A Mathematical Model for Nibrin Expression in Oral Squamous Cell Carcinoma by using Log Normal Distribution

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Abstract

In this paper, we introduce the lognormal distribution. Log-normal distributions are usually characterized in terms of the log-transformed variable, using as parameters the expected value, or mean of its distribution, and the standard deviation [7]. Two parameters are needed to specify a log-normal distribution. Traditionally, the mean μ and the standard deviation σ are used. This paper study sought to discover the role of Nibrin protein in 100 patients with oral squamous cell carcinoma (OSCC) and its potential relationship with clinic pathological parameters. The present study included 20% of patients with stage I disease, 22% of patients with stage II disease, 18% of patients with stage III disease, and 40% of patients with stage IV disease. Nibrin showed a significant positive correlation with moderately/poorly differentiated tumor tissues (P = 0.028), while significant inverse correlation of Nibrin expression was observed with tumor size (P = 0.018) and tumor stage (P = 0.039). Further, using univariate survival analysis it was observed that strong Nibrin expression was significantly associated with disease relapse in early stage OSCC patients (P = 0.049). Thus, the present study revealed that Nibrin could be used as a prognostic marker in patients with early stage OSCC. The application part is fitted with the Mathematical model and conclusion is compared with the medical report this will be helpful for the medical professional.

Keywords: Nibrin protein, oral squamous cell carcinoma, lognormal distribution

I. INTRODUCTION

Carcinomas of the oral cavity, including cancer originating from the buccal mucosa and tongue are of 10 most common cancers in the world with an increasing trend of incidence [2, 10]. Squamous cell carcinoma (SCC) is the most common type of oral cancer which accounts for more than 90% of oral malignancies which is characterized by an aggressive growth pattern, high-degree of local invasiveness, and cervical lymph node spread [2,14] . In India, oral squamous cell carcinoma (OSCC) is the leading cause of death which stands for 35-40% of all malignancies which is owed to the increased prevalence of lifestyle habits like chewing areca-nut/betel nut quid/tobacco and smoking with heavy alcohol consumption serving as a potent cofactor [5,6,12]. The survival of patients with oral cancer has remained unchanged even with the improved therapeutic modalities, over the last 3 decades [12]. The resultant poor prognosis is owed to a late stage diagnosis, low response rate to current therapeutic strategies, high risk of primary site recurrence and aggressive metastases to loco-regional lymph nodes, strongly suggestive of an urge to improve the treatment efficacy and diagnostic capabilities. Over the last decade, scientific research related to the specific pathways which are relevant to the development and progression of this disease has been performed to investigate biological, diagnostic and prognostic parameters [3,9,11,13,]. On the basis of this information, the aim of this study was to assess whether the Nibrin expression would relate to clincopathological variables and if it could predict.

II. APPLICATION

A total of 100 untreated patients with histolpathologically confirmed OSCC of tongue and buccal mucosa. Out of total 100 OSCC patients, for overall survival analysis, only 90 patients could be followed for a period of 24 months or until death within that period. On the other hand, for relapse-free survival study, 78 of 100 patients with or without recurrence within that period were considered. The remaining 12 patients could not be included for relapse-free survival study due to presence of persistent disease. Of the tongue and buccal mucosa cancer tissue, Nibrin protein expression was evaluated with nuclear location of the immunoreactions, Nibrin was expressed in 99% of tumors and 92% of the adjacent normal squamous epithelium [Figure 2.1]. Although we were unable to obtain any significant findings in total patients, we further sub grouped patients into early and advanced stage disease and surprisingly, we observed that in patients with early stage disease, a significant high incidence of disease relapse was observed in patients with strong Nibrin expression (43%, 10/23, log-rank = 3.884, df = 1, P = 0.049) as compared to patients with weak Nibrin expression (8%, 1/12) [Figure 2.2].

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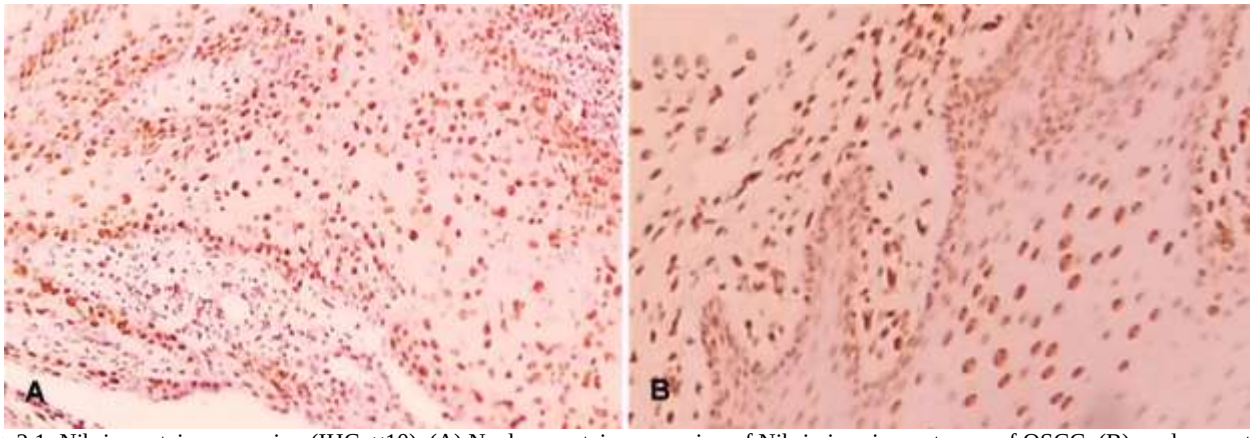

Fig. 2.1: Nibrin protein expression (IHC, ×10). (A) Nuclear protein expression of Nibrin in primary tumor of OSCC; (B) nuclear protein expression of Nibrin in adjacent normal tissue of primary OSCC tumor tissue. OSCC: oral squamous cell carcinoma

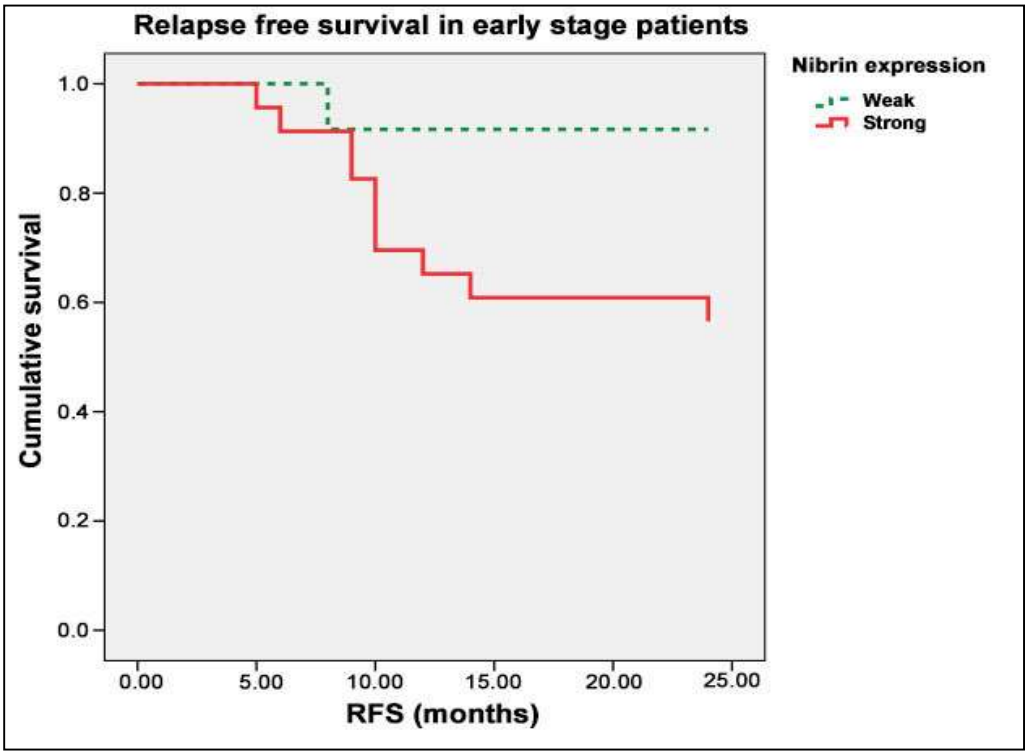

Fig. 2.2: Kaplan-Meier univariate survival analysis of patients with early stage disease indicating significant high incidence of disease relapse in patients with strong Nibrin expression (P = 0.049). RFS: relapse-free survival

III. MATHEMATICAL MODEL

A random variable X is log normally distributed if log(X) has a normal distribution. Usually, natural logarithms are used, but other bases would lead to the same family of distributions, with rescaled parameters. The probability density function of such a random variable has the form

$$f(x) = \frac{1}{x\sigma\sqrt{2\pi}} \exp\left(-\frac{1}{2\sigma^2} (\log(x) - \mu)^2 \right)$$

A shift parameter can be included to define a three-parameter family. This may be adequate if the data cannot be smaller than a certain bound different from zero[7]. The product of two independent log-normally distributed random variable has the shape parameter.

The mean of the log-normal distribution is

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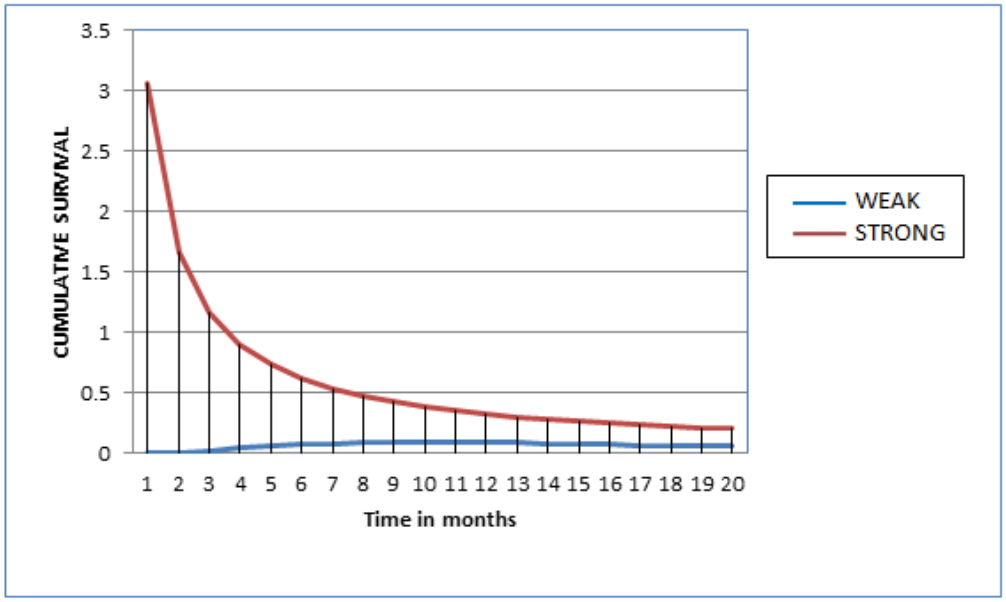
$$E(X) = \exp\left(\mu + \frac{\sigma^2}{2}\right)$$

and the variance of log-normal distribution is $\text{var}(X) = \exp\left(2\left(\mu + \sigma^2\right)\right) - \exp\left(2\mu + \sigma^2\right)$

IV. MATHEMATICAL RESULTS



V. DISCUSSION

Nibrin expression is up-regulated in adjacent normal tissues of OSCC tissue which is compatible with the hypothesis that Nibrin is a tumor suppressor gene. In contrast with our findings, Hsu et al.[8] showed that Nibrin over expression was significantly correlated with high tumor size and metastatic dieses in OSCC patients which may be because of the inclusion of more number of patients with locally advanced diseases. Ehlers et al.[4] also showed that Nibrin was associated with strong tumor severity and metastatic death marker in uveal melanoma. However, similar expression of NBS1 in class 1 tumors and normal uveal melanocytes suggests that up-regulation of NBS1 may be a late event in melanoma progression.

Kaplan-Meier univariate survival analysis showed that in patients with early stage disease high number of patients relapsed with strong Nibrin expression. However, our findings not only observed increased expression pattern of Nibrin in early stage patients but also found a strong correlation between increased Nibrin expressions in the onset of the disease with higher probability of recurrence. This could be attributed to the fact that since Nibrin acts as a sensor molecule of MRN complex which further activates the other DNA repair molecules, it might have a plausible role in constitutively activating these downstream molecules eventually leading to disease relapse in patients. While Hsu et al. [8] found that in OSCC patients strong Nibrin expression was associated significantly with shorter overall survival compared with weak expression. Ehlers et al.[4] have also found that in uveal melanoma, the 6-year survival was 100% for the low NBS1 group and 22% for the high NBS1 group (P = 0.01). In the breast carcinoma, patients with NBS1-aberrant tumors seemed to have poorer survival than the patients with NBS1 normal tumors. This indicates that the NBS1 deficiency predicts poor survival of the breast carcinoma patients. [1]

VI. CONCLUSION

The present study revealed that Nibrin could be used as a prognostic marker in patients with early stage OSCC. We conclude that a Nibrin protein expression is significant in lower tumor size and early stage disease in OSCC indicating its role in early event of disease progression. Further, high incidence of disease relapse was found to be present in early stage patients with strong Nibrin expression. Thus, it could be used as a favorable prognostic factor in developing disease recurrence in patients with early stage disease. Further, among various cancers, the different patterns of the Nibrin expression have observed which indicates that the expression of Nibrin is important in cancer development and progression with cancer cell type. The medical curve and Mathematical curve for disease control is higher than the probability density functions which are monotonic functions. This will be helpful for the medical professional.

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