

# Clinical and capillaroscopic findings in patients with liver disease and proximal apparent leukonychia (Terry nails and its variants)

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## Abstract

Terry nails and Lindsay nails are similar forms of proximal apparent leukonychia (PAL). A change in nail bed vascularity is thought to be responsible for PAL. The study was aimed at investigating the frequency of PAL in patients attending a liver disease clinic, the factors associated with its presence, its value for detecting cirrhosis, its prognostic value for mortality, and associated capillaroscopic findings.

A total of 521 patients were included (age range, 18–94 years; 69% men). Systematic nail photographs were evaluated by 2 independent investigators. Disease-related data were obtained from the medical records. Mortality was evaluated after 7 years of follow-up. Nailfold capillaroscopy was performed on a subset of 80 patients.

PAL was present in 228 patients (43.8%; Terry nails in 205, Lindsay nails in 20, and both in 3). The kappa-coefficient of interobserver agreement was 0.82. The presence of PAL was associated with cirrhosis and, accordingly, with portal hypertension and hepatocellular dysfunction. The positive likelihood ratio of PAL for the diagnosis of cirrhosis was 1.6 (95% CI 1.3–1.92). PAL was independently associated with chronic alcohol abuse and was not a significant predictor of mortality. Venous loop dilatation and prominence of the venous plexus were observed on capillaroscopy in patients with cirrhosis but were not significantly associated with PAL.

In summary, PAL is a common finding in patients from a liver clinic; it is associated with liver cirrhosis and with alcohol abuse. PAL is not associated with specific capillaroscopic findings. We propose the generic term *proximal apparent leukonychia* instead of classic eponymous titles to avoid confusion in the literature.

**Abbreviations:** MELD = model for end-stage liver disease, PAL = proximal apparent leukonychia.

**Keywords:** alcohol, cirrhosis, leukonychia, Lindsay nails, Terry nails

## 1. Introduction

Leukonychia (*white nail discoloration*) can be broadly classified into true and apparent.<sup>[1]</sup> True leukonychias (*punctata*, *striata*, or *totalis*) derive from alterations in the nail plate itself, whereas

apparent leukonychias are due to abnormalities in the nail bed.<sup>[1]</sup> Contrary to true leukonychias, the position of apparent leukonychias does not change as the nail grows.<sup>[1]</sup> Richard Terry (1954) reported “a ground-glass-like opacity of almost the entire nail bed” in 82 of 100 consecutive patients with liver cirrhosis, which was of alcoholic cause in more than 90% of patients.<sup>[2]</sup> Later, Terry observed a similar finding in patients with congestive heart failure.<sup>[3]</sup> Terry nail is a form of apparent leukonychia that is evident as a bilaterally symmetrical whitening of the fingernails that involves the basal or proximal part of the nail bed, sparing only a narrow pink-to-brown segment at the distal border.<sup>[2]</sup> Any whiteness of the nail bed is unaffected by the venous congestion induced by finger pressure and indeed is accentuated by the contrast with the congested distal zone.<sup>[2]</sup> The lunula can be indistinguishable in most severe cases.<sup>[2]</sup>

In 1984, Holzberg and Walker consecutively studied 512 hospitalized patients and observed Terry nails in 25.2% of them. Furthermore, they confirmed a statistically significant association between Terry nails and cirrhosis, chronic heart failure, adult-onset diabetes, and age.<sup>[4]</sup> Similarly, Park et al (1992) studied fingernails in 444 medical inpatients with chronic systemic diseases and observed Terry nails in 30.6% of them. They also confirmed an association with cirrhosis, congestive heart failure, and diabetes mellitus.<sup>[5]</sup> More recently, Nelson et al (2018) studied the fingers and toes of 503 medical outpatients with a variety of disorders and found Terry nails in 3% to 8%,

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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depending on the observer. Again, the authors found an association between Terry nails and liver cirrhosis in these outpatients.<sup>[6]</sup>

The width of the pink-to-brown distal transverse band in the nail is a matter of discussion and potential confusion in the literature. The definition in Terry classical series included a band of 1 to 2 mm in width.<sup>[2]</sup> The Holzberg and Walker criteria expanded that width to 0.5 to 3 mm.<sup>[4]</sup> Similar criteria have been employed in subsequent series.<sup>[5,6]</sup> Expanding the width of the distal band further creates an overlap with the so-called Lindsay nails, also a form of proximal apparent leukonychia (PAL), with a broader pink-to-brown band that occupies 20% to 60% of the nail bed; hence, these are also known as half-and-half nails.<sup>[7]</sup> Lindsay nails are associated with chronic renal failure.<sup>[7]</sup> Clinical distinction among these forms of PAL can be difficult<sup>[8,9]</sup> and there are also intermediate forms.<sup>[8]</sup>

The pathophysiology and pathology of this condition (Terry nails and its variants) remain undetermined. A change in nail bed vascularity, secondary to overgrowth of connective tissue, is thought to be responsible.<sup>[10]</sup> Nail bed biopsies in 3 patients with Terry nails revealed telangiectasias in the distal band, further supporting microvascular involvement.<sup>[4]</sup>

There is continuing interest in Terry nails and its variants, as revealed by recent case reports.<sup>[9–12]</sup> Physical signs are diagnostic tests that can be evaluated according to evidence-based medicine.<sup>[13]</sup> As noted above, studies of this type of nail abnormality have been performed in a selected sample of patients with liver cirrhosis,<sup>[2]</sup> and on general medical patients, both inpatients<sup>[4,5]</sup> and outpatients.<sup>[6]</sup> To the best of our knowledge, no studies have been conducted on patients from a liver disease clinic, with or without liver cirrhosis. The present study was aimed at investigating the frequency of PAL, the factors associated with its presence, its diagnostic value (for cirrhosis) and its prognostic significance (for mortality) in a series of patients attending a liver disease clinic. Furthermore, we performed nail fold capillaroscopy on a subset of these patients to determine whether PAL was associated with any specific abnormality in vascularization.

## 2. Methods

### 2.1. Study population and design

This observational study started with a cross-sectional design to evaluate the prevalence of PAL. Subsequently, patients with the effect (PAL) were compared with individuals without it (case-control design). Finally, all patients were followed up to determine mortality and associated factors (prospective cohort design). All patients provided written informed consent for participation in the study, which was reviewed and approved by the Regional (Galician) Ethics Committee.

Consecutive adult (>18 years) outpatients attending a liver disease clinic from a university hospital in northwest Spain in 2011 were included. The study was powered to offer a precision to estimate a proportion of  $\pm 4\%$  in the most unfavorable case ( $P=q=50\%$ ) with a confidence level of 95%. The study profile is depicted in Figure 1. Exclusion criteria were (a) the absence of informed consent and (b) the presence of artifacts (eg, nail polish) that could hinder nail evaluation. From 560 initially eligible patients, 525 were included in the study. Suitable photographs (see below) were not available for 4 individuals. The final study population, therefore, included 521 patients (Fig. 1). The median

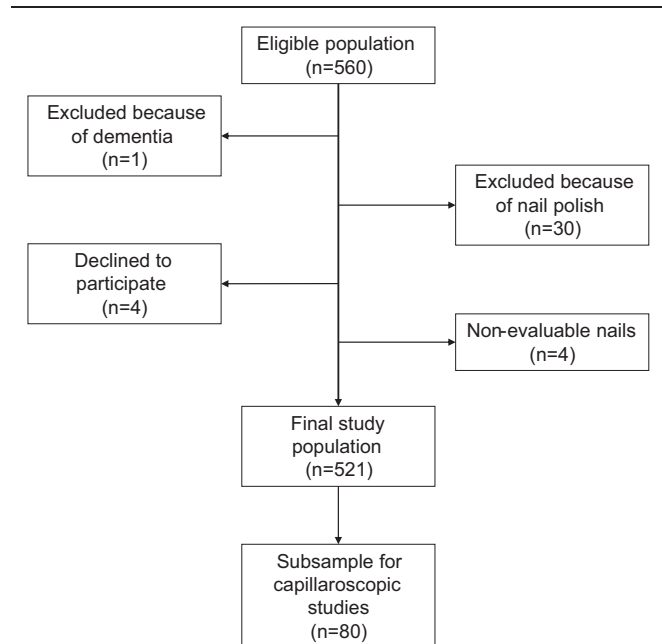


Figure 1. Study profile.

age was 55 years (range 18–94 years) and 69% were men. All patients were white, with the exception of 1 black patient.

Nail fold capillaroscopy (see below) was performed in a subsample of 80 patients who were stratified into 5 groups as follows: (a) patients without liver disease ( $n=9$ ); (b) patients with noncirrhotic liver disease, without PAL ( $n=20$ ); (c) patients with noncirrhotic liver disease, with PAL ( $n=16$ ); (d) patients with cirrhotic liver disease, without PAL ( $n=12$ ); and (e) patients with cirrhotic liver disease, with PAL ( $n=23$ ). Among the patients with noncirrhotic liver disease, 15 had been transplanted in the past and were considered apart in some analyses. Patients with active hepatitis B virus or hepatitis C virus infection were excluded from capillaroscopy to avoid any risk of transmission because small injuries in the nail fold are common and the study capillaroscope was of contact type (see below). As a result, liver cirrhosis was of alcoholic cause in all cases in this subsample.

### 2.2. Main determinations

**2.2.1. Demographic and clinical data.** Demographic and liver disease-related data were obtained from the electronic clinical records. Data related to liver disease included (a) the liver disease group (no evident liver disease, noncirrhotic liver disease, liver cirrhosis, and liver transplantation); (b) specific liver disease cause (or causes); (c) outcome and complications of liver disease (portal hypertension, gastrointestinal bleeding, ascites, splenomegaly, encephalopathy, hepatorenal syndrome, and transplantation); and (d) biological determinations, including kidney and liver function. The severity of the liver disease was graded according to the *Model for End-Stage Liver Disease* (MELD)<sup>[14,15]</sup> and Child-Pugh classification.<sup>[16]</sup>

**2.2.2. Macroscopic nail abnormalities (PAL forms).** Both front and side-facing photographs were taken of all fingers on both hands using a Canon EOS 500D with a 60-mm macro lens 1:2.8 USM in standard conditions. All photographs were blindly and independently evaluated by 2 independent researchers (a

general internist and a dermatologist) when the recruitment period was concluded. The 2 researchers established the presence or absence of the nail abnormality and the number of fingers involved, in categories (1, several, or all fingers). Their findings were transcribed to a database. After calculation of the agreement index (see below), discrepancies were resolved upon consensus.

PAL was defined by the presence of a white or light pink appearance of the basal part of the nail (with or without lunula) and a distal thin pink-to-brown transverse band.<sup>[2,4]</sup> Initially, PAL was classified as Terry nails or Lindsay nails following the simplified criterion of Iorizzo et al<sup>[17]</sup> as follows: when the leukonychia occupied >80% of the nail area, they were classified as Terry nails; when the area was <80%, they were classified as Lindsay nails. These abnormalities were considered both separately and together as PAL, the common feature of both conditions.

**2.2.3. Nail fold capillaroscopy.** The subsample of 80 patients underwent a capillaroscopy of all fingernail folds, excluding thumbs, following standard methods,<sup>[18]</sup> by means of a contact capillaroscope (AM4013-N5UT Dino-Lite Premier, Digital Microscope) with interposition of cedar oil. The following abnormal findings were registered as yes/no variables: (a) low capillary density (avascular areas >500  $\mu\text{m}$ ); (b) long capillaries (>400  $\mu\text{m}$ ); (c) capillary dilatation (>25  $\mu\text{m}$  in diameter; megacapillaries if >50  $\mu\text{m}$ ); (d) abnormal capillary morphology (tortuosities, crossings [simple, double, or complex], ramifications [simple and complex]; neoangiogenic pattern [irregular, different-stage, tortuous ramified capillaries]; or *shoal of fish* pattern [abundant and short capillaries]); (e) flow abnormalities (intermittent, granular [very slow], or the presence of thrombi); (f) abnormally prominent (visible) venous plexus (chandelier pattern); and (h) abnormalities in the pericapillary area (edema, half-moon hemorrhages, and exudates).<sup>[18]</sup>

**2.2.4. Overall mortality.** The day of examination was used as the baseline. The clinical records of the 521 participants were reviewed in 2018 to estimate the risk (cumulative incidence) of death at 7 years of follow-up, and potential associated baseline factors, including PAL. The monitoring of the vital status of the patients was done with the information provided by the national registry of mortality, which is connected with the electronic medical record, regardless of patient's address.

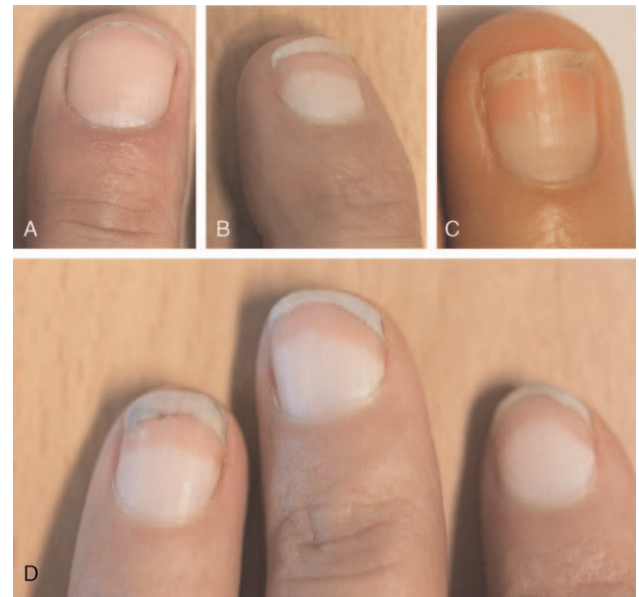
### 2.3. Statistical analyses

Agreement between observers was estimated using the kappa index. Nonparametric statistics were used to compare numerical variables among groups. The  $\chi^2$  test, with trend estimation and continuity correction when appropriate, was used to assess associations between categorical variables. Logistic regression models were constructed for the multivariate analyses. Covariates potentially associated with the outcome were forced to enter the equation in those models. The diagnostic accuracy of nail abnormalities for the diagnosis of liver cirrhosis was estimated, including sensitivity, specificity, predictive values, and likelihood ratios, with corresponding 95% CI.

## 3. Results

### 3.1. Prevalence of PAL

PAL was present in 228 patients (43.8%; 95CI, 39.5%–48.1%). Of these, the vast majority (205 patients) corresponded to Terry



**Figure 2.** Representative examples of proximal apparent leukonychia. (A) Terry nails. The proximal part of the nail shows a white-ground-glass appearance, with a distal pink-to-brown transversal band at the onychodermal junction. (B) Proximal apparent leukonychia with a broader distal band. (C) Lindsay nail. (D) Proximal apparent leukonychia in all fingers. Depending on distal bandwidth criteria, cases B and D could be classified either as Lindsay or Terry nails.

nails. A total of 20 patients presented Lindsay nails and 3 patients presented both types of nails (Fig. 2). The kappa index of concordance in the diagnosis of PAL between the 2 observers was 0.823 (standard error, 0.025). PAL was present in all fingers in 82 patients, in 2–4 fingers in 124 patients, and in only 1 finger in 22 patients. The nail lunula was absent in 174 patients with PAL (76.3%) and in 152 patients without it (51.9%,  $P < 0.001$ ).

### 3.2. Factors associated with the presence of PAL

The characteristics of individuals with and without PAL are shown in Table 1. There was no significant association between PAL and either age or sex. Regarding the most common causes of liver disease, the presence of PAL was associated with a history of alcohol abuse (Table 1). The association was stronger in current drinkers than in ex-drinkers (Table 1). Conversely, PAL was not associated with a history of hepatitis C virus infection. PAL was strongly associated with liver cirrhosis. The association was even stronger among patients with *present* liver cirrhosis than in those with *past* liver cirrhosis (ie, those who had liver transplants because of cirrhosis, Table 1). The association between PAL and liver cirrhosis varied depending on the number of fingers affected. In general, the higher the number of fingers with PAL, the higher the risk of underlying liver cirrhosis. Liver cirrhosis was present in 78 of 293 (26.6%) patients without PAL, 7 of 22 (31.8%) of patients with PAL in 1 finger, 49 of 124 (39.5%) of patients with PAL in several fingers, and 47 of 82 (57.3%) patients with PAL in all fingers ( $P$  for trend, <0.001). Along these lines, PAL was associated with the presence of portal hypertension (with or without esophageal varices) and ascites. Similarly, patients with PAL tended to have more prominent alterations in markers of hepatocellular dysfunction, such as serum bilirubin, albumin,

**Table 1**  
**Epidemiological and clinical characteristics of patients with and without proximal apparent leukonychia.**

Variable	Proximal apparent leukonychia				P-value
	No (n = 293)		Yes (n = 228)		
	N		N		
Age (yrs)	293	55 (44–63)	228	55 (47–65)	0.202
Sex (male)	293	195 (66.6)	228	165 (72.4)	0.154
History of alcohol abuse	293	112 (38.2)	228	122 (53.5)	0.001
Categories of alcohol abuse	293		228		
Never drinker		181 (61.8)		106 (46.5)	<0.001
Current drinker		28 (9.6)		46 (20.2)	
Ex-drinker		84 (28.7)		76 (33.3)	
History of HCV infection	293	59 (20.1)	228	41 (18.0)	0.536
Categories of HCV infection	293		228		
Never		234 (79.9)		187 (82.0)	0.810
Active		47 (16.0)		32 (14.0)	
Past		12 (4.1)		9 (3.9)	
History of liver cirrhosis	293	78 (26.6)	228	103 (45.2)	<0.001
Categories of liver cirrhosis	293		228		
Never		215 (73.4)		125 (54.8)	<0.001
Current		45 (15.4)		72 (31.6)	
Transplanted		33 (11.3)		31 (13.6)	
Liver transplantation	293	43 (14.7)	228	40 (17.5)	0.375
Ascites (current)	293	15 (5.1)	228	34 (14.9)	<0.001
Portal hypertension	293	38 (13.0)	228	64 (28.1)	<0.001
Esophageal varices	293	31 (10.6)	228	50 (21.9)	<0.001
Fatty liver	293	115 (39.2)	228	76 (33.3)	0.164
No significant liver disease	293	26 (8.9)	228	6 (2.6)	0.003
Serum bilirubin (mg/dL)	292	0.6 (0.5–0.9)	226	0.7 (0.5–1.0)	0.006
Serum albumin (g/dL)	288	4.4 (4.2–4.7)	221	4.3 (4.0–4.6)	0.037
Prothrombin time (INR)	267	0.95 (0.91–1.01)	204	0.98 (0.92–1.07)	0.001
Serum AST (IU/L)	293	21 (15–30)	227	23 (16–34)	0.028
Serum ALT (IU/L)	293	25 (17–41)	227	26 (18–42)	0.489
Serum GGT (IU/L)	293	37 (18–77)	226	47 (22–105)	0.009
Serum alk. phosphatase (IU/L)	292	146 (118–190)	226	167 (115–227)	0.035
MELD score	266	6 (6–8)	203	7 (6–10)	<0.001
Serum creatinine (mg/dL)	293	0.9 (0.8–1.1)	227	0.9 (0.8–1.1)	0.722
Blood hemoglobin (g/dL)	293	14.5 (13.3–15.6)	225	14.2 (13.1–15.2)	0.022

Data are absolute numbers and percentages with respect to individuals with or without leukonychia (within parentheses) or medians and interquartile ranges (within parentheses). ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, HCV = hepatitis C virus, INR = international normalized ratio, MELD = Model for end-stage liver disease.

prothrombin time, and MELD score than patients without it (Table 1). There was no clear association between PAL and markers of acute liver damage, although serum aspartate aminotransferase and, particularly, serum gamma-glutamyl transferase tended to be higher in patients with PAL than in patients without it (Table 1). There was no significant association between PAL and markers of renal dysfunction (serum creatinine, Table 1).

On multivariate analyses (logistic regression) present liver cirrhosis (but not liver cirrhosis that underwent transplantation) and current alcohol abuse (but not a history of alcohol abuse in the past) were independently associated with the presence of PAL, that is, these associations were still present after adjusting for each other as well as for age and sex (Table 2). Liver cirrhosis was the stronger predictor of having PAL (Table 2).

The associations between PAL and liver cirrhosis and its consequences were similarly present when Terry nails and Lindsay nails were considered separately (data not shown). Liver cirrhosis was present in 44.9% of the patients with Terry nails, 47.8% of the patients with Lindsay nails, and only 26.6% of the patients with neither Terry nor Lindsay nails.

### 3.3. Accuracy of PAL for detecting liver cirrhosis

The diagnostic accuracy of PAL in the diagnosis of liver cirrhosis is shown in Table 3. Sensitivity was rather low. Specificity was

**Table 2**  
**Factors associated with the presence of proximal apparent leukonychia. Multivariate analysis (logistic regression).**

Variable	Odds ratio	95% Confidence interval	P-value
Age (yrs)	1.005	0.991–1.019	0.524
Sex (male)	1.062	0.705–1.598	0.775
Categories of alcohol abuse			
Never drinker	1 (reference)		
Current drinker	2.057	1.164–3.635	0.013
Ex-drinker	0.947	0.569–1.576	0.834
Categories of liver cirrhosis			
Never	1 (reference)		
Current	2.522	1.524–4.173	<0.001
Transplanted	1.655	0.872–3.141	0.124

All variables entered the equation. A total of 521 patients were included.

**Table 3**

**Accuracy of proximal apparent leukonychia in the diagnosis of liver cirrhosis.**

<b>(a) Diagnostic value of proximal apparent leukonychia in at least 1 finger</b>		
	<b>Estimate</b>	<b>95% Confidence interval</b>
Sensitivity	61.5%	52.1%–70.2%
Specificity	61.4%	56.4%–66.1%
Positive predictive value	31.6%	25.7%–38.1%
Negative predictive value	84.6%	79.9%–88.5%
Positive likelihood ratio	1.6	1.3–1.9

**(b) Diagnostic value of proximal apparent leukonychia in all fingers**

	<b>Estimate</b>	<b>95% Confidence interval</b>
Sensitivity	28.2%	20.5%–37.4%
Specificity	87.9%	84.2%–90.8%
Positive predictive value	40.2%	29.7%–51.7%
Negative predictive value	80.9%	76.8%–84.4%
Positive likelihood ratio	2.4	1.9–2.9

Patients with past (transplanted) liver cirrhosis were considered as not having liver cirrhosis. A total of 521 patients were included.

higher when PAL affected all fingernails. Accordingly, the negative predictive value of PAL in this context of liver cirrhosis prevalence is high. The positive likelihood ratio of PAL for the diagnosis of liver cirrhosis was modest, but statistically significant (Table 3).

**3.4. Prognostic value of PAL in patients with liver disease**

According to the official mortality registry, a total of 99 patients from the 521 who were present at baseline have died after 7 years

**Table 4**

**Factors associated with all-cause mortality after 7 years of follow-up. Multivariate analysis (logistic regression).**

<b>Baseline characteristic</b>	<b>Odds ratio</b>	<b>95% Confidence interval</b>	<b>P-value</b>
Age (yrs)	1.062	1.039–1.087	<0.001
Sex (male)	1.917	1.047–3.511	0.035
Categories of liver cirrhosis			
Never	1 (reference)		
Current	5.813	3.366–10.040	<0.001
Transplanted	1.901	0.934–3.870	0.077
Proximal apparent leukonychia	0.562	0.523–1.423	0.562

All variables entered the equation. A total of 521 patients were included.

of follow-up (cumulative incidence or risk of death, 19.0%; 95% CI, 15.7%–22.6%). Overall mortality tended to be higher among patients with PAL (50/228, 21.9%) at baseline than among patients without PAL at baseline (49/293, 16.7%;  $P=0.133$ ). The presence of PAL at baseline was not significantly associated with overall mortality at 7 years after adjusting for age, sex, and the presence of liver cirrhosis. In this model, both age and liver cirrhosis were significantly and independently associated with all-cause 7-year mortality (Table 4).

**3.5. Capillaroscopic findings**

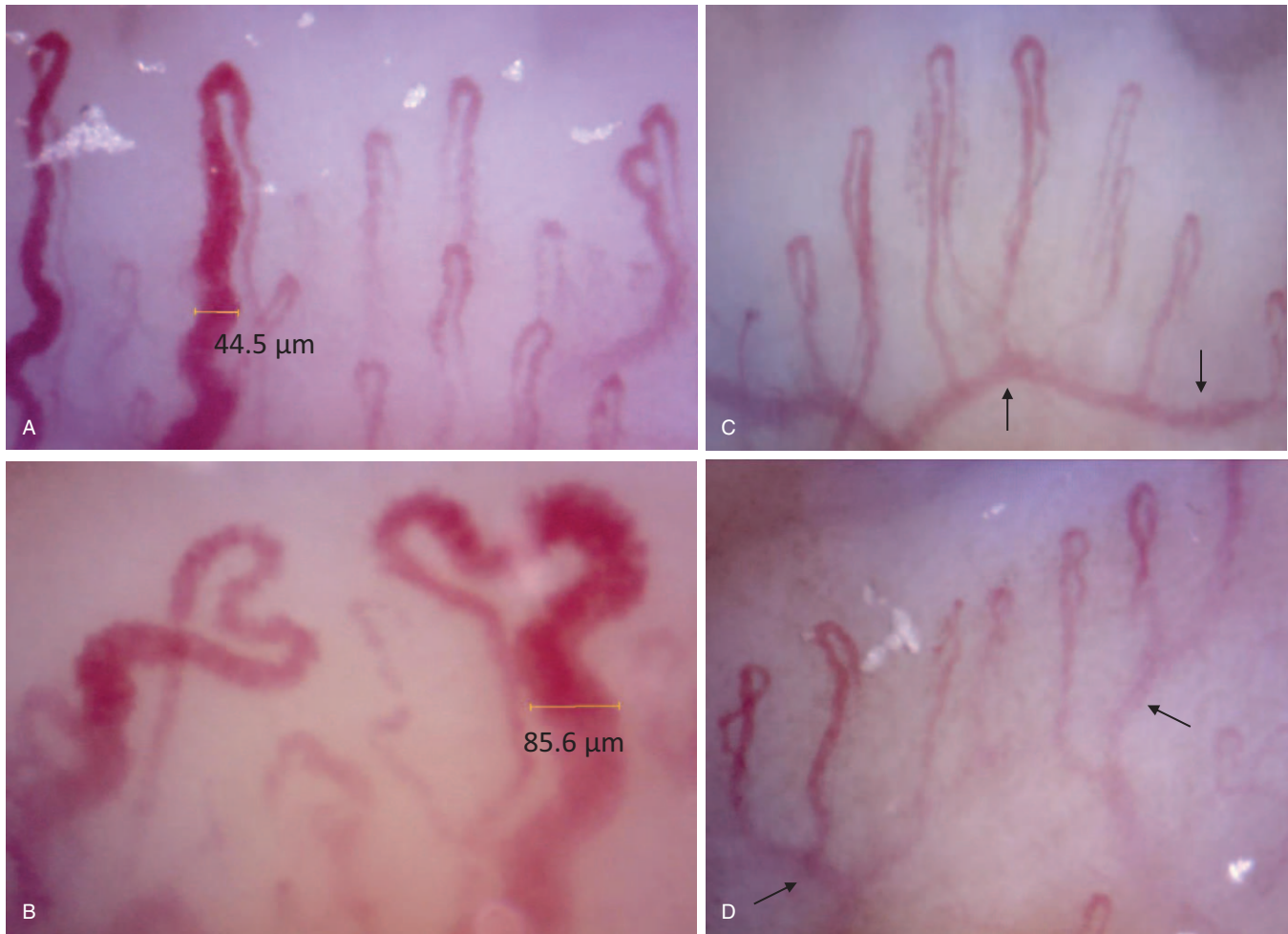
The most common abnormal findings in nail fold capillaroscopy, stratified by study group, are shown in Table 5. No alteration was significantly associated with the presence of PAL. Venous dilatations (sometimes as megacapillaries) and prominent (visible) venous plexus (Fig. 3) were associated with each other

**Table 5**

**Capillaroscopic abnormalities stratified by study group.**

<b>Capillaroscopic abnormality</b>	<b>No liver disease</b>		<b>Noncirrhotic liver disease</b>		<b>Liver cirrhosis</b>		<b>P-value</b>
	<b>Without PAL (n=9)</b>	<b>Without PAL (n=20)</b>	<b>With PAL (n=16)</b>	<b>Without PAL (n=12)</b>	<b>With PAL (n=23)</b>		
Density							
Capillary loss	1 (11.1)	3 (15.0)	3 (18.8)	2 (16.7)	7 (30.4)		0.659
Avascular areas	0 (0.0)	0 (0.0)	1 (6.3)	1 (8.3)	0 (0.0)		0.415
Length							
Very long capillaries	0 (0.0)	3 (15.0)	1 (6.3)	1 (8.3)	1 (4.3)		0.604
Diameter							
Dilatations	6 (66.7)	13 (65.0)	11 (68.8)	10 (83.3)	17 (73.9)		0.834
Venous dilatations	0 (0.0)	7 (35.0)	7 (43.8)	7 (58.3)	12 (52.2)		0.055
Megacapillaries	1 (11.1)	1 (5.0)	1 (6.3)	2 (16.7)	4 (17.4)		0.662
Morphology							
Tortuosities	5 (55.6)	9 (45.0)	5 (31.3)	5 (41.7)	17 (73.9)		0.088
Ramifications	3 (33.3)	13 (65.0)	11 (68.8)	5 (41.7)	9 (39.1)		0.170
Pattern							
Tortuous	2 (22.2)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)		0.117
Ramified	0 (0.0)	5 (25.0)	2 (12.5)	1 (8.3)	1 (4.3)		0.188
Neoangiogenesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.0)		0.102
Shoal of fish	1 (11.1)	1 (5.0)	2 (12.5)	0 (0.0)	0 (0.0)		0.349
Flow							
Intermittent	2 (22.2)	4 (20.0)	6 (37.5)	1 (8.3)	0 (0.0)		0.029
Granular	2 (22.2)	2 (10.0)	6 (37.5)	1 (8.3)	0 (0.0)		0.015
Venous plexus							
Prominent (visible)	0 (0.0)	9 (45.0)	4 (25.0)	8 (66.7)	12 (52.2)		0.014
Pericapillary area							
Edema	0 (0.0)	0 (0.0)	2 (12.5)	1 (8.3)	1 (4.3)		0.445
Hemorrhage	3 (33.3)	2 (10.0)	5 (31.3)	3 (25.0)	8 (34.8)		0.400

Figures are absolute numbers and percentages, within parentheses. PAL=proximal apparent leukonychia. P-values were obtained with the  $\chi^2$  test after comparison among the 5 groups.



**Figure 3.** Representative capillaroscopic findings in patients with liver disease. (A and B) Vascular dilatation ( $>25\ \mu\text{m}$ ) of the venous loop, sometimes as megacapillaries ( $>50\ \mu\text{m}$ ). (C and D) Prominent (visible) venous plexus (arrows) with *chandelier* pattern.

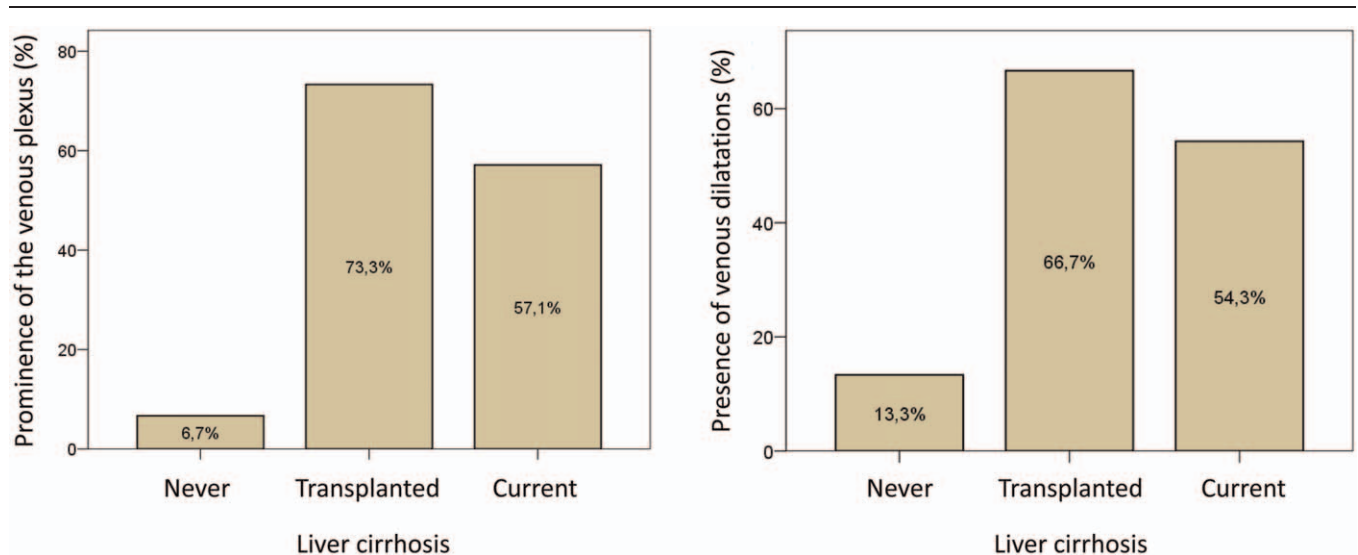
as well as with liver cirrhosis. Venous dilatations were not observed among individuals without liver disease and were observed in 33 of 71 (46.0%) patients with liver disease ( $P=0.008$ ). The finding was present in 19 of 35 (54.3%) patients with liver cirrhosis and in 14 of 36 (38.9%) patients with noncirrhotic liver disease ( $P=0.193$ ). However, significant differences were observed when patients with non-cirrhotic liver disease were further stratified by the antecedent of liver transplantation (Fig. 4). Venous dilatations were more common in patients with present liver cirrhosis and in patients who underwent transplantation for liver cirrhosis than in patients who never had cirrhotic liver disease (Fig. 4). Prominent (visible) venous plexus was present in 33 patients (41.2%). Of these, 25 (75.8%) also presented venous dilatations. Prominent (visible) venous plexus was similarly associated with a history of liver cirrhosis (Fig. 4). Conversely, data revealing a slow blood flow (intermittent and granular flow) tended to be less common in patients with liver cirrhosis (Table 5).

#### 4. Discussion

The results of the present study show that (a) the prevalence of PAL is high ( $>40\%$ ) among patients attending a liver disease

clinic; (b) interobserver agreement for the finding of PAL is good; (c) PAL is more common in patients with liver disease than without it; (d) the presence of PAL is strongly associated with liver cirrhosis and, consequently, PAL is associated with portal hypertension and markers of hepatocellular dysfunction; (e) PAL is associated with chronic alcohol abuse, independently of the presence of liver cirrhosis; (f) PAL has a sizeable value for the diagnosis of cirrhosis, particularly when all fingers are affected; (g) PAL is not an independent marker of long-term mortality among patients with liver disease; and (h) no specific vascular findings are observed on capillaroscopy of the nail fold in patients with PAL.

Our results support the notion that a general term of “*proximal apparent leukonychia*” is preferable to classic eponymous titles such as Terry nails and Lindsay nails. Horan et al added the designation “*Neapolitan nails*” (based on band similarity to the homonymous ice cream) in a series of institutionalized elderly people.<sup>[8]</sup> This additional eponymous title could only add further confusion given these individuals actually had Terry nails, Lindsay nails, and intermediate forms.<sup>[9]</sup> The term PAL would include all eponymous titles as well as intermediate types, and is more convenient for several reasons. First, both Terry nails and Lindsay nails are both forms of apparent leukonychia affecting



**Figure 4.** Prevalence of venous dilatations and prominence (visibility) of the venous plexus on nail fold capillaroscopy. The study population is stratified according to the presence of liver cirrhosis: never ( $n=30$ ), past (patients with liver cirrhosis who underwent liver transplantation,  $n=15$ ), and present ( $n=35$ ). There are significant differences among groups for both abnormalities ( $P<0.001$ ).

the basal (proximal) part of the nail bed, with a distal pink-to-brown transverse band.<sup>[2,7]</sup> Second, the relative extension of the bands (the proximal white and the distal pink-to-brown), which is used for the definition of either Terry or Lindsay nails, is somewhat arbitrary.<sup>[8,17]</sup> Third, there was a good interobserver agreement for the diagnosis of PAL in the present series, however, the agreement on the differentiation between Terry nails and Lindsay nails was poor (data not shown). Fourth, both types of PAL (Terry nails and Lindsay nails) may be present in the same individual. Finally, both types of PAL are associated with similar clinical conditions, at least in patients attending a liver clinic. Certainly, the PAL forms with the widest pink-to-brown distal band (the so-called half-and-half nails) are more common in other settings, such as chronic renal disease.<sup>[7]</sup> As Raffle (1984) had proposed, eponymous titles for these conditions would be better dispensed with.<sup>[19]</sup> In general, eponyms bring colour, history, and culture to medicine;<sup>[20]</sup> however, eponyms should be probably abandoned because they lack accuracy, lead to confusion, and hamper scientific discussion.<sup>[21]</sup> We, therefore, propose the generic name of “*proximal apparent leukonychia*,” which could further prevent unnecessary confusion in the literature.

The association between PAL and liver cirrhosis is consistent with previous studies.<sup>[2,4–6]</sup> Terry initial description included only patients with liver cirrhosis.<sup>[2]</sup> Other series included general inpatients<sup>[4,5]</sup> and outpatients<sup>[6]</sup> with a small number of patients with cirrhosis. Furthermore, no studies focused on patients attending a liver disease clinic, which is likely a more appropriate setting for the use of PAL as a clinical marker. The prevalence of liver cirrhosis is high in liver clinics and subsequent pre-test probability may modify the diagnostic accuracy of a given sign.<sup>[13]</sup> In liver clinics, a common question is “*does this patient with liver disease have liver cirrhosis?*,” and PAL, as a test, could aid in the diagnosis.<sup>[22]</sup> According to our experience in this high-prevalence context, PAL is specific for that purpose, particularly when it affects all fingers (ie, the proportion of patients without cirrhosis who test negative is high). The negative predictive value

is also high (ie, there is a significant probability that subjects with a negative test truly do not have cirrhosis). However, the sensitivity of PAL is poorer (ie, the proportion of patients with cirrhosis who test positive is low); therefore, the positive likelihood ratio (ie, the change in the odds of having cirrhosis in patients with PAL) is modest (1.6; 95% CI 1.3–1.92), although it is higher when all fingers are affected (positive likelihood ratio, 2.4; 95% CI 1.9–2.9).

Chronic alcohol abuse was found to be associated with PAL independent of the presence of cirrhosis in our series. This association is mentioned in general reviews of systemic manifestations of alcohol abuse<sup>[23]</sup> and in anecdotal reports;<sup>[24]</sup> to the best of our knowledge, however, it has never been systematically studied in the literature. Of note, the vast majority (>90%) of cirrhosis cases in the classic Terry nails series were of alcoholic cause.<sup>[2]</sup> Alcohol consumption was not investigated in other series of general inpatients, which included a small number of patients with liver cirrhosis.<sup>[4]</sup> Contrary to previous reports,<sup>[4,8]</sup> PAL was not significantly associated with age in our series.

The mechanisms responsible for PAL and its underlying pathological findings are largely unknown. As a form of apparent leukonychia, alterations should not be present in the nail plate but in the nail bed.<sup>[1]</sup> A change in nail bed vascularity, secondary to overgrowth of connective tissue in the nail matrix, is thought to be responsible for PAL.<sup>[10]</sup> It should be noted that the distal, pink-to-brown onychodermal band is not simply a healthy section of the nail, but a distinct part of the nail abnormality.<sup>[21,25]</sup> Biopsies of the distal band have been reported in only 3 cases, none of them with liver cirrhosis.<sup>[4]</sup> Hematoxylin-eosin preparations have shown underlying changes in vascularity, such as telangiectasias in the upper dermis in all 3 patients; the Fontana technique and Gomori stain did not show abnormal melanin or iron deposition in the distal band area, and the toluidine-blue stain showed normal progression of decreasing nuclear fragments distally in the nail plate.<sup>[4]</sup> In the original Terry series, this form of PAL was found to be associated with the presence of spider *naevi*, and the

author suggested that white nails could be additional endocrine stigmata, comparable with spiders, palmar erythema, cutaneous striae, and gynecomastia.<sup>[2]</sup> To investigate the potential microvascular findings associated with PAL, we performed capillaroscopy of the nail fold on a subset of patients with and without PAL, and with and without liver cirrhosis of alcoholic cause. Capillaroscopy of the nail fold is a useful, safe technique to investigate alterations in the microcirculation in vivo.<sup>[18,26]</sup> Vascularization of the nail fold is closely linked to that of the nail bed.<sup>[27]</sup> Very few capillaroscopy studies have been performed in patients with liver disease, and most were focused on patients with primary biliary cholangitis,<sup>[28,29]</sup> an entity associated with Raynaud phenomenon, the main indication for capillaroscopy in clinical practice.<sup>[26]</sup> Red blood cell acceleration and functional capillary density on capillaroscopy in patients with liver cirrhosis were lower than that of controls in a study.<sup>[30]</sup> We found significant alterations in patients with liver cirrhosis, particularly dilatations of the venous loop and prominence of the venous plexus. These alterations have not received much attention in the literature, although they could be similar to those described by Pirovino et al at the beginnings of capillaroscopy.<sup>[31]</sup> In patients with liver cirrhosis, there were also indirect signs of faster blood flow as revealed by a lower frequency of both intermittent and granular flow. Taken together, these abnormalities are consistent with the well-known state of systemic vasodilatation, low arterial resistance, and high cardiac output in patients with liver cirrhosis.<sup>[32]</sup> However, these abnormalities were still present after transplantation for liver cirrhosis. Further studies are needed to ascertain the mechanisms and clinical significance of these venous alterations. Of note, neither these venous alterations nor other specific capillaroscopic abnormalities were linked to the presence of PAL.

The study has limitations. The study was focused on patients attending a liver clinic and the results can only be extrapolated to similar settings. Nearly all participants were white; thus, the conclusions might not be relevant to patients of other skin colors. The study was restricted to fingernails; toenails were not investigated. To minimize classification bias, 2 independent observers analyzed all nail pictures in the study, which further allowed for estimation of concordance. The study was based on nail photographs, which precluded evaluation of additional signs depending on touch or pressure, eg, to evaluate the effect of nail congestion. Finally, as is common practice in clinical hepatology, liver cirrhosis was not biopsy-proven but based on clinical, biological, and image findings in most cases.

Despite the enormous development of diagnostic tools, the physical examination still plays a pivotal role in clinical medicine, as textbooks of evidence-based physical diagnosis point out.<sup>[13]</sup> *All human beings carry the record of their personality and recent past health in a flat sheet of keratin of the nail plate.*<sup>[27]</sup> A wealth of information can be gained from shaking hands and examining the hands at the same time<sup>[11]</sup> because nail changes can serve as an important clinical sign for underlying systemic disease.<sup>[10,12,33]</sup> The present study adds quantitative evidence to an old physical sign that indicates the presence of cirrhosis or a history of chronic alcohol abuse in patients with liver disease. Liver cirrhosis is associated with megacapillaries and venous dilatations on capillaroscopy, but these are not associated with PAL. Further studies are needed to investigate the underlying pathological features in the nail bed and the pathogenetic mechanisms that are responsible for this intriguing sign.

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