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Medicine

MALARIA INDUCED AKI- A STUDY IN A TERTIARY CARE CENTRE

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KEYWORDS :

INTRODUCTION

One of the most prevalent endemic diseases in India is Malaria. It caused by a protozoan of the genus Plasmodium, which has various species- P. falciparum, P. vivax, and P. malariae. P. knowlesi, P. ovale. Tertian malaria is caused by P. vivax and P. ovale, while quartan malaria is caused by P. malariae. P.falciparum is the most notorious in terms of systemic complications involving the hepatic, renal and sometimes even the central nervous system. The causative organism invades the RBC during the erythrocytic phase of the cycle and the parasitemia levels are directly proportional to the severity of the disease. [1]

In 2015, WHO reported an estimated 214 million cases of malaria and due to complications 438,000 deaths followed consequently .Female Anopheles mosquito acts as a vector and inoculates infective sporozoites in the bloodstream of a human and thus begins the vicious cycle of infection. During the evolutionary sexual cycle of plasmodium, schizonts are formed, which get converted into merozoites that invade erythrocytes, ultimately leading to hemolysis. P. vivax and P. ovale are commonly associated with the acute form of the disease. Whereas, P. falciparum is responsible for fulminant malaria. In acute malaria, patient complains of fever associated with chills and sweating. On examination hepato splenomegaly can be a common finding. On the other hand, Fulminant malaria can present with acute kidney injury, shock, anemia, electrolyte disturbances, respiratory failure, disseminated intravascular coagulation, diarrhea, jaundice, and even coma. Interestingly, P. ovale and P. vivax have been known to cause reactivation of infection, by formation of the quiescent forms called as 'hypnozoites'.[2] Malaria was one of the first parasitic infections associated with glomerular diseases. Severe malaria causes abnormalities and disease in the glomeruli, tubules and also in the interstitium.

AIMS AND OBJECTIVES

1) To evaluate the clinical profile of Malaria Induced AKI (MIAKI)
2) To classify MIAKI according to its clinical presentation - MIAKI per se, and MIAKI with Multi Organ Dysfunction Syndrome (MODS)

STUDY SETTING

The study has been conducted in Department of Medicine, Sri Ram Murti Medical Institute of Medical Sciences, Bareilly

PERIOD OF STUDY

The period of study was from 1st August 2018 to 1st December 2018, for duration of 4 months.

SAMPLE SIZE

A total of 242 patients with proven malaria , admitted in the Medicine IPD within the study period have been included .They were chosen randomly and were those who fulfilled the inclusion and exclusion criteria.

STUDY DESIGN

It is a Retrospective observational study.

METHODOLOGY

The diagnosis of malaria has been done using Rapid Diagnostic Test or peripheral smear examination from the venous blood samples. Investigations - Complete Blood Count , Renal profile , serum electrolytes , Liver function tests , Random blood glucose and Urine routine microscopy were performed Patients were also physically examined and any investigations deemed necessary were done. A written and informed consent was obtained from these patients. The patients of Acute Kidney Injury (AKI) were diagnosed using the KDIGO criteria:

- Increase in Sr. Creatinine by 0.3mg/dl or more within 48 hours or
- Increase in Sr.Creatinine to 1.5 times baseline or more within last 7 days or
- Urine output less than 0.5ml/kg/hour for 6 hours.

Multi-organ dysfunction syndrome (MODS) defined by using the Sequential Organ Failure Assessment score (SOFA score) of greater than 2.

Organ System	Score				
	0	1	2	3	4
Respiratory: PaO2/ FiO2	>400	≤400	≤300	≤200	≤100
Renal: Creatinine (mg/dl)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 urine output ≤500 ml/day	>5.0: Urine output <200 ml/day
Hepatic: Bilirubin (mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular: Hypotension	No hypotension	MAP <70mmhg	Dopamine ≤5a, Dobutamine (any dose)	Dopamine >5a or norepinephrine ≤0.1a	Dopamine >15a or epinephrine >0.1a or norepinephrine ≤0.1a
Hematologic: Platelet count (103/mcL)	>150	≤150	≤100	≤50	≤20
Neurologic: Glagow coma scale score	15	13-14	10-Dec	06-Sep	<6

INCLUSION CRITERIA

1) The patients with malaria with AKI (as per the KDIGO criteria)
2) Patients who were willing.
3) Age > 18 years.

EXCLUSION CRITERIA

1) Patients with any pre-existing Kidney diseases.
2) Unwilling patients.
3) Any known cause leading to AKI- such as bladder obstruction , nephrolithiasis

RESULTS AND OBSERVATIONS

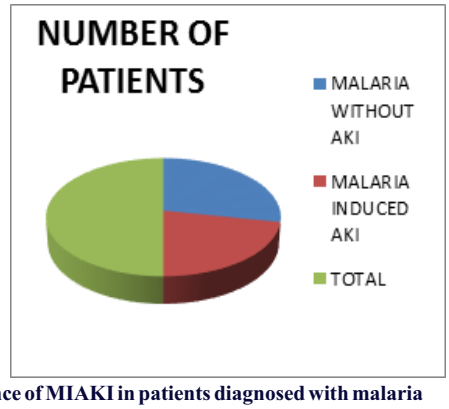
A total of 268 patients suffering with malaria were hospitalized between August 2018 and November 2018. 26 cases had to be excluded due to pre-specified criteria.

Out of 242 patients eligible for the study, AKI was diagnosed in 106(43.8%) patients. However, 136 (56.1%) patients had no evidence of AKI.

MALARIA INDUCED AKI (MIAKI)

Incidence of MIAKI in the present study was 43.8% .

Malaria Cases	Number of patients	Percentage
MALARIA WITHOUT AKI	136	56.1%
MALARIA WITH AKI (MIAKI)	106	43.8%
TOTAL	242	100%

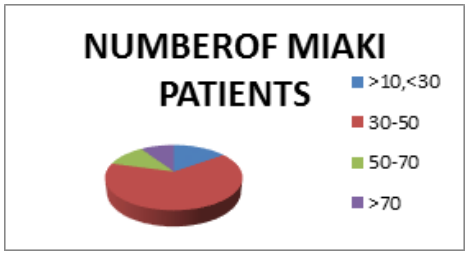


Incidence of MIAKI in patients diagnosed with malaria

AGE

In the present study the age group with most cases of MIAKI was 30 to 50 (64.1%) followed by the age group, 10-30 (15.9%), 50-70 (12%) and least in >70yrs (9.4%). Thus, MIAKI can be considered to be occurring maximally in the age group of 30 – 50.

Age Group	Number of patients	Percentage
10-30	16	15.09%
30-50	68	64.1%
50-70	12	11.3%
>70	10	9.4%
TOTAL	106	100%

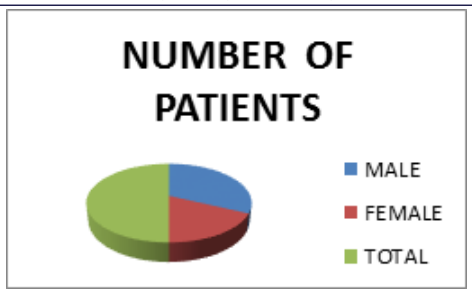


Age distribution seen in MIAKI patients.

SEX

In this study, a higher incidence of MIAKI was noted in the male population (64.1%) while affected female cases were 35.8%.

Sex	Number of patients	Percentage
MALE	68	64.1%
FEMALE	38	35.8%
TOTAL	106	100%

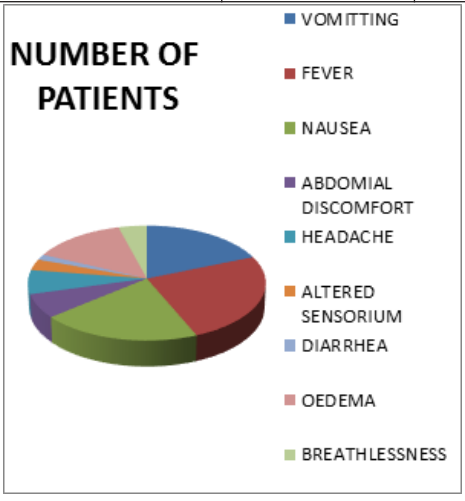


Sex distribution in MIAKI patients

CLINICAL FEATURES

In the present study the commonest presenting features have been, fever (90%), nausea (73%) and vomiting (67.9%) and oliguria – 62%.

Symptoms	Number of Patients	Percentage
VOMITTING	72	67.9%
FEVER	96	90.56%
NAUSEA	78	73.5%
ABDOMINAL DISCOMFORT	26	24.5%
HEADACHE	26	24.5%
ALTERED SENSORIUM	12	11.3%
DIARRHOEA	6	5.6%
OEDEMA	53	50%
OLIGURIA	66	62.2%
BREATHLESSNESS	16	15.0%

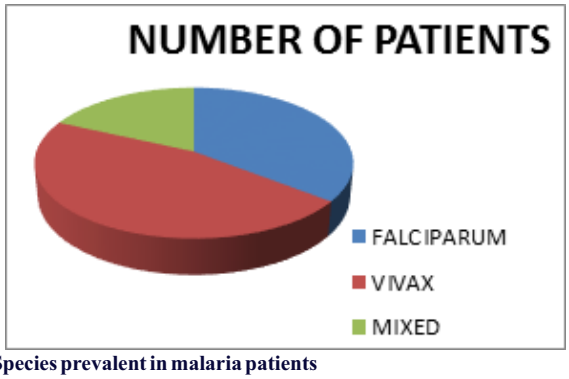


Clinical presentations of symptoms in patients

SPECIES DETECTED IN ALL MALARIA PATIENTS.

It was found that plasmodium species causing malaria most commonly were vivax (46.2%), next by falciparum (35.5%), followed by mixed (falciparum and vivax) (18.1%).

Species	Number of patients	Percentage
P.FALCIPARUM	86	35.5%
P. VIVAX	112	46.28%
MIXED	44	18.1%
TOTAL	242	100%

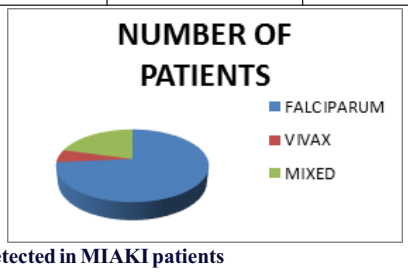


Species prevalent in malaria patients

SPECIES DETECTED IN MIAKI CASES.

Our study indicated that the plasmodium species showing highest causation of MAKI was P. falciparum (73.5%) followed by mixed falciparum and vivax infections (20.75%), followed by P. vivax infections (5.66%).

Species	Number of patients	Percentage
P. FALCIPARUM	78	73.5%
P.VIVAX	6	5.66%
MIXED	22	20.75%

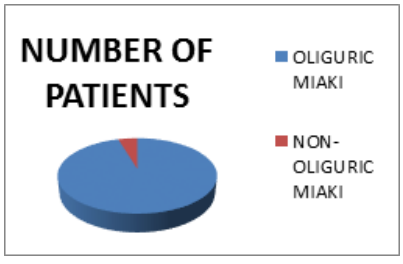


Species detected in MIAKI patients

OLIGURIC MAKI VS. NON-OLIGURIC MAKI

Our study indicated that oliguric AKI is found in 62.2% cases whereas non-oliguric AKI was found only in 37.73% cases.

MAKI Cases	Number of patients	Percentage
OLIGURIC MIAKI	66	62.2%
NON-OLIGURIC MIAKI	40	37.73%
TOTAL	106	100%

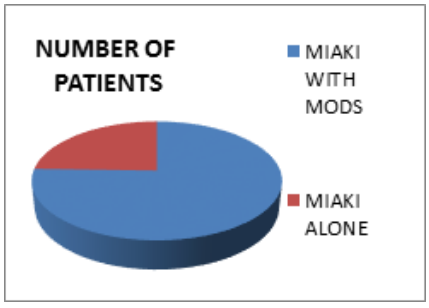


Ratio of oliguric MIaki vs. non-oliguric Miaki

MAKI WITH MODS AND MAKI ALONE.

Our study indicated the occurrence of Multi-organ dysfunction as defined by the SOFA score (75.4%).It concluded that significant mortality was seen in MODS.

MAKI Cases	Number of patients	Percentage
MIAKI WITH MODS	80	75.4%
MIAKI ALONE	26	24.5%
TOTAL	106	100%

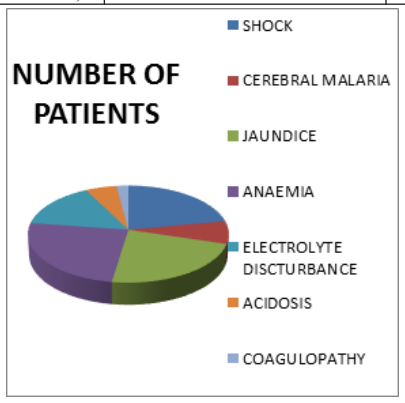


Association of MODS with MIAKI

INCIDENCE OF ASSOCIATED COMPLICATIONS.

Numerous complications have been associated with MIAKI like-shock (80%) jaundice (82.5%), cerebral malaria (27.5%), and anemia (80%).

Complications	Number (out of 80) of patient	Percentage
SHOCK	64	80%
CEREBRAL MALARIA	22	27.5%
JAUNDICE	66	82.5%
ANEMIA	72	80%
ACIDOSIS	16	20%
COAGULOPATHY	6	7.5%
BIOCHEMICAL CHANGES(ELECTROLYTE DISTURBENCE)	44	55%

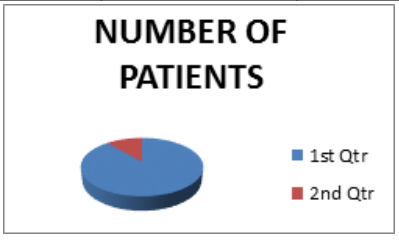


Frequency of associated complications

RELATION OF LEVELS OF S. BILIRUBIN IN AKI PATIENTS

Our study indicated that the majority of the patients had Bilirubin levels ranging from 3-10mg/dl out of the total 66 patients who had associated jaundice. (Out of the 80 patients who had AKI associated with MODS)

level of S. Bilirubin	No. of cases	Percentage
3-10	61	92.4%
>10	5	7.6%
TOTAL	`66	100%

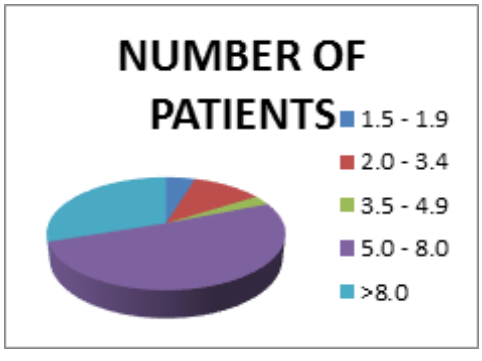


Relation of levels of S. Bilirubin with Renal dysfunction

DISTRIBUTION OF PATIENTS AS PER CREATININE LEVELS.

Almost 50% of the patients found to have creatinine levels of >5mg/dl. Similar findings were seen in various other studies

Creatinine Level (mg/dl)	Number of Patients	Percentage
1.5 - 1.9	5	4.7%
2.0 - 3.4	12	11.3%
3.5 - 4.9	3	2.8%
5.0 - 8.0	54	50.9%
>8.0	32	30.1%
TOTAL	106	100%

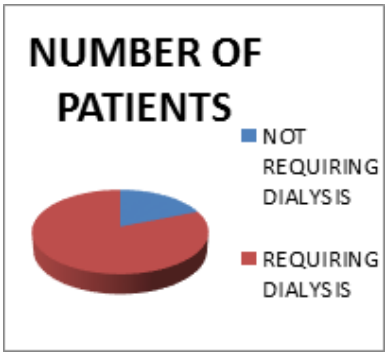


Distribution of patients as per creatinine levels.

MIAKI PATIENTS REQUIRING DIALYSIS.

In our study, it was noted that dialysis was needed to be done in 81.1% patients.

Maki Patients	Number of patients	Percentage
NOT REQUIRING DIALYSIS	20	18.8%
REQUIRING DIALYSIS	86	81.1%
TOTAL	106	100%

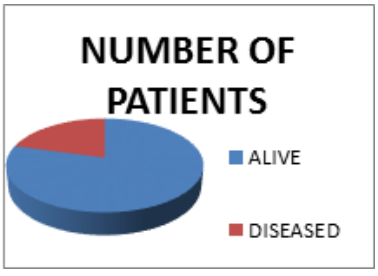


Number of MIAKI patients requiring dialysis.

INCDENCE OF DISEASED INDIVIDUALS

20.7% of in-hospital mortality has been seen in our study.

MAKI Cases	Number of patients	Percentage
ALIVE	84	79.2%
DISEASED	22	20.7%
TOTAL	106	100%



Outcome of the patients

DISCUSSION

As of today the combination of hepatic dysfunction and renal failure is a more common manifestation in cases of severe malaria. Kidney involvement is mainly attributed to the RBC abnormalities. The parasitized erythrocytes and platelets adhere to the endothelium of the capillaries, forming characteristic patterns like rosettes and clumps. [1] Microcirculation is impaired which can cause kidney injury due to hypovolemia shock. Endothelial activation leads to activation of inflammatory mediators causing kidney injury. P. malariae can also lead to complement activation due to activation of Th1 and Th2. Deposition of immune complexes can manifest as glomerulonephritis. P. falciparum can cause hypovolemia and shock which leads to acute tubular necrosis. With Th1 activation, acute interstitial nephritis and acute glomerulonephritis may also occur. Many factors like hypovolemia, hepatic dysfunction, vasoconstriction, hemolysis can cause hemoglobinuria, erythrocyte parasitemia, immune complex deposition within the glomeruli, microcirculation dysfunction and rhabdomyolysis can lead to acute kidney injury (AKI), and liver dysfunction causing hepato-renal syndrome. Relative hypovolemia can cause an increase in the catecholamine's, renin, vasodilators prostaglandins and vasopressin, which may cause AKI. [2] [3] Acute Kidney Injury has been noticed in infection by Plasmodium species (P. falciparum, P. vivax, P. malariae and P. ovale).

Kidney involvement by P. falciparum

The most severe form of malaria is caused by P.falciparum, which is responsible for maximum number of cases of AKI. [4] Clinically, patients infected by P. falciparum can have oligo-anuria, severe metabolic acidosis, electrolyte disturbances and a hyper catabolic state. [4] [5] The histopathological finding in kidney is usually acute tubular necrosis (ATN) followed by interstitial nephritis and are very rarely associated with glomerulonephritis. [6]

Mild proteinuria, microalbuminuria and urinary casts have been seen in a few cases. The new kidney injury biomarkers investigated in malaria include neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1). It has been seen that they can detect AKI earlier than other markers such as creatinine. One of the recent studies has found that 31% of patients with malaria-associated AKI had normal levels of creatinine. Hence, the NGAL can be considered a more dependable biomarker for malaria-associated AKI. [7]Hypergammaglobulinemia is also frequently present in malaria patients. The infection can lead to immunosuppression which is secondary to cytokine production which results in widespread reduction of macrophages and T cells. The organism further causes activation of B cells leading to an increased production of immunoglobulins which further leads to immune complex formation and causes glomerular injury.

IgM, IgG and C3 deposits can be seen in P. falciparum malaria through immunofluorescence. [8] [9] Kidney involvement by infection of P. malariae is less severe, but it can be related to renal complications like AKI and glomerulopathies. [10] Proteinuria and microhematuria can also occur. Complement levels are mostly normal, and there are deposits of immune complexes, which can lead to mesangiocapillar glomerulonephritis but, in a few cases, nephrotic syndrome can also develop. The patient can present with or without renal dysfunction. Most common glomerular disease associated with P. malariae infection is membranoproliferative glomerulonephritis. Thickening of glomerular capillary walls which is caused by subendothelial deposits, showing "tram track" appearance and mesangial proliferation can be seen. [11] AKI due to P. vivax infection is not very common, though P. vivax infection has been evidenced by some studies in endemic areas. Incidence of MIAKI in the present study was 43.8% whereas Thanachartwet et al. had found a high incidence of 44.7%. [12]Mehta et al found an incidence of 22.4%. [13]The study of Philips et al. found an incidence of 17.2 %.[14] These findings corroborate with our study. Koopmans et al. in their study on 485 patients found a low incidence of 8%.[15] In the present study the age group with most cases of MIAKI was 30 to 50 (64.1%) followed by the age group, 10-30 (15.9%), 50-70 (12%) and least in >70yrs (9.1%).Mehta et al conducted a study suggesting that 75% of the cases were of the age group of 20 to 40. [13] Gupta et al. conducted another study which indicated that the mean age of MIAKI patients was 38.3 years.[16] Prakash et al conducted another study which revealed that the mean age was found to be 36.3 years. [17] Thanachartwet et al noted a majority of patients were of the age group of 22- 40 with. [12] Thus, MIAKI can be considered to be occurring maximally in the age group of 30 – 50.

In this study, a higher incidence of MIAKI was noted in the male population (64.1%) while affected female cases were 35.8%. Gupta et al. conducted a study which proposed a male to female ratio to be 4:1. [16] Prakash et al. conducted a study which indicated that maximum of male cases were involved (Males- 69.14% and Females- 30.85%). [17] Thanachartwet et al. also saw a majority of male cases (74.3%) being involved. [12]

In the present study the commonest presenting features have been, fever (90%), nausea (73%) and vomiting (67.9%) and oliguria – 62% .Mehta et al. in his study showed that the commonest features were fever, abdominal discomfort, oliguria and vomiting.

It was found that plasmodium species causing malaria most commonly were vivax (46.2%), next by falciparum (35.5%), followed by mixed (18.1%).Our study indicated that the plasmodium species showing highest causation of MIAKI was P. falciparum (73.5%) followed by mixed falciparum and vivax infections (20.75%), followed by P. vivax infections (5.66%).Mehta et al. gave similar findings, commonest cause was found to be falciparum, followed by mixed.[13] Maheshwari et al. found that P falciparum attributed to 97.53% cases and P vivax caused 2.47% cases.[18] Naqvi et al. found P. falciparum caused 97.5% cases and P. vivax had 2.5% cases. [19] Reports of Indian Government stated that about 35% of all the cases from various regions of the country were caused by plasmodium falciparum every year.

Our study indicated that oliguric AKI is found in 62.2% cases whereas non-oliguric AKI was found only in 37.73% cases. In the study by Prakash et al. ,oliguric AKI as 69% and occurrence of non-oliguric AKI as 31%.[17]Misra et al. concluded that the occurrence of oliguric AKI (70.2%) was more than non-oliguric AKI (29.8%).[20] But , Mehta et al. showed that the occurrence of non-oliguric renal failure (58%) was more than oliguric renal failure (42%).

Our study indicated the occurrence of Multi-organ dysfunction as defined by the SOFA score was (75.4%).It concluded that significant mortality was seen in MODS. Gupta et al. in his study found that patients who had MODS with 3, 4 or 5 organ system failures suffered 100% mortality. [16]

It was also noted that numerous complications have been associated with MIAKI like- shock (80%) jaundice (82.5%), cerebral malaria (27.5%), and anemia (80%).RE Philips et al. in his study in Thailand , showed that cerebral malaria and MAKI were seen in 30%.[14]Studies by Krishnan et al. and Prakash et al. indicated an increased incidence of cerebral malaria. [21] [20] Misra et al. reported that 60%patients were found to be anemic. [20] SK Misra et al. in his study in Rourkela, India proved that incidence of co-existence of cerebral malaria and MIAKI was 29%. These findings tally with the current study. In view of renal function study, almost 50% of the patients found to have creatinine levels of >5mg/dl. Similar findings were seen in various other studies.

The current study noted that dialysis was needed to be done in 81.1% patients. Mehta et al indicated that 92% required dialysis. [13] Gupta et al. in his study quoted that 70% of MAKI patients underwent dialysis. [16] Prakash et al. noted the need for dialysis in 76.6% cases. [17] It was thus noted that there was an increased requirement of dialysis. However, a slightly lower dialysis requirement was seen in the studies conducted by Thanachartwet et al. (45.2%) and Krishnan et al. (36.26%).[12][21]

In terms of mortality, 20.7% of in-hospital mortality has been seen in our study. Thanachartwet et al in his study indicated that the in-hospital mortality to be 31.9%. Mehta et al. found the mortality as 29 %[13] and Prakash et al. noted a mortality rate of 20 %.[17]

CONCLUSION

Our study concluded that P.falciparum attributed to maximum cases of Acute Kidney Injury associated with oliguria .It was seen more commonly in males .MODS was a common presentation and there was an increased requirement for dialysis.

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