

- Cystic fibrosis
- Autoimmune
- Idiopathic

The gallstone disease and **alcohol** are the two most common causes for acute Pancreatitis.

Gallstones continue to be the leading cause of acute pancreatitis in most series (30-60%). The risk of acute pancreatitis in patients with at least one gallstone <5 mm in diameter is fourfold greater than that in patients with larger stones.

Alcohol is the second most common cause responsible for 15-30% of cases. The incidence of pancreatitis in alcoholics is surprisingly low (5/100000) indicating that in addition to the amount of alcohol ingested, other factors affect a person' s susceptibility to pancreatic injury such as cigarette smoking.

Acute pancreatitis occurs in 5-10% of patients following endoscopic retrograde cholangiopancreatography (ERCP). Use of a prophylactic pancreatic duct stent and rectal nonsteroidal anti-inflammatory drugs

(NSAIDs) has been shown to reduce pancreatitis after ERCP.

Risk factors for post-ERCP pancreatitis

- minor papilla sphincterotomy,
- sphincter of Oddi dysfunction,

- prior history of post-ERCP pancreatitis,
- age <60 years,
- >2 contrast injections into the pancreatic duct,
- endoscopic trainee involvement

Hypertriglyceridemia is the cause of acute pancreatitis in l.3-3.8% of cases; serum triglyceride levels are usually > 1l.3 mmol/L (> 1000 mg/dL). Most patients with hypertriglyceridemia when subsequently examined show evidence of an underlying derangement in lipid metabolism probably unrelated to pancreatitis. Such patients are prone to recurrent episodes of pancreatitis. Any factor (e.g., drugs or alcohol) that causes an abrupt increase in serum triglycerides can precipitate a bout of acute pancreatitis. Patients with a deficiency of apolipoprotein CII have an increased incidence of pancreatitis; apolipoprotein CII activates lipoprotein lipase which is important in clearing chylomicrons from the bloodstream. Patients with diabetes mellitus who have developed ketoacidosis and patients who are on certain medications such as oral contraceptives may also develop high

triglyceride levels.

Approximately 0.1-2% of cases of acute pancreatitis are drug related Drugs cause pancreatitis either by a hypersensitivity reaction or by the generation of a toxic metabolite.

Pathologically acute pancreatitis varies from interstitial pancreatitis (pancreas blood supply maintained) which is generally self-limited to necrotizing pancreatitis (pancreas blood supply interrupted) in which the extent of necrosis may correlate with the severity of the attack and its systemic complications. Autodigestion is a currently accepted pathogenic theory; according to this theory pancreatitis results when proteolytic enzymes (e.g., trypsinogen chymotrypsinogen proelastase and lipolytic enzymes such as phospholipase A_2) are activated in the pancreas acinar cell rather than in the intestinal lumen. A number of factors (e.g. endotoxins exotoxins viral infections ischemia oxidative stress lysosomal calcium and direct trauma) are believed to facilitate premature activation of trypsin. Activated proteolytic enzymes especially trypsin not only digest pancreatic and peripancreatic tissues but also can activate other enzymes such as elastase and phospholipase A_2. Spontaneous activation of trypsin also can occur.

PATHOGENESIS OF ACUTE PANCREATITIS

The initial phase is characterized by intra pancreatic digestive enzyme activation and acinar cell injury. Trypsin activation appears to be mediated by lysosomal hydrolases such as cathepsin B that become colocalized with digestive enzymes in intracellular organelles; it is currently believed that acinar cell injury is the consequence of trypsin activation.

The second phase of pancreatitis involves the activation, chemo attraction and sequestration of leukocytes and macrophages in the pancreas resulting in an enhanced intrapancreatic inflammatory reaction. Neutrophil depletion induced by prior administration of an ant neutrophil serum has been shown to reduce the severity of experimentally induced pancreatitis. There is also evidence to support the concept that neutrophils can activate trypsinogen. Thus, intrapancreatic acinar cell activation of trypsinogen could be a two-step process (i.e.an early neutrophil-independent and a later neutrophil-dependent phase).

The third phase of pancreatitis is due to the effects of activated proteolytic enzymes and cytokines, released by the inflamed pancreas, on distant organs. Activated proteolytic enzymes, especially trypsin, not only digest pancreatic and peripancreatic tissues but also activate other enzymes such as elastase and phospholipase A_2. The active enzymes and cytokines

then digest cellular membranes and cause proteolysis, edema, interstitial hemorrhage, vascular damage, coagulation necrosis, fat necrosis and parenchymal cell necrosis. Cellular injury and death result in the liberation of bradykinin peptides, vasoactive substances, and histamine that can produce vasodilation, increased vascular permeability, and edema with profound effects on many organs.

The systemic inflammatory response syndrome (SIRS) and acute respiratory distress syndrome (ARDS), as well as multiorgan failure may occur as a result of this cascade of local and distant effects.

A number of genetic factors can increase the susceptibility and/or modify the severity of pancreatic injury in acute pancreatitis recurrent pancreatitis and chronic pancreatitis. All of the major genetic susceptibility factors center on the control of trypsin activity within the pancreatic acinar cell in part because they were identified as candidate genes linked to intrapancreatic trypsin control.

Five genetic variants have been identified as being associated with susceptibility to pancreatitis.

(1) Cationic trypsinogen gene (PRSSl)

(2) Pancreatic secretory trypsin inhibitor (SPINKl)

(3) The cystic fibrosis transmembrane conductance regulator gene (CFTR)

(4) The chymotrypsin C gene (CTRC)

(5) The calcium-sensing receptor (CASR)

Clinical features of acute pancreatitis

Abdominal pain

- major symptom of acute pancreatitis
- Pain may vary from a mild discomfort to severe, constant & incapacitating nature
- onset is rapid and reaches maximal intensity in 10 to 20 minutes
- Characteristically steady and boring type that is located in the epigastrium and periumbilical region & may radiate to the back, chest, flanks & lower abdomen.

Nausea, *vomiting* & *abdominal distention* - also frequent complaints

Physical examination

Low-grade fever

Tachycardia

Hypotension

Jaundice

Erythematous skin nodules

Respiratory system - basilar rales, atelectasis & pleural effusion (left sided)

Abdomen - tenderness and muscle rigidity, Bowel sounds diminished or absent

Cullen's sign - a faint blue discoloration around the umbilicus (due to hemoperitoneum).

Turner's sign - a blue red purple or green-brown discoloration of the flanks (due to tissue catabolism of hemoglobin from severe necrotizing pancreatitis with hemorrhage)

LABORATORY DATA

Serum amylase and lipase

- > 3 fold above normal
- Serum lipase is the preferred test
- No correlation between the degree of serum lipase and amylase elevations & severity of pancreatitis
- After 3-7 days, total serum amylase values tend to return toward normal.
- Pancreatic isoamylase and lipase levels may remain elevated for 7-14 days.

- Amylase elevations in serum and urine occur in many conditions other than pancreatitis
- patients with arterial pH < 7.32, may have spurious elevations of serum amylase
- Serum lipase activity is more specific than amylase & it increases in parallel with amylase activity
- Serum lipase measurement can be useful in differentiating a pancreatic or non-pancreatic cause for hyperamylasemia.

Leukocytosis

- 15000 to 20000 leukocytes/micL occurs frequently

Hemoconcentration

- Hematocrit values >44%

- More severe disease

Prerenal azotemia

- Blood urea nitrogen (BUN) level >22 mg/Dl

- Risk factor for mortality

Hyperglycemia

- due to decreased insulin release, increased glucagon release, an increased output of adrenal glucocorticoids & catecholamine's **Hypocalcemia**

- Occurs in -25% of patients

Hyperbilirubinemia

- occurs in 10% of patients
- transient, returns to normal in 4-7 days
- SGOT,SGPT & ALP levels also transiently elevated

Hypertriglyceridemia

- occurs in 5-10% of patients,
- spuriously normal serum amylase levels in these individuals

Hypoxemia

- arterial $PO_2 < 60$ mmHg
- indicates the onset of ARDS

ECG

- ST-segment & T-wave abnormalities

Abdominal ultrasound

- initial diagnostic imaging modality
- Most useful to evaluate for gallstone disease and the pancreatic head

CT Abdomen

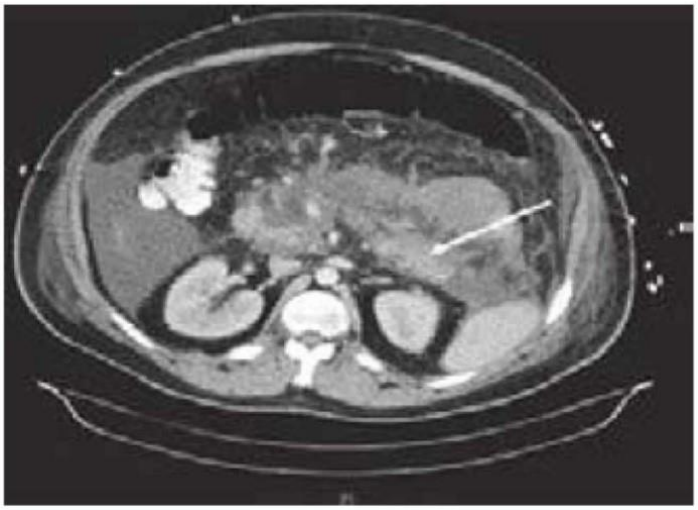
- best evaluated 3-5 days
- Interstitial or necrotizing pancreatitis are recognized by imaging based on pancreatic perfusion.

REVISED ATLANDA DEFINITIONS OF MORPHOLOGIC FEATURES OF ACUTE PANCREATİTIS

1. Interstitial pancreatitis

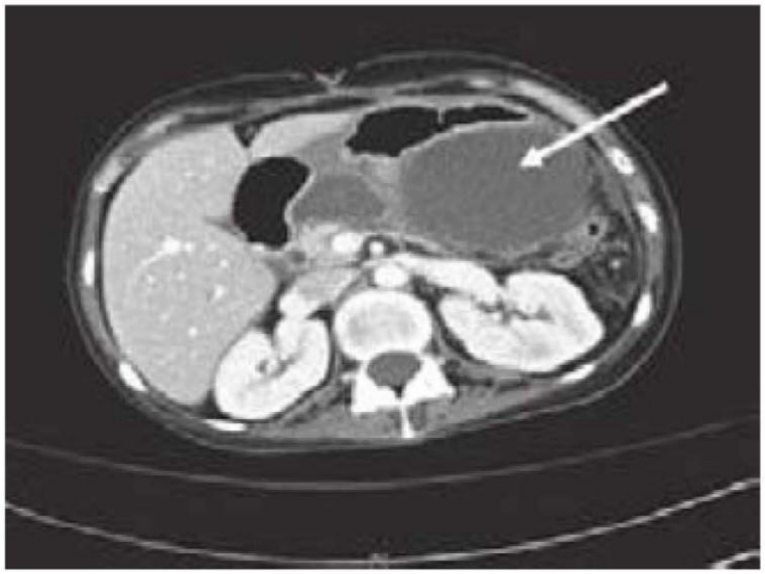
- Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis
- Pancreatic parenchyma enhancement by IV contrast agent;
- No findings of peripancreatic necrosis

2. Necrotizing pancreatitis

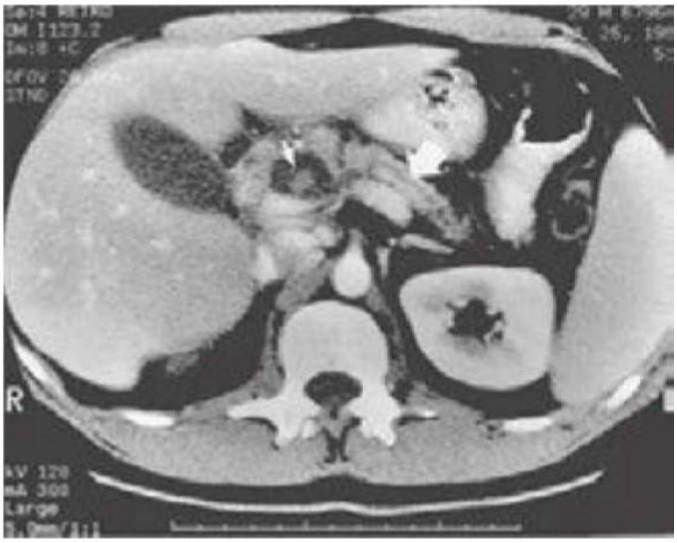


- Inflammation associated with pancreatic parenchymal necrosis and/or presence peripancreatic necrosis
- Lack of pancreatic parenchymal enhancement by IV contrast agent and/ or presence of findings of peripancreatic necrosis

3. Acute pancreatic fluid collection



- Peripancreatic fluid associated with (<4 weeks) interstitial edematous pancreatitis
- Not associated with peripancreatic necrosis / pseudocyst / pseudocyst **4. Pancreatic pseudocyst**



- An encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrosis

- This entity usually occurs >4 weeks after onset of interstitial edematous pancreatitis.

- Well circumscribed, usually round or oval Homogeneous fluid density

-No nonliquid component

- Well-defined wall; that is completely encapsulated

5. Acute necrotic collection (ANC)

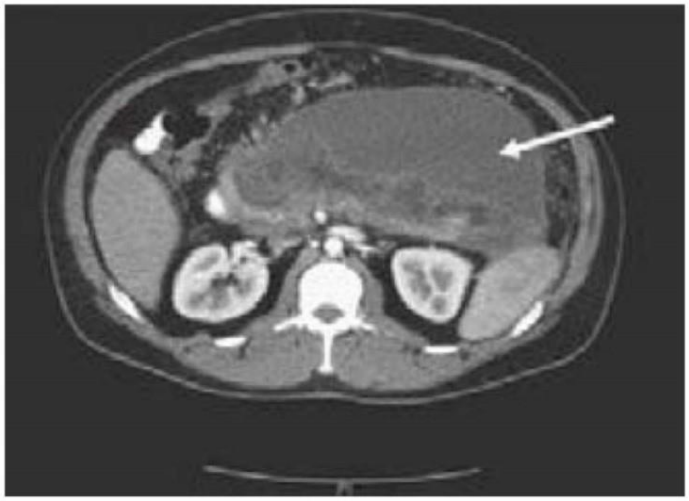
- Occurs only in the setting of acute necrotizing pancreatitis

- Heterogeneous and nonliquid density of varying degree in different locations

- No definable wall encapsulating the collection

-intrapancreatic and/or extra pancreatic

6. Walled-off necrosis (WON)



- Usually occurs >4 weeks after onset of necrotizing pancreatitis

- Heterogeneous with liquid and nonliquid density with varying degrees of loculation

- Well-defined wall; that is completely encapsulated

-intrapancreatic and/or extra pancreatic

The diagnosis is established by 2 of the following 3 criteria

(1) Typical abdominal pain in the epigastrium that may radiate to the back.

(2) Threefold or greater elevation in serum lipase and/or amylase

(3) Confirmatory findings of acute pancreatitis on cross-sectional abdominal imaging.

DIFFERENTIAL DIAGNOSIS

(1) Perforated viscus, especially peptic ulcer

(2) Acute cholecystitis and biliary colic

(3) Acute intestinal obstruction

(4) Mesenteric vascular occlusion

(5) Renal colic

(6) Inferior myocardial infarction

(7) Dissecting aortic aneurysm

(8) Connective tissue disorders with vasculitis

(9) Pneumonia

(10) Diabetic ketoacidosis

PHASES OF ACUTE PANCREATITIS

TWO PHASES

Early (<2 weeks)

- Lasts 1-2 weeks
- Severity is defined by clinica1 parameters rather than morphologic findings.
- predisposed to organ failure

Late (>2 weeks)

- protracted course of illness
- require imaging to evaluate for local complications
- Develops persistent organ failure.

Three organ systems should be assessed to define organ failure: ***respiratory, cardiovascular & renal***.

Organ failure

- Defined as a score of 2 or more for one of these three organ systems using the modified Marshall scoring system.

Persistent organ failure (>48 h)

- Most important clinical finding in regard to severity of the acute episode.

- **Multisystem organ failure** Organ failure that affects more than one organ is considered.

SEVERITY OF ACUTE PANCREATITIS

mild, moderate1y severe, and severe

MILD ACUTE PANCREATITIS

- Without local complications or organ failure.
- Mostly associated with interstitia1 acute pancreatitis
- the disease is self-limited and subsides spontaneously

MODERATELY SEVERE ACUTE PANCREATITIS

- Transient organ failure (resolves in <48 h) or local or systemic complications in the absence of persistent organ failure.
- These patients may or may not have necrosis
- may develop local complication such as a fluid collection that requires a prolonged hospitalization greater than 1 week

SEVERE ACUTE PANCREATITIS

- Characterized by persistent organ failure (>48 h).
- Organ failure can be single or multiple

Risk Factors for Severity

- Age >60 years
- Obesity
- BMI >30
- comorbid disease (Charlson comorbidity Index)

Markers of Severity at Admission or Within 24 hrs.

- SIRS defined by presence of 2 or more criteria
- Core temperature $<36^0$ or $>38^0$ C
- Heart rate >90 beats/mt
- Respirations >20/min or Pco2 <32 mmHg
- White blood cell count > 12000/micL or <4000/micL or 10% bands
- APACHE II
- Hemoconcentration (hematocrit >44%)
- Admission BUN (>22 mg/dL)
- BISAP 5core

  (B) BUN >25 mg/dL

  (I) impaired mental status

  (S) SIRS > 2 of 4 present

  (A) Age >60 years

  (P) Pleural effusion

- Organ failure (Modified Marshall 5core) Cardiovascular: systolic BP <90 mmHg, heart rate > 130 beats/min.

Pulmonary: Pao2 <60 mmHg

Renal: serum creatinine >2.0 mg%

Markers of Severity during Hospitalization

- Persistent organ failure
- Pancreatic necrosis

Complications of acute pancreatitis

Local

- Necrosis
- Sterile Infected Walled-off necrosis
- Pancreatic fluid collections
- Pancreatic pseudocyst
- Disruption of main pancreatic duct or secondary branches
- Pancreatic ascites
- Involvement of contiguous organs by necrotizing pancreatitis
- Thrombosis of blood vessels (splenic vein, portal vein)
- Pancreatic enteric fistula
- Bowel infarction
- Obstructive jaundice

Systemic

Pulmonary

- Pleural effusion
- Atelectasis
- Mediastinal fluid
- Pneumonitis
- Acute respiratory distress syndrome
- Hypoxemia (unrecognized)

Cardiovascular

- Hypotension
- Hypovolemia
- Nonspecific ST-T changes in electrocardiogram
- Pericardial effusion

Hematologic

- Disseminated intravascular coagulation

Gastrointestinal hemorrhage

- Peptic ulcer disease
- Erosive gastritis
- Hemorrhagic pancreatic necrosis with erosion into major blood vessels
- Portal vein & splenic vein thrombosis,

- variceal hemorrhage

Renal

- Oliguria (<300 ml/d)
- Azotemia
- Renal artery / renal vein thrombosis
- Acute tubular necrosis

Metabolic

- Hyperglycemia
- Hypertriglyceridemia
- Hypocalcemia
- Encephalopathy
- Sudden blindness (Purtscher's retinopathy)

Central nervous system

- Psychosis
- Fat emboli

Fat necrosis

- Subcutaneous tissues (erythematous nodules)
- Bone
- Miscellaneous (mediastinum,pleura,nervous system) **MANAGEMENT OF ACUTE PANCREATITIS**

- Usually acute pancreatitis are self-limited in 85 -90% subside within 3-7 days after starting treatment.
- 4 important factors that determine the recoveries are

  Aggressive fluid resuscitation

  Intravenous analgesics

  Severity assessment

  Search for etiologies
- If complications occur hemodynamic monitoring and management of necrosis or organ failure are important.

Fluid Resuscitation

- Safe & aggressive intravenous fluid resuscitation is the most crucial step in intervention of acute pancreatitis.
- For giving rest to the pancreas, patient is made NPO.
- To control abdominal pain, give intravenous narcotic analgesics & supplemental O_2 (2 L) via nasal cannula.
- Intravenous fluids of Ringer's lactate or normal saline are given. Initially bolus of 15-20 ml/kg (1050-1400 ml) followed by 3 mg/kg per hour (200-250 mL/ hr.) to maintain urine output >0.5 ml/kg per hour.
- Every 6-8 hrs. Serial bedside monitoring of vital signs, oxygen saturation & change in physical examination is mandatory.

- RL is better crystalloid than normal saline because it decreases systemic inflammation.
- Higher in-hospital mortality is associated with rising BUN during hospitalization. So “targeted resuscitation strategy” with measurement of hematocrit & BUN every 8-12 h is recommended for ensure adequacy of fluid resuscitation and monitor response to therapy.
- First 12-24 h, decrease in hematocrit & BUN is strong evidence for sufficient volume replacement.
- Adjustments in volume replacement may be required in patients with cardiac, pulmonary or renal disease.
- Increase in hematocrit or BUN during monitoring should be treated with a repeat volume challenge with bolus of 2-L crystalloid followed by 1.5 ml / kg per hour of fluids.

Special Considerations Based on Etiology

In GALLSTONE PANCREATITIS, Patients are increased risk of recurrence. If patients with evidence of ascending cholangitis within 24-48 h of admission they must undergo ERCP.so performing a cholecystectomy or endoscopic biliary sphincterotomy during the same admission or within 4-6 weeks of discharge is advisable.

In HYPERTRIGLYCERIDEMIA (Serum triglycerides > 1 000 mg/ dL) initial therapy may include insulin, heparin, or plasmapheresis, lipid-lowering agents, weight loss, avoidance of drugs that elevate lipid levels.

Other potential causes that may impact outcomes are

- Hypercalcemia (treatment of hyperparathyroidism or malignancy)
- Autoimmune pancreatitis (responsive to glucocorticoid administration)
- Post-ERCP pancreatitis (Pancreatic duct stenting and rectal indomethacin administration are effective)
- Drug-induced pancreatitis (Drugs should be discontinued)

Nutritional Therapy

In Mild acute pancreatitis, a low-fat solid diet can be given if abdominal pain subside.

In case of more severe pancreatitis, enteral nutrition should be considered 23 days after admission this maintains gut barrier integrity, limits bacterial translocation, less expensive & fewer com plications than TPN.

Management of Local Complications

If Patients shows signs of clinical deterioration even after aggressive fluid resuscitation & hemodynamic monitoring, they should be assessed for local complications.

“A multidisciplinary team approach” is recommended including gastroenterology, surgery, interventional radiology, and intensive care specialists, and consideration should also be made for transfer to a pancreas center.

Necrosis

“Percutaneous aspiration of necrosis with Gram stain and culture” must be performed if patient present with sustained leukocytosis, fever or organ failure.

Currently “no role for prophylactic antibiotics in necrotizing pancreatitis” If patient appears toxic, while awaiting the results of Gram stain and cultures, start broad-spectrum antibiotics then cultures are negative discontinue antibiotics minimize the risk of developing opportunistic or fungal superinfection.

If presence of persistent fever, repeated FNAC and Gram stain with culture of pancreatic necrosis should be done in every 5-7 days.

If presence of complications, repeated CT or MRI imaging should also be considered.

In general sterile necrosis is most often managed conservatively unless complications arise. If infected necrosis is present & an organism identified

targeted antibiotics should be instituted. Definitive management of infected necrosis is necrosectomy.

PSEUDOCYST

Incidence is low & collections resolves1 in most acute cases.

After 6 weeks, less than 10% of patients have persistent fluid collections. "Only symptomatic collections should be drained with surgery or endoscopy or by percutaneous route."

PANCREATlC DUCT DISRUPTION

In the setting of an enlarging fluid collection, pancreatic duct disruption may present with symptoms of dyspnea & increasing abdominal pain.

Diagnosis can be confirmed on MRCP or ERCP.

"Placement of a bridging pancreatic stent" for at least 6 weeks is >90% effective at resolving the leak. Nonbridging stents are less effective.

PERIVASCULAR COMPLICATlONS

- Splenic vein thrombosis with gastric varices
- Pseudo aneurysms.

Gastric varices bleed less than 5%.

Life-threatening bleeding can occur it must be diagnosed and treated with "mesenteric angiography and embolization"

EXTRAPANCREATIC INFECTIONS

Incidence of Hospital acquired infections are up to 2 to 20%.

Mostly as pneumonia, urinary tract infection and line infection.

Routine urine culture, monitoring of chest x-rays & routine changing of intravenous lines are important during hospitalization.

Follow-Up Care

For assessment of

- Development of diabetes
- Exocrine insufficiency
- Recurrent cholangitis
- Development of infected fluid collections.

PROGNOSIS

- Mortality rates for acute pancreatitis have declined from at least 10% to around 5% since the 1980s, but the mortality rate for severe acute pancreatitis remains at least 20%, with rates of 10% and 25% in those with sterile and infected necrosis, respectively.

- Severe acute pancreatitis is predicted by features of the systemic inflammatory response on admission.

- Half of the deaths occur within the first 2 weeks, usually from multiorgan failure.
- Multiorgan failure is associated with a mortality rate of at least 30%, and if it persists beyond the first 48 hours, the mortality rate is over 50%.
- Later deaths occur because of complications of infected necrosis.
- The risk of death doubles when both organ failure and infected necrosis are present.
- Moreover, hospital acquired infections increase the mortality of acute pancreatitis, independent of severity.

Readmission to the hospital for acute pancreatitis within 30 days may be predicted by a scoring system based on five factors during the index admission:

- Eating less than a solid diet at discharge
- Nausea, vomiting, or diarrhea at discharge;
- Pancreatic necrosis;
- Use of antibiotics at discharge;
- Pain at discharge.

- Recurrences are common in alcoholic pancreatitis but can be reduced by repeated, regularly scheduled interventions to eliminate alcohol consumption after discharge from the hospital.
- The risk of chronic pancreatitis following an episode of acute alcoholic pancreatitis is 13% in 10 years and 16% in 20 years.

CHRONIC PANCREATITIS

Chronic pancreatitis occurs most often in patients with alcoholism (45–80% of all cases). The risk of chronic pancreatitis increases with the duration and amount of alcohol consumed, but pancreatitis develops in only 5–10% of heavy drinkers.

Tobacco smoking is a risk factor for idiopathic chronic pancreatitis and has been reported to accelerate progression of **alcoholic** chronic pancreatitis. About 2% of patients with **hyperparathyroidism** develop pancreatitis. In tropical Africa and Asia, **tropical pancreatitis**, related in part to malnutrition, is the most common cause of chronic pancreatitis. A **stricture, stone, or tumor** obstructing the pancreas can lead to obstructive chronic pancreatitis.

Autoimmune pancreatitis is associated with hyper gamma globulinemia (IgG4 in particular) and often with autoantibodies and other autoimmune diseases and is responsive to corticosteroids.

Type 1 autoimmune pancreatitis is a multisystem disease characterized by lymphoplasmacytic sclerosing pancreatitis on biopsy, associated bile duct strictures, retroperitoneal fibrosis, renal and salivary gland lesions, and a high rate of relapse after treatment.

Type 2 affects the pancreas alone and is characterized by idiopathic duct centric pancreatitis on biopsy, lack of systemic IgG4 involvement, an association with inflammatory bowel disease, and a lower rate of relapse after treatment. Between 10% and 30% of cases of chronic pancreatitis are idiopathic, with either early onset (median age 23) or late onset
(median age 62).

Genetic factors may predispose to chronic pancreatitis in some of these cases and include mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the pancreatic secretory trypsin inhibitory gene (PSTI, serine protease inhibitor, SPINK1), and possibly the gene for uridine 5′-diphosphate glucuronosyltransferase. Mutation of the cationic trypsinogen gene on chromosome 7 (serine protease 1, PRSS1) is associated with hereditary pancreatitis, transmitted as an autosomal dominant trait with variable penetrance. A useful mnemonic for the predisposing factors to chronic pancreatitis is TIGAR-O: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive. The

pathogenesis of chronic pancreatitis may be explained by the SAPE (sentinel acute pancreatitis event) hypothesis by which the first (sentinel) acute pancreatitis event initiates an inflammatory process that results in injury and later fibrosis ("necrosis-fibrosis"). In many cases, chronic pancreatitis is a self-perpetuating disease characterized by chronic pain or recurrent episodes of acute pancreatitis and ultimately by pancreatic exocrine or endocrine insufficiency (sooner in alcoholic pancreatitis than in other types). After many years, chronic pain may resolve spontaneously or as a result of surgery tailored to the cause of pain. Over 80% of adults develop diabetes mellitus within 25 years after the clinical onset of chronic pancreatitis.

CLINICAL FINDINGS

SYMPTOMS AND SIGNS

- Persistent or recurrent episodes of epigastric and left upper quadrant pain with referral to the upper left lumbar region

  Are typical.
- The pain results in part from impaired inhibitory pain modulation by the central nervous system.
- Anorexia, nausea, vomiting, constipation, flatulence, and weight loss are common.

During attacks tenderness over the pancreas, mild muscle guarding, and ileus may be noted. Attacks may last only a few hours or as long as 2 weeks; pain may eventually be almost continuous. Steatorrhea (as indicated by bulky, foul, fatty stools) may occur late in the course.

LABORATORY FINDINGS

- Serum amylase and lipase may be elevated during acute attacks; however, normal values do not exclude the diagnosis.
- *Serum alkaline phosphatase and bilirubin* may be elevated owing to compression of the bile duct.
- *Glycosuria* may be present.
- *Excess fecal fat* may be demonstrated on chemical analysis of the stool. - Pancreatic insufficiency generally is confirmed by response to therapy with pancreatic enzyme supplements; **the secretin stimulation test** can be used if available, as can detection of **decreased fecal chymotrypsin or elastase levels**, although the latter tests lack sensitivity and specificity.
- *Vitamin B12 malabsorption* is detectable in about 40% of patients, but clinical deficiency of vitamin B12 and fat-soluble vitamins is rare.

Accurate diagnostic tests are available for the major trypsinogen gene mutations, but because of uncertainty about the mechanisms linking

heterozygous CFTR and PSTI mutations with pancreatitis, genetic testing for mutations in these two genes is not currently recommended.

Elevated IgG4 levels, ANA, and antibodies to lactoferrin and carbonic anhydrase II are often found in patients with autoimmune pancreatitis (especially type 1).

Antibodies *to peptide A1P1-7 and to ubiquitin-protein ligase E3 component n-recognin 2* have been reported in a high percentage of patients with autoimmune pancreatitis but also in some patients with pancreatic cancer.

Pancreatic biopsy, if necessary, shows a lymphoplasmacytic inflammatory infiltrate with characteristic IgG4 immunostaining, which is also found in biopsy specimens of the major papilla, bile duct, and salivary glands, in type 1 autoimmune pancreatitis.

IMAGING

- **Plain films** show calcifications due to pancreaticolithiasis in 30% of affected patients.
- **CT** may show calcifications not seen on plain films as well as ductal dilatation and heterogeneity or atrophy of the gland. Occasionally, the findings raise suspicion of pancreatic cancer ("tumefactive chronic pancreatitis").

- **ERCP** is the most sensitive imaging study for chronic pancreatitis and may show dilated ducts, intraductal stones, strictures, or pseudocyst, but the results may be normal in patients with so-called minimal change pancreatitis.
- **MRCP** (including secretin-enhanced MRCP) and endoscopic ultrasonography (with pancreatic tissue sampling) are less invasive alternatives to ERCP.
- **Endoscopic ultra-sonographic ("Rosemont") criteria** for the diagnosis of chronic pancreatitis include hyperechoic foci with shadowing indicative of calculi in the main pancreatic duct and lobularity with honeycombing of the pancreatic parenchyma.

Characteristic imaging features of autoimmune pancreatitis include diffuse enlargement of the pancreas, a peripheral rim of hypo attenuation, and irregular narrowing of the main pancreatic duct.

COMPLICATIONS

- Opioid addiction is common.
- Other frequent complications include often
- Brittle diabetes mellitus,
- Pancreatic pseudocyst or abscess,
- cholestatic liver enzymes with or without jaundice,
- Bile duct stricture,

- Steatorrhea
- Malnutrition
- Peptic ulcer.
- Pancreatic cancer develops in 4% of patients after 20 years; the risk may relate to tobacco and alcohol use. In patients with hereditary pancreatitis, the risk of pancreatic cancer rises after age 50 years and reaches 19% by age 70 years

TREATMENT

- Correctable coexistent biliary tract disease should be treated surgically.

MEDICAL MEASURES

- A low-fat diet should be prescribed.
- Alcohol is forbidden because it frequently precipitates attacks. Opioids should be avoided if possible.
- Preferred agents for pain are acetaminophen, nonsteroidal antiinflammatory drugs, and tramadol, along with pain-modifying agents such as tricyclic antidepressants, selective serotonin uptake inhibitors, and gabapentin or pregabalin.
- Steatorrhea is treated with pancreatic supplements that are selected on the basis of their high lipase activity. A total dose of 40,000 units of lipase in capsules is given with meals. Higher doses may be required in some

cases. The tablets should be taken at the start of, during, and at the end of a meal.

- Concurrent administration of a H2-receptor antagonist (eg, ranitidine, 150 mg orally twice daily), a proton pump inhibitor (eg, omeprazole, 20–60 mg orally daily), or sodium bicarbonate, 650 mg orally before and after meals, decreases the inactivation of lipase by acid and may thereby further decrease steatorrhea. In selected cases of alcoholic pancreatitis and in cystic fibrosis, enteric-coated microencapsulated preparations may offer an advantage.
- However, in patients with cystic fibrosis, high-dose pancreatic enzyme therapy has been associated with strictures of the ascending colon.
- Pain secondary to idiopathic chronic pancreatitis may be alleviated in some cases by the use of pancreatic enzymes (not enteric-coated) or octreotide, 200 mcg subcutaneously three times daily.
- Micronutrient therapy to correct electrophilic stress on key macromolecules in the pancreas by toxic metabolites has shown promise in early studies.
- Associated diabetes mellitus should be treated
- Autoimmune pancreatitis is treated with prednisone 40 mg/d orally for 1–2 months, followed by a taper of 5 mg every 2–4 weeks.

- Nonresponse or relapse occurs in 45% of cases (particularly in those with concomitant IgG4-associated cholangitis); azathioprine appears to reduce the risk of relapse.
- Other immunosuppressive therapies are under study.

SURGICAL AND ENDOSCOPIC TREATMENT

Endoscopic therapy or surgery may be indicated in chronic pancreatitis to treat underlying biliary tract disease, ensure free flow of bile into the duodenum, drain persistent pseudocysts, treat other complications, eliminate obstruction of the pancreatic duct, and attempt to relieve pain, or exclude pancreatic cancer. Liver fibrosis may regress after biliary drainage. Distal bile duct obstruction may be relieved by endoscopic placement of multiple bile duct stents. When obstruction of the duodenal end of the pancreatic duct can be demonstrated by ERCP, dilation of or placement of a stent in the duct and pancreatic duct stone lithotripsy or resection of the tail of the pancreas with implantation of the distal end of the duct by pancreaticojejunostomy may be performed. Many patients treated endoscopically eventually require surgery. When the pancreatic duct is diffusely dilated, anastomosis between the duct after it is split longitudinally and a defunctionalized limb of jejunum (modified Puestow procedure), in some cases combined with resection of the

head of the pancreas (Beger or Frey procedure), is associated with relief of pain in 80% of cases.

In advanced cases, subtotal or total pancreatectomy may be considered as a last resort but has variable efficacy and causes pancreatic insufficiency and diabetes mellitus. Perioperative administration of somatostatin or octreotide may reduce the risk of postoperative pancreatic fistulas. Endoscopic or surgical (including laparoscopic) drainage is indicated for symptomatic pseudocysts and, in many cases, those over 6 cm in diameter. Endoscopic ultrasonography may facilitate selection of an optimal site for endoscopic drainage. Pancreatic ascites or pancreaticopleural fistulas due to a disrupted pancreatic duct can be managed by endoscopic placement of a stent across the disrupted duct. Pancreatic sphincterotomy or fragmentation of stones in the pancreatic duct by lithotripsy and endoscopic removal of stones from the duct may relieve pain in selected patients. For patients with chronic pain and nondilated ducts, a percutaneous celiac plexus nerve block may be considered under either CT or endoscopic ultrasound guidance, with pain relief (albeit often short-lived) in approximately 50% of patients. A single session of radiotherapy to the pancreas has been reported to relieve Chronic pancreatitis often leads to disability. The prognosis is best in patients with recurrent acute pancreatitis caused by a remediable condition, such as cholelithiasis,

choledocholithiasis, stenosis of the sphincter of Oddi, or hyperparathyroidism, and in those with autoimmune pancreatitis. Medical management of hyperlipidemia, if present, may also prevent recurrent attacks of pancreatitis. In alcoholic pancreatitis, pain relief is most likely when a dilated pancreatic duct can be decompressed. In patients with disease not amenable to decompressive surgery, addiction to opioids is a frequent outcome of treatment. The quality of life is poorer in patients with constant pain than in those with intermittent pain.

REDCELL DISTRIBUTION WIDTH (RDW)

- RDW measures variation in RBC size or volume.
- It is elevated along with variation in red cell size (anisocytosis), i.e. when elevated RDW is reported on complete blood count, with on peripheral blood smear there is marked anisocytosis (increased variation in red cell size) is expected.

Normal reference range (vary depending on the individual laboratory and patient's age)

- RDW-SD 39-46 fL
- RDW-CV 11.6-14.6%

Depending on the types of hematology analyzer RDW can be statistically reported as coefficient of variation (RDW-CV) and/or standard deviation (RDW-SD).

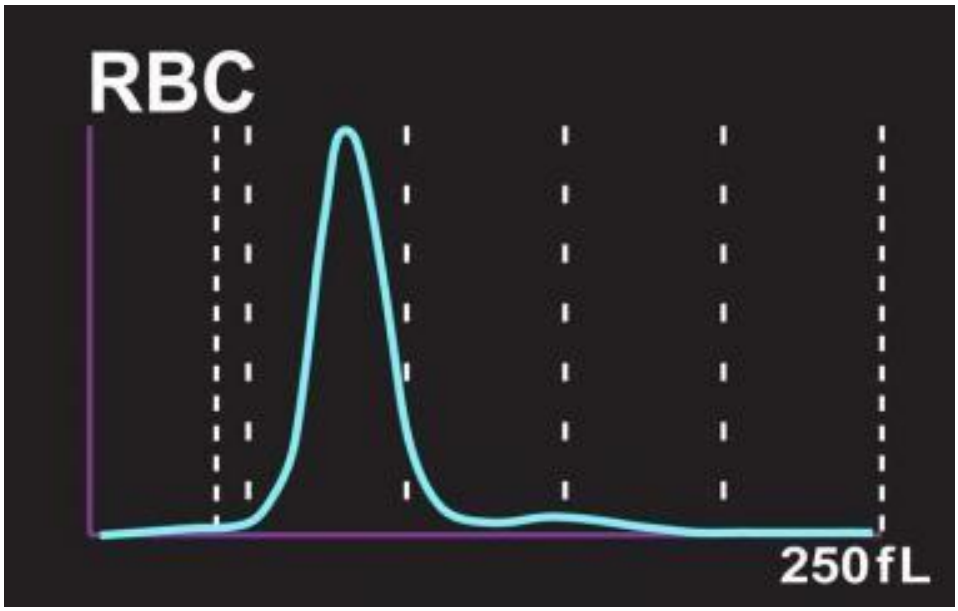
RDW-SD

- Expressed as fL
- It is an actual measurement of the width of the RBC size distribution histogram & measured by calculating the width (in fL) at the 20% height level of the RBC size distribution histogram
- This parameter is therefore not influenced by the average RBC size (mean corpuscular volume, MCV).

RDW-CV

- express in %
- It is calculated from standard deviation and MCV

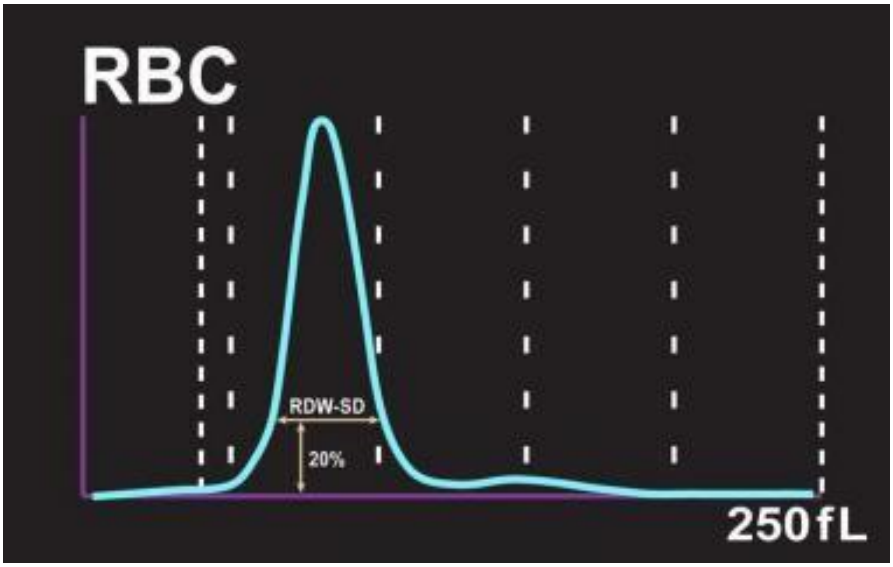
RDW-CV (%) = 1 standard deviation of RBC volume/MCV x 100% So it is mathematically derived from MCV, affected by the average RBC size (MCV).



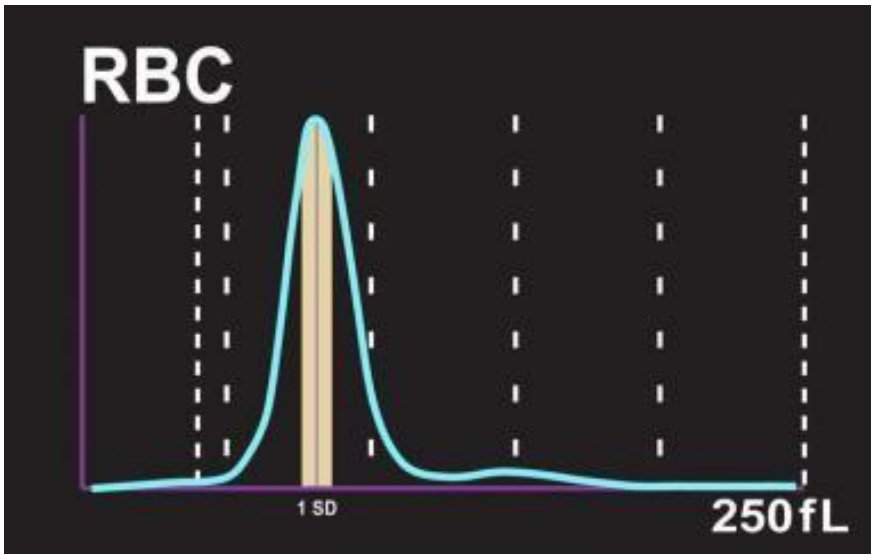
Sysmex SE-2100 analyzer- RBC size distribution histogram Here MCV of 81.4 fL, RDW-SD of 38.2 fL, & RDW-CV of 12.8%.

Determination of RDW-SD measurement.

Here, RDW-SD is 38.2 fL



Determination of RDW-SD measurement. In this example, RDW-SD is 38.2 fL



Calculation of RDW-CV measurement, which is derived from 1SD divided by MCV times 100%. In this example, RDW-CV is 12.8%.

RDW useful in

- Early nutritional deficiency (iron, folate, or vitamin B12 deficiency)

  Here RDW elevated earlier than other red blood cell parameters.

- Useful in differentiate uncomplicated iron deficiency anemia

  (Elevated RDW, normal to low MCV) & uncomplicated heterozygous thalassemia (normal RDW, low MCV)

- Useful in differentiate megaloblastic anemia (folate or vitamin B12 deficiency anemia -elevated RDW) & from other causes of macrocytosis (often normal RDW).

- Elevated RDW indicate red cell fragmentation, agglutination, or dimorphic red blood cell populations.

RDW & mean corpuscular volume (MCV)

- Both useful in narrowing the cause of anemia

Normal RDW and low MCV

- Anemia of chronic disease
- Heterozygous thalassemia
- Hemoglobin E trait

Elevated RDW and low MCV

- Iron deficiency
- Sickle cell-β-thalassemia

Normal RDW and high MCV

- Aplastic anemia
- Chronic liver disease
- Chemotherapy/antivirals/alcohol

Elevated RDW and high MCV

- Folate or vitamin B12 deficiency
- Immune hemolytic anemia
- Cytotoxic chemotherapy
- Chronic liver disease
- Myelodysplastic syndrome

Normal RDW and normal MCV

- Anemia of chronic disease
- Acute blood loss or hemolysis
- Anemia of renal disease

Elevated RDW and normal MCV

- Early iron, vitamin B12, or folate deficiency
- Dimorphic anemia (for example, iron and folate deficiency)
- Sickle cell disease
- Chronic liver disease
- Myelodysplastic syndrome

Role of RDW in acute pancreatitis

- RDW is an inflammatory marker & it is positively correlated with inflammation.
- Inflammation impairs the bone marrow function, iron metabolism and erythrocyte homeostasis. Increased inflammatory cytokines (such as tumor necrosis factor α, interleukin-1 and interleukin-6) due to sepsis in acute pancreatitis, leads to suppress maturation of erythrocytes leading to entry of immature erythrocytes in to the circulation causing elevation in RDW.
- Inflammatory markers such as CRP, pro-calcitonin and tumor necrosis factor (TNF) have been used as a prognostic marker in acute

pancreatitis.

Neutrophil lymphocyte ratio (NLR)

- It indicates the balance of neutrophils and lymphocytes in the body & it is a sign of systemic inflammation.
- WBC as an indicator of infection and inflammation & it is part of the acute pancreatitis prognostic scoring systems (such as APACHE II, Ranson, Imrie, and the Simplified Acute Physiology Score).
- Neutrophils and lymphocytes are significant constituents of WBC.
- Neutrophil to lymphocyte ratio (NLR) is used as a marker of subclinical inflammation.
- It is calculated by dividing the number of neutrophils by number of lymphocytes, usually from peripheral blood sample, but sometimes also from cells that infiltrate tissue, such as tumor.
- NLR can simply be determined from the routine work-up of patients with AP, additional cost is not necessary.
- NLR is better than total WBC in predicting adverse outcomes in acute pancreatitis.

MATERIALS AND METHODS

STUDY POPULATION:

This study is to be conducted among 30 patients with acute pancreatitis attending the Department of Medicine & Department of Medical gastroenterology, Govt. Rajaji Hospital, Madurai.

Inclusion criteria:

- Patients with features of acute pancreatitis
- Age > 12 years
- patients with recurrent pancreatitis (only on first admission)

Exclusion criteria

- Age less than 12 years
- Traumatic / Autoimmune pancreatitis
- Diabetes mellitus
- Tumor or liver failure

ANTICIPATED OUTCOME

The RDW & NLR can simply be determined from an element of the routine work-up of patients with AP and therefore accumulates no additional cost, and appears to correlate with outcome. Continuous RDW & NLR

monitoring on each day of admission provides a dynamic reflection of the variable course of AP, with optimal NLRs varying with changes in patient status.

Aim of this study is to optimize the RDW & NLR and investigate if incorporation in to current AP prognostic scoring systems increases the accuracy of current methods.

DATA COLLECTION:

- A Brief history with detailed clinical examination

LABORATORY INVESTIGATIONS:

- White cell count (WBC), RBC count, RDW, platelet count, hemoglobin level, MCV and mean platelet volume (MPV)
- Serum Amylase, creatinine , total protein, albumin, total calcium, total bilirubin, glucose, lactate dehydrogenase , aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities levels.
- ULTRASOUND & CT ABDOMEN

STUDY PROTOCOL:

- A diagnosis of Acute Pancreatitis required two of three features:

(1) Prolonged abdominal pain characteristic of AP

(2) Threefold elevation of serum amylase and/or lipase levels above the normal range

(3) Characteristic findings of AP on abdominal ultrasonography and/or CT scan.

- Mild AP (MAP) is defined as an absence of organ failure and an absence of local or systemic complications.
- Moderately SAP (MSAP) is defined as no evidence of persistent organ failure, but the presence of local or systemic complications and/or organ failure that resolved within 48 hours.
- SAP is defined as persistent organ failure (>48 hours).
- The Red cell distribution width (RDW) & white cell differential count to be analyzed and the NLR determined by calculating the ratio between the absolute neutrophil and lymphocyte counts on days 0, 1, and 2, and correlated with severity
- Sensitivity, specificity, Positive predictive value, negative predictive value, diagnostic accuracy of both tests are calculated.

DESIGN OF STUDY:

Prospective analytical study

PERIOD OF STUDY:

April 2017 TO August 2017

COLLABORATING DEPARTMENTS:

Department of Medicine, Department of Medical gastroenterology, Biochemistry, Radiology

CONSENT*:* Individual written and informed consent.

ANALYSIS*:* Statistical analysis

CONFLICT OF INTEREST*:* Nil

FINANCIAL SUPPORT*:* Nil

PARTICIPANTS*:* patients with acute pancreatitis attending the Department of Medicine & Department of Medical gastroenterology, Govt. Rajaji Hospital, Madurai.

Method of study

This study was conducted in Govt. Rajaji Hospital, Madurai which is affiliated to Madurai Medical College. This study subjects were selected from the patients admitted in Department of Medicine and Department of medical gastroenterology, Govt. Rajaji Hospital Madurai.

The study was conducted in 30 patients; the patients had acute pancreatitis diagnosed by clinical background and further evaluated and confirmed with biochemical and radiological investigations.

The patients are examined clinically with the following parameters and only 30 patients are taken for study.

Clinical criteria to diagnose acute pancreatitis

1. Patient diagnosed as a case of Acute Pancreatitis by two of following three features:
2. Prolonged abdominal pain characteristic of Acute Pancreatitis
3. Threefold elevation of serum amylase and/or lipase levels above the normal range
4. Characteristic findings of AP on abdominal ultrasonography and/or CT scan.

Study protocol

Patients with clinical, biochemical and radiological evidence of acute pancreatitis that fulfilling above criteria are included in this study.

In all the patients following investigation are done for further evaluation and monitoring of clinical course.

INVESTIGATIONS DONE

White cell count (WBC), RBC count, RDW, platelet count, haemoglobin level, MCV and mean platelet volume (MPV).

Serum Amylase, creatinine, total protein, albumin, total calcium, total bilirubin, glucose, lactate dehydrogenase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities levels Ultrasound and / or CT abdomen

- The Red cell distribution width (RDW) & white cell differential count analysed and the NLR determined by calculate the ratio between the absolute neutrophil and lymphocyte counts on days 0, 1, and 2, and this correlated with clinical severity.

After 48 hours patient classified as mild / severe acute pancreatitis by based on clinical, biochemical & radiological criteria.

Mild Acute Pancreatitis is defined as an absence of organ failure and an absence of local or systemic complications.

Severe Acute Pancreatitis is defined as persistent organ failure, (presence of local or systemic complications and/or organ failure) that persist after 48 hours.

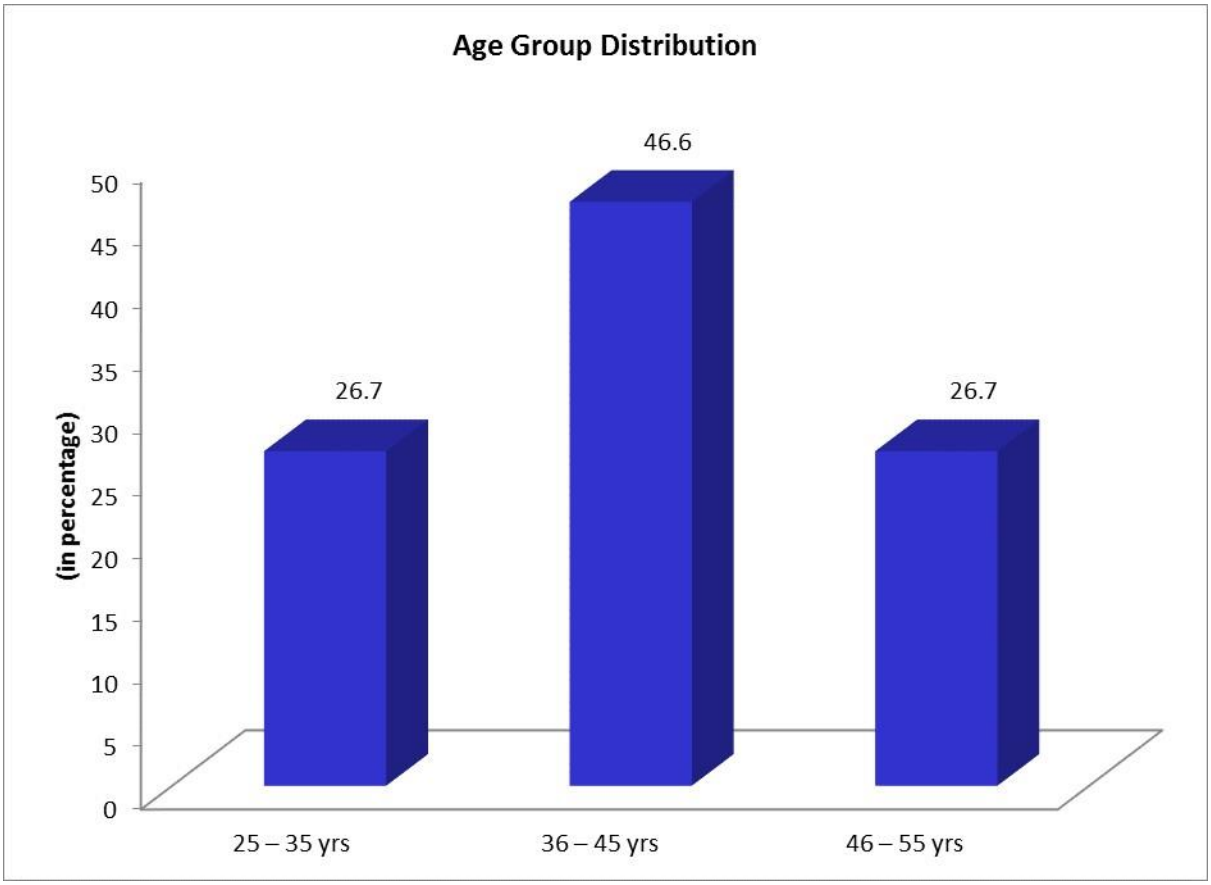
The Red cell distribution width (RDW) & NLR on days 0, 1, and 2, are correlated with clinical severity.

- Sensitivity, specificity, Positive predictive value, negative predictive value, diagnostic accuracy of both tests are calculated

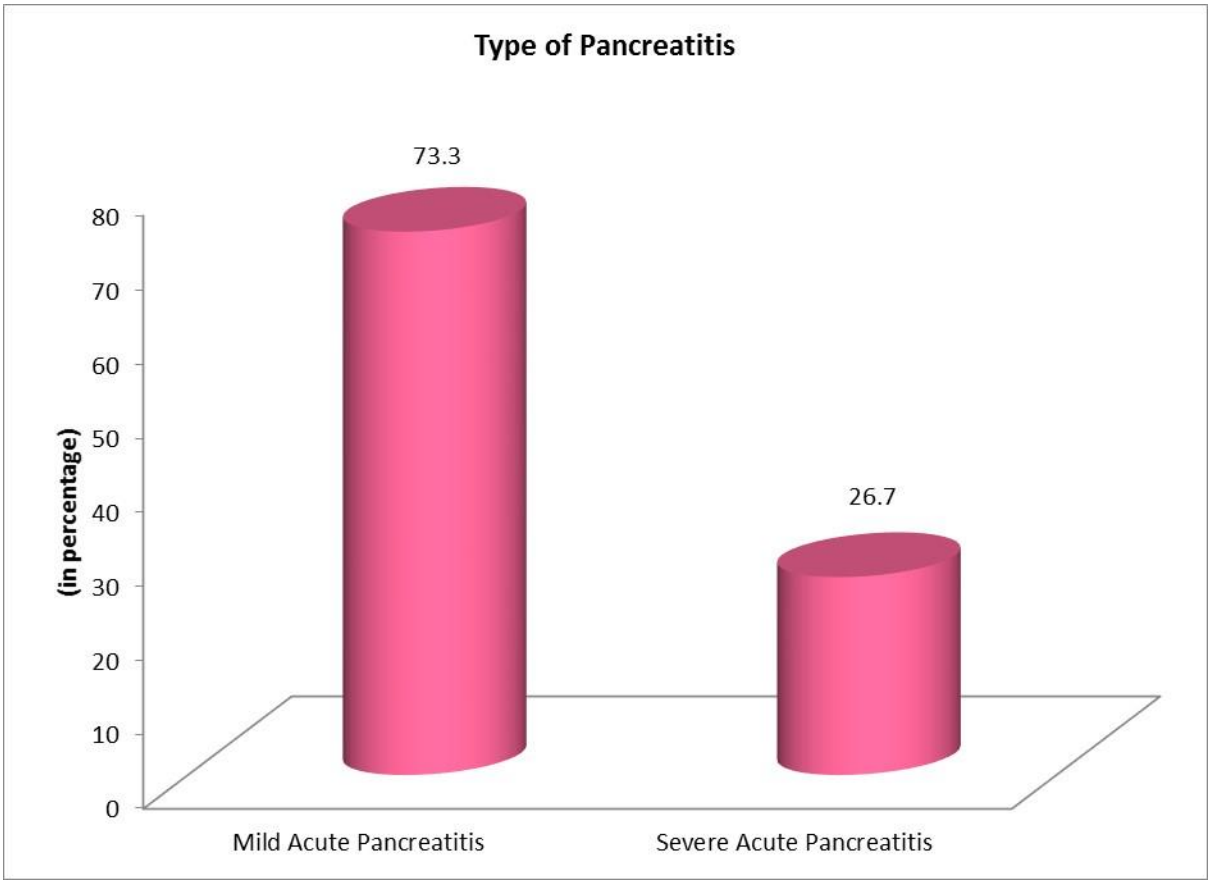
RESULTS AND INTERPRETATION

Age (in yrs)	
N	30
Mean	39.9
SD	7.0
Minimum	25
Maximum	50

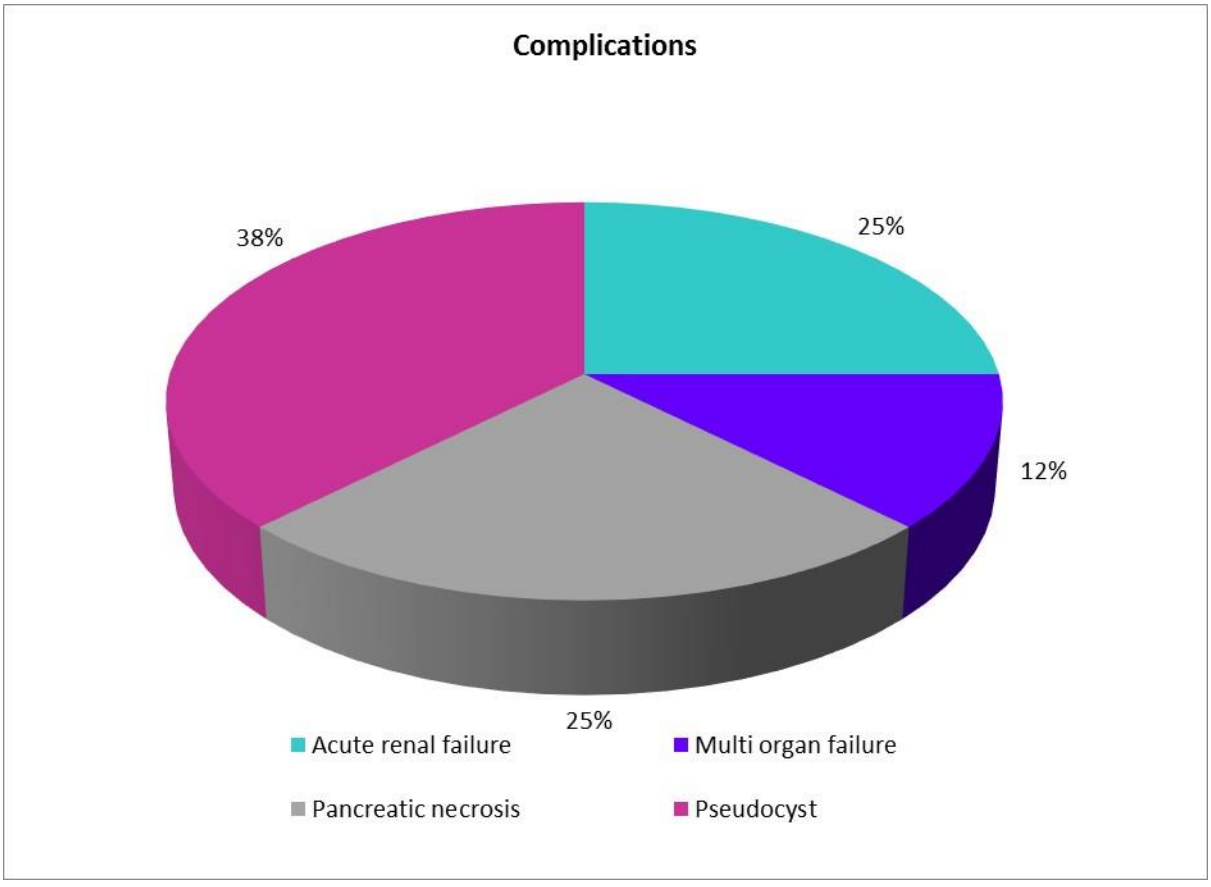
Age group (in yrs)	n (%)
25 – 35	8 (26.7)
36 – 45	14 (46.6)
46 – 55	8 (26.7)
Total	30 (100.0)



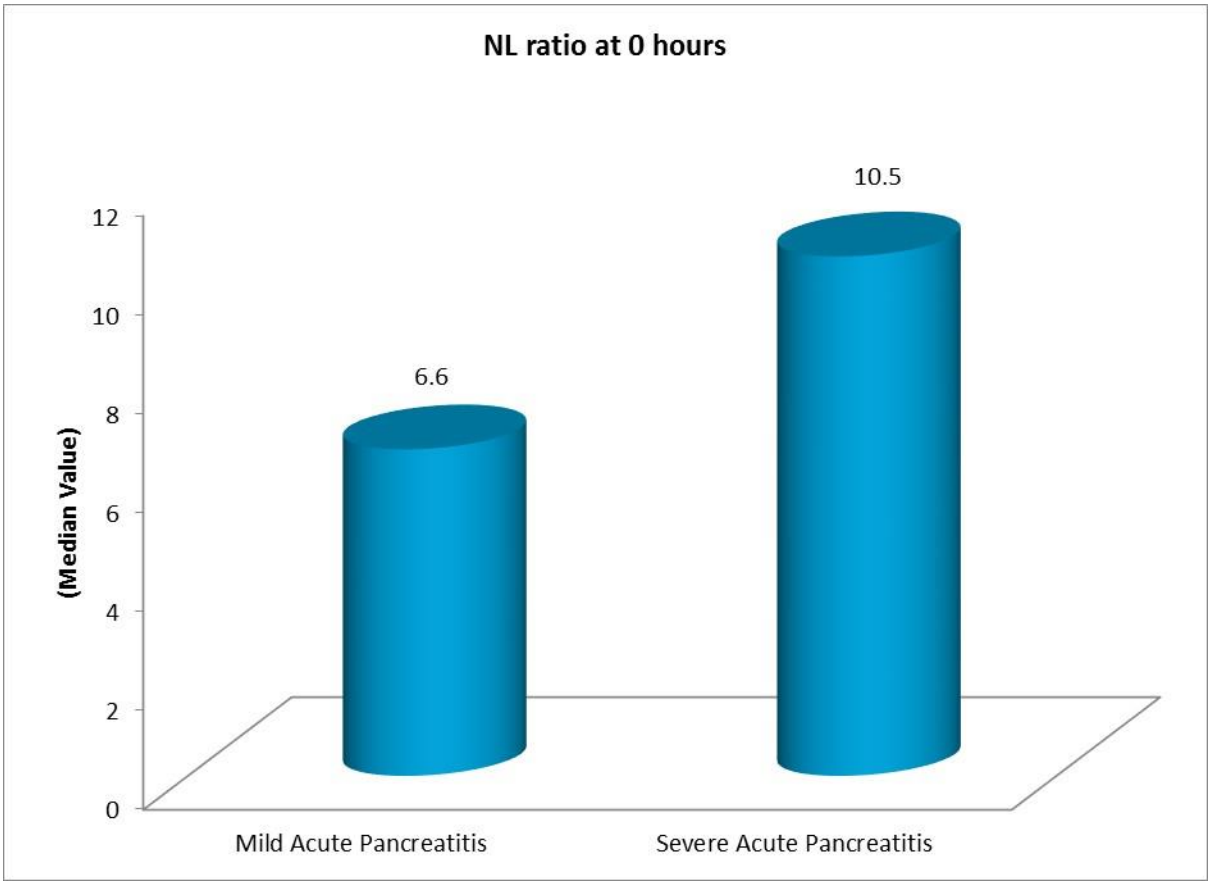
Type of Pancreatitis	n (%)
Mild Acute Pancreatitis	22 (73.3)
Severe Acute Pancreatitis	8 (26.7)
Total	30 (100.0)



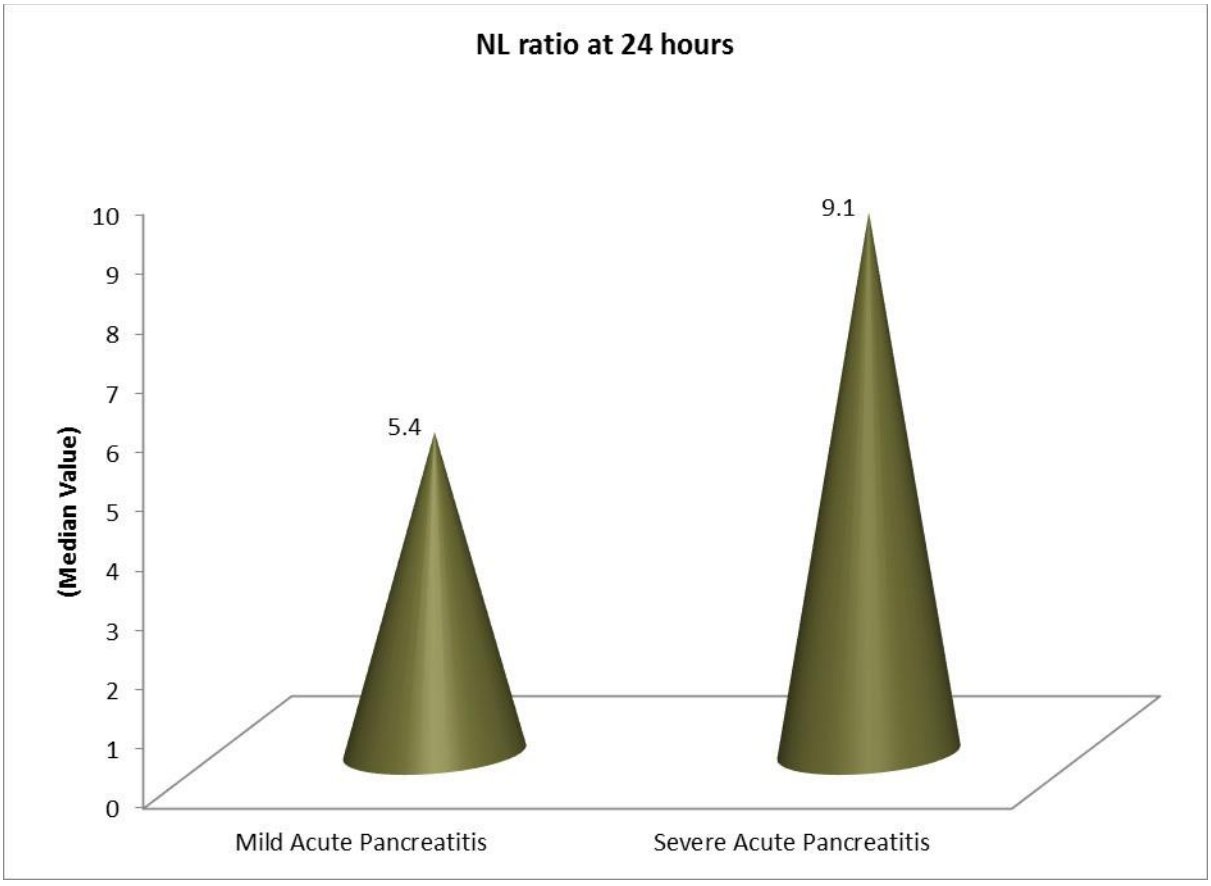
Complications	n (%)
Acute renal failure	2 (25.0)
Multi organ failure	1 (12.5)
Pancreatic necrosis	2 (25.0)
Pseudocyst	3 (37.5)
Total	8 (100.0)



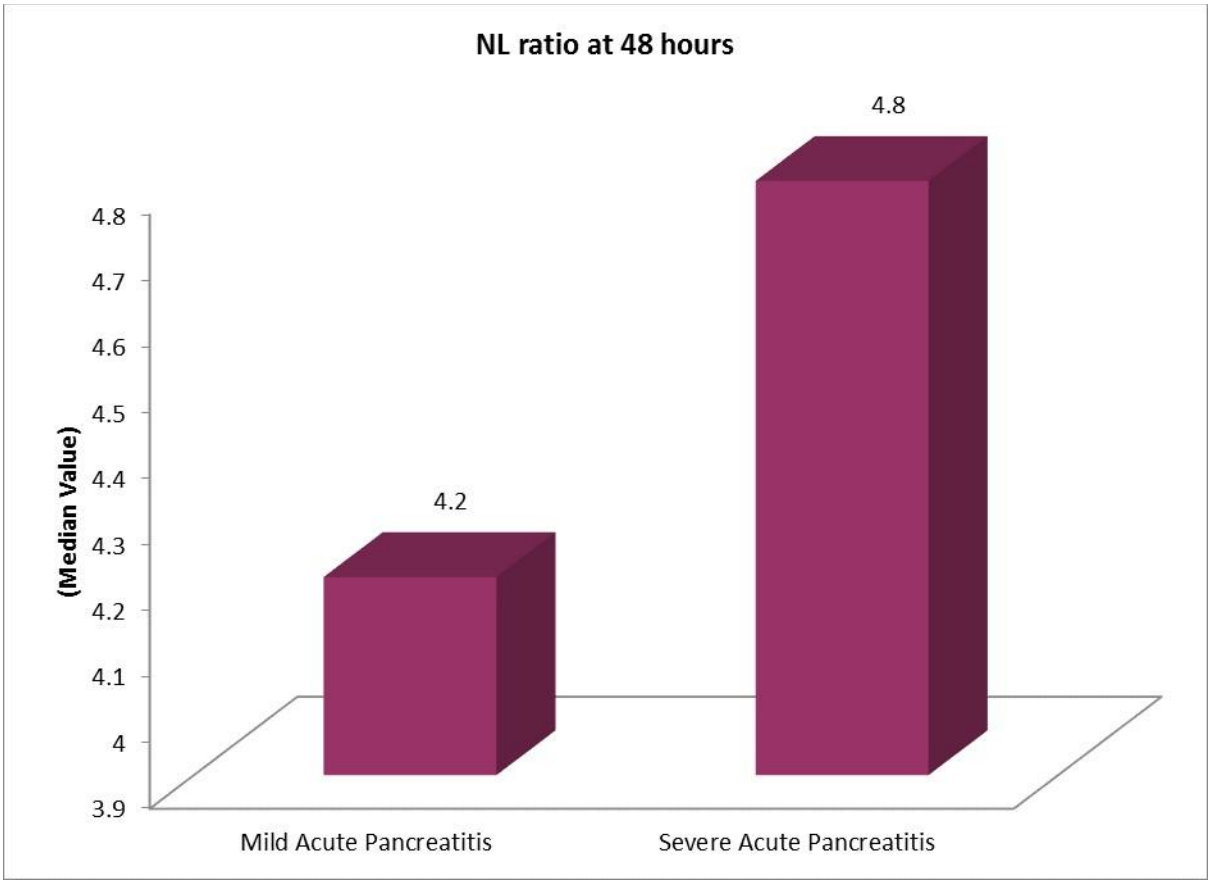
	Type of Pancreatitis	
	Mild Acute Pancreatitis (n=22)	Severe Acute Pancreatitis (n=8)
	Median (IQR)	Median (IQR)
NL ratio at 0 hours	6.6 (5.0, 7.5)	10.5 (9.9, 11.0)
p-value	<0.001 (Significant)	



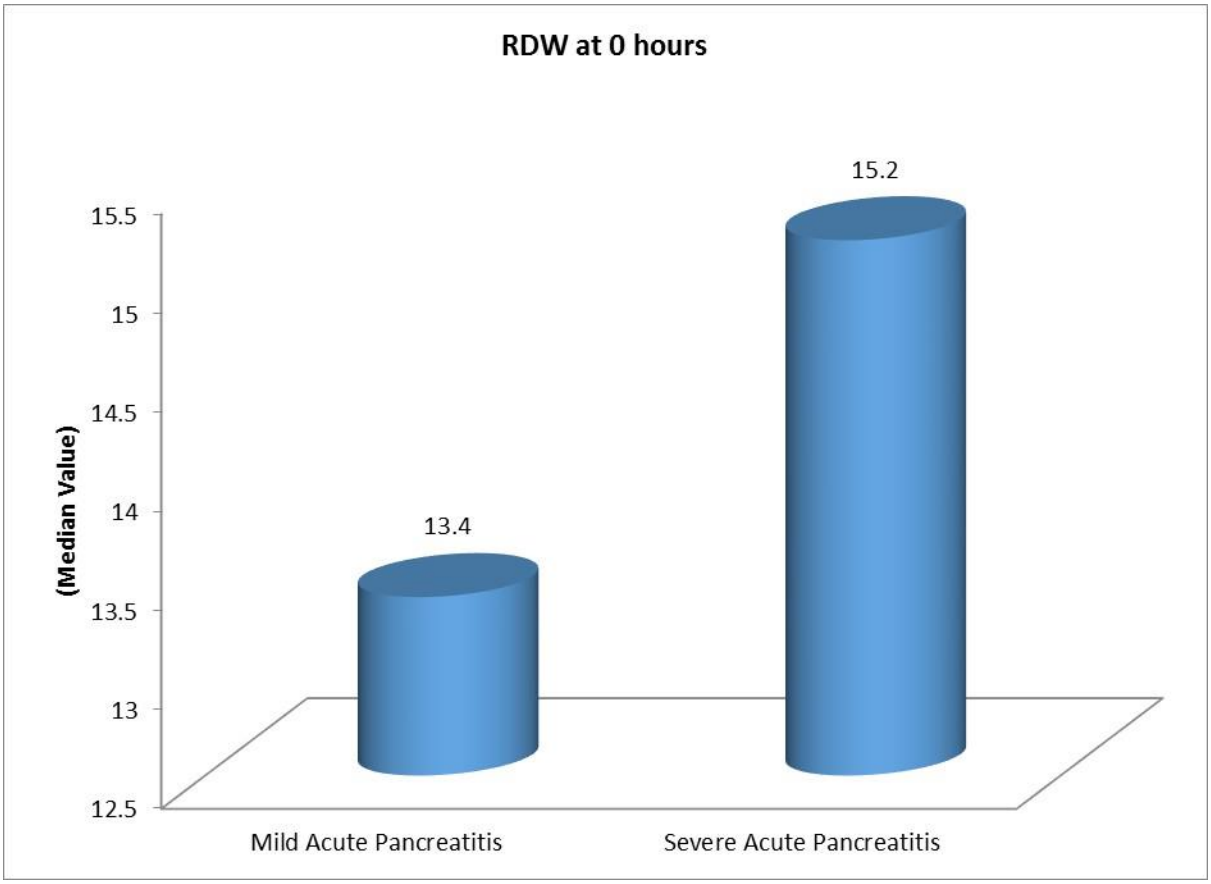
	Type of Pancreatitis	
	Mild Acute Pancreatitis (n=22)	Severe Acute Pancreatitis (n=8)
	Median (IQR)	Median (IQR)
NL ratio at 24 hours	5.4 (4.9, 6.1)	9.1 (8.5, 9.7)
p-value	<0.001 (Significant)	



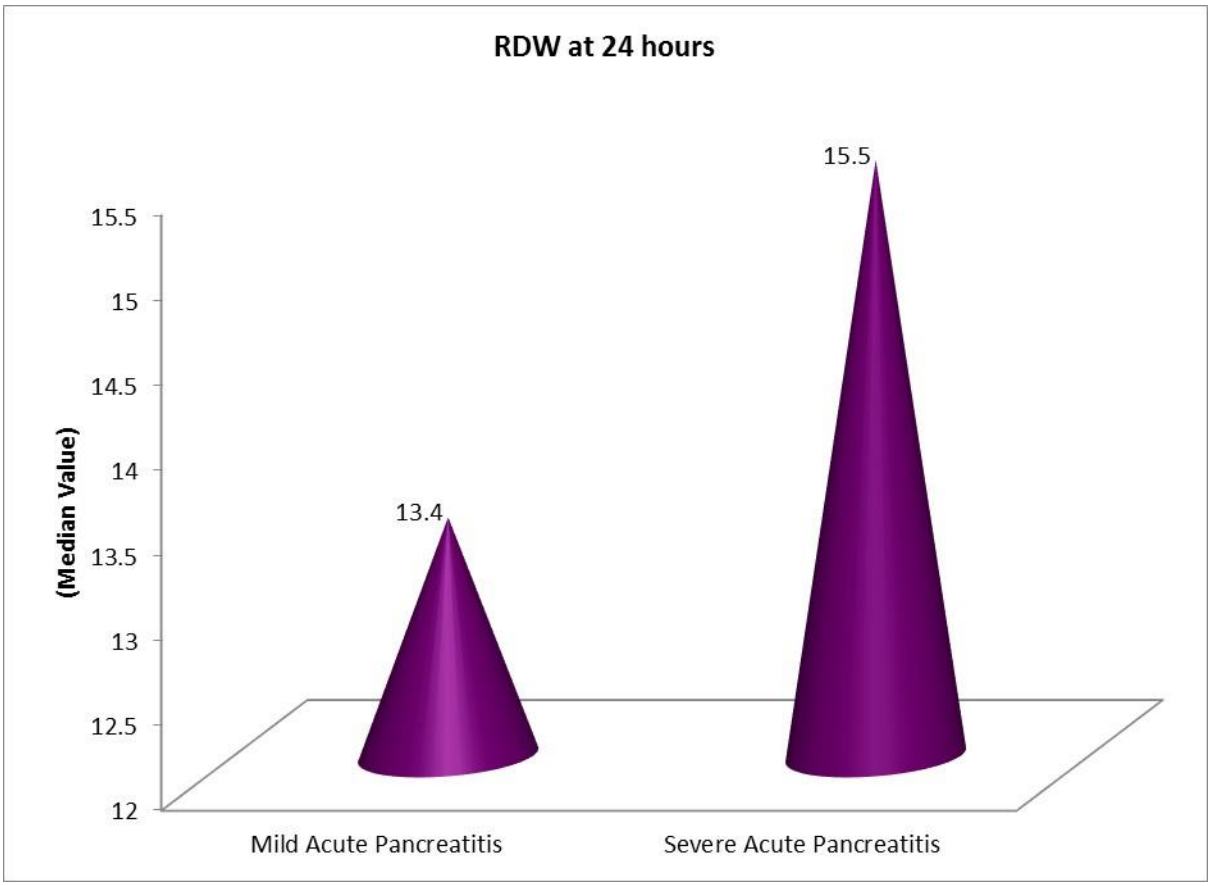
	Type of Pancreatitis	
	Mild Acute Pancreatitis (n=22)	Severe Acute Pancreatitis (n=8)
	Median (IQR)	Median (IQR)
NL ratio at 48 hours	4.2 (3.8, 4.6)	4.8 (4.3, 5.2)
p-value	0.035 (Significant)	



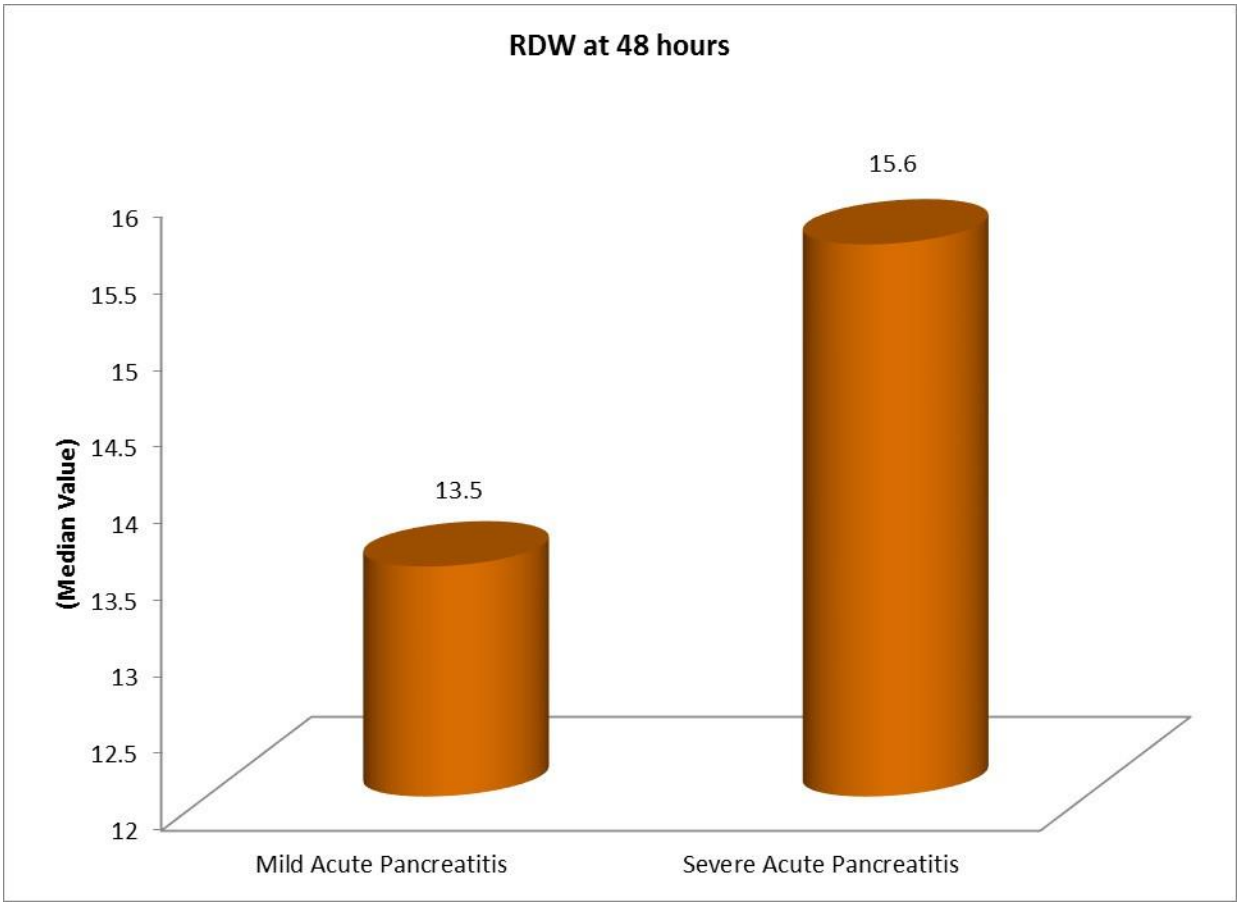
	Type of Pancreatitis	
	Mild Acute Pancreatitis (n=22)	Severe Acute Pancreatitis (n=8)
	Median (IQR)	Median (IQR)
RDW at 0 hours	13.4 (13.0, 13.9)	15.2 (14.6, 16.1)
p-value	<0.001 (Significant)	



	Type of Pancreatitis	
	Mild Acute Pancreatitis (n=22)	Severe Acute Pancreatitis (n=8)
	Median (IQR)	Median (IQR)
RDW at 24 hours	13.4 (13.0, 14.1)	15.5 (14.8, 17.0)
p-value	<0.001 (Significant)	



	Type of Pancreatitis	
	Mild Acute Pancreatitis (n=22)	Severe Acute Pancreatitis (n=8)
	Median (IQR)	Median (IQR)
RDW at 48 hours	13.5 (12.8, 13.8)	15.6 (14.4, 17.1)
p-value	0.004 (Significant)	



Age group (in yrs)	**%**
25 – 35 yrs	26.7
36 – 45 yrs	46.6
46 – 55 yrs	26.7
Type of Pancreatitis	**n (%)**
Mild Acute Pancreatitis	73.3
Severe Acute Pancreatitis	26.7
Complications	**n (%)**
Acute renal failure	25
Multi organ failure	12.5
Pancreatic necrosis	25
Pseudocyst	37.5

	Type of Pancreatitis	
	Mild Acute Pancreatitis	Severe Acute Pancreatitis
NL ratio at 0 hours	6.6	10.5
	Type of Pancreatitis	
	Mild Acute Pancreatitis	Severe Acute Pancreatitis
NL ratio at 24 hours	5.4	9.1
	Type of Pancreatitis	
	Mild Acute Pancreatitis	Severe Acute Pancreatitis
NL ratio at 48 hours	4.2	4.8

	Type of Pancreatitis	
	Mild Acute Pancreatitis	Severe Acute Pancreatitis
RDW at 0 hours	13.4	15.2
	Type of Pancreatitis	
	Mild Acute Pancreatitis	Severe Acute Pancreatitis
RDW at 24 hours	13.4	15.5
	Type of Pancreatitis	
	Mild Acute Pancreatitis	Severe Acute Pancreatitis
RDW at 48 hours	13.5	15.6

RESULTS

Age and sex distribution of the population in our study is as follows

26.7% of the study subjects were in the age group of 25-35years, 46.6% were in the age group of 36-45yrs, 26.7% were in the age group of 46-55 years.

All of the study subjects were males (100%)

Severity of pancreatitis in our study is as follows:

In our study about 73.3 % of the study subjects were classified as mild acute pancreatitis while 26.7% were developed complications, so called severe acute pancreatitis.

Among the severe acute pancreatitis group, about 37.5% of study groups developed pseudocyst of pancreas, 25% of patients developed pancreatic necrosis, 25 % developed acute renal failure and remaining 12.5% developed multi organ dysfunction syndrome.

Red cell distribution width

By observing RDW, no significant change in values on 0, 24 & 48 hrs in both acute and chronic pancreatitis.

But there is significant change observed in between acute & chronic pancreatitis; that is rise in RDW observed in severe acute pancreatitis. This change is more significant in 0 hr & 24 hrs than 48 hrs.

	Type of Pancreatitis		**P VALUES**
	Mild Acute Pancreatitis (n=22)	Severe Acute Pancreatitis (n=8)	
	Median (IQR)	Median (IQR)	
RDW at 0 hours	13.4 (13.0, 13.9)	15.2 (14.6, 16.1)	<0.001 (Significant)
RDW at 24 hours	13.4 (13.0, 14.1)	15.5 (14.8, 17.0)	<0.001 (Significant)
RDW at 48 hours	13.5 (12.8, 13.8)	15.6 (14.4, 17.1)	0.004 (Significant)

Neutrophil lymphocyte ratio

By observing NLR, there is significant change observed in between acute & chronic pancreatitis; that is rise in NLR observed in severe acute pancreatitis. This change is more significant in 0 hr & 24 hrs than 48 hrs. Similarly NLR ratio is higher than the normal population in acute pancreatitis; more significant rise observed in initial presentation than in 24 & 48 hours.

	Type of Pancreatitis		**P VALUES**
	Mild Acute Pancreatitis (n=22)	Severe Acute Pancreatitis (n=8)	
	Median (IQR)	Median (IQR)	
NLR at 0 hours	6.6 (5.0, 7.5)	10.5 (9.9, 11.0)	<0.001 (Significant)
NLR at 24 hours	5.4 (4.9, 6.1)	9.1 (8.5, 9.7)	<0.001 (Significant)
NLR at 48 hours	4.2 (3.8, 4.6)	4.8 (4.3, 5.2)	0.035 (Significant)

DISCUSSION

Rise in RDW is associated with the inflammation status of the disease, which may explain why patients with higher RDW values have a higher mortality rate.

It has been proposed that inflammation promotes deaths of RBCs or inhibits the maturation of RBCs, which is associated with an increase in RDW. Some inflammatory mediators influence bone marrow function and iron metabolism and suppress erythropoietin-induced maturation of RBCs. Therefore, RDW values reflect the inflammation status of acute pancreatitis and thus, may be used for predicting the severity of AP.

The WBC is a marker of infection and inflammation, and is part of many Acute Pancreatitis prognostic scoring systems including Ranson, Imrie, APACHE II, and the Simplified Acute Physiology Score (SAPS II). Neutrophils and lymphocytes are important components of the WBC count. Neutrophils propagate inflammation and tissue destruction in Acute pancreatitis via activation of a "cascade of inflammatory cytokines (IL-6, IL8, and TNF-α), proteolytic enzymes (myeloperoxidase, elastase, collagenase, and βglucoronidase), and oxygen free radicals"

A rise in neutrophil numbers corresponds with the development of

SIRS and progression to MODS, which are hallmarks of severe acute pancreatitis. Lymphocyte numbers increase following the initial stress and mediate the subsequent inflammatory response.

The traditional view is that neutrophilia is the primary cause of an elevated NLR, SIRS, and poor prognosis, while lymphocyte count remains static. Lymphopenia with in 24h of admission and persistent lymphopenia beyond this period is just as much a contributor to increased NLR and poor prognosis as neutrophilia.

This is replicated in our study where persistent lymphopenia is an independent marker of progressive inflammation, bacteremia, or sepsis in emergency admissions and intensive care patients. Uncontrolled inflammation is thought to precipitate lymphopenia by lymphocyte redistribution and accelerated apoptosis, and lymphopenia is associated with a higher mortality in patients with septic shock. The extent of lymphopenia, as with neutrophilia, also correlates with the severity of the insult.

SUMMARY OF PRIOR PUBLICATIONS

1. "The Prognostic Value of the Neutrophil–Lymphocyte Ratio (NLR) in Acute Pancreatitis: Identification of an Optimal NLR

Aravind Suppiah & Deep Malde & Tameem Arab & Mazin Hamed & Victoria Allgar & Andrew M. Smith & Gareth Morris-Stiff

Conclusion: Elevation of the NLR during the first 48 h of admission is significantly associated with severe acute pancreatitis and is an independent negative prognostic indicator in AP"

2. "Association between red cell distribution width and acute pancreatitis: a cross-sectional study

Jinmei Yao, Guocai Lv,

Department of Laboratory Medicine, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Conclusion: There is significant association between RDW and mortality of patients with AP"

3. "Effect of harmless acute pancreatitis score, red cell distribution width and neutrophil/lymphocyte ratio on the mortality of patients with non-traumatic acute pancreatitis at the emergency department

Bedia Gülen1, Ertan Sonmez1, Serpil Yaylaci2, Mustafa Serinken3, Cenker Eken4, Ali Dur1, Figen Tunali Turkdogan5, Özgür Söğüt1

Department of Internal Medicine, Gastroenterology, Emergency Medicine, General Surgery Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey; Department of Internal Medicine, Umraniye Training and Research Hospital, Istanbul, Turkey

Conclusion: HAPS, neutrophil/lymphocyte ratio and RDW were not effective in determining the mortality of non-traumatic acute pancreatitis cases within the first 48 hours. The only independent variable for determining the mortality was Balthazar classification"

DEFINITIONS

Diagnostic accuracy: “This is the probability that a randomly selected subject is correctly diagnosed by the test”.

Negative Predictive Value: “The probability that a person who has tested negative on a diagnostic test (T−) actually does not have the disease (D−)”

Positive Predictive Value: “This is the probability that a person who has tested positive on a diagnostic test (T+) actually has the disease (D+)”.

Sensitivity: “This is the probability that a person with disease (D+) will correctly test positive based on the diagnostic test (T+)”

Specificity: “This is the probability that a person without disease (D−) will correctly test negative based on the diagnostic test (T−)”

D – Disease., **T** – Test

CONCLUSION

In this study we evaluated the ability of RDW & NLR values predicting the outcome of acute pancreatitis and found that NLR is more valuable than RDW; both are important prognostic marker in acute pancreatitis patients. Increased RDW can be used as a new indicator of mortality in patients with acute pancreatitis.

In addition, *optimal cut-off RDW value of 15.2 on admission and 15.5 at 24 hours* are predict severe acute pancreatitis. Similarly *optimal neutrophil lymphocyte ratio (NLR) of 10.5 on admission 9.1 at 24 hours* also indicate severe acute pancreatitis.

These results indicate that NLR & RDW is convenient, economic, and sensitive monitoring method for helping clinicians predict complications in AP patients.

So NLR & RDW values in combination with other scoring systems will be useful for properly evaluating & predicting the severity of acute pancreatitis.

SUMMARY

Even though so many prognostic criteria's and markers are widely available in acute pancreatitis for predicting outcome, they all are not suitable for stratifying patients at the time of admission. Some of investigations like procalcitonin, interleukin-6, and interleukin-8 e are expensive, non-validated in the clinical arena, and not readily available.

So simplified investigations like complete hemogram that are routinely done in all patients and easily available investigation. Through this we can easily derive RDW & NLR as a routine workup. This will give clue to predicting the outcome of acute pancreatitis & they serve as important mortality indicator.

So we can change the treatment plan and managing protocol according to the NLR & RDW values; it will help to categorize the patients & predict the outcome even before developing clinical and other biochemical abnormalities.

In future both NLR & RDW may include in available scoring systems for predicting mortality of acute pancreatitis

Limitations of this study

1. smaller study population
2. shorter duration of follow up of cases
3. effect of recurrent pancreatitis on inflammation not considered
4. delayed complications and its correlation with haematological abnormality not considered

Further recommendations

1. A longer duration of study in larger population should be considered in the future.
2. Combination of NLR & RDW along with other haematological parameters must be included in the prognostic criteria
3. Treatment details such as antibiotics and other specific managements that alter inflammation must be consider in further study.

BIBLIOGRAPHY

1. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, Whitcomb DC. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. Am J Gastroenterol 2010;105(2): 435–441; quiz 442.
2. Dambrauskas Z, Gulbinas A, Pundzius J, Barauskas G. Value of the different prognostic systems and biological markers for predicting severity and progression of acute pancreatitis. Scand J Gastroenterol 2010;45(7–8): 959–970.
3. Pavlidis TE, Pavlidis ET, Sakantamis AK. Advances in prognostic factors in acute pancreatitis: a mini-review. Hepatobiliary Pancreat Dis Int 2010;9(5): 482–486.
4. Minne L, Abu-Hanna A, de Jonge E. Evaluation of SOFA-based models for predicting mortality in the ICU: A systematic review. Crit Care 2008;12(6): R161
5. AounE,ChenJ,ReighardD,GleesonFC,WhitcombDC,Papachristou GI.Diagnosticaccuracyofinterleukin-6andinterleukin-8inpredicting severe acute pancreatitis: a meta-analysis. Pancreatology 2009;9 (6): 777–785.

6. Mofidi R, Suttie SA, Patil PV, Ogston S, Parks RW. The value of procalcitonin at predicting the severity of acute pancreatitis and development of infected pancreatic necrosis: systematic review. Surgery 2009;146(1): 72–81.
7. Pezzilli R, Billi P, Miniero R, Fiocchi M, Cappelletti O, MorselliLabate AM, Barakat B, Sprovieri G, Miglioli M. Serum interleukin-6, interleukin-8, and beta 2-microglobulin in early assessment of severity of acute pancreatitis. Comparison with serum C-reactive protein. Dig Dis Sci 1995;40(11): 2341–2348.
8. England JM, Down MC. Red-cell-volume distribution curves and the measurement of anisocytosis. Lancet 1974;1:701–3.
9. Demir A, Yarali N, Fisgin T, et al. Most reliable indices in differentiation between thalassemia trait and iron deficiency anemia. Pediatr Int 2002;44:612
10. 10. Makhoul BF, Khourieh A, Kaplan M, et al. Relation between changes in red cell distribution width and clinical outcomes in acute decompensated heart failure. Int J Cardiol 2013;167:1412–16.
11. Hong N, Oh J, Kang SM, et al. Red blood cell distribution width predicts early mortality in patients with acute dyspnea. Clin Chim Acta 2012;413:992–7.

12. Braun E, Domany E, Kenig Y, et al. Elevated red cell distribution width predicts poor outcome in young patients with community acquired pneumonia. Crit Care 2011;15:R194.
13. Dabbah S, Hammerman H, Markiewicz W, et al. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. Am J Cardiol 2010;105:312–17
14. Wang YZ, Wang SW, Zhang YC, Sun ZJ. Protective effect of exogenous IGF-I on the intestinalmucosal barrier in rats with severe acutepancreatitis. World J Emerg Med 2012; 3: 213– 220.
15. Li XY, Wang XB, Liu XF, Li SG. Prevalence and risk factors of organ failure in patients with severe acutepancreatitis.World J Emerg Med 2010; 1: 201–204.

PROFORMA

Name:

Age/Sex

Occupation:

Presenting complaints:

H/o upper abdominal pain with or without guarding and/or rebound tenderness.

Past history:

H/o Tuberculosis, Chronic liver disease, coronary artery disease, chronic kidney disease

Clinical examination:

General examination:

Consciousness, Pallor, jaundice, Clubbing, Lymphadenopathy,

Vitals: PR, BP, RR, SpO2, Temperature

Systemic examination:

CVS:

RS:

Abdomen:

CNS:

LABORATORY INVESTIGATIONS:

1. White cell count (WBC), RBC count, RDW, platelet count, haemoglobin level, MCV and mean platelet volume (MPV).

2. Serum Amylase, creatinine, total protein, albumin, total calcium, total bilirubin, glucose, lactate dehydrogenase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) 3. Ultrasound and / or CT abdomen

					O hr		24 hrs		48 hrs		according to LABORATORY VALUES ON 48hrs	
S. No	**NAME**	**AGE**	**SEX**	**DIAGNOSIS**	**N / L RATIO**	**RDW**	**N / L RATIO**	**RDW**	**N / L RATIO**	**RDW**	**complication**	**type of pancreatitis**
1	MUTHU KARUPAN	45	M	ACUTE PANCREATITIS	4.9	13.2	5.3	13.4	3.9	13.5	_	mild acute pancreatitis
2	PANDI	36	M	ACUTE PANCREATITIS	10.4	15.6	8.3	15.8	4.6	15.8	acute ranal failure	severe acute pancreatitis
3	SAMAYAN	43	M	ACUTE PANCREATITIS	5.1	12.9	6.4	13.1	3.8	13.6	_	mild acute pancreatitis
4	MUTHU	28	M	ACUTE PANCREATITIS	4.3	13.4	4.9	15.2	4.2	14.3	_	mild acute pancreatitis
5	RAGU	47	M	ACUTE PANCREATITIS	10.7	14.9	8.4	15.2	4.9	15.6	multi organ failure	severe acute pancreatitis
6	MURUGAN	42	M	ACUTE PANCREATITIS	4.7	13.8	6.1	13.4	3.8	13.2	_	mild acute pancreatitis
7	RAVI	32	M	ACUTE PANCREATITIS	6.3	13.1	5.2	13.8	4.9	14.7	_	mild acute pancreatitis

8	AYYAVU	38	M	ACUTE PANCREATITIS	4.4	13.6	3.9	14.1	3.6	14.3	_	mild acute pancreatitis
9	SELVA MANI	29	M	ACUTE PANCREATITIS	9.8	14.5	11.3	14.7	5.2	14.9	pseudocyst	severe acute pancreatitis
10	JAMES	48	M	ACUTE PANCREATITIS	9.9	14.6	7.2	14.3	6.1	13.7	_	mild acute pancreatitis
11	CHANDRAN	46	M	ACUTE PANCREATITIS	7.2	12.8	5.6	12.9	3.9	12.8	_	mild acute pancreatitis
12	MARIMUTHU	38	M	ACUTE PANCREATITIS	10.5	17.2	8.9	17.3	4.3	17.7	pancreatic necrosis	severe acute pancreatitis
13	SENTHIL	44	M	ACUTE PANCREATITIS	8.2	13.5	4.9	12.4	3.2	12.2	_	mild acute pancreatitis
14	KANDHASAMY	49	M	ACUTE PANCREATITIS	5.7	13.9	5.3	15.3	4.2	15.9	_	mild acute pancreatitis
15	SOKKALINGAM	45	M	ACUTE PANCREATITIS	13.5	16.3	9.3	16.8	6.8	7.1	pseudocyst	severe acute pancreatitis
16	MANIKANDAN	38	M	ACUTE PANCREATITIS	7.2	13.2	5.9	13.4	4.6	13.6	_	mild acute pancreatitis

17	IRULAPPAN	35	M	ACUTE PANCREATITIS	4.9	12.6	4.1	12.8	3.8	12.8	_	mild acute pancreatitis
18	MARI MUTHU	49	M	ACUTE PANCREATITIS	5.3	12.7	4.8	13.1	4.1	13.7	_	mild acute pancreatitis
19	SONAI MUTHU	44	M	ACUTE PANCREATITIS	6.8	13.9	5.1	13.4	4.4	13.7	_	mild acute pancreatitis
				IS								
20	ARJUNAN	30	M	ACUTE PANCREATITIS	7.8	14.1	6.1	14.6	4.3	13.4	_	mild acute pancreatitis
21	KANNAN	41	M	ACUTE PANCREATITIS	11.2	13.8	9.6	13.9	5.3	14.3	pseudocyst	severe acute pancreatitis
22	RAMESH	50	M	ACUTE PANCREATITIS	6.2	12.2	4.6	12.4	3.4	12.6	_	mild acute pancreatitis
23	RANGAN	36	M	ACUTE PANCREATITIS	6.8	13.1	5.9	13.4	7.1	12.4	_	mild acute pancreatitis
24	PONAMBALAM	45	M	ACUTE PANCREATITIS	8.3	15.1	6.7	12.9	5.1	12.2	_	mild acute pancreatitis
25	RANGASAMY	39	M	ACUTE PANCREATITIS	7.5	13.8	5.9	13.6	4.4	13.4	_	mild acute pancreatitis

26	PRAKASH	46	M	ACUTE PANCREATITIS	8.2	13.7	6.8	13.2	4.9	13.2	–	mild acute pancreatitis
27	JAYAKUMAR	25	M	ACUTE PANCREATITIS	10.6	15.7	9.8	17.1	4.7	17.6	acute renal failure	severe acute pancreatitis
28	GANAPATHY	32	M	ACUTE PANCREATITIS	7.4	14.7	5.6	14.2	4.3	14.1	–	mild acute pancreatitis
29	RAJENDRAN	46	M	ACUTE PANCREATIT	6.5	13.4	5.2	13.4	4.1	13.5	–	mild acute pancreatitis
				IS								
30	GURUMOORTHY	33	M	ACUTE PANCREATITIS	8.2	14.9	8.8	15.3	3.9	15.7	pancreatic necrosis	severe acute pancreatitis

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
(Affiliated to The Tamilnadu Dr.MGR Medical University, Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate : Dr.R.Pon Raj

Course : PG in MD., General Medicine

Period of Study : 2015-2018

College : MADURAI MEDICAL COLLEGE

Research Topic : The Prognostic significance of the Red cell distribution width (RDW) and Neutrophil-Lymphocyte Ratio (NLR) in acute Pancreatitis: Identification of an Optimal values

Ethical Committee as on : 02.06.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary

Chairman
Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc (Neuro) Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

Dean / Convenor
Madurai Medical College
Madurai-20

← Reply ← Reply all → Forward Archive Delete Set flag •••

N noreply@urkund.se
10/10/2017 3:06 PM

[URKUND] Confirmation of receipt - ponraj thesis-rdw nlr in acutepancreatitis.doc
To: drponz@gmail.com

URKUND has received the document - ponraj thesis-rdw nlr in acute pancreatitis.doc - 10/10/2017 11:34:00 AM. It was sent from drponz@gmail.com to drponz.mgrmu@analysis.urkund.com. The document has been allocated a reference ID - D31179106.

Please fill in your name so that we can link your name to your e-mail address.

https://secure.urkund.com/account/account/submitter/6743100-447941-961000

At no point are any documents in URKUND's archive/repository browsable, nor are they sorted and they cannot be accessed through Google or any other search engine.
Your university/school will have chosen a default setting; clicking the link below will take you to a page where you can change this setting. If you have questions about this, please contact your university or school.

https://secure.urkund.com/account/document/exemptionstatus/31179106-484228-413382

Exempted: Documents which are marked "exempted" will not have their content disclosed to other universities/schools if there is a match within the document.

Unexempted: These documents will have their content shown to other users if the other users have a match in the document.

Regards,
URKUND automatic registrar

This is an automated e-mail message. You cannot reply to it. If you have questions about URKUND and its use, contact our Customer Support: +46 (0)8 738 5210 (Mon-Fri 08.00-16.30 CET) or by e-mail to support@urkund.com.

From: report@analysis.urkund.com
Sent: Tuesday, October 10, 2017 3:11 PM
To: drponz@gmail.com
Subject: [Urkund] 5% similarity - drponz@gmail.com

Document sent by: drponz@gmail.com
Document received: 10/10/2017 11:34:00 AM
Report generated 10/10/2017 11:41:16 AM by Urkund's system for automatic control.

Student message: kindly do pilagiarism for my thesis topic

Document : ponraj thesis-rdw nlr in acute pancreatitis.doc [D31179106]

IMPORTANT! The analysis contains 1 warning(s).

About 5% of this document consists of text similar to text found in 26 sources. The largest marking is 95 words long and is 93% similar to its primary source.

PLEASE NOTE that the above figures do not automatically mean that there is plagiarism in the document. There may be good reasons as to why parts of a text also appear in other sources. For a reasonable suspicion of academic dishonesty to present itself, the analysis, possibly found sources and the original document need to be examined closely.

Click here to open the analysis:
https://secure.urkund.com/view/30852096-992166-268431

Click here to download the document:
https://secure.urkund.com/archive/download/31179106-484228-413382

URKUND

Urkund Analysis Result

Analysed Document: ponraj thesis-rdw nlr in acute pancreatitis.doc (D31179106)
Submitted: 10/10/2017 11:34:00 AM
Submitted By: drponz@gmail.com
Significance: 5 %

Sources included in the report:

Sugu Plagiarism.docx (D31021602)
plag thesis.docx (D31003014)
Final version thesis_170831.pdf (D30416626)
https://quizlet.com/216913552/usmle-gi-flash-cards/

Instances where selected sources appear:

16