



Research Article

Serum Interleukin 6 As Potential Biomarker for Head And Neck Squamous Cell Carcinoma

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ABSTRACT

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Head and neck cancers constitute one- third of the cancer burden in India. Despite advances in cancer management, the morbidity and mortality rates have not significantly improved. Therefore, early detection or prevention of this disease will be most effective. Interleukin-6 (IL-6) is a pleiotropic cytokine which plays an important role in a number of cellular processes and has been identified in a wide variety of malignancies, including head and neck squamous cell carcinomas (HNSCC). The aim of this study was to investigate the serum levels of interleukin-6 in early diagnosis of patients with head and neck squamous cell carcinoma.

The circulating level of IL-6 in sera from patients with various HNSCC as well as from healthy normal controls were investigated by ECLIA principle. IL-6 serum concentrations were observed to be significantly higher in the HNSCC patients ($p < 0.05$). Furthermore, the correlation of the IL-6 serum concentration with tumor stage was observed to be significant. IL-6 serum levels can serve as a biological marker for early diagnosis of patients with head and neck cancer.

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INTRODUCTION:

Head and neck cancers (HNCs) continue to remain a significant public health burden worldwide, causing significant mortality and morbidity, despite significant clinical advances. Head and neck cancer accounts for more than 550,000 cases worldwide, and 380,000 deaths annually.^[1] In India, head and neck cancers are a significant problem, constituting approximately one-third of all cancer cases in contrast to 4–5% in the developed world. Despite advances in surgery, radiation and chemotherapy, the morbidity and mortality rates have not significantly improved in the past 30 years.^[2] Therefore, early detection or prevention of this disease is likely to be most effective. The absence of definite early warning signs, in cases of Squamous cell carcinoma (SCC) of head and neck, causes delay in the diagnosis of these patients. Therefore, the availability of sensitive and specific markers will be of utmost importance for screening the high-risk patients enabling their early diagnosis and treatment.

A number of molecular markers have been used to detect these tumors with varying degrees of specificity and sensitivity. However, no biological markers have been shown to universally identify HNSCC.^[3] Since the release of cytokines by tumor cells have been reported, the serum levels of these molecules may be useful as additional cancer markers.^[3] IL-6 is a multifunctional cytokine, produced by a wide variety of cell types including immune cells (macrophages, dendritic cells and B-cells), endothelial cells and tumor cells.^[4, 5, 6, 7] It plays an important role in a number of biological processes including immune regulation, hematopoiesis, inflammation and oncogenesis.^[8, 9, 10]

IL-6 plays a central role as a growth factor in the differentiation of a variety of cells, such as hematopoietic precursor cells, B-cells, T-cells, keratinocytes, neuronal cells, osteoclasts and endothelial cells.^[11] Elevated expression of IL-6 has been detected in multiple epithelial tumors (12). Several studies have shown elevated levels of IL-6 in HNSCC. (13, 14, 15,

16). Interleukin-6 (IL-6) is one of the key molecules that has been implicated in poor clinical outcomes in HNSCC patients.^[13, 14, 17, 18, 19.]

However, very few studies have been conducted on the role of interleukins in head and neck carcinomas as diagnostic and prognostic marker, in the Indian population. The purpose of this study was to investigate the relationship between serum levels of IL-6 and the severity and extent of the disease based on tumor staging, in order to explore use of this biomarker as a diagnostic and prognostic factor. It may then be used as a promising marker and further immunologic approaches could be used for the treatment of patients in the future.

MATERIAL AND METHODS

Subjects: The subjects in this study included 54 patients who have been diagnosed with Head and Neck Squamous cell carcinoma. Fifty healthy individuals served as controls.

All patients had recently been diagnosed with primary disease, and had not received any prior treatment in the form of chemotherapy, radiotherapy, surgery, or alternative remedies. Tumor staging is performed based on the sixth edition of the TNM system, published by the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC).^[20] Depending on the tumor staging, patients were divided into four groups: Stage I, Stage II, Stage III and Stage IV.

Exclusion criteria included a history of recent traumas, acute infections, recent burns, lacerations, previous surgery, chemotherapy or radiotherapy. In the control group, no subjects had a record of recent trauma, laceration, infection, illness, previous surgery, smoking or drinking problems. Control subjects underwent a physical examination before selection. All patient and control subject details have been documented in a detailed proforma. The study was approved by the Ethics Committee of the institution. Informed consent was obtained from all participants

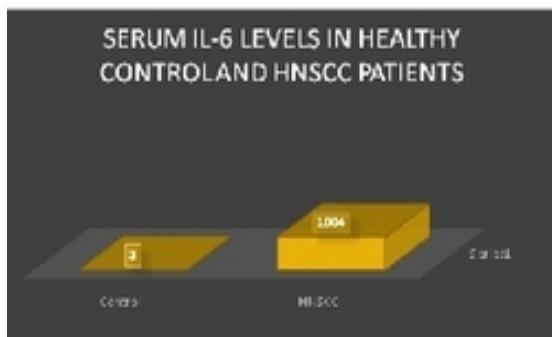
METHODS:

Peripheral venous blood samples were taken

and collected in sterile test tubes, centrifuged and further processed. IL-6 detection was carried out by the ECLIA principle, on the ELECSYS 2010, Roche. Statistical Analysis was carried out for the data obtained. $P < 0.05$ was set as the critical level of significance.

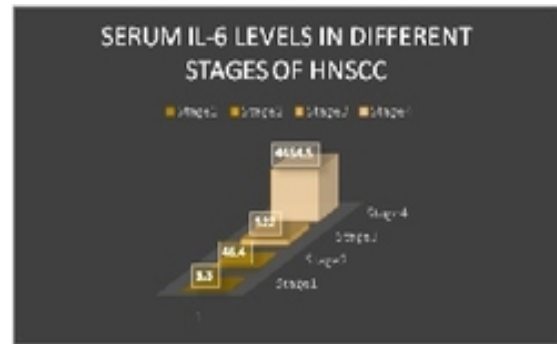
RESULTS AND DISCUSSION

In this study, 104 individuals were examined; 54 of whom were patients with Head and neck cancer and 50 of whom were in the control group. Forty-seven patients (87%) were male and eight (13%) were female. The average age of patients was 52 years. IL-6 levels were 1075.9 pg/ml in male patients and 858.9 pg/ml in female patients. When measuring IL-6, we found that the majority of the patients with HNSCC had high concentrations of serum IL-6. The levels of IL-6 in the sera of patients with cancer ranged from 1.5 to 5000 pg/ml (mean, 1004 pg/ml). In contrast, the IL-6 serum levels in 50 healthy individuals ranged from 1.4 to 10.4 pg/ml (mean, 2.6 pg/ml) (Fig. 1). Thus, IL-6 serum concentrations were significantly higher in the HNSCC patients ($p \leq 0.05$).



Serum levels of IL-6 in Healthy control group and HNSCC patients.

Of the 54 patients with head and neck cancer, 8 patients were in Stage I, 11 patients were in Stage II, 26 patients were in Stage III and 9 patients were in Stage IV. Mean serum IL-6 levels in Stage I was 3.3pg/ml, 46.4pg/ml in Stage II, 522pg/ml in Stage III and 4454.5pg/ml in Stage IV (Fig 2).



Serum IL-6 levels in different stages of HNSCC patients.

Thus, IL-6 levels were clearly observed to increase dramatically with the progression of malignancy in advanced stages, as compared to early stages of the disease. Also, a study by Riedel *et al.* in 2005 showed that IL-6 levels increased with increasing severity of disease. [14]

The t test was performed to determine the exact statistical difference between the various control / patient groups. The comparison of controls with the Head & neck squamous cell cancer patients showed a statistically significant difference with $p < 0.05$.

Also, statistically significant differences were observed between the patients with respect to their staging. Stage 1 and stage 2 patients showed significant differences with $p < 0.05$. Similar statistical differences were also seen between stages 1 & 3, stages 1 & 4, stages 2 & 3, stages 2 & 4 and stages 3 & 4.

CONCLUSION

In summary, our data clearly indicates that the serum levels of IL-6 in HNSCC patients were significantly elevated and directly associated with disease status and severity of Head and neck squamous cell carcinoma. Thus, serum IL-6 can be a promising candidate as a new marker for diagnosis and prognosis of HNSCC, particularly for advanced stage tumors.

Serum IL-6 determinations may find clinical applications in the follow-up of cancer therapy. Further studies with longitudinal follow-ups of patients are required to determine the value of serum IL-6 measurements in the detection of recurrent cancer.

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