

CLINICAL STUDIES

Cutaneous signs of liver disease: value for prognosis of severe fibrosis and cirrhosisClaus Niederau¹, Stefan Lange², Martin Frühauf¹ and Andreas Thiel³

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Abstract

Background/Aims: Although physicians have looked for cutaneous signs of liver disease for more than a century, their prognostic value has never been evaluated systematically. **Methods:** Therefore, cutaneous changes were prospectively recorded in all patients referred for liver biopsy from June 2000 to May 2004. Fibrosis was staged from F0 to F4 according to Desmet and Scheuer. The analysis included 744 patients, 520 of whom had chronic hepatitis C while the remaining had other diseases. **Results:** By univariate analysis, the frequency of several skin changes was associated with the degree of fibrosis. In general, at fibrosis F0–1 skin changes were infrequent; they became more frequent at F2 and were frequent at F3–4. To analyse the predictive value of skin changes, patients with fibrosis F0–2 were compared with those with F3–4. Final logistic regression included spider naevi, palmar erythema, teleangiectasia, bleeding signs and dry skin as well as age and gender. When routine laboratory values were included in the analysis, prothrombin time, γ -glutamyltransferase and albumin proved to be significant. Receiver operating characteristic (ROC) showed a good discrimination of fibrosis F0–2 from F3–4 by the modelled score on combining skin changes and laboratory tests: at the cost of 2% of non-diagnosed patients with F3–4, one might have saved 60% of biopsies. ROC was less useful in discriminating fibrosis F0–1 from F2–4. The discriminative power of skin changes was better than the laboratory values and the aspartate aminotransferase/platelet ratio. **Conclusions:** The results prove that it is quite useful to look for skin changes in patients with liver disease.

For more than a century, physicians and medical students have been told to look for cutaneous signs of liver disease during the regular physical examination. These signs include spider naevi, palmar erythema, glossy tongue and lips, symptoms and signs of a dry skin and pruritus, bleeding signs and various nail changes. However, the prognostic value of such cutaneous signs for the severity of liver disease has never been evaluated systematically to our knowledge. Currently, liver biopsy remains the standard for evaluation of liver fibrosis and thus for the prognosis of the disease (1–4). Although various laboratory, sonographical and radiological methods as well as a combination of such techniques and scores have been put forward to substitute liver biopsy, none has been

introduced as a routine in clinical medicine. The same is true for fibrosis markers and scores which value are still a matter of debate.

The present study prospectively assessed various skin changes in patients undergoing liver biopsy in order to evaluate their predictive value. In addition, we recorded several routine laboratory measurements in order to evaluate whether these tests might add to the predictive value of the cutaneous signs.

Methods

This study included all patients referred for liver biopsy to the St Josef Hospital Oberhausen between June 2000 and May 2004. Cutaneous changes were

recorded at the initial clinical examination before liver biopsy by one of the two authors (C. N. and M. F.), who are attending physicians at the St Josef Hospital following a prospective list that included:

Spider naevi, other forms of teleangiectasia, palmar erythema, nail changes (white nails, Muehrke nails, watch-glass deformity), gynaecomastia (in men), reduction/loss of pubic and axillary hair, reduction/loss of main hair, paper-money skin, caput medusae, glossy tongue, glossy lips, petechial and other bleeding signs, acne and jaundice. The nail changes were determined as individual characteristics (i.e. white nails, Muehrke nails and watch-glass deformity) as well as a sum of all nail changes (positive if either one of the individual changes was present). Similarly, we summarized glossy tongue and glossy lips as glossy tongue/lips, petechial and other bleeding as bleeding signs, loss/reduction of pubic/body hair and main hair as hair changes. The signs and symptoms of Dupuytren's contracture and carpal tunnel syndrome as well their sum (as an indication of palmar fibrotic changes) were recorded separately. Jaundice and caput medusa as well their sum (as indications of hepatic failure/portal hypertension) were recorded separately. The specific skin diseases lichen ruber, porphyria cutanea tarda, psoriasis and vitiligo were recorded separately and also summed up as specific skin diseases. We also noted the total number of spider naevi. Patients were asked about pruritus/itching and about complaints of dry skin and were examined for signs of scratching.

The physical findings were assessed as they are assessed in routine clinical practice; i.e. by the clinical judgement of the physician. We intended not to define special definitions arbitrarily for any physical finding because such a procedure would not mirror the daily clinical practice. The observer had no knowledge regarding the laboratory or imaging data, but was allowed to perform a complete physical examination and to obtain the medical history.

The duration of the disease was assessed by clinical means or by the first documentation of liver disease. Patients were routinely asked for the daily amount of alcohol consumption.

Inflammatory and fibrotic changes on liver biopsy were graded and staged according to Desmet and Scheuer (5) by one of the authors (A. T.) who was not aware of the cutaneous changes. In terms of grading fibrosis, the score is similar to that proposed by Batts and Ludwig and to the Metavir score (6–7); stage F0 represents the absence of fibrosis, stage F1 minimal (portal) fibrosis, stage F2 mild portal fibrosis with some septal fibrosis, stage F3 marked portal and septal fibrosis and stage F4 cirrhosis.

All laboratory values were taken from the routine panel. Haemoglobin (g/dl), thrombocytes ($\times 1000/\mu\text{l}$) and leucocytes ($\times 1000/\mu\text{l}$) were measured in a radio-meter analyser. All other values such as liver enzymes, prothrombine time (%), bilirubin (mg/dl), albumin (g/L), γ -globuline (g/L) and creatinine (mg/dl) were measured by an automated Behring analyser. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ -glutamyltransferase values are given in U/L for measurement at 25 °C.

This study was supported by the German 'Hepatitis Competence Network' project (Hep-Net) and was approved by the local ethical committee. No part of the study altered medical decisions in an individual patient.

The association between the fibrosis stage and the cutaneous signs of liver disease and other clinical and laboratory characteristics were analysed by a χ^2 -test for qualitative data, and for quantitative data by analysis of variance or the Kruskal–Wallis test depending on the underlying distribution assumptions.

In order to analyse the value of the various characteristics for prediction of severe fibrosis, patients with liver fibrosis F0–2 were compared with patients with fibrosis F3–4 by uni- and multivariate logistic regression analysis. For the analyses of AST, ALT, γ -glutamyltransferase and bilirubin logarithmically transformed values were used.

The reproducibility between the two observers was analysed in 27 patients with various degrees of fibrosis (F0 $n=9$, F1 $n=8$, F2 $n=4$, F3 $n=2$, F4 $n=4$) for the following physical findings: loss of hair, nail changes, glossy tongue/lips, for spider naevi, teleangiectasia, bleeding signs and palmar erythema. Reproducibility was calculated and expressed by κ coefficients and the corresponding 95% confidence intervals (CIs).

A total of 744 patients were randomly divided into a learning sample that consisted of two-third of the total cohort ($n=496$) and an evaluation sample that consisted of one-third of the total cohort ($n=248$). In a first step, univariate regression analysis was performed in the learning sample to determine which characteristics were significantly associated with fibrosis F3–4 vs. F0–2. Only those variables were included in the following multivariate regression analysis that were significant at the first step with a P -value < 0.01 ; however, age and gender were included in the model regardless of their significance at the univariate analyses. Stepwise logistic regression analysis was performed to develop a prediction model; variables were entered into and removed from the model using a P -value of 0.15. Finally, the prediction model from the learning sample was applied to the evaluation sample, and it was checked whether the prediction properties

were comparable between the two samples. The regression coefficients taken from the final model were rounded to obtain a suitable prediction score. A constant was chosen so that the score always has a positive value; greater score values are associated with a greater probability of having liver fibrosis F3–4.

Prediction scores were calculated for (i) the combination of cutaneous signs and laboratory values, (ii) the cutaneous signs of liver disease only, (iii) the laboratory values only, (iv) the AST to platelet ratio index (APRI) (8) and (v) the combination of cutaneous signs and the APRI.

Finally, receiver operating characteristic (ROC) analyses were performed to calculate sensitivity and specificity for the differentiation between liver fibrosis F0–2 and fibrosis F3–4 at various score levels. The areas under the ROC curves (AUC) were calculated to compare the different scores with regard to their predictive properties. The ROC curves from the learning and evaluation samples were very similar (data not shown); thus, a further calculation included both samples for final ROC analyses.

Statistical analyses were performed with the SAS software package, version 8.2.

Results

The analysis included 744 patients, 379 men and 365 women. The mean age was 49.2 ± 14.5 years (standard deviation), with a range from 6 to 85 years. The duration of liver disease ranged from 0 to 60 years, with a mean of 8.1 ± 6.4 years. The mean alcohol consumption was 13.0 ± 24.6 g/day, with a range from 0 to 200 g/day. Of the total 744 patients, 520 had chronic hepatitis C, 80 had chronic hepatitis B, 55 had fatty liver disease, 22 had autoimmune hepatitis, 13 had primary biliary cirrhosis, three had primary sclerosing cholangitis, 13 had genetic haemochromatosis, 23 had idiopathic liver disease and 15 had various other liver diseases. Thus, chronic hepatitis C was the diagnosis in 69.9% of the patients, while 30.1% had various other liver diseases.

The degrees of fibrosis are presented in Tables 1 and 2 (27% F0, 41% F1, 12.2% F2, 8.9% F3, 10.9% F4), which also show various clinical and laboratory data for fibrosis stages F0–4. By univariate analysis, several characteristics differed significantly among patients with different stages of liver fibrosis. In general, at fibrosis stages 0–1, skin changes, usually thought to represent cutaneous signs of liver disease, were infrequent such as spider naevi, palmar erythema, nail and hair changes, bleeding signs and glossy tongue or lips; these changes began to occur somewhat more

frequently at fibrosis stage F2 and were frequent at fibrosis stages F3–4. For example, almost none of the patients with fibrosis F0–1 had spider naevi, while spider were seen in almost 50% of the patients with stage F3 and in 84% of the patients with stage F4 (cirrhosis). Somewhat more non-specific skin changes and symptoms like itching, scratching and dry skin were also found to some degree in patients with none or minor fibrosis, but they were significantly more frequent in severe fibrosis and cirrhosis. Some specific skin diseases like lichen ruber, porphyria cutanea tarda, psoriasis and vitiligo have also been found to occur more frequently in patients with liver disease and cirrhosis; in the recent systematic analysis, however, the association of these alteration with the stage of liver fibrosis was weak or even absent (Table 1). The frequency of Dupuytren's contracture significantly increased with the stage of liver fibrosis, but was seen only infrequently (4.5 and 8.6% respectively) in patients with fibrosis F3–4. Symptoms and signs of a carpal tunnel syndrome were not significantly associated with liver fibrosis. Cutaneous signs of severe or decompensated liver disease or portal hypertension, such as jaundice and caput medusae, were relatively infrequent even in patients with cirrhosis probably because patients with clear clinical evidence of cirrhosis usually do not need a liver biopsy and were probably underrepresented in the recent cohort.

Male gender and age of the patients as well as the duration of liver disease and daily alcohol consumption were significantly associated with liver fibrosis and cirrhosis (Table 1).

Most patients were biopsied for chronic hepatitis C (69.9%) and the remaining patients because of various other liver diseases. The aetiology of liver disease was significantly associated neither with the occurrence of any of the skin changes nor with severe fibrosis (F3–4 vs. F0–2) ($P > 0.05$, data not shown). Thus, the conclusions are probably true not only for patients with chronic hepatitis C but also for patients with most other liver diseases.

Various clinical and laboratory characteristics were significantly associated with the stage of liver fibrosis (see Table 1 for univariate analysis).

The final prediction score resulting from the combination of cutaneous signs and laboratory values consisted of the following characteristics: presence of spider naevi, palmar erythema, nail changes, signs and symptoms of dry skin, sex, age, platelets, prothrombin time and serum albumin. The prediction equation was $25 + \text{dry skin (with a 1 if present, else 0)} \times 0.5 + \text{spider naevi (1/0)} \times 2 + \text{nail changes (1/0)} \times 0.5 + \text{palmar erythema (1/0)} \times 1 + \text{age (years)} \times 0.04 - \text{sex (1 if male,$

Table 1. Frequency and distribution of various clinical characteristics and laboratory values among patients with different stages of liver fibrosis

Clinical characteristics (n)	% positive characteristics at various fibrosis scores					Total number (744)	χ^2	P
	0 (201)	1 (305)	2 (91)	3 (66)	4 (81)			
Male sex	46.3	48.9	57.1	45.5	67.9	379	13.8	0.008
Spider naevi	1.0	1.3	3.3	48.5	84.0	109	454.3	< 0.001
Teleangiectasia	6.5	10.0	13.2	37.9	72.8	141	205.1	< 0.001
Palmar erythema	0	1.0	5.5	25.8	70.4	82	364.6	< 0.001
All nail changes	4.0	4.3	3.3	21.2	61.7	88	233.9	< 0.001
White nails	2.0	1.3	1.1	13.6	44.4	54	199.8	< 0.001
Muehrke nails	0.5	0.3	1.1	9.1	23.5	28	109.6	< 0.001
Watch-glass deformity	1.5	3.0	1.1	3.0	8.6	22	11.7	0.20
Glossy tongue or lips	1.0	1.3	2.2	4.5	33.3	38	150.9	< 0.001
Glossy tongue	1.0	1.3	2.2	3.0	30.9	35	139.3	< 0.001
Glossy lips	0	0	0	1.5	22.1	19	141.9	< 0.001
Paper money skin	1.0	1.3	3.3	3.0	33.3	38	150.4	< 0.001
Bleeding signs	1.0	1.3	2.2	4.5	17.3	25	56.4	< 0.001
Petechial bleeding	0.5	1.3	2.2	4.5	12.3	20	35.7	< 0.001
Other bleeding signs	0.5	1.3	1.1	1.5	12.3	17	41.6	< 0.001
Itching or scratching	7.0	13.8	20.9	25.8	59.3	140	112.6	< 0.001
Itching	6.5	13.4	20.9	25.8	56.8	136	106.8	< 0.001
Scratching	1.0	1.6	4.4	9.1	33.3	44	129.8	< 0.001
Dry skin	6.0	13.4	19.8	40.9	60.5	147	135.2	< 0.001
Jaundice or caput medusae	0	0.7	0	6.1	24.7	26	127.1	< 0.001
Jaundice	0	0.7	0	6.1	16.0	19	74.6	< 0.001
Caput medusae	0	0	0	0	8.6	7	57.8	< 0.001
Hair changes	8.5	14.8	17.6	50.0	70.4	168	169.1	< 0.001
Reduction or loss body or pubic hair	3.5	2.6	5.5	25.8	50.6	78	188.4	< 0.001
Reduction or loss of main hair	8.5	14.8	17.6	50.0	70.4	168	169.1	< 0.001
Gynecomastia	7.5	8.1	3.8	16.7	58.2	58	93.1	< 0.001
Acne	5.0	4.9	3.3	6.1	13.6	43	10.7	0.030
Dupuytren or cts	0.5	2.0	2.2	7.6	8.6	21	20.3	< 0.001
Carpal tunnel syndrome (cts)	0	1.0	0	3.0	1.2	6	6.7	0.15
Dupuytren's contracture	0.5	1.0	2.2	4.5	8.6	16	22.6	< 0.001
Specific skin diseases*	1.5	3.0	12.1	10.6	6.2	35	23.3	< 0.001
Lichen ruber ¹	1.5	0.7	1.1	3.0	2.5	10	3.5	0.5
Psoriasis vulgaris ²	0	1.6	1.1	0	0	6	5.6	0.2
Vitiligo ³	0	0.3	6.6	3.0	2.5	11	23.8	< 0.001
Porphyria cutanea tarda ⁴	0	1.0	3.3	4.5	2.5	11	10.4	0.034

*Including the for skin diseases indicated by the superscript 1–4.

else 0) \times 0.5 – platelets (no. in thousands) \times 0.01 – prothrombine time (%) \times 0.1 – serum albumin (g/L) \times 2.

The prothrombine time in per cent of normal (Quick) can be transferred to prolongation of prothrombine time by the calculation: Quick = $10^{[(1/-0.7) \times \log_{10} (\text{prolongation in prothrombine time}) + 3.414]}$

The calculated score showed that with an increase in the score by 1 the chance to have fibrosis stages F3–4 vs. stages F0–2 increased by 3.3-fold (95% CI: 2.7–4.1). At a score of 8, the sensitivity and specificity were about 90%, and at a score of 7 only 2% of patients with fibrosis F3–4 were misdiagnosed (sensitivity 98%) while the specificity was still 75%. At the cost of 2% of non-diagnosed patients with fibrosis F3–4, one might have saved 60% of liver biopsies (449/744).

The ROC curves are shown in Figure 1, which demonstrates that the calculated model is valuable to discriminate fibrosis F0–2 from F3–4.

The second analysis included only cutaneous changes, age and gender, thus not considering laboratory markers. The ROC analysis shows that the use of only the cutaneous signs instead of adding laboratory variables resulted in a slightly worse prediction of fibrosis F3–4 vs. F0–2. At a specificity of 90%, the sensitivity was now only 85% (instead of 90% when laboratory variables were included), and the specificity was reduced to 70% at a sensitivity of 90%. Thus, the score including only cutaneous signs of liver disease is somewhat less specific without laboratory variables added. Correspondingly, at the cost of 2% of non-

Table 2. Frequency and distribution of various clinical characteristics and laboratory values among patients with different stages of liver fibrosis

Clinical and laboratory characteristics	Means and interquartile regions (IQR) of various characteristics at different fibrosis scores										Kruskal–Wallis	
	F0		F1		F2		F3		F4			
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	χ^2	$P <$
Number of spider naevi (n)	0	0	0	0	0	0	2	6	6	6	430.7	0.001
Age (years)	42	19	47	21	51	18	49	19	60	21	92.1	0.001
Duration of hepatitis (years)	6	5	7	6	7	5	8	10	9	9	41.4	0.001
Alcohol consumption (g/day)	0	20	0	10	10	30	2.5	20	10	40	44.8	0.001
AST (U/L)	21	18	24	28	39	46	35	42	54	57	111.5	0.001
ALT (U/L)	33	28	43	48	59	62	49	54	50	60	49.4	0.001
γ -glutamyltransferase (U/L)	32	43	33	43	50	46	52	84	104	138	94.3	0.001
Haemoglobin (g/dl)	14.7	1.6	14.6	1.8	14.2	2.0	14.2	1.8	13.1	2.6	41.4	0.001
Leucocytes ($\times 1000/\mu\text{l}$)	6.7	2.5	6.5	2.2	5.4	2.3	6.2	2.3	5.0	2.2	55.6	0.001
Thrombocytes ($\times 1000/\mu\text{l}$)	243	94	234	90	198	83	148	108	103	54	181.3	0.001
Prothrombine time (%)	100	2	100	5	100	6	89	23	76	28	206.5	0.001
Bilirubin (mg/dl)	0.9	0.3	1.0	0.4	1.0	0.3	1.0	0.4	1.2	0.8	46.6	0.001
Albumin (g/L)	4.4	0.5	4.3	0.5	4.2	0.5	4.0	0.5	3.6	0.9	143.4	0.001
γ -globulin (g/L)	1.2	0.4	1.3	0.4	1.4	0.4	1.8	0.6	2.0	0.7	193.6	0.001
Creatinine (mg/dl)	0.8	0.3	0.8	0.3	0.9	0.21	1.0	0.2	1.0	0.3	59.4	0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

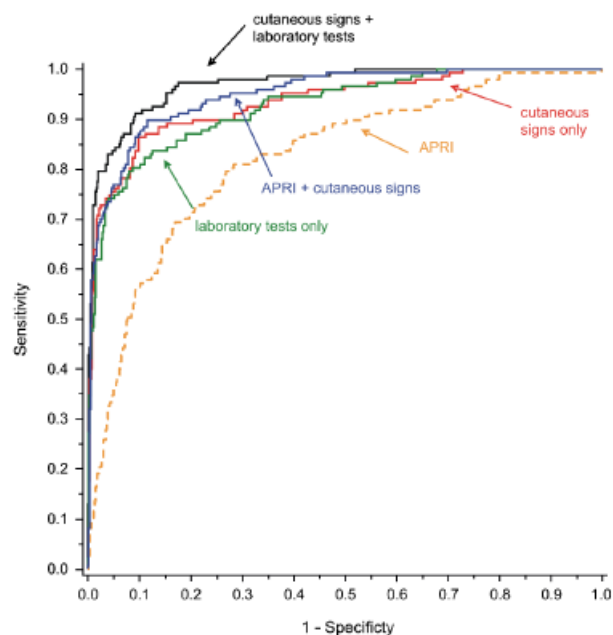


Fig. 1. ROC curves for discrimination of fibrosis stages F0–2 from F3–4 in 744 patients.

diagnosed patients with fibrosis F3–4, only 30% of biopsies might have been saved when using only the cutaneous signs.

The third ROC analysis only considered the laboratory values without the cutaneous changes; the resulting ROC curve was located just slightly to the right of the ROC curve considering only the cutaneous sign without the laboratory values and clearly located to the right when compared with the ROC analysis, which considered both cutaneous and laboratory changes (Fig. 1). In any case, the combination of skin changes and routine laboratory tests improved the non-invasive assessment for liver fibrosis.

A separate analysis calculated a ROC curve using the APRI in the literature (8). The ROC curve was located most right of all the other ROC curves, showing that the APRI does not predict liver fibrosis as well as the more complex index of further laboratory values or the clinical assessment of skin changes (Fig. 1). Again, the combination of the APRI and the clinical assessment of skin changes resulted in a quite useful ROC curve, which was only slightly less powerful when compared with the combination of various other routine laboratory measurements and skin changes (Fig. 1).

We also used the models described to evaluate their predictive value for differentiating fibrosis F0–1 vs. F2–4. The resulting ROC curves were clearly lying nearer to the 45° line of non-discrimination when compared with ROC curves calculated for predicting fibrosis F0–2 vs. F3–4 (Fig. 2). It might have been necessary to calculate a new model in order to better

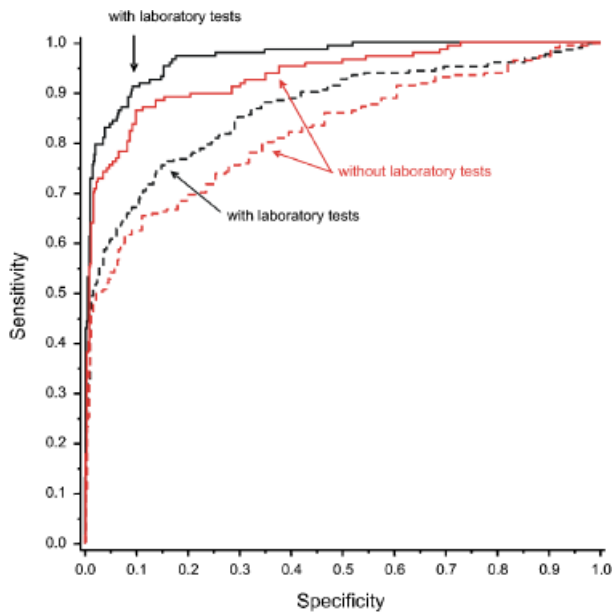


Fig. 2. ROC curves for discrimination of fibrosis stages F0–1 from F2–5 (dashed lines) and ROC curves for discrimination of fibrosis stages F0–2 from F3–4 (unbroken lines) in 744 patients.

differentiate fibrosis F0–1 vs. F2–4. However, just by looking at the raw data in Table 1, it is evident that most cutaneous signs of liver disease are very frequent only at fibrosis stages F3–4; thus, we did not further analyse potential models to better differentiate stages F0–1 from F2–4.

A further analysis calculated the percentage of severe fibrosis (F3–4) and cirrhosis (F4) in the absence of any of four typical cutaneous signs of liver disease (spider naevi, palmar erythema, nail changes, bleeding signs) or of abnormal values for four typical laboratory signs of liver fibrosis (platelets, prothrombine time, γ -globulins, albumin). Only 0.6% of the patients had cirrhosis (F4) in the absence of all these skin changes while already 37.1% had cirrhosis (F4) when only one cutaneous sign was present. In the absence of any of the four cutaneous signs, 5.1% of the patients had F3–4 fibrosis, while 57.1% had severe fibrosis (F3–4) when either one of the four skin changes was present. Similarly, only 0.5% of the subjects had cirrhosis (F4) when all four laboratory tests were normal, while 15.0% had cirrhosis when either one of the four tests was abnormal. Only 2.4% of the subjects with normal values for all four laboratory tests had severe fibrosis (F3–4), while 26.6% had severe fibrosis when one of the tests was abnormal. In subjects with absence of both the four cutaneous and the four laboratory changes, only 0.6% had cirrhosis (F4), while 14.2% had cirrhosis when either a cutaneous sign or a laboratory test was abnormal. Of the subjects with

absence of all these cutaneous and laboratory abnormalities, only 2.2% had fibrosis F3–4, while 25.4% had severe fibrosis when either one cutaneous sign was present or one laboratory test was abnormal. On the other hand, patients with cirrhosis did not often have all of the four cutaneous signs analysed; e.g. only 10.9% of the cirrhotic patients (F4) had all these skin changes. Similar results were obtained for the laboratory values (data not given).

The κ coefficients indicated that the reproducibility was moderate for loss of hair [κ coefficient 0.51 (95% CI 0.15–0.88)], good for nail changes [0.69 (0.33–1.00)] and glossy tongue/lips [0.71 (0.33–1.00)] and excellent for spider naevi [0.92 (0.54–1.00)], teleangiectasia [0.92 (0.55–1.00)], bleeding signs [1.00 (0.62–1.00)] and palmar erythema [1.00 (0.62–1.00)].

Discussion

Nowadays, most liver biopsies are not carried out anymore for diagnosis of a specific liver disease, but to determine the degree of inflammation (grading) and fibrosis (staging) and thus in order to predict the prognosis of the disease (1–7). In particular, the degree of fibrosis determines the patient's prognosis for almost all liver diseases (1–7). Thus, many further medical decisions such as antiviral or immunomodulatory therapies depend on the degree of liver fibrosis. Although various non-invasive fibrosis tests and scores have been put forward to substitute liver biopsy, none has been introduced as a routine in clinical medicine as yet (1). In this context, it is quite astonishing that the value of clinical and particular cutaneous signs of liver disease has never been evaluated properly although all these signs are recorded during every regular physical examination.

The present results prove that it is indeed useful to carefully look for skin changes in patients with liver disease. Several of these cutaneous changes are indeed signs of liver disease and in particular signs of severe liver fibrosis and cirrhosis. The value of such skin changes for determining the severity of fibrosis is of clinical value because severe fibrosis is the most important factor for predicting the patients' prognosis. For generations, physicians have in particular looked for the presence of spider naevi, palmar erythema, bleeding signs and nail changes in patients with suspected or known liver disease; now, we know that such a clinical evaluation is meaningful. In addition to such a clinical evaluation, simple laboratory measurements add some value in order to assess the severity of liver fibrosis. These laboratory values are routinely determined and thus available in virtually every liver patient without additional costs. The

combination of cutaneous signs and simple laboratory tests is helpful to estimate the prognosis in the routine clinical setting and may make some liver biopsies unnecessary. In the absence of most typical cutaneous signs of liver disease severe fibrosis is unlikely and cirrhosis is even very unlikely; on the other hand, even patients with cirrhosis do not necessarily have all the typical cutaneous signs analysed.

Clinical decisions, which depend on an assessment of the degree of liver fibrosis and thus on a prediction of prognosis, are based on recognition of various further data including clinical assessment of liver consistency and imaging methods such as ultrasound, computed tomography or magnetic resonance tomography. In addition, the complaints and the history of the patients as well as potential signs of oesophageal varices during endoscopy are important. It may be difficult to combine all these characteristics in a statistical model; probably, the brain of an experienced hepatologist is currently still the best tool in assessing the risk of the patient by combining and weighing all these data. The current analysis also shows that the reproducibility of the physical findings is in general good and even very good for the parameters that are included in the final score.

Along this line, it remains doubtful whether complex mathematical fibrosis scores and indices will be widely used in clinical practice. Some recent tests (Forns index, FibroTest, HCV FibroSure, ActiTest, Fibrospect I and II) include new laboratory and imaging methods such as sonographical or magnetic resonance elastography (FibroScan, Echosens, Paris, France) and serum protein glycans or a combination of laboratory tests such as procollagen-III-peptide, α_2 -macroglobulin, haptoglobin, apolipoprotein A1, tissue inhibitors of metalloproteinases 1–4 and hyaluronic acid (9–16); many of these parameters are not measured in a routine panel and thus add to the costs. Some tests are commercialized and require a complex mathematical modelling because of a non-published algorithm (17). Interestingly, none of these tests considers or includes information obtained by clinical examination. The present results strongly argue against such neglect of clinical data.

Another recent test put forward for prediction of liver fibrosis is at least easy to perform without additional costs: the APRI (8). The APRI is amenable to mental calculation in clinical practice while most other recently proposed tests include several laboratory tests that are not performed in a clinical routine or require mathematical calculation beyond mental power. Thus, the APRI ratio may be useful for a clinical routine and was therefore compared with the

clinical data obtained in the present study; the comparison shows that looking at cutaneous signs of liver disease is at least as useful and probably even better for prediction of severe fibrosis. Combining the clinical data with the APRI improves the predictive power of both means.

In the present cohort, patients with cirrhosis and bad liver function may be underrepresented because many patients with clinical signs of decompensated cirrhosis do not need a liver biopsy. This bias may explain why there are only a few patients with jaundice and caput medusae in the present cohort; almost all patients with cirrhosis on liver biopsy were staged as Child–Pugh A. This selection of rather milder liver disease, however, does not cause problems for the interpretation of the data. When one can clinically determine the presence of cirrhosis, no further tests and no liver biopsy are necessary anyway. The results also show that the cutaneous signs of liver disease are less helpful to indicate the presence of mild fibrosis (stage 2; i.e. some septal fibrosis). When further medical decisions may depend on such discrimination between fibrosis stages F0–1 and stages F2–4, liver biopsy may not be substituted by clinical examination and laboratory values. The same problem is also true for various other ‘fibrosis tests’ as stated by consensus conferences.

Patients without any cutaneous signs of liver disease such as spider naevi, palmar erythema, nail changes and others are extremely unlikely to have cirrhosis and very unlikely to have severe fibrosis. In this regard, the clinical examination is very useful and at least as good as routine laboratory data to rule out severe fibrosis or cirrhosis. The combination of the clinical examination of the skin and the determination of routine laboratory tests again adds some information in order to rule out severe fibrosis and cirrhosis when neither one of the cutaneous and laboratory signs is abnormal. On the other hand, patients with cirrhosis do not need to show all the skin changes that may indicate severe liver disease.

The present study emphasizes that clinical data such as cutaneous signs of liver disease are at least as good or better than various laboratory values and indices. The current analyses also demonstrate that the combination of routine clinical and laboratory data further improves the predictive power to assess the prognosis. Probably the same is true when one would add information from other clinical and imaging studies. We do not interpret the present results in the way that we do not need to perform liver biopsies any longer. Similarly, we do not propose that our mathematical model should be used in clinical practice in order to

assess the degree of liver fibrosis by non-invasive means. However, the present results strongly emphasize that careful clinical evaluation and simple routine laboratory values already do allow a quite valid prediction or exclusion of severe fibrosis and cirrhosis in the individual patient. This information needs to be kept in mind when the medical decision on liver biopsy is made and discussed with the patient.

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