Master's Thesis

The analysis of changes over time in acral nevi, considering the Automatic Evaluation Score (Fotofinder)

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Dr. med. Iryna Zalevska

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Declaration of Authorship:

I hereby declare that the submitted thesis is my own work. All direct and indirect sources are acknowledged in the references. This Master's thesis has not been used in the same or similar version to obtain any academic degree.

Dr. Iryna Zalevska Vienna 21.08.2024

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Zusammenfassung

Akrale Nävi, die sich an den Handflächen und Fußsohlen befinden, sind im Vergleich zu Nävi an anderen Körperstellen relativ selten. Diese Hautareale sind einzigartig, da sie häufig mechanischer Belastung und Reibung ausgesetzt sind. Akrale Nävi weisen spezifische dermatoskopische Muster auf, deren Untersuchung für die Differenzialdiagnose zum akralen lentiginösen Melanom entscheidend ist. In dieser Studie wurden 30 Fälle von akralen Nävi im Zeitraum von 2014 bis 2023 mit dem Fotofinder-Gerät und dem Automatic Evaluation Score (AES) analysiert. Zur Bewertung der Ergebnisse wurde eine Analyse der Differenzen durchgeführt, die zu zwei wichtigen Schlussfolgerungen führte: Es wurden geringe Unterschiede zwischen den Messungen beobachtet, obwohl ein linearer Trend festgestellt wurde. Außerdem gab es eine minimale Verbesserung des Zustands der Nävi auf der Grundlage des AES-Indikators.

Abstract

Acral nevi, located on the palms and soles, are relatively rare compared to nevi on other parts of the body. These areas of the skin are unique in that they are frequently subjected to mechanical stress and friction. Acral nevi have specific dermoscopic patterns, the study of which is crucial for the differential diagnosis with acral lentiginous melanoma. In this study, 30 cases of acral nevi were analyzed over the period from 2014 to 2023 using the Fotofinder device and the Automatic Evaluation Score (AES). Differential analysis was applied to assess the results, leading to two key conclusions: minor differences were observed between measurements, although a linear trend was noted, and there was also minimal improvement in the condition of the nevi based on the AES indicator.

1. Introduction

Palmoplantar nevi, or melanocytic lesions that appear on the palms of the hands and soles of the feet, represent a unique challenge in dermatology due to their rare occurrence and the distinctive characteristics of the skin in these areas. These regions are subject to frequent mechanical stress and friction, leading to nevi that often differ in appearance from those on other parts of the body. Typically, these nevi manifest as flat, brown to black spots, varying in shape, color, and size, with borders that are usually not well-defined. Despite their benign nature, palmoplantar nevi are associated with a slightly higher risk of progression to melanoma, particularly due to the difficulty in monitoring changes over time in these less-observed areas.

Dermoscopy plays a crucial role in the evaluation of these nevi, serving as an important tool that bridges clinical examination and histopathological analysis. By providing a detailed visualization of the skin's surface, dermoscopy enhances the diagnostic accuracy of a wide range of dermatoses, especially in the assessment of pigmented lesions. The specific patterns observed in acral nevi, such as the parallel furrow pattern, lattice-like pattern, and fibrillar pattern, are key to distinguishing benign from potentially malignant lesions. Additionally, recognizing atypical patterns, such as the parallel ridge pattern, which is highly suspicious for melanoma, is essential for early detection of acral lentiginous melanoma, a particularly aggressive form of melanoma.

Given the challenges in diagnosing palmoplantar nevi and the potential risk of malignant transformation, this study aims to analyze the dermoscopic changes in acral nevi over time using advanced imaging techniques like the FotoFinder system. This system offers high-resolution imaging coupled with automated analysis, providing a comprehensive approach to tracking nevi and assessing their risk of malignancy. By systematically documenting and analyzing changes in nevi at multiple time points, this study seeks to improve the understanding of acral nevi behavior over time and enhance the early detection of melanoma in these high-risk areas.

The conducted study involves the assessment of a sample of patients with acral nevi using the FotoFinder system and its Automatic Evaluation Score, as well as the analysis of changes at three different time points. It is hypothesized that a detailed analysis of these changes will reveal a dynamic pattern, indicating either stability or progression of changes in acral nevi, which, in turn, will provide a better understanding of the changes in acrale nevi over time.

2. Palmoplantar nevi

2.1. Palmoplantar nevi

Nevus palmaris (palmar nevus) and nevus plantaris (plantar nevus) refer to pigmented skin lesions that appear on the palms of the hands (palmar) and the soles of the feet (plantar). These areas are unusual locations for nevi (moles), which are typically found on sun-exposed parts of the body. Nevi occur in 3 to 30% cases **(1, 2).** Due to the unique architecture, palmar and plantar melanocytic nevi exhibit specific morphology which is reflected in the dermoscopic findings.

Nevi on the palms and soles are relatively rare compared to other body areas. These skin regions are unique because they are subject to frequent mechanical stress and friction. These nevi often appear as flat, brown to black spots. They can vary in shape, color, and size and are usually symmetric with not well-defined borders.

2.2. Dermoscopic features

Dermoscopy is an in vivo assessment method that serves as a bridge between clinical and histological examination. The diagnostic accuracy of a wide range of dermatoses is significantly enhanced through the use of dermoscopy, which allows for a detailed inspection of the entire skin surface. This method is particularly crucial in the evaluation of both pigmented and non-pigmented skin tumors **(3, 4)**.

In the literature, various dermoscopic patterns of nevi are distinguished **(5, 6, 7).** In the following sections, I will describe the patterns of acral nevi that were most frequently observed during this study.

In this study, several distinct dermoscopic patterns commonly observed in benign acral nevi were identified. The most frequently encountered pattern was the parallel furrow pattern, characterized by pigmentation aligned with the natural furrows between the skin ridges, reflecting the underlying topography.

A variant of this, the lattice-like pattern, displayed a grid-like arrangement of pigmentation with intersecting pigmented lines forming a net-like structure.

Additionally, the fibrillar (filamentous) pattern, often observed in areas subjected to mechanical friction, was marked by fine, parallel, linear streaks of pigment radiating outward from a central point.

The globular pattern, defined by round, evenly distributed globules, was another key pattern observed, particularly in congenital or early-onset nevi, and was typically associated with benign melanocytic activity.

The homogeneous pattern, frequently observed in acral nevi, was characterized by uniform pigmentation across the lesion without visible internal structures, presenting as a solid area of color varying from light brown to dark brown or black depending on melanocyte density.

These patterns are crucial in the dermoscopic assessment and diagnosis of acral nevi, providing important insights into their benign nature.

In the present study, the reticular pattern and the peas-in-a-pod pattern in acral nevi were also observed, which are significant in the dermoscopic evaluation of these lesions.

The reticular pattern is characterized by a network of interconnected pigmented lines, forming a mesh-like structure that resembles a net. This pattern typically reflects a more superficial distribution of melanocytes and is often seen in benign acral nevi.

Additionally, the peas-in-a-pod pattern, a less commonly reported pattern, is distinguished by the presence of multiple small, round, evenly spaced pigmented areas that resemble peas lined up within the furrows of the skin. This pattern is indicative of a clustered arrangement of melanocytes, and its recognition can be crucial in differentiating benign acral nevi from other lesions.

Both patterns contribute to the spectrum of dermoscopic features that are essential for accurately diagnosing acral nevi and understanding their benign nature.

2.3. Atypical dermatoscopic patterns

For further accurate diagnosis, it is important to highlight specific pathological patterns of acral nevi.

In the analysis of acral melanocytic nevi, several atypical dermoscopic patterns were identified, each carrying significant implications for the diagnosis of melanoma. The parallel ridge pattern is particularly noteworthy, as it deviates from the benign parallel furrow pattern by showing pigmentation that follows the ridges (raised lines) of the skin, rather than the furrows. This pattern is highly suspicious for melanoma, especially acral lentiginous melanoma, and is rarely seen in benign nevi.

Another concerning feature is irregular diffuse pigmentation, where the pigmentation is unevenly distributed across the lesion, lacking a clear, consistent pattern. Such irregular, blotchy, or asymmetrical pigmentation warrants further investigation due to its potential indication of melanoma **(8)**.

The multicomponent pattern further raises concern, as it presents multiple distinct dermoscopic structures within a single lesion, such as a mix of parallel ridge patterns, irregular pigmentation, and atypical dots or globules. The presence of more than one pattern within a nevus is often considered a sign of atypia or malignancy.

While most nevi are benign, those located on the palms and soles, referred to as palmar and plantar nevi, are associated with a slightly higher risk of progressing to melanoma, a severe form of skin cancer. This heightened risk is partly due to the challenges in detecting changes in these nevi, as these areas are less frequently observed compared to other parts of the body. Moreover, the unique anatomical and functional characteristics of the skin on the palms and soles—such as its increased thickness and exposure to mechanical stress—can further hinder the early detection and diagnosis of malignant changes. Notably, the presence of a parallel ridge pattern in palmar and plantar nevi has been identified as particularly indicative of melanoma, and irregular diffuse pigmentation in these areas should also raise concern, necessitating closer examination and potential biopsy. **(9)**

Therefore, differential diagnosis is crucial in the identification and management of acral nevi. Below, we will discuss the main differential diagnoses that must be considered in clinical practice.

2.3. Differential diagnosis of acral nevi

Acral nevi, melanocytic lesions located on the palms, soles, and beneath the nails, present distinct diagnostic challenges due to the unique characteristics of acral skin and the presence of various other pigmented lesions in these regions.

Differentiating benign acral nevi from potentially malignant conditions, such as acral lentiginous melanoma (ALM), is crucial for effective clinical management. ALM is a rare form of melanoma which occurs on acral surfaces and represents approximately 4% of melanoma cases in Caucasian populations, with higher prevalence in other ethnic groups. **(10)**

Dermoscopically, ALM is characterized by the parallel ridge pattern, where pigmentation aligns with the ridges of the skin, as well as irregular borders and variegated coloration, including shades of brown, black, blue, and red, indicative of heterogeneous melanin distribution. These features distinguish ALM from benign acral nevi, which typically exhibit a parallel furrow pattern. **(11)**

Other conditions that must be differentiated from acral nevi include subungual hematoma **(12)**, which is a collection of blood under the nail usually resulting from trauma, and glomus tumors **(13)**, which are rare, benign vascular tumors often presenting with severe pain and a bluish or reddish hue under the nail. Additionally, pigmented warts **(14)**, caused by the human papillomavirus (HPV), display a rough, verrucous surface and distinct dermoscopic features such as a mosaic pattern, which differentiates them from the smooth, symmetrical appearance of acral nevi.

Pigment deposition from tattoos or foreign bodies can also mimic pigmented lesions, but the absence of structured dermatoscopic patterns and a history of trauma or tattooing are distinguishing factors **(15)**.

Tinea nigra **(16)**, a superficial fungal infection producing pigmented macules on acral surfaces, can be differentiated by its uniform pigmentation and the absence of specific dermatoscopic patterns.

Lastly, intraepidermal ephelides (freckles), which are small, flat, pigmented spots **(17)** resulting from sun exposure, are generally lighter, smaller, and more symmetrical than nevi, and are typically found in sun-exposed areas, unlike acral nevi.

The differential diagnosis of acral nevi is vital due to the risk of melanoma, particularly ALM, which, despite its distinctive clinical presentation, can be challenging to distinguish from benign lesions.

Dermoscopy is an essential tool in this diagnostic process, providing detailed insights into the patterns and features of various pigmented lesions. In cases where clinical or dermoscopic features are ambiguous, biopsy or referral to a specialist is necessary to ensure accurate diagnosis and appropriate management.

2.4. Dermoscopy of palmoplantar nevi (with FotoFinder)

The FotoFinder method **(18, 19)** represents an advanced approach in dermatology, particularly in the imaging and analysis of skin lesions and nevi. As a leader in digital dermoscopy systems, FotoFinder provides a comprehensive suite of tools designed to improve the accuracy and efficiency of mole evaluation and monitoring.

The system leverages high-resolution dermoscopic imaging to offer clinicians detailed visualizations of the skin's surface, which is essential for the precise examination of nevi and other cutaneous lesions, offering diagnostic advantages over traditional visual inspection methods.

A key feature of the FotoFinder method is its automated mole mapping technology, enabling systematic documentation and longitudinal tracking of moles across the entire body, particularly beneficial for patients with numerous nevi or those at higher risk for melanoma, facilitating the early detection of suspicious changes.

The integration of artificial intelligence within the FotoFinder system allows for the automated analysis of dermoscopic images, with AI-based algorithms assessing moles for potential malignancy and providing objective risk stratification that supports clinical decision-making. This automated scoring system, which will be described in detail below, is designed to assist healthcare professionals in evaluating and diagnosing skin conditions more efficiently. Whether it serves as a valuable adjunct to the clinician's expertise, particularly in the early identification of malignant transformations, will be assessed in the present study.

Furthermore, FotoFinder enhances its diagnostic utility by enabling comparative analysis between current and previous images, allowing clinicians to detect subtle changes in nevi characteristics, such as alterations in size, shape, or pigmentation, which may indicate the early stages of melanoma or other skin disorders.

The method also ensures meticulous documentation of dermatological findings, with detailed records that support continuous patient care. The system generates comprehensive reports that can be seamlessly integrated into patient management protocols, thereby enhancing continuity of care and facilitating informed clinical decision-making.

FotoFinder is widely utilized in clinical practice for the early detection and management of skin cancers, particularly melanoma, combining high-resolution imaging, AI-driven diagnostics, and extensive documentation capabilities, making it an essential tool in dermatology. This approach contributes to improved patient outcomes through enhanced diagnostic accuracy and timely intervention.

3. Materials, Methods & Hypothesis

3.1. Materials

Changes in melanocytic nevi on the palms and soles have been documented, yet the relationship between these changes over time due to the rare localization remains poorly understood. Thus, the aim of this study was to conduct a review to identify dermatoscopic changes occurring in acral nevi over time.

As part of the assessment, the automated scoring system (the „Automatic Evaluation Scale“, hereafter: AES) provided by the FotoFinder software was employed. The AI-based system evaluates parameters such as the lesion's area in mm², size in mm, diameter in mm, aspect ratio, structure, and the presence of a pigmented network. The software then calculates an automatic score based on these parameters, which can be assessed using the AES. A score of 0.0-0.2 is considered „normal“ and is highlighted in yellow, 0.21-0.49 is classified as „borderline“ and marked in gray, while 0.5-1.0 is deemed „pathological“ and is marked in red. This automated scoring system aids healthcare professionals by classifying lesions into different categories based on calculated values, thereby enhancing the efficiency of evaluating and diagnosing skin conditions.

The study conducted comparative analyses of the AES of several moles. Typically, the AES used for comparison was that of moles observed dynamically two or more times. For further consideration, only patients under observation at the University Clinic of Graz, Dermatology Department, who had acral nevi and underwent dermatoscopic examination using the FotoFinder device were included. Patients were selected based on the presence of relevant acral nevi and a documented history of follow-up observations. An archive of acral nevi was used, and it was intentionally not divided into palmar and plantar nevi in order to avoid reducing the representativeness of the sample.

A sample from the FotoFinder archive covering the period from 2014 to 2023 was used. The data was extracted and analyzed in April 2023. All patients were assigned digital identifiers instead of names to ensure confidentiality and anonymity of the data.

Initially, a sample of 36 patients with 45 acral nevi was presented. However, since not all nevi met the specified research parameters, the sample was reduced to 30 nevi that fit the criteria.

The data from the AES for acral nevi were used for analysis, with three time points being analyzed and designated in this study as A, B, and C. Here, A corresponds to the first recorded observation, B to the intermediate observation, and C to the final observation of the nevus.

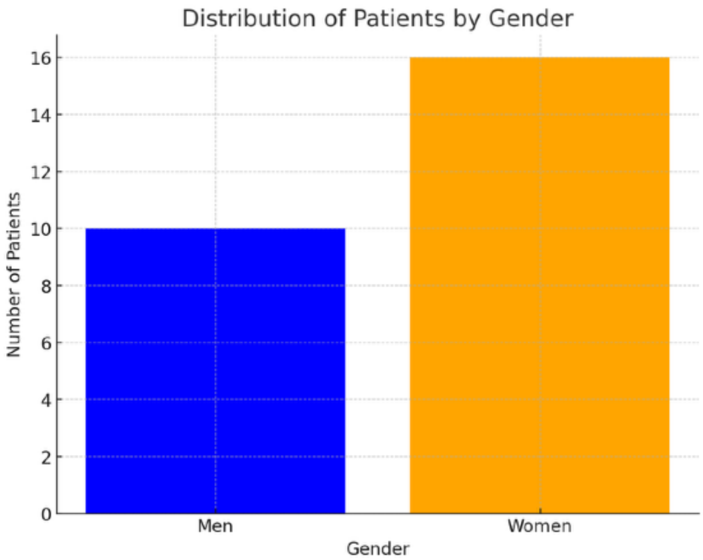
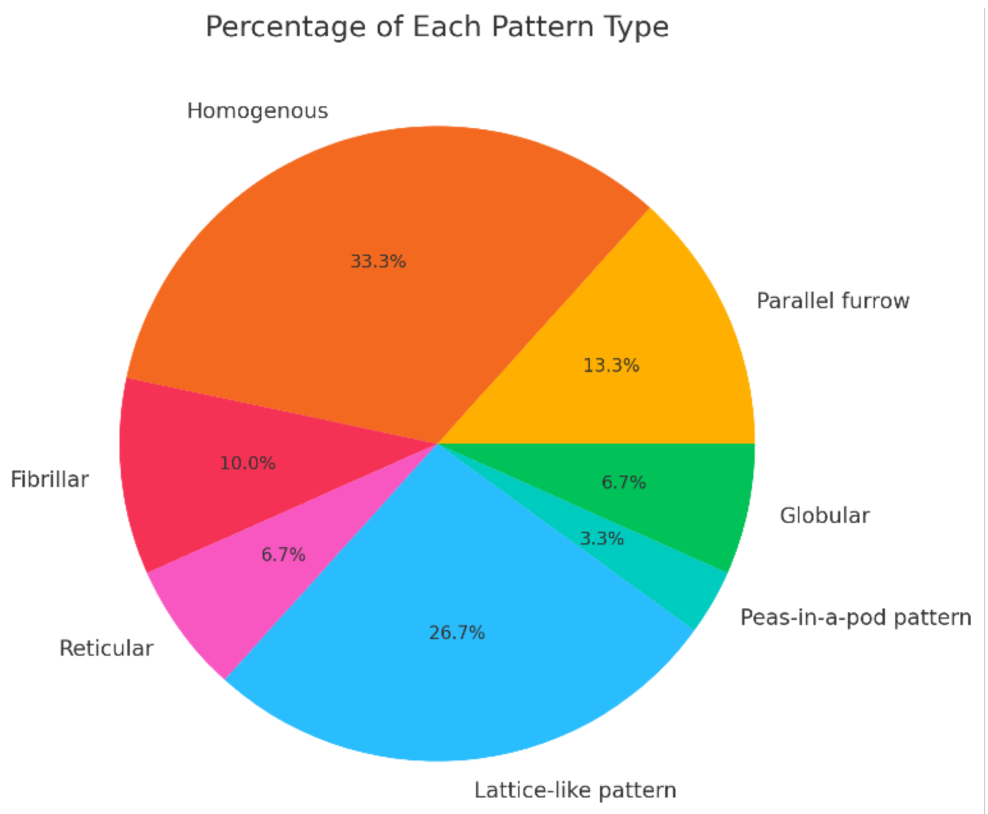


Table 1: Distribution of Patients by Gender

The histogram (Table 1) illustrates the gender distribution of 26 patients with identified moles. Among these patients, 16 are women, representing 61,5% of the total, and 10 are men, accounting for the remaining 38,5%. The chart visually emphasizes the proportion of female to male patients, highlighting that women constitute a larger percentage of the patient group in this study.

The study utilized data from 30 moles, each exhibiting different dermoscopic patterns. The patterns were analyzed by the researcher using a pattern analysis method based on the database. The frequency analysis of the patterns is presented in Table 2.



The patients are in the age range of 27 to 78 years old. The dataset is predominantly composed of older adults, with no representation from the younger age groups (under 25 years). This age distribution suggests that the findings are primarily applicable to individuals 35 years and older, which may reflect the age-related nature of the conditions being studied.

Age (in years)	0-15	15—25	25–35	35
Number of patients	0	0	2	24

Table 3: Age Distribution of the Study Sample

3.2. Methods: Analysis of Differences

The goal is to determine whether the automatic score readings from the FotoFinder (AES) have clinical significance, as the linear relationship in pathological moles over time is being investigated by clinicians. A linear development was intended to be demonstrated using AES, which is why an analysis of differences was selected for the study.

The analysis of differences is a method used to examine changes in a measured value over different points in time. The differences in the measured values between two consecutive points in time are calculated to determine whether the value increases, decreases or remains constant. This allows a detailed examination of the patterns of change and helps to identify trends or irregular patterns over time.

The analysis of the differences is particularly suitable for the question at hand, as changes in a specific measured value, the AES, are to be examined over three points in time. This analysis makes it possible to precisely quantify whether the condition of the moles improves, deteriorates or remains unchanged, and whether there is possibly an irregular pattern of change.

The main components of an analysis of differences, which were used in the present study, include: the determination of the differences between two measured values, and the determination of various statistical measures, such as mean, median, maximum, minimum and standard deviation.

In this work, the initial (first) value and the second value were each compared with the final (third) value (first period/set: $\Delta 1 = C - A$, second period/set: $\Delta 2 = C - B$). The mean value of the individual sets was then determined from the sets of differences calculated in this way in order to identify the general tendency in both groups. The calculation of the standard deviation serves to measure the variability of the changes. Determining the median has the additional advantage of being less susceptible to outliers or extreme values in the data set than the mean. If the differences contain strong outliers, the median can provide a more accurate indication of the trend within a data set.

While the strengths of the method lie in the simplicity of its application and in the quantitative determination of trends, it also has significant weaknesses that must be taken into account in the present study. Firstly, the method is sensitive to outliers. Large differences in the data can distort the results. Secondly, this method cannot be used to make any statements about causality. Although the method identifies changes, it does not provide any information about their cause. These points are taken up again in the discussion of the results.

A third key weakness of the method is that it implicitly assumes a linear pattern of change, which may not always be the case. This point has already been taken into account in the selection of methods.

In addition to an analysis of the differences, a manual examination of irregular patterns (e.g. improvement followed by deterioration) was therefore carried out. For this purpose, the individual cases were sorted according to ascending, descending, constant or inconsistent trends.

This triangulation method makes it possible to correlate the general dynamics of the changes with individual changes.

All analysis were carried out using the spreadsheet program “Numbers”.

3.3. Research question & Hypothesis

During the period from 2014 to 2023, changes in the condition of acral moles were observed and assessed using the „Automatic Evaluation Scale“ (AES) of the FotoFinder device. It is hypothesized that, since moles tend to change over time, acquiring pathological features, an analysis of objective indicators of these changes will allow us to establish patterns in their development.

Thus, this study aims to evaluate the changes from value A (initial value) to value C (final value), as well as the relationship between value B (intermediate value) and the final value C. It is expected to find a linear development of AES between the changes in A and C, as well as between the values of B and C, which would suggest the presence of linear changes in the overall condition of moles over time.

4. Results & Discussion

4.1. Results

Calculation of the differences: The calculated differences for each birthmark can be seen in Figures 1 & 2 in the Appendix.

Quantification of the changes: The mean values of the differences indicate a general trend in both periods analyzed. In period 1 ($\Delta 1 = C - A$) the mean value is -0.0332. In period 2 ($\Delta 2 = C - B$) the mean value is -0.0258. A negative trend can therefore be observed in both periods. The negative sign of the mean value of the differences means an improvement in the AES in both periods. The mean value is very small in both periods, which indicates a very slight change in the AES over the three measurement times.

In addition, the standard deviation is also relatively large compared to the mean value in both data sets (period 1: 0.1038; period 2: 0.1468). This circumstance makes it necessary to take an additional look at the median of the two groups.

The median of the differences is 0 in both periods, indicating that the AES for most of the moles analyzed did not change over the entire observation period. The corresponding cases therefore show a constant tendency in the change of their AES.

Identification of change patterns: A manual comparison of the individual cases showed that 9 cases exhibited linear changes in the AES. Four cases show a negative development, 5 cases a positive one. In 19 cases, no change in the AES could be identified. 2 of the analyzed cases show incoherent changes. The AES increases between time A and B, and then falls between time B and C.

4.2. Discussion

Two main conclusions can be drawn from the study:

Low Differences Between Measurements: The differences between individual measurements tend to be minimal. Approximately 30% of the cases exhibit a linear change in score, with 16.7% showing a linear increase and 13.4% a linear decrease in the score.

As the standard deviation is relatively high in both time periods, a look at the median provides a more reliable view of the trend of the calculated differences. The median in both comparison periods is equal to 0, which indicates a constant trend in the development of the AES. In fact, the majority of the cases analyzed show a constant AES across all three measurement points. This could explain why the trend difference in the measured values is very small despite strong outliers.

Another reason for the presence of outliers in this study could be varying examination intervals. Follow-up periods have not been consistent across the entire sample.

Improvement in the AES: Although 5 out of 30 cases show a higher score in the final measurement (and only 4 out of 30 showing a lower score), the overall AES of the moles under study has improved. Given that the score categorizes mole changes into "normal," "borderline," and "pathological," this improvement suggests that the moles examined in this study have shown a slight improvement over the observed period.

To gain a deeper understanding of these processes, additional visual analysis of mole patterns in these specific cases could be conducted to confirm or rule out any errors. It should be noted that this study was not the primary objective of the work.

5. Limitations

When analyzing data, especially related to changes in moles over time, there are certain limitations that need to be considered:

Sample Size Limitations: The statistical significance of the results can be reduced, and the conclusions may be made less reliable if the sample size is small. In the present case, it is important to note that access had been established to a database provided by the Medical University of Graz, which included a total of 45 clinical cases. However, only 30 of these cases met the criteria for our study.

Skewed Age Distribution:. The results presented here may not be applicable to younger age groups, as the sample, which primarily represents individuals aged 25 and older, does not include children and adolescents. This also means that any findings or conclusions from the study will be most relevant to middle-aged and older populations.

Another factor limiting the study is the **time parameter.** To obtain a more detailed and comprehensive analysis, the time factor could have been utilized, but the dataset was constrained by a very random sample, from which it was impossible to identify a specific, frequently recurring time parameter.

Outliers: The presence of anomalous values in the data can significantly distort the results, especially in smaller samples. In the present study, it is important to note that access had been established to a database provided by the Medical University of Graz, which included a total of 45 clinical cases. However, only 30 of these cases met the criteria for our study. In future studies with a larger overall study sample outliers could be removed to ensure more robust data.

Non-linear Relationships: Linear analysis assumes that the relationship between variables is linear. If the actual relationships are more complex and non-linear, the results of the linear analysis may be inadequate or misleading. Despite the fact that our study identified linear or constant trends in the majority of cases, the quantitative analysis showed a tendency for very weak differences between time points (A and C, as wells as B and C). This could suggest that additional factors, beyond the AES (i. e. medical history, the pattern of changes in nevi, the time over which these changes occurred, etc.), should be considered to achieve more accurate results.

6. Conclusion

The study aimed to assess the dermoscopic changes in acral nevi over time using the FotoFinder system's „Automatic Evaluation Scale“. The analysis of the differences accord out focused on a sample of 30 acral nevi from patients observed at the University Clinic of Graz's Dermatology Department, with evaluations conducted at three distinct time points.

The results of the study indicate that the differences between individual measurements were generally minimal, with approximately 30% of the cases showing linear changes in the automated score. Among these, 16.7% of the nevi exhibited a linear increase in score, while 13.4% showed a linear decrease. Despite the small magnitude of these changes, the overall automatic score for the nevi in this study indicated a slight improvement over the observed period. This suggests that the majority of the nevi remained stable or even showed a trend towards benign behavior.

The study also identified a relatively large standard deviation in the data, which could be attributed to varying examination intervals, highlighting the need for further research to explore the impact of consistent follow-up periods. Moreover, the study was limited by the small sample size and skewed age distribution, which predominantly included older adults. These factors may limit the generalizability of the findings to a broader population.

In conclusion, the use of the FotoFinder system for longitudinal assessment of acral nevi provided valuable insights into the stability and progression of these lesions. The minimal changes observed suggest that most acral nevi remain benign over time. However, the study underscores the importance of consistent monitoring and further research to better understand the dynamics of acral nevi, particularly in the context of early melanoma detection.

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Appendix

Analyse der Differenzen C - B

Case #	B	C	Differenz (C - B)	Data exploration
25	0,1	0,1	0	
34	0,11	0,1	-0,01	**Mean value**
39	0,1	0,1	0	-0,0258064516129032
44	0,1	0,1	0	
10	0,1	0,11	0,01	**Median**
22	0,1	0,12	0,02	0
27	0,1	0,11	0,01	
28	0,1	0,13	0,03	**Standardabweichung**
32	0,11	0,12	0,01	0,146836369950465
6	0,17	0,1	-0,07	
23	0,9	0,1	-0,8	**Minimum**
1	0,1	0,1	0	-0,8
2	0,1	0,1	0	
4	0,1	0,1	0	**Maximum**
7	0,1	0,1	0	0,03
12	0,1	0,1	0	
16	0,1	0,1	0	
17	0,1	0,1	0	
19	0,1	0,1	0	
20	0,1	0,1	0	
26	0,1	0,1	0	
29	0,1	0,1	0	
30	0,1	0,1	0	
35	0,1	0,1	0	
36	0,1	0,1	0	
38	0,1	0,1	0	
40	0,1	0,1	0	
42	0,1	0,1	0	
43	0,1	0,1	0	
45	0,1	0,1	0	

Figure 1: Analysis of the differences (C - B)

Figure 2: Analysis of the differences (C - A)

Analyse der Differenzen C - A

Case #	A	C	Differenz (C - A)	Data exploration
25	0,14	0,1	-0,04	
34	0,56	0,1	-0,46	**Mean value**
39	0,23	0,1	-0,13	-0,0332258064516129
44	0,32	0,1	-0,22	
10	0,1	0,11	0,01	**Median**
22	0,1	0,12	0,02	0
27	0,1	0,11	0,01	
28	0,1	0,13	0,03	**Standardabweichung**
32	0,11	0,12	0,01	0,103779718081413
6	0,1	0,1	0	
23	0,36	0,1	-0,26	**Minimum**
1	0,1	0,1	0	-0,46
2	0,1	0,1	0	
4	0,1	0,1	0	**Maximum**
7	0,1	0,1	0	0,03
12	0,1	0,1	0	
16	0,1	0,1	0	
17	0,1	0,1	0	
19	0,1	0,1	0	
20	0,1	0,1	0	
26	0,1	0,1	0	
29	0,1	0,1	0	
30	0,1	0,1	0	
35	0,1	0,1	0	
36	0,1	0,1	0	
38	0,1	0,1	0	
40	0,1	0,1	0	
42	0,1	0,1	0	
43	0,1	0,1	0	
45	0,1	0,1	0	

Figure 3:

Linear Changes

Case #	A	B	C	Linear Changes
25	0,14	0,1	0,1	**Negative Linear Changes**
34	0,56	0,11	0,1	4
39	0,23	0,1	0,1	
44	0,32	0,1	0,1	
10	0,1	0,1	0,11	**Positive Linear Changes**
22	0,1	0,1	0,12	5
27	0,1	0,1	0,11	
28	0,1	0,1	0,13	
32	0,11	0,11	0,12	
6	0,1	0,17	0,1	**Incoherent changes**
23	0,36	0,9	0,1	2
1	0,1	0,1	0,1	**No changes**
2	0,1	0,1	0,1	19
4	0,1	0,1	0,1	
7	0,1	0,1	0,1	
12	0,1	0,1	0,1	
16	0,1	0,1	0,1	
17	0,1	0,1	0,1	
19	0,1	0,1	0,1	
20	0,1	0,1	0,1	
26	0,1	0,1	0,1	
29	0,1	0,1	0,1	
30	0,1	0,1	0,1	
35	0,1	0,1	0,1	
36	0,1	0,1	0,1	
38	0,1	0,1	0,1	
40	0,1	0,1	0,1	
42	0,1	0,1	0,1	
43	0,1	0,1	0,1	
45	0,1	0,1	0,1	