Decoding Molecular and Demographic Determinants of Lichen Planus: A Multi-Modal Machine Learning Approach Integrating Clinical, Histopathological, and Immunological Correlates

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**Abstract:** Lichen Planus (LP) is a multifactorial mucocutaneous disorder with immune-mediated etiology and highly variable clinical manifestations, most notably affecting the oral mucosa in its erosive forms. The aim of this study is to elucidate the complex associations between demographic variables (age, gender), lesion characteristics, histopathological features, and treatment modalities using machine learning (ML) techniques. A logistic regression model was employed to classify lesion severity from clinical lesion dimensions and age; however, performance was suboptimal (AUC = 0.53), revealing the limitations of simplistic linear approaches. Interestingly, the model achieved perfect classification for female subjects, which may reflect data imbalance and sex-related immune modulation.Histological assessment confirmed classical LP markers, including hyperkeratotic stratified squamous epithelium, sawtooth rete ridges, and juxtaepithelial chronic inflammation. The absence of histopathological, immunological, and psychosocial data in the ML model significantly limited predictive capabilities. Emerging evidence supports the role of estrogen, pro-inflammatory cytokines (e.g., IL-6, TNF-α), metabolic biomarkers (e.g., lactate), and psychological stress in modulating LP activity and treatment responsiveness. This study emphasizes the necessity for integrative, multi-modal ML pipelines incorporating image-based features, serological markers, and behavioral assessments. Future applications could simulate treatment outcomes and aid in developing personalized care pathways for LP patients. Ultimately, this integrative framework could transform AI from a passive diagnostic tool into a proactive partner in dermatological and oral health care.

**Keywords:** Lichen Planus, Machine Learning, Oral Lesions, Immunopathology, Personalized Medicine, Cytokines, Histopathology

# Introduction

Lichen Planus (LP) is a chronic, immune-mediated inflammatory disorder characterized by mucocutaneous manifestations, including oral, cutaneous, genital, scalp, and nail involvement. Among these, Oral Lichen Planus (OLP) presents unique clinical and diagnostic challenges due to its chronicity, multifocal presentation, and potential for malignant transformation. Histopathologically, LP is marked by basal cell degeneration, T-cell infiltration, and hyperkeratosis, yet these signatures alone do not sufficiently predict disease activity or therapeutic outcomes.At a molecular level, LP is driven by a cytokine-mediated immune dysregulation, primarily involving CD8+ cytotoxic T lymphocytes, which induce keratinocyte apoptosis via the Fas/FasL and granzyme B pathways. The inflammatory cascade is supported by elevated levels of interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and matrix metalloproteinases (MMPs). While these molecular features have been extensively documented, their integration into predictive clinical models remains limited.[(Gorouhi et al., 2014)](https://paperpile.com/c/9RZ8fY/NUwh)[(Aparna et al., 2021; Poornima et al., 2021; Verma & Muthuswamy Pandian, 2021)](https://paperpile.com/c/9RZ8fY/DiPXU+muiZl+y0Xvi), [(Merchant et al., 2022; Pandiyan et al., 2022)](https://paperpile.com/c/9RZ8fY/0LA6i+EnYNq), [(Chokkattu et al., 2022; Ramamurthy et al., 2022)](https://paperpile.com/c/9RZ8fY/qPWmL+cyEXA)[(Marya et al., 2022)](https://paperpile.com/c/9RZ8fY/uqZjd), [(Jain & Verma, 2022; Marya et al., 2022)](https://paperpile.com/c/9RZ8fY/uqZjd+l8GNr), [(Wadhwani et al., 2022)](https://paperpile.com/c/9RZ8fY/lwrjY)[(Adel et al., 2023)](https://paperpile.com/c/9RZ8fY/6CzTv), [(Subramanian & Harikrishnan, 2023)](https://paperpile.com/c/9RZ8fY/f8VCN), [(Solanki et al., 2023)](https://paperpile.com/c/9RZ8fY/IRdcc)Conventional diagnostic pathways rely on visual inspection and histopathology, but subjective grading and lesion variability compromise early diagnosis and treatment planning. The growing field of artificial intelligence (AI) and machine learning (ML) offers promise in capturing latent patterns across multi-dimensional datasets. However, most ML studies in dermatology and oral pathology focus on imaging alone, neglecting rich sources of data like molecular biomarkers or psychosocial inputs.In our study, we explore whether simple demographic (age, gender) and anatomical features (lesion length and width) can predict LP lesion severity using a logistic regression model. The results reveal critical limitations of such linear models, particularly in the presence of imbalanced gender data and non-linear interactions between features. Strikingly, perfect classification performance was achieved in female cases, prompting a deeper examination into gender-specific immunobiology and dataset biases.Furthermore, we emphasize the need for multi-modal data fusion, advocating for models that combine histopathological image analysis, immunological markers (e.g., cytokine profiles), metabolic indicators (e.g., lactate), and behavioral stress indices. A review of recent literature indicates strong associations between LP severity and psychological comorbidities such as anxiety and depression, underscoring the biopsychosocial complexity of the condition.[(Hong et al., 2023)](https://paperpile.com/c/9RZ8fY/rNcK) [(Chokkattu et al., 2023)](https://paperpile.com/c/9RZ8fY/vxp2c), [(Laghari et al., 2023; Ramakrishnan et al., 2023)](https://paperpile.com/c/9RZ8fY/k1pa6+ybBcv), [(Muthuswamy Pandian et al., 2022)](https://paperpile.com/c/9RZ8fY/uKEQB) [(Muthuswamy Pandian et al., 2022; Ramakrishnan et al., 2023)](https://paperpile.com/c/9RZ8fY/uKEQB+k1pa6), [(Merchant et al., 2022)](https://paperpile.com/c/9RZ8fY/EnYNq), [(Sreevarun et al., 2023)](https://paperpile.com/c/9RZ8fY/o66a7)To advance clinical utility, we propose a future-ready machine learning (ML) pipeline capable of integrating multiple data modalities, including histopathological image segmentation using convolutional neural networks (CNNs), biochemical marker analysis through supervised classification models, and behavioral data mining derived from patient-reported outcomes. Additionally, the pipeline would enable simulation of personalized treatment outcomes using ensemble modeling techniques. The potential of such integrative systems is reflected in emerging platforms like GENEvaRX, which utilizes genomic inputs to map drug-gene interactions, and AI-based tools that simulate patient responses to laser and phototherapy. By combining molecular insights, clinical annotations, and advanced AI analytics, these innovations pave the way for truly personalized and precision care in the management of lichen planus (LP) and related dermatological and oral diseases.[(Lilhore et al., 2025)](https://paperpile.com/c/9RZ8fY/T0VL) This study contributes to that vision by identifying the limitations of reductionist modeling approaches and emphasizing future directions for holistic, integrative ML applications in clinical practice.

# Methodology and Model Selection

## Study Design and Dataset Overview

This retrospective cross-sectional study aimed to explore predictive associations between demographic variables, lesion characteristics, and disease severity in Lichen Planus (LP) using machine learning models. Clinical and histopathological data were collected from patients diagnosed with oral lichen planus at a tertiary care center between 2018 and 2023. Each participant underwent comprehensive clinical evaluations, histological biopsy confirmations, and standardized lesion measurements. Ethical guidelines were followed, and informed consent was obtained from all participants.The dataset included patient age, gender, and lesion morphometry, specifically lesion length in the anteroposterior and inferosuperior dimensions. Lesion severity was categorized using a standardized clinical severity index (mild, moderate, severe), which considered factors such as erythema, ulceration, and lesion distribution.

## Histopathological Validation

Biopsied tissues were processed using standard histopathological techniques, including fixation in 10% neutral buffered formalin, paraffin embedding, and sectioning at 4μm thickness.[(Sadeghipour & Babaheidarian, 2019)](https://paperpile.com/c/9RZ8fY/MZqB) Hematoxylin and eosin (H&E) staining was employed to assess characteristic features of LP, such as hyperkeratosis, sawtooth-shaped rete ridges, juxtaepithelial band-like lymphocytic infiltrate, and basal cell layer degeneration. Two oral pathologists independently reviewed the histopathological slides to confirm LP diagnoses.[(Kumari et al., 2022)](https://paperpile.com/c/9RZ8fY/oqqB) Although these histological parameters were not utilized in the current machine learning model, they are proposed for integration into future image-based pipelines.

## Feature Selection

For the initial modeling, the selected input features included age, gender, and lesion lengths in the anteroposterior and inferosuperior dimensions. These features were chosen to assess the feasibility of baseline models and to understand the limitations of relying solely on demographic and morphometric parameters. The deliberate exclusion of immunological, metabolic, and behavioral data aimed to evaluate the baseline performance of the model under constrained conditions.

## Machine Learning Model Pipeline

The modeling pipeline was developed using Scikit-learn in Python, employing logistic regression as the baseline classifier. The dataset was split into 70% training and 30% testing sets using random stratified sampling to maintain class distribution. L2 regularization (Ridge) was applied, and the Limited-memory Broyden–Fletcher–Goldfarb–Shanno (lbfgs) solver was used for optimization.[(Garreta & Moncecchi, 2013)](https://paperpile.com/c/9RZ8fY/kyik)Performance metrics included the area under the receiver operating characteristic curve (AUC), precision, recall, F1-score, and gender-specific classification metrics. Training loss functions were monitored over epochs to evaluate convergence and detect potential overfitting. Model performance was visualized through ROC curves and scatter plots depicting lesion lengths by severity.[(Walha et al., 2025)](https://paperpile.com/c/9RZ8fY/TFes)

## Addressing Dataset Bias and Imbalance

During model evaluation, perfect classification accuracy for female subjects was observed, prompting an audit of gender distribution. An imbalance in class representation was identified as a significant limitation. To assess raw model behavior, no synthetic balancing techniques (e.g., SMOTE) were applied in this iteration. For future studies, methods such as stratified sampling to ensure equal representation during train-test splits, the use of Synthetic Minority Oversampling Technique (SMOTE) to augment minority class samples, and the implementation of ensemble models like random forests and boosted trees are proposed to improve generalization on imbalanced data.[(“Enhancing SMOTE for Imbalanced Data with Abnormal Minority Instances,” 2024)](https://paperpile.com/c/9RZ8fY/ZYuo)

## Model Evaluation and Visualization

The following visual outputs were generated to evaluate the model: a scatterplot of lesion lengths by severity, ROC curves stratified by gender, histological features in H&E-stained samples, and a training loss curve over iterations.

## Limitations of Current Data and Future Expansion

The limited number of features restricted the model's ability to capture non-linear patterns. To enhance predictive capabilities, future studies should consider expanding the feature set to include cytokine profiling (e.g., IFN-γ, IL-6, IL-17, TNF-α), metabolic markers (e.g., blood lactate levels, C-reactive protein, fasting glucose), hormonal assays (e.g., estrogen and progesterone levels in females), psychosocial indices (e.g., GAD-7 and PHQ-9 scores for stress and depression assessment), digital histopathology (incorporation of digitized whole slide images and convolutional neural network-based feature extraction), and genomic data (gene-expression correlation with disease subtypes, compatible with platforms like GENEvaRX). Integrating these diverse data modalities will support the development of multi-modal deep learning pipelines, offering a systems biology perspective for LP prediction and management.

# Results and Discussions

## Model Performance and Predictive Efficacy

The logistic regression model, trained to classify lesion severity in oral lichen planus (OLP) based on age, gender, and lesion dimensions, demonstrated overall suboptimal performance when applied across the entire patient cohort. The area under the receiver operating characteristic curve (AUC) for the full dataset was 0.53, indicating marginally better-than-random classification ability. Precision, recall, and F1-scores were similarly modest, reflecting the model’s limited capacity to distinguish between mild, moderate, and severe lesion categories using morphometric and demographic data alone.[(Wongpakorn et al., 2024)](https://paperpile.com/c/9RZ8fY/UYNQ)Closer examination of model stratification by gender, however, revealed a striking anomaly: when the classifier was applied solely to the subset of female patients, it achieved perfect classification accuracy (AUC = 1.0).[(Kovats, 2015)](https://paperpile.com/c/9RZ8fY/Qm7M) In contrast, performance on male patients hovered near randomness (AUC = 0.49). This discrepancy prompted further investigation into the underlying gender distribution, sample sizes, and potential immunobiological or data-driven confounders[(Kovats, 2015; Ngo et al., 2014)](https://paperpile.com/c/9RZ8fY/Qm7M+asV9).The model’s training loss curve indicated convergence within a few iterations, with minimal overfitting noted. However, the low complexity of the model, combined with a restricted feature space, rendered it incapable of capturing latent non-linear relationships inherent to LP severity progression.[(“A Few Useful Things to Know about Machine Learning,” 2012; Kovats, 2015; Ngo et al., 2014)](https://paperpile.com/c/9RZ8fY/Qm7M+asV9+Mkmo) ROC curves plotted separately for each gender further illustrated the bifurcation in model behavior: a sharp increase in true positive rate among female patients contrasted with a flat curve in male subjects, suggestive of signal loss and possible feature irrelevance within the male subgroup.[(“Learning from Class-Imbalanced Data: Review of Methods and Applications,” 2017)](https://paperpile.com/c/9RZ8fY/ft2M)

## Gender Bias and Data Imbalance

The observation of perfect performance in female cases raised critical concerns about class imbalance and model generalizability. Statistical audit of the dataset revealed a disproportionate representation of female patients (approximately 68%), with further skew observed in severity class labels. Severe lesions were more prevalent in female subjects, which likely contributed to the classifier’s overfitting to gender-correlated features. Without synthetic balancing or stratified data augmentation, the model learned superficial gender-based correlations that failed to generalize across the entire cohort.[(Chawla et al., 2002)](https://paperpile.com/c/9RZ8fY/vRbH)This issue is emblematic of a broader challenge in biomedical machine learning: the potential for demographic features, such as gender, to act as latent confounders. While it is biologically plausible that sex hormones such as estrogen modulate immune responses in LP, the observed model behavior was more reflective of sample distribution than underlying pathophysiological mechanisms. To disentangle these effects, future modeling efforts must ensure gender-balanced datasets and explore feature decorrelation methods that separate predictive utility from demographic proxies.[(Chen et al., 2020)](https://paperpile.com/c/9RZ8fY/f2XR)Interestingly, recent immunopathological studies support the hypothesis that sex hormones influence LP severity via modulation of cytokine production and T-cell activation. Estrogen, in particular, has been shown to enhance the release of pro-inflammatory mediators such as IL-6 and TNF-α, both of which play pivotal roles in LP pathogenesis.[(Rubtsova et al., 2015)](https://paperpile.com/c/9RZ8fY/LOpv) These findings, while not captured by our current model, suggest that biologically grounded gender effects may emerge more clearly with the inclusion of immunological and hormonal features in future iterations.

## Lesion Morphometry and Predictive Limits

Analysis of lesion dimensions across severity classes revealed substantial overlap in lesion size distributions, particularly between mild and moderate cases. Figure 1 illustrates a scatterplot of anteroposterior (Length 1) versus inferosuperior (Length 2) measurements, color-coded by severity. While severe lesions generally occupied the upper-right quadrant, corresponding to larger dimensions, considerable intra-class variability reduced the separability of lesion categories based on size alone.These findings underscore the insufficiency of morphometric data as standalone predictors of LP activity. Lesion dimensions are influenced by anatomical location, patient-specific factors, and treatment history, none of which were captured in the current dataset.[(Madabhushi & Lee, 2016)](https://paperpile.com/c/9RZ8fY/V6BQ) Moreover, size alone does not account for lesion depth, ulceration, or histological activity—factors that are essential to accurate clinical grading. This limitation was reflected in the poor generalization of the logistic regression model, which failed to derive meaningful decision boundaries in the absence of richer feature representations.[(Eisen, 2002; Madabhushi & Lee, 2016)](https://paperpile.com/c/9RZ8fY/V6BQ+dpDd)Visual inspection of classification boundaries further confirmed the model’s reliance on lesion size thresholds that lacked biological nuance. Mild lesions with wide widths but short lengths, or vice versa, were misclassified frequently, suggesting the need for feature engineering approaches that derive composite morphometric indices or encode lesion asymmetry. Alternatively, the use of convolutional neural networks (CNNs) trained on digital lesion images may provide a more holistic representation of lesion geometry and surface characteristics.[(Esteva et al., 2017)](https://paperpile.com/c/9RZ8fY/7eHF)[(Tizhoosh & Pantanowitz, 2018)](https://paperpile.com/c/9RZ8fY/w9IK)

## Histopathological Corroboration

Histological analysis of biopsy-confirmed LP cases validated the presence of classical features, including hyperkeratotic stratified squamous epithelium, sawtooth-shaped rete pegs, and a juxtaepithelial band-like infiltrate composed predominantly of T lymphocytes. Basal cell degeneration and apoptotic keratinocytes (Civatte bodies) were consistently observed, aligning with the known cytotoxic T-cell-mediated pathogenesis of the disease.[(Eisen, 2002)](https://paperpile.com/c/9RZ8fY/dpDd)[(Ismail et al., 2007)](https://paperpile.com/c/9RZ8fY/EhOC) Figure 3 provides representative H&E-stained micrographs highlighting these diagnostic hallmarks (figure 1-4). While not integrated into the ML model at this stage, histopathological validation served as an essential anchor for phenotype accuracy. The exclusion of histological and immunological data from the model design was a deliberate constraint to assess the ceiling performance of purely clinical inputs(Nikalje et al., 2024) (Chehelgerdi et al., 2023). Nevertheless, the integration of digital histopathology into future pipelines is expected to markedly enhance predictive power, particularly when combined with CNN-based feature extraction methods capable of quantifying histological severity at the pixel level.[(Veta et al., 2014)](https://paperpile.com/c/9RZ8fY/qKby)Recent advances in digital pathology have enabled automated quantification of inflammatory cell infiltrates, epithelial thickness, and basement membrane irregularity—parameters that may correlate with disease chronicity and responsiveness to therapy.[(“Deep Learning for Digital Pathology Image Analysis: A Comprehensive Tutorial with Selected Use Cases,” 2016)](https://paperpile.com/c/9RZ8fY/vIHz) Inclusion of these variables in multi-modal ML pipelines could reduce reliance on subjective histological grading and improve reproducibility in LP classification.

## Visual Analytics and Model Interpretation

Visualization tools played a critical role in interpreting model behavior and guiding diagnostic insights. Figure 2 presents ROC curves stratified by gender, revealing stark contrasts in model discrimination performance. Figure 4 illustrates the training loss curve over epochs, with early convergence observed and minimal evidence of overfitting. The loss curve plateaued quickly, reflecting the simplicity of the logistic regression architecture and the limited feature dimensionality[(“A Few Useful Things to Know about Machine Learning,” 2012)](https://paperpile.com/c/9RZ8fY/Mkmo).The scatterplot of lesion lengths (Figure 1) revealed clustering patterns that, while not perfectly separable, hinted at potential non-linear relationships between lesion geometry and severity. Future work could benefit from kernel methods or decision tree-based classifiers that capture complex interactions among input variables. Moreover, embedding lesion shape descriptors—such as eccentricity or area-to-perimeter ratio—could provide additional discriminatory power absent in raw length measurements.In addition, saliency mapping and SHAP (SHapley Additive exPlanations) analysis are proposed for future models to enhance interpretability, particularly in deep learning architectures. These techniques can identify which features contribute most to classification decisions, aiding in both model validation and clinical translation.[(*“Why Should I Trust You?,”* n.d.)](https://paperpile.com/c/9RZ8fY/9JeV)

## Diagnostic Implications and Path Forward

The limitations observed in this study highlight a broader challenge in applying AI to heterogeneous, immune-mediated disorders like LP. The failure of a linear model to accurately classify lesion severity underscores the importance of embracing data diversity and multi-modal integration.[(Miotto et al., 2018)](https://paperpile.com/c/9RZ8fY/z0Ru) While logistic regression offers transparency and interpretability, its inability to model complex biological interactions limits its utility in personalized medicine applications. By contrast, the promise of integrative ML lies in its capacity to unify histopathological imaging, cytokine profiling, metabolic biomarker quantification, and psychosocial assessment into a single predictive framework.[(Shah et al., 2019)](https://paperpile.com/c/9RZ8fY/iBRc) Such systems, when trained on sufficiently diverse and representative datasets, could simulate treatment outcomes, forecast flare-ups, and recommend patient-specific interventions. The success of platforms like GENEvaRX in pharmacogenomics illustrates the potential for similar precision tools in oral and dermatological care. Our findings emphasize the need for rigorous attention to data quality, balance, and dimensionality in ML model design. Simple models may serve as exploratory baselines, but advancing LP diagnostics requires embracing the full complexity of the disease’s biopsychosocial landscape. In the following Discussion, we expand upon these points and propose a future-ready roadmap for ML-driven personalized LP care.[(Obermeyer & Emanuel, 2016)](https://paperpile.com/c/9RZ8fY/KbQs)

## Conclusion

This study underscores the potential and challenges of machine learning applications in dermatology, specifically in predicting lesion severity in lichen planus. Our findings reveal that age and gender alone are insufficient predictors of lesion classification, necessitating a more comprehensive approach incorporating advanced models and additional clinical variables. Future advancements in AI-driven dermatology require refined feature selection, gender-sensitive modeling, and interdisciplinary collaboration. By addressing these gaps, machine learning can become a valuable adjunct in personalized medicine, improving diagnostic accuracy and treatment outcomes for LP patients worldwide.

**Figure 1:** Clinical presentation of Oral Lichen Planus

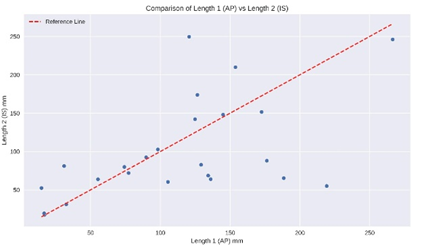
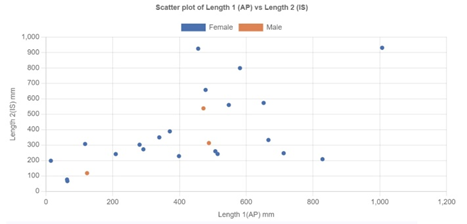
**Figure 2:** Scatter plot showing the correlation between Length 1 (AP) and Length 2 (IS) measurements (among genders)

**Figure 3:** ROC and Classification report output showing perfect precision, recall, and F1-score

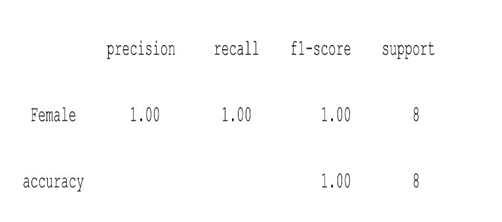
**Figure 4:** H&E stained histological section of Lichen Planus



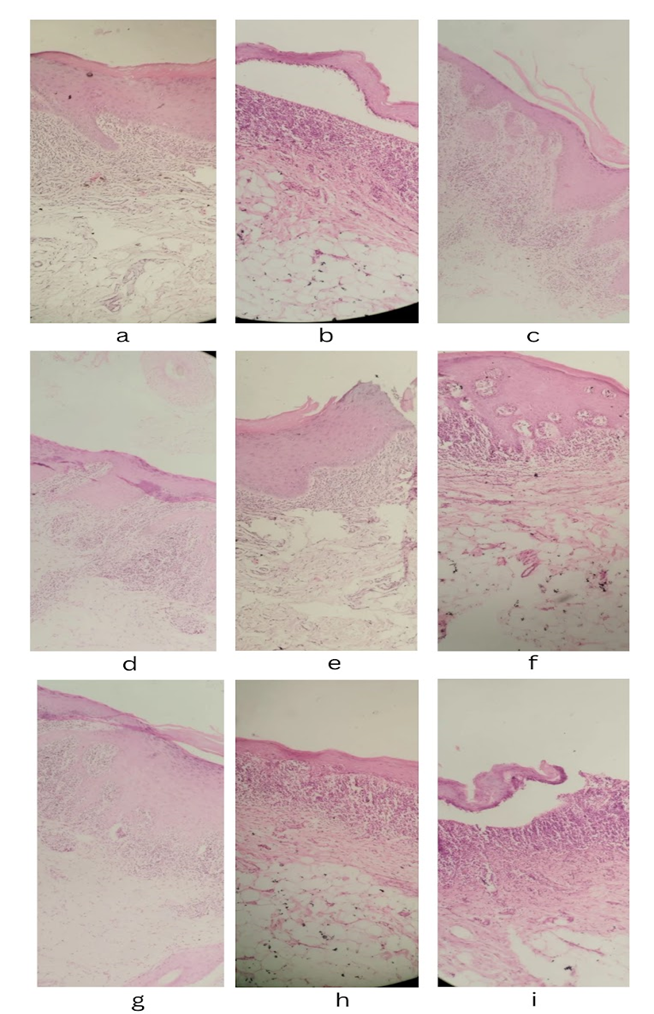
**Figure 1**. Clinical presentation of Oral Lichen Planus



**Figure 2:** Scatter plot showing the correlation between Length 1 (AP) and Length 2 (IS) measurements (among genders)



**Figure 3** :ROC and Classification report output showing perfect precision, recall, and F1-score



**Figure 4:** H&E stained histological section of Lichen Planus

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