Prognostic Value Of Platelet-To-Lymphocyte Ratios Among Critically Ill Patients With Acute Kidney Injury

by

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Dissertation submitted to

In partial fulfillment for the degree of

DOCTOR OF MEDICINE
IN
GENERAL MEDICINE

Under the Guidance of

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PROFESSOR

DEPARTMENT OF MEDICINE

BLDE (DEEMED TO BE UNIVERSITY)

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2019

LIST OF ABBREVATIONS

AKI	**Acute kidney injury**
ICU	**Intensive care unit**
PLR	**Platelet lymphocyte ratio**
ESRD	**End stage renal disease**
GFR	**Glomerular filteration rate**
BUN	**Blood urea nitrogen**
ATN	**Acute tubular necrosis**
CKD	**Chronic kidney disease**
AGN	**Acute glomerular nephritis**
AIN	**Acure interstitial nephritis**
ADQI	**Acute Dialysis Quality Initiative**
ISN	**International Society of Nephrology**
ASN	**American Society of Nephrology**
NKF	**National Kidney Foundation**
APACHE III	**Acute Physiology and Chronic Health evaluation**
SOFA	**Sequential Organ Failure Assessment**

ABSTRACT

Background

Inflammation plays a key role in the initiation and progression of acute kidney injury. Evidence regarding the prognostic effect of the platelet-to-lymphocyte ratio, an easily available systemic inflammation marker, among patients with acute kidney injury is less. In this study, we investigated the value of the Platelet-to-lymphocyte ratio in predicting the outcomes of Intensive care unit patients with acute kidney injury.

Methods

The study included 91 critically ill patients with acute kidney injury of Intensive care unit and Emergency ward. Informed consent was obtained from all patients. Period of study was from November 2017 to June 2019. Platelet-to-lymphocyte ratio cut-off values were determined using Reciever Operating Characterstic analysis.

Results

A total of 91 Intensive care unit patients with acute kidney injury were enrolled. A total of 24 deaths occurred,15 worsened and 52 improved. A U-shaped relationship was observed between the Platelet-to-lymphocyte ratio and prognosis at discharge, with the lowest risk being at values ranging from 100 to 299. Out of the parameters assessed, ESR, Blood urea and platelet count was significantly higher in high Platelet-to-lymphocyte ratio (>299) group. Lymphocyte counts showed significantly lower levels in the high Platelet-to-lymphocyte ratio (>299) group.

Conclusions

The preoperative Platelet-to-lymphocyte ratio was associated in a U-shaped pattern with survival among patients with acute kidney injury. The Platelet-to-lymphocyte ratio appears to be a novel, independent prognostic marker of outcomes in critically ill patients with acute kidney injury. Its clinical impact must be validated with appropriate study design and sample size.

Keywords: Platelet-to-lymphocyte ratio, Acute kidney injury, Prognosis, Intensive care unit

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INTRODUCTION

About higher than five million patients are admitted to intensive care units (ICUs) every year around worldwide.[1]6–24% of these patients have acute kidney injury (AKI).[2] In the presence of AKI, patient mortality and morbidity increases to 60–70%, especially within one year after ICU admission. [3,4] Keeping the point of high incidence of AKI in the ICU and its poor prognosis, an increased number of observational studies over the past two decades have been oriented in identifying the clinical predictors of mortality in AKI.

Systemic inflammation is one of the part of disease progression in critical illness and is most commonly associated with sepsis, leading to an increased risk of mortality and morbidity.[5] Inflammation plays a key role in the initiation and progression of AKI,[6] morphological &functional changes in vascular endothelial cells and/or in the tubular epithelium are observed in patients with AKI. Lymphocytes, including leukocytes, infiltrate the injured kidneys & the entire body via the circulation system and induce the generation of inflammatory mediators such as cytokines & chemokines, which will damage the kidney and other organ system.[7]

The anti-thrombotic effects of platelets can evolve into atherogenesis via the secretion of pro-inflammatory cytokines[8], whereas the attaching of platelets to endothelial cells can trigger leukocyte trans-migration & adhesion.[9]

The platelet-to-lymphocyte ratio (PLR) has been introduced as a bio-marker of inflammation in cardiovascular disease (CVD) & tumours, which are considered as inflammationrelated diseases. A positive correlation between increased PLR &poor prognosis for these diseases has been reported.[10][11]

Chen-Fei Zheng et al.,[12]studied the pre-operative PLR association with survival among patients with AKI. The PLR appears to be a novel, independent prognostic biomarker of outcomes in critically ill patients with AKI. Based on these facts, it is reasonable to speculate that the PLR might affect the prognosis of AKI.

So the present study was undertaken to know the prognostic value of platelet-to-lymphocyte ratio among critically ill patients with AKI.

AIMS AND OBJECTIVE OF THE STUDY

Prognostic value of platelet-to-lymphocyte ratios among critically ill patients with acute kidney injury.

REVIEW OF LITERATURE

About higher than five million patients are admitted to intensive care units (ICUs) every year around worldwide.[1] 6–24% of these patients have acute kidney injury (AKI).[2] In the presence of AKI, patient mortality and morbidity increases to 60–70%, especially within one year after ICU admission. [3,4] Keeping the point of high incidence of AKI in the ICU and its poor prognosis, an increased number of observational studies over the past two decades have been oriented in identifying the clinical predictors of mortality in AKI.

ACUTE KIDNEY INJURY

Acute kidney injury is the abrupt deterioration of function of kidney, leads in retention of urea and other nitrogenous waste products or decreased urine output or both and there is irregulation of extracellular fluid volume & electrolytes.

AKI - The term has widely replaced the term acute renal failure (ARF), it reflects that, the understanding of smaller decrements in renal function will not result in overt organ failure are of important clinical relevance and are associated with increased mortality & morbidity. The term acute renal failure is now used for severe AKI, usually indicates the need for renal replacement therapy.[13] Acute Kidney Injury (AKI) is defined by "an abrupt increase in serum creatinine over 48 hours resulting from an injury or insult that causes a functional or structural change in the kidney." It predisposes to chronic kidney disease and progresses thereafter to ESRD and death. **(Figure 1)** In critically ill patients severe renal failure requiring dialysis occurs in 4-5 % with a mortality rate of 60%. About 8-22% of these patients continue to require maintenance dialysis support thereafter. [14]

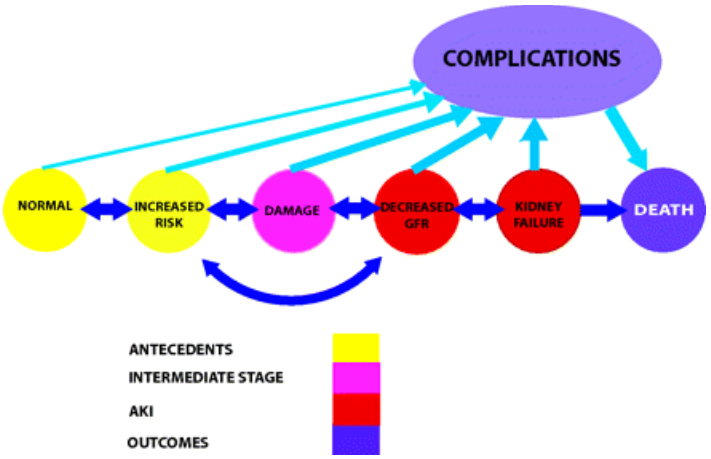


Figure 1.Progression of AKI and complications. (14)

AKI is mainly detected by measurement of serum creatinine. Creatinine is used for estimation of the glomerular filtration rate (GFR). Using serum creatinine to quantitatively define AKI are associated with three problems:

(i) Serum creatinine will not precisely reflect the GFR of a patient in whom the GFR is not in steady state. (a) In early stages of AKI, the sr. creatinine would be low, though the actual GFR is grossly reduced, because there may not have been enough time for sr. creatinine to accumulate. (b) If the serum creatinine is increasing, estimates of GFR depends on creatinine values will overestimate the real GFR (c) Estimation of GFR will underestimate the actual GFR during recovery of renal function, when the sr. creatinine concentration is reducing.

(ii) During dialysis the creatinine is removed. As a result, once dialysis is initiated it is commonly not possible to assess renal function by measuring the serum creatinine. But the exception is if the serum creatinine continues to fall on days where haemodialysis is not performed, denotes the recovery of kidney function.

(iii) Multiple epidemiologic analysis & clinical trials have used various cut-off values for sr. creatinine to quantitatively define AKI[13]

EPIDEMIOLOGY

In acute care hospital admission AKI affects 5 to 7 % of patients, up to 30% of admissions in the critical care unit. In the developing world along with many other disease AKI is also a major medical complication, especially in the setting of diarrheal illnesses, infectious diseases like leptospirosis and Malaria. The incidence of AKI has increased by more than fourfold in the US since 1988 and is been calculated to have annual incidence of 500 per 1 lakh population, higher than annual incidence of stroke.[15] AKI is associated with a remarkably increased risk of death in inpatients, particularly in patients admitted to the critical care unit where the hospital mortality percentage may exceed 50%.[15]

PREVALENCE OF AKI IN DEVELOPING WORLD

The epidemiology of AKI differs enormously between developing and developed countries, because of differences in geography, economics, demographics, and comorbid disease burden. Whereas in developed zone elderly patients predominate, in developing countries, AKI is a disease of the young and children, in whom volume responsive “pre-renal” mechanisms are common. AKI is a worsening problem, but its true incidence is unknown. From a worldwide perspective, there is a clear need to understand the epidemiology of AKI more accurately.[16]

ETIOLOGY

Most of the aetiologies for AKI are geographic-specific such as envenomation's from spiders, snakes, bees and caterpillars; infectious aetiologies such as leptospirosis and malaria and rhabdomyolysis due to crush injuries from earthquakes.

AKI is broadly classified into 3 important categories;

(i) Pre-renal azotemia,

(ii) Intrinsic renal parenchymal disease

(iii) Post renal obstruction

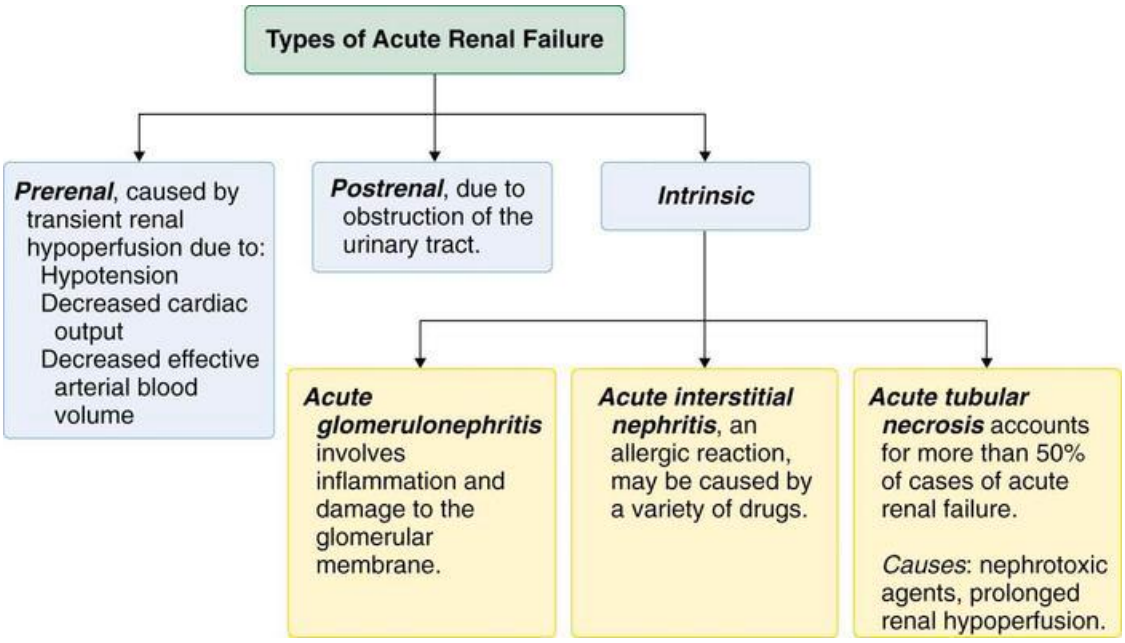


Figure 2.Types of AKI.(17)

PRE-RENAL AZOTEMIA

Adequate renal perfusion is mandatory to maintain a normal GFR. Pre-renal azotemia is due to decline in GFR caused by decrease in renal perfusion pressure with no damage to the renal parenchyma.[17]Failure of the circulation in the body or exclusive failure of the intra renal circulation can show a large impact on the renal perfusion.

Decreased renal flow causes salt and water retention for restoring pressure and volume. When pressure and volume is decline the baro-receptor reflexes which is located in carotid sinuses and aortic arch are gets activated. Which leads to sympathetic nerve stimulations results in afferent arteriolar vasoconstriction and through B1 receptors Renin secretion.[2]

Afferent arteriolar constriction leads to decline in intra glomerular pressure, which decreases the GFR in proportion. Angiotensin I is converted angiotensin II by renin; in turn release aldosterone.

Reduction in pressure or volume is a non-osmotic stimulus for anti-diuretic hormones from hypothalamus; which causes effect in collecting duct especially medullary collecting duct for water reabsorption. Through unidentified mechanism stimulation of sympathetic nervous system causes increased proximal tubular reabsorption of water and salt, also calcium, creatinine, uric acid and BUN. The net result of above four mechanisms of water and salt retention is decline in output and urinary excretion sodium [<20 meq/l].[17]

Causes for pre-renal azotemia:

(i) Volume loss:

- Diarrhoea
- Vomiting
- Heat exhaustion
- Extreme sweat loss
- Burns
- Haemorrhage

(ii) Escape of fluid from circulation

- Dengue
- Leptospirosis
- Malaria & etc.

(iii) Cardiac causes

- Cardiac failure
- Shock
- Pericardial tamponade
- Severe pulmonary hypertension

(iv) Interruption of blood flow to kidney

- Renal artery embolism
- Renal artery occlusion

(v)Renal loss

- Diuretics

(vi) Decreased vascular resistance -peripheral vasodilatation

- Sepsis
- Vasodilator medications
- Autonomic neuropathy
- Anaphylaxis

INTRINSIC AKI

Sepsis, nephrotoxins, and ischemia are the most common causes of intrinsic AKI. Nephrotoxins are broadly separated as endogenous toxins and exogenous toxins. Many cases of prerenal azotemia progressed to tubular injury. Though classically named "ACUTE TUBULAR NECROSIS," renal biopsy confirmation of tubular necrosis is lacking in patients of ischemia and sepsis; whereas, pathological processes such as apoptosis, inflammation, and altered perfusion in various regions of kidney may be relevant pathophysiologically. There are other causes of intrinsic AKI; which are less common. Intrinsic kidney injury is anatomically conceptualised according to the site of parenchymal damage of kidney. (i) Glomeruli (ii)Tubulo-interstitium, and (iii)vessels.[17]

ACUTE TUBULAR NECROSIS

Acute tubular necrosis (ATN) is a condition in which there is death of tubular epithelial cells that forms the tubules of the kidney. ATN is one among the cause of intrinsic acute kidney injury but it is more common and often seen in patients who has been hospitalized. The causes of

ATN are: Surgery especially abdominal surgery or cardiovascular surgery, trauma to the kidney, extensive muscle injury or extreme physical exercise, toxic Substances to the kidneys many a times substances that are not toxic to the kidneys in a healthy individual may become toxic in a person who contracts diseases like CKD, diabetes, heart failure, or multiple myeloma.[18]

ACUTE GLOMERULONEPHRITIS

Acute Glomerulonephritis is a renal disease where there is an active inflammation of the Glomeruli. Both kidneys are composed of 2 million filtering screens known as glomeruli. Glomeruli screens and selectively remove nitrogenous waste products. In AGN the microvasculature in the kidneys become inflamed and damaged. The inflammatory process usually starts after injury (trauma) or infection; there by the protective immune system of the body fight against the infection; leads to scar tissue formation; and then the process would be completed. When the glomeruli is damaged it will not do proper filtering function. AGN may also be caused by an abnormal immune response of the body.[19]

Causes of diffuse glomerulo nephritis:

- Lupus nephritis
- Cryoglobulinemia
- Good pasture's syndrome
- Wegener's granulomatosis
- Henoch- schonleinpurpura
- Peri arteritis nodosa
- other forms of vasculitis
- Bacterial or viral infections

Causes of AGN primarily affects kidney:

- IgA nephropathy
- MPGN
- Post infectious GN

ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis is resulting from immune mediated inflammatory tubule interstitial injury, commonly initiated by medications like Antibiotics such as Methicilin, Non-steroidal anti-inflammatory drugs like brufen, naproxen, infection & other causes. Reaction to drugs causes 71% to 92% of AIN cases. Better to advice a patient to not to consume over counter medications.[20]

Causes of AIN:[20]

Medications:

- NSAID
- Penicillin
- Methicillin
- Sulphonamides
- Furosemide
- Thiazide diuretics
- Allopurinol
- Cyclosporine etc...,

Infection

- Legionella
- Leptospira
- Cytomegalo virus
- Mycobacterium tuberculosis
- Ebstien-Barr virus
- Polyoma virus
- Ecoli etc...,

Autoimmune disorders

- Kawasaki disease
- Sjogrens syndrome
- Systemic lupus erythematosis
- Wegenersgranulomatosis

Signs and symptoms of AKI:

- Oliguria (though patients may have normal urine output)
- Fluid retention – Pedal edema
- Drowsiness
- Fatigue
- Shortness of breath
- Confusion, Coma
- Nausea, Vomiting

- Seizures
- Hypertension
- Easy bruising
- Decreased appetite
- Jaundice (in Liver disease)

POST RENAL ACUTE KIDNEY INJURY

Post-acute renal kidney injury developed when there is an obstruction in the urinary tract below the level of kidneys which in turn directs wastes to concentrate in the kidneys. Post renal acute kidney injury is not as common like intrinsic acute kidney injury. An obstruction in the urinary tract may cause urine to accumulate in one or both kidneys. Over a period of time, this fluid which is build up will prevent the normal flow of urine out of the kidney.

Causes of Post Renal Acute Kidney Injury

- Stones - Ureteric calculus, Bladder stones
- Prostate enlargement –BPH, CA prostate
- Blood clots in urethra and ureter
- Cancer cervix
- Renal cell carcinoma
- Carcinoma colon
- Neurologic disorders - that impair bladder emptying- eg.., spinal cord injury, stroke, multiple sclerosis, and Parkinson's disease.

Relieving the obstruction is the mainstay of treatment. If the blockage is removed, the kidney gets recovered in 1 to 2 weeks if there is no other infection associated with.[21]

Signs and symptoms of Post Renal Acute Kidney Injury

Pain: severity- varies

- Location – Depends upon the type of obstruction. Pain felt in the lower back,
- Lower abdomen, groin, genitalia
- Difficult urination
- Bladder Distension
- Anasarca
- Hypertension
- Hematuria

Diagnosis of Post Renal AKI:

Post renal AKI is diagnosed after an elaborate medical history and complete clinical examination with supra pubic distension of abdomen. Large amount of urine {2–3 litres} after catheterization of a bladder hold us to make the diagnosis. Following which the bladder swelling is resolved.

Risk factors[22]

Risk factors for ARF: age; hypotension; sepsis; hypovolaemia; pre-existing renal, cardiac dysfunction,hepatic; diabetes mellitus; immunosuppressive agents, exposure to nephrotoxins (e.g., aminoglycosides, NSAIDs, amphotericin, intravenous contrast media,ACE inhibitors).

Aetiology in critically ill individuals: Isolated episodes of ARF are rarely seen in critically ill subjects, but are usually part of multiple organ failure. ARF requiring dialysis is rarely seen in isolation. The kidneys are often the first organs to fail.

PATHOPHYSIOLOGY OF AKI

AKI has a common pathophysiological process despite its multifactorial etiology. (Figure 3) The commonest injury in hospital is ischemic or toxic, resulting in a downward spiral to AKI and ESRD if not evaluated or managed early. Once renal perfusion is reduced ischemic tubular dysfunction leads to loss of tubular cell polarity, followed by apoptosis and necrosis. Loss of ß-integrins and adhesion molecules cause sloughing of the tubular cells and the sloughed viable as well as necrotic cells lead to tubular obstruction and production of inflammatory mediators. These induce interstitial inflammation & vascular congestion. Once cells are sloughed, back-leak of filtrate occurs owing to increased intra-tubular pressure, worsening the inflammation cascade and ischemia as a result of vasoconstriction. The kidney may recover if the underlying insult is reversed early by a process of intact epithelial cells migrating over the denuded areas of the basement membrane, cell de-differentiation &proliferation to restore structural and functional integrity over a period of time. Time is of essence in this process of healing, with timely intervention resulting in regression of injury and recovery.[23]

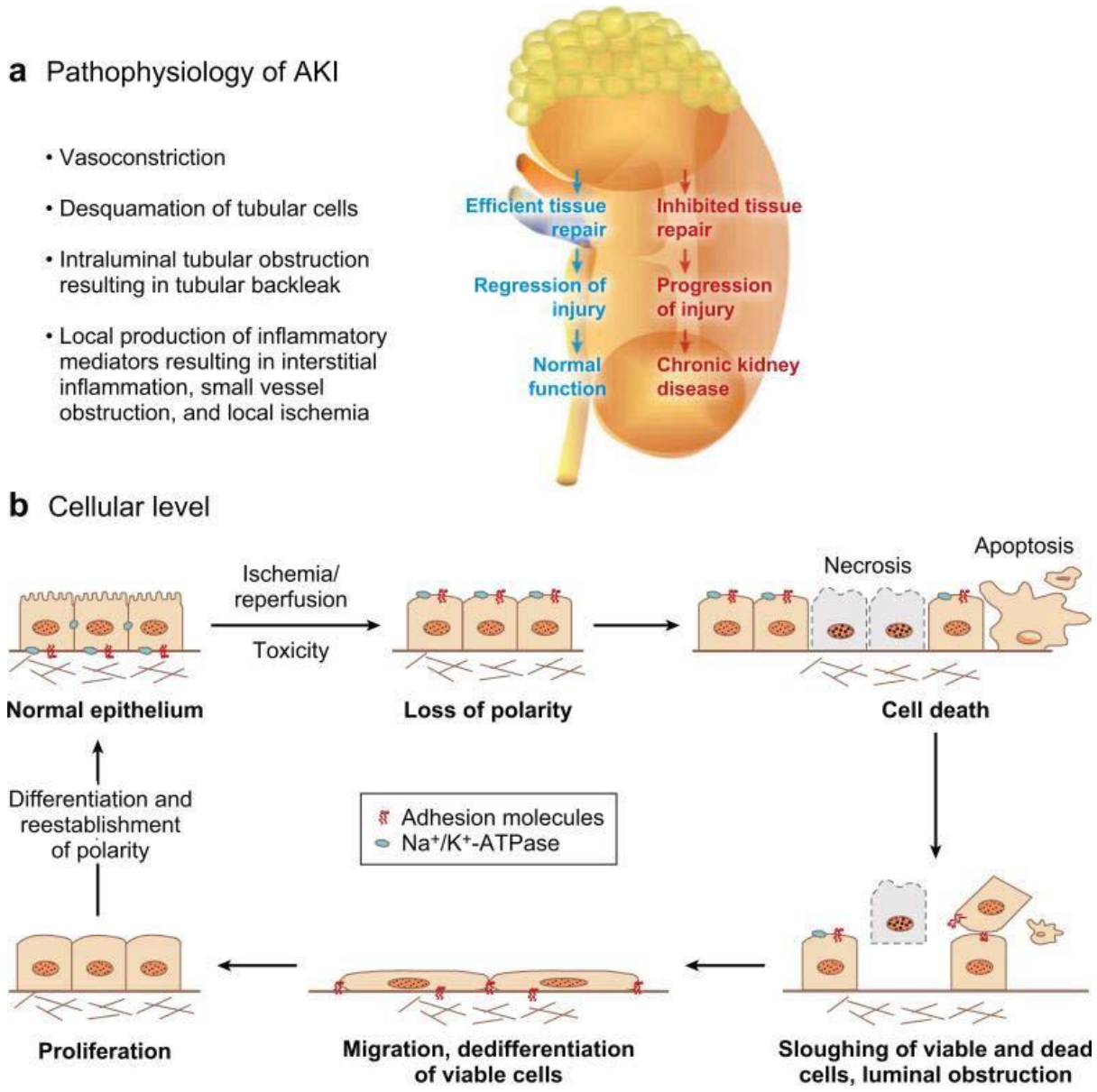


Figure 3.Pathophysiology of AKI.[23]

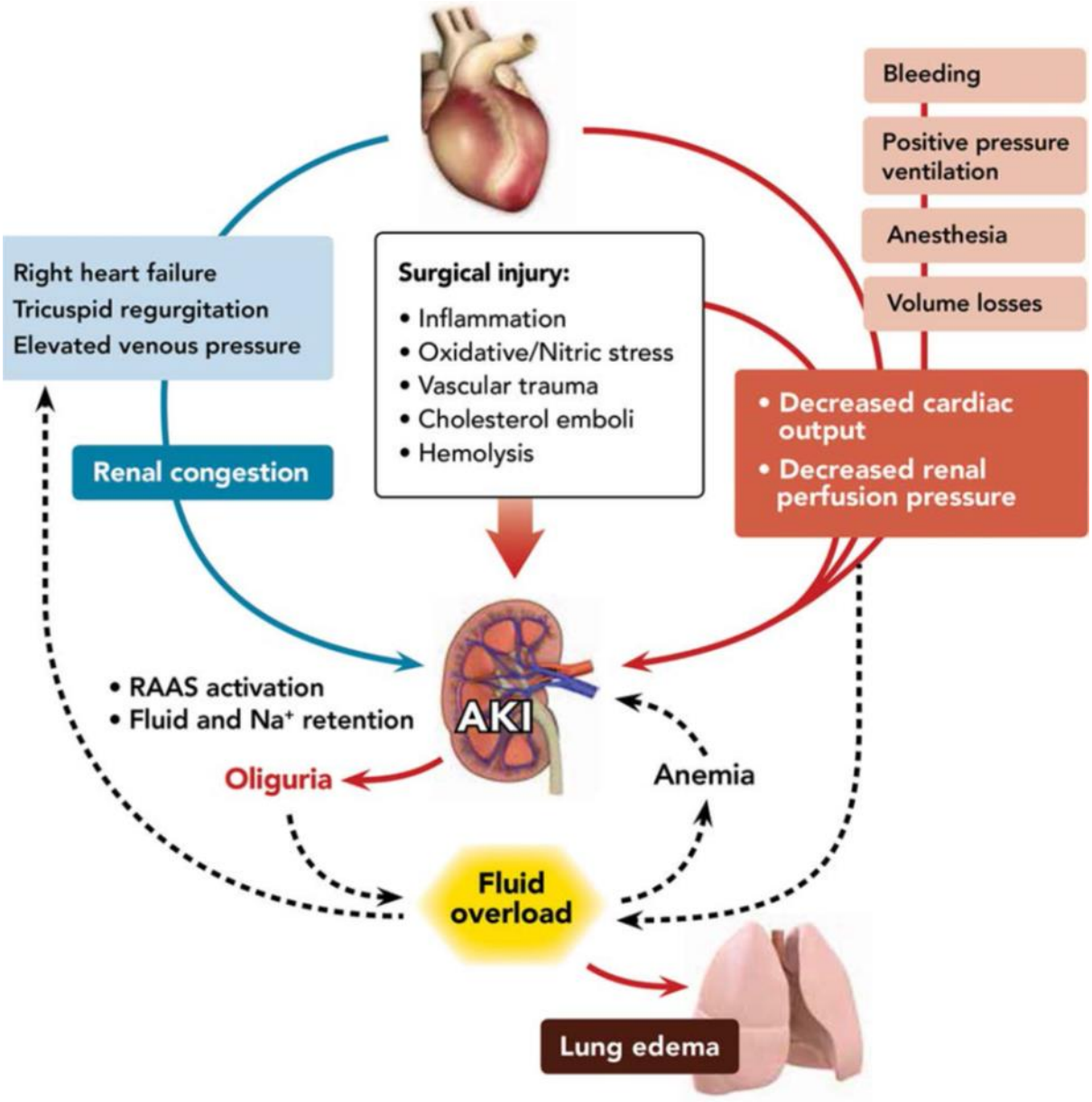


Figure 4.Etiopathogenesis of AKI.

ACUTE KIDNEY INJURY: THE PROCESS OF DEVELOPMENT.

Acute Kidney Injury: The process of development. “The exact definition of a problem with a detailed description and accurate measurement of the factors involved provides already

half the solution."—Anonymous. The problem with definitions like the above mentioned one is poor standardization both in terms of diagnosis and grading the severity of AKI. It was noticed that even modest increases in creatinine from the baseline translated to increased risk of mortality. A need to factor the risk associated with this rise in a manner that would sensitize treating physicians to treat early as well as grade / prognosticate patients based on the severity of AKI was felt.

The Acute Dialysis Quality Initiative (ADQI) was born out of this long felt need to address AKI and related issues. The group comprised intensivists and nephrologists from the American Society of Nephrology (ASN), International Society of Nephrology (ISN), National Kidney Foundation (NKF) and the European Society of Intensive Care. They met in Vicenza, Italy, in September 2004 to generate protocols and guidelines aiming to standardize care and dialysis for the critically ill with AKI.

Their guidelines called the RIFLE criteria **(Figure 5)** graded AKI based on the rise in creatinine and decrease in urine output into Risk (R) where renal failure can be prevented, Injury (I) where damage is ongoing and Failure (F) where renal failure is established. Creatinine was used despite reservations regarding its applicability as it is widely available and affordable as a marker for tubular dysfunction. [24]

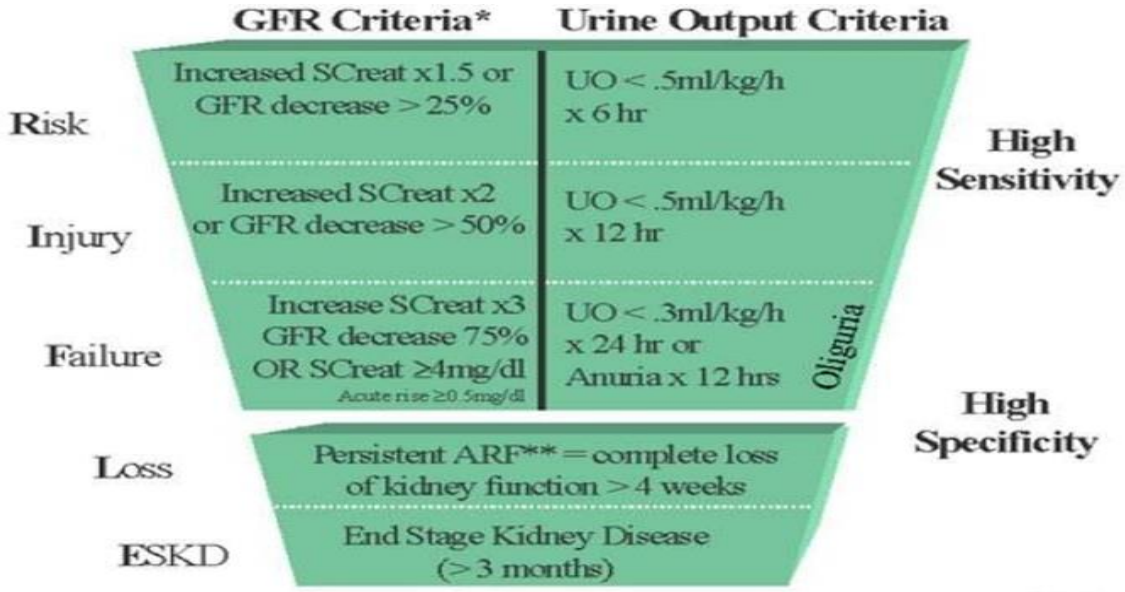


Figure 5.RIFLE Criteria.[24]

However with increasing applicability AKI using the RIFLE criteria, the need to establish a better, comprehensive and sensitive tool was felt along with a focused, multidisciplinary group to formulate these guidelines. Members of the ADQI collaborated with critical care societies to establish the Acute Kidney Injury Network (AKIN).

One of the fundamental tasks of this group was to improve outcomes for the risk grade as it was felt that they were most likely to benefit from early detection and intervention. They redefined AKI as "an abrupt (within 48 h) reduction in kidney function defined as an absolute increase in serum creatinine level of ≥26.4 mol/l (0.3mg/dl) OR a percentage increase in serum creatinine level of ≥50% (1.5-fold from baseline) OR a reduction in urine output (documented oliguria of <0.5 ml/kg/h for >6 h).These criteria are applied in the context of the clinical presentation and following adequate fluid resuscitation when applicable." The revised RIFLE criteria based on the above requirements was referred to as the AKIN classification. **(Table 1)** This was done in their first meeting in 2005 and published as the AKIN guidelines. It

staged the patients as Stage I, II and III and removed the Loss (L) and E (ESRD) categories in RIFLE which were considered to be outcomes.[25]

Table 1: AKIN Classification of AKI.[25]

Stage	Serum creatinine criteria	Urine output criteria
1	Increase of ≥26.4 μmol/l (0.3 mg/dl) OR to 150–200% of baseline (1.5–2.0-fold)	<0.5 ml/kg/h for >6 h
2	Increase to >200–300% of baseline (>2–3-fold)	<0.5 ml/kg/h for >12 h
3[a]	Increase to >300% of baseline (>3-fold; or serum creatinine ≥354 μmol/l [4.0 mg/dl] with an acute rise of at least 44 μmol/l [0.5 mg/dl])	<0.3 ml/kg/h for 24 h OR anuria for 12 h

Only one criterion (creatinine or urine output) needs to be fulfilled to qualify for a stage. [a]Patients who receive renal replacement therapy are considered to have met the criteria for Stage 3, irrespective of the stage that they are in at the time of commencement of renal replacement therapy. Permission obtained from BioMed Central © Mehta RL *et al.* (2007) *Crit Care* **11:** R31.

RIFLE Classification

AKI has been a significant component of critical care scoring systems constituting 20% and 16.6% of the APACHE III (Acute Physiology and Chronic Health evaluation) (26) and SOFA (Sequential Organ Failure Assessment) scores. [27] ADQI formulated RIFLE grading AKI based on increasing severity (assessed by fall in urine output and rise in creatinine from baseline) as R (Risk), I (Injury) and F (Failure) and outcomes as L (Loss) and E (End Stage Renal Disease).(24) In ICU s the incidence of AKI in patients in the R and I categories is 55% placing them at a higher risk of mortality.(28) In patients requiring renal replacement therapy (RRT) the overall in hospital mortality in a studies was 50.2%.[29]

Limitations

Although the introduction of RIFLE provided insight into the high incidence of AKI and enabled early diagnosis and management, the criteria per se is not without limitations, in a practical scenario. Although urine output serves as a sensitive and specific parameter in the criteria, its accuracy in terms of measurement in a patient who is not on continuous bladder drainage or post diuretic use is questionable. Comparing these parameters has shown creatinine criteria to be a better marker for mortality, but in conjunction with urine output a stable result is likely.[30] The absence of a baseline creatinine in most patients presenting with AKI does hamper accuracy of the criteria, although back calculation of baseline GFR using the MDRD equation has been advocated.[31]

RIFLE has also been validated successfully in non ICU based situations. In a retrospective study RIFLE; R, I and F were found in 9.1%, 5.2% and 3.7% respectively with overall mortality of 8.0%. An incremental mortality was observed from the non AKI patients across to those in failure (non AKI- 4.4%; R - 15.1%; I - 29.2%; and F - 41.1%). [32]

Acute Kidney Injury Network Criteria

AKIN is an international group of nephrologists including adult, paediatric and critical care specialists with a focused interest in AKI and development of evidenced based guidelines for improvement in care and outcomes of AKI.(25) They defined AKI as “an abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥26.4 μmol/l), a percentage increase in serum creatinine of more than

or equal to 50% (1.5-fold from baseline), or a reduction in urine output (oliguria of less than 0.5 ml/kg per hour for more than six hours)."

Urine output is used as a diagnostic criterion as it often heralds renal dysfunction before a rise in serum creatinine. It needs to be assessed in the clinical scenario of reliable measurement, optimal hydration, absence of diuretic use and urinary obstruction with the recognition that it may not be specific for in AKI stage I.[25]

AKIN versus RIFLE Criteria

A recent analysis of the Australian New Zealand Intensive Care Society (ANZICS) database found agreement with both RIFLE and AKIN criteria. There was <1% difference in the overall number of identified AKI with AKIN, slightly increasing the number of patients classified as Stage I injury as compared to category R in RIFLE (18.1 versus 16.2%) but reducing those with Stage II injury as compared to category I in RIFLE (10.1% versus 13.6%). ROC curves for hospital mortality were similar (0.67 for AKIN and 0.66 for RIFLE. [33] This similarity has been demonstrated in other studies with a similar design.[34]

As there seem to be no additional benefits to the AKIN criteria at this point, future efforts aim to focus on successful application and extended use of either of these criteria, particularly RIFLE, as a surrogate marker for outcomes in trials to prevent and alleviate AKI.[33]

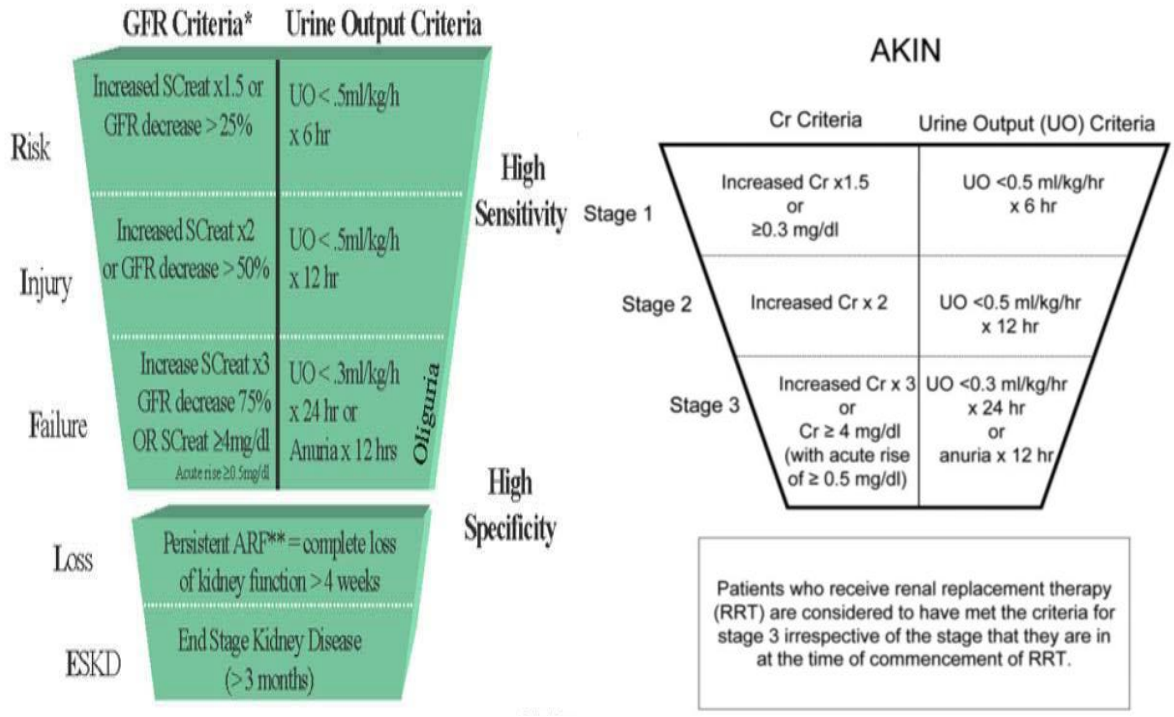


Figure.6 AKIN versus RIFLE Criteria[34]

MANAGEMENT OF ACUTE KIDNEY INJURY

AKI is a worldwide problem with varied aetiologies&manifestations, but the results are similar. With this wide global variation in the natural history & management of AKI, it is essential to develop system for sharing information &collaboration among centres be developed. So a standard for diagnosing &classifying AKI would enhance the ability to improve the management of these patients.[25]

The evaluation &initial management of patients with AKI should include:

1. An assessment of the contributing causes of the kidney injury,
2. An assessment of the clinical course including comorbidities,

3. A careful assessment of volume status, and
4. The institution of appropriate therapeutic measures designed to reverse or prevent worsening of functional or structural kidney abnormalities.[35]

AKI : Clinical Assessment; Investigations[36]

It is recommend that all patients presenting with AKI should have appropriate baseline investigations performed which should include anurinanalysis and a renal tract ultrasound within 24 hours (if renal obstruction is suspected).

Audit measures

1. Proportion of patients who had a urinanalysis performed within 24 hours of the diagnosis of AKI unless anuric

2. Proportion of patients developing AKI secondary to obstruction who had a renal ultrasound examination < 24 hrs after a diagnosis of AKI established

Rationale

Clinical assessment to establish a working diagnosis requires a number of investigations to be performed.

A baseline set of laboratory investigations should be sent including:

 Biochemistry: Urea &electrolytes

 Haematology: Complete blood count

 Urinalysis: Microscopy

 Microbiology: Urine culture, blood culture.

 Renal immunology

 Urinary biochemistry: electrolytes, osmolality

 ECG

 Chest x-ray

 Abdominal x-ray

 Renal tract ultrasound (within 24hrs if obstruction suspected or esoteric cause suspected requiring a kidney biopsy)

 Kidney biopsy

Urinalysis can give hint to patients with AKI. Positive protein values of 3+ and 4+ on reagent strip testing of the urine suggest intrinsic glomerular disease.

Haematuria may be useful in identifying in cases of lower urinary tract obstruction often in association with tumours and less commonly associated with calculi, infection or severe renal ischaemia due to arterial or venous thrombosis.[37]

Urine microscopy can be informative in particular clinical scenarios such as suspected poisoning. The presence of crystalluria may provide clue in case of ethylene glycol poisoning.[38]

Patients with pre-renal AKI not on diuretics have both low FENa (<1%) & decreased FEUrea. However patients with pre-renal AKI on diuretics have levels of FENa greater than 2%

but still have low levels of FEUrea. In comparison, patients with ATN have both high FENa and high FEUrea.[39][40]

The diagnostic criteria for hepatorenal failure include a urine sodium of less than 10 mmol/L (although not a major diagnostic criterion).(41)

USG is the gold standard test for diagnosis of upper tract obstruction through the finding of hydronephrosis and/or hydroureter. However upper urinary tract(UUT) obstruction may not be initially detected by USG in patient whose volume is depleted. It is therefore recommended to repeat the renal tract USG, if UUTobstruction is suspected once the patient is adequately fluid resuscitated.

In some circumstances USG may not be diagnostic, such as in retroperitoneal fibrosis, in such case additional imaging studies may be considered such as dynamic nuclear medicine studies or CT. Dynamic nuclear medicine studies will be of less diagnostic use if the patient has oligoanuric AKI.[36]

Early in the course of AKI, optimization of the hemodynamic status &correction of volume deficit will have a salutary effect on kidney function, which will help to minimize further extension of the kidney injury,&will potentially facilitate recovery from AKI with minimization of any residual chronic impairment of kidney function.[35] However a positive fluid balance after the development of AKI is associated with increased mortality, as well as progression to more severe grades of AKI and increased requirement for renal support.[42]

Patients with AKI receiving renal replacement therapy (RRT) should be referred to a dietician for individual assessment. They should receive 25-35 kcal/kg/day &up to a maximum

of 1.7g amino acids/kg/day if hypercatabolic&receiving continuous RRT. Micronutrients should be supplemented as required.[36]

Interventions to enhance renal blood flow &decrease tubular reabsorption seem to be a logical approach for the prevention of outer medullary hypoxic injury. Loop diuretics block the active sodium-potassium co-transport in the apical membrane of the thick ascending limb renal tubular cells. The loop diuretic frusemide has been shown to reduce medullary demand by inhibiting solute reabsorption and to decrease the severity of AKI in animal models. It is hypothesisedthat it may protect the human kidney from ischaemic injury.[43]

In critically ill patients with ARF, there is no evidence to suggest that the use of loop diuretics reduces morbidity &mortality, reduces the length of ICU/hospital stay, or increases the recovery of renal function.[43]

The choice of renal replacement therapy modality should be guided by the individual patient's clinical status, medical and nursing expertise, and availability of modality.[36]

FIGURE 7.AN APPROACH TO ACUTE KIDNEY INJURY[36]

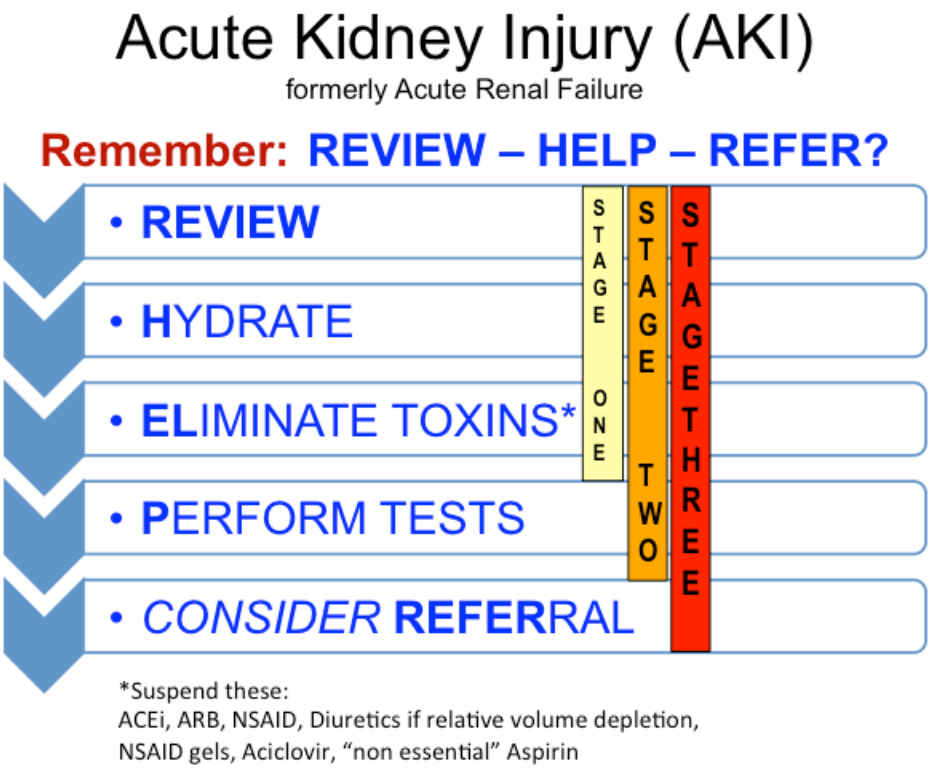


Figure 8.Management approach of AKI.[36]

BIOMARKERS OF ACUTE KIDNEY INJURY

The urine has yielded the most promising biomarkers for early detection of AKI &these biomarkers as useful tools for the earlier diagnosis, identification of mechanism of injury, &assessment of site and severity of injury.[23]

Serum creatinine, although used routinely in clinical practice and in clinical trials, is a poor marker of renal dysfunction. Changes in creatinine can be non-specific as they may occur as a result of several non-renal factors, such as muscle mass & nutrition.[44]

Some of the urinary biomarkers of acute kidney injury are cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), NAG, c-glutamyltranspeptidase, IL-18, and kidney injury molecule-1 (KIM-1).

N-acetyl-β-glucosaminidase (NAG)

A proximal tubule lysosomal enzyme, has been extensively studied and has proven to be a sensitive, persistent, and robust indicator of tubular injury.[45]

β2-microglobulin (β2M)

β2M is 11.8-kDa protein that is the light chain of the major histocompatibility class (MHC) I molecule expressed on the cell surface of all nucleated cells. β2M is typically filtered by the glomerulus and almost entirely reabsorbed and catabolized by the proximal tubular cells, a process that may be impeded in AKI.(23)

α1-microglobulin

α1-microglobulin is a 27−33-kDa protein synthesized by the liver with approximately half of the circulating protein complexed to IgA found in routine clinical practice, making it a preferred marker of tubular proteinuria in human bioassays.[23]

Retinol binding protein (RBP)

Is a 21-kDa protein that is hepatically synthesized and responsible for transporting vitamin A from the liver to other tissues. Bernard et al. monitored patients with AKI from various etiologies and found urinary RBP to be a highly sensitive indicator of renal tubule dysfunction, preceding urinary NAG elevation.[23]

Cystatin-C

Cys-C is freely filtered by the glomerulus, reabsorbed and catabolized, but not secreted, by the tubules which is independent of age, sex & muscle mass.Vaidya et al.,observed Cys-C as sensitive serum marker of GFR and a stronger predictor than serum creatinine of risk of death and cardiovascular events in older patients.[23]

Kidney Injury Molecule-1

Kidney injury molecule-1 (KIM-1) is a type I cell membrane glycoprotein containing a unique six-cysteine immunoglobulin-like domain and a mucin domain in its extracellular region. KIM-1 mRNA levels increase more than any other known gene after kidney injury.[23]

Clusterin

Clusterin is induced in the kidney and urine of rats after various forms of preclinical AKI such as ischemia/reperfusion injury, toxicant-induced kidney injury, or subtotal nephrectomy.[23]

Urine IL-18 levels were significantly increased in patients with AKI compared with prerenal azotemia, urinary tract infection, chronic renal insufficiency, and nephrotic syndrome.[44]

PROGNOSTIC ROLE OF PLATELET-TO-LYMPHOCYTE RATIO (PLR) AMONG CRITICALLY ILL PATIENTS

There are many scoring systems used in the prediction of prognosis in Intensive Care Unit (ICU) patients. Of these scoring systems, the Acute Physiology and Chronic Health Evaluation (APACHE) score measures mortality numerically using laboratory parameters

together with physiological parameters that may affect mortality. It is one of the most frequently used scoring systems in ICUs. Although there are several scoring systems, the APACHE II score is still one of the most frequently used risk scoring systems as physiological, hematological and biochemical parameters are evaluated together and it has high success rate for the prediction of mortality.[46]

In recent years, in addition to these scoring systems, different indicators have been studied which may be useful for the prediction of mortality. Hematological parameters are considered important because they are readily available and easy to interpret. With the exception of WBC and hematocrit levels, which are also included in the APACHE II score, hematological parameters which are not included in scoring systems are being investigated, such as platelet count, platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR) and MPV.

Thrombocytopenia is the most frequently seen coagulation abnormality in critically ill patients.[47] It is quite difficult to identify the reason for a decreased platelet count in ICU and it is often thought to be multifactorial.[48] Although it may differ based on how it is defined (<100000 or <150000, x106/L) and the patient categories studied, thrombocytopenia prevalence and incidence in ICU patients has been reported to vary between 8.3- 67.6% and 13-44% respectively.[49] In several previous reports,[48][49][50] thrombocytopenia has been defined as an independent risk factor for mortality in ICU patients. In a cohort study by Williamson et al.,[51] reported that both thrombocytopenia at the time of admission and the development of thrombocytopenia during the follow-up period were independent risk factors for mortality and length of stay of patients admitted to internal medicine, surgery and cardiovascular ICUs. Regardless of the cause of admission to ICU, the increased systemic inflammatory response is evident, and it is an important cause of mortality and morbidity in critically ill patients.[1] WBC

and neutrophil count increased C - reactive protein (CRP) levels and, hypoalbuminemia are usually studied as biochemical parameters related to the systemic inflammatory response.[52] It has also been reported by some researchers in various studies [53][54][55][56] that PLR may be used as an inflammatory marker and it is related to poor prognosis in many diseases especially chronic inflammatory diseases like acute kidney injury, cardiovascular diseases, diabetes and malignancies. Liu et al.,[57] reported, higher PLR presents a higher risk for re-admission and mortality in critically ill patients. In addition to PLR, NLR and its effect on intensive care mortality has become a research topic in current studies.[58]

The platelet activation products that are available in circulation have a very important role in the pathogenesis of vascular and inflammatory diseases.[59] PLR is a simple and cheap test which is routinely measured, and easy to interpret. It has been previously reported that is altered in diseases such as AKI, diabetes mellitus, myocardial infarction, and hyperthyroidism. Moreover, PLR has prognostic value in some other diseases.[60]

PROGNOSTIC VALUE OF PLATELET-TO-LYMPHOCYTE RATIO (PLR) AMONG CRITICALLY ILL PATIENTS WITH ACUTE KIDNEY INJURY

About higher than five million patients are admitted to intensive care units (ICUs) every year around worldwide.[1] 6–24% of these patients have acute kidney injury (AKI).[2] In the presence of AKI, patient mortality and morbidity increases to 60–70%, especially within one year after ICU admission. [3,4] Keeping the point of high incidence of AKI in the ICU and its poor prognosis, an increased number of observational studies over the past two decades have been oriented in identifying the clinical predictors of mortality in AKI.

AKI represents a systemic inflammatory condition. AKI shows direct cause and effect relationship with inflammation.[1][2][61] Systemic inflammation is an integral part of disease progression in critical illness & is commonly associated with sepsis, leading to an increased risk of morbidity &mortality.[5][62] Inflammation plays vital role in the initiation &progression of AKI[63] , and morphological and/or functional changes in vascular endothelial cells and/or in the tubular epithelium are observed in patients with AKI. Many observational studies have described increased circulating levels of inflammatory mediators &adverse outcomes for these conditions. These inflammatory mediators include blood cells, platelets, components of endothelial cells, macrophages, lymphocytes, mast cells& fibroblasts.[64]

Lymphocytes, including leukocytes, infiltrate the injured kidneys & the entire body via the circulation system and induce the generation of inflammatory mediators such as cytokines &chemokines, which will damage the kidney and other organ system.[7] The anti-thrombotic effects of platelets can evolve into atherogenesis via the secretion of pro-inflammatory cytokines[8], whereas the attaching of platelets to endothelial cells can trigger leukocyte trans-migration & adhesion.[9]

The platelet-to lymphocyte ratio (PLR) has been introduced as a potential biomarker of inflammation in cardiovascular disease (CVD) and tumors, which are considered as inflammation related diseases.[55] In a study of 2563 patients, Velibey et al.[65]demonstrated that increased PLRs are independently associated with a greater risk of contrast-induced AKI in patients undergoing primary percutaneous coronary intervention. High PLRs in patients with ESRD were also associated with increased levels of inflammation. Balta et al.[66]showed that inflammation is better predicted by the PLR than by the neutrophil-to-lymphocyte ratio in ESRD. On the basis of the association between PLR related inflammation &disease severity, we

speculated that excessively high PLRs could predict the same poor outcomes as other inflammation biomarkers in AKI populations. A positive correlation between a high PLR and a poor prognosis among critically ill patients with AKI has been reported.[10][55][57] On the evidence of similar previous studies, it is reasonable to speculate that the PLR might affect the prognosis of AKI.[67]

So the present study was undertaken to know the prognostic value of platelet to lymphocyte ratio among critically ill patients with acute kidney injury.

METHODOLOGY

The study included critically ill patients with AKI of ICU and emergency ward of BLDE's Shri B.M. Patil Medical College hospital and research centre, Vijayapura. The patients were informed about study in all respects and informed consent was obtained. Period of study was from November 2017 to June 2019. Detailed history and thorough physical examination as indicated for a particular case was done. Relevant blood and urine investigations were sent. Other investigations as needed for a patient condition were performed. Each patient in the study group was followed till discharge or death.

Sample collection

Oral and written consent was taken from the subjects prior to the collection of specimens. Sample was collected in a clean dry test tube and transported to the biochemistry laboratory at B.M. Patil medical college, Vijaypura.

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. ROC analysis for Sensitivity- specificity was done to check relative efficiency. If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007

RESULTS

A hospital based prospective, double blinded, randomized, comparative study was conducted from November 2017 to June 2019. A total of 91 cases of critically ill patients with acute kidney injury were included in the study.

DISTRIBUTION OF CASES ACCORDING TO AGE

Mean age of the patients was 58.4±17.9 years (Table 2). Majority of the patients (37.4%) were between 61 to 75 years of age followed by 46 to 60 years (25.3%) (Table 3, Figure 9).

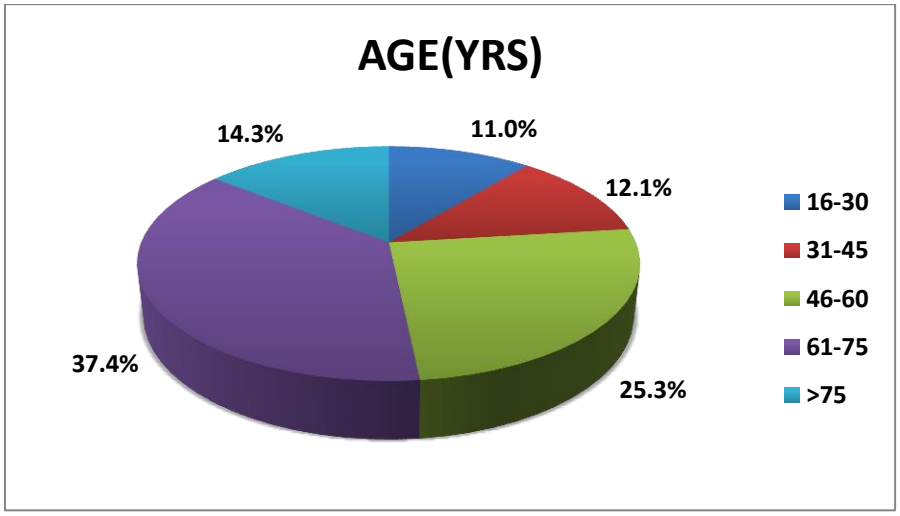
Table 2: Mean age

	Range	Mean	SD
AGE (YRS)	16-92	58.4	17.9

Table 3: Distribution of cases according to age

AGE(YRS)	N	%
16-30	10	11.0
31-45	11	12.1
46-60	23	25.3
61-75	34	37.4
>75	13	14.3
TOTAL	91	100.0

FIGURE 9: DISTRIBUTION OF CASES ACCORDING TO AGE



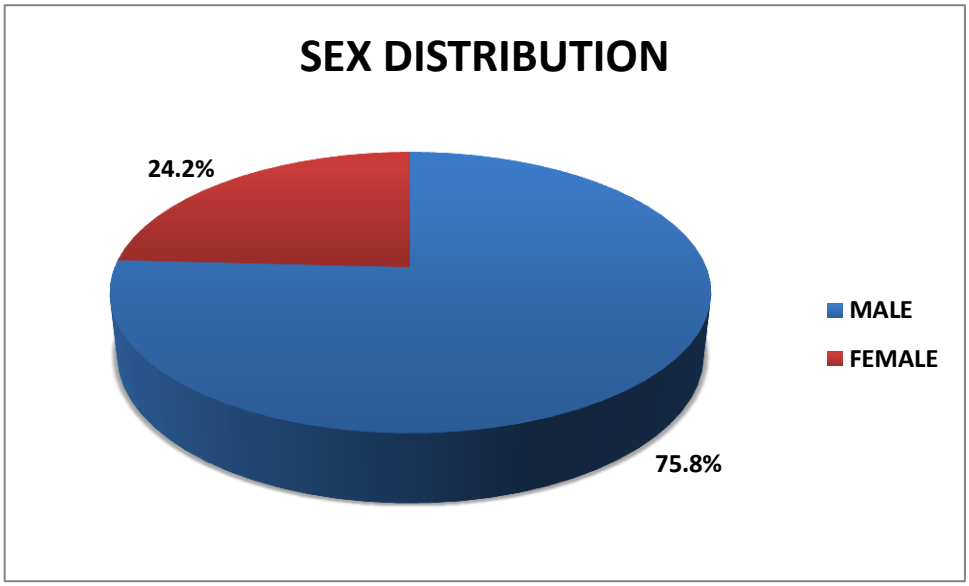
DISTRIBUTION OF CASES ACCORDING TO SEX

Out of the 91 patients enrolled, 75.8% of the patients were male whereas 24.2% patients were female. Males were predominant in our study (Table 4)(Figure 10).

Table 4: Distribution of cases according to sex

SEX	N	%
MALE	69	75.8
FEMALE	22	24.2
TOTAL	91	100.0

FIGURE 10: DISTRIBUTION OF CASES ACCORDING TO SEX



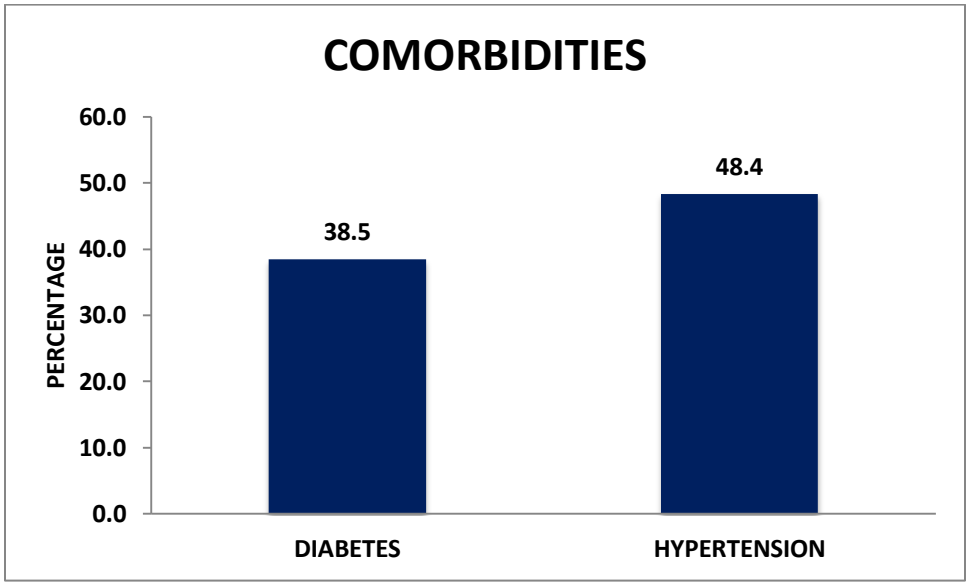
DISTRIBUTION OF CASES ACCORDING TO COMORBIDITIES

Out of the patients enrolled, 48.4% were known cases of hypertension and 38.5% were known cases of type 2 diabetes mellitus. (Table 5, Figure 11)

Table 5: Distribution of cases according to comorbidities

COMORBIDITIES	N	%
DIABETES	35	38.5
HYPERTENSION	44	48.4

FIGURE 11: DISTRIBUTION OF CASES ACCORDING TO COMORBIDITIES



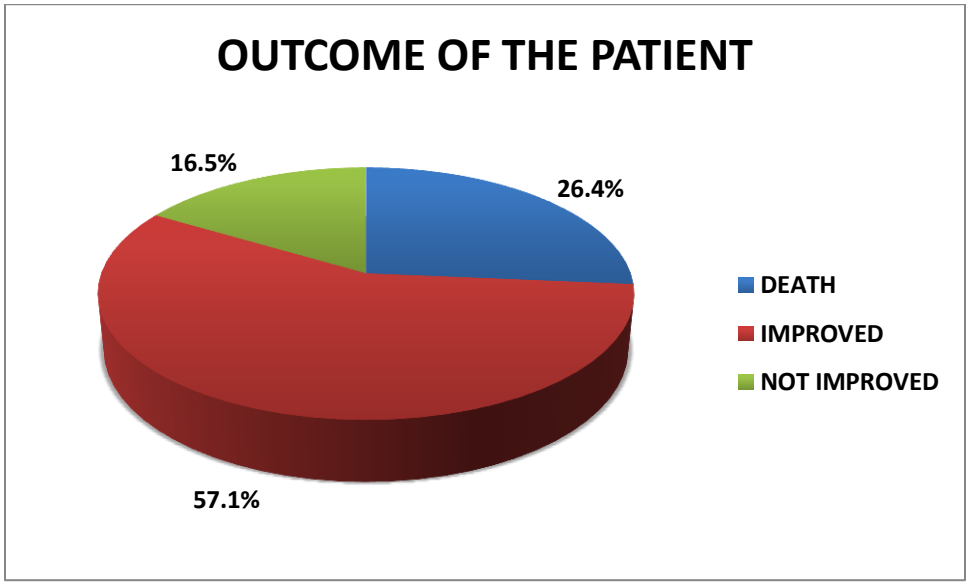
DISTRIBUTION OF CASES ACCORDING TO OUTCOME OF THE PATIENT AT DISCHARGE

Fifty seven percent of the critically ill patients with acute kidney injury had improved in condition at the time of discharge, 26.4% died and 16.5 patients had worsened (Table 6, Figure 12).

Table 6: Distribution of cases according to outcome of the patient at discharge

OUTCOME OF THE PATIENT AT DISCHARGE	N	%
DEATH	24	26.4
IMPROVED	52	57.1
NOT IMPROVED	15	16.5
TOTAL	91	100.0

FIGURE 12: DISTRIBUTION OF CASES ACCORDING TO OUTCOME OF THE PATIENT



After calculating PLR, patients were divided into the following groups:

- **PLR <105**
- **PLR =105-299**
- **PLR >299**

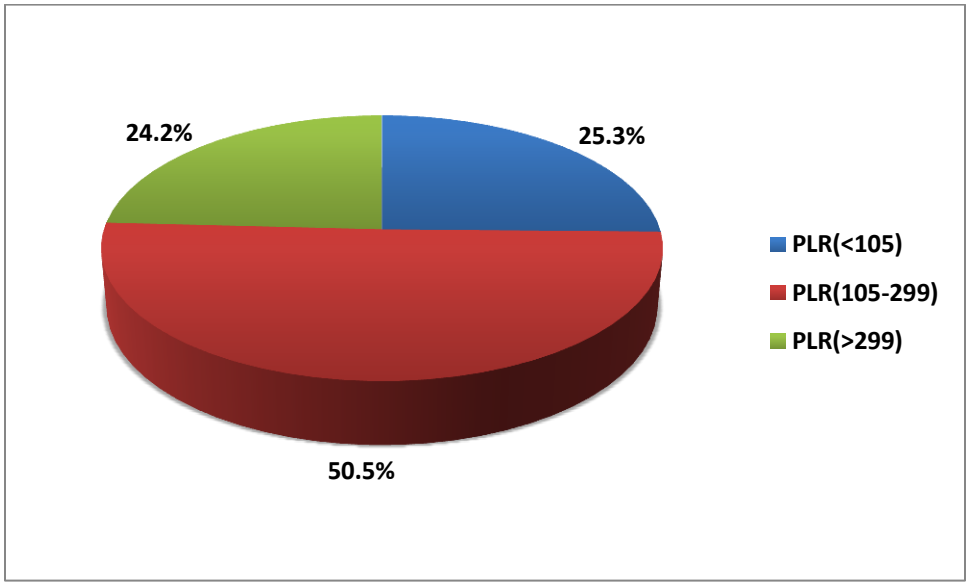
DISTRIBUTION OF CASES ACCORDING TO PLR

Majority (50.5) of the patients belonged to PLR group of 105 to 299 (Table 7, Figure 13).

Table 7: Distribution of cases according to PLR

RISK GROUPS	N	%
PLR(<105)	23	25.3
PLR(105-299)	46	50.5
PLR(>299)	22	24.2
TOTAL	91	100

FIGURE 13: DISTRIBUTION OF CASES ACCORDING TO PLR



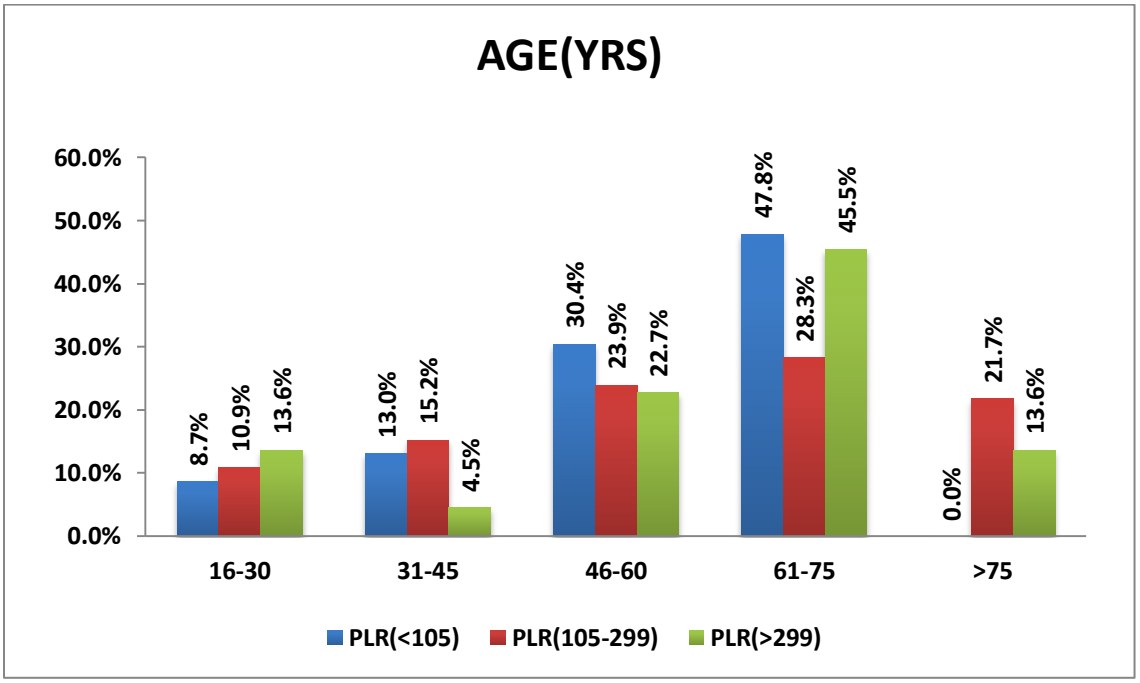
DISTRIBUTION OF AGE ACCORDING TO PLR

Irrespective of age, all PLR groups showed that majority of the patients belonged to the age group of 61-75 years. There was no significant difference between the age of all three groups (Table 8, Figure 14).

Table 8: Distribution of age according to PLR

AGE(YRS)	PLR(<105)		PLR(105-299)		PLR(>299)		p value
	N	%	N	%	N	%	
16-30	2	8.7%	5	10.9%	3	13.6%	0.328
31-45	3	13.0%	7	15.2%	1	4.5%	
46-60	7	30.4%	11	23.9%	5	22.7%	
61-75	11	47.8%	13	28.3%	10	45.5%	
>75	0	0.0%	10	21.7%	3	13.6%	
TOTAL	23	100.0%	46	100.0%	22	100.0%	

FIGURE 14: DISTRIBUTION OF AGE ACCORDING TO PLR



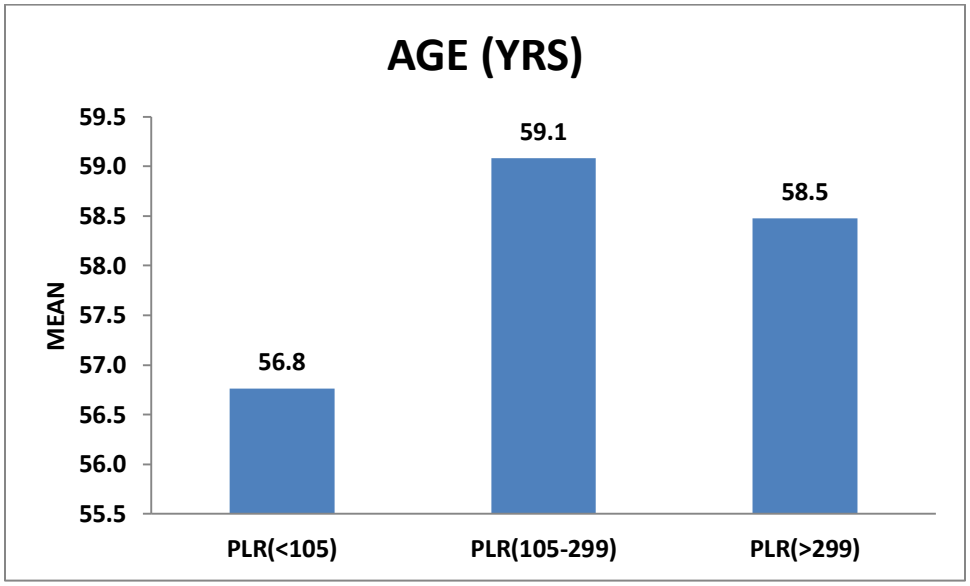
MEAN AGE ACCORDING TO PLR

There was no significant difference between the mean age of all three groups (Table 9, Figure 15).

Table 9: Mean age according to PLR

Paramaters	PLR(<105)		PLR(105-299)		PLR(>299)		p value
	Mean	SD	Mean	SD	Mean	SD	
AGE (YRS)	56.8	14.8	59.1	19.0	58.5	18.7	0.886

FIGURE 15: MEAN AGE ACCORDING TO PLR



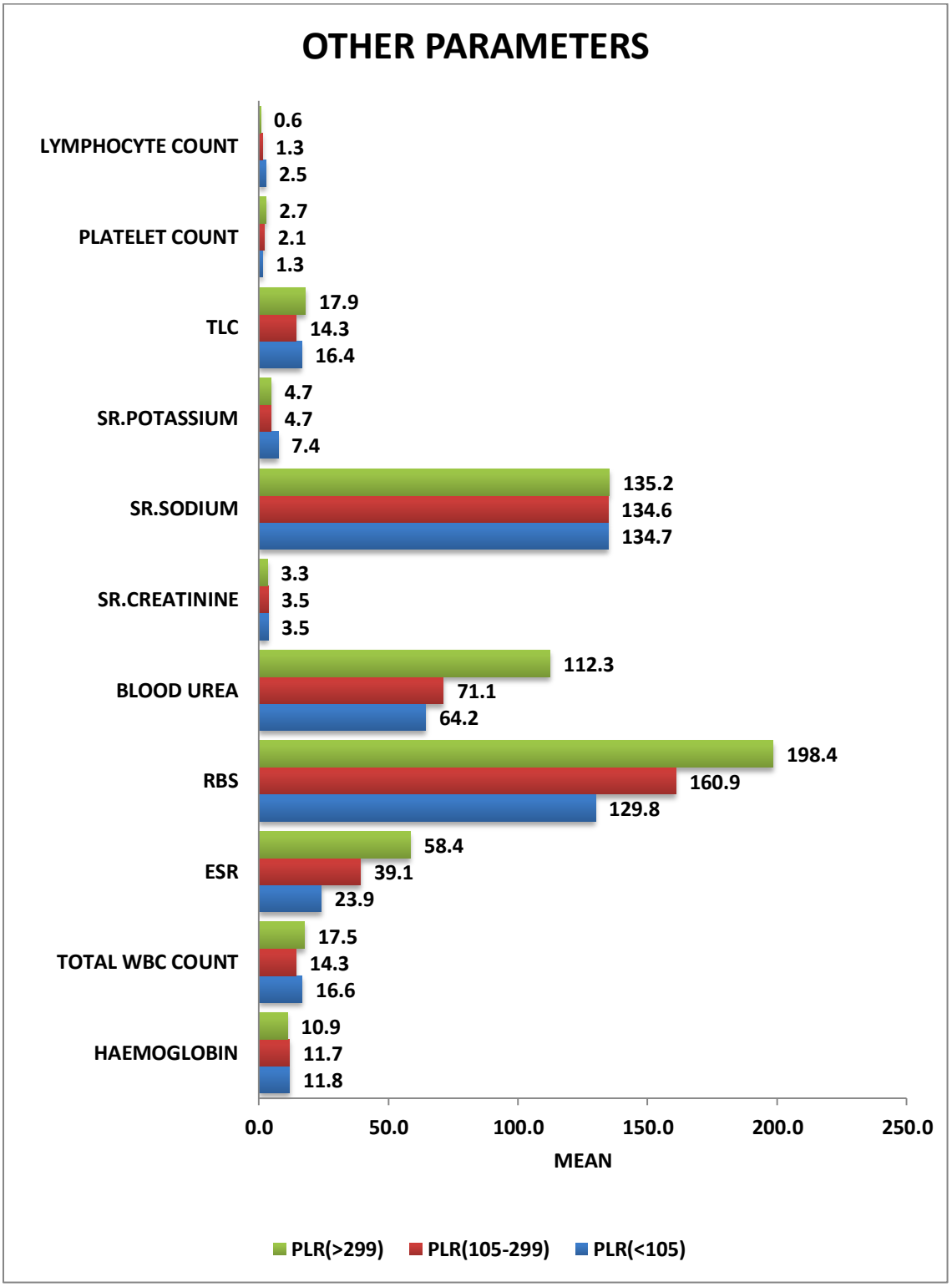
OTHER PARAMETERS ACCORDING TO PLR

Out of the parameters assessed, ESR, Blood urea and platelet count was significantly higher in high PLR(>299) group. Lymphocyte counts showed significantly lower levels in the high PLR(>299) group. Other parameters such as total counts, random blood sugar, sodium and potassium levels were not significantly associated with any PLR groups.(Table 10, Figure 16)

Table 10: Other parameters according to PLR

OTHER PARAMETERS	PLR(<105)		PLR(105-299)		PLR(>299)		p value
	Mean	SD	Mean	SD	Mean	SD	
ESR	23.9	24.7	39.1	31.1	58.4	42.7	0.021*
RBS	129.8	73.5	160.9	110.6	198.4	163.3	0.207
BLOOD UREA	64.2	58.5	71.1	49.9	112.3	63.4	0.041*
SR.CREATININE	3.5	2.6	3.5	2.8	3.3	2.3	0.955
SR.SODIUM	134.7	4.4	134.6	6.0	135.2	7.5	0.935
SR.POTASSIUM	7.4	13.0	4.7	0.9	4.7	1.1	0.235
TLC('000)	16.4	10.1	14.3	7.0	17.9	8.1	0.219
PLATELET COUNT	1.3	1.1	2.1	0.9	2.7	1.5	0.001*
LYMPHOCYTE COUNT	2.5	2.0	1.3	0.7	0.6	0.4	<0.001*

FIGURE 16: OTHER PARAMETERS ACCORDING TO PLR



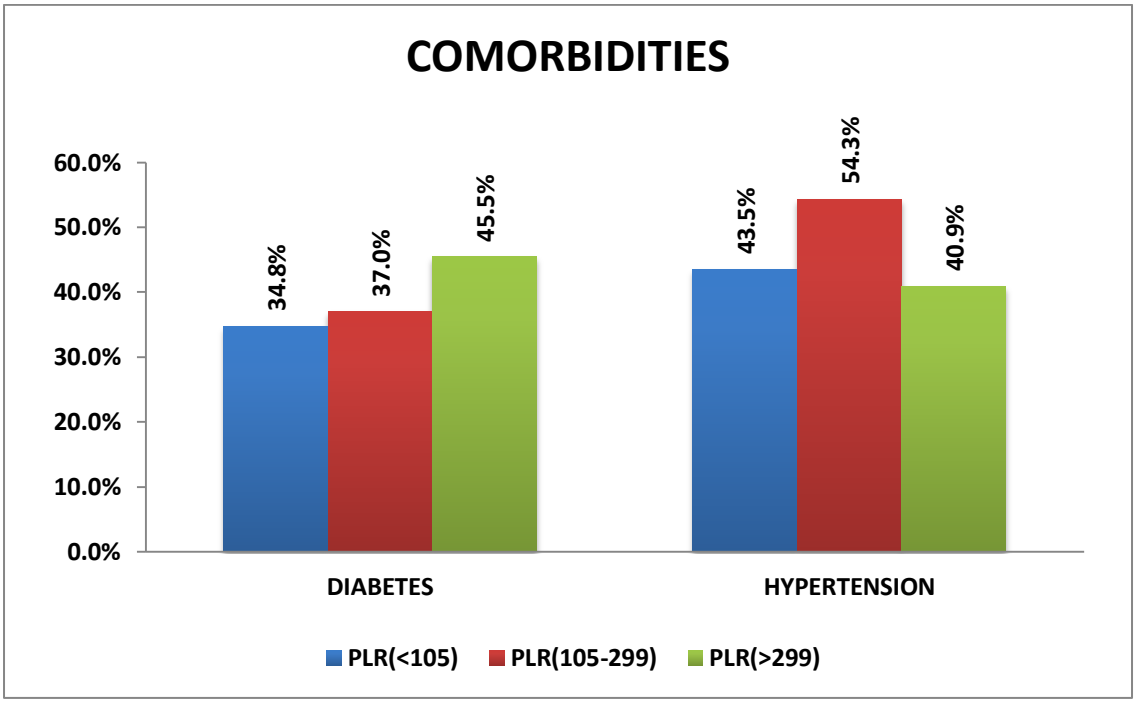
COMORBIDITIES ACCORDING TO PLR

Comorbidities like type 2 diabetes and hypertension were not significantly related to any of the PLR groups (Table 11, Figure 17).

Table 11: Comorbidities according to PLR

COMORBIDITIES	PLR(<105)		PLR(105-299)		PLR(>299)		p value
	N	%	N	%	N	%	
DIABETES	8	34.8%	17	37.0%	10	45.5%	0.731
HYPERTENSION	10	43.5%	25	54.3%	9	40.9%	0.504

FIGURE 17: COMORBIDITIES ACCORDING TO PLR



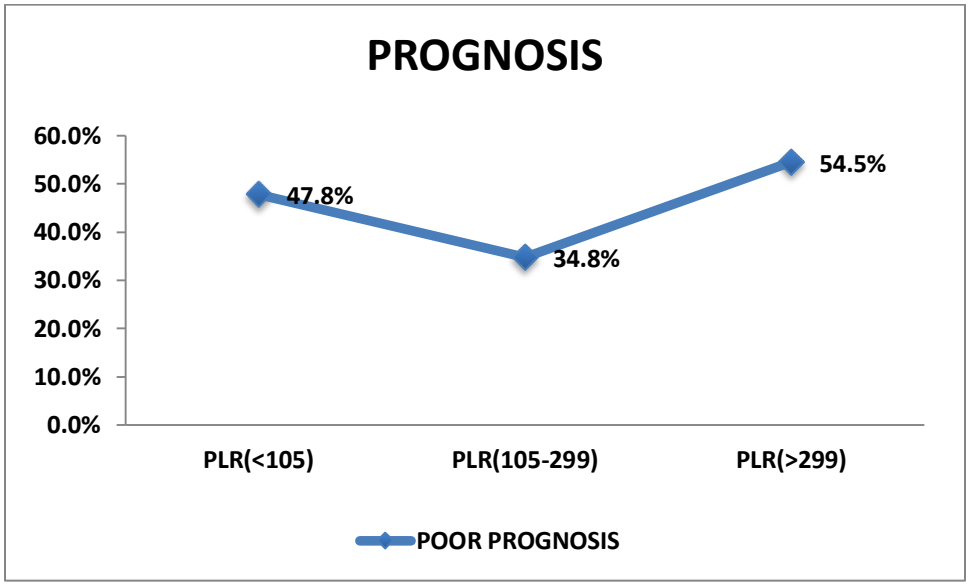
PROGNOSIS ACCORDING TO PLR

Both low and high PLR groups exhibited higher percentage of patients with poor prognosis as compared to PLR group of 105-299. However this was not statistically significant. Most patients who improved in condition belonged to PLR group of 105-299(Figure 18, Table 12).

Table 12: Prognosis according to PLR

PROGNOSIS	PLR(<105)		PLR(105-299)		PLR(>299)		p value
	N	%	N	%	N	%	
POOR PROGNOSIS	11	47.8%	16	34.8%	12	54.5%	0.261
IMPROVED	12	52.2%	30	65.2%	10	45.5%	
TOTAL	23	100.0%	46	100.0%	22	100.0%	

FIGURE 18: PROGNOSIS ACCORDING TO PLR



ROC ANALYSIS OF PLR IN PREDICTING POOR PROGNOSIS

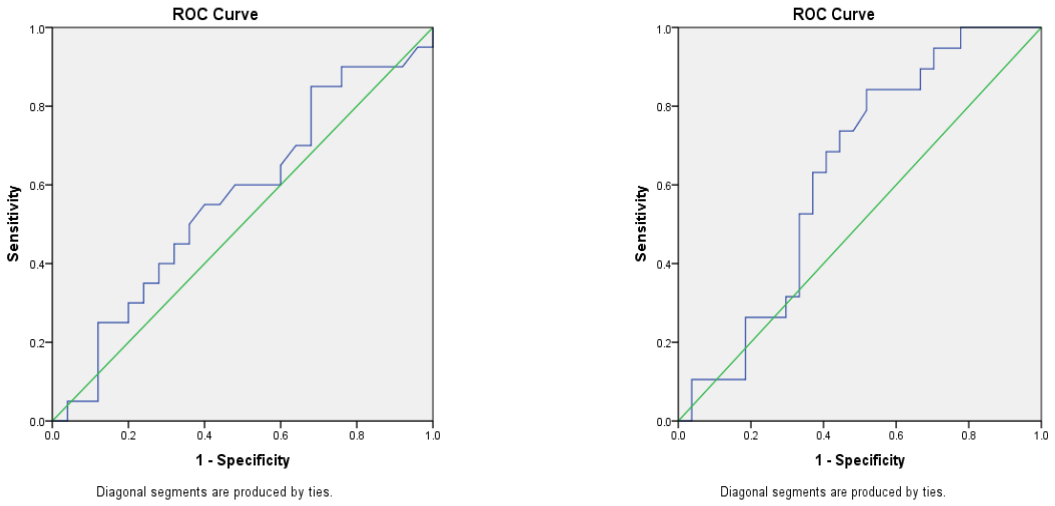
The table below shows the cutoff value for PLR in predicting poor prognosis of patients. It was found that the risk of poor prognosis was significantly higher with PLR <105 and >299 (with sensitivity of 60% and specificity of 52% for lower cut off and sensitivity of 63.2% and specificity of 63% for upper cut off)(Table 13, Figure 19).

Table 13: ROC analysis of PLR in predicting poor prognosis

PLR	Area Under the Curve	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
LOWER PLR	0.564	0.087	0.465	0.393	0.735
UPPER PLR	0.631	0.082	0.135	0.47	0.792

Parameters	CUT OFF	Sensitivity	Specificity
LOWER PLR	105	60.0%	52.0%
UPPER PLR	299	63.2%	63.0%

FIGURE 19: ROC CURVE OF LOWER AND UPPER PLR CUTOFF IN PREDICTING POOR PROGNOSIS



DISCUSSION:

A hospital based prospective, single blinded study with 91 cases of critically ill patients with acute kidney injury was conducted.

Mean age of the patients was 58.4±17.9 years which was similar to a study by Zheng *et al.*[12] with a mean age of 65.4 years. After calculating PLR, patients were divided into three groups based on PLR cutoff:

- PLR <105
- PLR =105-299
- PLR >299

Majority of the patients were between 61 to 75 years of age. There was no significant difference between the mean age of all three groups. Irrespective of age, all PLR groups showed that majority of the patients belonged to the age group of 61-75 years. There was no significant difference between the age of all three groups. There is insufficient data about the importance of interplay between age and PLR. In a recent study conducted on Indian population, Sairam *et al.*[68] elderly people were found to have lower platelet values. Majority (50.5) of the patients in our study belonged to PLR group of 105 to 299.

Out of the parameters assessed, ESR, blood urea and platelet count was significantly higher in high PLR (>299) group. Lymphocyte counts showed significantly lower levels in the high PLR (>299) group. Both acute and chronic renal diseases correlate with local and systemic inflammation. Blood cells, endothelial cells, platelets, lymphocytes, macrophages, mast cells, and fibroblasts mediate this inflammation.

Balta*et al.* [66]reported that PLR is proportionally a better predictor of inflammation in ESRD. This association asserts that undue elevation of PLRs could foresee the same poor prognosis as other inflammation biomarkers in subjects with acute kidney injury.

Both low and high PLR groups exhibited, although insignificant, but higher percentage of patients with poor prognosis as compared to PLR group of 105-299. Most patients who improved in condition belonged to PLR group of 105-299. U-shaped relationship between the PLR and mortality, and both low and high PLRs were associated with increased mortality due to all causes as corroborated by a study conducted by Zheng *et al.* *(12)*

Proctor *et al.* [69] investigated the correlation between the PLR and overall survival which contrary to our study showed a positive correlation between the PLR and mortality when using a similar PLR cutoff.

Yaprak *et al.* [70] in a recent study correlated PLR and mortality with a small cohort of patients with end-stage renal disease (ESRD) and established that the PLR could autonomously predict several causes of mortality in this population. A core cause for this difference is the deficient number of patients with reduced PLRs.

The PLR has been scrutinized as a novel inflammatory marker for predicting major complications associated with CVD [55]. In a study by Velibey *et al.* [65]they reported that elevated PLRs are self-sufficiently liked to a greater possibility of contrast-induced AKI in patients who have previously undergone primary percutaneous coronary intervention. A recent study exhibited that a raised PLR is correlated with coronary artery disease, C-reactive protein and fibrinogen values [71].

Out of the patients enrolled, 48.4% were known cases of hypertension and 38.5% were known cases of type 2 diabetes mellitus. Comorbidities like type 2 diabetes and hypertension were not significantly related to any of the PLR groups. Other parameters such as total counts, random blood sugar, sodium and potassium levels were not significantly associated with any PLR groups. Variables affecting the outcome of AKI are multifactorial including blood pressure [(72)], renal function [(73)], urine output [(72)] and other clinical parameters (i.e., S Cr, BUN, and pH [(74)] as well as comorbidities (e.g., cardiac disease)[(74)]A study by Zheng *et al.*[(12)]also showed no significant interactions for sex, PO2, GCS, SBP, potassium, S Cr, urine output or BUN which was similar to findings in our study.

Fifty seven percent of the critically ill patients with acute kidney injury had improved in condition at the time of discharge, 26.4% died and 16.5 patients had worsened. Patients who worsened or died were included among patients with poor prognosis. In a study comparing the mortality rates of critical patients with those of patients suffering from acute renal failure (ARF), Mehta *et al.* [(75)]observed that the risk of mortality is greater than threefold higher with low platelet count patients as compared to controls with normal platelet values.

In an observational study, Chertow *et al.* [(76)] scrutinized the correlation of mortality with thrombocytopenia at the time of consultation which was associated with mortality in ARF patients. Similar potential risk factor with low platelet count was seen in another study. [(77)]

Thrombocytopenia is not uncommon among critically ill patients and is often connected to poor prognosis. The reduced platelet manufacture or unwarranted platelet destruction due to underlying disease and therapeutic interventions plays a key role in establishment of thrombocytopenia [(78)]. Combined, these discoveries show that reduction in platelet counts could

result in a low PLR in AKI patients and could pave the way for high mortality, thus, asserting our observation of a U-shaped association between the PLR and mortality.

It was found that the risk of poor prognosis was significantly higher with PLR <105 and >299 (with sensitivity of 60% and specificity of 52% for lower cut off and sensitivity of 63.2% and specificity of 63% for upper cut off).

Limitations of this study are as follows:

- CKD status among patients with AKI could not be assessed and the role of CKD in the association between the PLR and mortality could not be established.
- PLR was calculated in the study subjects only on admission.
- A cross sectional recording of PLR does not completely demonstrate ongoing inflammation, a better assessment of which would be by synergistically measuring several inflammatory mediators.
- Sepsis and shock, both of which may escalate patient morbidity and predict higher mortality among patients with AKI was not considered [(79)].

The preliminary data from our study advocates the importance of PLR as a risk adjustment tool with prognostic implications for AKI. However, to substantiate PLR as a prognostic marker, its clinical impact must be validated with appropriate study design and sample size. The cutoff value must be established in one large cohort of patients and tested in another large cohort, and the number of patients in each group needs to be considered in statistical analyses for statistically significant validation of PLR as prognostic marker, not only in AKI, but in an array of critical diseases.

CONCLUSION

A hospital based prospective, single blinded study with 91 cases of critically ill patients with acute kidney injury was conducted.

After calculating PLR, patients were divided into three groups based on PLR cutoff:

- PLR <105
- PLR =105-299
- PLR >299

Majority (50.5) of the patients in our study belonged to PLR group of 105 to 299. Importance of interplay between age and PLR was not significant.

Out of the parameters assessed, ESR, Blood urea and platelet count was significantly higher and lymphocyte counts showed significantly lower levels in the high PLR (>299) group. Since both acute and chronic renal diseases correlate with local and systemic inflammation, PLR is proportionally a better predictor of inflammation in ESRD and can foresee the same poor prognosis in acute kidney injury.

U-shaped relationship between the PLR and mortality, and both low and high PLRs were associated with increased mortality.

. Comorbidities like type 2 diabetes and hypertension as well as other parameters such as total counts, random blood sugar, sodium and potassium levels were not significantly associated with any PLR groups.

Fifty seven percent of the critically ill patients with acute kidney injury had improved in condition at the time of discharge, 26.4% died and 16.5 patients had worsened. Patients who worsened or died were included among patients with poor prognosis. Risk of mortality was

greater with low platelet count in our study making it a potential risk factor for mortality. Thrombocytopenia is not uncommon among critically ill patients and is often connected to poor prognosis with all-cause mortality.

From our study , we can conclude that reduction in platelet counts could result in a low PLR in AKI patients and could pave the way for high mortality, thus, asserting our observation of a U-shaped association between the PLR and mortality.

SUMMARY

A hospital based prospective, single blinded study with 91 cases of critically ill patients with acute kidney injury was conducted.

- Mean age of the patients was 58.4±17.9 years
- After calculating PLR, patients were divided into three groups based on PLR cutoff: PLR <105, PLR =105-299, PLR >299.
- Irrespective of age, all PLR groups showed that majority of the patients belonged to the age group of 61-75 years.
- Majority (50.5) of the patients belonged to PLR group of 105 to 299.
- Out of the parameters assessed, ESR, Blood urea and platelet count was significantly higher and lymphocyte counts showed significantly lower levels in the high PLR (>299) group.
- U-shaped relationship between the PLR and mortality, and both low and high PLRs were associated with increased mortality.
- Comorbidities like type 2 diabetes and hypertension as well as other parameters such as total counts, random blood sugar, sodium and potassium levels were not significantly associated with any PLR groups.
- It was found that the risk of poor prognosis was significantly higher with PLR <105 and >299 (with sensitivity of 60% and specificity of 52% for lower cut off and sensitivity of 63.2% and specificity of 63% for upper cut off)
- From our study, we can conclude that reduction in platelet counts could result in a low PLR in AKI patients and could pave the way for high mortality.

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ANNEXURE I

PROFORMA

B.L.D.E UNIVERSITY

SHRI B. M. PATIL MEDICAL COLLEGE VIJAYAPUR, KARNATAKA.

"PROGNOSTIC VALUE OF PLATELET-TO-LYMPHOCYTE RATIOS AMONG CRITICALLY ILL PATIENTS WITH ACUTE KIDNEY INJURY"

SCHEME OF CASE TAKING

Name: CASE NO:

Age: OP/IP NO:

Sex: DOA:

Religion: DOD:

Occupation:

Address:

Presenting complaints with duration:

History of presenting complaints:

Past History:

Family History:

Personal History:

Diet

Appetite

Sleep

Bladder and bowel habits:

Others

Treatment History: treatment for diabetes/hypertension

General Physical Examination

Pallor: present/absent

Icterus:present/absent

Cyanosis: present/absent

Clubbing: present/absent

Generalized lymphadenopathy: present/absent

Odema:present/absent

Built:

Nourishment:

Vitals

PR:

BP: in mm of mercury (mm hg)

RR:

Temp:

SYSTEMIC EXAMINATION:

- Cardiovascular system
- Respiratory system
- Per abdomen
- Central nervous system

INVESTIGATIONS

PATHOLOGY

1.)Complete blood count:

Hb	gm/dl
Total count	Cells/cumm
Lymphocytes	%
Platelet count	

Platelet : Lymphocyte ratio (PLR):

2.) ESR

3.) Urine Routine

Sugar

Albumin

Cell type

Cell count

BIOCHEMISTRY

- Random blood sugar
- Fasting blood sugar
- Post prandial blood sugar
- Liver function test
- Renal function test
- ABG

Other relevant investigations will be done when required.

Sequential Organ Failure Assessment (SOFA) score

FINAL DIAGNOSIS:

PROGNOSIS:

ANNEXURE II

CONSENT FORM

INFORMED CONSENT FOR: Prognostic value of platelet-to-lymphocyte ratio among critical ill patients with acute kidney injury"

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is to assess Prognostic value of platelet-to-lymphocyte ratio among critical ill patients with acute kidney injury"

PROCEDURE:

I understand that I will undergo detailed history and clinical examination and investigations.

RISKS AND DISCOMFORTS:

I understand that there is no risk involved in this study and I may experience mild pain during the above mentioned procedures.

BENEFITS:

I understand that my participation in this study will help to assess prognostic value of platelet to lymphocyte ratio in critically ill patients with AKI

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulation of hospital. If the data is used for publication the identity will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw from study at any time.

INJURY STATEMENT:

I understand in the unlikely event of injury to me during the study I will get medical treatment but no further medical compensation.

(Signature of Guardian) (Signature of patient)

STUDY SUBJECT CONSENT FORM:

I confirm that _____has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all above in detail in my own language and I understand the same. I agree to give my consent to participate as a subject in this research project.

SIGNATURE OF PARTICIPANT DATE

SIGNATURE OF WITNESS DATE

ANNEXURE IV

KEY TO MASTERCHART

AKI	ACUTE KIDNEY INJURY
DM	DIABETES MELLITUS
HTN	HYPERTENTION
IHD	ISCHEMIC HEART DISEASE
STEMI	ST ELEVATION MYOCARDIAL INFARCTION
GI	GASTROINTESTINAL
GTCS	GENERALIZED TONIC CLONIC SEIZURES
ALD	ALCHOHIOLIC LIVER DISEASE
CLD	CHRONIC LIVER DISEASE
ARDS	ACUTE RESPIRATORY DISTRESS SYMDROME
CVA	CEREBROVASCULAR ACCIDENT
COPD	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
B/L	BILATERAL
LV	LEFT VENTRICLE
CCF	CONGESTIVE CARDIAC FAILURE