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Unveiling molecular clues: Exploring IFNγ, IL-10, and MMP7 blood levels in gastric carcinoma patients

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ABSTRACT

Objective: Gastric carcinoma is a leading cause of morbidity and mortality worldwide. Early detection can help reduce mortality rates. Biomarkers are being investigated globally for their potential in disease screening, monitoring, and follow-up in various cancers. However, currently, there is insufficient data on the role of biomarkers in gastric carcinoma.

Material and Methods: This single center case control study was conducted from June 2018 to March 2021 from South India. Blood samples were collected from 85 patients diagnosed with gastric carcinoma and 85 apparently healthy individuals serving as the control group. The samples were collected in a fasting state. The serum levels of biomarkers interferon gamma (IFNγ), interleukin 10 (IL-10), and matrix metalloproteinase 7 (MMP7) were measured using enzyme-linked immunosorbent assay (ELISA) and compared between the two groups. Additionally, the levels of biomarkers were compared within the gastric cancer group based on disease location, stage, and histotype.

Results: The serum levels of IFNγ and IL-10 were found to be significantly elevated in gastric carcinoma patients compared to the healthy control group. Both biomarkers exhibited high sensitivity and specificity in detecting carcinoma of the stomach. However, there was no significant difference in the serum level of MMP7 between gastric cancer patients and control group.

Conclusion: IFNγ and IL-10 show promise as potential molecular biomarkers for the detection of gastric carcinoma. Further, well designed studies, involving larger and more diverse populations matched for stage and histological types, are necessary to establish the screening and monitoring utility of these biomarkers in gastric carcinoma.

Keywords: Matrix metalloproteinase 7, interferon gamma, interleukin 10, enzyme-linked immunosorbent assay, gastric cancer, screening

INTRODUCTION

According to Global Cancer Statistics (GLOBACON) 2020, gastric cancer ranks as the fifth most common cancer worldwide and the fourth leading cause of cancer-related mortality. The current annual burden of gastric cancer amounts to approximately 1.1 million new cases per year and is expected to rise to 1.8 million per year by 2040 (1). However, the diagnosis of early-stage gastric carcinoma remains below 20% of cases, which results in poor prognosis and overall survival (2). To reduce disease burden, early detection and efficient monitoring of gastric carcinoma are crucial, necessitating the identification of novel screening, monitoring, and prognostic tools such as biomarkers.

The tumor microenvironment encompasses a variety of cells and inflammatory mediators, each exhibiting unique patterns in different tumors. These mediators can be detected and measured in peripheral plasma, offering potential for tumor detection and monitoring. Inflammatory molecules play a significant role in immune responses, chronic inflammation, tissue injury, and the development of cancer, invasion, and metastasis. The balance between pro-inflammatory and anti-inflammatory chemical mediators influence tumor growth (3).

Interferon gamma (IFNγ) is an important inflammatory mediator within the cancer microenvironment, released by invading immune cells. The role of IFNγ in gastric carcinogenesis remains controversial as it has been associated with both pro-carcinogenic and anti-carcinogenic properties (4). Interleukin 10 (IL-10) is an anti-inflammatory molecule produced by tumor infiltrating B lymphocytes, Th2 cells, macrophages, and tumor cells. Like IFNγ, IL-10 has been found to exhibit both tumor-supportive and tumor-inhibitory roles within the cancer microenvironment (5).

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Some recent studies, including one conducted by Shokrzadeh et. al., suggest that there may be an increase in serum levels of IL-10 and IFNγ, potentially indicating their usefulness as diagnostic markers for early detection of gastric carcinoma (6). Matrix metalloproteinase 7 (MMP7) is an enzyme known for its involvement in tumorigenesis, metastasis, and inflammatory processes through the remodeling of extracellular matrix components.

Limited studies have been conducted in the Indian subcontinent involving the serum levels of IFNγ, IL-10, and MMP7 in gastric carcinoma patients (7-11). The significance of these biomarkers in gastric carcinoma is yet to be confirmed with larger and more diverse populations. In this study, we assessed the circulating levels in blood of three important biomolecules IFNγ, IL-10, and MMP7 in gastric carcinoma patients and compared them with their levels in an apparently healthy control population.

MATERIAL and METHODS

The project received approval from the Institutional Ethics Committee in 2018, and the study was conducted from June 2018 to March 2021 in a tertiary care centre from South India.

Study Population and Sampling

The sample size was calculated using OPENEPI software for unmatched case-control studies with proportions, considering a 10% dropout rate, 80% power, and 95% confidence interval. Fasting blood samples were collected from 85 patients diagnosed with gastric carcinoma before treatment and 85 volunteers as controls. All participants were aged 18 years or older and provided informed consent to participate in the study. Venous blood samples of 5 mL were collected, centrifuged, and stored at -80°C until analysis.

Biomarker Analysis

The samples were processed using commercially available enzyme linked immunosorbent assay (ELISA) kits to assess the levels of the selected biomarkers, following the methodology provided in the respective user manuals. IL-10 levels were assessed using the Diaclone IL-10 ELISA kit. IFNγ levels were assessed using the fine test human IFNγ ELISA kit. MMP7 levels were assessed using the human matrix metalloproteinase-7 ELISA kit from Bioassay Technology Laboratories.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software version 20.0 for Windows. A few extreme outlier values were excluded from the study as they were due to ELISA well defects. Demographic data was compared and analysed using unpaired t-test for age and Chi-square test for gender. The serum levels of biomarkers were expressed in their respective quantitative units and compared using the Mann-Whitney U test. The variation of biomarkers based on the stage of the disease, location, and histology was calculated, and analysed using the Kruskal-Wallis and Mann-Whitney U tests.

RESULTS

A total of 170 participants were included (85 in each group) in the study. On comparing the mean age between the groups, it was found that there was a significant difference between age; however, the difference in proportion of sex between the groups was not significant. Half of the study patients presented with abdominal pain (Table 1). The statistical difference between the median values of IFNγ and IL-10 (not MMP7 levels) in these two groups were found to be significant ($p< 0.001$) (Table 2). Statistical significance of individual biomarker level difference between the stages of gastric carcinoma was found to be statistically insignificant (Table 3).

Table 1. Comparison of demographic data between gastric carcinoma patients cases and controls

Parameters		Cases, n= 85	Controls, n= 85	Significance* (p)
Age (years)	Mean	54.45	44.92	<0.001[a]
	Standard deviation	12.02	15.06	
Sex	Male (%)	64.7	52.9	0.07[b]
	Female (%)	35.3	47.1	
Symptoms	Presenting symptoms		Patients presented (%)	
	Abdominal pain		56.47	
	Vomiting		41.17	
	Distension		15.29	
	Hematemesis or melaena		5.8	
	Regurgitation		3.5	
	Others		18.82	

*p< 0.05 is considered significant; a: Unpaired t-test; b: Chi-square test.

Table 2. Comparison of biomarker levels in patients and controls

Biomarker	Cases M (IQR)	Control M (IQR)	p (*)
IFNγ (pg/mL)	9.6 (9.2-10.8)	6.4 (6.0-7.6)	<0.001
IL-10 (pg/mL)	12.1 (9.2-18.0)	3.9 (3.3-5)	<0.001
MMP7 (ng/mL)	0.7 (0.5-1.2)	0.8 (0.6-1.2)	0.188

*Statistical significance was determined by Mann-Whitney U test.
M (IQR): Median with inter quarter range.
IFNγ: Interferon gamma, IL-10: Interleukin 10, MMP7: Matrix metalloproteinase 7.

Table 3. Comparison of serum levels of biomarkers in different stages, locations and histotypes of gastric cancer

Parameters		IFNγ [M (IQR)] (pg/mL)	IL-10 [M (IQR)] (pg/mL)	MMP7 [M (IQR)] (pg/mL)
Stage	Early	11.42 (9.62 to 11.57)	13.8 (12.3 to 18.2)	1.21 (0.55 to 1.31)
	Locally advanced	9.6 (9.2 to 10.5)	11.2 (8.4 to 14.3)	0.73 (0.47 to 1.13)
	Metastatic	9.5 (9.2 to 9.8)	13.4 (9.1 to 17.8)	0.9 (0.43 to 1.29)
	P value[a]	0.75	0.46	0.88
Site	Proximal	9.3 (9.2 to 10.0)	10.4 (9.5 to 13.8)	0.7 (0.4 to 1)
	Distal	9.7 (9.2 to 10.8)	12.2 (9.3 to 15.8)	0.7 (0.5 to 1.1)
	Body	9.5 (9.1 to 10)	9.4 (5.3 to 13.3)	0.6 (0.3 to 0.7)
	P value[b]	0.5	0.22	0.33
Histology	Diffuse adenocarcinoma	9.5 (9.0 to 10.2)	11.3 (8.4 to 17.1)	0.85 (0.58 to 1.21)
	Intestinal adenocarcinoma	9.6 (9.2 to 10.8)	11.7 (9.3 to 14.8)	0.7 (0.38 to 1.16)
	p value[c]	0.39	0.69	0.08

M (IQR): Median with inter quarter range; a: Kruskal Wallis test; b: Kruskal Wallis test; c: Mann-Whitney U test. IFNγ: Interferon gamma, IL-10: Interleukin 10, MMP7: Matrix metalloproteinase 7.

It also showed the variation in serum levels of biomarkers according to the histology of gastric cancer. Statistical significance was not established when the biomarker values were compared between diffuse and intestinal types of adenocarcinoma. Other variants like GIST and lymphoma were not compared as their frequency in the data was too less to compare.

ROC Curve for Interleukin 10

A point of maximum sensitivity 86% (85.9%) and specificity 88% (88.2%) was selected as the cut-off point for IL-10 level, which corresponds to the serum level of 7.73 pg/mL and the area under curve was 0.9. This implied that IL-10 level at 7.73 pg/mL can classify the population into gastric carcinoma patients and healthy population with high accuracy (Figure 1).

ROC Plot for Interferon Gamma

A point of 95% (95.3%) sensitivity and 81% (81.2%) specificity was selected, which corresponds to serum level of 8.7 pg/mL as the cut off value and the area under curve was 0.9. This implied that IL-10 level at 8.7 pg/mL can classify population into gastric carcinoma patients and healthy population with high accuracy (Figure 2).

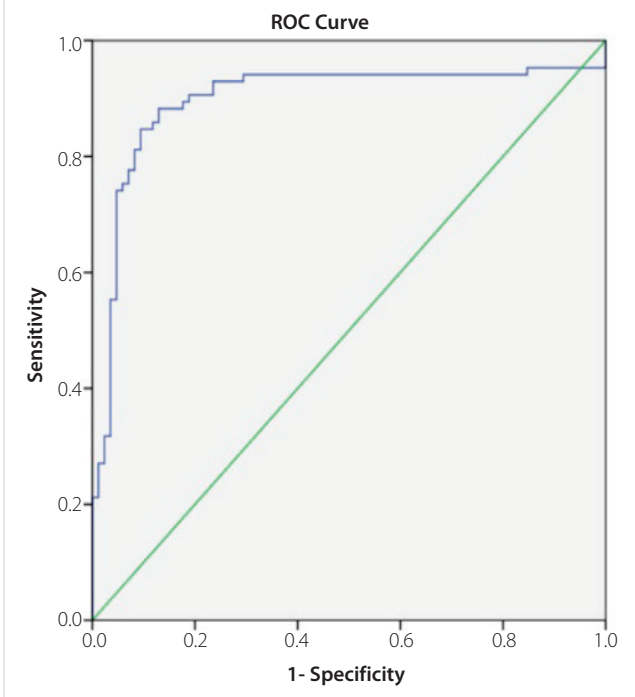

Figure 1. ROC curve for IL-10.

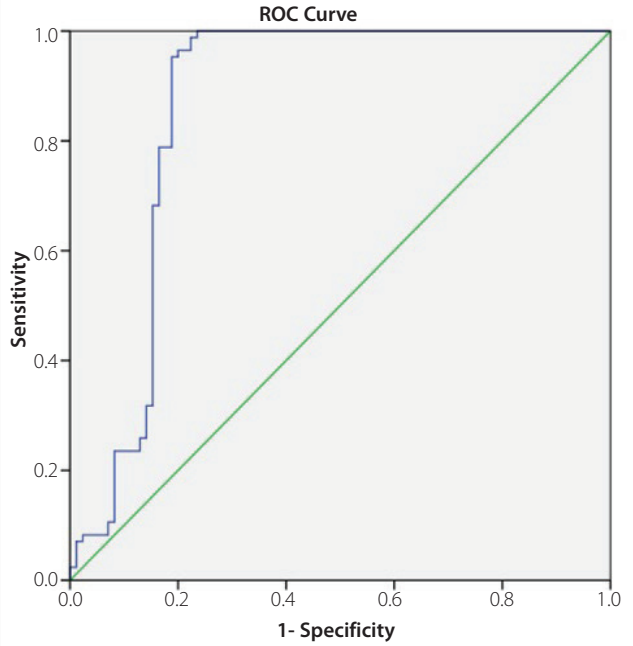

Figure 2. ROC curve for IFNγ.

DISCUSSION

Despite numerous research efforts and advancements, late-stage diagnosis remains a hindrance to the prognosis of gastric carcinoma in most cases. In developed countries like Japan and Korea, pre-emptive screening using upper gastrointestinal endoscopy has proven to enhance survival rates through early detection. However, the feasibility of implementing such screening programs on a day-to-day basis in developing countries is questionable. Ongoing studies aim to discover affordable and economical screening, diagnostic, monitoring, and prognostic tools for gastric carcinoma. Biomarkers play a crucial role in tumor management, overcoming the limitations of invasive, technically demanding, and expensive monitoring tools currently in use. Various biomarkers are being studied worldwide for their potential application in gastric carcinoma.

In our study, the average age of gastric carcinoma patients was found to be 54 years, which aligns with similar studies conducted in South India (average age of 60 years) and Eastern India (average age of 55 years) (8,9). The male-to-female ratio among gastric carcinoma patients in our study was 1.83:1. Comparable male predominance ratios have been observed in the northeastern population of India (2.16:1) and in other Indian studies (2:1) (10,11). A recent study reported a male predominance ratio of 2.2:1 worldwide for gastric carcinoma (12). Similar trends were observed in Korean patients younger than 45 years (13). This difference in sex difference may be attributed to the protective effects of female hormones as well as higher exposure to environmental agents like tobacco and alcohol in males (14,15).

Abdominal pain was the most common symptom reported by 56% of the gastric carcinoma patients in our study, followed by vomiting (41%), weight loss (10%), abdominal distension (15%), bleeding manifestations (6%), and regurgitation (3.5%). Similar studies have reported abdominal discomfort, pain, and anorexia as the most common presenting symptoms in gastric carcinoma patients (8,11).

Regarding tumor location, 15% of the patients in our study had proximal gastric cancer (fundus and cardia growths), 14% had cancer of the body of the stomach, and 71% had distal stomach carcinoma (antrum and pylorus growths). Other Indian studies have also shown that distal stomach is the most common location for gastric carcinoma (9,10). However, a Chinese analysis has reported a higher prevalence of gastric cardia tumors in their study population (16).

At presentation, 74% of the patients in our study had locally advanced gastric carcinoma, 20% had metastasis, and only 6% presented in the early stage. Similar findings have been reported by other studies, suggesting that late-stage presentation of gastric carcinoma is a common occurrence due to symptoms developing as the disease progresses and limited access to advanced healthcare and diagnostic tools in developing countries (10,16-18). Adenocarcinoma accounted for 92% of the gastric carcinoma cases in our study, with 41% classified as diffuse type and 59% as intestinal type. Other studies have also observed a higher frequency of intestinal type adenocarcinoma in gastric cancer patients (19,20). However, contrasting results have been reported in different populations, indicating that the prevalence of adenocarcinoma types may vary in different regions (21).

Helicobacter pylori and T cell inflammatory reactions can increase IFNγ in the gastric mucosa, leading to high serum IFNγ levels in gastric cancer patients (7,22,23). In our study, a significant rise in serum levels of IFNγ was observed in gastric carcinoma cases compared to controls. It is not clear if this increase is related to EBV or *H. pylori* infections (24,25). However, conflicting results have been reported by other studies, with some showing decreased levels of IFNγ in gastric cancer patients compared to healthy controls (26). Nonetheless, our study found a high sensitivity of 95% and specificity of 81% for IFNγ at a level of 8.7 pg/mL in differentiating gastric carcinoma patients from controls. Similarly, our study revealed higher serum levels of IL-10 in gastric carcinoma patients compared to controls. Similar trends have been reported by other studies emerging from India and other countries with average IL-10 levels ranging from 16-27 pg/mL in gastric carcinoma patients (6,23,27,28). A high sensitivity of 86% and specificity of 88% at a level of 8.7 pg/mL were observed for IL-10 in our study. The high sensitivity and specificity observed for IL-10 (86% sensitivity; 88% specificity) and IFNγ (95% sensitivity; 81%

specificity) support their utility in differentiating gastric carcinoma patients. This is in line with the proposed utility of IFNγ and IL-10 by Sánchez-Zauco et al. (22). Comparison of IL-10 and IFNγ values among different tumor locations, histological types, and stages of gastric carcinoma in our study did not yield statistically significant differences. However, further studies with larger sample sizes are needed to conclusively determine the significance of these biomarkers according to these variables.

MMP7 levels were analyzed in our study, but no significant relationship could be established between gastric carcinoma patients and controls. Contrasting results have been reported in other studies, with high MMP7 levels associated with poor prognosis in gastric carcinoma patients in some analyses (29-31). On the other hand, one study even observed immunonegative staining for MMP7 in majority of gastric cancer patients (32). Genetic polymorphism of the MMP7 gene and genotypic influences on its expression may contribute to the variability in results.

CONCLUSION

The introduction of novel biomarkers and the exploration of the tumor microenvironment have opened up a wide scope for early diagnosis and treatment approaches for numerous diseases, including gastric carcinoma. Our study has revealed higher serum levels of IFNγ and IL-10 in gastric carcinoma, suggesting the potential utility of these biomarkers for screening and monitoring gastric carcinoma patients. Further studies involving larger and more heterogeneous populations can help establish the effectiveness of these biomarkers in the management of gastric carcinoma.

Ethics Committee Approval: The study was approved by the Jawaharlal Institute of Postgraduate Medical Education Research Institutional Ethics Committee (Human Studies) (Decision no: JIP/IEC/2018/0215 Date: 23.05.2018).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - SGS; Design - AA, SGS; Materials - AA, CV, SS; Data Collection and/or Processing - AA; Analysis and/or Interpretation - TPE, BV; Literature Search - AA, CV, SS; Writing Manuscript - AA; Critical Reviews - SGS, BV, TPE.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ORİJİNAL ÇALIŞMA-ÖZET
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Moleküler ipuçlarının ortaya konulması: Mide karsinomu hastalarında IFNγ, IL-10 ve MMP7 kan düzeylerinin araştırılması

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ÖZET

Giriş ve Amaç: Mide karsinomu dünya çapında morbidite ve mortalitenin önde gelen nedenidir. Erken teşhis ölüm oranlarının azaltılmasına yardımcı olabilir. Biyobelirteçler, çeşitli kanserlerde hastalık taraması, izleme ve takipteki potansiyelleri açısından küresel olarak araştırılmaktadır. Ancak şu anda mide karsinomunda biyobelirteçlerin rolüne ilişkin yeterli veri bulunmamaktadır.

Gereç ve Yöntem: Bu tek merkezli vaka kontrol çalışması Haziran 2018'den Mart 2021'e kadar Güney Hindistan'da gerçekleştirildi. Mide kanseri tanısı alan 85 hastadan ve kontrol grubu olarak görev yapan sağlıklı görünen 85 kişiden kan örnekleri toplandı. Örnekler aç olarak toplandı. İnterferon gama (IFNy), interlökin 10 (IL-10) ve matriks metalloproteinaz 7 (MMP7) biyobelirteçlerinin serum seviyeleri, enzim bağlantılı immünosorbent tahlili (ELISA) kullanılarak ölçüldü ve iki grup arasında karşılaştırıldı. Ek olarak mide kanseri grubunda hastalığın lokasyonu, evresi ve histotipine göre biyobelirteçlerin seviyeleri karşılaştırıldı.

Bulgular: IFNy ve IL-10'un serum seviyelerinin mide karsinomu hastalarında sağlıklı kontrol grubuyla karşılaştırıldığında anlamlı derecede yüksek olduğu bulundu. Bu biyobelirteçlerin her ikisi de mide karsinomunun tespitinde yüksek hassasiyet ve spesifiklik sergiledi. Ancak mide kanseri hastaları ile kontrol grubu arasında serum MMP7 düzeyi açısından anlamlı bir fark yoktu.

Sonuç: IFNy ve IL-10, mide karsinomunun tespiti için potansiyel moleküler biyobelirteçler olarak ümit vericidir. Ayrıca, evre ve histolojik tiplere göre eşleştirilmiş daha büyük ve daha çeşitli popülasyonları içeren iyi tasarlanmış çalışmalar, bu biyobelirteçlerin mide karsinomunda tarama ve izleme yararlılığını belirlemek için gereklidir.

Anahtar Kelimeler: Matris metaloproteinaz 7, interferon gama, interlökin 10, enzime bağlı immünosorbent tahlili, mide kanseri, tarama

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