Appropriateness of Oral Proton Pump Inhibitors Prescribing in Sri Aman Hospital

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ABSTRACT

Introduction:
Given the utility, safety profile, efficacy, and tolerability of proton pump inhibitors (PPIs), these medications have been overprescribed globally. Recently, reported adverse events associated with PPIs have raised safety concerns. This study aimed to determine the appropriateness of oral PPIs prescribing pattern in Sri Aman Hospital, the factors associated with them and the costs incurred.

Methods:
In this study, all prescriptions for adults prescribed at the outpatient clinics between 1st April 2024 and 30th June 2024 that fulfilled the inclusion criteria were reviewed, together with patient's clinic card, to determine the appropriateness of PPIs prescribing based on the 2024 National Health Service (NHS) guidelines. Data such as patient demographics, types of PPIs, indication, dosage, duration, prescribing discipline and concurrent medications were recorded. Chi-square test was used to analyse the associated factors of inappropriate oral PPIs prescribing.

Results:
We found that 58.1% of the oral PPIs were inappropriate with the majority (51.0%) lacking proper or documented indication. Among the documented indications, PPIs were mostly used for nonsteroidal anti-inflammatory drug (NSAIDs) prophylaxis, which recorded 6.6% of inappropriate indication. Inappropriate PPIs prescribing was associated with several factors, including age (P<0.001), number of concurrent medications (P=0.005) and the concomitant use of anticoagulants (P=0.001) and corticosteroids (P=0.045). The inappropriate use of PPIs was most prevalent among patients aged below 65 years (n=80, 70.8%). Inappropriate PPIs prescribing was also most commonly observed in patients receiving 2–4 concurrent medications (n=31, 75.6%). Additionally, a high prevalence of inappropriate PPIs prescriptions was identified among patients receiving concurrent anticoagulants (n=26, 86.7%) and corticosteroids (n=11, 84.6%). Approximately 53.0% of PPIs were prescribed for duration of more than 52 weeks. The inappropriate prescribing of oral PPIs was estimated to incur RM20882.40 during the study period in our setting.

Conclusion:
It is imperative that prescribers adhere to prescribing guidelines and review the need for continued therapy to ensure rational use of PPIs and reduce unnecessary healthcare costs.

Keywords:
Prescribing, proton pump inhibitors, appropriateness

INTRODUCTION

Proton pump inhibitors (PPIs) are the most effective medications currently available to reduce gastric acid secretion. They are the cornerstone in the treatment for gastro-oesophageal reflux disease (GERD), upper gastrointestinal (GI) bleeding secondary to peptic ulcer disease or non-steroidal anti-inflammatory drug (NSAIDs)-induced ulcer, *Helicobacter pylori* eradication, dyspepsia and hypersecretory disorders such as Zollinger-Ellison syndrome.[1,2] Besides, they are widely used for stress ulcer prophylaxis, as well as the prophylaxis of GI bleeding in patients on NSAIDs or dual antiplatelet therapy.[1,3,4] In Malaysia, there are currently 6 PPIs registered with the Drug Control Authority, namely pantoprazole, omeprazole, esomeprazole, rabeprazole, lansoprazole, and dexlansoprazole,. These PPIs are available in oral or parenteral formulations, either as single-ingredient products, fixed-dose combinations, or combination packs.[5]

Given the broad utility of these medications, favorable safety profile, demonstrated efficacy, and good tolerability, PPIs have been overprescribed globally.[1,6-12] Their use is widespread and on the increasing trend, with annual sales worldwide exceeded US $25 billion.[6] In Germany, PPIs prescribing increased from 44 million defined daily doses (DDD) in 1993 to 1,674 million DDD in 2008, accounting for a drastic increase of 3,805%, costing 540 million Euros per year.[6] According to the Malaysian Statistics on Medicine 2017, by ranking of expenditures on drugs in Malaysia, pantoprazole was ranked 13th (cost RM51.1 million per year) and esomeprazole was ranked 27th (cost RM48.7 million per year). All these frequently used PPIs had fallen into the top 50 drugs by expenditures in 2017.[13]

The prevalence of inappropriate PPIs prescribing has been reported to be between 45.9% to 86.0% in the hospital setting according to a few observational prevalence studies in other countries.[10-12,14,15] A multicentre prospective study carried out in France in 2014 showed that the overprescribing of PPIs was found in 73.9% older patients.[16] Additionally, a recent narrative review in 2025 summarised that 25–70% of PPIs prescriptions lack an appropriate indication and overprescribing is particularly common in both primary care and hospital settings.[17] It is also common for the duration of use of PPIs to be longer than necessary once started.[2,18]

According to a multicentre study carried out in Sibu Hospital and also three main government health clinics in the Sibu area in 2017, more than half (53.0%) of the oral PPIs were inappropriately prescribed for its indication.[19]

The increase in PPIs prescribing patterns could be influenced by prescribers' consideration that patients are at a higher risk of developing stress ulcer especially those who are on NSAIDs, aspirin, corticosteroids, those receiving chemotherapy and older adult patients.[16,20] A cross-sectional observational study conducted in 35 primary care practices in North-Eastern Germany found that 54.5% of PPIs were prescribed without valid indications upon discharge.[6] Inappropriate use of stress ulcer prophylaxis (SUP) in non-intensive care unit settings and failure to discontinue SUP prior to discharge often resulted in patients being discharged on oral PPIs.[21] The multicentre study carried out in Sibu also showed that 62.3% of the PPIs were prescribed for more than 1 year.[19]

While PPIs are safe in the short-term, emerging evidence shows risks associated with long-term use. Reported adverse events associated with PPIs highlighted safety concerns under the review of National Pharmaceutical Regulatory Agency (NPRA), such as subacute cutaneous lupus erythematosus, hypomagnesemia, osteoporotic fractures, risk of pneumonia, *Clostridium difficile* infection, and dementia.[22] A meta-analysis of nine studies involving 115,455 patients found statistical significance between PPIs use and the risk of hypomagnesemia.[23] In a meta-analysis of 11 international observational studies, PPIs modestly increased the risk of hip, spine, and any-site fractures.[24] In one meta-analysis of 23 studies encompassing 300,000 patients, PPIs use increased the incidence of *Clostridium difficile* infection by 65.0%.[25] A systematic review of 33 studies and meta-analysis of 26 studies spanning over 20 years reported that outpatient use of PPIs was found to confer a 1.5-fold increased risk of developing community-acquired pneumonia.[26] A large scale longitudinal observational study published recently examining the link between PPIs use and the risk of developing dementia in the German population has revealed a significantly increased risk of dementia with regular use of PPIs.[27] NPRA recently received safety notifications from local product registration holders about the new labelling requirements by the United States FDA regarding the risk of erectile dysfunction associated with PPIs.[28]

From January 2024 to April 2024, pantoprazole tablet was ranked 9th in the top 20 drugs by expenditures in Sri Aman Hospital. Hence, the study of the prescribing pattern of PPIs in this local setting is imperative considering the potential adverse effects linked with unnecessary prolonged continuation of PPIs. This study aimed to determine the appropriateness of prescribing oral PPIs in Sri Aman Hospital, specifically the prevalence of inappropriate indications of oral PPIs prescribed, duration of oral PPIs prescribed, associated factors leading to inappropriate prescribing of oral PPIs, and the cost expenditure associated with inappropriate use of oral PPIs.

This study may provide clinically meaningful statistics of local prescribing patterns that serve as helpful feedback for prescribers in our hospital. This study might also serve as a preliminary study for future pharmacist-led intervention in improving the prescribing pattern of PPIs.

METHODS

Study design

In this retrospective observational study, all outpatient clinic prescriptions for adults aged 12 years old and above, prescribed between 1st April 2024 and 30th June 2024, were screened for PPIs using the Pharmacy Information system (PhIS). However, prescriptions without an available clinic card were excluded. Thus, prescriptions containing PPIs included in this study were then reviewed.

Data collection

Prescriptions and the patient's medical record in the clinic card were reviewed to determine the rationale of the PPIs prescription. History of peptic ulcer or GI bleeding and *Helicobacter pylori* infection were determined based on endoscopy result and diagnosis in patient's medical record. Patients' demographic data (age, gender), types of PPIs, indication, prescribed dose, frequency and the PPIs initiation date as well as the prescribing discipline, concurrent medications and cost were recorded using a structured data collection form as shown in Appendix 1. The cost was calculated using the formula: Number of tablets prescribed per day x Duration of PPIs prescribed x Cost per tablet (RM).

Definition

Appropriateness of the prescribed oral PPIs was evaluated by assessing the indications based on the NHS guidelines.[29] The indications of oral PPIs considered appropriate or acceptable are shown in Table 1. Therefore, other indications than those listed in Table 1 were considered inappropriate or has no clear indications.

Sample size

The sample size was calculated using the sample size calculator by Naing *et al.*[34] Sample size required for this study is 222 patients with a precision of 0.05. Based on the list generated from PhIS, a total of 524 adult outpatients at Sri Aman Hospital were prescribed oral PPIs between 1st April 2024 and 30th June 2024. Prescriptions were stratified by oral PPIs type, and systematic random sampling technique was applied in each subgroup, in which the odd-numbered prescriptions were selected from the list.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS version 20.0). Descriptive analysis was used to describe prevalence of inappropriate oral PPIs prescribing. Categorical variables were expressed as frequencies and percentages, while categorical data was analysed using Chi-square tests. A *P*-value of <0.05 was considered statistically significant.

Table 1. Indications of oral PPIs considered appropriate or acceptable for use

Indication	Criteria for indication
Appropriate for use	
Treatment of upper GI bleeding (UGIB) or peptic ulcer	Patients with major peptic ulcer bleeding (active bleeding or non-bleeding visible vessel) following endoscopic hemostatic therapy[30,31]
Treatment of gastro-oesophageal reflux disease (GERD) or dyspepsia	A chronic condition in which the lower oesophageal sphincter allows gastric acids to reflux into the oesophagus, causing heartburn, acid indigestion, and possible injury to the oesophageal lining[30,32]
For *Helicobacter pylori* eradication	Test for the presence of *Helicobacter pylori* and eradicate if present[30]
Acceptable for use	
Prophylaxis of NSAIDs (including low-dose aspirin) related GI ulcer	Patients on NSAIDs with ≥ 1 risk factor(s): 1. Previous history of a gastric ulcer 2. Age >65 years 3. Previous history of *Helicobacter pylori* infection 4. Concurrent use of aspirin (including low dose) 5. Concurrent use of corticosteroids 6. Concurrent use of anticoagulants[33]
Uninvestigated dyspepsia / gastritis (empirical treatment)	Treatment of symptomatic gastritis without evidence from endoscopic investigations[10, 33]

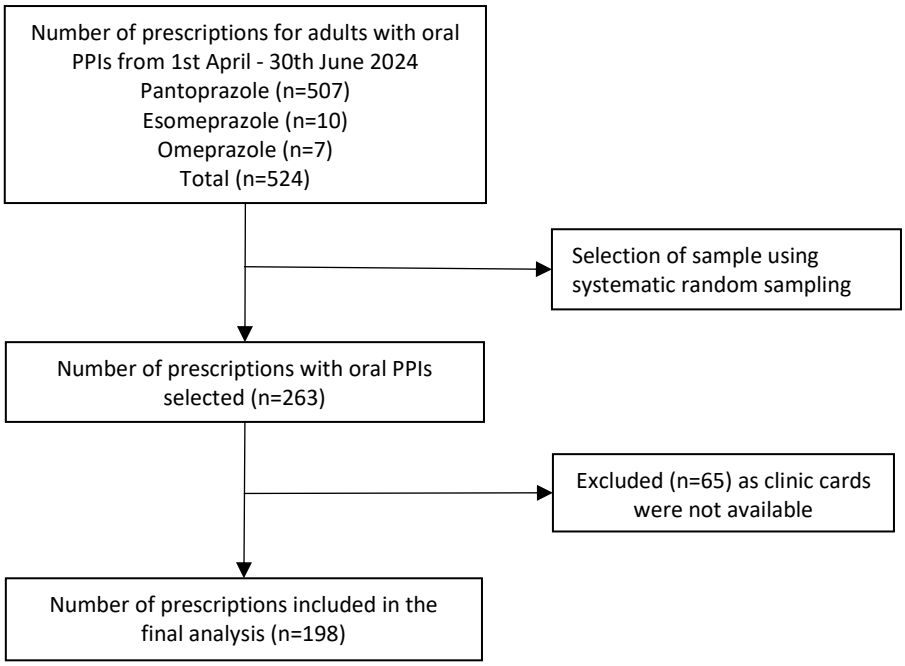

Figure 1: Flow diagram of study sample

RESULTS

Prevalence of inappropriate indications of oral PPIs prescribed

More than half of the oral PPIs prescribed (n= 115, 58.1%) fall under the category of inappropriate indication. Among patients prescribed PPIs for NSAIDs prophylaxis, a small proportion (n=13, 6.6%) had inappropriate indication. The majority of the inappropriately prescribed PPIs had no proper or documented indication (n=101, 51.0%). Table 2 summarises the appropriateness of oral PPIs prescribed based on the indication.

Duration of PPIs prescribed

More than half (n=105, 53.0%) of the PPIs were prescribed for a duration of more than 52 weeks, of which 27.3% (n=54) were continued for unknown indications and 21.2% (n=42) for NSAIDs prophylaxis.

Factors associated with inappropriate prescribing of oral PPIs

The study found that age was significantly associated with inappropriate oral PPIs prescribing. It was also found that PPIs were mostly prescribed inappropriately in patients with 2-4 concurrent medications. Notably, inappropriate PPIs prescription was highly prevalent in patients on concurrent anticoagulants (86.7%, *P*=0.001) and corticosteroids (84.6%, *P*=0.045).

Cost Incurred from Inappropriate Use of PPIs

Inappropriate use of PPIs in our facility had resulted in a total expenditure of RM20,882.40 during the study period, which amounted to more than half (57.9%) of the total PPIs expenditure.

Table 2. Appropriateness of oral PPIs prescribed based on indication (n=198)

Indication	n (%)			Total
	Appropriate indication	Acceptable indication	Inappropriate / no clear indication	
GI ulcer	6 (3.0)	0 (0.0)	0 (0.0)	**6 (3.0)**
GERD	4 (2.0)	0 (0.0)	0 (0.0)	**4 (2.0)**
Helicobacter pylori eradication	6 (3.0)	0 (0.0)	0 (0.0)	**6 (3.0)**
NSAIDS prophylaxis	0 (0.0)	56 (28.3)	13 (6.6)	**69 (34.9)**
Gastritis	0 (0.0)	11 (5.6)	0 (0.0)	**11 (5.6)**
Others	0 (0.0)	0 (0.0)	1 (0.5)	**1 (0.5)**
Unknown	0 (0.0)	0 (0.0)	101 (51.0)	**101 (51.0)**
Total	**16 (8.0)**	**67 (33.9)**	**115 (58.1)**	**198 (100.0)**

Table 3: Duration of oral PPIs prescribed (n=198)

Indication	n (%)				
	<2 weeks	2-4 weeks	5-8 weeks	8-52 weeks	>52 weeks
GI ulcer	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	2 (1.0)
GERD	0 (0.0)	0 (0.0)	2 (1.0)	2 (1.0)	0 (0.0)
Helicobacter pylori eradication	0 (0.0)	0 (0.0)	3 (1.5)	2 (1.0)	1 (0.5)
NSAIDS prophylaxis	0 (0.0)	0 (0.0)	0 (0.0)	27 (13.6)	42 (21.2)
Gastritis	0 (0.0)	1 (0.5)	1 (0.5)	3 (1.5)	6 (3.0)
Others	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (0.5)	1 (0.5)	2 (1.0)	43 (21.7)	54 (27.3)
Total	**1 (0.5)**	**3 (1.5)**	**8 (4.0)**	**81 (40.9)**	**105 (53.0)**

Table 4. Factors associated with inappropriate prescribing of oral PPIs

Associated factors	*n*	Appropriate/ acceptable indication of PPIs, n (%)	Inappropriate indication of PPIs, n (%)	χ^2 statistic[a] *(df)*	*P*-value[a]
Gender					
Male	122	56 (45.9)	66 (54.1)	2.07 (1)	0.150
Female	76	27 (35.5)	49 (64.5)		
Age (years)					
13-40	19	3 (15.8)	16 (84.2)	19.17 (2)	<0.001
41-65	94	30 (31.9)	64 (68.1)		
>65	85	50 (58.8)	35 (41.2)		
Prescriber's discipline					
Medical	175	71 (40.6)	104 (59.4)	1.12 (1)	0.289
Others	23	12 (52.2)	11 (47.8)		
Number of concurrent oral medications					
≤1	14	10 (71.4)	4 (28.6)	10.45 (2)	0.005
2-4	41	10 (24.4)	31 (75.6)		
≥5	143	63 (44.1)	80 (55.9)		
Concurrent medication with Aspirin/ NSAIDs					
Yes	94	61 (64.9)	33 (35.1)	38.80 (1)	<0.001
No	104	22 (21.2)	82 (78.8)		
Concurrent medication with Clopidogrel					
Yes	34	27 (79.4)	7 (20.6)	23.70 (1)	<0.001
No	164	56 (34.1)	108 (65.9)		
Concurrent medication with Anticoagulant					
Yes	30	4 (13.3)	26 (86.7)	11.87 (1)	0.001
No	168	79 (47.0)	89 (53.0)		
Concurrent medication with Corticosteroid					
Yes	13	2 (15.4)	11 (84.6)	4.02 (1)	0.045
No	185	81 (43.8)	104 (56.2)		

[a] Chi-square test for independence

* *P*<0.05 is considered statistically significant

DISCUSSION

Prevalence of inappropriate indications of oral PPIs prescribed

Our study is consistent with a recent narrative review on PPIs prescriptions which showed that the ballpark figure for inappropriate PPIs use ranged from 25% to 70%.[17] A similar study carried out in Singapore also showed that about half of the PPIs prescribed did not have clear indications.[10]

Among the documented indications of PPIs prescribing in our facility, NSAID prophylaxis tops the list (n=69, 34.9%). Current guidelines recommend peptic ulcer prophylaxis in patients on NSAIDs with ≥ 1 risk factor(s) stated as: previous history of a gastric ulcer; age >65 years; previous history of *Helicobacter pylori* infection; concurrent use of aspirin (including low dose); concurrent use of

corticosteroids; and concurrent use of anticoagulants.[33]

Our study showed that a small fraction of patients (n=13, 6.6%) was prescribed PPIs despite having no risk factor as stated above. We believed that prescribers' non- adherence to guidelines and lack of knowledge about practice parameters are highly associated with inappropriate use of PPIs, which is highlighted in another study by Perwaiz et al.[21] All patients taking PPIs should be reassessed regularly for its ongoing indications and to consider de-prescribing PPIs if there is no absolute indication upon review.

Duration of PPIs prescribed

Our finding is consistent with a systematic review which reported widespread and often inappropriate long-term PPIs use, including when PPIs were started for NSAID or SUP and then continued after the risk period ended.[2]

The utilization of PPIs for SUP in hospitalized patients is shown to increase steadily worldwide.[35] More often than not, these patients were discharged with PPIs without information on the recommended treatment duration. Failure to discontinue SUP and the absence of treatment reassessment during follow up in clinic as outpatients, have led to endless continuation of PPIs, and therefore the inappropriate prolongation of the medication.[16,35] Furthermore, many patients continued using PPIs unnecessarily after stopping NSAIDs or low-dose aspirin.[36]

Although PPIs were initially considered safe, recent pharmacoepidemiological studies have shown an association between PPIs use and long-term adverse effects, such as *Clostridium difficile* infection, hip fracture and dementia.[16,21-23,27] Given that a substantial number of patients in our facility were on prolonged duration of PPIs, it is imperative to re-evaluate the risk and benefit of PPIs.

Factors associated with inappropriate prescribing of oral PPIs

In this study, age is a significant associated factor. Oral PPIs were mostly prescribed for patients aged 41-65 (n=94, 47.5%), followed by patients aged over 65 (n=85, 42.9%) and a small proportion for patients aged 13-40 (n=19, 9.6%). Out of these three age groups, most of the PPIs prescribed for patients age 13-40 are of inappropriate indication. This warrants the need of deprescribing of PPIs, which can be done by switching to "when required" use, and using alternative antacid medication along with non-drug approaches to avoid or manage heartburn.[37] On the other hand, the proportion of inappropriate indication is lowest among patients aged 65 and above. Clinical and epidemiological data indicate that the incidence of NSAID- and aspirin-related peptic ulcers increases with age.[38] It is well established that elderly (>65 years old), especially those who are also taking NSAID, aspirin or corticosteroid have a higher chance than younger people of developing GI bleeding (5.5-fold vs. 1.65-fold).[39,40] Hence, the use of PPIs in the elderly was justified.

Number of concurrent medications was also found to be significantly associated with inappropriate PPIs prescribing. More than half (n=143, 72.2%) of the patients prescribed PPIs from our study had ≥5 concurrent oral medications. This is consistent with the result from another study, which demonstrated that the odds for PPIs prescribing increase with the increase in the total number of concurrent medications.[12] These patients were likely to have several comorbidities, with follow-up visits under multiple disciplines.[12] Healthcare providers tend to prescribe PPIs for patients with comorbidities and multiple medications for a longer period of time as PPIs are believed to have beneficial effects on the overall health of such patients.[12,41] Furthermore, prescribers are less likely to question prescriptions under other disciplines even if the medications are deemed unnecessary.[12] To date, no evidence suggests the need to prophylactically prescribe PPIs for patients with multiple medications.

It was also observed from our study that when it comes to the percentage of inappropriate PPIs prescribed, patients in the category of 2-4 concurrent medications came out on top of the list (n=31, 75.6%), followed by patients with ≥5 concurrent medications (n=80, 55.9%). The possible explanation for this finding is that the patients with ≥5 concurrent meds are more likely to have cardiovascular diseases that are treated with dual antiplatelet therapy or triple antithrombotic therapy, thereby justifying the prescription of prophylactic PPIs.

Besides, this study revealed an association between inappropriate PPIs prescribing and concurrent medications that pose a GI risk, in which 86.7% (n=26) of patients on anticoagulant monotherapy were inappropriately prescribed PPIs (P=0.001). Due to their gastroprotective effects, PPIs were often prescribed for patients on anticoagulants. However, a large retrospective observational study has shown that in patients treated with anticoagulant, the use of PPIs significantly reduced the risk of upper gastrointestinal bleed hospitalizations among those concurrently using antiplatelet drugs, but not in anticoagulant monotherapy.[42] Thus, oral anticoagulant and PPIs co-therapy is not recommended due to lack of evidence of the protective role of PPIs.[42,43]

Our study also showed that 84.6% (n=11) of patients on corticosteroids were inappropriately prescribed with PPIs (P=0.045). This is owing to the beliefs of practitioners that corticosteroids are ulcerogenic. The association between corticosteroids and peptic ulceration has been a source of debate since the 1950s.[42] While increased risk of GI bleeding applied to hospitalized patients on corticosteroid therapy, meta-analyses indicated that peptic ulcer is a rare complication of systemic corticosteroid therapy occurring in less than 0.4-1.8% of patients in ambulatory care.[44,45] Corticosteroids become

ulcerogenic only if they are administered together with NSAID.[46,47] Therefore, the administration of PPIs to prevent the development of peptic ulcers in treatment of corticosteroid alone is not routinely indicated.[44-47]

On the other hand, the incidences of inappropriate indications in patients with PPIs co- therapy with NSAID/ aspirin and clopidogrel are 35.1% (n=33) and 20.6% (n=7) respectively. These results from our study showed that a large proportion of prescribers adhered to the current treatment guideline.

Therefore, it is plausible that the use of oral anticoagulants and corticosteroids may have contributed to the higher frequency of inappropriate PPIs prescriptions observed in our facility.

Cost Incurred from Inappropriate Use of PPIs

According to the Malaysian Statistics on Medicine 2018-2022, the usage and expenditure of PPIs have been progressively increasing, reflecting the negative impact of PPIs overuse on healthcare costs.[48] Exacerbating this trend, a significant proportion of PPIs expenditure is attributable to prescriptions that deviate from established clinical guidelines, thereby amplifying the economic burden without corresponding therapeutic gains. To achieve long-term cost-effectiveness, stringent adherence to guidelines in prescribing and de-prescribing of PPIs is warranted.

Limitations

As this study was carried out retrospectively, indications of PPIs were identified solely based on documentation in patients' home- based cards. We might underestimate the number of PPIs prescriptions with actual indications by assuming the indications were unknown as it is possible that some of these prescriptions might have been justified by physicians during patient interviews or assessments, but were not documented in the medical records. Furthermore, endoscopy might have been performed, which justified the use of PPIs, however the reports were not attached to the patients' home- based cards. Despite efforts to recruit the calculated sample size of 222, only 198 participants were included due to time and resources constraints. This limitation may affect the study's statistical power.

CONCLUSION

In conclusion, this study provides preliminary insight into the prescribing pattern of oral PPIs in Hospital Sri Aman. The findings suggest a relatively high prevalence of potentially inappropriate PPIs prescribing within the facility. While PPIs overuse has been associated in previous literatures with increased healthcare costs, polypharmacy, and a higher risk of adverse events, the present study did not directly assess these outcomes. Nonetheless, the results highlight the need for prescribers adhere to prescribing guidelines and review the need for continued therapy to ensure rational use of PPIs and reduce unnecessary healthcare costs.

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CONFLICT OF INTEREST

The investigators declared they have no conflict of interest.

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ETHICAL APPROVAL

This study was registered with the National Medical Research Register (NMRR ID-24-02014-EFF) and was approved by the Medical Research and Ethics Committee, Malaysia.

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Appendix 1. Prescribing pattern of Proton Pump Inhibitors (PPIs) in Sri Aman Hospital

No	Date	Study ID	Male (M) / Female (F)	Age (years)	Type of PPIs (Esomeprazole / Omeprazole / Pantoprazole)*	Prescribed Dose & Frequency	Duration of PPI (weeks)	Prescribing Discipline (Medical / Surgical / Ortho / Eye / ENT / O&G / Psychiatry / ETD)	Diagnosis / Indication of PPIs (GERD / *Helicobacter pylori* eradication / GI ulcer / NSAIDs prophylaxis / gastritis / Others / Unknown)	No. of concurrent oral medicines	Concurrent Medication(s) (√)						Previous history GI ulcer(√)	Previous history of *Helicobacter pylori* infection (√)	No. of GI risk factor (s)**	Appropriate / Accepted / No indication
											NSAIDs	Aspirin	Ticlopidine	Clopidogrel	Anticoagulant	Steroids				
1																				
2																				
3																				
4																				
5																				
6																				
7																				
8																				

*Refer to the latest course of PPIs (if there is a switch of types of PPIs)

**Refer definition for the NSAIDs prophylaxis.