The Log Odds Of Positive Lymph Nodes (Lodds) Staging System As A Prognostic Predictors For Gastric Cancer- A Single Center Study

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ABSTRACT:

Background: The latest edition of American Joint Committee on Cancer/International Union against Cancer (UICC/AJCC 8th Edition) tumor–node–metastasis (TNM) classification recommends the examination of no less than 16 regional lymph nodes for nodal metastatic status determination. Compliance with this recommendation is poor with > 15 nodes assessed in only 29% of patients. The aim of the study is to compare the 8th pN system with ratio-based and Log odds of positive lymph nodes (LODDS) staging systems for predicting the overall survival (OS) of gastric cancer (GC) patients after curative resection

Methods: We analyzed, retrospectively, clinicopathologic and prognostic data from our tertiary care center, on 250 patients from January 2014 to December 2020 who underwent curative surgery for GAC. We formulated tumor-LODDS-metastasis (TLM) and tumor ratio- metastasis (TRM) staging system. The relative discriminative abilities of the different staging systems were assessed using Akaike's Information Criterion (AIC), a linear trend chi-square test, and a likelihood ratio chi-square test.

Results: The cut-off points of the LODDS were set as: ≤ -1, -1 to -0.5, -0.5 to 0.0, 0 to 0.5, and > 0.5. There were significant differences in the survival of patients in different LODDS classifications for each pN or LNR group. The modified TLM staging system had better discriminatory ability and promising prognostic indicator than the 8th TNM or the TRM staging systems for patients with GC.

Conclusions: The LODDS staging system was superior to other lymph-node staging as a predictor of prognosis for GC. LODDS may be included into a GC staging system.

Introduction:

Globally Gastric adenocarcinoma (GAC) is fifth most common malignancy and second leading cause of cancer related mortality [1]. GAC is most prevalent in East Asian countries which contributes 2/3rd of cases worldwide [2]. Despite phenomenal progress in surgical techniques and chemotherapy regimens, the overall five year survival is still only 28% [3]. The major determinant of prognosis and survival in GAC is lymph node status [4]. The latest edition of American Joint Committee on Cancer/International Union against Cancer (UICC/AJCC 8th Edition) tumor–node–metastasis (TNM) classification proposed atleast 16 lymph nodes to be retrieved for adequate staging as well as to avoid *will Rogers phenomenon* [5]. As per AJCC 8th edition, the total number of affected nodes and not the site of involvement determines the prognosis [6]. However compliance with this recommendation is poor with > 15 nodes assessed in only 29% of patients [6]. The reason for this poor compliance could be inadequate nodal dissection during surgery or improper nodal sampling during pathological evaluation. In order to provide more precise nodal staging system than pTNM, other system has been proposed like lymph node ratio (LNR) and Log odds of positive nodes (LODDS) [7, 8]. LNR is calculated based on number of affected node (n+) divided by total number of nodes examined (nT). The flaws in LNR system is when patient doesn't have positive node, LNR will be zero hence LNR will not give meaningful prognostic evaluation [9]. Log odds of positive nodes (LODDS), defined as the log of the ratio between the number of positive nodes and the number of negative nodes, which gives more accurate and reliable prognostic value [10]. LODDS system will give prognostic information even with less number of nodal sampling [11]. The aim of the study is to compare the 8th pN system with ratio-based (LNR) and Log odds of positive lymph nodes (LODDS) staging systems for predicting the overall survival (OS) of gastric cancer (GC) patients after curative resection. To the best of our knowledge, no such studies published so far from our country where GAC are more prevalent.

Patients and methods:

All patients with GAC who were treated at Institute of Surgical Gastroenterology and Liver Transplantation, Government Stanley Medical College, Chennai, Tamil Nadu, India from January 2014 to December 2020 were entered into a prospectively maintained dataset. A total of 250 patients of GAC were entered. 43 patients were excluded due to peritoneal disease, mesenteric deposit, liver metastasis, palliative resections, and margin positive on HPE. Hence 207 patients underwent curative surgery (D2 or D1 plus lymphadenectomy) for GAC are included for the study. All patients with stage II and higher were treated with adjuvant chemotherapy as per our institute protocol. The baseline demographic parameters like age, sex, tumor characteristics like grade, Laurens type of GAC (diffuse or intestinal), type of surgery (subtotal or total gastrectomy), and number of nodes harvested were analyzed. The LNR and LODDS were calculated and staged as follows

pN stage (TNM)	LNR	LODDS
pN0	0	LODDS <-1
pN1	0.01-0.1	$-1 \leq LODDS < -0.5$
pN2	0.1-0.25	$-0.5 \leq LODDS < 0$
pN3	>0.25	$0 \leq LODDS < 0.5$
		$LODDS \geq 0.5$

All patients were followed up every 3 months during the first 2 years and every 6 months thereafter. Follow up visit include enquiry about new onset of symptoms, complete physical examination, blood investigations, imaging and upper GI scopy as indicated. Overall Survival (OS) is defined as the time from diagnosis to disease-related death (or) was censored at the last follow-up date if no events had occurred.

Statistical analysis:

Clinicopathological and follow-up data for each patient were collected in a computerized dataset, regularly data's were enters about tumor recurrence and survival status, and retrospectively reviewed. The collected data were analyzed with IBM SPSS Statistics for Windows, Version 23.0.(Armonk, NY: IBM Corp). To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. Post hoc analysis by GPower for Windows, version 3.0, was conducted in order to evaluate power estimation with the aim of assessing the adequacy of group and subgroup sample sizes. Overall survival rates were calculated by Kaplan-Meier method, and the logrank test was used to assess the statistical differences between the groups. The univariate and multivariate analyses by the one way ANOVA with Tukey's Post-Hoc test to identify the most significant N classification correlated with prognosis. To elucidate how LODDS contributed to the accuracy of the N classification, scatter plots of the relationship between LODDS and the number or the ratio of node metastasis were plotted. Then, overall survival rates, based on pN, LNR, and LODDS classifications, were compared. The accuracy of the prognosis assessment of each staging method was compared using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). Multivariate analysis was performed with the Cox proportional hazard method. The correlations between the number of retrieved lymph nodes, number of metastatic lymph nodes, NR, and LODDS were calculated by the Pearson correlation coefficient. Statistical significance was conventionally defined as $p < 0.05$.

Results:

The study population comprised of 150 males and 57 females, with mean age of 54 years (range 23-84 years). As per Lauren's classification intestinal type GAC are more frequent (74.9%) than diffuse type (25.1%). Grade G1 tumors were 5%, G2 tumors were 72.4% and G3 were 22.2%. A total of 114 (55.1%) patients underwent total gastrectomy against 93 (44.1%) patients underwent subtotal gastrectomy. Of the 207 patients, 21 were node negative (10.1%), 186 were node positive disease (89.8%).

The mean and median numbers of retrieved lymph nodes were 11.4 and 11 respectively with range of 3 to 40 and standard deviation of 4.73. About 173 patients had less than 15 nodes retrieved (Mean ±SD 23.23±19.2) as compared to 34 patients only had more than 15 nodes retrieved (Mean ±SD 17.09±10.7). Of 207 patients, 5 were T1, 54 patients were T2, 113 patients were T3 and 35 were T4.

The distribution of LNR are as follows, 22 patients were LNR 0, 11 patients were LNR 0.01-0.1, 43 patients were LNR 0.12-0.25, 131 patients were LNR >0.25. LODDS distribution as shown. 18 patients were LODDS <-

1, 39 patients were $-1 \leq \text{LODDS} < -0.5$, 97 patients were $-0.5 \leq \text{LODDS} < 0$, 38 patients were $0 \leq \text{LODDS} < 0.5$ and 15 patients were $\text{LODDS} \geq 0.5$.

Overall survival for the whole population was 5.7% at 5 years since most of our study population were within last 5 years of study duration (2016-2020) and median survival was 68 months. Overall survival curves of various lymph node staging system were shown in figure-1. These survival curves revealed survival advantage of early LODDS staging system were comparable to other staging system. Table -1 shows comparison of survival among patient's demographics and tumor characteristics. Factors that significantly correlated with survival were Grade of tumor, Lauren's type, gastrectomy type, number of lymph nodes retrieved, pT, pN, and LODDS. Whereas no correlation with survival was found in age, sex, LNR. At multivariate analysis in Table-2, there was significant correlation between survival and pN, pT, LODDS. LNR was not significantly correlated with survival.

The median survival of the 207 patients after surgery was used as the gold standard to draw the ROC curve as shown in Table-2 to compare the accuracy of the three staging methods in the prognostic assessment of gastric cancer patients. The corresponding AUC for pN, LNR, and LODDS was 0.76 (95% CI 0.63 - 0.89), 0.76 (95% CI 0.61 - 0.91) and 0.79 (95% CI 0.68 - 0.91)

To determine the superiority LODDS classification when compared to the pN and LNR classifications, we drawn scatter plots of the relationship between LODDS and the ratio of node metastasis. As shown in Fig. 3, the value of LODDS increased with the ratio of metastatic lymph nodes, indicating that there was a close correlation between LODDS and the LNR. However, this correlation was not linear. When the ratio of nodal metastasis was less than 0.2 or more than 0.8, it increased at a slower rate than LODDS. The most interesting finding was that when the ratio of node metastasis was 0 or 1, the value of LODDS was still diverse, indicating that the LODDS system has the potential to discriminate among patients with the same LNR classification with different prognoses, especially for those whose ratio of nodal metastasis was 0 and 1.

Correlation Between the pN Staging, LNR, and LODDS Methods and the Total Number of Lymph Nodes. A Pearson test (Table 4) showed a strong correlation between the number of metastatic nodes and LODDS system with survival, as compared to LNR (p value 0.0005). This indicates that the LODDS classification has more power to minimize the "stage migration" phenomenon caused by insufficient nodes retrieved.

VARIABLE	PATIENTS (n)	MEDIAN SURVIVAL (MONTHS)	p value (univariate analysis)
Age			0.574
<65	178	18	
>65	29	15	
Sex			0.436
male	150	18	
female	57	15	
Tumor grade			**0.0005**
G1-G2	161	19	
G3	46	11.5	
Number of lymph nodes retrieved			
<15	173	18	**0.011**
>15	34	13.5	
Lauren type			**0.0005**
intestinal	155	19	
diffuse	52	11.5	
Gastrectomy type			**0.001**
subtotal gastrectomy	114	15	
total gastrectomy	93	19	
pN stage			**0.001**
pN0	21	25	
pN1	42	20	
pN2	108	18	
pN3	36	12.5	
pT stage			**0.002**
T1	5	10	
T2	54	24	
T3	113	18	
T4	35	8	
LNR			0.081
0	22	23.5	
0.01-0.1	11	24	
0.1-0.25	43	20	
>0.25	131	15	
LODDS			**0.0003**
LODDS <-1	18	26	
$-1 \leq LODDS < -0.5$	39	27	
$-0.5 \leq LODDS < 0$	97	18	
$0 \leq LODDS < 0.5$	38	14	
$LODDS \geq 0.5$	15	9	

Table -1 shows comparison of survival among patient's demographics and tumor characteristics

VARIABLE	SE	P value	95% Confidence Interval
T stage	3.373	.014	1.49 - 18.97
N stage	4.202	.024	1.15 - 22.93
LNR	5.927	0.248	-4.32 - 26.38
LODDS	3.913	.002	4.26 - 25.80

Table-2 shows Multivariate analysis (Post Hoc Tests) between various nodal staging systems which clearly revealed significant results on LODDS system (p value 0.002)
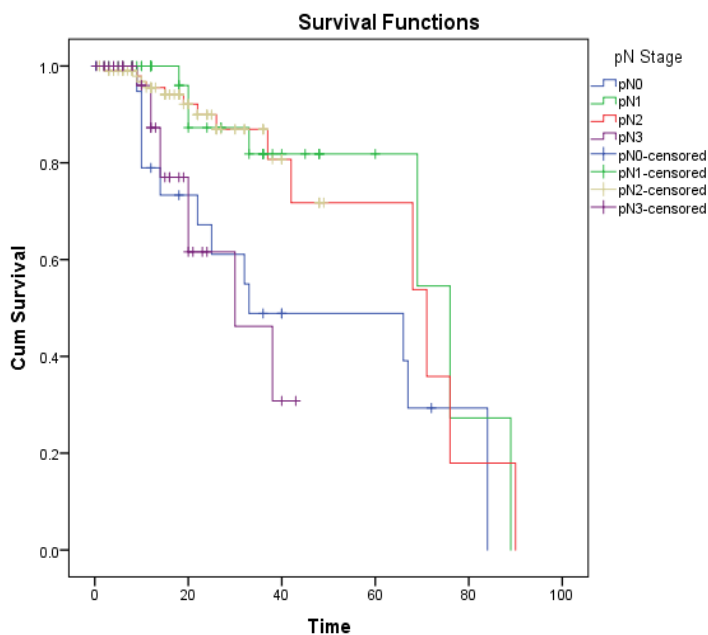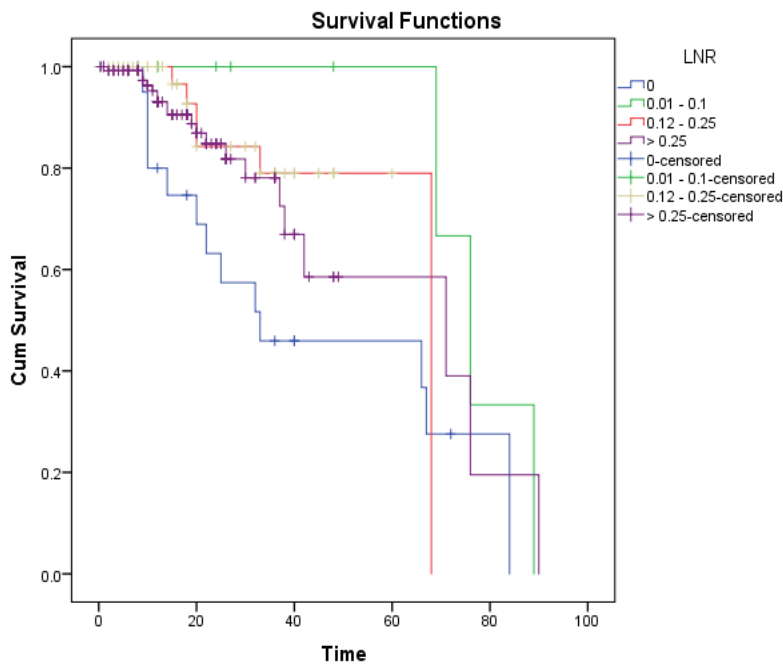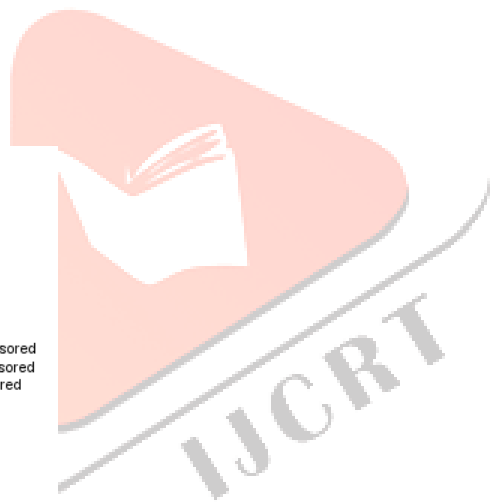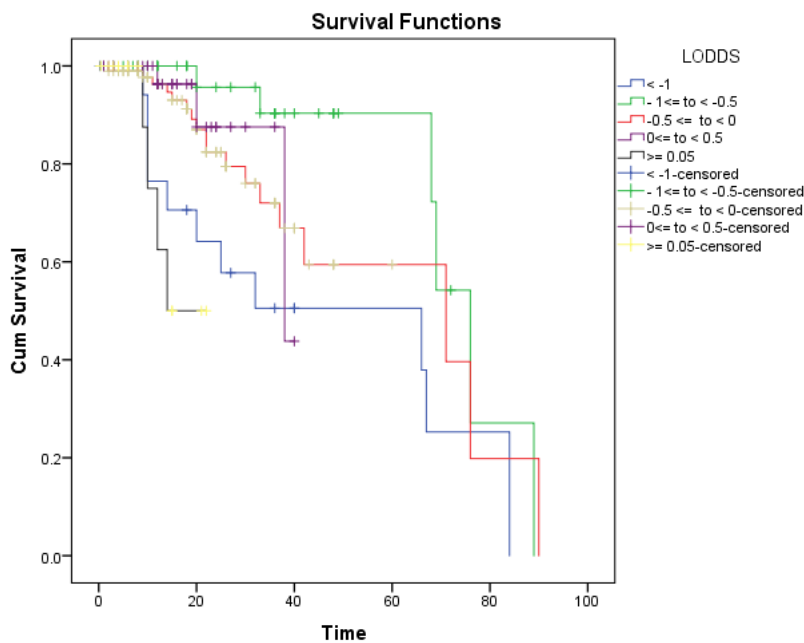
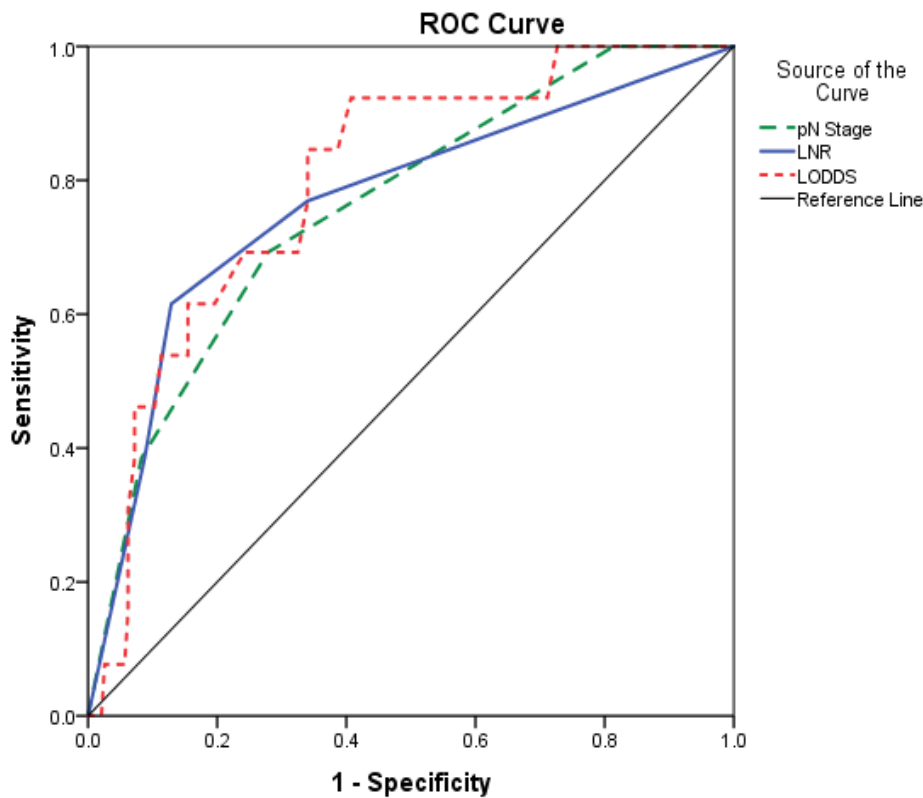**Figure-a:**

Figure-b:

Figure-c:

Figure-1: Overall survival according to the different staging methods: **a)** AJCC 8th edition pN stage, **b)** LNR and **c)** LODDS. *LNR* lymph node ratio

Figure-2: ROC curves comparison of pN, nodal ratio, and LODDS

Area Under the Curve					
				Asymptotic 95% Confidence Interval	
			p-value		
Test Result Variable(s)	Area	Std. Error[a]		Lower Bound	Upper Bound
pN Stage	.761	.067	.002	.630	.891
LNR	.767	.076	.001	.619	.915
LODDS	.799	.056	.0003	.688	.910

The test result variable(s): pN Stage, LNR, LODDS has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

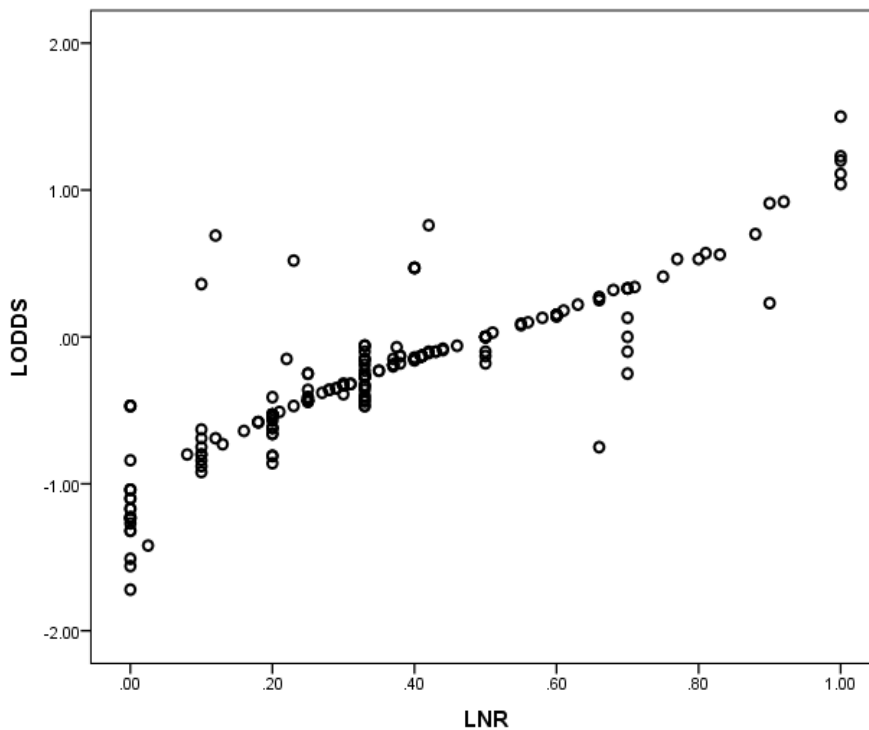**Table-3 Area under curve between various staging systems**

Figure- 3: Scatter plot of relationship between LODDS and LNR

		LODDS	LNR
LODDS	Pearson Correlation	1	.869**
	Sig. (2-tailed)		.000
	N	207	206
LNR	Pearson Correlation	.869**	1
	Sig. (2-tailed)	.000	
	N	206	206

Table -4: Pearson test showed a strong correlation between the number of metastatic nodes and LODDS system with survival, as compared to LNR (p value 0.0005)

Discussion:

The key determinant of prognostic assessment for GAC is lymph node status. The number of metastatic lymph nodes influences the survival. The main drawback of AJCC 8th edition is significant dependency on larger number of harvested nodes (>16 nodes) without which staging couldn't be done or considered as under staging so called stage migration. Hence prognosis could not be assessed upon incomplete nodal sampling which holds true for many studies [12].

In the present study as well, only 34 patients had adequate nodal sampling, 173 patients had less than 15 nodes harvested. It has been shown that the phenomenon of stage migration happens in more than 15% of cases, especially when the number of resected nodes is lower than 15.

The NR is a simple method to improve nodal staging, less affected by the extension of the lymphadenectomy by the surgeon and by the accuracy of nodal sampling of the pathologist [12, 13]. However, the LNR is unable to distinguish patients without metastatic nodes irrespective of the total number of nodes harvested that is LNR 0/8 is as equal as 0/16 nodes. Another limitation of LNR is same prognosis for same LNR viz, LNR will be same for two patients with 3/3 metastatic nodes and 16/16 metastatic nodes (NR=1), also for patients with 4/8 nodes and 8/16 nodes (LNR=0.5).

LODDS are a novel indicator of lymph node status, developed with the aim of enhancing the accuracy of N classification for prognostic evaluation [14]. Wang et al., in their study on stage III colon cancer, suggest that LODDS may be superior to LNR for several statistical reasons [15] LODDS is a function of the number of negative lymph nodes. In a study by Sun Z et al., pointed out that LODDS are an independent prognostic factor and are more predictable than pN and NR in prognostic patient stratification; they are particularly beneficial in case of limited lymphadenectomy [5]. Another study by Wang X et al, also concluded that LODDS provide better discriminatory capacity and higher predictive accuracy than either pN or LNR and that LODDS influence much less from stage migration [16].

Our study evaluated 207 patients subjected to curative gastrectomy for GAC. The extent of lymphadenectomy was D2 or D1 plus gastrectomy. Indeed, the mean number of lymph nodes retrieved was less, and only a small group of patients received optimal lymphadenectomy with more than 15 lymph nodes examined. Hence prognostic assessment for these patients as per AJCC classification was difficult.

Survival analysis showed that there were significant association between these pN, LNR, and LODDS staging system with overall survival. Multivariate analyses also confirmed strong significant associations of these nodal staging systems with overall survival.

Limitation and Recommendation of the study:

Our study was a Single center Retrospective study. Influence of chemotherapy on nodal status and its prognosis were not assessed. The number of early stage gastric cancer were less hence there was overlap in early months of survival curves.

Hence we recommend future studies with more sample size to make definitive conclusion on prognosis assessment. Atleast 3 years of follow-up is needed for predicting survival (since our study included 2020 patients). More studies are needed to further clarify the role LODDS and to understand if they may be superior to pN and LNR in prognosticating early subgroups of gastric adenocarcinoma patients.

Conclusion:

LODDS is more useful than the UICC/AJCC 8th edition pN and LNR classifications for predicting the prognosis. LODDS may be included into a GAC staging system.

Employment: Not applicable

Financial interests: The authors have no relevant financial or non-financial interests to disclose.

Conflicts of interest: The authors declare that they have no conflict of interest.

Availability of data and material (data transparency): The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions: "All authors have contributed equally to the work"

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