"A ONE YEAR CROSS SECTIONAL STUDY OF CUTANEOUS MANIFESTATIONS IN PATIENTS WITH CHRONIC LIVER DISEASE AND ITS ASSOCIATION WITH LIVER FUNCTION TESTS"

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LIST OF ABBREVIATIONS USED

/Cumm	-	Per cubic millimeter
^{0}C	-	Degree centigrade
A:G	-	Albumin to globulin ratio
AC	-	Alcoholic cirrhosis
ALD	-	Alcoholic liver disease
CLD	-	Chronic liver disease
e.g.	-	For example
g/dL	-	Grams per deciliter
gm	-	Gram
HBsAg	-	Hepatitis B surface antigen
HBV	-	Hepatitis B virus
HCC	-	Hepatocellular carcinoma
HCV	-	Hepatitis C virus
IgG	-	Immunoglobulin G
IgM	-	Immunoglobulin M
INH	-	Isoniazid
IU/L	-	International units per liter
Kgs	-	Kilogram
LPA	-	Lysophosphatidic acid
mg/dL	-	Milligrams per deciliter
mm Hg	-	Millimeters of mercury
n	-	Total number
NAFLD	-	Non alcoholic fatty liver disease

NALD	-	Non alcoholic liver disease
NASH	-	Non alcoholic steatohepatitis
p	-	Probability
PAN	-	Polyarteritis nodosa
PCT	-	Porphyria cutanea tarda
PNC	-	Post necrotic cirrhosis
RNA	-	Ribonucleic acid
SD	-	Standard deviation
SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamate-pyruvate transaminase
TLC	-	Total leucocyte count
U/L	-	Units per liter
USA	-	United States of America
vs	-	Versus
WHO	-	World Health Organization
α	-	Alpha

ABSTRACT

Background and objectives

Chronic liver disease may present with numerous dermatological conditions. The present study explored the spectrum of cutaneous features in patients with chronic liver disease and its association with liver function tests.

Methodology

This one year cross sectional study was done under the settings of Department of Dermatology Venereology and Leprosy, of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2014 to December 2014. A total of 75 patients who presented with chronic liver disease during the study period were included in the study. Patients were subjected to complete dermatological examination and liver function tests.

Results

Majority (96%) of the patients were males. The male to female ratio was 24:1. The commonest age group was 41 to 50 years (34.67%) and the mean age was 51.09 ± 11.69 years. 66.67% of the patients had duration of CLD of less than or equal to one year and alcoholic cirrhosis (61.33%) was the commonest type liver disease. Out of 75 patients studied, 64 (85.33%) had cutaneous manifestations and jaundice was the commonest manifestation (53.33%). The prominent nail change observed was onycholysis (8%). Most of the patients had raised direct biliruibin (93.33%), SGOT (93.33%), SGPT (81.33%), and total

bilirubin (68%) levels and low A:G ratio (78.67%) and serum albumin (48%). The mean total and direct bilirubin levels were significantly high in patients with cutaneous manifestations ($p<0.001$). Also, positive association of cutaneous manifestations was noted with age ($p=0.005$) and the mean age was significantly low in patients with cutaneous manifestations ($p=0.004$).

Conclusion

There is high rate of cutaneous manifestations in patients with chronic liver disease. The common cutaneous manifestatons are jaundice and pruritus while shiny nails and finger clubbing are common nail features. There is direct relationship between raised total and direct bilirubin levels with cutaneous manifestations and cutaneous manifestations are common in younger age group.

Key words:

Chronic liver disease; Cutaneous manifestations; Nail changes;

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF PHOTOGRAPHS

INTRODUCTION

Chronic liver disease (CLD) is increasingly prevalent in developed countries, probably reflecting an increase in alcohol intake, the emerging obesity epidemic and the impact of viral hepatitis.[1] Available data suggests that about 0.1% of the European population is affected by cirrhosis, corresponding to 14 to 26 new cases per 100,000 inhabitants per year or an estimated 170,000 deaths per year.[2] However, literature on the prevalence and incidence of cirrhosis in India is scarce.

The liver synthesizes proteins such as clotting factors, complements, and albumin; neutralizing toxins; and metabolizing lipids and carbohydrates. Insults to the liver can compromise any of these functions, affecting visceral organs, joints, gastrointestinal tissues, and the skin. Dysfunction in the body's second largest organ, the liver, often yields changes in the body's largest organ, the skin. It is postulated that, the cutaneous changes may be the first clue that a patient has liver disease.[3,4] Although many of these changes are nonspecific, some are associated with distinct liver diseases and correlate with the severity of hepatic pathology.[5]

The cutaneous manifestations of liver disorders are protean. In addition to the well-recognized stigmata of liver cirrhosis, various infectious, metabolic, autoimmune, hereditary, developmental, and neoplastic liver disorders can result in various cutaneous and mucosal changes as well as in pruritus and abnormal hair and nail growth. Although many of these changes are nonspecific, some are associated with distinct liver diseases and correlate with the severity of hepatic pathology. Familiarization with the spectrum of these manifestations is important for early detection and treatment of hepatic diseases.[6]

Chronic liver disease can give rise to numerous extrahepatic disorders among which dermatological diseases occupy a central place and at times point to etiology of disease.[7] Jaundice, pigmentation, spider telangiectasias,[8] striae distensae, leukonychia, palmar erythema,[9] xerosis and loss of pubic and axillary hair are recognized sequelae of CLD.[10] Besides, these certain dermatoses are frequently associated with hepatobiliary disorders including lichen planus,[11,12] pyoderma gangrenosum, urticaria, porphyria cutanea tarda, vitiligo and hepatocutaneous syndrome. Other skin disorders which may be linked to CLD are erythema multiforme and nodosum, Behcet's disease and malakoplakia.[13,14]

Often the first clue to a liver disease is manifested through skin and cutaneous manifestations may also give a clue to the type of the liver disease the patient is suffering from.[15] However, there is scanty data available on the cutaneous manifestations of CLD in India. As to our knowledge, no large study has been done to explore cutaneous manifestations of CLD and correlate them with liver function tests in this part of the country. Hence the present study was planned to find out the spectrum of cutaneous features in patients suffering from CLD and to assess association between cutaneous features and liver function tests.

OBJECTIVES

The objectives of the present study were;

Primary

- To study the spectrum of cutaneous features in patients suffering from chronic liver disease.

Secondary

- To assess if any association exists between cutaneous features and liver function tests in chronic liver disease.

REVIEW OF LITERATURE

CHRONIC LIVER DISEASES

The liver is a vital organ in the upper right abdomen that aids in digestion and removes waste products from the blood. The liver aids greatly in the maintenance of metabolic homeostasis by processing dietary amino acids, carbohydrates, lipids, and vitamins; metabolizing cholesterol and toxins; producing clotting factors; and storing glycogen. Liver disease refers to any disorder of the liver and includes steatosis or fatty deposits in the liver, hepatitis or inflammation of the liver, fibrosis or scarring of the liver and cirrhosis. Injury to the liver parenchyma associated with an influx of acute or chronic inflammatory cells is termed hepatitis. Fibrosis previously was thought to be an irreversible scarring process formed in response to inflammation or direct toxic insult to the liver, but current evidence suggests that fibrosis may be reversible in some patients with chronic hepatitis B after antiretroviral therapy.[16]

Cirrhosis is a condition where scarring and inflammation spread through the liver and irreversibly disrupt its shape or function causing permanent cell damage and ultimately liver failure. It can lead to liver cancer which is a major cause of mortality.[17]

The word cirrhosis comes from the Greek word kirrhos, which means orange yellow.[18] Laennec gave cirrhosis its name kirrhos in 1819 in a brief footnote to his treatise De l'auscultation mediate.[19] The definition of cirrhosis remains morphological, described by a working party for the World Health Organization

(WHO) in 1978 as: "A diffuse process characterized by fibrosis and the conversion of normal liver architectures into structurally abnormal nodules".[20]

Cirrhosis is a chronic disease of the liver in which diffuse destruction and regeneration of hepatic parenchymal cells has occurred as well as diffuse increase in connective tissue has resulted in disorganization of the lobular architecture. The triad of parenchymal necrosis, regeneration and scarring is always present regardless of individual clinical manifestations.[21]

In the evolution of many chronic liver diseases cirrhosis is a stage that is considered to be irreversible. Cirrhosis can be stabilized by controlling the primary pathology but its presence implies consequences such as portal hypertension, intrahepatic shunting of blood, impaired parenchymal function affecting protein synthesis, hormone metabolism and excretion of bile and bile salts. The most common complications are: gastrointestinal hemorrhage, ascites, encephalopathy, bacterial infections, renal failure, hepatocellular carcinoma and hepatic failure.[22]

Certain reversible components of cirrhosis have been indicated where significant histological improvement have occurred with regression of cirrhosis but complete resolution with a return to normal architecture seems unlikely.[23]

The underlying immunological response has usually been acting for months or years where inflammation and tissue repairing are in progress simultaneously which leads in the end to fibrosis and cirrhosis.[24]

The past 30 years have witnessed major progress in the knowledge and management of liver disease. Cirrhosis and primary liver cancer are key to understanding the burden of liver disease. They represent the end-stage of liver pathology and thus are indicative of the associated mortality.[1]

Epidemiology

In the United States (USA) there has been an increase in the proportion of patients with HCV compared to ALD in the recent years.[25] Studies on patients characteristics at diagnosis show that the mean age is around 60 years and majority of the patients are males with the male/female ratio ranging from 1.3-4.[26] The highest mortality from liver cirrhosis is in the age group of 60-70 years.[27]

Literature on the prevalence and incidence of cirrhosis in India is scarce. Available data suggest that about 0.1% of the European population is affected by cirrhosis, corresponding to 14-26 new cases per 100,000 inhabitants per year or an estimated 170,000 deaths per year.[2]

In developing countries viral hepatitis is the leading cause of cirrhosis and in the developed countries ALD, HCV and NASH are the most significant causes of cirrhosis.[24]

Etiology

Any chronic insult to the liver can cause progression to cirrhosis. Although numerous pathophysiologic mechanisms of injury exist, the final common pathway is persistent wound healing resulting in hepatic parenchymal fibrosis. In most persons, approximately 80 to 90 percent of the liver parenchyma will be destroyed

before liver failure is manifested clinically. When complications of cirrhosis occur, they typically are related to impaired hepatic function or actual physical disruption and reorganization of the liver parenchyma.[16]

Etiologies of Hepatic Cirrhosis[16,28,29]

Most common causes

- Alcohol (60 to 70 percent)
- Biliary obstruction (5 to 10 percent)
    - Biliary atresia/neonatal hepatitis
    - Congenital biliary cysts
    - Cystic fibrosis
- Primary or secondary biliary cirrhosis
- Chronic hepatitis B or C (10 percent)
- Hemochromatosis (5 to 10 percent)
- NAFLD (10 percent)—most commonly resulting from obesity; also can occur after jejunoileal bypass

Less common causes

- Autoimmune chronic hepatitis types 1, 2, and 3
- Drugs and toxins
    - Alpha-methyldopa
    - Amiodarone
    - Isoniazid (INH)
    - Methotrexate
    - Oxyphenisatin
    - Troglitazone

  - Perhexiline
  - Vitamin A
- Genetic metabolic disease
  - α_1-Antitrypsin deficiency
  - Amino acid disorders (e.g., tyrosinemia)
  - Bile acid disorders
  - Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycogen storage diseases)
  - Lipid disorders (e.g., abetalipoproteinemia)
  - Porphyria
  - Urea cycle defects (e.g., ornithine carbamoyltransferase deficiency)
  - Wilson's disease
- Idiopathic/miscellaneous
  - Granulomatous liver disease (e.g., sarcoidosis)
  - Idiopathic portal fibrosis
  - Indian childhood cirrhosis
  - Polycystic liver disease
- Infection
  - Brucellosis
  - Congenital or tertiary syphilis
  - Echinococcosis
  - Schistosomiasis
- Vascular abnormalities
  - Chronic, passive hepatic congestion caused by right-sided heart failure, pericarditis

- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)
- Veno-occlusive disease

Natural history and complications of liver cirrhosis

Clinical features of cirrhosis derive from morphological alterations and usually reflect severity of hepatic damage rather then the etiology of the underlying liver disease. The loss of hepatocellular mass may lead to jaundice, edema, coagulopathy, and a variety of metabolic abnormalities.

Fibrosis and distorted vasculature lead to portal hypertension and its sequelae, including gastroesophageal varices and splenomegaly. Ascites and hepatic encephalopathy result from both portal hypertension and hepatocellular insufficiency. Other major complications of liver cirrhosis and portal hypertension are spontaneous bacterial peritonitis, hepatorenal syndrome and heptocellular carcinoma. The other sequelae are thrombocytopenia as a result of hypersplenism and in the alcoholic patients, direct bone marrow suppression by ethanol. Diminished protein synthesis can lead to reduced production of factors I, II, V, VII, IX and X. This may also be worsened by concomitant malabsorption of the fat-soluble vitamin K due to cholestasis.[30]

It has been observed that liver cirrhosis also affects other organs and organ systems such as the gastrointestinal tract and nutrition as well as the kidneys cardiovascular, respiratory and the skeletal system. The prognosis of liver cirrhosis ranges according to the severity of the liver disease and is significantly reduced after the development of decompensation.

A new scheme for the analysis of the natural history of cirrhosis and the identification of prognostic factors was proposed and agreed upon at the International Consensus Workshop of Baveno IV. The scheme identifies four clinical stages of cirrhosis: stage 1 which is characterized by the absence of esophageal varices and of ascites; stage 2 which is characterized by the presence of esophageal varices without ascites and without bleeding. The development of ascites, with or without varices, in a patient who has never bled is the hallmark of stage 3. Gastrointestinal bleeding with or without ascites characterizes stage 4. Cirrhosis is defined as compensated when the patient is in stages 1 and 2, decompensated in stages 3 and 4. Dividing the patients in to these 2 groups of compensated and decompensated cirrhosis is very useful in terms of prognosis as these are two distinct stages of cirrhosis with different predictors of survival.[31,32]

The yearly mortality rates have been calculated based on a large natural history study and the yearly risk of death according to the clinical stage is: in stage 1: 1.0%, in stage 2: 3.4%, in stage 3: 20% and in stage 4: 57%.[33] Even among patients with cirrhosis and mild portal hypertension the survival rate is significantly decreased compared to the general population.[34]

Clinical Presentation

History

Cirrhosis often is a silent disease, with most patients remaining asymptomatic until decompensation occurs. Physicians should inquire about risk factors that predispose patients to cirrhosis.Quantity and duration of alcohol consumption is an important factor in the early diagnosis of cirrhosis.[28] Other risk

factors include those for hepatitis B and C transmission (e.g., birthplace in endemic areas, sexual history exposure risk, intranasal or intravenous drug use, body piercing or tattooing, accidental contamination with blood or body fluids), as well as transfusion history and personal or family history of autoimmune or hepatic diseases.[28]

Early and well-compensated cirrhosis can manifest as anorexia and weight loss, weakness, fatigue, and even osteoporosis as a result of vitamin D malabsorption and subsequent calcium deficiency. Decompensated disease can result in complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal bleeding from portal hypertension.[16,35] Clinical symptoms at presentation may include jaundice of the eyes or skin, pruritus, gastrointestinal bleeding, coagulopathy, increasing abdominal girth, and mental status changes. Each of these clinical findings is the result of impaired hepatocellular function with or without physical obstruction secondary to cirrhosis. Because hepatic enzyme synthesis is required for drug metabolism, heightened sensitivity and medication toxicity may occur in patients with impaired hepatic enzyme synthesis.[16,28,36]

Physical examination

Physical examination of patients with cirrhosis may reveal a variety of findings that should lead to a targeted hepatic- or gastrointestinal-based work-up.[16,37] Many patients will already have had serologic or radiographic tests or an unrelated surgical procedure that incidentally uncovered signs of cirrhosis.

Common Physical Examination Findings in Patients with Cirrhosis[16]

- Abdominal wall vascular collaterals (caput medusa)
- Ascites
- Asterixis
- Clubbing and hypertrophic osteoarthropathy
- Constitutional symptoms, including anorexia, fatigue, weakness, and weight loss
- Cruveilhier-Baumgarten murmur—a venous hum in patients with portal hypertension
- Dupuytren's contracture
- Fetor hepaticus—a sweet, pungent breath odor
- Gynecomastia
- Hepatomegaly
- Jaundice
- Kayser-Fleischer ring—brown-green ring of copper deposit around the cornea, pathognomonic for Wilson's disease
- Nail changes:
    - Muehrcke's nails—paired horizontal white bands separated by normal color
    - Terry's nails—proximal two thirds of nail plate appears white, whereas the distal one third is red
- Palmar erythema
- Scleral icterus
- Vascular spiders (spider telangiectasias, spider angiomata)

- Splenomegaly
- Testicular atrophy

Complications of Cirrhosis[38]

Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding, and hepatorenal syndrome.

Cutaneous manifestations of chronic liver disease

Chronic liver disease is associated with several cutaneous manifestations. Although many of these changes are nonspecific, some are associated with distinct liver diseases and correlate with the severity of hepatic pathology. Often the first clue to a liver disease is manifested through skin. It is important for physicians to be familiar with the spectrum of these manifestations, to recognize, help detect, and treat the underlying hepatic disease.[5]

The cutaneous manifestations of liver disorders are protean. In addition to the well-recognized stigmata of liver cirrhosis, various infectious, metabolic, autoimmune, hereditary, developmental, and neoplastic liver disorders can result in various cutaneous and mucosal changes as well as in pruritus and abnormal hair and nail growth. Although many of these changes are nonspecific, some are associated with distinct liver diseases and correlate with the severity of hepatic pathology. Familiarization with the spectrum of these manifestations is important for early detection and treatment of hepatic diseases.[6,39]

Skin functions as a window to overall health and a number of systemic diseases result in various cutaneous changes. The presence of a constellation of signs and symptoms is more useful in pointing toward an underlying hepatobiliary condition.[40]

The spectrum of skin manifestations that may be found in various liver diseases are mentioned below.

Skin changes that may represent liver disease

Pruritus

Pruritus is the commonest, and at times the most distressing symptom of hepatobiliary diseases. It can be transient and mild or persistent and severe. Conditions associated with cholestasis such as primary sclerosing cholangitis and obstructive gallstone disease commonly present with pruritus, where it tends to be generalized but worse on hands and feet.[40,41]

The pathophysiological basis of pruritus in liver diseases is incompletely understood. Historically, the accumulation of bile salts, bile acids, and bilirubin has been considered to be responsible for cholestatic pruritus. Improvement of pruritus with the use of bile acid chelating resins and the disappearance of pruritus after dilating major bile duct stenosis in patients with longstanding intractable cholestatic pruritus are evidences to support the causative role of these substances.[42,43]

However, not all patients with elevated levels of bile salts or acids manifest with pruritus and also many patients do not respond to bile acid chelating resins. Further concentration of bile salts seems unrelated to the intensity of pruritus. Bile

salts possibly play a complex role in mediating cholestatic pruritus by interacting with other pruritogens. A number of potential pruritogens including endogenous opioids, histamine, tryptase, and substance P have been investigated. Dramatic improvement in cholestatic pruritus with the use of μ-receptor antagonist naltrexone strongly supports the role of endogenous opioids in the pathogenesis of cholestatic pruritus; however, no correlation has been found between the intensity of itch and opioid levels.[40,44]

Recently, lysophosphatidic acid (LPA) has been identified as a major pruritogen. It is produced from lysophosphatidylcholine by the action of enzyme autotaxin.40

In a study done by Kremer et al,[45] the levels of autotaxin and LPA were markedly increased in cholestatic patients with pruritus when compared with those without pruritus. Also, autotaxin activity significantly correlated with the intensity of pruritus; while that of serum bile salts, histamine, substance P, and μ-opioids failed to do so.

Pruritus of cholestasis does not get relieved by scratching and usually no visible skin lesions other than excoriations are seen. Sometimes, patients can develop lichenified plaques and prurigo nodularis like lesions.[46]

The documentation of pruritus and its severity was elicited by direct inquiry of patients using a direct inquiry of patients using a scale in which grade 0 = none, grade 1 = mild, grade 2 = some interference with sleep (moderate), and grade 3 = excoriations and substantial sleep disturbance (severe).[46]

Pruritus of liver diseases is quite resistant to therapy. Bile acid resins like cholestyramine form the first line of therapy. Other treatment options include selective serotonin re-uptake inhibitors, plasmapheresis, and opioid antagonists (naloxone). Rifampicin has also shown good results in some studies by promoting metabolism of endogenous pruritogens.[47,48]

Jaundice

Jaundice or icterus is a yellowish discoloration of tissue resulting from the deposition of bilirubin. Tissue deposition of bilirubin occurs only in the presence of serum hyperbilirubinemia and is a sign of liver disease. Slight increase in serum bilirubin is best detected by examining the sclera, which have high affinity for bilirubin due to their high elastin content. The major differential diagnosis of jaundice is carotenoderma. Carotenoderma is the yellow discoloration of the skin due to the presence of carotene. It occurs in healthy individuals who ingest excessive amounts of vegetables, fruits that contain carotene, such as carrots, leafy vegetables, squash, peaches and oranges. In carotinoderma, the pigment is concentrated on palms and soles, forehead and nasolabial folds. Carotinoderma can be differentiated from jaundice by the sparing of the sclera.[49] Skin discoloration following mepacrine or busulfan therapy may simulate jaundice, but these usually also cause subungual pigmented bands.[50]

Vascular Signs

*Spider Angiomata (*Vascular spiders , spider telangiectasias)

These are collection of dilated blood vessels near the skin surface. Spider angiomas are composed of a central feeding arteriole surrounded by radiating

tortuous capillaries. Blanching of lesion when pressure is applied over central arteriole is the hallmark sign. Most common site of occurrence is the trunk and face. Their presence in patients with alcoholic liver disease (ALD) indicates the associated risk of esophageal varices.[51]

Contributory factors include decreased hepatic metabolism of oestrogen leading to hyperoestrogenemia which accounts for loss of secondary male pattern hair, gynaecomastia and testicular atrophy; alcohol induced vasodilatation and altered cental vasomotor control may also be involved.[50]

Vascular spiders are not specific for cirrhosis: they also occur during pregnancy, in patients with severe malnutrition, and in healthy persons. The number and size of vascular spiders have been shown to correlate with the severity of chronic liver disease. Patients with numerous large vascular spiders are at increased risk for variceal hemorrhage.[52]

Further, their presence in increased number acts as a clinical marker of hepatopulmonary syndrome. Their presence in adults should prompt to investigate for underlying liver disease. Spontaneous regression with improvement in hepatic status or after liver transplant has been observed.[53] For cosmetic purpose, these can be treated with laser therapy.[40]

Palmar Erythema

Palmar erythema or liver palms can present as generalized redness of palms, dorsum of hands, fingertips, and nail bed. At times, it is localized only to hypothenar eminence. Similar changes can be seen over soles. Erythema blanches on the pressure and flushes synchronously with pulse rate. Patient may complain of

throbbing and tingling sensation. Exact pathogenesis of this mechanism is not known, but prostacyclins and nitric oxide are thought to play some role.[54,55]

The disturbed androgen balance in patients with ALD leads to local vasodilatation presenting as erythema. Patients of cirrhosis may have accompanied muscle atrophy of thenar and hypothenar eminence which appear to be myogenic in origin and not related to hormonal fators.[51]

Paper Money Skin

Patients with cirrhosis have many randomly scattered thin superficial capillaries over the upper trunk in association with spider angiomas. This resembles the silk threads in American dollar bills and hence is named dollar paper markings or paper money skin.[56]

Other Vascular Changes

Other vascular changes include corkscrew scleral vessels and caput medusae. Patients can also have purpuric lesions, epistaxis, and gingival bleeding either due to vascular fragility or due to acquired clotting factor deficiency.[3] Sometimes, small irregularly shaped hypopigmented patches are seen over arms and legs. These are considered to be due to venous stasis and are known as Bier spots. Their characteristic feature is that they disappear when pressure is applied or when the affected limb is raised from dependent position.[57]

Increased peripheral blood flow with the dilatation of digital pulp arteriovenous anastomoses leads to finger clubbing; seen in about 15% patients of hepatic cirrhosis. In progressive liver disease with portal hypertension, collateral

blood flow creates visible coiled varicose veins on the abdominal wall. When these occur in pattern radiating from the umbilicus, the appearance is termed 'caput Medusae'.[50]

Xanthelasma

Liver diseases can result in various forms of secondary dyslipoproteinemias. Most common are hypertriglyceridemia and low levels of high-density lipoproteins. Cutaneous manifestation is in the form of xanthelasmas which present as soft, yellowish asymptomatic plaques especially over the eyelids. The PBC is especially known to be associated with hypercholesterolemia and presents as planar, tuberous, and tendinous xanthomas.[58]

Pigmentary Changes

Patients with chronic liver disease often have a muddy gray colored hyperpigmentation predominantly over sunexposed areas.[29.] It is due hypermelanosis with normal number of melanocytes with precise mechanism being uncertain.[50] It may be blotchy or diffuse, at times exaggerated in perioral, periocular areas, and palmar creases. Men often have increased areolar pigmentation in association with testicular atrophy and gynaecomastia. Patients with hemochromatosis commonly develop metallic brown discoloration of the skin due to increased melanin production secondary to the cutaneous deposition of hemosiderin, known as Bronze diabetes.[40]

Nutritional Deficiencies

A number of hepatic diseases predominantly those causing steatorrhea result in the malabsorption of proteins, carbohydrates, minerals, trace elements, and vitamins. Further hypovitaminosis also results from decreased hepatic storage and failure of liver to convert vitamins to metabolically active forms. Also, vitamins are essential to repair the damaged cells and to produce new hepatocytes. Patients with hepatocellular disease including ALD have deficiency predominantly of vitamin B-complex and folic acid, while those with biliary obstruction have deficiency of fat-soluble vitamins (A, D, E, and K). Deficiency of these vitamins leads to changes in skin, nails, hair, and mucosae.[40]

Deficiency of iron and zinc is also commonly present in patients with chronic liver disease. Iron deficiency manifests as angular stomatitis, glossitis, brittle nails, and alopecia. Zinc deficiency can result in the development of dermatitis lesions over body and erosions over genital, perianal, and perioral areas.[40]

Mucocutaneous manifestatons of vitamin deficiencies in patients with chronic liver disease[40]

Vitamin deficiency	Mucocutaneous manifestations
Vitamin A	Xerosis Deep skin fissures (dermomalacia) Follicular hyperkeratotis (Phrynoderma) Xerophthalmia
Vitamin D	Alopecia
Vitamin E	Follicular hyperkeratosis
Vitamin K	Purpura Ecchymosis Gingival bleeding
Vitamin C	Follicular hyperkeratosis Perifollicular hemorrhages Stomatitis, epistaxis, bleeding gums (scurvy)
Vitamin B2 (Riboflavin)	Seborrheic dermatitis Stomatitis, gingivitis Conjunctivitis, corneal vascularization
Vitamin B6 (pyridoxine)	Seborrheic dermatitis Photodermatitis Glossitis, cheilitis
Vitamin B12 (cyanocobalamin)	H yperpigmentation of flexures, knuckles, palms, and fingers Pigmented streaks over nails Enlarged red tongue
Vitamin B3 (niacin)	Pellagra (dermatitis, dementia, and diarrhea)
Biotin	Alopecia Eczema around nose and mouth Conjunctivitis
Folic acid	G ray brown pigmentation on sun-exposed areas Cheilitis Glossitis Mucosal erosions

Hormonal Changes

In patients with chronic liver disease, there can be loss of forearm, axillary and pubic hair in both sexes. Men experience a decrease in the growth rate of facial hair and development of female pubic hair pattern along with the loss of libido, testicular atrophy, and oligospermia.[51]

Hair and Nail Changes

The body hair is often thinned or partially lost ,and males tend to develop a female pubic hair pattern. This is due to the fact that there is both increased production and decreased metabolism of oestrogens, as well as decreased production and increased metabolism of testosterone. Also, zinc deficiency leads to severe loss of hair.[50]

Nail abnormalities can be a revealing sign of a systemic disease including liver cirrhosis. Nail changes include a diffuse white colour with an invisible lunula, proximal white colour with distal pink colour (Terry nails) and white bands called Muehrke bands. Altered digital blood flow, soft tissue overgrowth and hypoalbuminaemia are the contributing factors.[50]

Those with advanced cirrhosis can present with Terry's nails characterized by a ground glass opacity of nail plate which turns powdery white at its proximal end.31 The condition is bilaterally symmetrical, with a tendency to be more marked in the thumb and forefinger.[50]

Another classical presentation of Terry's nails is a distal thin brown to pink transverse band of 0.5-2.0 mm in width. This needs to be differentiated from half-

and-half nails, which are typically seen in chronic renal failure, as well as in cirrhotic patients with severe hypoalbuminemia.[50]

Terry's nails are only a visual diagnosis and validated diagnostic criteria are absent, and some patients with Terry's fingernails show inhomogeneous changes in all nails in a random fashion.[50]

Longitudinal striations, dystrophic nails, brittle nails, onychorrhexis and true leukonychia can be found in hepatitis B and hepatitis C. Splinter hemorrhages and hypertrophic osteopathy can also occur in cirrhosis.

Bluish lunula known as Azure lunulae have been observed in Wilsons disease and in hemochromatosis, where in a blackish pigment, presumably melanin, appears on the nails.[59] Nails are white, brittle, and often triangular in Crockhite-Canada syndrome.[60]

Nail plate changes include clubbing and its milder variant, the watch glass deformity; flattened nails, or koilonychia may occur due to poor nutrition or altered metabolism in conditions such as Haemochromatosis.[59]

Collagen changes

Striae occur in both sexes, especially on the lower abdomen, thighs and buttocks. Chronic alcoholism also alters metabolism of corticosteroids, leading to 'pseudo-Cushing's syndrome'.[50]

Liver diseases with their typical cutaneous manifestations

Viral Hepatitis

Hepatitis A Virus

This is generally a transient infection and does not lead to chronic liver disease. The cutaneous manifestations include jaundice, urticaria, and exanthema which are present in a minority of cases.[61] In its relapsing variant, itching, purpura, and small vessel vasculitis can be seen.[62]

Hepatitis B Virus

This is transmitted parenterally and sexually. It may be associated with the presence of other sexually transmitted diseases and include a variety of cutaneous findings.[40]

Urticaria and Angioedema

Serum sickness like syndrome occurs in around 10% patients of acute HBV infection in the preicteric phase.[51] This may range from a mild erythema to a severe illness characterized by fever, malaise, and arthralgia. Circulating immune complexes are considered to be pathogenic.[63] Histopathology reveals small vessel vasculitis with direct immunofluorescence positive for IgG, IgM, C3, and hepatitis B surface antigen (HBsAg). Erythema multiforme and erythema nodosum like lesions can also be present. These cutaneous changes many a times precede the onset of other features of liver disease.[40]

Polyarteritis Nodosa

Hepatitis B virus infection is present in around 20% patients of polyarteritis nodosa (PAN). The frequency of HBV infection in patients with PAN has considerably declined over the past two decades. About 7–8% patients of acute HBV infection develop PAN and in most of them anti-neutrophil cytoplasmic antibody is negative unlike the classical PAN. Antigen–antibody complexes possibly involving hepatitis Be antigen (HBeAg) are thought to be pathogenic.[64]

Cryoglobulinemic Vasculitis

Cryoglobulins are detectable in 15% patients with HBV infection and this is generally asymptomatic.[65]

Gianotti Crosti Syndrome (Papular Acrodermatitis of Childhood)

It is characterized by small umbilicated papules predominantly affecting the extremities, buttocks, and cheeks. It has now been described in association with a number of other viral infections but was initially linked to HBV infection and vaccination. Lesions resolve spontaneously over 6–8 weeks and therefore management is only symptomatic.[65]

Other Skin Lesions

Pyoderma gangrenosum, dermatomyositis, and lichen planus have all been reported to be associated with HBV infection. There are few case reports of the development of urticaria, lichen planus, Gianotti Crosti syndrome, and granuloma annulare with HBV vaccination.[40]

Hepatitis C Virus

This is predominantly transmitted parenterally and 75% of patients develop chronic hepatitis.[40]

Cryoglobulinemia

Majority (70%) of type II cryoglobulinemia (polyclonal IgG and monoclonal IgM rheumatoid factor) and a minority of type III cryoglobulinemias (polyclonal IgG and polyclonal IgM rheumatoid factor) are HCV-associated. Common presenting features include small vessel vasculitis affecting the lower extremities, acrocyanosis, livedo reticularis, glomerulonephritis, arthralgia, hepatosplenomegaly, and hypocomplementemia.[66]

Studies have demonstrated the presence of HCV-RNA in organs affected in cryoglobulinemia mainly the skin and kidneys. All patients with mixed cryoglobulinemia complicating HCV infection should receive anti-virals as firstline therapy.[67]

Polyarteritis Nodosa

A small percentage of patients (30%) with PAN have preceding history of HCV infection.[68]

Porphyria Cutanea Tarda

This is characterized by blistering leading to scarring and hyperpigmentation predominantly over sun-exposed areas and facial hypertrichosis. There are wide variations in the prevalence of HCV-seropositivity in patients of porphyria cutanea

tarda (PCT) ranging from 10% to 90% depending on the geography. Other common associations of PCT are ALD and hemochromatosis. All patients of PCT should be screened for the presence of HCV infection and if positive require interferons for management in addition to regular iron removal.[40]

Necrolytic Acral Erythema

This has been recently described as a specific cutaneous feature of HCV infection.[69] It presents with well-defined acral dusky discoloration with blistering progressing to erythrokeratoderma clinically resembling necrolytic migratory erythema and pseudoglucagonoma.[70] Positive HCV serology with normal glucagon levels help in arriving at the diagnosis. Its development has also been linked to acquired zinc deficiency secondary to chronic liver disease but it needs further confirmation.1 Resolution of lesions has been seen in patients with interferon-based regimens.[71]

Red Finger Syndrome

This is due to capillary dilatation resulting in erythema. Earlier description of this syndrome was in patients with concomitant HIV and HCV infections.[40]

Lichen Planus

Lichen planus has been found to be positively associated with chronic liver diseases including PBC, chronic active hepatitis, and cirrhosis of unknown cause. Studies have both supported and refuted the claims of association between lichen planus and HCV infection.[40,72]

A recent meta-analysis has reported that there is significantly higher risk of lichen planus patients being HCV-seropositive.[73] Thus, all patients of lichen planus should ideally be screened for HCV-seropositivity.[40]

Other Skin Diseases

Autoimmune thrombocytopenic purpura, Behcet's disease, vitiligo, and Sjogren's syndrome are some of the autoimmune disorders associated with HCV-seropositivity.[40,65]

Other Hepatitis Viruses

Hepatitis D virus infection can cause cutaneous features similar to that of HBV infection. Hepatitis F, G, and E viruses cause infections which are generally mild and are rarely associated with dermatological manifestations.[65]

Primary Biliary Cirrhosis

It is an autoimmune disorder predominantly affecting women. Presence of concomitant autoimmune disorders is common including Sjogren's syndrome, CREST syndrome, morphea, and lichen planus.[74]

Typical clinical picture is of a middle-aged lady with jaundice and pruritus, showing features suggestive of cholestasis on liver function tests and the presence of anti-mitochondrial antibodies. Fifty percent patients of PBC present with pruritus as the initial and predominant feature resulting in excoriations and also postinflammatory hyperpigmentation. Butterfly sign characterized by normal looking skin over the upper back and surrounding hyperpigmentation is frequently observed.[75]

This is because of the inability of the patient to scratch the upper back. Secondary hyperlipidemia presenting with xanthelasma palpebrarum, palmar crease, tuberous, and tendinous xanthomas is also a hallmark manifestation.[65]

A series of 49 PBC patients has reported fungal infections to be the commonest cutaneous manifestation (31.5%); followed by neoplastic lesions (18.4%), urticaria (15.7%), and pigmentary changes (12.4%).[76]

Hemochromatosis

It is a multi-system disorder resulting in the deposition of iron in tissues and organs including liver, pancreas, heart, pituitary, and other endocrine organs. Predominant clinical features include skin pigmentation, diabetes, hepatic cirrhosis, and cardiac failure. Apart from the presence of stigmata of chronic liver disease, two characteristic cutaneous abnormalities are seen which include hyperpigmentation and ichthyosiform changes.[40]

Hyperpigmentation which is more marked over sun-exposed areas is an early sign of hemochromatosis and acts as a surrogate marker of iron deposition in other organs. It has a grayish or bronze hue and hence named bronze diabetes. Deposition of iron in skin stimulates melanocytes resulting in enhanced melanin production; this is further aggravated by sun exposure. Another important cutaneous change seen is the development of fish like dry scales known as ichthyosis usually in association with koilonychia of nail plate. The exact pathogenesis of this disorder remains unclear.[3]

Therapies that lower serum iron levels reverse the cutaneous manifestations; however, skin pigmentation takes a long time to resolve.[77,78]

Alcoholic Cirrhosis

Chronic alcoholism is recognized as one of the common causes of cirrhosis, resulting in end-stage liver disease. Defective synthesis of clotting factors due to cirrhosis leads to bleeding disorders. Spider angiomas, palmar erythema, and Dupuytren's contracture are seen in around 72% of patients with alcoholic cirrhosis.[77]

Most distinct lesions of alcoholic cirrhosis include paper money skin and Dupuytren's contracture. Other than these, alcoholic cirrhosis patients are also found to be more prone to develop disseminated superficial porokeratosis which resolve completely with the improvement of liver function.[40]

Acquired zinc deficiency in patients of ALD can present as crackled and reticulate eczema over the trunk and extensor of extremities. Also, there can be crusted erosions over the perianal and genital areas, cheilitis, hair loss, and transverse (Beau's) lines over nails.[65] Apart from specific dermatological manifestations of chronic liver disease, patients of chronic alcoholism can present with a number of associated diseases having cutaneous changes.[40]

Cutaneous manifestations of chronic alcoholism[40]

Chronic alcoholism-associated diseases with cutaneous abnormalities

- Marasmus: Dry wrinkled skin
- Kwashiorkor:
    - Scaling and fissuring over flexures
    - A lternating bands of dark and light hair (flag sign)
- Vitamin deficiencies
- Hypogonadism: Reduced facial hair growth
- Hyperestrogenemia
    - Loss of body hair
    - Spider angiomas
    - Gynecomastia
- Pseudo-Cushing's syndrome
    - Abdominal striae
    - Moon facies, buffalo hump, truncal obesity
- Porphyria cutanea tarda
- Pancreatitis
    - Subcutaneous fat necrosis
    - Cullen's sign, Grey Turner sign
- Dupuytren's contracture

Cutaneous diseases aggravated by alcohol

- Psoriasis
- Rosacea
- Discoid eczema

Hepatic Neoplasm

Skin changes are rarely seen in patients with hepatocellular carcinoma (HCC). Cutaneous metastasis presenting as single or multiple firm, painless, reddish-blue nodules Other are seen in only 1–5% cases.[79]

Hepatocellular carcinoma can be associated with a PCT-like presentation and there is also a case report of dermatomyositis in a patient of HCC with HBV infection.[80]

Pityriasis rotunda presenting as round to oval patches of dry ichthyotic skin has been found to be more common in patients with HCC.[81] Hemangioendo thelioma, leiomyosarcoma, and sarcomatoid carcinoma are other hepatic tumors which can present with cutaneous metastasis.[40]

Alagille Syndrome

It is a hereditary and developmental liver disease characterized by chronic cholestasis, peculiar facies, cardiovascular abnormalities, and vertebral arch defects.[82]

The syndromic form has autosomal dominant inheritance and the nonsyndromic form is associated with α1-anti-trypsin deficiency and viral infections (rubella, cytomegalovirus, and HBV). Specific cutaneous manifestations include jaundice, xanthomas, and pruritus. Xanthomas are seen in 29% cases and are widespread involving palmar and plantar creases, inguinal area, popliteal fossae, elbows, and knees. Xanthomas are the result of chronic cholestasis and hypercholesterolemia and tend to improve following liver transplant.[83]

Overall, patients with liver diseases can present with a number of cutaneous manifestations. These at times are quite specific and thus help in identifying the underlying disorder. Thorough knowledge of these cutaneous changes is essential both for dermatologists and for hepatologists, so as to make a timely diagnosis aiding in prompt intervention. However, to-date very few studies[14,84] have evaluated the cutaneous manifestations in patients with chronic liver disease.

In a study by Sayal S.K et al[84] who had done a comparative analysis of liver function tests in patients with chronic liver disease, found that cutaneous manifestations were seen in 58.7% cases. These included 28.3% cases of alcoholic liver disease, 15.2% cases of post necrotic cirrhosis, 8.7% cases of chronic active hepatitis and 6.5% cases of hepatocellular carcinoma. Common cutaneous manifestations seen in chronic liver disorders were prominent dilated veins on abdomen (30.4%), icterus (26.0%), clubbing of nails (19.5%), ichthyosis (15.2%), hyperpigmentation (13%) and pruritus (10.8%). Other less common cutaneous manifestations were telangiectasia, palmar erythema, spider naevi, leukonychia and loss of body hair in 4.3% cases each and purpura, stria distensae and pellagra in 2.2% cases each. It was observed that serum bilirubin level was high in patients with cutaneous manifestations while the level of serum alkaline phosphatase and serum glutamic pyruvic transaminase were high in patients of chronic liver disorder without cutaneous manifestation.

Another study by Khan MM, et al.[14] determined the cutaneous manifestations of chronic liver disease (CLD) and particular pattern associated with aetiology of disease. Patients suffering from chronic liver disease of any aetiology presenting to Department of Gastroenterology Hayatabad Medical Complex,

Peshawar from 1st December 2004 to 30th April 2005 were enrolled in the study. A total of fifty patients, 32 males and 18 females were included. Thirty (60%) patients were suffering from chronic hepatitis C virus infection, 14 patients were suffering from Chronic hepatitis B virus infection and 2 patients each were suffering from primary biliary cirrhosis and Wilson's disease. In two cases the aetiology could not be ascertained. Different manifestations included pigmentation (82%), Terry's nails (80%), xerosis and excoriations (72%), nonscarring hair loss from axilla and pubic region (64%), and spider naevi and palmar erythema (36%). Lichen planus was seen in 4%, vitiligo and hepatocutaneous syndrome in (2%) of patients each. The authors commented that, cutaneous manifestations in chronic liver disease are non-specific and do not point towards specific aetiology. Physicians caring for patients with chronic liver disease should pay attention to its multisystemic nature.

METHODOLOGY

The present study was carried out in the Department of Dermatology Venereology and Leprosy, of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi over a period of one year from January 2014 to December 2014.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2014 to December 2014.

Place

This study was carried out at Department of Dermatology, Venereology and Leprosy, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi attached to Jawaharlal Nehru Medical College, Belagavi.

Source of Data

Patients with chronic liver disease attending Out Patient and In patient services at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi were studied.

Sample size

The present study was comprised of 75 patients with chronic liver disease.

Sampling method

The sample size was determined based on the following formula.

$n = (z^2 \times p \times q)\ d^2$

where

z = Constant (1.96 ~ 2 at 95% confidence interval)

p = Prevalence (58.7% considered from previous study)

q = 100 – p = 100 -58.7 = 41.3

d = Absolute error that is 10%

Therefore

$n = 2^2 \times 58.7 \times 41.3 / 10^2$

$= 96.97 \approx 97$

Revised sample size for finite population:

$n = n / [1 + (n/N)]$

Where, N was calculated from total no. of diagnosed cases of chronic liver disease.

$= 97 / [1 + (97/300)]$

$= 97/1.32$

$= 73.5 \approx 75$

Hence the sample size of 75 was planned.

Selection criteria

Inclusion Criteria

- All confirmed (old and new) cases of chronic liver disease, willing to participate in the study.
- Presence of cirrhosis (clinically/radiologically suspected and/or histologically proven).
- Presence of severe cholestatic liver disease(serum bilirubin level more than three time the upper limit of normal for more than six months).

Exclusion criteria

- Patients who do not provide informed consent.

Ethical clearance

Prior to the commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed consent

Patients who fulfilled the selection criteria were briefed about the nature of study and a written informed consent was obtained (Annexure I).

Data collection

The selected patients were interviewed for demographic features like age, sex and detailed history was taken regarding chronic liver disease including duration and type of chronic liver disease. Presence of other associated illnesses was noted.

Patients were subjected to clinical and systemic examination. These findings were noted on a predesigned proforma (Annexure II).

Dermatological examination

A complete dermatological examination was done to assess the cutaneous manifestations.

Investigations

Following investigations were done in all the patients.

- Haemoglobin
- Total leucocyte count
- Liver function tests:
    - Total bilirubin
    - Direct bilirubin
    - SGOT
    - SGPT
    - Serum albumin
    - Alkaline phosphatase
    - A:G ratio
- Skin biopsy
- KOH mount preparation

Skin biopsy

Skin biopsy was performed for dermatoses such as Eczema and Leucocytoclastic vasculitis.

Procedure

After an informed consent, thorough cleaning of biopsy site was done with 70% alcohol. The area was then anasethetized by infiltrating 2% lignocaine subcutaneously. A round body skin biopsy punch was held vertically and twisted as it descends perpendicularly through the dermis and subcutis . The punch was then slowly withdrawn and specimen was elevated and cut at its base. This was transferred to 10% formalin for histopathological examination.

KOH mount preparation

For diagnosing Superficial Dermatophyte infections and Pityriasis versicolor.

Procedure

For direct microscopic examination, a small amount of specimen was spread over the centre of the glass slide and a drop of 10% KOH was added and a cover slip was placed on it. Slide was slightly warmed by passing over naked flame and after the material softened, gentle pressure was applied over the cover slip to force out any trapped air and to facilitate thinning of the specimen. Examination was conducted first under low power and then under high power objective.

Statistical analysis

The data obtained was coded into Microsoft excel spreadsheet (Annexure III). The continuous data was expressed as mean ± standard deviation (SD). Categorical data was expressed in terms of rates, ratios and percentages and comparison was done using chi-square test or fishers exact test and continuous data was compared

using independent sample 't' test. A probability value ('p' value) of less than or equal to 0.050 was considered as statistically significant.

RESULTS

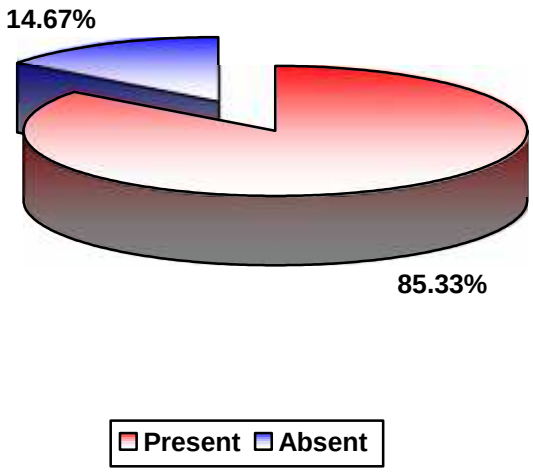
The present one year cross sectional study was carried out in the Department of Dermatology Venereology and Leprosy, of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. A total of 75 patients with chronic liver disease during the study period from January 2014 to December 2014 were studied.

The data was analysed and the final results and interpretations were tabulated as below.

Table 1. Incidence of cutaneous manifestations

Cutaneous manifestations	Distribution (n=75)	
	Number	**Percentage**
Present	64	85.33
Absent	11	14.67
Total	**75**	**100.00**

Graph 1. Incidence of cutaneous manifestations

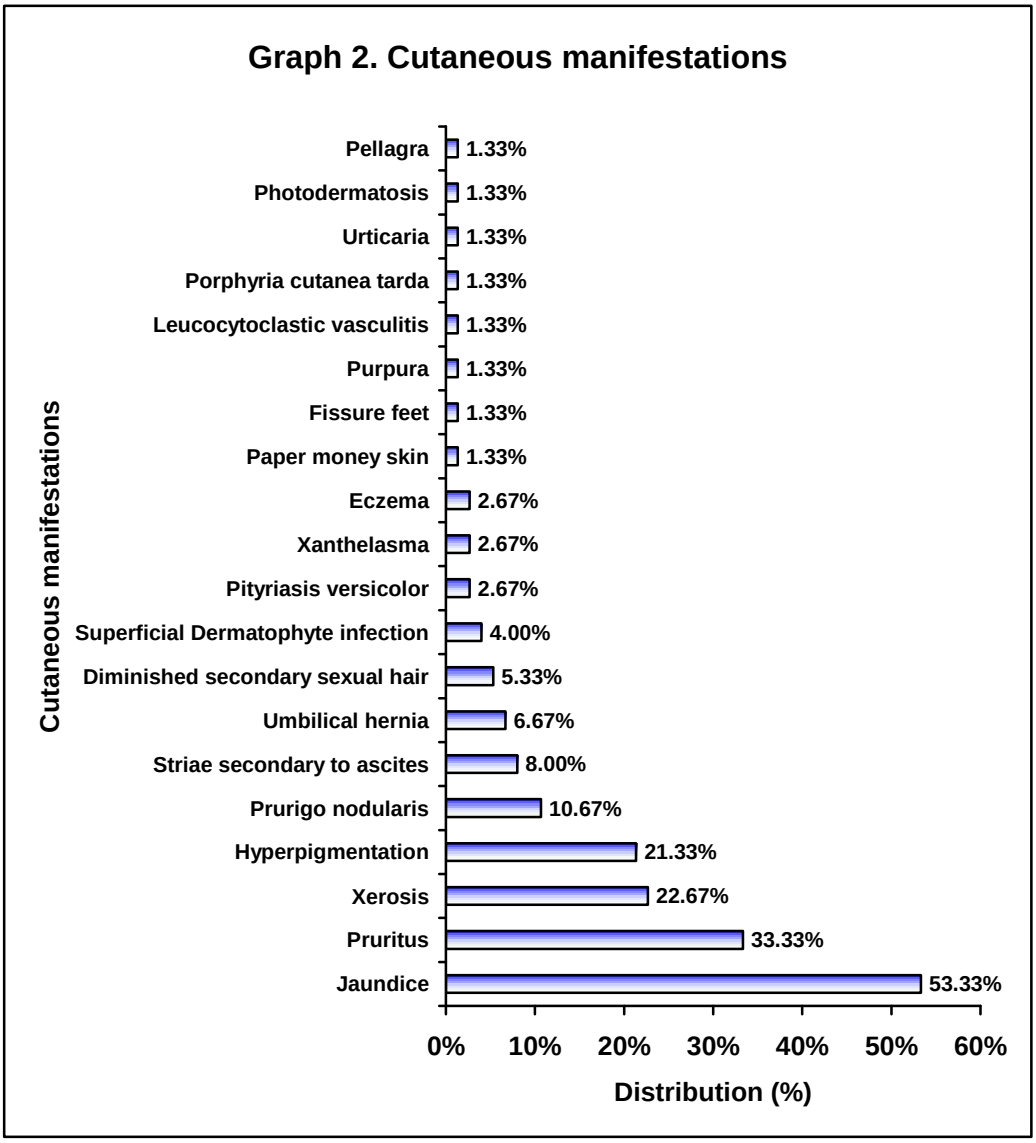


In the present study out of 75 patients studied 64 (85.33%) patients had cutaneous manifestations.

Table 2. Cutaneous manifestations

Cutaneous Manifestations	Distribution (n=75)	
	Number	**Percentage**
Jaundice	40	53.33
Pruritus	25	33.33
Xerosis	17	22.67
Hyperpigmentation	16	21.33
Prurigo nodularis	8	10.67
Striae secondary to ascites	6	8.00
Umbilical hernia	5	6.67
Diminished secondary sexual hair	4	5.33
Superficial Dermatophyte infection	3	4.00
Pityriasis versicolor	2	2.67
Xanthelasma	2	2.67
Eczema	2	2.67
Paper money skin	1	1.33
Fissure feet	1	1.33
Purpura	1	1.33
Leucocytoclastic vasculitis	1	1.33
Porphyria cutanea tarda	1	1.33
Urticaria	1	1.33
Photodermatosis	1	1.33
Pellagra	1	1.33

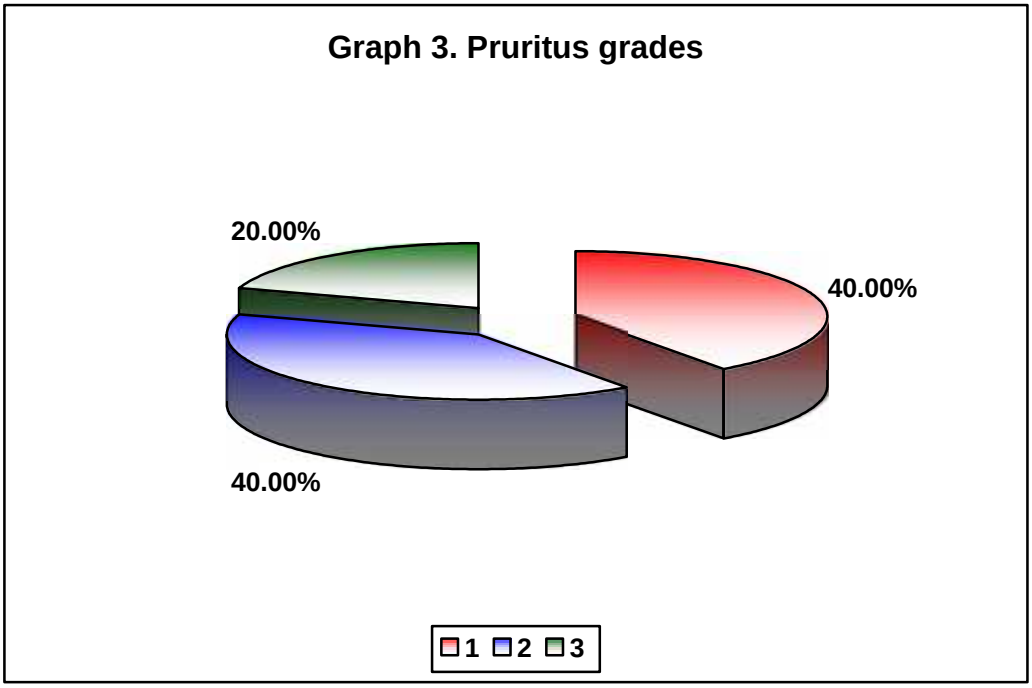
Multiple conditions present hence total not shown



In this study Jaundice was the commonest manifestation (53.33%) followed by Pruritus (33.33%), Xerosis (22.67%), Hyperpigmentation (21.33%) and Prurigo nodularis (10.67%). Few patients also presented with Striae secondary to ascites (8%), Umbilical hernia (6.67%), Diminished secondary sexual hair (5.33%), Superficial Dermatophyte infection (4%), Pityriasis versicolor (2.67%), Xanthelasma, Eczema (2.67% each), Paper money skin, Fissure feet, Purpura, Leucocytoclastic vasculitis, Porphyria cutanea tarda, Urticaria, Photodermatosis and Pellagra (1.33%).

Table 3. Pruritus grades

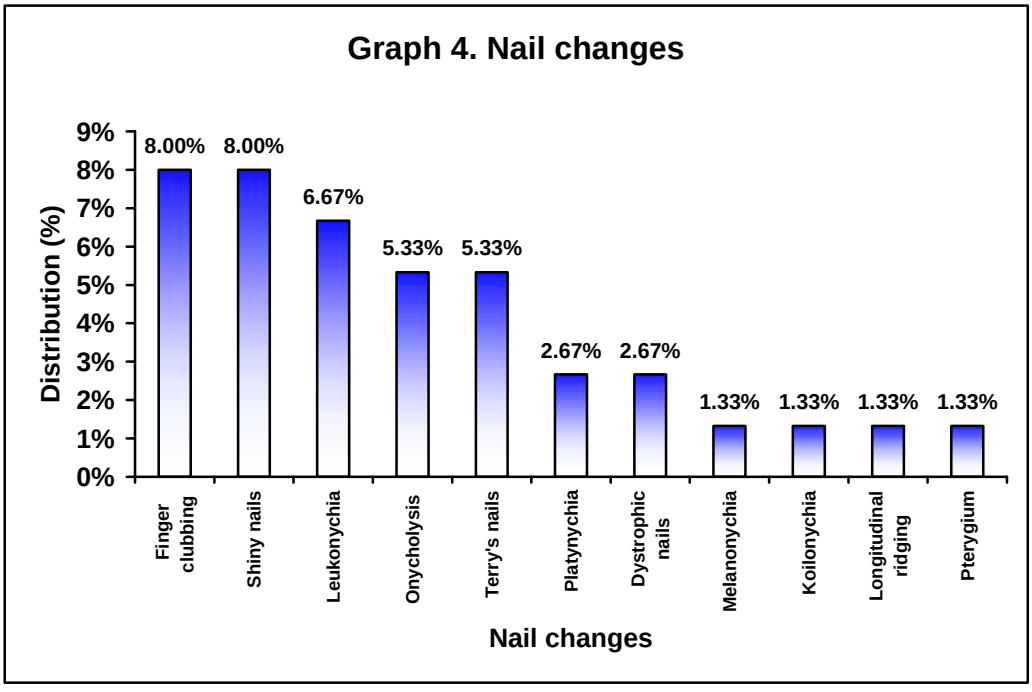
Grades	Distribution (n=25)	
	Number	**Percentage**
1	10	40.00
2	10	40.00
3	5	20.00
Total	**25**	**100.00**



In the present study, of the 25 patients with pruritus, 10 each (40% each) had grade 1 and 2 while 5 patients (20%) had grade 3 pruritus.

Table 4. Nail changes

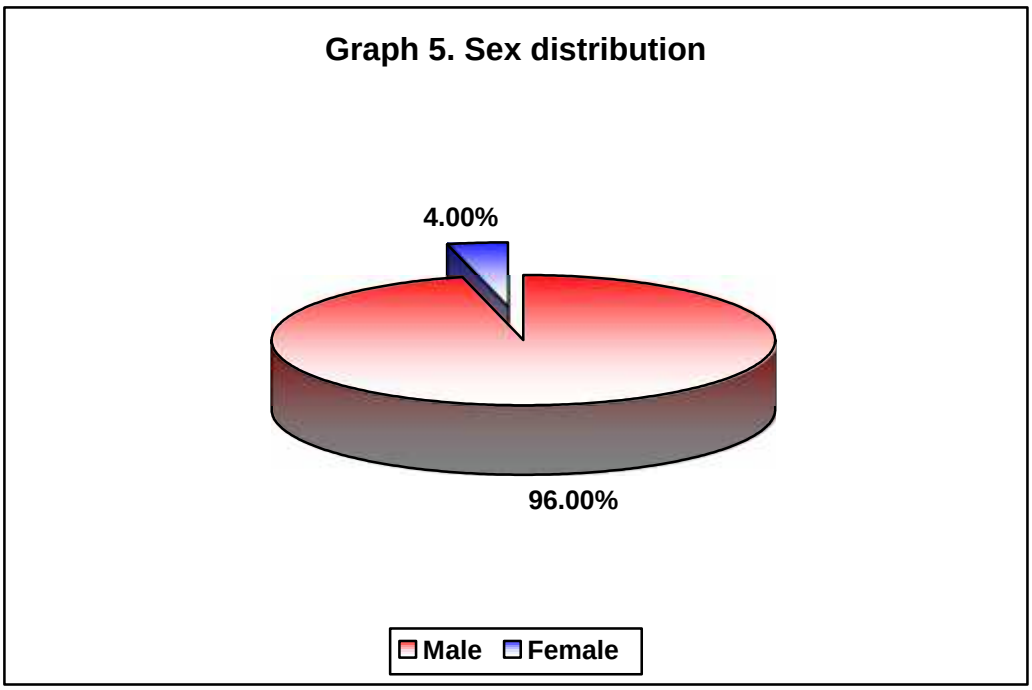
Nail changes	Distribution (n=75)	
	Number	Percentage
Finger clubbing	6	8.00
Shiny nails	6	8.00
Leukonychia	5	6.67
Onycholysis	4	5.33
Terry's nails	4	5.33
Platynychia	2	2.67
Dystrophic nails	2	2.67
Melanonychia	1	1.33
Koilonychia	1	1.33
Longitudinal ridging	1	1.33
Pterygium	1	1.33



In this study nail changes Finger clubbing and Shiny nails were noted in 8% of the patients each while Leukonychia was noted in 6.67% of the patients.

Table 5. Sex distribution

Sex	Distribution (n=25)	
	Number	**Percentage**
Male	72	96.00
Female	3	4.00
Total	**75**	**100.00**

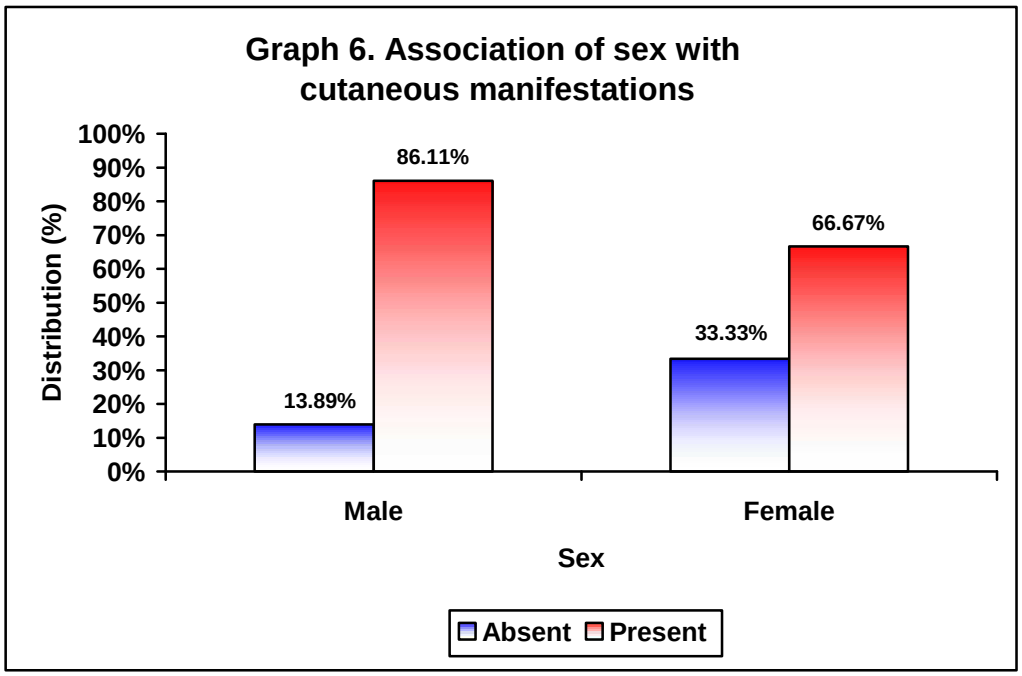


In the present study, majority (96%) of the patients were males and male to female ratio was 24:1.

Table 6. Association of sex with cutaneous manifestations

Sex	Cutaneous manifestations			
	Absent		Present	
	Number	Percentage	Number	Percentage
Male	10	13.89	62	86.11
Female	1	33.33	2	66.67
Total	**11**	**14.67**	**64**	**85.33**

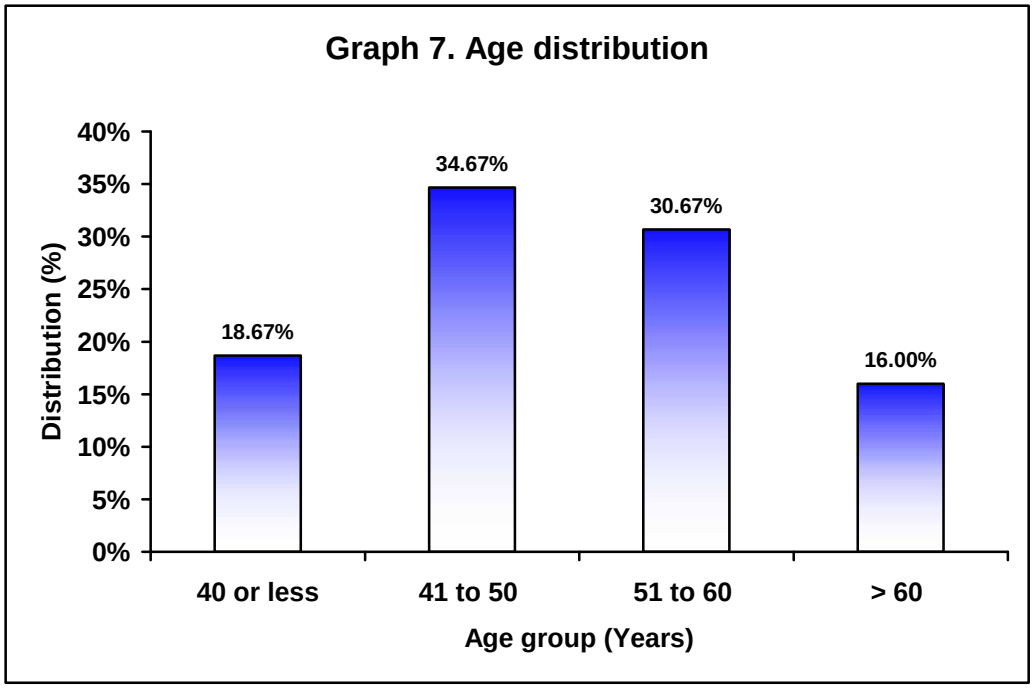
p = 0.383



In the present study majority of the patients that is 72 patients were males of which 62 (86.11%) had cutaneous manifestations compared to 2 females out of 3 (66.67%). However the cutaneous manifestations were common in both the sexes (p=0.383).

Table 7. Age distribution

Age group (Years)	Distribution (n=25)	
	Number	**Percentage**
40 or less	14	18.67
41 to 50	26	34.67
51 to 60	23	30.67
> 60	12	16.00
Total	**75**	**100.00**

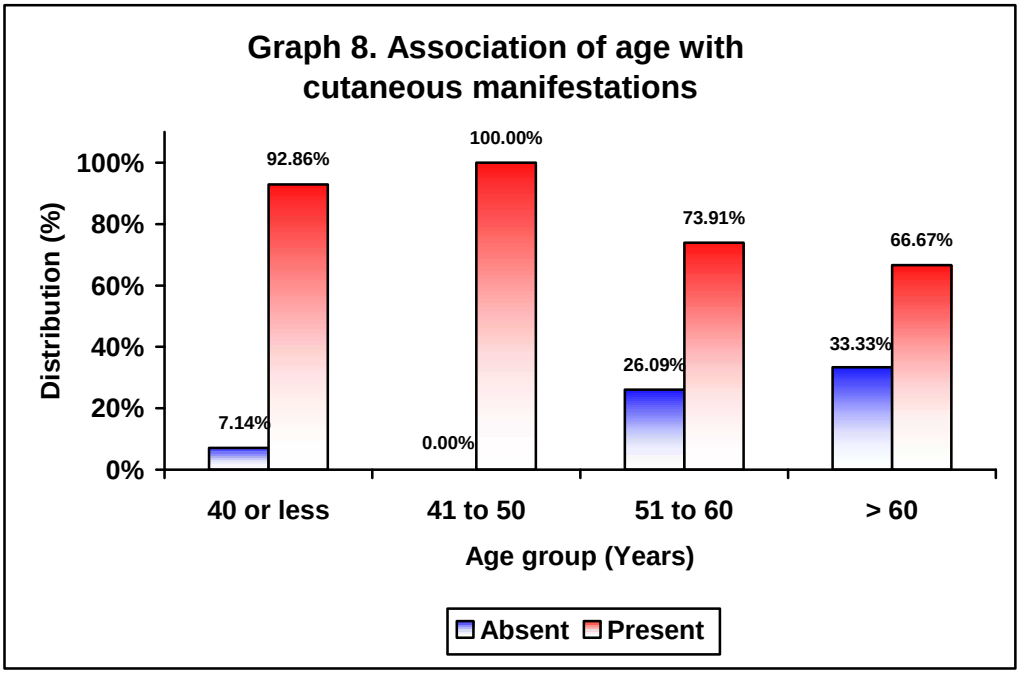


In the present study most of the patients were aged between 41 to 50 years (34.67%) and 51 to 60 years (30.67%).

Table 8. Association of age with cutaneous manifestations

Age group (Years)	Cutaneous manifestations			
	Absent		Present	
	Number	Percentage	Number	Percentage
40 or less	1	7.14	13	92.86
41 to 50	0	0.00	26	100.00
51 to 60	6	26.09	17	73.91
> 60	4	33.33	8	66.67
Total	**11**	**14.67**	**64**	**85.33**

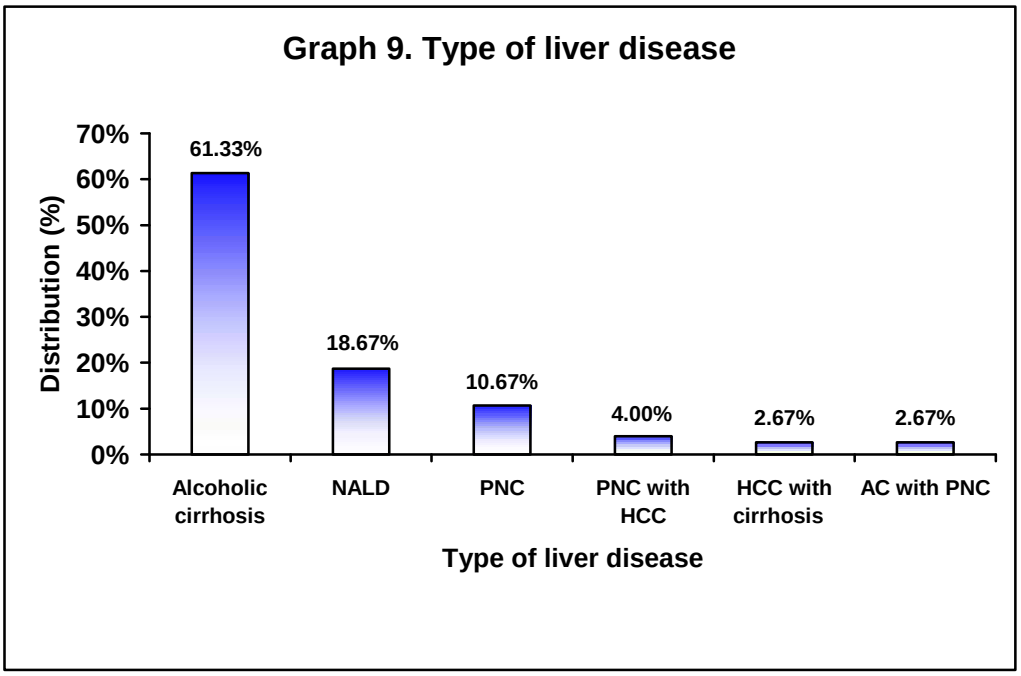
p = 0.005



In this study cutaneous manifestations were widely prevalent in patients with < 40 years and 41 to 50 years (92.86% and 100% respectively) compared to age > 50 years (p=0.005).

Table 9. Type of liver disease

Type of liver disease	Distribution (n=25)	
	Number	**Percentage**
Alcoholic cirrhosis	46	61.33
NALD	14	18.67
Post necrotic cirrhosis	8	10.67
Post necrotic cirrhosis with HCC	3	4.00
Hepatocellular carcinoma with cirrhosis	2	2.67
Alcoholic cirrhosis with post necrotic cirrhosis	2	2.67
Total	**75**	**100.00**



In the present study Alcoholic cirrhosis (61.33%) was the commonest type liver disease followed by NALD (18.67%) and PNC (10.67%).

Table 10. Association of type of liver disease with cutaneous manifestations

Type	Cutaneous manifestations			
	Absent		Present	
	No.	%	No	%
Alcoholic cirrhosis	5	10.87	41	89.13
NALD	3	21.43	11	78.57
Post necrotic cirrhosis	2	25.00	6	75.00
Hepatocellular carcinoma with cirrhosis	0	0.00	2	100.00
Post necrotic cirrhosis with HCC	1	33.33	2	66.67
Alcoholic cirrhosis with post necrotic cirrhosis	0	0.00	2	100.00
Total	**11**	**14.67**	**64**	**85.33**

p = 0.484

In the present study, the frequency of cutaneous manifestations was comparable in different types of liver diseases (p=0.484).

Table 11. Distribution of patients according to type of liver disease and cutaneous manifestations

Cutaneous manifestation	Type of liver disease											
	Alcoholic cirrhosis (n=46)		NALD (n=14)		Post necrotic cirrhosis (n=8)		HCC with cirrhosis (n=3)		PNC with HCC (n=2)		AC with PNC (n=2)	
	No	%	No	%	No	%	No	%	No	%	No	%
Jaundice	27	58.70	4	28.57	6	75.00	1	33.33	1	50.00	1	50.00
Xanthelasma	1	2.17	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00
Eczema	1	2.17	0	0.00	1	12.50	0	0.00	0	0.00	0	0.00
Paper money skin	0	0.00	0	0.00	1	12.50	0	0.00	0	0.00	0	0.00
Umbilical hernia	3	6.52	2	14.29	0	0.00	0	0.00	0	0.00	0	0.00
Fissure feet	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pruritus	18	39.13	3	21.43	2	25.00	0	0.00	1	50.00	1	50.00
Hyperpigmentation	12	26.09	1	7.14	2	25.00	1	33.33	0	0.00	0	0.00
Prurigo nodularis	6	13.04	0	0.00	1	12.50	0	0.00	1	50.00	0	0.00
Striae secondary to ascites	4	8.70	0	0.00	2	25.00	0	0.00	0	0.00	0	0.00
Purpura	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Leucocytoclastic vasculitis	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Porphyria cutanea tarda	0	0.00	0	0.00	1	12.50	0	0.00	0	0.00	0	0.00
Diminished secondary sexual hair	2	4.35	0	0.00	2	25.00	0	0.00	0	0.00	0	0.00
Urticaria	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Photodermatosis	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Xerosis	11	23.91	2	14.29	1	12.50	0	0.00	1	50.00	2	100.00
Pellagra	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Pityriasis versicolor	1	2.17	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00
Superficial Dermatophyte infection	3	6.52	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Multiple conditions present hence total not shown

In this study Alcoholic cirrhosis was noted in 46 (61.33%) patients. Among them, Jaundice was noted in 27 patients (58.7%), Pruritus in 18 patients (39.13%), Hyperpigmentation in 12 (26.09%) and Xerosis in 11 patients (23.91%).

Table 12. Distribution of patients according to the type of liver disease and nail changes

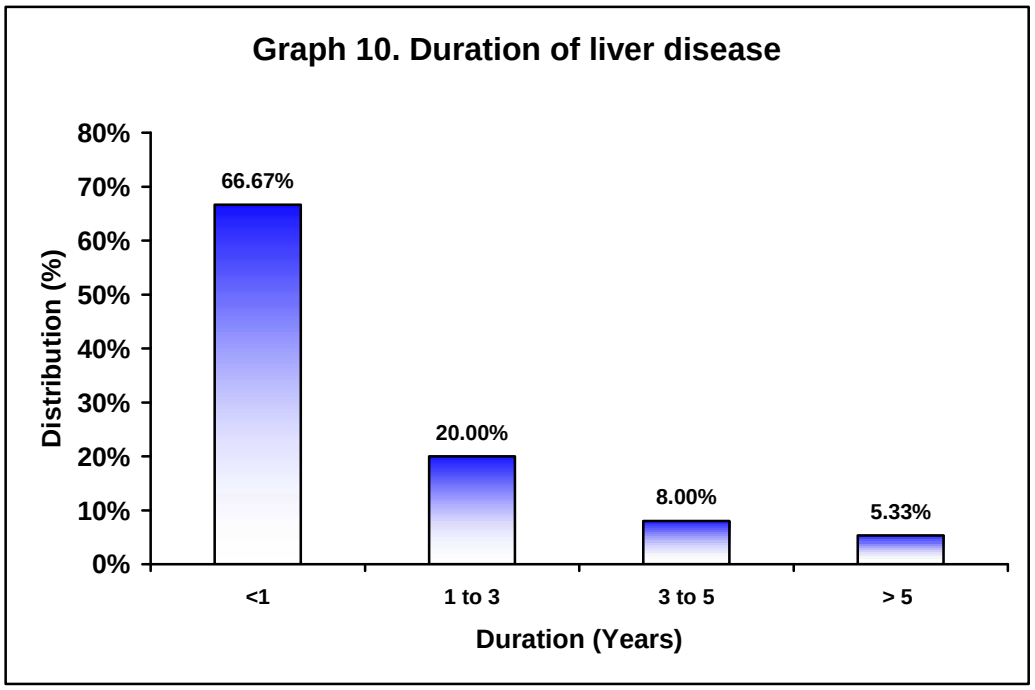
Nail changes	Type of liver disease											
	Alcoholic cirrhosis (n=46)		NALD (n=14)		Post necrotic cirrhosis (n=8)		HCC with cirrhosis (n=3)		PNC with HCC (n=2)		AC with PNC (n=2)	
	No	%	No	%	No	%	No	%	No	%	No	%
Finger clubbing	2	4.35	0	0.00	4	50.00	0	0.00	0	0.00	0	0.00
Onycholysis	0	0.00	1	7.14	1	12.50	1	33.33	0	0.00	1	50.00
Dystrophic nails	0	0.00	0	0.00	1	12.50	0	0.00	0	0.00	0	0.00
Terry's nails	4	8.70	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Koilonychia	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Leukonychia	2	4.35	0	0.00	1	12.50	0	0.00	1	50.00	1	50.00
Platynychia	2	4.35	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Shiny nails	3	6.52	1	7.14	1	12.50	0	0.00	0	0.00	1	50.00
Longitudinal ridging	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Melanonychia	0	0.00	0	0.00	1	12.50	0	0.00	0	0.00	0	0.00
Pterygium	1	2.17	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Multiple conditions present hence total not shown

In the present study 46 patients (61.33%) had Alcoholic cirrhosis of which 4 patients (8.7%) had Terry's nails and 3 patients (6.52%) had Shiny nails.

Table 13. Duration of liver disease

Duration (Years)	Distribution (n=75)	
	Number	**Percentage**
< 1	50	66.67
1 to 3	15	20.00
3 to 5	6	8.00
> 5	4	5.33
Total	**75**	**100.00**



In this study 66.67% of the patients had duration of CLD less one year.

Table 14. Association of duration of liver disease with cutaneous manifestations

Duration (Years)	Cutaneous manifestations			
	Absent		Present	
	No.	%	No	%
< 1	9	18.00	41	82.00
1 to 3	1	6.67	14	93.33
3 to 5	1	16.67	5	83.33
> 5	0	0.00	4	100.00
Total	**11**	**14.67**	**64**	**85.33**

p=0.590

In this study, the frequency of cutaneous manifestations were comparable in patients with different duration of CLD (p=0.590).

Table 15. Distribution of patients according to duration of liver disease and cutaneous manifestations

Cutaneous manifestations	Duration of liver disease (Years)							
	< 1 (n=50)		1 to 3 (n=15)		3 to 5 (n=6)		> 5 (n=4)	
	No	%	No	%	No	%	No	%
Jaundice	24	48.00	10	66.67	3	50.00	3	75.00
Xanthelasma	1	2.00	1	6.67	0	0.00	0	0.00
Eczema	1	2.00	1	6.67	0	0.00	0	0.00
Paper money skin	0	0.00	1	6.67	0	0.00	0	0.00
Umbilical hernia	0	0.00	4	26.67	0	0.00	1	25.00
Fissure feet	1	2.00	0	0.00	0	0.00	0	0.00
Pruritus	12	24.00	8	53.33	4	66.67	1	25.00
Hyperpigmentation	11	22.00	4	26.67	1	16.67	0	0.00
Prurigo nodularis	6	12.00	1	6.67	1	16.67	0	0.00
Striae secondary to ascites	5	10.00	1	6.67	0	0.00	0	0.00
Purpura	1	2.00	0	0.00	0	0.00	0	0.00
Leucocytoclastic vasculitis	0	0.00	1	6.67	0	0.00	0	0.00
Porphyria cutanea tarda	1	2.00	0	0.00	0	0.00	0	0.00
Diminished secondary sexual hair	1	2.00	2	13.33	0	0.00	1	25.00
Urticaria	0	0.00	4	26.67	0	0.00	0	0.00
Photodermatosis	1	2.00	0	0.00	0	0.00	0	0.00
Xerosis	10	20.00	5	33.33	2	33.33	0	0.00
Pellagra	1	2.00	0	0.00	0	0.00	0	0.00
Pityriasis versicolor	1	2.00	0	0.00	0	0.00	0	0.00
Superficial Dermatophyte infection	1	2.00	1	6.67	0	0.00	0	0.00

Multiple conditions present hence total not shown

In this study 50 patients had duration of < 1 year duration of CLD. Among them, 24 patients (48%) had Jaundice, 12 patients (24%) had Pruritus, 11 patients (22%) had Hyperpigmentation, and 10 patients (20%) had Xerosis.

Table 16. Distribution of patients according to the duration of liver disease and nail changes

Nail changes	Duration of liver disease (Years)							
	< 1 (n=50)		1 to 3 (n=15)		3 to 5 (n=6)		> 5 (n=4)	
	No	%	No	%	No	%	No	%
Finger clubbing	4	8.00	1	6.67	0	0.00	1	25.00
Onycholysis	1	2.00	1	6.67	1	16.67	1	25.00
Dystrophic nails	1	2.00	0	0.00	0	0.00	0	0.00
Terry's nails	4	8.00	0	0.00	0	0.00	0	0.00
Koilonychia	1	2.00	0	0.00	0	0.00	0	0.00
Leukonychia	2	4.00	1	6.67	1	16.67	1	25.00
Platynychia	2	4.00	0	0.00	0	0.00	0	0.00
Shiny nails	1	2.00	3	20.00	2	33.33	0	0.00
Longitudinal ridging	1	2.00	0	0.00	0	0.00	0	0.00
Melanonychia	0	0.00	0	0.00	1	16.67	0	0.00
Pterygium	0	0.00	0	0.00	0	0.00	1	25.00

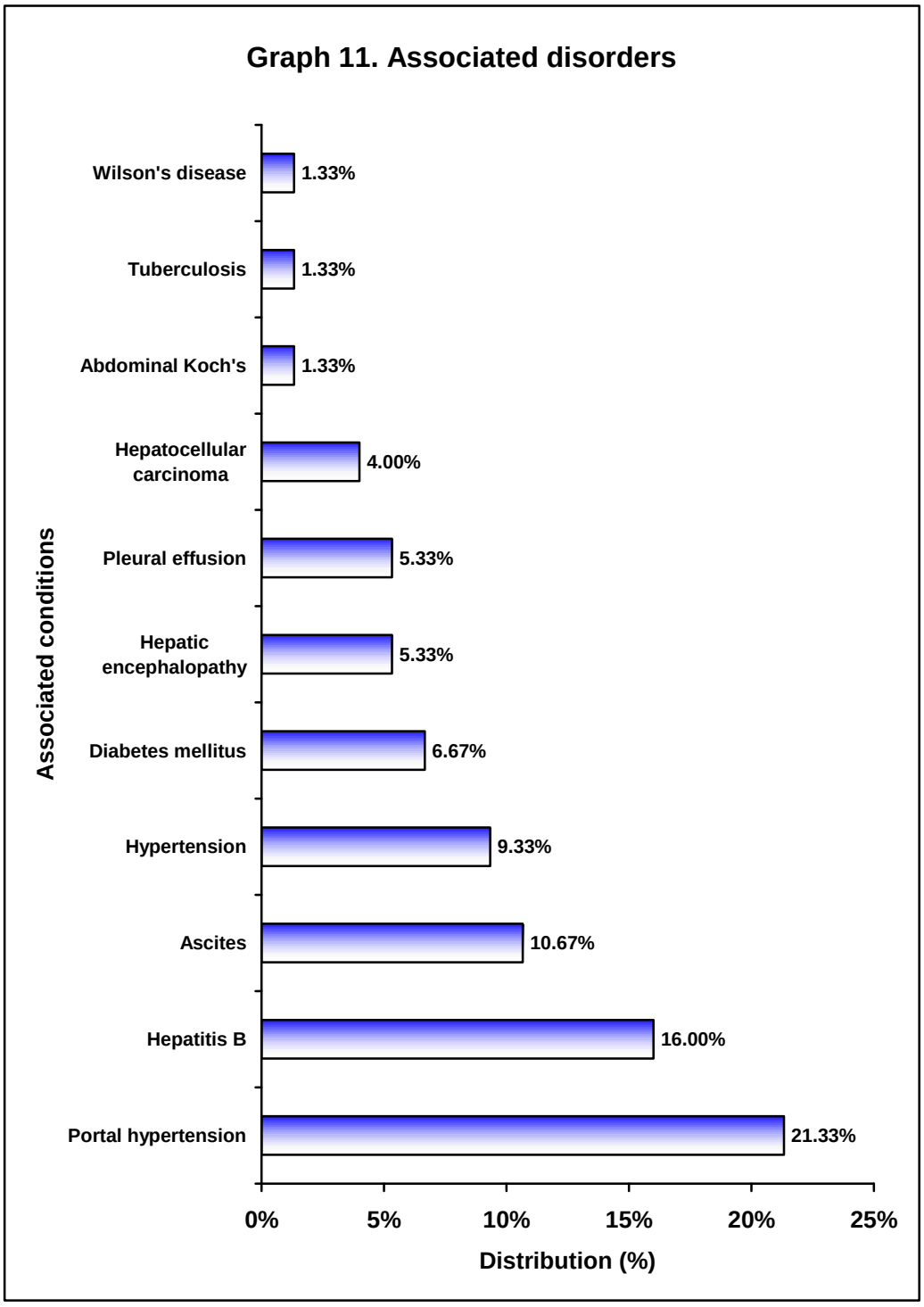
Multiple conditions present hence total not shown

In this study 50 patients had duration < 1 year of CLD. Among them 4 patients each (8%) had Finger clubbing and Terry's nails and 2 each (4%) had Leukonychia and Platynychia.

Table 17. Associated disorders

Associated conditions	Distribution (n=75)	
	Number	**Percentage**
Portal hypertension	16	21.33
Hepatitis B	12	16.00
Ascites	8	10.67
Hypertension	7	9.33
Diabetes mellitus	5	6.67
Hepatic encephalopathy	4	5.33
Pleural effusion	4	5.33
Hepatocellular carcinoma	3	4.00
Abdominal Koch's	1	1.33
Tuberculosis	1	1.33
Wilson's disease	1	1.33

Multiple conditions present hence total not shown

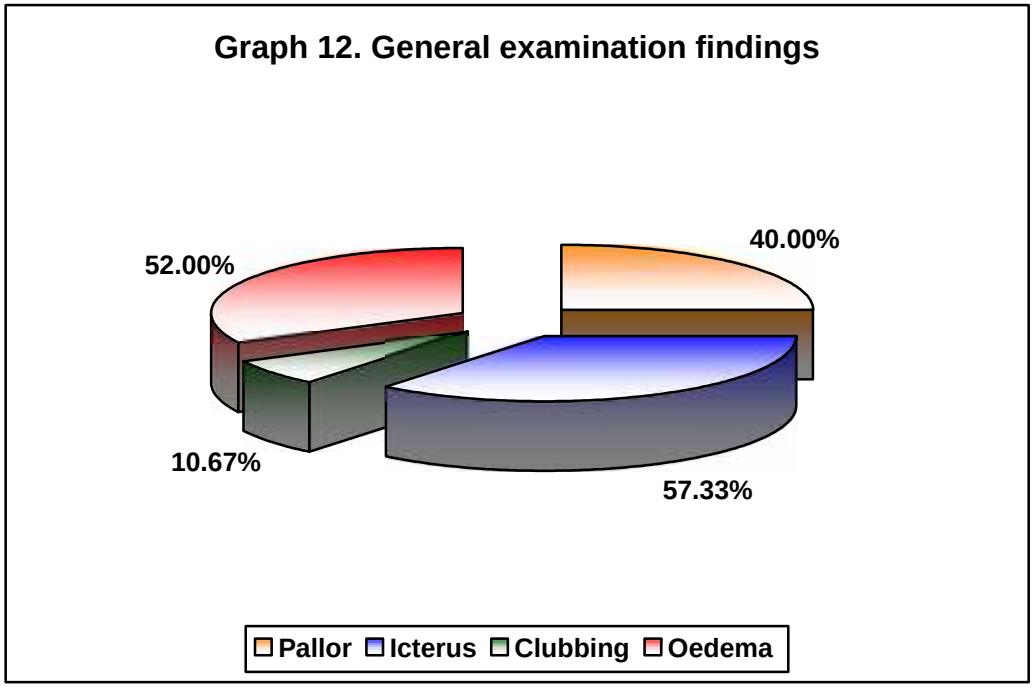


In this study portal hypertension was the commonest associated disorder noted in 21.33% of patients followed by hepatitis B which was present in 16%.

Table 18. General examination findings

Findings	Distribution (n=75)	
	Number	**Percentage**
Pallor	30	40.00
Icterus	43	57.33
Clubbing	8	10.67
Oedema	39	52.00

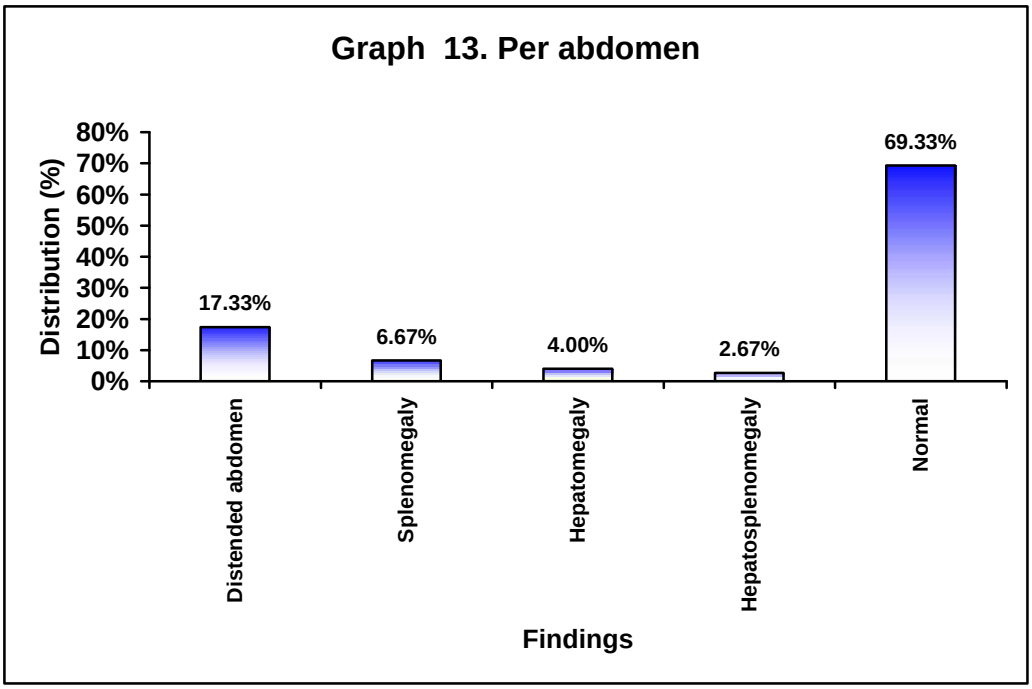
Multiple conditions present hence total not shown



In the present study general examination revealed pallor (40%), icterus (57.33%), clubbing (10.67%) and oedema (52%).

Table 19. Per abdomen

Findings	Distribution (n=75)	
	Number	**Percentage**
Distended abdomen	13	17.33
Splenomegaly	5	6.67
Hepatomegaly	3	4.00
Hepatosplenomegaly	2	2.67
Normal	52	69.33
Total	**75**	**100.00**



In this study distended abdomen was noted in 17.33% of the patients.

Table 20. Association of cutaneous manifestations with haemoglobin, total count and liver profile

Variables	Findings	Cutaneous manifestations				Total		p value
		Absent		Present				
		No.	%	No.	%	No.	%	
Haemoglobin	Low	2	15.38	11	84.62	13	17.33	0.611
(gm%)	Normal	9	14.52	53	85.48	62	82.67	
	Total	**11**	**14.67**	**64**	**85.33**	**75**	**100.00**	
Total count	> 11000	2	15.38	11	84.62	13	17.33	0.611
(/Cumm)	4000-11000	9	14.52	53	85.48	62	82.67	
	Total	**11**	**14.67**	**64**	**85.33**	**75**	**100.00**	
Total bilirubin	≥ 2.0	4	7.84	47	92.16	51	68.00	0.558
(mg/dL)	< 0.20	7	29.17	17	70.83	24	32.00	
	Total	**11**	**14.67**	**64**	**85.33**	**75**	**100.00**	
Direct bilirubin	≥ 0.20	10	14.29	60	85.71	70	93.33	0.288
(mg/dL)	< 0.20	1	20.00	4	80.00	5	6.67	
	Total	**11**	**14.67**	**64**	**85.33**	**75**	**100.00**	
SGOT	≥ 37	10	14.29	60	85.71	70	93.33	0.244
(IU/L)	< 37	1	20.00	4	80.00	5	6.67	
	Total	**11**	**14.67**	**64**	**85.33**	**75**	**100.00**	
SGPT	≥ 65	10	16.39	51	83.61	61	81.33	0.343
(IU/L)	< 65	1	7.14	13	92.86	14	18.67	
	Total	**11**	**14.67**	**64**	**85.33**	**75**	**100.00**	
Serum albumin	<3.40	6	16.67	30	83.33	36	48.00	0.638
(g/dL)	3.40 to 5.00	5	12.82	34	87.18	39	52.00	
	Total	**11**	**14.67**	**64**	**85.33**	**75**	**100.00**	
A:G ratio	<0.8	9	15.25	50	84.75	59	78.67	1.000
	0.8-2.0	2	13.33	13	86.67	15	20.00	
	>2.0	0	0.00	1	100.00	1	1.33	
	Total	**11**	**14.67**	**64**	**85.33**	**75**	**100.00**	

Table 20 shows abnormalities pertaining to haemoglobin, total count and liver profile and its association with cutaneous manifestations. It was observed that, most of the patients had raised direct biliruibin (93.33%), SGOT (93.33%), SGPT (81.33%), and total bilirubin (68%) while A:G ratio (78.67%) and serum albumin

(48%) levels were low. Also raised total count and low haemoglobin levels were present in 17.33% of the patients each. However no association was found between cutaneous manifestations and liver function test parameters (p>0.050).

Table 21. Clinical and biochemical profile of the patients

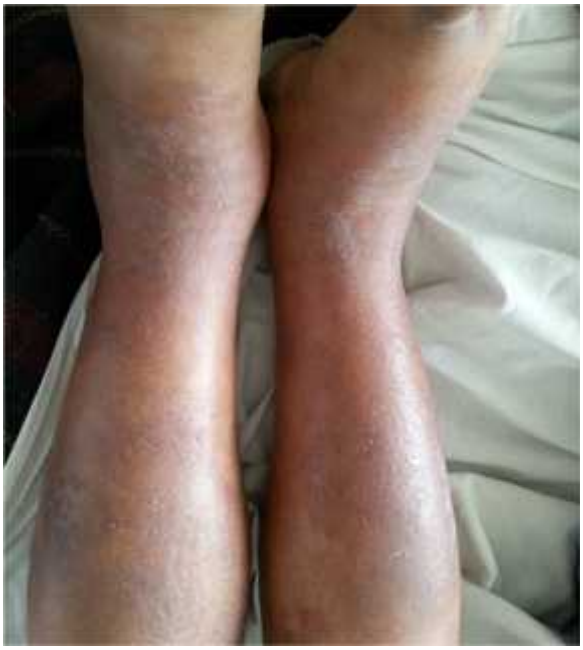
Variables	Mean (n=75)		Median		
	Mean	SD		Minimum	Maximum
Age (Years)	51.09	11.67	50.00	21.00	77.00
Weight (Kgs)	59.97	9.41	60.00	40.00	80.00
Systolic (mm Hg)	117.89	9.71	120.00	100.00	144.00
Diastolic (mm Hg)	75.57	7.20	78.00	60.00	90.00
Pulse rate (/Minute)	78.04	6.59	78.00	62.00	98.00
Respiraory rate (/Minute)	28.23	41.95	20.00	14.00	252.00
Temperature	98.36	0.30	98.60	98.00	98.80
Haemoglobin (gm%)	10.60	2.53	10.70	5.20	15.20
TLC (/Cumm)	10667.20	4926.97	9800.00	4900.00	44100.00
Total (mg/dL)	5.90	7.23	2.75	0.20	30.34
Direct (mg/dL)	3.85	5.57	1.40	0.05	22.67
SGOT (IU/L)	82.69	62.15	61.00	11.00	351.00
SGPT (IU/L)	56.86	44.57	48	17	362
Serum albumin (g/dL)	2.49	0.88	2.30	1.00	4.30
Alkaline phosphatase (IU/L)	148.71	62.58	133.00	41.00	407.00
A:G ratio	0.68	0.79	0.60	0.30	6.90

The clinical and biochemical profile of the patient is as depicted in table 21.

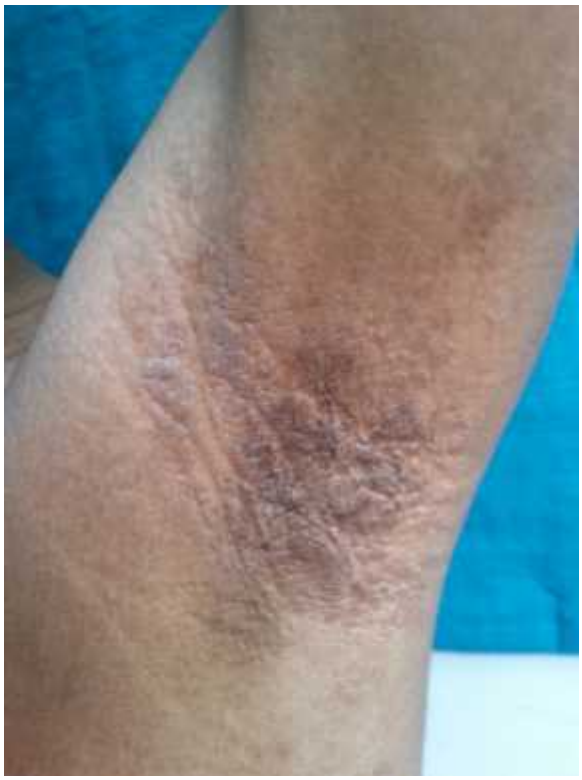
Table 22. Comparison of clinical, biochemical and liver profile in patients with and without cutaneous changes

Variables	Cutaneous changes				p value
	Absent (n=11)		Present (n=64)		
	Mean	SD	Mean	SD	
Age (Years)	60.73	10.01	49.44	11.18	**0.004**
Weight (Kgs)	57.82	5.71	60.34	9.90	0.246
Systolic (mm Hg)	117.27	11.91	118.00	9.39	0.850
Diastolic (mm Hg)	71.82	7.51	76.22	7.00	0.093
Pulse rate (/Minute)	75.55	5.47	78.47	6.70	0.134
Respiratory rate (/Minute)	19.27	1.62	29.77	45.28	0.069
Temperature (^{0}C)	98.33	0.31	98.37	0.30	0.690
Haemoglobin (gm%)	11.00	2.24	10.53	2.59	0.540
TLC (/Cumm)	15820.00	9685.72	9781.56	2861.79	0.066
Total bilirubin (mg/dL)	1.80	1.43	6.60	7.60	**<0.001**
Direct bilirubin (mg/dL)	0.70	0.61	4.40	5.86	**<0.001**
SGOT (U/L)	67.91	49.06	85.23	64.11	0.318
SGPT (U/L)	55.09	52.72	57.17	43.49	0.903
Serum albumin (g/dL)	2.83	0.65	2.43	0.91	0.095
Alkaline phosphatase (U/L)	150.82	58.24	148.34	63.72	0.900
A:G ratio	0.55	0.22	0.70	0.85	0.234

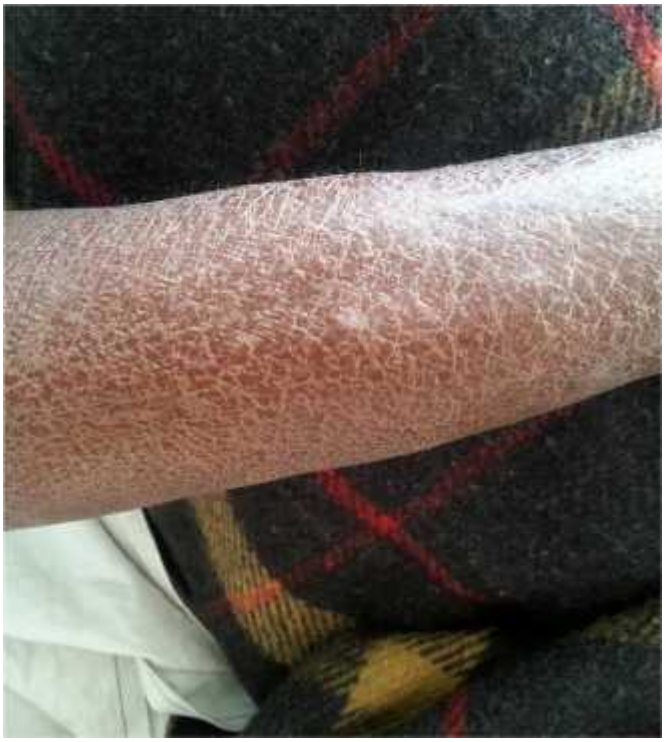
Table 22 shows comparison of clinical, biochemical and liver profile in patients with and without cutaneous changes. It was observed that, mean age in patients with cutaneous manifestations was significantly low (49.44 ± 11.18 vs 60.73 ± 10.01 years; p=0.004). Also the mean total and direct bilirubin were raised in patients with cutaneous manifestations (p<0.001).



Photograph 1. Pedal oedema with xerosis

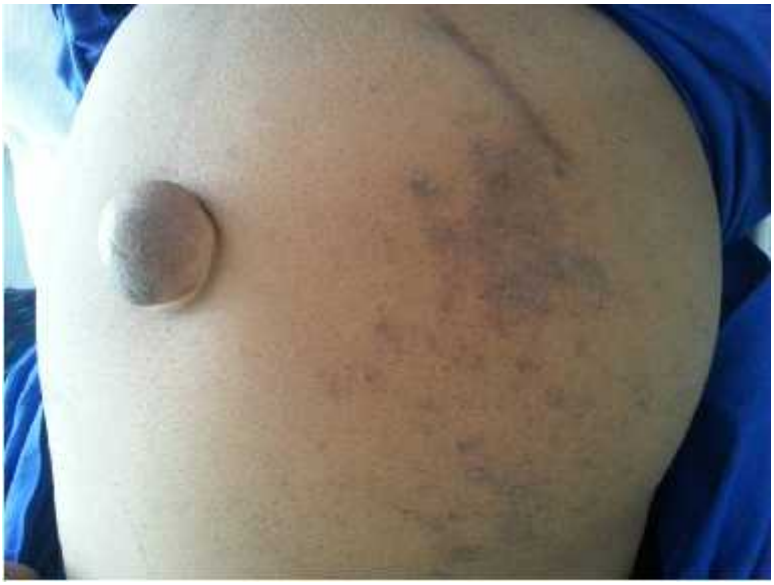


Photograph 2. Loss of axillary hair

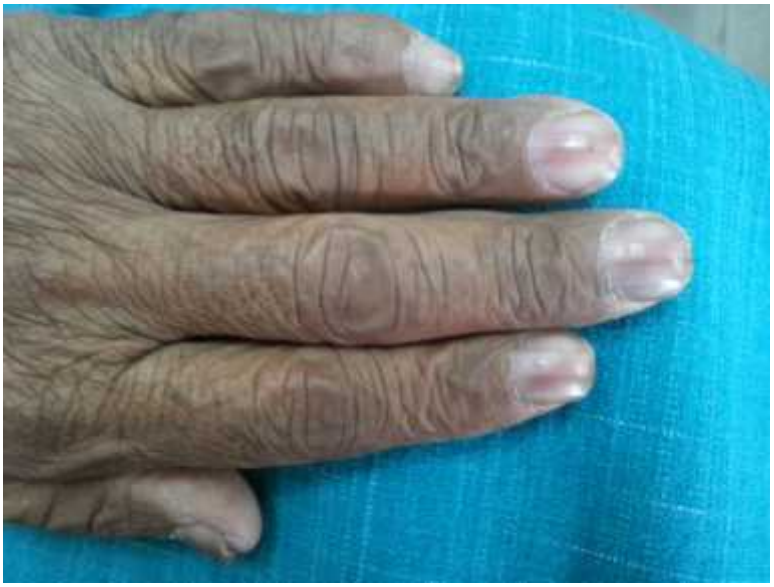


Photograph 3. Xerosis

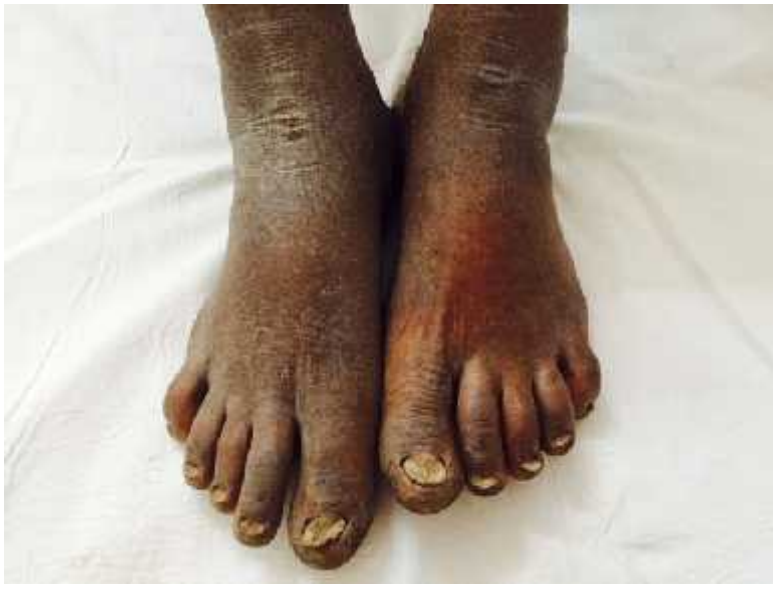
Photograph 4. Jaundice



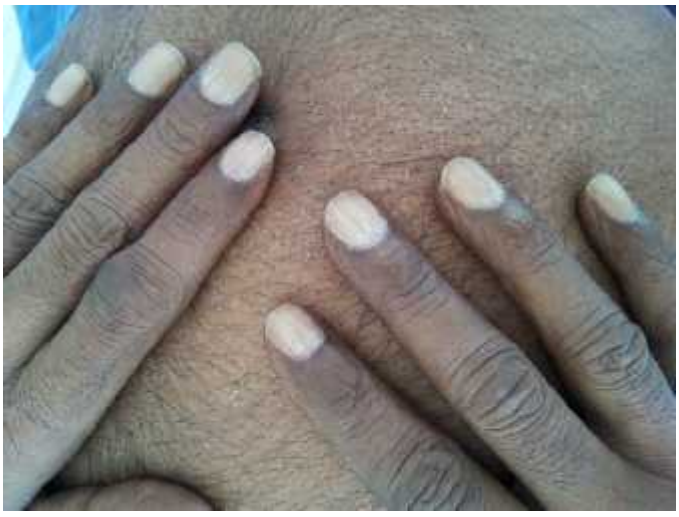
Photograph 5. Umbilical hernia with eczema



Photograph 6. Melanonychia

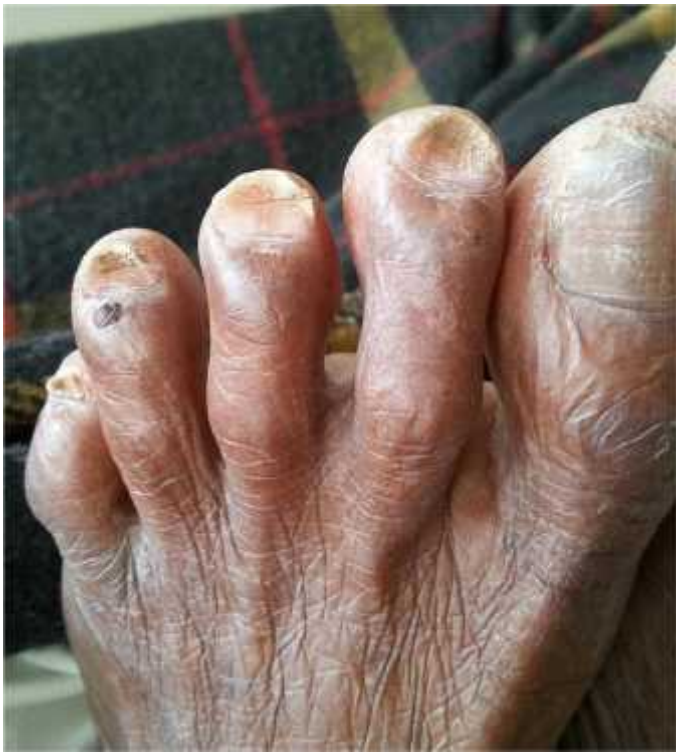


Photograph 7. Dystrophic nails



Photograph 8. Leukonychia

Photograph 9. Terry's nails



Photograph 10. Platynychia

DISCUSSION

Skin functions as a window to our overall health and a number of systemic diseases result in various cutaneous changes. Knowledge of these manifestations helps in suspecting an underlying systemic illness.[39]

Cutaneous abnormalities are quite common in patients with liver diseases. However, cutaneous manifestations seen in patients with liver disease though common are nonspecific. They can also be seen in patients without liver diseases and generally do not indicate about a specific underlying hepatic disorder. The presence of a constellation of signs and symptoms is more useful in pointing towards an underlying hepatobiliary condition. The cutaneous abnormalities may be the first clue to the underlying liver disease.[39]

The commonest symptom in patients with liver disease is pruritus which is often protracted and disabling. Other common features include spider angiomas, palmar erythema, paper money skin, xanthelasmas, pigmentary changes, and nutritional deficiencies.[39]

Identifying the cutaneous manifestations is crucial for early diagnosis and better management. However, the data on cutaneous manifestations is scant[14,84] and limited data is available on correlation of these manifestations with liver function tests.[84] This prompted us to investigate the spectrum of cutaneous manifestations in patients with CLD and to find the association between cutaneous features and liver function tests.

This one year cross sectional study was done on 75 patients with chronic liver disease in the Department of Dermatology Venereology and Leprosy, of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2014 to December 2014. Patients were examined for the presence of cutaneous manifestations and subjected to estimation of liver function tests.

In the present study majority of the patients that is, 85.33% had cutaneous manifestations. A similar study by Sayal SK. et al.[84] reported cutaneous manifestations in 58.7% of the patients. The frequency of cutaneous manifestations observed in the present study was very high when compared to the study by Sayal SK. et al.[84]

In the present study jaundice was the commonest cutaneous manifestation seen in nearly half of the study population (53.33%). The other common manifestations were pruritus (33.33%), xerosis (22.67%), hyperpigmentation (21.33%) and prurigo nodularis (10.67%). The less frequent cutaneous manifestations included striae secondary to ascites (8%), umbilical hernia (6.67%), diminished secondary sexual hair (5.33%), superficial dermatophyte infection (4%), pityriasis versicolor (2.67%), xanthelasma, eczema (2.67% each), paper money skin, fissure feet, purpura leucocytoclastic vasculitis, porphyria cutanea tarda, urticaria, photodermatosis and pellagra (1.33%).

A study by Sayal SK. et al.[84] reported prominent dilated veins in abdomen (30.4%), icterus (26.0%), clubbing of nails (19.5%), ichthyosis (15.2%), hyperpigmentation (13%) and pruritus (10.8%) as common cutaneous manifestations seen in patients with chronic liver disorders and telangiectasia, palmar erythema,

spider naevi, leukonychia and loss of body hair (4.3% cases each) and purpura, stria distensae and pellagra (2.2% cases each) as less common cutaneous features.

Another study by Khan MM. et al.[14] reported pigmentation as the commonest finding observed in 82% of the cases and xerosis (dryness) of the skin and excoriations in 72% of the patients.

In this study, the commonest nail changes seen were onycholysis and shiny nails which were present in 8% of the patients each. The other nail changes were leukonychia (6.67%), Terry's nails (5.53% each), platynychia, dystrophic nails (2.67% each), melanonychia, koilonychia, longitudinal ridging and pterygium (1.33% each). These findings were comparable with other studies in the literature. Salem et al[85] in his study showed that among nail changes: onycomycosis was the most common finding seen in 18% cases followed by in descending order, longitudinal striations, brittle nails, clubbing of nails, dystrophic nails, leukonychia and longitudinal melanonychia. Leukonychia, brittle nails and clubbing was seen in 12.5% of cases each. The study done by Sayal SK et al[85] 1997 reported clubbing in 16.3% and leukonychia in 4.1% cases. Another study done by Gupta and Sayal et al[84] showed clubbing in 19.5% and leukonychia in 4.3% cases while shiny nails were seen in 37.5% of patients.

In contrast to the findings of the present study, higher rate of nail changes is reported by Mohammad Khan M et al.,[14] Salem et al. and Ghosn SH et al.[9] A study by Khan MM. et al.[14] reported Terry's nails, a proximal white nail and distal pinkish margin a characteristic sign of CLD in 80% of the cases. Salem et al[86] in 2010 demonstrated most common nail changes as Terry's nail seen in 75% of the cases.

Ghosn SH et al.[9] 1988 reported Terry's nail in 80% of the cases with cirrhosis and onycomycosis in 50% of the cases.

In the present study jaundice was the commonest cutaneous manifestations seen in 53.33% of the patients. Similar study by Sayal and Gupta et al[84] during 1997 showed icterus in 26% cases. Another study done by Sayal et al[85] 1997 observed icterus in 20% patients. Recently a study by Shaikh NA et al[10] in 2010 showed jaundice in 35.4% cases. It is reported that, yellowish discoloration of skin and eyes (icterus) is due to accumulation of bilirubin under the skin and becomes clinically apparent when level is more than 2.5 mg%.[14] The higher rate of jaundice in the present study can be attributed to higher total and direct bilirbin levels observed as mean total bilirbin levels were 5.90 ± 7.23 mg/dL and median levels were 2.75 mg/dL (Range 0.20 to 30.34 mg/dL) and mean direct bilirubin levels were 3.85 ± 5.57 mg/dL and median levels were 1.40 mg/dL (Range 0.05 to 22.67 mg/dL).

Impaired liver function leads to accumulation of toxins and bile salts in body and deposition in skin, causes irritation and itching. In the present study, pruritus was the second most common cutaneous manifestations noted in one third of the study population (33.33%). Of the 25 patients with pruritus, 10 each (40% each) had grade 1 and 2 while 5 patients (20%) had grade 3 pruritus. These findings were consistent with an earlier study by Ghosn SH et al.[9] in 1988 which reported 40% patients of alcoholic liver disease with generalized pruritus. In contrast, Kochhar AM et al.[88] in 2003 reported pruritus in as high as 92% of the cases while Sayal and Gupta et al[84] 1997 reported lower rate of pruritus that is, 10.8% of the patients. In another study by Sayal et al[85] also the frequency of pruritus was low (8.2%).

Xerosis, a protean manifestation of liver dysfunction due to prolonged and decompensated nature of disease and complemented by malnutrition and catabolic state was noted in 22.67% of the patients in this study as the third most common cutaneous manifestation. In contrast to our findings, a study by Miraj et al.[14] in 2005 reported Xerosis in as high as 72% cases of the cases.

In the present study commonest etiology of chronic liver disease was alcoholic cirrhosis (61.33%) followed by NALD (18.67%) and post necrotic cirrhosis (10.67%). The other etiologies were PNC with HCC (4%), HCC with cirrhosis (2.67%) and alcoholic cirrhosis with PNC (2.67% each). In patients with alcoholic cirrhosis and NALD jaundice was the commonest cutaneous manifestation (58.7% and 28.57% respectively). However, the frequency of cutaneous manifestations in different types of liver disease was comparable (p=0.484). The etiology of chronic liver disease observed in the present study was comparable to the study by Sayal SK et al.[84] who reported 19 patients with alcoholic liver disease (hepatitis/cirrhosis), 12 with post necrotic cirrhosis, 12 with chronic active hepatitis and 3 with hepatocellular carcinoma out of 46 cases.

In this study nearly two third of the study population (66.67%) had ≤ 1 year duration of CLD. The common cutaneous manifestations in these patients were jaundice (48%), pruritus (24%), hyperpigmentation (22%) and xerosis (20%). The common nail changes observed were finger clubbing and Terry's nails (8% each), leukonychia and platynychia (4% each). However, the prevalence of cutaneous manifestations did not vary significantly in different durations of CLD (p=0.590). These findings could not be compared with other studies due to scanty data in the literature.

In the present study age of the patients with chronic liver disease ranged from 21 to 77 years. Most of the patients were aged between 41 to 50 years (34.67%) and 51 to 60 years (30.67%). The mean age was 51.09 ± 11.69 years and median age was 50 years. Surprisingly, the cutaneous manifestations were widely prevalent in patients who were aged <40 years (92.86%) and 41 to 50 years (100%) (p=0.005). Also the mean age in patients with cutaneous manifestations was significantly low (49.44 ± 11.18 vs 60.73 ± 10.01 years; p=0.004). These findings suggest a strong relationship between age and cutaneous manifestations among the patients with chronic liver disease. The age range observed in the present study was comparable with a study by Khan MM et al.[14] where patients age ranged from 28 to 77 years.

In the present study males outnumbered females as 96% of the patients were males with male to female ratio of 24:1. However the frequency of cutaneous manifestations was comparable among males (86.11%) and females (66.67%) (p=0.383). The gender distribution pattern observed in the present study was consistent with a study by Khan MM et al.[14] who reported 64% of the males and 36% of female. In contrast, a similar study by Niaz A et al.[87] in 2010 reported 53.7% males and 46.3% females. The male preponderance observed in the present study can be explained by higher rate of alcoholic liver disease (61.33%) which is one of the common type of liver disease in males.

In this study liver function tests revealed most of the patients with raised direct biliruibin (93.33%), SGOT (93.33%), SGPT (81.33%), and total bilirubin (68%). The A:G ratio (78.67%) and serum albumin (48%) levels were low. However no positive association was noted between liver function tests and cutaneous

manifestations. However, the mean total (6.60 ± 7.60 vs 1.80 ± 6.60 mg/dL; p<0.001) and direct bilirubin (4.40 ± 5.86 vs 0.70 ± 0.61 mg/dL; p<0.001) were raised in patients with cutaneous manifestations. These findings suggest that, patients presenting with chronic liver disease having cutaneous manifestations are likely to have abnormal liver profile in terms of total and direct bilirubin and reflect the disease severity. The cutaneous changes in hepatic disorders may be secondary to intrinsic liver disorders or metabolic enzyme deficiencies or may be a miscellaneous association.[89] Some of these disorders are clearly related with severity of liver dysfunction especially icterus which becomes clinically apparent when serum bilirubin level is in excess of 2.5 mg%.[89]

These findings were in agreement with a study by Sayal SK et al.[84] who demonstrated that, in chronic liver disorders, there was mild to moderate derangement of liver function. The values of serum bilirubin and serum alkaline phosphatase were moderately high in almost all cases while SGOT and SGPT levels remained within normal limits in majority of cases except in alcoholic liver disease. All the cases who had icterus had serum bilirubin level more than 2.5 mgm% while serum bilirubin in nonicteric patients was less than 2.5 mgm% Almost any disorder affecting the liver may cause moderate increase in serum alkaline phosphatase and this is attributed to increased liver enzyme in serum.[90]

Overall the present study showed that cutaneous manifestations are common in chronic liver disease and total and direct bilirubin level were high in patients with cutaneous manifestations.

CONCLUSION

The present study highlighted the spectrum of cutaneous manifestations in patients with chronic liver disease. It is evident that there is a high rate of cutaneous manifestations in patients with chronic liver disease.

The spectrum of common manifestations include jaundice, pruritus, xerosis, hyperpigmentation and prurigo nodularis. Though less frequent, other cutaneous manifestations like striae secondary to ascites, umbilical hernia, diminished secondary sexual hair, superficial dermatophyte infection, pityriasis versicolor, xanthelasma, eczema, paper money skin, fissure feet, purpura, leucocytoclastic vasculitis, porphyria cutanea tarda, urticaria, photodermatosis and pellagra are also prevalent.

With regard to nail changes onycholysis and shiny nails are common and leukonychia, Terry nails, platynychia, dystrophic nails, melanonychia, koilonychia, longitudinal ridging and pterygium are less common.

Patients presenting with cutaneous manifestations are likely to present with raised direct bilirubin, SGOT, SGPT, and total bilirubin while they may have lower A:G ratio and serum albumin levels. Also there is direct relationship between raised total and direct bilirubin levels with cutaneous manifestations.

Furthermore the cutaneous manifestations were widely prevalent among younger age group.

SUMMARY

Chronic liver disease may present with numerous cutaneous manifestations. Often the first clue to a liver disease is manifested through these cutaneous manifestations. The present study explored the spectrum of cutaneous features in patients with chronic liver disease and its association with liver function tests.

This one year cross sectional study was done under the settings of Department of Dermatology Venereology and Leprosy, of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2014 to December 2014. A total of 75 patients who presented with chronic liver disease during the study period were included in the study. Patients were subjected to complete dermatological examination and liver function test.

Majority (96%) of the patients were males. The male to female ratio was 24:1. The commonest age group was 41 to 50 years (34.67%) and the mean age was 51.09 ± 11.69 years. 66.67% of the patients had duration of CLD of less than or equal to one year and alcoholic cirrhosis (61.33%) was the commonest type liver disease. The other commonest associated disorder was portal hypertension (21.33%). Out of 75 patients studied, 64 (85.33%) had cutaneous manifestations and jaundice was the commonest manifestation (53.33%) followed by pruritus (33.33%), xerosis (22.67%), hyperpigmentation (21.33%) and prurigo nodularis (10.67%). The prominent nail changes were onycholysis and shiny nails (8% each). Most of the patients had raised direct biliruibin (93.33%), SGOT (93.33%), SGPT (81.33%), and total bilirubin (68%) levels and low A:G ratio (78.67%) and serum albumin (48%). The mean total and direct bilirubin levels were significantly high in patients with

cutaneous manifestations ($p<0.001$). Also, positive association of cutaneous manifestations was noted with age ($p=0.005$) and the mean age was significantly low in patients with cutaneous manifestations (49.44 ± 11.18 vs 60.73 ± 10.01 years; $p=0.004$). However, no association was found between cutaneous manifestations with liver function test parameters ($p>0.050$), sex ($p=0.383$), duration ($p=0.590$) and type of liver disease ($p=0.484$).

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ANNEXURE I – CONSENT FORM

I.D.NO. _____ INFORMED CONSENT FORM

A one year cross sectional study of cutaneous manifestations in patients with chronic liver disease and its association with liver function tests.

The study is conducted by Dr. **** *****, Post graduate student in M.D Dermatology under guidance of Dr. ******** *, Professor of Dermatology, J N Medical College, Belagavi.

Respected Sir/Madam, we invite you to participate in our study as, you are eligible for the same. During the study you will be asked some questions in detail regarding your present complaints.

Purpose of the study

The purpose of this study is to find out the prevalence of cutaneous features in patients with chronic liver disease. You are being asked to participate in this research because you have been diagnosed to have chronic liver disease. All patients admitted in the Gastroenterology ward, who are diagnosed to have this disease, will be requested to participate in this study during the period of one year.

Need for the study

Cutaneous manifestations may give a clue that a patient has liver disease. Recognising these signs is crucial in diagnosing the liver conditions early.

Procedure and treatment

Should you choose to participate, you will be asked to give a detailed history of your disease, undergo a physical examination, and consent to retrieve previous reports of the investigations undergone.

Benefits of the study

The result of you taking part in this research would help health care providers towards a better understanding of this disease, and thus we will be able to provide improved patient care.

Alternatives

If you decide not to participate in this study, you will still be receiving the usual standard care for your disease.

Privacy and confidentiality

Your privacy will be respected and all information collected about you during the course of this study will be kept confidential. Your identity will remain undisclosed.

Financial incentives

You shall not be receiving any payment or any financial incentives for participating in this study.

Authorization to publish results

The results of this study may be published for scientific purpose or presented to a scientific group. Your identity, however, will be maintained confidential at all times.

Voluntary participation

Your participation in this study is voluntary. Your decision whether or not to participate will neither affect the care of your current disease, nor your future relations with the doctor or the hospital. In case you need further information regarding your rights as a study participant, you may contact Dr ***** * Post graduate, Dermatology, mobile number ***** ******, Dr * *******, Professor, Department of Dermatology, telephone No. ****** ****** and Dr. **** ******,

Professor and HOD, Pathology, Chairman of the Ethical Committee On Human subjects, J N Medical College, Belagavi on telephone No.***** ******, extension number ****, mobile number ***** ******.

Statement of Consent:

I.D.NO:_____

I Mr/Ms/Mrs _____ volunteer and consent to participate in this study. I have read the consent document or it has been read to me in my vernacular language. I accept to participate in the study. All the information regarding this study is provided to me and I have understood the same. I have been given the opportunity to ask questions and obtain appropriate answers.

Participant's name:

Signature or left thumb print of participant:

Witness name:

Signature of witness & Date :

Signature of the investigator & Date :

If the participants are Minors (under 18), the parents sign the form, rather than the participants.

ANNEXURE II – PROFORMA

Name of the patient -

Hospital ID No. -

Age -

Sex -

Address -

Contact No. -

Type of chronic liver disease

1) Alcoholic cirrhosis

2) Non alcoholic liver disease

3) Post Necrotic Cirrhosis

4) Hepatocellular Carcinoma with cirrhosis

Duration of disease

1) <1 year

2) 1-3 years

3) 3-5 years

4) >5 years

General Physical examination:

Vital	Present	Absent
Pallor		
Icterus		
Cyanosis		
Clubbing		
Lymphadenopathy		
Edema		

Essentials

Blood pressure :

Pulse rate :

Temperature :

Respiratory rate :

Weight :

Mucocutaneous changes	Present	Absent
Jaundice		
Xanthelasma		
Rhinophyma		
Spider angioma		
Paper-money skin		
Palmar erythema		
Rosacea		
Pruritis		
Hyperpigmentation		
Prurigo Nodularis		
Striae secondary to Ascitis		
Purpura		
Porphyria cutanea tarda		
Diminished secondary sexual hair		
Urticaria		
Leucocytoclastic vasculitis		
Slate Grey Skin		
Gynaecomastia		

Nail changes	Present	Absent
Terry's nails		
Leukonychia		
Finger clubbing		
Onycholysis		
Other changes		

Any other cutaneous finding :

Associated Disorders:

Systemic Examination:

Cardiovascular system:

Respiratory system:

Nervous system:

Per abdomen:

Investigations

LIVER FUNCTION TESTS	
Serum Total Bilirubin	
Serum Direct Bilirubin	
SGOT	
SGPT	
Serum Albumin	
Alkaline phosphatase	
A:G ratio	

Investigator signature _____

Guide signature _____

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
A:G	-	Albumin to globulin ratio
BP	-	Blood pressure
CLD	-	Chronic liver disease
cumm	-	Cubic millimeters
D	-	Dystrophic nails
dL	-	Deciliter
Ds	-	Distended abdomen
Duration		
1	-	< 1 year
2	-	1 to 3 years
3	-	3 to 5 years
4	-	> 5 years
F	-	Female
gm	-	Gram
HEP	-	Hepatomegaly
HSM	-	Hepatosplenomegaly
IU/L	-	International units per liter
K	-	Koilonychia
Kg	-	Kilogram
L	-	Leukonychia
LR	-	Longitudinal ridging

M	-	Male
m	-	Melanonychia
mg	-	Milligram
mm Hg	-	Millimeters of mercury
N	-	Normal
P	-	Platynychia
Pt	-	Pterygium
SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamate-pyruvate transaminase
SN	-	Shiny nail
SPL	-	Splenomegaly
TLC	-	Total leucocyte count
Tn	-	Terry's nails

Type of liver disease

1	-	Alcoholic cirrhosis
2	-	Non alcoholic liver disease
3	-	Post necrotic cirrhosis
4	-	Hepatocellular Carcinoma with cirrhosis