CLINICAL BIOCHEMICAL AND VIROLOGICAL PROFILE OF HEPATOCELLULAR CARCINOMA

DISSERTATION SUBMITTED FOR

THE FULFILLMENT OF

DOCTOR OF MEDICINE

BRANCH I – GENERAL MEDICINE

MARCH 2008

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU.

CERTIFICATE

This is to certify that this dissertation entitled **"CLINICAL BIOCHEMICAL AND VIROLOGICAL PROFILE OF HEPATOCELLULAR CARCINOMA"** submitted by **Dr.S.Jayaprakash,** to The Tamil Nadu Dr.M.G.R. Medical University, Chennai is in partial fulfillment of the requirement for the award of M.D. degree- Branch I (General Medicine) and is a bonafide research work carried out by him under our direct supervision and guidance.

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I, **Dr.S.Jayaprakash** solemnly declare that I carried out this work on **"CLINICAL BIOCHEMICAL AND VIROLOGICAL PROFILE OF HEPATOCELLULAR CARCINOMA"** at Department of General Medicine, Government Rajaji Hospital during the period of July, 2006 - April, 2007. I also declare this bonafide work or a part of this work was not submitted by me or any other for any award, degree, and diploma to any university, board either in India or abroad.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the M.D. in General Medicine Degree examination.

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ACKNOWLEDGEMENT

At the outset, I thank our Dean **Dr.V.Raji,M.D,** for permitting me to carry out this study in our hospital.

I am greatly indebted to my beloved Chief& Head of the Department **Prof. Dr.A.AYYAPPAN, M.D.,** for his guidance, encouragement and support during the study period.

I am grateful to our chief **Prof.Dr.M.KAMARAJ,M.D**, professor, Department of Medicine, for his guidance and support during this period.

I express my gratitude to my assistant professors **Dr.M.Sooriyakumar M.D, Dr.C.Dharmaraj M.D, Dr.P.Manimegalai, M.D**, for their valuable suggestions.

I am obliged to my guide **Prof.Dr.L.THAYUMANAVAN,M.D, D.M.** Professor and Head, Department of Medical Gastroenterology, **Dr.A.S.A.Jeganathan,D.M** , **Dr.M.Kannan,D.M,** and **Dr.Ramani,D.M,** Asst. Professors, Dept. of MGE for their guidance and valuable suggestion.

I sincerely thank **Prof.R.Sethuraman,M.Sc,M.Phil.,** Head of the Department, Biochemistry, Madurai Medical College, for guidance & co-operation in conducting this study.

I specially thank **Dr.P.Thirumalaikolundhu Subramanian, M.D,** former professor and Head of the Department, Medicine, Govt.Rajaji Hospital, for motivating me in this research.

CONTENTS

INTRODUCTION

The incidence of hepatocellular carcinoma varies greatly with geographic location, ethnic background, and sex. For instance, incidence rates among men in sub-Saharan Africa and Asia may be 20 times higher than those among men in the United States (see the map). This disparity between countries is probably related to endemic rates of viral hepatitis and environmental carcinogens.

HCC frequently arises in the setting of cirrhosis, appearing 20-30 years following the initial insult to the liver. However, 25% of patients have no history or risk factors for the development of cirrhosis. The extent of hepatic dysfunction limits treatment options, and as many patients die of liver failure as from tumor progression. The prevalence of HCC worldwide parallels that of viral hepatitis and the majority of cases are associated with HBV and HCV. The increase in HCC incidence in the developed world is likely to be a direct result of the HCV epidemic occurring some 20–30 years after the rise in this infection in target populations. Alcohol, genetic hemochromatosis, and rarely primary biliary cirrhosis are associated[9].

Although it is currently one of the most common worldwide causes of cancer death, a major impact on the incidence of HCC should be achieved

through current vaccination strategies for hepatitis B virus (HBV) infection, screening and treatment for hepatitis C virus (HCV) infections, and from the reduction of alcoholic liver disease. However, because the latency period from hepatic damage to HCC development is very long, it may be many years until the incidence of HCC decreases as a result of these interventions.

HCC is the fifth most common cancer in men and the eighth most common cancer in women worldwide. An estimated 560,000 new cases are diagnosed annually. The incidence of HCC worldwide varies according to the prevalence of hepatitis B and C infections. Areas such as Asia and sub-Saharan Africa with high rates of infectious hepatitis have incidences as high as 120 cases per 100,000 populations[9].

In India, though it is a relatively uncommon disease, some increase is suspected in South India. The Madras Metropolitan Tumour Registry (MMTR), a Population Based Cancer Registry, was established at the Cancer Institute (W.I.A) in 1981 in the network of National Cancer Registry Programme (NCRP) of Indian Council of Medical Research, New Delhi, to study the pattern and trend of Cancer incidence and mortality in Chennai City (formerly Madras).Recent reports from the registry (2001-2003) shows an incidence of liver cancer about 2.5 per 100,000 male population ; 0.8 per 100,000 female

population. For Liver cancer, the relative proportion of cancers of all sites in men is 2.6%; female 0.8%[18].

Reddy et al have reported an incidence of 1.6 per cent from Madras in an autopsy study of liver cell cancer. However, information regarding the clinical and virological profile of hepatocellular carcinoma in India is limited.

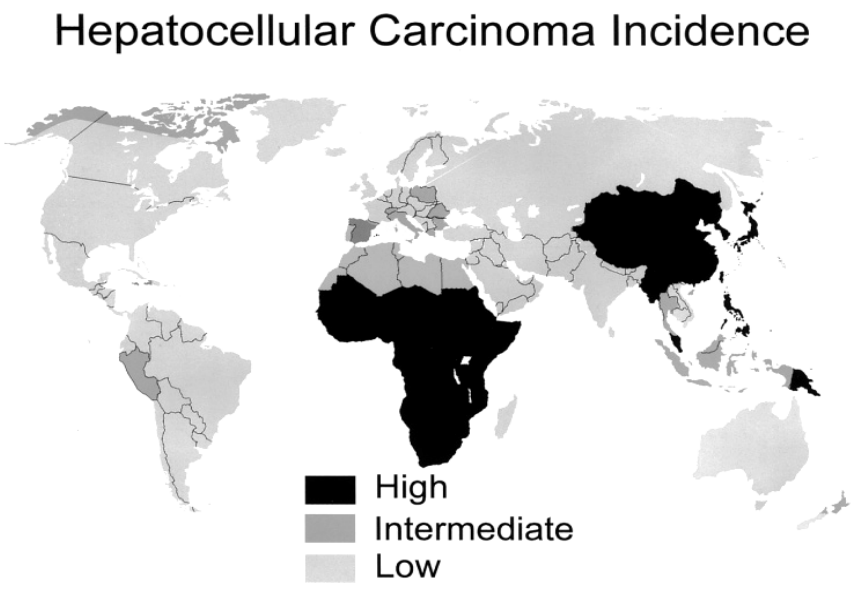

Figure 1. High-15 per 100,000 populations per annum, Intermediate: 5 – 15 per 100,000 populations per annum, Low: less than 5 per 100,000 populations per annum.

AIM OF STUDY

1. To study the clinical & demographic pattern of hepatocellular carcinoma in our centre.
2. To study the biochemical parameters &imaging characteristics of hepatocellular carcinoma.
3. To analyze the virological pattern of HCC with the help of serology.

REVIEW OF LITERATURE

In adults in most parts of the world, hepatic metastases are more common than primary malignant tumors of the liver, although the converse is true in sub-Saharan Africa and parts of the Far East. HCC (Hepatocellular carcinoma) is an uncommon tumor in the Western world, where it represents only 0.5–2.0% of all cancers, and has an incidence of only three to five cases per 100,000 population per year in the United States, it has an attack rate as high as 150 per 100,000 population in areas of Sub-Saharan Africa and Southeast Asia. Worldwide, it is the most common visceral cancer and may be the single most common cancer[21].

EPIDEMIOLOGY:

The incidence of HCC varies dramatically around the globe, ranging from 150 cases per 100,000 population per year in areas such as Taiwan, Mozambique, and Southeast China to a low of three to seven cases per 100,000 population in North and South America, North and Central Europe, and Australia. Intermediate rates from 5 to 20 cases per 100,000 population per year are found in Japan, the Middle East, and European countries bordering on the Mediterranean. The attack rate in Western developed countries is rising, however, with the incidence in the United States increasing by 71% between 1976–1980 and 1991–1995. Similar changes have been noted in France, Italy,

the United Kingdom, Canada, Australia, and Japan. This increasing incidence is particularly linked to the rising numbers of patients with chronic hepatitis C. But Indian studies have shown the predominant association with Hepatitis B virus infections[16].

Although these generalities hold true, marked differences can be seen within the same geographic area. Native black South Africans and native Maori males in New Zealand have attack rates 28- and 7-fold greater than whites in their respective countries. Blacks in Southern California have an attack rate four times greater than that of whites. Although the above findings suggest racial and/or genetic factors, environmental differences may play an even bigger role. It is commonly found that when natives move from areas with a high attack rate to one with a low attack rate, the incidence falls as they adapt the Western life-style. In contrast, individuals who move from highly developed countries to third-world countries tend to retain their low attack rate, possibly because they maintain their original life-style rather than that of their adopted country. HCC is considerably more common in males (8:1 in areas of high incidence and 2:1 to 3:1 in areas of low incidence)[1].

Race:

HCC is most commonly found among Asians, due to childhood infections with hepatitis B. However, due to the implementation of childhood

hepatitis B vaccination programs in many Asian countries, a decrease in the incidence of HCC among Asians is expected[9].

Sex:

HCC occurs more commonly in men than in women. In high-risk areas (China, sub-Saharan Africa, Japan), the difference between genders is more pronounced, with male-to-female ratios as high as 8:1. In industrialized countries, patients with hepatocellular carcinoma in the absence of cirrhosis have an approximately equal sex distribution[9].

Age:

The incidence of hepatocellular carcinoma increases progressively with advancing age in all populations, although it tends to level off in the oldest age groups. However, in ethnic Chinese and even more in black African populations, the mean age is definitely younger. This phenomenon is most striking in Mozambique, where more than 50% of Shangaan men with hepatocellular carcinoma are younger than 30 years of age, and their mean age is 33 years. Hepatocellular carcinoma is rare in children.Age at diagnosis varies widely according to geographic distribution. In the United States and Europe, the median age at diagnosis is 65 years. HCC is rarely diagnosed before age 40 years. However, between 1975 and 1998, the 45- to 49-year age group had the highest rate, a 3-fold increase in the incidence of HCC[1].

In Africa and Asia, age at diagnosis is substantially younger, occurring in the fourth and fifth decades of life, respectively. Diagnosis at a younger age is thought to reflect the natural history of hepatitis B and C related HCC.

PATHO PHYSIOLOGY:

A number of factors have been associated with the pathogenesis of HCC, including physical, chemical, infectious, and metabolic/hereditary etiologies. This multistep model of hepatocarcinogenesis includes four steps. Initiation occurs when an infection or chemical exposure produces a fixed genetic change that makes the initiated cell responsive to promotion. During promotion, hepatocyte necrosis, inflammation with production of cytokines and growth factors, or exposure to specific chemicals (anabolic steroids, alcohol, iron) leads to liver regeneration and active or inactive cirrhosis. This “fixes” the genetic defect, preventing the liver from eliminating the cell with its altered genome. Progression occurs when these “growth-advantaged” malignant cells are stimulated to produce microscopic foci of HCC by clonal expansion. Phenobarbital and other chemicals are particularly effective in producing progression. Ultimately, continued growth stimulation and clonal expansion of the malignant cells lead to one or more macroscopic foci of HCC and clinically apparent cancer. Most explanations of hepatocellular carcinogenesis attempt to

recapitulate these steps and generally no single agent is felt to be sufficient by itself to induce HCC[1].

The blend of risk factors differs in different parts of the world, and this may explain in part the diverse biologic characteristics of hepatocellular carcinoma in different populations.

PHYSICAL AND CHEMICAL AGENTS

1. Radiation:

Ionizing radiation causes liver tumors in mice, but does not appear to be a significant factor in the development of human HCC. Long-term follow-up of those who survived the atomic bombing of Nagasaki and Hiroshima has not demonstrated an increase in HCC, although veno-occlusive disease and the Budd-Chiari syndrome are increased following radiation exposure. The low rate of cell turnover in the adult liver with the limited opportunity for fixation of genetic alterations may account for resistance to radiation-induced tumors. Long-term continuous exposure to radiation, however, can produce tumors in the human liver. The unfortunate use of thorotrast, one of the original radiologic contrast agents and the radionuclide of choice from the late 1920s to the mid-1950s, has produced hemangiosarcomas and even HCCs. This a-radiation emitter has a biological half-life of approximately 400 years, and well over 50,000 adults remain at risk for the development of HCC[1].

2. Chemical carcinogenesis:

Because of the liver's unique anatomic position in the body, and its dual blood flow, everything taken by mouth traverses the liver via the portal drainage of the abdominal viscera before reaching the systemic circulation. Compounds that enter the body via other routes also find their way to the liver, which receives 25% of the cardiac output. Over 12,350,000 unique chemical compounds have been identified and this total grows by more than 11,500 each week as new compounds are synthesized or found in the environment. Over 90,000 are in regular use, including some 800 as food additives. In animal models, more than 3,000 chemicals are known to be carcinogenic and, as noted above, the rodent liver has been the standard model used to delineate the multistep model of hepatic carcinogenesis. Despite the overwhelming evidence of carcinogenicity of chemicals, and the massive daily exposure of the human liver to chemicals, only two chemicals are clearly documented human hepatic carcinogens: aflatoxin and vinyl chloride monomer.

Aflatoxin B_1

Aflatoxin B_1, derived from *Aspergillus flavus* and *Aspergillus parasiticus*, is an important risk factor for hepatocellular carcinoma in parts of Africa and Asia. *A. flavus* is ubiquitous in nature and contaminates a number of staple foodstuffs in tropical and subtropical regions. Epidemiologic studies have shown a strong positive correlation between the dietary intake of aflatoxin B_1

and the incidence of hepatocellular carcinoma. Aflatoxin B_1 and HBV may interact in the pathogenesis of hepatocellular carcinoma. One possible way in which aflatoxin B_1 may contribute to hepatocarcinogenesis is suggested by the correlation between heavy dietary exposure to this mycotoxin and an inactivating mutation of the third base of codon 249 of the p53 tumor suppressor gene. It is the most powerful human hepatocarcinogen known and promotes tumors, in part, by leading to inactivation of p53 through specific G-T mutations at codon 249.

Vinyl chloride monomer induces angiosarcomas in animal models as well as in industrial workers manufacturing polyvinyl chlorides.

3. Viral and other infectious agents:

There are many examples of virus-induced tumors in animal models. In most cases, the viral genome becomes incorporated into the host cells' genetic material either directly, if it is a DNA virus, or following reverse transcriptase production of a DNA copy, if it is an RNA virus. Insertion of the viral material into the host cell genome may then act as a mutagen or as a promoter to alter gene expression to produce new proteins, particularly oncogenes, or may cause over expression of normal genes, which leads to malignant transformation. The hepatitis B virus has the strongest association with the development of HCC and hepatitis B viral DNA has been found integrated into the genome of the host DNA in up to 80% of patients with HCC who are hepatitis B carriers.

However, there is no consistent site of integration. In contrast, hepatitis C, which is also strongly associated with HCC, is an RNA virus with no reverse transcriptase activity; thus, it is unlikely that it exerts its effect by insertion into the host cell genome. In Japan, where 70% of patients with HCC are hepatitis C positive, patients with chronic hepatitis C are three times more likely to develop HCC than those with chronic hepatitis B. Unlike in hepatitis B, however, HCC occurs only after the development of cirrhosis and the continuous necroinflammatory reaction with subsequent regeneration may account for its tumorigenic behavior[27].

4. Cirrhosis:

Cirrhosis is a common feature in almost all cases of HCC. In some cases, such as hepatitis C, it may be the necroinflammatory reaction and continuous regeneration that ultimately "fix" the mutation that leads to malignant transformation and allows it to flourish. In other cases, such as hereditary hemachromatosis in which 3–27% of patients develop HCC, tumor develops only in patients with cirrhosis. If timely phlebotomy is performed in hemachromatosis prior to the development of cirrhosis, the lifelong risk of developing HCC is reduced to that of the normal population.

However, cirrhosis is clearly only another cofactor in the development of HCC. In Western industrialized countries where HCC is uncommon, 80–90% of patients who develop HCC will have underlying cirrhosis and it occurs

primarily in older individuals. In contrast, in Africa, where chronic hepatitis B and aflatoxin exposure are common cofactors, HCC occurs at an earlier age, and only 60–70% of patients have underlying cirrhosis. A combination of hepatitis B with cirrhosis increases the risk of developing HCC by at least four-fold over those who are hepatitis B negative. Virtually any form of cirrhosis appears to increase the risk of developing HCC, but the overall rates may vary from 40 to 50% in those with hepatitis B to 5 to 15% in those whose cirrhosis is caused by alcohol. The highest rate is found in hereditary tyrosinemia[1].

5. Drugs and alcohol:

In the Western industrialized world, HCC is most commonly associated with alcohol. The lifetime risk of developing HCC appears to be about 15% in alcoholic cirrhosis, and this continues even after cessation of alcohol ingestion. In one study, 55% of patients who had stopped drinking had HCC at autopsy. As noted in the section on chemicals, many drugs act as initiators, promotors, or progression factors in the development of HCC in animals. Surprisingly few have been proven to produce HCC in humans. Possible exceptions are anabolic steroids and estrogens, which may play a role in the development of HCC, hepatic adenomas, and hemangiomas as discussed below. Phenobarbitol and diphenylhydantoin (Dilantin) are among the most potent promotors and inducers in animals, but have shown no association with HCC in humans. Similarly, tolazamide, oxytetracycline, and aminopyrine have not been

recognized as hepatic carcinogens in humans, despite their ability to be metabolized to carcinogenic nitrosamines.

6. Genetic:

Hereditary tyrosinemia has the clearest association with the development of HCC. Close to 40% of patients in one study developed HCC despite good dietary control. Tumors have also been reported in association with ataxia telangiectasia. Most other associations have not been borne out by more careful study, and convincing evidence of a genetic predisposition to the development of HCC is lacking. Familial clustering of HCC is seen in patients with chronic hepatitis B, but this is probably related to vertical and horizontal transmission of the hepatitis B. Differences between ethnic and geographic groups have been discussed above, and are probably more environmental than genetic. The association with Fanconi's anemia is probably related to the androgens used to treat the anemia rather than the underlying disease. Probably the best recognized and most striking association of a hereditary disease with the development of HCC is that with hereditary hemachromatosis. Hepatocellular carcinoma also may develop in patients with other inherited metabolic disorders that are complicated by cirrhosis, such as α_1-antitrypsin deficiency and type 1 hereditary tyrosinemia, whereas in patients with other diseases, for example type 1 glycogen storage disease, tumors develop in the absence of cirrhosis[1].

Hepatocellular carcinoma develops in as many as 45% of patients with hereditary hemochromatosis. Malignant transformation was thought to occur only in the presence of cirrhosis (and is certainly more likely to do so), but in recent years this complication has been reported in a few patients without cirrhosis. This observation suggests that excessive free iron in tissue per se may be carcinogenic, perhaps by generating mutagenic reactive oxygen species, a possibility that has gained further support from the observation that black Africans with dietary iron overload are at greatly increased risk of hepatocellular carcinoma. Hepatocellular carcinoma develops occasionally in patients with Wilson disease, but only in the presence of cirrhosis. Malignant transformation has been attributed to the cirrhosis but also may result from oxidant stress secondary to the accumulation of copper in the liver.

A statistically significant correlation between the use of oral contraceptive steroids and the occurrence of hepatocellular carcinoma has been demonstrated in countries in which the incidence of the tumor is low and there is no overriding risk factor for the tumor. This group of patients, however, constitutes a small proportion of all patients with hepatocellular carcinoma. The patients are usually relatively young. The increased risk persists for more than 10 years after the agents are discontinued. Epidemiologic evidence of a link between cigarette smoking and the occurrence of hepatocellular carcinoma is conflicting, although most of the evidence suggests that smoking is a minor risk

factor. Heavy smokers have an approximately 50% higher risk than nonsmokers. The cytochrome P450 system, which is responsible for the metabolic activation of a number of chemical carcinogens, is highly inducible by smoking.

Hepatocellular carcinoma develops in about 40% of patients with membranous obstruction of the inferior vena cava, a rare congenital or acquired anomaly. Continuous cycles of hepatocyte necrosis followed by regeneration resulting from the severe and unremitting hepatic venous congestion render the cells susceptible to environmental mutagens and spontaneous mutations[1].

TABLE 1.

S.No	Etiological factors	Incidence in HCC
1.	Cirrhosis	80 – 90 %
2.	HBV infection	80 %
3.	HCV infection	70-90 %(Japan), 60-65 %(Italy), 20 -50 %(US)

PATHOLOGY

Definitive diagnosis of hepatocellular carcinoma depends on demonstrating typical histologic features. Suitable tissue samples generally can be obtained by percutaneous biopsy or fine-needle aspiration. The yield and

safety of the procedure can be increased by aiming the needle under ultrasonographic guidance. Laparoscopically directed biopsy is an alternative approach. Because there is a risk of local, regional, or systemic dissemination of hepatocellular carcinoma by needle biopsy or aspiration of the tumor, many clinicians believe that these procedures should be avoided if the tumor is thought to be operable[1].

Gross Appearance

Hepatocellular carcinoma may take three forms—nodular, massive, or diffuse. The nodular variety accounts for about 75% of hepatocellular carcinomas and usually coexists with cirrhosis. It is characterized by numerous round or irregular nodules of various sizes scattered throughout the liver, some of which are confluent. The massive type is more common in younger patients with a noncirrhotic liver. It is characterized by a large circumscribed mass, often with small satellite nodules. This type of tumor is most prone to rupture. The diffusely infiltrating variety is rare. In this type, a large part of the liver is infiltrated homogeneously by indistinct minute tumor nodules, which may be difficult to distinguish from the regenerating nodules of cirrhosis that are almost invariably present. Hepatocellular carcinoma rarely, if ever, umbilicates. The tumor may be monoclonal (with intrahepatic metastases accounting for other tumor deposits) or polyclonal.

In the nodular and massive varieties, the tumor tissue is usually soft and bulges above the surrounding cut surface of the liver. Areas of necrosis and hemorrhage are common. Well-differentiated tumors are light brown, whereas anaplastic tumors are yellowish white or gray. Bile production may cause greenish brown discoloration of the tumor. The portal vein and its branches are infiltrated by tumor in up to 70% of cases seen at necropsy; the hepatic veins and bile ducts are invaded less often.

Microscopic Appearance

Hepatocellular carcinoma is classified histologically into well-differentiated, moderately differentiated, and undifferentiated (pleomorphic) forms.

Well-differentiated Appearance

Despite the aggressive nature and poor prognosis of hepatocellular carcinoma, most tumors are well differentiated. Trabecular and acinar (pseudoglandular) varieties occur, sometimes in a single tumor. In the trabecular variety the malignant hepatocytes grow in irregular anastomosing plates separated by sinusoids lined by flat cells resembling Kupffer cells. The sinusoids may be inconspicuous, however. The trabeculae resemble those of normal adult liver, although they are often thicker and may be composed of several layers of cells. Scanty collagen fibers may be seen adjacent to the sinusoid walls. The malignant hepatocytes are polygonal, with abundant,

slightly granular cytoplasm that is less eosinophilic than that of normal hepatocytes. The nuclei are large and hyperchromatic with prominent nucleoli. Bile production is the hallmark of hepatocellular carcinoma, regardless of the pattern.

A variety of glandlike structures are present in the acinar variety. They are composed of layers of malignant hepatocytes surrounding the lumen of a bile canaliculus, which may contain inspissated bile. A tubular or pseudopapillary appearance may be produced by degeneration and loss of cells, or cystic spaces may form in otherwise solid trabeculae. The individual cells may be more elongated and cylindrical than in the trabecular variety.

Moderately Differentiated Appearance

Solid, scirrhous, and clear cell varieties are described. In the solid variety, the cells are usually small, although they vary considerably in shape. Pleomorphic multinucleated giant cells are occasionally present. The tumor grows in solid masses or cell nests. Evidence of bile secretion is rare, and connective tissue is inconspicuous. Central ischemic necrosis is common in larger tumors. In the scirrhous variety, the malignant hepatocytes grow in narrow bundles separated by abundant fibrous stroma. Ductlike structures are occasionally present. In most tumors the cells resemble hepatocytes. In an occasional tumor, the malignant hepatocytes are predominantly or exclusively clear cells. More often, tumors contain areas of clear cells. The appearance of

these cells usually results from a high glycogen content, although in some cases fat is the cause.

Undifferentiated Appearance

The cells are pleomorphic, varying greatly in size and shape. The nuclei are also extremely variable. Large numbers of bizarre-looking giant cells are present. The cells may be spindle-shaped, resembling those of sarcomas.

Globular hyaline structures may be seen in all types of hepatocellular carcinoma. These reflect the presence of α-fetoprotein, α_1-antitrypsin, or other proteins. Mallory's hyaline is occasionally present.

Extrahepatic metastases are present at necropsy in 40% to 57% of patients with hepatocellular carcinomas. They are more common (70%) in patients without coexisting cirrhosis than in those with cirrhosis (30%). The most common sites are the lungs (up to 50% in some populations) and regional lymph nodes (20%).

Fibro lamellar Hepatocellular Carcinoma

This variant of hepatocellular carcinoma typically occurs in young patients, has an approximately equal sex distribution, does not secrete α-fetoprotein, is not caused by chronic hepatitis B (HBV) or C (HCV) virus infection, and almost always arises in a noncirrhotic liver. Fibrolamellar hepatocellular carcinoma is more often amenable to surgical treatment and, therefore, generally has a better prognosis than conventional hepatocellular

carcinoma. It does not, however, respond to chemotherapy any better than other forms of hepatocellular carcinoma. The hepatocytes are characteristically plump and deeply eosinophilic and are encompassed by abundant fibrous stroma composed of thin, parallel fibrous bands that separate the cells into trabeculae or nodules. The cytoplasm is packed with swollen mitochondria and, in approximately half the tumors, contains pale or hyaline bodies. Nuclei are prominent, and mitoses are rare[26].

CLINICAL PRESENTATION:

HCC must always be suspected in a patient with rapid and dramatic change in previously stable cirrhosis. On routine visits, liver size (both and right and left lobes), the presence or absence of Ascites, numbers of spider angiomata, and degree of palmar erythema, as well as status of nutrition, muscle mass, and presence or absence of jaundice, should be recorded. Significant or rapid changes in any of these parameters, as well as the development of new symptoms or signs, should prompt the immediate search for possible development of HCC. Unfortunately, the disease is often clinically silent until it is well advanced or tumor diameter exceeds 10 cm[9].

History: Patients generally present with symptoms of advancing cirrhosis.

- Pruritus
- Jaundice

- Splenomegaly
- Variceal bleeding
- Cachexia
- Low grade fever
- Increasing abdominal girth (Rapid development of ascites)
- Hepatic encephalopathy
- Right upper quadrant pain

Physical signs:

- Jaundice
- Ascites
- Hepatomegaly
- Alcoholic stigmata (Dupuytren's contracture, spider angiomata)
- Asterixis
- Pedal edema
- Periumbilical collateral veins
- Enlarged hemorrhoidal veins

Paraneoplastic Manifestations:

The majority of paraneoplastic syndromes in hepatocellular carcinoma are rare. One of the more important is type B hypoglycemia, which occurs in fewer than 5% of patients and manifests as severe hypoglycemia early in the

course of the disease. Characteristically, the hypoglycemia is the reason that the patient seeks medical attention. Affected patients present with confusion, delirium, acute neuropsychiatric disturbances, convulsions, stupor, or coma. Not surprisingly, the presence of the underlying tumor is easily overlooked. Type B hypoglycemia is believed to result from the defective processing by malignant hepatocytes of the precursor to insulin-like growth factor II (pro-IGF-II)[1].

Another important paraneoplastic syndrome is polycythemia (erythrocytosis), which occurs in fewer than 10% of patients with hepatocellular carcinoma. If polycythemia develops in a patient known to have cirrhosis, hepatocellular carcinoma is highly likely. This syndrome is probably caused by the synthesis of erythropoietin by malignant hepatocytes.

A patient with hepatocellular carcinoma, especially the sclerosing variety, may present with hypercalcemia in the absence of osteolytic metastases. When hypercalcemia is severe, the patient is drowsy and lethargic and may be stuporous. The probable cause is secretion of parathyroid hormone-related protein (PTHrP) by the tumor. Cutaneous manifestations of hepatocellular carcinoma are rare except for *pityriasis rotunda*, which may be a useful cutaneous marker of the tumor in black Africans. The disorder is characterized by single or multiple, round or oval, hyperpigmented scaly lesions on the trunk and thighs that range in size from 0.5 to 25 cm.

DIAGNOSIS:

Conventional tests of hepatic function do not distinguish hepatocellular carcinoma from other hepatic masses or from cirrhosis. Accordingly, they contribute little to the diagnosis of this tumor**.** Often the most striking laboratory finding in HCC is the lack of abnormal tests. Transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] are most often normal or only minimally elevated. Alkaline phosphatase (AP) and g-glutamyltransferase are the most frequently abnormal tests, but are rarely more than two- to three-fold elevated. Lactate dehydrogenase (LDH) can be strikingly and disproportionately elevated in patients with metastatic liver disease, particularly if of hematogenous origin.

Serum Tumor Markers

Many of the substances synthesized and secreted by hepatocellular carcinoma are not biologically active. Nevertheless, a few are produced by a sufficiently large proportion of tumors to warrant use as serum markers of the tumor. The most helpful of these is α-fetoprotein.

- **Alpha-fetoprotein** (AFP) is elevated in 75% of cases.
    - The level of elevation correlates inversely with prognosis.
    - An elevation of AFP greater than **400 ng/mL** predicts for HCC with specificity greater than 95%. In the setting of a growing mass, cirrhosis, and the absence of acute hepatitis, many centers

use a level greater than **1000 ng/mL** as presumptive evidence of HCC (without biopsy)[9].

α-Fetoprotein is a α_1-globulin normally present in high concentration in fetal serum but in only minute amounts thereafter. Reappearance of high serum levels of α-fetoprotein strongly suggests the diagnosis of hepatocellular carcinoma (and hepatoblastoma). This finding is especially true in populations in which hepatocellular carcinoma is most prevalent: the great majority of ethnic Chinese and black African patients have a raised serum concentration (more than 20 ng/mL [20μg/L]), and about 75% have a diagnostic level (more than 500 ng/mL [500μg/L]). These percentages are lower in populations at low or intermediate risk of the tumor, and consequently, α-fetoprotein is a less useful tumor marker in these groups. The mean serum value of α-fetoprotein in affected patients in high incidence regions of hepatocellular carcinoma is 60,000 to 80,000 ng/mL, compared with about 3000 ng/mL in regions with a low or intermediate incidence of the tumor. Raised serum values range over six orders of magnitude, although concentrations of greater than 1 million are rare. The reason 500 ng/mL (500μg/L) is used as a diagnostic level is that serum concentrations below this value may be found in patients with a variety of acute and chronic benign liver diseases, such as acute and chronic hepatitis and cirrhosis. False-positive results may also occur in patients with tumors of endodermal origin and undifferentiated teratocarcinomas or embryonal cell

carcinomas of the ovaries or testis. A progressively rising serum α-fetoprotein concentration, even if below the diagnostic level, is highly suggestive of hepatocellular carcinoma.

Because not all hepatocellular carcinomas produce α-fetoprotein, its presence is not essential to hepatocellular carcinogenesis, and there is no evidence that tumors that do not produce α-fetoprotein are biologically different from the majority of hepatocellular carcinomas. Synthesis of α-fetoprotein by a tumor is permanent and age-related: the younger the patient, the more likely the serum value is to be raised and the higher the level attained. Provided that patients are age-matched, there is no sex difference in α-fetoprotein production. No obvious correlation exists between the serum concentration of α-fetoprotein and any of the clinical or biochemical features of the tumor or the survival time after diagnosis. However, small presymptomatic tumors are associated with an appreciably lower serum level of α-fetoprotein than are symptomatic tumors. Attempts to correlate the degree of differentiation of hepatocellular carcinoma with production of α-fetoprotein have produced conflicting results.

Fucosylated α-Fetoprotein

The α-fetoprotein secreted by malignant hepatocytes contains unusual and complex sugar chains that are not found in the α-fetoprotein present in the nontransformed hepatocytes. The sugar chains have the same core structure, but the number of the outer chain trisaccharides differs. This refinement is

particularly useful in the differential diagnosis of hepatocellular carcinoma when the serum α-fetoprotein concentration is less than 500 ng/mL [500 μg/L], and it may improve the diagnostic yield of α-fetoprotein in presymptomatic tumors. Unfortunately, the method now used to measure fucosylated α-fetoprotein is rather complex and costly[1].

Des-γ-carboxy Prothrombin

Serum concentrations of *des-γ-carboxy prothrombin* (also known as prothrombin produced by vitamin K absence or antagonism II [PIVKA II]) are raised in the majority of patients with hepatocellular carcinoma. In populations in which the incidence of hepatocellular carcinoma is low, the abnormal prothrombin may prove to be a better marker than α-fetoprotein, and it could be used as a first-line tumor marker[1].

CA 125, tissue polypeptide antigen, and tumor-associated isoenzymes of 5'-nucleotide phosphodiesterase have high sensitivity but poor specificity. Tumor-associated isoenzymes of γ-glutamyl transpeptidase and variant alkaline phosphatase have high specificity but low sensitivity, and both sensitivity and specificity are low for ferritin, carcinoembryonic antigen, CA 19-9, and calcitonin.

Two tumor markers—*abnormal vitamin B_{12}-binding protein and neurotensin*—have been linked specifically to the fibrolamellar variant of

hepatocellular carcinoma. When present, they provide useful confirmatory evidence of this variant, but both markers have low sensitivity.

TABLE 2

Tumor markers	Sensitivity	Specificity
Alpha-fetoprotein	80 – 90%	90%
Des-γ-carboxy prothrombin	58 - 91 %	84 %
α-L-Fucosidase	75 %	70 – 90%

IMAGING:

Liver imaging is done using ultrasonography, CT scanning, or MRI. When performed for suspected HCC due to a rising AFP, each test has a 70-85% chance of finding a solitary lesion; sensitivity is higher with multiple tumors. Chest radiography may demonstrate pulmonary metastases[1].

Ultrasonography

Ultrasonography detects the majority of hepatocellular carcinomas but does not distinguish this tumor from other solid lesions in the liver. Its advantages include safety, availability, and cost effectiveness, although it has the drawbacks of being nonstandardized and examiner-dependent. Approximately two thirds of symptomatic hepatocellular carcinomas are uniformly hyperechoic, whereas the remainder is partly hyperechoic and partly hypoechoic. Tumors located immediately under the right hemidiaphragm may

be difficult to detect. Ultrasonography with Doppler is useful for assessing the patency of the inferior vena cava, portal vein and its larger branches, hepatic veins, and biliary tree[25].

Ultrasound is probably the most accurate imaging modality for visualizing small liver nodules, even compared with more advanced techniques such as helical CT, CT during arterial portography, digital subtraction angiography, CT arteriography, and T1/T2 weighted MRI. The probability of HCC undoubtedly increases when nodule diameter exceeds 10 mm (approximately 90%) but well over half (approximately 68%) of the smaller nodules we examined proved to be HCC and about 15% were considered to be premalignant. While Ultrasound and other imaging techniques (even the more advanced) are of limited use for the diagnosis of these small nodules, close to 90% can be safely, rapidly, and reliably identified by means of US guided fine needle biopsy[25].

Computed Tomography

Spiral (helical) CT and CT during arterial portography have greatly improved the diagnosis of hepatocellular carcinoma by CT. The images of hepatocellular carcinoma obtained with CT are, however, not specific. Nevertheless, CT is especially useful in defining the extent of the tumor within and beyond the liver and showing the course, caliber, and patency of blood

vessels. Because iodized poppy seed oil (Lipiodol) is concentrated and retained in hepatocellular carcinoma tissue, injection of this material at the end of hepatic arteriography can be used in conjunction with CT, performed after a suitable delay, to detect small tumors[1].

Magnetic Resonance Imaging

MRI provides another way of distinguishing hepatocellular carcinoma from normal liver tissue. Most tumors have a low signal intensity on T_1-weighted images and a high signal intensity on T_2-weighted images. Gradient-echo sequences and turbo spin-echo sequences have greatly reduced the time needed for MRI. Furthermore, the use of a contrast agent, such as gadopentetate dimeglumine and superparamagnetic iron oxide, increases the accuracy of MRI, especially in detecting small hepatocellular carcinomas in cirrhotic livers and distinguishing small hepatocellular carcinomas from hemangiomas or dysplastic nodules discovered in surveillance programs[1].

Hepatic Angiography

Hepatic digital subtraction angiography is helpful in recognizing small hypervascular hepatocellular carcinomas but may miss early, well-differentiated hypovascular tumors. Dynamic contrast-enhanced ultrasonography with intra-arterial infusion of CO_2 microbubbles can be used to detect these hypovascular tumors and also to differentiate hepatocellular carcinoma from other hepatic

nodules. Angiography is also essential in delineating the hepatic arterial anatomy when planning surgical resection, transplantation, bland or chemoembolization of the tumor, or infusion of cytotoxic drugs directly into the hepatic artery or its branches[1].

LIVER BIOPSY:

Core biopsy is favored over fine needle biopsy since larger amounts of tissue, often with normal surrounding parenchyma, can be obtained. Biopsy may be omitted in a clinical setting of a growing mass in a cirrhotic liver (>2 cm) noted on 2 coincident imaging techniques with at least one imaging showing contrast enhancement. Likewise, a growing mass in a cirrhotic liver on one imaging modality with an associated AFP level greater than 500-1000 ng/mL is clinically diagnostic of HCC. The need for biopsy should be carefully evaluated, especially if the risk for complications is high. Lesions that are 2-3 cm or smaller may be dysplastic nodules in a cirrhotic background. These are probably premalignant, and obtaining a biopsy is especially important to distinguish them from HCC. Obtaining a biopsy may be unnecessary in patients who will undergo resection regardless of diagnosis or if definitely indicated then it will paramount to burn the tract to avoid seedling[1].

Differential Diagnosis

HCC must be distinguished from all of the other malignant and benign masses like Dysplastic nodules in cirrhosis, Fibrous nodular hyperplasia, Metastatic disease, Primary hepatic lymphoma. Usually the use of appropriate imaging studies, plus testing for α-fetoprotein, is sufficient. In fact, in a patient with cirrhosis with another risk factor such as hepatitis C, hepatitis B, hemochromatosis, or alcohol, the presence of a typical lesion on ultrasound and CT imaging, plus a high or rapidly rising a-fetoprotein, is sufficient to make the diagnosis without histological verification[9].

TREATMENT:

1. Surgical resection:

Resection or liver transplantation offers the best chance of cure for hepatocellular carcinoma. For resection to be considered, the tumor must be confined to one lobe of the liver and be favorably located, and ideally, the nontumorous liver tissue should not be cirrhotic. Resection can, however, be considered if the tumor is limited to the left lobe and the cirrhosis of the right lobe is not severe, or if the tumor is favorably located in either lobe, allowing the surgeon to perform a segmentectomy or limited nonanatomic resection. Overall, resection is feasible in only about 15% of patients. Resection carries an operative mortality rate of around 5% in noncirrhotic and 10% to 15% in

cirrhotic livers. One of the most disappointing aspects of resecting hepatocellular carcinoma is the very high recurrence rate.

2. Radio frequency Ablation:

Radiofrequency ablation of HCC is a relatively newly described technique using a probe placed into the tumour mass, usually percutaneously. It uses high frequency ultrasound to generate heat at the probe tip which can destroy tissue. A single probe can destroy lesions of up to 3 cm and a multiple tipped probe has been used to target lesions of up to 6 cm in diameter. Larger tumours can be treated by radiofrequency ablation; the largest series is 126 HCCs greater than 3 cm in diameter. Complete necrosis was produced in 47%.

3. Chemotherapy

Of chemotherapeutic agents, only *doxorubicin (Adriamycin)* has shown a better than 20% response rate. There have been essentially no cures with chemotherapy given systemically, either as a single agent or in combination. Site-directed chemotherapy via intraarterial perfusion has shown only a modest increase in response rate by allowing delivery of larger doses of chemotherapeutic agents directly to the tumor site. More promising, but primarily for short- or long-term palliation, is the recent approach of embolizing the vessels feeding the tumor with Gel foam or Lipiodol, an oily substance that becomes trapped in the tumor. An extension of these two approaches combines

embolization of the tumor vessels with chemotherapy, thus producing a combination of anoxic necrosis with high local concentrations of trapped chemotherapeutic agents. This approach with *chemoembolization* has shown some promise. For small tumors, less than 5 cm and preferably less than 3 cm in size, percutaneous ethanol, acetic acid, and even hot saline injections have proved quite beneficial in improving 3- to 5-year survival.

4. Liver Transplantation:

Liver transplantation is performed in patients in whom the tumor is not resectable but is confined to the liver or in whom advanced cirrhosis and poor liver function preclude resection. Orthotopic liver transplantation (OLT) can be considered for patients who meet the ***Milan criteria***—one tumor less than 5 cm or up to 3 tumors all less than 3 cm. These highly selected patients have excellent survival rates, similar to those of patients who undergo liver transplantation for end-stage liver disease without HCC. OLT in combination with chemoembolization and post-transplant adjuvant chemotherapy have been reported to produce 5-year survival rates of 60–70% in highly selected patients.

Prognosis

The overall prognosis for HCC remains very poor. Mean survival after diagnosis of large tumors, if not treated, is less than 6 months. Small tumors have a considerably better prognosis, with one study reporting 90% survival at 3 years in patients with tumors smaller than 3 cm; another found 63% survival

at 3 years in patients with tumors less than 5 cm in size, and Child– Pugh class A cirrhosis (compensated cirrhosis). Surgical resection of small tumors or possibly percutaneous ethanol injection or radiofrequency ablation provides the only reasonable chance for cure[9].

Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults: (British society of Gastroenterology)

Surveillance using *abdominal ultrasound* and *α-fetoprotein (AFP)* estimation can detect HCC of a smaller size than those presenting without screening. The only potentially curative therapies depend on detection of small HCC. If surveillance is offered, it should be six monthly abdominal ultrasound assessments in combination with serum AFP estimation.

Diagnosis of HCC:

The commonest clinical scenario is a patient with a mass discovered on ultrasound where AFP may or may not be raised. If the patient is known to have pre-existing cirrhosis and the mass is greater than 2 cm in diameter, there is a greater than 95% chance that the lesion is a HCC. If AFP is raised, this confirms the diagnosis and further investigation is only required to establish the most appropriate therapy. The normal range for AFP is 10–20 ng/ml and a level **>400** ng/ml is usually regarded as diagnostic. Two thirds of HCCs less than 4 cm however have AFP levels less than 200 ng/ml and up to 20% of HCC do not

produce AFP, even when very large. If AFP is normal, further radiological imaging (CT, MRI, or lipiodol angiography with follow up CT) will usually allow a confident diagnosis to be made and proceed to assessment of treatment without the need for biopsy. In the few cases where real diagnostic doubt persists, biopsy may be indicated. Using AFP testing also produces false positives; levels in the range 20–250 ng/ml are frequently seen in regenerating nodules in viral cirrhosis. A rising AFP over time, even if the level does not reach 400 ng/ml, is virtually diagnostic of HCC.

A focal lesion in the liver of a patient with cirrhosis is highly likely to be HCC. Initial assessment should be by spiral computed tomography (CT) of the liver (local spread) and thorax (metastases).Magnetic resonance imaging (MRI) with contrast enhancement or angiography with lipiodol injection and follow up CT may increase the accuracy of detection of other liver lesions. Biopsy is rarely required for diagnosis, and seeding of tumour in the needle tract occurs in 1–3%. Biopsy of potentially operable lesions should be avoided where possible.

Treatment of HCC:

The only proven potentially curative therapy for HCC remains surgical, either hepatic resection or liver transplantation, and patients with single small HCC (<5 cm) or up to three lesions <3 cm should be referred for assessment for these treatment modalities.

Liver transplantation should be considered in any patient with cirrhosis and a small (5 cm or less single nodule or up to three lesions of 3 cm or less) HCC. Patients with replicating HBV had a worse outlook due to HBV recurrence and were previously not considered candidates for transplantation. Effective antiviral therapy is now available and patients with small HCC, as defined above,should be assessed for transplantation.Hepatic resection should be considered as primary therapy in any patient with HCC and a non-cirrhotic liver (including fibro lamellar variant).Resection can be carried out in highly selected patients with hepatic cirrhosis and well preserved hepatic function (Child-Pugh A) who are unsuitable for liver transplantation. Such surgery carries a high risk of postoperative decompensation and should be undertaken in units with expertise in hepatic resection and management of liver failure[8].

PREVENTION:

Given the poor prognosis and lack of effective therapies for hepatocellular carcinoma, programs for prevention are desperately needed. Nonspecific measures to ensure sterile needles, safe laboratory practices, a clean donor blood supply, good general hygiene, effective public health policies and HBV vaccination should be every country's priority[3].

PROGNOSIS:

The prognosis of patients with hepatocellular carcinoma is assessed by the following methods:

- Child-Turcotte-Pugh scoring system
- Okuda staging
- Cancer of the Liver Italian program (CLIP) scoring system
- Barcelona Clinic Liver Cancer (BCLC) staging

Child scoring system can be used to assess the severity of any liver disease including hepatocellular carcinoma. Cirrhosis can also be staged clinically. A reliable staging system is the modified Child-Pugh classification with a scoring system of 5 to 15. This scoring system was initially devised to stratify patients into risk groups prior to undergoing portal decompressive surgery. The Child-Pugh score is a reasonably reliable predictor of survival in many liver diseases and predicts the likelihood of major complications of cirrhosis such as bleeding from varices and spontaneous bacterial peritonitis[5,20,22].

Table 3. Child-Turcotte-Pugh scoring system[5]

Clinical and biochemical measurements	Points scored for increasing abnormality		
	1	**2**	**3**
Albumin (g/dl)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dl)	1-2	2-3	>3
For cholestatic diseases: Bilirubin (mg/dl)	<4	4-10	>10
PT (secs prolonged)	1-4	4-6	>6
Or			
INR	<1.7	1.7-2.3	>2.3
Ascites	Absent	Slight	Moderate
Encephalopathy (grade)	None	1 and 2	3 and 4

Table 4 – Child's class

Class	Total points
A	5 - 6
B	7 - 9
C	10 - 15

OKUDA staging:

Tumour staging, which is the basis for therapeutic management, has traditionally been based on the Okuda system (table 19), which was developed 18 years ago. At that time, early diagnosis of HCC was relatively rare, and the staging system was therefore based on data from patients with advanced disease[11].

Staging of HCC is based on four criteria: tumor size (<or > 50% of the liver), ascites (absent or present), bilirubin (< or > 3 mg/dL), and albumin (< or >3 g/dL) to establish Okuda stages I (no positive criteria), II (1or 2 positives), and III (3 or 4 positives). The Okuda system predicts clinical course better than the American Joint Cancer Commission TNM system. The natural history of each stage without treatment is as follows: stage I- 8 months; stage II-2 months; stage III-less than 1 month.

Cancer of the Liver Italian program (CLIP) scoring system:

The Cancer of the Liver Italian Program (CLIP) score is a newer staging system that has been validated in case series from various parts of the world. Although its predictive power has been found to be superior to that of the Okuda system in most cases, doubts have been raised regarding its value in certain populations[11].

CLIP scoring system:

Score of 0-2 is assigned for each of the 4 features listed below; cumulative score ranging from 0-6 is the CLIP score.

1. Child-Pugh stage : Stage A = 0; Stage B = 1; Stage C = 2

2. Tumor morphology:

Uninodular and extension less than 50% = 0

Multinodular and extension less than 50% = 1

Massive and extension greater than 50% = 2

3. Alpha-fetoprotein: Less than 400 = 0; Greater than 400 = 1

4. Portal vein thrombosis: Absent = 0; Present = 1

Estimated survival based on CLIP score: Patients with a total CLIP score of 0 have an estimated survival of 31 months; those with score of 1, about 27 months; score of 2, 13 months; score of 3, 8 months; and scores 4-6, approximately 2 months. The CLIP staging is simple, uses common clinical criteria, and is more accurate than the Okuda and Child-Pugh staging systems. Until a better system comes along it should be implemented as a useful staging system for HCC.

Barcelona Clinic Liver Cancer (BCLC) staging:

Among the prognostic variables considered in BCLC staging are performance status (PS) and portal hypertension, which are not taken into account in either the CLIP or Okuda system. These additional criteria should make it especially suitable for staging HCCs diagnosed early in patients with well compensated cirrhosis[11,20,22].

Table 3 shows Definition of the Barcelona Clinic Liver Cancer (BCLC) staging for hepatocellular carcinoma.

Stages A and B: all criteria should be fulfilled. Stage C: at least one criterion; PST 1–2 or vascular invasion/ extra hepatic spread. Stage D: at least one criterion; PST 3–4 or Okuda stage III/ Child-Pugh C.

Table 5: Definition of the Barcelona Clinic Liver Cancer (BCLC) staging for hepatocellular carcinoma[11]:

BCLC stage	PST	Tumour status		Liver function status
		Tumour stage	Okuda stage	
Stage A: early HCC	0		I	
A1	0	Single, <5 cm	I	No portal hypertension and normal bilirubin
A2	0	Single, <5 cm	I	Portal hypertension and normal bilirubin
A3	0	Single, <5 cm	I	Portal hypertension and abnormal bilirubin
A4	0	3 tumours <3 cm	I – II	Child-Pugh A–B
Stage B: intermediate HCC	0	Large multinodular	I – II	Child-Pugh A–B
Stage C: advanced HCC	1 - 2	Vascular invasion or extrahepatic spread	I – II	Child-Pugh A–B
Stage D: end stage HCC	3 - 4	Any	III	Child-Pugh C

MATERIALS AND METHODS

This is a prospective observational study conducted in Government Rajaji Hospital, Madurai from July 2006 to April, 2007.

All patients with clinical and biochemical evidence of cirrhosis were screened with Abdominal ultrasonogram and serum alpha-fetoprotein estimation.

A total of 45 cases were selected for the study from department of Medicine, and department of Medical gastroenterology based on the following criteria proposed by British society of Gastroenterology.

Inclusion criteria:

- All patients with histopathological evidence of hepatocellular carcinoma in Liver biopsy

-Any patient with mass lesion (>2cm) in liver with

- Serum Alpha-fetoprotein level more than 400ng/ml
- Rising AFP levels even if the value is less than 400ng/ml

Exclusion criteria:

- Any liver mass (<2cm) with normal alpha-fetoprotein level
- Any liver mass with primary malignancy of GIT, Testis, Breast, and Lung

Patients with features of chronic liver disease were screened for Hepatocellular carcinoma by detailed clinical history taking& clinical examination.

Patients with evidence of cirrhosis were subjected to Liver imaging to detect any mass lesion. In patients with liver mass, serum alpha-fetoprotein level (AFP) was done. Serum AFP level more than 400ng/ ml was considered diagnostic of HCC, irrespective of the size of liver mass. For those patients with AFP level <400ng/ ml, CT / MRI Abdomen was done to assess tumour characteristics.

Patients with insignificant AFP levels and inconclusive imaging features were subjected to liver biopsy under ultrasound guidance. Liver biopsy was not done for mass lesion with features of resectability.

Features of resectability are: single mass lesion confined to one lobe of liver in a cirrhotic liver, without vascular invasion and metastases.

Following investigations were done:

Complete Blood cell count

Blood sugar, Urea, Creatinine

Serum sodium, Potassium

Serum bilirubin (Total, Direct, Indirect)

SGOT, SGPT, Serum alkaline phosphatase

Serum proteins, Albumin, Globulin

Serum Alpha-fetoprotein

Liver imaging – Abdominal ultrasonogram, CT / MRI

Upper GI endoscopy

Liver biopsy in selected cases

During Abdominal imaging, following features were noted:

Liver size, Features of cirrhosis, Mass lesion (if any), Site of mass lesion (Lobe), Number of lesions, Size of lesion(s), Well-defined lesion or not, Portal vein invasion.

Complete virological profile was done for all cases. Markers for HBV infection (HBsAg, IgG Anti-HBc, HBeAg, HBV DNA), Markers for HCV infection (Anti-HCV antibodies, HCV RNA) were done and analyzed. Incidence of Chronic HBV infection, Chronic HCV infection, and Occult HBV infection were calculated. Occult HBV infection is present if HBsAg is negative, and HBV DNA is positive.

Prognosis of the cases were assessed by Child-Pugh scoring system, Okuda staging.

Consent	:	Obtained
Financial support	:	Nil
Ethical committee clearance	:	Obtained
Conflict of interest	:	Nil

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002).Using this software, frequencies, percentage, mean, standard deviation, were calculated.

RESULTS

The results of clinical evaluation were shown below. The age distribution of the study is shown in Table No.6.

TABLE 6

AGE DISTRIBUTION

Age Group (in years)	**Cases**	
	Number	**Percentage**
≤ 30	4	8.9
31-40	1	2.2
41-50	7	15.6
51-60	19	42.2
>60	14	31.1
Total	45	100
Mean Standard deviation	55.1 yrs 13 yrs	

The Mean age of patients in our study was 55.1 ± 13 yrs. Majority of patients were in sixth decade at the time of presentation.

TABLE 7

SEX DISTRIBUTION

Sex	Cases	
	No.	%
Males	40	88.9
Females	5	11.1
Total	45	100

Table 7 shows sex distribution of the study. Majority of the patients were males. Male to female ratio was 8:1.

TABLE 8

SYMPTOMS

Symptoms	Cases	
	No.	%
Fever	17	37.8
Anorexia	36	80
Nausea	15	33.3
Vomiting	15	33.3
Abdominal pain	41	91.1
Hematemesis	10	22.2
Pruritus	8	17.8
Arthalgia	5	11.1
Weight loss	29	64.4
High coloured urine	23	51.1
Clay coloured stool	10	20.8
Malena	11	24.4

Table 8 shows list of clinical symptoms and its frequency in the study group. Commonest symptoms are abdominal pain, anorexia, weight loss, high coloured urine. Mean duration of symptoms was 6 months.

TABLE 9

RISK FACTORS

Risk Factors	Cases	
	Number	Percentage (%)
Alcohol use	20	44
Tobacco	25	55
Oral contraceptives	0	-
Past H/o jaundice	5	11
IV drug abuse	0	-
Multiple sex partners	4	8
Blood transfusion	3	6

Table 9 shows risk factors for cirrhosis and hepatocellular carcinoma. All those alcohol users were males. Among tobacco users 23 were males; 2 were females. The incidence of cirrhosis was 35% in the study.

TABLE 10

CLINICAL SIGNS

Signs present	Cases	
	No.	%
Consciousness		
a) Conscious	37	82
b) Drowsy	7	15
c) Coma	1	2.2
Pedal Edema	28	62
Ascites	27	60
Hepatomegaly		
i. Mild	14	31
ii. Moderate	6	13
iii. Massive	17	37
Splenomegaly		
i. Mild	6	13
ii. Moderate	3	6
iii. Massive	1	2.2

Table 10 shows distribution of signs in the study group. Only one patient presented with hepatic encephalopathy.

TABLE 11

HEMATOLOGICAL PARAMETERS

PARAMETERS	Mean	S.D.
Hemoglobin	9.24	2.26
Urea	43.5	50.7
Creatinine	1.1	0.6
Bilirubin- Total	4.29	5.32
Bilirubin- Direct	2.74	4.1
Total protein	6.24	0.92
Albumin	3.46	0.79
Globulin	2.82	0.82
SGOT(AST)	148.8	123.8
SGPT(ALT)	74.5	79.6
Alkaline phosphatase	409.9	297.2

Table 11shows hematological and biochemical parameters of the study group. Mean and standard deviation (S.D) of the parameters were calculated.

TABLE 12

LABORATORY PARAMETERS

S.No	Features	CASES	
		Number	Percentage (%)
1.	Anemia	42	93
2.	Elevated renal parameters	9	20
3.	Hypoglycemia	1	2.2
4.	Hyperbilirubinemia	33	73
5.	Hypoalbuminemia	18	40
6.	Raised Alkaline phosphatase	33	73

Table 12 shows hematological and biochemical parameter abnormalities in the study group. Anemia was the commonest abnormality detected with a mean Hb 9.2g/dl.

TABLE 13

Upper GI Endoscopy

S.No	Findings	Number (Total-34)	Percentage (%)
1.	Normal	18	53
2.	Esophageal varices alone	9	26
3.	Esophageal varices + Portal hypertensive gastropathy	7	21

Table 13 shows the upper gastro-intestinal endoscopy findings of the study group. Endoscopy was done in 34 patients. Esophageal varices were detected in 16 patients (47%).Portal hypertensive gastropathy was found in 7 patients (21%).Upper GI endoscopy was normal in 18 patients (53%).

TABLE 14

IMAGING FEATURES

Features	No.	%
Cirrhosis	41	91
Lobe involvement		
Right	22	49
Left	3	7
Both	20	44
No. of Lesions		
Single	22	49
Multiple	23	51
Single Lesion - Size		
≤ 5 cm	4	9
> 5 cm	18	40
Multiple lesion- Size		
≤ 3 cm	2	4
> 3 cm	21	47
Portal vein Thrombosis	13	29
Splenomegaly	12	26.7

Table 14 shows the imaging characteristics of the study group. Incidence of cirrhosis in imaging was 91% with predominantly right lobe involvement.

TABLE 15

VIRAL MARKERS

S.No	STATUS	Number	Percentage (%)
1.	HBV Infection	24	53
2.	HCV Infection	9	20
3.	HBV & HCV Co-infection	1	2
4.	Occult HBV Infection	3	7
5.	HCV positivity among occult HBV infection	0	-

Table 15 shows the virological profile of the study group. Markers of HBV infection (HBsAg; Anti-HBc IgG), markers of HCV infection (Anti-HCV; HCV RNA) were studied and the above conclusions were drawn.

HBV infection was dominant among the study group (53%).

TABLE 16

ALPHA-FETOPROTEIN

S.No	Serum alpha-fetoprotein	Number (Total-38)	Percentage (%)
1.	<10 ng / ml	6	16
2.	10 – 400ng / ml	6	16
3.	>400ng/ml	26	68

Table 16 shows serum alpha-fetoprotein pattern in the study group. Normal alpha-fetoprotein levels were found in 6 patients (16%). Insignificant values were found in 6 patients (16%). Significant diagnostic levels (>400ng/ml) were found in 26 patients (68%).

TABLE 17

LIVER BIOPSY

S.No	Biopsy findings	Number (Total-19)	Percentage (%)
1.	Positive for HCC	19	
	i) Classical HCC	18	95
	ii) Fibro lamellar variant	1	5
2.	Not suggestive of HCC	-	-

Liver biopsy was deferred in 26 (57% of study group) patients for the following reasons: Poor general condition, prolonged prothrombin time, Operable tumors.

TABLE 18

CHILD'S CLASSIFICATION

S.No	Child class	Number of cases	Percentage (%)
1.	A	21	46.6
2.	B	21	46.6
3.	C	3	6.7

Table 18 shows staging of cases according to Modified child's classification. Majority of patients were in Class A & B (93%) with equal distribution.

TABLE 19

OKUDA STAGING

S.No	Okuda Stage	Number of cases	Percentage (%)
1.	1	2	4.4
2.	2	31	68.8
3.	3	12	26.6

Table 19 shows classification of the study group according to okuda staging. Majority of patients were in stage 2 (68%).

DISCUSSION

In western countries, numerous studies are being conducted in hepatocellular carcinoma. In India, the clinical trials regarding hepatocellular carcinoma are limited. Particularly, data on cancer epidemiology in southern parts of India is under-reported. To rectify this defect, Government has started a cancer registry in Tamil nadu. For southern parts of the Tamil nadu, a cancer registry is started in Dindugal. This is an attempt to emphasize the magnitude of the problem and to highlight the importance of early cancer screening program.

In this study, all the patients with features of cirrhosis, and any patient presented with a liver mass without the evidence of primary tumor were screened for the presence of hepatocellular carcinoma. More than 100 patients were screened and 45 among those were recruited for the study, based on the guidelines suggested by the British society of Gastroenterology (Published in "Gut "journal in 2003)[8].

The study shows major occurrence of cases in sixth and seventh decade (See Table 6). About 19 cases (42%) are in the age group of 51- 60 years (sixth decade). The mean age in this study is 55.1±13 yrs. The mean age of presentation depends on endemicity of HBV infection in the population. Population with high endemicity of HBV carrier state (Incidence>8%) shows

younger age of presentation. India comes under intermediate endemic region (4%) in this regard. There is an increase in incidence of HCC as the age advances in our study which is similar to many studies from literature. There are two patients in the adolescent age group[17,27].

There is a male preponderance noted in this study which is supported by literature world wide. Proportion of male patients in the study group is 89%. The male to female ratio is 8: 1. It is found in the literature that male to female ratio may vary from 4:1 to 9:1[1].

Commonest symptoms found in our study are abdominal pain & swelling (91%), anorexia (80%), weight loss (64%), jaundice (51%), and fever (37%). The incidence of symptoms in our study is not different from the literature.

Commonest signs in our study are Hepatomegaly (81%), Ascites (60%), and Splenomegaly (21%) which are also not different from the literature.

The incidence of cirrhosis in our study (By imaging) is 91%, which is relatively higher than the incidence (80%) found in literature from western countries. In liver imaging, right lobe (49%) is involved more commonly than left lobe (7%) of the liver in our study[1].

Number of lesions share relatively equal incidence. Among cases with single lesion (22 cases), only 3 patients (6% of study group) were suitable to undergo resection. Among patients with multiple lesions (23 cases), only one patient (2%) was suitable to undergo resection. The incidence of operable and inoperable cases in our study was 9% and 91% respectively. Features of resectability are single lesion (<5cm) confined to one lobe (preferably left lobe or right inferior segments) without vascular invasion and metastasis. Features of unresectable tumors are bi-lobar or four segmental involvement, portal vein thrombus, vena caval involvement or tumor thrombus. The incidence of portal vein invasion in our study is 29%. In literature, 35% cases of HCC show portal vein invasion[4].

The incidence of Chronic HBV and HCV infection in our study are 53% and 20% respectively, which is similar to other Indian studies. The incidence of occult HBV infection in our study is 7%, an important data which is often not found in many studies[15,10].

Serum alpha-fetoprotein levels were elevated in 32 patients (84%) in the study group. But, diagnostic levels (>400ng/ml) were found in 68% of cases. Data from western literature show that 80% of HCC cases have elevated alpha-fetoprotein[4].

Liver biopsy was done in 19 cases where there was an unresectable liver mass with insignificant AFP elevation. Among 19 cases, only one fibro lamellar variety noted which was inoperable (multiple lesions >3cm) due to late presentation. Among 19 biopsy proven cases, 10 (53%) were positive for HBV infection; 3 cases (16%) were positive for HCV infection. The following table illustrates the relation between viral infection and alcoholism among biopsy proven cases.

TABLE 20

RISK FACTORS AMONG BIOPSY PROVEN HCC (19 CASES)

S.No.	Associated Risk factor	Number of cases	Percentage (%)
1.	HBV Positivity	10	53
2.	HCV Positivity	3	16
3.	Both HBV & HCV positive	0	-
4.	Total No. of Alcohol abuse	8	42
	i) With HBV positivity	5	26
	ii) With HCV positivity	1	5
	iii) Without HBV& HCV	2	10

Prognostic scoring based on Child's classification showed higher number of cases (46%) were in class A (compensated cirrhosis). Only patients in Child's class A are suitable to undergo hepatic tumor resection. According to okuda staging, about 68% of cases were under stage 2.

There are two Indian studies on clinical profile of hepatocellular carcinoma, which is comparable in most aspects.

First study was from *Department of Gastroenterology, GB Pant Hospital, New Delhi.* about Profile of hepatocellular carcinoma in India[10]:

Seventy-four consecutive cases of HCC were studied. A detailed history, tests for hepatitis B virus, hepatitis C virus infection, liver histopathology and HBV-DNA integration by using Southern blot hybridization were studied. Hepatocellular carcinoma patients were predominantly males (mean age 49.5 ± 14.0 years). Portal hypertension and cirrhosis were seen in 56 (76%) patients. A majority (78.5%) of the chronic alcoholics had associated viral infection. The etiology of HCC remained undetermined in 15 (20%) patient. The conclusions of the study were: (i) HBV infection is the predominant factor for the development of HCC, often related to mutant forms of HBV; (ii) a majority of the HCC patients have overt cirrhosis of the liver; and (iii) HCV and alcohol per se are uncommonly associated.

Another study was from *Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh on 2005*." Evaluation of clinical and biochemical parameters in hepatocellular carcinoma"[15].

Forty seven patients of HCC (Male = 43, Female = 4) diagnosed on the basis of history, clinical examination, imaging (USG, CT/MRI), α-fetoprotein (AFP) and by USG/CT guided FNAC, were included. Patients were screened for HBV, HCV and history of alcohol. Tumor size was assessed on imaging and UGI endoscopy for the presence of varices. The mean age was 53.4 ± 14.6 y. Clinical presentation included anorexia in 32 (68%), abdominal pain in 28 (60%), loss of weight in 23 (49%), fever in 12 (26%), and jaundice in 6 (13%) patients. Seventeen percent had normal AFP (< 10 ng/ml) and the remaining 83% had raised AFP [< 10 ng/ml = 7, 10–400 ng/ml = 27, > 400 ng/ml = 8]. Thirteen patients (28%) were consuming alcohol in cirrhogenic doses and 10 (21%) were smokers. More than half of the HCC cases had underlying cirrhosis. Hepatitis B virus infection was commonly associated. Most of patients had a large tumor (> 5 cm) at presentation. This study results were similar to our study results. See the following table for comparison.

TABLE 21- Comparison Between Studies on HCC in India:

S.No	Features	Our study(GRH) (2007)	PGI study (2005)	New Delhi (2001)
1.	Number of cases	45	47	74
2.	Male: female ratio	8:1	10:1	-
3.	Mean age	55.1 ± 13 yrs	53.4 ± 14.6yrs	49.5 ± 14 yrs
4.	Symptoms:			
	Abdominal pain	91 %	60 %	-
	Anorexia	80 %	68 %	-
	Weight loss	64 %	49 %	-
	Jaundice	51 %	13%	-
	Fever	37 %	26 %	-

TABLE 22- Comparison Between Studies on HCC in India:

S.No	Risk factors	Our study(GRH) (2007)	PGI study (2005)	New Delhi (2001)
1.	Cirrhosis	91 %	62 %	76 %
2.	Alcoholism	44 %	28 %	-
3.	HBV infection	53 %	54 %	71%
4.	HCV infection	20 %	27 %	4 %
5.	Occult HBV infection	7 %	-	-

Current studies in various centre focus on therapeutic interventions for hepatocellular carcinoma. The findings of this preliminary study need confirmation from large multi-centric study.

CONCLUSIONS

1. We conclude that hepatocellular carcinoma is not an uncommon malignancy in south India.

2. Hepatocellular carcinoma has a Predominantly Male Preponderance. The major occurrence of HCC is in the sixth decade.

3. Commonest symptoms found are abdominal pain & swelling, anorexia, weight loss, jaundice, and fever.

4. Commonest signs are Hepatomegaly, Ascites, and Splenomegaly. Jaundice at presentation is not uncommon.

5. Majority of cases of HCC occur in the background of cirrhosis. Nearly half of the patients present with esophageal varices.

6. Commonest site of tumor is right lobe of the liver.

7. Majority of cases are in decompensated stage of cirrhosis and inoperable at presentation.

8. HBV infection is the leading cause of HCC in our study. The importance of occult HBV infection is also emphasized in this study.

9. Majority of cases present with significant elevation of alpha-fetoprotein. This helps to make the diagnosis without the need for liver biopsy.

10. The clinical, biochemical and virological profile of hepatocellular carcinoma in south India is similar to data from north India.

SUMMARY

BACKGROUND:

Hepatoma is a common malignancy seen in India. However, information regarding the clinical profile of hepatocellular carcinoma in India is limited. We decided to study the clinical profile of hepatoma cases in our centre.

AIM:

To study the clinical, biochemical & imaging profile of hepatocellular carcinoma in our centre (Madurai medical college).

METHODS:

All patients with histological evidence of hepatocellular carcinoma or clinical features of HCC with alpha-fetoprotein levels more than 400ng per dl were included in the study. A total of 45 cases from Govt. Rajaji hospital, Madurai were recruited. The duration of study was from July, 2006 to April, 2007.The history, Clinical features, biochemistry, imaging, endoscopic findings, viral markers and prognostic scores (using okuda, Child) were analyzed.

RESULTS:

The Mean age of patients in our study was 55.1 ± 13 yrs. Majority of patients were in sixth decade at the time presentation. Majority of the patients were males. Male to female ratio was 8:1. Commonest symptoms are

abdominal pain, anorexia, weight loss, high coloured urine. Only one patient presented with hepatic encephalopathy. Mean duration of symptoms was 6 months. The incidence of cirrhosis was 91% in the study group. Anemia was found in 93% cases. Jaundice was noted in 73% of cases. The incidence of esophageal varices was 47%. Right lobe involvement was seen in nearly half the patients. The incidence of HBV and HCV infection is 53% and 20% respectively. Serum alpha-fetoprotein was elevated significantly (>400ng/ml) in 68% cases. The incidence of operable and inoperable cases in our study was 9% and 91% respectively.

CONCLUSION:

- Hepatocellular carcinoma had a Predominantly Male Preponderance.
- Major occurrence of cases in sixth decade.
- The Lesions were unresectable at presentation in 91% cases.
- HBV infection was the leading cause for HCC in the study.

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A STUDY ON CLINICAL BIOCHEMICAL AND VIROLOGICAL PROFILE OF HEPATOCELLULAR CARCINOMA

PROFORMA

NAME: AGE/SEX:

WARD NO. /UNIT:

ADDRESS:

Date of Investigation:

HISTORY:

SYMPTOMS	PRESENT / NOT	DURATION
Fever		
Loss of appetite		
Abdominal pain		
Abdominal swelling		
Weight loss		
Vomiting		
Hematemesis		
Melena		
High coloured urine		
Pruritus		
Clay coloured stools		

RISK FACTORS:

H/O Blood transfusion	YES / NO
H/O Intravenous drug abuse	YES / NO
H/O Tattooing / Acupunture	YES / NO
H/O Long term dialysis	YES / NO
H/O Any systemic illness	YES / NO
H/O Any occupational exposure to blood products	YES / NO
H/O Multiple sexual partners	YES / NO
H/O Homosexuality	YES / NO
H/O Use of any drugs for any systemic illness	YES / NO
H/O Exposure to professional barbers	YES / NO
H/O Other member of community being affected with jaundice	YES / NO
H/O Jaundice in the past	YES / NO
H/O Alcohol intake	YES / NO
If YES	Currently / Occasionally / Former
	Year of starting alcohol :
	Amount / (day/week) :
H/O Smoking / Tobacco chewing	YES / NO
H/O Oral contraceptive pill usage	YES / NO
H/O Similar illness in the family members	

CLINICAL ASSESSMENT:

GENERAL EXAMINATION:

Level of consciousness:	Conscious& alert / Restless / Drowsy / Comatose
Built	Well built / Thin-built / Emaciated
Fever	YES / NO
Pallor	YES / NO
Icterus	YES / NO
Clubbing	YES / NO
Pedal edema	YES / NO
JVP	Raised / Not raised
Purpurae	YES / NO

Signs of Alcoholism:

Palmar erythema	YES / NO
Parotid enlargement	YES / NO
Spider naevi	YES / NO
Dupuytren's contracture	YES / NO

Examination of ABDOMEN*:*

Inspection: Normal contour / distended

Engorged veins Present / Not

Any Visible swelling

Palpation: Tenderness in any region

Hepatomegaly YES / NO If yes Mild / Moderate / Massive

Hepatic bruit YES / NO

Splenomegaly YES / NO If yes Mild / Moderate / Massive

Ascites YES / NO

INVESTIGATIONS:

BLOOD:

Hemoglobin :

WBC-Total count :

Differential count :

Platelet count :

Glucose :

Urea :

Creatinine :

Serum Electrolytes :

Sodium :

Potassium :

Chloride :

Bicarbonate :

LIVER FUNCTION TESTS:

Serum Bilirubin – Total :

Direct :

Indirect :

SGOT (AST) :

SGPT (ALT) :

Serum Proteins- Total :

Albumin :

Globulin :

Serum Alkaline Phosphatase:

VIROLOGICAL PROFILE:

S.No	MARKER	STATUS
1.	**HBV**	
	HBsAg	
	HBeAg	
	IgG Anti-HBc	
	HBV DNA	
2.	**HCV**	
	Anti-HCV	
	HCV RNA	

Serum Alpha-fetoprotein :

UPPER GI ENDOSCOPY:

Reg.no: Date:

Oesophagus:

Stomach:

Duodenum:

Impression:

LIVER IMAGING:

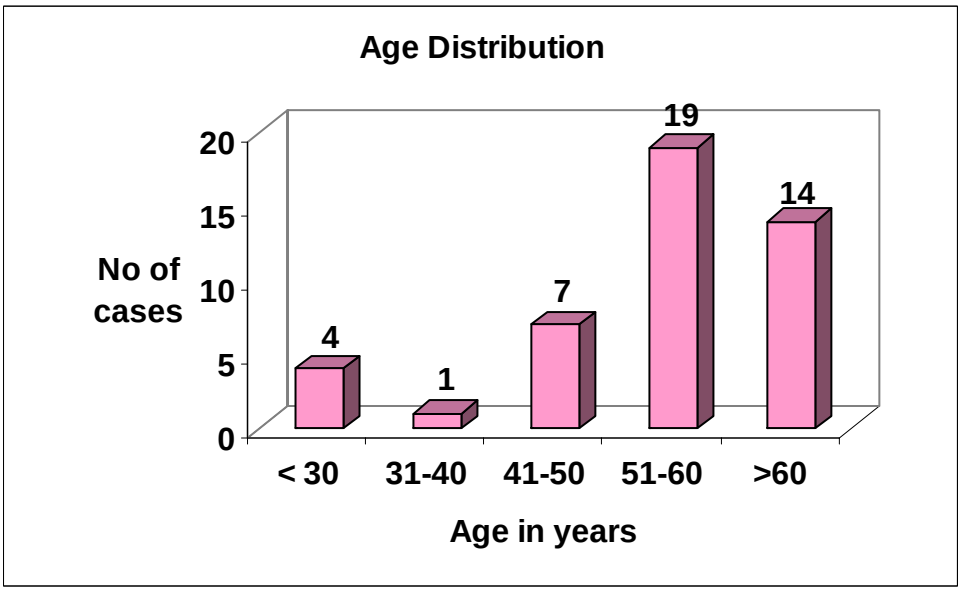
Abdominal Ultrasonogram (USG):

Reg.no: Date:

Computed Tomogram (CT):

Reg.no: Date:

GRAPH 1



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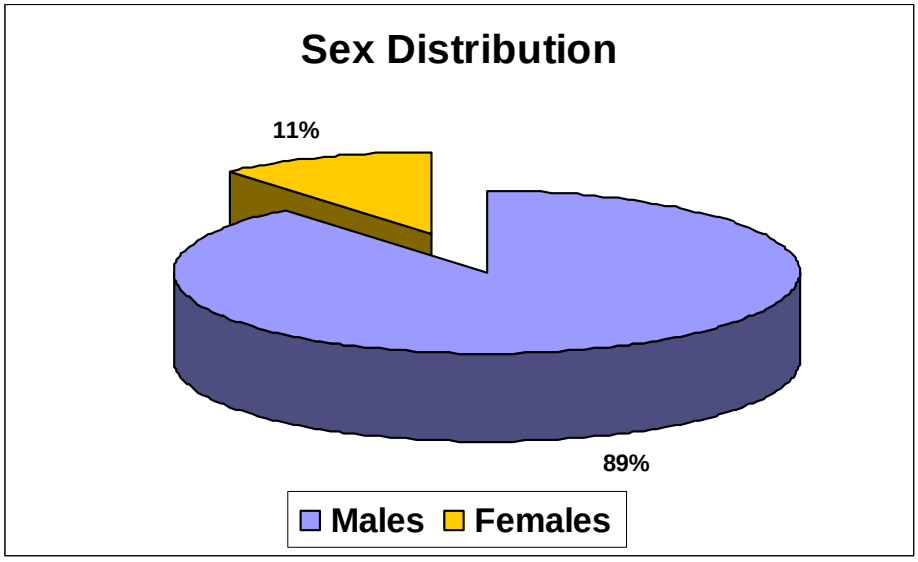

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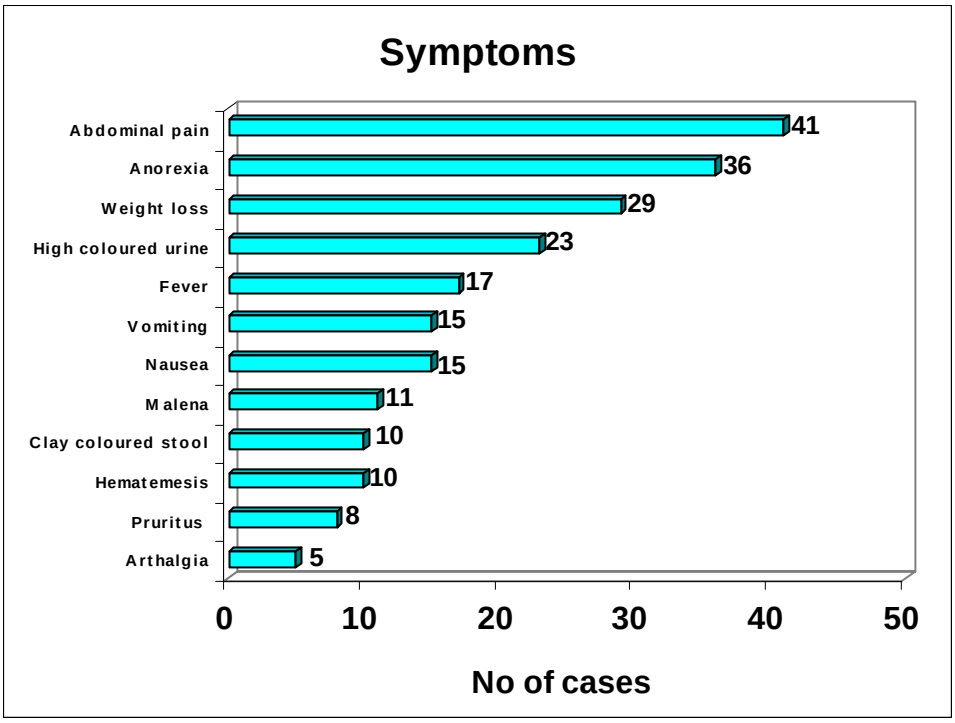

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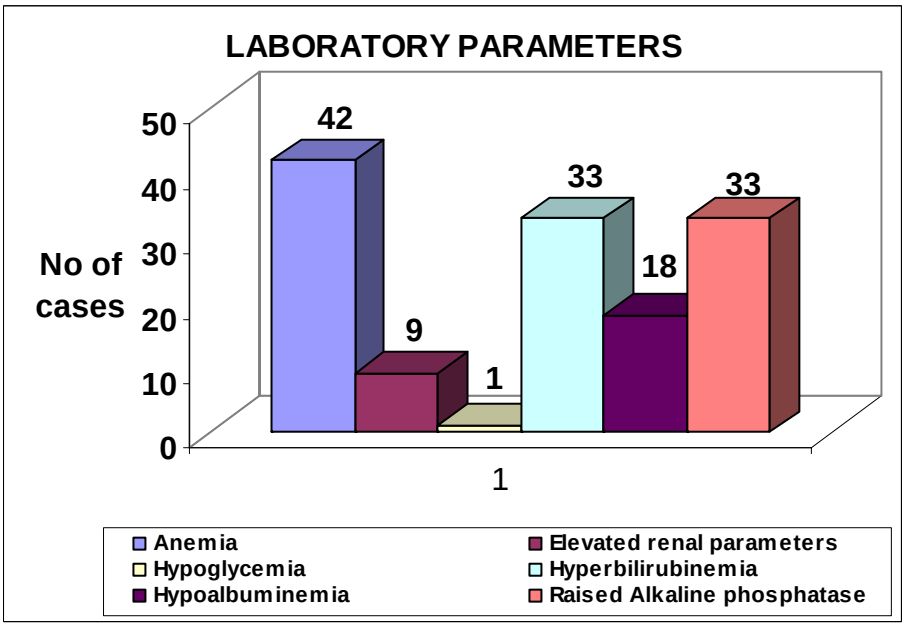

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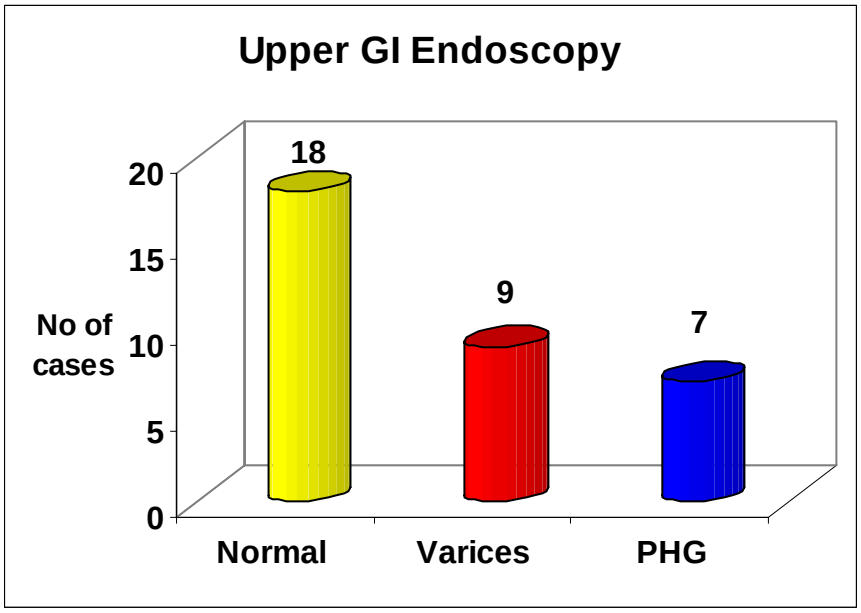

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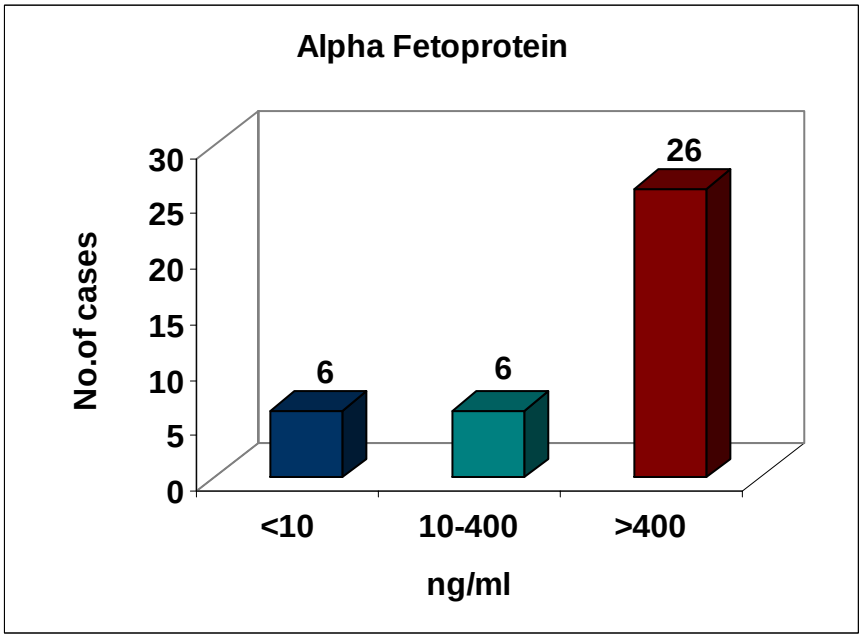

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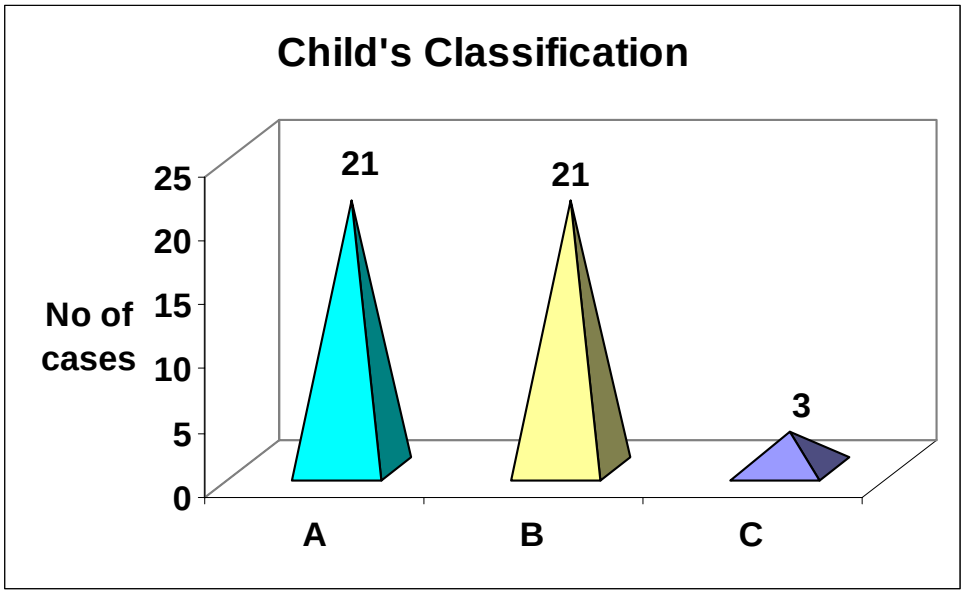

GRAPH – 8