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Differences of IL-12 Levels between Positive and Negative Helicobacter Pylori Gastritis

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What is Important?

IL-12 is one of several inflammatory cytokines in response to bacterial infection. In gastritis patients, a significant increase in IL-12 was reported. A significant difference between IL-12 levels in gastritis patients with *H. pylori* was seen compared with gastritis without *H. pylori*.

ABSTRACT

Introduction: Gastritis is inflammation of the stomach that can occur either acutely or gradually as a chronic condition. The incidence of gastritis in Indonesia reaches 40.8%. One of the most common causes of gastritis is *Helicobacter pylori* (*H. pylori*). Gastric mucosal damage due to inflammation will induce natural body defense cells and increase inflammatory cytokines, one of which is IL-12.
Methods: The study was conducted on 80 samples obtained through consecutive sampling in March-June 2019. Gastritis was diagnosed through endoscopic examination (Olympus, Tokyo, Japan). *H. pylori* was determined by a change in color to red, magenta, pink or orange on Campylobacter Like Organism (CLO) examination. IL-12 level was determined using a Human IL-12 ELISA kit (ab46035) | Abcam. All data were collected and analyzed with SPSS version 23.
Results: A total of 80 subjects were enrolled with male predominant. The mean of Body Mass Index (BMI) was 23.16 kg/m^2 and the mean of total IL-12 levels was 49.38 $\pm$ 19.71 pg/mL. IL-12 levels were significantly higher in positive *H. pylori* gastritis (65.36 $\pm$ 16.58 pg/mL) than negative *H. pylori* gastritis (40.77$\pm$15.5 pg/ml), p <0.001.
Conclusion: There was a significant difference between IL-12 levels in patients with *H. pylori* gastritis compared with gastritis without *H. pylori*.

Key Words: IL-12, Gastritis, *Helicobacter Pylori*

INTRODUCTION

Gastritis is an inflammation of gastric mucosa that caused by *Helicobacter pylori* (*H. pylori*) which can be acute, diffuse or chronic localized [1]. Data from World Health Organization in 2012 showed that some incidence of gastritis in the world, including the UK 22%, China 31%, Japan 14.5%, Canada 35%, and France 29.5%. In the world, the incidence of gastritis is around 1.8-2.1 million of the population every year. While in Indonesia the percentage of gastritis was found to reach 40.8% [2].

H. pylori is a spiral, microaerobic gram-negative bacterium. Epidemiologic studies reveal that about 50% of people worldwide are infected with *H. pylori* [3]. *H. pylori* plays an important role in the occurrence of gastritis and peptic ulcer. *H. pylori* infection is estimated to occur in 50% of the world's population where the majority of these infections occur in developing countries [4,5]. During the infection, gastric epithelial cells produce a variety of cytokines that are involved in the

inflammatory gastric environment after infection with *H. pylori*. Besides, many immune cells, such as neutrophils, lymphocytes, and plasma cells, are releasing inflammatory factors in the stomach of *H. pylori* infection [6].

In gastritis patients with *H. pylori*, there is an increase in several inflammatory cytokines in the gastric mucosa, one of them is interleukin 12 (IL-12) [7]. IL-12 is a cytokine that is directly produced after a bacterial infection. Cellular sources of IL12 in response to infection are dendritic cells and phagocytes. IL-12 has two subunits IL12-p35 and p40-encoded by different genes, each named IL12A and IL12B, which are unrelated and located on separate chromosomes (3p12 - q13.2 and 5q31-33) [8]. This increase in IL-12 level will further induce the formation of IFN-γ which will further increase the body's defense response by forming Th 1. This cascade will be followed by the formation of other inflammatory cytokines. The study by Karttunen, *et al.* reported a significant increase in IL-12 in gastritis patients with *H. pylori*. This is in accordance with research by Bauditz, *et al.* which showed a significant relationship between IL-12 levels and the degree of histopathology in chronic gastritis [7]. It has previously been shown that IFN-γ-producing T cells are induced by IL-12, and that macrophages are potent producers of IL-12 at sites of bacterial infection [6]. The gastric concentrations of IFN-γ and IL-12 were significantly higher in patients infected with *H. pylori* than in uninfected individuals [9].

To the authors' knowledge, there is no previous study about differences of IL-12 levels between positive and negative *H. pylori* in Indonesia. The aimed of this study to determine the differences of IL-12 levels between positive and negative H. pylori.

MATERIALS AND METHOD

Patient Selected

There were 80 samples obtained through consecutive sampling in March-July 2018. Gastritis was ensured by endoscopy (Olympus, Tokyo, Japan). Mucosa undergoes edema, erythema (spotted, patchy, linear), exudate, bleeding, erosion and histopathology (marked by inflammatory cells in the gastric mucosa) is diagnosed with gastritis. *H. pylori* is determined through a change in color from yellow to red, magenta, pink, and orange in the examination of Campylobacter Like Organism test (CLO). IL-12 level examination using a Human IL-12 ELISA kit (ab46035) | Abcam.

Data analysis

Data analysis of IL 12 level between positive and negative *H. pylori* were univariate and bivariate. Univariate analysis was used in determining the characteristics of *H. pylori* gastritis patients and the prevalence of *H. pylori* gastritis patients. Bivariate analysis was used in determining the ratio of IL 12 level between positive and negative *H. pylori* gastritis patients using independent T-test. All data were analysed by SPSS 23 version. A value of $p< 0.05$ with a 95% confidence interval was considered statistically significant.

RESULT

Table 1. Baseline and clinical characteristic of subjects

Characteristic	n = 80
Gender [a]	
Male	49 (61.25)
Female	31 (38.75)
Age (years) [b]	47 (24 – 66)
Ethnic [a]	
Batak	46 (57.5%)
Java	28 (35%)
Acehnese	6 (7.5%)
Occupation [a]	
Private employee	35 (43.8%)
Housewive	18 (22.5%)
Entrepreneur	22 (27.5%)
Civil servants	5 (6.3%)
Education [a]	
Elementary school	3 (3.8%)
Junior High School	20 (25%)
High School	41 (51.3%)
University	16 (20%)
BMI (kg/m^2) [b]	23.36 ± 3.75
H. pylori [a]	
Positive	28 (35%)
Negative	52 (65%)
IL-12 (pg/mL) [c]	49.38 ± 19.71

[a] *Categoric data: n(%)*
[b] *Numeric data, not normal distribution: median (min-max)*
[c] *Numeric data, normal distribution: mean ± SD*

Table 2. The difference of IL-12 levels between positive and negative *Helicobacter pylori*-associated gastritis

H. pylori	IL-12 levels (pg/mL)	p
Positive	65.36± 16.58	<0.001
Negative	40.77 ± 15.5	

The proportion of gastritis was more in male (61.25%) than in female (38.75%). Based on *H. pylori* status, patient with *H. pylori* positive was 35% and *H. pylori* negative was 65%. Based on ethnicity, the highest proportion of gastritis sufferers was Batak (57.5%), and the lowest was Acehnese (7.5%). Based on the occupation, the highest was private employee (43.8%) and civil servants (6.3%) become the lowest. Based on education, the highest proportion of patients is at high school level (51.3%) and the lowest proportion at the elementary school (3.8%). Mean of body mass index (BMI) was 23.16 kg/m^2 and mean of total IL 12 levels obtained in the study was 49.38 ± 19.71 pg/mL (Table 1). IL-12 levels were significantly higher in positive *H. pylori* gastritis (65.36 ± 16.58 pg/mL) than negative *H. pylori* gastritis (40.77 ± 15.5 pg/ml), p <0.001. (Table 2).

DISCUSSION

In this study, it was showed that majority of gastritis patients were male (62.5%). This result is similar to the research conducted by Chen, *et al* in China with 2,051 people (51.7%) of whom were men [10]. Other study by Dairi, *et al* in Indonesia also showed similar results that 24 people (60%) patients with gastritis are men [11]. However, study by Mahmoud *et al* in Egypt did not show the same result that 255 people (63.8%) gastritis sufferers are women [12]. This difference may be due to the influencing by various other factors, such as racial, demographic, and other comorbid factors such as Gastroesophageal Reflux Disease disorders [13]. Some factors in the work are known to affect the virulence of *H. pylori* and also the immune response to infection. In this study, housewives were obtained the highest percentage. A study by Tajalli *et al* found things be related to the findings of this study, where gastritis is more common among women who live in a crowded environment. This is because these women are more likely to have close contact with children, which is said to often transmit *H. pylori* infection. Most gastritis sufferers were found in the Batak tribe (57.5%), followed by Javanese (35%) and Acehnese (7%). Previous study also showed similar results where gastritis sufferers were most often found in the Batak tribe (57.5%) followed by Javanese (30%) and Acehnese (12.5%).

There were 28 cases (35%) positive *H. pylori* gastritis and 52 other cases (65%) were negative *H. pylori* gastritis. Epidemiological data suggest that the spread of *H. pylori* infection depends largely on geography, socio-economic status, hygiene and the environment in which it lives [14]. In this study there were differences in the mean levels of total IL-12 status between gastritis due to *H. pylori* and non *H. pylori* gastritis. This finding was supported by Mario *et al* study in Italy which found the increasing of circulating IL-12 in patients infected by Cag-positive/Vac-positive strain of *H. pylori.* IL-12, together with IL-18 and IL-23, play a key role in natural host defense by inducing natural killer cell IFN-γ production and by favoring the differentiation of IFN-γ –secreting Th1 cell [15]. Bagheri *et al* also found that IL 12 increased in *H. pylori-NAP* gastritis patients. *H. pylori-NAP* can induce the innate immune cells including monocytes and neutrophils to produce IL-23 and IL-12 and elicit an antigen-specific Th1-polarized T-cell response in the gastric mucosa of *H. pylori*-infected patients [16]. Study by Bauditz *et al* also found the same result that secretion of IL-12 was significantly associated with inflammatory activity in *H. pylori* associated gastritis in contrast to *H. pylori*-negative gastritis (P < 0·0001). It was produced mainly by macrophages and monocytes in host defence against bacteria, bacterial products or intracellular parasites was thought to play an initiating role in the inflammatory cascade [7].

In other study, it was found that gastric concentrations of IFN-γ and IL-12 were significantly higher and the concentrations of IL-4 and IL-10 were lower in patients infected with *H. pylori* than in uninfected patients. Comparison of cytokine concentration (IFN-γ, IL-12, IL-4, and IL-10) in the gastric mucosa revealed differences between patients with different gastrointestinal diseases. The levels of IFN-γ and IL-12 were higher in the groups with gastric ulcer and gastric cancer and lower levels of IL-4 and IL-10 were detected in these groups when compared to patients with gastritis and duodenal ulcer. Analysis of cytokine concentration in gastric biopsies of patients infected with different bacterial strains showed higher concentrations of IFN-γ and IL-12 in patients infected with the virulent s1m1cagA+ genotype compared to those carrying other strains. Comparison between cytokine concentration in the gastric mucosa and the histopathological findings showed higher levels of IFN-γ and IL-12 in patients with a higher degree of inflammation and neutrophil activity and a greater relationship with the presence of intestinal metaplasia.[9]

To our knowledge, this is the first study regarding the differences of IL-12 levels between positive and negative *H. pylori* in Indonesia. However, this study has several limitations. Further study with larger population and multicenter study regarding IL-12 level association with the severity of gastritis with *H. pylori* infection are suggested.

CONCLUSION

There was a significantly different of IL-12 levels between positive and negative *H. pylori* gastritis patient. There were higher total IL-12 levels in positive *H. pylori* gastritis patient.

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Conflict Of Interest Disclosure

The authors declare that there are not conflicts of interest.

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