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Immune Cell Profiling in Peptic Ulcer Disease: Investigation of MAIT Cells and Key Inflammatory Cytokines IL-17 and IFN- γ

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ABSTRACT

Peptic ulcer disease (PUD) is a common gastrointestinal disorder associated with chronic mucosal inflammation and immune dysregulation. Recent evidence suggests that Mucosal-associated invariant T (MAIT) cells, a subset of T cells expressing CD161 and V α 7.2, are involved in mucosal immunity and inflammatory responses. However, their precise role in PUD remains unclear. Given their dual function in immune defense and inflammation, investigating MAIT cell alterations in PUD could provide novel insights into disease pathogenesis and potential therapeutic targets.

A cross-sectional study was performed, including 25 patients with endoscopically verified PUD and 25 healthy controls. Flow cytometry was used to quantify circulating MAIT cells (V α 7.2⁺CD161⁺⁺) and their subsets (CD4⁺, CD8⁺, and double-negative). Serum interleukin-17 (IL-17) and interferon- γ (IFN- γ) levels were measured using ELISA in 21 PUD patients and 21 healthy controls. Correlations between MAIT cell frequencies and cytokine levels were analyzed using the Spearman correlation coefficient.

PUD patients exhibited a substantially elevated frequency of circulating MAIT cells compared to controls. Among subsets, CD8⁺ MAIT cells showed the most pronounced increase, correlating positively with serum IFN- γ levels ($r=0.5819$). Furthermore, levels of IL-17 and IFN- γ were substantially elevated in individuals with PUD in comparison to controls.

Our results indicate that MAIT cells, particularly the CD8⁺ subset, may contribute to immune activation in PUD. The observed increase in MAIT cells, along with elevated IL-17 and IFN- γ levels, highlights their potential involvement in disease progression. These findings support the potential role of MAIT cells as biomarkers or therapeutic targets in PUD.

Keywords: *Helicobacter pylori*; Inflammation; Mucosal-associated invariant T (MAIT) cells ; Peptic Ulcer

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INTRODUCTION

Peptic ulcer disease (PUD) is recognized as one of the most prevalent causes of mortality worldwide. Approximately 10% of individuals worldwide develop PUD throughout their lifetime.¹ This disease results from an imbalance of invasive components (acid, pepsin, and bacterial toxins) and gastric protective mechanisms. In fact, PUD occurs when the protective mucosal barrier is disrupted by aggressive factors, leading to acid-induced injury. In other words, stomach acid erodes the mucosal lining, creating an ulcer that exposes the submucosa. These ulcers predominantly occur in the stomach and duodenum but can also develop in the esophagus.²

Clinical symptoms of PUD vary and are often nonspecific. The most common symptoms include epigastric discomfort, bloating, nausea, heartburn, and back pain in cases of posterior ulcers. Symptoms typically improve with antacids, but can be asymptomatic in some patients. Complications, such as hemorrhage and perforation, are major contributors to mortality and morbidity in patients with PUD.³

Numerous risk factors have been found, including chronic stress, obesity, an unhealthy diet, *Helicobacter pylori* (*H. pylori*) infection, and nonsteroidal anti-inflammatory drug (NSAID) use. Frequent use of low-dose aspirin and other medications can also contribute to ulcer development.⁴ Among these risk factors, *H. pylori* infection is the primary etiological factor in PUD.¹ This spiral-shaped, Gram-negative bacterium colonizes the gastric mucosa and infects more than 50% of the global population.⁵

Although most (>80%) infected patients remain asymptomatic, approximately 10% to 20% will progress to develop PUD.⁶ The pathogenesis of *H. pylori*-induced PUD is linked to its virulence factors, particularly CagA and VacA toxins, which trigger IL-8 secretion, neutrophil infiltration, and inflammatory damage. Recent investigations have elucidated the pivotal role of host immune responses in mucosal inflammation, resulting in PUD and gastric cancer (GC).⁷ Among immune cell populations, mucosal-associated invariant T (MAIT) cells have gained attention due to their role in antibacterial immunity and mucosal homeostasis. MAIT cells express a T-cell receptor (TCR) with an invariant V α 7.2-J α 33 α -chain and high levels of CD161, distinguishing them as an innate-like T cell subset.⁸

The predominant population of human MAIT cells exhibits a CD8⁺ phenotype, while CD4⁺CD8⁺ (double-negative [DN]) and CD4⁺ subsets are less frequent.⁹ MAIT cells recognize bacterial vitamin B precursors (riboflavin derivatives) presented by MHC-related 1 (MR1), which is restricted by major histocompatibility complex (MHC). These cells are found in mucosal surfaces, particularly in the lamina propria of the gut, as well as in lymph nodes, liver, and peripheral blood (where they constitute ~8% of all circulating T cells).¹⁰ Upon activation, MAIT cells quickly generate proinflammatory cytokines, including interleukin-17 (IL-17), interferon- γ (IFN- γ), and tumor necrosis factor (TNF), playing a crucial role in bacterial immunity.^{11,12} They may also be triggered in a TCR-independent manner by cytokines, such as IL-12 and IL-18.^{13,14} Several studies have highlighted correlations between MAIT cell frequency and disease severity in chronic inflammatory conditions, including inflammatory bowel disease (IBD), multiple sclerosis (MS), celiac disease, and rheumatoid arthritis, suggesting a potential role in immune dysregulation.¹⁵

In patients with IBD, including Crohn disease and ulcerative colitis, phenotypic and functional analyses of MAIT cells have revealed a complex pattern of distribution. Peripheral blood MAIT cell frequencies were found to be decreased compared to healthy individuals, whereas MAIT cells were markedly enriched in inflamed intestinal tissues. These cells exhibited increased production of IL-22 and IL-17, but reduced IFN- γ secretion. Subset analysis showed a decreased proportion of CD8⁺ MAIT and DN MAIT cells in patients compared to controls, while the proportion of CD4⁺ MAIT cells was elevated.⁹

Similarly, alterations in MAIT cell frequencies have been reported in cancer patients. Eundeag Won et al observed that circulating MAIT cells were significantly reduced in patients with mucosa-associated cancers, such as gastric, hepatic, pulmonary, breast, and thyroid cancers, although their capacity to produce IFN- γ , IL-17, and TNF- α remained intact.¹⁶ Chunyan Shao et al reported a marked decrease in peripheral blood MAIT cells in gastric cancer patients, with most cells being CD8⁺ or DN and a small fraction being CD4⁺.¹⁷ Liwian et al demonstrated that circulating MAIT cells were significantly reduced in colorectal cancer patients, with CD8⁺ and DN subsets predominating, but CD4⁺ MAIT cells were notably increased compared to healthy

controls.¹⁸ Juanfen Mo et al further confirmed that CD4⁺CD8⁻, CD4⁻CD8⁺, and CD4⁻CD8⁻ MAIT cells were elevated in the peripheral blood of colorectal cancer patients, and CD161 expression in tumor tissues was higher than in adjacent non-tumor tissues. These findings highlight the dynamic redistribution and functional alterations of MAIT cells in inflammatory and neoplastic conditions, suggesting their potential role in disease pathogenesis. While their role in various inflammatory diseases has been studied, their contribution to PUD remains unclear. We hypothesized that MAIT cell frequencies and inflammatory cytokines would be increased in PUD patients compared to healthy controls. Therefore, we aimed to investigate the involvement of MAIT cells in PUD by analyzing their frequency, subpopulations, and cytokine levels in peripheral blood, which may provide novel insights into disease mechanisms and potential therapeutic targets.

MATERIALS AND METHODS

Study Population

A total of 25 patients with endoscopically confirmed PUD were recruited from Rouhani Hospital, Babol, Iran. A control group of 25 age- and sex-matched healthy individuals with no history of gastrointestinal disorders was also included. The average age of PUD patients was 50.92±15.75 years, while the average age of healthy people was 50.52±16.18 years (Table 1). Patients with chronic heart, kidney, lung, or liver diseases, prior gastric

surgery were excluded. To eliminate the potential confounding influence of *H. pylori* infection on immune cell profiles, all participants were screened for *H. pylori* using enzyme-linked immunosorbent assay (ELISA). In both the patient and healthy control groups, only individuals who tested positive for *H. pylori* were included. This matching strategy guaranteed that any immunological disparities between groups could not be attributed to variation in *H. pylori* infection status. Patients who had taken NSAIDs within the last 2 weeks were excluded to avoid confounding effects on peptic ulcer development.

Flow Cytometry

Peripheral blood mononuclear cells (PBMCs) were isolated and stained with fluorescent-labeled monoclonal antibodies, including anti-TCR Vα7.2 (PE, BioLegend, USA, Cat# 351706, dilution: 5 μL/test), anti-CD161 (PerCP/Cyanin5.5, BioLegend, USA, Cat# 339908, dilution: 5 μL/test), anti-CD8α (FITC, BioLegend, USA, Cat# 301006, dilution: 5 μL/test), and anti-CD4 (APC, BioLegend, USA, Cat# 300514, dilution: 5 μL/test). The stained cells were fixed with 1% paraformaldehyde and analyzed using a FACS Calibur flow cytometer (BD Biosciences, USA). Gating was performed sequentially for lymphocytes (forward scatter [FSC] vs. side scatter [SSC]), single cells (forward scatter height vs. forward scatter area), and MAIT cells (CD161⁺ TCR Vα7.2⁺). Data were analyzed using FlowJo software (TreeStar, USA).

Table 1. Baseline demographic characteristics of the study participants

Variable	Controls (n=25)	Patients (n=25)	p
Age, y	50.52±16.18	50.92±15.75	0.91
Gender (M/F)	12/13	14/11	0.78

Age is presented as mean±standard deviation and was compared using an independent samples *t*-test.

Gender distribution is shown as count (male/female) and was analyzed using Fisher exact test. No statistically significant differences were observed between the two groups, indicating successful matching. Statistical analyses were performed using GraphPad Prism version 9. F: female; M: male.

Enzyme-linked Immunosorbent Assay (ELISA)

Serum concentrations of IFN-γ and IL-17 were measured using Karmania Pars Gene ELISA kits (Rafsanjan, Iran), following the manufacturer's instructions. Briefly, 50 μL of serum was added to wells pre-coated with monoclonal antibodies against human IFN-γ and IL-17 and incubated at 37°C for 60 minutes.

The plates were washed 3 times with washing buffer before adding a conjugated detection antibody and incubating at 37°C for another 60 minutes. After 3 additional washes, 50 μL of Avidin-HRP solution was added, followed by a 30-minute incubation at 500 RPM. The reaction was developed using 50 μL of substrate solution in the dark, and stopped using concentrated

H₂SO₄. Optical density was measured at 450 nm. Values below the limit of detection (LOD) were assigned half of the lowest detectable concentration; this approach, while commonly used, represents a potential limitation of the assay.

Statistical Analysis

Data were presented as median (first quartile to third quartile [Q1–Q3]) as applicable. The Shapiro-Wilk test was employed to evaluate the normality of data distribution. Due to the non-normal distribution of the data, group comparisons were conducted utilizing the Mann-Whitney U test. The Spearman rank correlation test was employed to evaluate correlations between variables. A *p* value of less than 0.05 was regarded as statistically significant. To control for multiple comparisons across different MAIT cell subsets and cytokines, Bonferroni correction was applied where appropriate. Statistical analyses were performed utilizing GraphPad Prism 9 (GraphPad Software, USA). The lower limit of detection (LOD) for IFN- γ and IL-17 was 5 pg/mL. For statistical analysis, values that were less than the LOD were reported as <5 and considered as 2.5 pg/mL (half the LOD).

RESULTS

MAIT Cell Phenotype and Frequency in the Peripheral Blood of PUD Patients

Flow cytometry was used to assess the phenotype and frequency of MAIT cells in fresh peripheral blood (PB) from both healthy donors and PUD patients. MAIT cells were identified based on CD161 and TCR Va7.2 expression and further characterized into subsets using CD4 and CD8 markers; the gating strategy for identifying CD8⁺ MAIT cells, DN MAIT cells, and CD4⁺ MAIT cells is shown in Figure 1A–B.

The proportion of CD8⁺ MAIT cells in the PB of PUD patients (2.7 [1.63–4.3], *n*=25) was substantially increased in comparison to healthy donors (1.23 [0.75–1.95], *n*=25, *p*<0.0002). Similarly, the frequency of DN MAIT cells in PUD patients (0.37 [0.23–0.74]) was significantly elevated compared to that in healthy donors (0.15 [0.08–0.36], *p*<0.004). The CD4⁺ MAIT cell subset was also significantly higher in patients with PUD (0.14 [0.1–0.16]) compared with healthy individuals (0.05 [0.03–0.1], *p*<0.05) (Figure 2).

Correlation Between Circulating MAIT Cells and Serum Cytokines in PUD Patients

Serum levels of IL-17A and IFN- γ were significantly higher in PUD patients compared to healthy donors (IFN- γ : 14.33 [11.1–18.2] pg/mL vs. 6.21 [2.5–7.3] pg/mL; IL-17A: 28.7 [21.2–35.9] pg/mL vs. 9.8 [2.5–12.8] pg/mL, *p*=0.0001) (Figure 3).

A significant positive correlation was observed between serum IFN- γ levels and CD8⁺ MAIT cell frequency in PUD patients (*r*=0.5819, *p*=0.005). Likewise, a significant positive correlation was observed between the frequency of CD4⁺CD8⁺ MAIT cells and serum IFN- γ levels (*r*=0.472, *p*=0.031), suggesting a potential role of this subset in IFN- γ -mediated inflammation in PUD. In contrast, the frequency of CD4⁺ MAIT cells showed a trend toward a negative correlation with IFN- γ levels (*r*=−0.4299, *p*=0.0517), which was not statistically significant (Figure 4).

Additionally, IL-17A levels did not show a significant correlation with any of the MAIT cell subsets (*p*>0.05) (Figure 5). These findings suggest that CD8⁺ MAIT cells may contribute to immune activation in PUD through IFN- γ production, potentially exacerbating inflammation and mucosal damage. In contrast, the lack of correlation between MAIT cell subsets and IL-17A suggests that other immune pathways may regulate IL-17A levels in PUD, independent of MAIT cell involvement. Further studies are required to clarify the mechanistic link between MAIT cells and cytokine-driven immune responses in PUD.

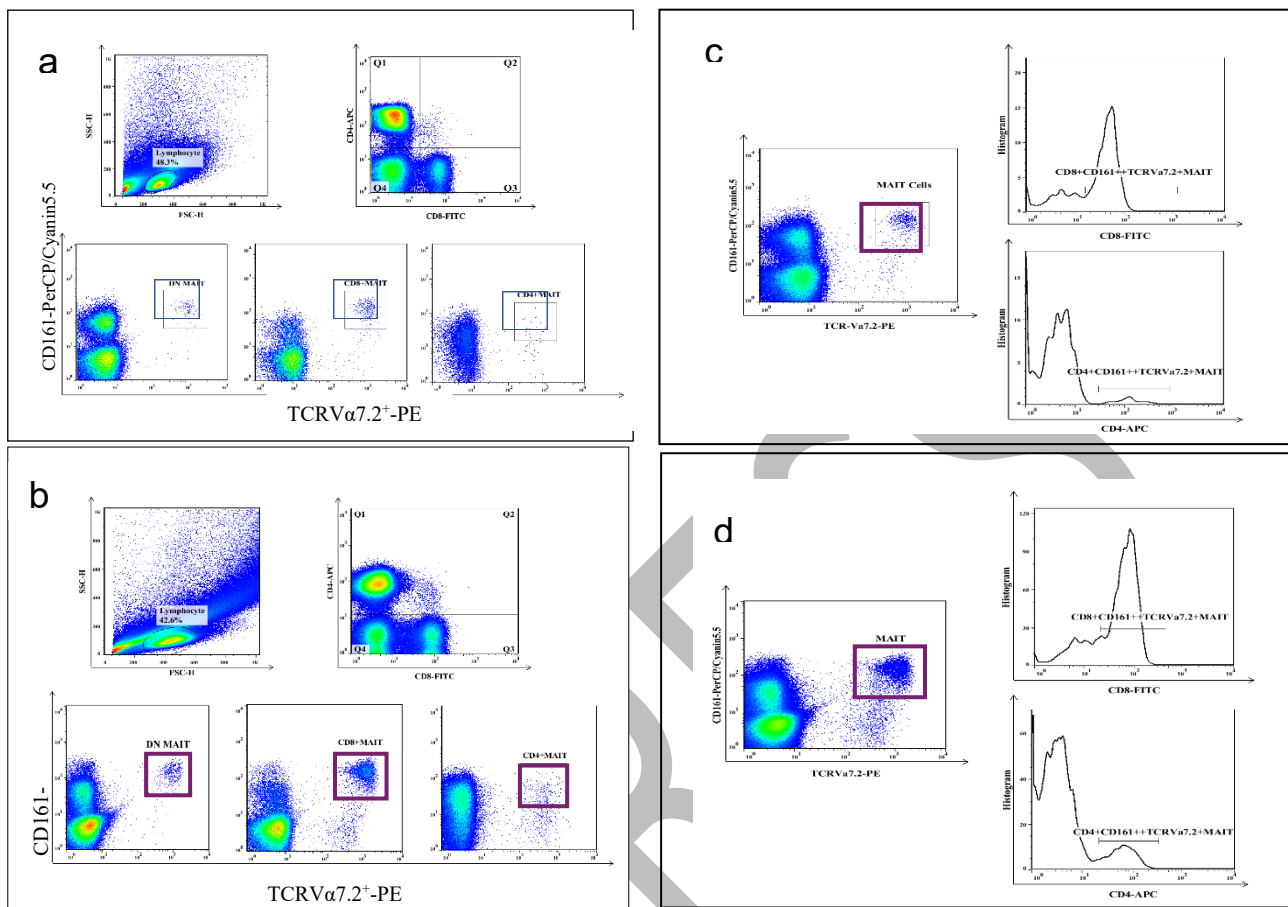


Figure 1. A. Flow cytometry analysis of mucosal-associated invariant T (MAIT) cell subsets in peripheral blood from a healthy control (A) and a patient with peptic ulcer disease (B). Lymphocytes were gated based on FSC and SSC, then categorized into CD4⁺, CD8⁺, and CD4⁻CD8⁻ (double-negative [DN]) populations. MAIT cells were identified as TCR V α 7.2⁺CD161⁺⁺ within each subset. Data shown represent typical dot plots analyzed using FlowJo software. In the healthy control, the percentage of MAIT cells was: CD4⁺ MAIT 0.03%, CD8⁺ MAIT 1.29%, DN MAIT 0.15%. In the patient group, the percentages were: CD4⁺ MAIT 0.5%, CD8⁺ MAIT 4.1%, DN MAIT 0.2%. (n=25). **B.** Histogram plots corresponding to the flow cytometry data shown in Figure 1A, illustrating CD4 and CD8 expression within the gated MAIT (TCR V α 7.2⁺CD161⁺⁺) cell population in a healthy control (C) and a patient with peptic ulcer disease (D).

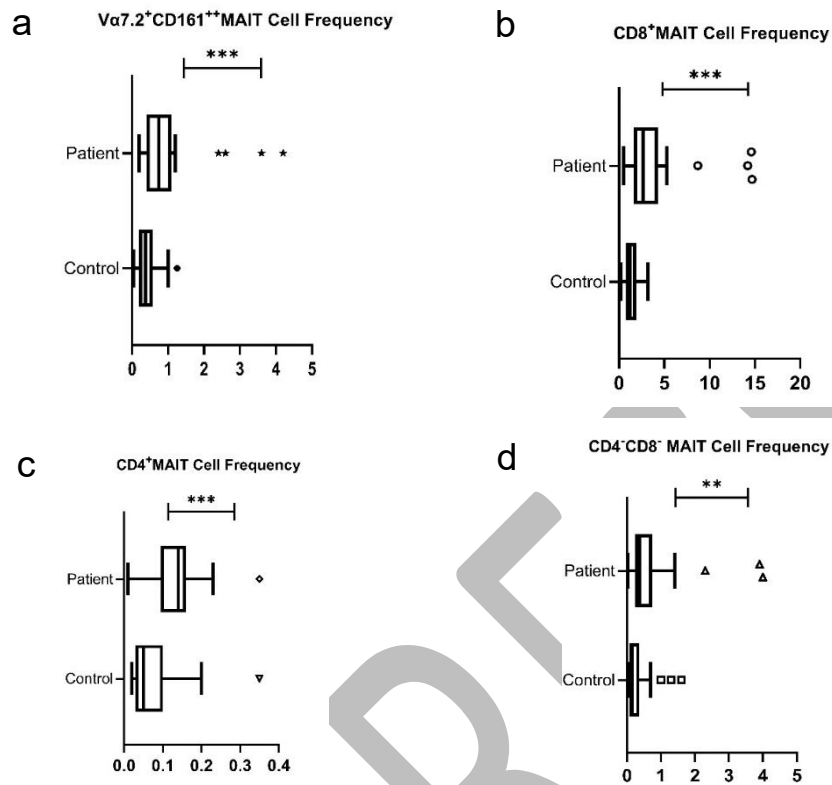


Figure 2. MAIT cell frequencies in the peripheral blood of healthy controls and patients with peptic ulcer disease. A. Frequency of total MAIT cells (Va7.2⁺CD161⁺⁺). B. CD8⁺ MAIT cell frequency. C. CD4⁺ MAIT cell frequency. D. Double-negative (CD4⁺CD8⁻) MAIT cell frequency. Data are presented as median (IQR). Statistical comparisons were performed using the Mann-Whitney U test. **p*<0.05, ***p*<0.01, ****p*<0.001, *****p*<0.0001. Statistical analyses were performed using GraphPad Prism version 9. (n=25)

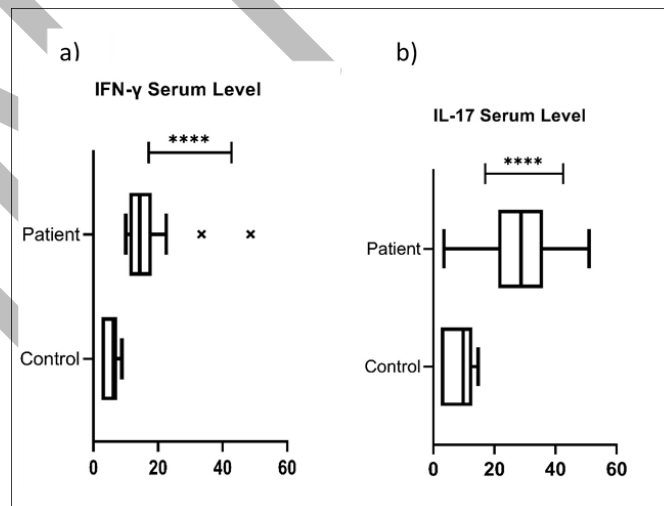


Figure 3. Comparison of serum cytokine levels between healthy controls and patients with peptic ulcer. A. IFN-γ and B. IL-17 concentrations were significantly higher in the patient group. Results are expressed as median (IQR). Statistical significance was determined using the Mann-Whitney U test. ***p*<0.0001. Statistical analyses were performed using GraphPad Prism version 9. (n=21)

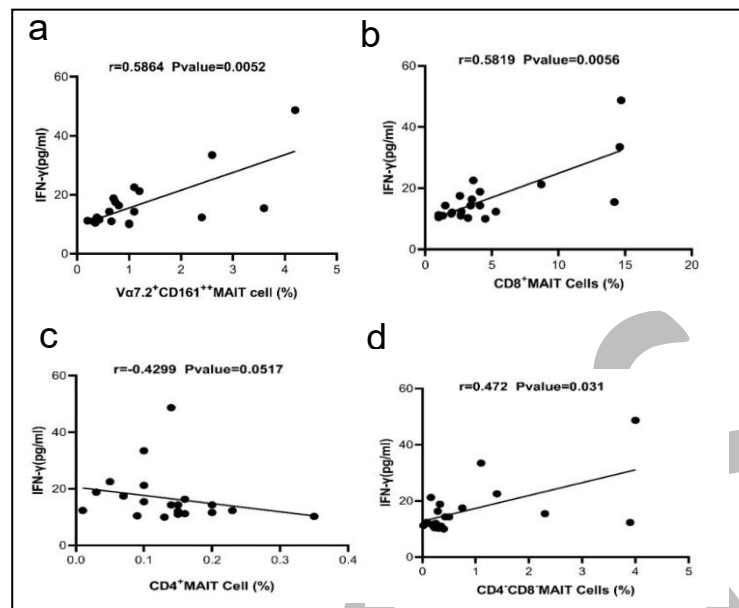
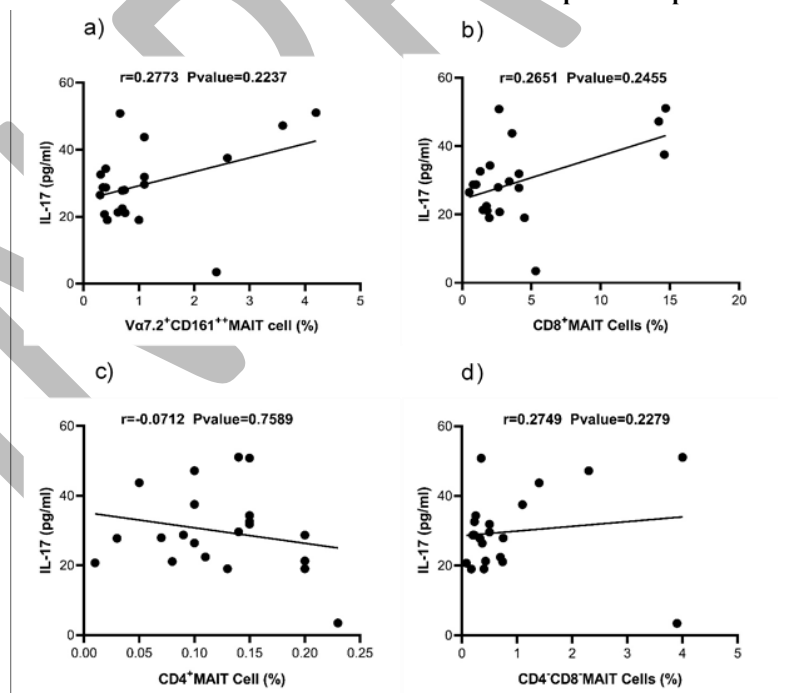


Figure 4. Spearman correlation analysis between serum IFN- γ concentrations and the frequency of MAIT cell subsets in patients with gastric ulcer. **A.** A significant positive correlation was observed between IFN- γ levels and the percentage of Va7.2⁺CD161⁺⁺ MAIT cells ($r=0.5864$, $p=0.0052$). **B.** IFN- γ levels showed a strong positive correlation with CD8⁺ MAIT cell frequency ($r=0.5819$, $p=0.0056$). **C.** A negative, but not statistically significant, correlation was detected between IFN- γ levels and CD4⁺ MAIT cells ($r=-0.4299$, $p=0.0517$). **D.** A statistically significant positive correlation was found between IFN- γ levels and CD4⁺CD8⁻ MAIT cells ($r=0.4712$, $p=0.031$). *Statistical analyses were performed using GraphPad Prism version 9.

Figure 5. Correlation between IL-17 serum levels and MAIT cell subsets in patients. Spearman's rank correlation analysis



revealed no statistically significant associations between IL-17 levels and the frequency of **A.** Va7.2⁺CD161⁺⁺ MAIT cells ($r=0.2773$, $p=0.2237$), **B.** CD8⁺ MAIT cells ($r=0.2651$, $p=0.2455$), **C.** CD4⁺ MAIT cells ($r=-0.0712$, $p=0.7589$), or **D.** CD4⁺CD8⁻ MAIT cells ($r=0.2749$, $p=0.2279$). Despite the observed trends, none of the correlations reached statistical significance.

*Statistical analyses were performed using GraphPad Prism version 9.

DISCUSSION

PUD is a prevalent gastrointestinal disorder worldwide, often leading to a reduced health-related quality of life. Chronic and untreated PUD is linked to a heightened risk of GC, which ranks as the fourth most prevalent malignancy worldwide and the second most common cause of cancer-related mortality.^{7,19} Genetic predisposition, environmental factors, and persistent mucosal inflammation contribute to the development of PUD and its potential progression to GC. Chronic inflammation in PUD not only increases the risk of GC but also affects immune cell populations involved in mucosal defense.²⁰ Among these, MAIT cells have emerged as key players in mucosal immunity, yet their role in PUD remains poorly understood.

The purpose of this investigation was to quantify the frequency of MAIT cells and their subsets in the PB of PUD patients and to evaluate their functional involvement by assessing cytokine production, particularly IFN- γ and IL-17A. Understanding the distribution and activation of MAIT cells in inflammatory diseases like PUD can provide valuable insights into disease monitoring and potential therapeutic targets.

Our analysis revealed a substantial negative correlation between MAIT cell frequency and age in healthy individuals, while no significant gender-related differences were observed. Given these demographic influences, we next explored the distribution of MAIT cell subsets to determine whether specific populations play distinct roles in PUD pathogenesis (Table 2).

Table 2. Comparison of MAIT cell subpopulations and cytokine levels between control and patient groups

Parameter (Unit)	Control	Patient	<i>p</i>
TCR V α 7.2 ⁺ CD161 ⁺⁺ MAIT Cell (% of PBMC)	0.37 (0.19–0.57)	0.74 (0.4–1.1)	0.0004
CD8 ⁺ TCR V α 7.2 ⁺ CD161 ⁺⁺ MAIT Cell (% of CD8 ⁺ T Cells)	1.23 (0.75–1.95)	2.7 (1.63–4.3)	0.0002
CD4 ⁺ TCR V α 7.2 ⁺ CD161 ⁺⁺ MAIT Cell (% of CD4 ⁺ T Cells)	0.05 (0.03–0.1)	0.14 (0.1–0.16)	0.0006
CD4 ⁺ CD8 ⁺ TCR V α 7.2 ⁺ CD161 ⁺⁺ MAIT Cell (% of DN T Cells)	0.15 (0.08–0.36)	0.37 (0.23–0.74)	0.004
IFN- γ (pg/mL)	6.21 (2.5–7.3)	14.33 (11.1–18.2)	<0.0001
IL-17 (pg/mL)	9.8 (2.5–12.8)	28.7 (21.2–35.9)	<0.0001

Data are presented as median (25th–75th percentile). Differences between groups were analyzed using the Mann-Whitney U test. *p*<0.05 was considered statistically significant. *Statistical analyses were performed using GraphPad Prism version 9.

CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; DN: double-negative; IFN- γ : interferon- γ ; IL-17: interleukin-17; MAIT: mucosal-associated invariant T; PBMC: peripheral blood mononuclear cell; TCR: T-cell receptor.

STATEMENT OF ETHICS

The Ethics Committee of Aja University of Medical Sciences approved the study (No: IR.AJAUMS.REC.1402.098). Written informed consent was obtained from all participants.

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This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

The authors used Grammarly (Grammarly Inc.) and QuillBot for language editing and paraphrasing assistance.

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