



Estimation Of Clic1 Plasma Concentration In Patients With Oral Squamous Cell Carcinoma And Its Clinicopathological Correlation

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Abstract

Background

Oral Squamous Cell Carcinoma (OSCC) is one of the most prevalent malignancies of the oral cavity, particularly in developing countries. Early diagnosis and prognostic assessment remain challenging despite advances in treatment modalities. Chloride Intracellular Channel Protein 1 (CLIC1) has emerged as a potential biomarker in various cancers due to its role in cell proliferation, migration, invasion, and tumor progression.

Aim

To estimate plasma CLIC1 concentration in patients with OSCC and evaluate its correlation with clinicopathological parameters.

Materials and Methods

A case-control study was conducted involving patients diagnosed with histopathologically confirmed OSCC and healthy controls. Plasma samples were collected from all participants and analyzed for CLIC1 concentration using enzyme-linked immunosorbent assay (ELISA). Clinicopathological parameters including age, gender, tobacco habits, tumor site, TNM stage, histopathological grade, lymph node status, and tumor size were recorded. Statistical analysis was performed to compare plasma CLIC1 levels between groups and determine correlations with clinicopathological variables.

Results

Plasma CLIC1 concentrations were significantly elevated in OSCC patients compared with healthy controls. Increased CLIC1 levels demonstrated a positive association with advanced TNM stage, larger tumor size, lymph node metastasis, and poor histological differentiation. Significant correlations suggested that CLIC1 expression may reflect tumor aggressiveness and disease progression.

Conclusion

Plasma CLIC1 concentration is significantly increased in OSCC patients and exhibits strong clinicopathological correlations. CLIC1 may serve as a promising non-invasive biomarker for diagnosis, prognosis, and disease monitoring in OSCC.

Keywords: Oral Squamous Cell Carcinoma, CLIC1, Biomarker, Plasma Concentration, ELISA, Clinicopathological Correlation

Introduction

Oral squamous cell carcinoma (OSCC) is one of the most common malignancies of the oral cavity and represents the predominant histological type of oral cancer. The global burden of oral cancer remains substantial, with considerable geographic variation and a particularly high burden in South and Southeast Asia. Tobacco use, smokeless tobacco, areca nut, alcohol consumption and other environmental and behavioural factors contribute substantially to oral carcinogenesis.^{1–5} Despite advances in surgery, radiotherapy and systemic treatment, prognosis remains strongly dependent on stage at diagnosis, and delayed diagnosis continues to contribute to poor outcomes.^{3–5}

Early diagnosis and accurate prognostic assessment are therefore essential for improving patient outcomes. Conventional diagnosis is primarily based on clinical examination followed by biopsy and histopathological assessment. Although histopathology remains the diagnostic gold standard, considerable interest has developed in minimally invasive biomarkers that could assist in early detection, risk stratification, prognosis and treatment monitoring. Serum, plasma and salivary biomarkers have consequently been investigated as potential adjunctive tools in oral cancer diagnosis and prognosis.^{6–10}

Cancer development and progression are associated with multiple molecular alterations, including uncontrolled cellular proliferation, resistance to apoptosis, altered cell adhesion, epithelial–mesenchymal transition, oxidative stress and dysregulation of intracellular signalling pathways. These alterations have led to the investigation of proteins, nucleic acids, metabolites and other cellular molecules as potential biomarkers of malignant transformation and tumour behaviour.^{6–10}

Ion channels are membrane proteins involved in maintaining cellular homeostasis and regulating several physiological processes. Chloride channels participate in the regulation of cell volume, intracellular pH, membrane potential, proliferation, migration and apoptosis. Increasing evidence suggests that dysregulation of ion-channel activity contributes to tumour development and progression, making ion channels potential molecular targets in cancer biology.^{11,12}

The chloride intracellular channel (CLIC) family consists of six members, CLIC1–CLIC6. CLIC1 is one

of the most extensively studied members of this family and is unusual because it exists in both soluble cytoplasmic and membrane-associated forms. Its conformational and functional state is influenced by cellular redox conditions. CLIC1 has been implicated in cell-cycle progression, oxidative stress, intracellular signalling, migration and invasion.^{11–15}

The involvement of CLIC1 in tumour biology has been demonstrated in several malignancies. Increased CLIC1 expression has been reported in glioblastoma, gastric cancer, colorectal cancer, prostate cancer, hepatocellular carcinoma, breast cancer, ovarian cancer, pancreatic cancer and oesophageal squamous cell carcinoma.^{13–24} Functional studies have shown that CLIC1 can promote tumour-cell proliferation, migration, invasion, angiogenesis and survival through different signalling mechanisms, including MAPK/ERK, ROS-related pathways, PI3K/AKT and mTOR signalling.^{16–24}

In oral squamous cell carcinoma, Xu *et al.* demonstrated that CLIC1 was significantly increased in both tumour tissue and plasma. Their study further showed associations between CLIC1 expression and histological grade, TNM stage and tumour size, while high CLIC1 expression was associated with poorer overall survival.²⁵ These findings provide direct evidence supporting the investigation of circulating CLIC1 as a potential biomarker in OSCC.

Feng *et al.* further demonstrated that CLIC1 promotes OSCC progression by enhancing proliferation, migration, invasion and angiogenesis. CLIC1 depletion decreased integrin $\alpha v/\beta 1$, phosphorylated ERK, vimentin, MMP-2 and MMP-9, while increasing E-cadherin and apoptosis-related proteins. These findings suggest that CLIC1 may contribute to OSCC progression through integrin-associated MAPK/ERK and related signalling pathways.²⁶

More recently, Wojtera *et al.* evaluated plasma CLIC1 in patients with OSCC and reported an association between plasma CLIC1 concentration and lymph-node metastasis, further supporting the potential value of circulating CLIC1 as a prognostic biomarker.²⁷

The biological importance of CLIC1 is also supported by studies in other malignancies. CLIC1 has been shown to regulate ROS/ERK-dependent migration and invasion in colorectal cancer,²⁸ MAPK/ERK-mediated proliferation and migration in prostate cancer,²⁹

angiogenesis through VEGFA modulation in hepatocellular carcinoma,²³ and mTOR-dependent proliferation in oesophageal squamous cell carcinoma.²⁴ Recent work has also demonstrated a role for CLIC1 in pancreatic tumour growth and metabolic adaptation.³⁰

Considering the increasing evidence linking CLIC1 with tumour progression and its detectability in plasma, the present study was undertaken to estimate plasma CLIC1 concentration in patients with histopathologically confirmed OSCC and to evaluate its correlation with clinicopathological parameters. The findings may contribute to determining whether plasma CLIC1 can serve as a minimally invasive biomarker for disease progression and prognosis in OSCC.

Materials and Methods

Study Design

A hospital-based case-control study.

Study Population

The study included patients diagnosed with histopathologically confirmed OSCC attending the Department of Oral Pathology and related oncology units.

Sample Size

The study comprised:

Group 1: Healthy controls (n = 45)

Group 2: Patients with OSCC (n = 45)

Inclusion Criteria

Group 1 – Healthy Controls

Inclusion criteria -

1. Healthy individuals

Exclusion criteria -

1. Presence of any oral disease, Oral squamous Cell carcinoma, Oral Potentially Malignant Disorders
2. Individuals with any systemic disease.
3. Individuals with history of prior malignancy

Group 2- Oral Squamous Cell Carcinoma (OSCC):

Inclusion criteria

Patients with histopathologically diagnosed Oral squamous cell Carcinoma.

Exclusion criteria

1. Patients with any other soft tissue or bony lesions.
2. Patients with any systemic disease.
3. Patients with any of the following: second any primary tumor, local recurrence, or a history of previous chemotherapy or radiotherapy.

Data Collection

Clinical details including:

1. Age
2. Gender
3. Tobacco and alcohol habits
4. Tumor site
5. TNM stage
6. Histopathological grade

were recorded using a standardized proforma.

Blood Sample Collection

Approximately 2 mL of venous blood was collected under aseptic conditions. Plasma was separated by centrifugation and stored at -20°C until analysis.

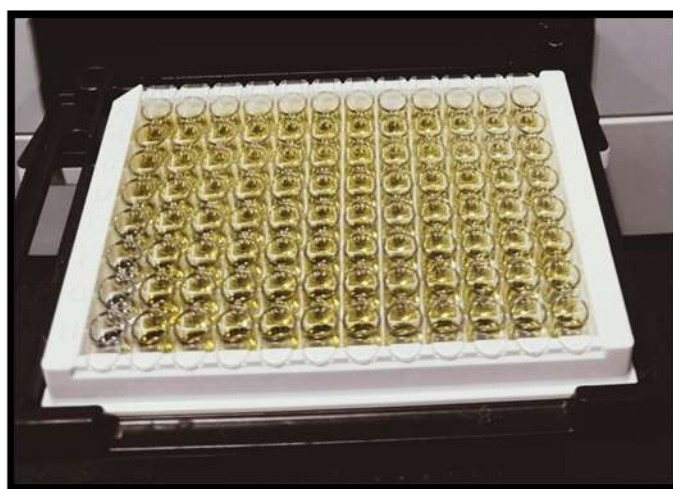
Estimation of Plasma CLIC1

Plasma CLIC1 concentrations were measured using a commercially available ELISA kit (Bioassay technology Lab.) according to the manufacturer's protocol. Optical density values were recorded and concentrations were calculated using standard calibration curves.

Photograph No. 1: ELISA reagents used for estimation of Plasma CLIC1 concentration (Bioresource)



Photograph No. 2: Micro ELISA Plate pre-coated with an antibody specific to Human CLIC1



Statistical Analysis

Data obtained was compiled on a MS office excel sheet (v 2010, Microsoft Redmond Campus, Redmond, Washington, United States).

1. Data was subjected to statistical analysis using a statistical package for social sciences (SPSSv 21.), IBM).
2. Descriptive statistics like frequencies and percentage for categorical data, mean and SD for numerical data has been depicted.

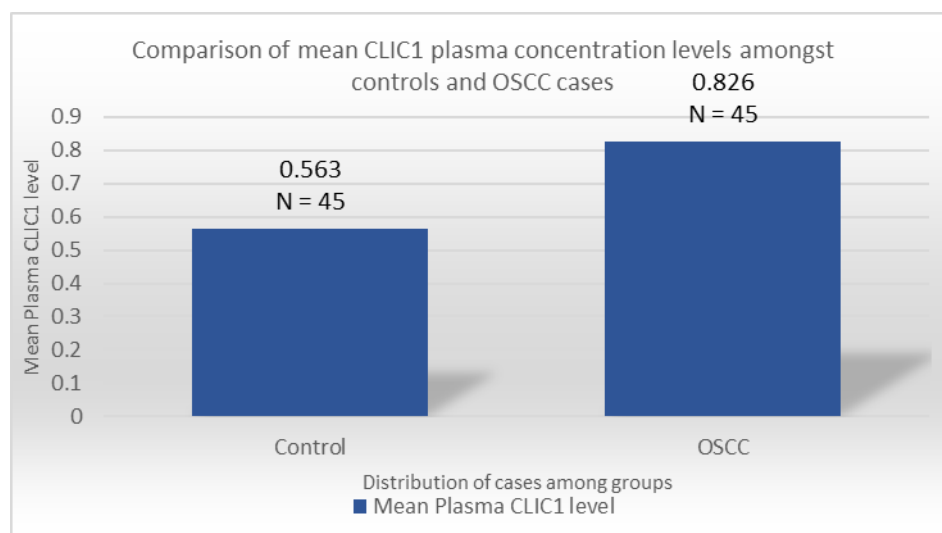
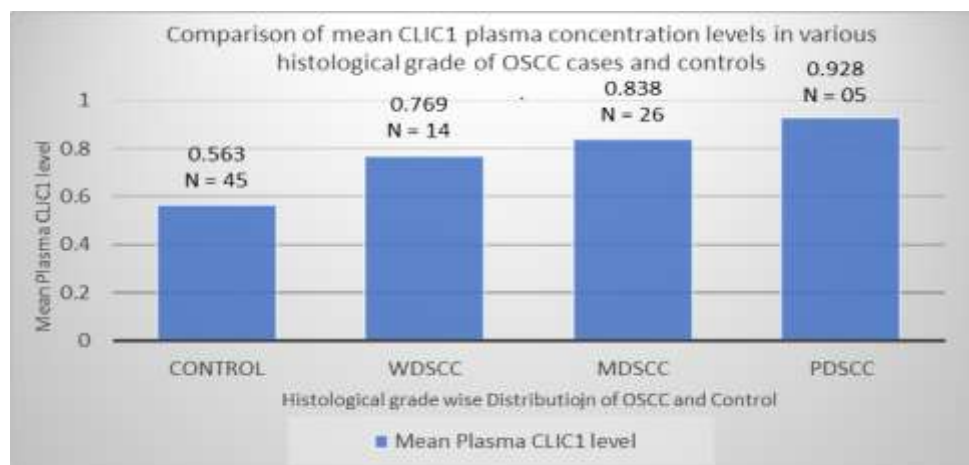
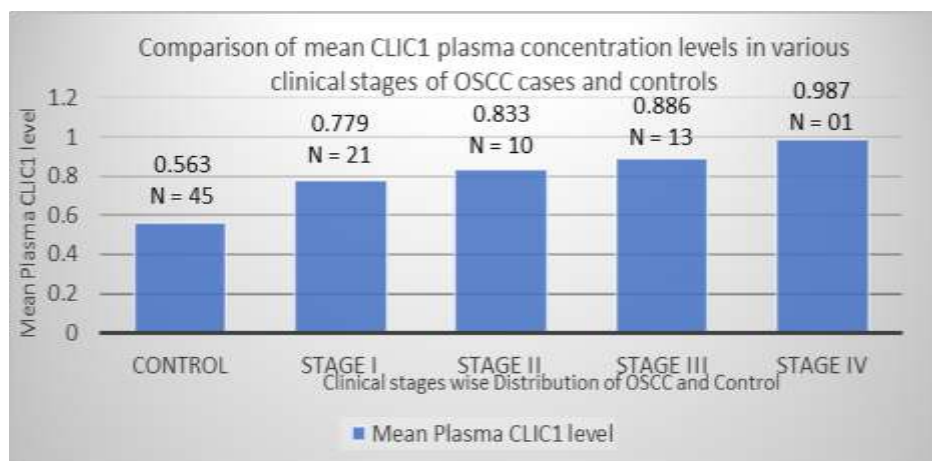
3. Inter-group comparison (> 2 groups) was done using one way ANOVA followed by pair-wise comparison using a post hoc test.
4. For all the statistical tests, $p < 0.05$ was considered to be statistically significant, keeping α error at 5 % and β error at 20% , thus giving a power to the study as 80 %.

Results

The present study included 45 Oral Squamous Cell Carcinoma (OSCC) and 45 Healthy controls. Demographic findings of all study subjects were

recorded. Estimation of CLIC1 plasma concentration level were done using a commercially available ELISA Kit. Clinical staging of all patients having OSCC was done by TNM classification given by AJCC cancer staging atlas 2018 and histopathological grading was done according to Anneroth G et al; 1987

The results were tabulated according to age, gender, anatomical site, oral habits, clinical staging and histopathological grading for OSCC cases along with plasma CLIC1 concentration.



The mean plasma CLIC1 concentration was significantly higher in OSCC patients compared to healthy controls ($p < 0.05$).

Higher plasma CLIC1 levels were observed among:

- Advanced TNM stage patients.
- Cases with lymph node metastasis.
- Poorly differentiated carcinomas.

A statistically significant positive correlation was identified between plasma CLIC1 concentration and disease severity indicators.

Discussion

Oral squamous cell carcinoma remains a major global health problem and represents the predominant malignant neoplasm of the oral cavity. Its burden is particularly significant in countries such as India, where tobacco and areca-nut consumption remain important risk factors.^{1-5,31} Despite advances in treatment, delayed presentation and advanced disease continue to influence prognosis. Consequently, the identification of reliable and minimally invasive biomarkers remains an important area of OSCC research.⁶⁻¹⁰

The present study evaluated plasma CLIC1 concentration in OSCC patients and healthy controls and examined its relationship with clinicopathological characteristics. The results demonstrated a significantly higher mean plasma CLIC1 concentration in OSCC patients compared with healthy controls. This observation is consistent with the findings of Xu et al., who reported significant overexpression of CLIC1 in OSCC tissue and plasma and demonstrated associations with tumour size, histological grade and TNM stage.²⁵

The increased plasma concentration of CLIC1 observed in OSCC may reflect the biological involvement of CLIC1 in malignant transformation and tumour progression. CLIC1 is a redox-sensitive protein that can undergo changes between soluble and membrane-associated forms. Its membrane-associated form can function as an ion channel, whereas its intracellular functions are associated with cell-cycle regulation, oxidative stress and signalling pathways.¹¹⁻¹⁵ These properties provide a biological basis for the association between increased CLIC1 and malignant behaviour.

In the present study, the majority of OSCC patients belonged to the fifth and sixth decades of life, with a marked male predominance. Similar demographic patterns have been reported in epidemiological studies of oral cancer, particularly in populations with substantial exposure to tobacco and areca nut.^{3-5,31} The predominance of buccal mucosa in the present study is also consistent with the widespread use of smokeless tobacco products, which are frequently placed in the buccal vestibule. Tobacco and smokeless tobacco exposure are established risk factors for oral cancer in India.^{4,5,31}

All OSCC patients in the present study had a history of tobacco-related habits. This observation reinforces the established relationship between tobacco exposure and oral carcinogenesis. Systematic reviews of Indian studies have demonstrated a significant association between smokeless tobacco use and malignant and potentially malignant oral lesions.⁵ Areca nut is also an established carcinogenic exposure and contributes substantially to the oral cancer burden in South and Southeast Asia.^{4,31}

The principal finding of the present study was the significantly increased plasma CLIC1 concentration in OSCC patients compared with controls. The mean plasma CLIC1 concentration increased from 0.563 ± 0.032 ng/ml in controls to 0.826 ± 0.046 ng/ml in OSCC patients. This finding is particularly relevant because Xu et al. directly demonstrated increased CLIC1 protein levels in the plasma of OSCC patients using ELISA and reported that CLIC1 was associated with clinicopathological characteristics and overall survival.²⁵

The present findings are also supported by Wojtera et al., who investigated plasma CLIC1 concentration in OSCC and demonstrated an association with lymph-node metastasis.²⁷ Taken together, these studies suggest that circulating CLIC1 may reflect biological features associated with tumour aggressiveness and metastatic potential.

In the present study, no statistically significant association was observed between plasma CLIC1 concentration and age, sex, anatomical site or oral habits. Although slightly higher CLIC1 levels were observed in females and in patients with labial mucosal lesions, these observations should be interpreted cautiously because of the small sample size and uneven distribution of subjects across these

subgroups. The absence of statistical significance in these demographic comparisons does not necessarily exclude a biological association; rather, larger cohorts with more uniform subgroup distribution would be required to investigate these relationships adequately.

A significant association was observed between plasma CLIC1 concentration and clinical stage. Plasma CLIC1 levels progressively increased from Stage I to Stage IV, with the highest concentration observed in Stage IV disease. This progressive increase suggests that circulating CLIC1 may parallel increasing tumour burden and disease severity. The observation is consistent with Xu et al., who reported an association between CLIC1 expression and TNM stage in OSCC.²⁵

The association between CLIC1 and tumour progression is also biologically supported by experimental studies. Feng et al. demonstrated that CLIC1 depletion inhibited OSCC-cell proliferation, migration, invasion and angiogenesis. CLIC1 silencing was associated with reduced integrin $\alpha v/\beta 1$, phosphorylated ERK, vimentin, MMP-2 and MMP-9, together with increased E-cadherin and apoptosis-related proteins.²⁶ These findings indicate that CLIC1 may promote a more aggressive tumour phenotype through pathways involved in cell adhesion, epithelial-mesenchymal transition, extracellular matrix degradation and intracellular signalling.

The relationship between CLIC1 and aggressive tumour behaviour is not restricted to OSCC. CLIC1 has been implicated in ROS/ERK-dependent migration and invasion in colorectal cancer,²⁸ MAPK/ERK-dependent proliferation and migration in prostate cancer,²⁹ and mTOR-dependent proliferation in oesophageal squamous cell carcinoma.²⁴ In hepatocellular carcinoma, increased CLIC1 expression has also been associated with angiogenesis and poorer survival.²³ These observations support the concept that CLIC1 may act as a broadly relevant regulator of malignant behaviour.

Histopathological grading in the present study also demonstrated increasing plasma CLIC1 concentrations with poorer differentiation. Poorly differentiated OSCC showed the highest mean CLIC1 concentration, followed by moderately and well-differentiated tumours. This finding is consistent with the study by Xu et al., in which CLIC1 expression was significantly associated with histological grade.²⁵ The

association may indicate that increased CLIC1 expression accompanies dedifferentiation and acquisition of more aggressive biological characteristics.

The biological significance of CLIC1 may be explained partly by its role in redox regulation and signalling. CLIC1 can exist in soluble and membrane-associated conformations and its membrane localisation and activity are influenced by the cellular redox environment.¹¹⁻¹⁵ CLIC1-related signalling has been associated with ROS production, ERK activation, cell-cycle progression, migration, invasion and angiogenesis.^{16-20, 28, 29} Thus, increased CLIC1 in OSCC may represent both a marker and a contributor to malignant progression.

The potential therapeutic relevance of CLIC1 is supported by experimental studies in other malignancies. In glioblastoma, CLIC1 targeting has been shown to inhibit cancer-stem-cell proliferation and tumourigenic properties.¹⁷⁻²⁰ CLIC1 inhibition has therefore been proposed as a potential therapeutic strategy, although translation into clinical oncology remains preliminary. These findings provide a rationale for further investigation of CLIC1-targeted approaches in OSCC, particularly because CLIC1 has demonstrated functional involvement in OSCC-cell proliferation, invasion and angiogenesis.²⁶

Overall, the present study demonstrates that plasma CLIC1 concentration is significantly elevated in OSCC and increases progressively with advancing clinical stage and histopathological grade. The findings, together with previous OSCC studies, support the potential role of CLIC1 as a minimally invasive biomarker associated with tumour progression.²⁵⁻²⁷ However, the present findings should be interpreted in the context of the relatively small sample size and unequal distribution of patients among clinical stages and histopathological grades. Larger prospective, multicentric studies with appropriate subgroup representation and long-term follow-up are required to determine the diagnostic, prognostic and therapeutic utility of plasma CLIC1.

CONCLUSION

The findings of the present study demonstrate that plasma CLIC1 concentration is significantly elevated in patients with OSCC compared with healthy controls and increases with advancing clinical stage and

histopathological grade. These findings are consistent with previous studies demonstrating increased CLIC1 expression in OSCC and its association with tumour progression and metastatic behaviour.²⁵⁻²⁷

The significant association between increased plasma CLIC1 levels and advanced disease supports its potential role as a minimally invasive prognostic biomarker. In view of the demonstrated involvement of CLIC1 in OSCC proliferation, migration, invasion and angiogenesis,²⁶ CLIC1 may also represent a potential therapeutic target. Nevertheless, larger multicentric studies with long-term follow-up and independent validation are necessary before plasma CLIC1 can be considered for routine clinical application.

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