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CONCORDANCE AND DISCORDANCE IN DERMATOLOGICAL DIAGNOSES: A COMPREHENSIVE REVIEW OF CLINICAL, HISTOLOGICAL AND IMMUNOFLUORESCENCE CORRELATION

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ABSTRACT

Dermatological diagnosis relies on integrating clinical examination, histological analysis, and immunofluorescence to ensure accuracy in identifying skin diseases. This study evaluates the concordance between clinical, histopathological, and direct immunofluorescence (DIF) diagnoses in 75 cases of skin lesions, encompassing both bullous and non-bullous types. Conducted at Saveetha Medical College, Chennai, from March 2023 to June 2024, the research utilized descriptive statistics and the Chi-square test to analyze data. Results underscored the pivotal role of immunofluorescence in enhancing diagnostic accuracy, particularly in immunobullous diseases characterized by autoantibodies targeting skin adhesion structures. Understanding the interplay among diagnostic modalities provides insights into improving diagnostic precision and treatment outcomes in dermatology. This study contributes to refining clinical practices by highlighting the significance of immunofluorescence in dermatological diagnostics. Bullous Pemphigoid emerged as the predominant diagnosis, comprising 54.7% of cases, followed by Systemic Lupus Erythematosus (20%), Cutaneous Small Vessel Vasculitis (12%), Pemphigus Vulgaris (8%), and Pemphigus Foliaceus (5.3%). Concordance between clinical, histopathological, and immunofluorescence findings was high across all diagnoses, with 69 cases showing agreement among all three diagnostic methods. Discordance, observed in 6 cases, underscores challenges in diagnosis despite comprehensive evaluation. These findings emphasize the critical role of integrating diagnostic modalities to enhance accuracy in managing autoimmune skin diseases effectively.

INTRODUCTION

Dermatological diagnosis is a complex and multifaceted process that relies on the integration of clinical examination, histological analysis, and immunofluorescence studies. Each diagnostic modality offers unique insights and contributes to a comprehensive understanding of skin diseases. Clinical examination involves visual inspection and assessment of the patient's history, providing initial clues based on the morphology and distribution of skin lesions. Histological analysis, often considered the gold standard, involves microscopic examination of skin biopsies to reveal detailed architectural and cellular characteristics. Immunofluorescence, including direct and indirect techniques, detects specific antibodies or antigens in the skin, offering critical diagnostic information, particularly for autoimmune and blistering diseases.

The concordance between these diagnostic methods is vital for accurate diagnosis and effective treatment planning. While high concordance can reinforce diagnostic confidence, discordance poses challenges and necessitates further

investigation. This review aims to comprehensively analyse the concordance and discordance in dermatological diagnoses, examining the relationships and potential discrepancies among clinical, histological, and immunofluorescence findings. By understanding these correlations, clinicians and pathologists can improve diagnostic accuracy and patient outcomes in dermatology.

AIMS AND OBJECTIVES

The aim of this study was to evaluate the concordance between clinical, histopathological, and direct immunofluorescence (DIF) diagnoses in skin lesions, specifically focusing on both bullous and non-bullous types. By thoroughly analyzing the agreement between these diagnostic methods, the study sought to provide a comprehensive understanding of their interrelationship and diagnostic value. A key objective was to ascertain the extent to which direct immunofluorescence influences and enhances the overall diagnostic process. By identifying the level of concordance among these three diagnostic approaches, the study aimed to highlight the significance and impact of immunofluorescence in improving diagnostic accuracy for various skin lesions.

Immunological diseases encompass a wide range of disorders characterized by abnormal immune responses. These diseases are classified primarily based on their clinical presentation, histopathology, and immunopathology. Among these, immunobullous diseases represent a distinct category marked by the presence of pathogenic autoantibodies targeting specific antigens involved in cell adhesion processes. Understanding the nuances of these diseases and their diagnostic techniques is crucial for accurate diagnosis and effective treatment.

Classification and Pathogenesis

Immunobullous diseases are primarily classified according to their clinical features, histopathological findings, and immunopathological characteristics. Clinically, these diseases manifest as blisters or bullae on the skin and mucous membranes. Histopathologically, they are defined by the presence of specific changes in the skin layers, often observed through biopsy samples. Immunopathologically, the presence of autoantibodies that target components of the skin's adhesion structures is a hallmark of these diseases.

The pathogenesis of immunobullous diseases involves autoantibodies directed against target antigens that play a critical role in maintaining the structural integrity of the skin. These target antigens are located either within the desmosomes—structures responsible for cell-to-cell adhesion within the epidermis—or within the adhesion complex of the basement membrane zone, which anchors the epidermis to the dermis. The disruption of these adhesion structures leads to the formation of blisters.

MATERIALS AND METHODS

The study was conducted in Saveetha Medical College, Thandalam, Chennai from March 2023 to June 2024. A total of 75 cases of skin biopsies were studied for each of the skin biopsies to separate containers were received one for Histopathology and one for direct immune of fluorescence. Patients of all ages and both genders were included (Graph-1,2 and Table-1). Two biopsies of each case were taken after taking informed consent, One biopsy was kept in 10% neutral buffered formalin and the second biopsy was kept in Michelle's medium for Direct Immunofluorescence.

In this study, descriptive statistics were utilized to present general data. The Chi-square test was employed to compare nominal or ordinal variables between oral cancer patients and non-oral cancer patients. Furthermore, the logistic regression model was used to analyze the crucial factors that contribute to the contraction of oral cancer. SPSS for Windows, version 10.1 (SPSS Inc., Chicago, IL, USA), was used to perform the statistical analysis. A statistical significance level of P-value of <0.05 was considered as significant.

INCLUSION CRITERIA

Skin biopsies warranting immunofluorescence to be considered for study.

OBSERVATIONS AND RESULTS

A total of 75 patients were included in the study out of which 43 were males and 32 were females and the patients were present across all age groups.

Graph 1: Gender distribution

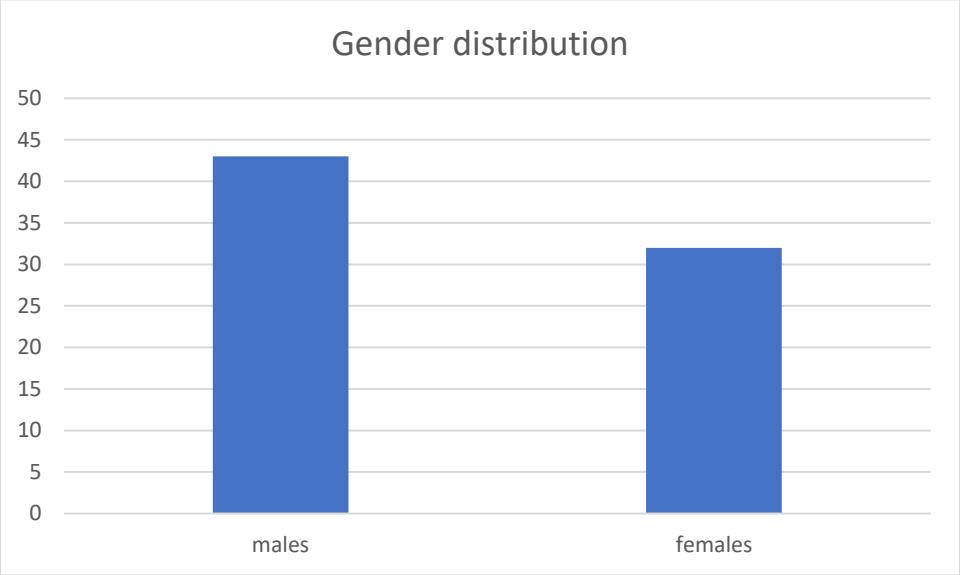


Table 1: Age distribution of patients included in the study

Age Interval	Number of cases
0 to 9	0
10 to 19	6
20 to 39	18
30 to 39	11
40 to 49	8
50 to 59	10
60 to 69	12

Graph 2: Age distribution

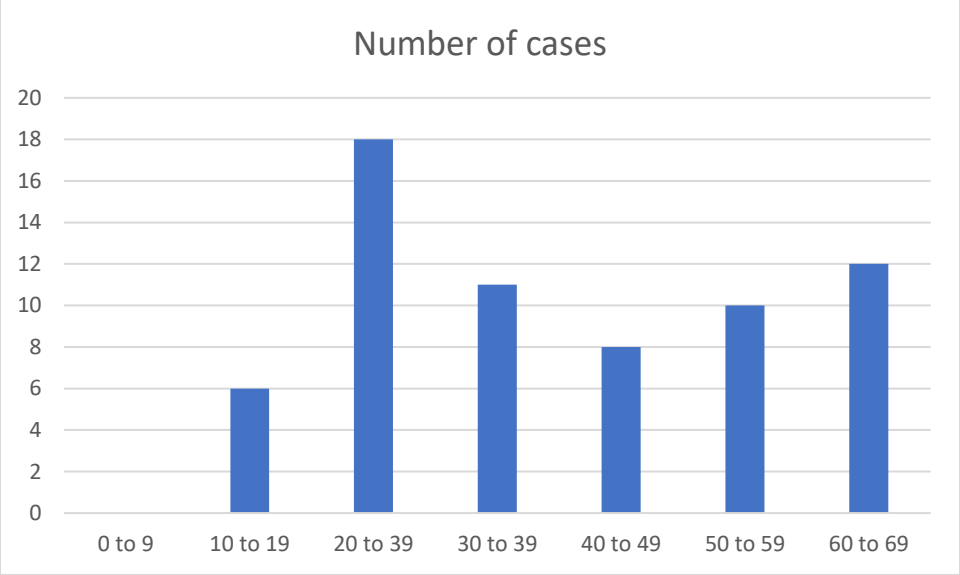
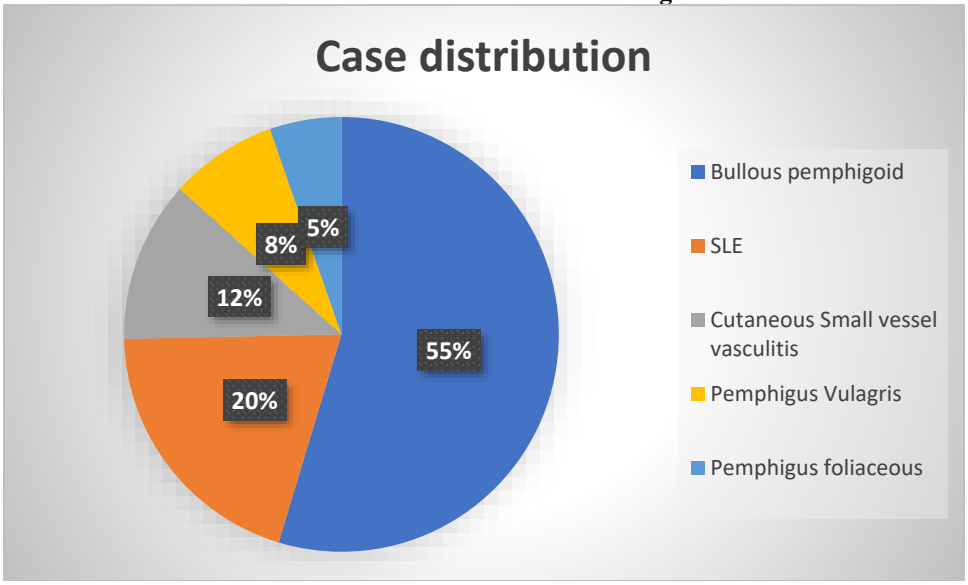


Chart 1: Number of cases of each diagnosis



Out of the 75 cases, Bullous Pemphigoid (Fig.4), with 41 cases, is the most frequently diagnosed condition among the listed autoimmune disorders. Systemic Lupus Erythematosus (SLE) follows with 15 cases, indicating a significant but lower prevalence compared to Bullous Pemphigoid. Cutaneous Small Vessel Vasculitis (Fig.5) has been diagnosed in 9 cases, highlighting its less frequent occurrence relative to the others. Pemphigus Vulgaris (Fig.1 and 2 shows DIF results) and Pemphigus Foliaceus (Fig.3), with 6 and 4 cases respectively, represent relatively rarer conditions within this group of autoimmune diseases (Chart-1).

Table 2: Immunofluorescence findings

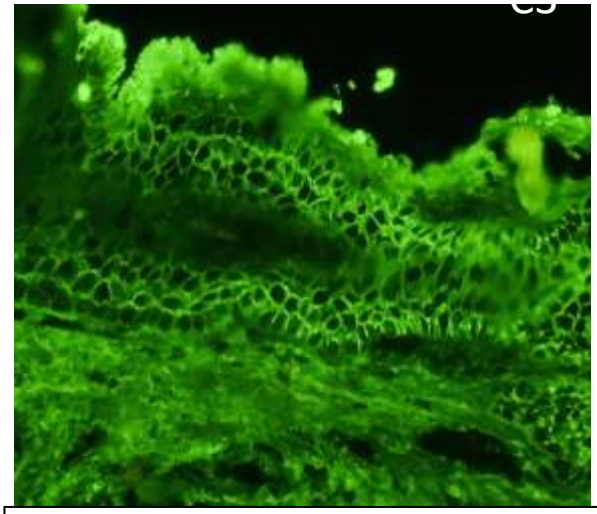
S.No	FINDINGS	PV	PF	BP	SLE	CSVV
1	IgG deposition					
	Intercellular	6	4	-	-	-
	BMZ	-	2	39	-	-
2	IgA deposition					
	Intercellular	-	3	-	-	-
	BMZ	-	1	-	2	-
3	IgM deposition					
	Intercellular	-	2	-	-	-
	BMZ	-	-	-	-	-

4	C3 deposition					
	Intercellular	6	5	-	2	-
	BMZ	-	1	2	1	-
5	Fibrinogen deposition					
	Intercellular	-	-	-	-	-
	BMZ	-	-	1	-	-

Table3: Number of cases showing concordance between clinical, histopathological and immunofluorescence

Diagnosis	**Clinical Only**	**Clinical + Histopathological**	**Clinical + Immunofluorescence**	**Total**
Concordant Cases	69	69	69	69
Discordant Cases	6	6	6	6
Total				75

Immunofluorescence was positive in all the cases pointing to the diagnosis of the case (Table 2). Therefore the positive predictive value of Immunofluorescence is 100%. All these cases were diagnosed on Histopathology and no discordance was observed between the histopathology and immunofluorescence. However, the discordance was seen in 6 cases between clinical and histopathology cases4 of them were cutaneous small vessel vasculitis and 2 of them were Pemphigus vulgaris (Table-3).



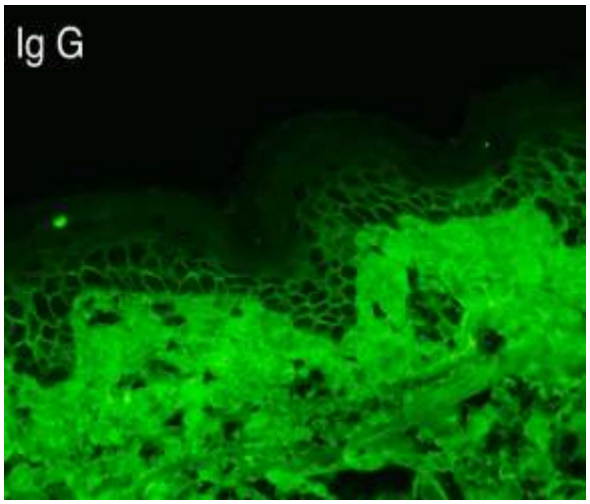
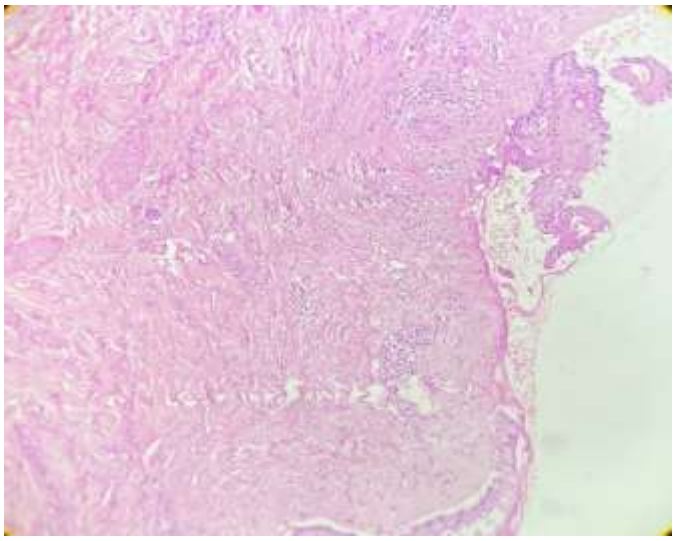


Fig 1 and 2: Direct immunofluorescence- Intercellular deposition of C3 and IgG like “fishnet or chicken-wire pattern” in case of Pemphigus vulgaris.

Fig-3: Subcorneal separation in case of Pemphigus foliaceous, H&E stain (10x)



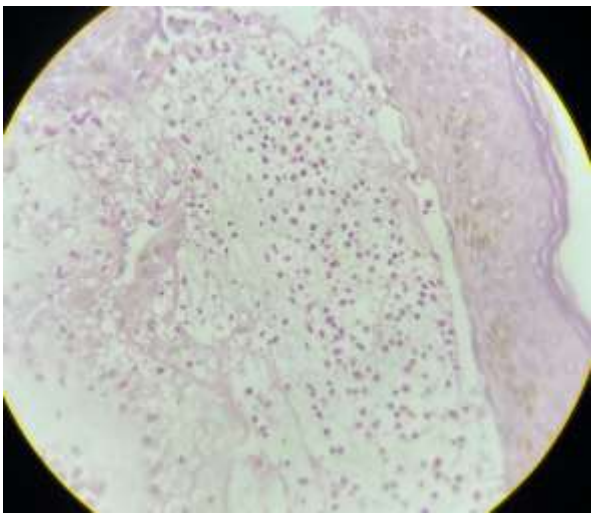


Fig-4: Basement membrane separation in case of Bullous pemphigoid, H&E stain (10x)

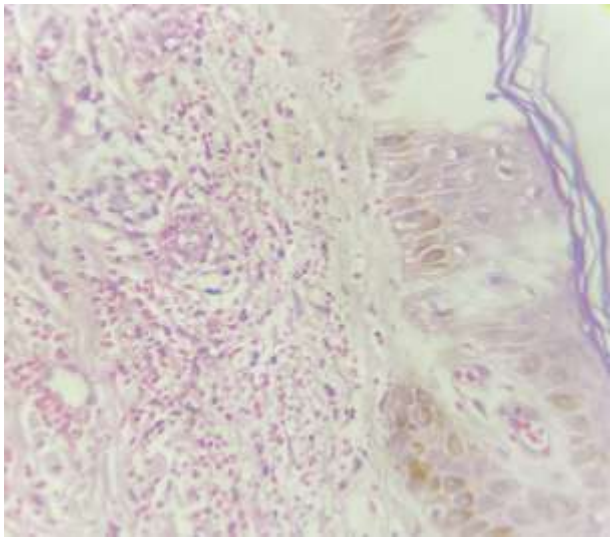


Fig-5: Perivascular mononuclear infiltrate in case of Small vessel leukocytoclastic vasculitis, H&E stain (10x)

Therefore the overall concordance is 92% and overall discordance is 8 %. The highest concordance was seen in cases of Bullous Pemphigoid, SLE and Pemphigus foliaceous (100%).
The highest discordance was seen in case of Cutaneous small vessel vasculitis which was 44% followed by Pemphigus vulgaris (33%).

DISCUSSION

In our study, we found a high degree of agreement among clinical assessments, histopathological examinations, and findings from direct immunofluorescence (DIF) testing. DIF proved to be an essential tool in accurately diagnosing immune-mediated skin disorders. However, there were a few cases where discordance was observed, particularly in instances of pemphigus vulgaris and bullous pemphigoid. DIF played a crucial role in cases where clinical features or histological findings were ambiguous, aiding in both confirming diagnoses when these were typical and guiding towards the exclusion of immunological causes in cases with atypical presentations. It is noteworthy that false-positive DIF results were not encountered during our study, highlighting its reliability in clinical practice.
The findings of our study align closely with published research on the concordance between clinical, histopathological, and direct immunofluorescence (DIF) diagnoses in autoimmune skin diseases.

Role of DIF in Diagnosing Autoimmune Skin Diseases: DIF is consistently highlighted as an essential diagnostic tool, particularly for autoimmune bullous diseases. Mysorekar et al. (2015) reported a very high concordance rate of 93.4% ($\kappa = 0.90$) between clinical, histological, and DIF results, underscoring its diagnostic precision. Similarly, Kudligi et al. emphasized the efficacy of histopathological examination alongside DIF, especially in cases with strong clinical suspicion. This reinforces the notion that DIF serves as a confirmatory test when other diagnostic methods are inconclusive, thereby enhancing diagnostic accuracy in dermatological practice

Concordance Rates: Our study's overall concordance rate of 92% is supported by similar findings in the literature. Studies have shown that the concordance for pemphigus vulgaris is around 81%, while it is lower for pemphigus foliaceus and bullous pemphigoid, with rates of 60% and 50%, respectively. These variations highlight the importance of considering DIF results alongside clinical and histopathological data to achieve comprehensive and accurate diagnoses. Such findings are in line with those reported by Mysorekar et al. and Karattuthazhathu et al., who confirmed the complementary role of DIF in diagnosing autoimmune skin diseases.

Challenges and Discordance: The discordance observed in our study, particularly in cases of cutaneous small vessel vasculitis and pemphigus vulgaris, is consistent with other findings. Slight to moderate discordance among clinical, histopathological, and DIF diagnoses is a common challenge in dermatology. For instance, De et al. highlighted that while DIF is invaluable, discrepancies can arise due to various factors such as the timing of biopsies and treatment-induced changes. This underscores the necessity of integrating multiple diagnostic modalities to achieve a comprehensive and accurate diagnosis.

Efficacy Across Different Conditions: Our study's observation that DIF was most effective in diagnosing bullous pemphigoid, systemic lupus erythematosus (SLE), and pemphigus foliaceus aligns with existing research. DIF is particularly useful in detecting immunocomplex deposition in these diseases, contributing significantly to accurate diagnosis and management. Ben Mordehai et al. noted similar findings, emphasizing the role of DIF in distinguishing these conditions from other dermatological disorders, thereby aiding in targeted treatment approaches

Recommendations for Clinical Practice: The integration of DIF with clinical and histopathological assessments, as emphasized in our study, is crucial for improving diagnostic accuracy. Kudligi et al. and Karattuthazhathu et al. both support this integrated approach, noting that DIF should be used as a complementary tool rather than an alternative to histopathological examination. This holistic approach ensures a more reliable diagnosis and better patient management in autoimmune skin diseases.

The study focused on the utility of DIF in diagnosing various immune-mediated skin disorders, particularly those characterized by vesiculobullous lesions. These disorders accounted for a significant proportion of the cases studied, with DIF proving diagnostically useful in the vast majority. Specifically, in cases of pemphigus vulgaris, DIF demonstrated a high sensitivity rate of 100% , confirming its effectiveness in identifying characteristic immunofluorescence patterns even in cases where clinical or histopathological features were not entirely typical. Similarly, in bullous pemphigoid, DIF was positive in 100% of cases

DIF's efficacy extended beyond vesiculobullous disorders to include other immune-mediated conditions such as lupus erythematosus and vasculitis. In these disorders, where clinical and histopathological features alone might not suffice for a conclusive diagnosis, DIF proved instrumental in confirming the presence of characteristic immunofluorescence patterns indicative of specific autoimmune processes. For instance, lupus band test (LBT) positivity was observed in all cases of lupus erythematosus included in the study, underscoring DIF's role in distinguishing lupus-specific skin manifestations from other dermatological conditions.

Additionally, the study addressed challenges and limitations associated with DIF. Treatment-induced changes were noted as potential causes of false-negative DIF results in some cases, particularly in diseases like pemphigus where treatment may alter immunofluorescence patterns over time. Strategies to mitigate these challenges, such as careful timing of biopsies relative to treatment cycles, were discussed to optimize the diagnostic yield of DIF in clinical practice.

Furthermore, the study acknowledged variations in DIF sensitivity across different immune-mediated disorders. While DIF showed high sensitivity rates in disorders like pemphigus vulgaris and bullous pemphigoid, its sensitivity in conditions such as dermatitis herpetiformis (DH) was lower. In DH, the study noted that histopathological and DIF findings often lacked specificity, necessitating reliance on a combination of clinical features, serological tests, and response to treatment for accurate diagnosis.

Beyond diagnostic applications, the study also explored prognostic implications of DIF findings, particularly in pemphigus where DIF positivity early in the disease course and changes in complement deposition patterns were

suggestive of disease activity and potential for relapse. However, it cautioned against using DIF as the sole prognostic marker due to its persistence even after clinical remission.

In conclusion, the study highlighted DIF as a valuable adjunctive tool for diagnosing immune-mediated dermatological disorders, particularly when clinical and histopathological features are inconclusive. Its ability to detect characteristic immunofluorescence patterns not only aids in confirming diagnoses but also plays a crucial role in excluding immunological causes when results are negative. The absence of false-positive results underscores its reliability, although challenges such as treatment-induced changes and variable sensitivity across different conditions necessitate careful interpretation and integration with clinical context. Overall, DIF remains indispensable in the diagnostic armamentarium for dermatologists, contributing significantly to the accurate classification and management of diverse autoimmune skin disorders.

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CONFLICT OF INTEREST:-The authors have no conflict of interest and nothing to declare.

AUTHOR CONTRIBUTIONS:-

R. Sowmya and *Nithin Diwagar* were responsible for the conceptualization, visualization, and overall administration of the study. *R. Sowmya* contributed to data curation and the initial drafting of the manuscript, while *Nithin Diwagar* oversaw validation and formal analysis. Both authors were actively involved in the manuscript revision process and have approved the final version for submission.

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