"STUDY OF CLINICAL PROFILE OF LEPTOSPIROSIS; MANAGEMENT AND FACTORS PREDICTING THE OUTCOME."

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Under the guidance of

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Dr. SRIRAMA A.G

LIST OF ABBREVATIONS:

ARDS-Acute respiratory distress syndrome,

ARF- Acute renal failure,

BU-Blood urea,

SC-Serum creatinine,

CSF- Cerebrospinal fluid,

CPK- Creatine Phosphokinase,

CXR-Chest x-ray,

DC-Differential count

DGM- Dark ground microscopy,

DOHS-Duration of hospital stay,

DIC- Disseminated intravascular coagulation,

ELISA-Enzyme linked immunosorbent assay,

ECG- Electrocardiogram,

ESR-Erythrocyte sedimentation rate

Hb-Heamoglobin

HLA- Human leukocyte antigen,

Ig- Immunoglobulin,

IHA- Indirect haemagglutination assay,

L-Leptospira,

LAMP-Loop mediated isothermal amplification,

LPS-Lipopolysaccharide,

MAT-Microscopic agglutination test,

MFC- Modified Faine's criteria,

MODS-Multi organ dysfunction syndrome,

MP-Malarial parasite,

MSAT- Macroscopic slide agglutination test,

NAD- No abnormality detected,

NPV-Negative predictive value,

NRA-No radiological abnormality

PCR- Polymerase chain reaction,

PBPs- Penicillin binding proteins,

PPV-Positive predictive value,

RBS-Random blood sugar,

SAT-Slide agglutination test,

SGOT- Serum glutamic oxaloacetic transaminases,

SGPT- serum glutamic pyruvic transaminase

SPHS- Severe pulmonary hemorrhage syndrome,

TC-Total count,

TNF- Tumor necrosis factor,

TLR- toll-like receptor,

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ABSTRACT:

BACKDROUND:

Leptospirosis is one of the important causes of acute febrile illness in India. Leptospirosis is now being increasingly reported from many parts of India. In humans, leptospirosis may range from a very mild and self-limited illness to severe multisystem illness that includes high fever, renal failure, jaundice, and aseptic meningitis and if not recognized early it can lead to increase to increased rates of mortality in infected patients. Various factors like oliguria, pulmonary rales, hepatitis, acute renal failure, and multi organ failure are associated with poor prognosis. Therefore it important to know the clinical profile of leptospirosis, it's management and also the factors predicting the outcome.

OBJECTIVES:

To study the CLINICAL PROFILE OF LEPTOSPIROSIS, it's management and to determine the factors predicting the outcome of leptospirosis.

METHODS:

30 Patients with fever testing Leptospira positive by ELISA IgM admitted in R.L Jalappa Hospital, Tamaka, Kolar, for the duration of one year from February 2012 to March 2013 will be selected for the study. Every patient will be evaluated by history, clinical examination and relevant investigations.

RESULTS:

The age group ranged from 18 to 77 years. Majority were in the age group of 21 to 40 years (53.4%). 76.7% were from rural areas and 23.3% were from urban areas. Most of the patients were females (63.3%) and 36.7% were males. Agriculture (63.3%) was the most common occupation of the patients. Common symptoms of the patients were fever (100%), myalgia (80%), headache (66.7%) and cough (43.3%). 6.7% of the patients had oliguria and there was a significant association between oliguria and mortality (p=0.011). Important signs seen were conjunctival suffusion (66.7%), Hepatomegaly (40%) and pulmonary rales(13.3%).

56.7% of the patients had thrombocytopenia (platelet count < 150000/cumm). CPK was elevated in 13.3 % of patients. 23.3% and 13.3% of patients had elevated blood urea and serum creatinine levels respectively. Hyponatremia was seen in 50% and hyperkalemia was seen in 3.3% of the patients. Elevated Blood urea (P=0.0001), Serum Creatinine (P=0.0001), Hyponatremia (P=0.06) and Hyperkalemia (P=0.002) were important parameters in predicting the outcome and were associated with poor prognosis of the patients. 33.3% of the patients had multi organ dysfunction.

CONCLUSION:

Leptospirosis is common among rural people and agriculturists. Fever, headache and myalgia are the common symptoms, and conjunctival suffusion and hepatomegaly were the common clinical findings. Oliguria, elevated CPK, blood urea, serum creatinine, hyponatremia and hyperkalemia were poor prognostic indicators. Multi organ dysfunction is associated with increased mortality.

INTRODUCTION

Leptospirosis is a well known worldwide zoonotic disease with a greater incidence in tropics. In India, Leptospirosis is a grossly underreported disease probably due to lack of awareness of the disease among physicians.[1]

It is known by many different local names (e.g. mud, swamp, sugar cane, Fort Bragg and Japanese autumnal fevers).

The etiological agent is Leptospira interrogans which has 23 serogroups and >250 serovars, while L.biflexa is a free living organism and is not pathogenic to humans.

Primarily a disease of wild and domestic mammals, man is infected through contact with an infected animal either directly or indirectly by water or soil contaminated with the urine of an infected animal.[2]

Leptospirosis may present with a wide variety of clinical manifestations. These may range from a mild "flu"-like illness to a serious and sometimes fatal disease. It may also mimic many other diseases, e.g. dengue fever and other viral hemorrhagic diseases.

After the usual incubation period of 5 to 14 days, individuals develop an acute febrile illness that can be followed by a more severe, occasionally fatal illness.

Severe leptospirosis is characterized by jaundice, renal dysfunction, and hemorrhagic diathesis and is referred to as Weil's Syndrome, but majority present with a self-limited systemic illness.

The diagnosis is confirmed by laboratory tests,

Leptospirosis has been under reported and under diagnosed from India due to a lack of awareness of the disease and lack of appropriate laboratory diagnostic facilities in most parts of the country.

Combining clinical expertise and awareness with confirmatory laboratory back up dramatically increases the recognition of patients with leptospirosis.

OBJECTIVES

1. To study the CLINICAL PROFILE OF LEPTOSPIROSIS and its management.

2. To determine the factors predicting the outcome of leptospirosis.

The various outcomes of leptospirosis can be influenza like illness, Weil's syndrome, meningitis/meningoencephalitis and pulmonary haemorrhage with respiratory failure following which there can be either recovery or death of the patient.

Factors predicting the outcomes include varied symptoms the patient may present with for e.g.: fever, headache, myalgia, altered mental status, meningism, icterus, oliguria, dyspnoea.

Patients with findings like respiratory failure, ARDS, Haemoptysis, ARF, higher serum potassium levels, high serum bilirubin levels, and higher levels of hepatic enzymes are considered as poor prognostic indicators of leptospirosis.

All these factors predicting the outcome will be studied in patients presenting with ELISA IgM positive for leptospirosis.

REVIEW OF LITERATURE

HISTORICAL REVIEW:

Adolf Weil described leptospirosis as a disease entity in 1886. His name is still attached to a serious form of leptospirosis called Weil's disease, traditionally attributed to rat transmitted which is caused by *Leptospira interrogans*, serovar *icterohaemorrhagiae* or *copenhageni*.[3]

Leptospires had been seen at that time, but were not cultured and were named *Spirocheta interrogans* by Stimson as early as 1907, in silver stained preparations of liver from a patient believed to have expired of yellow fever, the viral origins of which were then unrecognized.[4]

Its contagious nature and microbial origin were proved independently, first in Japan by Inada et al. *(Spirochaetaicterohaemorrhagiae)* in 1915, [5] and soon after in Germany (*Spirochaeta icterogenes*) by Uhlenhuth andFromme.[6]

Noguchi proposed the name 'Leptospira' (thin spirals) in 1918, following detailed microscopical and cultural observations.[7]

In 1929 Taylor and Goyle isolated Leptospira from 24 patients in the Andaman Islands and proved the existence of the disease in India.[8]

Electron microscopy revealed much of the detail of the structure during the 1960s and 1970s.

Yanagawa and Faine (1966) showed that Leptospires were analogous to other bacteria in structure and that characteristic antigens are associated with structural elements.[9]

ELISA methods were developed to analyze non-agglutinating as well as agglutinating antigens, [10] and monoclonal antibodies were used to identify epitopes involved in immunity, or for classification.[11]

Historically important developments in the last 15 years include lipopolysaccharide derivation of the antigens involved in immunity and molecular techniques for identification and genetic speciation; currently, PCR methods are being developed for identification and diagnosis.[12]

AETIOLOGY:

The causative agents belong to the genus *Leptospira*.

It is a fine spiral bacteria of 0.1 μm in diameter and 6–20 μm in length.[13] Has a spinning motility, when viewed under dark ground microscopy, along their long axis which may disguise the spiral nature of the organisms.[14]

The family of Leptospiraceae has been subdivided into three genera – the *Leptospira, Leptonema* and *Turneria* (previously *Leptospira parva*). The genus *Leptospira* comprises two species: *L. interrogans* (Pathogenic) and *L. biflexa* (Saprophytic).

The species *L. interrogans* is divided into serogroups (e.g. *canicola*) and then into many serovars, and strains are identified by cross-agglutination. *L. interrogans* comprises the parasitic and pathogenic strains that can cause disease in humans and animals, whereas *L. biflexa* includes those that are considered non-pathogenic.

The species *L. interrogans* can be divided into more than 200 recognized serovars. Leptospira interrogans is an obligate which can be grown on various media which incorporate vitamins. B1 and B12, long chained fatty acids (>C15) and ammonium salts. The optimal growth conditions are pH 7.2 to 7.6 with media enriched with fresh serum or albumin, with incubation at a temperature of 28°C to 30°C.

The organism survives in anticoagulated blood (oxalated) for many days, but not in citrated blood.

EPIDEMIOLOGY AND TRANSMISSION:-

Rodents, particularly species of rat, are the most important maintenance hosts of leptospires that may infect humans.

However, it is likely that every mammal has the potential to become a carrier of some serovar and is capable of spreading the disease among its own kind and to other species, including humans.

In maintenance hosts, the organisms continue to replicate in the renal tubules after primary infection and may then be excreted in the urine asymptomatically for months or years.

Rural seroprevalence surveys in some developing countries indicate 15–20% of the population has been exposed.

The first case of leptospirosis was reported in the Andaman Islands in 1929 and since then, it has been reported in different parts of the country.[15]

The highest positivity rate of 25.6% has been reported in southern India. The reported positivity rates are 8.3%, 3.5%, 3.1% and 3.3% in northern, western, eastern and central India, respectively.[16]

Humans acquire infection by direct or indirect contact with the urine of maintenance hosts, which include rodents and other wild animals, some domestic animals (e.g. dogs excreting *L.canicola*) and farm animals (e.g. cattle excreting *L. hardjo*).

Leptospires are naturally aquatic bacteria, and their prolonged survival in urine contaminated water is an extremely important factor with regard to transmission of infection.

In order for humans to be infected, the organism generally gains entry through fresh cuts or grazes on the skin and possibly through intact mucous membranes.

Immersion in heavily contaminated fresh water carries a high risk; Working closely with infected animals also carries a risk, as does working in an environment heavily contaminated with infected urine.

The survival of leptospires in the environment is favored by warm, moist conditions and neutral or slightly alkaline pH. They survive in fresh water at neutral pH for up to 4 weeks but at pH5, survival is reduced to about 2 days.

The incidence of leptospirosis relates directly to the daily maximum rainfall[17] and increases during some disasters, including floods[18] and hurricanes.[19]

Occupations associated with leptospirosis include mining, farming, animal slaughter, veterinary medicine, fish farming and processing, sewage and canal work, sugar cane harvesting and trench warfare.

Certain agricultural laborers are at high risk, and intense exposure to leptospirosis has been documented in rice, sugarcane and rubber plantation workers. [20, 21]

More recently, the disease has been described in those taking part in recreational water sports, such as canoeing, white-water rafting, swimming in canals or windsurfing.

Military recruits involved in jungle training and those taking ‘safari holidays’ in tropical areas are at risk of infection.[22, 23]

PATHOGENESIS

Leptospires enter the body through cuts and abrasions, mucous membranes or conjunctivae, or aerosol inhalation of microscopic droplets.

After penetrating intact mucous membrane or abraded skin, leptospires enter the blood stream and are rapidly carried to all parts of the body, including the CSF and eye.[24]

Trans-endothelial migration of spirochetes is facilitated by a systemic vasculitis, accounting for a broad spectrum of clinical illness.

Severe vascular injury can ensue, leading to pulmonary hemorrhage, ischemia of the renal cortex and tubular-epithelial cell necrosis, and destruction of the hepatic architecture, resulting in jaundice and liver cell injury, with or without necrosis.[25]

The mechanisms whereby leptospires cause disease are not clearly understood. Potential virulence factors include immune mechanisms, toxin production, adhesins, and other surface proteins.

Human susceptibility to leptospirosis may be related to poor recognition of leptospiral LPS by the innate immune system. [26, 27]

Human toll-like receptor (TLR), which responds to extremely low concentrations of gram-negative LPS (endotoxin), appears to be unable to bind leptospiral LPS[27, 28,] perhaps because of the unique methylated phosphate residue of its lipid A.[29]

Direct tissue damage may also be caused by production of hemolytic toxins, which may act as sphingomyelinases, phospholipases, or pore-forming proteins.[30]

Immune-mediated mechanisms have been postulated as one factor influencing the severity of symptoms.[31]

Investigation of the 1998 Springfield Illinois Triathlon outbreak identified the HLA- DQ6 as an independent risk factor for leptospirosis.[32]

The structural location of HLA-DQ6 polymorphisms associated with disease suggested that leptospires produce a super-antigen that can cause nonspecific T-cell activation in susceptible individuals. Other immune mechanisms, including circulating immune complexes, anti cardiolipin antibodies, and antiplatelet antibodies, have been proposed but their significance is unproven.

A number of studies have focused on the roles of surface lipoproteins in leptospiral pathogenesis.[33]The major surface lipoprotein, LipL32, is highly conserved among pathogenic serovars.[34] LipL32 is a major target of the human immune response and appears to be involved in the pathogenesis of tubulointerstitial nephritis.[35]

Virulent leptospires respond to the increased osmolarity of host tissues by inducing expression of the multifunctional Lig surface proteins that mediate interactions with fibronectin, fibrinogen, and other extracellular matrix factors.[36]

The Lig proteins are early antigens; IgM antibodies to their immunoglobulin-like repeats develop early in infection, offering an approach to improved detection of acute infection.

The endostatin-like LenA protein binds the complement regulatory protein, factor H, suggesting an important role in serum resistance.[37]

Kidney: -

There are three possible mechanisms for development of renal failure.

1. **Direct bacterial invasion**:-Leptospires after entering the renal artery are found in the glomeruli, peritubular capillaries, renal interstitium, renal tubular cells and tubular lumen (Acute tubular necrosis).The time sequence of these lesions and their correlation with the presence of Leptospires suggests that the leptospirosis in some way directly causes various lesions.[38,39]

Possible mechanisms of direct renal injury include,

a) Mechanical corkscrew movement

b) Leptospiral endotoxin

c) Hyaluronidase

d) Hemolysin

e) TNF secreted by monocytes in response to the peptidoglycan of the Leptospiral cell wall. However Leptospiral endotoxin is present only in certain serotypes. The roles of the other factors in causing renal injury have not been fully understood.

2. **Non-specific factors**: -

Combination of hypovolemia, hyper viscosity and intravascular coagulation may lead to acute renal failure.

In addition cytokines, complement activation and low-grade intravascular coagulation may also be involved.

3. **Hypovolemia** is common and is attributed to decrease fluid intake, increased insensible fluid loss and increased capillary permeability.

There may also be myocardial dysfunction secondary to leptospiral myocarditis. The outcome of these factors could be prolonged renal hypoperfusion and ischemic acute tubular necrosis.[38]

Liver:-

Jaundice is the most noticeable clinical finding in cases of hepatic dysfunction. Neither hemolytic anemia nor hepato-cellular necrosis is a prominent feature of leptospirosis.

Tunnel assay revealed apoptosis of liver cells, probably related to 30kDa glycoprotein and 32KDa fibronectin adhesions to liver cells. Leptospira induced cytoplasmic effects in liver cell culture has been shown.[38, 39]

Meninges: -

Organisms easily enter the CSF during leptospiremia. Symptoms of meningitis coincide with the development of antibodies and disappearance of leptospires from the CSF suggesting an immunologic mechanism.

Cardiopulmonary system:-

Pulmonary involvement in Leptospirosis is generally the result of hemorrhage rather than of inflammation.

Localized or confluent hemorrhages may be noted throughout the lung, pleura and tracheobronchial tree. Focal hemorrhagic myocarditis has been reported.[41, 42, 43]

ECG abnormalities can occur in form of P-R interval lengthening, repolarisation abnormalities and atrial fibrillation. Cardiac failure is rare.

Skeletal muscle:-

The mylagias typical of early disease appear due to active invasion of skeletal muscle by leptospires. Muscle pain ends as antibody titers develop and organisms are cleared from the blood.

Eyes:

The aqueous humor provides a protective environment for leptospires, which readily enter the anterior chamber of the eyes during the leptospiremic phase of disease.

Uveitis is frequent, appearing weeks or 3 months after the onset of disease and has been attributed to the persistence of organisms in the anterior chamber.[42, 43]

PATHOLOGY:

Kidneys:-

Macroscopically, the kidneys are swollen with a pale cortex and a congested medulla.

In human leptospirosis the basic renal lesions is acute tubular necrosis followed by acute interstitial nephritis.[44]

On microscopic examination the glomeruli are essentially normal.

Electron microscopy showed changes in the proximal convoluted tubule like degeneration, necrosis thickening of the basement membrane and fusion of foot processes are shown by electron microscopy.

Renal lesions on progression of the disease were seen associated with circulating immune complexes and deposition of complement components and electron dense bodies in glomeruli, suggesting immune-complex glomerulonephritis.[45]

Liver:-

Hepatic damage is primarily subcellular. [46] Hepatic lesions consist of focal centrilobular necrosis with focal lymphocytic infiltration and disorganization of liver cell plates.[44]

The liver is not enlarged and microscopic damage ranges from no appreciable changes on light microscopy, to unicellular damage with oedema, to multiple necrotic foci, seen only in those who die soon after onset of symptoms[47]. Normally, regeneration of the liver

begins rapidly and reorganization will have begun even in a patient who dies later from renal failure

Lungs:-

In experimental leptospirosis induced in guinea pigs, lung lesions showed an evolving pattern of capillary congestion, local hemorrhages, and generalized hemorrhages.

Immuno-histochemistry revealed fibrin agglutination in vessel lumen (DIC), fibrin in alveoli (ARDS), and positive leptospiral antigen in lung. Electron Microscopy showed endothelial cell swelling and platelet adherence to the endothelium. [49]

Striated Muscle:-

Myalgia may be prominent early and can be severe, histological changes in muscle are often unimpressive.

Early changes include cytoplasmic vacuoles in the myofibrils.[46]

Focal areas of degeneration of individual muscle fibrils and loss of architecture associated with inflammation in the skeletal muscle are considered specific for leptospirosis.

Leptospira antigens have been demonstrated in these lesions by fluorescent antibody technique.[45]

CLINICAL PRESENTATION

Leptospiral infection is associated with a very broad spectrum of severity, ranging from subclinical illness followed by seroconversion to two clinically recognizable syndromes—a self-limited systemic illness seen in approximately 90% of infections, and a severe, potentially fatal illness accompanied by any combination of renal failure, liver failure, and pneumonitis with hemorrhagic diathesis.[49,50,51]

In some patients, the disease has two distinct phases, an initial septicemic stage followed by a temporary decline in fever followed by an immune phase in which the severe symptoms occur.

However, in many severe cases, the distinction between these two phases is not apparent; in addition, many patients present only with the onset of the second phase of the illness.

Early non-specific bacteraemic phase

The incubation period is usually 7–12 days, although in a very few cases it may be as short as 2 days or as long as 30 days.

There follows an acute febrile, influenza-like illness with chills, sore throat, headache, myalgia, back pain, anorexia, nausea and vomiting and, sometimes, herpes labialis. Sometimes the acute phase is severe; the patient is prostrate and has a persistently high fever (39–40°C) with exquisitely tender muscles, some cough and perhaps even haemoptysis, with dyspnoea and persistent vomiting.

Abdominal pain is common and the patient tends to be constipated.

Aseptic meningitis is common in some series. Aseptic meningitis, with or without symptoms, is characteristic of the immune phase of illness, occurring in up to 80% of cases.

In endemic areas, a significant proportion of all aseptic meningitis cases may be caused by leptospiral infection.[52]

Symptomatic patients present with an intense, bi-temporal, and frontal throbbing headache, with or without delirium.

A lymphocytic pleocytosis occurs, with total cell counts generally below 500/mm3. CSF protein levels are modestly elevated, between 50 and 100 mg/ml; the CSF glucose concentration is normal. Severe neurologic complications such as coma, meningo-encephalitis, hemiplegia, transverse myelitis, or Guillain-Barré syndrome occurs only rarely.[53]

During this phase, leptospires may be cultured from blood and cerebrospinal fluid (CSF) and other tissues, but not from urine.

Serological tests are negative until at least 5 days after the onset of symptoms. This so-called bacteraemic phase lasts around 4–7 days.

There may be a transient skin rash; e.g. in Fort Bragg fever there is a pretibial rash with raised erythematous patches (2–5 cm in diameter) with some induration but much less tenderness than would be expected with erythema nodosum.

It seems to be more common following infection with *L. autumnalis* or pomona than with *L. canicola* or *icterohaemorrhagiae*.

Myalgia and tender musculature, with raised serum creatine phosphokinase levels, and conjunctival suffusion are characteristic.

There may be moderate hepatomegaly but splenomegaly is less common.

The platelet count may fall and thrombocytopenic purpura and frank bleeding ensue. Urinalysis shows proteinuria but creatinine clearance usually remains normal until tubular necrosis or glomerulonephritis occurs.

Second (immune) phase

After the initial illness, a second phase begins, characteristically the patient having developed antibodies to the infecting organism.

The antibody response is predominantly in the IgM class, which has strong agglutinating properties and may persist for many months. In mild cases, the second phase may be

associated with minimal symptoms and signs but in a proportion of more severe infections, meningeal or hepato-renal manifestations predominate.

In the severe form of the disease, the first and second phases merge imperceptibly; with persistent high fever the patient deteriorates, becoming jaundiced and starting to bleed into the skin, mucous membranes and lungs.

The liver enlargement is now more prominent. As the sclera become icteric, the suffused vessels glow orange.

Purpura and ecchymoses are seen.

Oliguric renal failure, shock and myocarditis follow and are associated with a high mortality rate.

The patient develops pulmonary oedema and sub-pleural pulmonary haemorrhages with haemoptysis. Severe pulmonary hemorrhage syndrome (SPHS) can be a prominent manifestation of infection and may occur in the absence of hepatic and renal failure.[54]

Frank hemoptysis can arise simultaneously with the onset of cough during the acute phase of illness.[55] However, hemorrhage is often not seen until patients are intubated;

Clinicians should suspect SPHS in patients with signs of respiratory distress, whether or not they have hemoptysis.

With progressive pulmonary involvement, radiographic abnormalities seen most frequently in the lower lobes evolve from small nodular densities (snowflake-like) to patchy alveolar infiltrates; confluent consolidation is uncommon but may occur.[56]

The pathophysiology of SHPS is consistent with acute respiratory distress syndrome (ARDS) with diffuse lung injury, impaired gas exchange, and hemodynamic changes indicative of septic shock.[57]

At autopsy, the lungs appear grossly congested and demonstrate focal areas of hemorrhage.[58]

Acute adult respiratory distress syndrome occurs occasionally and, in these cases, smoking may be an important risk factor.[59]

The patient will deteriorate rapidly if significant gastrointestinal haemorrhage occurs, but pulmonary haemorrhage is an important cause of death.[60, 61]

The electrocardiogram is often abnormal, reflecting myopericarditis.

Kidney involvement is initially characterized by a unique non-oliguric hypokalemic form of renal insufficiency.

Hallmarks are impaired sodium reabsorption, increased distal sodium delivery, and potassium wasting.

The impairment in sodium reabsorption appears to be caused by selective loss of the ENaC sodium channel in the proximal tubular epithelium.

The blood urea nitrogen level is usually below 100 mg/dL, and the serum creatinine level is usually below 2 to 8 mg/dL during the acute phase of illness.[62]

Patients who develop oliguria, then anuria with rising plasma creatinine concentrations require renal dialysis.

The bilirubin concentration is high, but often without marked enzyme abnormalities and the combination of high bilirubin and creatinine levels should immediately raise the question of leptospirosis.

Renal failure is the usual cause of death but myocarditis, adrenal failure, haemorrhage and cerebral artery thrombosis may also be contributory.

In those who survive without renal support, the creatinine concentration begins to fall at the end of the second week of the illness, indicating rapid resolution of the tubular necrosis. All renal function parameters will have returned to normal by 6 months except urinary concentrating ability.[63]

Abdominal pain may occur with sufficient increases in the level of amylase and lipase, despite renal failure, to suggest that pancreatitis is the cause, especially in younger patients.[64, 65]

The most distinctive form of severe illness that may develop after the acute phase of illness is Weil's disease, characterized by impaired hepatic and renal function.

More severe cases may progress directly from the acute phase without the characteristic brief improvement in symptoms to a fulminant illness, with fever higher than 40° C and the rapid onset of liver failure, acute renal failure, hemorrhagic pneumonitis, cardiac arrhythmia, or circulatory collapse.[66]

Altered mental status has been found to be the strongest predictor of death[67].Other poor prognostic signs include acute renal failure (oliguria, hyperkalemia, serum creatinine > 3.0 mg/dL), respiratory insufficiency (dyspnea, pulmonary rales, chest x-ray infiltrates), hypotension, and arrhythmias.[68]

In jaundiced patients, disturbance of liver function is out of proportion to the rather mild and nonspecific pathologic findings. Conjugated serum bilirubin levels may rise to 80 mg/dL, accompanied by more modest elevations of serum transaminases, alanine aminotransferase, and aspartate aminotransferase, which rarely exceed 200 U/L.[69]

This is in marked contrast to viral hepatitis. Jaundice is slow to resolve, but death caused by liver failure almost never occurs in the absence of renal failure.

DIFFERENTIAL DIAGNOSIS:-

Jaundice and renal failure with an acute febrile illness should immediately include leptospirosis in the differential diagnosis, and a full history of occupational, recreational and animal exposure must be taken.

In practice, most cases of jaundice will at first be thought to be due to viral hepatitis: a raised bilirubin level with relatively unchanged enzymes and polymorphonuclear leukocytosis with negative viral serology should point away from viral infection.

Many other acute fevers are associated with jaundice (e.g. malaria, acute schistosomiasis, visceral leishmaniasis, melioidosis, plague, tularaemia and relapsing fever). The most important clinical clue is the link with renal failure.

The haemolytic–uraemic syndrome may be caused by toxins produced by gut pathogens such as *Shigella* spp. and *Escherichia coli* (serotype O157), but dysentery is a prominent feature in such cases.

In one series from Mumbai, leptospirosis presented as acute liver failure in 5/28 patients.[99]

If petechiae are present, meningococcal disease must be excluded. Examination of the CSF is, therefore, very important when there is any hint of meningitis. Any patient with acute lymphocytic meningitis must have a full history for possible exposure to leptospirosis taken.

DIAGNOSIS OF LEPTOSPIROSIS:-

Clinical clues that may suggest the diagnosis of leptospirosis over other causes of acute fever are disproportionate myalgia, jaundice, conjunctival suffusion, pretibial rash and lymphocytic meningitis.

If the diagnosis is suspected at this early stage, it is important to discuss with the microbiologist to arrange for appropriate specimens to be examined.

However rapid results are not always possible: cultures may take 2–3 weeks to prove positive and antibodies are unlikely to be detected until at least 5–6 days after the onset of symptoms.

Diagnosis of Leptospirosis Utilizing Modified Faine's Criteria.

Faine had evolved a criterion (WHO Guidelines) for diagnosis of Leptospirosis on the basis of clinical (A), epidemiological (B) and laboratory data (C) (A+B+C).

This criterion (Modified Faine's Criteria) has been modified from the original WHO criteria (Faine's criteria). [95]

The most important modification has been made in the diagnostic criteria, where simple and easily available tests such as Elisa and macroscopic slide agglutination test (MSAT) have been included in addition to MAT and culture.

The original criteria had included only MAT, which is a complicated test and is not easily available.

Modified Faine's Criteria Table:-

Part A : Clinical Data		**Part B: Epidemiological Factors**		**Part C: Bacteriological and Lab Findings**	
Headache	2	Rainfall	5	Isolation of leptospira in culture-Diagnosis certain	
Fever	2	Contact with contaminated environment	4	**Positive Serology**	
Temp > 39ºC	2	Animal contact	1	ELISA IgM Positive	15
Conjunctival suffusion	4	Total score		SAT – Positive	15
Meningism	4			MAT – Single High titre	15
Muscle pain	4			Rising titre (Paired sera)	25
Conjunctival suffusion + Meningism + Muscle pain	10			TOTAL SCORE	
Jaundice	1				
Albuminuria/Nitrogen retention	2				
Total score					

Presumptive diagnosis of leptospirosis is made of:
Part A or Part A and Part B score: 26 or more
Parts A, B, C (Total) : 25 or more
A score between 20 and 25 suggests leptospirosis as a possible diagnosis.

The modified Faine's criteria have two objectives:- [96]

(1) Confirmation of leptospirosis utilizing laboratory tests. The clinical features of leptospirosis are nonspecific and hence confirmation by diagnostic tests is essential.

Simple rapid tests such as Elisa and MSAT have been included along with MAT and cultures to confirm the diagnosis with appropriate scores (A + B + C = 25 or more). This is the most important aspect of the criteria. It is very important that rapid tests are made easily available in both urban and rural hospitals.

(2) Since these tests become positive only after a week, a scoring based on clinical and epidemiological criteria has been used for the first week (A + B = 26 or more). This scoring system is valuable in diagnosis of severe leptospirosis. But this has less sensitivity than A + B + C as milder cases tend to be missed. [97]

Therefore, it is very essential that investigations to diagnose leptospirosis are definitely done. The A + B criteria should be used to start empiric therapy even for possible leptospirosis (A + B = 20 – 25).

(PART A+B)	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Standard Faine's Criteria	41.9%	84.9	41.9%	84.9%
Modified Faine's criteria	58%	97.4	85.7%	89.9%
Statistical Significance	NS	p value <0.001	p value <0.001	NS

The above table shows the advantage of modified Faine's criteria over Faine's criteria in a study [96].

Dark Ground Microscopy:-

It is an indispensable method for the study of leptospira, but it has its own limitations as a diagnostic aid. Dark ground microscopy is the ideal technique for demonstration of leptospires in cultures.[70] However, it is often used in demonstrating leptospires in clinical specimens especially blood and urine with less than satisfactory results.

The sensitivity and specificity of the DGM are 47.7% to 46.4% respectively indicating high levels of false positive and false negative results. Moreover reading the results are always subjective. [70]

It can be applied in any laboratory where serology or culture is not possible.[71]

ISOLATION AND IDENTIFICATION

Culture into special media is more sensitive than direct microscopy. Leptospires can be isolated from blood, CSF, and peritoneal dialysate fluids during the first 10 days of illness.

Specimens should be collected while the patient is febrile and before antibiotic therapy is initiated.

One or two drops of blood should be inoculated directly into culture medium at the bedside. Survival of leptospires in commercial blood culture media for several days has been reported.[72]

Urine can be cultured after the first week of illness.

Specimens should be collected aseptically into sterile containers without preservatives and must be processed within a short time of collection; best results are obtained when

the delay is less than 1 hour, because leptospires do not survive well in acidic environments.[73]

Cultures are performed in albumin-polysorbate media such as EMJH (Ellinghausen-McCullough-Johnson-Harris) medium, which is available commercially.[74]

Primary cultures are performed in semisolid medium, to which 5-fluorouracil is usually added as a selective agent. Cultures are incubated at 30° C for several weeks, because initial growth may be very slow.

Isolated leptospires are identified to serovar level by traditional serologic methods or by molecular methods, such as pulse field gel electrophoresis.[75]

These techniques are limited in availability to a few reference laboratories. Powerful molecular techniques such as multilocus sequence typing (MLST) and multiple-locus variable number tandem repeat analysis (MLVA) have been applied to the epidemiologic analysis of leptospirosis, but have yet to be widely used.[76, 77]

Indirect Detection Methods-Serological Tests For Leptospirosis :-

Microscopic Agglutination test (MAT)

Most leptospirosis cases are diagnosed by serology. The reference standard assay is the Microscopic agglutination test (MAT), in which live antigens representing different serogroups of leptospires are reacted with serum samples and then examined by darkfield microscopy for agglutination.[73]

The sensitivity of the MAT is low (30%) in the first acute phase specimen, increasing to 63% in the second acute phase and 76% in the convalescent specimen. The specificity of MAT was 97% in all specimens.[78]

This is a complex test to maintain, perform, and interpret, and its use is restricted to a few reference laboratories.

Its main advantage is that it is a good indicator of infecting serogroups, especially late in the illness or in survey, since it detects serovar specific antibodies which tend to peak later.

ELISA:-

ELISA (IgM) is more sensitive than the MAT and simple to perform in a hospital diagnostic laboratory, but it cannot determine the infecting serogroups.

The detection of specific IgM, which usually develops a few days after the onset of fever helps in the fairly rapid diagnosis of current infection.[79, 80]

A titer of 1:40 in non-endemic areas and a titre of 1:80 in endemic areas are considered as significant titre for leptospirosis in early stages.[79]

The sensitivity of IgM detection by ELISA was 52% in the first acute phase, increasing to 89% and 93% in the second acute phase and convalescent specimen respectively. The specificity of IgM ELISA was as high as 94% in all specimens.[78]

Indirect Haemagglutination Assay:-

IHA detects both IgM and IgG classes of antibodies in human sera. The sensitivity of IHA for the detection of leptospirosis was 100%, the specificity was 94%, the positive predictive value was 95%, and the negative predication value was 100%. Performance of IHA was simple, and IHA requires no specialized equipment.[74]

DNA detection

Isolation of leptospires from clinical specimens requires a couple to several weeks for growth, and current serological tests exhibit low sensitivity in the acute phase and require paired sera for definitive sero-diagnosis.

Therefore, detection of leptospiral DNA by PCR has been applied for early diagnosis of leptospirosis in the last two decades. Leptospiral DNA has been amplified from blood, urine, CSF, aqueous humor and tissues.[81]

Recently, real-time PCR has been introduced not only as a rapid and sensitive tool for leptospiral DNA detection but also as a technique to reduce the risk of carryover contamination. [82]

It has been demonstrated that both conventional and real-time PCR are useful for early diagnosis during which antibody production has not begun;

More recently, a **loop-mediated isothermal amplification (LAMP)** method has been developed for detecting pathogenic leptospires.[83]

Unlike PCR, the LAMP method amplifies a target DNA sequence under isothermal conditions for approximately 1 h with high specificity and efficiency, and the results can be assessed with the naked eye, [84] promising lower expenses for equipment.

The LAMP method was applied for detecting leptospiral DNA from mouse kidneys but remains unevaluated for its sensitivity and specificity for human clinical specimens.[82]

Role of diagnostic tests for leptospirosis .[85]

Culture	PCR	MAT	MSAT/Elisa IgM and other rapid screening tests
• Isolation of leptospira organism by culture of blood, CSF and urine are the most definite way of confirming leptospirosis • Culture does not contribute to an early diagnosis as results come late, weeks or even months after inoculation of culture medium.	• PCR is the only available diagnostic test available in the first week of leptospirosis • It is a complicated and expensive test • The serovar cannot be identified by this test	• Gold standard • Complicated, DFM required. • Titers peak late (2nd or 3rd week), but persist longer (5 to 10 years) • Valuable in sero epidemiologic studies • Less sensitive for current diagnosis • Repeat samples required for confirming diagnosis • Requires 24 live serogroup cultures • Cut-off titers controversial **Interpretation of MAT** Single titer • 1:100— significant criteria	• Single positive sample adequate for diagnosis • Simple, sensitive and specific tests • Becomes positive earlier than MAT • Cannot identify the serogroup • Can be done also in small rural hospitals. • Can be easily done for a large number of patients during an epidemic **Other rapid tests are:** • Latex agglutination test • Lepto dipstick • Lepto tek lateral flow • Lepto tek Dri-Dot test

		Diagnostic criteria • Endemic area—1:400 (1:800, 1:1,600) • Non-endemic area—1:100, 1:200 • Serosurvey—1:50 Repeat titer • Four-fold rise/seroconversion	

Abbreviations: CSF, Cerebrospinal fluid; PCR, Polymerase chain reaction; MAT, Microscopic agglutination test; MSAT, Macroscopic slide agglutination test

TREATMENT OF LEPTOSPIROSIS:-

Antibiotic therapy should be initiated as early in the course of the disease as suspicion allows. OD dose of Inj. ceftriaxone has been shown to be as effective as penicillin.[86]

Jarisch-Herxheimer reactions have been reported in patients treated with penicillin[87]. Patients receiving penicillin should be monitored because of the increased morbidity and mortality of such reactions.

Supportive therapy is essential for hospitalized patients. Patients with early renal disease with high-output renal dysfunction and hypokalemia should receive aggressive volume repletion and potassium supplementation to avoid severe dehydration and acute tubular necrosis.

In patients who progress to oliguric renal failure, rapid initiation of hemodialysis reduces mortality and is typically required only on a short-term basis. Renal dysfunction caused by leptospirosis is typically completely reversible.[88]

Patients requiring intubation for SPHS have decreased pulmonary compliance and should be managed as cases of ARDS. Protective ventilation strategies involving low tidal volumes (lower than 6 mL/kg) to avoid alveolar injury caused by high ventilation pressures have been shown to improve survival rates in ARDS dramatically.[89]

Management of leptospirosis [85]

Mild leptospirosis	– Doxycycline 100 mg bd for 7-10 days – Amoxycillin 500 mg qid for 7–10 days – Ampicillin 500–750 mg qid for 7–10 days – Azithromycin 500 mg od for 3 days
Severe leptospirosis	– Penicillin 1.5 million units IV qid for 7 days – Ceftriaxone 1 g IV od for 7 days – Start treatment before 5 days – Empirical therapy recommended (WHO)
Fluid therapy	– Indication: Hypovolemia/Hypotension/Hemorrhage – Fluids: IV saline/Blood transfusion
ARDS/Pneumonia	– Ventilatory support

Prevention:-

Prevention of leptospirosis may be achieved by avoidance of high-risk exposures, adoption of protective measures, immunization, and use of chemoprophylaxis, in varying combinations depending on environmental circumstances and the degree of human activity.

High-risk exposures include immersion in fresh water, as in swimming, and contact with animals and their body fluids.[90]

Reducing direct contact with potentially infected animals and indirect contact with urine-contaminated soil and water remains the most effective preventive strategy available.

Consistent application of rodent control measures is important in limiting the extent of contamination.

Appropriate protective measures depend on the activity, but include wearing boots, goggles, overalls, and rubber gloves. In tropical environments, walking barefoot is a common risk factor.[91]

Immunization of animals with killed vaccines is widely practiced, but the immunity is short-lived and animals require periodic (usually annual) boosters.[92]

Human immunization is not widely practiced. A vaccine containing serovar Icterohaemorrhagiae is available in France for workers in high risk occupations, and a vaccine has been developed for human use in Cuba.[93]

Immunization has been more widely used in Asia, to prevent large-scale epidemics in agricultural laborers. For those who will be unavoidably exposed to leptospires in endemic environments, chemoprophylaxis is recommended.

Weekly doxycycline (200 mg) has been shown to be effective in military personnel without previous exposure who underwent jungle training.[94]

Material and methods:

Source of Data

30 Patients with fever testing Leptospira positive by ELISA IgM admitted in R.L Jalappa Hospital, Tamaka, Kolar, for the duration of one year from February 2012 to March 2013 were selected for the study.

Method of collection of data:

Each patient was evaluated by detailed history, clinical examination & modified Faine's criteria.

These patients underwent the following investigations:-

IgM anti leptospiral antibody by ELISA,

Complete blood count,

Creatine phosphokinase,

Random Blood sugar,

Electrocardiogram,

Chest x-ray,

Blood Urea and Serum Creatinine,

Liver function test (LFT),

Serum electrolytes,

Peripheral smear for MP,

Dengue serology.

CSF analysis, Ultrasound abdomen, CT scan brain, coagulation profile was done as and when required.

Statistical analysis:

Data was entered into Microsoft data sheet after coding and analyzed using EPI info 7 software.

Frequencies and proportions were computed for qualitative data.

Mean and standard deviation was computed for quantitative data. Chi square test was used for categorical data as a test of significance.

Fisher Exact test was used when expected count in 2x2 tables was less than 5. Student t-test was used as test of significance for continuous data.

P value less than 0.05 was considered as statistically significant.

RESULTS:

Statistical analysis:

Table 1: Age distribution of patients

Age in years	No. of patients	%
<20	5	16.7
21-30	8	26.7
31-40	8	26.7
41-50	4	13.3
>50	5	16.7
Total	30	100.0

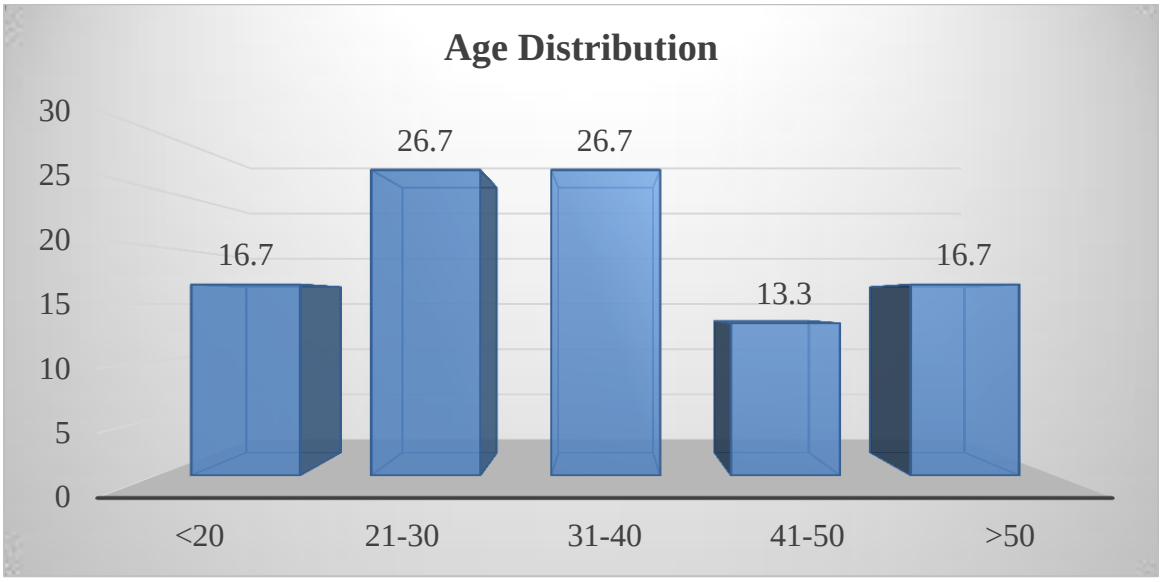


Figure 1: Bar Diagram showing age distribution of patients

In this study it was observed that the mean age group of patients was 36.67±15.66. Majority of them were within the age group of 21 to 40 i.e. 53.4%.

Table 2: Gender distribution of patients

Gender	No. of patients	%
Female	19	63.3
Male	11	36.7
Total	30	100.0

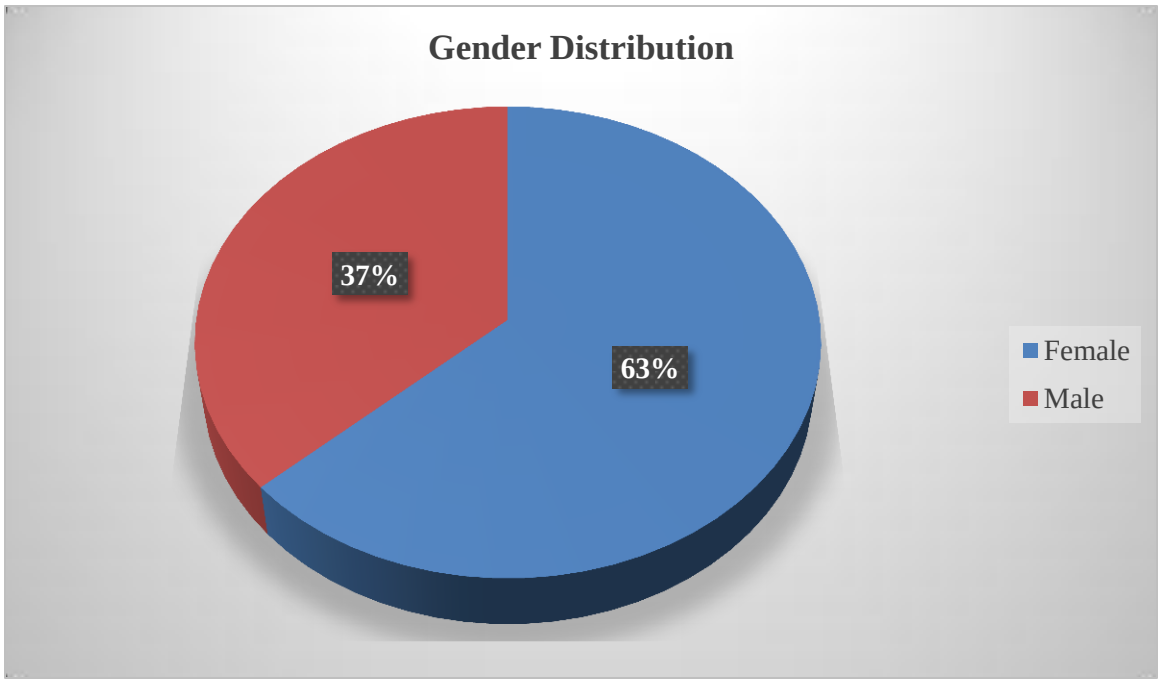


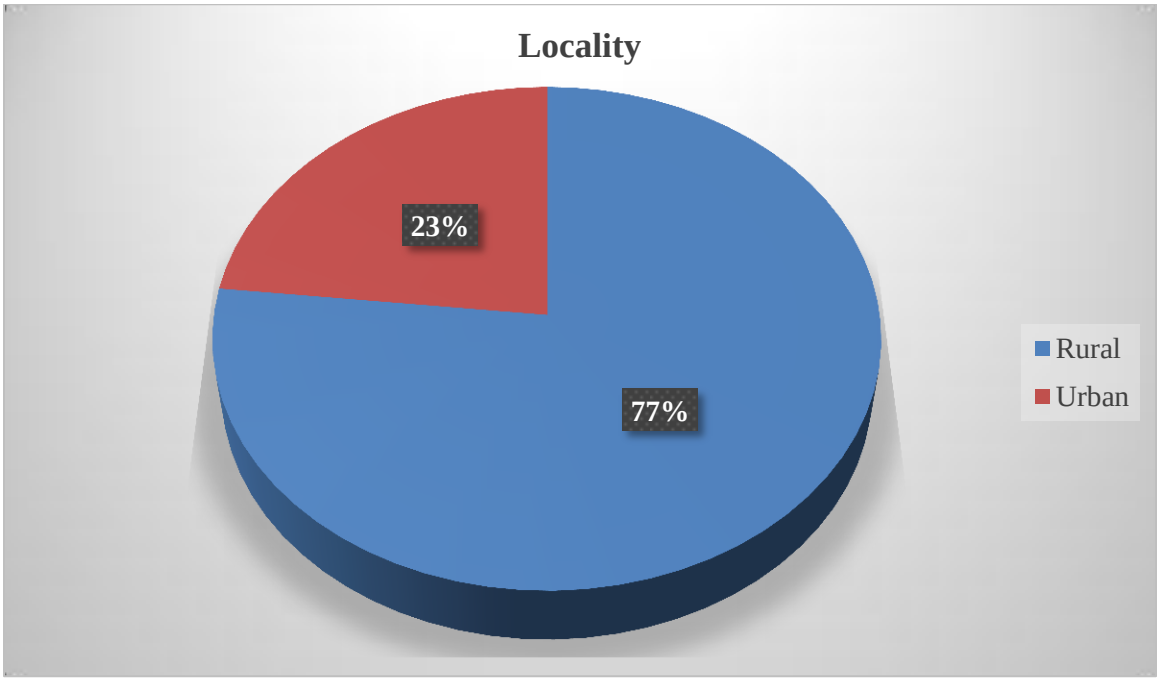
Figure 2: Pie diagram showing Gender distribution

In this study it was observed that majority of the patients was females i.e. 63.3% and 36.7% were males.

Table 3: Showing Distribution of patients according to locality

Locality	No. of patients	%
Rural	23	76.7
Urban	7	23.3
Total	30	100.0

Figure 3: Pie Diagram showing Distribution according to Locality



In this study it was observed that majority of cases are from rural set up i.e. 76.7% and 23.3% from urban area. Hence rural people are at more risk of getting Leptospirosis.

Table 4: Distribution of patients according to Occupation

Occupation	No. of patients	%
Agriculture	19	63.3
House wife	9	30
Mason	1	3.3
Student	1	3.3
Total	30	100.0

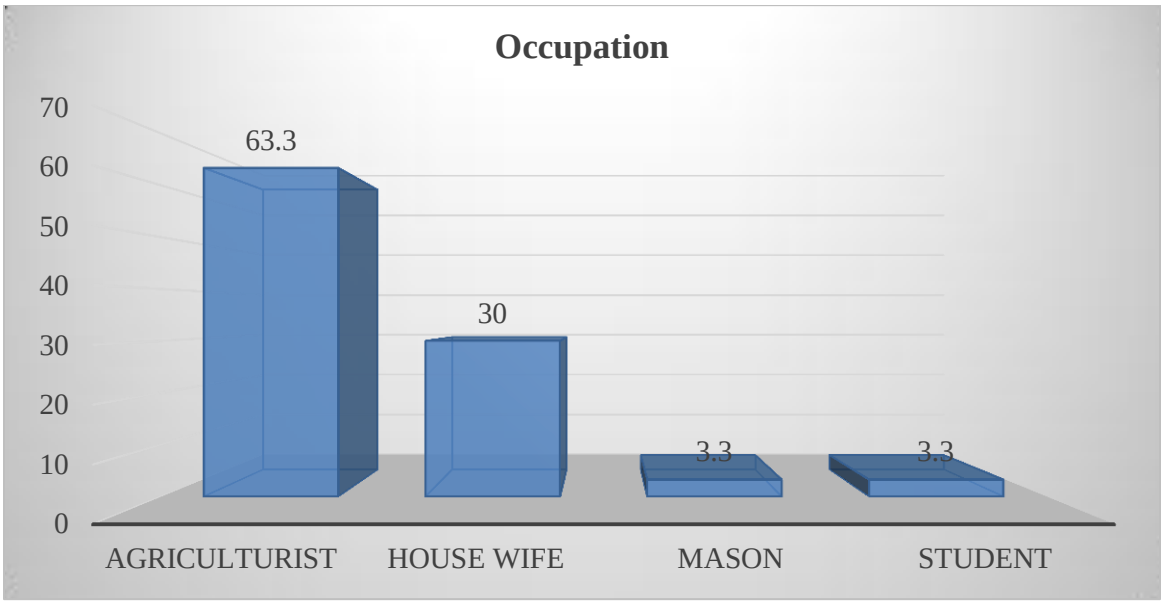


Figure 4: Bar Diagram showing Distribution of Occupation

In this study it was observed that majority of the patients are agriculturists (63.3%) by occupation and 30% are housewives.

Table 5: Distribution of patients according to Clinical Manifestations

Clinical Manifestations	No. of patients (n=30)	%
Fever	30	100.0
Headache	20	66.7
Vomiting	9	30.0
Myalgia	24	80.0
Arthralgia	7	23.3
Cough	13	43.3
Breathlessness	4	13.3
Jaundice	4	13.3
Oliguria	2	6.7
Purpura/Ecchymosis	7	23.3
Altered Sensorium	1	3.3

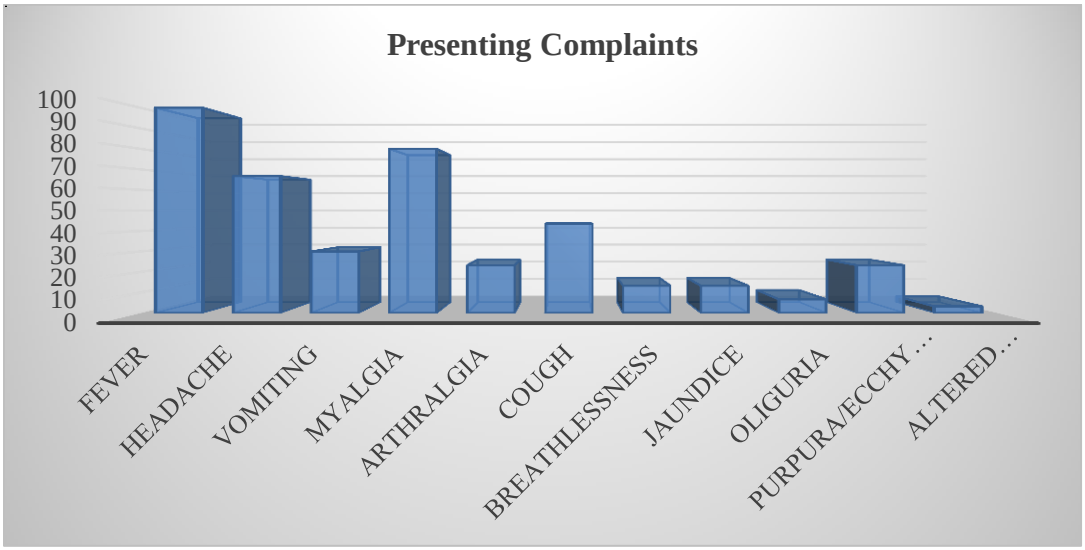


Figure 5: Bar Diagram showing Distribution of patients according to presenting complaints

In this study it was observed that all the patients presented with Fever i.e. 100%. Second most common presentation was Myalgia i.e. in 80%, followed by Headache in 66.7%, Cough in 43.3% and Vomiting in 30% of cases.

Table 6: Distribution of patients according to MFC A+B score

MFC A+B	Frequency	Percent
<26	29	96.7
>26	1	3.3
Total	30	100.0

In the study it was observed that MFC A+B score was <26 in 96.7% of patients and 3.3% had >26 MFC Score

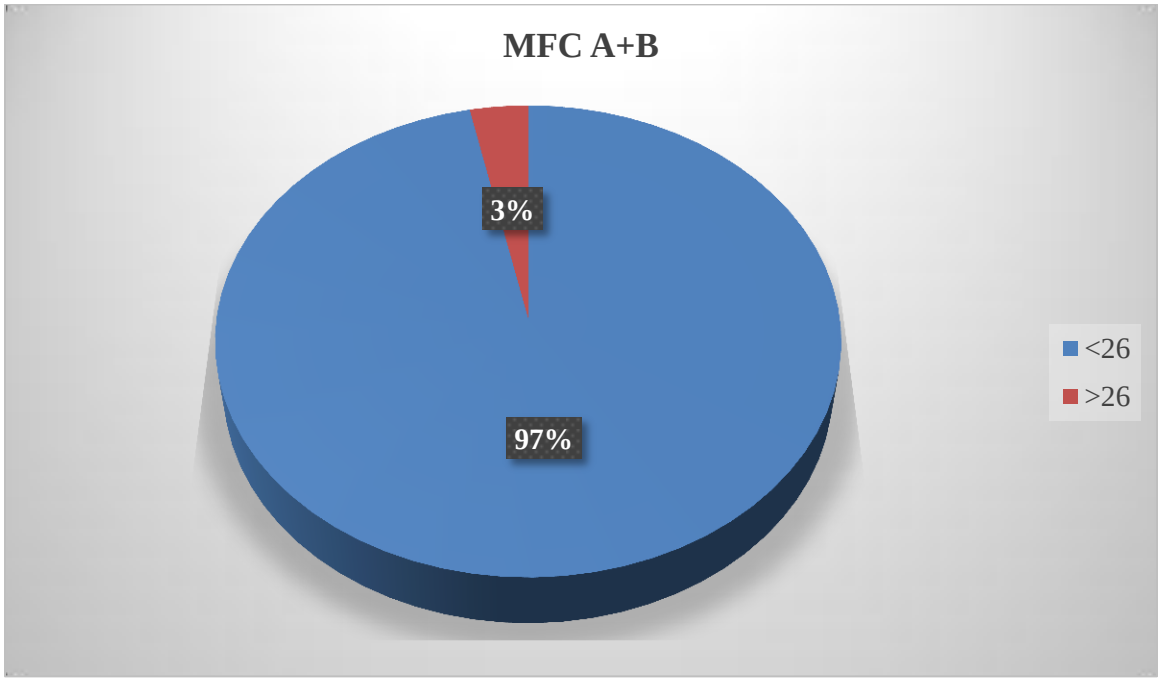


Figure 6: Pie diagram showing distribution of patients with respect to MFC A+B Score

Table 7: Distribution of patients according to MFC A+B +C Score

MFC A+B +C Score	Frequency	Percent
>25	27	90.0
20 to 25	2	6.7
<20	1	3.3
Total	30	100.0

In this study it was observed that majority of the patients had MFC A+B+C score >25 i.e. in 90%. 6.7% had score 20 to 25 and 3.3% had score <20.

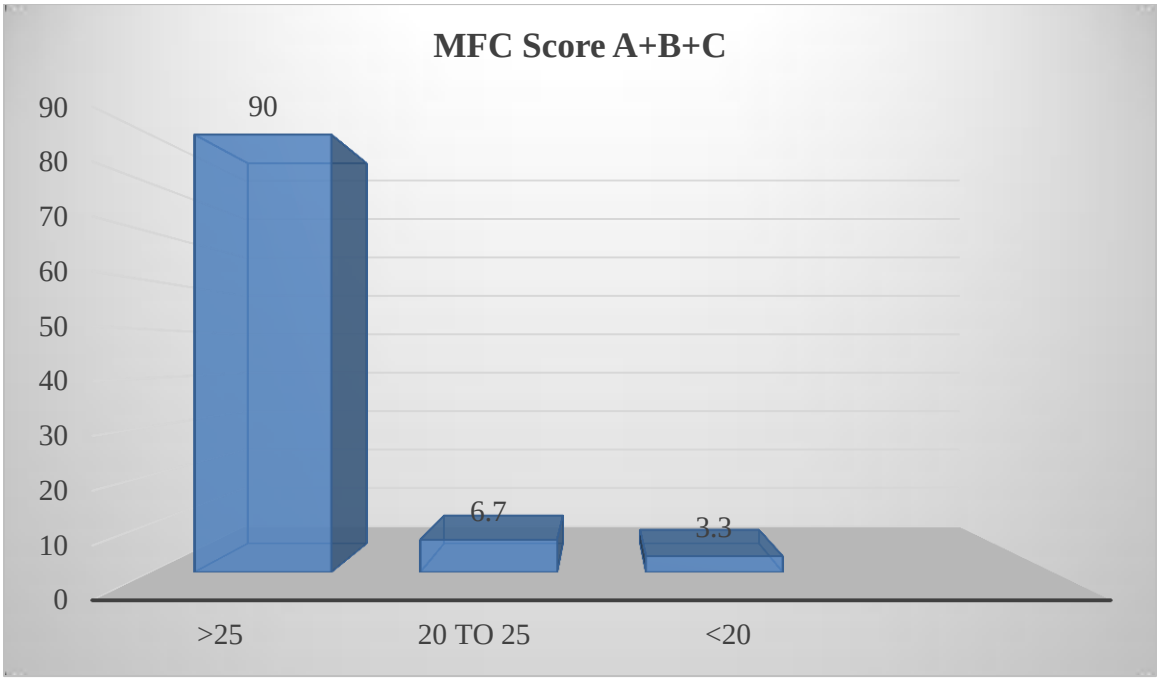


Figure 7: Bar Diagram showing Distribution of patients according to MFC A+B+C score

Table 8: Distribution of Patients according to Signs

Investigations	**No. of patients**	**%**
Conjunctival Suffusion		
• Negative	10	33.3
• Positive	20	66.7
Pallor		
• Negative	25	83.3
• Positive	5	16.7
Icterus		
• Negative	25	83.3
• Positive	5	16.7
Significant Lymph node enlargement		
• Negative	29	96.7
• Positive	1	3.3
Hepatomegaly		
• Negative	18	60.0
• Positive	12	40.0
Splenomegaly		
• Negative	24	80.0
• Positive	6	20.0
RS		

• Crepitations present	4	13.3
• NAD	26	86.7
CNS		
• Altered sensorium +	1	3.3
• NAD	29	96.7

In this study it was observed that 66.7% had conjunctival suffusion, 16.7% had pallor, 16.7 had Icterus, 3.3% had significant lymph node enlargement, 40% had Hepatomegaly, 20% had splenomegaly, 13.3% had crepitations and 3.3% had altered sensorium.

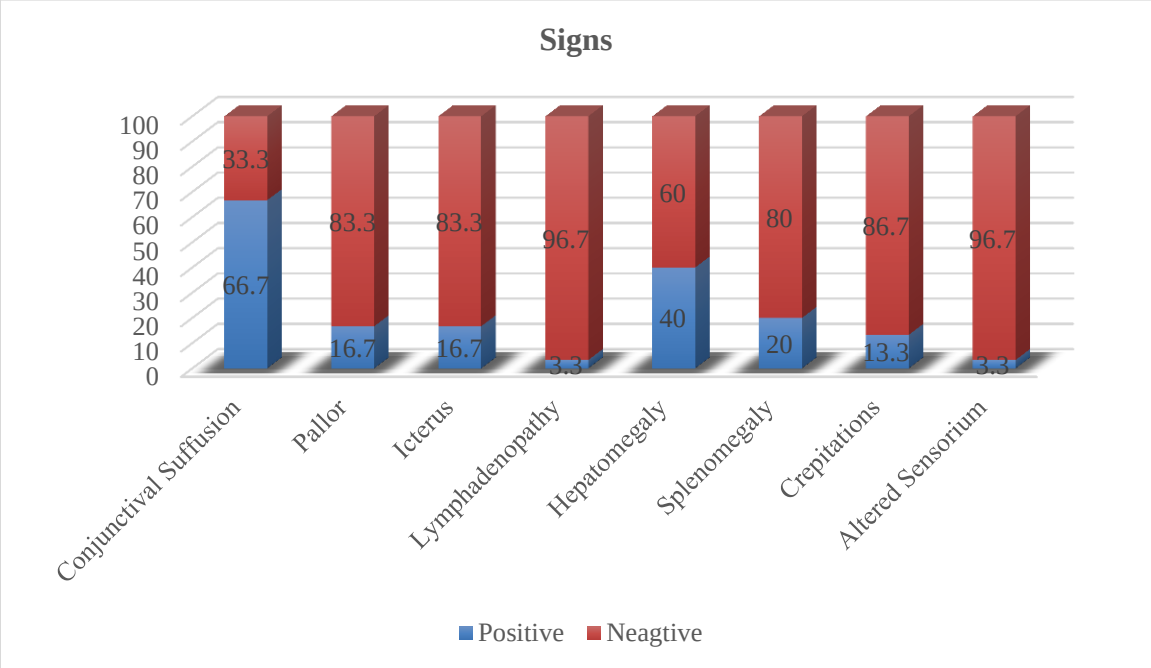


Figure 8: Bar Diagram showing Distribution of patients according to signs

Table 9: Distribution of Patients according to Investigations Hb%, Total Leucocyte count, Platelet count

Investigations	**No. of patients**	**%**
Hb%		
• <11	14	46.7
• >11	16	53.3
Total Leucocyte count		
• <4000	7	23.3
• 4000 -11,000	15	50.0
• >11,000	8	26.7
Platelet count		
• <20,000	1	3.3
• 20,000 to 30,000	1	3.3
• 30,000 to 40,000	2	6.7
• 40,000 to 50,000	3	10.0
• 50,000 to 1,00,000	7	23.3
• 1,00,000 to 1,50,000	3	10.0
• >1,50,000	13	43.3

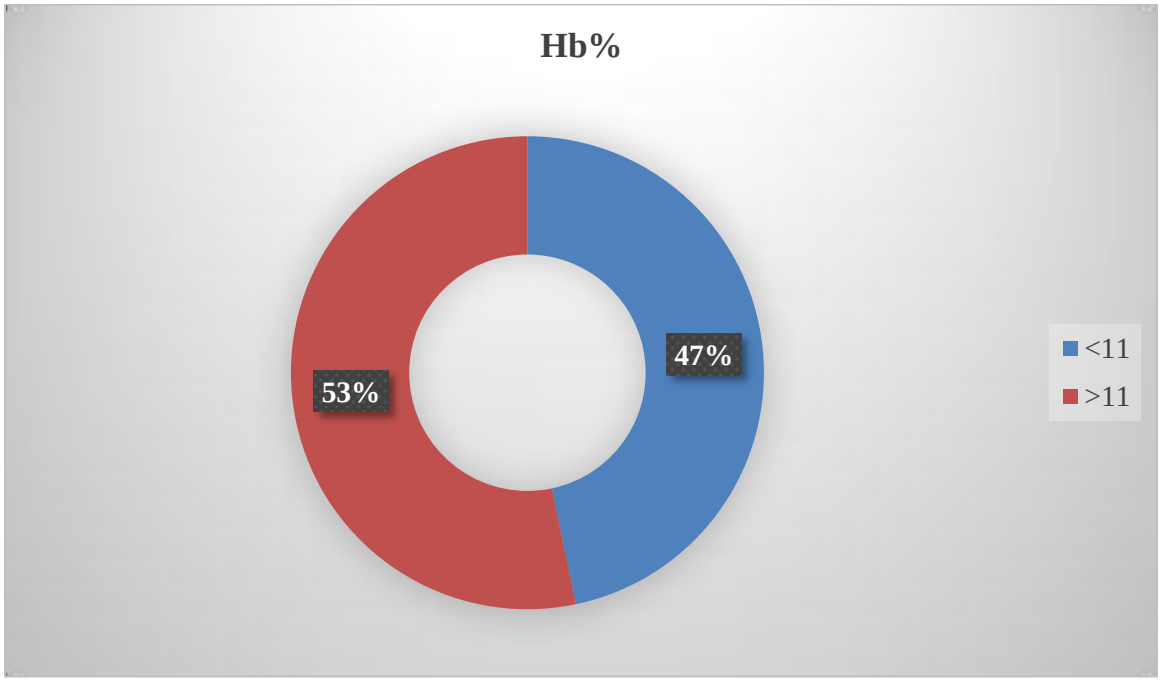


Figure 9: Pie diagram showing distribution of patients according to Hb%

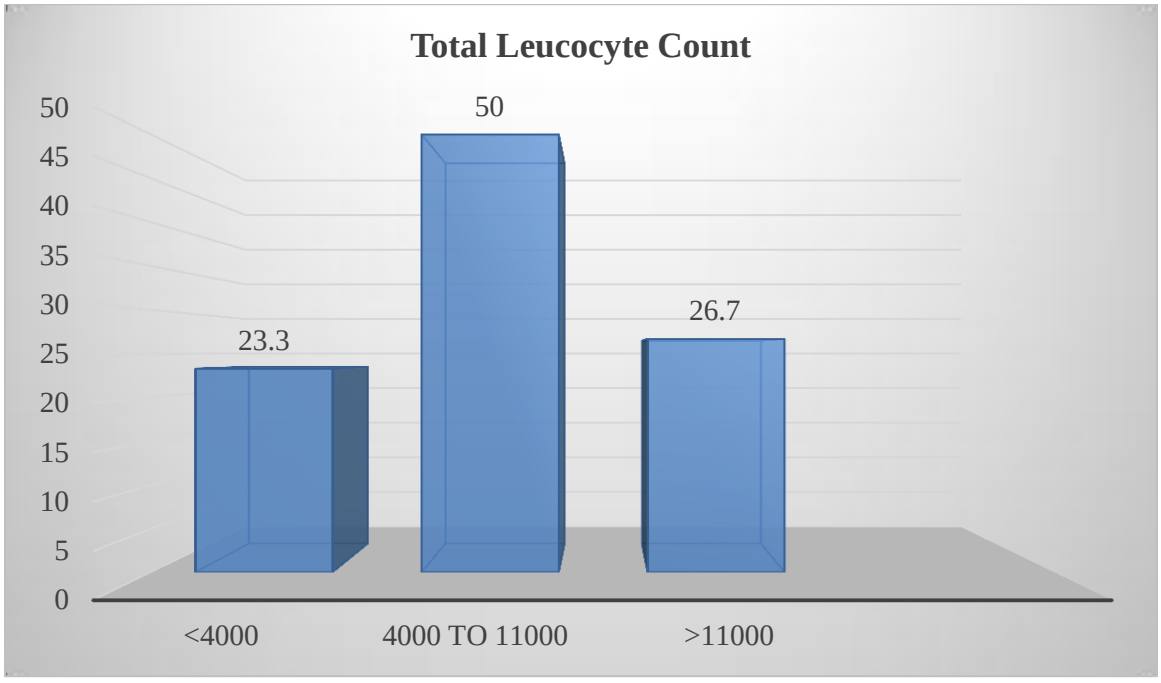


Figure 10: Bar Diagram Showing Distribution of patients according to Total Leucocyte count

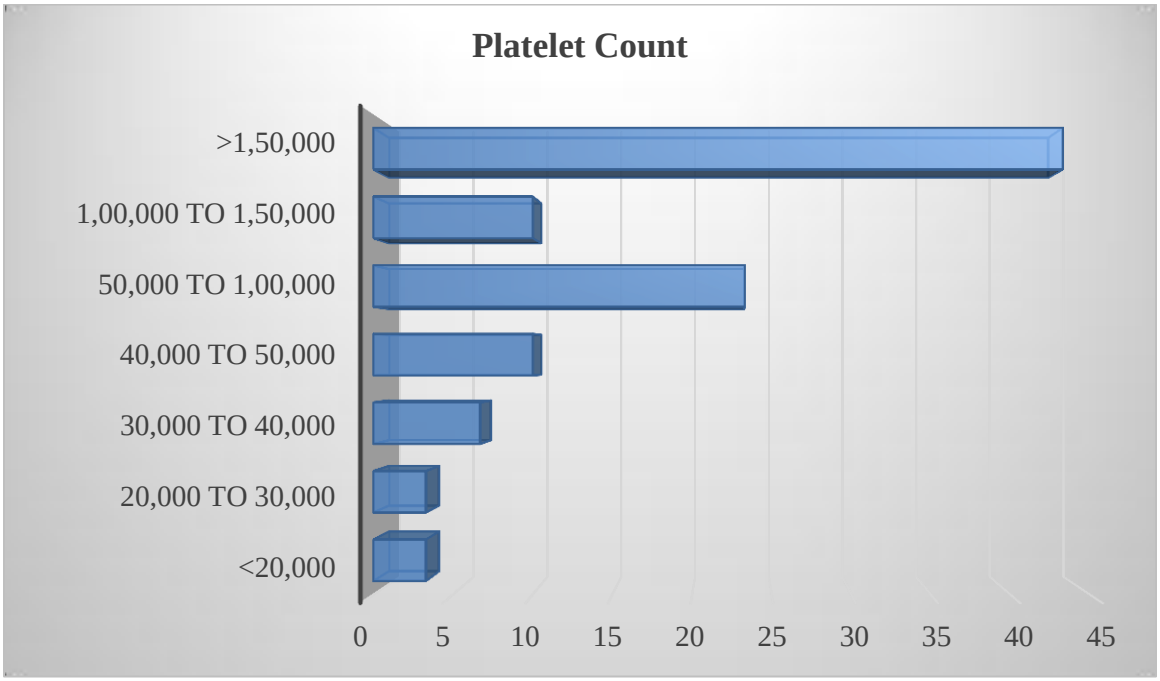


Figure 11: Bar Diagram showing Distribution of patients according to Platelet count

In this study it was observed that 46.7% had anemia, 23.3% had leucopenia, 26.7% had Leucocytosis and 56.7% had platelet count less than 1,50,000/cumm.

Table 10: Distribution of Patients according to Investigations CPK, Urine Routine and RBS

	No of Patients	**%**
CPK		
• 24 to 195	26	86.7
• >195	4	13.3
Urine Routine		
• WBC	2	6.7
• RBC	1	3.3
• Albumin	8	26.7
• Bile Salts	1	6.3
• Normal	18	60
RBS		
• <70	3	10.0
• 70 to 140	21	70.0
• >140	6	20.0

In this study it was observed that 13.3% had increased CPK levels, 6.7% had WBC in urine, 3.3% had RBC, 26.7% had Albumin in urine.

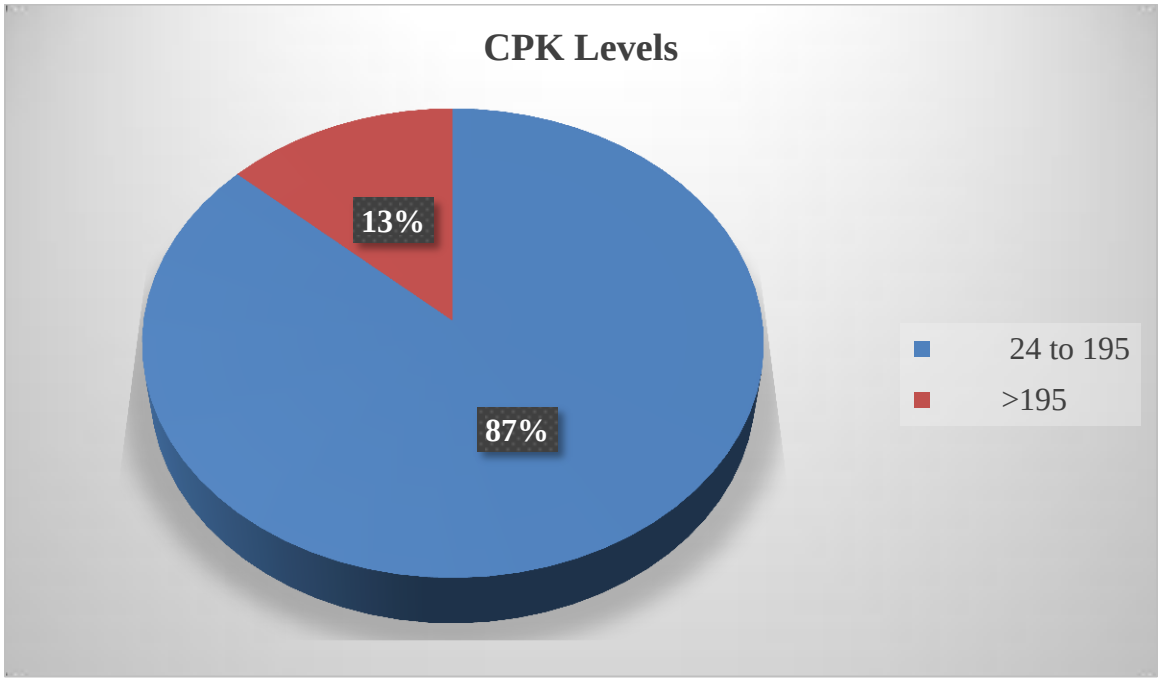


Figure 12: Pie diagram showing distribution of patients according to CPK levels

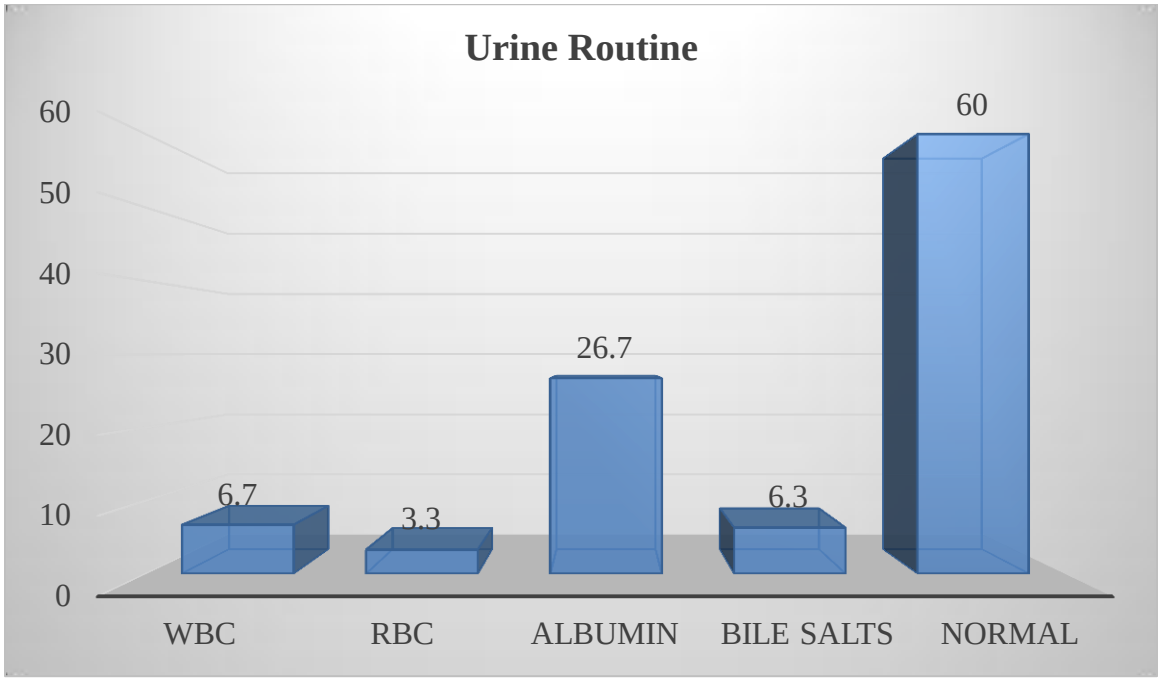


Figure 13: Bar Diagram showing distribution of patients according to Urine investigations

Table 11: Distribution of Patients according to Investigations of Renal Function

	No of Patients	%
Blood Urea		
• <40	23	76.7
• >40	7	23.3
Serum Creatinine		
• <1.4	26	86.7
• >1.4	4	13.3

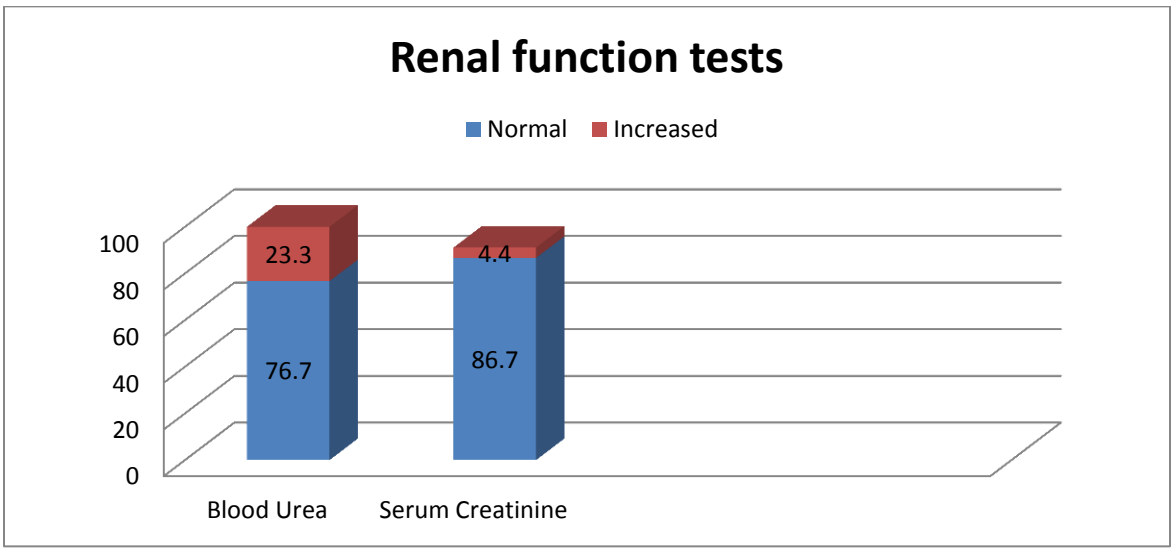


Figure 14: Bar diagram showing distribution of patients according to Renal function tests.

In this study it was observed that 23.3% had increased Blood urea and 13.3 had increased Serum creatinine.

Table 12: Distribution of Patients according to Electrolytes

Electrolytes	**No of Patients**	**%**
Na		
• <135	15	50.0
• 135 to 145	15	50.0
K		
• <3.5	4	13.3
• 3.5 to 4.5	25	83.3
• >4.5	1	3.3

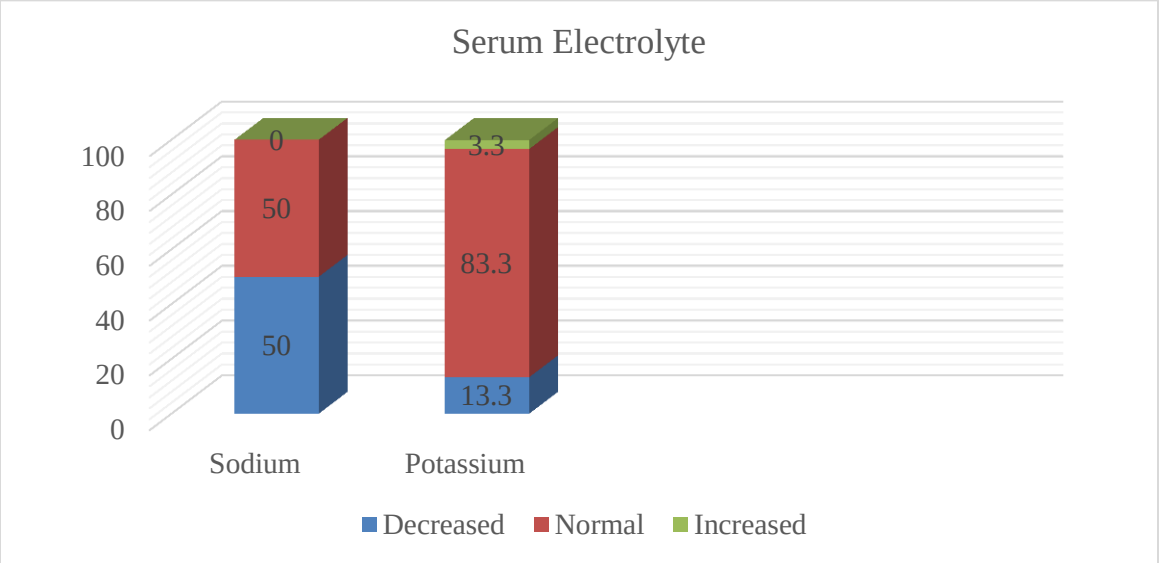


Figure 15: Bar diagram showing distribution of patients according to Serum Electrolyte

In this study it was observed that 50% had decreased sodium levels and 13.3% had decreased potassium, 3.3% had increased potassium levels.

Table 13: Distribution of Patients according to Investigations of Liver Function

LFT	**No of Patients**	**%**
Total bilirubin		
• <1.2	23	76.7
• >1.2	7	23.3
Direct bilirubin		
• 0.2-0.4	20	66.6
• >0.4	10	33.4
SGOT		
• <40	12	60.0
• >40	18	40.0
SGPT		
• <40	18	60.0
• >40	12	40.0
Albumin		
• <3.5	11	36.7
• >3.5	19	63.3

In this study it was observed that 40% had increased Total Bilirubin, 36.7% had increased direct bilirubin, 60% had increased SGOT, 40% had increased SGPT and 36.7% had hypoalbuminemia.

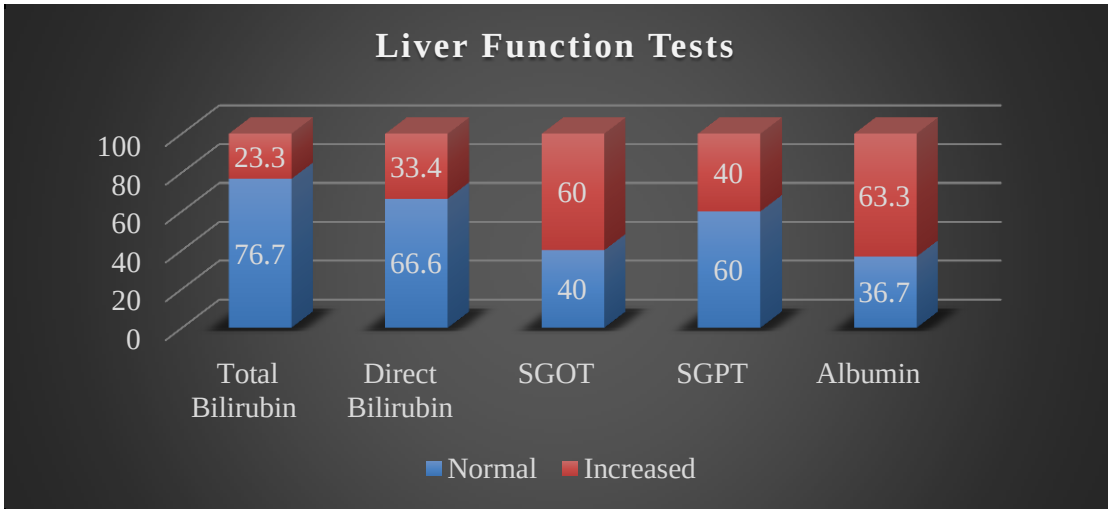


Figure 16: Bar diagram showing distribution of patients according to Liver function tests

Table 14: Distribution of patients according to Chest X-ray findings

CXR	No. of patients	%
NRA	23	76.7
X ray changes present (Opacity, patches, infiltrates)	7	23.3
Total	30	100.0

In this study it was observed that 23.3 had chest x ray findings like opacity and patches.

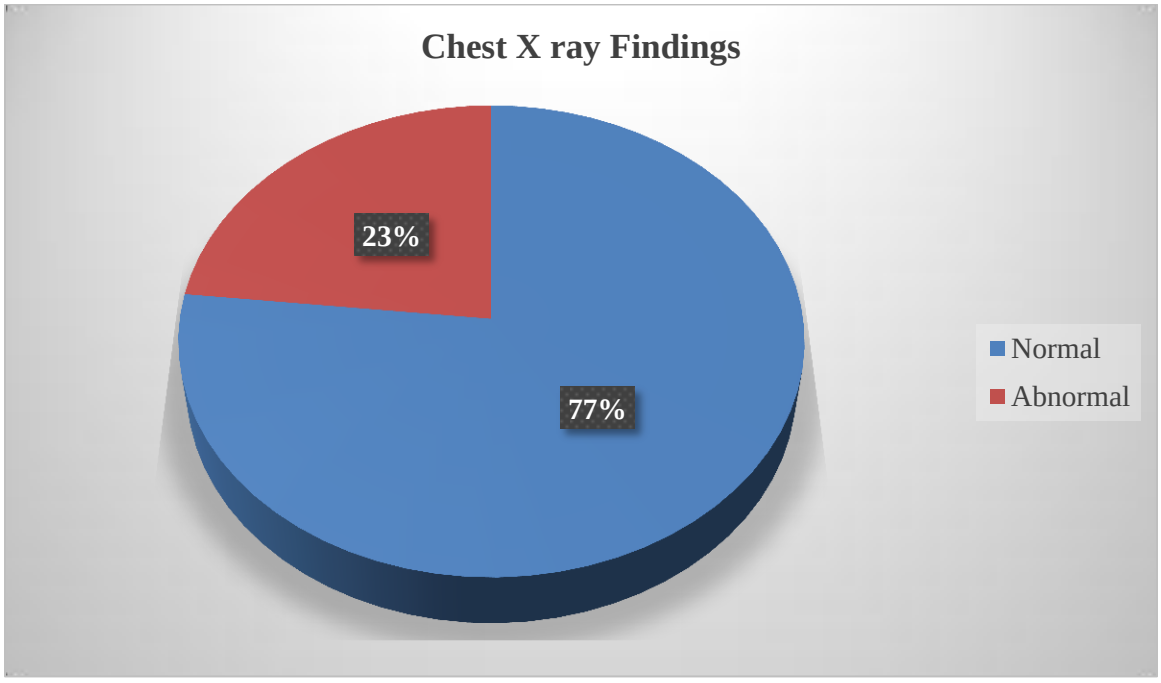


Figure 17: Pie diagram showing Chest X ray findings among patients

Table 15: Distribution of patients according to antibiotic treatment

Antibiotic	No of Patients	%
Inj Ceftriaxone		
• Given	23	76.7
• Not Given	7	23.3
Inj CP		
• Given	10	33.3
• Not Given	20	66.7
Doxycycline		
• Given	22	73.3
• Not Given	8	26.4
Two or More antibiotics		
• Given	23	76.7
• Not Given	7	23.3

In this study it was observed that ceftriaxone was given for 76.7% of patients, crystalline penicillin was given for 33.3% of patients, doxycycline was given for 73.3% of patients and among 76.7% of patients two or more antibiotics was used for treatment.

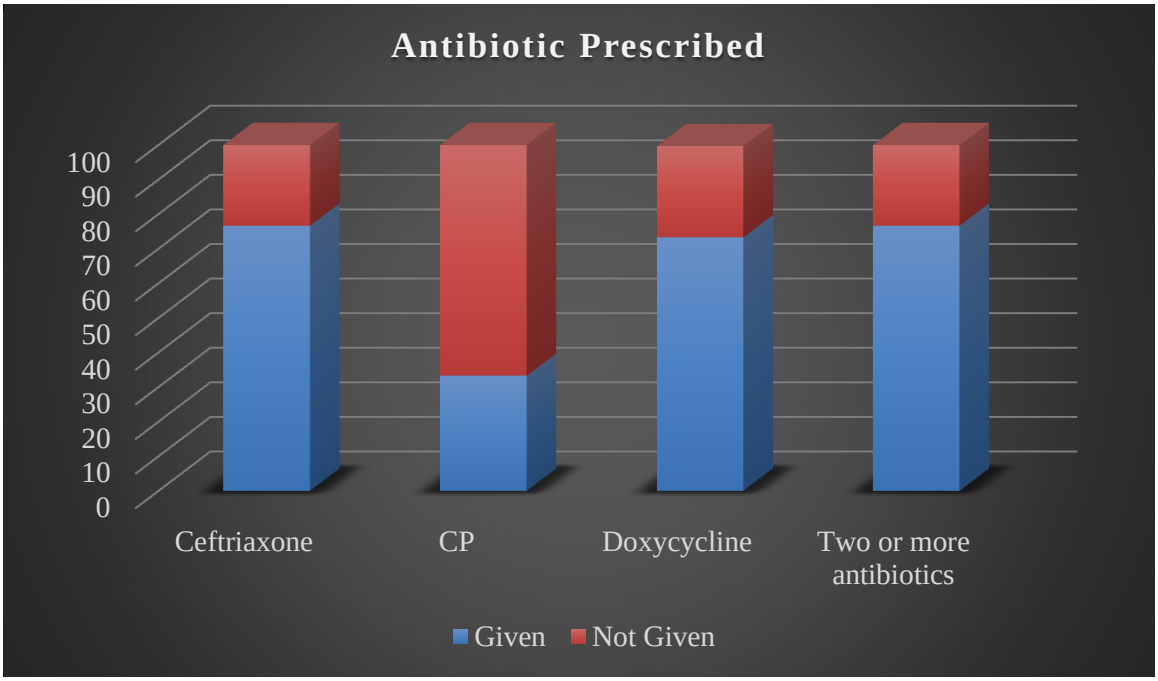


Figure 18: Bar diagram showing distribution of patients according to antibiotic prescription

Table 16: Distribution of patients according to Platelet transfusion

Transfusions	No. of patients	%
Not transfused	25	83.3
Transfused	5	16.7
Total	30	100.0

In this study it was observed that only 20% of patients required platelet transfusion.

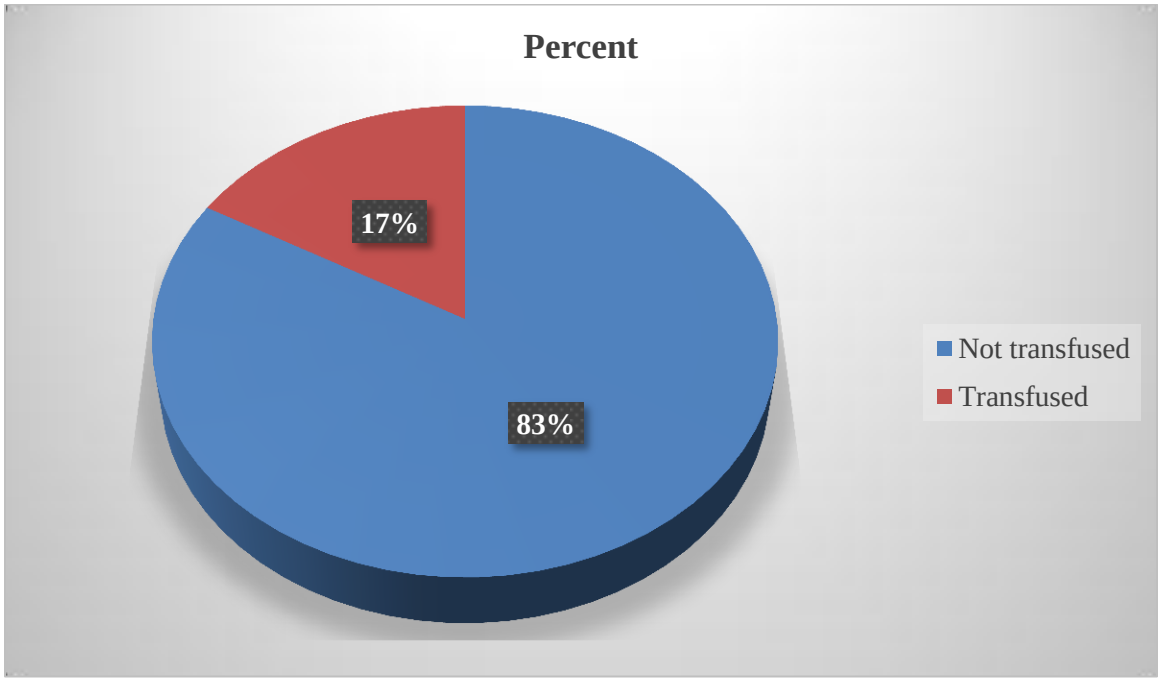


Figure 19: Pie diagram showing distribution of patients according to Platelet transfusion

Table 17: Distribution of patients according to Duration of Hospital stay

Duration of Hospital stay	No. of patients	%
1-2 days	2	6.7
3-5 days	14	46.7
>5 days	14	46.7
Total	30	100.0

In this study it was observed that majority of the patients had a duration of stay more than 2 days i.e. 93.7%

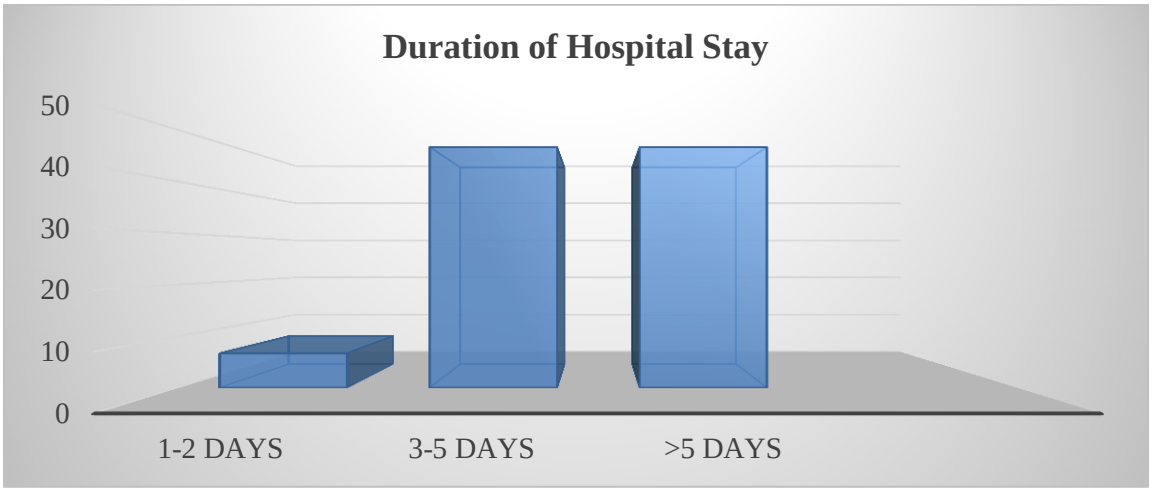


Figure 20: Bar diagram showing distribution of patients according to Duration of Hospital Stay

Table 18: Showing association between Fever and Outcome among the Leptospirosis cases

		Outcome		Total
		Expired	Recovered	
Fever	Present	2	28	30
Total		2	28	30

All the 30 patients in this study presented with fever and among them only 2 cases expired. There is no significant association between Fever and poor outcome.

Table 19: Showing association between Headache and Outcome among the Leptospirosis cases

		Outcome		Total	
		Expired	Recovered		
Headache	Absent	1	9	10	X^2= 0.268, df =1, p=0.605
	Present	1	19	20	
Total		2	28	30	

In this study it was observed that majority of the patients with headache i.e. 19 out of 20 recovered and only one patient expired, therefore there is no significant association between Headache and poor outcome.

Table 20: Showing association between Myalgia and Outcome among the Leptospirosis cases

		Outcome		Total	
		Expired	Recovered		
Myalgia	Absent	1	5	6	X^2= 1.205, df =1, p=0.272
	Present	1	23	24	
Total		2	28	30	

In this study it was observed that majority of the patients with Myalgia i.e. 23 out of 24 recovered and only one patient expired, hence there is no significant association between Myalgia and poor outcome.

Table 21: Showing association between Oliguria and Outcome among the Leptospirosis cases

		Outcome		Total	
		Expired	Recovered		
Oliguria	Absent	1	27	28	X^2= 6.467, df =1, p=0.011*
	Present	1	1	2	
Total		2	28	30	

*p value significant at 0.05

In the study it was observed that only 2 patients presented with oliguria and among them 1 patient recovered and one patient expired. Similarly among the 28 patients there was no

oliguria and only one patient expired among them. There was significant association between Oliguria and poor outcome in leptospirosis.

Table 22: Showing association between Jaundice and Outcome among the Leptospirosis cases

		Outcome		Total	
		Expired	Recovered		
Jaundice	Absent	1	25	26	X^2= 2.493, df =1, p=0.114
	Present	1	3	4	
Total		2	28	30	

In the study it was observed that only 4 patients presented with Jaundice and among them 3 patients recovered and one patient expired. Similarly among the 26 patients there was no jaundice and only one patient expired among them, this showed that there was no significant association between Jaundice and poor outcome in leptospirosis.

Table 23: Showing association between Altered Sensorium and Outcome among the Leptospirosis cases

		Outcome		Total	
		Expired	Recovered		
Altered Sensorium	Absent	2	27	29	X^2= 0.074, df =1, p=0.786
	Present	0	1	1	
Total		2	28	30	

In the study it was observed that only 1 patient presented with Altered Sensorium and 29 patients without altered sensorium.

The patient who presented with altered sensorium recovered and was discharged.

There was no significant association between altered sensorium and poor outcome in leptospirosis.

Table 24: Showing association between Breathlessness and Outcome among the Leptospirosis cases

		Outcome		Total	
		Expired	Recovered		
Breathlessness	Absent	1	25	26	X^2= 2.493, df =1, p=0.114
	Present	1	3	4	
Total		2	28	30	

In the study it was observed that only 4 patients presented with dyspnea and among them 3 patients recovered and one patient expired. Similarly among the 26 patients there was no dyspnea and only one patient expired among them. There was no significant association between Dyspnea and poor outcome in leptospirosis.

Table 25: showing mean difference of Hb%, Total count, ESR and Platelet count among Recovered and Expired Leptospirosis cases

	Outcome	N	Mean	Std. Deviation	t value	df	p-value (two sided)
Hb (gm %)	Recovered	28	10.5286	3.04532	-0.867	28	0.393
	Expired	2	12.4500	2.47487			
TC (Cells/cumm)	Recovered	28	9078.57	8285.344	-0.593	28	0.558
	Expired	2	12700.00	9899.495			

ESR	Recovered	28	36.54	20.646	-1.244	28	0.224
	Expired	2	55.00	1.414			
Platelet count (cumm)	Recovered	28	157646.43	127209.205	1.169	28	0.252
	Expired	2	50500.00	48790.368			

In the study it was observed that among the leptospirosis patients there is no significant mean difference between the recovered and Expired for Hb%, Total Count, ESR and Platelet count. Hence these parameters will not be useful in predicting the outcome in leptospirosis.

Table 26: showing mean difference of CPK and RBS among Recovered and Expired Leptospirosis cases

	Outcome	N	Mean	Std. Deviation	t value	df	p value (two sided)
CPK(U/I)	Recovered	28	92.14	78.164	-3.419	28	0.002**
	Expired	2	343.50	342.947			
RBS(mg/dl)	Recovered	28	109.18	42.736	-0.138	28	0.891
	Expired	2	113.50	45.962			

**p value significant at 0.01

In the study it was observed that among the leptospirosis patients there is no significant mean difference between the recovered and expired for RBS but there was significant difference for CPK among the recovered and expired cases i.e. Mean CPK levels among

the recovered patients was 92.14 ± 78.16 and among the expired patients mean CPK was 343.50 ± 342.94 and the mean difference of 251.36 was significant.

Hence high values of CPK will act as an important parameter in predicting the poor outcome among patients with leptospirosis.

Table 27: showing mean difference of Renal Parameters among Recovered and Expired Leptospirosis cases

	Outcome	N	Mean	Std. Deviation	t value	df	p value (two sided)
BU(mg/dl)	Recovered	28	31.04	19.049	-6.787	28	0.0001*
	Expired	2	127.50	27.577			
SC (mg/dl)	Recovered	28	0.8193	0.28930	-8.373	28	0.0001*
	Expired	2	2.9500	1.06066			

**p value significant at 0.01

In the study it was observed that among the leptospirosis patients there was significant difference for Blood Urea and Serum Creatinine among the recovered and expired cases. Hence elevated blood urea and serum creatinine levels will act as important parameters in predicting the poor outcome among leptospirosis.

Table 28: showing mean difference of Sodium and Potassium among Recovered and Expired Leptospirosis cases

	Outcome	N	Mean	Std. Deviation	t value	df	p value (two sided)
Na^+(mEq/L)	Recovered	28	132.93	6.104	-1.953	28	0.06
	Expired	2	141.50	.707			
K^+(mEq/L)	Recovered	28	3.9857	.45356	-3.448	28	0.002**
	Expired	2	5.1500	.63640			

**p value significant at 0.01

In the study it was observed that among the leptospirosis patients there was significant difference for Sodium and Potassium levels among the recovered and expired cases.

Hence Sodium and potassium levels will act as important parameters in predicting the outcome among leptospirosis.

Table 29: showing mean difference of Liver Function Tests among Recovered and Expired Leptospirosis cases

	Outcome	N	Mean	Std. Deviation	t value	df	p value (two sided)
TB(mg/dl)	Recovered	28	2.2818	5.15188	-0.631	28	0.533
	Expired	2	4.6500	4.31335			
DB	Recovered	28	1.6918	4.34364	-0.743	28	0.464
	Expired	2	4.0500	4.17193			
SGOT	Recovered	28	67.79	56.717	-2.366	28	0.025*
	Expired	2	166.00	56.569			
SGPT	Recovered	28	49.54	39.512	-2.601	28	0.015*
	Expired	2	128.00	73.539			

*p value significant at 0.05

In the study it was observed that among the leptospirosis patients there was significant difference for SGOT and SGPT levels among the recovered and expired cases. SGOT and SGPT levels were higher among the expired patients, Hence SGOT and SGPT will act as important parameters in predicting the outcome among leptospirosis.

Table 30: Mean difference in optical density values of IgM ELISA Leptospira with respect to outcome.

	Outcome	N	Mean	Std. Deviation	t value	df	p value (two sided)
Optical Density	Recovered	28	14.82	1.611	0.699	28	0.490
	Expired	2	14	1.41			

In the study it was observed that there is no significant difference among recovered and expired patients with respect to Optical density of IgM.

DISCUSSION

This study was undertaken with an objective to study the clinical profile of leptospirosis, its management and factors predicting the outcome.

Factors associated with outcome are oliguria, dyspnoea, pulmonary rales, altered mental status, and higher serum potassium levels. The outcome of the patient taken in to consideration in the study was either recovery or death of the patient.

Haemoptysis, meningism, muscle tenderness and high serum bilirubin levels were also significant predictors of mortality.[99]

A high CPK level was also associated with mortality.[100]

A total of 30 Patients testing ELISA IgM positive for Leptospirosis above 18yrs of age was taken up for the study.

ELISA IgM is a simple and sensitive test which measure IgM antibodies, it is used to diagnose current leptospirosis at a very early stage and a single sample is adequate. It is useful in making an early diagnosis, as it is positive as early as 2 days into illness, a time when the clinical manifestations may be nonspecific. It was found to be 100% sensitive and 93% specific in one study.[101]

Age of the patients in the study ranged from 18 - 77 years. In the study it was observed that the mean age group of patients was 36.67±15.66. Majority of them were within the age group of 21 to 40 i.e. 53.4%. This was comparable to a study by Singh et al, where the commonest age group affected was also between 21 to 40 years.[102]

Majority of the cases are from rural set up i.e. 76.7% and 23.3% from urban area. Exposure to cattle and rodents is more common in a rural setting; hence rural people are at more risk of getting Leptospirosis.

Certain agricultural laborers are at high risk, and intense exposure to leptospirosis has been documented in rice, sugarcane and rubber plantation workers.[20, 21]

In the study it was observed that majority of the patients was females i.e. 63.3% and 36.7% were males, which is in contrast to a study by Muthusethupathi et al, where 88% of patients were males. [103]

Out of the 19 women who tested positive for Leptospirosis by ELISA IgM positive, 10 (52.6%) were agriculturists by occupation and 9 (47.4%) were housewives by occupation.

Majority of the patients in the study were agriculturists by occupation (63.3%) and 30% were housewives.

A study done in Madras in 1990-91 by M.A Muthusethupathi et al, which included 57 cases showed outdoor manual workers accounted for 49% of their cases.[103]

Leptospirosis was traditionally considered an occupational risk among persons exposed to contaminated water or infected animal urine, which is now being recognized as one of the common causes of febrile illness in tropical environments worldwide.

Clinical Features: In this study it was observed that all the patients presented with Fever i.e. 100%. Second most common presentation was Myalgia i.e. in 80%, followed by Headache in 66.7%, Cough in 43.3% and Vomiting in 30% of cases. Purpura/Ecchymosis

was seen in 23.3 % of the cases. Less common features were jaundice 13.3 %, breathlessness 13.3 %, oliguria 2% and altered sensorium in 3.3 % of the cases.

Muthusethupathi et al, have found clinical features of fever (100%), myalgia (82%), jaundice (85%), Oliguria (72%), bleeding (25%) and altered sensorium (49%).

Deodhar et al, found clinical features of headache in (89%), myalgias in (56%), jaundice in (53.5%), ecchymosis and/or petechiae were seen in (28.5%) and altered sensorium in (3%) of their study patients.[104]

The nonspecific constitutional symptoms reported in the study are comparable to the above mentioned studies but the incidence of organ involvement is different. This may be due to different infecting serovars, environment and host factors.

All the 30 patients presented with fever and among them only 2 cases expired. 20 (66.7%) patients in the study had headache of which 19 recovered one patient expired. Majority of the patients with Myalgia i.e. 23 out of 24 (80%) recovered and one patient expired.

Four (13.3%) patients presented with Jaundice and among them 3 patients recovered and one patient expired. Similarly among the 26 patients there was no jaundice and only one patient expired among them. One patient presented with Altered Sensorium and 29 patients without altered sensorium. The patient recovered and was discharged, so there was no significant association with mortality with the above mentioned symptoms.

Also 4 (13.3%) patients presented with dyspnea and among them 3 patients recovered and one patient expired. Similarly among the 26 patients there was no dyspnea and only one patient expired among them. There was no significant association between dyspnea (p=0.114) and outcome in leptospirosis.

Also in this study it was observed that only 2(6.7%) patients presented with oliguria and among them 1 patient recovered and one patient expired. Similarly among the 28 patients there was no oliguria and only one patient expired among them, therefore there was significant association between oliguria (p=0.011) and mortality in leptospirosis.

B. Doudier et al noted that oliguria was an independent prognostic factor in leptospirosis, [105] and also Seguro et al noted that the mortality rate for oliguric patients with acute renal failure appeared to be higher than that for patients with persistent diuresis.[106]

Conjunctival suffusion was a feature in 20 (66.7%) of patients, 5 (16.7%) patients had pallor, 5 (16.7%) patients had Icterus, 1 (3.3%) patient had Lymphadenopathy, 12 (40%) patients had Hepatomegaly, 6 (20%) patients had splenomegaly, 4 (13.3%) pateints had crepitations and 1 (3.3%) patient had altered sensorium.

In a study by Deodhar et al 65.5% had conjunctival suffusion and 67% had hepatomegaly [104] and in the study by Muthusethupathi et al 58% of the patients had conjunctival suffusion.[103] The findings in the study are comparable to the above mentioned studies.

Four (13.3%) of patients presented with hypotension (B.P <90/60mmhg), of which 3 of them recovered and 1 patient expired due to multi organ dysfunction. None of the patients had myocarditis. Their ECG findings were not suggestive of myocarditis and all the 3 patients who recovered responded to parentral administration of fluids.

In this study it was observed that 14 (46.7%) patients had anemia, 7 (23.3%) patients had leucopenia, 8 (26.7%) patients had Leucocytosis and 17 (56.7%) patients had platelet count less than 150000 of which 1 (3.3%) patient had platelet count less than 20,000/cumm, 2 (6.7 %) patients had a platelet count between 30,000 to 40,000/cumm and 7 (23.3%) patients had platelet count between 50,000 to 1,00,000/cumm. The lowest platelet count recorded in this study was 16,000/cumm.

In the study by Deodhar et al 9% had a haemoglobin value <10 g/dl and 26% of the cases had leucocytosis.[104]

In this study it was observed that among the leptospirosis patients there is no significant mean difference between the recovered and expired for Hb%, Total Count, ESR and Platelet count. Hence these parameters were not useful in predicting the outcome.

The increased incidence of anemia could be due nutritional deficiency or anemia that was pre-existing prior to admission.

In this study 4 (13.3%) of patients had increased CPK levels, and in urine routine 6.7% had WBC in urine, 3.3% had RBC, 8 (26.7%) patients had Albumin in urine.

There was significant difference for CPK among the recovered and expired cases i.e. Mean CPK levels among the recovered patients was 92.14 ± 78.16 and among the expired patients mean CPK was 343.50 ± 342.94 and the mean difference of 251.36 was significant and the p-value is 0.002 which is significant. Hence high CPK will act as important parameter in predicting poor outcome among leptospirosis and is associated with high mortality.

High CPK (>500 IU/L) and hyponatremia (<130 mEq/L) were associated with mortality in a study by Dilip Unnikrishnan et al.[100]

Renal parameters like Blood urea was elevated in 7 (23.3%) of the patients and 4 (13.3%) had increased Serum creatinine levels. In a study by Deodhar et al the serum creatinine was >1.5 mg/dl in 8.5%. [104]

It was also observed in the study that 15 (50%) patients had decreased sodium levels and 4 (13.3%) patients had decreased potassium, 1 (3.3%) patient had increased potassium levels. Hyponatremia is because of impaired sodium reabsorption, increased distal sodium delivery, and potassium wasting.

The impairment in sodium reabsorption appears to be caused by selective loss of the ENaC sodium channel in the proximal tubular epithelium.

There was significant difference for Blood Urea, Serum Creatinine, Sodium and Potassium levels among the recovered and expired cases. Hence elevated Blood urea (p=0.0001), Serum Creatinine (p=0.001), sodium (p=0.06) and potassium (p=0.002) levels will act as important parameters in predicting the outcome among leptospirosis, and higher values were associated with poor prognosis.

In a study of 1016 patients, with a case fatality rate of 14.5%, advanced age, higher serum creatinine, and higher admission serum potassium, longer duration of symptoms, and icteric leptospirosis were associated with high in-hospital fatality.[107]

Liver was the most common organ involved in the study. Clinical jaundice was seen in only 13.3% of the patients, 40% had hepatomegaly. 40% of the patients had increased Total Bilirubin, 36.7% had increased direct bilirubin, 60.0% had increased SGOT, 40% had increased SGPT and 36.7% had hypoalbuminemia. Hepatic encephalopathy was not seen in our study.

According to Deodhar et al, Elevated transaminases were present in 81% and the bilirubin was raised in 60% of the cases.[104]

Only 7(23.3%) of patients had chest radiographic abnormalities.

Only one (3.3%) patient presented with altered sensorium, with CSF showing elevated protein and lymphocytic pleocytosis. CT scan of brain did not reveal any abnormalities, and patient did not have any other neurological abnormalities. The patient improved with treatment and was discharged.

Inj. Ceftriaxone 1gm i.v was given twice daily for 76.7% of patients, inj. crystalline penicillin 20 lakh units i.v was given Qid for 33.3% of patients, tab. doxycycline 100mg bd was given for 73.3% of patients and among 76.7% of patients two or more antibiotics was used for treatment. Majority of the patients (76.7%) were given two antibiotics, 50% of patients were given a combination of inj. ceftriaxone and tab. doxycycline and 26.7% of patients were given a combination of inj. crystalline penicillin and tab.doxycycline.

Platelets was transfused for 5 (17%) of the patients.

Out of 30 patients, 12 (40%) patients did not have any complications, the rest 18 (60%) had developed complications. In them it was observed that the most common

complication was hepatic damage which was seen in 26.7 % of the patients. 23.3% of them had hepatic damage and ARF, 6.7% had hepatic damage, ARDS and ARF and only 3.3% of them had altered sensorium along with hepatic damage.

Out of the 30 patients, 10 (33.3%) patients had multi organ dysfunction (2 or more organs are involved) and 2 (6.7%) patients have expired in the study, among them, one patient had developed ARDS, ARF and hepatic dysfunction and was on ventilator support for 3 days, hemodialysis was started on day 2 of admission, but patient succumbed on 3rd day of admission and the other patient had developed ARF & hepatic dysfunction.

CONCLUSION

Leptospirosis has a wide spectrum of clinical signs and symptoms which necessitates a high degree of clinical suspicion for timely diagnosis. In this study,

- Leptospirosis was more common in agriculturists (63.3%).
- People hailing from rural areas (76.7%) are more prone to this disease than those from urban areas (23.3%).
- Females (63.3%) were more commonly affected than males (36.7%).
- Fever was the commonest symptom at presentation (100%).
- Myalgia (80%), headache (66.7%), and cough (43.3%) were the other common symptoms at presentation.
- Conjunctival suffusion (66.7%) and hepatomegaly (40%) were the common findings and has to be looked carefully into.
- Thrombocytopenia (56.7%) was also a common feature.
- Oliguria, elevated blood urea, serum creatinine, hyponatremia and hyperkalemia was associated with poor prognosis.
- 13.3% of patients had elevated CPK and was associated with poor prognosis of the patient.
- MODS were significantly associated with mortality.
- Early diagnosis & initiation of treatment of leptospirosis prevents mortality and morbidity.

SUMMARY

30 patients with fever who tested positive for IgM anti leptospiral antibody by ELISA were studied for clinical profile, laboratory findings, their management and the factors predicting their outcome.

- The age group commonly involved was 21-40 years (53.4%).
- Most of the patients were females (63.3%), with their predominant occupation being agriculture (52.6%).
- 76.7% of the patients are from rural areas.
- Fever was present in all patients.
- Other common symptoms encountered were Myalgia (80%) and headache (66.7%). Jaundice, oliguria and oliguria were less common.
- Important signs seen were conjunctival suffusion, hepatomegaly.
- Liver and kidneys were the most common organs involved.
- The incidence of pulmonary involvement was less.
- 60% of the patients had elevated liver enzymes.
- Renal involvement was seen in 23.3% of patients. One patient in our study required hemodialysis.
- Thrombocytopenia was seen in 56.7% patients.

- Two patients expired in the present study with all of them having hepatic and renal involvement and thrombocytopenia. Respiratory system involvement was seen in only one of the expired patients.
- Oliguria, elevated CPK, BU & SC, hyponatremia and hyperkalemia were associated with poor prognosis in our study.

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ANNEXURES:

PROFORMA :

PATIENT DETAILS :-

Name: D.O.A:

Age: Sex: D.O.D:

Hospital No:

Rural/Town:

Occupation:

CHIEF COMPLAINTS:-
Fever
Headache
Vomiting
Myalgia
Arthralgia
Cough
Breathlessness
Jaundice
Oliguria
Sub con.haemorrage
Epistaxis
Haematuria
Bleeding gums
Ecchymosis.

HOPI:-

MODIFIED FAINES CRITERIA:

Part A : Clinical Data	Points	Score
Headache	2	
Fever	2	
Temp > 39ºC	2	
Conjunctival suffusion	4	
Meningism	4	
Muscle pain	4	
Conjunctival suffusion + Meningism + Muscle pain	10	
Jaundice	1	
Albuminuria/Nitrogen Retention	2	
Total score		

Part B: Epidemiological Factors	Points	Score
Rainfall	5	
Contact with contaminated environment	4	
Animal contact	1	
Total score		
Part C: Bacteriological and Lab Findings	Points	Score
Isolation of leptospira in culture Diagnosis certain		
Positive Serology		
ELISA IgM Positive	15	
SAT – Positive	15	
MAT – Single High titer	15	
Rising titer (Paired sera)	25	
TOTAL SCORE		

PAST HISTORY:

PERSONAL HISTORY:

OCCUPATIONAL HISTORY:

ON EXAMINATION:
GPE
Conjunctiva: PR: BP:

Other findings:

SE:-
CVS:

RS:

PA

CNS

INVESTIGATIONS:
ELISA IgM:

CBC: Hb: g%; TC /cumm; DC: N %, L %, E %; PLT /cumm; ESR

CPK:

RBS:

Urine Routine:
Renal Function Test: BU: mg/dl SC: mg/dl
Liver function test (LFT):

Serum electrolytes: Na^+: mEq/L K^+: mEq/L

Peripheral smear for MP:

Dengue serology:

MAT (On Availability):

Rising Titres (On Availability):

CT-Brain (If Indicated):

LP CSF (If Indicated):

ECG

Chest x-ray:

Treatment:

Duration of Hospital Stay:

Outcome:

Signature of Guide:

Signature of Co-Guide:

Case No :	Hosp. No. :	Age:	Sex:	Rural/Town:	Occupation:	Fever (days)	Headache	Vomiting	Myalgia	Arthralgia	Cough	Breathlessness	Jaundice	Oliguria	Haematuria	Bleeding Gums	Purpura/Ecchym	Altered Sensorium	MFI Score(A+B)	MFI Score(A+B+C)	Temp °F	Conjunctival Suffusion	Pallor	Icterus	Lymphandeno	BP(mm/Hg)	Hepatomegal	Spleenomeg	CVS	RS
1	772052	40	f	Rural	House wife	+	-	-	+	-	+	-	-	-	-	-	-	-	8	23	102	-	+	-	-	110/60	-	-	NAD	NAD
2	771627	35	f	Rural	Agriculturist	+	+	-	+	-	+	-	-	-	-	-	-	-	16	31	102	-	+	-	-	116/70	+	-	NAD	NAD
3	769718	65	m	Rural	Agriculturist	+	+	-	-	-	+	+	-	-	-	-	-	-	18	33	102.8	-	-	-	-	120/80	-	-	NAD	rt. Basal crepts +
4	776329	28	m	Rural	Agriculturist	+	+	+	+	-	+	-	-	-	-	-	-	-	21	36	102.2	+	-	-	-	110/80	+	+	NAD	NAD
5	779878	26	f	Rural	House wife	+	+	-	+	+	-	-	-	-	-	-	+	-	21	36	102.2	+	+	-	-	100/40	-	-	NAD	NAD
6	794164	40	f	Rural	House wife	+	-	-	+	-	-	-	+	-	-	-	+	-	18	33	103.6	-	-	+	-	100/70	+	+	NAD	NAD
7	819630	40	f	Rural	Agriculturist	+	+	-	+	+	-	-	-	-	-	-	-	-	24	39	102.6	+	-	-	-	110/70	-	-	NAD	NAD
8	820304	32	f	Rural	Agriculturist	+	+	-	+	+	-	-	-	-	-	-	-	-	22	37	102.2	+	-	-	-	120/70	-	+	NAD	NAD
9	822028	46	f	Rural	Agriculturist	+	-	-	+	-	+	-	-	-	-	-	-	-	22	37	102.8	+	-	-	-	130/86	+	-	NAD	NAD
10	826949	25	m	Rural	Agriculturist	+	+	+	-	-	-	-	-	-	-	-	-	-	14	29	102	+	-	-	-	110/80	-	-	NAD	NAD
11	826692	38	f	Town	House wife	+	+	+	+	-	-	-	+	-	-	-	-	-	21	36	103.2	+	-	+	+	120/70	+	+	NAD	NAD
12	831983	45	f	Town	House wife	+	-	-	+	+	+	+	-	-	-	-	-	-	21	36	103	+	-	-	-	106/60	-	-	NAD	NAD
13	849795	20	f	Rural	Agriculturist	+	+	-	+	-	+	-	-	-	-	-	-	-	22	37	100.1	+	-	-	-	110/70	-	-	NAD	NAD
14	864431	48	m	Rural	Agriculturist	+	+	-	+	-	-	-	-	-	-	-	-	-	20	35	100	-	+	-	-	100/70	-	-	NAD	NAD
15	865913	60	f	Rural	Agriculturist	+	-	+	+	-	+	+	+	+	-	-	+	-	22	37	103.4	+	-	+	-	80/'60	+	-	NAD	B/L crepts +
16	866936	38	f	Town	House wife	+	+	-	-	-	+	-	-	-	-	-	-	-	13	28	101	-	-	-	-	100/60	-	-	NAD	NAD
17	870583	45	m	Rural	Agriculturist	+	-	-	+	-	-	-	-	+	-	-	-	-	22	37	103	+	-	-	-	70/50	+	+	NAD	NAD
18	875817	20	f	Rural	Agriculturist	+	+	+	+	-	+	-	-	-	-	-	-	-	22	37	102.6	+	-	+	-	80/70	+	-	NAD	B/L crepts +
19	775842	77	m	Rural	Agriculturist	+	-	-	+	-	-	-	-	-	-	-	-	-	13	28	100.2	-	-	-	-	108/70	-	-	NAD	NAD
20	899376	23	F	Town	House wife	+	-	-	-	-	-	-	-	-	-	-	-	-	2	17	100.4	-	+	-	-	110/70	-	-	NAD	NAD
21	900229	60	m	Rural	Agriculturist	+	+	+	+	+	-	-	+	-	-	-	+	-	27	42	102.8	+	-	+	-	120/70	+	-	NAD	NAD
22	908104	20	m	Town	Mason	+	+	+	-	-	-	-	-	-	-	-	-	-	21	36	102.6	+	-	-	-	120/80	+	+	NAD	NAD
23	805176	20	f	Town	House wife	+	+	-	+	+	-	-	-	-	-	-	-	-	12	27	99.8	-	-	-	-	112/70	-	-	NAD	NAD
24	920242	27	m	Rural	Agriculturist	+	+	+	+	+	+	-	-	-	-	-	-	-	24	39	102.2	+	-	-	-	120/80	-	-	NAD	NAD
25	927457	25	f	Rural	Agriculturist	+	+	-	+	-	-	-	-	-	-	-	-	-	20	35	100.6	+	-	-	-	90/50	-	-	NAD	NAD
26	931687	18	m	Rural	Student	+	-	-	+	-	-	-	-	-	-	-	+	-	19	34	101.8	+	-	-	-	110/70	+	-	NAD	NAD
27	931664	22	f	Rural	Agriculturist	+	-	-	-	-	+	-	-	-	-	-	-	-	9	24	100	-	-	-	-	118/70	-	-	NAD	NAD
28	825816	22	f	Town	House wife	+	+	-	+	-	-	-	-	-	-	-	+	-	24	39	102.8	+	-	-	-	126/60	-	-	NAD	NAD
29	932400	35	M	Rural	Agriculturist	+	+	+	+	-	-	-	-	-	-	-	+	+	23	38	103	+	-	-	-	100/70	+	-	NAD	NAD
30	944969	60	f	Rural	Agriculturist	+	+	-	+	-	+	+	-	-	-	-	-	-	21	36	102.4	+	-	-	-	100/60	-	-	NAD	B/L crepts +

Abbrevations:

f	female
m	male
NAD	No abnormalities detected
N	Normal
WNL	Within normal limits
NRA	No radiological abnormality
MFI	Modified Faines criteria
CVS	cardio vascular system
RS	Respiratory system
CNS	Central nervous System
Hb	hemoglobin
Tc	Total Count
PLT	Platelet
CPK	Creatinine phosphokinase
RBS	Random blood sugar
Na+	Sodium
K+	Pottasium
BU	Blood urea
SC	Serum Creatinine
TB	total bilirubin
DB	Direct bilirubin
SGOT	Serum Glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

CNS	Lepto ELISA IGM	OD (optical Density)	Dengue Rapid Card	Malaria RC/PSMP	Hb(g%)	TC (Cells/ cumm)	ESR	PLT (/cumm)	CPK (U/l)	Urine Routine	RBS (mg/dl)	BU (mg/dl)	SC (mg/dl)	Na+ (mEq/L)	k+ (mEq/L)	TB (mg/dl)	DB	SGOT	SGPT	Alb	CT Brain	LP CSF	ECG	CXR	Inj. Ceftriaxonem)(1g	Inj. CP (20lkh units)	DOXY	PCM	IVF	Transfusions	DOHS (days)	Outcome
NAD	+	15	-	-	6.2	38,000	10	1,60,000	50	N	146	26	0.8	133	3.8	0.6	0.4	30	18	3.6	NI	NI	WNL	NRA	BDx5d	-	BDx5d	+	+	-	5days	Recovered
NAD	+	14	-	-	5.9	7600	22	2,41,000	80	Albumin +;WBC : 8-10; RBC 1-2	88	36	0.4	136	3.8	0.8	0.44	35	22	4.2	NI	NI	WNL	NRA	-	Qidx5d	BDx5d	+	+	-	7days	Recovered
NAD	+	12	-	-	13	12300	10	2,04,000	40	Albumin+	109	40	1.1	140	3.3	1.1	0.55	28	12	4	NI	NI	WNL	Rt.Basal pneumonic patch +	BDx7d	-	BDx5d	+	+	-	7	Recovered
NAD	+	16	-	-	14.2	8600	18	48,000	30	Albumin+	69	55	1.7	120	4.4	0.2	0.42	147	128	2.5	NI	NI	WNL	NRA	-	Qidx7d	BDx7d	+	+	-	7	Recovered
NAD	+	13	-	-	4.5	11400	30	32,000	88	N	62	25	0.65	129	4.3	0.4	0.46	46	16	4.4	NI	NI	WNL	NRA	BDx3d	Qidx7d	BDx7d	+	+	2 units packed cells & 5 units of platelets.	13	Recovered
NAD	+	14	-	-	9.9	33,600	80	2,07,000	326	Albumin +;Bile salts & Pigments +	73	31	0.8	127	3.2	23.5	21.2	184	156	2.1	NI	NI	WNL	Rt. Pleural effusion	BDx7d	-	-	-	+	-	11	Recovered
NAD	+	16	-	-	12.5	9200	28	71,000	42	N	194	12	0.78	131	4.1	0.6	0.4	44	32	4.6	NI	NI	WNL	NRA	BDx6d	-	BDx5d	+	-	-	7	Recovered
NAD	+	16	-	-	13.1	2,600	60	60,000	44	N	139	16	0.7	142	3.8	0.4	0.56	18	28	5	NI	NI	WNL	NRA	BDx1d	-	BDx1d	+	-	-	1	Recovered
NAD	+	18	-	-	11.8	3,400	44	1,60,000	72	N	191	15	0.7	132	3.8	0.5	0.3	44	34	4.3	NI	NI	WNL	Rt. Lower zone opacity	BDx5d	-	BDx5d	+	+	-	5	Recovered
NAD	+	13	-	-	15	3700	32	60,000	66	N	209	13	0.7	129	4.4	0.6	0.4	20	28	3.8	NI	NI	WNL	NRA	BDx7d	-	BDx7d	+	-	-	7	Recovered
NAD	+	14	-	-	12.7	7,900	80	1,60,000	320	N	100	22	0.72	128	3.5	1.8	1.2	149	75	2.6	NS	Protien-62mg/ dl, sugar-49 mg/dl, chloride-120mEq/L; Cell count-12cells, lymphocytes;no growth.	WNL	NRA	BDx5d	Qidx7d	-	+	+	-	11	Recovered
NAD	+	13	-	-	9.9	8,400	42	90,000	110	N	108	43	0.7	121	4.3	0.7	0.2	14	21	3.2	NI	NI	WNL	Rt.Basal pneumonic patch +	-	Qidx5d	BDx5d	+	-	-	5	Recovered
NAD	+	15	-	-	9.2	7,600	25	1,08,000	55	N	80	36	0.4	136	4	0.5	0.3	24	20	4.1	NI	NI	WNL	NRA	BDx5d	-	-	+	+	-	5	Recovered
NAD	+	13	-	-	5.9	4,300	36	1,86,000	56	N	81	23	0.8	136	4.3	0.8	0.4	48	32	3.5	NI	NI	WNL	NRA	-	Qidx4d	BDx4d	+	-	-	4	Recovered
NAD	+	15	-	-	10.7	5,700	54	16,000	586	Albumin+; RBC 5-10;	146	147	3.7	142	5.6	7.7	7	126	76	1.9	Ni	NI	Sinus Tachycardia	Right lower lobe patchy opacity	BDx3d	Qidx3d	-	+	+	3 units platelets	3	Expired
NAD	+	13	-	-	14.2	19,700	56	85,000	101	Albumin+,WBC 8-10cells, RBC 10-20 cells,casts +	81	108	2.2	141	4.7	1.6	1.1	206	180	2.9	NI	NI	WNL	NRA	BDx3d	-	BDx3d	+	+	-	3	Expired
NAD	+	14	-	-	11.1	6,400	38	27,000	112	N	67	41	1.1	129	4.8	1.1	0.2	114	98	1.9	NI	NI	WNL	NRA	-	Qidx7d	BDx7d	+	+	2units platelets tranfused	8	Recovered
NAD	+	16	-	-	11	13,000	22	38,000	186	Albumin++	77	26	0.74	137	3.7	5.2	4.4	205	113	2	NI	NI	WNL	B/L Lower zone infiltrates +	BDx7d	-	-	+	+	-	10	Recovered
NAD	+	18	-	-	5.3	2,300	30	2,89,000	65	N	78	17	0.78	139	3.9	0.9	0.4	55	34	3.8	NI	NI	WNL	NRA	BDx7d	-	BDx5d	+	+	2 Units packed cells.	12	Recovered
NAD	+	17	-	-	7.5	7,800	88	5,85,000	43	N	199	12	0.51	144	4.4	1.1	0.8	65	60	4.2	NI	Ni	WNL	NRA	BDx5d	-	BDx5d	+	+	-	5	Recovered
NAD	+	14	-	-	8.1	3,600	46	60,000	210	Albumin++	73	107	1.6	126	3	16.3	10.7	53	49	1.8	NI	NI	WNL	NRA	-	Qidx10d	BDx7d	sos	+	6 units platelets	11	Recovered
NAD	+	13	-	-	12.2	5,500	28	98,000	90	Albumin+	75	30	0.88	133	3.7	1	0.45	138	109	4.4	NI	NI	WNL	NRA	BDx5d	-	BDx5d	+	+	-	6	Recovered
NAD	+	16	-	-	11.7	13,000	10	3,60,000	40	N	120	10	0.7	138	4.1	0.6	0.2	16	22	4.2	NI	NI	WNL	NRA	BDx5d	-	BDx5d	+	-	-	5	Recovered
NAD	+	15	-	-	11.3	2,500	18	45,000	122	Albumin+	114	35	0.8	130	5	0.4	0.2	38	26	4.6	NI	NI	WNL	NRA	BDx4d	-	BDx4d	+	+	12 units platelets	4	Recovered
NAD	+	16	-	-	9.2	5,000	24	2,50,000	24	N	90	30	0.6	141	4.1	0.52	0.13	29	19	3.3	NI	NI	WNL	NRA	BDx5d	-	-	-	-	-	5	Recovered
NAD	+	15	-	-	13.7	5,100	34	1,13,000	28	Albumin++	118	35	0.88	136	3.9	1.39	0.75	169	94	3.1	NI	NI	WNL	NRA	BDx5d	-	BDx5d	+	-	-	5	Recovered
NAD	+	17	-	-	9.1	4,800	44	2,10,100	56	Albumin++	118	28	0.6	136	4.2	0.68	0.46	34	26	4	NI	NI	WNL	NRA	BDx5d	-	-	+	-	-	3	Recovered
NAD	+	14	-	-	15.1	3,800	24	46,000	78	N	87	17	1	137	3.6	0.7	0.35	30	27	N	NI	NI	WNL	NRA	BDx3d	-	-	+	+	-	3	Recovered
Altered sensorium +	+	15	-	-	13.2	13,200	48	1,50,000	80	N	101	37	0.9	131	3.8	0.4	0.3	44	26	3.8	NI	NI	WNL	NRA	BDx6d	-	BDx5d	+	+	-	6	Recovered
NAD	+	13	-	-	12.5	9,600	52	3,56,000	67	N	91	51	0.9	125	4.4	1.1	0.8	77	62	4.5	NI	NI	WNL	left lower zone non-homogenous opacity	-	Qidx7d	BDx7d	+	+	-		Recovered