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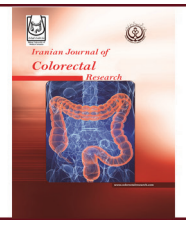

Investigation of Serum PIVKA-II Levels in Patients with *Helicobacter pylori* Infection and Normal Group

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Abstract

Background: *Helicobacter pylori* is a highly prevalent microorganism and risk factor for gastric cancer. In this study, we evaluated the serum levels of PIVKA-II in patients with and without *H. pylori*.
Methods: This study was performed on 90 patients (45 with *H. pylori* infection and 45 in the control group). After recording demographic information, serum levels of PIVKA-II were measured by the ELISA method.
Results: We found no significant difference in PIVKA-II levels between all patients with and without *H. pylori* infection (P=0.08), but among individuals aged below 40 years old, *H. pylori* infection was associated with significantly lower serum PIVKA levels in patients vs. controls (P=0.026). Among men, *H. pylori* infection was associated with a significantly lower serum PIVKA level than controls (P=0.038). Among all *H. pylori*-infected patients, women had higher PIVKA levels than men (P=0.037).
Conclusion: Our results indicate that (i) serum PIVKA-II levels are lower in *H. pylori*-infected individuals under 40 years old and men than in non-infected controls, and ii) among all *H. pylori*-infected patients, serum PIVKA-II levels are lower in men than women and in those under 40 years of age compared to those 40 or above.

Keywords: *Helicobacter pylori*, PIVKA-II, Gastritis, Infection

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Introduction

Helicobacter pylori is a major risk factor for gastric cancer and causes gastrointestinal diseases such as gastritis and gastric ulcers, with its eradication reducing the incidence of gastric cancer (1-3). Gastric cancer is the fourth most common cancer globally and the second deadliest. This cancer does not have a favorable prognosis; five-year survival is observed only in 5 to 20% of patients, so early diagnosis is critical (4).

PIVKA-II, also known as des-γ-carboxy-prothrombin (DCP), is a large glycoprotein that has been identified as a biomarker in the diagnosis of hepatocellular carcinoma (HCC) (5, 6). Due to the lack of sufficient resources, the relationship between *H. pylori* infection (a major risk factor for gastric cancer) and changes in serum PIVKA-II levels remains unknown (7).

Biomarkers such as CEA (carcinoembryonic

antigen), CA19-9 (cancer antigen 19-9), and CA72-4 (cancer antigen 72-4) have long been commonly used to diagnose gastric cancer. The ability of these biomarkers to help in the early diagnosis of gastric cancer is limited due to their low sensitivity (7, 8). Therefore, considerable attention has been devoted to discovering new biomarkers for the timely diagnosis of this disease. PIVKA-II has been identified as a biomarker in the diagnosis of HCC (9), though several case reports have revealed a possible association between PIVKA-II and gastric cancer (10-12). As of 2010, only 16 cases of PIVKA-II-producing gastric cancers have been reported (13). PIVKA-II-producing gastric cancers do not show any specific symptoms and have general symptoms such as fatigue, loss of appetite, and upper abdominal pain. However, AFP (alpha-fetoprotein) levels are elevated in 80% of patients, and portal vein thrombosis is seen in 20% of cases (10, 14). Considering the positive relationship between *H. pylori* infection and the incidence of gastric cancer, as well as the lack of sufficient sources for the association between gastric cancer and changes in serum PIVKA-II levels, we investigated the potential relationship between *H. pylori* infection and serum PIVKA-II levels.

Patients and Methods

This study included 45 patients with *H. pylori* infection and 45 uninfected controls. Patients were selected among those referring to a gastroenterologist with gastrointestinal upset, with *H. pylori* infection confirmed by endoscopy and *H. pylori* tests. The control group included 45 healthy people corresponding to the patient group regarding age and sex, selected from those who donated blood to the blood transfusion organization. The inclusion criteria were those with no history or clinical evidence of medication use, surgery, asthma, cancer or immunodeficiency, autoimmune, metabolic, or cardiovascular disease, and who had no infectious or inflammatory disease for at least the past three months. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (IR.SUMS.MED.REC.1399.613). Informed consent was obtained from all subjects.

From each participant, 5 ml of venous blood was taken in the morning after overnight fasting. After transferring the sample to the laboratory, the serums were stored at -20 °C until testing. Serum PIVKA-II levels were measured using a PIVKA-II ELISA kit (Shanghai Crystal Day Biotech, Yangpu District, China) according to the manufacturer's instructions.

SPSS software (v.23.0; JBM, NY, USA) was used for statistical analysis. The chi-squared test was used to evaluate differences between groups in qualitative variables. The Mann-Whitney U test was used to compare the groups regarding quantitative variables. P-values equal to or below 0.05 were considered statistically significant for all analyses.

Results

This study was performed on 90 individuals (45 patients with *H. pylori* infection and 45 controls). Of the 90 participants, 30 (33.3%) were men and 60 (66.7%) were women. The mean age of the subjects was 43.64±12.14 years (18 to 75 years). There was no significant difference between *H. pylori*-infected and uninfected individuals regarding age and gender.

The average serum level of PIVKA-II in the subjects of the two study groups did not have a statistically significant difference (P=0.08). Among individuals aged below 40, *H. pylori* infection was associated with significantly lower serum PIVKA levels in patients vs. controls (P=0.026). Among all cases positive for *H. pylori* infection, the higher age group (≥40 years) had significantly higher PIVKA levels (P=0.04) (Table 1).

Among men, *H. pylori* infection was associated with a significantly lower serum PIVKA level than controls (P=0.038). Among all *H. pylori*-infected patients, women had higher PIVKA levels than men (P=0.037) (Table 2).

Finally, we categorized *H. pylori*-infected patients into two groups based on histopathological diagnosis: chronic gastritis and chronic active gastritis. Among individuals aged below 40, the level of PIVKA-II was significantly lower in chronic active gastritis patients than in the uninfected group (P=0.02) (Figure 1).

Table 1: The serum levels of PIVKA-II in infected and control groups, with age classification

Age	*H. pylori* (+) (Mean±SD)	*H. pylori* (-) (Mean±SD)	P value
<40	78.27±10.04	161.98±33.73	0.026
>40	108.75±15.37	116.16±2.89	0.52
P value	0.04	0.1	

Table 2: The serum levels of PIVKA-II in infected and control groups, with gender classification

Sex	*H. pylori* (+) (Mean±SD)	*H. pylori* (-) (Mean±SD)	P value
Men	78.31±12.24	135.6±27.1	0.038
Women	108.74±15.12	140.35±29.61	0. 81
P value	0.037	0.52	

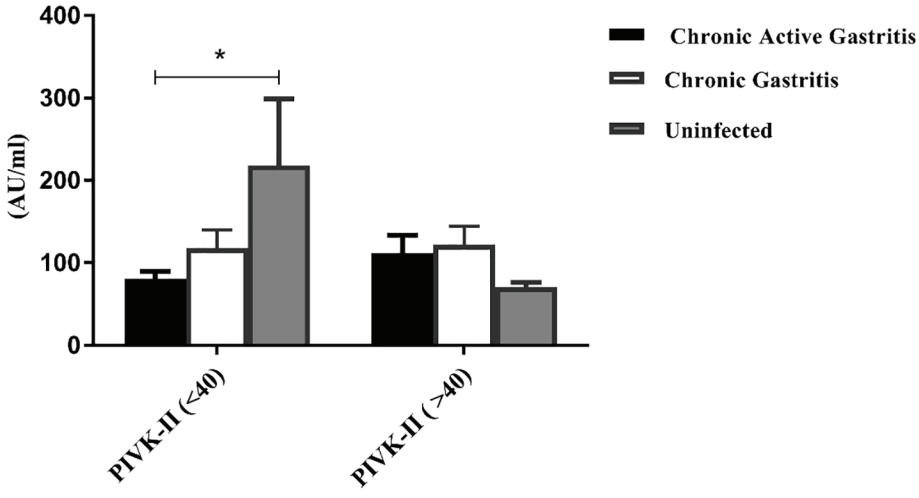

Figure 1: The serum levels of PIVK-II, in H pylori-infected (chronic active gastritis and chronic gastritis), and uninfected patients in two different age groups. (*P≤0.05)

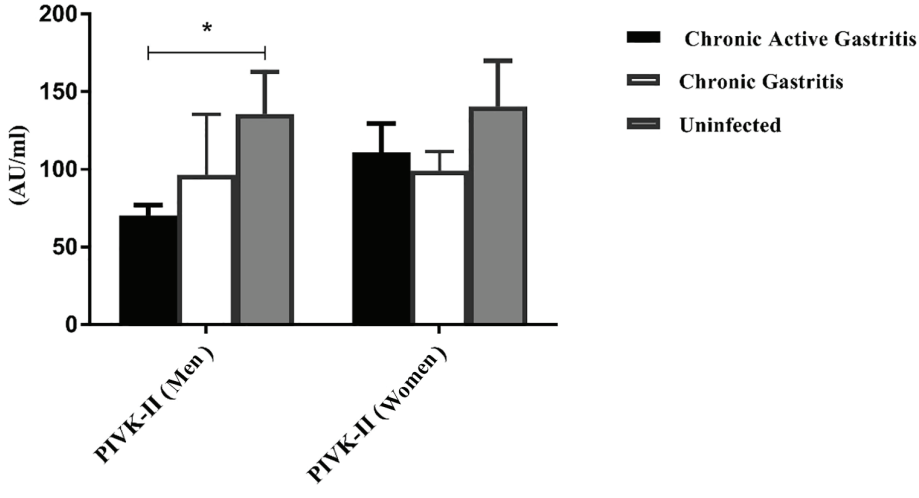

Figure 2: The comparison of the serum concentrations of PIVK-II, in the patients with chronic active gastritis and chronic gastritis due to H pylori infection and uninfected groups in male and female patients. (*P≤0.05)

Among men, those with chronic active gastritis had significantly lower PIVKA-II levels than uninfected controls (P=0.05). However, this difference was insignificant in women (Figure 2).

Discussion

As *H. pylori* is a known cause of gastric cancer and since there have been contradictory reports on the relation between PIVKA-II and cancers in recent years, we examined the levels of PIVKA-II in patients infected with *H. pylori* compared to controls.

Kucera et al. examined different biomarkers (PIVKA-II, pepsinogen I, pepsinogen II, and gastrin) and *H. pylori* infection, suggesting a lack of connection between PIVKA-II levels and pathological findings in the patients' stomachs (15). Based on the findings of our study, the reduction in the level of PIVKA-II in patients infected with *H. pylori* was not significant compared with the control group. However, we examined the PIVKA-II marker from other aspects as well, revealing that its level in patients with *H. pylori* infection increased significantly at the age of ≥40 years, while at the age of less than 40 years, there was a significant reduction in PIVKA-II levels compared with the control group.

Lim et al. reported a 75-year-old male patient with a rare type of gastric cancer called HAC (hepatoid adenocarcinoma) with elevated serum AFP (alpha-fetoprotein) and PIVKA-II levels, which returned to normal after the removal of the cancerous tissues (16). Takahashi et al. described a 56-year-old man with gastric adenocarcinoma, where the plasma levels of AFP and PIVKA-II were considerably high (13). Our study found that PIVKA-II levels were significantly higher in women compared to men infected with *H. pylori*. Takahashi et al. also described an 87-year-old woman with gastric cancer and HCC, where high levels of AFP and PIVKA-II were observed (17). Meanwhile, the level of PIVKA-II in *H. pylori*-infected patients with chronic active gastritis aged below 40 was significantly lower than in the control group.

Conclusion

Our results indicate that (i) serum PIVKA-II levels

are lower in *H. pylori*-infected individuals under 40 and men than in non-infected controls; ii) among all *H. pylori*-infected patients, serum PIVKA-II levels are lower in men than women and in those under 40 compared to those 40 or above; and (iii) PIVKA-II levels are lower in *H. pylori*-infected individuals aged below 40 and men with chronic active gastritis patients than in their respective uninfected controls. Future studies should investigate whether PIVKA-II levels provide any predictive/prognostic value in the mentioned groups in relation to gastric cancer.

Authors' Contribution

Study conception and design: SA Shamsdin, MJ Fattahi. Analysis and interpretation of data: SA Shamsdin, H Samani, Y Nikmanesh, H Akrami. Statistical analysis: SA Shamsdin. Drafting of the manuscript: SA Shamsdin, H Samani, MJ Fattahi, Y Nikmanesh, H Akrami. All authors have reviewed and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest: None declared.

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