Evaluation of the Pro Inflammatory Cytokine Profile in Patients with Early Onset Gastric Cancer Under 40 Years of Age

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Abstract: *Background:* Early-onset gastric cancer (EOGC) is gastric cancer diagnosed in patients aged below 40 years; EOGC is increasing in frequency, although the immune profile of EOGC is not well studied. Although a major part of gastric carcinogenesis is attributed to chronic inflammation that is frequently due to Helicobacter pylori, the cytokine profiles in the young gastric cancer patients have not been clearly defined.

Purpose: The paper will focus on the assessment of the serum pro-inflammatory cytokine profile in EOGC patients and discuss how this parameter is associated with clinicopathological characteristics (tumor stage, grade, and metastasis).

Methods: The retrospective observational study design was applied to 50 EOGC patients and 50 healthy age-matched controls. Blood samples were collected, and cytokine levels (IL-1β, IL-6, IL-8, TNF-alpha, IFN- gamma, and IL-18) were determined by ELISA and multiplex bead-based assays. The levels of cytokines were compared in the two groups, and the correlations of the levels with clinical and pathological features were examined. The diagnostic potential of cytokines was investigated using ROC analysis.

Findings: The patients of EOGC had a great amount of serum cytokines compared to the healthy controls. There was also a significant increase in IL-6 and IL-1β, which was linked to advanced stages of tumor and metastasis. The ROC analysis revealed that the diagnostic performance of IL-6 and IL-1β was high, with the AUC of 0.85 and 0.82, respectively.

Conclusion: Patients with EOGC exhibit a distinctive pro-inflammatory cytokine profile, which suggests that inflammation plays a part in the disease's development. High cytokines like IL-6 and IL-1β can be used as potential biomarkers of early diagnosis and prognosis. These findings should be confirmed with further studies to investigate the therapeutic approach to address the inflammatory pathways in the management of EOGC.

Keywords: Early-onset gastric cancer (EOGC), Pro-inflammatory cytokines, Tumor progression, Biomarkers, Helicobacter pylori.

INTRODUCTION

Gastric cancer (GC), which occurs in people younger than 40 years of age, is attracting attention because of its growing prevalence in the world over time, which is referred to as EOGC [1, 2]. Although gastrointestinal cancer was traditionally linked to older people, it is increasingly being acknowledged that the incidence of the cancer is on the increase among younger groups of the population [3, 4]. This trend has contributed to an increase in interest in the learning of the specific clinicopathological and molecular peculiarities of EOGC, not corresponding to the regular GC of normal age. Gastric cancer causes a lot of burden in terms of incidence and mortality in the world, and more so in regions like East Asia and South America [5, 6]. The age at which gastric cancer occurs has been inconsistently defined in the literature; most frequently, the age cut-offs are 40 and 50 years [7, 8]. This research identified EOGC as gastric cancer that had been diagnosed under the age of 40 to narrow on a more homogenous group with clearer clinical and molecular features [9].

Nor is EOGC an exceptional example of age demographics, but also biological conduct. It is believed, based on the studies, that younger patients with GC tend to have more aggressive disease features, such as a higher percentage of diffuse histology, higher stages of tumor at diagnosis, and lower prognoses than their older counterparts. The connection of chronic inflammation and gastric carcinogenesis is proven, and a central role is played by chronic gastritis, which occurs as a result of infection with Helicobacter pylori, and leads to the development of a pro-inflammatory microenvironment. This chronic inflammation is mediated by a number of pro-inflammatory cytokines, including interleukins (IL-1β, IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-0 (IFN-γ).

Pro-inflammatory cytokines have been shown to be elevated in patients with stomach cancer and may be associated with the prognosis, tumor stage, and disease risk [10]. These cytokines comprise the body's immune response that can alter the tumor microenvironment by regulating the immune cell invasion, angiogenesis, and metastasis. A number of studies have proposed that cytokine profiles in GC patients could serve as promising biomarkers for early

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detection and management of disease progression, although most data have been obtained from typical-age GC patients.

Although limited information exists on cytokines in gastric carcinogenesis in young patients aged <40 years, the immune and cytokine subsets unique to this age group remain poorly understood. The aim is to regulate the serum pro-inflammatory cytokine profile of patients with EOGC (<40 years) and compare it with clinicopathological parameters (tumor stage, grade, and metastasis). It is postulated that the EOGC patients have a different profile of pro-inflammatory cytokines than the controls of the same age, which can provide new information about the particular pathophysiology of gastric cancer in younger patients.

Though many studies have been conducted on the cytokine profile of gastric cancer in typically-aged patients, there has been relatively less emphasis laid on studies involving young patients. This study aims to investigate the pro-inflammatory cytokines in the serum of young patients with gastric cancer and compare their levels with clinical parameters such as tumor stage, grade, and metastasis. Through this study better understand the inflammatory process unique to young-onset gastric cancer patients, in contrast to previously published results.

Key Contribution

This paper expounds new knowledge on the unique profile of pro-inflammatory cytokines in EOGC patients below the age of 40. The analysis of serum concentrations of major cytokines reveals a significant increase in these parameters compared with healthy controls. It is of interest to note that IL-6 and IL-1β were significantly linked with higher tumor stages and metastasis, which may be promising diagnostic and prognostic EOGC biomarkers. The paper also indicates the importance of chronic inflammation, particularly when associated with the infection of H. pylori, in the development of gastric cancer in younger individuals.

The paper discusses the pro-inflammatory cytokine signature of patients with early-onset gastric cancer (EOGC) who are below the age of 40 years when compared to healthy controls. Section I presents EOGC and the importance of chronic inflammation. Section II describes the study design, patient selection, and assays of cytokines. Section III displays findings of high concentrations of cytokines such as IL-6 and IL-1, which are associated with tumor stage and metastasis. These findings are discussed in Section IV and their diagnostic potential. Section V ends with future research directions on therapeutic interventions for inflammation in EOGC.

MATERIALS AND METHODS

Study Design and Setting

It was retrospective design research that involved analyzing data from the past. This research took place at a particular hospital and lasted for only one year. The purpose of the study was to measure the concentration of proteins in the blood responsible for causing inflammation in EOGC cases. The data were obtained from the hospital's cancer treatment unit since EOGC cases resided there. The institutional review board approved the study, and the ethical considerations were met, and the data confidentiality was maintained. The research design used in this study was in line with the best ethical practices, and informed consent was acquired before any research participant was included in the study.

The subjects were randomly chosen from the oncology ward of the study site over a period of one year. Patients were selected depending on the following inclusion criteria: being below 40 years old, treatment naive (no previous exposure to chemotherapy, radiotherapy, or immunotherapy), and histological confirmation of adenocarcinoma of the stomach. Patients were excluded if they had existing autoimmune disease, systemic infection, previous treatment for their illness, or any other comorbidity that would influence the measurement of cytokines. Fifty patients diagnosed with early gastric cancer and fifty controls within the same age group were involved in the study. The sample size was calculated based on pilot results from previous studies investigating cytokines in relation to gastric cancer, with an aim of 0.80 power at a significance of 0.05 for medium effects.

Schematic illustration of the study design and workflow, showing patient selection, sample collection, and cytokine analysis phases. This figure is a conceptual overview and does not represent actual experimental data.

Figure **1** illustrates the research plan on investigating the serum cytokine pattern in EOGC patients. The research is classified into three stages, namely, Phase 1, which will involve the choice of a study population, where 50 EOGC patients (younger than 40, treatment-naïve, with histology-confirmed disease) and 50 healthy controls of the same age as

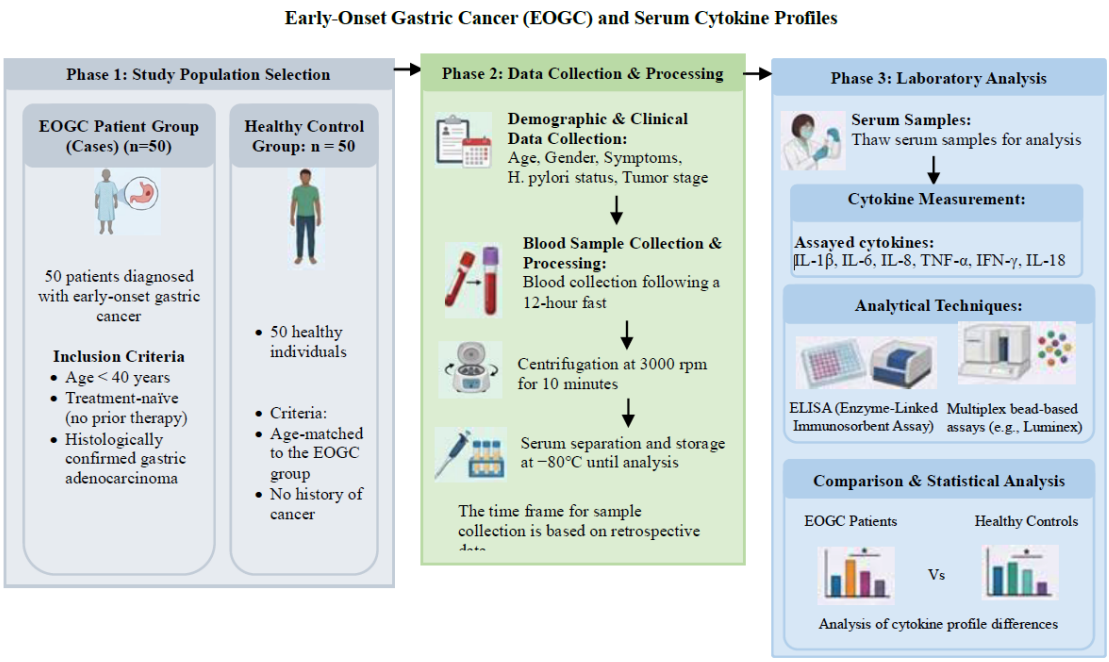

Figure 1: Study Design for EOGC and Serum Cytokine Profiling.

the EOGC patients will be included. Phase 2 involves a collection of demographic and clinical information, and then a blood sample is taken following 12 hours of fasting, and serum is stored at -80°C. Phase 3 is dedicated to laboratory analysis, where the thawed serum samples are measured with ELISA and multiplex bead-based assays to determine levels of cytokines, compare and analyze cytokine profiles between EOGC patients and healthy controls.

Study Population

The population sample was composed of patients who had a diagnosis of gastric adenocarcinoma at an age of below 40 years. The inclusion criteria were that the study subjects must have gastric cancer that has been confirmed using histology and must be treatment-naïve during blood collection. The treatment-naïve status played an important role in removing any possible confounding variables associated with the effects of previous therapeutic interventions on the levels of cytokines. The patients were not to include those patients who have autoimmune diseases, active systemic infection, or who have previously received chemotherapy or radiotherapy, so that the cytokine profile observed is not determined by other medical conditions or treatments.

Along with the EOGC group, age-matched healthy controls were also incorporated in the study. These controls never had any history of gastric cancer or other known gastrointestinal diseases and formed a control group. A comparative cohort was optional, where gastric cancer patients aged 40 and above were compared to further test whether there are any differences in cytokine profile when the cancer was diagnosed early or at a normal age.

Clinical and Pathological Data

Detailed clinical and pathological information concerning each participant was obtained. The demographic data, including age, sex, and history of gastric cancer in the family, were taken. Data regarding comorbidities and infection with H. pylori were also obtained. The tumor features were recorded, such as the location of the tumor, its histological type (Lauren classification), and the cancer stage based on the TNM system (tumor size, the involvement of lymph nodes, and metastasis). The histological differentiation (poorly differentiated, moderately differentiated, and well-differentiated) was used to classify the grade of the tumor. In addition, the presence or absence of metastatic cancer to other organs was recorded to study the influence of metastasis on the expression of signaling proteins. The presence of H. pylori infection was tested either using a rapid urease test or microscopic analysis of biopsy tissues.

Extensive data on clinical and pathological features were gathered for every subject involved in the study. Tumor staging was performed following the TNM classification system, and a staged I–III distribution table was generated. The histological subtypes were

classified on the basis of the Lauren classification system (intestinal, diffuse, mixed). Naïve to any form of treatment before sampling was confirmed in all patients to avoid interference with cytokine concentration. Any possible confounders, including co-morbid conditions (such as diabetes, hypertension), current infection, autoimmune conditions, and inflammation states, were meticulously documented; patients with these characteristics were excluded from the study.

Possible sources of confounding were carefully controlled for. Helicobacter pylori infection was excluded by rapid urease testing and histopathology among all patients. Patients who had an autoimmune disorder, systemic infection, or any other inflammatory disease were not included in the study because they could interfere with the evaluation of cytokines. Moreover, demographic data and the medical history of patients in relation to any concomitant disease, such as diabetes and hypertension, were collected. Thus, differences in cytokine levels will be mainly attributed to early gastric cancer.

Blood Sampling and Cytokine Assays

A 12-hour overnight fast was performed to ensure that no recent food consumption had affected any cytokine levels of the participants, and then the samples of blood were taken. Centrifugation of the collected blood at 3000 rpm and 10 minutes was done to isolate serum, which was stored in -80 °C until the time cytokine analysis was done.

The choice of cytokines to be measured in the study was IL-1β, IL-6, IL-8, TNF-8, IFN-8, and IL-18, which have been previously shown to facilitate inflammatory and gastric carcinogenesis. These cytokines play different roles, including the recruitment of immune cells, angiogenesis, and tumor development, and have already been demonstrated in the tumor microenvironment of gastric cancer.

The concentrations of the cytokines, such as IL-1β, IL-6, IL-8, TNF-α, IFN-γ, and IL-18 in the serum specimens were quantified by using ELISA kits obtained from R&D Systems, Minneapolis, USA, and also by the bead-based assay in the Luminex System provided by Bio-Rad, Hercules, USA. All experiments were performed thrice to obtain reproducible results. The manufacturer's instructions for limit of detection and the coefficient of variations (CV) in the inter-assay and intra-assay were strictly followed. Positive and negative controls were included in each test plate to confirm the efficacy of the test and standard curve was constructed for all cytokines.

Outcome Measures

The main result of the study was to compare the levels of cytokines in patients with gastric cancer who have developed early and healthy controls. Secondary outcomes were based on exploring how associations between cytokine levels and different clinicopathology characteristics, including tumor stage, tumor grade, and metastasis. The other secondary goal was to assess whether the level of cytokines was related to the H. pylori status and tumor histological type. Moreover, the research was carried out to evaluate whether these cytokines can be a diagnostic or prognostic biomarker to early detect and the progression of gastric cancer among younger patients.

Statistical Analysis

All statistical analysis procedures were done using SPSS software version 25 or other equivalent packages. $P<0.05$ was taken as statistically significant. To compare the serum cytokine levels between EOGC subjects and healthy controls, t-test was performed in case the data was normally distributed while if not then Mann-Whitney U-test was applied. One-way ANOVA was used in case the data was normally distributed and Kruskal-Wallis test when it was not for comparing multiple groups like those having various stages of tumors and histological types.

Pearson/Spearman correlation was calculated for analyzing the association between serum cytokines in relation to clinicopathological features in terms of their distributions. Multiple linear regression was done to determine which factors independently predicted tumor stages and grades. To calculate the diagnostic efficiency of each cytokine for early diagnosis of EOGC, ROC curve analysis was done which included the computation of sensitivity, specificity and area under the curve of each cytokine separately for differentiation between GC and non-GC individuals.

The Shapiro-Wilk test was utilized to test whether the data followed the normal distribution. In case the data followed the normal distribution, parametric tests were used including independent samples t-tests or one way ANOVA while non-parametric tests were utilized in cases where the data did not follow a normal distribution and included the Mann Whitney U test or Kruskal Wallis test. The Bonferroni correction was utilized whenever subgroup analyses were performed, particularly for multiple comparisons of groups in relation to tumor staging or type, to maintain the overall alpha level at 0.05. Regression analysis had cytokines

as the independent variable while tumor stage, grade and metastasis as the dependent variable.

Ethics

The research was conducted in compliance with ethical standards, and the approval of the institutional review board was sought for all activities that involved human subjects. All patients gave informed consent, and they were aware of the aim of the study, the procedures used, and the risks involved in the study. The analysis of all patient data was anonymized in order to ensure the preservation of patient confidentiality.

RESULTS

Study Population Description

The total sample size comprising the EOGC patients for conducting this experiment included 50 patients below 40 years of age and 50 controls, which were also below 40 years of age. Table **1** presents information regarding the patients that participated in this experiment. The mean age of the patients with EOGC was 34.5 years, including 30 male and 20 female participants. The tumor stage for the majority of these patients was between I and III. Moreover, 60% of the patients suffered from the H. pylori infection. The occurrence rate of the infection among patients with EOGC was much higher compared to controls ($p < 0.01$).

Cytokine Levels: Early-Onset GC vs Healthy Controls

The EOGC patients' serum cytokine levels were significantly different from those of the healthy controls. As shown in Table **2**, the EOGC group had higher median levels of IL-1β, IL-6, IL-8, TNF-alpha, IFN-gamma, and IL-18. The greatest variation was noted in IL-6 and IL-1β, where 85.0 [65-100] and 28.5 [15-45], respectively, compared with 25.0 [15-45] and 14.2 [8-22] in the healthy controls ($p < 0.01$ each). Cytokine levels of the two groups are presented in Figure **2**, which displays the boxplot comparison.

The boxplots represent the initial experimental data regarding the concentration of cytokines, namely, IL-1β, IL-6, IL-8, TNF-α, IFN-γ, and IL-18 in sera obtained from patients with early-onset gastric cancer and healthy participants.

The serum concentrations were measured by ELISA and multiplex bead assay. As one can see in Figure **2**, there was a substantial increase in the level of cytokines in the case of patients with early-onset gastric cancer compared to the control group.

Association with Clinicopathologic Features

The increased level of cytokines in the group with EOGC has been correlated with some important clinicopathological characteristics. There was a strong association between IL-6 and IL-1β levels in the presence of tumor (stage II and III) and metastasis.

Table 1: Demographic and Clinicopathologic Characteristics of Study Participants

Characteristic	Early-Onset GC (n=50)	Healthy Controls (n=50)	p-value
Age (mean ± SD)	34.5 ± 5.2	35.0 ± 4.8	0.69
Sex (Male: Female)	30:20	30:20	1.00
Family History of GC (%)	10%	5%	0.58
H. pylori Positive (%)	60%	25%	<0.01
Tumor Stage (Stage I-III)	70%	N/A	N/A

Table 2: Serum cytokine levels (pg/mL) in early-onset GC patients and healthy controls

Cytokine	Early-Onset GC (Median [IQR])	Healthy Controls (Median [IQR])	p-value
IL-1β	28.5 [15-45]	14.2 [8-22]	<0.01
IL-6	85.0 [65-100]	25.0 [15-45]	<0.01
IL-8	120.0 [100-160]	45.0 [30-60]	<0.01
TNF-α	85.5 [70-110]	40.0 [25-50]	<0.01
IFN-γ	52.0 [35-70]	20.0 [10-30]	<0.01
IL-18	500 [400-600]	250 [150-350]	<0.01

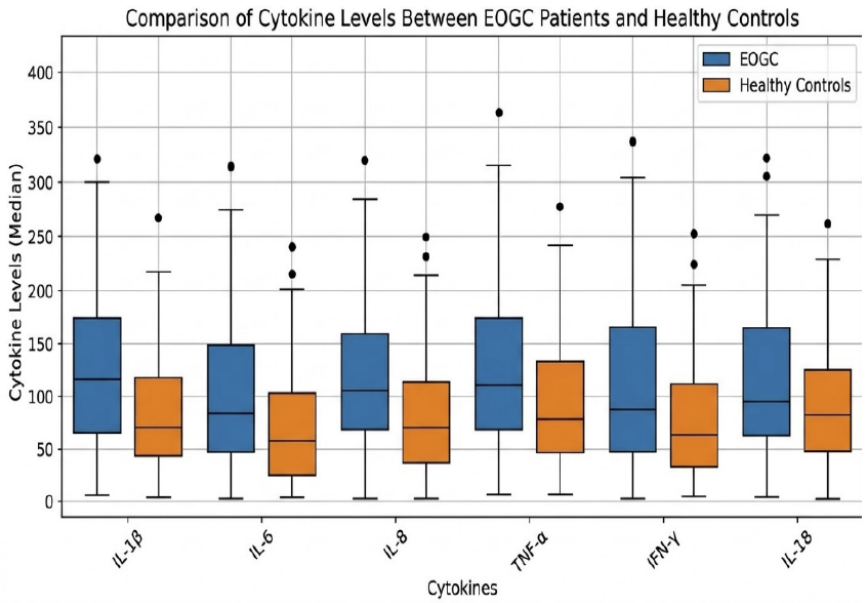

Figure 2: Comparison of serum cytokine levels (pg/mL) between EOGC patients and healthy controls.

Compared to patients with intestinal gastric cancer, those with diffuse histological gastric cancer had much higher levels of cytokines such as IL-1β and IL-6.

Indicatively, the levels of IL-1, which were found to be highest in stage III tumors, were a median of 45.0 and 100.0, whilst the median in stage I tumors was 15.0 and 65.0, respectively. On the same note, metastasis was also linked with a much-increased level of TNF- α and IL- 8.

Diagnostic and Prognostic Analyses

The ROC curve was analyzed to determine the diagnostic value of cytokines in distinguishing between EOGC and healthy controls. Figure **3** shows that IL-6 and IL-1β performed well in diagnostics, with respective AUCs of 0.85 and 0.82. These cytokines were also sensitive and specific to detect very early gastric cancer in this cohort.

ROC curves derived from experimental cytokine measurements in early-onset gastric cancer patients, showing the discriminative performance of IL-6 and IL-1β for differentiating patients from healthy controls.

Diagnostic ability of IL-6 and IL-1β was also assessed by ROC analysis, as indicated in Figure **3**. The correlations of both IL-6 and IL-1β with the AUC value of 0.85 and 0.82, respectively, demonstrate that they can be used as biomarkers in differentiating between EOGC and healthy patients, but IL-6 has a higher discriminative ability.

While the ROC curves showed high discriminative power of IL-6 and IL-1β (with AUC values 0.85 and 0.82, respectively) for distinguishing between EOGC patients and controls, this information is based on a unique sample. Confirmation through an independent validation study would be needed in order to evaluate the clinical applicability of this set of biomarkers. Consequently, one should proceed with caution regarding the results obtained in the course of the present investigation.

Exploratory Analyses

A clustering of cytokine profiles based on an exploratory analysis was used to define possible subgroups of the EOGC cohort. The study found two distinguishable subgroups of gastric cancer patients depending on their cytokine profiles, which may support the idea that cytokine signatures can be used to further subdivide EOGC patients. Nevertheless, this investigative finding needs to be confirmed on a broader scale in multicenter research.

Also, a comparison was made of cytokine profiles of the early-onset and old gastric cancer cohorts (patients ≥40 years). Surprisingly, some cytokines, such as IL-6, were increased in both groups, whereas IL-1β was much higher in the younger group, which could be because of the peculiar inflammatory state of EOGC.

DISCUSSION

This paper provides an insight into finding that patients with gastric cancer, which develops in early

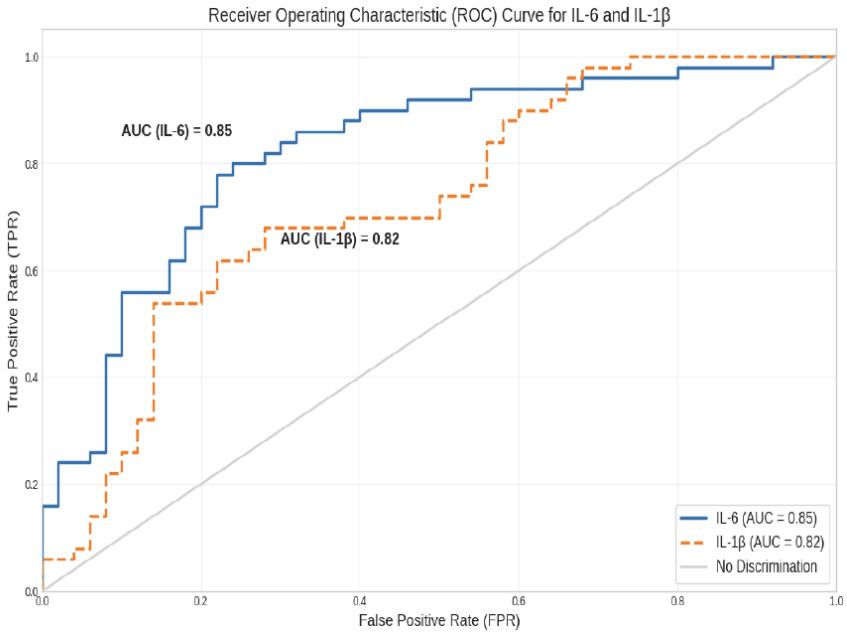

Figure 3: ROC Curve for IL-6 and IL-1β.

years (EOGC), have a unique pro-inflammatory cytokine profile when compared to healthy controls, indicating that several major cytokines, such as IL-6, IL-1β, IL-8, TNF-α, IFN-γ, and IL-18, are highly elevated [11]. The most significant results were the high levels of IL-6 and IL-1β, which were also correlated with advanced tumor stages and the occurrence of tumor metastasis. These findings indicate that these cytokines might be very significant in the pathogenesis of EOGC and that they might have a major effect on tumor development, metastases, and the general outcomes of the disease. The increase in the inflammatory condition in EOGC patients also indicates the role of inflammation in the pathogenesis of gastric cancer, especially among the younger population, and provides additional evidence of the peculiarities of the biological behavior of this cancer [12]. The increase in cytokines of EOGC implies that they could cause the aggressive character of the disease, which is frequently diagnosed at more advanced stages in younger patients, and it is more difficult to treat. Although individuals with autoimmune and inflammatory diseases were excluded from this study, Helicobacter pylori infection was prevalent among EOGC patients (60%), which might play a role in high cytokine levels. Stratified analysis should be incorporated in future investigations to distinguish between the influence of H. pylori infection and tumor-induced cytokine changes.

The results are in line with the earlier studies on gastric cancer; the role of pro-inflammatory cytokines, especially IL-6 and IL-1β, has been established as an important aspect of tumor development [13, 14]. These cytokines are also known to take part in several biological events like immune regulation, cell growth, angiogenesis, and tissue remodeling. Nevertheless, this study has a certain advantage in that it has been specifically dedicated to a cytokine profile of patients under the age of 40, and this cohort has not been as widely studied in the context of gastric cancer [15]. The observed differences in the cytokine profiles of this group of EOGC patients should be considered as a useful diagnostic or prognostic biomarker of this group of patients, which allows monitoring disease progression in a non-invasive way and provides information about the prognosis. The aggressive character of EOGC, as well as late stages of diagnosis among the younger population groups, makes early diagnosis and proper monitoring a very important issue in treating the disease.

This research shows that the expression of both IL-6 and IL-1β is significantly increased among early-onset gastric cancer patients and depends on the staging and metastasis of the tumor. Although this may imply that the cytokines can have a potential role as biomarkers for the disease, the results are based solely on one cohort. Hence, any conclusions about their diagnostic/prognostic potential should be regarded as preliminary until confirmed by further research using an independent group of patients. In addition, although manipulating IL-6 and IL-1β can affect tumor growth, no evidence is provided concerning this issue. Thus, these assumptions are merely theoretical [16]. The idea of modulating the inflammatory cascades triggered

by IL-6 and IL-1β could be a novel method of treating EOGC, specifically in younger individuals who might respond to combination therapy involving the use of anti-inflammatory treatments in association with the existing treatment measures, including immunotherapy. The results provide opportunities to conduct further studies on the use of cytokine inhibitors or other anti-inflammatory interventions to slow down the disease development, enhance patient outcomes, and provide a new horizon in the treatment of gastric cancer [17, 18].

Nevertheless, the research does not go without limitations. It is a retrospective and single-center study, which restricts the external validity of the findings. In addition, the cross-sectional design of the study does not allow for the determination of the temporal variation in cytokine levels, especially in relation to the treatment. To establish such findings, longitudinal research, especially multicenter studies with bigger sample sizes, is required to give more concrete evidence of the role of cytokines in the pathogenesis of EOGC. Moreover, research in the future must be directed towards combining cytokine profiling with genetic and molecular data to gain more insight into the underlying processes that contributed to the distinct cytokine profiles in EOGC. The results of such research would give a better insight into the disease and may produce specific drugs that would help to improve the prognosis and treatment of young gastric patients with cancer [19, 20].

CONCLUSION

To sum up, this study gives strong evidence that the pro-inflammatory cytokine profile between patients with EOGC and healthy control groups differs, with high levels of IL-6, IL-1β, IL-8, TNF-alpha, IFN- gamma, and IL-18. It is noteworthy to mention that IL-6 and IL-1β had a high correlation with high tumor stages and metastasis, which is important in the development and aggressiveness of EOGC. These observations highlight inflammation as the primary focus of the pathophysiology of gastric cancer among younger people who are below 40 years old and most of the time have more advanced and aggressive strains of the disease. Since the disease is frequently discovered at advanced stages and there are limited treatment options, the high levels of cytokines found in EOGC patients may be helpful biomarkers utilized in early diagnosis, prognosis, and monitoring. The distinct cytokine pattern identified in this cohort can thus be used to come up with more precise diagnostic tools as well as non-invasive monitoring procedures, which could be used to monitor the progress of the disease. Also, the experiment hypothesizes that the pro-inflammatory cytokines, such as IL-6 and IL-1β, can increase tumor progression, invasion, and metastasis, and hence they can be used as therapeutic targets. Inhibiting these inflammatory pathways, including cytokine blockers or anti-inflammatory therapy, would provide new ways of treating EOGC in combination with immunotherapy. Nonetheless, the study is associated with several limitations, such as a retrospective, single-centered design and a cross-sectional design, which limit it. Further investigation, such as larger, multi-centered, and longitudinal research that has been proposed to verify these results and even deeper examine cytokine profiling in the context of genetic and molecular conditions, is necessary to eventually enhance personalized treatment plans and patients' survival in younger gastric cancer patients.

REFERENCE

[1] Baek S, Park E, Park EY. Association of Pro-inflammatory Cytokines with Gastric Cancer Risk: A Case-Cohort Study. Cancer Research and Treatment: Official Journal of Korean Cancer Association 2025; 57(3): 760-769. https://doi.org/10.4143/crt.2024.718

[2] Nouri Z, Choi SW, Choi IJ, Ryu KW, Woo SM, Park SJ, *et al.* Exploring connections between oral microbiota, short-chain fatty acids, and specific cancer types: a study of oral cancer, head and neck cancer, pancreatic cancer, and gastric cancer. Cancers 2023; 15(11): 2898. https://doi.org/10.3390/cancers15112898

[3] Aljeboury GH, Risan MH, Algafari RN. Effect of probiotic extracted from lactobacillus sp. antagonist helicobacter pylori of human stomach ulcer. Journal of Global Pharma Technology 2019; 11(5): 731-737.

[4] Milne AN, Sitarz R, Carvalho R, Carneiro F, Offerhaus GJA. Early onset gastric cancer: on the road to unraveling gastric carcinogenesis. Current Molecular Medicine 2007; 7(1): 15-28. https://doi.org/10.2174/156652407779940503

[5] Qi Q, Peng Y, Zhu M, Zhang Y, Bao Y, Zhang X, *et al.* Association between serum levels of 12 different cytokines and short-term efficacy of anti-PD-1 monoclonal antibody combined with chemotherapy in advanced gastric cancer. International Immunopharmacology 2023; 114: 109553. https://doi.org/10.1016/j.intimp.2022.109553

[6] Sakhri S, Othman RB, Jerbi C, Ceylan Hİ, Naija L, Zemni I, *et al.* Effect of Perioperative Supplementation with Arginine and Omega-3 on Postoperative Complications in Patients Undergoing Gastrointestinal Cancer Surgery: A Pilot Open-Label Randomized Controlled Trial. Nutrients 2026; 18(4): 651. https://doi.org/10.3390/nu18040651

[7] Sitarz R, de Leng WWJ, Polak M, Morsink FHM, Bakker O, Polkowski WP, *et al.* IL-1B−31T>C promoter polymorphism is associated with gastric stump cancer but not with early onset or conventional gastric cancers. Virchows Archiv 2008; 453(3): 249-255. https://doi.org/10.1007/s00428-008-0642-5

[8] Liu L, Wu M, Liu Y. Prognostic integration of tumor microenvironment and parthanatos-related genes in gastric

cancer: a machine learning-driven risk model and immune landscape profiling. Frontiers in Immunology 2026; 17: 1636331.
https://doi.org/10.3389/fimmu.2026.1636331

[9] He M, Liu L, Chen Z, Liu Y, Liu C, Ma M, *et al.* A two-step scoring model incorporating visceral-to-subcutaneous fat ratio and systemic immunoinflammatory index for predicting cytokine release syndrome severity in patients with gastric cancer receiving Claudin18.2-targeted CAR-T cell therapy. Cancer Immunology, Immunotherapy: CII 2026; 75(4): 96.
https://doi.org/10.1007/s00262-026-04341-y

[10] Yarmohammadi R, Najafi K, Noroozbeygi M, Didehvar K, Rastin A, Ataei F, *et al.* The Role of IL-6, IL-10 and CRP in Gastrointestinal Cancers. Cell Biology International 2025; 49(9): 1061-1078.
https://doi.org/10.1002/cbin.70050

[11] Kesharwani A, Dighe OR, Lamture Y, Dighe O. Role of helicobacter pylori in gastric carcinoma: A review. Cureus 2023; 15(4).
https://doi.org/10.7759/cureus.37205

[12] Wang Y, Zou J, Li Y, Jiao X, Wang Y, Zhuo N, *et al.* Serological biomarkers predict immune-related adverse events and clinical benefit in patients with advanced gastrointestinal cancers. Frontiers in Immunology 2022; 13: 987568.
https://doi.org/10.3389/fimmu.2022.987568

[13] Smirnova O, Sinyakov A, Kasparov E. Cytokine Regulation and Oxidative Stress in Helicobacter Pylori-Associated Gastric Adenocarcinoma at Different Stages: Insights from a Cross-Sectional Study. International Journal of Molecular Sciences 2025; 26(15): 7609.
https://doi.org/10.3390/ijms26157609

[14] Jardim SR, de Souza LMP, de Souza HSP. The rise of gastrointestinal cancers as a global phenomenon: unhealthy behavior or progress?. International Journal of Environmental Research and Public Health 2023; 20(4): 3640.
https://doi.org/10.3390/ijerph20043640

[15] Della Bella C, D'Elios S, Coletta S, Benagiano M, Azzurri A, Cianchi F, *et al.* Increased IL-17A serum levels and gastric Th17 cells in Helicobacter pylori-infected patients with gastric premalignant lesions. Cancers 2023; 15(6): 1662.
https://doi.org/10.3390/cancers15061662

[16] Li X, Sun Z, Peng G, Xiao Y, Guo J, Wu B, *et al.* Single-cell RNA sequencing reveals a pro-invasive cancer-associated fibroblast subgroup associated with poor clinical outcomes in patients with gastric cancer. Theranostics 2022; 12(2): 620.
https://doi.org/10.7150/thno.60540

[17] Bartchewsky Jr W, Martini MR, Masiero M, Squassoni AC, Alvarez MC, Ladeira MS, *et al.* Effect of Helicobacter pylori infection on IL-8, IL-1β and COX-2 expression in patients with chronic gastritis and gastric cancer. Scandinavian Journal of Gastroenterology 2009; 44(2): 153-161.
https://doi.org/10.1080/00365520802530853

[18] Sexton RE, Al Hallak MN, Diab M, Azmi AS. Gastric cancer: a comprehensive review of current and future treatment strategies. Cancer and Metastasis Reviews 2020; 39(4): 1179-1203.
https://doi.org/10.1007/s10555-020-09925-3

[19] Khan S, Huda B, Bhurka F, Patnaik R, Banerjee Y. Molecular and immunomodulatory mechanisms of statins in inflammation and cancer therapeutics with emphasis on the NF-κB, NLRP3 inflammasome, and cytokine regulatory axes. International Journal of Molecular Sciences 2025; 26(17): 8429.
https://doi.org/10.3390/ijms26178429

[20] Wu M, Tian C, Zou Z, Jin M, Liu H. Gastrointestinal microbiota in gastric cancer: Potential mechanisms and clinical applications—A literature review. Cancers 2024; 16(20): 3547.
https://doi.org/10.3390/cancers16203547

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https://doi.org/10.30683/1929-2279.2026.15.12