ARTÍCULO ORIGINAL

Gac Méd Caracas 2025;133(3):666-674
DOI: 10.47307/GMC.2025.133.3.2

Effect of proton pump inhibitor therapy on serum vitamin B12 levels and hematologic parameters in the blood of patients with laryngopharyngeal reflux

Efecto de la terapia con inhibidores de la bomba de protones sobre los niveles séricos de vitamina B12 y los parámetros hematológicos en la sangre de pacientes con reflujo laringofaringeo

Muhammad Amsyar Akil[1a*], Uleng Bahrun[1b], Foppy Puspitasari[1]

SUMMARY

Introduction: *Laryngopharyngeal reflux (RLF) is an inflammation of the aerodigestive tract where the retrograde flow of gastric contents into the larynx and pharynx encounters the upper aerodigestive tract. Proton pump inhibitors (PPIs), especially Omeprazole, are often used to manage RLF. Some studies have shown that prolonged use of PPIs can result in anemia.* **Objective:** *To analyze the relationship of PPIs to serum Vitamin B12 and hematological parameters in RLF patients.* **Methods:** *This is an analytical study with a cross-sectional approach conducted at the Ear, Nose, and Throat (ENT) polyclinic of Dr. Wahidin Sudirohusodo Hospital, Makassar, by comparing vitamin B12 levels, hemoglobin, MCV, MCH, and MCHC before and after Omeprazole therapy for 3 months.* **Results:** *The study consisted of 20 RLF patients. There was a significant effect of Omeprazole therapy for 3 months on RSI and RFS scores ($p<0.001$ and $p<0.001$). There was no significant effect on Hemoglobin, MCV, MCH, and MCHC before and after Omeprazole therapy for 3 months ($p=0.129$; 0.694; 0.514; 0.847). There was no significant effect on vitamin B_{12} levels before and after Omeprazole therapy for 3 months ($p=0.150$).* **Conclusion:** *Omeprazole therapy for 3 months in patients with RLF does not affect vitamin B12 levels, hemoglobin, MCV, MCH, or MCHC.*

Keywords: *Hematology, laryngopharyngeal reflux, omeprazole, vitamin B12.*

DOI: https://doi.org/10.47307/GMC.2025.133.3.2

ORCID: 0000-0001-8011-8292[a]
ORCID: 0000-0002-8284-5351[b]

[1]Department of Otorhinolaryngology-Head and Neck Surgery, Medical Faculty of Hasanuddin University, Makassar

*Corresponding author: Muhammad Amsyar Akil
E-mail: kedokteran.fkuh@gmail.com

Recibido: 14 de noviembre 2024
Aceptado: 19 de junio 2025

RESUMEN

Introducción: *El reflujo laringofaríngeo (RLF) es una inflamación del tracto aerodigestivo donde el flujo retrógrado del contenido gástrico hacia la laringe y la faringe entra en contacto con el tracto aerodigestivo superior. Los inhibidores de la bomba*

de protones (IBP), especialmente el omeprazol, se utilizan a menudo para el tratamiento del RLF. Algunos estudios han demostrado que el uso prolongado de IBP tiene el efecto secundario de la anemia. **Objetivo:** *Analizar la relación de los IBP con la vitamina B12 sérica y los parámetros hematológicos en pacientes con RLF.* **Métodos:** *Se trata de un estudio analítico con abordaje transversal realizado en el policlínico de otorrinolaringología del Hospital Dr. Wahidin Sudirohusodo de Makassar comparando los niveles de vitamina B12, hemoglobina, MCV, MCH, MCHC antes y después de la terapia con omeprazol durante 3 meses.* **Resultados:** *El estudio estuvo integrado por 20 pacientes con RLF. Hubo un efecto significativo con el tratamiento con omeprazol durante 3 meses sobre las puntuaciones de RSI y SSR (p<0,001 y p<0,001). No hubo efecto significativo sobre los niveles de vitamina B12 antes y después del tratamiento con omeprazol durante 3 meses (p=0,150).* **Conclusión:** *El tratamiento con omeprazol durante 3 meses en pacientes con RLF no tiene efecto sobre los niveles de vitamina B12, hemoglobina, MCV, MCH, MCHC.*

Palabras clave: *Reflujo laringofaríngeo, omeprazol, vitamina B12, hematología.*

INTRODUCTION

Laryngopharyngeal reflux (LPR) is a disease characterized by symptoms, signs, and tissue changes in the upper aerodigestive tract caused by the retrograde movement of gastric contents into the laryngopharynx, which is highly susceptible to both acidic and non-acidic components of reflux. RLF disease occurs due to inflammatory reactions in the mucous membranes of the pharynx, larynx, and other respiratory organs caused by the reflux of gastric contents into the esophagus (1,2).

The prevalence of LPR is estimated to be approximately 10 % of all patients attending the Ear, Nose, and Throat (ENT) polyclinic. More than 50 % of patients with hoarseness are found to have reflux-related disease. Adriani (2011) showed that there were 51 patients with LPR in 6 months among patients with complaints of LPR who came to the ENT polyclinic, Wahidin Sudirohusodo Hospital, Makassar, with the highest prevalence of women (62.75 %) and the highest age group was 41-50 years (54.9 %) (2,3). Omeprazole is the first-choice Proton pump inhibitor (PPI) used for LPR, as it has been proven effective in treating LPR and is also relatively inexpensive and easily available compared to other PPIs (4).

Although PPIs are considered safe and approved for long-term use, several studies have reported that they are associated with vitamin B_{12} deficiency in two ways: by decreasing gastric acidity, which interferes with the release of vitamin B12 from proteins in the stomach, and by increasing gastric pH, which reduces vitamin B12 absorption (5-7). Swarnakari et al. (2022) reported that long-term use of PPIs causes vitamin B_{12} deficiency (8). Dado et al. (2017) also reported decreased hemoglobin (Hb), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) after 12 years of PPI use (9).

A systematic literature review published between 2010 and 2020 showed that long-term PPI use can reduce vitamin B12 levels and lead to hematological abnormalities. However, studies such as those by Hartman et al. (2016) have argued that using PPIs for more than 12 months does not increase the risk of vitamin B12 deficiency. There is no uniform timeframe for assessing the effect of long-term PPI use on the risk of vitamin B12 deficiency and hematological disorders (10).

Based on this, this study aimed to assess the effect of Proton Pump Inhibitor therapy on serum Vitamin B12 levels and hematology parameters in the blood of patients with laryngopharyngeal reflux.

METHODS

This research is a quasi-experimental study employing a group pre-post-test design, aiming to determine the effect of Proton Pump Inhibitor therapy on serum vitamin B12 levels and Hematological Parameters in patients with laryngopharyngeal reflux. The sampling technique was carried out purposively, specifically targeting all patients with laryngopharyngeal reflux (LPR) (based on RSI > 13 and RFS > 7) who met the inclusion criteria.

Furthermore, 5 mL of peripheral blood was sampled before administering empirical PPI therapy (Omeprazole 20 mg, administered orally

every 12 hours). Patients were given empirical PPI therapy (Omeprazole 20 mg / 12 hours / orally) for 3 months and a drug use control card; the patient will check if they are taking PPIs. Patients were instructed to take Omeprazole 20 mg orally every 12 hours. A reminder message was sent via a WhatsApp group message to ensure daily medication adherence. Patients were also controlled for the use of omeprazole 20 mg / 12 hours / orally every day via personal chat to ensure patients consume. Patients with laryngopharyngeal reflux who stopped Omeprazole 20 mg / 12 hours / oral therapy by themselves or did not complete treatment for 3 months were considered dropouts.

After 6 and 12 weeks of oral Omeprazole 20 mg every 12 hours, the evaluation was conducted by retaking peripheral blood samples and calculating RSI and RFS. The results of serum vitamin B12 and hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) was analyzed before and after 6 weeks and 12 weeks of empirical therapy with Omeprazole 20 mg orally every 12 hours. Confidentiality of the subject's identity was guaranteed.

This study has obtained ethical clearance with number 314 / UN4.6.4.5.31 / PP36 / 2022, Protocol No. UH22040199 from the Research Ethics Commission, Faculty of Medicine, Hasanuddin University.

RESULTS

Respondent Characteristics

This study was conducted on 20 patients with laryngopharyngeal reflux (LPR) at Wahidin Sudirohusodo Hospital, Makassar, who met the inclusion and exclusion criteria. The distribution of respondent characteristics is shown in Table 1.

Table 1. Respondent Characteristics

Variables	Mean±SD	Frequency	Percentage
Gender			
Male		8	40
Female		12	60
Age (years)	47.55±12.05		
RSI	17.20±3.43		
RFS	11.85±3.15		
Hemoglobin (g/dL)	13.55±1.60		
Normal		20	100
Not Normal		0	0
MCV (fl)	85.60±5.53		
Microcytic		20	100
Macrocytic		0	0
MCH (pg)	28.90±2.61		
Microcytic		19	95
Macrocytic		1	5
MCH (pg)	28.90±2.61		
Microcytic		19	95
Macrocytic		1	5
MCHC (g/dL)	33.75±1.58		
Hypochrome		1	5
Hyperchrome		19	95
Serum Vitamin B12 (pmol/L)	818.45±326.831		
Normal		20	100
Deficiency		0	

Based on Table 1, female gender was found to be more prevalent in this study, with 12 individuals (60.0 %) identified, compared to 8 men (40.0 %). The mean (mean±SD) age of the respondents who participated in this study was 47.55±12.05 years old. The mean (mean±SD) RSI score of respondents in this study was 17.20±3,43. The mean (mean±SD) RFS score of the respondents in this study was 11.85±3,15.

The mean (mean±SD) hemoglobin value of the respondents in this study was 13.55±1.60 g/dL. All respondents had normal hemoglobin values. The mean (mean±SD) value of MCV levels in this study was 85.60±5.53 fl. All respondents had MCV values in the microcytic category. The mean value (mean±SD) of MCH levels was 28.90±2.61 pg. Nineteen respondents had microcytic MCH levels (95.0 %), and one respondent had macrocytic MCH levels (5.0 %). The mean (mean±SD) of MCHC levels in this study was 33.75±1.58 g/dL. Nineteen respondents had hyperchrome MCHC levels (95.0 %), and one respondent had hypochrome MCHC levels (5.0 %). The mean (mean±SD) of serum vitamin B12 was 818.45±326.831 pmol/L. All respondents had normal serum vitamin B12 levels.

Mean Omeprazole Therapy on RSI and RFS

The administration of Omeprazole therapy to respondents for 3 months (12 weeks) yields comparative results of RSI and RFS before and after Omeprazole therapy (Tables 2 and 3).

Table 2. Mean RSI and RFS Before and After Omeprazole Therapy

Variables	Before Omeprazole Therapy	After 6 Weeks of Omeprazole Therapy	After 12 Weeks of Omeprazole Therapy
RSI	17.20±3.47	10.95±3.63	6.10±1.48
RFS	11.85±3.16	7.15±3.16	4.20±1.93

Table 2 shows decreased RSI scores after Omeprazole therapy for 12 weeks. The mean (mean±SD) RSI score before therapy was 17.20±3.47. After being given Omeprazole therapy for 6 weeks, the mean (mean±SD) RSI score decreased to 10.95±3.63, and after 12 weeks of therapy, the mean RSI score decreased again to 6.10±1.48. The same was true for the RFS score. There was a decrease in RFS score after 12 weeks of Omeprazole therapy. The mean (mean±SD) RFS score before therapy was 11.85±3.16. After being given Omeprazole therapy for 6 weeks, the mean (mean±SD) RFS score decreased to 7.15±3.16, and after 12 weeks of therapy, the mean RFS score decreased again to 4.20±1.93.

Table 3. Comparison of Omeprazole Administration on RSI and RFS Values

Variables	Before Therapy Omeprazole	After 12 Weeks of Omeprazole Therapy	P-value
RSI	17.20±3.47	6.10±1.48	0.0001*
RFS	11.85±3.16	4.20±1.93	0.0001*

*Analysis using paired t-test. A significant effect of Omeprazole therapy for 3 months on RSI score (p=0.0001) and RFS score (p=0.0001). *p<0.05.

Effect of Omeprazole on Hematology Parameters

Table 4 presents the results of comparing hematological parameters (hemoglobin, MCV, MCH, and MCHC) before and after 6 weeks and 12 weeks of Omeprazole therapy.

Table 4. Comparison of Hematology Parameters Before and After Therapy with Omeprazole

Variables	Before Omeprazole Therapy	After 6 Weeks of Omeprazole Therapy	After 12 Weeks of Omeprazole Therapy
Hemoglobin (g/dL)	13.55±1.60	13.42±1.55	13.35±1.47
MCV (fl)	85.60±5.53	85.35±6.02	85.30±5.43
MCH (pg)	28.90±2.61	29.15±2.41	28.65±2.64
MCHC (g/dL)	33.75±1.58	33.80±1.47	33.70±1.55

Table 5 shows no significant effect of Omeprazole therapy for 3 months on hemoglobin levels (p=0.129). However, the mean hemoglobin level had a slight tendency to decrease. The mean hemoglobin before treatment was 13.55 g/dL; after 6 weeks of Omeprazole therapy, it decreased to 13.42 g/dL, and after 12 weeks of Omeprazole therapy, it further reduced to 13.35 g/dL (Table 5).

Omeprazole therapy did not significantly affected MCV levels for 3 months (p=0.694). The mean MCV before therapy was 85.60 fl; after 6 weeks of Omeprazole therapy it was 85.35 fl, and after 12 weeks of Omeprazole therapy, 85.30 fl (Table 5).

The same applies to MCH and MCHC levels. There was no significant effect of Omeprazole therapy for 3 months on MCH (p=0.514) and MCHC (p=0.847) levels (Table 5).

Table 5. Relationship of Hematology Parameters with the Administration of Omeprazole Therapy

Variables	Before Omeprazole Therapy	After 12 Weeks of Omeprazole Therapy	P-value
Hemoglobin(g/dL)	13.55±1.60	13.35±1.47	0.129
MCV (fl)	85.60±5.53	85.30±5.43	0.694
MCH (pg)	28.90±2.61	28.65±2.64	0.514
MCHC (g/dL)	33.75±1.58	33.70±1.55	0.847

Analysis using paired t-test.

Table 6 shows that serum vitamin B12 decreases during Omeprazole therapy, however this effect was statistically significant (p=0.150). The mean (mean±SD) serum vitamin B12 before PPI therapy was 818.45±326.831 pmol/L; after 6 weeks of PPI therapy, the mean (mean±SD) serum vitamin B12 was 773.85±288.31 pmol/L and 732.40±237.95 pmol/L after 12 weeks of Omeprazole therapy.

Table 6. Comparison of Serum Vitamin B12 Before and After Therapy with Omeprazol

Variables	Before Omeprazole Therapy	After 12 Weeks of Omeprazole Therapy	P-value
Serum Vitamin B12 (pmol/L)	818.45±326.831	732.40±237.95	0.150

Analysis using paired t-test.

DISCUSSION

The present results indicate that females are more likely to suffer from laryngopharyngeal reflux (11). This is related to hormonal factors that can increase acid production in the stomach (12). While female hormonal factors can influence gastric acid and pepsin production, the direct involvement of the hypothalamus-pituitary-adrenal (HPA) axis, particularly through ACTH and cortisol, is not the primary pathway for regulating parietal cell and peptic gland activity. Instead, these cells are primarily regulated by local factors and neural inputs, with hormonal influences playing a supporting role. Increased stomach acid and pepsin, however, can contribute to laryngopharyngeal reflux (13).

Regarding age, patients with laryngopharyngeal reflux in this study had an average age of 47.55 ± 12.05 years. This finding aligns with Kurniawati's research (2012), which also revealed that patients with laryngopharyngeal reflux were more commonly found to be at an average age of over 40 years (12). The occurrence of LPR above the age of 40 is due to changes in the laryngeal mucosa, where there is edema of the superficial layer of the lamina propria, especially in women who experience menopause. Changes occur in the glands in the larynx, causing reduced mucus production. Histologically, granular endoplasmic reticulum and the Golgi apparatus are found in the mucosa and serosa of the larynx. This causes the quality and quantity of mucus secretion in the larynx to decrease. Laryngopharyngeal reflux (LPR) is associated with several changes in the larynx and surrounding areas. These include thinning of the plica vocalis epithelial mucosa, making it more susceptible to acid damage and increasing the risk of LPR. Additionally, there's atrophy in the muscles of the face, pharynx, and masticatory muscles, along with weakness of the esophageal sphincter, which can exacerbate reflux more easily (11,13).

Laryngopharyngeal reflux is a chronic inflammatory disease with no apparent cause. It is easy to misdiagnose because its clinical symptoms are similar to those of many other laryngopharyngeal diseases. The Reflux Symptom Index (RSI) and Reflux Finding Score (RFS) are primarily used to assess and diagnose laryngopharyngeal reflux by evaluating symptoms and clinical indicators. These scales are also valuable for monitoring treatment effectiveness in patients with LPR (14,15). Sore throat and hoarseness are relatively obvious symptoms of the disease. Symptoms such as persistent cough, a foreign body in the throat, and shortness of breath can have a profoundly negative impact on patients' lives. Prompt diagnosis and effective treatment are crucial for promoting a good prognosis and recovery in patients with laryngopharyngeal reflux disease (15).

Proton pump inhibitors (PPIs) are potent drugs that strongly and persistently reduce gastric acid secretion, including pepsin, by targeting the final step in the acid production pathway. This mechanism enables PPIs to effectively inhibit acid secretion, regardless of the factors that stimulate it (13,16). In this study, Omeprazole was used as the PPI, and a comparison of serum vitamin B12 and hematological parameters was assessed before and after Omeprazole therapy for 3 months (12 weeks). Our results indicated a significant effect of Omeprazole therapy for 3 months on RSI and RFS scores. The decrease in RSI and RFS scores was observed after administering Omeprazole therapy for 1.5 months (6 weeks) and continued to decrease until the completion

of the 3-month Omeprazole therapy, showing that administration of Omeprazole for 3 months is highly effective in reducing RSI and RFS in patients with laryngopharyngeal reflux. These results are in line with the study of Pizzorni et al. (17), who showed a decrease in RSI and RFS scores after the administration of Omeprazole for 2 months. However, these results contradict the study by Wei et al. (14), a meta-analysis assessing the efficacy of PPIs in treating LPR symptoms, which found no significant difference in laryngoscopic signs between LPR patients treated with PPIs and those treated with placebo (14). Several factors may have influenced the results. Lifestyle modification has also been suggested as an effective strategy to improve the symptoms of chronic laryngopharyngitis. However, as our study did not assess these factors, we cannot demonstrate the effect of combined therapy between Omeprazole (PPI) and lifestyle modification on clinical improvement, as evaluated by RSI and RFS, in patients with laryngopharyngeal reflux. However, the study by Pizzorni et al. (17) suggested that combining long-term PPI treatment with lifestyle modification may be an effective strategy for preventing and managing laryngopharyngeal reflux symptoms.

Despite Omeprazole therapy being effective in treating laryngopharyngeal reflux, several reports have noted that patients on chronic Omeprazole use can develop iron deficiency anemia (18). In effect, Boxer's (2020) study which involved 43 patients reported iron deficiency possibly due to iron malabsorption and PPI use (19). Similarly, Lam et al. (2016), indicted that the use of gastric acid inhibitors for at least 2 years was associated with an increased risk of iron deficiency anemia among patients without known risk factors for iron deficiency. The risk increased with increasing acid inhibition potency and decreased after treatment discontinuation (20). Usually, iron is absorbed through the small intestine via the protein ferroportin, an iron transporter regulated by hepcidin. Whereas in patients taking PPIs, experimentally, Omeprazole has been shown to increase hepcidin levels and downregulate ferroportin, providing an additional mechanism by which Omeprazole may inhibit iron absorption in specific individuals (18).

This study showed no significant effect of Omeprazole therapy for 3 months on hemoglobin, MCV, MCH, and MCHC. This may be because the current study administered Omeprazole therapy for only 3 months. At the same time, some studies have shown a decrease in hemoglobin, hematocrit, and MCV levels among individuals using PPIs for more than one year, which suggests that iron deficiency will develop among long-term PPI users (21). However, although this study did not show a significant effect, it can still be seen that there was a tendency for a decrease in hemoglobin and MCV during Omeprazole therapy for 3 months.

Long-term use of proton pump inhibitors can lead to vitamin B12 deficiency, potentially causing anemia, especially in older adults (21). This is because PPIs reduce stomach acid production, which is crucial for releasing vitamin B12 from food and its subsequent absorption (22). This finding is consistent with Mumtaz et al. (2022), who demonstrated that 12 months of PPI use resulted in reduced vitamin B12 levels in the body, with this effect being more pronounced among PPI users compared to those who did not use PPIs. Long-term use of proton pump inhibitors (PPIs), a class of medications used to reduce stomach acid, can increase the risk of vitamin B12 deficiency. This occurs primarily due to two factors: impaired release of vitamin B12 from food in the stomach because of reduced acidity, and increased bacterial growth in the small intestine, which can interfere with B12 absorption. While studies have shown a link, there's an ongoing debate about the best ways to monitor and manage this relationship (23).

Several possible theories have been proposed to explain their interaction, which can lead to vitamin B12 deficiency. A healthy stomach lining, specifically the gastric corpus mucosa that houses the oesophageal glands, including the parietal cells, is crucial for vitamin B12 absorption. These cells produce intrinsic factor, a protein that binds to vitamin B12, enabling its absorption in the small intestine. Proton pump inhibitors reduce stomach acid by inhibiting the H^+/K^+ ATPase pump in parietal cells, which is responsible for pumping H^+ ions from within the gastric parietal cells into the gastric lumen, where they react with Cl ions to form hydrochloric acid.

This effect may hinder the release of vitamin B12 from food and its subsequent absorption. Gastric acid converts pepsinogen into pepsin to release vitamin B12 from food proteins. Lack of gastric acid due to the use of PPIs or histamine H2 receptor antagonist (H2RA) (or pathophysiological conditions affecting gastric acid production, such as atrophic gastritis) will reduce the digestive capacity to release vitamin B12 from food and thus reduce the amount of Vitamin B12 absorbed in the body (8).

However, our results are not in line with these concepts since they showed no significant effect of Omeprazole therapy for 3 months on serum vitamin B12 levels. It is possible that this is due to the fact that Omeprazole was used for only 3 months in this study. At the same time, existing studies have shown that the effect of vitamin B12 deficiency has been proven at least 12 months of PPI use.

This study may help to illustrate that Omeprazole can provide effective therapy to patients with laryngopharyngeal reflux. In addition, this study may also demonstrate that the use of Omeprazole for 3 months does not cause changes in hematological parameters, particularly those used to assess iron deficiency anemia and vitamin B12 deficiency.

One notable limitation of this study is the relatively short duration of PPI therapy (three months). While our findings offer insight into early changes in vitamin B12 levels and hematologic parameters, it is essential to recognize that many previously reported adverse effects—particularly vitamin B12 deficiency—are typically associated with prolonged PPI use, often exceeding 12 months (21,23). Therefore, caution should be exercised when extrapolating these results to long-term clinical scenarios. Future studies with extended follow-up periods are warranted to more comprehensively evaluate the chronic effects of PPI therapy on vitamin B12 status and hematologic outcomes. Secondly, we did not assess the risk factors that may affect the effectiveness of omeprazole in laryngopharyngeal reflux therapy, nor did we examine the potential side effects, such as anemia and vitamin B12 deficiency. Lastly, the relatively small sample size of this study is an inherent limitation, as it reduces statistical power and may limit the ability to detect subtle or clinically meaningful differences in outcomes. While the findings provide preliminary insight into the short-term effects of PPI therapy, they should be interpreted with caution. Future studies with larger, more diverse patient populations are needed to validate these results and enhance the generalizability and robustness of the conclusions.

CONCLUSIONS

Omeprazole therapy for 3 months did not significantly reduce serum levels of vitamin B12 and hematological parameters (Hemoglobin, MCV, MCH, MCHC) in patients with LPR.

Acknowledgments

Thank you to all those who have supported and helped to complete this research article, Department of Otorhinolaryngology-Head and Neck Surgery, Faculty of Medicine, Hasanuddin University, as well as several parties who have helped, but cannot be mentioned one by one.

REFERENCES

1. Salihefendic N, Zildzic M, Cabric E. Refluks laringofaring Disease - RLFD. Medical Archives (Sarajevo, Bosnia and Herzegovina). 2017;71(3):215-218.
2. Ford CN. Clinician's Corner of Reflux Laringofaring. JAMA. 2005;294(12):1534-1540.
3. Andriani Y, Akil MA, Gaffar M, Punagi AQ. Deteksi pepsin pada penderita refluks laringofaring yang didiagnosis berdasarkan reflux symptom index dan reflux finding score. Oto Rhino Laryngol Indonesiana. 2011;41(2):121.
4. Marlina L, Poluan FH, Zebua RL. Improvement of the Life Quality for Laryngopharyngeal Reflux Patients After Receiving Proton Pump Inhibitor (PPI) Therapy At the Ent-Kl Polyclinic of Uki Hospital January 2021 - February 2021. Internat J Res -Granthaalayah. 2021;9(4):281-296. .
5. Sarzynski E, Puttarajappa C, Xie Y, Grover M, Laird-Fick H. Association between proton pump inhibitor use and anemia: A retrospective cohort study. Digest Dis Scienc. 2011;56(8):2349-2353.

6. Permono, Bambang. Buku Ajar Hematologi – Onkologi Anak. Jakarta: Badan Penerbit IDAI; 2010.
7. Amalia A, Tjiptaningrum A. Diagnosis dan Tatalaksana Anemia Defisiensi Besi Diagnosis and Management of Iron Deficiency Anemia. Majority. 2016;5:166-169.
8. Swarnakari KM, Bai M, Manoharan MP, Raja R, Jamil A, Csendes D, et al. The Effects of Proton Pump Inhibitors in Acid Hypersecretion-Induced Vitamin B12 Deficiency: A Systematic Review (2022). Cureus. 2022;14(11):e31672.
9. Dado DN, Loesch EB, Jaganatha SPA. Case of Severe Iron Deficiency Anemia Associated with Long-Term Proton Pump Inhibitor Use. Current Therapeutic Research - Clinical and Experimental. 2017;84:1-3.
10. Hartman B, Donnelly-VanderLoo M, Watson T, O'Connor C, Madill J. Proton-pump inhibitor therapy and vitamin B12 status in an inpatient hospital setting. Applied Physiology, Nutrition and Metabolism. 2016;41(10):1071-1076.
11. Widiantari IAA, Sucipta IW. Karakteristik penderita laryngopharyngeal reflux yang didiagnosis berdasarkan reflux symptom index dan reflux finding score di Poliklinik THT-KL RSUP Sanglah Tahun 2015-2017. Medicina. 2019;50(3):457-461.
12. Kurniawati T, Madiadipoera T, Sarbini TB, Saifuddin OM. Perbandingan Efektivitas antara Omeprazole dan Lansoprazol terhadap Perbaikan Kualitas Hidup Penderita Rinosinusitis Kronik Akibat Refluks Laringofaring. Majalah Kedokteran Bandung. 2012;44(3):138-146.
13. Marlina L, Hendrika W, Paembonan TS. Description of Laryngopharyngeal Reflux Patients Based on Reflux Symptom Index (RSI) After PPI Administration at UKI General Hospital. Internat J Modern Pharmac Res. 2015;6(1):19-29.
14. Wei C. A meta-analysis for the role of proton pump inhibitor therapy in patients with laryngopharyngeal reflux. Eur Arch Oto-Rhino-Laryngol. 2016;273(11):3795-3801.
15. Jin X, Zhou X, Fan Z, Qin Y, Zhan J. Meta-analysis of Proton Pump Inhibitors in the Treatment of Pharyngeal Reflux Disease. Computat Mathema Meth Med. 2022;2022:9105814.
16. Liu X, Jiang Y, Luo H, Liu H. Proton pump inhibitors for the treatment of laryngopharyngeal reflux disease: A protocol for systematic review and meta-analysis. Medicine. 2020;99(49):e23297.
17. Pizzorni N, Ambrogi F, Eplite A, Rama S, Robotti C, Lechien J, et al. Magnesium alginate versus proton pump inhibitors for the treatment of laryngopharyngeal reflux: A non-inferiority randomized controlled trial. Eur Arch Oto-Rhino-Laryngol. 2022;279(5):2533-2542.
18. Kobets A, Kobets K. An Unusual Presentation of Iron-Deficiency Anemia: An Autobiographical Case Report. Cureus. 2021;13(12):10-13.
19. Boxer M. Iron deficiency anemia from iron malabsorption caused by proton pump inhibitors. eJHaem. 2020;1(2):548-551.
20. Lam JR, Schneider JL, Quesenberry CP, Corley DA. Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use and Iron Deficiency. Gastroenterology. 2017;152(4):821-829.e1.
21. Imai R, Higuchi T, Morimoto M, Koyamada R, Okada S. Iron deficiency anemia due to the long-term use of a proton pump inhibitor. Internal Med. 2018;57(6):899-901.
22. Humphrey ML, Barkhordari N, Kaakeh Y. Effects of Omeprazole on vitamin and mineral absorption and metabolism. J Pharm Technol. 2012;28(6):243-248.
23. Mumtaz H, Ghafoor B, Saghir H, Tariq M, Dahar K, Ali SH, et al. Association of Vitamin B12 deficiency with long-term PPIs use: A cohort study. Ann Med Surg. 2022;82:104762.