

## Cutaneous manifestations in disorders of hepatobiliary system

### Abstract

**Background:** Hepatobiliary diseases are associated with various mucocutaneous changes that are directly and indirectly associated with these diseases. There is a dearth of studies from India dealing with cutaneous manifestations in liver disorders. **Aim:** This study was conducted to know the spectrum of cutaneous changes and their correlation with liver function tests in patients with disorders of hepatobiliary system. **Methods:** This was a descriptive study conducted among in patients and outpatients with primary hepatobiliary disorders at a tertiary care center in South India. Detailed history taking and examination was done. Visual analog score (VAS) and 5D itch score was employed to quantify pruritus. Correlation of liver function tests with pruritus and comparison of skin changes in the major disease groups was attempted. **Results:** A total of 303 patients were recruited. Hepatic mass/malignancy followed by nonalcoholic liver disease were the most common diagnoses. Icterus followed by pruritus were the most common cutaneous complaints. The mean VAS and 5D itch scores among the patients with pruritus were  $4.7 \pm 1.9$  and  $13.6 \pm 4.9$ . The most common mucocutaneous findings observed were icterus (241 patients; 79.5%), ichthyosis/xerosis (172 patients; 56.7%), pallor (131 patients; 43.2%), excoriations (118 patients; 38.9%), hyperpigmented palmar creases (118 patients; 38.9%), clubbing (113 patients; 37.2%), and pedal edema (85 patients; 28%). There was statistically significant correlation between serum bilirubin levels and pruritus. **Conclusion:** The common mucocutaneous manifestations associated with primary hepatobiliary disorders were icterus, ichthyosis/xerosis, pallor, excoriations, hyperpigmented palmar creases, clubbing, and pedal edema.

**Key Words:** Hepatitis, liver disorders, skin changes

### Introduction

The skin being the largest organ of the body, often provides a clue to the underlying systemic diseases, and hence cutaneous manifestations of systemic diseases are frequently encountered by dermatologists.<sup>[1,2]</sup> The liver is the second largest organ of the body, and liver dysfunction often results in changes in the body's largest organ, the skin. There are few studies published in the literature that have assessed the cutaneous manifestations of specific hepatobiliary disorders such as alcoholic cirrhosis, primary biliary cirrhosis, Wilson's disease, Alagille syndrome, hepatitis B, and hepatitis C infection. However, there is dearth of studies on the spectrum of cutaneous manifestations of various hepatobiliary diseases establishing the prognostic value of such cutaneous signs for the severity of liver disease, especially in Indian patients. Most of the studies are from western literature, and those findings cannot be extrapolated on Indian skin.

Hence, this study was conducted to study the spectrum of cutaneous changes and their correlation with the liver function tests in patients with disorders of hepatobiliary system.

### Materials and Methods

This was descriptive study conducted at a tertiary care center in South India. Consecutive consenting patients diagnosed with primary hepatobiliary disease presenting to the outpatient and inpatient departments of medical and surgical gastroenterology and pediatrics, and conforming to the inclusion and exclusion criteria, from November 2013 to June 2015, were included in the study.

All primary hepatobiliary disorders with cutaneous manifestations were included. Diseases with both cutaneous and liver involvement, liver pathology due to skin diseases, liver damage by drugs used to treat skin diseases, and liver transplant

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patients were excluded from the study. The diagnosis of the liver pathology (biochemical, serological, and/or histopathological) was obtained from the patient records, as already diagnosed patients who were on follow-up in our gastroenterology and pediatric outpatient departments were recruited. Detailed history regarding the type and duration of primary hepatobiliary disorder, treatment details, alcohol consumption, nature, and duration with evolution of specific and nonspecific cutaneous manifestations was elicited. Thorough clinical examination was performed to look for evidence of specific and nonspecific cutaneous changes of liver disease. Cutaneous diagnosis was made after careful clinical assessment by two dermatologists. Biopsy was done in doubtful cases. Other primary skin diseases and cutaneous reactions to drugs used for the treatment of these disorders were also recorded. Patients were interrogated in detail regarding the characteristics of pruritus to assess the severity by visual analog scale (VAS) and 5D itch scale, which included description of perception of pruritus, disability caused, distribution, relieving and aggravating factors, treatment received, and response to various treatments. 5D itch score is a single page questionnaire classifying patients with pruritus according to 5Ds, namely, duration, degree, direction, distribution, and disability. A score of 5 means no pruritus whereas 25 implies the most severe pruritus. In VAS, the patient marked his level of pruritus between 0 and 10 on a scale. The laboratory investigations done for the patients, along with other relevant investigations pertaining to the primary disorder were also recorded separately.

Statistical analysis was performed using IBM's Statistical package for the social sciences (SPSS) version 20 software (Armonk, NY: IBM). Unpaired *t*-test was used for comparing biochemical parameters and clinical features.

## Results

Three hundred and three consecutive consenting patients who were diagnosed with primary hepatobiliary disease from November 2013 to June 2015 were included in the study. Because there is a dearth of data on the prevalence of liver diseases in rural population of South India, a convenient sample size was calculated based on the average number of patients attending the concerned departments in the last 2 years. The mean age of the study population was  $43.9 \pm 20.2$  years (ranging from 2 months to 85 years with a median age of 49 years), in which males outnumbered females with a sex ratio of 2.1:1. Out of the 303 patients recruited, 40 patients (13.2%) were children (<14 years) with a mean age of  $4.3 \pm 4.4$  years. The maximum number of patients included in the study were those with malignancies/mass lesions (56 patients; 18.4%) followed by nonalcoholic steatohepatitis (55 patients; 18.2%), cholelithiasis (48 patients; 15.8%), and cirrhosis (42 patients; 13.9%). Genetic liver diseases were

present in 35 patients (11.6%). The mean disease duration of our study population was  $25.7 \pm 22.5$  months.

The most common complaint noted in our study population was icterus (241 patients; 79.8%) followed by generalized pruritus in 159 patients (52.5%), hair loss/texture changes (62 patients; 20.5%), and dryness of skin (52 patients, 17.2%) [Figure 1]. Pruritus was more common in patients with malignancies (40 patients; 25.1%), namely, periampullary carcinoma (19 patients; 11.9%) and hepatocellular carcinoma (12 patients; 7.5%). Nonalcoholic steatohepatitis (32 patients; 20.1%) and cirrhosis (23 patients; 14.4%) were other disorders commonly associated with pruritus. The mean VAS and 5D itch scores among the patients with pruritus were  $4.7 \pm 1.9$  and  $13.6 \pm 4.9$ , respectively. The most severe degree of pruritus (5D itch score = 21–25) and minimal pruritus (5D itch score = 5–10) was noticed in 6 patients each (3.8%).



Figure 1: Ichthyosis in a child with Wilson's disease



The most common mucocutaneous findings observed were icterus (241 patients; 79.5%), ichthyosis/xerosis (172 patients; 56.7%), pallor (131 patients; 43.2%), excoriations (118 patients; 38.9%), hyperpigmented palmar creases (118 patients; 38.9%), clubbing (113 patients; 37.2%), and pedal edema (85 patients; 28%). Mucosal manifestations such as atrophic glossitis, hyperpigmentation, coated tongue, and oral candidiasis were noticed in 56 patients (18.4%), 44 patients (14.5%), 36 patients (11.8%), and 34 patients (11.2%), respectively. The detailed record of the mucocutaneous features in various primary hepatic disorders is given in Table 1.

**Table 1: Mucocutaneous manifestations of hepatobiliary diseases**

Mucocutaneous examination	N (%)
Icterus	241 (79.5)
Ichthyosis/xerosis	172 (56.7)
Pallor	131 (43.2)
Excoriations	118 (38.9)
Hyperpigmented palmar creases	118 (38.9)
Clubbing	113 (37.2)
Pedal edema	85 (28)
Cutaneous hyperpigmentation	73 (24)
Thenar/hypothenar atrophy	71 (23.4)
Atrophic glossitis	56 (18.4)
Parotid swelling	54 (17.9)
Striae distensae	47 (15.6)
Mucosal hyperpigmentation	44 (14.5)
Coated tongue	36 (11.8)
Oral candidiasis	34 (11.2)
Paper money skin	31 (10.3)
Gynecomastia	27 (8.9)
Palmar erythema	25 (8.2)
Caput medusa	21 (7)
Spider angioma	18 (5.9)
Cutaneous lichen planus	13 (4.3)
Dupuytren contracture	12 (4)
Nail findings	
Terry's nails	112 (36.9)
Brittle nails	100 (33)
Longitudinal ridging	83 (27.3)
Watch glass deformity	56 (18.4)
Leukonychia	45 (14.8)
Hair findings	
Sparse body hair	81 (26.8)
Chronic telogen effluvium	60 (19.8)
Brittle/lusterless hair	42 (13.9)
Premature graying	7 (2.3)
Alopecia areata	2 (0.6)
Associated systemic findings	
Ascites	63 (20.8)
Splenomegaly	8 (2.6)
Generalized lymphadenopathy	2 (0.6)

Nail examination in our study revealed Terry's nails in 112 patients (36.9%) followed by brittle nails in 100 (33%), longitudinal ridging in 83 (27.3%), watch glass deformity in 56 (18.4%), and leukonychia in 45 (14.8%) [Figure 2].

Scalp examination revealed chronic telogen effluvium and brittle hair in 60 patients (19.8%) and 42 patients (13.9%), respectively. Premature graying was noticed in 7 patients (2.3%), and alopecia areata in 2 patients (0.7%).

The most common mucocutaneous findings in each type of primary liver disease are presented in Table 2.

### Disease-wise analysis of mucocutaneous manifestations

On comparing alcoholic ( $n = 31$ ) versus non-alcoholic liver disease ( $n = 272$ ), edema (51.6% vs 25.4%,  $P = 0.005$ ) and ecchymosis (38.7% vs 16.9%,  $P = 0.005$ ) were significantly more common in patients with alcoholic liver disease than other disorders. Similarly, thenar/hypothenar atrophy [Figure 3] (51.6% vs 26.5%), sparse body hair (45.2% vs 25%), and palmar erythema (25.8% vs 6.2%) were among the nonspecific cutaneous findings; whereas, caput medusa (22.6% vs 5.14%) and spider angioma (22.6% vs 4%) were among the specific cutaneous manifestations seen significantly more in patients with alcoholic liver disease.

Patients with cirrhosis ( $n = 42$ ) had significantly more clubbing (59.5% vs 29.1%), edema (42.9% vs 25.7%), ecchymosis (38.1% vs 16%), palmar erythema (21.4% vs 6.1%), and atrophic glossitis (31% vs 16.5%) than the non-cirrhotic patients. Lichen planus (11.9% vs 3.1%) was also significantly more common among the cirrhotic patients [Figure 4]. Among the nail findings, brittle nails, longitudinal ridging, and watch glass deformity were also more common in patients with cirrhosis, however, the findings were statistically insignificant. Similarly other mucosal findings such as mucosal hyperpigmentation (16.7% vs 14.9%), coated



**Figure 2: Terry's nails**

**Table 2: The most common mucocutaneous manifestations in each group**

Hepatobiliary disorders	Mucocutaneous manifestations
Genetic liver disease	
Idiopathic neonatal hepatitis (N=15)	Icterus (15 patients), leukonychia, longitudinal ridging (4 patients each) followed by pallor (3 patients)
Wilson's disease (N=14)	Icterus (13 patients), Terry's nails (9 patients), ichthyosis/xerosis (8 patients), and excoriations (8 patients)
Progressive familial intrahepatic cholestasis (N=6)	Icterus (5 patients) and leukonychia (3 patients)
Viral hepatitis	
Hepatitis C infection (N=14)	Ichthyosis/xerosis (8 patients), clubbing (7 patients), and icterus (7 patients)
Hepatitis B infection (N=9)	Icterus (8 patients) and Terry's nails (3 patients)
Immune and autoimmune liver disease	
Autoimmune hepatitis (N=4)	Icterus (4 patients) and hyperpigmented palmar creases (3 patients)
Primary biliary cirrhosis (N=3)	Icterus, pallor, and ichthyosis (3 patients each)
Primary sclerosing cholangitis (N=1)	Icterus, excoriation, mucosal hyperpigmentation, brittle nails, and leukonychia
Malignancy/mass lesions	
Periapillary carcinoma (N=22)	Hyperpigmented palmar creases (16 patients), excoriations (16 patients) and ichthyosis/xerosis (15 patients)
Hepatocellular carcinoma (N=19)	Ichthyosis/xerosis (14 patients), icterus (11 patients), and excoriations (9 patients)
Cholangiocarcinoma (N=13)	Terry's nails and brittle nails (10 patients each) followed by icterus, ichthyosis/xerosis, and pallor (8 patients each)
Carcinoma of gall bladder (N=2)	Icterus, ichthyosis/xerosis, and Terry's nails (2 patients each)
Acute alcoholic hepatitis (N=31)	Icterus (22 patients); pallor (16 patients), pedal edema (16 patients), thenar atrophy (14 patients), and Terry's nails (14 patients)
Nonalcoholic fatty liver (N=55)	Icterus (40 patients) and ichthyosis/xerosis (36 patients), and excoriations (28 patients)
Cholestatic syndrome	
Biliary atresia (N=3)	Icterus (3 patients) and leukonychia (2 patients)
Cholelithiasis (N=48)	Icterus (36 patients) and ichthyosis/xerosis (31 patients), hyperpigmented palmar creases (27 patients), and pallor (18 patients)
Cirrhosis (N=42)	Icterus (31 patients) and ichthyosis/xerosis (29 patients), clubbing (25 patients), and pallor (20 patients)



Figure 3: Hypothenar and thenar atrophy in cirrhosis



Figure 4: Lichen planus in a hepatitis C patient



tongue (16.7% vs 11.5%), and oral candidiasis (16.7% vs 10.3%), though more prevalent in patients with cirrhosis, were statistically insignificant. One patient of hepatitis C had biopsy proven small plaque parapsoriasis [Figure 5].

On comparing children < 14 years ( $n = 40$ ) with adults ( $n = 263$ ), icterus was noted in all the children (40 patients, 100%) as compared to adults (197 patients; 74.9%) whereas clubbing (35.7% vs 17.5%,  $P < 0.0001$ ) and pedal edema (30.8% vs 10%,  $P = 0.0047$ ) were significantly more common in adults [Figure 6]. Among the nonspecific cutaneous manifestations, ichthyosis (62.4% vs 27.5%), excoriations (42.2% vs 20%), thenar/hypothenar atrophy (33.5% vs 0), hyperpigmented creases (42.2% vs 17.5%), sparse body hair (31.2% vs 0), and striae distensae (17.9% vs 0) were significantly more prevalent in adults. Paper money skin was seen exclusively in adults (11.8%,  $P = 0.02$ ) and brittle nails (38% vs 12.5%), mucosal hyperpigmentation (17.1% vs 2.5%), and coated tongue (13.7% vs 2.5%) were also significantly more common in the adult population.

There was a statistically significant correlation between the serum bilirubin levels and the incidence of pruritus. Among patients with pruritus ( $n = 159$ ), the mean bilirubin levels were  $7.2 \pm 7.4$ , whereas in those without pruritus ( $n = 144$ ), the bilirubin levels were  $4.8 \pm 5.5$  ( $P = 0.0018$ ). The mean values of other liver function parameters such as alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were also higher in patients with pruritus but were statistically insignificant [Table 3].

## Discussion

Mucocutaneous manifestations are the most common extra-hepatic manifestations in disorders of the hepatobiliary system.<sup>[1,3]</sup> In our study, pruritus was the most common dermatological complaint by the patients (52.5%). This was in accordance with the previous studies,<sup>[3-5]</sup> which showed that pruritus is noticed in up to 70% patients with hepatobiliary disorders.<sup>[3,6,7]</sup>

In our study, the most common mucocutaneous finding on examination were icterus (79.5%) followed by ichthyosis/xerosis, pallor, excoriations, hyperpigmented palmar creases, clubbing, pedal edema, and cutaneous hyperpigmentation. This was similar to the results of Sayal *et al.*<sup>[8]</sup> in their study among 46 Indian patients with chronic liver disorders. They observed that the most common cutaneous manifestations were prominent dilated veins in the abdomen (30.4%), icterus (26.0%), clubbing of nails, ichthyosis, hyperpigmentation, and pruritus.

Alcoholic liver disease is commonly associated with cutaneous manifestations such as spider angiomas (whose number might correlate with the frequency of esophageal varices),<sup>[9]</sup> caput medusa, palmar erythema, icterus, pruritus, hyperpigmentation, urticaria, atrophic glossitis, parotid



Figure 5: Small plaque parapsoriasis in a patient of hepatitis C, probably an incidental finding

Table 3: Correlation of mean values of liver function test in patients who were having pruritus ( $n=159$ ) versus those not having pruritus ( $n=144$ )

Lab parameter	With pruritus ( $n=159$ )	Without pruritus ( $n=144$ )	P
Bilirubin	7.208+7.39	4.817+5.463	0.0018
Alkaline phosphatase	558.10+526.88	480.11+399.87	0.1631
Aspartate aminotransferase	100.71+146.6	85.73+85.55	0.289
Alanine aminotransferase	92.84+136.24	69.02+70.154	0.062

swelling, clubbing, watch glass deformity, and Terry's nails.<sup>[10-12]</sup> We had similar findings. However, there was a decreased incidence of features such as spider angiomas, palmar erythema, and Dupuytren's contracture (18%) compared to other studies in Caucasian population (72%), possibly due to darker skin type.<sup>[3]</sup> In patients with cirrhosis also, a decreased incidence of spider angiomas was seen in comparison with that reported in the Caucasian population, as noticed in previous Indian studies.<sup>[13,14]</sup>

Pruritus was the most common skin manifestation seen in hepatitis C virus (HCV) infection in studies by Raslan *et al.*<sup>[15]</sup> (45.8%), Asim *et al.*<sup>[16]</sup> (35%), and Soyly *et al.*<sup>[17]</sup> (48%), followed by pigmented purpuric eruption (5.2%), aphthous ulcer, lichen planus (3.9% each), and leukocytoclastic vasculitis (2.6%).<sup>[15]</sup> In our study also, pruritus was observed in 50% of patients with HCV infection with other common manifestations being ichthyosis/xerosis (57.1%), icterus (50%), clubbing (50%), and pallor (42.8%). Hepatitis C infection is associated with lichen planus, especially the oral subtype, and its prevalence can vary from 3.8–65% depending on the geographical location, virus characteristics, and genetic susceptibility of the population to develop lichen planus.<sup>[4,7,18]</sup> In our study,



**Figure 6:** Icterus, ascites, and umbilical hernia in a child with idiopathic neonatal hepatitis

classical cutaneous lichen planus and oral lichen planus were noted in two and one patients, respectively, which is lower than that reported by Udayshankar *et al.*<sup>[7]</sup> but higher than that noted by Harman *et al.* (3.9%),<sup>[18]</sup> which might be explained by genetic differences in different geographic regions. Other commonly associated manifestations with HCV such as urticaria, porphyria cutanea tarda, and cryoglobulinemic vasculitis were not observed in any of our patients.<sup>[1,19,20]</sup> In hepatitis B patients, although the incidence of oral lichen planus and pitted keratolysis was not very high as reported by Dogan,<sup>[21]</sup> other features such as icterus, Terry's nails, longitudinal ridging, excoriations, and parotid swelling were seen. Among the nail changes in viral hepatitis, along with the already described features such as higher prevalence of onychomycosis, longitudinal striations, brittle nails, onychorrhexis, clubbing, dystrophic nails, leukonychia, and melanonychia,<sup>[22]</sup> features such as Terry's nails and watch glass deformity, hitherto Unreported, were noticed in this study.

Seyhan *et al.*<sup>[23]</sup> in their study among 37 children with Wilson's disease, observed xerosis as the most common finding (45.7%) followed by leukonychia (18.9%), keratosis pilaris, spider angioma, and cheilitis (10.8% each). We also noticed ichthyosis/xerosis in 57% patients with Wilson's disease with other common manifestations being icterus (93%), Terry's nails (64.2%), excoriations, hyperpigmented palmar creases, and clubbing. The specific nail finding, blue/azure lunula,<sup>[1]</sup> was noticed only in one patient in our study. Among patients of primary biliary cirrhosis, pruritus was the most common manifestation, as is previously described in the literature.<sup>[24]</sup> In contrast to an observation of pruritus preceding the primary diagnosis in 75% patients by Rishe *et al.*,<sup>[25]</sup> onset of pruritus coincided with primary diagnosis in all our patients.

Hepatic malignancies, especially hepatocellular carcinoma, can rarely have cutaneous manifestations such as cutaneous metastasis, pityriasis rotunda (round-to-oval ichthyotic patches), porphyria cutanea tarda-like and dermatomyositis-like presentation.<sup>[2,26,27]</sup> In our study also, we noticed pityriasis rotunda and small plaque parapsoriasis (digitate subtype) in one patient each with hepatocellular carcinoma. Basal cell carcinoma (noduloulcerative type) was also noticed in one patient with hepatocellular carcinoma. We, however, did not notice any of the other mentioned features, and instead the common manifestations observed were ichthyosis/xerosis, icterus, excoriations, clubbing, and Terry's nails.

The correlation of pruritus with serum bilirubin levels seen in our study is similar to what is described in the literature.<sup>[8]</sup>

The disease-wise comparison of dermatological features is unique to our study and significant because it gives a clue to the causation of liver disease in any given patients. Though further validation is required, increased incidence of edema, ecchymosis, thenar/hypothenar atrophy, sparse body hair, palmar erythema, caput medusa, and spider angioma in alcoholic liver disease versus non-alcoholic liver disease and that of clubbing, edema, ecchymosis, palmar erythema, atrophic glossitis, and lichen planus in cirrhotic versus non-cirrhotic patients can help in clinical evaluation and appropriate treatment.

### Limitations of the study

This was an observational study conducted for a short duration with a small sample size. In addition, most of the patients recruited had already diagnosed primary hepatobiliary disorder, and hence the earliest mucocutaneous manifestations of these disorders could not be recorded. Because the study was done in a tertiary care center, there were higher number of patients having rare liver disorders such as genetic liver diseases, malignancies, and autoimmune disorders than what is generally seen in the population.

### Conclusion

In our study on 303 patients with hepatobiliary disorders, the most common mucocutaneous manifestations noted were icterus followed by ichthyosis/xerosis, pallor, excoriations, hyperpigmented creases, clubbing and Terry's nails. The other common manifestations described in Caucasian population such as spider angioma in cirrhosis and alcoholic liver disease, oral lichen planus in HCV, and azure lunulae in Wilson disease were not found to be common in our study population, possibly due to different Fitzpatrick skin type and geographical factors. The most common cutaneous manifestations of hepatobiliary disorders, i.e., pruritus and icterus are associated with elevated serum bilirubin, transaminase levels, and also

correlate with the severity of the underlying disorder. The results of this study give a better insight into the dermatological features in patients suffering from primary hepatic diseases in south India. This would help the dermatologist to pay closer attention to the possibility of an underlying liver disease in a patient who presents with these manifestations; moreover, it will also enable the hepatologists to consider the cutaneous complaints of their patients significant.

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### *Conflicts of interest*

There are no conflicts of interest.

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