"THE INCIDENCE OF ACUTE KIDNEY INJURY IN NEONATES WITH CONGENITAL HEART DISEASE IN A TERTIARY CARE HOSPITAL OVER A PERIOD OF ONE YEAR"

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LIST OF ABBREVIATIONS

ABBREVATION	EXPANSION OF ABBREVATION
nAKI	Neonatal Acute Kidney Injury
NICU	Neonatal Intensive Care Unit
CHD	Congenital Heart Disease
AKI	Acute Kidney Injury
GFR	Glomerular filtration rate
RBF	Renal Blood Flow
RVR	Renal Vascular Resistance
NO	Nitric Oxide
ADH	Anti diuretic hormone
ARF	Acute Renal Failure
UO	Urine Output
SCr	Serum Creatinine
AWAKEN	Assessment of Worldwide Acute Kidney Epidemiology in Neonates
KDIGO	Kidney Disease: Improving Global Outcomes
ATN	Acute Tubular Necrosis
NSAIDs	Non Steroidal Anti Inflammatory Drugs
IVIG	Intravenous Immunoglobulin

CKD	Chronic Kidney Disease
ELBW	Extremely Low Birth Weight
VLBW	Very Low Birth Weight
LBW	Low Birth Weight
MRI	Magnetic Resonance imaging
HIE	Hypoxic Ischemic Encephalopathy
PDA	Patent Ductus Arteriosus
NINJA	Nephrotoxic Injury Negated by Just-in-time Action
ACE	Angiotensin Converting Enzyme
ECMO	Extra Corporeal Life Support
NEC	Necrotizing Enterocolitis
CSF	Cerebro Spinal Fluid
MDRD	Modification of Diet in Renal Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
SGA	Small for Gestational Age
AGA	Appropriate for Gestational Age
LGA	Large for Gestational Age
LSCS	Lower Segment Caesarian Section
NVD	Normal Vaginal Delivery
IUGR	Intra Uterine Growth Restriction

PROM/PPROM	Premature Rupture Of Membranes/ Preterm Premature Rupture Of Membranes
BMV	Bag and Mask Ventilation
ASD	Atrial Septal Defect
VSD	Ventricular Septal Defect
TAPVC	Total Anomalous Pulmonary Venous Connection
TOF	Tetralogy of Fallot
TGA	Transposition of Great Arteries
AVSD	Atrio-Ventricular Septal Defect
COA	Coarctation of Aorta
MS	Mitral Stenosis
CPAP	Continuous Positive Airway Pressure
MV	Mechanical Ventilation

ABSTRACT

"THE INCIDENCE OF ACUTE KIDNEY INJURY IN NEONATES WITH CONGENITAL HEART DISEASE IN A TERTIARY CARE HOSPITAL OVER A PERIOD OF ONE YEAR"

Background: Neonatal acute kidney injury (nAKI) is an underexplored yet critical issue in neonatal intensive care units (NICUs), particularly in neonates with congenital heart disease (CHD). Given the increased risk of morbidity and mortality associated with nAKI, early detection using reliable biomarkers is essential for timely intervention.

Objective: This study aims to compare serum creatinine and serum cystatin-C as biomarkers for early detection of neonatal AKI in neonates with CHD and determine the incidence of acute kidney injury in neonates with congenital heart disease, identify associated risk factors, and assess the outcomes.

Methods: A cross-sectional study was conducted at KLES Prabhakar Kore Hospital and Research Centre over one year, involving 40 neonates diagnosed with CHD in their first week of life. Serum creatinine and serum cystatin-C levels were measured between days 4 and 7 of life. The diagnosis of AKI was based on modified neonatal KDIGO guidelines. Demographic data, clinical history, and neonatal outcomes were analysed ßstatistically.

Results: Among the study cohort, 60% were male, and 67.5% had acyanotic CHD. The overall incidence of AKI was significantly associated with cyanotic CHD. Serum cystatin-C demonstrated higher sensitivity in detecting early AKI compared to serum creatinine. The mortality rate was notably higher among neonates diagnosed with

AKI, with serum creatinine-based criteria showing the strongest association with adverse outcomes.

Conclusion: Neonates with CHD are at a considerable risk of developing AKI, with cyanotic CHD showing a stronger correlation. Serum cystatin-C proved to be a more reliable biomarker for early AKI detection. Early identification of AKI can help guide interventions to improve neonatal outcomes. Further studies with larger sample sizes are needed to validate these findings.

Keywords: Neonatal acute kidney injury, congenital heart disease, serum creatinine, serum cystatin-C, neonatal outcomes, biomarkers.

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INTRODUCTION

The 'neonatal acute kidney injury (nAKI) is a common occurrence in 'neonatal intensive care unit (NICU) requiring prompt diagnosis and treatment which is challenging in our country.

Neonatal acute kidney injury itself is an independent risk factor for mortality, and associated with adverse outcomes including prolonged mechanical ventilation and hospital stay and increased risk of progression to chronic kidney disease is seen among neonates surviving an episode of acute kidney injury thus requiring long term follow up[1,2].

The exact prevalence of neonatal acute kidney Injury is unknown, and the incidence is 30% with AWAKEN study [3]. The risk factors contributing to acute kidney injury in neonates include prematurity and low birth weight, congenital heart disease and cardiac surgery, hypoxic ischemic encephalopathy, necrotizing enterocolitis, nephrotoxic medications[4].

Congenital Heart Disease (CHD) is the most common congenital disorder, responsible for 28% of cases. The prevalence of congenital heart disease varies between 8 to 12 per 1000 live births[5,6] and in India every year approximates 2,40,000 cases of CHD[7]. Among these, the incidence of acute kidney injury in neonates with congenital heart disease is around 10 to 12% and risk factors include prematurity, hypotension, hypercapnia, hypochloremia, metabolic alkalosis[8].

Neonatal acute kidney injury remains to be an understudied topic and represents a rapidly evolving area in clinical research, but a significant amount of work needs to be done to improve the outcomes in these babies. This study is being

undertaken with the aim of studying the incidence of acute kidney injury in neonates with congenital heart disease and its risk factors and outcomes using serum creatinine and serum cystatin-C to detect acute kidney injury[9].

AIMS AND OBJECTIVES

AIM

- The incidence of acute kidney injury in neonates with congenital heart disease in a tertiary care hospital over a period of one year.

OBJECTIVES

PRIMARY OBJECTIVE

- To compare serum Creatinine and serum Cystatin C in detecting early AKI

SECONDARY OBJECTIVE

1. To study the incidence of early AKI in neonates with congenital heart disease using serum creatinine and serum cystatin C.
2. To investigate the risk factors causing acute kidney injury in congenital heart disease neonates
3. To find the outcome of the study

REVIEW OF LITERATURE

DEVELOPMENT OF KIDNEY

Human kidney development begins in the third week of gestation and continues until birth[10,11]. During this process, three sequential kidney structures appear: the pronephros, mesonephros, and metanephros. The first two, the pronephros and mesonephros, develop temporarily before regressing, while the metanephros matures into the permanent kidney. By the fifth week of gestation, the ureteric bud, an outgrowth from the mesonephric duct, extends into the metanephros[12,13].

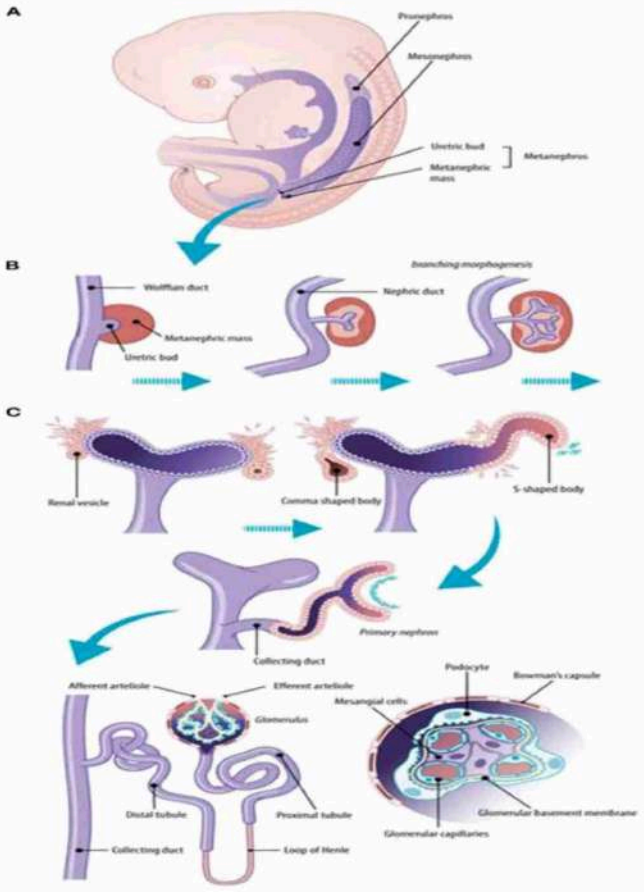


Figure 1: Normal renal development. (A)The early ureteric bud interacts with metanephric mesenchyme to form pronephros. The more caudal mesonephric ducts are the first "glomeruli-like" structures (mesonephros) that form transiently active

filtration units while the metanephros is created. (B)Early development of the kidney implies branching morphogenesis through interaction between ureteric bud and metanephric mass. (C) The metanephric mass undergoes mesenchymal-to-epithelial transformation to form nephrons, including the glomeruli and tubuli [17].

The interaction between the ureteric bud and the surrounding metanephric mesenchyme is essential for nephron formation and to promote ureteric bud branching [14]. The formation of nephrons occurs at the end of each branch, and this branching ultimately decides the total number of nephrons[13,15,16].

Nephron progenitor cells are located in the mesenchymal cap at the tip of each branch[18,19,20]. A carefully controlled balance exists between the factors that encourage differentiation and those that sustain the progenitor cell populations[18,19,20,21]. The nephrons that are the deepest mature first, while nephrogenesis persists in the outer nephrogenic zone[18].

Nephrogenesis continues till 36 weeks of gestation and results in ~1,000,000 nephrons in each human kidney[22]. However, the number of nephrons in each kidney at birth can differ greatly, ranging from 300,000 to 1.8 million[22]. This variation is mainly due to genetic factors and the conditions present in the fetal environment during development[23].

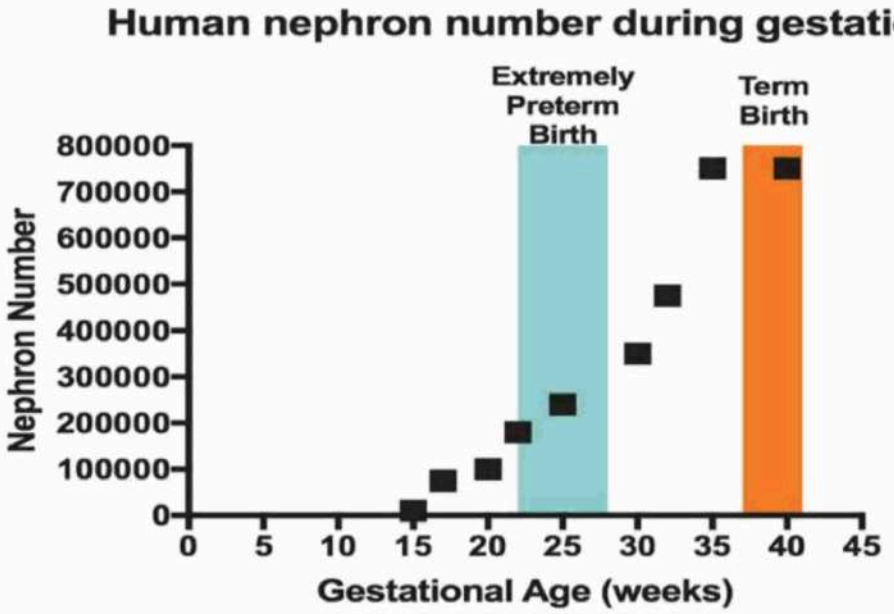


Figure 2: Relation between gestational age and number of nephrons,at 15 weeks glomerular number was estimated to be 15,000 and increased to 740,000 by 40 weeks, demonstrating the exponential increase in nephron formation in the third trimester[24].

And between 19 and 28 weeks of gestation, the number of nephrons increases at an exponential rate[25,26]. In fact, nearly two-thirds of the total number of nephrons in the human kidney are formed during the third trimester of pregnancy[27], which emphasizes the potential consequences of preterm birth on nephron development [28].

The exact mechanisms behind the wide variation in nephron numbers in humans, along with the factors that trigger the end of nephrogenesis, remain largely unclear[29].

RENAL ADAPTATIONS

Knowing the renal adaptations that occur in the postnatal period is essential for diagnosis and management of neonatal AKI.

Fetal urine production begins at 9 to 10 weeks of gestation and contributes to the amniotic fluid. The volume increases as the pregnancy advances[30].

Fetal hemostasis is controlled by the placenta, while the kidneys play key roles in urine production, lung maturation, and hormone production[31]. Glomerular filtration rate (GFR), renal blood flow (RBF), and tubular functions progresses as gestational age advances and allow the adaptation to extrauterine life.

The adult renal blood flow is 20 % of cardiac output whereas neonatal renal blood flow as soon as the baby is delivered is around 3 to 5 % of cardiac output, and reaches about 10% of cardiac output by first week of life and adult renal blood flow value by 2 years of age[32].

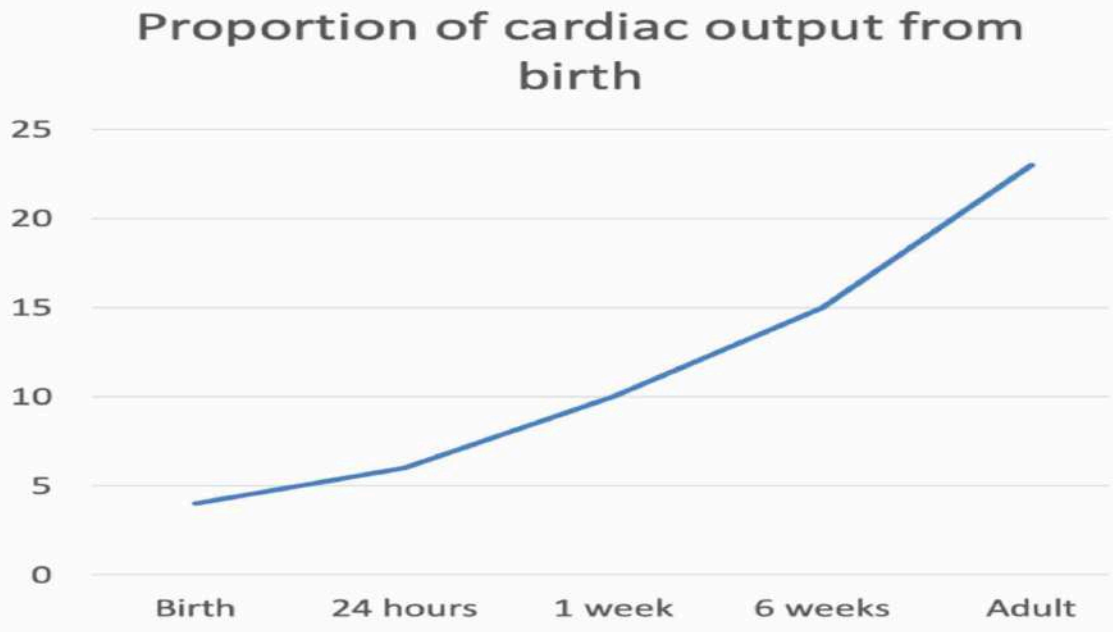


Figure 3: Relation between cardiac output and age[33].

Meanwhile, GFR increases from about 5 to 40 mL/min/1.73 m2 during the first postnatal week and continues to increase to 65 mL/min/1.73 m2 by two months of age and reaches the adult value of 120 mL/min/1.73 m2 by two years of age. The

rise in GFR is due to rise of RBF and fall off renal vascular resistance (RVR)[34]. Renal vascular resistance is regulated by various vasoactive factors, including angiotensin II, prostaglandins, nitric oxide (NO), and catecholamines[32].

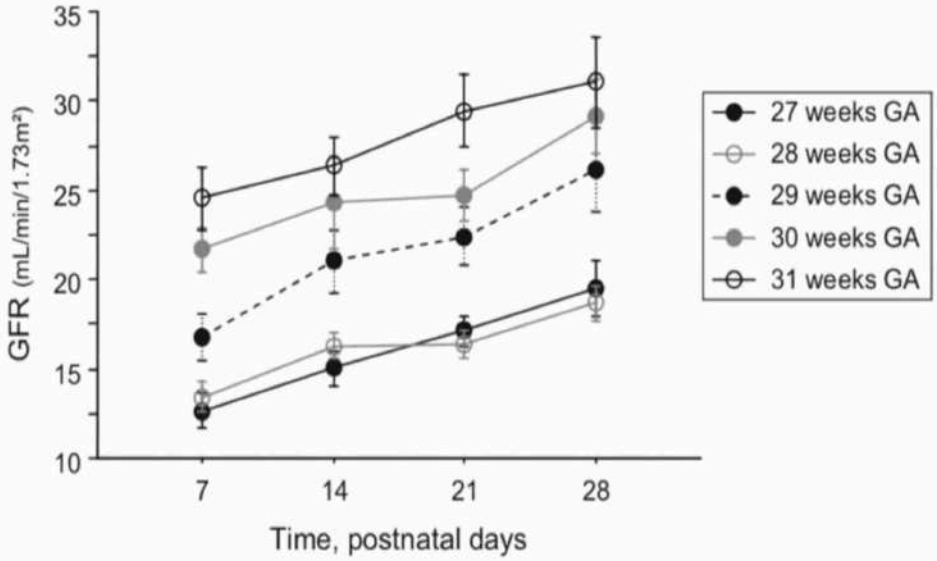


Figure 4: Relation between GFR and postnatal age according to gestational age[34].

Angiotensin II levels are elevated in newborns compared to adults. These levels decrease during the neonatal period and early childhood, reaching adult levels by the age of 6 to 9 years[32,35]. Angiotensin II being an effective vasoconstrictor increases RVR and reduces the GFR[35], whose effects are antagonised by prostaglandins and NO (nitric oxide) vasodilatory effect, specifically on afferent arteriole[31,36]. The levels of NO decrease as endothelial NO synthase production is downregulated at the completion of nephrogenesis[31].

Similarly, the urinary flow rate rises by 10 times during fetal life from 6 mL/h at 2nd trimester to 60 mL/h at the end of 3rd trimester. The osmolarity of fetal urine is between 100 to 250 mOsm/kg H2O (hypotonic)[31] and that of a term newborn is

around 700mOsm/kg H2O, which is half the concentrating capacity of adult kidney (~1400mOsm/kg H2O), attained between 6 to 12 months of age[37].

The diminished concentrating capacity is due to reduced medullary interstitium tonicity, subdued expression of aquaporins and poor tubular sensitivity to Arginine Vasopressin (also known as ADH)[38].

Similarly, electrolyte homeostasis is also achieved during extrauterine transition.

1) Sodium: its secretion decreases as gestational age advances[35]. The increased rate of sodium secretion initially is due to elevated circulating concentrations, heightened sensitivity to natriuretic factors, huge extracellular fluid volume, poor sensitivity to aldosterone, and immature sodium reabsorption in the tubules[39]. Unlike adults, sodium reabsorption occurs in distal tubules of fetus[39].
2) Potassium: positive balance of potassium is needed for growth of fetus. In preterm neonates, hyperkalaemia is common due to immature distal tubules, and potassium permeability causing transfer of potassium ions from intracellular space to extracellular space[40].

As the extrauterine adaptation continues, potassium levels are regulated with the onset of diuresis which facilitates the excretion of it. Also the newborn kidneys have reduced threshold for bicarbonate excretion[40].

Researches have shown that, nephrogenesis continues beyond 36 weeks period of gestation in preterm neonates as compared to term neonates where cessation of nephrogenesis is noted[41,42]. Faa et al., concluded similar findings by human autopsy samples in preterm neonates[43].

Thus nephrogenesis remains to be a continuous process, not only confined to antenatal period, but also to postnatal period where environmental factors and other risk factors including the presence of acute kidney injury impacting it[26,28].

NEONATAL ACUTE KIDNEY INJURY

Acute kidney injury (AKI), earlier known as acute renal failure(ARF), is defined as a sudden decline in renal function along with acute and reversible rise of serum creatinine with or without reduced urine output (UO) and resulting in deranged fluid balance, electrolytes and waste product clearance[4,45,46].

There are several endogenous biomarkers, which aid in the assessment of renal function but there is no gold standard which has been approved so far. Each biomarker has its merits and demerits, making it difficult to standardise and use for detecting acute kidney injury in neonates.

The gold standard technique for estimating GFR is to measure the clearance of inulin and other exogenous markers which are freely filtered by the glomerulus and are neither metabolized, reabsorbed, nor secreted by the renal tubules[47,48]. But, repeated blood sampling, urine collection, and administration of exogenous markers restricts the use of it[47]. Additionally, these procedures are time consuming, costly, and difficult[49].

There has been a lot of research to develop a more precise and accurate definition to define neonatal AKI and recently modified neonatal KDIGO has been attaining acceptance[50].

AKI stage	Serum creatinine (SCr) criteria	Urine output criteria (hourly rate)
0	No change in SCr or SCr rise < 0.3 mg/dL	≥0.5 ml/kg/h
1	SCr rise ≥ 0.3 mg/dL rise within 48 h *or* SCr rise ≥ 1.5–1.9 x baseline SCr[a]	<0.5 ml/kg/h x 6–12 h
2	SCr rise ≥ 2.0–2.9 x baseline SCr[a]	<0.5 ml/kg/h for >12 h
3	SCr rise ≥ 3 x baseline SCr[a] *or* SCr ≥ 2.5 mg/dL[b] or Kidney support therapy utilization	<0.3 ml/kg/h for ≥24 h or Anuria for ≥12 h

Table 1: Modified neonatal KDIGO criteria for nAKI. Baseline Serum Creatinine defined as lowest previous SCr value. Serum Creatinine value of 2.5 mg/dL represents glomerular filtration rate of <10 mL/min/1.73 metre square[51].

INCIDENCE OF NEONATAL AKI

AKI being common in neonates, is seen in 18 to 70% of babies admitted in NICU[52], with AWAKEN study showing incidence of approximately 30%[3]. Those neonates with AKI had four-times increased odds of death and longer hospital length of stay than those without AKI[53].

Moreover, the data on neonatal AKI from the Indian subcontinent is very small and risk factors predisposing newborns to develop AKI is not well-studied. Reported incidence of neonatal AKI in India ranges from 3.4 to 4.2% of all NICU admissions[54,55].

ETIOLOGY OF NEONATAL AKI

Renal hypoperfusion secondary to various conditions, i.e., prerenal azotemia is the major cause of neonatal AKI[56,57]. AKI in neonates is commonly non-oliguric[58].

Prerenal AKI	Renal or Intrinsic AKI	Postrenal AKI
Functional change without actual renal damage. Most commonly due to reduced renal perfusion, with an incidence of 85%[59,60]. It is seen in preterm neonates due to impaired skin barrier , sepsis due to increased capillary permeability, reduced cardiac output as in certain congenital heart diseases, asphyxia and antenatal or postnatal exposure to NSAIDs due to renal vasoconstriction[61].	Due to intrinsic injury of the renal parenchyma is the second most frequent cause of AKI in neonate with an incidence of 11% [59,62].Histopathological findings revealed Acute tubular necrosis (ATN) commonly. It is seen in UAC malposition[63] due to bilateral renal vein thrombosis [64], renal artery thrombosis, or renal infarct, antimicrobials such as aminoglycosides due to direct toxic effect on the tubular epithelium, intrarenal vasoconstriction and local glomerular and mesangial cell contraction[65]. Antenatal maternal administration of ampicillin and aminoglycosides reduces nephron number. Vancomycin has oxidative effects on cells of the proximal renal tubule[68], mechanism of amphotericin-induced nephrotoxicity is not completely understood. Amphotericin B inserts into cell membranes, resulting in the creation of pores that increase membrane permeability[69] and acyclovir nephrotoxicity is due to intratubular deposition of crystals; the nephron becomes obstructed leading to increased resistance to renal blood flow and subsequent elevation of the serum creatinine[66]. Intravenous immunoglobulin (IVIG) is another medication that may cause nephrotoxicity, attributed to osmotic insult caused by the high sucrose contents[61,67].	It is less frequent and accounts for about 3% of cases of neonatal AKI[59,60]. It is caused by intrinsic obstructions, such as fungal balls, extrinsic compression, such as tumors, or due to congenital causes of urinary tract obstruction such as posterior urethral valves, triad syndrome, bilateral ureteropelvic junction obstruction or unilateral obstruction in single kidney. Urethral strictures due to traumatic bladder catheterization, and malfunctioning urinary catheters. Relief of the obstruction results in improvement in renal function[61].

Table 2: Etiology of AKI

RISK FACTORS FOR AKI

Several risk factors contribute to the occurrence of acute kidney injury, the most common ones are described below.

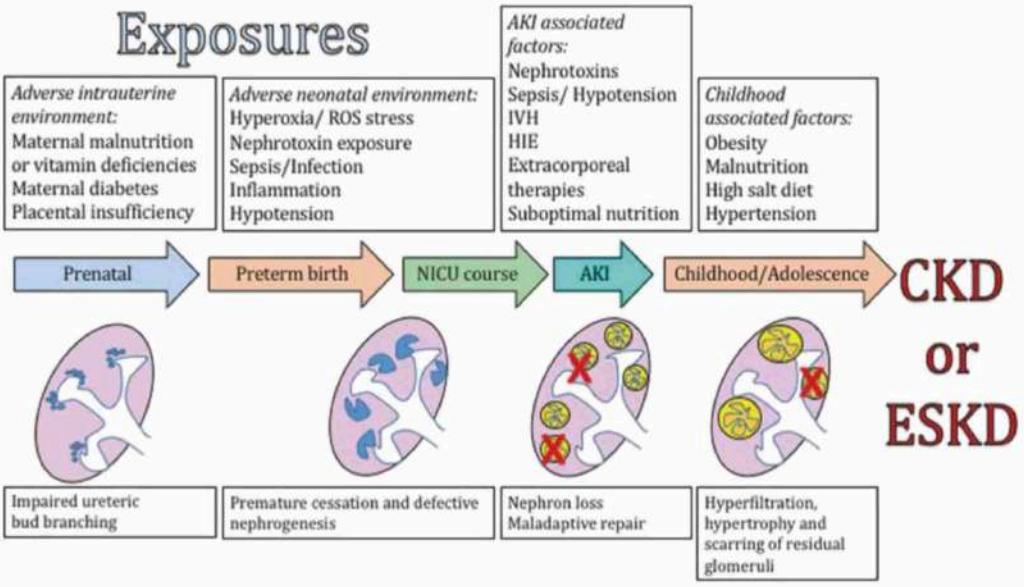


Figure 5: Exposures across the life course leads to an increased risk of CKD in preterms. There are many unique exposures incurred by preterm neonate that lead to an enhanced risk of acute kidney injury as well as chronic kidney disease [29].

1. PREMATURITY, LBW and AKI

Reported incidence of AKI in VLBW infants ranges from 12.5% to 39.8% with consistent reports of mortality being significantly higher in VLBW infants with AKI compared to those without AKI[52,70].

The incidence of AKI showed a U-shaped pattern across gestational age groups, with the highest rates in both the youngest (between 22 to 29 weeks of gestation) and oldest (>36 weeks) neonates. In the youngest group, the incidence was 48%[52,71-75], consistent with previous studies. Similarly, the incidence in neonates born

at 36 weeks or older was 37%[76-78], matching other research on term infants. The AKI rate for those born between 29 and 36 weeks was 18%[3], a finding not previously reported.

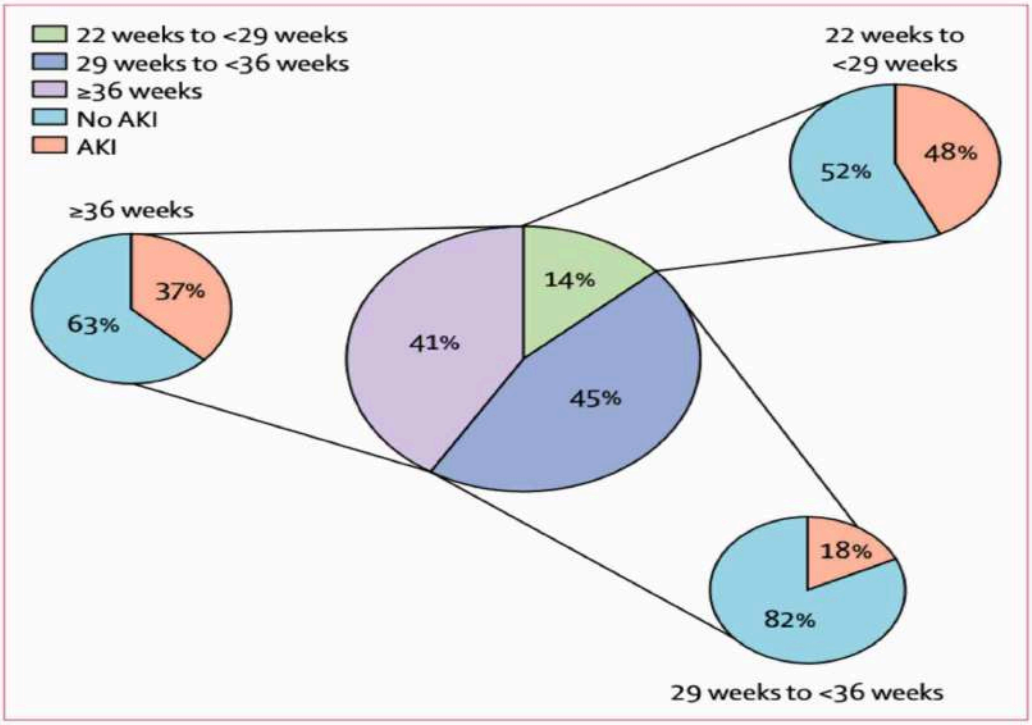


Figure 6: Distribution of AKI among various gestational ages[3].

2. PERINATAL ASPHYXIA AND AKI

Newborns with birth asphyxia, also known as HIE, commonly develop multiorgan failure. The incidence of AKI reported from various studies ranged between 38 to 72%[58,75,77-82].

A single centre study with 96 asphyxiated neonates, treated with therapeutic hypothermia , showed AKI in 38% of cases and was linked to prolonged mechanical ventilation and NICU stay[77].

A follow-up study found that AKI during therapeutic hypothermia was associated with abnormal MRI findings at 7-10 days postnatal[83].

The effect of therapeutic hypothermia on AKI incidence in HIE is still debated, as studies show contrasting results[84,85].

3. SEPSIS AND AKI

The incidence of AKI among septic term neonates was around 26% and can go higher up to 75% as in septic preterm neonates[4,86,87], due to inverse relation of sepsis with gestational age[88,89].

The study by Munyendo et al, revealed that AKI exacerbates the clinical course in late onset sepsis neonates[90] contrary to the study by Holda et al, which showed higher incidence of AKI in early onset sepsis neonates[91].

Sepsis is predicated to cause AKI by various mechanisms such as an inflammatory response causing hypotension and renal hypoperfusion leading to Acute Tubular Necrosis, microvascular and tubular dysfunction presenting as decreased GFR, histologically different from Acute Tubular Necrosis and pyelonephritis[45,92-95].

4. CONGENITAL HEART DISEASE, CHD SURGERY AND AKI

AKI occurred in about 10% to 12% of newborns with congenital heart disease as described by Ebishima et al[8], and can go up to 32% as described in a study by J.J.Binder et al[62].

Similarly, Patent Ductus Arteriosus among other CHDs has been associated with increased predisposition to risk of AKI due to poor systemic perfusion with an increase in the synthesis of vasodilatory prostaglandins to compensate for the hemodynamic effects of the duct[96,97,98].

But the studies on association between AKI and PDA are conflicting, because of the impact of treatment, especially with NSAIDs[101], which affect renal arterial perfusion[98-100].

Also, study Kent et al showed that association exists between drugs and the biomarkers including urinary podocyte number and albuminuria[102].

Also, cyanotic CHDs had more risk of developing AKI compared to acyanotic CHDs[164] due to chronic hypoxemia leading to secondary erythrocytosis, increasing blood viscosity and renal hypoperfusion.

Cardiac surgery is one of the most common causes of AKI in neonates, with a high risk of a prolonged hospital stay and mortality, which are impacted by prolonged cross-clamp time, a prolonged ventilation, a longer time to reach a negative fluid balance and inotropic support[103,104].

Hence, post-operative AKI in newborns after cardiac surgery is common, with incidence rates between 45% and 64% in various studies[62,105-107].

5. NEPHROTOXIC DRUGS AND AKI

At least, 70 to 75% of neonates in NICU are exposed to one or more nephrotoxic medications during their stay in NICU, during the first postnatal week, most commonly antibiotics[109-112]. The relation between AKI and nephrotoxic drugs remains to be understudied.

A study by Rhone et al, in VLBW neonates showed an inverse linear relationship between birth weight and nephrotoxic drugs received per day which increased the risk of AKI[112]. Moreover, low baseline serum creatinine value was

linked with increased risk of AKI in preterm neonates as small change in serum creatinine leads to classification of AKI using serum creatinine based definition.

The overall incidence of AKI due to nephrotoxic agents, reported varied between 8 to 24%[95,113]. It was around 17% in a study by Salerno et al., in 2021[114].

A latest study called Baby NINJA was adapted from NINJA (Nephrotoxic Injury Negated by Just-in-time Action) by Stoops et al., for studying the neonates at high risk of developing nephrotoxic AKI (defined as ≥3 nephrotoxic medications administration within 24 h or ≥4 calendar days of an intravenous aminoglycoside)[115]. It involved sending electronic alerts, which could help reduce nephrotoxic medications exposure.

The most common implicated antibiotics to cause nephrotoxicity in the decreasing order are: carbapenems > cephalosporins > penicillins > monobactams[116]. Contrary to this, third-generation cephalosporins do not induce renal damage[116].

Other medications, possessing the risk of nephrotoxicity, include Non-Steroidal Anti-Inflammatory Drugs[101,117], Acyclovir[66], Amphotericin-B[69], Immunoglobulins[61,67], maternal exposure of ACE inhibitors[118].

Contrastingly, a secondary analysis of the AWAKEN study found an association between caffeine and lower prevalence of AKI[119,120].

6. OTHER CAUSES OF AKI

Other factors like presence of NEC[33], ECMO(AKI incidence reported to be as high as 64–71%)[33,121,122], dehydration[123], chest compressions, respiratory distress syndrome[3], nutritional problems[124], use of mechanical ventilation and inotrope support [125] are also known to cause AKI.

LONG TERM SEQUALE OF NEONATAL AKI

Based on the AKI etiology and severity of AKI, most of the neonates up to 90% survive after AKI till NICU discharge, as mentioned in AWAKEN study[3,126,127].

Despite these, neonates surviving AKI have complications in the long run[128].

Also, available data from studies on preterm and term neonates shows that 31% (ranging between 9 to 83%) of neonatal AKI survivors develop Chronic Kidney Disease, though the attributable risk of AKI to CKD is not clear[129].

In a single centre study, particularly analysing long term outcomes of neonatal AKI, height was decreased in those with AKI after a two year follow up[107]. There can also be poor neurodevelopmental outcome following an episode of AKI such as poor hearing, language and motor developmental delay[130].

Few can experience proteinuria, albuminuria, reduction of renal mass and nephrocalcinosis over an 18-year period[128,131].

HISTORY OF CYSTATIN C

Cystatin C, was first identified in the year 1961 as a basic protein in human CSF(also known as γ CSF) by Jorgen Clausen[132].

Cystatin C was first named by Alan J Barrett in 1981 to describe a small egg protein isolated from chicken egg white and demonstrating the ability to inhibit lysosomal cysteine proteinases[133].

Its role as a marker of kidney function was studied widely after the 1990s[134,135].

STRUCTURE AND PROPERTIES OF CYSTATIN C

It is a single non-glycosylated polypeptide chain with 122 amino acid residues with 13k Da weight with molecular radius of 1.51nm[48,136,137].

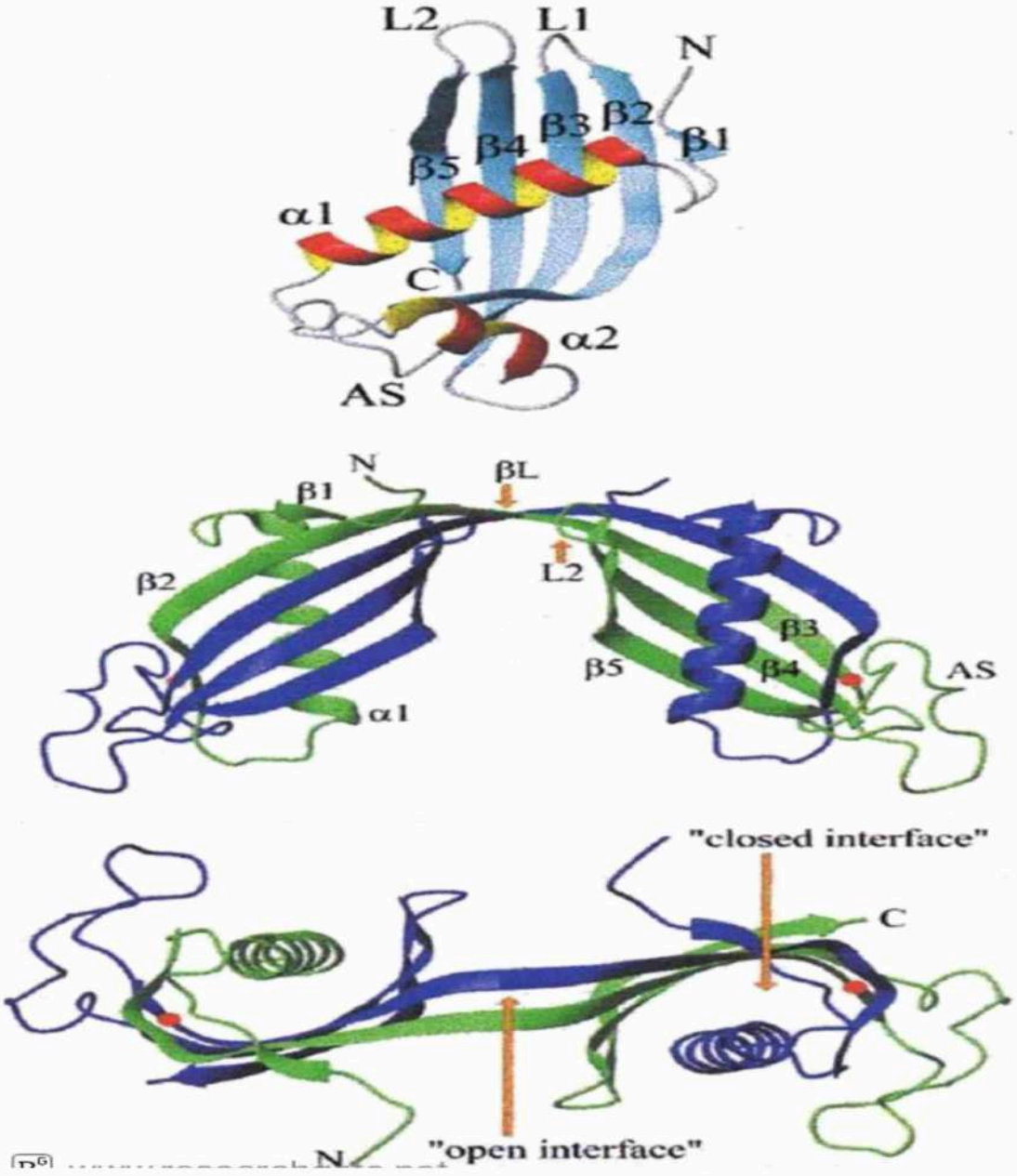


Figure 7: Structure of Cystatin C molecule. From top to bottom: fold of chicken cystatin (top), 3D domain-swapped dimer of human cystatin C in horizontal view, and perpendicular orientation (bottom)[138].

SYNTHESIS OF CYSTATIN C

The synthesis of Cystatin C is non tissue specific and is a product of the housekeeping gene expressed in all nucleated cells and produced at a constant rate in the body[139].

METABOLISM OF CYSTATIN C

Cystatin C is freely filtered through the glomerular membrane without significant peritubular uptake and then completely reabsorbed and degraded by the proximal tubule[48,136,140]. Relatively, small amounts of cystatin-C are excreted into the urine[48].

CYSTATIN C AS A MARKER OF GLOMERULAR FILTRATION RATE

The level of cystatin C is unaffected by age, gender, diet, and body composition, inflammation, infection or malignancy with the exception of thyroid disorder, where hypothyroidism decreases and hyperthyroidism increases the level of cystatin C[49,142-146].

There is an added advantage for cystatin C as it doesn't cross the blood placental barrier, making it better than other endogenous marker for measuring renal function[147,148].

CREATININE

Most routinely, GFR is assessed by measuring the clearance of creatinine, an endogenous substance derived from creatine and phosphocreatine in skeletal muscles, thus reflecting individual muscle mass.

Despite creatinine being used widely,it has many shortcomings.

1. Change in muscle mass alter serum creatinine level[136,148,149]
2. Creatinine levels at birth reflects maternal creatinine value as it crosses placenta, in first few days of life, the rate of fall being dependent on gestational age at birth.However in preterm infants, born with gestational age <30 weeks, and in those with impaired renal functions, the rate of fall is very slow and may take up to 2 months[136,150-154].
3. Due to the immature renal tubular system, a portion of creatinine is reabsorbed, resulting in raised creatinine levels in neonates causing underestimation of GFR[136].

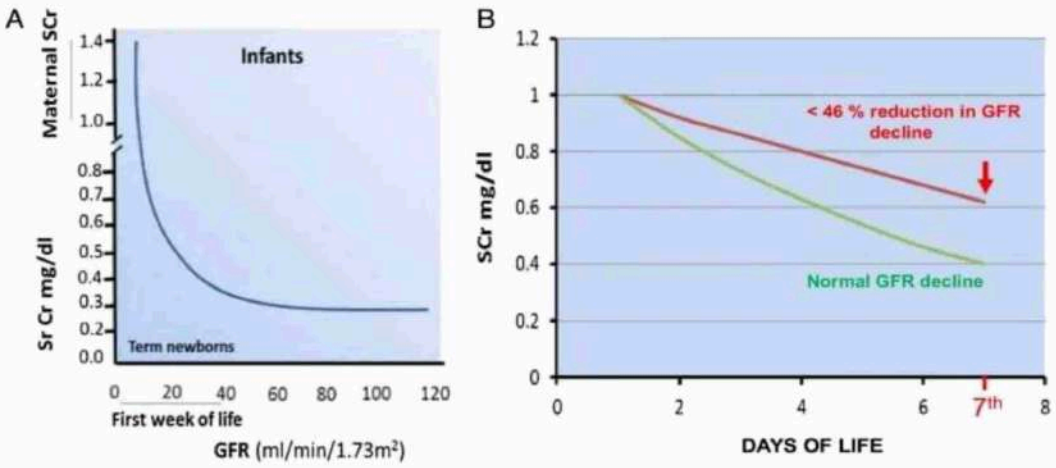


Figure 8: Panel A :shows relationship between the serum creatinine (SCr) and glomerular filtration rate (GFR). Panel B shows the predicted SCr decline in healthy term newborns (normal SCr decline) and those with impaired kidney function as reported by Gupta et al[44].

4. The most common method to measure serum creatinine-Jaffe method, has interactions due to certain cases like hyperbilirubinemia, hemolysis, and ketone bodies leading to false positive elevation of creatinine resulting in underestimation of GFR[49,136].

5. The rise of serum creatinine lags far behind renal injury as subsquent rise is often not witnessed until 48–72 hours of renal injury and after 25 to 50 % function is lost[147].

Despite having several limitations and being a substandard marker, serum creatinine and urine output has been widely in aiding the diagnosis of AKI.

COMPARISION OF CREATININE AND CYSTATIN C [155]

Characteristics	Creatinine	Cystatin C
Compound	Byproduct of creatine and phosphocreatine	Low Molecular Weight-Protein
Molecular weight	113 Dalton	13 kilo Dalton
Production	Variably produced	Constantly produced
Extrarenal degradation/secretion	tubular secretion increases with reduced GFR, Nothing significant	Not significant
Non-renal factors affecting plasma concentration	muscle mass, race, gender, age, and diet	Thyroid dysfunction, glucocorticoids
Equations for estimation of GFR	Cockcroft-Gault, MDRD, and CKD-EPI	Several
Validation of estimates	Well-validated (MDRD)	Not widely validated
Measurable	serum, urine	Serum, urine
Standardization of assays	available	available

Table 3: Comparision of Creatinine and Cystatin-C

REFERENCE RANGE

CYSTATIN C[156]

Gestational Age	Postnatal Age	Reference Interval
<28 weeks	0-3 days	1.18 -2.02 mg/l
	4-6 days	0.99-2.11 mg/l
	7-10 days	0.90-2.55 mg/l
29-32 weeks	0-3 days	1.01-2.11 mg/l
	4-6 days	1.12-1.95 mg/l
	7-10 days	1.18-2.31 mg/l
33-37 weeks	0-3 days	1.18-2.17 mg/l
	4-6 days	1.15-2.20 mg/l
	7-10 days	1.07-2.32 mg/l
>37 weeks	0-3 days	1.01-2.28 mg/l
	4-6 days	0.92-1.92 mg/l
	7-10 days	1.06-1.96 mg/l

Table 4: Reference range of serum Cystatin-C across various gestational age

CREATININE[157]

Gestational Age	Postnatal Age	Reference Interval
<28 weeks	0-3 days	0.78 -1.32 mg/dl
	4-6 days	0.59 -1.31 mg/dl
29-32 weeks	0-3 days	0.63-1.13 mg/dl
	4-6 days	0.57-1.31 mg/dl
33-37 weeks	0-3 days	0.56-1.0 mg/dl
	4-6 days	0.29-1.25 mg/dl
>37 weeks	0-3 days	0.55-0.95 mg/dl
	4-6 days	0.16-0.96 mg/dl

Table 5: Reference range of serum Creatinine across various gestational age

MATERIALS AND METHODS

STUDY POPULATION

Neonates with congenital heart disease admitted in NICU and post-natal wards of Dr. Prabhakar Kore Charitable Hospital, Belagavi, Karnataka.

STUDY DESIGN

The aims of the investigation were taken into consideration when selecting the cross-sectional study design. Cross-sectional studies are conducted either at a single moment in time or over a very short period of time. They are vastly used in the process of determining the frequency with which a specific outcome occurs in a particular group. It also give information about individual factors like exposure to risk factors and regarding details of outcome . These studies serves as a snapshot , at a particular point of time ,for outcome as well as its associated characteristics. Therefore, it was determined that this particular study design was suitable for the current investigation.

STUDY PERIOD

Research study was conducted over a period of 12 months from August 2023 to July 2024.

SAMPLING PROCEDURE

Sampling is defined as the process of selecting a number of subjects from all the subjects available in a particular group or universe. A conclusion based on sample results may be attributed only to the population sampled.

In this study we considered all eligible neonates consecutively admitted in the department of neonatology (NICU and post-natal wards) at Dr Prabhakar Kore Charitable Hospital & MRC, Belagavi with congenital heart disease till we meet the sample size.

INCLUSION CRITERIA

All the neonates diagnosed with congenital heart disease in their first week of life.

EXCLUSION CRITERIA

Neonates with Congenital Renal anomalies

Operated cases of Congenital Heart Disease

SAMPLE SIZE

Sample size was calculated assuring the proportion of Incidence of ACUTE KIDNEY INJURY as 10% as per the study by Ebishima H et al. The other parameters considered for sample size calculation were error which is 10% of prevalence and 95% confidence level. The following formula was used for sample size calculation.

Based on the previous hospital records, the approximate number of potential eligible subjects to be attending the study setting during the data collection period were considered as 40. Hence a finite population correction was applied for 40. The following formula was used for sample size as per the study by Daniel WW et al.

$$n' = \frac{NZ^2P(1-P)}{d^2(N-1) + Z^2P(1-P)}$$

Where *n'* = Sample size

N= Population Size= 40 (estimated number of neonates with congenital heart disease)

Z= Z statistic for a level of confidence level= 1.960

P = Expected prevalence/proportion of outcome= 10%

d = error = 10% of prevalence

The required sample size as per the above-mentioned calculation was 38.

METHOD OF DATA COLLECTION

All subjects were explained regarding the study method and due informed consent was taken verbally and in writing. Cases are those neonates with congenital heart diseases admitted in the Department of neonatology in NICU and post-natal wards at Dr Prabhakar Kore Charitable Hospital & MRC Belagavi.

Subjects were recruited according to the inclusion and exclusion criteria.

Detailed antenatal, natal and postnatal history were recorded.

Serum creatinine and serum cystatin C values were taken between day 4 of life to day 7 of life. Samples for serum creatinine and serum cystatin C were collected in a plain tube, 3ml venous blood and processed. The levels of serum creatinine was detected by modified Jaffe method and serum cystatin C was detected by Latex Enhanced Turbidimetric Immunoassay, which is a quantitative method.

Day of life, gender, gestational age, mode of delivery, resuscitation at birth, birth weight, antenatal scans, type of congenital heart disease, use of antibiotics,

NSAIDs, inotropes, decongestive therapy, oxygen support, presence of sepsis and other risk factors were all documented.

Criteria for the diagnosing neonatal AKI was according to modified neonatal KDIGO guidelines.

ETHICAL CONSIDERATION

Ethical clearance was taken from Internal Ethical Committee of Dr Prabhakar Kore Hospital & MRC Belagavi before conducting the study. Informed written consent was obtained and study was conducted.

BUDGET

Investigations: Rs. 21,000

Printing and copying supplies : Rs. 10,000

Total Cost: Rs. 31,000

STATISTICAL ANALYSIS

IBM SPSS version 22 and MS Excel were used for statistical analysis of the data. Descriptive analysis were carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. Data were also represented using appropriate diagrams like bar diagram, pie diagram and box plots.

The association between explanatory variables and categorical outcomes were assessed by cross tabulation and comparison of percentages. Chi square test was used to test statistical significance. P-value < 0.05 was considered statistically significant.

RESULTS

The data provided includes 40 subjects. The neonates in the study group were between 4 to 7 days of life. Demographic details are described in the below mentioned table.

Table 6: Distribution of subjects according to demographic details in the study population

Variables	Frequency	Percentages
Day of life		
4-5 days of life	22	55.00%
6-7 days of life	18	45.00%
Gender		
Male	24	60.00%
Female	16	40.00%

Out of 40 subjects, 24 were male and 16 were female.

Figure 9: Pie chart of gender distribution in the study population

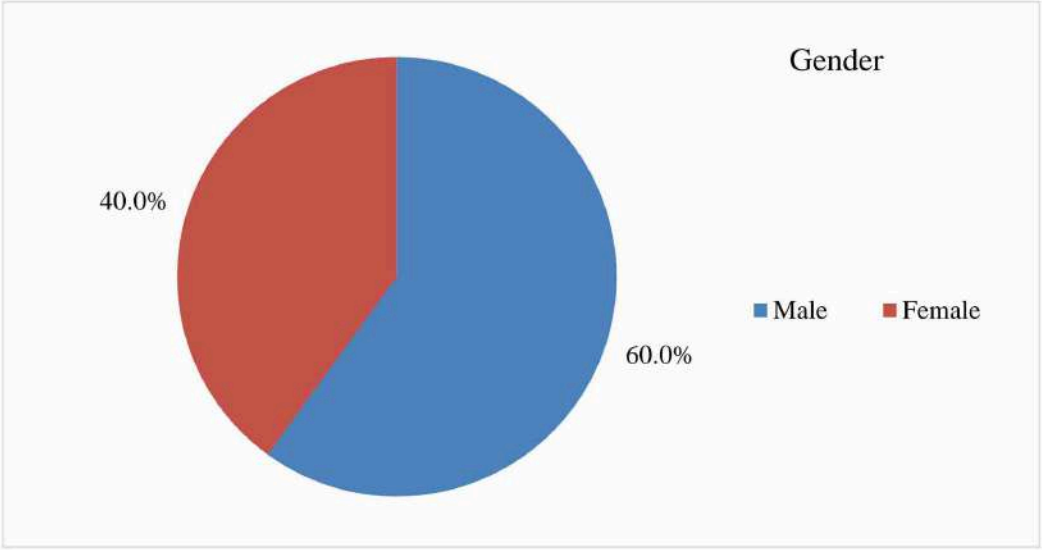


Table 7: Distribution of variables among different gestational age and birth weight in the study population

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Birth Weight (grams)	2293.5 ± 753.15	2350.0	780.0	4200.0	2052.6	2534.4
Gestational Age (weeks)	36.01 ± 3.68	37.1	27.6	41.7	34.8	37.2

Table 8: Distribution among birth weight category in the study population

Birth Weight (grams)	Frequency	Percentage
ELBW	1	2.50%
VLBW	6	15.00%
LBW	17	42.50%
Macrosomia	1	2.50%
Normal	15	37.50%

Table 9: Distribution among weight for gestational age in the study population

SGA/AGA/LGA	Frequency	Percentage
AGA	24	60.00%
SGA	15	37.50%
LGA	1	2.50%

Among the 40 neonates, most of them were low birth weight (42.5%) followed by normal birth weight (37.5%) followed by very low birth weight (15%) and least being macrosomia and extremely low birth weight category(2.5%each).

Among the 40 neonates, 24 (60%) were appropriate for gestational age, 15 (37.5%) were small for gestational age and 1 (2.5%) were large for gestational age.

Figure 10: Bar chart of distribution of birth weight in the study population

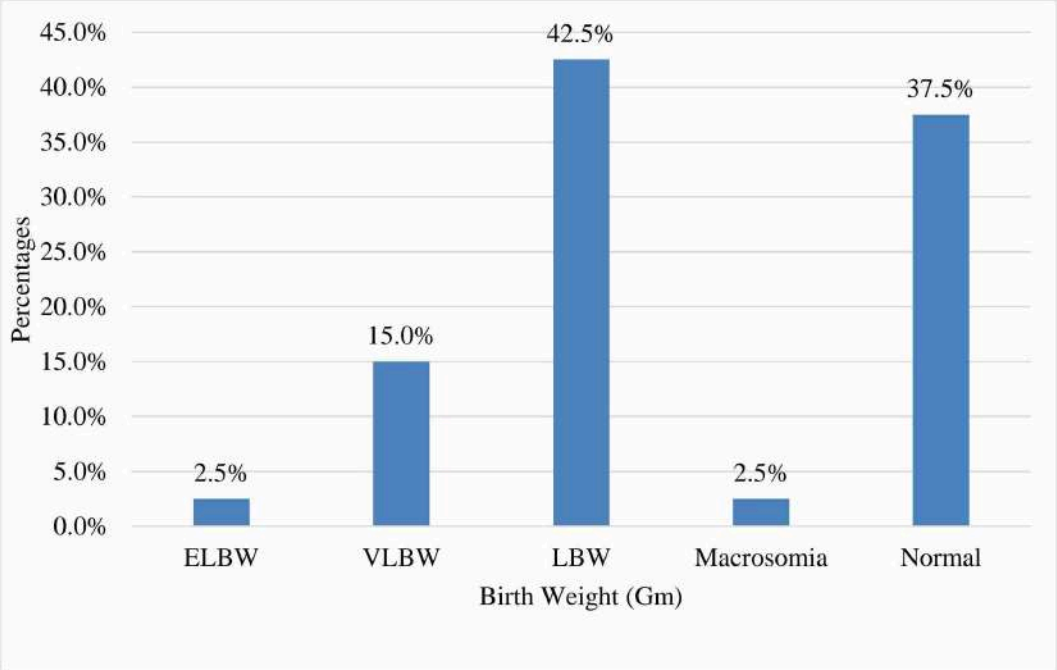


Figure 11: Pie chart of SGA/AGA/LGA in the study population

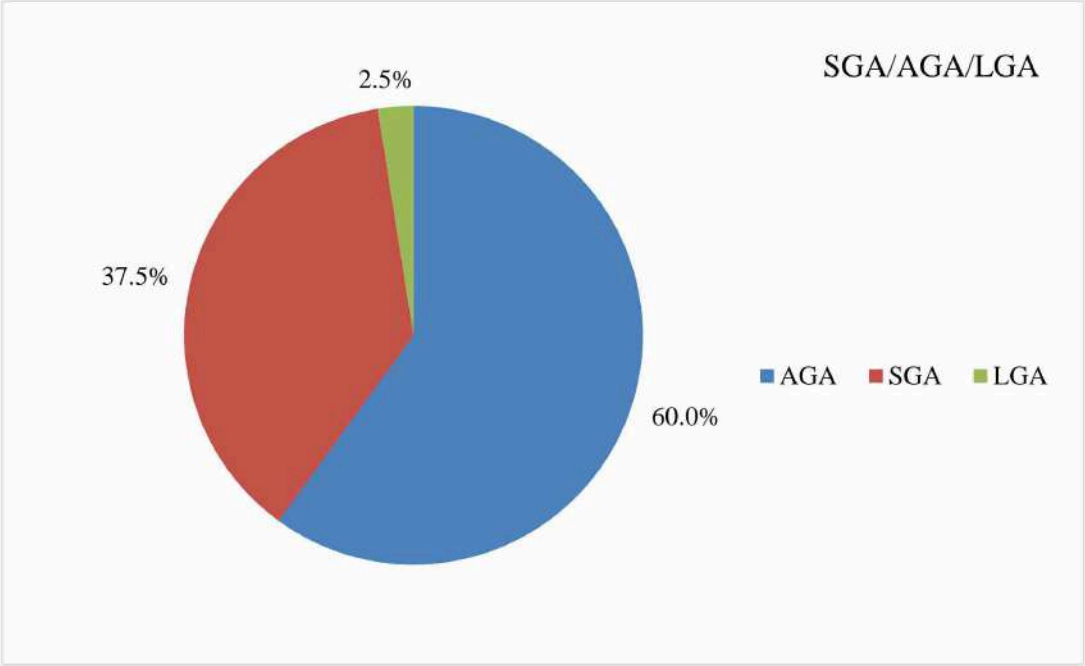


Table 10: Distribution among gestational age category in the study population

Gestational Age	Frequency	Percentage
Extremely Preterm	1	2.50%
Early Preterm	8	20.00%
Late Preterm	9	22.50%
Term	22	55.00%

Among the 40 neonate, more than half of them were term (55%), followed by late preterm (22.5%) and early preterm (20%) and least being extremely preterm(2.5%).

Figure 12: Bar chart of gestational age distribution in the study population

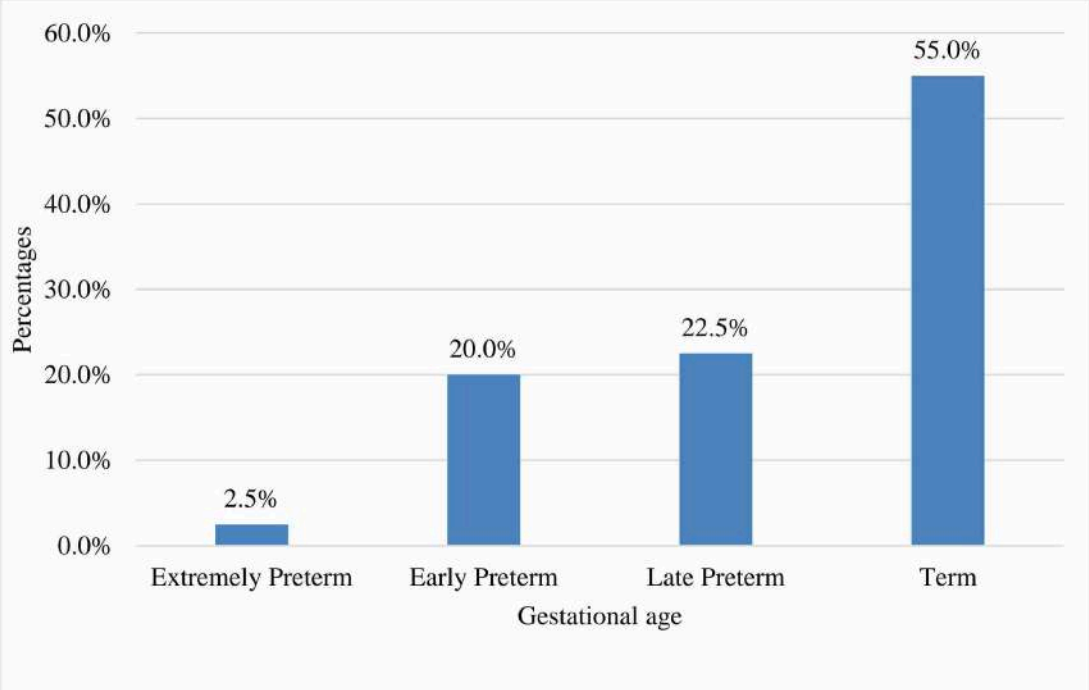


Table 11: Distribution of various risk factors in the study population

Variables	Frequency	Percentages
Mode Of Delivery		
LSCS	33	82.50%
NVD	7	17.50%
Obstetric Score		
Primi	12	30.00%
Multi	28	70.00%
Antenatal and natal risk factors		
IUGR	8	20.0%
PPROM/PROM	8	20.0%
Pre-eclampsia	3	7.5%
Oligohydramnios	3	7.5%
Resuscitation		
Cried Immediately After Birth	31	77.50%
Cried After BMV	5	12.50%
Weak Cry at Birth	3	7.50%
Cried After Stimulation	1	2.50%

Among the 40 subjects, 33 were delivered via LSCS (82.5%), remaining 7 via NVD (17.5%) and after delivery, majority of the neonates (77.5%) cried immediately after birth while 12.5% neonates cried after bag and mask ventilation, 7.5% had weak cry at birth, remaining (2.5%) cried after simulation.

Among the risk factors, 20% of mothers had IUGR and PROM/PPROM antenatally and around 7.5% of mothers had preeclampsia and oligohydramnios.

Figure 13: Pie chart of mode of delivery in the study population

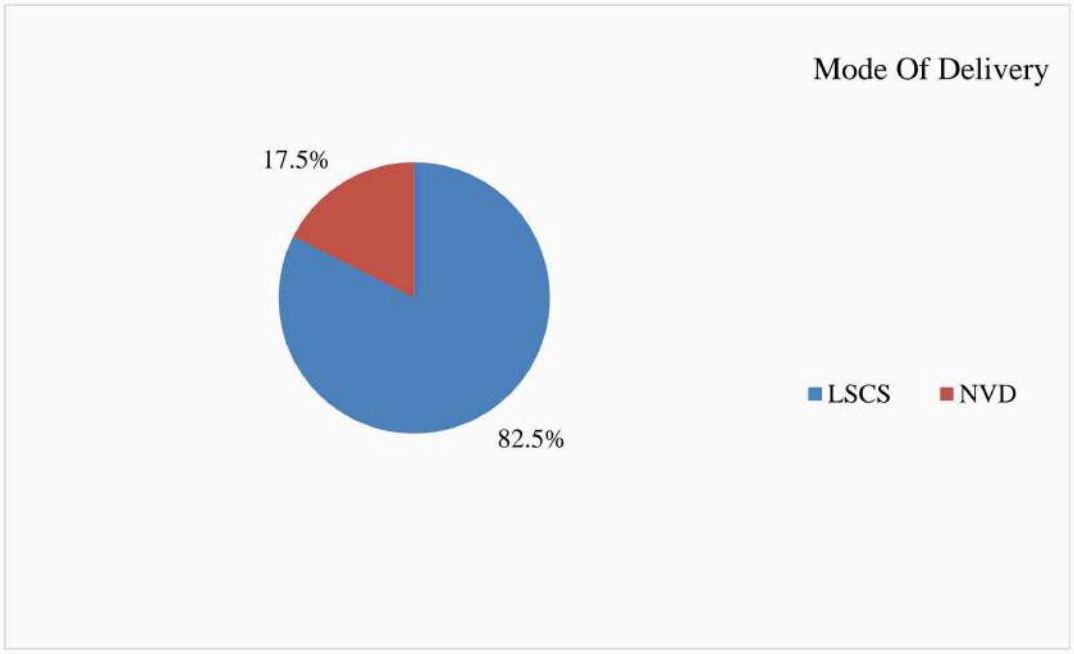


Figure 14: Pie chart of Obstetric Score in the study population

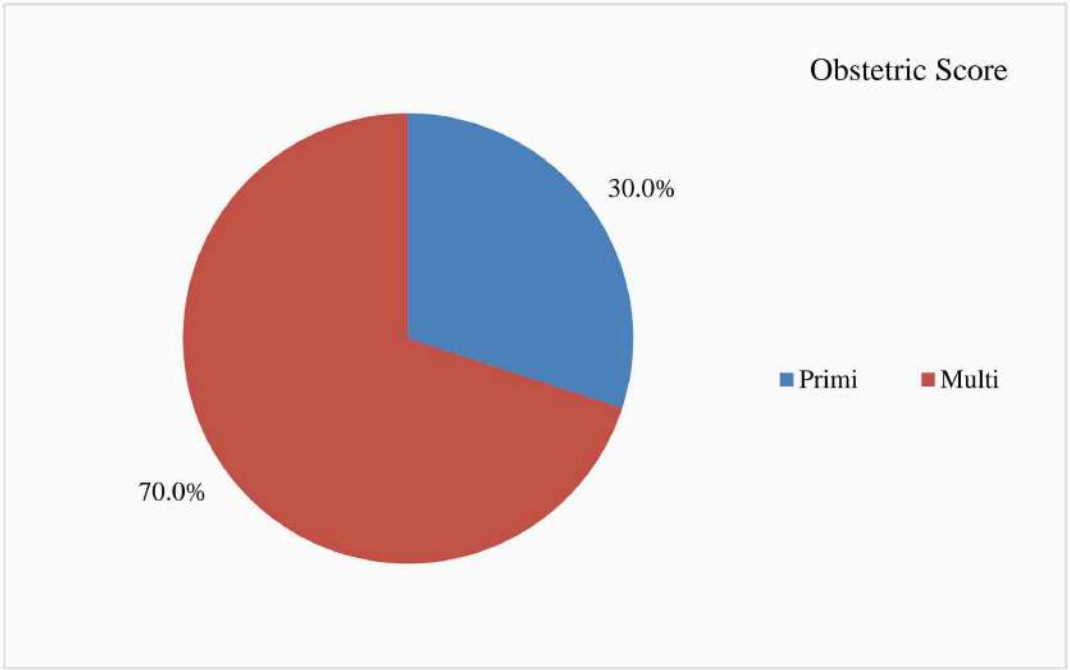


Figure 15: Bar chart of antenatal and natal risk factors in the study population

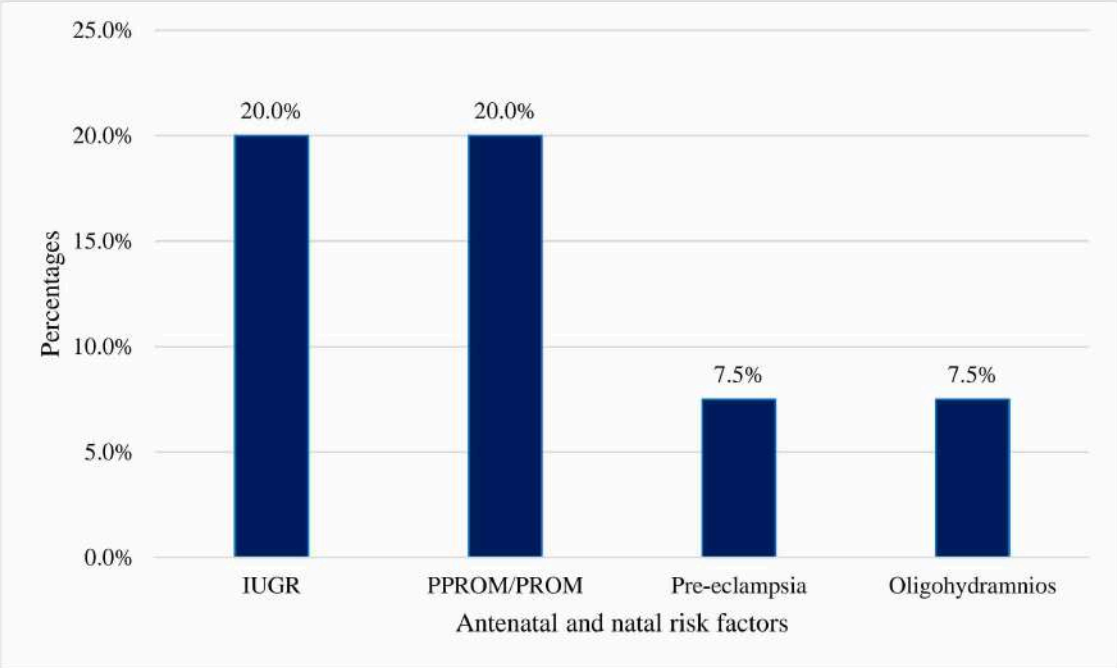


Figure 16: Bar chart of resuscitation at birth in the study population

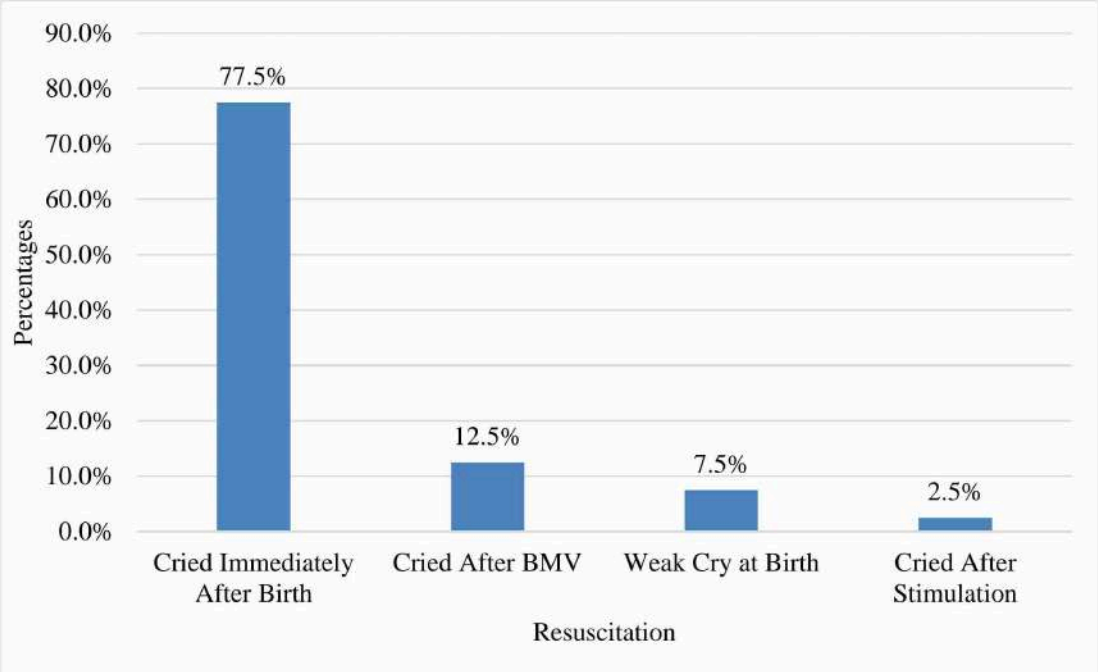


Table 12: Descriptive analysis of different variables of CHD in the study population

Variables	Frequency	Percentages
Antenatal Scans		
Normal	26	65.00%
Antenatally Diagnosed CHD	14	35.00%
Cyanotic Or Acyanotic		
Acyanotic	27	67.50%
Cyanotic	13	32.50%
CHD		
PDA	12	30.00%
Complex CHD	6	15.00%
ASD	5	12.50%
Single Ventricle Physiology	4	10.00%
VSD	4	10.00%
TAPVC	2	5.00%
TGA	2	5.00%
TOF	2	5.00%
AVSD	1	2.50%
COA	1	2.50%
MS	1	2.50%

Among the 40 neonates with Congenital heart disease, 14 were diagnosed to have CHD antenatally (35%).

27 neonates, had Acyanotic CHD (67.5%) while 13 neonates had Cyanotic CHD (32.5%).

PDA was the most common CHD found among the neonates (30%), followed by complex CHD (15%) and ASD (12.5%).

Figure 17: Pie chart of antenatal scans in the study population

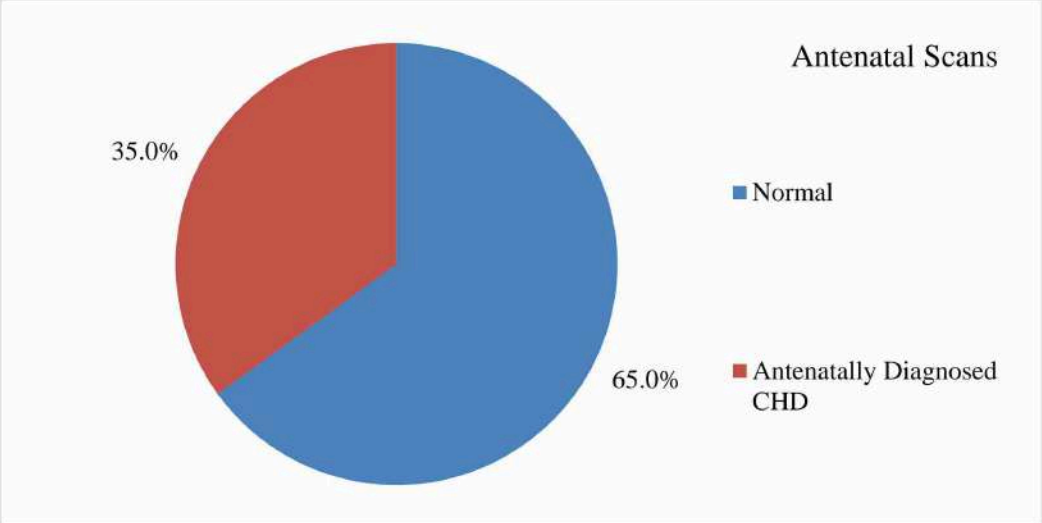


Figure 18: Pie chart of distribution of cyanotic and acyanotic CHDs in the study population

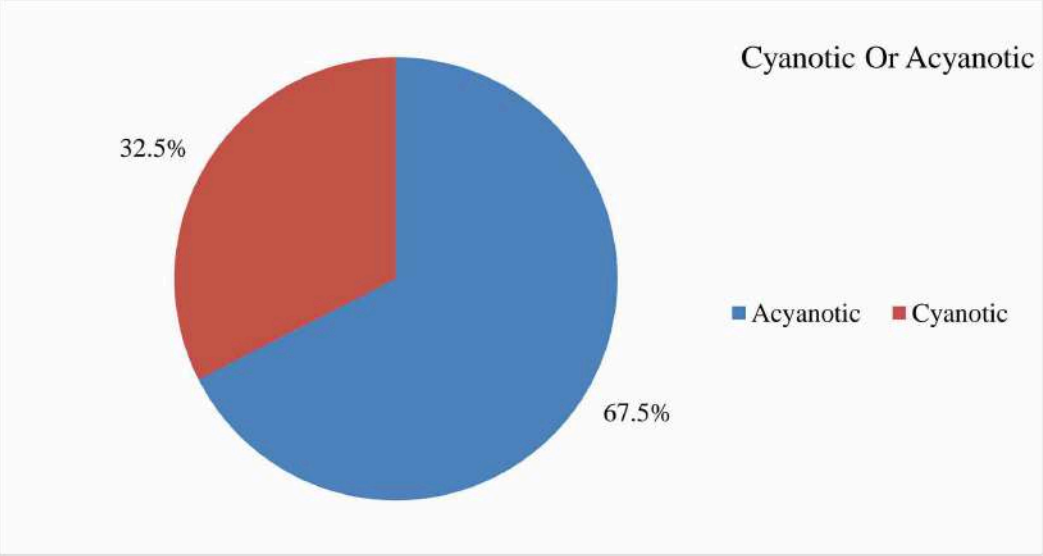


Figure 19: Bar chart of CHD in the study population

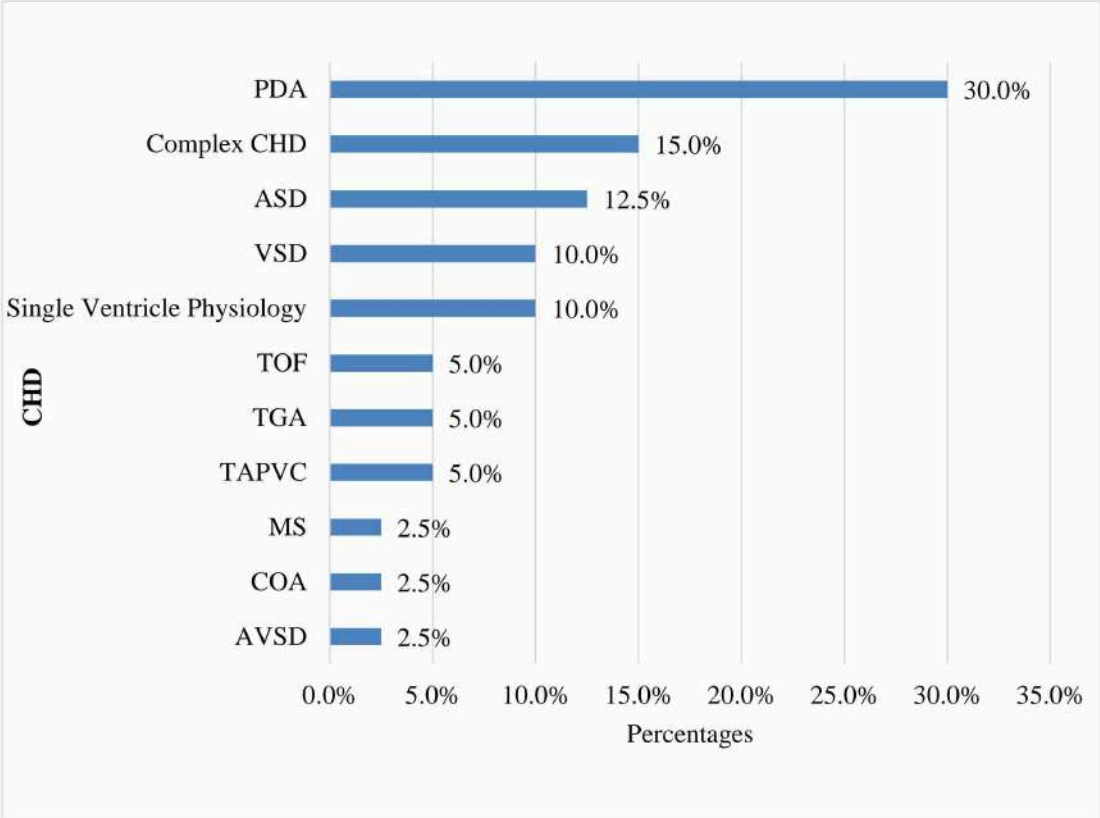


Table 13: Descriptive analysis of serum creatinine and serum cystatin C in study population

Parameter	Mean ± SD	Median	Minimum	Maximum	95% C.I	
					Lower	Upper
Sr Creatinine(mg/dl)	0.89 ± 0.32	0.8	0.4	1.5	0.8	1.0
Sr Cystatin C (mg/L)	1.79 ± 0.5	1.7	0.8	2.9	1.6	2.0

Table 14: Descriptive analysis of AKI in the study population

Parameter	Frequency	Percentages
AKI (Serum Creatinine)		
Yes	9	22.50%
No	31	77.50%
AKI (Serum Cystatin-C)		
Yes	14	35.00%
No	26	65.00%
AKI (Overall)		
Yes	16	40.00%
No	24	60.00%

Among the 40 neonates, overall 16 neonates had AKI, of which 9 neonates showed elevated serum Creatinine and 14 neonates showed elevated serum Cystatin-C.

Table 15: Descriptive analysis of AKI (stage) in the study population (N=40)

Aki (Stage)	Frequency	Percentages
Stage 1	4	10.00%
Stage 2	5	12.50%
Nil	31	77.50%

Figure 20: Pie chart of AKI (Serum Creatinine) in the study population

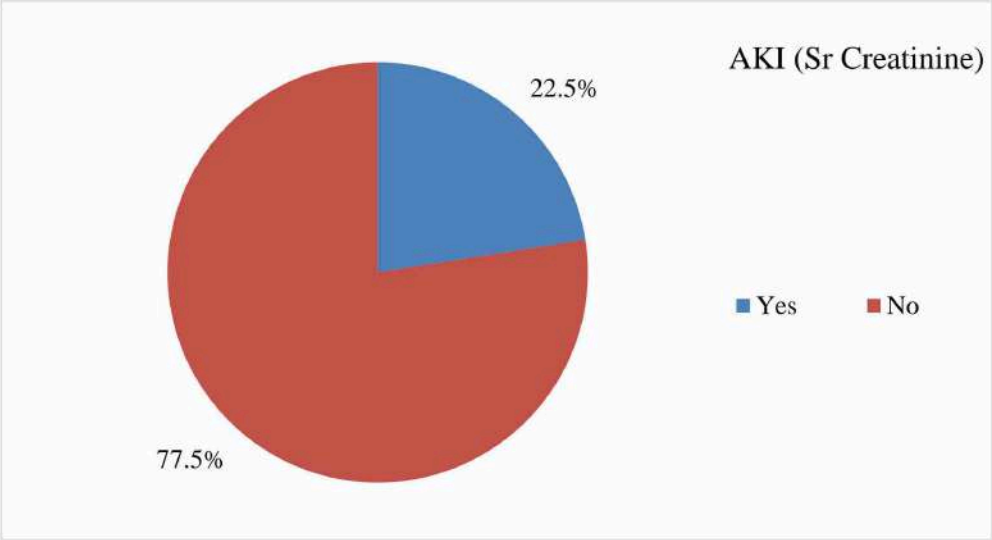


Figure 20: Pie chart of AKI (Serum Cystatin-C) in the study population

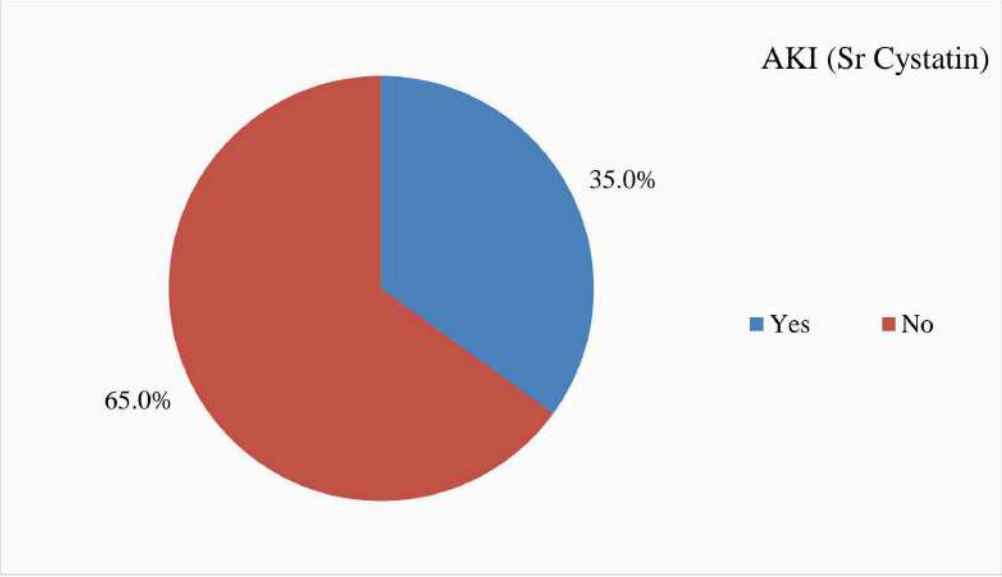


Figure 22: Pie chart of AKI in the study population

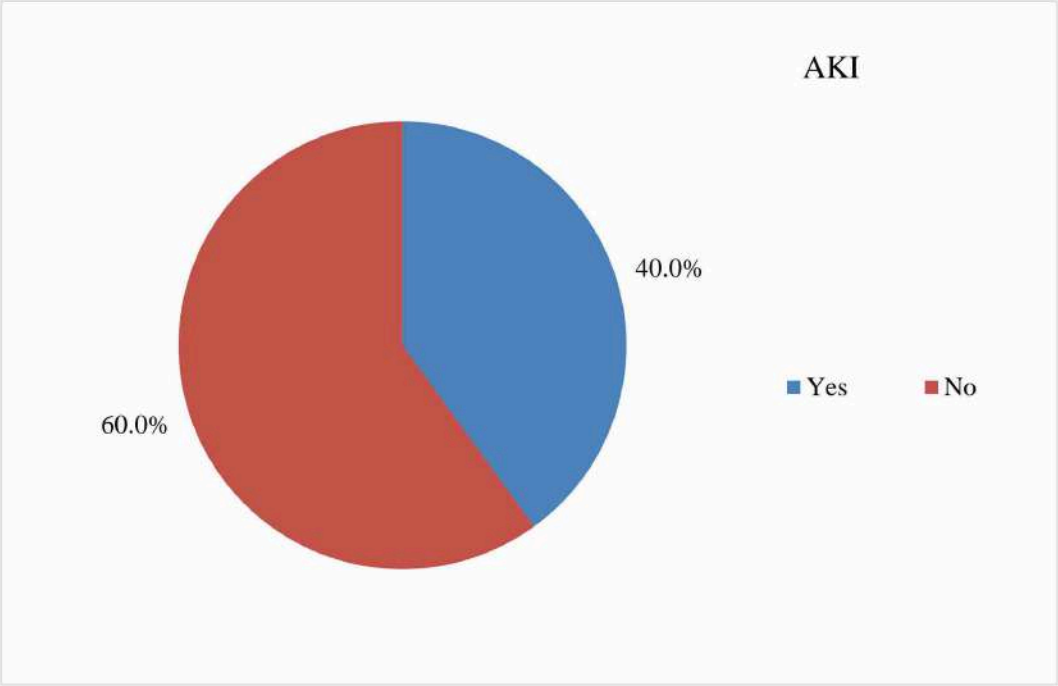


Figure 23: Pie chart of AKI (stage) in the study population using serum creatinine

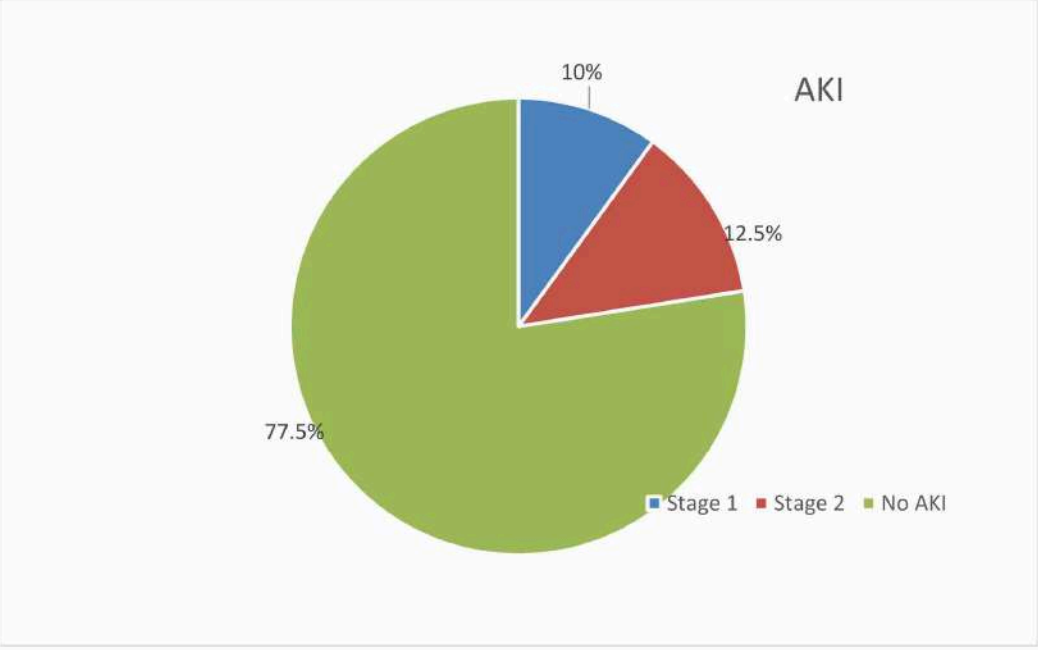


Table 16: Descriptive analysis of Postnatal risk factors of AKI in the study population

Variables	Frequency	Percentages
Sepsis		
Yes	5	12.50%
No	35	87.50%
NICU Stay		
Yes	35	87.50%
No	5	12.50%
Inotropes		
Yes	6	15.00%
No	34	85.00%
Antibiotics		
Aminoglycoside	27	67.50%
Meropenem	3	7.50%
Fluconazole	8	20.00%
NSAIDs		
Yes	7	17.50%
No	33	82.50%
Caffeine Citrate		
Yes	9	22.50%

No	31	77.50%
Decongestives		
Yes	11	27.50%
No	29	72.50%
Other Medications		
Surfactant	5	12.50%
Prostaglandin	7	17.50%

Among the 40 neonates, 5 neonates were positive for sepsis(12.5%), 6 neonates required inotropic support(15%), 7 neonates received NSAIDs (17.5%) , 27 neonates received aminoglycosides (67.5%), 3 neonates received meropenem (7.5%), 8 neonates received fluconazole (20%). 2 neonates received all the 3 groups of antibiotics (5%) whereas 7 neonates received 2 groups of antibiotics (17.5%). 9 neonates received caffeine citrate (22.5%) and 11 neonates required decongestive therapy (27.5%).

87.5% of neonates (35)with congenital heart disease required NICU stay.

Figure 24: Pie chart of sepsis in the study population

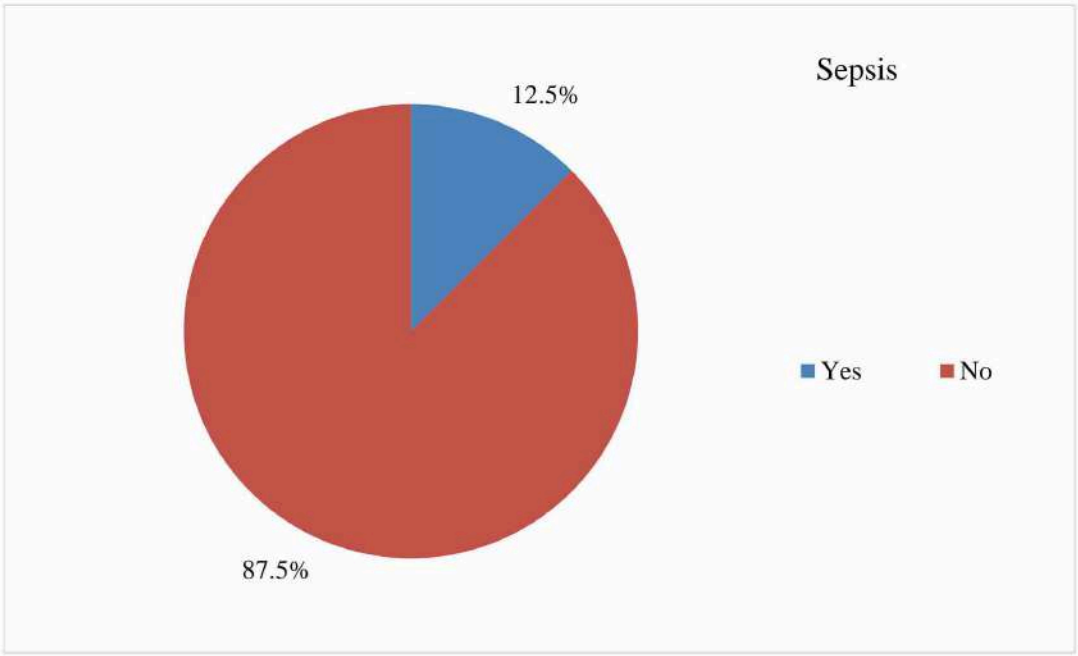


Figure 25: Pie chart of NICU Stay in the study population

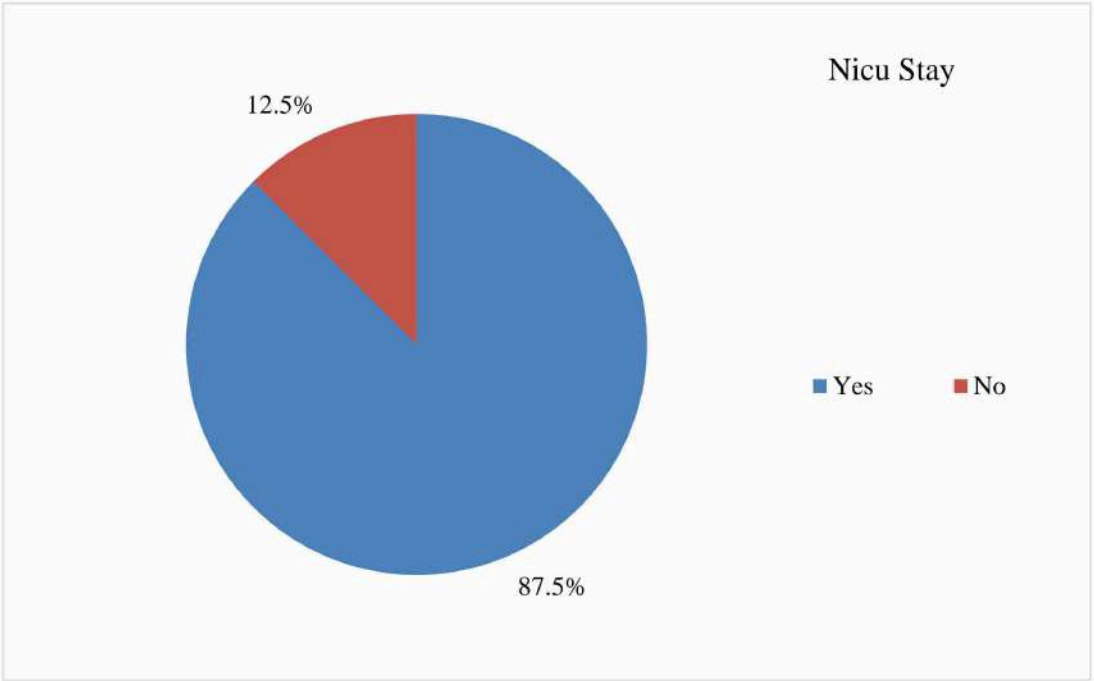


Figure 26: Pie chart of Inotropes in the study population

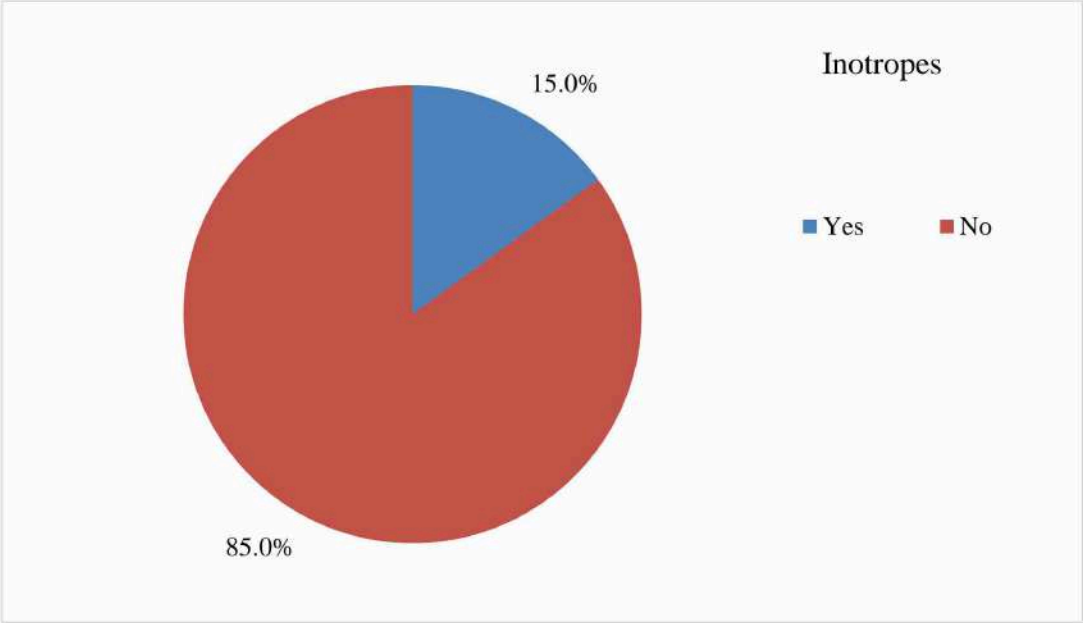


Figure 27: Bar graph of Antibiotics in the study population

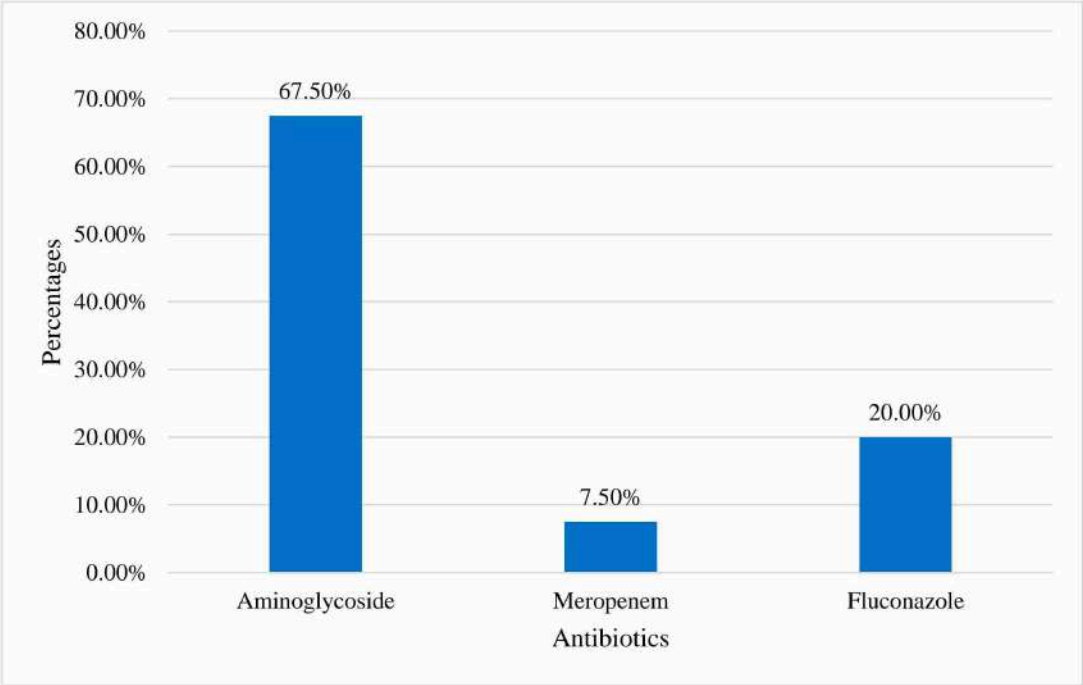


Figure 28: Pie chart of NSAIDS in the study population

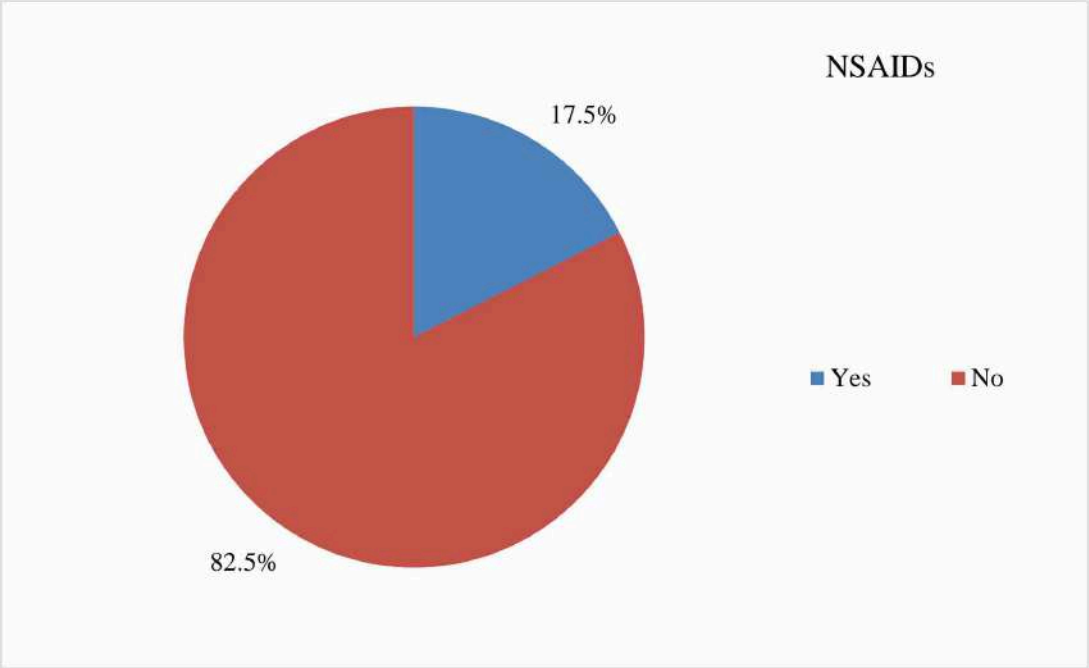


Figure 29: Pie chart of caffeine citrate in the study population

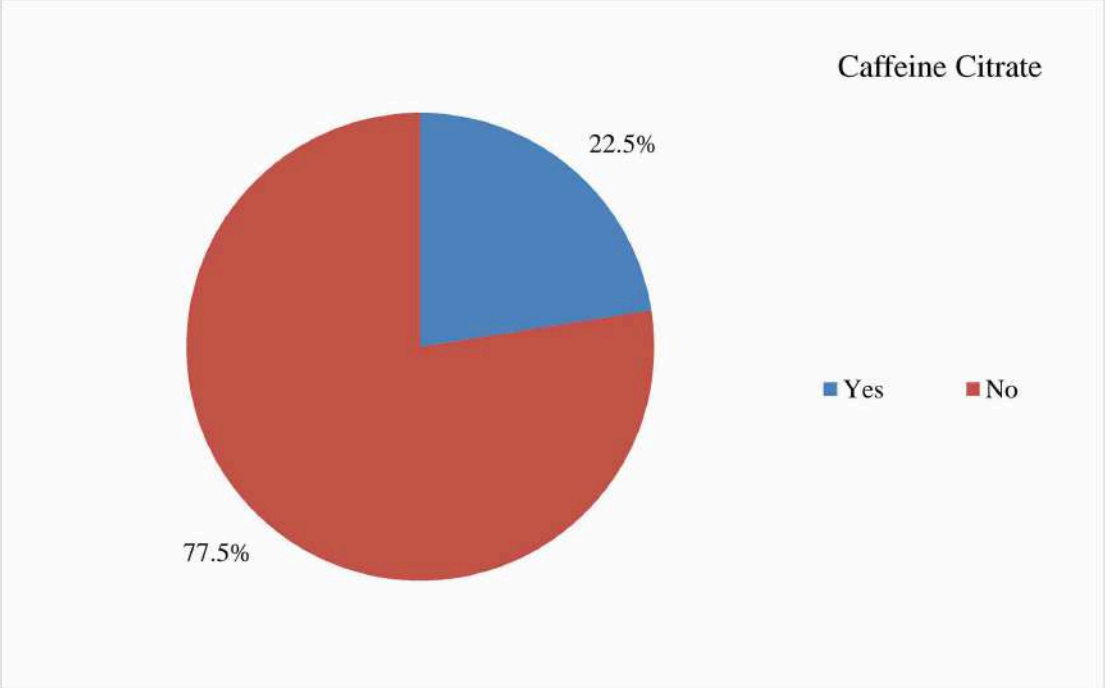


Figure 30: Bar chart of Other Medication in the study population

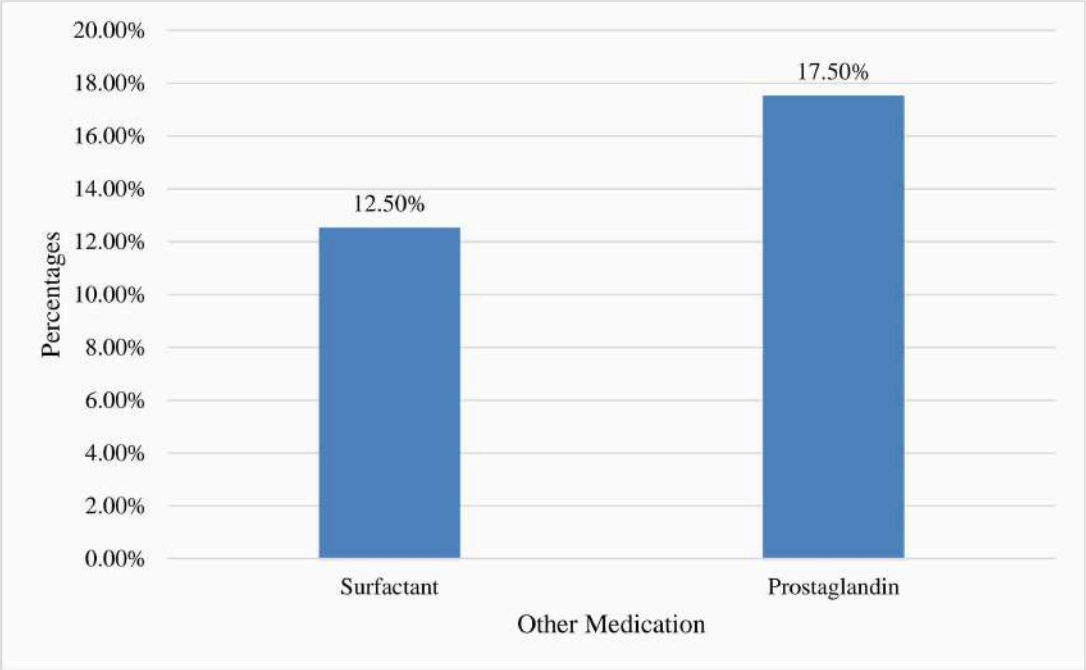


Figure 31: Pie chart of Decongestive citrate in the study population

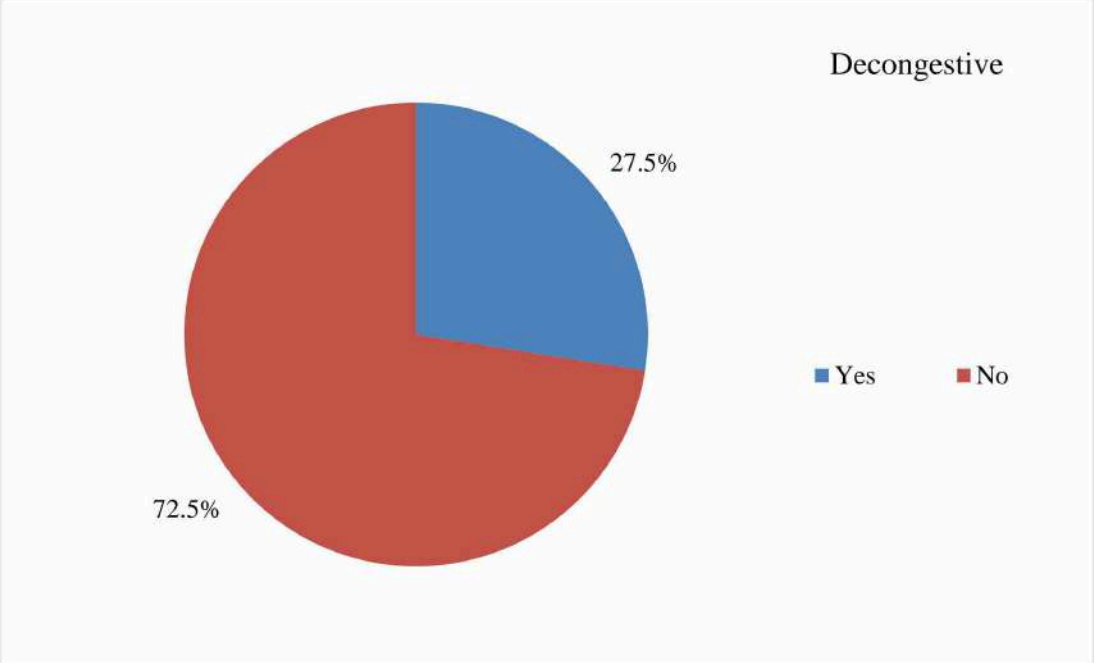


Table 17: Descriptive analysis of Oxygen support in the study population

Oxygen support	Frequency	Percentages
Mechanical ventilation	5	12.50%
CPAP	11	27.50%
Nasal Prongs	7	17.50%

Among the 40 neonates with CHD, majority did not require oxygen support (57.5%), 27.5% required CPAP support, 17,5% required nasal prongs whereas only 12.5% required mechanical ventilation.

Figure 32: Bar chart of oxygen support in the study population

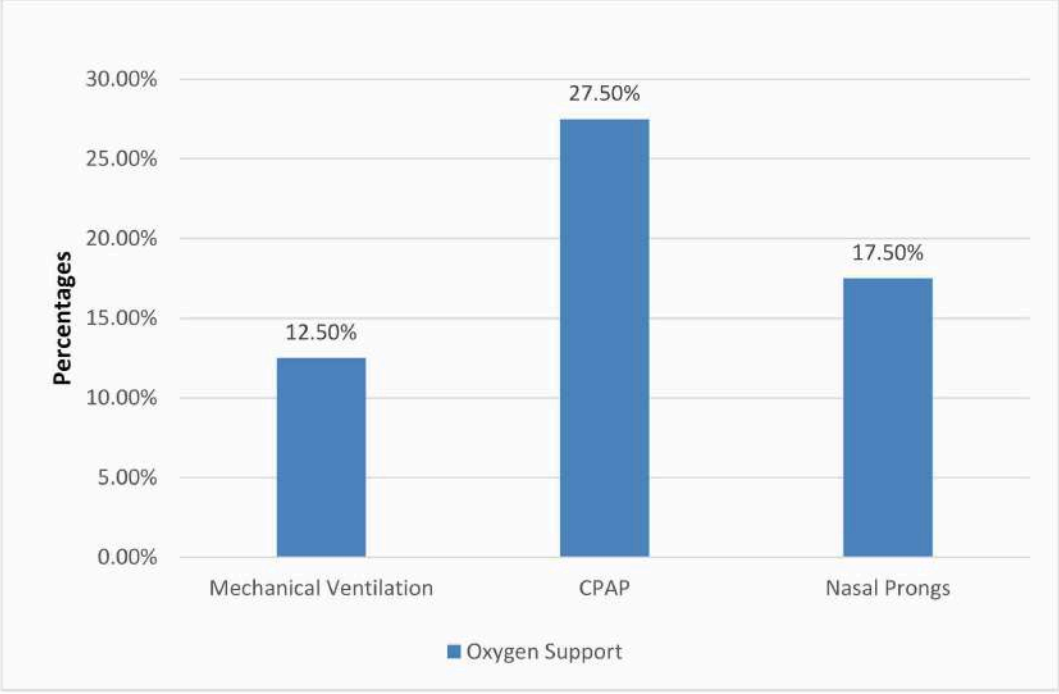


Table 18: Descriptive analysis of outcome in the study population

Outcome	Frequency	Percentages
Discharged	36	90.00%
Expired	4	10.00%

10% of neonates with CHD (4 in number) expired during the study period.

Figure 33: Pie chart of outcome in the study population

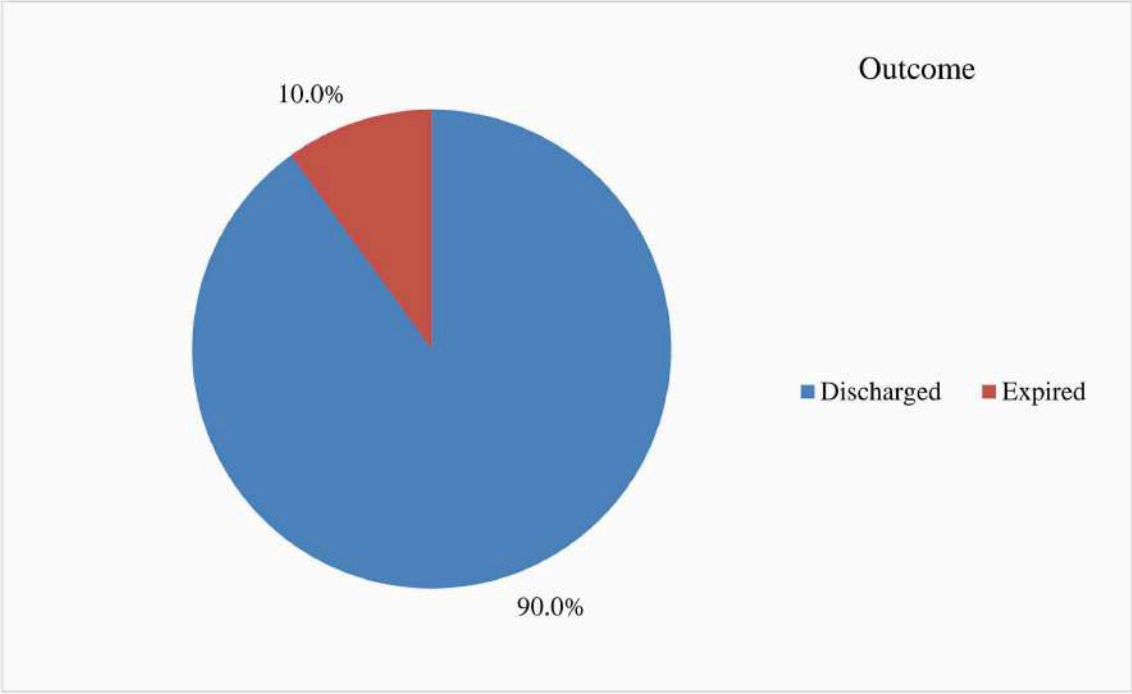


Table 19: Comparison of AKI (Sr creatinine) between AKI (Sr cystatin)

Aki (Sr Creatinine)	AKI (Sr Cystatin)		Chi square	P value
	Yes (N=14)	No (N=26)		
Yes	8 (57.14%)	1 (3.85%)	14.824	<0.001
No	6 (42.86%)	25 (96.15%)		

The table compares AKI diagnosis using serum creatinine and serum cystatin, showing that among 14 patients diagnosed with AKI by serum creatinine, 8 (57.14%) were also identified by serum cystatin, while 6 (42.86%) were not. Among the 26 patients not diagnosed with AKI by serum creatinine, 25 (96.15%) were also negative by serum cystatin, while 1 (3.85%) was positive. The chi-square value of 14.824 and a highly significant p-value (<0.001) indicate a strong correlation between the two biomarkers, suggesting that serum cystatin may be a reliable marker for AKI diagnosis.

Figure 34: Cluster bar chart of comparison of AKI (Sr creatinine) between AKI (Sr cystatin)

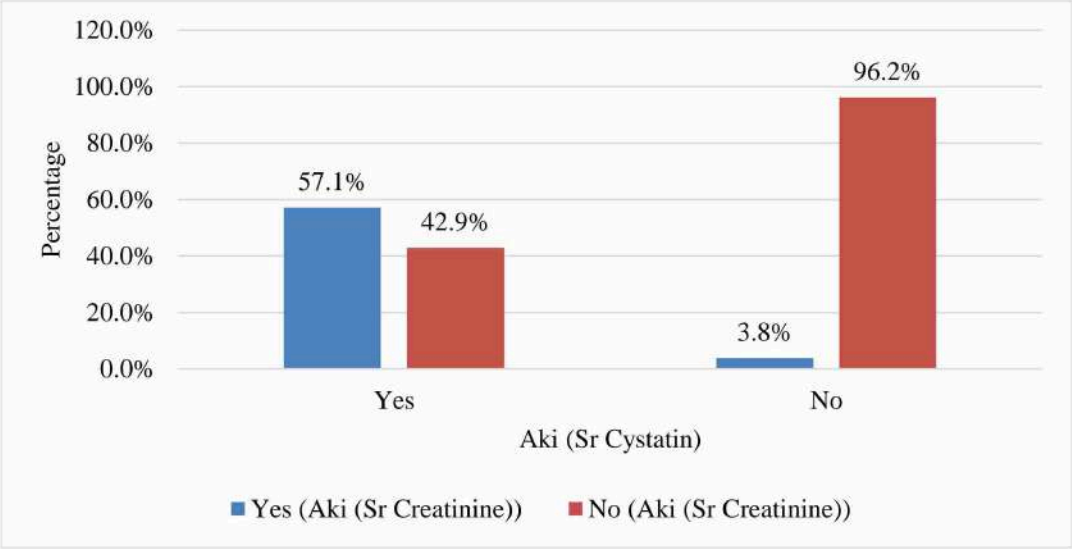


Table 20: Comparison of AKI between male and female in the study population

Gender	AKI		Chi square	P value
	Yes (N=16)	No (N=24)		
Male	10 (62.5%)	14 (58.33%)	0.069	0.792
Female	6 (37.5%)	10 (41.67%)		

Table 21: Comparison of AKI (Sr Cystatin) between male and female in the study population

Gender	AKI (Sr Cystatin)		Chi square	P value
	Yes (N=14)	No (N=26)		
Male	8 (57.14%)	16 (61.54%)	0.073	0.787
Female	6 (42.86%)	10 (38.46%)		

Table 22: Comparison of AKI (Sr Creatinine) between male and female in the study population

Gender	Aki (Sr Creatinine)		Chi square	P value
	Yes (N=9)	No (N=31)		
Male	6 (66.67%)	18 (58.06%)	0.215	0.717
Female	3 (33.33%)	13 (41.94%)		

The three tables compare the incidence of AKI across gender using different markers (general AKI, Sr Cystatin, and Sr Creatinine) in a sample of 40 neonates. In all three comparisons, males had a higher proportion of AKI cases than females, although the differences were not statistically significant (P-values > 0.7 in all cases). In the first table, 62.5% of AKI cases were male, while 37.5% were female. The second table (Sr Cystatin) shows a similar trend, with 57.14% of AKI cases being male and 42.86% female. The third table (Sr Creatinine) further reinforces this pattern, with 66.67% of AKI cases in males and 33.33% in females. Despite the observed male predominance, the lack of statistical significance suggests that gender alone may not be a strong predictor of AKI in this cohort.

Figure 35: Cluster bar chart of comparison of AKI male and female in the study population

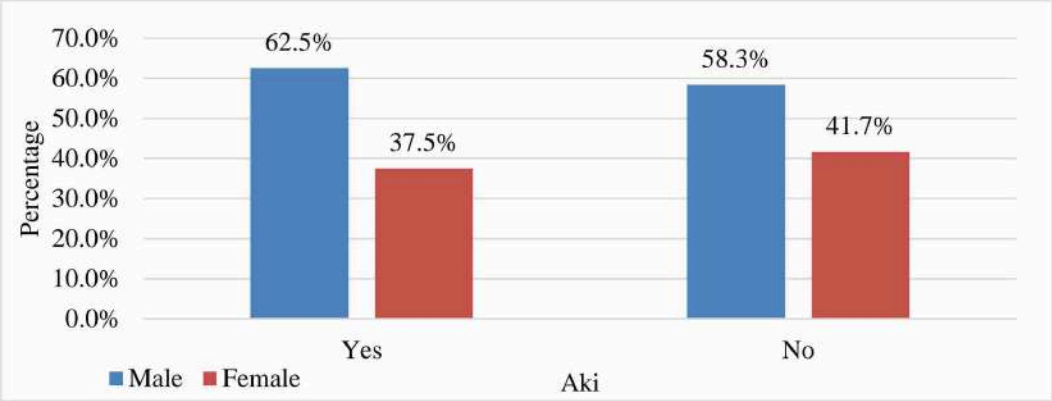


Figure 36: Cluster bar chart of comparison of AKI between male and female (Sr cystatin) in the study population

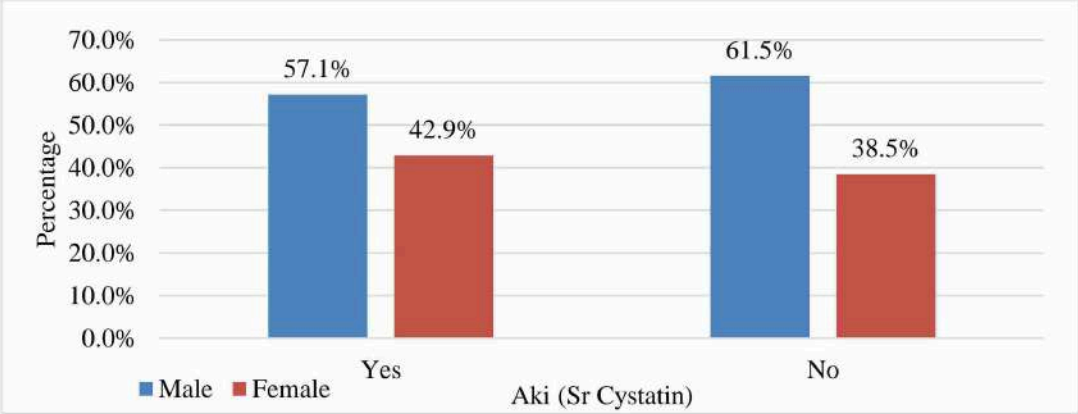


Figure 37: Cluster bar chart of comparison AKI between male and female (Sr Creatinine) in the study population

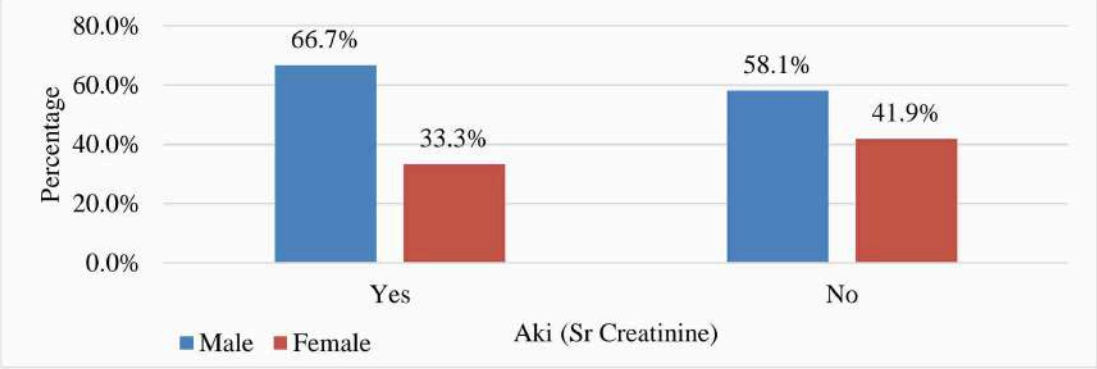


Table 23: Comparison of AKI among birth weight category in the study population

Birth Weight	AKI		Chi square	P value
	Yes (N=16)	No (N=24)		
ELBW	0 (0%)	1 (4.17%)	2.91	0.573
VLBW	2 (12.5%)	4 (16.67%)		
LBW	8 (50%)	9 (37.5%)		
Macrosomia	1 (6.25%)	0 (0%)		
Normal	5 (31.25%)	10 (41.67%)		

Table 24: Comparison of AKI (Sr Cystatin) among birth weight category in the study population

Birth Weight	AKI (Sr Cystatin)		Chi square	P value
	Yes (N=14)	No (N=26)		
ELBW	0 (0%)	1 (3.85%)	4.83	0.306
VLBW	1 (7.14%)	5 (19.23%)		
LBW	8 (57.14%)	9 (34.62%)		
Macrosomia	1 (7.14%)	0 (0%)		
Normal	4 (28.57%)	11 (42.31%)		

Table 25: Comparison of AKI (Sr Creatinine) between Demographic in the study population

Birth Weight	Aki (Sr Creatinine)		Chi square	P value
	Yes (N=9)	No (N=31)		
ELBW	0 (0%)	1 (3.23%)	6.26	0.181
VLBW	1 (11.11%)	5 (16.13%)		
LBW	7 (77.78%)	10 (32.26%)		
Macrosomia	0 (0%)	1 (3.23%)		
Normal	1 (11.11%)	14 (45.16%)		

The three tables compare AKI occurrence across birth weight categories using different diagnostic criteria: general AKI , AKI based on serum cystatin , and AKI based on serum creatinine. In all three, low birth weight (LBW) had the highest AKI incidence (50% in general AKI, 57.14% in cystatin-based AKI, and 77.78% in creatinine-based AKI), while extremely low birth weight (ELBW) had no AKI cases in any method. Normal birth weight had a varying AKI occurrence (31.25% in general, 28.57% in cystatin, and 11.11% in creatinine). The chi-square values were 2.91 (p=0.573) for general AKI, 4.83 (p=0.306) for cystatin, and 6.26 (p=0.181) for creatinine, all indicating no statistically significant association between birth weight and AKI regardless of the diagnostic criteria used.

Figure 38: Cluster bar chart of comparison of Birthweight between AKI in the study population

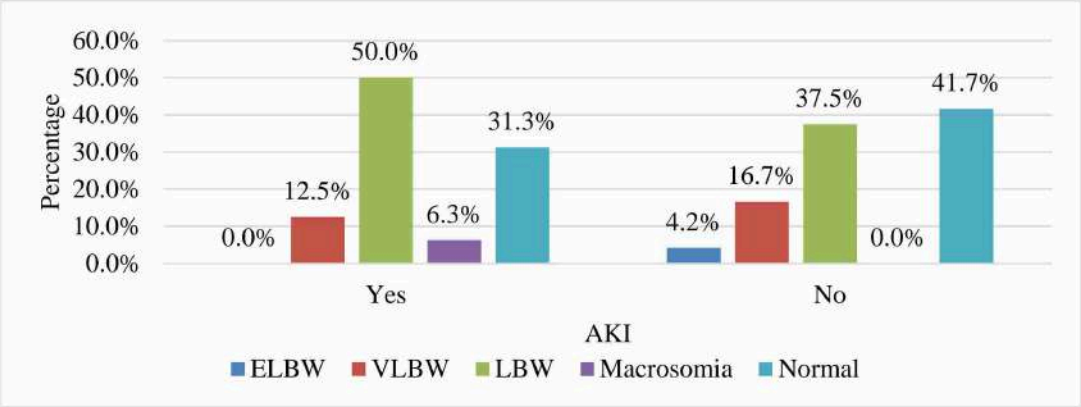


Figure 39: Cluster bar chart of comparison of Birthweight between AKI (Sr cystatin) in the study population

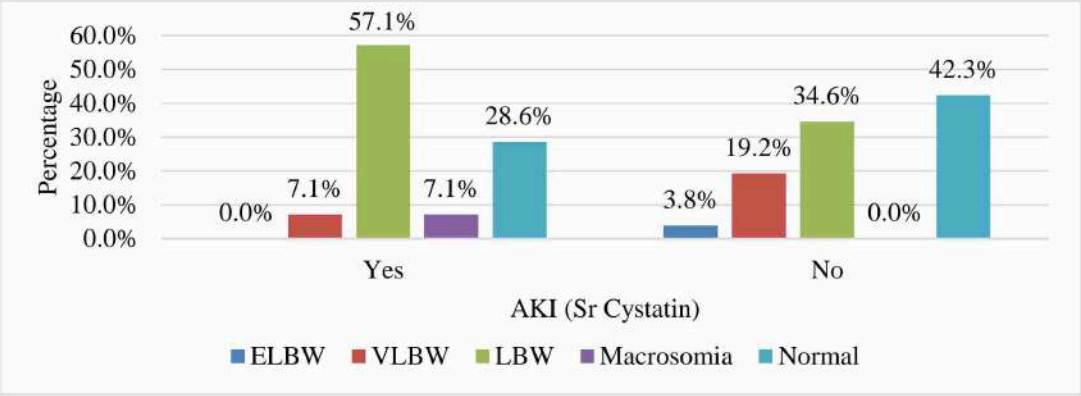


Figure 40: Cluster bar chart of comparison of Birthweight between AKI (Sr Creatinine) in the study population

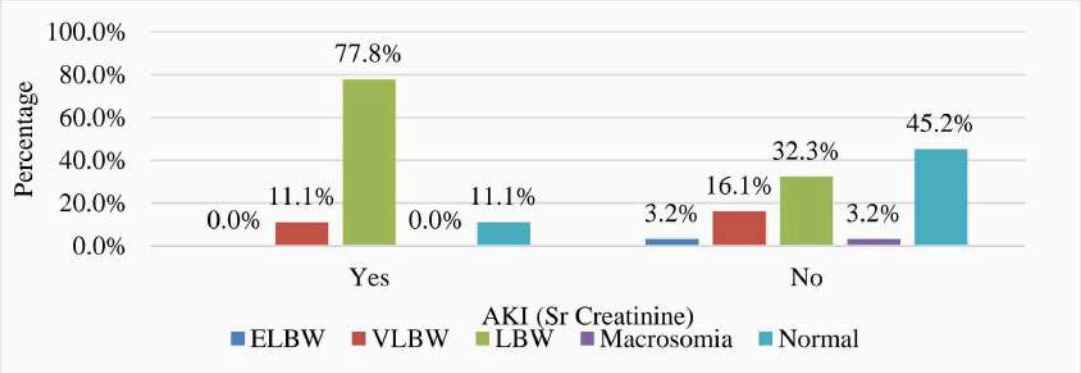


Table 26: Comparison of AKI among gestational age category in the study population

Gestational Age	AKI		Chi square	P value
	Yes (N=16)	No (N=24)		
Extremely Preterm	1 (6.25%)	0 (0%)	4.37	0.224
Early Preterm	1 (6.25%)	7 (29.17%)		
Late Preterm	4 (25%)	5 (20.83%)		
Term	10 (62.5%)	12 (50%)		

Table 27: Comparison AKI (Sr cystatin) among gestational age category in the study population

Gestational Age	AKI (Sr Cystatin)		Chi square	P value
	Yes (N=14)	No (N=26)		
Extremely Preterm	1 (7.14%)	0 (0%)	7.23	0.065
Early Preterm	0 (0%)	8 (30.77%)		
Late Preterm	3 (21.43%)	6 (23.08%)		
Term	10 (71.43%)	12 (46.15%)		

Table 28: Comparison of AKI (Sr Creatinine) among gestational age category in the study population

Gestational Age	Aki (Sr Creatinine)		Chi square	P value
	Yes (N=9)	No (N=31)		
Extremely Preterm	0 (0%)	1 (3.23%)	1.36	0.716
Early Preterm	1 (11.11%)	7 (22.58%)		
Late Preterm	3 (33.33%)	6 (19.35%)		
Term	5 (55.56%)	17 (54.84%)		

The three tables compare AKI occurrence among different gestational age categories using general AKI criteria, serum cystatin-based AKI, and serum creatinine-based AKI. In all three, term infants had the highest AKI incidence (62.5% in general AKI, 71.43% in cystatin-based AKI, and 55.56% in creatinine-based AKI), while early preterm had the lowest. Late preterm showed moderate AKI occurrence across all methods (25% in general, 21.43% in cystatin, and 33.33% in creatinine). Chi-square values were 4.37 (p=0.224) for general AKI, 7.23 (p=0.065) for cystatin, and 1.36 (p=0.716) for creatinine, indicating no statistically significant association between gestational age and AKI in any of the three diagnostic methods. However, the cystatin-based test showed a trend toward significance (p=0.065), suggesting a possible association.

Figure 41: Cluster bar chart of comparison of AKI among gestational age category

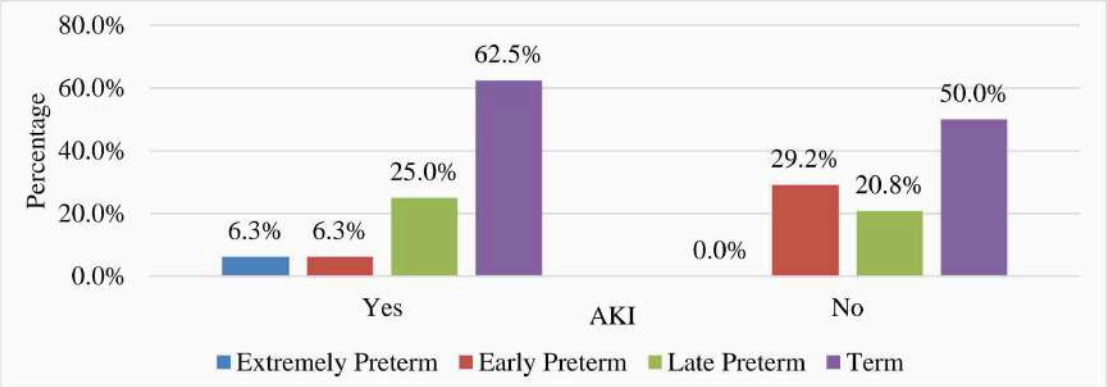


Figure 42: Cluster bar chart of comparison of AKI (Sr cystatin) among gestational age category in the study population

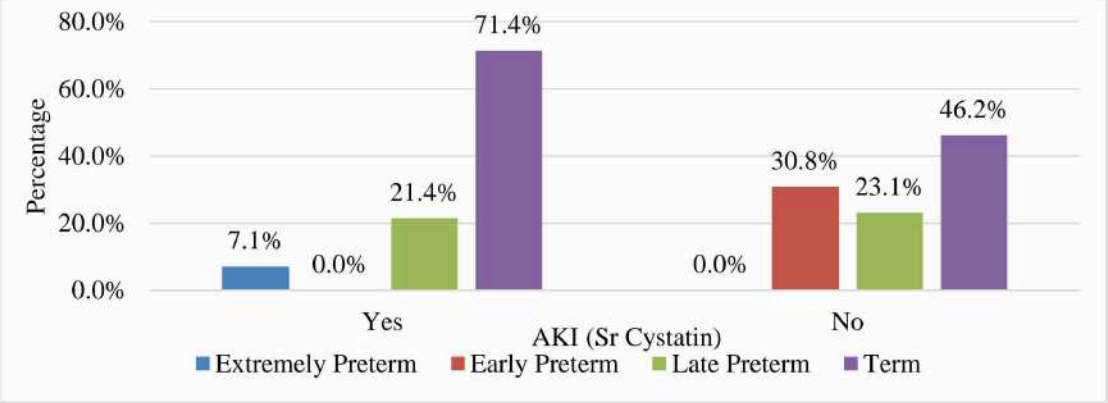


Figure 43: Cluster bar chart of comparison of AKI among gestational age category (Sr Creatinine) in the study population

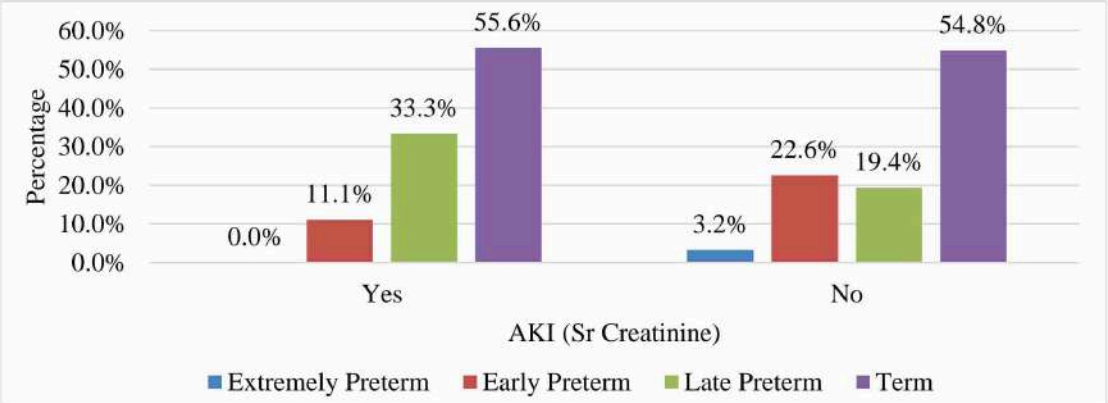


Table 29: Comparison of AKI due to various risk factors in the study population

Variables	AKI		Chi square	P value
	Yes (N=16)	No (N=24)		
Antenatal and natal risk factors				
IUGR	4 (25%)	4 (16.67%)	0.417	0.690
PPROM/PROM	3 (18.75%)	5 (20.83%)	0.026	1.00
Pre-eclampsia	1 (6.25%)	2 (8.33%)	0.060	1.00
Oligohydramnios	0 (0%)	3 (12.5%)	2.16	0.141
Resuscitation				
Cried Immediately After Birth	11 (68.75%)	20 (83.33%)	2.652	0.448
Cried After BMV	3 (18.75%)	2 (8.33%)		
Weak Cry at Birth	1 (6.25%)	2 (8.33%)		
Cried After Stimulation	1 (6.25%)	0 (0%)		

Table 30: Comparison of AKI due to various risk factors (Sr cystatin) in the study population

Variables	AKI (Sr Cystatin)		Chi square	P value
	Yes (N=14)	No (N=26)		
Antenatal and natal risk factors				
IUGR	4 (28.57%)	4 (15.38%)	0.989	0.414
PPROM/PROM	1 (7.14%)	7 (26.92%)	2.23	0.222
Pre-eclampsia	1 (7.14%)	2 (7.69%)	0.004	1.00
Oligohydramnios	0 (0%)	3 (11.54%)	1.75	0.186
Postnatal Period				
Cried Immediately After Birth	10 (71.43%)	21 (80.77%)	2.018	0.569
Cried After BMV	2 (14.29%)	3 (11.54%)		
Weak Cry at Birth	1 (7.14%)	2 (7.69%)		
Cried After Stimulation	1 (7.14%)	0 (0%)		

Table 31: Comparison of AKI due to various risk factors (Sr Creatinine) in the study population

Variables	AKI (Sr Creatinine)		Chi square	P value
	Yes (N=9)	No (N=31)		
Antenatal and natal risk factors				
IUGR	4 (44.44%)	4 (12.9%)	4.34	0.059
PPROM/PROM	1 (11.11%)	7 (22.58%)	0.573	0.655
Pre-eclampsia	1 (11.11%)	2 (6.45%)	0.218	0.545
Oligohydramnios	0 (0%)	3 (9.68%)	0.942	0.332
Postnatal Period				
Cried Immediately After Birth	5 (55.56%)	26 (83.87%)	5.246	0.155
Cried After BMV	2 (22.22%)	3 (9.68%)		
Weak Cry at Birth	1 (11.11%)	2 (6.45%)		
Cried After Stimulation	1 (11.11%)	0 (0%)		

The above three tables compare the association of various risk factors of Acute Kidney Injury (AKI) using different biomarkers-general AKI, AKI diagnosed by serum cystatin C, and AKI diagnosed by serum creatinine. Across all three tables, Intrauterine Growth Restriction (IUGR) is more frequently observed in AKI cases, with a higher percentage in the serum creatinine group (44.44%). However, statistical significance is not reached ($P > 0.05$). Other factors like PPROM/PROM, pre-

eclampsia, and oligohydramnios show variations but lack significant associations. In the postnatal period, cried immediately after birth is the most common response, but the percentage is slightly lower in the AKI groups. The chi-square and p-values across all tables indicate no statistically significant association between these risk factors and AKI, suggesting that while these factors might contribute to AKI development, stronger statistical evidence is needed.

Figure 44: Cluster bar chart of AKI due to various risk factors in the study population

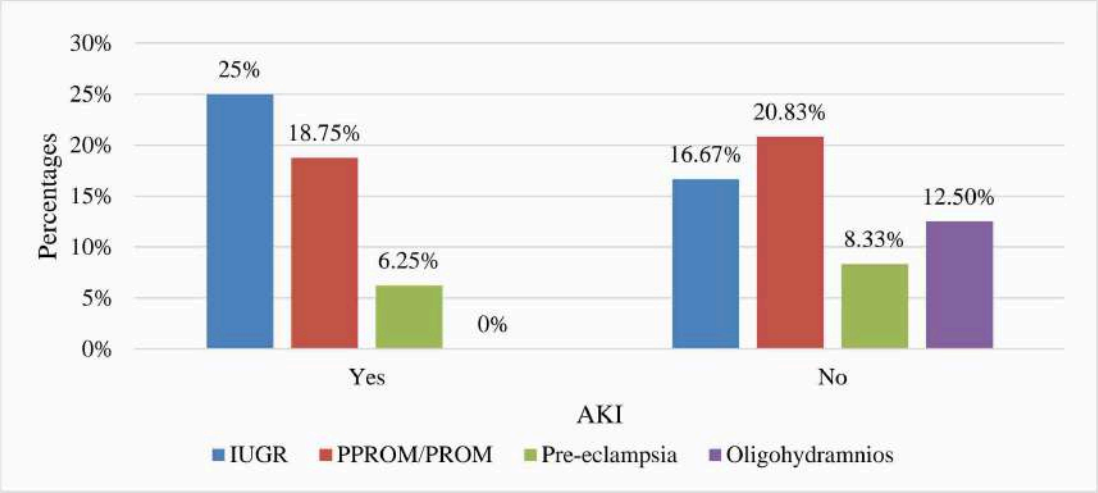


Figure 45: Cluster bar chart of AKI due to various risk factors (Sr cystatin) in the study population

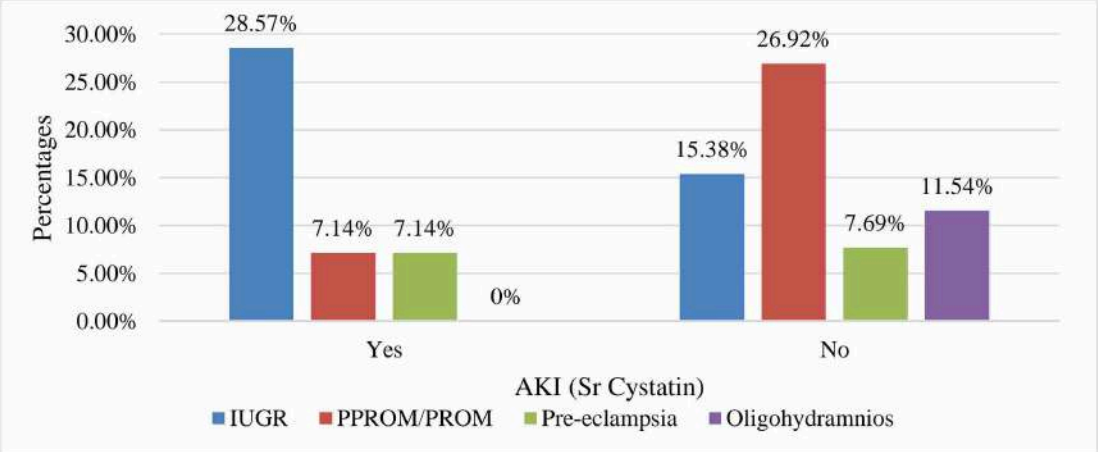


Figure 46: Cluster bar chart of AKI due to various risk factors (Sr Creatinine) in the study population

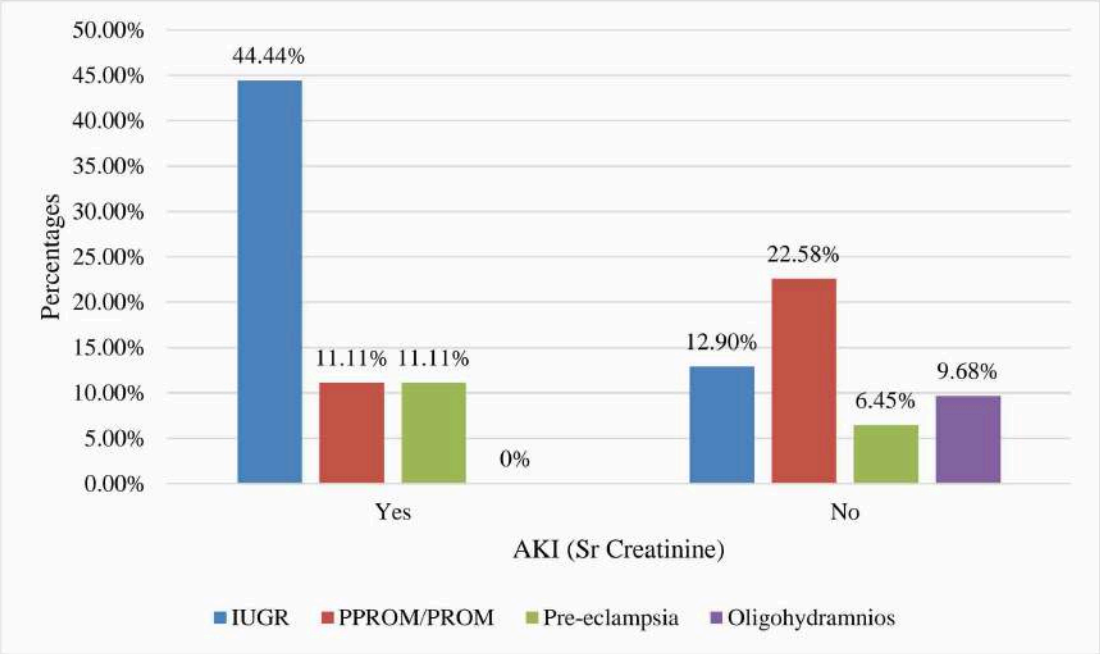


Figure 47: Cluster bar chart of AKI due to birth asphyxia in the study population

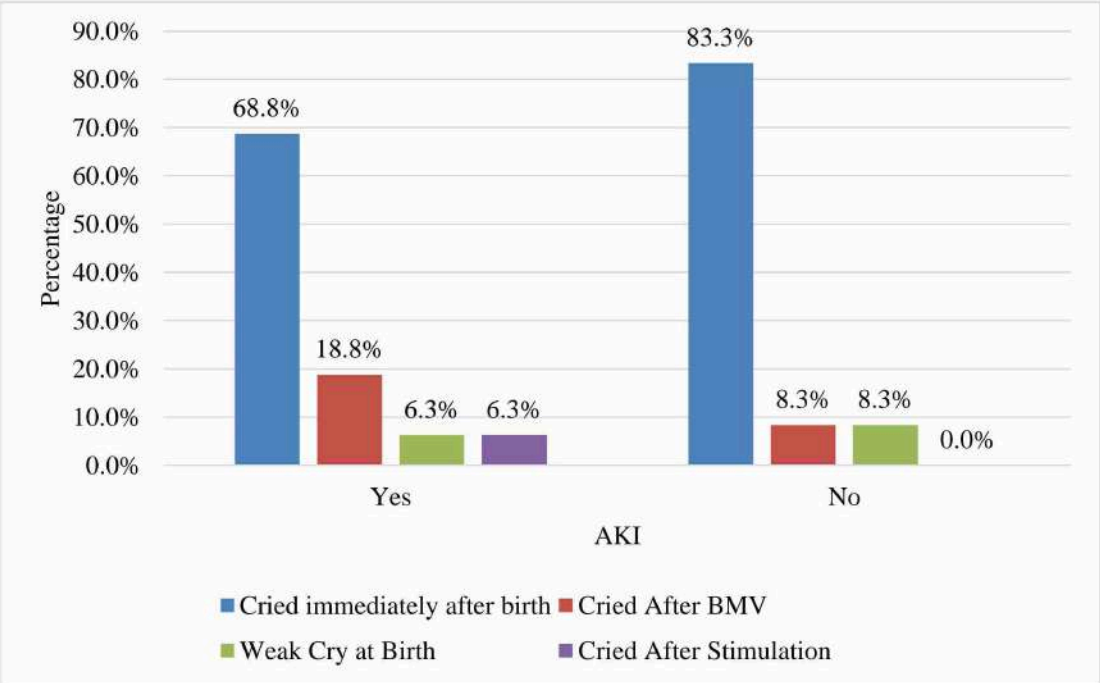


Figure 48: Cluster bar chart of AKI due to birth asphyxia (Sr cystatin) in the study population

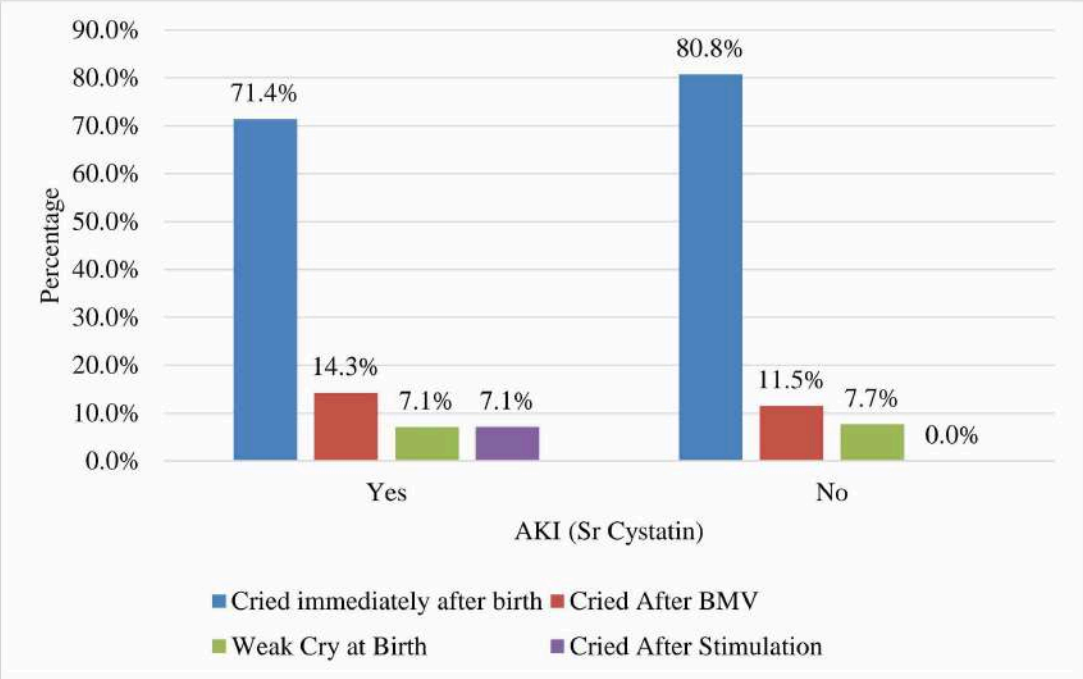


Figure 49: Cluster bar chart of AKI due to birth asphyxia (Sr Creatinine) in the study population

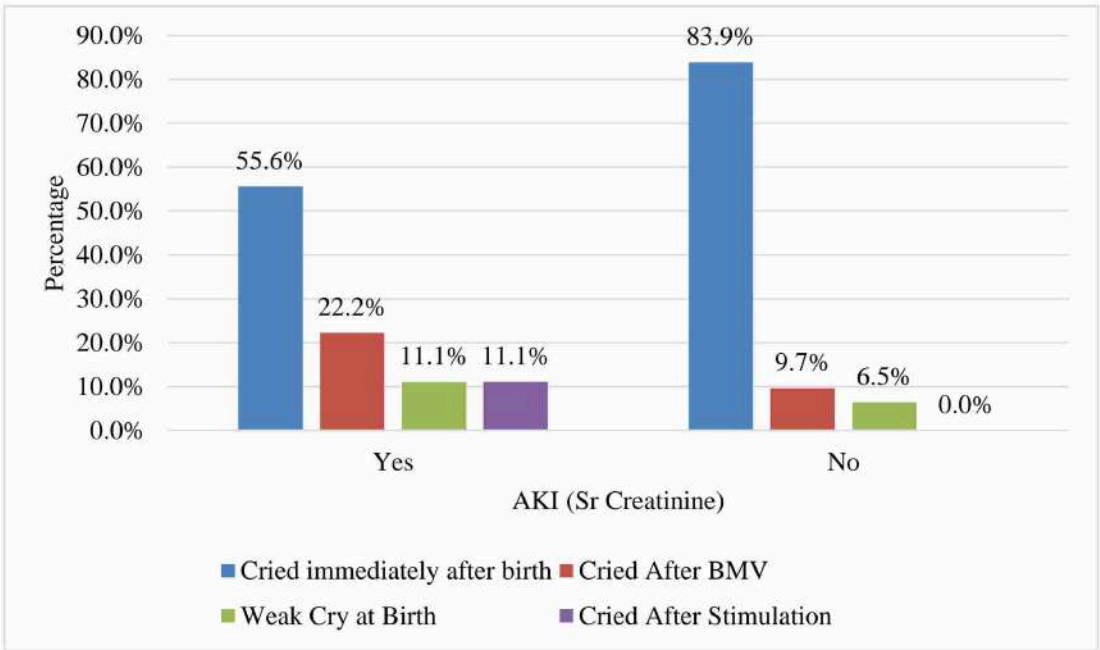


Table 32: Comparison of AKI between cyanotic or acyanotic CHD in the study population

Cyanotic Or Acyanotic	AKI		Chi square	P value
	Yes (N=16)	No (N=24)		
Acyanotic	8 (50%)	19 (79.17%)	3.723	0.054
Cyanotic	8 (50%)	5 (20.83%)		

Table 33: Comparison of AKI between cyanotic or acyanotic CHD (Sr cystatin C) in the study population

Cyanotic Or Acyanotic	Aki (Sr Cystatin)		Chi square	P value
	Yes (N=14)	No (N=26)		
Acyanotic	6 (42.86%)	21 (80.77%)	5.962	0.031
Cyanotic	8 (57.14%)	5 (19.23%)		

Table 34: Comparison of between cyanotic or acyanotic CHD (Sr Creatinine) in the study population

Cyanotic Or Acyanotic	Aki (Sr Creatinine)		Chi square	P value
	Yes (N=9)	No (N=31)		
Acyanotic	4 (44.44%)	23 (74.19%)	2.814	0.120
Cyanotic	5 (55.56%)	8 (25.81%)		

The three tables compares the occurrence of Acute Kidney Injury (AKI) in patients with cyanotic and acyanotic congenital heart disease (CHD) using general AKI diagnosis, serum cystatin C, and serum creatinine as biomarkers. In all three tables, a higher proportion of cyanotic CHD cases is associated with AKI. The chi-square and p-values show varying levels of significance. The general AKI table shows a near-significant association ($p = 0.054$), indicating a trend towards higher AKI in cyanotic CHD. The cystatin C-based AKI table shows a statistically significant association ($p = 0.031$), suggesting that cyanotic CHD has a notable impact on AKI diagnosis using this biomarker. However, the creatinine-based AKI table does not show statistical significance ($p = 0.120$), implying that serum creatinine may not be as sensitive in detecting AKI differences between cyanotic and acyanotic CHD. These findings suggest that cyanotic CHD may contribute to a higher risk of AKI, particularly when assessed using cystatin C.

Figure 50: Cluster bar chart of comparison of AKI between cyanotic or acyanotic CHD in the study population

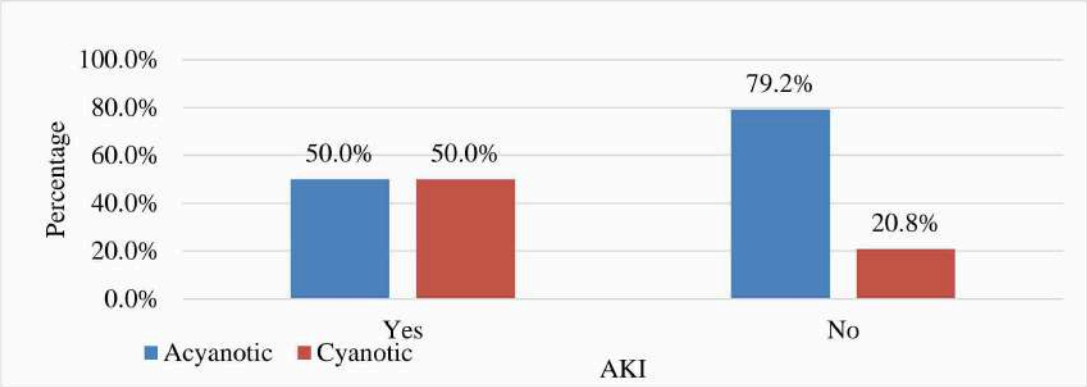


Figure 51: Cluster bar chart of comparison of AKI between cyanotic or acyanotic CHD (Sr cystatin C) in the study population

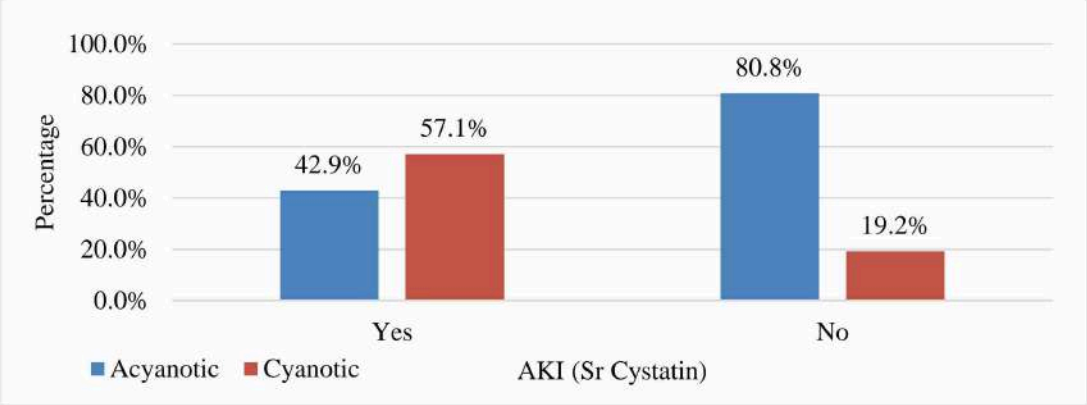


Figure 52: Cluster bar chart of comparison of AKI between cyanotic or acyanotic CHD (Sr Creatinine) in the study population

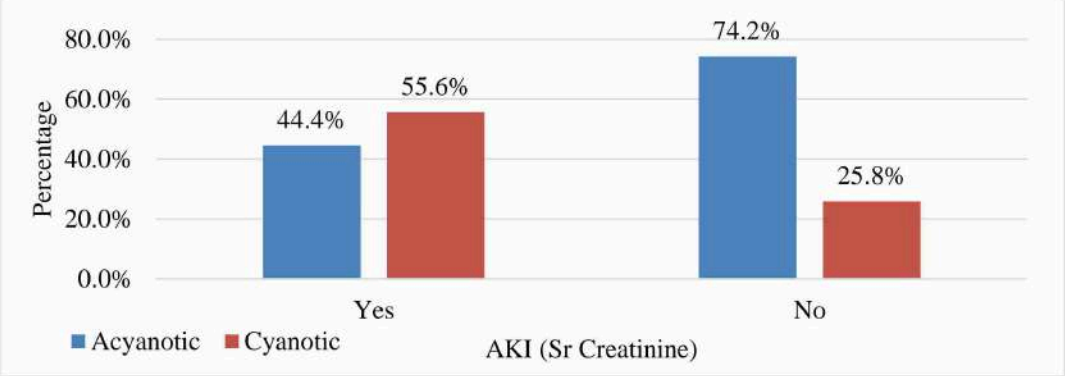


Table 35: Comparison of AKI among various CHDs in the study population

CHD	AKI		Chi square	P value
	Yes (N=16)	No (N=24)		
ASD	1 (6.25%)	4 (16.67%)	8.92	0.09
AVSD	0 (0%)	1 (4.17%)		
COA	1 (6.25%)	0 (0%)		
Complex CHD	3 (18.75%)	3 (12.5%)		
MS	0 (0%)	1 (4.17%)		
PDA	5 (31.25%)	7 (29.17%)		
Single Ventricle Physiology	2 (12.5%)	2 (8.33%)		
TAPVC	1 (6.25%)	1 (4.17%)		
TGA	0 (0%)	2 (8.33%)		
TOF	2 (12.5%)	0 (0%)		
VSD	1 (6.25%)	3 (12.5%)		

Table 36: Comparison of AKI among various CHDs (Sr cystatin) in the study population

CHD	AKI (Sr Cystatin)		Chi square	P value
	Yes (N=14)	No (N=26)		
ASD	1 (7.14%)	4 (15.38%)	9.01	0.0531
AVSD	0 (0%)	1 (3.85%)		
COA	1 (7.14%)	0 (0%)		
Complex CHD	2 (14.29%)	4 (15.38%)		
MS	0 (0%)	1 (3.85%)		
PDA	4 (28.57%)	8 (30.77%)		
Single Ventricle Physiology	2 (14.29%)	2 (7.69%)		
TAPVC	1 (7.14%)	1 (3.85%)		
TGA	0 (0%)	2 (7.69%)		
TOF	2 (14.29%)	0 (0%)		
VSD	1 (7.14%)	3 (11.54%)		

Table 37: Comparison of AKI among various CHDs (Sr Creatinine) in the study population

CHD	Aki (Sr Creatinine)		Chi square	P value
	Yes (N=9)	No (N=31)		
ASD	1 (11.11%)	4 (12.9%)	7.69	0.659
AVSD	0 (0%)	1 (3.23%)		
COA	1 (11.11%)	0 (0%)		
Complex CHD	1 (11.11%)	5 (16.13%)		
MS	0 (0%)	1 (3.23%)		
PDA	3 (33.33%)	9 (29.03%)		
Single Ventricle Physiology	1 (11.11%)	3 (9.68%)		
TAPVC	1 (11.11%)	1 (3.23%)		
TGA	0 (0%)	2 (6.45%)		
TOF	1 (11.11%)	1 (3.23%)		
VSD	0 (0%)	4 (12.9%)		

The three tables compare the incidence of Acute Kidney Injury (AKI) among different types of congenital heart diseases (CHDs) using general AKI diagnosis, serum cystatin C, and serum creatinine as biomarkers. Across all tables, complex CHD, single ventricle physiology, and Tetralogy of Fallot (TOF) appear to have

higher AKI occurrences. The chi-square and p-values indicate that the cystatin C-based AKI table ($p = 0.031$) shows a near-significant association, suggesting that some CHDs may have a stronger correlation with AKI when using this biomarker. The general AKI table trends similarly but lacks significance, while the creatinine-based AKI table has the highest p-value (0.689), implying the weakest association. Overall, these findings suggest that AKI occurrence varies among CHD types, with complex CHDs showing a higher prevalence, and that cystatin C may be a more sensitive marker for detecting AKI in this population.

Figure 53: Cluster bar chart of AKI among various CHDs in the study population

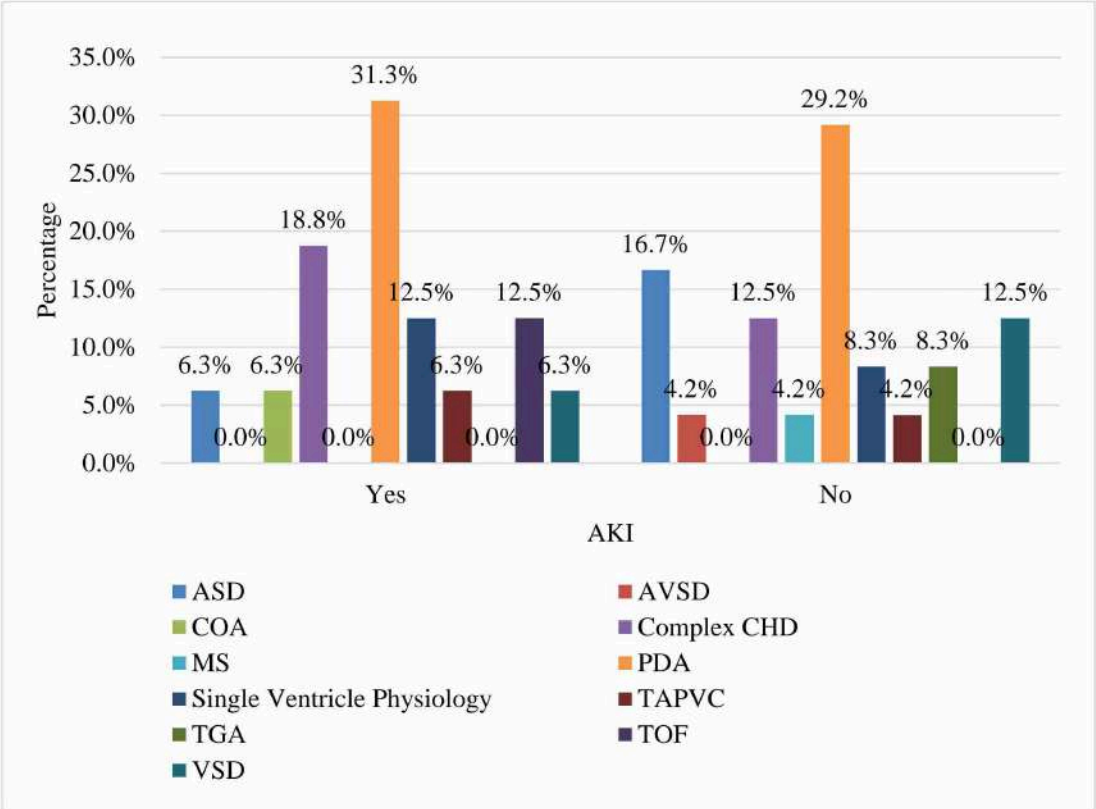


Figure 54: Cluster bar chart of AKI among various CHDs (Sr cystatin) in the study population

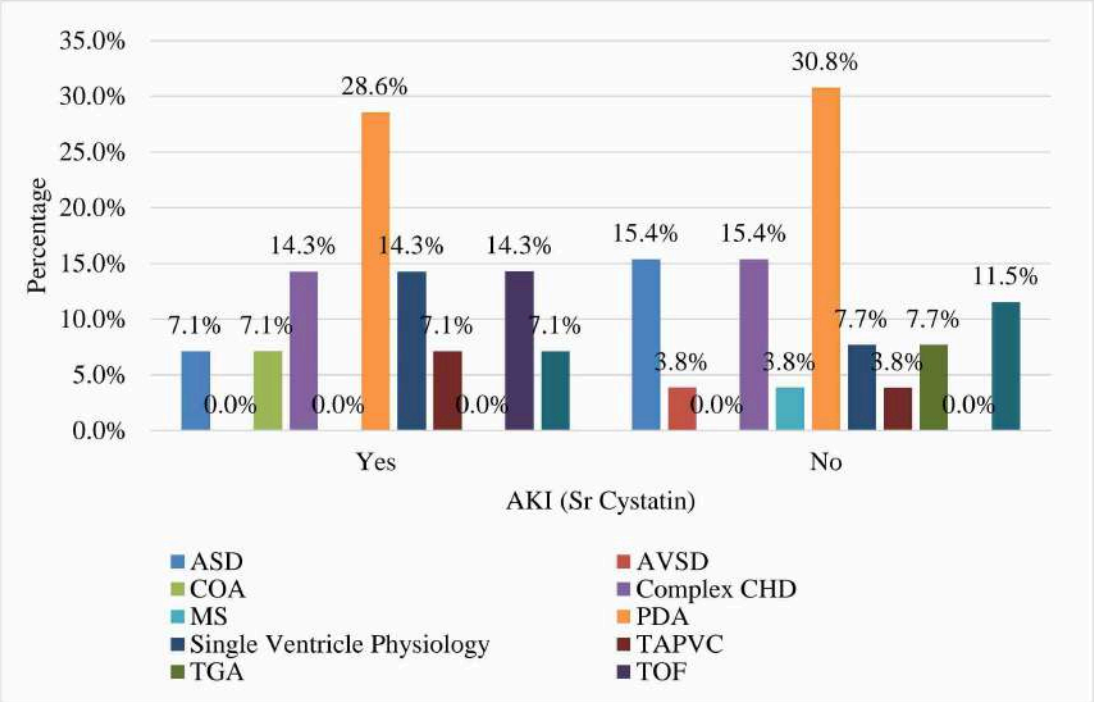


Figure 55: Cluster bar chart of AKI among various CHDs (Sr Creatinine) in the study population

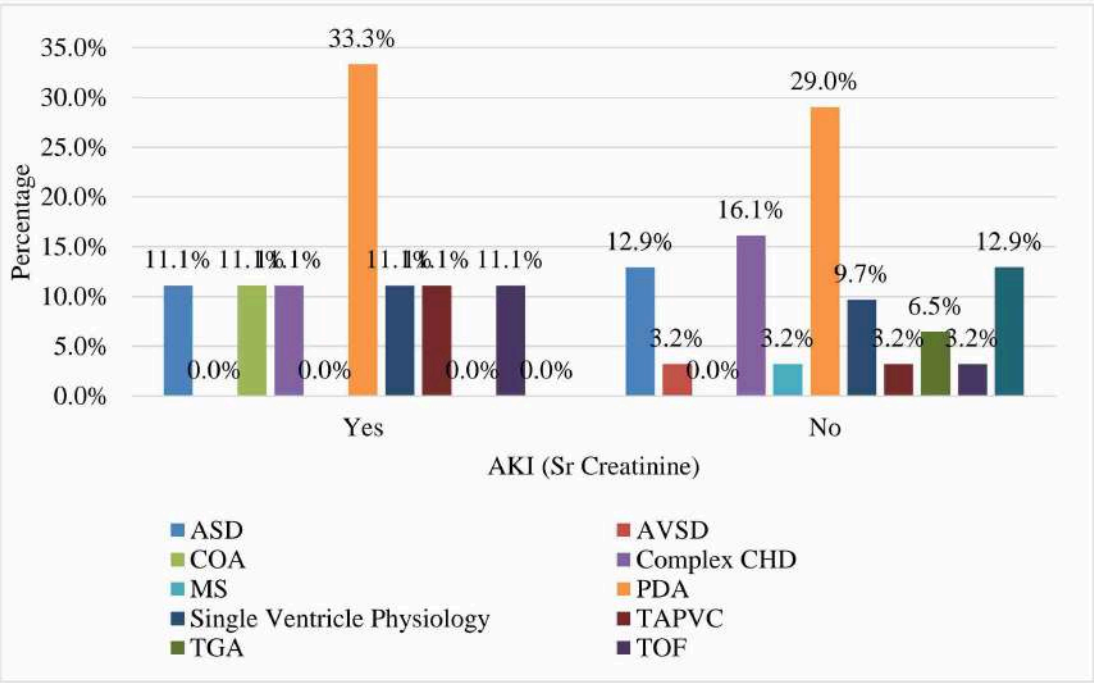


Table 38: Comparison of AKI due to various postnatal risk factors in the study population

Variables	AKI		Chi square	P value
	Yes (N=16)	No (N=24)		
Sepsis				
Yes	1 (6.25%)	4 (16.67%)	0.952	0.631
No	15 (93.75%)	20 (83.33%)		
Inotropes				
Yes	4 (25%)	2 (8.33%)	2.092	0.195
No	12 (75%)	22 (91.67%)		
Antibiotics				
Aminoglycoside	11 (68.75%)	16 (66.67%)	0.019	0.890
Meropenem	0 (0%)	3 (12.5%)	2.16	0.141
Fluconazole	2 (12.5%)	6 (25%)	0.938	0.439
NSAIDS				
Yes	3 (18.75%)	4 (16.67%)	0.029	1.000
No	13 (81.25%)	20 (83.33%)		
Caffeine Citrate				
Yes	2 (12.5%)	7 (29.17%)	1.529	0.272
No	14 (87.5%)	17 (70.83%)		

The table presents a comparison of acute kidney injury (AKI) occurrence in neonates based on various postnatal risk factors such as sepsis, inotrope use, antibiotic type, NSAID use, and caffeine citrate administration. The table includes statistical analyses with chi-square values and p-values to determine the significance of each factor's association with AKI. Notably, no factor shows a statistically significant association with AKI, as all p-values are greater than 0.05.

Figure 56: Cluster bar chart of comparison of AKI among septic and non-septic neonates in the study population

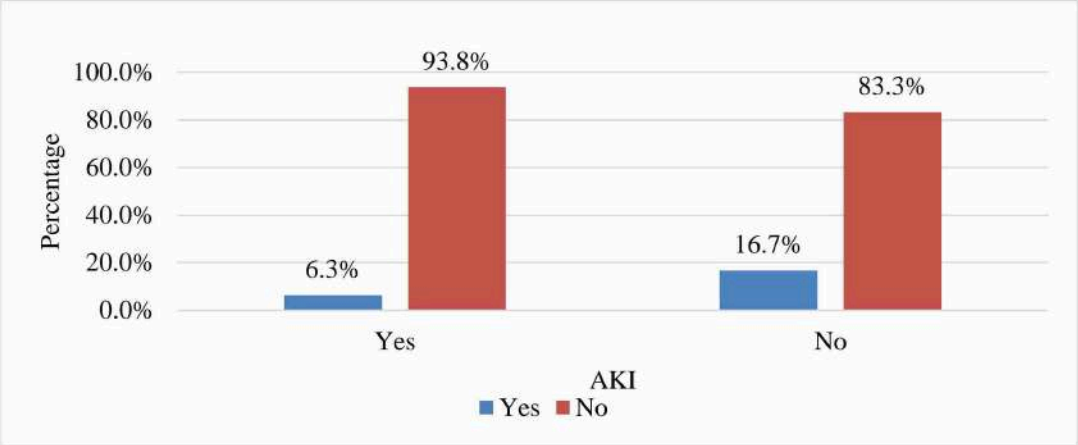


Figure 57: Cluster bar chart of comparison of AKI among neonates with and without inotropic support in the study population

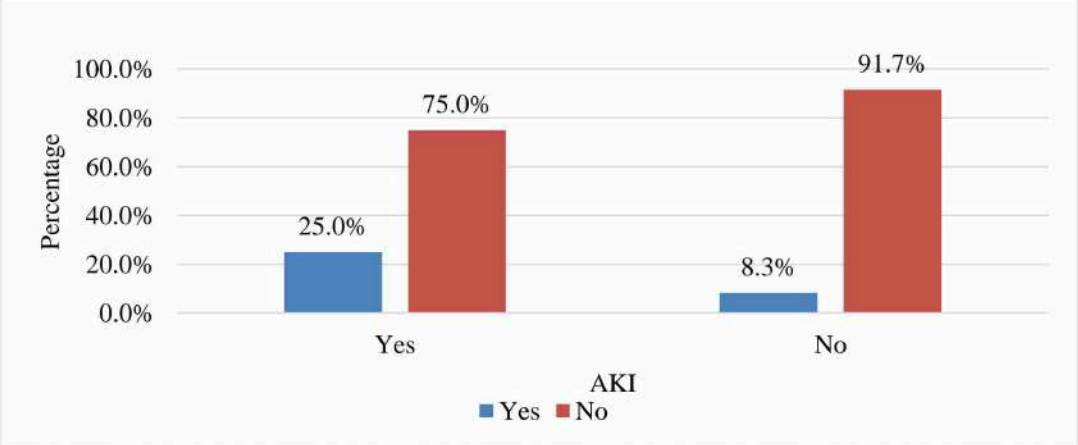


Figure 58: Cluster bar chart of comparison of AKI among various antibiotics in the study population

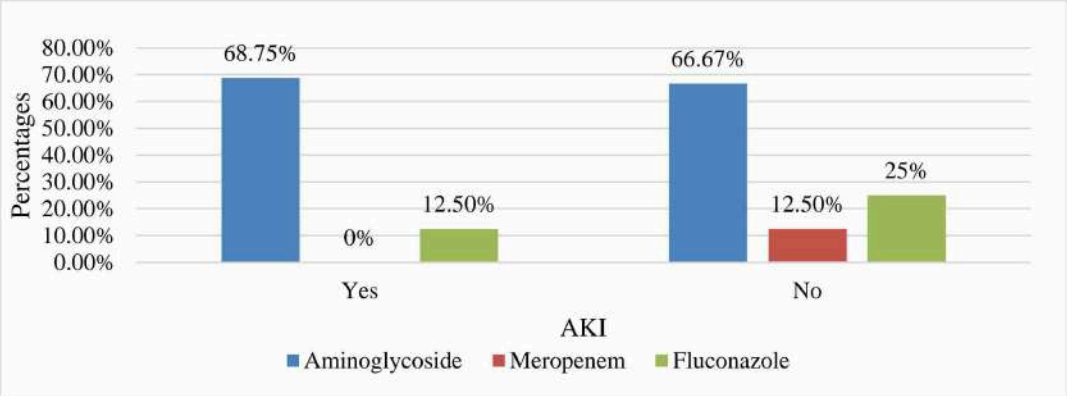


Figure 59: Cluster bar chart of comparison of AKI among neonates who received NSAIDs and neonates not receiving NSAIDs in the study population

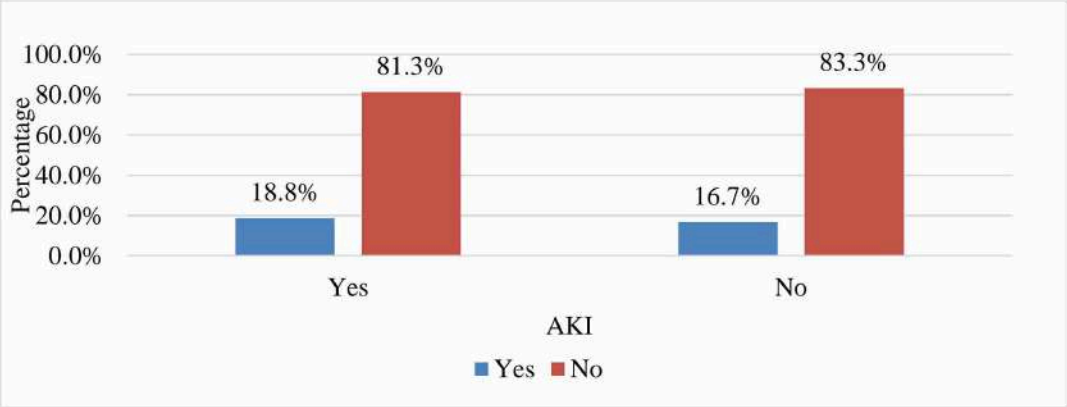


Figure 60: Cluster bar chart of comparison of AKI among neonates receiving caffeine citrate and neonates not receiving it in the study population

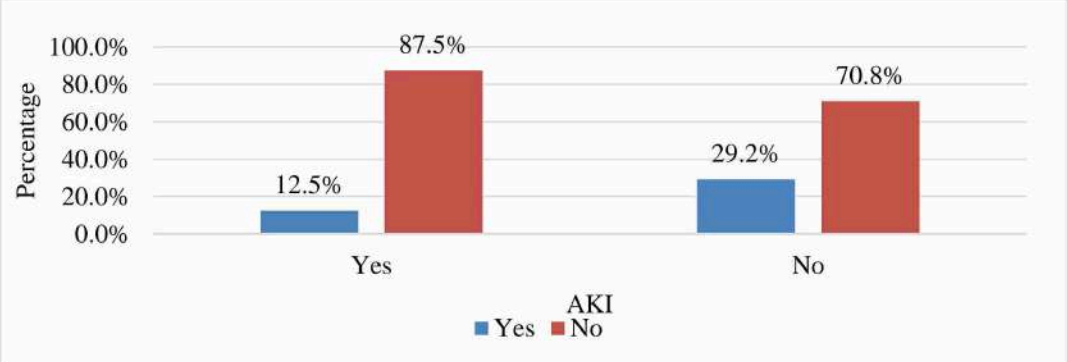


Table 39: Comparison of Oxygen Support between AKI in the study population

Variable	AKI		Chi square	Fisher exact P value
	Yes (N=16)	No (N=24)		
MV				
Yes	2 (12.5%)	3 (12.5%)	0.000	1.000
No	14 (87.5%)	21 (87.5%)		
CPAP				
Yes	3 (18.75%)	8 (33.33%)	1.024	0.473
No	13 (81.25%)	16 (66.67%)		
Nasal Prongs				
Yes	5 (31.25%)	2 (8.33%)	3.492	0.094
No	11 (68.75%)	22 (91.67%)		

Table 40: Comparison of Oxygen Support between AKI (Sr cystatin) in the study population

Variables	Aki (Sr Cystatin)		Chi square	Fisher exact P value
	Yes (N=14)	No (N=26)		
MV				
Yes	1 (7.14%)	4 (15.38%)	0.565	0.640
No	13 (92.86%)	22 (84.62%)		
CPAP				
Yes	2 (14.29%)	9 (34.62%)	1.886	0.270
No	12 (85.71%)	17 (65.38%)		
Nasal Prongs				
Yes	5 (35.71%)	2 (7.69%)	4.949	0.039
No	9 (64.29%)	24 (92.31%)		

Table 41: Comparison of Oxygen Support between AKI (Sr Creatinine) in the study population

Variables	Aki (Sr Creatinine)		Chi square	Fisher exact P value
	Yes (N=9)	No (N=31)		
MV				
Yes	1 (11.11%)	4 (12.9%)	0.020	1.000
No	8 (88.89%)	27 (87.1%)		
CPAP				
Yes	2 (22.22%)	9 (29.03%)	0.162	1.000
No	7 (77.78%)	22 (70.97%)		
Nasal Prongs				
Yes	3 (33.33%)	4 (12.9%)	2.016	0.316
No	6 (66.67%)	27 (87.1%)		

The three tables compare the association between different oxygen support methods (Mechanical Ventilation, CPAP, and Nasal Prongs) and Acute Kidney Injury (AKI) based on general criteria, Cystatin C levels, and Creatinine levels. In the first table (general AKI), none of the oxygen support methods showed a significant association with AKI, though Nasal Prongs had a higher chi-square value (3.492, p=0.094), suggesting a possible trend. The second table (AKI based on Cystatin C) revealed a statistically significant association between Nasal Prongs and AKI

(p=0.039), while MV and CPAP remained non-significant. In the third table (AKI based on Creatinine), none of the oxygen support methods demonstrated a significant relationship with AKI. Overall, while most comparisons indicate no strong correlation, the significant association between Nasal Prongs and AKI (Cystatin C-based).

Figure 61: Cluster bar chart of comparison of oxygen support among neonates with AKI and without AKI in the study population

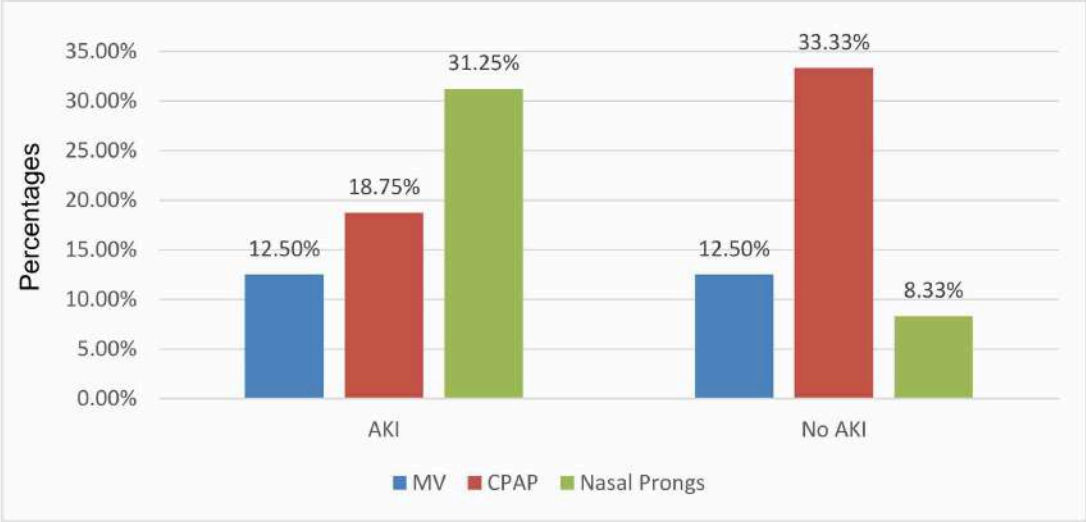


Figure 62: Cluster bar chart of comparison of oxygen support among neonates with AKI and without AKI (Sr Cystatin C) in the study population

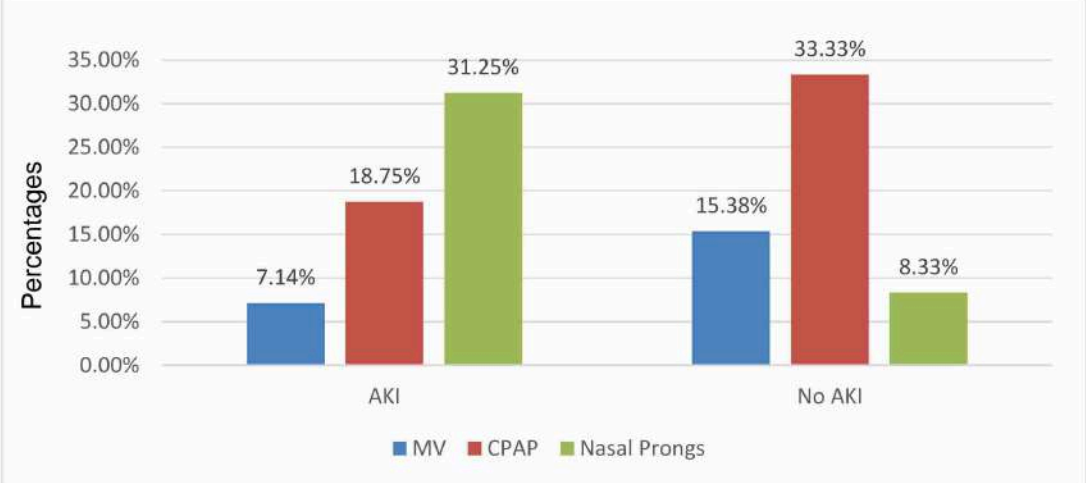


Figure 63: Cluster bar chart of comparison of oxygen support among neonates with AKI and without AKI (Sr Creatinine) in the study population

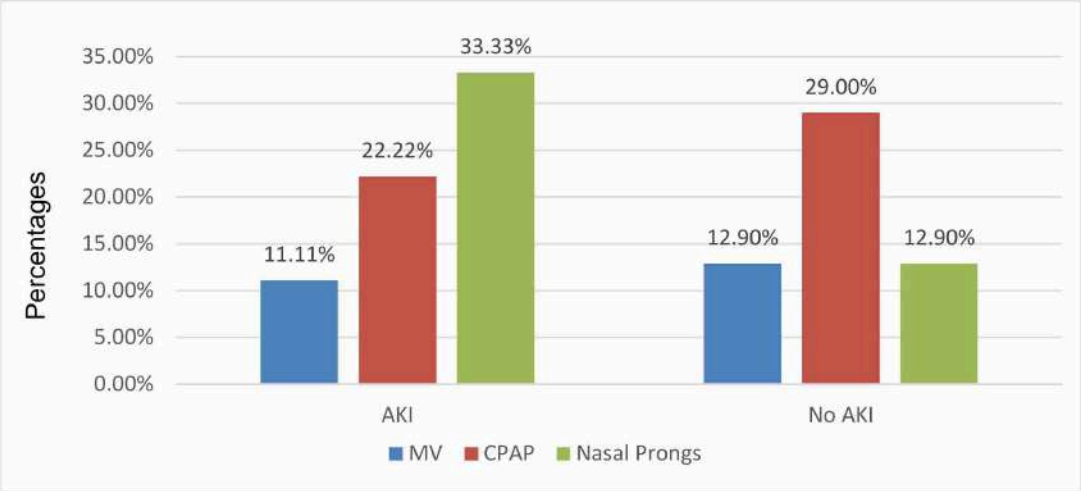


Table 42: Comparison of Outcomes among neonates with and without AKI in the study population

Outcome	AKI		Chi square	P value
	Yes (N=16)	No (N=24)		
Discharged	13 (81.25%)	23 (95.83%)	2.269	0.283
Expired	3 (18.75%)	1 (4.17%)		

Table 43: Comparison of Outcomes among neonates with and without AKI (Sr cystatin) in the study population

Outcome	AKI (Sr Cystatin)		Chi square	P value
	Yes (N=14)	No (N=26)		
Discharged	12 (85.71%)	24 (92.31%)	0.440	0.602
Expired	2 (14.29%)	2 (7.69%)		

Table 44: Comparison of Outcomes among neonates with and without AKI (Sr Creatinine) in the study population

Outcome	AKI (Sr Creatinine)		Chi square	P value
	Yes (N=9)	No (N=31)		
Discharged	6 (66.67%)	30 (96.77%)	7.025	0.030
Expired	3 (33.33%)	1 (3.23%)		

The above three tables compare neonatal outcomes (discharged vs. expired) among those with and without Acute Kidney Injury (AKI) based on general criteria, Serum Cystatin C levels, and Serum Creatinine levels. In the first table (general AKI), 18.75% of neonates with AKI expired compared to 4.17% without AKI, but this difference was not statistically significant (p=0.283). In the second table (AKI based on Cystatin C), the mortality rate was slightly lower (14.29% in AKI cases vs. 7.69% in non-AKI cases), but the difference remained statistically insignificant (p=0.602). However, in the third table (AKI based on Creatinine), the mortality rate was significantly higher in neonates with AKI (33.33% vs. 3.23% in non-AKI cases), with a statistically significant chi-square value of 7.025 and a p-value of 0.030. This suggests that AKI defined by Serum Creatinine levels may be more strongly associated with adverse neonatal outcomes compared to other definitions. Among the 4 expired neonates, 2 (50%)of them had stage-2 AKI, 1 had stage-1 AKI and there one did not have AKI.

Figure 64: Cluster bar chart of comparison of Outcomes among neonates with and without AKI in the study population

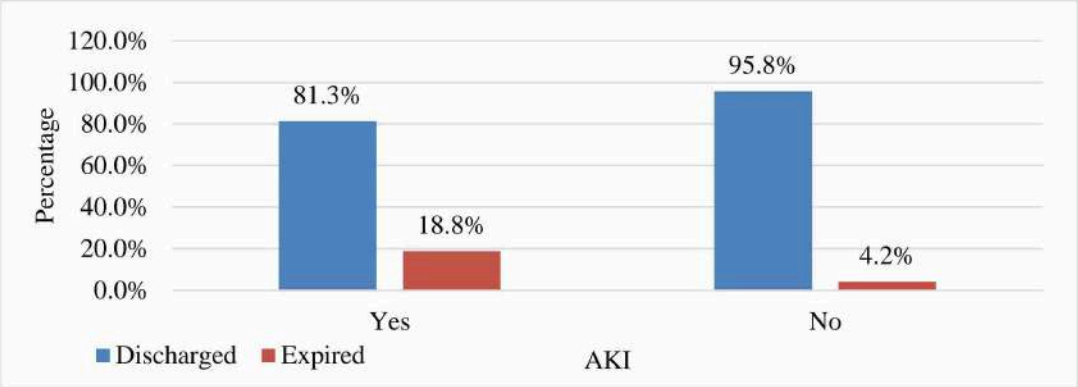


Figure 65: Cluster bar chart of comparison of Outcomes among neonates with and without AKI (Sr cystatin) in the study population

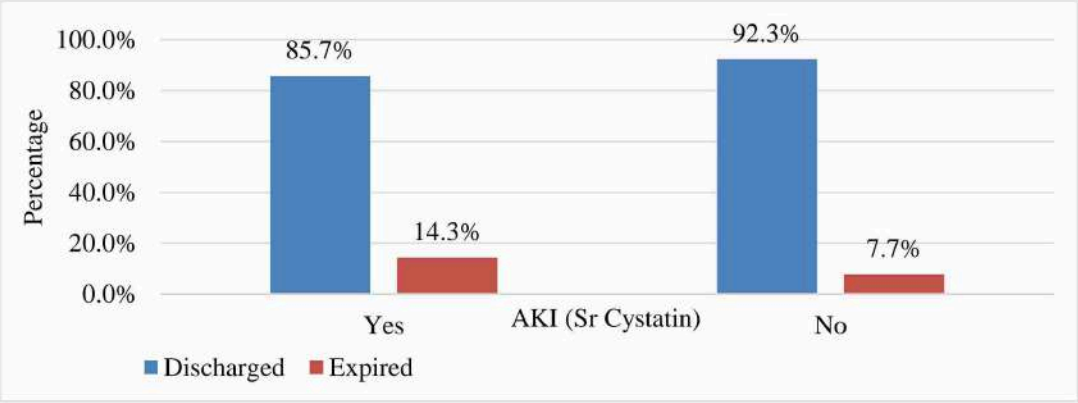
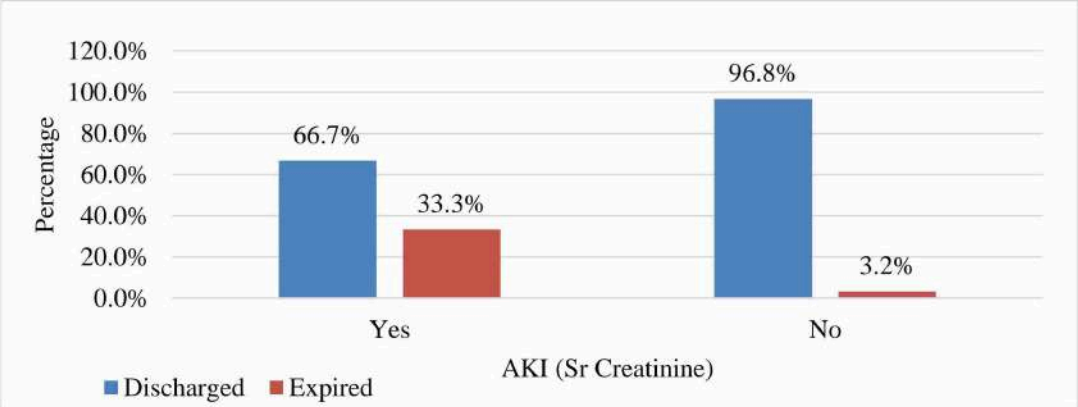


Figure 66: Cluster bar chart of comparison of Outcomes among neonates with and without AKI (Sr Creatinine) in the study population



DISCUSSION

Neonatal acute kidney injury (nAKI) is an understudied yet critical area in neonatal care, with evolving research highlighting its impact on morbidity and mortality. Despite advancements in neonatal intensive care, there remains a need for better diagnostic markers, early intervention strategies, and standardized management protocols to improve outcomes. Further research focusing on prevention, early detection, and targeted therapies is essential to enhance survival and long-term kidney health in neonates.

Our study was a cross sectional study conducted at KLES Prabhakar Kore Hospital and Research Centre from August 2023 to July 2024. Over one year, 40 neonates with congenital heart disease (CHD) in their first week of life, admitted to NICU, postnatal wards of the KLE'S Prabhakar Kore Charitable hospital were enrolled.

After obtaining the approval from ethical committee, written informed consent from each of neonate's parent/guardian were obtained. Detailed antenatal, natal and postnatal history, physical examination was done. Serum creatinine and serum cystatin C values were taken between day 4 of life to day 7 of life. Neonatal AKI was diagnosed using modified neonatal KDIGO guidelines[51].

In our study we compared serum Creatinine and serum Cystatin C in detecting early AKI and the incidence of early AKI in neonates with congenital heart disease was determined, the risk factors causing acute kidney injury in congenital heart disease neonates and the outcome was discussed.

In our study group, out of 40 neonates with CHD, **24 (60%) were male and 16 (40%) were female**, showing male predominance , which is similar to study done by Pugnaloni F et al.[159], and concluded that males have a greater risk of being born with severe CHD, while females are more prone to milder CHD subtypes. Contrary to this, study done by Azakie A et al.[160], showed no gender predominance for CHD.

The incidence of acute kidney injury (AKI) across gender groups in our study aligns with existing literature, showing a higher proportion of AKI cases among males than females across different biomarkers (Sr Cystatin and Sr Creatinine). The AWAKEN study[3] and study by Jetton et al.,[45] reported similar findings, noting that male neonates had a higher incidence of AKI than females, but the association did not reach statistical significance.

In the present study, the mean gestational age for the study population was 36 weeks with standard deviation of 3 weeks and median gestational age was 37 weeks with a range between 27 weeks and 42 weeks. The 95% confidence interval for the mean gestational age was between 34 and 37 weeks which indicates, study cohort primarily including late preterm neonates.

Similarly, mean birth weight for the study population was 2.29kg with standard deviation of 750gms and median gestational age was 2.35kg with a range between 780gmsand 4.2kgs. The 95% confidence interval for the mean gestational age was between 2kg and 2.5kg which indicates, study cohort primarily including low birth weight neonates.

The findings from our current study indicate a higher prevalence of AKI in neonates with lower birth weights, though the statistical significance is limited (as shown by the chi-square values and p-values). Viswanathan et al., [73]and Stojanovic et

al., [74] Carmody et al., [52,112] highlighted a similar pattern in very low birth weight (VLBW) infants, where AKI was commonly underreported despite its clinical significance. Their study found that AKI incidence in VLBW infants was around 40–50%, which is contrary to our study.

The AWAKEN study[3] reported a U-shaped pattern in AKI incidence across gestational age groups, with higher rates in both extremely preterm (48%) and term neonates (37%), while neonates born between 29–36 weeks had an AKI rate of 18%, which aligns with our current study, that term neonates are at higher risk of AKI.

Additionally, Carmody et al., [52,112] emphasized that very low birth weight (VLBW, <1500g) infants are particularly vulnerable to AKI, which is consistent with the higher AKI rates observed in the lower birth weight.

In our study, the AKI prevalence is distributed among gestational age groups, with a higher percentage among late preterm and term infants. However, the statistical significance varies, as seen in the p-values, showing marginally significant association ($p = 0.065$) for AKI based on cystatin C, which suggests cystatin C may be a more sensitive marker than creatinine[134,145].

In a study by Selewski et al.[33], term infants showed a high incidence of AKI, which aligns with our current study.

Several antenatal risk factors, such as IUGR, PROM, preeclampsia, oligohydramnios and birth asphyxia were known to increase the risk of AKI but it showed no statistical significance. IUGR alone had a positive correlation which was similar to the findings from AWAKEN study[3].

In our study group, pre-eclampsia had no significant p-value , showing no association with AKI, which is contrary to the study done by Lee et al.,[161] stating pre-eclampsia in preterm deliveries to be a protective factor for AKI. Studies by Mol et al.,[162] and Bilano et al.,[163] Asekenazi et al.,[57] and AWAKEN study[3]showed pre-eclampsia to cause AKI in preterm neonates, which doesn't align with our study group.

Similarly, in our study group, oligohydramnios and PPROM/PROM had no significant association with AKI, whose findings are similar to the AWAKEN study[3] but is contrary to the study done by Stojanovic et al.,[74] which states PPROM to be a major predictor of AKI.

Contrary to studies by Karlowicz MG et al.,[58] Alaro D et al.,[76] Selewski DT et al.,[77] Durkan A et al.,[79] Kaur S et al.,[80] , perinatal asphyxia showed no significant association with AKI.

In our study group, AKI was noted in 50% of both cyanotic and acyanotic CHD cases with a p-value of 0.054, suggesting borderline statistical significance. The incidence of AKI using serum Cystatin C showed a higher occurrence among cyanotic CHDs (57.14%) than acyanotic CHDs (42.86%) with a significant p-value of 0.031. Similarly the occurrence of AKI using serum creatinine showed higher occurrence among cyanotic (55.56%) compared to acyanotic CHDs (44.44%) , despite being statistically insignificant. The findings were similar to study done by Amornchaicharoensuk Y et al., [164] Zheng J et al.[165]

Patent ductus arteriosus (PDA) was the most frequent type of CHD (30%), followed by complex CHD (15%), atrial septal defect (ASD) (12.5%), and ventricular septal defect (VSD) (10%) observed in our study group. Although, PDA (31.25%)

and single ventricle physiology (21.43%) were associated with higher AKI rates, but the difference was with a borderline significant p-value of 0.0531 when serum Cystatin C was used a biomarker compared to serum creatinine which was statistically limited. The findings of our study, align with existing literature, which highlights that PDA is independently associated with AKI, as described by Radicioni M et al.,[96] Ronnie Guillet et al.,[98] and increased risk of AKI among extremely preterm neonates with PDA as described by study of Majed B et al.[100]

In our study group, the mean serum creatinine level was 0.89 ± 0.32 mg/dL, with a median value of 0.8 mg/dL, ranging from a minimum of 0.4 mg/dL to a maximum of 1.5 mg/dL. The 95% confidence interval (CI) for serum creatinine was between 0.8 mg/dL and 1.0 mg/dL. On the other hand, the mean serum cystatin C level was higher at 1.79 ± 0.5 mg/L, with a median of 1.7 mg/L and a wider range of 0.8 mg/L to 2.9 mg/L. The 95% CI for serum cystatin C lies between 1.6 mg/L and 2.0 mg/L.

Similarly in our study group, based on serum creatinine levels, AKI was identified in 22.5% of neonates, while 35% had AKI based on serum cystatin C levels. The overall incidence of AKI was 40%, indicating that serum cystatin C might be a more sensitive marker for detecting AKI compared to serum creatinine. The comparison of AKI identified by serum creatinine and serum cystatin C shows a significant association, with a chi-square value of 14.824 and a p-value of <0.001, suggesting that cystatin C may detect renal dysfunction earlier than creatinine. The above findings from our study group, align with the study done by Cho SY et al.,[9] Finney H et al.,[48] Bostom AG et al.,[134] Johan Lassus et al.,[155] Xin Xu et al.,[166] Yang et al.,[167] thus indicating that cystatin C-based diagnosis identifies a higher proportion of AKI cases and may allow earlier intervention, potentially improving neonatal

outcomes. Of the 9 neonates diagnosed with AKI based on serum creatinine using the modified neonatal KDIGO criteria, 4 were classified as having stage 1 AKI, while the other 5 had stage 2 AKI[51].

In our study group, sepsis was present in 12.5% of cases, while 87.5% did not have sepsis and was more common in neonates without AKI (16.67%) compared to those with AKI (6.25%), but the association was not statistically significant, which are contrary to the studies done by Munyendo et al.,[90] Holda et al.,[91] Deirdre U. Sweetman,[4] N.B. Mathur et al.,[86] and AWAKEN study[3].

Use of inotropes was seen in 15% of cases and was higher among AKI cases (25%) versus non-AKI cases (8.33%), but the difference was not significant ($p = 0.195$) which are conflicting to the Walker M et al., study [125].

Regarding antibiotics in our study group , aminoglycosides were the most frequently used (67.5%), followed by fluconazole (20%) and meropenem (7.5%), and no statistical significance was noted which goes against the Barhight, M et al.,[109] Murphy, H.J.,[110] Mohamed, T.H.,[111] Rhone et al.,[112] and Salerno S et al[114] studies

Similarly, use of NSAIDs was noted in 17.5% of cases and was slightly higher in AKI cases (18.75%), but not statistically significant ($p = 1.000$) which doesn't align with the Van der Heijden B et al.,[117] and Bensman A et al.,[101] studies.

Caffeine citrate was used in 22.5% of neonates and showed no statistical significance in the occurrence of AKI which is contrasting to the secondary analysis from AWAKEN study[119] and Carmody JB et al., study[120] which showed reduced prevalence of AKI among neonates.

In our study population, 12.5% underwent mechanical ventilation (MV), 27.5% received continuous positive airway pressure (CPAP), and 17.5% were supported with nasal prongs. A significant association was found between nasal prong usage and acute kidney injury (AKI) when defined by elevated cystatin C level (p=0.039), while MV and CPAP did not show significant associations with AKI which is opposite to the finding by Walker M et al., study[125] and Kraus AC et al., study[141].

In our study group, an overall neonatal mortality rate of 10% was reported, with a higher mortality rate of 33.33% among neonates diagnosed with acute kidney injury (AKI) based on serum creatinine levels. These finding aligns with several studies highlighting the significant impact of AKI on neonatal outcomes including AWAKEN study[3] with affected infants experiencing a higher mortality rate (9.7%) compared to those without AKI (1.4%).

These studies consistently demonstrate that neonatal AKI is associated with increased mortality rates, underscoring the critical need for early identification and management of AKI in neonatal intensive care settings.

LIMITATIONS

Despite several strengths, the study has certain limitations:

- The study largely relied on serum biomarkers such as serum creatinine , serum cystatin C and urine output was not considered in view of limited availability of neonatal catheters and risk of sepsis involved in the process of securing the catheter.
- A larger sample size would have helped in better understating of risk factors and early detection of AKI.
- In this study, the role of Confounding factors on the development and prognosis of the AKI were not studied. Also matching, stratification, adjusted analysis occur less meaningful with the small sample size.

CONCLUSION

Serum Cystatin-C was able to detect AKI earlier than serum Creatinine in around 35 to 40% of our study population.

Early detection of Congenital Heart Disease within 48 to 72 hours of life, helps to recognise AKI and other complications including the duration of hospital stay, duration of mechanical ventilation, inotropes and to take adequate care to prevent progression.

Neonates being a vulnerable group of population with several risk factors, the probability of blood and urinary biomarkers to detect AKI in the early period is an invaluable tool.

SUMMARY

The study was conducted over one year from August 2023 till July 2024 at KLEs Dr Prabhakar Kore Charitable Hospital .All the samples of neonates with echocardiologically confirmed congenital heart disease in their first week of postnatal life was collected from NICU and postnatal wards.

Results were recorded in tabular and graphical forms Mean , Median , SD and ranges were accounted for quantitative data. Chi square analysis was useful in testing for major differences between proportions and frequencies. T test was useful in testing for major differences between two means. The confidence interval was set to be at ninety five % limit, with level of significance to be at $p < 0.05$.

The study included 40 neonates from whom blood sample was taken for serum creatinine and serum cystatin-C values and detailed history was evaluated.

Neonatal AKI was diagnosed using modified neonatal KDIGO guidelines.

- The mean gestational age for the study population was 36 weeks with standard deviation of 3 weeks and most of the neonates were term.
- Among the subjects, **24 (60%) were male and 16 (40%) were female**, showing male predominance.
- Among the subjects, 14 were diagnosed to have CHD antenatally (35%). 27 neonates, had Acyanotic CHD (67.5%) while 13 neonates had Cyanotic CHD (32.5%).
- PDA was the most common CHD found among the neonates (30%), followed by complex CHD (15%) and ASD (12.5%).

- In the study group, AKI diagnosed using serum cystatin had a highly significant p-value (<0.001) indicating that serum cystatin could serve as a reliable marker for early AKI diagnosis compared to creatinine.

- In our study group, PPROM, IUGR was noted in 18.75% and 25% of neonates with AKI despite being statistically insignificant.

- In the study group, among the 9 neonates diagnosed with AKI based on serum creatinine using the modified neonatal KDIGO criteria, 4 had stage-1 AKI with a mortality of 25%, while the remaining 5 were classified as stage-2 AKI which had a mortality of 40%.

- The cystatin C-based AKI table shows a statistically significant association (p = 0.031), suggesting that cyanotic CHD has a positive association with AKI.

- In our study group, despite caffeine citrate being largely used, it did not show any negative with AKI.

- The mortality rate was significantly higher in neonates with AKI (33.33% vs. 3.23% in non-AKI cases), with a statistically significant chi-square value of 7.025 and a p-value of 0.030, suggesting AKI defined by serum Creatinine can be more strongly associated with adverse neonatal outcomes.

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ANNEXURES

ANNEXURE – I - INFORMED CONSENT FORM

"THE INCIDENCE OF ACUTE KIDNEY INJURY IN NEONATES WITH CONGENITAL HEART DISEASE IN A TERTIARY CARE HOSPITAL OVER A PERIOD OF ONE YEAR"

Name of Student/Principal Investigator: _____

Name of Guide/Co Investigators: _____

Introduction: you are being invited to participate in this study to find out the incidence of acute kidney injury in neonates with congenital heart disease using serum creatinine and serum cystatin c. Your kind consent and cooperation is required for participating in this study,

Explanation of procedure: neonates with congenital heart disease born/admitted in NICU of Prabhakar Kore hospital are enrolled in the study. Detailed antenatal, natal and postnatal history will be taken and urine output and baseline serum creatinine values are taken. Following which serum cystatin C and serum creatinine values are taken on day 6 15 to 7 day) Samples for serum creatinine and serum cystatin C are collected in a plain tube, Jini venous blood and processed

Withdrawal from participation in the study: Participation in this study in voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will not get any benefits hy participating in this study. The data gathered will help population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study

Privacy and confidentiality: The information collected from you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Cost of investigations done during the course of study will be paid by the principal investigator/Participant.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups.

However, your identity will never be revealed.

Questions: If you have any question or complaints with regard to your right as study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights

CONSENT STATEMENT

I am making a voluntary decision to participate in the study "the incidence of acute kidney injury in neonates with congenital heart disease in a tertiary care hospital over a period of one year". My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE II-PROFORMA

TITLE OF THE STUDY: INCIDENCE OF ACUTE KIDNEY INJURY IN NEONATES WITH CONGENITAL HEART DISEASE IN A TERTIARY CARE CENTER OVER A PERIOD OF 1 YEAR

NAME: **AGE/GENDER:** **IP/OP NO.:**

MOTHER'S NAME:

FATHER'S NAME:

DIAGNOSIS:

MODE OF DELIVERY: NVD/ LSCS

GESTATIONAL AGE:

TERM/PRETERM

ANTENATAL SCANS:

NATAL HISTORY:

POSTNATAL HISTORY:

CHD: CYANOTIC/ ACYANOTIC

INVESTIGATIONS:

	SERUM CREATININE	**CYSTATIN-C**
BASELINE		
DAY 4 TO 7 OF ADMISSION		

VITALS:

GENERAL EXAMINATION-

SYSTEMIC EXAMINATION-

TREATMENT GIVEN-

OUTCOME-

ANNEXURE III-MASTER CHART

Sample number	Name of the baby	Day of life	Gender	Classification based on weight	Birth Weight	Mode of Delivery	Term/ Preterm	Gestational age	Antental Scans	Postnatal Period	Mother Diagnosis					Cyanotic or Acyanotic	CHD	CHD simplified	Sr Creatinine(mg/dl)	AKI (Creatnine	AKI stage	Sr. Cys C (mg/l)	AKI (Cystatin C	Other risk factors	AKI	IP Number	Sepsis	NICU stay	SGA/AGA/LGA	Inotropes	Antibiotics			NSAIDs	Oxygen support			Caffeine citrate	Decongestives	Others		Outcome
											Obstetric Score	IUGR	Pre-eclampsia	Oligohydraminios	PPROM/PROM															AMINOGLYCOSIDE	MEROPENEM	FLUCONAZOLE		MV	CPAP	Nasal prongs			Surfactant	Prostaglandin	
1	Bo Divya Sushanth Patil	Day 5	Male	LBW (low birth weight)	2200gm	LSCS	Term	39w 3d	Normal	Cried immediately after birth	Primi	No	No	Yes	Yes	Acyanotic	Large Perimembranous VSD	VSD	0.46	No		1.63	No		No	1207144	Yes	No	SGA	No	No	No	No	No	No	No	-	No	No	No	No	
2	Bo Fouziya Banu Mohammed Waseem Jamad	Day 6	Male	VLBW (very low birth weight)	1180gm	LSCS	Early Preterm	28w4d	Normal	cried after 1 cycle of BMV	G3P2L2	No	No	No	Yes	Acyanotic	Large PDA	PDA	1.46/0.96/1.5	Yes	Stage 2	0.83	No	PPROM	yes/No	10009612	Yes	Yes	AGA	Yes (adrenaline, dobutamine)	Yes	No	Yes	Yes (PCT)	Yes	No	-	Yes	No	Yes	No	Expired
3	Bo Girija Anand Adaki	Day 5	Female	Normal	2700gm	LSCS	Term	38w6d	Normal	Cried immediately after birth	G2A1	No	No	No	No	Acyanotic	Large Fossa Ovalis ASD	ASD	0.51	No		1.43	No	PPROM	No	10012456	No	Yes	AGA	No	Yes	No	No	No	No	Yes	-	No	No	No	No	
4	Bo Bhakti Sanjeev Alarwad	Day 4	Male	Normal	2700gm	LSCS	Late Preterm	36w6d	Normal	Cried immediately after birth	Primi	No	No	No	Yes	Acyanotic	Large Fossa Ovalis ASD with large PDA with PAH	Complex CHD	0.82/0.92/1.23	No		1.71	No		Borderline/No	10012163	No	Yes	AGA	No	Yes	No	No	No	No	Yes	-	No	No	No	No	
5	Bo Soniya Pramod Bastawadkar	Day 5	Male	LBW	2000gm	LSCS	Term	37w	Normal	Cried immediately after birth	G4P3L3	Yes	No	No	No	Acyanotic	PFO with small PDA with mild TR	PDA	1.15	No		1.31	No	Hypoglycemia	No	10012932	No	Yes	SGA	No	No	No	No	No	No	No	-	No	No	No	No	
6	Bo Haseenabanu Mahamadeliyas	Day 6	Male	LBW	2300gm	NVD	Late Preterm	35w	Normal	Cried immediately after birth	G3P1L1A1	No	No	No	No	Acyanotic	Perimembranous VSD	VSD	0.60/0.78	No		1.84	No		No	10012516	No	Yes	AGA	Yes (dobutamine)	Yes	No	No	No	No	Yes	-	No	Yes	No	No	
7	Bo Laxmi Gaddi	Day 5	Female	Normal	2900gm	NVD	Term	39w 4d	Normal	Cried immediately after birth	G3P1L1A1	No	No	No	No	Cyanotic	Large Perimembranous VSD with R to L shunt with Pulmonary Atresia with RVH	TOF	0.74	No		1.92	AKI		No/AKI	10021961	No	Yes	AGA	Yes (dobutamine, dopamine)	Yes	No	No	No	No	No	Yes	No	Yes	No	No	
8	Bo Lalita Mallappa Rotti	Day 4	Female	LBW	1800gm	LSCS	Late Preterm	36w	T2-slight discrepency in size of heart(R>L), aorta relatively of same size/ T3 Stage 1 FGR	Cried immediately after birth	G2A1	Yes	No	No	No	Cyanotic	Large PDA with bidirectional shunt with large ASD with COA with moderate to severe PAH	COA	1.38	AKI	Stage 2	2.39	AKI		AKI	10025234	No	Yes	SGA	No	No	No	No	No	No	No	-	No	Yes	No	No	

9	Bo Saniya Tippu Hubli	Day 4	Male	LBW	2100gm	LSCS	Late Preterm	36w	Normal	Cried immediately after birth	G3P1L1A1	No	Yes	No	No	Cyanotic	VSD with pulmonary atresia with PDA	Complex CHD	1.23/1.09	AKI	Stage 1	2.24	AKI		AKI	10028981	No	Yes	SGA	No	Yes	No	No	No	No	No	-	No	Yes	No	Yes	Expired
10	Bo Asha Basavaraj	Day 6	Male	Normal	2600gm	NVD	Term	37w3d	Normal	Cried immediately after birth	G2A1	Yes	No	No	No	Acyanotic	Large Anterior Muscular VSD with PDA with moderate PAH	Complex CHD	1.02/0.85	No		1.72	No	Hypoglycemia	No	10036253	No	Yes	AGA	No	Yes	Yes	No	No	No	Yes	-	No	Yes	No	No	
11	Bo Jayasree Malanagouda Tuppad	Day 4	Female	Macrosomia	4200gm	LSCS	Term	37w4d	T2-dextrocardia/single atria and ventricle status	Cried immediately after birth	G3P2L1D1	No	No	No	No	Cyanotic	Complex CHD-Dextrocardia/Univentricular physiology with Pulmonary Stenosis/Large PDA	Single Ventricle Physiology	0.88	No		2.03	AKI		No/AKI	10039813	No	Yes	LGA	No	Yes	No	No	No	No	No	Yes	No	No	No	Yes	
12	Bo Shilpa Umesh Nadugeri	Day 5	Male	LBW	2900gm	LSCS	Term	37w2d	T2-increased nuchal fold thickness,scalp edema, increased prenasal thickness T3-fetal aascites, scalp edema, flat facies, prominent third ventricle	cried after 1 cycle of BMV	Primigravida	No	No	No	No	Acyanotic	Moderate sized ASD/dilated RA/RV/moderate TR/moderate PAH	ASD	0.68/0.58	No		1.58	No	Syndromic	No	10043855	No	Yes	AGA	No	No	No	No	No	No	No	Yes	No	No	No	No	
13	Bo Renuka Mahesh Nandanwada	Day 6	Male	LBW	2400gm	LSCS	Term	41w5d	Normal	Cried immediately after birth	G2P1L1/Post-dated pregnancy	No	No	No	No	Cyanotic	TOF with large ostium secundum ASD	TOF	1.45/0.86	AKI	Stage 2	2.5	AKI		AKI	10059850	No	Yes	SGA	No	Yes	No	No	No	No	No	Yes	No	No	No	Yes	Expired
14	Bo Laxmi Lagamappa Naik	Day 6	Male	LBW	1740gm	LSCS	Early Preterm	32w	Normal	Cried immediately after birth	G2P1L1	No	No	No	Yes	Acyanotic	Moderate sized PDA	PDA	0.62/0.85	No		1.45	No	Surfactant given	No	10057309	No	Yes	AGA	No	Yes	No	No	No	Yes	No	-	Yes	No	Yes	No	
15	Bo Shilpa Parasharam Kumbhar	Day 6	Female	ELBW (extremely low birth weight)	780gm	LSCS	Early Preterm	31w1d	Normal	weak cry at birth	G2P1L1	No	Yes	Yes	No	Acyanotic	Moderate sized ASD/Mild RV Dilatation	ASD	0.64/0.84/1.46	No		1.07	No		No	10052951	Yes	Yes	SGA	No	Yes	Yes	Yes	No	No	Yes	-	Yes	No	No	No	
16	Bo Reema Anil Chauhan	Day 5	Female	VLBW	1080gm	LSCS	Extremely Preterm	27w4d	Normal	cried after 2 cycles of BMV	G4P1D1A1E1	No	No	No	Yes	Acyanotic	Large PDA with severely dilated LA/LV	PDA	1.02/1/1.14	No		2.84	AKI	MV/Surfactant	No/AKI	10053566	No	Yes	AGA	No	Yes	No	Yes	Yes (Ibuprofen)	Yes	No	-	Yes	No	No	No	
17	Bo Durgavva Talawar	Day 7	Female	LBW	2100gm	LSCS	Term	37w	Normal	Cried immediately after birth	G3A2	No	No	No	No	Cyanotic	Complex CHD-PDA/Pulmonary Stenosis/Large ASD/Cardiomegaly with Hypoplastic RV/Double SVC	Single Ventricle Physiology	0.6	No		1.71	No	single umbilical artery/tethered cord	No	10062611	No	Yes	SGA	No	Yes	No	No	No	No	No	-	No	Yes	No	Yes	

18	Bo Sakshi Sanket Sansuddi	Day 7	Male	LBW	1800gm	LSCS	Term	37w4d	Normal	Cried immediately after birth	Primi	No	No	No	No	Acyanotic	Large PDA with dilated LA/LV with severe PPHN	PDA	0.76	No		1.44	No		No	10064457	Yes	Yes	SGA	No	Yes	No	Yes	No	No	No	-	No	No	No	No	
19	Bo Tangevva Dyamanni Gorav.	Day 5	Male	LBW	1970gm	NVD	Late Preterm	36w6d	Normal	Cried immediately after birth	G3P2L2	Yes	No	No	No	Acyanotic	Large Perimembranous VSD/moderate sized fossa ovalis ASD/hyperkinetic PAH	AVSD	0.37	No		0.76	No		No	10027454	No	No	SGA	No	No	No	No	No	No	No	-	No	Yes	No	No	
20	Bo Deepa Laxmikant Kuri	Day 4	Male	Normal	2570gm	LSCS	Late Preterm	35w1d	T2- echogenic foci in right ventricle of heart, mild diffuse sub chorionic hemorrhage	Cried immediately after birth	G7P4L2D2A2	No	No	No	No	Acyanotic	Large Fossa Ovalis ASD	ASD	0.73	No		1.86	No		No	10067390	No	No	AGA	No	No	No	No	No	No	No	-	No	No	No	No	
21	Bo Laxmi Mahadev Sutar	Day 7	Male	Normal	2800gm	NVD	Term	40w	T2- bilateral chorid plexus cyst/T3- normal	Cried immediately after birth	G2P1L1	No	No	No	No	Acyanotic	Large Perimembranous VSD with L to R shunt with mild pulmonary atresia with mild overriding of aorta	VSD	0.49	No		2.02	AKI		No/AKI	10065917	No	No	SGA	No	No	No	No	No	No	No	-	No	No	No	No	
22	Bo Rasikava Mallapa	Day 5	Male	Normal	2700gm	LSCS	Term	38w4d	Normal	Cried immediately after birth	Primi	No	No	No	No	Acyanotic	Moderate sized PDA	PDA	0.76	No		2.94	AKI		No/AKI	10066956	No	No	AGA	No	No	No	No	No	No	No	-	No	No	No	No	
23	Bo Pooja Sagar Gurav	Day 6	Female	LBW	1820gm	LSCS	Late Preterm	34w	T2- bilateral ventricles prominent with cleft lip	cried after 2 cycles of BMV	G2P1D1/Placenta previa/ early onset FGR/	Yes	No	No	No	Acyanotic	Large PDA with left to right shunt/ moderate LVH	PDA	0.69/1.12	AKI	Stage 2	2.29	AKI		AKI	10072603	No	Yes	AGA	Yes (dobutamine)	Yes	No	No	No	No	Yes	-	No	Yes	No	No	
24	Bo Anushree Suresh	Day 7	Male	VLBW	1080gm	LSCS	Early Preterm	29w1d	Normal	weak cry at birth	G2P1L1	No	No	Yes	Yes	Acyanotic	Large PDA/left to right shunt/dilated LA	PDA	0.92/0.79	No		1.64	No		No	10073065	No	Yes	AGA	No	Yes	No	Yes	Yes (PCT)	No	Yes	-	Yes	No	No	No	
25	Bo Dundavva Annayya Hiremath	Day 4	Male	LBW	2460gm	LSCS	Term	38w1d	T2- echogenic foci in left ventricle, persistent blaker pouch cyst, megacisterna magna/ T3- persistent blaker pouch cyst, megacisterna magna	Cried after stimulation	G3P1L1A1	No	No	No	No	Acyanotic	Large PDA/left to right shunt/Severe PAH	PDA	0.89/1.08	AKI	Stage 1	1.93	AKI	Hydrocephalus	AKI	10077286	No	Yes	SGA	No	Yes	No	No	Yes (PCT)	No	No	-	No	No	No	No	

26	Bo Akshata Chaitanya Budni	Day 7	Male	Normal	2500gm	LSCS	Term	38w1d	Normal	Cried immediately after birth	G2P1L1	No	No	No	No	Cyanotic	Pulmonary atresia/Small PDA/Hypoplastic right ventricular	Single Ventricle Physiology	0.52	No		1.83	No		No	10078104	No	Yes	SGA	No	Yes	No	No	No	No	No	Yes	No	No	No	Yes	Expired
27	Bo Rekha Santosh Patil twin 2	Day 4	Female	Normal	3400gm	LSCS	Term	37w4d	T2- twin A- no anomaly, twin B- hydrocephalus, B/L cleft lip and cleft palate	Cried immediately after birth	G2P1L1	No	No	No	No	Acyanotic	Small Mid muscular VSD	VSD	0.91	No		1.7	No	Toxoplasma IgM.IgG+/ cleft lip &palate hydrocephalus	No	10078709	No	Yes	AGA	No	No	No	No	No	No	No	-	No	No	No	No	
28	Bo Laxmi Gangappa	Day 5	Female	Normal	3700gm	NVD	Term	40w4d	Normal	Cried immediately after birth	G3P1LA1	No	No	No	No	Cyanotic	Total Anamolous Pulmonary Venous Connection with ASD with PAH with dilated RA and RV	TAPVC	0.75	No		1.85	No		No	10082741	No	Yes	AGA	No	Yes	No	No	No	No	No	-	No	No	No	No	
29	Bo Shobha Irappa	Day 5	Male	LBW	2300gm	LSCS	Term	37w2d	Normal	weak cry at birth	G2A1	Yes	No	No	No	Cyanotic	Total Anamolous Pulmonary Venous Connection/ large ASD/mild PAH	TAPVC	0.87/1.2	AKI	Stage 2	2.27	AKI		AKI	10089122	No	Yes	SGA	No	Yes	No	No	No	No	Yes	-	No	No	No	No	
30	BO Arati Sidharth Kalkambhar	Day 5	Male	VLBW	1300gm	LSCS	Early Preterm	29w3d	Normal	Cried immediately after birth	Primi	No	No	No	Yes	Acyanotic	Moderate sized PDA	PDA	0.88	No		1.6	No		No	10090921	No	Yes	AGA	No	Yes	No	Yes	No	No	Yes	-	Yes	No	No	No	
31	Bo Mariya Arbaz Nalband	Day 4	Male	VLBW	1220gm	LSCS	Early Preterm	30w4d	Normal	Cried immediately after birth	G3P2L2	No	Yes	No	No	Acyanotic	Large PDA with left to right shunt with PAH	PDA	1.02/1.04	No		1.64	No		No	10093504	No	Yes	AGA	No	Yes	No	Yes	Yes (PCT)	Yes	No	-	Yes	No	Yes	No	
32	Bo Aishwarya Itagi	Day 7	Female	Normal	3000gm	LSCS	Early Preterm	36w	T2- hypoplastic RA with mitral valve stenosis	Cried immediately after birth	Primi	No	No	No	No	Acyanotic	severe congenital Mitral Stenosis	MS	0.41/0.52/0.37	No		1.58	No		No	10096308	No	Yes	AGA	Yes (dobutamine)	No	No	No	No	No	Yes	-	No	Yes	No	No	
33	Bo Bhagyashree Basappa Chalavadi	Day 5	Male	LBW	2400gm	LSCS	Term	38w5d	T2- TOF	Cried immediately after birth	Primi	No	No	No	No	Cyanotic	Large Perimembranous VSD with bidirectional shunt with small PDA with left to right shunt with severe PAH	Complex CHD	0.56	No		1.99	AKI		No/AKI	10101215	No	Yes	SGA	No	No	No	No	No	No	No	-	No	No	No	No	

34	Bo Safiya Jamadar.	Day 7	Female	VLBW	1250gm	LSCS	Early Preterm	28w	Normal	cried after 1 cycle of BMV	Primi	No	No	No	Yes	Acyanotic	Large Fossa Ovalis ASD with large PDA with PAH	Complex CHD	0.73/0.78/0.55	No		1.22	No		No	10084005	Yes	Yes	AGA	No	Yes	Yes	Yes	Yes (PCT)	No	No	-	Yes	Yes	Yes	No	
35	Bo Espiosa Agostinho Cardozo	Day 5	Female	Normal	2690gm	LSCS	Late Preterm	35w6d	T2- single ventricle morphology, small atretic pulmonary artery	Cried immediately after birth	G3A2	No	No	No	No	Cyanotic	Transposition of Great Arteries/Pulmonary atresia/Tricuspid atresia/large OS ASD/dextrocardia/ single LV morphology	TGA	0.48/0.43/0.37	No		1.48	No		No	10107847	No	Yes	AGA	No	Yes	No	No	No	No	Yes	-	No	No	No	No	
36	Bo Anitha Shankar Shelake	Day 7	Female	Normal	2700gm	LSCS	Term	39w	Normal	Cried immediately after birth	Primi	No	No	No	No	Acyanotic	Moderate sized PDA	PDA	0.76/0.29	No		1.62	No	ABO incompatability	No	10111790	No	Yes	AGA	No	No	No	No	No	No	No	-	No	No	No	No	
37	Bo Geeta Shridhar.	Day 7	Male	Normal	3200gm	NVD	Term	38w4d	Normal	Cried immediately after birth	G2P1L1	No	No	No	No	Cyanotic	Transposition of great arteries/small VSD	TGA	0.41/0.48	No		0.84	No		No	10092799	No	Yes	AGA	No	Yes	No	No	No	No	No	-	No	No	No	Yes	
38	Bo Mahek Tajoddin.	Day 6	Female	Normal	3100gm	LSCS	Term	38w1d	T2- Pulmonary stenosis and RV hypertrophy	Cried immediately after birth	Primi	No	No	No	No	Acyanotic	Large fossa ovalis ASD/severe TR/small PDA/moderate PAH	ASD	1.05/0.72	AKI	Stage 1	2.32	AKI		AKI	10050804	No	Yes	AGA	Yes (dobutamine)	Yes	No	No	No	No	No	Yes	No	Yes	No	No	
39	Bo Renuka Berappa Hirekodi	Day 4	Male	LBW	2300gm	LSCS	Term	39w1d	T2- small thick walled left ventricle with reduced contactility with right atrium and ventricle enlargement- suspected hypoplaastic left heart syndrome with evolving coarctation of aorta	Cried immediately after birth	G3P2L2	Yes	No	No	No	Cyanotic	Hypoplastic left heart syndrome /Mitral Atresia/Extremely Hypoplastic Aortic Valve/Large ASD with left to right shunt/Large PDA	Single Ventricle Physiology	1.34/1.42	AKI	Stage 1	2.56	AKI		AKI	10104564	No	Yes	SGA	No	No	No	No	No	No	No	Yes	No	No	No	Yes	
40	Bo Asmitha Ankush Birajdar	Day 7	Female	LBW	1800gm	LSCS	Late Preterm	34w6d	T2- early onset FGR stage 1	Cried immediately after birth	Primi	Yes	No	No	No	Acyanotic	Large Fossa Ovalis ASD with large PDA with dilated LA/LV with severe PAH	Complex CHD	0.81	No		1.97	No		No	10065221	No	Yes	AGA	No	Yes	No	No	Yes (PCT)	Yes	No	-	Yes	No	Yes	No	