e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(11); 685-691

Original Research Article

Nephropathy in Sickle Cell Anaemia Children in a Tertiary Health Care Centre

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Received: 25-08-2023 / Revised: 28-09-2023 / Accepted: 30-10-2023

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Conflict of interest: Nil

Abstract:

Introduction: When sickled erythrocytes are present in the renal medulla, it causes ischemia, microinfarcts, and papillary necrosis in the kidneys. This condition is known as sickle cell nephropathy (SCN), which is the renal manifestation of sickle cell disease (SCD). Clinically presenting as increased GFR as a result of localised prostaglandin production and enhanced nitric oxide synthase in response to hypoxia, glomerular hyper filtration is the initial sign of SCN. This leads to an increase in renal blood flow and albuminuria 2. Proteinuria types 1 and 4 affect 20–30% of SCD patients.

Material and Methods: We also measured height and weight using anthropometric techniques. The individuals' shoes and top clothing were taken off before these measurements were taken. Every subject's weight was recorded using digital weighing equipment, which was calibrated as needed and had its accuracy confirmed on a regular basis, to the nearest 0.1 kg. Using a portable stadiometer, the standing height was measured to the closest 1 cm. Weight (in kilogrammes) divided by height (in metres squared) was used to calculate BMI (kg/m2). Using a suitable blood pressure cuff size for the child's upper arm and a relaxed forearm on the examination table, the resting Systolic blood pressure (SBP) was measured.

Results: Similar to earlier studies, we discovered 5.83% of AKI patients in our investigation. According to Baddam S et al., 17% of vaso-occlusive pain crises had an AKI3 connection. Vasoocclusive pain crises were a frequent side effect in kids with SCA and a known risk factor for AKI, with 2.5–17% of kids admitted to the hospital due to a VOC going on to develop AKI136–38. Acute infection (malaria and sepsis), hypovolemia (insensible loss due to fever, reduced intake, diarrhoea, and vomiting), and the use of NSAIDs to manage Vaso-occlusive crises are recognised risk factors for AKI.

Conclusion: Hospital based cross-sectional study design with selection bias, lead time bias and diagnosis bias which limits its potential to make conclusion. Estimated GFR (e GFR) using Schwartz formula is inferior to ideal measured GFR using cystatin-C or inulin and noble biomarkers for diagnosing AKI like KIM-1 & NGAL are quite expensive which was beyond the scope of our study.

Keywords: Nephropathy, Anaemia Children, SCD.

Introduction

Sickle Cell Nephropathy (SCN) is renal manifestation of Sickle Cell disease (SCD) characterized by the presence of sickled erythrocytes in the renal medulla that results in decreased medullary blood flow, ischemia, micro infarct & papillary necrosis in the kidneys. The earliest manifestation of SCN is glomerular hyper filtration clinically manifested as elevated GFR due to localized prostaglandins release & increased nitric oxide synthase in response to hypoxia resulting in increase in renal blood flow and Albuminuria [2]. Approximately 20-30% of patients with SCD develops proteinuria [1,4]. Medullary ischemia & haemolysis both can adversely impact tubulo-interstitium through several mechanisms. Renal ischemia caused by micro vascular occlusion has been thought to be the primary pathophysiologic mechanism of both acute

& chronic kidney disease in SCD patients [2]. The most common renal complication in SCD patients is impaired urinary concentrating ability attributed to loss of deep juxtamedullary nephrons while the urinary diluting mechanisms are intact [2].

Dysfunction in the distal tubules may lead to impaired potassium & H+ ion excretion and subsequently develop hyperkalemia & metabolic acidosis respectively [2]. Haematuria appears to result from the polymerization of HbS & red cell sickling in medulla with subsequent vascular obstruction and red cell extravasation. Microscopic haematuria is common in paediatric SCN with cross-sectional studies reporting a prevalence of up to in 30% cases [5]. Out of the 122 children with SCA studied 5(4.1%) had persistent hematuria done by Uzoamaka C. Akubuilo et al. Significant hematuria found in 6.7% of sickle cell children reported by Nnaji et al.

Increased serum phosphorus levels thought to be due to supranormal proximal tubule function leading to increase in maximal tubular absorption of phosphorus [2]. AKI is due to volume depletion, severe sepsis, rhabdomyolysis and NSAIDs used to treat pain crises. AKI were associated with 17% vaso-occlusive pain crises [3].

Renal medullary carcinoma is rare but aggressive neoplasm of kidney associated with SCD. Patients generally presents as gross haematuria, flank pain, weight loss [2]. SCD patients may develop CKD with features similar to other forms of CKD features such as electrolyte disturbances, oedema, hypertension, anaemia & mineral bone disease.

Patients with Sickle cell disease are at risk of development of numerous renal complications collectively known as Sickle Cell Nephropathy. Given the potential for significant mortality & morbidity associated with Sickle cell nephropathy it is imperative to screen sickle cell children routinely for renal involvement, in particular attention to patient treated with NSAIDs. Southern Odisha is endemic for sickle cell disease and a lot of patients from KBK districts of Odisha are coming to MKCG medical college & hospital for health care benefits. Studies related to nephropathy in sickle cell children are limited across India so it's of paramount importance for such study.

Materials and Methods

Study Type: Prospective observational study

Study Design: Cross sectional study

Study Setting: PG department of Paediatrics, MKCG Medical College and Hospital, Berhampur

Study Period: November 2020- October 2022

Inclusion Criteria:

1. All sickle cell anaemia children between 1 year to 14 years of age admitted to paediatrics ward in MKCG medical college and hospital.
2. All SCA children with other associations like thalassemia, Hb C, Hb D and Hb E.

Exclusion Criteria:

1. Patients who died within 24 hr of hospitalisation.
2. Patients with known case of any renal disease due to other systemic causes.

Sample size calculated using following formula:

Sample size=$Z^2 \times P \times (1-P)/d^2$

Where, Z=1.96(Standard deviation at 95% confidence interval)

P=Expected percentage of population (50%)

d =0.10(Expected margin of error)

Nonresponse rate=20%

Methodology

During the study period 120 sickle cell anaemia children fitting to inclusion criteria were included in the study group. Different demographic parameters such as name, age, sex, socioeconomic status, birth order, history of child born out of consanguineous marriage, sibling history and family history of SCD. Detailed history of mode of presentation like fever, pain abdomen, joint pain, pallor, jaundice, decreased urination, passage of high coloured urine, dysuria etc were recorded.

Thorough general examination like pallor, icterus and organomegaly etc with proper systemic examination special reference to Urinary system were made. Past history of hospitalisation for VOC symptoms, requirement of blood transfusion, h/o any blood product related infection, jaundice etc were recorded.

Proper nutrition, immunization and Developmental history were taken, then laboratory investigations were sent in each patient as per case proforma after taking consent from parents.

We also performed anthropometric measurements including weight and height. These measurements were performed after the subjects have removed their shoes and upper garments. Weight of each subject was measured to the nearest 0.1 kg using digital weighing machine which was periodically checked for accuracy and calibrated as necessary.

The standing height was measured to the nearest 1 cm with a portable stadiometer. BMI (kg/m2) was computed using weight (in kilogram) divided by height (in meters squared). The resting Systolic blood pressure (SBP) measurement was obtained from the right upper arm with an appropriate BP cuff size for children with his/her forearm relaxed

on the examination table. The state of kidneys of these patients was assessed by carrying out following laboratory tests.

Results

Table 1: Age Distribution in Sickle Cell Anaemia

Age(in years)	Number of cases	Percent
1-4	20	16.7
5 TO 9	59	49.2
10 and More	41	34.2
Total	120	100.0

Total number of patients presenting with Sickle cell disease were 120. Most of them, belonged to 5-9 years comprising 49.2% of total cases.

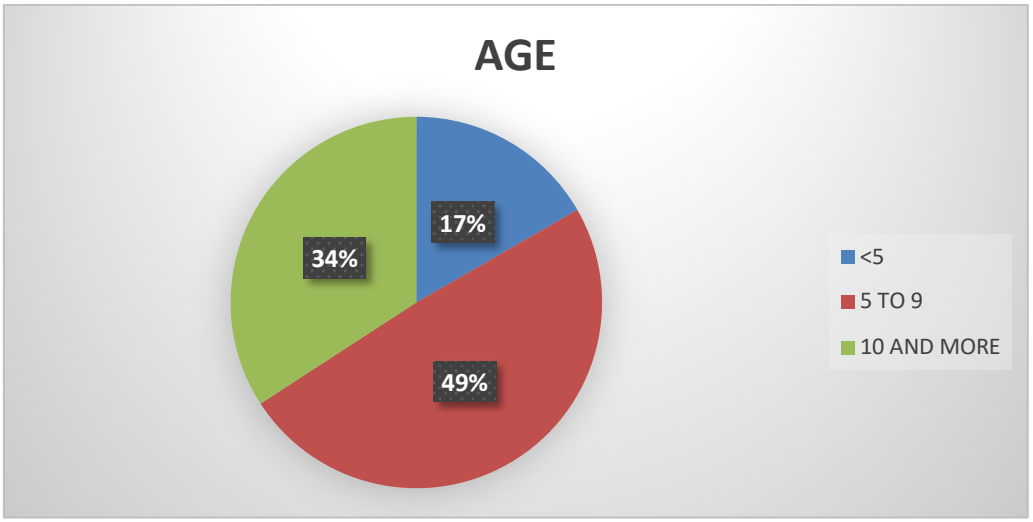

Figure 1: Age

Table 2: Sex Distribution in Sickle Cell Anaemia

Sex	Numbers	Percent
Male	76	63.3
Female	44	36.7
Total	120	100.0

Males in the study participant were 63.3% while females were 36.7%.

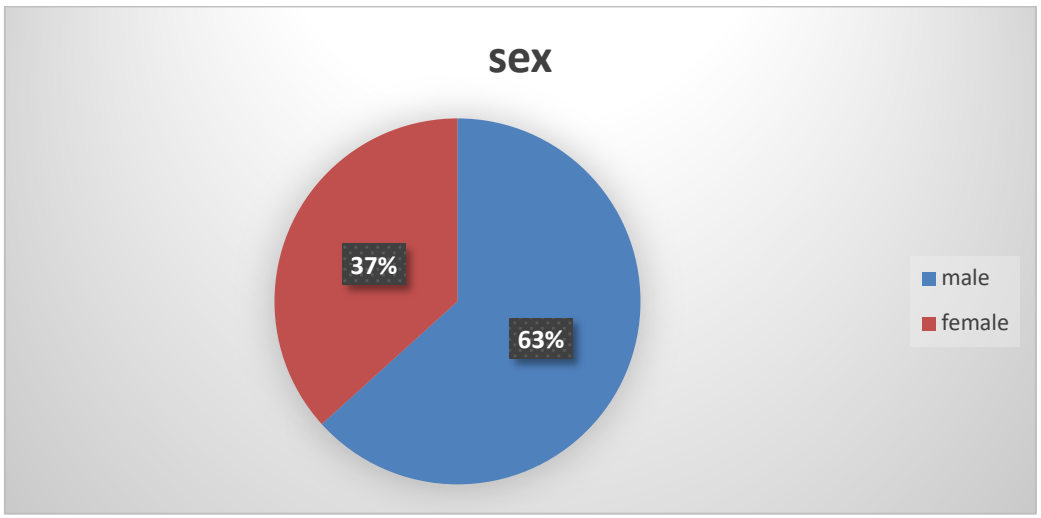

Figure 2:Sex

Table 3: Socio Economic Status of Sickle Cell Anaemia (According to Modified Kuppuswamy Scale)

S.E.S	Number	Percent
Upper	4	3.3
Upper Middle	10	8.4
Lower Middle	25	20.8
Upper Lower	73	60.8
Lower	8	6.7
Total	120	100

According to modified Kuppuswamy socio economic status scale (2019) most of the sickle cell children belonged to upper lower class 73(60.8%).

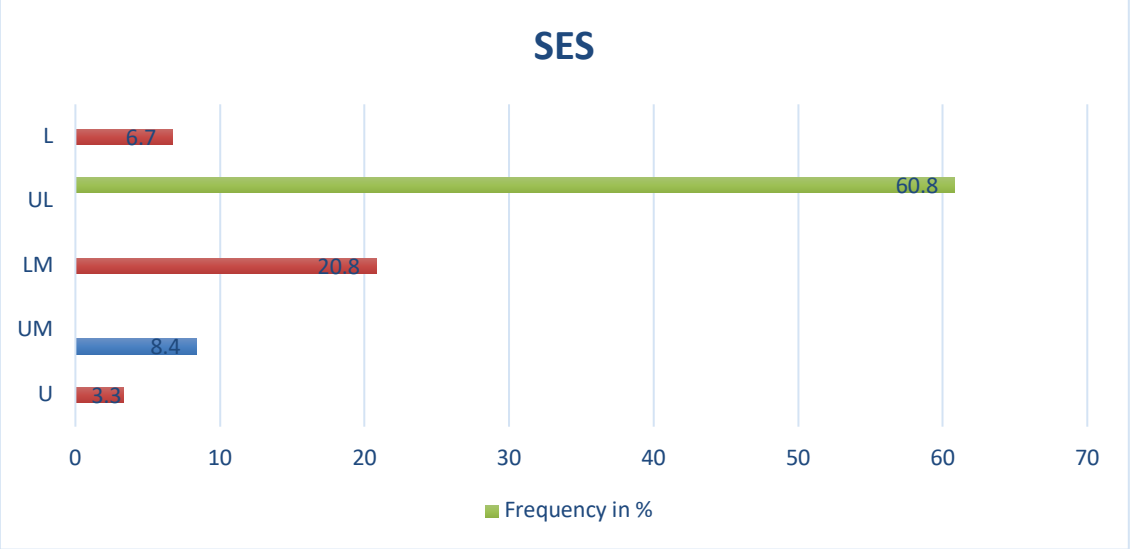

Figure 3: SES

Table 4: Consanguinity in Sickle Cell Anaemia

Consanguinity	Number	Percent
Absent	106	88.3
Present	14	11.7
Total	120	100.0

Child born to a consanguineous marriage was seen only in 11.7% of cases.

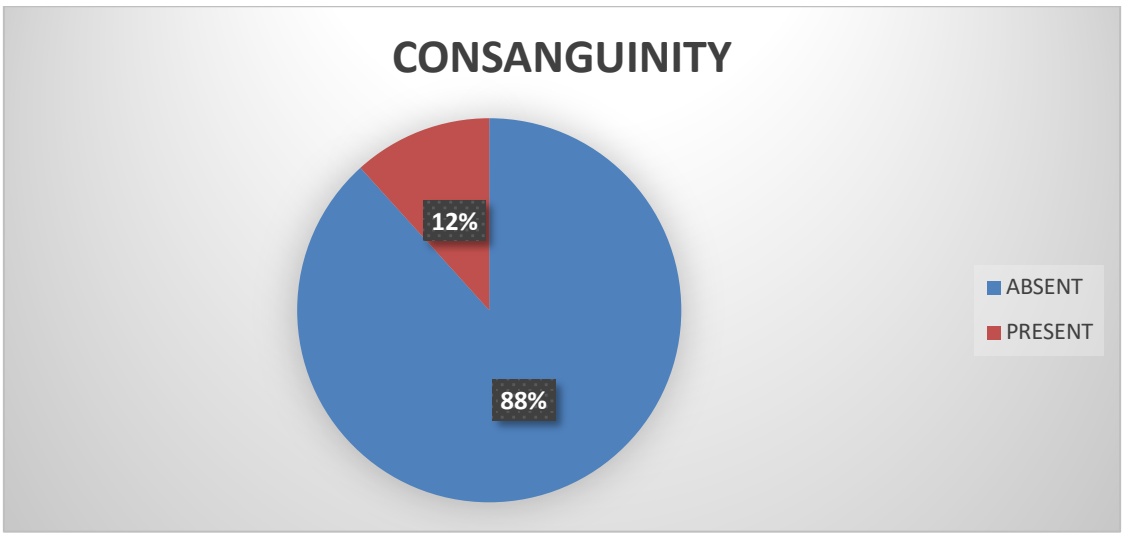

Figure 4: Consanguainity

Table 5: Hemoglobin Pattern in Sickle Cell Anaemia

HPLC/Electrophoresis	Number	Percent
HBSS	88	73.3
HBSA	20	16.7
HBSB	11	9.2
HBS alpha	1	.8
Total	120	100.0

Most of the children (73.3%) were having Hb S fraction >60% suggesting to be Sickle cell Homozygous/Sickle cell Anaemia.

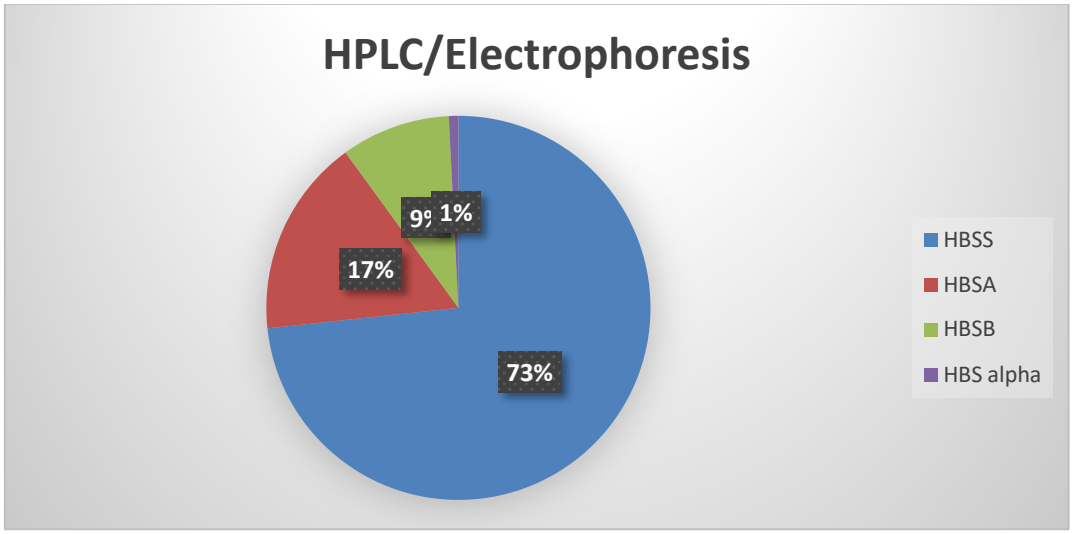

Figure 5: HPLC/Electrophoresis

Table 6: Hemoglobin Level in Sickle Cell Anaemia

Hb%	Frequency	Percent
<5	16	13.3
5-10	89	74.2
>10	15	12.5
Total	120	100.0

Most of the sickle cell children i.e 89 (74.2%) of all cases were having some pallor with haemoglobin % between 5-10 gm%.

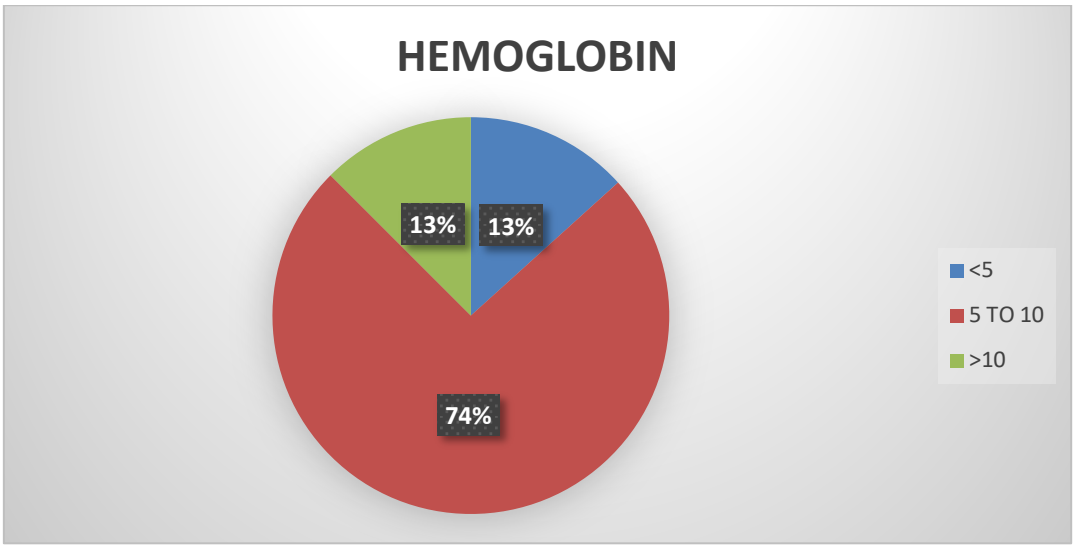

Figure 6: Hemoglobin

Discussion

The table-1 & 2 describe the age and sex distribution of sickle cell disease, where maximum number of cases (49.2%) observed in the age group of 5-9 years with male preponderance. In a hospital based clinical study from western Odisha, the investigators found 52% of sickle cell disease patients were within 15 years of age [20]. Maximum frequency of cases (24.4%) was found in 5-9 years age group. According to B.C Kar et al, 50% of children had their manifestation within 5 years of life and another 25% manifested by 10 year of age. The more number of cases in higher age group is probably due to early detection and higher rate of survival in modern times.

Table-3 depicts distribution of cases according to different socioeconomic class, in which maximum number of cases (60.8%) were from upper lower, followed by 20.8% in lower middle and 6.7% in lower SE class. Thus total 67.5% of cases were from low SE class. Although there is no comparable literature regarding distribution of the disease in different social classes, various authors like Kar B.C [18] and Bolgir R.S have observed high frequency of the disease in lower socio economic community which indirectly supports our findings.

Table-4 depicts the history of consanguinity in only 11.7% cases. Nanda et al [16] observed higher incidence of consanguinity in the Agharia caste which resulted in high incidence of SCD in that particular caste. It is well known that with consanguineous marriage transmission of recessive disorder manifest as diseases in off springs.

Table-5 shows most cases (73.3%) of study group were of sickle cell homozygous. Majority of the cases had some pallor (Table-6), Hb% 5-10gm% (74.2%). Kar BC et al demonstrated, 77% of SCD patients had total haemoglobin between 4-10 gm/dl. Mean Hb level in Indian SS disease were found to be 8.73±1.69 gm/dl and the raised foetal Hb level was attributed to mild to moderate anaemia in these children which is similar to our findings. Hb status may not be steady throughout, but affected by crisis and other intercurrent infection aggravating morbidity in children. Most (73.3%) haemoglobin patterns were of Hb SS type (Table-5) might be due to consanguineous marriage.

We found Proteinuria-15.8% (Table-7) out of different manifestation of sickle cell nephropathy, similar findings also been reported in other studies. The prevalence of albuminuria in the first three decades of life is up to 27% increasing to 68% in older SCD patients. Proteinuria is a frequent finding in SCD, and is present in 30% of patients during long term follow up. Approximately 20-30% of patients with SCD develops proteinuria [1,4] Proteinuria is more common in mid to late adolescent group of children and adults due to lack of significant glomerular dysfunction and nephropathy secondary to sickling process might be the reason why we got less number of cases as compared to previous studies. Microscopic hematuria is common in pediatrics SCN with cross-sectional studies reporting a prevalence of upto 30% [20]. Out of the 122 children with SCA studied 5(4.1%) had persistent hematuria done by Uzoamaka C. Akubuilo et al. We also reported 10% cases of hematuria (Table-8) cases.

Hyper filtration as a manifestation of sickle cell nephropathy was reported to be 13.3% in our study similar to other studies (Table-9). In the study by Etteldorf and colleagues, children with SCD aged 4–11 years had a significantly higher mean measured glomerular filtration rate (m GFR) (169 mL/min/1.73 m2) than normal controls (128 mL/min/1.73 m2). In the BABY HUG trial, 176 children aged 9–19 months had a measured GFR at baseline of 125 mL/min/1.73 m^2, which was significantly higher than published normal values for the same age group. Hyper filtration is a well-known phenomenon in SCD even though the pathogenesis and pathophysiology is less well understood. As a result of hyper perfusion, increased amount of fluids is presented to the proximal tubule triggering more tubular reabsorption of sodium and water in order to restore glomerulotubular balance.

We found 5.83% cases of AKI in our study similar to other study (Table-10). Baddam S et al described 17% vaso-occlusive pain crises were associated with AKI[3].Vasoocclusive pain crises were a common complication in children with SCA and a risk factor for AKI with an estimated 2.5-17% of children hospitalized with a VOC developing AKI Known risk factors for AKI includes acute infection (malaria & sepsis) and hypovolemia (insensible loss secondary to fever, decreased intake, diarrhea and vomiting) and NSAID use to treat Vaso-occlusive crises.

Conclusion

Hospital based cross-sectional study design with selection bias, lead time bias and diagnosis bias which limits its potential to make conclusion.

Estimated GFR (e GFR) using Schwartz formula is inferior to ideal measured GFR using cystatin-C or inulin and noble biomarkers for diagnosing AKI like KIM-1 & NGAL are quite expensive which was beyond the scope of our study.

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