The Inflammatory Prognostic Index; A Potential Predictor In Stage-4 Gastric Cancer

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Research Article

Keywords: inflammatory prognostic index, stage-4 gastric cancer, Prognostic factor

Posted Date: February 3rd, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1264323/v1>

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Abstract

Background: Clinical researches regarding the determination of effective and simple prognostic markers for gastric cancer are still being carried out effectively. Inflammatory prognostic index (IPI) has been accepted as a promising prognostic marker in patients with Non-Small Cell Lung Cancer.

Aims: To evaluate the usability of the inflammatory prognostic index in stage 4 gastric cancer, which has been shown to be effective in lung cancer.

Methods: A total of 152 patients with stage 4 gastric cancer, whose laboratory progression-free survival and overall survival data could be accessed, were evaluated. Kaplan Meier analysis was used to show survival curves. Hazard ratios (HRS) were expressed as 95% CIs in the analyses. All methods were performed in accordance with the relevant guidelines and regulations

Results: Median age at diagnosis is 63 (range: 32 to 88 years). The number of patients who received first-line chemotherapy was 129 (84.9%). Progression-free survival in first line treatment was median 5.3 months, Progression-free survival in second line treatment was 3.3 months, and median overall survival (os) was 9.4 months. Median IPI score was 22.2. We evaluated overall survival in the roc analysis and set the threshold value for the IPI score as 14.6. Low IPI score was significantly associated with longer PFS and OS compared with high IPI (PFS in high vs low IPI, 3.6 vs 7 months; $p < 0.001$) (OS in high vs low IPI, 6.6 vs 14.2 months; $p < 0.001$)

Conclusions: IPI score can be an independent prognostic index that is inexpensive, easy to access and evaluate for metastatic gastric cancer patients, and may be useful in predicting survival in daily practice.

Introduction

Gastric cancer is the 5th most common cancer and the 3rd among cancer-related deaths.[1, 2] Cancer-associated systemic inflammatory response is triggered by tumor microenvironment and is associated with tumor development, invasion, and metastasis.[3] Systemic inflammatory response is clinically reflected in the predisposition to cachexia and deterioration of the patient's performance.[4] Some inflammatory biomarkers generated using hematological and biochemical parameters may predict some adverse effects such as decreased overall survival or resistance to chemotherapy. Therefore, these inflammatory biomarkers have been investigated in a number of tumor types.[5, 6] The link between inflammation and cancer is closely related and just as complex. The interaction of cells responsible for inflammation and tumor cells varies with the effect of suppressors or activators at various steps. Inflammation plays an important function in tumor development, invasion and metastasis. CRP produced by liver cells; is an acute phase protein regulated by IL-1, IL 6 and tumor necrosis factor.[7] Many studies have shown that increased CRP negatively affects the prognosis. And many previous studies have shown that the neutrophil/lymphocyte ratio (NLR) is associated with poor prognosis in various cancers. It has been confirmed that NLR is a reliable marker in this respect.

Significant variation in this association has been observed between studies, and the sources of this variation are poorly understood. NLR strikes a balance between the harmful effects of neutrophil and the beneficial effects of adaptive immunity. [8] The prognostic potential of NLR may not be the same in all patient subgroups and in all solid tumors. [9]

Clinical researches regarding the determination of effective and simple prognostic markers for gastric cancer are still being carried out effectively. Various combinations of parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) or the Glasgow prognostic score (GPS) have been used, as in our investigation of the role of the IPI score in metastatic gastric cancer.[10, 11] Subsequently, increasing evidence showed that prognostic markers could be used as an independent prognostic index in various malignant tumors. Inflammatory prognostic index (IPI), a measure based on CRP, NLR and serum albumin, has been accepted as a promising prognostic marker in patients with Non-Small Cell Lung Cancer and has been shown in various publications. [12]

In our study, we aimed to investigate the effects of inflammatory prognostic index on results such as PFS and OS in patients with stage-4 gastric cancer.

Methodology

In our study, patients who were diagnosed with metastatic gastric cancer (GC) between 2013 and 2020 in Manisa Celal Bayar University and İzmir City Hospital Oncology Center were retrospectively analyzed. Clinicopathological findings such as performance status (PS), age, gender, laboratory parameters and treatments received were recorded with the electronic medical record system. Since it is easier to implement, The performance status of the patients was evaluated with ECOG performance scoring.

A total of 152 patients with stage 4 gastric cancer, whose laboratory progression-free survival and overall survival data could be accessed, were evaluated. This retrospective study was approved by the ethics committee of Manisa Celal Bayar University. The present study was approved by the Manisa Celal Bayar University Faculty of Medicine ethics committee/institutional review board and was exempted from informed consent requirements owing to its retrospective design.

Laboratory data included hemogram data such as neutrophil, lymphocyte, platelet count, hemoglobin level, and biochemical parameters such as serum albumin, creatinine, lactate dehydrogenase (LDH), serum calcium, CRP and CEA, CA19-9. As in the original study, IPI was calculated using the formula: $\text{CRP} \times \text{NLR} / \text{serum albumin}$.

Kaplan Meier analysis was used to show survival curves. Univariate and multivariate analyzes were performed using the Cox proportional hazards model to assess the survival difference. Hazard ratios (HRS) were expressed as 95% CIs in the analyses. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the date of last follow-up. Progression-free survival (PFS) was calculated as the interval between the date of diagnosis and progression or death.

Categorical variables are presented in tables as patient numbers and percentages. Compared with odds ratio (OR) and corresponding 95% confidence interval (CI) using chi-square or Fisher's exact test.

ROC analysis was used to determine the discriminative power of the IPI score and to determine the appropriate positivity threshold. All statistical evaluations were a p-value of 0.05 was considered statistically significant. SPSS 22.0 statistical program was used for all analyzes. All methods were performed in accordance with the relevant guidelines and regulations

Results

A total of 152 patients were included for analysis in the present study. All patients were staged 4. Median age at diagnosis is 63 (range: 32 to 88 years). 30.9% (47) of the patients were female, 69.1% (105) were male. Demographic data are given in Table-1 and clinical features are given in Table-2.

83.6% (127) of the patients had de novo metastatic disease. The patients with an ECOG performance score of 3-4 was 23 (15.1%). None of the patients with an ECOG performance score of 3-4 received chemotherapy. The number of patients who received chemotherapy as 1st line was 129 (84.9%). The number of patients who could receive chemotherapy as 2nd was 67 (44.1%). In our retrospective study, 143 (94.1%) of the patients died during data collection.

There were 45 (29.6%) patients who had previously been operated palliatively or curatively for gastric cancer, and 107 (70.4%) were not operated. The number of Cerbb2 positive cases was 14 (9.2%). All of these cases received trastuzumab together with chemotherapy in the first-line treatment.

Progression-free survival 1 (PFS1) was median 5.3 months, Progression-free survival 2 (PFS2) was 3.3 months, and median overall survival (os) was 9.4 months. OS was 2.2 months in patients with ECOG 3-4, and OS was 11 months in patients with ECOG 0-1-2. ($p < 0.0001$) (mOS) is 11.9 months in patients with 2 or less metastatic areas, and 7.5 months in patients with 3 or more. ($p: 0.028$)

The IPI ratio ranged from 0.238,7 (median, 22.2), and NLR ranged from 0.4136.00 (median, 3.61)

We evaluated overall survival in the ROC analysis and set the threshold value for the IPI score as 14.6. Low IPI score was significantly associated with longer OS and PFS compared with high IPI score (median OS in high vs low IPI, 6.6 vs 14.2 months; $p < 0.001$) (median PFS in high vs low IPI, 3.6 vs 7 months; $p < 0.001$). Survival function patterns by IPI low and IPI high group has shown in figure - 1

We evaluated overall survival in the ROC analysis and set the threshold value for the NLR score as 3. Low NLR score was significantly associated with longer OS compared with high NLR score (median OS in high vs low IPI, 7.2 vs 13.6 months; $p < 0.001$) (median PFS in high vs low NLR, 3,5 vs 6.6 months; $p < 0.001$). Survival function patterns by NLR low and NLR high group has shown in figure - 2

Notably, IPI and NLR classification were identified as an independent prognostic factor for OS and PFS. Univariate and multivariate analysis of overall survival and progression free survival by prognostic factors are given in Table-3 and Table-4.

Discussion

Three inflammatory markers are very important for prediction of survival in gastric cancer. These are NLR, CRP and serum albumin level. [13]. There are several prognostic marker systems that allow us to interpret the prognosis based on inflammation in solid malignant tumors.

High NLR has been identified as an unfavorable prognostic factor in various cancers.

IL-1, IL-6 and tumor necrosis factor (TNF)- α are at the root of the increase in CRP, an acute phase inflammation protein. Therefore, CRP contributes to aggressive cancer behavior. CRP is known as an independent negative prognostic factor in various solid tumor types.[14]

Hypoalbuminemia, another important variable, has been shown to be significantly associated with short survival time in cancer patients. Hypoalbuminemia and high CRP levels are frequently observed in advanced cancer patients and are generally reported to be associated with worse survival.[15] The protein digestion and absorption were decreased in patients with gastric cancer, resulting in a negative nitrogen balance [16]

For this reason, it is thought that the inflammatory prognostic index, which is the combination of these three important parameters, can serve as a more effective scoring system in predicting the prognosis of cancer patients. A higher IPI score indicates more severe inflammation and a weaker immune response in patients.

In this analysis of 152 gastric cancer patients, we confirmed that NLR and IPI correlated with overall survival. We demonstrated that IPI score and NLR correlates with poor progression free survival in stage 4 gastric cancer patients. The NLR is a reproducible, cost-effective and available prognostic marker for gastric cancer patients.[17]

Several prognostic scores have been developed to aid in the assessment of cancer prognosis based on serum CRP and albumin levels, such as the Glasgow prognostic score (GPS) inflammatory prognostic index (IPI). Like IPI, GPS scores showing high inflammation and poor immune response have also been shown to be associated with worse prognosis for a variety of different tumor types.[12, 18] We propose that patients with a high NLR and high IPI score should thus be recognized as a high-risk group in terms of progression and survival.

An important previously published study demonstrated that CRP/Albumin and NLR score serve as independent prognostic factors for overall survival in patients with gastric cancer.[19]

Cox regression analysis demonstrated that the IPI score could be used as a predictor for both OS and PFS.

Since this study was a retrospective two-center study with a relatively small number of patients, it would be appropriate to confirm these results with prospective studies with larger patient participation.

Conclusion

As a result of cox regression analysis, it was determined that IPI score could be a parameter predicting overall survival. The IPI score can be an independent prognostic index that is inexpensive, easy to access and evaluate for metastatic gastric cancer patients, and may be useful in predicting survival in daily clinical practice.

Declarations

ETHICAL APPROVAL: Study was approved by the Manisa Celal Bayar University's Non-Invasive Clinical Research Ethics Committee (approval No. E-85252386-050.04.04-49119, date: 22.03.2021).

PATIENTS' CONSENT: Since the study was a retrospective archive search, informed consent was not obtained from the patients.

CONFLICT OF INTEREST: The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION: A.O, A.P.E. and F.E. collected the patients data, A.O. had done the statistical analysis and wrote the main manuscript text. All authors reviewed the manuscript.

DATA AVAILABILITY STATEMENT: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Tables

Table-1 Demographic data and laboratuary findings of the stage-4 gastric cancer patients

	N	Median	Minimum	Maximum	Skewness	Std. Error of Skewness
Age	152	63	32	88	-0,319	0,197
Height	152	165	143	185	-0,11	0,197
Weight	152	62	38	120	1,024	0,197
CEA	152	4,275	0,1	1744	6,66	0,197
CA19-9	152	33	0,5	9868	5,183	0,197
Creatinine	152	0,775	0,38	3,33	3,755	0,197
Albumin	152	3,7	2,08	4,7	-0,619	0,197
CRP	152	2,3	0,11	29	1,848	0,197
Neutrophil	152	5,84	1,3	26	1,848	0,197
Lymphocyte	152	1,52	0,15	4,63	1,099	0,197
Platelet	152	306,5	34	1157	2,242	0,197
Hemoglobin	152	11,4	4,5	16,4	-0,518	0,197

Table-2 Clinical features of stage-4 gastric cancer patients

	Frequency	Percent		Frequency	Percent
sex			Lung met.		
Female	47	30,9	no	124	81,6
Male	105	69,1	yes	28	18,4
ECOG			Bone met.		
0-1-2	129	84,9	no	125	82,2
3-4	23	15,1	yes	27	17,8
Surgery			LN met.		
yes	45	29,6	no	7	4,6
no	107	70,4	yes	145	95,4
Denovo			1st line		
yes	127	83,6	no	23	15,1
No	25	16,4	yes	129	84,9
Liver met.			Exitus		
no	86	56,6	no	9	5,9
yes	66	43,4	yes	143	94,1

Table-3 Univariate and multivariate analysis of overall survival by prognostic factors

Characteristics	Univariate Analysis		Multivariate Analysis	
	OS HR (95%CI)	P value	OS HR (95%CI)	P value
IPI low vs high	2,21(1,56-3,13)	0,0001	1,1(0,47-1,77)	0,78
NLR low vs high	2(1,41-2,84)	0,0001	1,93(1,24-3,01)	0,004
PLR low vs high	1,16(0,83-1,61)	0,4	0,81(0,55-1,21)	0,3

Table-4 Univariate and multivariate analysis of progression free survival by prognostic factors

Characteristics	Univariate Analysis		Multivariate Analysis	
	PFS HR (95%CI)	P value	PFS HR (95%CI)	P value
IPI low vs high	2,13(1,47-3,07)	0,0001	1,16(0,59-2,29)	0,67
NLR low vs high	2(1,4-2,89)	0,0001	1,89(1,21-2,95)	0,005
PLR low vs high	1,18(0,83-1,67)	0,36	0,88(0,59-1,33)	0,55

Figures

Figure 1

Survival function patterns by IPI low and IPI high group

Figure 2

Survival function patterns by NLR low and NLR high group

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [gastricipi.zip](#)