Risk Factors of Drug-Resistant Enterobacterales Infections in Patients Receiving Proton Pump Inhibitors

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ABSTRACT

Introduction:
Proton pump inhibitors (PPI) are commonly prescribed as stress ulcer prophylaxis in non-critical patients, especially those with major adverse cardiac and cerebrovascular events (MACCE). However, PPI use has been associated with a higher risk of drug-resistant Enterobacterales (DRE) infections. It is still unclear whether PPI use in patients with cerebrovascular accidents (CVA) and acute coronary syndromes (ACS) further increases their risk of DRE infections. This study aimed to explore the risk factors, including MACCE, and the incidence of DRE infections among patients receiving PPI.

Methods:
This retrospective cohort study examined all adult patients who received PPI and were admitted to Hospital Sultanah Maliha, Langkawi, Kedah, Malaysia, between March 1, 2022, and February 28, 2023. The study analyzed the relationship between MACCE and other covariates, with the risk of DRE infections using Cox regression. The first positive DRE culture identified during the study period was treated as an event for the analysis. The effects of covariates on DRE infections were reported as hazard ratios (HR).

Results:
During the study period, 2,585 hospitalized patients were prescribed PPI. Of these, 434 patients (16.8%) were diagnosed with either ACS, CVA or both. The overall incidence of DRE infections among patients prescribed with PPI was relatively low, affecting only 41 patients (1.6%). However, the risk of DRE infections was notably higher among those with concurrent CVA and ACS (10.0%) and those with CVA alone (6.4%). Patients with CVA had a 3.84-fold increased risk of DRE infections compared to those without CVA (95% CI: 1.65 to 8.96; *P*=0.002). Additionally, patients with frequent hospitalizations (adjusted HR = 1.46, 95% CI: 1.22 to 1.75; *P*<0.001) and those with a history of antibiotic use (adjusted HR = 2.29, 95% CI: 1.13 to 4.64; *P*=0.021) also had significantly elevated risks of contracting DRE infections.

Conclusion:
In addition to PPI use, patients with CVA who experienced frequent hospitalizations and had a history of antibiotic use were found to have a higher risk of DRE infections.

Keywords:
Proton pump inhibitors, drug-resistant Enterobacterales, ischaemic stroke, major adverse cardiac and cerebrovascular events

INTRODUCTION

Proton pump inhibitors (PPI) are widely used gastric acid suppressants, prescribed for stress ulcer prophylaxis, upper gastrointestinal bleeding, and various other gastric acid-related disorders. The European Society of Cardiology (ESC) had recommended PPI for patients on antithrombotic regimens who were at high risk of gastrointestinal bleeding, according to the criteria set by the Academic Research Consortium for High Bleeding Risk (ARC-HBR).[1,2] High bleeding risk factors, such as advanced age (≥75 years), moderate to severe chronic kidney disease (CKD), ischaemic stroke, and long-term oral anticoagulation use, are common reasons for prescribing PPI. Furthermore, the market withdrawal of ranitidine in 2019 due to elevated levels of N-nitrosodimethylamine (NDMA) had led to a sudden surge in PPI prescriptions from 2020 onwards.[3]

PPIs can reduce gastric acidity, disrupt gut ecology, and increase susceptibility to enteric pathogens such as *Salmonella*, *Escherichia coli*, and *Vibrio cholerae*.[4] Enterobacteriaceae, known for causing severe illnesses, have shown resistance to third-generation cephalosporins and carbapenems worldwide.[5] Numerous studies link PPI use to a higher risk of drug-resistant Enterobacterales (DRE) among hospitalized patients.[6–8] Although the impact of concurrent medication use has been widely studied, data on specific infections in DRE patients using PPIs remain limited. Research has associated PPI use with a higher risk of pneumonia in stroke and CKD patients, though the pathogens involved are often unspecified.[9,10] Positive associations between PPI exposure and DRE infections have been noted at 30 days, 90 days, and 6 months[6,8], but no conclusive link exists between PPI duration and pneumonia.[9,10]

Current guidelines did not recommend PPI for patients with acute coronary syndromes (ACS), yet the concurrent use of dual antiplatelet therapy (DAPT) had remained a prevalent reason for PPI prescriptions in Malaysia.[11] This pattern of PPI overuse had been observed globally, with Malaysia, being no expection, having a significant rate of inappropriate PPI use (>65%).[11,12]

Given that DAPT was frequently prescribed for patients with ACS and cerebrovascular accidents (CVA) or strokes, this study focused on the risk of DRE infections in these patient groups. For the purposes of this study, major adverse cardiac and cerebrovascular events (MACCE) encompassed myocardial infarction, unstable angina requiring hospitalization, ischaemic stroke, or transient ischaemic attack. The study aimed to investigate the risk factors including patient demographics, MACCE, other comorbidities, duration of PPI use and the incidence of DRE infections among patients receiving PPI.

METHODS

Study Design, Setting and Participants

This retrospective cohort study involved adult patients admitted to Hospital Sultanah Maliha in Langkawi, Kedah, Malaysia, a 110-bed district hospital, between March 1, 2022, and February 28, 2023. The study population included individuals aged 13 years and older who had received PPI either within the year prior to their admission or during their hospital stay. Data on patient demographics, medical and medication histories, and the initiation date of PPI were obtained from the Pharmacy Information System (PhIS). Results of positive DRE cultures were retrieved from the pathology department's system (iReportAG). For patients without prior follow-up at this hospital, medical and medication histories were sourced from their previous healthcare institutions. All enrolled patients were followed up until their discharge.

Variables

Patients recruited for this study were categorized into two groups: those diagnosed with MACCE, which included ACS and/or CVA, and non-MACCE patients. Ischaemic stroke was diagnosed based on neuroimaging that identified brain infarcts. The diagnosis of ACS was confirmed by persistent or dynamic changes on an electrocardiogram (ECG) or elevated serum cardiac markers. Active DRE infections were identified through positive DRE cultures that necessitated intravenous antibiotic treatment during the study period. Search terms for DRE in the iReportAG system included "ESBL", "MRO", "MDR", and "CRE".

The study also considered several covariates such as age, sex, the number of hospital admissions in the past year, exposure to antibiotics in the last three months, and prevalent comorbidities, such as hypertension, diabetes mellitus, and CKD. These comorbidities included both pre-existing or newly diagnosed conditions during the current admission. The estimated glomerular filtration rate (eGFR) was calculated using the 2021 CKD-EPI Creatinine Equation, which provides a more accurate eGFR across different race groups.[13] CKD was defined by an eGFR consistently below 60 mL/min/1.73 m^2 for more than three months before the study period, as outlined in the KDIGO guidelines.[14] Consequently, the most recent baseline eGFR upon admission was used for analysis.

The type of PPI referred to the most recent PPI prescribed during the study period. The duration of PPI use was based on medication history retrieved up to one year before the current admission. Any PPI use extending beyond one year prior to the admission was considered as one year for the purposes of the study.

Sample Size

The sample size was estimated using the Fleiss sample size calculation method for cohort studies.[15] The two-sided significance level was set at 0.05, and the power of the analysis was fixed at 80%. From the literature review, the prevalence of DRE acquisition among patients using PPIs was approximately 40%.[6–8] From the preliminary data, an estimated 2% of non-MACCE cases and 10% of MACCE cases acquired DRE infections.[8] Therefore, the minimum sample size required was 270 participants (135 patients with MACCE).

Statistical Analysis

Data analyses were performed using SPSS version 28, with results summarized through descriptive statistics. The Shapiro-Wilk normality test was used to assess the normality of numerical variables. Non-normal numerical data were presented as medians with interquartile ranges (IQR). Risk factors, such as MACCE and the incidence of DRE infections, were analyzed using Cox regression. All factors were included in both the simple and multivariable Cox regression analyses. The first positive DRE culture during the study period was considered an event, while the time from PPI initiation to the DRE infection was treated as the time-to-event variable in the analysis. Patients who did not develop a DRE infection during the study period were treated as right-censored data. Hazard ratios (HR) and confidence intervals (CI) were calculated for the risk factors associated with DRE infections, with P-values less than 0.05 considered statistically significant.

RESULTS

During the study period, 2585 patients using PPIs were hospitalized. Among these, 434 patients (16.8%) were diagnosed with either ACS, CVA or both (Figure 1). The overall incidence of DRE infections was relatively low, affecting 41 patients (1.6%). However, the incidence was higher among patients with MACCE at 2.5% (n = 11), particularly in those with CVA alone (6.4%) or concurrent ACS and CVA (10.0%), compared to 1.0% in ACS alone and 1.4% in non-MACCE patients. The median number of previous hospital admissions was 1 (IQR = 1), with a median hospital stay of 3 days (IQR = 3). The mortality rate among MACCE patients was 3.5%, compared to 0.3% in the non-MACCE group. Table 1 summarizes the demographic and clinical data of the study participants.

The majority of positive DRE cultures (n = 41) were obtained from urine samples (n = 11, 26.8%). Extended-spectrum beta-lactamase (ESBL) *Klebsiella pneumoniae* was the most commonly isolated microorganism (n = 18, 43.9%). The types of cultures and DRE infections are summarized in Table 2.

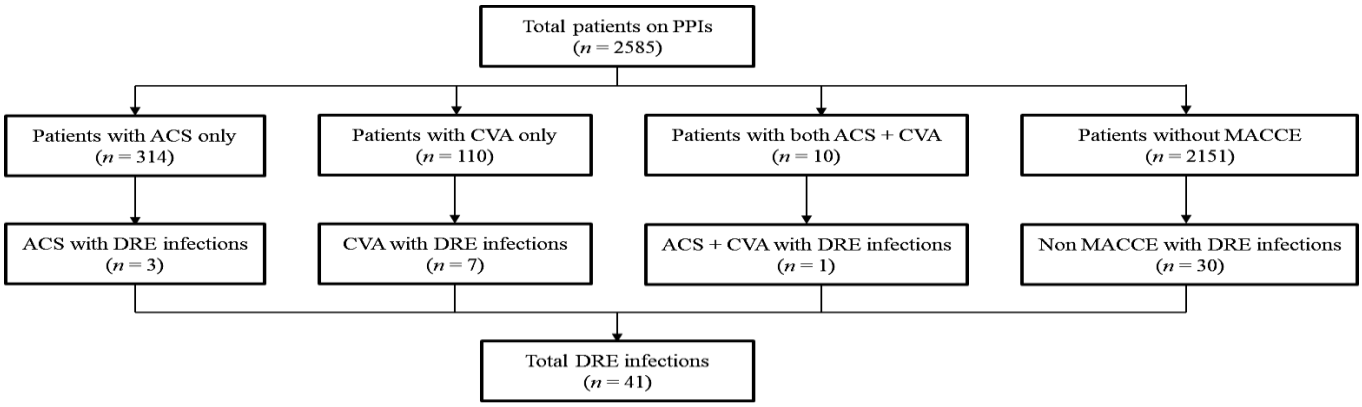


Figure 1. Classification of the participants' MACCE status and DRE infection

Table 1. Demographic and clinical data of the study participants (n = 2585)

Variables	MACCE, *n* (%) (n=434)	Non-MACCE, *n* (%) (n=2151)
Sex		
Male	233 (53.7)	1019 (47.4)
Female	201 (46.3)	1132 (52.6)
Ethnicity		
Malay	391 (90.1)	1893 (88.0)
Chinese	12 (2.8)	105 (4.9)
Indian	19 (4.4)	67 (3.1)
Others	12 (2.8)	86 (4.0)
Age group (years)		
<30	6 (1.4)	399 (18.5)
30 – 49	105 (24.2)	695 (32.3)
50 – 64	177 (40.8	555 (25.8)
≥65	146 (33.6))	502 (23.3)
Diagnosis of MACCE		
ACS only	314 (72.4)	-
CVA only	110 (25.3)	-
Both ACS and CVA	10 (2.3)	-
DRE infections		
Yes	11 (2.5)	30 (1.4)
No	423 (97.5)	2121 (98.6)
Type of PPIs		
Oral Pantoprazole	379 (87.3)	1376 (64.0)
IV Pantoprazole	38 (8.8)	690 (32.1)
Oral Esomeprazole	15 (3.5)	64 (3.0)
IV Esomeprazole	2 (0.5)	21 (1.0)
Comorbidities		
Hypertension	255 (58.8)	1769 (82.2)
Diabetes mellitus	199 (45.9)	368 (17.1)
CKD	129 (29.7)	157 (7.3)
Heart failure	23 (5.3)	13 (0.6)
Atrial fibrillation	20 (4.6)	35 (1.6)
Bronchial asthma	19 (4.4)	199 (9.3)
COPD	11 (2.5)	83 (3.9)
Malignancy	4 (0.9)	3 (0.1)
Antibiotic exposure in the past three months		
Yes	116 (26.7)	1113 (51.7)
No	318 (73.3)	1038 (48.3)
Discharge modality		
Discharge to home	419 (96.5)	2144 (99.7)
Deceased	15 (3.5)	7 (0.3)

ACS: acute coronary syndromes; CKD: chronic kidney disease;
COPD: chronic obstructive pulmonary disease;
CVA: cerebrovascular accident; IV: Intravenous;
MACCE: major adverse cardiac and cerebrovascular events;
PPI: proton pump inhibitor.

Table 2. Type of cultures and DRE infections (*n* = 41)

Variables	*n* (%)
Type of DRE infections	
ESBL *Klebsiella pneumoniae*	18 (43.9)
ESBL *Escherichia coli*	14 (34.1)
ESBL *Enterobacter cloacae*	3 (7.3)
ESBL *Proteus mirabilis*	1 (2.4)
MRO *Klebsiella pneumoniae*	2 (4.9)
CRE *Klebsiella pneumoniae*	1 (2.4)
More than one DRE infections	2 (4.9)
Type of cultures with DRE infections	
Urine	11 (26.8)
Blood	8 (19.5)
Tissue	4 (9.8)
Pus / Swab	4 (9.8)
Sputum	3 (7.3)
Tracheal aspirate	1 (2.4)
Catheter lumen	3 (7.3)
Body fluid	1 (2.4)
More than one positive cultures	6 (14.6)

CRE: carbapenem-resistant Enterobacterales;
DRE: drug-resistant Enterobacterales;
ESBL: extended-spectrum beta-lactamase;
MRO: multi-resistant organisms

Among patients with DRE infections, the median duration from PPI initiation to the first DRE infection was 16 days (IQR = 103). Table 3 summarizes the risk factors analyzed in the Simple Cox Regression. Covariates that showed significant associations in the analysis included CVA, eGFR, duration of PPI use, prior antibiotic exposure, and the number of hospital admissions.

In examining the risk factors for DRE infections among hospitalised patients, the Multivariable Cox Regression analysis has provided significant insights. Notably, CVA patients have a 3.84-fold increased hazard of DRE infections whereas ACS has a 90% lower hazard as compared to non-MACCE patients. It is also noteworthy that the duration of PPI, antibiotic exposure in the past three months, and the number of hospital admissions also increase the hazard of developing DRE infections substantially (Table 4).

Table 3. The association between covariates and DRE infections in univariable analysis

Covariates	Simple Cox Regression		
	Estimate	HR (95% CI)	*P*-value
Sex (Female)	0.469	1.60 (0.86, 2.97)	0.139
Age	0.012	1.01 (0.99, 1.03)	0.161
ACS	-0.382	0.68 (0.21, 2.24)	0.528
CVA	**1.542**	**4.67 (2.05, 10.64)**	**<0.001***
Both ACS and CVA	1.980	7.25 (0.99, 53.13)	0.051
Hypertension	0.426	1.53 (0.79, 2.96)	0.204
Diabetes mellitus	0.407	1.50 (0.81, 2.78)	0.196
eGFR (mL/min/1.73m²)	**-0.010**	**0.99 (0.98, 1.00)**	**0.028***
Duration of PPI (days)	**0.007**	**1.01 (1.00, 1.01)**	**<0.001***
Antibiotic exposure in the past three months	**0.873**	**2.39 (1.24, 4.62)**	**0.009***
Number of admissions in the past one year	**0.412**	**1.51 (1.33, 1.72)**	**<0.001***

Note: **P*<0.05; ACS: acute coronary syndromes;
CI: confidence interval;
CVA: cerebrovascular accident;
eGFR: estimated glomerular filtration rate;
HR: hazard ratio;
PPI: proton pump inhibitor.

Table 4. The association between covariates and DRE infections in multivariable analysis

Covariates	Multivariable Cox Regression		
	Estimate	aHR (95% CI)	*P*-value
ACS	**-2.299**	**0.10 (0.02, 0.45)**	**0.002***
CVA	**1.346**	**3.84 (1.65, 8.96)**	**0.002***
Both ACS and CVA	1.038	2.82 (0.37, 21.76)	0.319
Duration of PPI (days)	**0.014**	**1.01 (1.01, 1.02)**	**<0.001***
Antibiotic exposure in the past three months	**0.830**	**2.29 (1.13, 4.64)**	**0.021***
Number of admissions in the past one year	**0.380**	**1.46 (1.22, 1.75)**	**<0.001***

Note: **P*<0.05.
ACS: acute coronary syndromes;
aHR: adjusted hazard ratio;
CI: confidence interval; CVA: cerebrovascular accident;
PPI: proton pump inhibitor.
No multicollinearity and interaction were detected.
Proportional hazards assumption was fulfilled (hazard function plots, log-minus-log plots and partial Schoenfeld residuals)

DISCUSSION

Notably, the incidence of DRE infections was highest among patients with concurrent ACS and CVA. However, this observation is based on a single case, representing 10% of the total subjects in that group, which limits its statistical significance. The study also revealed that DRE infections were found in 6.4% of CVA (including stroke) patients, a figure comparable to the 9.3% of infections reported among stroke patients in a European study.[16] This similarity underscores the susceptibility of stroke patients to secondary infections. Patients with acute stroke are more likely to be prescribed PPIs due to several factors, including prolonged immobility, dysphagia, and the use of antiplatelet medications. Additionally, immunosuppression resulting from acute stroke, mediated through both humoral and neural pathways, significantly increases the risk of post-stroke infections.[17] However, the study did not specify whether the reported infections were DRE-related.

The findings of this study align with those of a Korean study, which demonstrated that the use of acid suppressants, such as PPIs, was also associated with an elevated risk of infections among stroke patients. This relationship persisted even after accounting for important covariates, including enteral tube feeding, mechanical ventilation, comorbid conditions, and concomitant medications.[18] Acid suppressant use is widely known to be associated with the DRE acquisition.[8,19] Furthermore, the higher prevalence of DRE detection in urine samples observed in this study is likely attributable to the prolonged use of urinary catheters. These devices are a well-documented cause of urinary tract infections in stroke patients and may have contributed to the increased detection of DRE in this population.[18]

Conversely, patients with ACS exhibited a reduction in the hazard of DRE infections. This contrasting finding underscores the complex interplay between underlying health conditions and their management in the context of DRE risk. The protective effect observed in ACS patients remains unclear and may be attributed to differences in clinical management practices or variations in the prophylactic use of medications, warranting further investigation. Our findings of a low DRE risk among patients with ischemic heart disease or hypertension align with other studies suggesting that the concurrent use of beta-antagonists, calcium channel blockers, renin-angiotensin system inhibitors, and lipid-modifying drugs does not contribute to DRE infections.[7,18]

Reconsideration of H2-receptor antagonists (H2RAs) for stroke patients may be warranted, especially following the withdrawal of ranitidine from the market in 2020.[20] Notably, no other H2RAs are currently listed in the Malaysian Ministry of Health Drug Formulary. This situation has necessitated the reliance on PPIs for patients requiring gastric acid suppression. However, American Society of Health-System Pharmacists guidelines suggest that PPIs are not indicated for primary stress ulcer prophylaxis, citing insufficient evidence to support their use as prophylactic agents.[21] Moreover, existing literature indicates that H2RAs are not significantly associated with infections when compared to PPIs.[6,8,10] Therefore, it is recommended to substitute PPIs with H2RAs for stress ulcer prophylaxis in this subgroup of patients to reduce the risk of DRE infections.

Previous literature has reported that prior exposure to antimicrobials might increase the risk of DRE infections.[22] This study also identified a significant association with prior antibiotic exposure. Additionally, the duration of PPI use and the frequency of hospital admissions were significantly linked to an increased hazard of DRE infections. These findings reveal gaps in understanding and suggest a cumulative effect of healthcare exposure and medication use on susceptibility to DRE infections. This highlights the importance of prudent medication management and stringent hospital infection control practices. Future research should focus on developing targeted interventions to minimise the risk of DRE infections, particularly among high-risk patient groups.

Patient eGFR values were not statistically significant in the multivariate analysis. This finding is likely attributable to the strong association between renal function and stroke status. Numerous studies have confirmed that eGFR is an independent risk factor for ischemic stroke. For instance, a decrease of 10 mL/min/1.73m² in eGFR corresponds to a 7% increased risk of stroke.[23] The underlying mechanisms involve vascular calcification and blood-brain barrier (BBB) disruption, leading to the accumulation of uremic toxins that cross the BBB. These processes result in altered cerebral perfusion, cognitive dysfunction, and neurodegeneration.[24]

Strengths and Limitations

Given the well-established association between PPI use and DRE infections in existing literature, our study focused on the subgroups of ACS and CVA patients who are potentially being prescribed PPIs inappropriately. We adopted a cohort study design to account for the temporal influence of PPI use on DRE infections. This approach enabled a more precise determination of the association between risk factors such as MACCE, other comorbidities, duration of PPI exposure, previous antibiotic exposure and DRE infections. The application of the time-to-event method with Cox regression further substantiated our findings.

To the best of our knowledge, this study is the first in Malaysia to investigate DRE infections among PPI users and has revealed a significant association among hospitalised CVA patients, irrespective of their age, kidney function, or comorbidities. The increased hazard of developing DRE infections compared to non-MACCE patients highlights a notable vulnerability within this patient subgroup.

This study has several limitations. Firstly, stroke severity measures, such as the NIH Stroke Scale (NIHSS) score, were not included due to the unavailability of data. Secondly, the relationship between DRE infections and both the type and route of administration of PPIs remains unclear, as patients may alternate between these agents during their treatment course. Furthermore, it has not yet been established whether transitioning from intravenous to oral PPIs early in the treatment course could reduce the risk of DRE infections. The evaluation of PPI compliance was also not included in this study, potentially introducing bias, particularly among long-term PPI users. Additionally, determining PPI use based on medication history up to one year before admission could result in an underestimation of the time to DRE infection.

Moreover, the percentage of DRE cases was relatively low in this study. Future research may consider conducting a case-control study to ensure a higher proportion of DRE cases for analysis. Lastly, this study exclusively recruited hospitalised patients. As a result, individuals who were not admitted to the hospital during the study period were not included, potentially limiting the generalisability of the findings to non-hospitalised populations.

CONCLUSION

In addition to the use of PPIs, a higher risk of DRE infections was found among patients who had frequent hospital admissions, previous antibiotic exposure, and diagnosed with CVA, irrespective of their kidney function and cardiovascular disease status. This finding suggests the need for implementing early measures to enhance the functional levels of stroke patients to help reduce their risk of infections. The study outcome also highlights the need for the use of H2RAs as an alternative to PPIs to promote more judicious use of gastric acid suppressants.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest or financial relationships relevant to this article to disclose.

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ETHICAL APPROVAL

The study complied with ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. Ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (NMRR ID-23-01835-RP2).

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