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# Prospective Lesion-Level Analysis of the Inverse Approach for Lentigo Maligna in Real-World Clinical Practice

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## ABSTRACT

**Introduction:** Lentigo maligna (LM) is a melanoma subtype that develops predominantly on photodamaged skin. Classic criteria may miss early lesions due to subtle or partially present malignancy-associated features or their overlap with benign or premalignant conditions related to photodamage. The recently introduced inverse approach, which focuses on the absence of typical non-melanoma dermoscopic features, has shown promise in identifying these challenging cases.

**Objectives:** This study prospectively evaluated the real-life performance of the inverse approach for differentiating LM from its mimickers and assessed its ability to detect lesions lacking classic criteria.

**Methods:** This prospective study enrolled consecutive patients presenting with pigmented flat lesion(s) on the head and neck region. Each lesion was photographed and independently assessed by two dermatologists using classic and inverse approach criteria. Lesions showing at least one classic LM criterion or that did not predominantly (≥50% of the surface area) display any inverse approach feature were considered suspicious for LM and underwent biopsy for histopathological evaluation.

**Results:** A total of 956 lesions from 68 patients were initially evaluated. Of these, 795 (83.2%) were diagnosed as solar lentigo or flat seborrheic keratosis and 145 (15.2%) as actinic keratosis. Classic criteria for lentigo maligna identified four lesions as suspicious, all of which were histopathologically confirmed; three additional lesions were suspicious only by the inverse approach and were likewise confirmed as LM.

**Conclusions:** In this real-life cohort, the inverse approach identified all observed LM cases, including those lacking classic criteria or showing only subtle classic criteria; this approach may serve as a practical adjunct for evaluating pigmented facial lesions. Larger multicenter studies with systematic verification are needed for broader validation.

## Introduction

Lentigo maligna (LM) is a subtype of malignant melanoma that predominantly develops on chronically photodamaged skin, especially in the head and neck region. According to the progression model of LM, early dermoscopic findings include dots clustered around follicles, short streaks, asymmetric follicular pigmentation, and a subtle annular-granular pattern. As the lesion progresses, dermoscopic features that facilitate recognition begin to emerge more clearly as the annular-granular pattern becomes more prominent, accompanied by perifollicular radial or curved linear projections, followed by the development of rhomboidal structures and eventually obliteration of follicular openings [1,2]. These LM-specific dermoscopic features are hereafter referred to as the classic criteria.

Several studies have indicated that the sensitivity of **classic criteria** is often lower than their specificity [3,4], primarily due to the subtle or partial appearance of malignancy-associated features, which is further diminished by photodamage-related lesions such as pigmented actinic keratosis, solar lentigo, or flat seborrheic keratosis, potentially obscuring the clinical picture [5,6]. Although advanced imaging techniques such as reflectance confocal microscopy and artificial intelligence-based analyses have been proposed to overcome these diagnostic challenges, their limited accessibility in routine clinical practice currently restricts their widespread adoption, leaving early-stage LM often undetected in real-life clinical settings.

In response to this limitation, Lallas et al. proposed a novel dermoscopic strategy, the inverse approach, which emphasizes the absence of typical non-melanoma features rather than the presence of classic criteria [7]. According to this method, six non-melanoma dermoscopic features were defined for flat pigmented lesions: scales, large white follicular openings, erythema, reticular or parallel brown lines, sharply demarcated borders, milia-like cysts, and comedo-like openings. Lesions that do not predominantly (in ≥50% of the surface area) display any of these features are considered suspicious for LM, even if no classic criteria are observed. This method demonstrated a sensitivity of 88.5% and specificity of 66.9% in a pilot study.

## Objectives

This study aimed to prospectively assess the diagnostic performance of the newly defined inverse approach in distinguishing LM from its benign mimickers via dermoscopy and to test the hypothesis that it can detect LM cases lacking classic features, thereby providing a complementary diagnostic perspective in clinical dermatology.

## Materials and Methods

This prospective descriptive study received approval from the Institutional Scientific Research Ethics Committee. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki (1964) and its later amendments. Sample size was not predetermined, and all consecutive eligible patients within the study period were enrolled. Written informed consent was obtained from all participants.

### Study Group

Consecutive patients presenting with pigmented flat lesion(s) on the head and neck region were evaluated and informed about the study objectives and procedures. Written informed consent was obtained from all patients who agreed to participate. In addition to lesion-specific data, contextual information on patients' Fitzpatrick skin phototypes, occupational sun exposure, photoprotection habits, and personal and familial skin cancer history was collected for risk assessment. Based on occupational sun exposure, patients were categorized as indoor, semi-indoor, or outdoor workers. Photoprotection behaviors were initially recorded in detail, then grouped into three categories: "effective photoprotection," "ineffective photoprotection," or "no photoprotection," depending on consistency and method of use.

### Photography

The head and neck regions of all patients were photographed both macroscopically and dermoscopically. Each lesion was numbered prior to image acquisition. Macroscopic images were taken using an iPhone XS. Dermoscopic images were acquired at 10x magnification using a DermLite DL4 dermoscope (3Gen, USA) attached to the iPhone XS via the DermLite MagnetiConnect system. All photographs were labeled with the corresponding patient and lesion numbers.

### Clinical Evaluation

Dermoscopic evaluations were independently performed by two dermatologists with expertise in dermoscopy. Each lesion was assessed using both classic criteria and the inverse approach. If dermoscopic findings outside these frameworks suggested another entity, the lesion entered the diagnostic pathway corresponding to the relevant provisional diagnosis. Inter-observer agreement on lesion classification (benign vs. suspicious) was formally assessed using Cohen's kappa statistic. Any discrepancies were resolved through consensus.

### Biopsy

Lesions deemed benign based on established dermoscopic criteria and lacking features suggestive of malignancy, whether according to classic criteria or the inverse approach, were classified as benign. Final classification in these cases relied on the dominant benign dermoscopic impression.

Lesions presenting at least one classic criterion or that did not predominantly (in ≥50% of the surface area) display any inverse approach benign features were considered suspicious for LM. These lesions were excised under local anesthesia with standard surgical margins, following written informed consent. All excised specimens were histopathologically examined by the same dermatopathologist.

In cases where other dermatological conditions or clinically suspicious lesions were identified during the examination, appropriate diagnosis and treatment were provided in accordance with standard clinical practice.

### Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY). Descriptive statistics are presented as frequencies (f) and percentages (%). Inter-observer agreement was evaluated using Cohen's kappa statistic. Diagnostic performance was assessed (observed sensitivity calculated; specificity not estimable due to lack of biopsy verification of benign-appearing lesions).

## Results

A total of 956 lesions from 68 patients (34 females, 34 males; mean age 59 ± 15.7 years, range: 22–84) were initially evaluated. The study flowchart is shown in Figure 1.

Most patients had Fitzpatrick phototypes II–III; outdoor work was the predominant occupational category, and photoprotection was commonly absent. The majority reported no personal or familial history of skin cancer. Detailed counts and percentages are provided in Table 1.

The average number of lesions per patient was 13 ± 15.3 (range: 1–67), with lesion sizes ranging from 2 mm to 32 mm (mean diameter, approximately 8 mm). Fifty-six patients (82.4%) presented with multiple lesions.

Of the 956 lesions, 795 (83.2%) were diagnosed as solar lentigo or flat seborrheic keratosis and 145 (15.2%) as actinic keratosis. Dermoscopic features of benign lesions are summarized in Table 2.

Classic criteria identified four lesions as suspicious for LM (Table 3), all of which were histopathologically confirmed; an illustrative example is shown in Figure 2. An additional three lesions, lacking classic criteria and not predominantly (in ≥50% of the surface area) displaying any inverse approach features, were flagged as suspicious using the inverse approach. These three lesions were also confirmed as LM; a representative case is shown in Figure 3.

In addition, eight (0.8%) lesions were deemed suspicious for pigmented superficial basal cell carcinoma and one (0.1%) for pigmented Bowen's disease on dermoscopy; all were subsequently confirmed histopathologically.

Inter-observer agreement on lesion classification (benign vs. suspicious) was substantial, with a Cohen's kappa ($\kappa$)=0.82. All discrepancies were resolved by consensus.

Classic criteria detected four of the seven histopathologically confirmed LM cases (observed sensitivity: 57.1%); among biopsied lesions, specificity was 100%, with no false positives. In contrast, the inverse approach correctly identified all seven LM lesions (observed sensitivity: 100%). Because lesions deemed benign by both methods were not biopsied, specificity for either method cannot be robustly estimated from this cohort. No false positive was observed among biopsied lesions, and there were no missing data.

## Discussion

Chronic sun exposure, lighter skin phototypes, and inadequate photoprotection are recognized risk factors for LM [8-10]. In our cohort, 69.1% had Fitzpatrick phototypes II-III, and 45.6% were outdoor workers. Photoprotection was generally suboptimal: 67.6% reported ineffective measures and 30.9% no protection, with only 1.5% reporting effective protection. Taken together, our findings reflect a literature-consistent high-risk profile for LM and clearly demonstrate a substantial cumulative burden of photodamage. Moreover, 82.4% of patients presented with multiple lesions, a high lesion burden in which LM can be overlooked among numerous benign-appearing macules. Therefore, diagnostic strategies that perform reliably in early or subtle presentations are essential.

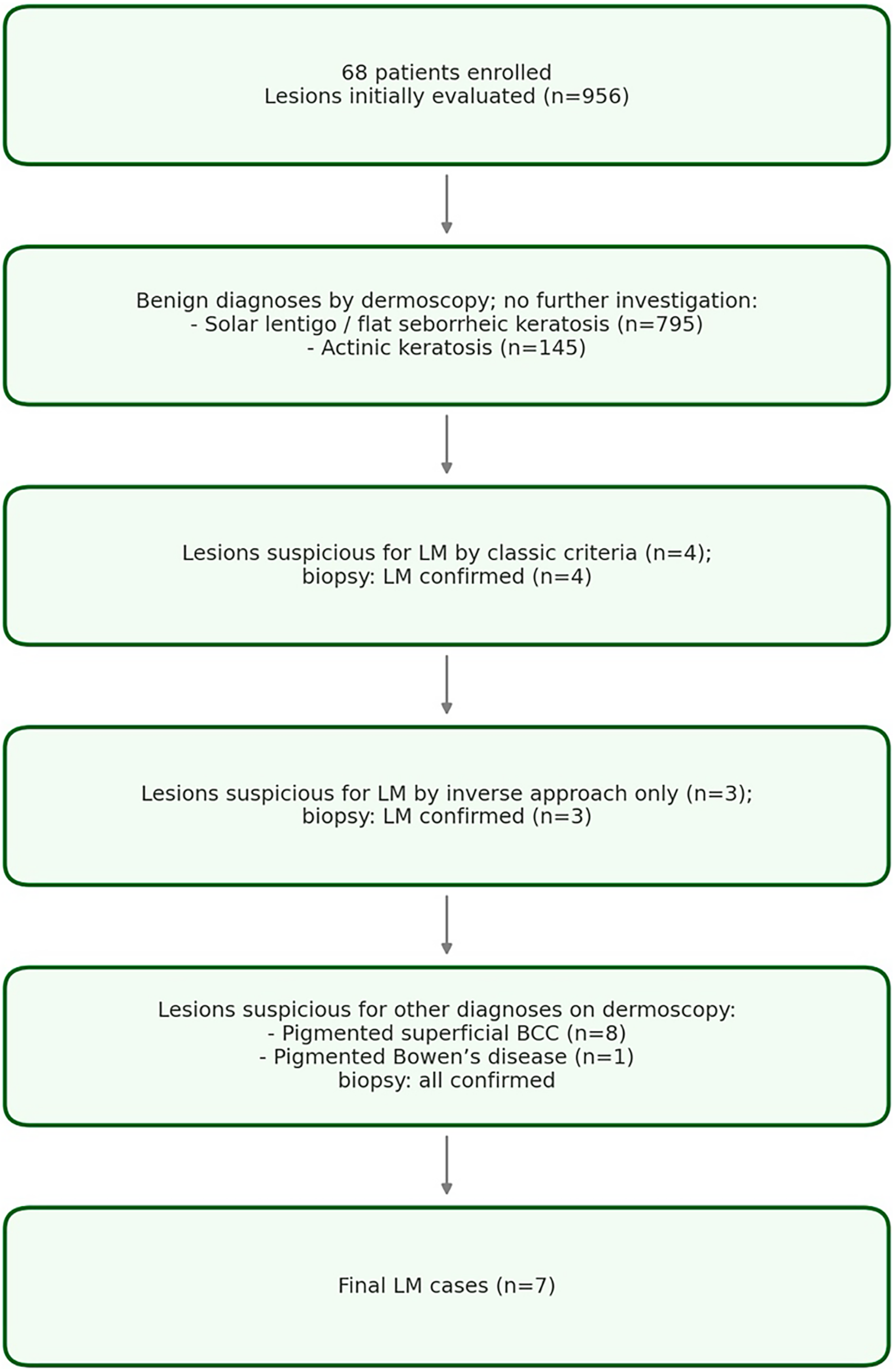


**Figure 1.** The study flow diagram. (Abbreviations: LM, lentigo maligna; BCC, basal cell carcinoma.)

Although classic criteria based on the LM progression model offer a structured evaluation framework, their sensitivity remains limited in early or subtle cases. Feature-based diagnostic scoring systems such as those proposed by Şahin et al. and Micantonio et al. provide detailed guidance but are often impractical for routine use due to their complexity [11,12]. The inverse approach was developed to address these limitations by focusing on the absence of benign features rather than on the presence of malignancy-specific ones. In our cohort, the classic criteria identified four out of seven LM cases (sensitivity: 57.1%), whereas the inverse approach successfully detected all seven (observed sensitivity 100%). However, specificity could not be reliably estimated because benign-appearing lesions were not biopsied. These results were superior to those reported by Lallas et al. [7], highlighting the potential of the inverse approach to identify

**Table 1. Distribution of Fitzpatrick skin phototypes, occupational sun exposure, photoprotection habits and levels, and personal and familial skin cancer history in the study group.**

| | N | % |
|---|---|---|
| **Fitzpatrick skin phototypes** | | |
| I | 10 | 14.7 |
| II | 25 | 36.8 |
| III | 22 | 32.3 |
| IV | 11 | 16.2 |
| **Occupational sun exposure** | | |
| Indoor worker | 20 | 29.4 |
| Semi-indoor worker | 17 | 25.0 |
| Outdoor worker | 31 | 45.6 |
| **Photoprotection habits** | | |
| Physical barrier and sunscreen | 11 | 16.2 |
| Physical barrier only | 14 | 20.6 |
| Sunscreen only | 22 | 32.3 |
| None | 21 | 30.9 |
| **Photoprotection levels** | | |
| Effective protection | 1 | 1.5 |
| Ineffective protection | 46 | 67.6 |
| No protection | 21 | 30.9 |
| **Personal and familial skin cancer history*** | | |
| Patients with personal melanoma history | 2 | 2.9 |
| Patients with personal non-melanoma skin cancer history | 9 | 13.2 |
| First degree relative with melanoma history | 2 | 2.9 |
| First degree relative with non-melanoma skin cancer history | 4 | 5.9 |
| Patient without personal/family history of skin cancers | 52 | 76.5 |

*Categories are not mutually exclusive; totals may exceed 100%.

**Table 2. Dermoscopic features of benign lesions.**

| | Solar lentigo/ Seborrheic keratosis (N=795) | | Actinic keratosis (N=145) | |
|---|---|---|---|---|
| | n | % | n | % |
| **Scale** | - | - | 69 | 47.6 |
| **Large white follicular openings** | - | - | 141 | 97.2 |
| **Erythema** | - | - | 110 | 75.8 |
| **Reticular or parallel brown lines** | 517 | 65.0 | - | - |
| **Border with sharp demarcation** | 196 | 24.6 | - | - |
| **Milia-like cysts/comedo-like openings** | 238 | 29.9 | - | - |

Categories are not mutually exclusive; totals may exceed 100%.

early-stage or featureless LM lesions that may evade conventional dermoscopic pattern recognition.

Importantly, our findings were derived from real-life clinical practice. We examined a large number of facial pigmented lesions, assessed independently by two experienced dermatologists using standardized dermoscopic criteria. Formal inter-observer agreement analysis confirmed the diagnostic consistency of our evaluations. In addition, the inverse approach was applied using predefined criteria, facilitating reproducibility in broader clinical settings.

The inverse approach may be particularly beneficial to clinicians with limited dermoscopic experience. It offers an

**Table 3. Dermoscopic features of lesions suspicious for lentigo maligna according to classic lentigo maligna criteria.**

| | LM1 | LM2 | LM3 | LM4 |
|---|---|---|---|---|
| **Asymmetric follicular pigmentation** | + | + | + | + |
| **Annular-granular pattern** | - | - | + | + |
| **Rhomboidal structures** | + | + | + | + |
| **Obliteration of follicular openings** | - | - | - | + |

Lentigo Maligna 1 (LM1). Patient No. 60. Lesion No. 1.
Lentigo Maligna 2 (LM2). Patient No. 61. Lesion No. 2.
Lentigo Maligna 3 (LM3). Patient No. 61. Lesion No. 3.
Lentigo Maligna 4 (LM4). Patient No. 67. Lesion No. 1.

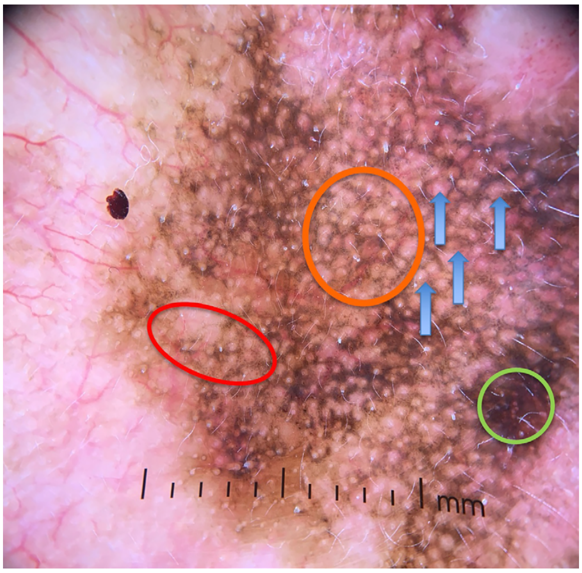


**Figure 2.** Patient No. 67. Lesion No. 1. Left cheek. Asymmetric follicular pigmentation (red ring), rhomboidal structures (blue arrow), annular-granular pattern (orange ring), homogeneous area obliterating the hair follicles (green ring). Histopathology: A lentiginous proliferation of atypical melanocytes is noted along an atrophic epidermis with marked solar elastosis. Diagnosis: Lentigo maligna.

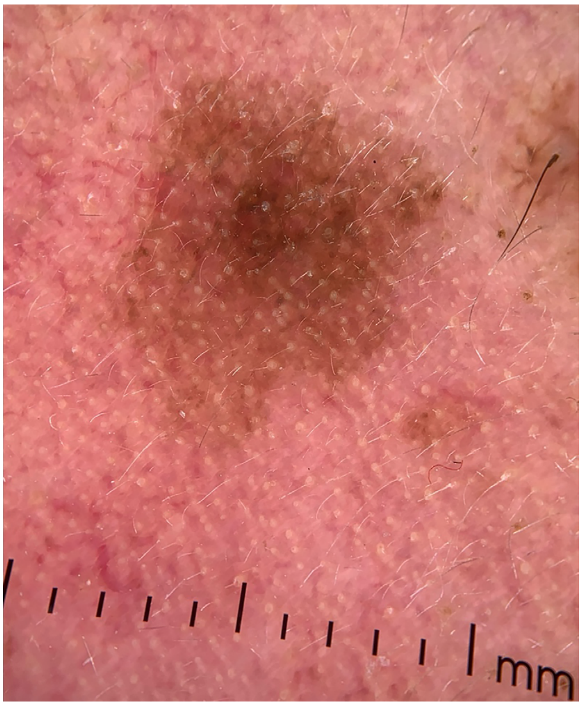


**Figure 3.** Patient No. 41. Lesion No. 3. Right infraorbital area. Hyperpigmented macule that did not predominantly (≥50%) display any inverse approach benign features. Histopathology: Scattered atypical melanocytes are present at the dermoepidermal junction, occasionally forming small nests. Diagnosis: Lentigo maligna.

intuitive, structured alternative for identifying lesions that fall outside typical diagnostic algorithms.

### Limitations and Strengths

This study's strengths include its prospective design, use of real-life dermoscopic data, and lesion-level analysis with independent double-reader assessment. One limitation of this study is the relatively small number of histopathologically confirmed LM cases (N=7), potentially affecting statistical power. While the number of individual patients was relatively modest (N=68), a total of 956 lesions were included and analyzed independently. This lesion-level approach increased the overall diagnostic dataset; however, it may still limit the representativeness of patient-level diversity and should be considered when interpreting the generalizability of the findings. Additionally, the single-center design may further limit generalizability. Histopathological confirmation was not obtained for lesions classified as benign, introducing verification bias and precluding reliable specificity estimation; however, this reflects routine clinical practice.

## Conclusion

This real-life, prospective cohort suggests that the inverse approach improves recognition of LM cases that lack classic criteria or have only subtle classic features. Applied in routine practice, it appears to be a useful adjunct to conventional dermoscopy, particularly in patients with extensive photodamage and multiple lesions. The approach identified all seven LM cases (observed sensitivity 100%). However, lesions deemed benign were not biopsied, so specificity cannot be robustly estimated and results should be interpreted in light of partial verification and the small number of LM cases. The inverse approach should be viewed as a complementary aid rather than a stand-alone algorithm. Larger, multicenter studies with systematic verification are warranted.

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