RESEARCH ARTICLE

SYSTEMIC MARKERS AND SURVIVAL OF ORAL CANCER PATIENTS IN EGYPT.

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Manuscript Info

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Abstract

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Background: Oral cancer is a common head and neck malignancy with poor survival rate specially with late diagnosis. Systemic markers have been shown to have a prognostic role in many cancers. The aim of the present study is to investigate the prognostic value of pretreatment systemic markers in a small group of oral cancer patients in Egypt as a pilot study.
Methodology: Twenty (20) oral cancer patients have been enrolled for the study. The systemic markers were assessed in relation with overall survival and recurrence free survival.
Results: Neutrophils count (NC), neutrophils to lymphocytes ration (NLR) and platelets to lymphocytes ratio (PLR) were higher in dead patients compared to survivors. PLR was higher in patients with recurrence compared to patients without. However, these differences were not statistically significant.
Conclusions: Systemic markers may help in predicting the survival of oral cancer patients. Further studies with larger samples are needed to verify their role.

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Introduction:-

Oral cancer represents one of the most frequently encountered malignancies of head and neck [1]. Classic prognostic factors of oral cancer include the size of the tumor, regional nodal & distant metastasis (TNM staging system). However, these factors can be insufficient in predicting individual patient's outcome. Recently, oncological research has analyzed the characterization of new markers. Ideally, they ought to be easily reproducible, readily available, inexpensive, and above all should be able to define patients with higher risk for recurrence as well as death [2].

The appropriate stratification of cancer patients and subsequent allocation to surgical, oncological and palliative treatments remains a challenge. Outcomes in cancer patients are not determined TNM staging alone, and the patient-related factors, of which systemic inflammatory response comes in the first place, are also key to outcome [3]. The aim of the present study is to investigate correlation of systemic markers with survival rates of oral cancer patients.

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Materials and methods:-

The study included 20 patients with biopsy-proven oral cancer admitted at Oncology Center Mansoura University (OCMU). The protocol of the study was approved by the committee of postgraduate research, Faculty of Dentistry, Mansoura University. The purpose of the study was explained to each subject & an informed consent was obtained.

The patients were 7 males and 13 females with age ranging from 26 to 71 years (mean 53.65 ± 13.82). The blood sampling was done at the time of diagnosis. The planned treatment (Surgery, surgery and radiotherapy, surgery and chemoradiotherapy, neoadjuvant chemoradiotherapy) was recorded. The clinical and pathological data of these patients are represented in Table (1). The patients were followed up till September 2015 for recurrence or death. Statistical analysis was performed using the IBM SPSS statistics 21 (IBM Corp., Armonk, NY). The follow up duration ranged from 8 to 633 days with a median of 65.5 (mean 163.95 ± 193.69).

The following laboratory investigations were performed:
*Complete blood count (CBC) markers including:
-   Heamoglobin (HGB).
-   RBCs count.
-   WBCs count.
-   Platelets count (PLT).
-   Neutrophils count (NC).
-   Lymphocytes count (LC).
-   Neutrophils to Lymphocytes ratio (NLR).
-   Platelets to Lymphocytes ratio (PLR).
*Liver function tests including:
-   SGPT.
-   SGOT.
-   Serum albumin (Alb.).
-   Serum total direct bilirubin.
*Serum creatinine.

Results:-

Table (2) shows the systemic markers of the oral cancer patients in the study. By the end of follow-up, 5 out of the 20 patients have died. Kaplan-Meier estimates of overall survival are shown in figure (1).Table (3) shows systemic markers of dead oral cancer patients compared to survived ones. NC, NLR and PLR were higher in dead patients compared to survivors. However, this difference was not statistically significant.

Only 2 cases out of the 20 cases included in the study showed recurrence within the follow-up duration. Kaplan-Meier estimates of recurrence free survival are shown in figure (2). Table (4) shows systemic markers of oral cancer patients with recurrence compared to those without. PLR was higher in patients with recurrence compared to patients without recurrence. However, this difference was not statistically significant.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff points of pretreatment PLR for predicting overall survival (Fig. 3). The optimal cutoff value was defined as the point on the ROC curve that maximizes Youden index. A cutoff value of 93.66 was defined (Sensitivity = 80%, specificity = 53.3%, corresponding AUC = 0.64).

Discussion:-

Oral cancers are malignant tumors that involve the structures or tissues of the oral cavity, with more than 90% squamous cell carcinomas arising in the mucous membranes of the mouth and oropharynx [4]. The relatively high rate of mortality in oral cancer patients is linked with regional or less frequently distant metastasis at the time of diagnosis, a commonly encountered feature due to late detection of the disease. This metastasis usually makes the expected survival rate drops approximately by half [5].

NLR has been emphasized as a poor prognostic indicator in multiple malignancies. One explanation is its association with inflammation. Neutrophilia as an inflammatory reaction suppresses the immune system through decreasing the cytolytic activity of immune cells, for example lymphocytes, natural killer cells and activated T cells

[6]. Another possible explanation is that neutrophils have been reported to secrete tumor growth promoting factors, such as circulating vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor and matrix metalloproteinases[7].

Out of the 20 oral cancer cases included in this study, 18 cases (90%) were diagnosed as squamous cell carcinoma (SCC) (Table 1). This is consistent with the ratio reported by a recent review article on oral and oropharyngeal SCC. More than half of OSCC cases in our study were in the tongue (55%). This is slightly higher than most of similar studies, which usually report a proportion ranging from 40% to 50% [8].

The finding that 60% of oral cancer cases were stage (IV a) and 5% were stage (IV b) is quite devastating. This means that approximately two thirds of patients were diagnosed at an advanced stage, which limits the treatment options and dramatically decreases survival rates. This is consistent with several reports stating late diagnosis as a major problem in managing oral cancer [9, 10].

Primary oral cancer lesions represented 60% of the cases included in this study, while about one third of the cases were recurrent lesions (30%). This recurrence rate comes in agreement with rates published in other reports. Recurrent cases represent a greater challenge in terms of defining the optimum management approach: limited number of cases are candidates for salvage surgery, those who are indicated for chemotherapy suffer from drug resistance, and the overall survival is very poor [11].

Table (3) shows the relation between systemic markers and survival in oral cancer patients. There was no statistically significant difference between survived and dead patients for any of these markers. Patients with and without recurrence also did not display any significant difference (Table 4). A possible justification is the small sample size (n=20). Survival statistics are almost always investigated on larger samples. These findings are consistent with the work of *Tsai et al.,* who reported that pretreatment total WBCs count, NC, LC and NLR were not significantly associated with cancer-specific survival in oral cancer patients. Instead, the authors found that pretreatment monocytes count had a significant association with survival in these patients [12].

Our results showed that NLR in dead patients had a median of 5.43, and in survived patients had a median of 2.44. However, this difference was not statistically significant. This contradicts with the results of *Perisanidis et al*[2] who recognized NLR as a marker of poor disease-specific survival in oral cancer patients. This difference can be attributed to the large sample that the investigators used (n=97).

Rachidi et al.[13] also reported different results in their work on head and neck squamous cell carcinoma (HNSCC). They found that NLR was associated with worse prognosis in HNSCC patients. They noted that neutrophils and/or lymphocytes count could be affected by comorbid diseases such as autoimmune diseases or the intake of medications prescribed for such conditions such as corticosteroids.

Another research on HNSCC patients concluded that higher NLR was associated with worse prognosis, which differs from our results. The authors suggest that elevated neutrophils count may be attributed – besides inflammation – to an increased infiltration of immature neutrophils from the bone marrow as a result of high leukocyte turnover [14].

Conclusions:-
In conclusion, CBC based markers may have a prognostic role in oral cancer patients. Further studies with larger samples and longer follow up duration are needed to establish our findings.

Table (1):- Clinical and pathological data of oral cancer patients.

Parameter	Number of patients (%)
-Smoking	
Yes	2(10%)
No	18 (80%)
-Site of lesion	
Tongue	11(55%)
Floor of the mouth (extending from tongue or lower lip)	2 (10%)

Cheeck	5(25%)
Maxilla (osteosarcoma)	2(10%)
Mandible (SCC)	1(5%)
Lips	1 (5%)
-Type of lesion	
Primary	12(60%)
Recurrent	6(30%)
Residual	1(5%)
Post chemoradiotherapy	1 (5%)
-Stage	
Stage II	6(30%)
Stage III	1(5%)
Stage IV a	12(60%)
Stage IV b	1 (5%)
-Grade of Differentiation	
G I	4(20%)
G II	12(60%)
G III	3(15%)
G IV	1 (5%)
-Treatment Plan	
Surgery	7(35%)
Surgery and Radiotherapy	6(30%)
Surgery and Chemoradiotherapy	2(10%)
Chemoradiotherapy	5 (25%)

Table (2):- Systemic markers of oral cancer patients.

Markers	Oral cancer (n=20)		
	Mean ± SD	Median	Min-Max
HGB	11.99±1.88	12.20	6.37-14.70
RBCs	4.72±.51	4.73	3.66-5.72
WBCs	9.28±3.61	8.63	4.10-18.60
PLT	247.70±81.94	230.50	114-403
NC	6.28±3.31	5.89	2.00-15.70
LC	2.34±1.77	2.30	.44-8.34
NLR	5.23±5.68	2.58	.41-17.56
PLR	167.86±128.77	98.52	35.25-463.47
SGPT	27.69±22.13	20.15	8.48-96
SGOT	23.99±13.01	20.48	1.09-51.95
Albumin	4.48±.61	4.46	3.10-5.50
Bilirubin	.60±.23	.63	.19-1.23
Creatinine	.97±.21	.90	.60-1.32

* The highlighted data are non-parametric
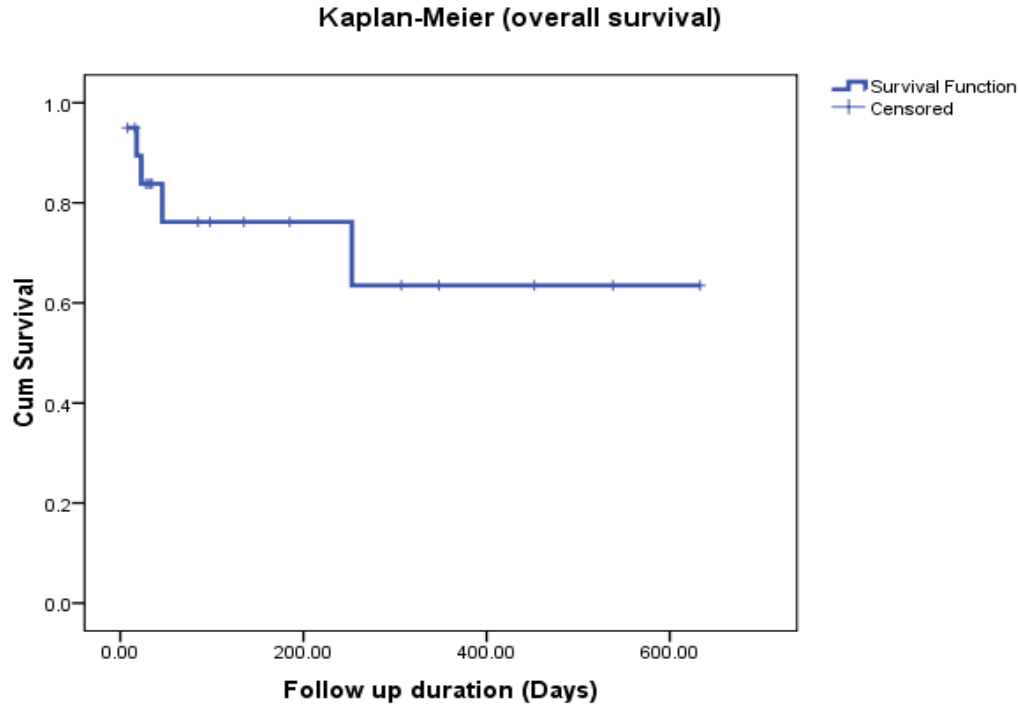
Kaplan-Meier (overall survival)

Fig. (1):- Kaplan-Meier estimates of overall survival time (days) in oral cancer patients.

Table (3):- Systemic markers of dead and survived oral cancer patients.

Items	Oral cancer (n=20)		Test of sign.
	Dead (n=5)	**Survived (n=15)**	**p-value**
HGB	12.36±1.76	11.87±1.97	t=.491 p=.630
RBCs	5±.83	4.63±.35	t=1.421 p=.172
WBCs	10.06±5.32 Median=8.28	9.03±3.06 Median=8.70	Z=.131 p=.896
PLT	228.40±72.41	254.13±86.24	t=.598 p=.557
NC	7.17±5.20 Median=5.98	5.98±2.60 Median=5.81	Z=.218 p=.827
LC	1.63±1.12 Median=1.50	2.58±1.91 Median=2.38	Z=1.35 p=.176
NLR	7.18±6.93 Median=5.43	4.59±5.31 Median=2.44	Z=.480 p=.631
PLR	213.58±163.810 Median=177.06	152.62±117.66 Median=93.33	Z=.917 p=.359
SGPT	32.30±35.69 Median=18	26.16±17.05 Median=23.10	Z=.131 p=.896
SGOT	24.74±15.09 Median=15.73	23.74±12.82 Median=21	Z=.393 p=.694
Albumin	4.25± .84	4.56±.53	t=.974 p=.343
Bilirubin	.65±.24	.58±.23	t=.606 p=.552
Creatinine	.94±.25	.97±.20	t=.260 p=.798

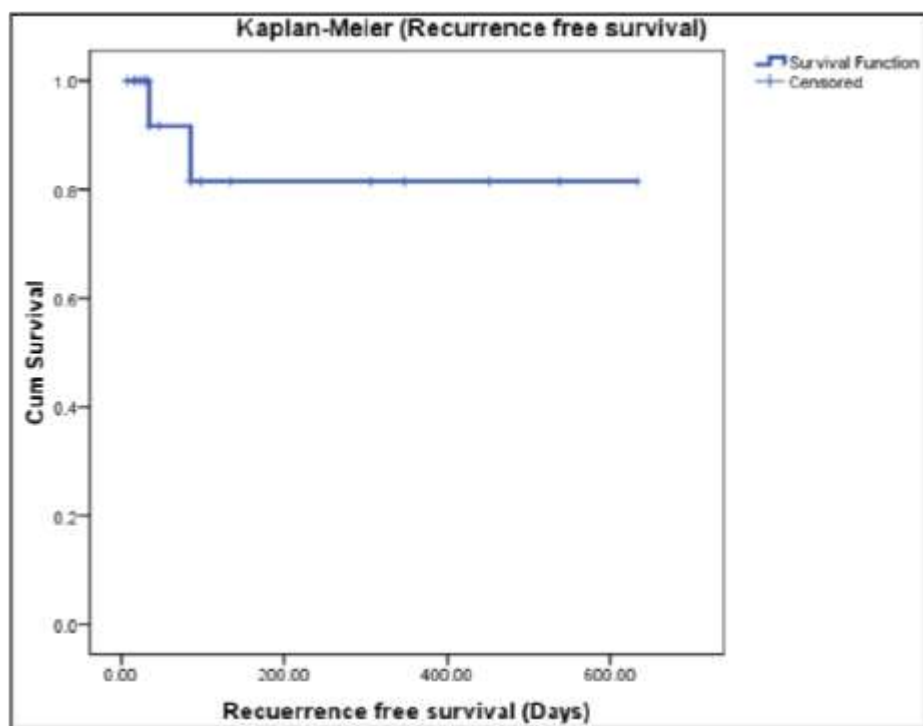*****Z for Mann–Whitney test. The highlighted data are non-parametric.

Fig. (2):- Kaplan-Meier estimates of recurrence free survival time (days) of oral cancer patients.

Table (4):-Systemic markers of oral cancer patients with and without recurrence.

Items	Oral cancer (n=20)		Test of sign. p-value
	Recurrence (n=2)	**No recurrence (n=18)**	
HGB	12.15±.21	11.97±1.99	t=.120 p=.906
RBCs	5.08±.86	4.68±.48	t=1.032 p=.316
WBCs	6.64±3.59 Median=6.64	9.58±3.60 Median=8.63	Z=.756 p=.450
PLT	327.50±37.47	238.83±81.18	t=1.498 p=.151
NC	4.14±3.03 Median=4.14	6.51±3.33 Median=5.89	Z=.882 p=.378
LC	2±.43 Median=2	2.38±1.86 Median=2.34	Z=.378 p=.705
NLR	1.94±1.09 Median=1.94	5.60±5.88 Median=2.70	Z=.882 p=.378
PLR	165.15±16.83 Median=165.15	168.16±136.07 Median=93.66	Z=630 p=.529
SGPT	12.75±.35 Median=12.75	29.35±22.76 Median=22.20	Z=1.386 p=.166
SGOT	15.36±.51 Median=15.36	24.95±13.40 Median=21.55	Z=1.324 p=.186
Albumin	4.98±.11	4.42±.62	t=1.214 p=.240
Bilirubin	.67± .03	.59±.24	t=.456 p=.654
Creatinine	1.07±.18	.95±.21	t=.690 p=.499

*Z for Mann–Whitney test. The highlighted data are non-parametric.
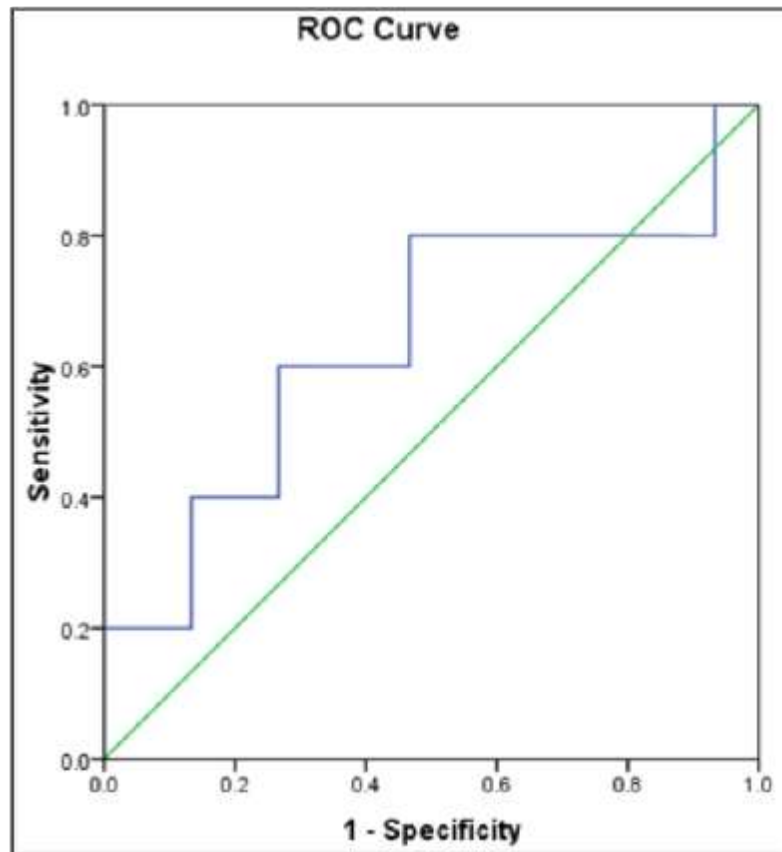
Fig. (3):- Receiver operating characteristic (ROC) curve for pretreatment PLR predicting overall survival in oral cancer patients.

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