# "SERUM CYSTATIN C CONCENTRATION LEVELS AS A MARKER OF ACUTE RENAL FAILURE IN CRITICALLY ILL PATIENTS – A CROSS SECTION STUDY"


**By**

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# Dissertation

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**Under the Guidance of**

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# LIST OF ABBREVIATIONS USED

ACEIs - Angiotensin-Converting Enzyme Inhibitors

AKI – Acute Kidney Injury

AKIN – Acute Kidney Injury Network

ANCA – Anti Neutrophil Cytoplasmic Antibody

APACHE – Acute Physiology And Chronic Health Evaluation

ARBs – Angiotensin Receptor Blockers

ARF – Acute Renal Failure

ATN – Acute Tubular Necrosis

BUN – Blood Urea Nitrogen

CBC – Complete Blood Count

$C_{Cr}$ – Creatinine Clearence

CHF – Congestive Heart Failure

Creat – Creatinine

CRF – Chronic Renal Failure

Cyst – Cystatin C

eGFR – Estimated Glomerular Filtration Rate

ESKD – End Stage Kidney Disease

FENa – Fractional Excretion of Sodium

FEUrea – Fractional Excretion of Urea

GFR – Glomerular Filtration Rate

GI – Gastrointestinal

HTN – Hypertension

HUS –Hemolytic Uremic Syndrome

ICU – Intensive Care Unit

LFT – Liver function test

NPV – Negative predictive value

NSAIDs – Nonsteroidal anti-inflammatory drugs

$P_{Cr}$ – Plasma Creatinine

PPV – Positive predictive value

$P_{urea}$ – Plasma Urea

RBC – Red Blood Cell

RBF – Renal Blood Flow

RIFLE – Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease;

RPGN – Rapidly Progressive Glomerulonephritis

Sr. – Serum

TSH – Thyroid Stimulating Hormone

TTP – Thrombotic Thrombocytopenic Purpura

$U_{Cr}$ – Urinary Creatinine

UO – Urine Output

$U_{urea}$ – Urinary urea

WBC – White Blood Cell

# ABSTRACT

## Background and objectives

Acute Renal Failure (ARF) is a common complication in patients admitted to the Intensive care unit (ICU). The present study was undertaken to assess serum Cystatin C (Sr. Cystatin C) concentration levels as a marker of ARF in critically ill patients.

## Methodology

The present one year cross sectional study was conducted on patients admitted in the Medical Intensive Care Unit of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. A total of 50 patients were studied. CBC, LFT, Sr. TSH, X-ray chest, ultrasound abdomen and other necessary tests to make a etiological diagnosis were done at admission. Sr. Cystatin C and Sr. Creatinine levels were determined at admission and these were considered as the first reading of Sr. Creatinine and Sr. Cystatin C. Sr. Creatinine and Sr. Cystatin C were repeated after the patient developed ARF and was considered as second reading and results were analyzed.

## Results

In the present study out of 50 patients, 33 (66%) were male and 17 (34%) were female. The male: female ratio was 1.94:1. In this study, out of 50 patients, there were 13 (26%) patients each in the age group of 18 to 30 years and more than 60 years. There were 18 (36%) patients each with primary gastrointestinal and respiratory disease and 6 (12%) patients with snake bite. The mean Sr.

Creatinine and Sr. Cystatin C values in ARF were 1.86 mg/dL and 3.14 mg/L respectively. The mean Sr. Creatinine and Sr. Cystatin C values in patients with out ARF were 0.68 mg/dL and 0.73 mg/L respectively. The sensitivity, specificity, PPV, NPV of Sr. Creatinine for second reading was 78.57%, 100%, 100%, 78.57% respectively and the sensitivity, specificity, PPV, NPV for second reading of Sr. Cystatin C was 100%.

**Interpretation and conclusion**

Sr. Creatinine was normal in some patients with ARF whereas Sr. Cystatin C was above the normal value in all ARF patients indicating that Sr. Cystatin C is more reliable marker than Sr. Creatinine.

**Keywords**

Acute renal failure; Serum Creatinine; Serum Cystatin C;

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# Chapter 1

# Introduction

# INTRODUCTION

Acute Renal Failure (ARF) is a common complication in patients admitted to the intensive care unit (ICU). It is common in hospitalized patients, with a mortality rate between 30% and 90% depending upon various causes.[1]

Numerous causes are responsible for development of ARF.[1] Moreover ARF is often due to multifactorial aetiology in critically ill patients. Increasing use of nephrotoxic drugs, invasive procedures, intravascular catheters and major surgical procedures (cardiovascular and abdominal surgeries) predispose patient to sepsis and renal failure.[2]

Acute renal failure is the abrupt loss of renal function sufficient to decrease urinary elimination of nitrogenous waste (urea nitrogen and creatinine) although there is consensus about this general definition, few agree on the magnitude of the rise in serum creatinine necessary to ascribe a diagnosis of ARF.

The differences in the definition plus variances in the methods of patients accrual, population analysed, categorization of causes, render development of broad based over view of ARF difficult. The high mortality of patients with ARF is not explained entirely by comorbid conditions. Recent data indicate that ARF per say increase the risk of development of multiple non renal conditions that lead to death and disability.

The relative importance of factors contributing to ARF will be different depending on the underlying pathology and patient characteristics. A patient

population of young trauma patients developing ARF can probably not be compared with older patients with ischemic and congestive heart disease developing ARF after cardiac surgery. The large differences in mortality for patients with ARF, as reported in recent trials (varying between 28 and 83%) can possibly be explained by differences in patient population.[3,4]

In clinical practice, the detection of ARF, which is characterized by a rapid decline of the glomerular filtration rate (GFR), is based on increase of serum creatinine (Sr. Creatinine). However, there are major limitations to the use of creatinine for estimating GFR. Minor changes of Sr. Creatinine, as typically seen early in acute renal failure, may already reflect substantial decline in GFR. Sr. Creatinine inaccurately estimates GFR due to tubular secretion and reabsorption of creatinine.[5] Sr. Creatinine can be affected by age, sex, muscle mass, drugs and diet.[6] The early and accurate detection of acute renal failure is crucial to prevent its progression, and thereby, to potentially improve its outcome.

Hence there is a need of a early and more reliable marker of ARF which can detect minor GFR reduction and which is not affected by age, sex, muscle mass, drugs and diet. Many international studies say that Serum Cystatin C (Sr. cystatin C) is one such marker but there is lack of Indian studies regarding Sr. Cystatine C levels as a marker of acute renal failure in critically ill patients. To date no studies on Sr. Cystatin C are done in Karnataka. Hence the present study was undertaken to assess whether Sr. Cystatin C is a early and more reliable marker of ARF.

# Chapter 2

# Objectives

# OBJECTIVES

The objective of the present study was to assess serum cystatin C concentration levels as a marker of ARF in critically ill patients.

# Chapter 3

# Review of Literature

# REVIEW OF LITERATURE

Acute renal failure, or acute kidney injury (ARF), as it is now referred to in the literature, is defined as an abrupt or rapid decline in renal function. This condition is usually marked by a rise in Sr. Creatinine concentration or by azotemia (a rise in blood urea nitrogen [BUN] concentration).[7]

However, immediately after a kidney injury, BUN or creatinine levels may be normal, and the only sign of a kidney injury may be decreased urine production.

A rise in the creatinine level can result from medications (aminoglycosides) that impair the renal function.

A rise in the BUN level can occur without renal injury, resulting instead from sources such as gastrointestinal (GI) or mucosal bleeding, steroid use, or protein loading. So a detailed history should be taken and relavent investigations should be done to determining whether renal injury is present.

## Categories

ARF may be classified into three general categories, as follows:

- **Prerenal** - as an adaptive response to severe volume depletion and hypotension, with structurally intact nephrons
- **Intrinsic(renal)** - in response to cytotoxic, ischemic, or inflammatory insults to the kidney, with structural and functional damage
- **Postrenal** – due to obstruction to the passage of urine

While this classification is useful in establishing a differential diagnosis, many pathophysiologic features are shared among the different categories.

**Oliguric and nonoliguric patients**

Patients who develop ARF can be oliguric or nonoliguric. They may have have a rapid or slow rise in creatinine levels, and may have qualitative differences in urine solute concentrations and cellular content. (Approximately 50-60% of all cases of ARF are nonoliguric).

This lack of a uniform clinical presentation reflects the variable nature of the injury.

Classifying ARF as oliguric or nonoliguric based on daily urine excretion has prognostic value. Oliguria is defined as a urine output of less than 400 mL/day and has a worse prognosis, except in prerenal failure.

Anuria is defined as a urine output of less than 100 mL/day and, if abrupt in onset, suggests bilateral obstruction or catastrophic injury to both kidneys. Stratification of renal failure along these lines helps in decision-making (timing of dialysis) and can be an important criterion for patient response to therapy.

**The RIFLE system**[8]

In 2004, the Acute Dialysis Quality Initiative work group set forth a definition and classification system for ARF, described by the acronym RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease; as shown in table, below). Investigators

have since applied the RIFLE system to the clinical evaluation of ARF, although it was not originally intended for that purpose. ARF research increasingly uses RIFLE.

**RIFLE Classification System for Acute Kidney Injury**

| Stage | GFR Criteria | Urine Output (UO) Criteria | Probability |
|---|---|---|---|
| Risk | Sr. Creat increased × 1.5<br>*or*<br>GFR decreased >25% | UO < 0.5 mL/kg/h × 6 h | High sensitivity (Risk >Injury >Failure) |
| Injury | Sr. Creat increased × 2<br>*or*<br>GFR decreased >50% | UO < 0.5 mL/kg/h × 12 h | |
| Failure | Sr. Creat increased × 3<br>*or*<br>GFR decreased 75%<br>*or*<br>Sr. Creat ≥4 mg/dL; acute rise ≥0.5 mg/dL | UO < 0.3 mL/kg/h × 24 h (oliguria)<br>*or*<br>anuria × 12 h | |
| Loss | Persistent ARF: complete loss of kidney function >4 wk | | High specificity |
| ESKD | Complete loss of kidney function >3 mo | | |

Patients can be classified by GFR criteria and/or UO criteria. The criteria that support the most severe classification should be used.

The superimposition of acute on chronic failure is indicated with the designation RIFLE-$F_C$; failure is present in such cases even if the increase in SCreat is less than 3-fold, provided that the new SCreat is greater than 4.0 mg/dL (350 μmol/L) and results from an acute increase of at least 0.5 mg/dL (44 μmol/L).

When the failure classification is achieved by UO criteria, the designation of RIFLE-$F_O$ is used to denote oliguria. The initial stage, risk, has high sensitivity; more patients will be classified in this mild category, including some who do not actually have renal failure. Progression through the increasingly severe stages of RIFLE is marked by decreasing sensitivity and increasing specificity.

**Complications**[9]

A vast array of fluid and electrolyte abnormalities can be seen with ARF.

Cardiovascular complications

Cardiovascular complications (congestive heart failure [CHF], myocardial infarction, arrhythmias, cardiac arrest) have been observed in as many as 35% of patients with ARF. Fluid overload secondary to oliguric ARF is a particular risk for elderly patients with little cardiac reserve.

Pericarditis is a relatively rare complication of ARF. When pericarditis complicates ARF, consider additional diagnoses, such as systemic lupus erythematosus (SLE) and hepatorenal syndrome.

Acute renal failure also can be a complication of cardiac diseases, such as endocarditis, worsening CHF, or atrial fibrillation with emboli. Cardiac arrest in a patient with ARF always should arouse suspicion of hyperkalemia. Many authors recommend a trial of intravenous calcium chloride (or gluconate) in all patients with ARF who experience cardiac arrest.

Pulmonary complications

Pulmonary complications have been reported in approximately 54% of patients with ARF and are the single most significant risk factor for death in patients with ARF. Pulmonary edema is one of the most common complication of ARF.

Several diseases exist that commonly present with simultaneous pulmonary and renal involvement, including pulmonary/renal syndromes (Goodpasture syndrome, Wegener granulomatosis, polyarteritis nodosa, cryoglobulinemia, sarcoidosis).

Hypoxia commonly occurs during hemodialysis and can be particularly significant in the patient with pulmonary disease. This dialysis-related hypoxia is thought to occur secondary to white blood cell (WBC) lung sequestration and alveolar hypoventilation.

Gastrointestinal complications

Gastrointestinal symptoms of nausea, vomiting, and anorexia are frequent complications of ARF and represent one of the cardinal signs of uremia. Gastrointestinal bleeding occurs in approximately one third of patients with ARF. Most episodes are mild, but GI bleeding accounts for 3-8% of deaths in patients with ARF.

Mild hyperamylasemia commonly is seen in ARF (2-3 times controls). Elevation of baseline amylase can complicate diagnosis of pancreatitis in patients with ARF. Lipase, which commonly is not elevated in ARF, often is necessary to make the diagnosis of pancreatitis. Pancreatitis has been reported as a concurrent illness with ARF in patients with atheroemboli, vasculitis, and sepsis from ascending cholangitis.

Jaundice has been reported to complicate ARF in approximately 43% of cases. Etiologies of jaundice with ARF include hepatic congestion, blood transfusions, and sepsis.

Hepatitis occurring concurrently with ARF should prompt the differential diagnosis of common bile duct obstruction, fulminant hepatitis B, leptospirosis, acetaminophen toxicity, and *Amanita phalloides* toxin.

Infectious complications

Infections commonly complicate the course of ARF and have been reported to occur in as many as 33% of patients with ARF. Most common sites are pulmonary and urinary tracts. Infections are the leading cause of morbidity and death in patients with ARF. Various studies have reported mortality rates of 11-72% in infections complicating ARF.

Neurologic complications

Neurologic signs of uremia are a common complication of ARF and have been reported in approximately 38% of patients with ARF. Neurologic sequelae include lethargy, somnolence, reversal of the sleep-wake cycle, and cognitive or memory deficits. Focal neurologic deficits are rarely solely due to uremia.

The pathophysiology of neurologic symptoms is still unknown, and do not correlate well with levels of BUN or creatinine.

A number of diseases express themselves with concurrent neurologic and renal manifestations (SLE, thrombotic thrombocytopenic purpura [TTP], hemolytic uremic syndrome [HUS], endocarditis, malignant hypertension).

**Etiology**[9]

The driving force for glomerular filtration is the pressure gradient from the glomerulus to the Bowman space. Glomerular pressure is primarily dependent on renal blood flow (RBF) and is controlled by combined resistances of renal afferent and efferent arterioles. Regardless of the cause of ARF, reductions in RBF represent a common pathologic pathway for decreasing GFR. The etiology of ARF consists of three main mechanisms.

- Prerenal failure - GFR is depressed by compromised renal perfusion. The renal tubular and glomerular function is normal.
- Intrinsic (renal) failure - Includes diseases of the kidney itself, predominantly affecting the glomerulus or tubule, which are associated with release of renal afferent vasoconstrictors. Ischemic renal injury is the most common cause of intrinsic renal failure.
- Post renal failure – is due to urinary outlet obstruction. Initially causes an increase in tubular pressure, decreasing the filtration driving force. This pressure gradient soon equalizes, and maintenance of a depressed GFR is then dependent on renal efferent vasoconstriction

Patients with chronic renal failure may also present with superimposed ARF from any of the aforementioned etiologies.

Depressed RBF eventually leads to ischemia and cell death. This may happen before frank systemic hypotension is present and is referred to as normotensive ischemic ARF. The initial ischemic insult triggers a cascade of events that includes production of oxygen free radicals, cytokines and enzymes, endothelial activation and leukocyte adhesion, activation of coagulation, and initiation of apoptosis. These events continue to cause cell injury even after restoration of RBF.

Tubular cellular damage results in disruption of tight junctions between cells, allowing back leak of glomerular filtrate and further depressing effective GFR. In addition, dying cells slough off into the tubules, forming obstructing casts, which further decrease GFR and lead to oliguria.

During this period of depressed RBF, the kidneys are particularly vulnerable to further insults. This is when iatrogenic renal injury is most common. The following are common iatrogenic combinations:

- Preexisting renal disease (elderly, diabetic patients, jaundiced patients) with radiocontrast agents, aminoglycosides, or cardiovascular surgery
- Small- or large-vessel renal arterial disease with Angiotensin-converting enzyme (ACE) inhibitors and diuretics,
- Congestive heart failure (CHF), hypertension (HTN), or renal artery stenosis with Nonsteroidal anti-inflammatory drugs (NSAIDs
- Hypovolumia with aminoglycosides, amphotericin, or radiocontrast agents

Restoration of renal blood flow and associated complications

Recovery from ARF is first dependent upon restoration of RBF. Early RBF normalization predicts better prognosis for recovery of renal function. In prerenal failure, restoration of circulating blood volume is usually sufficient. Rapid relief of urinary obstruction in postrenal failure results in a prompt decrease of vasoconstriction. With intrinsic renal failure, removal of tubular toxins and initiation of therapy for glomerular diseases decreases renal afferent vasoconstriction.

Once RBF is restored, the remaining functional nephrons increase their filtration and eventually hypertrophy. GFR recovery is dependent upon the size of this remnant nephron pool. If the number of remaining nephrons is below some critical value, continued hyperfiltration results in progressive glomerular sclerosis, eventually leading to increased nephron loss. A vicious cycle ensues; continued nephron loss causes more hyperfiltration until complete renal failure results. This has been termed the hyperfiltration theory of renal failure and explains the scenario in which progressive renal failure is frequently observed after apparent recovery from ARF.

Prerenal ARF

Prerenal ARF represents the most common form of kidney injury and often leads to intrinsic ARF if it is not promptly corrected. Volume loss due to acute gastroenteritis, burns, and internal or external hemorrhage can result in this syndrome. Prerenal ARF can also result from decreased renal perfusion in patients with heart failure or sepsis.

Special classes of medications that can induce prerenal ARF in volume-depleted states are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which are otherwise safely tolerated and beneficial in most patients with chronic kidney disease.

Arteriolar vasoconstriction leading to prerenal ARF can occur in hypercalcemic states, with the use of NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine, and catecholamines.

The hepatorenal syndrome can also be considered a form of prerenal ARF, because functional renal failure develops from diffuse renal vasoconstriction.

To summarize, volume depletion can be caused by the following:

- Renal losses (diuretics, polyuria)
- GI losses (vomiting, diarrhea)
- Hemorrhage
- Extra vascular sequestration
    - Pancreatitis and burns

Decreased renal perfusion can be caused by the following:

- Heart failure
- Pulmonary embolism
- Acute myocardial infarction
- Severe valvular disease

Systemic vasodilation can be caused by the following:

- Sepsis
- Anaphylaxis
- Antihypertensives

Afferent arteriolar vasoconstriction can be caused by the following:

- Hypercalcemia
- Drugs (NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine)
- Hepatorenal syndrome

Diseases that compromise renal perfusion include the following:

- Renal arterial stenosis - atherosclerotic, fibromuscular dysplasia,
- Renal artery embolism - septic, cholesterol

Intrinsic ARF

Structural injury in the kidney is the hallmark of intrinsic renal failure, and the most common form is acute tubular necrosis (ATN), either ischemic or cytotoxic. Frank necrosis is not prominent in most cases of ATN and tends to be patchy. Less obvious injury includes loss of brush borders, flattening of the epithelium, detachment of cells, formation of intratubular casts, and dilatation of the lumen. Although these changes are observed predominantly in proximal tubules, injury to the distal nephron can also be demonstrated. In addition, the distal nephron may become obstructed by desquamated cells and cellular debris.

In contrast to necrosis, the principal site of apoptotic cell death is the distal nephron. During the initial phase of ischemic injury, loss of integrity of the actin cytoskeleton leads to flattening of the epithelium, with loss of the brush border, loss of focal cell contacts, and subsequent disengagement of the cell from the underlying substratum.

Many endogenous growth factors that participate in the process of regeneration have not been identified; however, administration of growth factors exogenously has been shown to ameliorate and hasten recovery from ARF. Depletion of neutrophils and blockage of neutrophil adhesion reduce renal injury following ischemia, indicating that the inflammatory response is responsible, in part, for some features of ATN, especially in postischemic injury after transplant.

Intrarenal vasoconstriction is the dominant mechanism for the reduced GFR in patients with ATN. The mediators of this vasoconstriction are unknown, but tubular injury seems to be an important concomitant finding. Urine backflow and intratubular obstruction (from sloughed cells and debris) are causes of reduced net ultrafiltration. The importance of this mechanism is highlighted by the improvement in renal function that follows relief of such intratubular obstruction.

In addition, when obstruction is prolonged, intrarenal vasoconstriction is prominent in part due to the tubuloglomerular feedback mechanism, which is thought to be mediated by adenosine and activated when there is proximal tubular damage and the macula densa is presented with increased chloride load.

Apart from the increase in basal renal vascular tone, the stressed renal microvasculature is more sensitive to potentially vasoconstrictive drugs and otherwise-tolerated changes in systemic blood pressure. The vasculature of the injured kidney has an impaired vasodilatory response and loses its autoregulatory behavior. This latter phenomenon has important clinical relevance because the frequent reduction in systemic pressure during intermittent hemodialysis may provoke additional damage that can delay recovery from ATN. Often, injury results in atubular glomeruli, where the glomerular function is preserved, but the lack of tubular outflow precludes its function.

A physiologic hallmark of ATN is a failure to maximally dilute or concentrate urine (isosthenuria). This defect is not responsive to pharmacologic doses of vasopressin. The injured kidney fails to generate and maintain a high medullary solute gradient, because the accumulation of solute in the medulla depends on normal distal nephron function. (Failure to excrete concentrated urine even in the presence of oliguria is a helpful diagnostic clue in distinguishing prerenal from intrinsic renal disease; in prerenal azotemia, urine osmolality is typically more than 500 mOsm/kg, whereas in intrinsic renal disease, urine osmolality is less than 300 mOsm/kg.)

Rapidly progressive glomerulonephritis (RPGN) can be a cause of ARF. Glomerular crescents (glomerular injury) are found in RPGN on biopsy; if more than 50% of glomeruli contain crescents, this usually results in a significant decline in renal function. Although comparatively rare, acute glomerulonephritides should be part of the diagnostic consideration in cases of ARF.

To summarize, vascular (large and small vessel) causes of intrinsic ARF include the following:

- Renal artery obstruction (thrombosis, emboli, dissection, vasculitis)
- Renal vein obstruction (thrombosis)
- Microangiopathy (TTP, HUS, Disseminated Intravascular Coagulation, preeclampsia)
- Malignant hypertension
- Scleroderma renal crisis
- Transplant rejection

Glomerular causes include the following:

- Anti-glomerular basement membrane (GBM) disease (Goodpasture syndrome)
- Anti-neutrophil cytoplasmic antibody(ANCA)-associated glomerulonephritis, Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis
- Immune complex Glomerulonephritis (lupus, postinfectious, cryoglobulinemia, primary membranoproliferative glomerulonephritis)

Tubular etiologies may include ischemia or cytotoxicity.

Cytotoxic etiologies include the following:

- Heme pigment (rhabdomyolysis, intravascular hemolysis)
- Tumor lysis syndrome, seizures, ethylene glycol poisoning

- Drugs (aminoglycosides, lithium, amphotericin B, pentamidine, cisplatin, ifosfamide, radiocontrast agents, megadose vitamin C, acyclovir, indinavir, methotrexate)

Interstitial causes include the following:

- Drugs (penicillins, cephalosporins, NSAIDs, proton-pump inhibitors, allopurinol, rifampin, indinavir, mesalamine, sulfonamides)
- Infection (pyelonephritis, viral nephritides)
- Systemic disease (Sjögren syndrome, sarcoid, lupus, lymphoma, leukemia, tubulonephritis, uveitis)

Postrenal ARF

Mechanical obstruction of the urinary collecting system, including the renal pelvis, ureters, bladder, or urethra, results in obstructive uropathy or postrenal ARF

If the site of obstruction is unilateral, then a rise in the Sr. Creatinine level may not be apparent due to contralateral renal function. Although the Sr. Creatinine level may remain low with unilateral obstruction, a significant loss of GFR occurs, and patients with partial obstruction may develop progressive loss of GFR if the obstruction is not relieved. Causes of obstruction include calculi, stricture, and intraluminal, extraluminal, or intramural tumors.

Bilateral obstruction is usually a result of benign prostatic hypertrophy or prostate tumors in men and urologic or gynecologic tumors in women.

Patients who develop anuria typically have obstruction at the level of the bladder or downstream to it.

To summarize, causes of postrenal ARF include the following:

- Ureteric obstruction (calculi, tumor, fibrosis, ligation during pelvic surgery)
- Bladder neck obstruction (benign prostatic hypertrophy [BPH], prostate carcinoma, neurogenic bladder, tricyclic antidepressants, ganglion blockers, bladder tumor, calculi, hemorrhage/clot)
- Urethral obstruction (strictures, tumor, phimosis)

The patient's age has significant implications for the differential diagnosis of ARF.

**Epidemiology**

Incidence in the United States

Approximately 1% of patients admitted to hospitals have ARF at the time of admission. The estimated incidence rate of ARF is 2-5% during hospitalization.

Acute renal failure develops within 30 days postoperatively in approximately 1% of general surgery cases;[10] it develops in up to 67% of ICU patients.[11] Approximately 95% of consultations with nephrologists are related to ARF.

Feest and colleagues calculated that the appropriate nephrologist referral rate is approximately 70 cases per million population.[12]

Although reliable statistics on the prevalence of ARF amongst different tropical countries are not available, statistics based on referrals to dialysis units suggest that the condition is more common in the tropics. Kaufman recently reported a 0.1% incidence of community acquired intrinsic ARF from the US.[13] This contrasts with data from a institute, a large referral hospital in North India, where 1.5% of all hospital admissions were referred to the Nephrology services for management of moderate or severe ARF.[14]

Race predilection

No race predilection is recognized in ARF.

Sex predilection

Males and females are affected equally by ARF.

Prognosis

The prognosis for patients with ARF is directly related to the cause of renal failure and, to a great extent, to the duration of renal failure prior to therapeutic intervention.

On long-term follow-up (1-10 years), approximately 12.5% of survivors of ARF are dialysis dependent (rates range widely, from 1-64%, depending on the patient population) and 19-31% of them have chronic kidney disease.[11]

A study from Canada showed a much higher incidence of ARF than in previous reports, 18.3% (7,856 of 43,008) in hospitalized patients.[15] The incidence of ARF correlated inversely with estimated GFR (eGFR) and was associated with a higher mortality rate and a higher incidence of subsequent end-stage renal disease (ESRD) at each level of baseline eGFR; however, the greatest impact on mortality was seen in individuals with eGFR greater than 60 mL/min who developed ARF. Those with stage 3 ARF (AKIN criteria) had a mortality rate of 50% compared to individuals with eGFR greater than 60 mL/min who did not develop ARF (3%).

Conversely, individuals with eGFR less than 30 who did not develop ARF had a higher mortality rate (12.1%) than those with an eGFR of greater than 60 mL/min, but the mortality rate with stage 3 ARF in patients with advanced CKD was 40.7%, somewhat less than patients with eGFR greater than 60 mL/min. This study confirms the short- and the long-term mortality risk and ESRD risk associated with ARF and suggests that the condition may be a more common event than previously recognized.[15]

Mortality rates and associated factors[16]

If ARF is defined by a sudden increment of Sr. Creatinine of 0.5-1 mg/dL and is associated with a mild to moderate rise in Sr. Creatinine, the prognosis tends to be worse. (Increments of 0.3 mg/dL in Sr. Creatinine have important prognostic significance.)

Even if renal failure is mild, however, the mortality rate for patients is 30-60%. If these patients need dialysis therapy, the mortality rate is 50-90%. The mortality rate is 31% in patients with normal urine sediment test results and is 74% in patients with abnormal urine sediment test results. The survival rate is nearly 0% among patients with ARF who have an Acute Physiology and Chronic Health Evaluation II (APACHE II) score higher than 40; the survival rate is 40% in patients with APACHE II scores of 10-19.

The in-hospital mortality rate for ARF is 40-50%. The mortality rate for patients in the ICU is higher in those who have ARF, especially when ARF is severe enough to require dialysis treatment; the mortality rate in patients in intensive care settings with ARF is 70-80%.

In addition, evidence suggests that the relative risk of death is 4.9 in patients in the ICU who have renal failure that is not severe enough to require dialysis. This reflects that the high mortality rate in patients with ARF who require dialysis may not be related to the dialysis procedure or accompanying comorbidities and that ARF alone may be an independent indicator of mortality.

In one published post hoc analysis of the Fluid and Catheter Treatment Trial (FACTT),[17] which examined liberal versus conservative fluid management in intubated ICU patients, fluid balance and diuretic use were identified as prognostic factors for mortality in individuals with ARF. Specifically, greater cumulative fluid accumulation over an average of 6 days was associated with a higher mortality (10.2 L vs 3.7 L in the liberal vs conservative group), and higher furosemide use was associated with a lower mortality (cumulatively 562 mg vs

159 mg). Of note, more than one half of the individuals had Stage 1 ARF (AKIN criteria) CKD, so whether these results apply to more severe stages of ARF is not clear. One interpretation of this study is that patients who can be stabilized with less volume resuscitation fare better. From a practical standpoint, one conclusion is that aggressive prolonged volume resuscitation does not improve prognosis in ARF in the ICU setting.

Other prognostic factors include the following:

- Older age
- Multiorgan failure (the more organs that fail, the worse the prognosis)
- Oliguria
- Hypotension
- Vasopressor support
- Number of transfusions
- Noncavitary surgery

Prerenal azotemia due to volume contraction is treated with volume expansion; if left untreated for a prolonged duration, tubular necrosis may result and may not be reversible.

Postrenal ARF, if left untreated for a long time, may result in irreversible renal damage. Procedures such as catheter placement, lithotripsy, prostatectomy, stent placement, and percutaneous nephrostomy can help to prevent permanent renal damage.

Timely identification of pyelonephritis, proper treatment, and further prevention using prophylactic antibiotics may improve the prognosis, especially in females. Early diagnosis of crescentic glomerulonephritis via renal biopsy and other appropriate tests may enhance early renal recovery, because appropriate therapy can be initiated promptly and aggressively. The number of crescents, the type of crescents (cellular vs fibrous), and the Sr. Creatinine level at the time of presentation may dictate prognosis for renal recovery in this subgroup of patients

Approximately 20-60% of patients experiencing ARF require dialysis during their hospital stay. The majority of these patients recover, with only 25% requiring long-term renal replacement therapy.

A large cohort study demonstrated that proteinuria coupled with low baseline GFR is associated with a higher incidence of ARF and should be considered as an identifying factor for individuals at risk. An occurrence of ARF by itself also has significant negative prognostic implications.[18]

One published study[19] examining ARF after elective surgery in more than 200,000 patients older than 66 years suggested that patients taking statins had a lesser incidence and severity of ARF and lower mortality than individuals not on statins. Furthermore, the incidence and severity correlated with the potency of the statin as well. As the study was a retrospective review, the authors were not able to recommend routine preoperative administration of statins; however, the study certainly suggests that statins should not be routinely discontinued prior to elective surgery.

**History**[9]

A detailed and accurate history is crucial to the diagnosis of the type of ARF that a patient has and to determining the required treatment.

Distinguishing ARF from chronic renal failure is important, yet making the distinction can be difficult. A history of chronic symptoms - fatigue, weight loss, anorexia, nocturia, and pruritus and presence of diabetes or any chronic renal disease suggests chronic renal failure.

The following history should be asked

- Nephrotoxic drug ingestion
- History of trauma or unaccustomed exertion
- Blood loss or transfusions
- Exposure to toxic substances, such as ethyl alcohol or ethylene glycol
- Exposure to mercury vapors, lead, cadmium, or other heavy metals, which can be encountered in welders and miners
- Urine output

Findings during the physical examination:

- Hypotension
- Dehydration
- Congestive heart failure
- Abdominal tenderness
- Evidence of connective tissue disorders or autoimmune diseases

People with the following comorbid conditions are at a higher risk for developing ARF:

- Hypertension
- Congestive cardiac failure
- Diabetes
- Multiple myeloma
- Chronic infection
- Myeloproliferative disorder

Urine output history can be useful. Oliguria generally favors ARF. Abrupt anuria suggests acute urinary obstruction, acute and severe glomerulonephritis, or embolic renal artery occlusion. A gradually diminishing urine output may indicate a urethral stricture or bladder outlet obstruction due to prostate enlargement.

Because of a decrease in functioning nephrons, even a trivial nephrotoxic insult may cause ARF to be superimposed on chronic renal insufficiency. ARF has a long differential diagnosis. History can help classify the pathophysiology of ARF as prerenal, intrinsic renal, or postrenal failure, and it may suggest some specific etiologies.

Prerenal failure

Patients commonly present with symptoms related to hypovolemia, including thirst, decreased urine output, dizziness, and orthostatic hypotension. Elders with vague mental status change are commonly found to have prerenal or normotensive ischemic ARF. Ask about volume loss from vomiting, diarrhea, sweating, polyuria, or hemorrhage. Patients with advanced cardiac failure leading to depressed renal perfusion may present with orthopnea and paroxysmal nocturnal dyspnea. Insensible fluid losses can result in severe hypovolemia in patients with restricted fluid access and should be suspected in elderly patients and in comatose or sedated patients.

Intrinsic renal failure

Patients can be divided into those with glomerular etiologies and those with tubular etiologies of ARF. Hematuria, edema, and HTN indicates a glomerular etiology of ARF (Nephritic syndrome). Query about prior throat or skin infections. ATN should be suspected in any patient presenting after a period of hypotension secondary to cardiac arrest, hemorrhage, sepsis, drug overdose, or surgery. A careful search for exposure to nephrotoxins should include a detailed list of all current medications and any recent radiologic examinations (exposure to radiocontrast agents).

Pigment-induced ARF should be suspected in patients with possible rhabdomyolysis (muscular pain, recent coma, seizure, intoxication, excessive exercise, limb ischemia) or hemolysis (recent blood transfusion). Allergic interstitial nephritis should be suspected with fevers, rash, arthralgias, and exposure to certain medications, including NSAIDs and antibiotics.

Postrenal failure

Postrenal failure usually occurs in older men with prostatic obstruction and symptoms of urgency, frequency, and hesitancy. Patients may present with asymptomatic, high-grade urinary obstruction because of the chronicity of their symptoms. A history of prior gynecologic surgery or abdominopelvic malignancy often can be helpful in providing clues to the level of obstruction. Flank pain and hematuria should raise a concern about renal calculi or papillary necrosis as the source of urinary obstruction. Use of acyclovir, methotrexate, triamterene, indinavir, or sulfonamides implies the possibility of tubular obstruction by crystals of these medications.

**Physical Examination**[9]

Obtaining a thorough physical examination is extremely important when collecting evidence about the etiology of ARF.

Skin

- Livido reticularis, digital ischemia, butterfly rash, palpable purpura - Systemic vasculitis
- Maculopapular rash - Allergic interstitial nephritis
- Track marks (intravenous drug abuse) – Endocarditis
- Petechiae, purpura, ecchymosis, and livedo reticularis provide clues to inflammatory and vascular causes of AK.
- Infectious diseases, TTP, DIC, and embolic phenomena can produce typical cutaneous changes.

Eyes

- Keratitis, iritis, uveitis, dry conjunctivae - Autoimmune vasculitis
- Jaundice - Liver diseases
- Band keratopathy (hypercalcemia) - Multiple myeloma
- Signs of diabetes mellitus
- Signs of hypertension
- Atheroemboli (retinopathy)

Evidence of uveitis may indicate interstitial nephritis and necrotizing vasculitis. Ocular palsy may indicate ethylene glycol poisoning or necrotizing vasculitis. Findings suggestive of severe hypertension, atheroembolic disease, and endocarditis may be observed on careful examination of the eyes.

Ears

- Hearing loss - Alport disease and aminoglycoside toxicity
- Mucosal or cartilage ulcerations - Wegener granulomatosis

Cardiovascular system

- Irregular rhythms (atrial fibrillation) - Thromboemboli
- Murmurs - Endocarditis
- Increased jugulovenous distention, rales, $S_3$ - CHF

The most important part of the physical examination is the assessment of cardiovascular and volume status. The physical examination must include pulse rate and blood pressure recordings measured in the supine position and the

standing position; close inspection of the jugular venous pulse; careful examination of the heart, lungs, skin turgor, and mucous membranes; and assessment for the presence of peripheral edema.

In hospitalized patients, accurate daily records of fluid intake and urine output and daily measurements of patient weight are important. Hypovolemia leads to hypotension; however, hypotension may not necessarily indicate hypovolemia.

Severe CHF may also cause hypotension. Although patients with CHF may have low blood pressure, volume expansion is present and effective renal perfusion is poor, which can result in ARF. Severe hypertension with renal failure suggests renovascular disease, glomerulonephritis, vasculitis, or atheroembolic disease.

Abdomen

- Pulsatile mass or bruit - Atheroemboli
- Costovertebral angle tenderness - Nephrolithiasis, papillary necrosis
- Pelvic, rectal masses; prostatic hypertrophy; distended bladder – Urinary obstruction
- Limb ischemia, edema - Rhabdomyolysis

Abdominal examination findings can be useful to help detect obstruction at the bladder outlet as the cause of renal failure, which may be due to cancer or an enlarged prostate. The presence of tense ascites can indicate elevated intra-

abdominal pressure that can retard renal venous return and result in ARF. The presence of an epigastric bruit suggests renal vascular hypertension, which may predispose to ARF.

Pulmonary

- Rales - Goodpasture syndrome, Wegener granulomatosis
- Hemoptysis - Wegener granulomatosis

**Diagnosis**

Several laboratory tests are useful for assessing the etiology of ARF, and the findings can aid in proper management. These tests include complete blood count (CBC), serum biochemistries, urine analysis with microscopy, and urine electrolytes. In some cases, renal imaging is useful, especially if renal failure is secondary to obstruction. The American College of Radiology recommends ultrasonography, preferably with Doppler methods, as the most appropriate imaging method in ARF.[20]

Blood Urea Nitrogen and Sr. Creatinine[16]

Although increased levels of BUN and creatinine are the hallmarks of renal failure, the rate of rise is dependent on the degree of renal insult as well as on protein intake with respect to BUN. The ratio of BUN to creatinine is an important finding, because the ratio can exceed 20:1 in conditions in which enhanced reabsorption of urea is favored (in volume contraction); this suggests

prerenal acute renal failre (ARF). BUN may be elevated in patients with GI or mucosal bleeding, steroid treatment, or protein loading.

Assuming no renal function, the rise in BUN over 24 hours can be roughly predicted using the following formula: 24-hour protein intake in milligrams X 0.16 divided by total body water in mg/dL added to the BUN value. Assuming no renal function, the rise in Sr. Creatinine can be predicted using the following formulas:

- For males: weight in kilograms X [28 - 0.2(age)] divided by total body water in mg/dL added to the creatinine value
- For females: weight in kilograms X [23.8 - 0.17(age)] divided by total body water added to the Sr. Creatinine value

As a general rule, if Sr. Creatinine increases to more than 1.5 mg/dL/d, rhabdomyolysis must be ruled out.

CBC, Peripheral Smear, and Serology[16]

The peripheral smear may show schistocytes in conditions such as HUS or TTP. A finding of increased rouleaux formation suggests multiple myeloma, and the workup should be directed towards serum and urine immunoelectrophoresis. The presence of myoglobin or free hemoglobin, increased serum uric acid level, and other related findings may help to further define the etiology of ARF.

Serologic tests for antinuclear antibody (ANA), ANCA, anti-GBM antibody, hepatitis, and antistreptolysin (ASO) and complement levels may help to include and exclude glomerular disease. Although serologic tests can be informative, the costs can be prohibitive if these tests are not ordered judiciously.

Urinalysis[16]

Findings of granular, muddy-brown casts are suggestive of tubular necrosis. The presence of tubular cells or tubular cell casts also supports the diagnosis of ATN. Often, oxalate crystals are observed in cases of ATN. Reddish brown or cola-colored urine suggests the presence of myoglobin or hemoglobin, especially in the setting of a positive dipstick for heme and no red blood cells (RBCs) on the microscopic examination. The dipstick assay may reveal significant proteinuria as a result of tubular injury.

The presence of RBCs in the urine is always pathologic. Eumorphic RBCs suggest bleeding along the collecting system. Dysmorphic RBCs or RBC casts indicate glomerular inflammation, suggesting glomerulonephritis is present. The presence of WBCs or WBC casts suggests pyelonephritis or acute interstitial nephritis. The presence of urine eosinophils is helpful in establishing a diagnosis but is not necessary for allergic interstitial nephritis to be present.

The presence of eosinophils, as visualized with Wright stain or Hansel stain, suggests interstitial nephritis but can also be seen in urinary tract infections, glomerulonephritis, and atheroembolic disease. The presence of uric acid crystals

may represent ATN associated with uric acid nephropathy. Calcium oxalate crystals are usually present in cases of ethylene glycol poisoning.

Urine Electrolytes[16]

Urine electrolyte findings also can serve as valuable indicators of functioning renal tubules. The fractional excretion of sodium (FENa) is the commonly used indicator. However, the interpretation of results from patients in nonoliguric states, those with glomerulonephritis, and those receiving or ingesting diuretics can lead to an erroneous diagnosis.

FENa can be a valuable test for helping to detect extreme renal avidity for sodium in conditions such as hepatorenal syndrome. The formula for calculating the FENa is as follows:

$$FENa = (U_{Na}/P_{Na}) / (U_{Cr}/P_{Cr}) \text{ X } 100$$

Calculating the FENa is useful in acute kidney injury (AKI) only in the presence of oliguria. In patients with prerenal azotemia, the FENa is usually less than 1%. In ATN, the FENa is greater than 1%. Exceptions to this rule are ATN caused by radiocontrast nephropathy, severe burns, acute glomerulonephritis, and rhabdomyolysis.

In the presence of liver disease, FENa can be less than 1% in the presence of ATN. On the other hand, because administration of diuretics may cause the FENa to be greater than 1%, these findings cannot be used as the sole indicators in ARF. In patients who are receiving diuretics, a fractional excretion of urea

(FEUrea) can be obtained, since urea transport is not affected by diuretics. The formula for calculating the FEUrea is as follows:

$$FEUrea = (U_{urea}/P_{urea}) / (U_{Cr}/P_{Cr}) \text{ X } 100$$

FEUrea of less than 35% is suggestive of a prerenal state.

Bladder Pressure[16]

An intra-abdominal pressure of less than 10 mm Hg is considered normal and suggests that abdominal compartment syndrome is not the cause of ARF. Patients with an intra-abdominal pressure below 15-25 mm Hg are at risk for abdominal compartment syndrome, and those with bladder pressures above 25 mm Hg should be suspected of having ARF as a result of abdominal compartment syndrome.

Ultrasonography[16]

Renal ultrasonography is useful for evaluating existing renal disease and obstruction of the urinary collecting system. The degree of hydronephrosis does not necessarily correlate with the degree of obstruction. Mild hydronephrosis may be observed with complete obstruction if found early. Obtaining images of the kidneys can be technically difficult in patients who are obese or in those with abdominal distension due to ascites, gas, or retroperitoneal fluid collection. Ultrasonographic scans or other imaging studies showing small kidneys suggest chronic renal failure.

Doppler ultrasonography[16]

Doppler scans are useful for detecting the presence and nature of renal blood flow. Because renal blood flow is reduced in prerenal or intrarenal ARF, test findings are of little use in the diagnosis of ARF. However, Doppler scans can be quite useful in the diagnosis of thromboembolic or renovascular disease. Increased resistive indices can be observed in patients with hepatorenal syndrome.

Nuclear Scanning[16]

Radionuclide imaging with technetium-99m-mercaptoacetyltriglycine (99m Tc-MAG3),$^{99m}$ Tc-diethylenetriamine penta-acetic acid ($^{99m}$ Tc-DTPA), or iodine-131 ($^{131}$ I)-hippurate can be used to assess renal blood flow and tubular functions. Because of a marked delay in tubular excretion of radionuclide in prerenal disease and intrarenal disease, the value of these scans is limited.

Aortorenal Angiography[16]

This can be helpful in establishing the diagnosis of renal vascular diseases, including renal artery stenosis, renal atheroembolic disease, and atherosclerosis with aortorenal occlusion, and in certain cases of necrotizing vasculitis (polyarteritis nodosa).

Renal Biopsy[9,16]

A renal biopsy can be useful in establishing the diagnosis of intrarenal causes of ARF and can be justified if it will change management (initiation of

immunosuppressive medications). A renal biopsy may also be indicated when renal function does not return for a prolonged period and a prognosis is required to develop long-term management. In as many as 40% of cases, renal biopsy results reveal an unexpected diagnosis. Acute cellular or humoral rejection in a transplanted kidney can be definitively diagnosed only by performing a renal biopsy.

Emerging Biomarkers

A number of biomarkers are being investigated to risk stratify and predict ARF in patients at risk for the disease. The reason for this is because creatinine is a late marker for renal dysfunction and, once elevated, reflects a severe reduction in GFR. The most promising biomarker to date is urinary neutrophil gelatinase-associated lipocalin (NGAL), which has been shown to predict ARF in children undergoing cardiopulmonary bypass surgery.

**Serum cystatin C**

Glomerular filtration rate is considered the best marker of renal function, and Sr. Creatinine is the most commonly used biochemical parameter to estimate GFR in routine practice. However, there are some shortcomings to the use of this parameter. Factors such as muscle mass and protein intake can influence Sr. Creatinine, leading to an inaccurate estimation of GFR. Normal Sr. Creatinine may be observed in individuals with significantly impaired GFR.[21,22] Moreover, in unstable, critically ill patients, acute changes in renal function can make real-time evaluation of GFR using Sr. Creatinine difficult.[23]

In the absence of effective, specific therapies for ARF, the early and accurate detection of ARF is crucial to prevent its progression, and thereby, to potentially improve its outcome.[24,25,26]

In clinical practice, the detection of ARF, which is characterized by a rapid decline of the GFR, is based on an increase of Sr. Creatinine.[27]

However, there are major limitations to the use of creatinine for estimating GFR. Sr. Creatinine does not accurately reflect GFR during the nonsteady state of ARF by underestimating GFR.[28] Thus, minor changes of creatinine, as typically seen early in ARF, may already reflect substantial declines in GFR. Furthermore, Sr. Creatinine inaccurately estimates GFR due to tubular secretion and reabsorption of creatinine, and nonrenal factors that may apply to ARF patients who are predominantly critically ill.[28]

To overcome these obstacles, there is an extensive search for improved laboratory markers of impaired renal function. Cross-sectional studies in chronic renal insufficiency identified Sr. Cystatin C as a promising, easily measurable marker to estimate GFR with a higher diagnostic value than Sr. Creatinine.[29,30]

Cystatin C is a 13 kD endogenous cysteine proteinase inhibitor and is produced by nucleated cells at a constant rate. Cystatin C is freely filtered by the glomerulus, reabsorbed, and catabolized, but it is not secreted by the tubules.[31,32]

Further studies[33,34] demonstrated the superiority of Sr. Cystatin C compared to creatinine, especially to detect minor GFR reduction. This finding was confirmed by a recent meta-analysis.[35]

Previous longitudinal studies[36-40] on Sr. Cystatin C predominantly suggested that Sr. Cystatin C performed better than Sr. Creatinine as a marker to detect acute changes of GFR. However, these studies were limited because they examined either GFR changes in small patient samples or did not include controls.

Furthermore limiting, most studies[36-39] were conducted in renal transplant recipients early after transplantation, and high-dose glucocorticoid medication may have interfered with Sr. Cystatin C.[41,42]

Cystatin C is a nonglycosylated protein that belongs to the cysteine protease inhibitors, cystatin superfamily.[43]

These proteins play an important role in the regulation of proteolytic damage to the cysteine proteases. Cystatin C is produced at a constant rate by nucleated cells.[31] It is found in relatively high concentrations in many body fluids, especially in the seminal fluid, cerebrospinal fluid and synovial fluid.[44]

Its low molecular weight (13.3 kDa) and positive charge at physiological pH levels facilitate its glomerular filtration. Subsequently, it is reabsorbed and almost completely catabolized in the proximal renal tubule.[32,45] Therefore, because of its constant rate of production, its serum concentration is determined by glomerular filtration.[46-49]

Moreover, its concentration is not influenced by infections, liver diseases, or inflammatory diseases. Use of Sr. Cystatin C as a marker of GFR is well

documented, and some authors have suggested that it may be more accurate than Sr. Creatinine for this purpose.[50-56]

Monitoring renal function is extremely important in the management of critically ill patients. GFR, which can be measured by determining the clearance of various substances, is the 'gold standard' parameter for monitoring renal function. The ideal endogenous marker would be characterized by stable production rate, stable circulating levels (unaffected by pathological changes), lack of protein binding, free glomerular filtration, and lack of reabsorption or secretion; to date, no such marker has yet been identified. Some substances such as creatinine, urea, $\beta_2$-microglobulin and retinol-binding protein have been used as endogenous markers of GFR, by measuring either their plasma levels or their renal clearance. Among them, the most useful markers for assessing GFR are Sr. Creatinine and renal $C_{Cr}$. This is secondary to their correlations with the renal clearance of some exogenous substances (inulin, creatinine-EDTA, iothalamate) that are considered 'gold standards' for determining GFR.[23]

Creatinine production changes significantly according to the muscle mass of the body and dietetic factors. It is filtered by the glomeruli, but it is also secreted by the renal tubules. This tubular secretion contributes approximately 20% of the total creatinine excretion by the kidney, and it can increase as GFR decreases. All of these factors explain why Sr. Creatinine concentration may not be a good parameter for accurate determination of GFR, especially at lower rates.[23]

Cystatin C production in the body is a stable process that is not influenced by increased protein catabolism, or dietetic factors. Moreover, it does not change with age or muscle mass like creatinine does. Its biochemical characteristics allow free filtration in the renal glomerulus, and subsequent metabolism and reabsorption by the proximal tubule. For these reasons, Sr. Cystatin C has been suggested to be an ideal endogenous marker of GFR.[50-56]

# Chapter 4

# Methodology

# METHODOLOGY

The present study was conducted on patients admitted in the Medical Intensive Care Unit of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010.

**Study design**

One year Cross sectional study

**Study period**

The present study was conducted during January 2010 to December 2010

**Source of data**

Patients admitted in the Medical Intensive Care Unit of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum

**Sample size**

A total of 50 patients admitted in the Medical Intensive Care Unit of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum

**Sampling procedure**

As this is a cross sectional study sample size was calculated by the following formula

$N=4PQ/D^2$

Where N: Sample size

P: Prevalence of the disease which was taken as 50% as no records were available regarding the study.

Q: 100-P

D: Absolute error taken as 15%

**Selection criteria**

Inclusion

- Patients at risk of developing ARF (all patients of medical intensive care unit without co-exiciting/known acute or chronic renal failure).

**Exclusion**

- Acute and Chronic Renal Failure.

**Procedure**

The study was approved by the Ethical and Research Committee of J. N. Medical College Belgaum. Based on the selection criteria every fifth patient admitted in Medical Intensive Care Unit was screened for eligibility. The patients with normal Sr. Creatinine that is ≤ 1.3 mg/dl and willing to participate were included in the study after obtaining their informed consent (Annexure 1). Patients with acute or chronic renal failure that is Sr. Creatinine > 1.3 mg/dL were excluded from the study.[5]

Demographic data like age, gender, address and occupation was recorded on predesigned and pretested proforma (Annexure 2). At admission detailed history was taken in all patients and thorough general physical and systemic

examination was carried out with special attention to the symptoms of the patients. Clinical diagnosis was made depending on history and examination.

**Vital signs**

Temperature, pulse rate, blood pressure, respiratory rate, oxygen saturation were monitored hourly

**Intake and out put charting**

Meticulous fluid chart consisting of amount and type of intravenous fluid given and accurate urine output charting was maintained in all the patients. Most of the patients were catheterised as they were critically ill.

All base line investigations as per the predesigned and pretested proforma like complete blood count, liver function test, renal function test, urine routine and microscopy were done.

Sr. TSH, X-ray chest, ultrasound abdomen and other necessary tests to make a etiological diagnosis were done at admission. S. Cystatin C levels were determined at admission and these were considered as the first reading of Sr. Creatinine and Sr. Cystatin C.

Sr. Cystatin C was done by serum nephelometry method. Any value above 0.95 mg/l was considered high.[57]

Further Sr. Creatinine was done daily for five days in all the patients to know whether the patient has developed ARF.

Acute Renal Failure was defined as an abrupt decrease in renal function (over hours to days) sufficient to result in retention of nitrogenous waste products (blood urea nitrogen and creatinine) in the body. There is no consensus regarding the magnitude of elevation of Sr. Creatinine or blood urea nitrogen sufficient to ascribe a diagnosis of ARF. In this study ARF is detected according to first three RIFLE (the Risk of renal dysfunction, Injury to the kidney, Failure of the kidney function, Loss of kidney function and End Stage Renal Disease) criteria of the GFR domain.

First three RIFLE criteria of GFR domain are;[8]

- R-criteria is raise in creatinine by ≥ 50%
- I-criteria is raise in creatinine by ≥100%
- F-criteria is raise in creatinine by ≥200%

Once there was increase in Sr. Creatinine of more than or equal to fifty percentage from baseline, Sr. Cystatine C levels were repeated. The values of Sr. Creatinine and Sr. Cystatin C on this day were considered as the second readings.

The percentage rise of Sr. Creatinine and Sr. Cystatin C were calculated.

Patients were categorized depending upon the percentage rise of sr. Creatinine into R (creat), I (creat) and F (creat) in accordance to first three RIFLE criteria of the GFR domain.

Similarly the patients with rise in Sr. Cystatin C ≥ 50%. ≥100% and ≥ 200% were categorised as R(cyst), I(cyst) and F (cyst).

In the patients who did not develop ARF, Sr. Cystatin C was done on day 5. These patients were considered as controls.

Complete blood count, liver function tests, urine routine and microscopy, Chest X-ray was done at admission and repeated when required.

**Statistical methods**

The data was tabulated and analysed using rates, ratios, percentages. The comparison was done using chi-square test and student-t test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

# Chapter 5

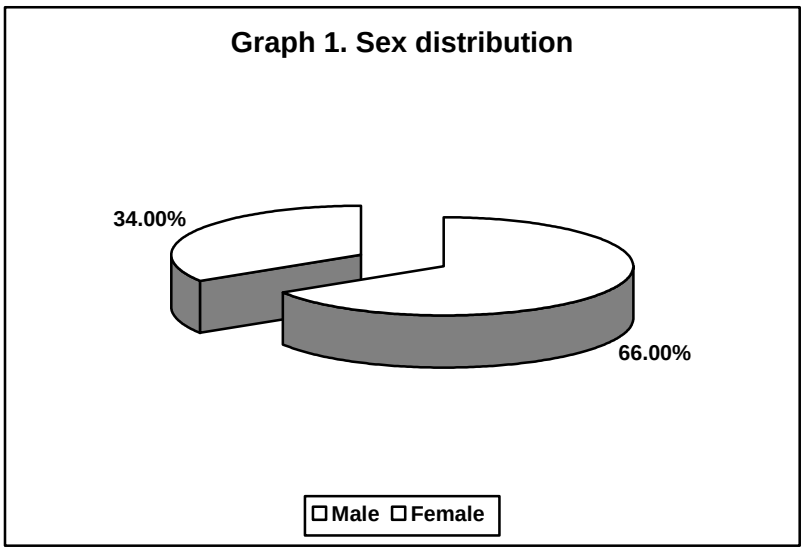
# Results

# RESULTS

The present one year cross sectional study was conducted on patients admitted in the Medical Intensive Care Unit of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. A total of 50 patients were studied. The data obtained was tabulated and analysed as below.

**Table 1. Sex distribution**

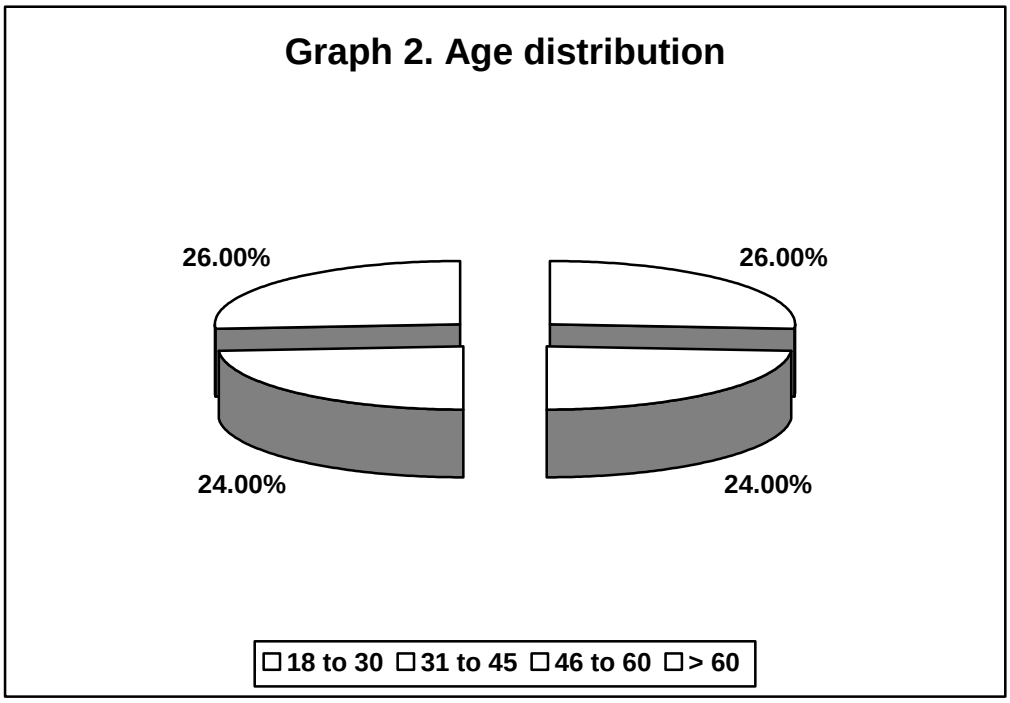
| Gender | Distribution (n=50) | |
|---|---|---|
| | **Number** | **Percentage** |
| Male | 33 | 66.00 |
| Female | 17 | 34.00 |
| **Total** | **50** | **100.00** |




In the present study out of 50 patients, 33 (66%) were male and 17 (34%) were female. The male: female ratio was 1.94:1.

**Table 2. Age distribution**

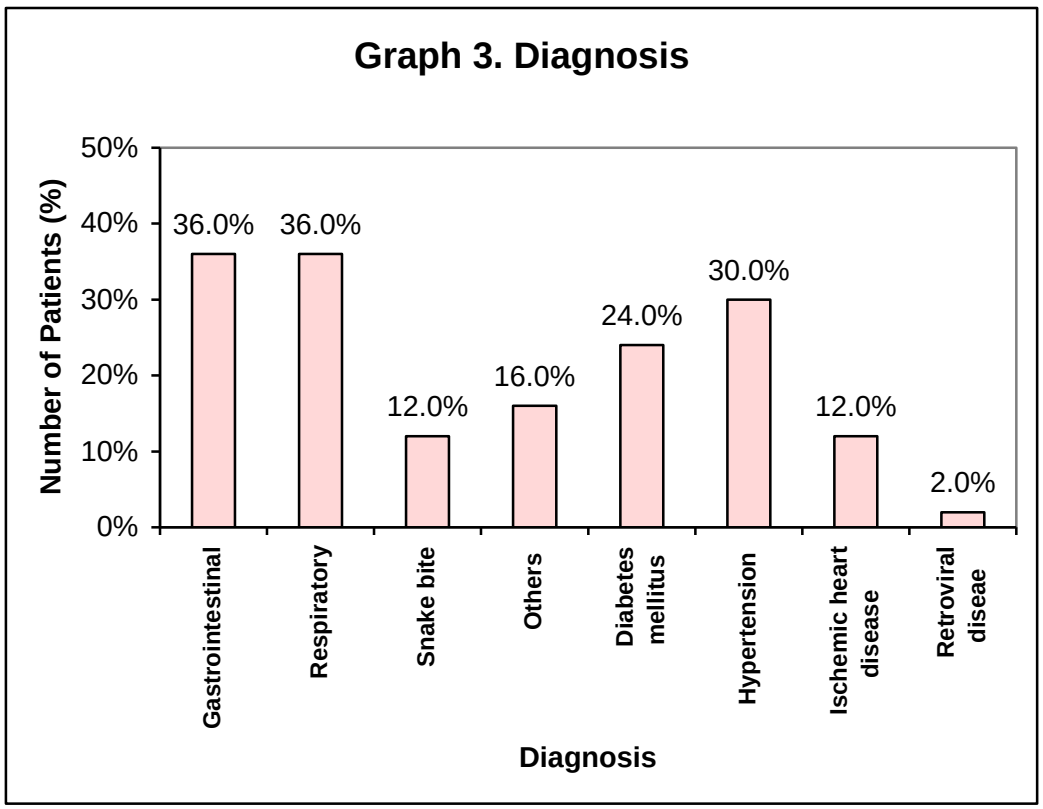
| Age group (Years) | Distribution (n=50) | |
|---|---|---|
| | **Number** | **Percentage** |
| 18 – 30 | 13 | 26.00 |
| 31 – 45 | 12 | 24.00 |
| 46 – 60 | 12 | 24.00 |
| > 60 | 13 | 26.00 |
| **Total** | **50** | **100.00** |




In this study, out of 50 patients, there were 13 (26%) patients each in the age group of 18 to 30 years and more than 60 years, and 12 (24%) patients each in the age group of 31 to 45 years and 46 to 60 years.

**Table 3. Primary diagnosis according to the system involved and associated conditions**

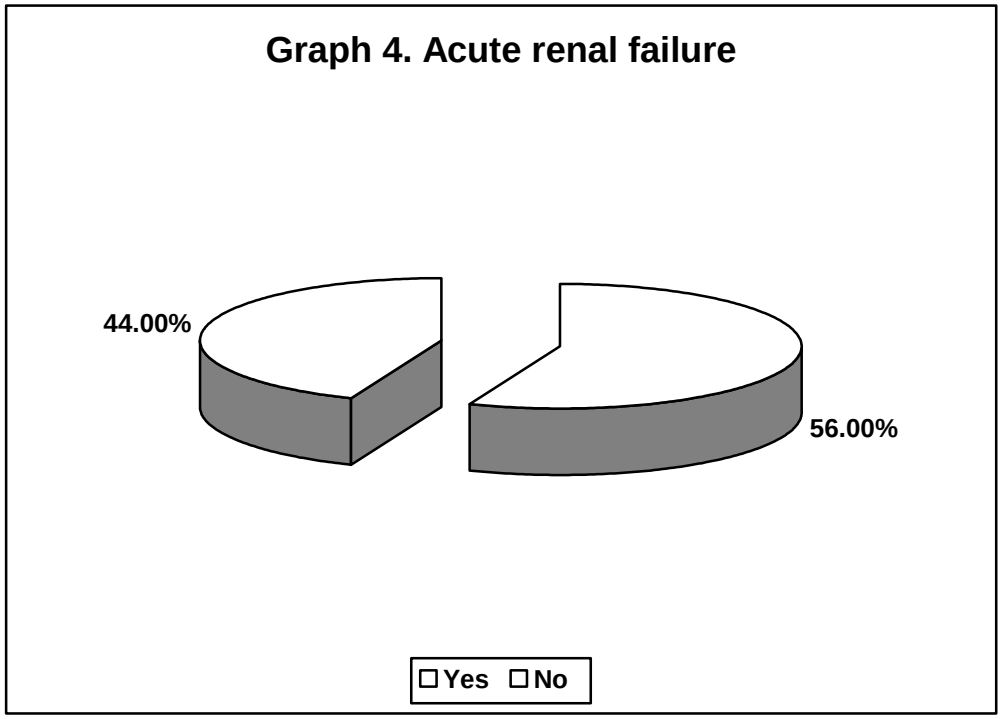
| Diagnosis | Distribution (n=50) | |
|---|---|---|
| | No. | % |
| Gastrointestinal | 18 | 36 |
| Respiratory | 18 | 36 |
| Snake bite | 6 | 12 |
| Others | 8 | 16 |
| Diabetes mellitus | 12 | 24 |
| Hypertension | 15 | 30 |
| Ischemic heart disease | 6 | 12 |
| Retroviral disease | 1 | 2 |




In the present study, there were 18 (36%) patients each with primary gastrointestinal and respiratory disease and 6 (12%) patients with snake bite.

**Table 4. Acute renal failure**

| Acute renal failure | Distribution (n=50) | |
|---|---|---|
| | **No.** | **%** |
| Yes | 28 | 56.00 |
| No | 22 | 44.00 |
| **Total** | **50** | **100.00** |




In the present study 28 (56%) patients developed ARF.

**Table 5. Sex distribution in ARF and Non ARF patients**

| Sex | ARF (n=28) | | Non ARF (n=22) | |
|---|---|---|---|---|
| | **Number** | **Percentage** | **Number** | **Percentage** |
| Male | 18 | 64.29 | 15 | 68.18 |
| Female | 10 | 35.71 | 7 | 31.82 |
| Total | **28** | **100.00** | **22** | **100.00** |
| $x^2$=0.083 | | DF=1 | | p=0.773 |

In the present study, there were 18 (64.29%) males and 10 (35.71 %) females in the patients with ARF. Among those who did not develop ARF 15 (68.18%) were males and 7 (31.82%) were females suggesting equal distribution of gender in both groups.

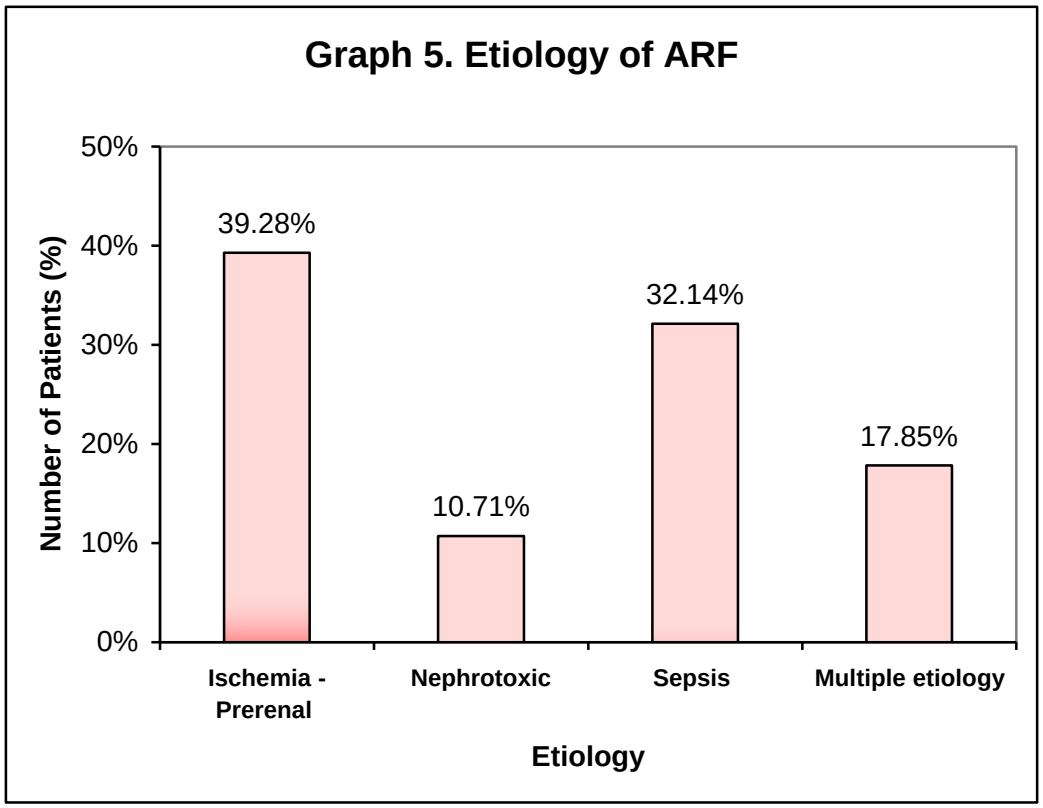
**Table 6. Comparison of mean age among patients with and without ARF patients**

| Acute renal failure | Mean age (Years) | |
|---|---|---|
| | **Mean** | **SD** |
| With ARF | 50.25 | 17.85 |
| Without ARF | 44.82 | 20.20 |
| t=0.937 | DF=48 | p=0.353 |

In the present study the mean age of patients with ARF was 50.25 ± 17.85 years and in patients who did not develop ARF the mean age was 44.82 ± 20.20 years suggesting that age in both the groups were comparable.

**Table 7. Etiology of ARF**

| Diagnosis | Distribution (n=28) | |
|---|---|---|
| | **No.** | **%** |
| Ischemia – Prerenal | 11 | 39.28 |
| Nephrotoxic | 3 | 10.71 |
| Sepsis | 9 | 32.14 |
| Multiple etiology | 5 | 17.85 |




In the present study, majority that is 11 (39.28%) patients developed ARF due to ischemia – prerenal etiology whereas nine, three and five patients developed ARF due to sepsis (32.14%), nephrotoxicity (10.71%) and combination of multiple etiologies (17.85%) respectively.

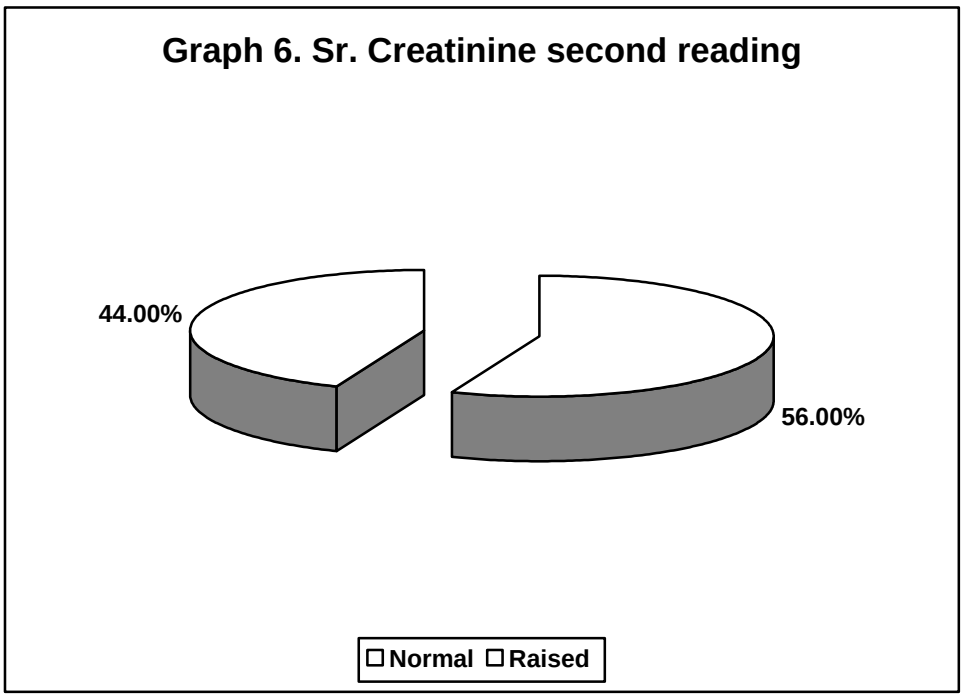
**Table 8. Sr. Creatinine on admission**

| Sr. Creatinine | Distribution (n=50) | |
|---|---|---|
| | **Number** | **Percentage** |
| Normal | 50 | 100.00 |
| Raised | 0 | 0.00 |
| **Total** | **50** | **100.00** |

In the present study Sr. creatinine on admission was normal in all 50 (100%) patients.

**Table 9. Sr. Creatinine second reading**

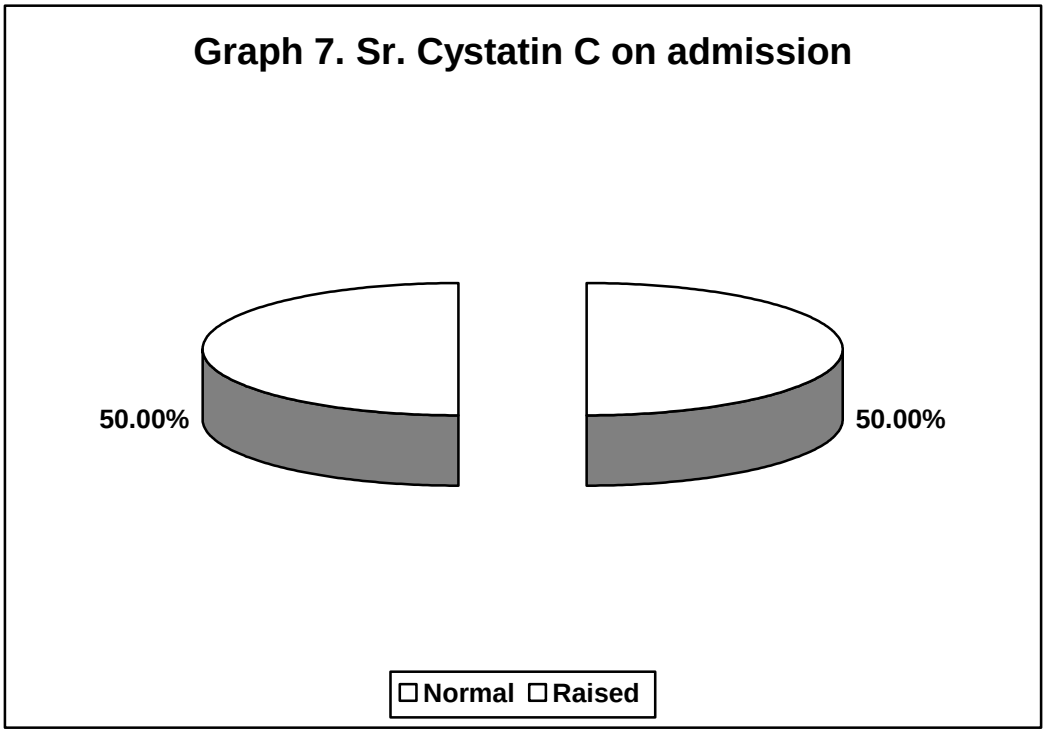
| Sr. Creatinine | Distribution (n=50) | |
|---|---|---|
| | **No.** | **%** |
| Normal | 28 | 56.00 |
| Raised | 22 | 44.00 |
| **Total** | **50** | **100.00** |




In the present study second reading of Sr. creatinine was normal in 28 (56%) patients and high in 22 (44%) patients

**Table 10. Sr. Cystatin C on admission**

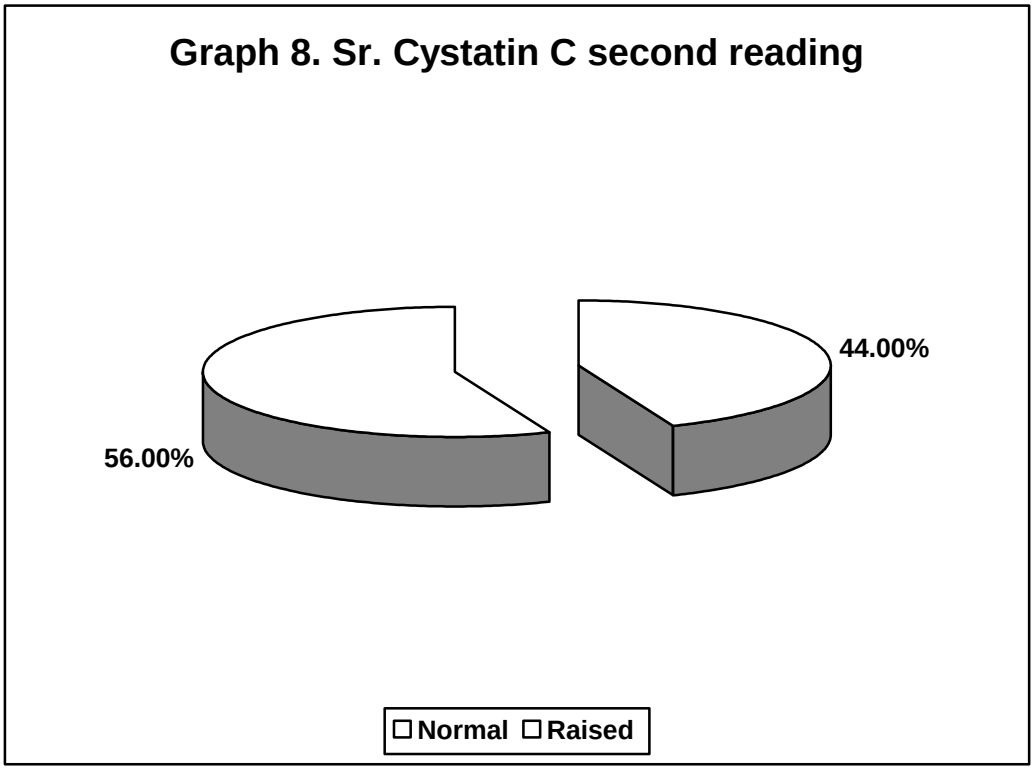
| Sr. Cystatin C | Distribution (n=50) | |
|---|---|---|
| | **Number** | **Percentage** |
| Normal | 25 | 50.00 |
| Raised | 25 | 50.00 |
| **Total** | **50** | **100.00** |




In the present study the first reading of Sr. Cystatin C was normal in 25 (50%) patients and high in 25 (50%) of patients.

**Table 11. Sr. Cystatin C second reading**

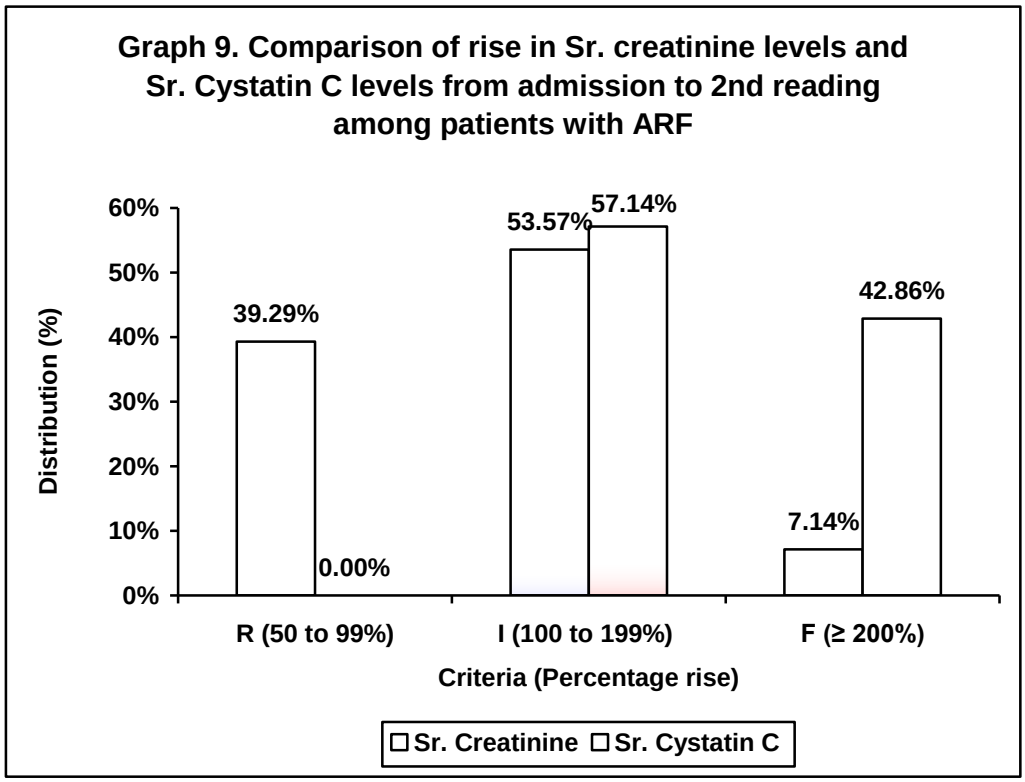
| Sr. Cystatin C | Distribution (n=50) | |
|---|---|---|
| | **No.** | **%** |
| Normal | 22 | 44.00 |
| Raised | 28 | 56.00 |
| **Total** | **50** | **100.00** |




In the present study the second reading of Sr. Cystatin C was normal in 22 (44%) patients and high in 28 (56%) patients.

**Table 12. Comparison of rise in Sr. creatinine levels and Sr. Cystatin C levels from admission to 2nd reading among patients with ARF**

| Criteria (Percentage Rise) | Sr. Creatinine (n=28) | | Sr. Cystatin C (n=28) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| R (50 to 99%) | 11 | 39.29 | 0 | 0.00 |
| I (100 to 199%) | 15 | 53.57 | 16 | 57.14 |
| F (≥ 200%) | 2 | 7.14 | 12 | 42.86 |
| **Total** | **28** | **100.00** | **28** | **100.00** |

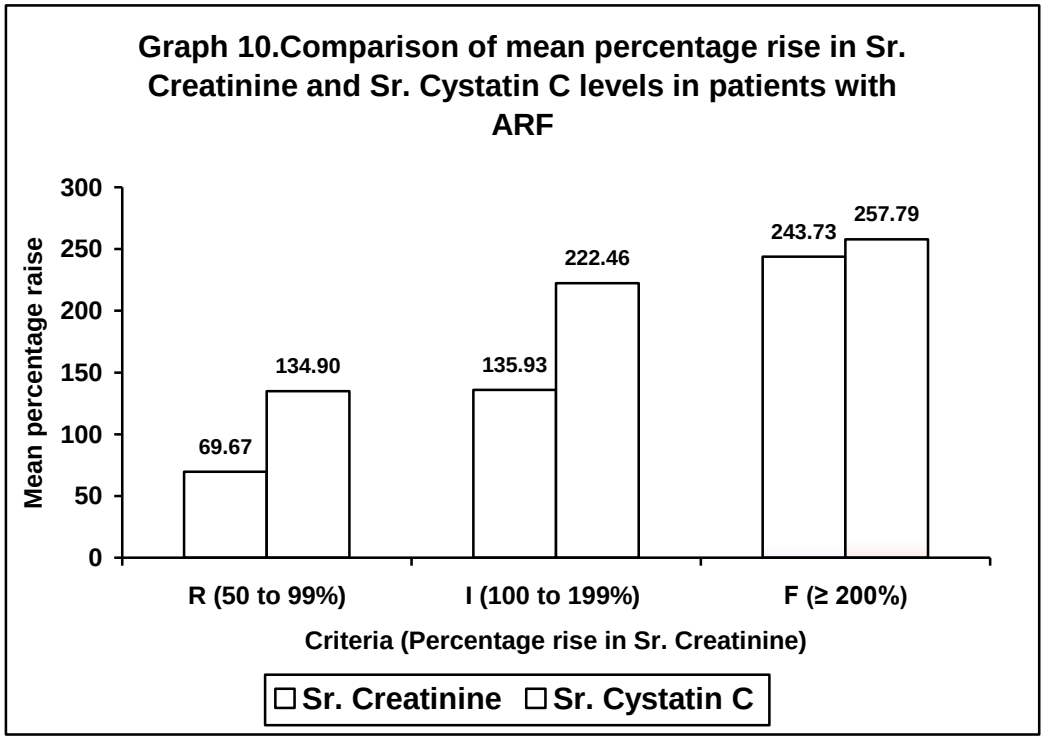



In the present study among patients who developed ARF 39.29%, 53.57% and 7.14% patients have satisfied $R_{Creat}$ (50 to 99%), $I_{Creat}$ (100 to 199%) and $F_{Creat}$ (≥ 200%) criteria respectively. Among patients with category $R_{Creat}$ rise of Sr. cystatin C was ≥ 100% and 57.14% patients had 100 to 199% rise in Sr. cystatin C levels and among 42.86% patients a rise of more than or equal 200% was noted.

**Table 13. Comparison of mean percentage rise in Sr. Creatinine and Sr. Cystatin C levels in patients with ARF**

| Criteria (Rise) | Mean percentage rise | | | | 't' | DF | 'p' value |
|---|---|---|---|---|---|---|---|
| | Sr. Creatinine | | Sr. Cystatin C | | | | |
| | Mean | SD | Mean | SD | | | |
| R (50 to 99%) | 69.67 | 11.33 | 134.90 | 24.18 | 8.143 | 20 | <0.001 |
| I (100 to 199%) | 135.93 | 26.65 | 222.46 | 43.88 | 6.506 | 28 | <0.001 |
| F (≥ 200%)* | 243.73 | 61.87 | 257.79 | 49.09 | - | - | - |

* Among patients with percentage rise ≥ 200% comparison could not be done as there were only two patients.

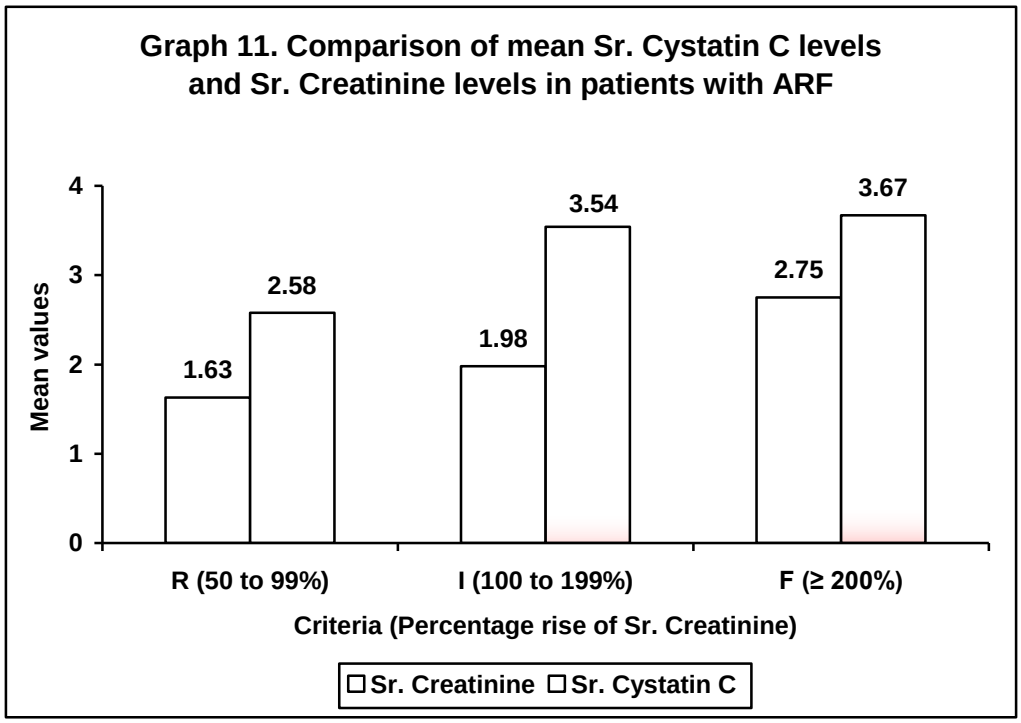



In this study among patients who developed ARF the mean percentage raise in Sr. creatinine levels in $R_{Creat}$ category was 69.67% ± 11.33% whereas

mean percentage raise in Sr. Cystatin were noted as 134.90% ± 24.18%. Similarly in those with category $I_{Creat}$ (100 to 199%) mean percentage raise in Sr. Creatinine levels was 135.93% ± 26.65% whereas mean rise in Sr. Cystatin C was recorded as 222.46% ± 43.88% suggesting significant raise in Sr. Cystatin C compared Sr. Creatinine ($p<0.001$). However among patients with $F_{Creat}$ (percentage rise ≥ 200%) comparison could not be done as there were only two patients.

**Table 14. Comparison of mean Sr. Creatinine and Sr. Cystatin C levels levels in patients with ARF**

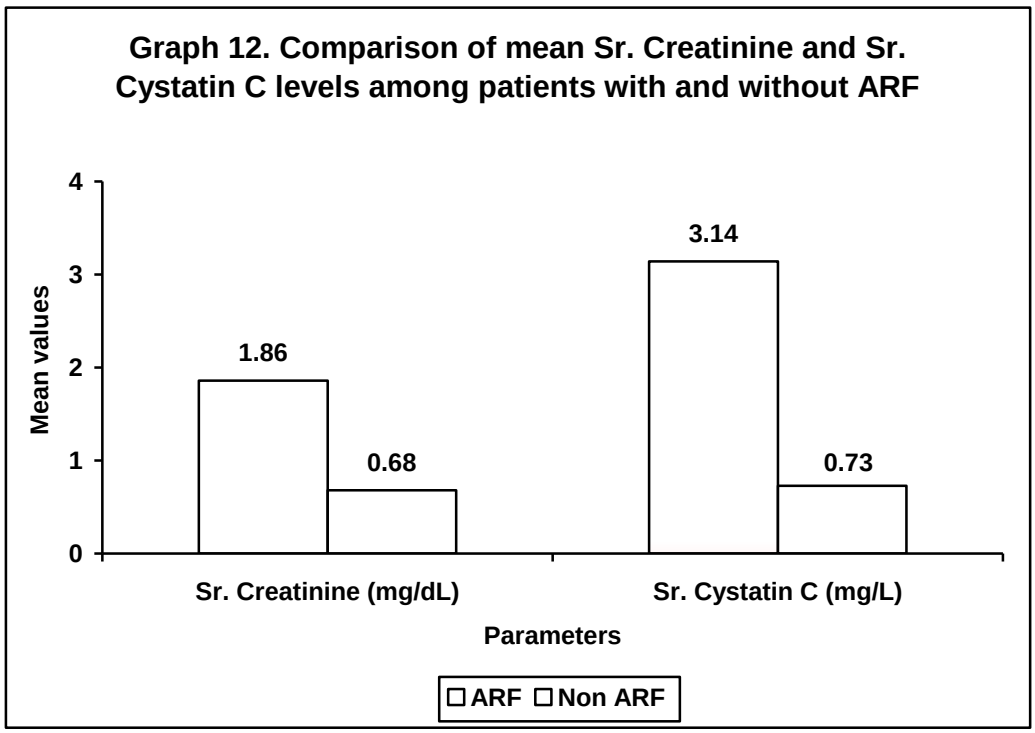
| Criteria (Rise) | Sr. Creatinine (mg/dL) | | | | Sr. Cystatin C (mg/L) | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean value | | Range | | Mean value | | Range | |
| | Mean | SD | Min | Max | Mean | SD | Min | Max |
| R (50 to 99%) | 1.63 | 0.36 | 0.90 | 2.10 | 2.58 | 0.37 | 2.20 | 3.36 |
| I (100 to 199%) | 1.98 | 0.66 | 1.20 | 3.30 | 3.54 | 0.59 | 2.60 | 4.40 |
| F (≥ 200%) | 2.75 | 0.49 | 2.40 | 3.10 | 3.67 | 0.75 | 3.14 | 4.20 |




In this study among patients who developed ARF the mean Sr. creatinine level of $R_{Creat}$ category was 1.63 ± 0.36 mg/dL whereas mean value of Sr. Cystatin C was noted as 2.58 ± 0.37 mg/L. Similarly in those with category $I_{Creat}$ (100 to 199%) mean Sr. creatinine levels was 1.98 ± 0.66 mg/dL whereas mean value of Sr. Cystatin was recorded as 3.54 ± 0.59 mg/L suggesting significantly high levels of Sr. cystatin C compared Sr. creatinine ($p<0.05$). However among patients with $F_{Creat}$ (percentage rise ≥ 200%) comparison could not be done as there were only two patients.

**Table 15. Comparison of mean Sr. Creatinine and Sr. Cystatin C levels among patients with and without ARF**

| Parameters | ARF | | Non ARF | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Sr. Creatinine (mg/dL) | 1.86 | 0.61 | 0.68 | 0.20 |
| Sr. Cystatin C (mg/L) | 3.14 | 0.69 | 0.73 | 0.10 |




In the present study the mean Sr. Creatinine and Sr. Cystatin C values in ARF were 1.86 mg/dL and 3.14 mg/L respectively. The mean Sr. Creatinine and Sr. Cystatin C values in patients with out ARF were 0.68 mg/dL and 0.73 mg/L respectively.

**Table 16. Comparison of accuracy of Sr. Creatinine and Sr. Cystatin C**

| | **Sr. Creatinine** | | **Sr. Cystatin** | |
|---|---|---|---|---|
| | **1st reading** | **2nd reading** | **1st reading** | **2nd reading** |
| Sensitivity | 0% | 78.57% | 85.71% | 100% |
| Specificity | 100% | 100% | 95.45% | 100% |
| PPV | 0% | 100% | 96.00% | 100% |
| NPV | 44% | 78.57% | 84.00% | 100% |

In this study the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of Sr. Creatinine for first reading was 0%, 100%, 0%, 44% respectively and the sensitivity, specificity, PPV, NPV for first reading of Sr. Cystatin C was 85.71%, 95.45%, 96% and 84% respectively.

The sensitivity, specificity, PPV, NPV of Sr. Creatinine for second reading was 78.57%, 100%, 100%, 78.57% respectively and the sensitivity, specificity, PPV, NPV for second reading of Sr. Cystatin C was 100%.

# Chapter 6

# Discussion

# DISCUSSION

This study is conducted on 50 patients admitted in the Medical Intensive Care Unit of KLES Dr Prabhakar Kore Hospital and Medical Research Center, Belgaum

In this study, out of 50 patients 33 (66%) patients were males and 17 (34%) patients were females with a male to female ratio of 1.94:1. These findings were comparable to a study conducted on patients admitted in ICU by villa et al[23] in which out of 50 patients, 34 (68%) were males and 16 (32%) were females.

In a study conducted by Herget et al[5] on medical and surgical ICU patients out of 85 patients, 54 (63.5 %) were males and 31 (36.5%) were females with a male:female ratio of 1.74:1. In a study by Nejat et al[58] out of 442 patients, 270 (61%) were males and 172 (39%) were females.

In the present study out of 50 patients, there were 13 (26%) patients each in the age group of 18 to 30 years and more than 60 years age, and 12 (24%) patients each in the age group of 31 to 45 years and 46 to 60 years with a mean age of 47.5 years. In a study by villa et al[23] conducted on 50 ICU patients the mean age was 54 years. In a study conducted by Herget et al[5] the mean age was 66.5 years. The mean age in Nejat et al[58], a study conducted on two ICU patients was 60 ± 18 years.

In the present study, there were 18(36%) patients each with gastrointestinal and respiratory disease and 6 (12%) patients with snake bite.

In a study conducted by Hoste et al[59] at the University of Pittburgh Medical Centre on 5383 patients admitted to the ICU 147 (2.73%) and 850 (18.8%) patients had primary gastrointestinal and pulmonary diseases respectively.

Tadashi et al[60] showed that out of the 259 patients, gastrointestinal and pulmonary disease as a primary reason for admission in 12 (4.6%) and 6 (2.3%) patients respectively.

In Villa et al[23] study there were 10 (20%) of patients with primary pulmonary disease.

In Herget et al[5] study on 85 ICU patients, patients with primary gastrointestinal and pulmonary disease were 13 (15.3%) and 7 (8.23%) patients respectively.

In the present study, out of 50 patients, 28 (56%) patients developed ARF based on RIFLE criteria[8] between one to three days of admission and 22 (44%) did not develop ARF. This was comparable to a study conducted by hoste et al[59] in the University of Pittsburg Medical Center, in which out of 5383 ICU patients, 1182 patients had ARF at admission and in the remaining 4201 patients, 2435 (57.9%) patients developed ARF during the hospital stay and 1766 (42.1%) patients did not develop ARF.

In a study conducted by Herget et al[5] on 85 ICU patients, 44 (51.7%) patients developed ARF and 41(48.3%) patients did not develop ARF.

In a study conducted by Villa et al[23], on 50 patients admitted in the ICU, 25(50%) patients developed ARF and 25 (50%) did not. In a study conducted by Ron Wald et al[61] on patients undergoing cardiopulmonary bypass surgery, out of 150 patients, 47 (31.3%) patients developed ARF postoperatively.

In the present study out of 28 ARF patients, there were 18 (64.29%) males and 10 (35.71 %) females. Among those who did not develop ARF that is 22 patients 15 (68.18%) were males and 7 (31.82%) were females suggesting equal distribution of gender in both groups. In a study by Herget et al[5] 66 and 34 percentage were males and females respectively among patients with ARF and among those who did not develop ARF 61% and 39% were male and females respectively suggesting equal distribution of gender in both groups.

In a study conducted by Ron Wald et al[61] on 150 cardiopulmonary bypass patients, there were 32 (68.11%) and 15 (31.89%) males and females respectively among patients with ARF and among patients who did not develop ARF there were 71 (68.9%) males and 32 (31.1%) females.

In the present study the mean age of patients with ARF was 50.25 ± 17.85 years and in patients who did not develop ARF the mean age was 44.82 ± 20.20 years suggesting that the age in both the groups were comparable. In a study by Herget et al[5] the mean age of patients with and without ARF was 70 ± 8 years and 63 ± 11 years respectively.

In Tadashi et al[60] study, the mean age of patients with and without ARF were 68 and 64 years respectively.

In the present study, majority that is 11 (39.3%) patients developed ARF due to ischemia – prerenal etiology whereas 9 (32.14%), 3 (10.71%) and 5 (17.85%) patients developed ARF due to sepsis, nephrotoxicity and combination of multiple etiologies respectively.

In a study conducted by Herget et al[5], majority of patients that is 27 (62%) developed ARF due to multiple etiologies. Patients developing ARF due to sepsis, ischemia prerenal and nephrotoxicity were 8 (18%), 5 (11%) and 4 (9%) respectively.

In this study the Sr. Creatinine during the first reading was normal in all ie 50 patients(inclusion criteria is normal creatinine). This finding was comparable to the study conducted by Hoste et al[62] in which the first reading of Sr. Creatinine was normal in all patients.

In this study second reading of Sr. Creatinine was normal in 28(56%) patients and high in 22 (44%) patients. Second reading of Sr. Creatinine was within normal limit in 6 patients with ARF that is, inspite of $\geq$ 50% rise in Sr. Creatinine

In this study the first reading of Sr. Cystatin C was normal in 25 (50%) patients and high in 25 (50%) of patients that is out of 28 ARF patients, 24 (85.71%) patients had high Sr. Cystatin C levels at admission which is one to three days prior to rise in Sr. Creatinine. However one patient with high Sr. Cystatin C at admission did not develop ARF. This was comparable to a study by Herget et al[5] where in all patients of ARF, Sr. Cystatin C had raised one to two days earlier to S.creatinine.

A study by Ron Wald et al[61] also showed that Sr. Cystatin C predated the identification of s.creatinine based ARF by one to two days.

In the present study the second reading of Sr. Cystatine C was normal in 22 (44%) patients and high in 28 (56%) patients that is second reading of Sr. Cystatin C was high in all ARF patients.

In the present study among patients who developed ARF 39.29%, 53.57% and 7.14% patients have satisfied $R_{Creat}$ (50 to 99%), $I_{Creat}$ (100 to 199%) and $F_{Creat}$ ($\geq$ 200%) criteria respectively. Among patients with category $R_{Creat,}$ rise of Sr. Cystatin C was $\geq$ 100% and hence 57.14% patients had 100 to 199% rise in Sr. Cystatin C levels and among 42.86% patients a rise of more than or equal 200% was noted.

In this study among patients who developed ARF the mean percentage raise in Sr. creatinine levels in $R_{Creat}$ category was 69.67% ± 11.33% whereas mean percentage raise in Sr. Cystatin C were noted as 134.90% ± 24.18%. Similarly in those with category $I_{Creat}$ (100 to 199%) mean percentage raise in Sr. Creatinine levels was 135.93% ± 26.65% whereas mean rise in Sr. Cystatin C was recorded as 222.46% ± 43.88% suggesting significant raise in Sr. Cystatin C compared Sr. Creatinine ($p<0.001$). However among patients with $F_{Creat}$ (percentage rise $\geq$ 200%) comparison could not be done as there were only two patients.

In Herget et al[5], a study on 85 ICU patients showed a mean percentage rise of Sr. Creatinine of 89% ± 34 %, 145% ± 39 %, 237 ± 24% in Rcreat, Icreat,

Fcreat groups,. where as the mean percentage rise in Sr. Cystatin C was 126% ± 51%, 172% ± 81% and 244% ± 92% in Rcreat, Icreat, Fcreat groups respectively.

In this study among patients who developed ARF the mean Sr. Creatinine level of $R_{Creat}$ category was 1.63 ± 0.36 mg/dL whereas mean value of Sr. Cystatin C was noted as 2.58 ± 0.37 mg/L. Similarly in those with category $I_{Creat}$ (100 to 199%) mean Sr. Creatinine level was 1.98 ± 0.66 mg/dL whereas mean value of Sr. Cystatin C was recorded as 3.54 ± 0.59 mg/L suggesting significantly high levels of Sr. Cystatin C compared Sr. Creatinine ($p<0.05$). However among patients with $F_{Creat}$ (percentage rise ≥ 200%) comparison could not be done as there were only two patients.

In the study conducted by Herget et al[5], the mean values of Sr. creatinine in patients with Rcreat, Icreat , Fcreat groups were 1.57 ± 0.2 mg/dL, 1.89 ± 0.38 mg/dL, 2.58 ± 0.36 mg/dL respectively. Where as the mean values of Sr. Cystatine C in patients with $R_{creat}$, $I_{creat}$ , $F_{creat}$ groups were 1.79 ± 0.36, 2.17 ± 0.61, 2.86 ± 0.75 mg/L respectively.

In the present study the mean Sr. Creatinine and Sr. Cystatin C values in patients with ARF were 1.86 mg/dL and 3.14 mg/L respectively. The mean Sr. creatinine and Sr. Cystatin C values in patients with out ARF were 0.68 mg/dL and 0.73 mg/dL respectively. In a study conducted by Ron wald et al[61], on 150 patients the mean Sr. Cystatine C levels were 1.27±0.44 and 0.92±0.23 mg/L in ARF and non ARF patients respectively.

In this study the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of Sr. Creatinine for first reading was 0%,

100%, 0%, 44% respectively and the sensitivity, specificity, PPV, NPV for first reading of Sr. Cystatin C was 85.71%, 95.45%, 96% and 84% respectively. The sensitivity, specificity, PPV, NPV of Sr. Creatinine for second reading was 78.57%, 100%, 100%, 78.57% respectively and the sensitivity, specificity, PPV, NPV for second reading of Sr. Cystatin C was 100%.

In a study conducted by Hoste et al[62] Sr. Creatinine proved a very insensitive screening test for the early detection of renal dysfunction in ICU patients.

The limitations of the study were smaller sample size and urine output criteria was not included in the diagnosis of ARF because many patients were on diuretics at admission. Also preadmission normal baseline Sr. Cystatin C and Sr. Creatinine were not available with many patients hence this study was limited to monitoring of patients from entry to the ICU and cannot be readily used to assess the status of patients on entry to the ICU. Lack of a 'gold standard' independent measure of GFR such as an inulin or radioisotope clearance, prevented from commenting on whether Sr. Cystatin C or Sr Creatinine correlated more accurately with a true decrease in GFR. Though none of the patients were a known case of thyroid disease and Sr. TSH levels were normal in all patients, thyroid disease could not be ruled out and the variation of Sr. Cystatin C in relation to thyroid disease could not be analysed. Though none of the patients were on steroids, the effect of cortisol on Sr. Cystatine C levels could not be analysed as Sr. Cortisol levels were not measured.

Further a large multicentric study is required to confirm these results.

# Chapter 7

# Conclusion

# CONCLUSION

In our study of 50 ICU patients, 28 patients developed Acute Renal Failure during the hospital stay. The first reading of Sr. Cystatin C in patients with ARF was high in significant number of patients where as the first reading of Sr. Creatinine was normal in all the patients with ARF indicating that Sr. Cystatin C is a early marker of ARF. Further the second reading of sr. Creatinine in patients with ARF was normal in 6 patients that is inspite of $\geq$ 50% rise in sr. Creatinine where as the second reading of Sr. Cystatin C was high in all patients with ARF. The percentage raise of Sr. Cystatin C was significantly greater than percentage raise of Sr. Creatinine in patients with ARF. This study concludes that Sr. Cystatin C is a early and more reliable marker of ARF than Sr. Creatinine in critically ill patients.

# Chapter 8

# Summary

# SUMMARY

Acute Renal Failure is a common complication in patients admitted to the ICU. The present study was undertaken to assess whether Sr. Cystatine C is a early and more reliable marker of acute renal failure.

The present one year cross sectional study was conducted on patients admitted in the Medical Intensive Care Unit of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2010 to December 2010. A total of 50 patients were studied. CBC, LFT, Sr. TSH, X-ray chest, ultrasound abdomen and other necessary tests to make a etiological diagnosis were done at admission. Sr. Cystatin C and Sr. Creatinine levels were determined at admission and these were considered as the first reading of Sr. Creatinine and Sr. Cystatin C. Sr. Creatinine and Sr. Cystatin C were repeated after the patient developed ARF and was considered as second reading and results were analyzed.

In the present study out of 50 patients, 33 (66%) were male and 17 (34%) were female. The male: female ratio was 1.94:1. In this study, out of 50 patients, there were 13 (26%) patients each in the age group of 18 to 30 years and more than 60 years. There were 18 (36%) patients each with primary gastrointestinal and respiratory disease and 6 (12%) patients with snake bite.

In the present study 28 (56%) patients developed ARF. The mean age of patients with ARF was 50.25 ± 17.85 years. The mean Sr. Creatinine and Sr. Cystatin C values in ARF were 1.86 mg/dL and 3.14 mg/L respectively. The

mean Sr. Creatinine and Sr. Cystatin C values in patients with out ARF were 0.68 mg/dL and 0.73 mg/L respectively.

In the present study among patients who developed ARF 39.29%, 53.57% and 7.14% patients have satisfied $R_{Creat}$ (50 to 99%), $I_{Creat}$ (100 to 199%) and $F_{Creat}$ ($\geq$ 200%) criteria respectively. Among patients with category $R_{Creat}$ rise of Sr. cystatin C was $\geq$ 100% and 57.14% patients had 100 to 199% rise in Sr. cystatin C levels and among 42.86% patients a rise of more than or equal 200% was noted.

The sensitivity, specificity, PPV, NPV of Sr. creatinine for second reading was 78.57%, 100%, 100%, 78.57% respectively and the sensitivity, specificity, PPV, NPV for second reading of Sr. Cystatin C was 100%.

Sr. Creatinine was normal in some patients with ARF whereas Sr. Cystatin C was above the normal value in all ARF patients indicating that Sr. Cystatin C is more reliable marker than Sr. Creatinine.

# Chapter 9

# Bibliography

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# *Annexures*

# Annexure I

# ANNEXURE I – CONSENT FORM

## "SERUM CYSTATIN C CONCENTRATION LEVELS AS A MARKER OF ACUTE RENAL FAILURE IN CRITICALLY ILL PATIENTS"

**Objective and purpose of the study:**

To study Serum Cystatin C concentration levels as a marker of acute renal failure in critically ill patients.

The principal investigator of the study is Dr.VEENA. P. MUNAVALLI under the guidance of Dr. A.J. DHUMALE. Your co-operation will be of great help to patients with acute renal failure in India.

**Procedure:**

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations

**Risk and Benefits:**

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

**Alternatives**

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may

stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

**Privacy and Confidentiality**

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

**Institution / Sponsor's policy**

Does not apply to this research

**Financial incentives for participation**

You will not be paid / offered any gifts /incentives for participating in the study.

**Authorization to publish the results**

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your rights as a participant you may call Dr. V. D. Patil, Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number 0831-2471350.

**CONSENT FORM**

CONSENT TO PARTICIPATE IN RESEARCH STUDY:

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

Name of the Participant or legally authorized representative: _____

Signature / Thumb print _____

In case of the queries during study or in future I may contact following person

Principal investigator : Dr. Veena P Munavalli

Guide : Dr. A J Dhumale

Name of the Witness _____

Signature _____

Investigator Name and Signature _____

Date: Place:

# *Annexures*

# Annexure II

# ANNEXURE II – PROFORMA

PROFORMA

Case No:

NAME:

AGE/SEX:

IP No.

ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

Fever:

Loose motions:

Vomiting:

Bleeding:

Giddiness:

Lose of conciousness:

Palpitations:

Jaundice:

Pain abdomen:

Abdominal distension:

Facial puffiness:

Treatment History:

Past history

Family history

Personal History

On Examination

Weight

Pallor

Icterus

Cyanosis

Edema

Vitals

Pulse:

Blood Pressure:

Systemic Examination

Cardiovascular system

Respiratory system

Per abdomen

Central nervous system

Investigations

Hemoglobin:

TLC: N: L: E: M: B:

ESR:

Platelet count:

Urine Routine and microscopy:

Random blood sugar

Liver function test:

Blood Urea:

Serum Creatinine:

Serum Cystatine C:

Serum TSH:

Others:

Signature of Patient Signature of Guide

| Serial Number | In Patients No. | Sex | Age (Years) | Clinical examination | | | Diagnosis | Diagnosis | Diagnosis | Diagnosis | Diagnosis | Investigations | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | BP (mm | | | | | | | | Sr. Creat (mg/dL) | | | Serum cystatin C (mg/L) | | | |
| | | | | Pulse rate (Min) | Systolic | Diastolic | | | | | | Blood urea (mg/dL) | On admission | 2nd Reading | Percentage raised | On admission | 2nd Reading | Percentage raised | Sr. TSH (µIU/dL) |
| 1 | 371245 | F | 45 | 110 | 90 | 70 | lepto (O.I) | Sep | - | - | - | 22 | 0.70 | 0.70 | - | 0.68 | 0.71 | - | 1.20 |
| 2 | 370816 | M | 81 | 120 | 80 | 60 | DM | HTN | Pne | Sep | - | 18 | 0.90 | 1.10 | - | 0.92 | 0.93 | - | 2.10 |
| 3 | 369332 | F | 57 | 90 | 110 | 70 | Sep | UTI (OI) | - | - | - | 24 | 1.30 | 0.60 | - | 0.82 | 0.80 | - | 3.00 |
| 4 | 376189 | M | 87 | 106 | 90 | 60 | COPD | HTN | pne | Sep | - | 20 | 0.90 | 0.80 | - | 0.80 | 0.90 | - | 0.90 |
| 5 | 390597 | M | 35 | 112 | 90 | 70 | A GE | - | - | - | - | 18 | 0.60 | 0.50 | - | 0.70 | 0.65 | - | 1.00 |
| 6 | 390739 | M | 30 | 126 | 80 | 60 | Pne | Sep | - | - | - | 21 | 0.80 | 0.70 | - | 0.70 | 0.72 | - | 2.20 |
| 7 | 398105 | F | 82 | 80 | 110 | 80 | COPD | DM | pne | Sep | - | 25 | 0.80 | 0.40 | - | 0.90 | 0.60 | - | 1.60 |
| 8 | 400874 | M | 60 | 96 | 110 | 70 | Lepto (O I) | HTN | ARDS | Sep | IHD | 28 | 1.10 | 1.10 | - | 1.00 | 0.90 | - | 1.20 |
| 9 | 352871 | M | 42 | 132 | 90 | 60 | Pne | Sep | - | - | - | 18 | 0.50 | 0.60 | - | 0.55 | 0.60 | - | 1.40 |
| 10 | 353152 | M | 36 | 140 | 80 | 60 | PCPne | RVD | Sep | - | - | 17 | 0.90 | 0.50 | - | 0.90 | 0.60 | - | 1.60 |
| 11 | 394468 | M | 25 | 80 | 110 | 70 | A GE | HTN | - | - | - | 23 | 0.50 | 0.70 | - | 0.56 | 0.70 | - | 1.00 |
| 12 | 392355 | M | 18 | 110 | 120 | 70 | A GE | - | - | - | - | 26 | 0.60 | 0.60 | - | 0.60 | 0.70 | - | 2.20 |
| 13 | 390909 | M | 56 | 128 | 110 | 70 | A GE | - | - | - | - | 20 | 1.00 | 0.50 | - | 0.90 | 0.70 | - | 3.00 |
| 14 | 387560 | M | 60 | 90 | 120 | 66 | Cirr | DM | A GE | - | - | 18 | 0.80 | 0.40 | - | 0.70 | 0.80 | - | 2.10 |
| 15 | 384706 | M | 26 | 118 | 120 | 80 | Pne | Sep | - | - | - | 28 | 1.30 | 0.60 | - | 0.94 | 0.70 | - | 1.80 |
| 16 | 394147 | M | 38 | 124 | 120 | 80 | pne | Sep | - | - | - | 30 | 1.20 | 0.90 | - | 0.93 | 0.80 | - | 1.30 |
| 17 | 384538 | F | 30 | 112 | 110 | 70 | malaria (OI) | Sep | - | - | - | 18 | 1.00 | 0.90 | - | 0.80 | 0.80 | - | 1.50 |
| 18 | 343663 | F | 60 | 122 | 100 | 70 | Br Asthma | pneu | Sep | - | - | 24 | 0.80 | 0.70 | - | 0.82 | 0.80 | - | 1.20 |
| 19 | 353994 | M | 33 | 98 | 120 | 70 | A GE | - | - | - | - | 26 | 0.60 | 0.60 | - | 0.60 | 0.70 | - | 1.40 |
| 20 | 396259 | F | 23 | 126 | 110 | 60 | T Fev (OI) | - | - | - | - | 24 | 0.40 | 0.50 | - | 0.56 | 0.60 | - | 0.80 |
| 21 | 400112 | M | 32 | 116 | 110 | 70 | A GE | - | - | - | - | 22 | 0.80 | 0.70 | - | 0.80 | 0.70 | - | 0.90 |
| 22 | 396263 | F | 30 | 110 | 90 | 60 | SB | - | - | - | - | 18 | 0.80 | 0.80 | - | 0.70 | 0.70 | - | 0.60 |
| 23 | 397913 | M | 46 | 128 | 110 | 74 | cirr | DM | pne | sep | IHD | 36 | 1.20 | 2.10 | 75.00 | 1.20 | 2.60 | ##### | 0.80 |
| 24 | 362238 | M | 64 | 110 | 110 | 60 | DM | HTN | Pne | sep | - | 38 | 0.70 | 1.30 | 85.71 | 1.00 | 2.22 | ##### | 0.50 |
| 25 | 368468 | M | 69 | 114 | 86 | 60 | A GE | HTN | - | - | - | 28 | 0.80 | 2.10 | ##### | 1.10 | 3.33 | ##### | 0.80 |
| 26 | 380888 | F | 86 | 132 | 100 | 70 | HTN | Pne | sep | IHD | - | 34 | 1.00 | 1.50 | 50.00 | 1.00 | 2.20 | ##### | 1.40 |
| 27 | 391571 | M | 75 | 129 | 80 | 50 | AGE | IHD | - | - | - | 40 | 0.80 | 2.40 | ##### | 1.30 | 4.20 | ##### | 2.00 |
| 28 | 355412 | F | 30 | 126 | 86 | 60 | Malaria | - | - | - | - | 46 | 0.90 | 1.40 | 55.56 | 1.10 | 2.20 | ##### | 2.10 |
| 29 | 357172 | M | 72 | 132 | 106 | 70 | DM | HTN | Pne | Sep | - | 28 | 1.20 | 2.00 | 66.67 | 1.30 | 3.04 | ##### | 1.60 |
| 30 | 394170 | M | 20 | 128 | 100 | 76 | Malaria | - | - | - | - | 52 | 0.50 | 0.90 | 80.00 | 1.10 | 2.50 | ##### | 1.80 |
| 31 | 391842 | M | 50 | 96 | 110 | 76 | A GE | HTN | - | - | - | 44 | 1.10 | 1.80 | 80.00 | 1.30 | 2.63 | ##### | 0.90 |
| 32 | 393800 | M | 50 | 118 | 86 | 60 | DM | HTN | IHD | Pne | Sep | 42 | 0.80 | 2.30 | ##### | 1.06 | 4.20 | ##### | 0.60 |
| 33 | 393730 | M | 67 | 122 | 110 | 76 | COPD | DM | HTN | Pne | Sep | 60 | 1.00 | 2.50 | ##### | 1.12 | 3.27 | ##### | 0.80 |
| 34 | 386752 | M | 38 | 128 | 120 | 70 | A GE | - | - | - | - | 58 | 1.10 | 2.00 | 81.82 | 1.04 | 2.80 | ##### | 0.90 |
| 35 | 390105 | M | 72 | 134 | 110 | 60 | DM | HTN | Pne | Sep | - | 62 | 1.10 | 1.80 | 63.64 | 1.00 | 2.40 | ##### | 1.40 |
| 36 | 384399 | M | 40 | 124 | 86 | 70 | Malaria | ARDS | MODS | - | - | 44 | 0.80 | 3.10 | ##### | 0.80 | 3.14 | ##### | 1.20 |
| 37 | 394756 | M | 38 | 116 | 86 | 60 | A GE | - | - | - | - | 40 | 1.30 | 3.30 | ##### | 1.40 | 4.20 | ##### | 2.10 |
| 38 | 401499 | M | 49 | 96 | 120 | 70 | A GE | - | - | - | - | 38 | 1.30 | 3.10 | ##### | 1.40 | 4.30 | ##### | 2.00 |
| 39 | 384410 | F | 62 | 120 | 120 | 70 | SB | HTN | - | - | - | 30 | 0.90 | 1.50 | 66.67 | 1.20 | 3.36 | ##### | 3.00 |
| 40 | 390018 | F | 58 | 110 | 78 | 60 | A GE | DM | - | - | - | 28 | 1.10 | 2.30 | ##### | 1.04 | 3.74 | ##### | 2.10 |
| 41 | 380145 | F | 63 | 116 | 80 | 60 | DM | SB | - | - | - | 34 | 0.80 | 1.80 | ##### | 1.06 | 3.96 | ##### | 2.40 |
| 42 | 386995 | F | 30 | 122 | 80 | 60 | A GE | - | - | - | - | 26 | 0.70 | 1.50 | ##### | 1.12 | 4.40 | ##### | 3.20 |
| 43 | 355341 | M | 36 | 130 | 74 | 50 | A GE | - | - | - | - | 46 | 0.80 | 1.60 | ##### | 1.10 | 3.00 | ##### | 4.00 |
| 44 | 368641 | M | 38 | 120 | 84 | 60 | A GE | - | - | - | - | 58 | 0.60 | 1.20 | ##### | 1.00 | 2.60 | ##### | 3.10 |
| 45 | 378412 | F | 54 | 112 | 110 | 70 | HTN | SB | - | - | - | 49 | 0.90 | 1.60 | 77.78 | 1.00 | 2.40 | ##### | 2.60 |
| 46 | 381515 | F | 26 | 96 | 126 | 70 | Pne | sep | - | - | - | 46 | 0.50 | 1.30 | ##### | 0.90 | 2.90 | ##### | 1.90 |
| 47 | 346812 | M | 64 | 90 | 120 | 70 | DM | SB | IHD | - | - | 36 | 0.60 | 1.30 | ##### | 1.10 | 3.20 | ##### | 0.90 |
| 48 | 368923 | F | 58 | 106 | 130 | 70 | HTN | Pne | sep | - | - | 48 | 0.70 | 1.60 | ##### | 1.00 | 3.10 | ##### | 1.60 |
| 49 | 338615 | M | 29 | 86 | 84 | 60 | A GE | - | - | - | - | 37 | 0.70 | 1.80 | ##### | 0.90 | 3.30 | ##### | 2.00 |
| 50 | 348484 | F | 26 | 84 | 70 | 50 | SB | - | - | - | - | 29 | 0.50 | 1.10 | ##### | 0.93 | 2.70 | ##### | 0.80 |

# *Annexures*

# Annexure III

## ANNEXURE III – KEY TO MASTER CHART

mg/dl – milligram per decilitre

mg/l – milligram per litre

IU/dl – International Units per decilitre

Lepto – Leptospirosis

Sep – Sepsis

HTN – Hypertension

DM – Diabetes Mellitus

COPD – Chronic Obstructive Pulmonary Disease

SB – Snake Bite

Pne – Pneumonia

A GE – Acute Gastroenteritis

UTI – Urinary Tract Infection

IHD – Ischemic Heart Disease

PCPne – Pneumocystic Pneumonia

RVD – Retro Viral Disease

Cirr – Cirrhosis

T Fev – Typhoid Fever

Sr Creat – Serum Creatinine

Sr Cystatin C– Serum Cystatin C

Sr TSH – Serum Thyroid Stimulating Hormone