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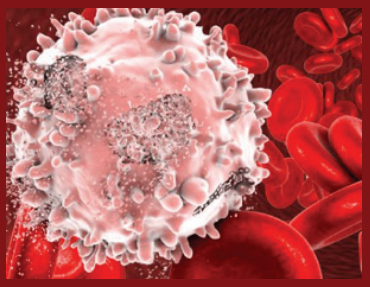
Research Article: Uric Acid, Serum Urea, Creatinine, And Profiling In Oral Cancer: A Prospective Comparative Study



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Abstract

Introduction: Oral squamous cell carcinoma (OSCC) is a prevalent global malignancy, imposing substantial social and financial burdens. Understanding the fundamental processes driving OSCC may yield novel therapeutic avenues to enhance disease management and patient survival. Our study seeks to evaluate serum urea, creatinine, and uric acid levels in oral cancer patients compared to a healthy control group.

Methodology: In this prospective comparative study, we enrolled 60 OSCC patients and 60 healthy controls. We assessed serum urea, creatinine, and uric acid levels at OSCC diagnosis and collected clinical and laboratory data. Subsequently, we examined these serum concentrations, correlating them with the disease's clinicopathological features.

Results: In our study, we observed that OSCC patients (mean age: 54.48±11.52 years) outnumbered controls (mean age: 53.24±10.19 years) with a male predominance (68.33%). Significant differences existed in smoking and alcohol use between the groups. TNM stage 4 (41.67%) was the most prevalent among cases, and most had advanced disease (TNM 3-4, 60.00%). Lymph node metastasis was frequent in positive neck cases (53.33%), and histologically, most cases were moderately differentiated (65.00%). Most cases were alive (71.67%) concerning disease-related survival. In linear regression analysis, OSCC patients displayed significantly lower serum urea levels compared to controls, with age, smoking, and lymph node invasion significantly influencing urea levels. Multiple linear regression confirmed these variables' impact on serum urea levels.

Conclusion: Patients with advanced OSCC exhibit reduced serum urea levels correlated with lymph node metastasis. Dysregulation of protein catabolism processes may potentially enhance the invasive characteristics of OSCC, fostering their aggressive behaviour.

Keywords: Oral Cancer, OSCC, Urea, Creatine, Uric Acid

Introduction

Oral squamous cell carcinoma (OSCC) stands as the predominant malignancy within the head and neck region, constituting approximately 92%-95% of all oral cancer cases. [1] This disease exhibits a notable predilection for males, with incidence rates two to three times higher than those for females, largely attributed to higher rates of tobacco and alcohol consumption among men. In 2005, the World Health Organization (WHO) defined potentially malignant disorders (PMDs) as conditions or lesions with the potential to progress to cancer in the future. [1] Several factors contribute to the genesis of oral cancer, and avoidance of established risk factors, such as tobacco use in any form, including chewing tobacco products like pan masala, khaini, and gutka, as well as areca nut, can significantly reduce the risk of developing oral cancer. Furthermore, it is well-documented that alcohol and nicotine exert a synergistic effect, compounding the risk. [2] Research indicates that most oral squamous cell carcinomas arise from premalignant states. [3-5]

Notably, patients afflicted with oral cancer and leukoplakia often exhibit elevated serum copper levels compared to the general population.

Conversely, these individuals tend to have significantly reduced serum zinc levels. Similarly, lower levels of iron and selenium are observed in oral cancer patients compared to their healthy counterparts. Elevated blood lactate dehydrogenase activity has been documented in individuals with OSCC, oral lichen planus (OLP), and oral submucous fibrosis (OSMF). Alkaline phosphatase levels also demonstrate an upward trend in OSCC cases. [6] Recent promising research has unveiled a potential link between OSCCs and metabolic indicators such as urea, uric acid (UA), and creatine. Researchers have compared the levels of urea, uric acid, and creatine in individuals with OSCC to those in a control group. Furthermore, there is a growing interest in evaluating the diagnostic potential of measuring creatine, urea, and uric acid levels for the early detection of oral cancer. [7,8] Accordingly, our study aimed to assess metabolic biomarkers such as serum urea, uric acid, and creatinine in OSCC patients, as this approach has the potential to enhance our understanding of OSCC pathogenesis and improve diagnostic strategies.

Material And Methods

We conducted this study at the Department of Biochemistry, U.P. University of Medical Sciences, Saifai, Etawah, Uttar Pradesh, from March 2022 to June 2023. After obtaining ethical clearance and patient/guardian consent, we enrolled 60 OSCC patients and 60 healthy controls. Primary tumour sites included the tongue, floor of the mouth, buccal mucosa, gingiva, palate mucosa, and lips. Patients underwent thorough assessments, including clinical examinations, blood tests, and imaging. Those with preexisting or newly diagnosed conditions affecting creatinine, urea, or uric acid levels, such as renal or hepatic failure, gout, or decompensated metabolic or systemic diseases or patients with a history of other malignancies, were excluded. Clinical TNM staging was determined based on clinical examinations and imaging findings, with treatment following national guidelines. All resectable lesions underwent radical tumour resection, and neck dissection (ipsilateral or bilateral) was performed when lymph node metastasis was suspected. Prophylactic neck dissection was conducted in cases with a high risk of nodal spread, particularly large oral tumours with ulcerative growth patterns in the posterior oral cavity. Adjuvant therapy was decided upon pathology evaluation. Follow-up consisted of regular clinical examinations and imaging. The control group, composed of individuals who underwent minor oral surgeries without systemic illnesses or abnormal blood values, had comparable demographics. We collected clinical and laboratory data at admission as part of the pre-treatment workup, including general and local clinical exams, imaging, cardiac and respiratory assessments, and complete blood tests, with additional investigations as needed. Laboratory markers, including serum urea, creatinine, and uric acid, were analyzed from pre-treatment samples.

Statistical Analysis:

We used IBM SPSS version 26 for statistical analysis. We assessed data distribution normality with Kolmogorov–Smirnov and Shapiro–Wilk tests. Parametric data were analyzed using the Independent Student T-test. Using Spearman correlation analysis, we selected significant biological parameters in OSCC vs. healthy controls for correlation analysis with clinicopathological characteristics. Subsequently, we conducted multiple regression analysis via the backward stepwise method. Data were presented as mean ± SD or median with IQR, and significance was set at $p < 0.05$.

Results

In this study, the mean age of cases was 54.48 ± 11.52 years, while for controls, it was 53.24 ± 10.19 years. Male patients (68.33%) outnumbered female patients (31.67%). Significant differences were observed in smoking status and alcohol abuse between cases and controls. Most cases were smokers (81.67%) compared to controls (25.00%). Similarly, cases had a higher rate of alcohol abuse (73.33%) than controls (21.67%). [Table-1] Among the cases, TNM staging 4 was the most common (41.67%), followed by stages 2 (28.33%), 3 (18.33%) and 1 (11.67%). [Figure-1] In terms of primary tumour dimensions among cases, small stages (T stages 1-2) were more common (63.33%) than large stages (T stages 3-4) (36.67%). Regarding disease status, most cases had advanced disease (TNM 3-4) (60.00%). Lymph node metastasis was observed more frequently in positive neck cases (53.33%) compared to negative neck cases (46.67%). Histological differentiation degree in cases showed that most patients were moderately differentiated (65.00%), followed by well-differentiated (23.33%) and poorly differentiated (11.67%). Regarding disease-related survival, most cases were alive (71.67%), while 28.33% had decreased secondarily due to disease progression. [Table-1] The OSCC group exhibited a statistically significant decrease in serum urea levels [34.48±9.84] compared to the control group [38.54±10.87]. However, there were no significant differences in creatinine and uric acid levels between the OSCC group [0.79±0.22 and 5.49±1.27] and the control group [0.80±0.20 and 5.34±1.07]. [Table-2, Figure- 2(a), 2(b) and 2(c)] Upon linear regression, the age (0.0054*), smoking status (0.0097*), and lymph node invasion (0.0195*) are important factors influencing serum urea level, while alcohol abuse (0.648), histological differentiation (0.758), T stage (0.698), and disease-related prognosis (0.448) do not appear to have a significant impact on the serum urea level. After applying multiple linear regression on the significant variable from linear regression, age, smoking status, and lymph node invasion significantly impacted the serum urea level. [Table-3]

Discussion

Protein catabolism generates nitrogen compounds, including toxic ammonia. Normally, organisms have mechanisms to eliminate excess ammonia by converting it into urea, a non-toxic, water-soluble metabolite excreted through urine. This detoxification process primarily occurs in the liver, known as the urea cycle. The complete urea cycle transforms two nitrogen molecules into one urea molecule, involving five catalytic enzymes and two membrane transporters. [9,10] Emerging research has highlighted a potential connection between this metabolic pathway, particularly the dysregulation of the urea

cycle, and cancer development. In cancer cells, aberrant urea cycle function redirects nitrogen molecules away from their usual disposal as urea, channelling them into anabolic processes for molecule biosynthesis, thereby promoting cancer growth. Altered activity of specific urea cycle enzymes has been observed in colorectal carcinoma, negatively impacting patient survival and therapy response in clinical settings. This insight underscores the importance of understanding urea cycle dysregulation in cancer pathogenesis. [11,12]

In the current investigation, we discerned no discernible differences in the demographic characteristics between the group afflicted with Oral Squamous Cell Carcinoma (OSCC) and the control group. Notably, a significant proportion of OSCC cases were habitual smokers (81.67%), in stark contrast to the control group (25.00%). Likewise, the incidence of alcohol abuse was markedly higher among the cases (73.33%) compared to the controls (21.67%), and these disparities were statistically significant ($p<0.0001$*) in our analysis. This observation aligns with the findings of **Caruntu A et al.** [13], who also documented a similar prevalence of smoking and alcohol abuse, with 97 of their patients being smokers and nearly half of them exhibiting alcohol abuse. Among the cases in our study, TNM staging revealed that stage 4 was the most prevalent (41.67%), followed by stages 2 (28.33%), 3 (18.33%), and 1 (11.67%). In terms of disease status, a majority of the cases were diagnosed with advanced disease (TNM 3-4) (60.00%). **Yadav KD et al.** [14] reported a high incidence of TNM stage 4 among OSCC cases, with nearly 70% of their patients diagnosed at an advanced stage. **Caruntu A et al.** [13] also concurred with these findings, reporting that a substantial proportion (38%) of their cases presented with stage 4 cancer.

In the present study, concerning the dimensions of the primary tumour among the cases, smaller stages (T stages 1-2) were more prevalent (63.33%). Notably, lymph node metastasis was more frequently observed in cases with positive neck nodes (53.33%). A study by **Caruntu A et al.** [13] found that regional spread to the cervical lymph nodes was confirmed in 42% of cases, further corroborating our findings. In our study, the histological differentiation degree among the cases revealed that the majority of patients were moderately differentiated (65.00%), followed by well-differentiated (23.33%), and poorly differentiated (11.67%). These findings are consistent with previous studies, including those by **Yadav et al.** [14] and **Caruntu et al.** [13], which also reported that more than half of the tumours were classified as moderately differentiated (55%), with 24% being poorly differentiated and the remainder well-differentiated.

Regarding disease-related survival, most cases in our study remained alive (71.67%), while 28.33% experienced a decline in health due to disease progression. Another research showed that 30 patients succumbed to the disease's progression throughout the follow-up period, while 115 remained alive at their last follow-up visit. [13] We observed that patients diagnosed with OSCC exhibited significantly lower levels of serum urea (mg/dL) compared to healthy controls. Additionally, we noted a consistent decrease in serum urea levels associated with disease progression to advanced stages. These findings are in agreement with those of **Caruntu et al.** [13], as well as other studies. [15,16] In contrast, the mean serum uric acid (mg/dL) and creatinine (mg/dL) levels were comparable between both groups. However, **Yadav KD et al.** [14] noted a significantly lower uric acid level in OSCC cases than controls.

Caruntu A et al. [13] reported age-related changes in serum urea levels, with increasing serum urea levels correlating with ageing, which aligns with our study's findings. Extensive research on healthy subjects has also demonstrated a progressive elevation of blood urea with ageing, with significant differences detected in each decade of life for both genders [17,18]. Furthermore, we identified a significant negative correlation between serum urea levels and smoking within our study group. Similar results were reported by **Wu C et al.** [19] and others [13], supporting the association between smoking and decreased serum urea levels. The precise mechanisms behind these changes remain unclear, but a direct link is suspected, given the significant differences detected in some urea cycle intermediate metabolites, such as aspartate, in smokers compared to non-smokers. [20] It's worth noting that serum urea is influenced by protein intake. [21]

Conversely, our study found significant correlations between decreased serum urea levels and the regional spread of the disease into the cervical lymph nodes in OSCC. [13] This observation is consistent with another study conducted on head and neck cancer patients, which assessed the predictive value of various pretreatment laboratory parameters and reported similar findings regarding blood urea levels. [22] A significant proportion of patients in our study, approximately two-thirds, presented with advanced stages of the disease. Notably, we detected low serum urea levels in these patients, although these levels did not carry prognostic value. However, they were significantly correlated with the presence of lymph node metastasis. Interestingly, in contrast to our findings, the authors of this study also reported significantly lower urea levels in patients with large tumours, particularly those staged as T3 and T4. This intriguing observation could potentially be attributed to impaired eating and swallowing, which are commonly encountered in patients with large head and neck tumours. Such difficulties may lead to changes in metabolic byproducts detected in body fluids. [23]

Recent studies have suggested a link between alterations in the urea cycle and an increased metastatic potential in cancer cells. These alterations are believed to be related to modifications within the tumour microenvironment that impair the local immune response and facilitate the migration of tumour cells to regional or distant sites. [11] Similarly, studies on other types of carcinomas have reported similar findings, revealing changes in urea cycle enzyme expression that correlate with an altered immune response. [25,26] However, impaired local immune responses are not the sole factors facilitating cancer cell metastasis. The plasticity of epithelial cancer cells, known as epithelial-mesenchymal transition, imparts specific features that enable cancer cell migration to regional or distant sites. It has been demonstrated that the deprivation of asparagine, a biosynthesis product of asparagine synthetase, can reduce metastatic behaviour in cancers. Ammonia and aspartate, both important components of the urea cycle, are the main substrates for asparagine biosynthesis. [27] This suggests that deviations in the levels of these molecules could manifest clinically as decreased serum urea levels in metastatic cancers. Uncovering the dysregulation of the urea cycle associated with cancer

pathogenesis offers therapeutic potential. This may enhance the arsenal of anticancer strategies, particularly in malignancies that have not shown significant improvements in disease control with currently available treatments. Various molecules, including vaccines, that target different components of the urea cycle, such as enzymes or intermediate metabolites, are currently under investigation, either alone or in combination, and preliminary results indicate promising anticancer effects. [28,29]

Conclusion

The pathogenesis of OSCC remains largely elusive. We have observed reduced serum urea levels in advanced disease stages correlated with lymph node metastasis, hinting at a potential link between disruptions in protein catabolic processes and the aggressive nature of OSCC. Given the intricate interplay of genetic, immune, and systemic factors influencing tumour progression and distant metastasis, there is a compelling need for a thorough investigation into the intricate connections with metabolic alterations. Such research can offer a more holistic understanding of cancer pathogenesis in OSCC. However, it's important to acknowledge the limitations of our study, including its single-centre nature and the relatively limited number of subjects. Additionally, a comprehensive assessment of protein intake in our patients could provide a more accurate perspective on the subsequent metabolic changes in OSCC. Nonetheless, one notable strength of this study is its exploration of the correlation between serum urea levels and OSCC, shedding light on potential metabolic biomarkers for disease progression. Furthermore, to enhance the research, future studies could consider multi-centre collaborations to increase the sample size and should delve deeper into the underlying mechanisms of urea cycle dysregulation in OSCC, possibly paving the way for targeted therapeutic interventions in this cancer type.

Conflict Of Interest - All authors declare no conflict of interest.
Source of Funding- None
Consent: As per international or university standards, the authors have collected and preserved written participant consent.
Ethical Approval: As per international or university standards, the author(s) has collected and preserved written ethical permission.

TABLE-1: Clinico-demographic parameters of OSCC patients and healthy controls (N=120).

Clinico-demographic parameters		CASES [N=60]		CONTROLS [N=60]		P-VALUE
		No.	%	No.	%	
AGE		54.48±11.52		53.24±10.19		t=0.6245 p=0.5335
GENDER	Males	41	68.33%	37	61.67%	X=0.5861 p=0.4439
	Females	19	31.67%	23	38.33%	
SMOKING STATUS	Yes	49	81.67%	15	25.00%	X=38.71 **p<0.0001***
	No	11	18.33%	45	75.00%	
ALCOHOL ABUSE	Yes	44	73.33%	13	21.67%	X=32.11 **p<0.0001***
	No	16	26.67%	47	78.33%	
DISEASE STATUS	Incipient (TNM 1-2)	24	40.00%	-		--
	Advanced (TNM 3-4)	36	60.00%	-		--
PRIMARY TUMOR DIMENSIONS	Small (T stages 1-2)	38	63.33%	-		--
	Large (T stages 3-4)	22	36.67%	-		--
LYMPH NODE METASTSIS	Positive neck	32	53.33%	-		--
	Negative neck	28	46.67%	-		--
HISTOLOGICAL DIFFERENTIATION DEGREE	Well-differentiated	14	23.33%	-		--
	Moderately differentiated	39	65.00%	-		--
	Poorly differentiated	7	11.67%	-		--
DISEASE RELATED SURVIVAL	Alive	43	71.67%	-		--
	Decreased secondarily to disease progression	17	28.33%	-		--

TABLE-2: Comparison of serum urea, uric acid and creatinine between OSCC and Control group.

	OSCC GROUP		CONTROL GROUP		P-VALUE
	Mean	SD	Mean	SD	
SERUM UREA	34.48	9.84	38.54	10.87	t=2.145 **p=0.0340 ***
CREATININE	0.79	0.22	0.80	0.20	t=0.2605 p=0.7949
URIC ACID	5.49	1.27	5.34	1.07	t=0.6997 p=0.4855

TABLE-3: Linear and Multiple regression analysis for serum urea in OSCC patients.

LINEAR REGRESSION ANALYSIS						
	Coefficients	***Standard Error***	***t Stat***	***P-value***	***Lower 95%***	***Upper 95%***
Intercept	14.578	8.255	24.846	**0.0001***		
Age	5.957	2.188	7.589	**0.0054***	0.124	3.641
Smoking Status	-4.586	2.396	6.987	**0.0097***	0.025	3.168
Alcohol Abuse	-0.697	0.441	2.841	0.648	-0.124	-4.951
Histological differentiation	0.198	0.025	0.329	0.758	0.005	2.984
T stage	0.218	0.325	0.694	0.698	0.128	1.985
Lymph node invasion	-3.958	0.628	5.987	**0.0195***	-0.026	-3.115
Disease related prognosis	0.295	0.335	0.891	0.448	0.021	1.264
MULTIPLE REGRESSION ANALYSIS						
INTERCEPT	22.957	4.985	36.957	**0.0001***		
Age	5.487	2.111	7.218	**0.0069***	0.114	3.517
Smoking Status	-4.498	2.158	5.998	**0.0169***	-0.019	-3.048
Lymph node invasion	-3.588	0.656	5.157	**0.0204***	-0.014	-3.015

FIGURE-1: TNM staging of the disease in the OSCC group.

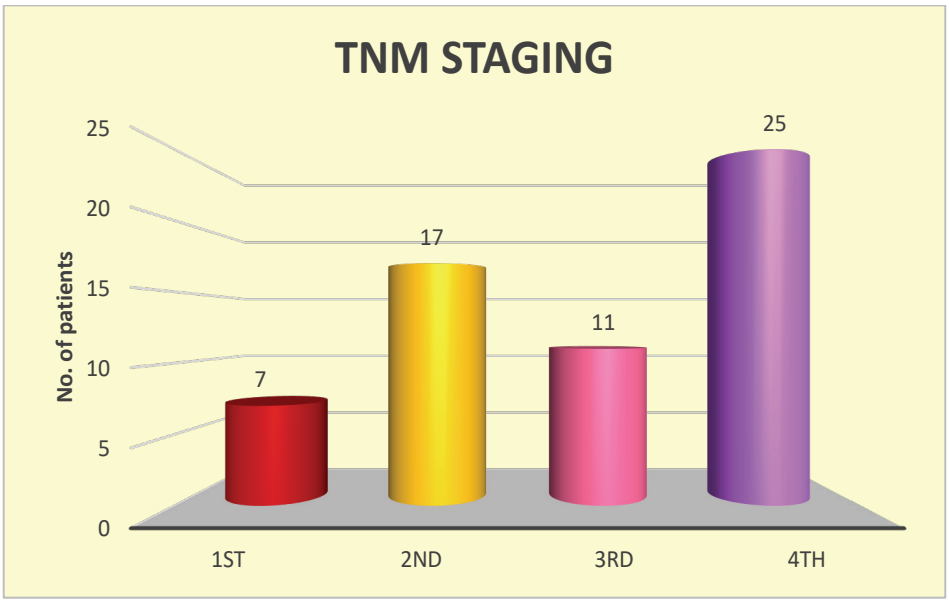

FIGURE- 2: Mean serum (a) urea, (b) creatinine, and (c) uric acid in OSCC cases and controls.

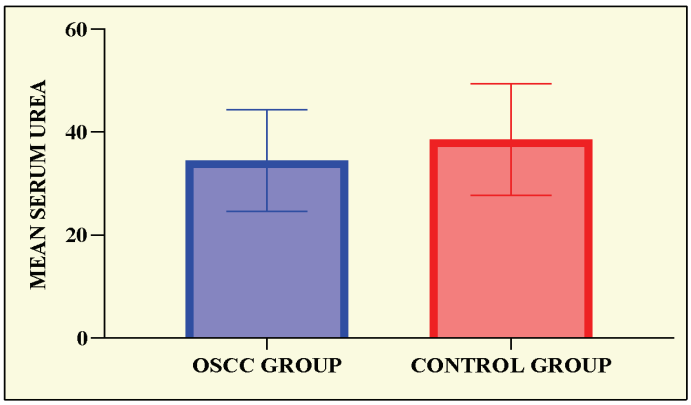

FIGURE- 2(a)

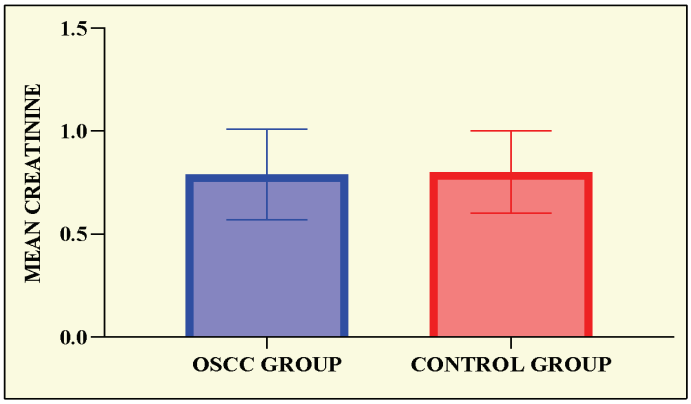

FIGURE- 2(b)

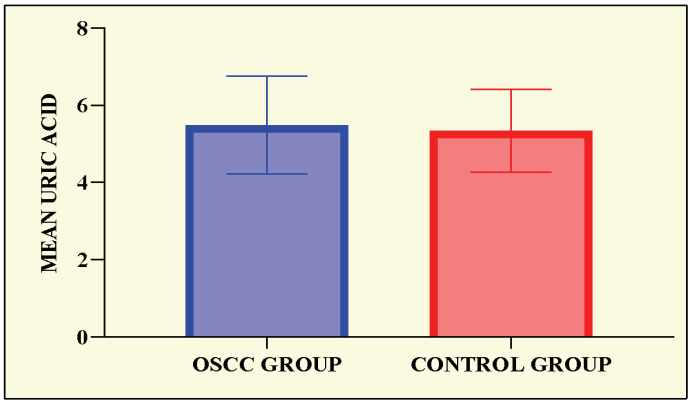

FIGURE- 2(c)

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