Dermatology Practical & Conceptual

Differential Expression of Claudin-3 and Claudin-1 in Mycosis Fungoides: Implications for Disease Monitoring

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Key words: Mycosis Fungoides, Claudin-1, Claudin-3, Disease Monitoring, Biomarker

Citation: Aktaş A, Erduran F, Tuğrul B, Eren F, Fırat Oğuz E. Differential Expression of Claudin-3 and Claudin-1 in Mycosis Fungoides: Implications for Disease Monitoring. *Dermatol Pract Concept*. 2025;15(4):5679. DOI: https://doi.org/10.5826/dpc.1504a5679

Accepted: June 28, 2025; **Published:** October 2025

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

ABSTRACT

Introduction: Claudins are integral transmembrane proteins that play a pivotal role in regulating tight junctions within epithelial and endothelial cells. In addition to their fundamental function in preserving cell-cell adhesion and barrier integrity, claudins are implicated in various biological processes, including those critical to cancer development and dermatological disorders. However, the role of claudin-1 and claudin-3 in mycosis fungoides (MF) pathogenesis remains unexplored and has yet to be comprehensively studied.

Objectives: This study aimed to investigate the serum levels of claudin-1 and claudin-3 in MF patients and assess their potential clinical significance as biomarkers for disease progression.

Methods: A total of 88 MF patients and 88 healthy controls were included in this case-control study. Serum claudin-1 and claudin-3 levels were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analyses were performed to compare claudin levels between groups and examine correlations with disease stage and duration.

Results: Serum claudin-3 levels were significantly higher in MF patients compared to controls ($P<0.001$), while no significant difference was observed in claudin-1 levels ($P=0.448$). Additionally, a weak but statistically significant positive correlation was found between claudin-3 levels and MF stage ($r=0.219$, $P=0.041$), suggesting its potential role in disease progression. No significant correlation was observed between claudin-1 levels and MF stage.

Conclusion: Our findings indicate that elevated serum claudin-3 levels are associated with MF and correlate with disease severity, suggesting that claudin-3 may serve as a valuable biomarker for monitoring disease progression. Further research is required to elucidate its underlying mechanisms and assess its potential as a therapeutic target in MF.

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Introduction

Claudins are integral membrane proteins that play a crucial role in the formation and function of tight junctions, which are essential to maintaining the integrity of epithelial and endothelial cell layers. They regulate paracellular permeability and are involved in various cellular processes, including growth and adhesion [1-3]. In recent years, these proteins have garnered significant attention and have been implicated in a variety of diseases [1,4]. Alterations in claudin expression have been implicated also in various malignancies, influencing tumor behavior, including proliferation, invasion, and metastasis [5].

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, characterized by the proliferation of malignant T lymphocytes in the skin. The pathogenesis of MF involves complex interactions between malignant cells and the skin microenvironment, leading to the disruption of normal skin architecture and function [6].

Among the claudin family, claudin-1 and claudin-3 have been identified as significant contributors to the structural and functional properties of the skin [1]. However, the specific roles of claudin-1 and claudin-3 in the pathogenesis of MF remain underexplored. Claudin-1 is a critical component of the skin's barrier function. Studies have shown that claudin-1-deficient mice experience significant water loss due to impaired tight junctions in the epidermis, highlighting its importance in maintaining skin integrity [7]. In the context of MF, although disruptions in skin barrier function are not directly studied, alterations in claudin expression could contribute to such barrier defects. Research on various skin cancers has demonstrated changes in claudin expression [8,9]. A previous study showed that claudins 1, 2, 3, 4, 5, and 7 exhibit distinct expression patterns in solar keratosis and cutaneous squamous cell carcinoma, supporting their involvement in the progression from premalignant to malignant lesions [10] Although MF is a distinct entity, these findings can imply that claudins may influence the behavior of skin malignancies.

Understanding the expression patterns of these proteins in MF could provide valuable insights into the mechanisms underlying the disease and may offer potential biomarkers for diagnosis and prognosis. Furthermore, monitoring serum claudin levels during treatment may provide insights into treatment efficacy and potential resistance mechanisms [4].

Objectives

Our study aimed to investigate the serum levels of claudin-1 and claudin-3 in patients with MF and to assess their potential clinical significance in the context of MF.

Methods

Ethical Approval and Study Design

Prior to the study, ethical approval was obtained from the Ankara Bilkent City Hospital Ethics Committee on 4 September 2024, under protocol number TABED 2-24-453. The study included 88 patients diagnosed with MF, and 88 age- and sex-matched healthy controls. All participants provided informed consent before the study. Data collected from patients included age, sex, disease duration, and disease stage.

Inclusion and Exclusion Criteria for the Participants

Participants aged 18 and over were included in the study. Exclusion criteria for the participants included individuals with inflammatory bowel disease, those who had experienced acute or chronic gastrointestinal infections within the three months preceding the study, individuals who had undergone any gastrointestinal surgery within the six months prior, unexplained weight loss, nonsteroidal anti-inflammatory drug use within the week before the study, individuals on a diet regimen, use of antibiotics, probiotics, or synbiotics within the three months prior, a history of malignancy, alcohol dependence, and/or chronic liver and pancreatic diseases; pregnant and breastfeeding females were also excluded.

Peripheral venous blood samples were collected after a 12-hour fasting period. After a 2-hour clotting period in serum separation tubes, samples were centrifuged at 1000×g for 20 minutes. The resulting serum aliquots were stored at –80° C until further analysis.

The concentrations of target proteins in the test samples were estimated based on previous studies [11], and an

appropriate dilution factor was selected to ensure that the diluted target protein concentrations fell within the optimal detection range of the kit. Concentrations read from the standard curve were multiplied by the dilution factor. All measurements were performed in accordance with the manufacturer's instructions.

To measure serum claudin-1 and claudin-3 levels (ng/ml), commercially available enzyme-linked immunosorbent assay (ELISA) kits from Elabscience, Texas, USA, were utilized. The kits used were:

- **Claudin-1** (Catalog No: E-EL-H0745; Lot No: WP-24FHJ89507; Detection Range: 0.16–10 ng/ml; Sensitivity: 0.09 ng/ml)
- **Claudin-3** (Catalog No: E-EL-H0754; Lot No: WP2346048679; Detection Range: 0.31–20 ng/ml; Sensitivity: 0.19 ng/ml)

Each measurement was performed in duplicate, and the average values were used for further analysis. For the aforementioned ELISA analyses, intra-assay and inter-assay coefficient of variation (CV) values were found to be below 10%.

Statistical Analysis

Data analysis was conducted using SPSS 11.5 software. Descriptive statistics for quantitative variables are reported as mean ± standard deviation and median (minimum-maximum), while qualitative variables are described by frequency (percentage). To assess the differences between two categories of a qualitative variable concerning quantitative variables, the Student's t-test was used if the normality assumption was met, and the Mann-Whitney U test was employed if normality was not assumed. To examine the relationship between two quantitative variables, the Spearman correlation test was used, as the normality assumption was not satisfied. The chi-square test was applied to assess the relationship between two qualitative variables. The statistical significance level was set at 0.05.

Results

Among the participants, 88 (50.0%) were diagnosed with MF, and 88 (50.0%) were in the control group. The average age of the patients with MF was 50.95 ± 13.98 years, whereas the average age of the control group was 52.39 ± 12.73 years. The mean age at disease onset and disease duration in MF patients were 41.97 ± 13.43 years and 8.85 ± 10.43 years, respectively. Regarding the disease stage, 38 (43.2%) patients were in stage 1A, 30 (34.1%) in stage 1B, 13 (14.8%) in stage 2A, five (5.7%) in stage 2B, one (1.1%) in stage 3A, and one (1.1%) in stage 4A. The mean claudin-1 and claudin-3 values for the participants were 13.45 ± 3.65 ng/mL and 1064.56 ± 261.71 ng/mL, respectively (Table 1).

There was no significant difference between the two groups in terms of sex and age (P=0.227 and P=0.079,

Table 1. Descriptors of Demographic Data.

Variables		Descriptive Statistics
Group, N (%)	MF	88 (50.0)
	Control	88 (50.0)
Sex, N (%)	Female	84 (47.7)
	Male	92 (52.3)
Age at disease onset (year)	Mean±SD	41.97±13.43
	Median (Min-Max)	43.00 (10.00-75.00)
Disease duration (year)	Mean±SD	8.85±10.43
	Median (Min-Max)	5.00 (0.50-78.00)
MF stage, N (%)	1A	38 (43.2)
	1B	30 (34.1)
	2A	13 (14.8)
	2B	5 (5.7)
	3A	1 (1.1)
	4A	1 (1.1)
Claudin-1 (ng/mL)	Mean±SD	13.45±3.65
	Median (Min-Max)	13.78 (4.85-23.80)
Claudin-3 (ng/mL)	Mean±SD	1064.56±261.71
	Median (Min-Max)	1037.26 (524.78-1724.92)

Abbreviations: SD: standard deviation, Min: minimum, Max: maximum, MF: Mycosis fungoide

Table 2. Comparisons of Variables between MF and Control groups.

Variables		MF	Control	p-value
Age (year)	Mean±SD	50.95±13.98	52.39±12.73	0.079[a]
	(Min-Max)	(18.00-82.00)	(30.00-83.00)	
Sex, N (%)	Female	38 (43.2)	46 (52.3)	0.227[c]
	Male	50 (56.8)	42 (47.7)	
Claudin-1 (ng/mL)	Mean±SD	13.66±3.73	13.24±3.58	0.448[a]
	Median (Min-Max)	13.77 (4.85-21,40)	13.78 (6,33.23,80)	
Claudin-3 (ng/mL)	Mean±SD	1223.45±226.09	905.67±188.65	**<0.001[b]**
	Median (Min-Max)	1202.35 (687.09-1724.92)	877.50 (524.78-1613.26)	

Abbreviations: SD: standard deviation Min: minimum, Max: maximum, a: Student's t-test b: Mann-Whitney U test c: chi-square test, MF: Mycosis fungoides.

respectively). However, a significant difference was found between the two groups regarding claudin-3 levels (P=0.079 and P<0.001, respectively). The mean claudin-3 (ng/mL) level was significantly higher in the MF group compared to the control group. Table 2 **presents the comparisons of variables between the MF and control groups.**

No significant correlation was found between MF stage and claudin-1 levels, whereas a weak but statistically significant positive correlation was observed between claudin-3 levels and MF stage (r=0.219, P=0.041). As the stage of MF increased, claudin-3 levels also increased. Table 3 **examines the relationship between claudin levels and the stage of MF.**

No significant correlation was found between claudin levels and either disease duration or disease onset age (P>0.05). Table 4 **examines the relationship between claudin levels and disease duration and disease onset age.**

Table 3. The Relationship between Claudin Levels and MF Stages.

Claudin Level		MF stage
Claudin-1 (ng/mL)	Correlation Coefficient	–0.002
	p value	0.982[a]
Claudin-3 (ng/mL)	Correlation Coefficient	0.219
	p value	**0.041[a]**

a: Spearman correlation test, MF: Mycosis fungoides

Discussion

The current study focused on evaluating serum claudin-1 and claudin-3 levels in patients with MF and their potential role as biomarkers for disease progression. Our findings demonstrate that serum claudin-3 levels were significantly elevated in the MF group compared to controls. Moreover, serum claudin-3 levels showed a positive correlation with disease stage, suggesting its involvement in the pathophysiology and progression of MF. In contrast, serum claudin-1 levels did not differ significantly between MF patients and controls, nor did it correlate with disease stage. These results suggest that claudin-3 may serve as a valuable biomarker for disease monitoring in MF, while claudin-1 appears to have limited utility in this context.

Alterations in claudin expression have been extensively documented in various malignancies. For instance, claudin-1 is one of the most widely studied claudins in cancer research, but its role as either a tumor promoter or suppressor remains controversial. In some cancers, reduced claudin-1 expression has been associated with enhanced tumor invasion and progression, whereas in others, its loss has been linked to improved patient outcomes [1,3,4,12]. In breast cancer, the expression of claudin-1 varies across pathological subtypes, with downregulation frequently associated with increased invasiveness and poor prognosis. Conversely, elevated claudin-1 expression has been observed in certain basal-like breast cancer subtypes [13]. Similarly, in esophageal squamous cell carcinoma, reduced claudin-7 expression is associated with enhanced invasiveness and metastatic potential , highlighting the complex role of claudins in cancer biology [14].

Claudin-3, primarily expressed in the epidermis and other epithelial tissues, plays a key role in regulating the permeability of tight junctions. Interestingly, both downregulation and upregulation of claudin-3 can contribute to tumor progression in a tumor-type-dependent manner [15]. In urothelial carcinomas, a strong correlation has been observed between claudin-3 upregulation and tumor grade and stage progression, aligning with findings from Nakanishi et al., who reported a link between high claudin-3 expression and advanced stage, high grade, and poor overall survival in a cohort of 129 upper urinary tract urothelial cancers [16]. In colorectal adenocarcinoma, nuclear localization of claudin-3 has been linked to tumor progression [17].

Table 4. The Relationship between Claudin Levels, Disease Duration, and Age at Disease Onset.

Claudin Level		Disease duration (year)	Disease onset - age (year)
Claudin-1 (ng/mL)	Correlation Coefficient	0.032	0.187
	p-value	0.768[a]	0.081[a]
Claudin-3 (ng/mL)	Correlation Coefficient	0.113	–0.095
	p-value	0.293[a]	0.381[a]

a: Spearman correlation test

In the context of MF, its overexpression may suggest either a compensatory response or a pathogenic factor contributing to disease progression. Elevated claudin-3 levels could enhance tumor development by strengthening cell-cell adhesion, facilitating the accumulation of malignant cells, or promoting the epithelial-to-mesenchymal transition, a crucial process in cancer metastasis [15]. We think the elevated claudin-3 expression observed in the current study may contribute to disease progression by enhancing tumor cell proliferation and invasiveness. The positive correlation between claudin-3 levels and disease stage further supports its potential role in MF advancement.

The role of claudin-3 as a biomarker extends to dermatology beyond oncology. Increased serum claudin-3 levels have been reported in psoriasis patients, indicating impaired intestinal permeability. This dysfunction suggests a potential avenue for therapeutic intervention by targeting the intestinal barrier [18]. Furthermore, claudin-1 has been evaluated as a potential biomarker in psoriasis, with reduced levels observed in specific subtypes and correlated with disease onset [19]. In another study, alterations in claudin expression were observed in chronic plaque psoriasis, with claudin-1 being absent in the epidermis of psoriatic plaques, while typical staining patterns are present in clinically normal skin [20]. These studies emphasize the diverse roles of claudins in various diseases and their potential as therapeutic targets.

To the best of our knowledge, there is a lack of studies in the current literature specifically assessing serum claudin-1 and claudin-3 levels in patients with MF or other cutaneous lymphomas. Our study contributes to this growing body of evidence by establishing a significant association between elevated serum claudin-3 levels and disease severity in MF. The findings align with prior research highlighting the involvement of tight junction proteins in cancer progression. While no significant association was identified between claudin levels and disease duration or age at onset, these findings may be influenced by the limited sample size of the study. Larger cohorts and longitudinal studies are needed to validate these results and explore the potential mechanistic pathways linking claudin-3 to MF pathogenesis.

Conclusions

In conclusion, this study provides compelling evidence that serum claudin-3 levels are significantly elevated in MF patients and correlate positively with disease stage. These findings suggest that claudin-3 may serve as a useful biomarker for assessing disease progression in MF. Further research is warranted to elucidate the precise role of claudin-3 in the pathogenesis of MF and to investigate its potential as a therapeutic target in this and other malignancies.

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