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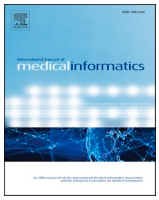

Reducing proton pump inhibitors overuse with an advisory, risk-based, context-aware electronic alert system: A controlled interrupted time series analysis

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ABSTRACT

Background: Proton pump inhibitors (PPI) are frequently overprescribed despite guidelines recommending cautious use. Electronic alert systems have shown potential in improving prescribing practices, but their effectiveness varies. This study evaluates a novel electronic alert system designed to reduce perioperative PPI overuse by leveraging real-time, patient-specific clinical data.

Methods: A retrospective controlled interrupted time series analysis was conducted from February 2015 to October 2021 in a tertiary care hospital. The intervention group comprised patients undergoing internal fixation surgeries in the orthopedic department, while the control group included patients receiving appendectomies in the general surgery department. A novel electronic alert system was integrated into the computerized physician order entry system, providing risk assessments and advisory alerts for intravenous PPI prescriptions. The system operated from July 2019 to November 2020. Key outcomes measured every two weeks included Defined Daily Doses (DDD) and Days of Therapy (DOT) per patient, prescription rates, and proportions of high-dose and alert-triggering orders.

Results: The study included 8,303 patients in the intervention group and 5,728 in the control group. Post-implementation, the intervention group showed a significant decrease in DDD per patient (β = -1.21, p = 0.003) and DOT per patient (β = -0.698, p = 0.011), primarily due to reduced intravenous administration. Prescription rates for PPI decreased significantly (OR = 0.710, p = 0.002), and there was a reduction in high-dose prescriptions (OR = 0.243, $p < 0.001$). While consumption metrics remained sustained after alert deactivation, quality indicators showed partial rebounds but remained improved compared to baseline.

Conclusions: The advisory, risk-based, context-aware electronic alert system effectively reduced PPI overuse and improved prescribing quality in a surgical department. The differential impact post-intervention, with more durable effects on consumption metrics than on prescribing quality, suggests a certain degree of sustainability in prescribing behaviors. Implementing advisory, context- aware electronic alerts may offer a scalable solution for optimizing medication use in healthcare settings.

1. Background

Proton pump inhibitors (PPI) are widely prescribed for acid-related disorders and, in surgical settings, primarily for the prevention of stress ulcers. However, their overuse remains a significant concern in healthcare systems globally. In China, while the overall rate of PPI use

Abbreviations: CPOE, Computerized Physician Order Entry; DDD, Defined Daily Dose; DOT, Days of Therapy; ICU, Intensive Care Unit; IT, Information Technology; ITS, Interrupted Time Series; IV, Intravenous; OR, Odds Ratio; PPI, Proton Pump Inhibitor.

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ranged from 3.5% to 6.2% across different cities, a concerning 32.6% to 56.8% of the PPI prescriptions were used for inappropriate indications, with PPI use accompanied by unapproved indications and excessive dosages [1]. Although PPIs are generally safe, especially for short-term use, their prolonged or excessive use is associated with gastric atrophy, enteric infections, bone fractures, pneumonia, vitamin B12 deficiency, and hypomagnesemia, as well as increased healthcare costs. [2] Despite guidelines recommending careful and appropriate use [3], implementation of these best practices remains suboptimal.

Electronic alert systems have emerged as a potential strategy to improve guideline adherence and clinical decision-making [4,5]. However, their effectiveness in PPI prescribing varies depending on design, frequency, and integration into clinical workflows, with alert fatigue potentially limiting long-term impact [6]. While studies have explored various approaches to improve PPI prescribing [6–9], evidence on the implementation and effectiveness of risk-based electronic alert systems specifically targeting PPI use is limited.

In response to persistent PPI overuse despite audits and feedback, our institution implemented a series of interventions. Initially, a strict policy control was established, followed by the development of a risk-based electronic alert system. This system, developed based on established clinical guidelines and piloted for perioperative PPI use, represents an innovative approach to promoting rational prescribing. This study aims to assess the effectiveness of our alert system in reducing PPI overuse and examine the sustainability of effect post-intervention.

2. Methods

2.1. Aim

We conducted a retrospective interrupted time series (ITS) analysis with comparison to evaluate the impact of the e-alert system on proton pump inhibitor prescribing patterns in a tertiary care hospital.

2.2. Study design

The study period spanned from February 1, 2015, to October 1, 2021, encompassing two major interventions:

1. Policy Control Intervention: February 1, 2018 – October 7, 2018
2. E-alert Implementation: July 1, 2019 – November 1, 2020

Despite ongoing quarterly medication audits and feedback, the hospital continued to observe persistent PPI overuse. In response to government concerns, on February 1, 2018, a stringent “circuit-breaker” policy was implemented, temporarily revoking PPI prescribing rights for surgical departments. Physicians were required to submit indications for each PPI order via a mobile or computer application, which were reviewed and approved by the pharmacy departments. Owing to its restrictive nature, this policy was discontinued on October 7, 2018, and prescribing rights were reinstated.

Following this period, as PPI use still increased, the hospital, in collaboration with the IT, Pharmacy departments, developed an electronic alert system, piloted specifically for patients undergoing internal fixation surgeries in the orthopedic department, typically requiring minimal PPI use. To track the alert system’s functionality, we conducted informal interviews with orthopedic surgeons and observed monthly PPI usage patterns during the first two months. On 2020-11-01, a major Hospital Information System (HIS) upgrade unintentionally disabled the alert system. Subsequently, the system’s status went undocumented, with periods of intermittent activation and deactivation.

2.3. Study groups

Intervention Group: Patients undergoing internal fixation surgery in the orthopedic department.

Control Group: Patients receiving appendectomies in the general surgery department, selected for their comparable surgical duration and trauma level to the intervention group.

2.4. Electronic alert system

The electronic alert system was seamlessly integrated into the existing Computerized Physician Order Entry (CPOE) system. Oral PPI orders remained unrestricted. The system operated as follows:

Trigger: The system activated silently when an orthopedic surgeon ordered an intravenous PPI via CPOE for a patient post-internal fixation surgery within five days, with no interface change.
Risk Assessment: It automatically calculated a stress ulcer risk score using predefined criteria based on recognized guidelines for stress ulcer prophylaxis [3] (Table 1) and real-time data collected from the electronic medical record, medication orders, laboratory information system.
Alert Mechanism: a. For scores ≥ 2: Prescription proceeded without alert if within standard dosage (DDD <= 1) or if “GI ulcer/bleeding” was indicated; b. For scores < 2 or excessive dosage (except for “GI ulcer/bleeding ”): Alert triggered, presenting a comprehensive list of PPI indications. (Fig. 1.A, B, C) This facilitated the identification of additional risk factors or justifications, while also ensuring that clinicians are consistently exposed to the PPI indications.
Pharmacist Review: Orders submitted for review were quickly assessed by pharmacists and approved, regardless of the justification, minimizing delays in patient care and illustrating the advisory nature of the alert (Fig. 1.E).
Follow-up Alert: After two doses, a one-time pop-up in CPOE prompted: “Consider discontinuing PPI or switching to oral.” (Fig. 1. D) This advisory alert excluded patients identified or selected in step 2 with “GI ulcer/bleeding”.

2.5. Risk factors for stress ulcer prophylaxis

We utilized a risk scoring system based on the recognized guideline for stress ulcer prophylaxis [3]. The system incorporates ten key risk factors, including postoperative fasting, ICU stay, immunosuppressant use, and others (Fig. 1.B, and Table 1).

2.6. Data collection

We conducted a retrospective analysis of medical records for both patient groups identified from the HIS during the study periods. This

Table 1
Risk factors for stress ulcer prophylaxis.

Risk factor	Points
1. NPO (postoperative fasting) or TPN > 3 days	2
2. ICU stay	1
3. Immunosuppressants	1
4. Fecal Occult blood positive	1
5. Age > 65 years	1
6. NSAIDs use	1
7. Antithrombotic use	1
8. High-dose corticosteroids	1
9. Male gender	1
10. Coagulation disorder (INR > 1.5, PLT < 50x10^9/L, or APTT > 65 s)	1
11. GI ulcer or GI bleeding	2

Risk factors and corresponding points used by the electronic alert system to automatically calculate patient-specific stress ulcer risk scores, based on recognized guideline [2].
NPO: Nil Per Os (Nothing by mouth); TPN: Total Parenteral Nutrition; ICU: Intensive Care Unit; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; INR: International Normalized Ratio; PLT: Platelet count; APTT: Partial Thromboplastin Time; GI: Gastrointestinal

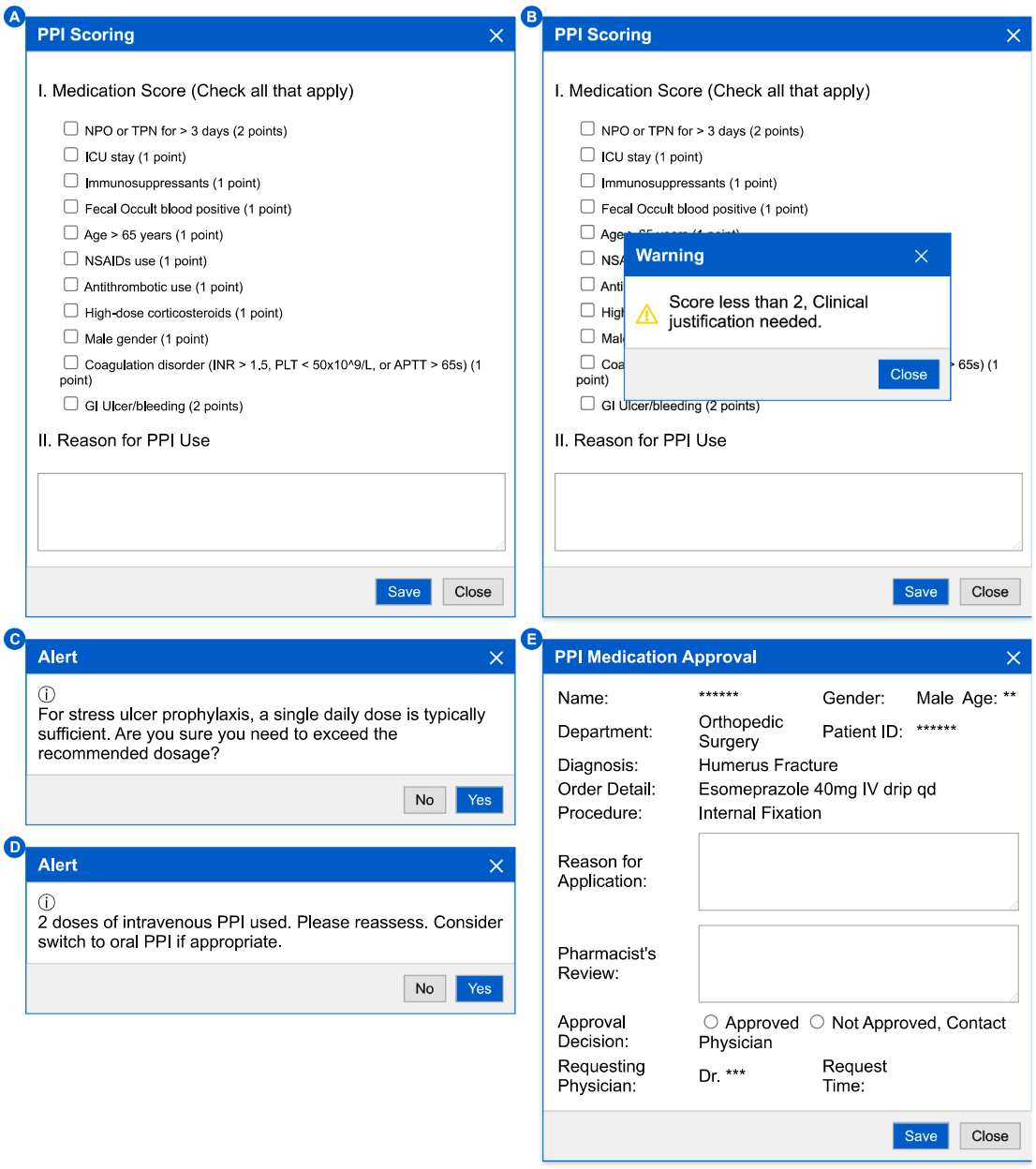

Fig. 1. Title: Key interfaces of the electronic alert system for PPI prescribing Legend: A: Risk assessment scoring interface B: Alert for low-risk patients (score < 2) requiring justification C: Alert for high dosage (DDD > 1) D: Follow-up alert after two doses of IV PPI E: Pharmacist review interface for order approval.

data included diagnoses, medication orders, laboratory results, and patient demographics, enabling us to reconstruct the clinical context for each PPI prescription. To ensure data accuracy, we standardized data extraction from the HIS and processed all data using consistent Python scripts.

2.7. Statistical analysis

2.7.1. Outcome measurements

We used several standardized measures to assess PPI consumption and prescribing patterns, calculated every two weeks:

1. Defined Daily dose (DDD): The assumed average maintenance dose per day for a drug's main indication in adults, as per world health Organization standards.
2. DDD-based measures: a) DDD per patient: Calculated as total DDD divided by the number of patients, representing the average PPI consumption per surgical patient. b) DDD per patient-day: Calculated as total DDD divided by the total number of patient-days, given the short-term nature of perioperative care in a surgical ward.
3. Days of Therapy (DOT) based measures: a) DOT per patient: Calculated as total DOT divided by the number of patients, representing the average duration of PPI therapy per surgical patient. b) DOT per patient-day: Calculated as total DOT divided by the total number of patient-days.
4. Prescription Rates: The number of PPI prescriptions per one hundred patients.
5. IV DDD Proportion: The proportion of PPI use administered intravenously.
6. Proportion of Orders Needing Alerts: We retrospectively applied the same alert criteria to pre-intervention orders to determine the proportion that would have triggered alerts.
7. High Dose Proportion: a) Proportion of cumulative daily doses exceeding 1 DDD; b) Proportion of single orders exceeding 1 DDD.

2.7.2. Interrupted time series regression

We employed a five-phases interrupted time series analysis model with a control group, based on the methodology described by Zhang et al. and Wagner et al. [10,11]. The five phases were: pre-policy control, during policy control, pre-electronic alert, during alert, and post-electronic alert. Our model can be represented by the equation:

$$\begin{aligned} Yt = {} & \beta 0 + \beta 1Tt + \beta 2X(1)t + \beta 3X(2)t + \beta 4X(3)t + \beta 5X(4)t \\ & + \beta 6(Tt - t1)X(1)t + \beta 7(Tt - t2)X(2)t + \beta 8(Tt - t3)X(3)t \\ & + \beta 9(Tt - t4)X(4)t + \beta 10G + \beta 11GTt + \beta 12GX(1)t + \beta 13GX(2)t \\ & + \beta 14GX(3)t + \beta 15GX(4)t + \beta 16G(Tt - t1)X(1)t \\ & + \beta 17G(Tt - t2)X(2)t + \beta 18G(Tt - t3)X(3)t \\ & + \beta 19G(Tt - t4)X(4)t + \epsilon t \end{aligned}$$

Where:

- Yt is the dependent variable.
- G is the binary indicator for treatment group or control group.
- Tt is the study time from start to end.
- X(1)t, X(2)t, X(3)t, X(4)t are binary indicators for phases 2–5 of the study.
- t1, t2, t3, t4 are the first time points after onset of interventions for phases 2–5.
- εt represents the random error term.

2.7.3. Coefficient Interpretation

β0 to β5: Baseline level and immediate changes in level at the onset of each phase in the control group. **β6 to β9**: Changes in the slope after each phase onset in the control group. **β10 to β15**: Differences in the initial level, slope, and immediate changes post-intervention between treatment and control groups for each phase. **β16 to β19**: Differences in trend changes post-intervention between treatment and control groups for each phase. The error terms may differ by treatment status, reflecting the independent and identically distributed process.

For linear outcomes, we employed an Ordinary Least Squares (OLS) model with Newey-West heteroskedasticity and autocorrelation consistent (HAC) adjustments. Proportional outcomes were analyzed using Generalized Estimating Equations (GEE) with a binomial distribution and logit link function. To address potential confounding due to variations in the distribution of PPI risk factors between groups and within each group over time, we adjusted our analyses using three models:(1) Robust, uses no covariates, (2) Full Covariate: adjusted for 10 PPI risk factors, and (3) Composite Score: adjusted for a composite score derived from these 10 risk factors. We implemented Box-Cox transformations to correct for non-normality in outcome variables as needed. Sensitivity analyses included a single group ITS analysis of the intervention group. For DDD/patient-day and DOT/patient-day, we modeled with patient-days as a covariate to adjust for patient-days changes. Statistical analyses were conducted using Python. We considered p-values < 0.05 as statistically significant.

3. Results

3.1. Patient demographics and baseline characteristics

From February 2015 to October 2021, a total of 14,031 patients were included in the analysis, with 8303 in the intervention group and 5728 in the control group. We analyzed 634,572 medication orders (421573 in the intervention group, 212,999 in the control group), of which 16,503 (2.60 %) were for PPI, 7958 (48.22 %) in the intervention group, 8545 (51.78 %) in the control group). Table 2 shows the baseline characteristics of patients in both groups, focusing on indications for PPI use. Significant differences across most indications led us to adjust for them as covariates in subsequent analyses. Additional analyses of patient characteristics across different study phases for both groups are provided in Supplementary Table 1 and 2.

Table 2
Patient demographics and baseline characteristics.

	Total (N = 14031)	Control (N = 5728)	Intervention (N = 8303)	P
Age > 65 Years, N (%)	3428 (24.4)	861 (15.0)	2567 (30.9)	**<0.001**
Male, N (%)	7680 (54.7)	2850 (49.8)	4830 (58.2)	**<0.001**
ICU Stay, N (%)	112 (0.8)	10 (0.2)	102 (1.2)	**<0.001**
NPO or TPN > 3 Days, N (%)	2746 (19.6)	365 (6.4)	2381 (28.7)	**<0.001**
Positive FOB, N (%)	556 (4.0)	129 (2.3)	427 (5.1)	**<0.001**
Coagulopathy, N (%)	120 (0.9)	25 (0.4)	95 (1.1)	**<0.001**
GI Ulcer/Bleeding, N (%)	173 (1.2)	80 (1.4)	93 (1.1)	0.167
Antithrombotic Use, N (%)	663 (4.7)	26 (0.5)	637 (7.7)	**<0.001**
NSAIDS Use N (%)	4725 (33.7)	1508 (26.3)	3217 (38.7)	**<0.001**
Immunosuppressant, N (%)	2 (0.0)	0	2 (0.0)	0.517
High-Dose Corticosteroid, N (%)	1425 (10.2)	586 (10.2)	839 (10.1)	0.831

Caption: Key patient characteristics used in the risk-based scoring for electronic alerts on PPI usage, including age, gender, ICU stay, and relevant clinical conditions. Statistically significant changes ($p < 0.05$) are highlighted in bold.
ICU: Intensive Care Unit; NPO: Nil Per Os (Nothing by mouth); TPN: Total Parenteral Nutrition; FOB: Fecal Occult Blood; GI: Gastrointestinal; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

3.2. Impact on PPI consumption

Table 3 presents key PPI consumption metrics, highlighting differences between the intervention and control groups in terms of immediate level changes and trend changes following both the implementation and cancellation of the alert. Our analysis revealed significant changes in major prescribing patterns post-implementation, with minimal changes post-cancellation. Primary results are reported from the Composite Score model, balancing confounder control and simplicity, while results of all three models are available in Supplementary Table 3.

3.2.1. DDD/patient and DDD/patient-day

DDD/patient decreased significantly post-implementation (β = -1.21, 95 % CI: −2.02 to −0.408, p = 0.003), with a very small but significant upward trend during the intervention period. The decrease was primarily driven by reductions in IV administration (β = -1.01, 95 % CI: −1.82 to −0.207, p = 0.014). Oral DDD/patient showed a non-significant increase post-implementation, but with a significant upward trend during the intervention (β = 0.0569, 95 % CI: 0.023 to 0.091, p = 0.001). Post-cancellation, changes were not statistically significant for total, IV, or oral DDD/patient. DDD/patient-day showed no significant immediate change but exhibited a very small increasing trend during the intervention (β = 0.0032, 95 % CI: 0.002 to 0.004, p < 0.001). Trends are illustrated in Fig. 2.A and 2.B.

3.2.2. DOT/patient and DOT/patient-day

DOT/patient significantly decreased post-implementation (β = -0.698, 95 % CI: −1.23 to −0.164, p = 0.011), primarily driven by reductions in IV administration (β = -0.522, 95 % CI: −0.966 to −0.078, p = 0.021), with no significant change in oral administration. There was no significant trend during the intervention period. DOT/patient-day showed no immediate change but a slight increasing trend during the intervention (β = 0.0012, 95 % CI: 0.001 to 0.002, p < 0.001), consistent across both IV and oral administration. Post-cancellation, neither metric exhibited significant changes. Trends are shown in Fig. 2.C and 2.D.

Table 3
Interrupted time series analysis of alert impact on PPI usage: level and trend changes following implementation and cancellation.

Indicators	Level Change (E-alert Implementation)			Trend Change (E-alert Implementation)			Level Change (E-alert Cancellation)			Trend Change (E-alert Cancellation)		
	Coef	**95 % CI**	**p**	**Coef**	**95 % CI**	**p**	**Coef**	**95 % CI**	**p**	**Coef**	**95 % CI**	**p**
DDD/Patient	−1.21	(−2.02, −0.408)	**0.003**	0.0059	(0.002, 0.01)	**0.003**	0.331	(−0.546, 1.21)	0.458	0.0006	(−0.004, 0.005)	0.78
IV DDD/Patient	−1.01	(−1.82, −0.207)	**0.014**	0.0033	(−0.001, 0.008)	0.14	0.422	(−0.425, 1.27)	0.327	0.0036	(−0.001, 0.008)	0.086
Oral DDD/ Patient	3.15	(−4.40, 10.70)	0.41	0.0569	(0.023, 0.091)	**0.001**	−7.33	(−15.2, 0.602)	0.07	0.0113	(−0.034, 0.057)	0.63
DDD/Patient-day	0.0583	(−0.13, 0.246)	0.54	0.0032	(0.002, 0.004)	**<0.001**	−0.0248	(−0.271, 0.221)	0.843	−0.0005	(−0.002, 0.001)	0.46
IV DDD/ Patient-day	0.0613	(−0.129, 0.251)	0.52	0.0026	(0.001, 0.004)	**<0.001**	−0.0147	(−0.255, 0.226)	0.905	−0.0002	(−0.002, 0.001)	0.81
Oral DDD/ Patient-day	3.04	(−3.85, 9.93)	0.39	0.0554	(0.024, 0.087)	**0.001**	−6.56	(−13.8, 0.72)	0.077	0.0096	(−0.032, 0.051)	0.65
DOT/Patient	−0.698	(−1.23, −0.164)	**0.011**	−0.0001	(−0.003, 0.003)	0.94	−0.0531	(−0.615, 0.508)	0.852	0.0002	(−0.002, 0.003)	0.88
IV DOT/Patient	−0.522	(−0.966, −0.078)	**0.021**	−0.0026	(−0.005, 0)	**0.016**	0.159	(−0.306, 0.625)	0.501	0.0046	(0.002, 0.007)	**<0.001**
Oral DOT/ Patient	4.40	(−4.10, 12.9)	0.31	0.0617	(0.023, 0.101)	**0.002**	−1.96	(−4.28, 0.37)	0.099	−0.0195	(−0.036, −0.003)	**0.021**
DOT/Patient-day	0.0378	(−0.065, 0.141)	0.47	0.0012	(0.001, 0.002)	**<0.001**	−0.0279	(−0.159, 0.104)	0.677	−0.0001	(−0.001, 0.001)	0.78
IV DOT/ Patient-day	0.0286	(−0.078, 0.136)	0.60	0.0006	(0.00001, 0.001)	**0.045**	−0.0085	(−0.136, 0.119)	0.896	0.0004	(0, 0.001)	0.27
Oral DOT/ Patient-day	4.34	(−3.58, 12.3)	0.28	0.0612	(0.025, 0.098)	**0.001**	−1.678	(−3.86, 0.501)	0.131	−0.0191	(−0.035, −0.004)	**0.016**

Caption: This table shows the immediate level changes and trend changes in PPI usage indicators following the implementation and cancellation of electronic alerts. Statistically significant changes ($p < 0.05$) are highlighted in bold.
Coef: estimated coefficient representing the magnitude of change; 95 % CI: 95 % confidence interval; p: p-value. **Level Change: immediate change in the outcome following the e-alert implementation or cancellation; Trend Change: change in the slope of the outcome over time following the e-alert implementation or cancellation.** DDD: Defined Daily Dose; IV: Intravenous; DOT: Days of Therapy. E-alert Implementation refers to the introduction of the electronic alert system, while E-alert Cancellation refers to its removal. Statistically significant results ($p < 0.05$) are highlighted in bold.

3.3. Impact on prescribing quality

Table 4 presents results of the interrupted time series analysis on PPI prescribing quality metrics. Odds ratios (ORs) are reported for proportion-based outcomes. Primary results are from the Composite Score model. Full results from all modeling approaches are in Supplementary Table 4.

3.3.1. Prescription rates

Total prescription rate decreased significantly post-implementation (OR = 0.710, 95 % CI: 0.570 to 0.884, p = 0.002), with a small increasing trend during intervention (OR = 1.002, 95 % CI: 1.0 to 1.003, p = 0.006). This decrease was mainly driven by IV prescription rate (OR = 0.690, 95 % CI: 0.514 to 0.926, p = 0.013), which showed a slight decreasing trend during intervention (OR = 0.998, 95 % CI: 0.996 to 1.00, p = 0.026). Oral prescription rate showed no significant immediate change post-implementation, but increased during intervention (OR = 1.05, 95 % CI: 1.03 to 1.07, p < 0.001) and subsequently decreased significantly post-cancellation (OR = 0.003, 95 % CI: 0.00 to 0.046, p < 0.001).

3.3.2. IV proportion in DDD

The proportion of IV administration in DDD showed no significant immediate change post-implementation of the alert system (OR = 0.526, 95 % CI: 0.072 to 3.85, p = 0.527). However, there was a significant decreasing trend during the intervention period (OR = 0.943, 95 % CI: 0.928 to 0.959, p < 0.001), indicating a gradual shift from IV to oral PPI administration. After the alert cancellation, there was a significant immediate increase in IV proportion (OR = 110, 95 % CI: 7.50 to 1626 p = 0.001), suggesting a rapid return to higher IV PPI consumption. The post-cancellation trend showed no significant change.

3.3.3. Proportion of alert-triggering orders

The proportion of PPI orders that would have triggered alerts decreased immediately after the alert implementation (OR = 0.519, 95 % CI: 0.342 to 0.790, p = 0.002). During the intervention period, there was a small but significant increasing trend (OR = 1.004, 95 % CI: 1.002 to 1.006, p < 0.001). After cancellation, there was a significant increase (OR = 3.56, 95 % CI: 1.96 to 6.50, p < 0.001), without further trend changes.

3.3.4. Proportion of high dose orders

Two indicators were used: proportion of cumulative daily dose DDD > 1 and proportion of single order DDD > 1. Post-implementation, both indicators decreased significantly (OR = 0.243, p < 0.001; OR = 0.221, p < 0.001 respectively). During intervention, both showed small increasing trends (OR = 1.004, p = 0.001; OR = 1.004, p = 0.002 respectively). Post-cancellation, both indicators increased significantly (OR = 2.98, p < 0.001; OR = 3.94, p < 0.001), with no subsequent trend changes.

3.4. Sensitivity analyses

To assess the robustness of our findings, we conducted several additional analyses:

3.4.1. Single-group interrupted time series analysis

We performed single group interrupted time series analyses without the control group on five indicators. Results largely supported our main findings, particularly for immediate effects post-implementation. Detailed results are provided in Supplementary Table 5.

3.4.2. Analysis accounting for patient-days as a covariate

The intervention significantly impacted patient-days (Supplementary Fig. 1), influencing DDD/patient-day and DOT/

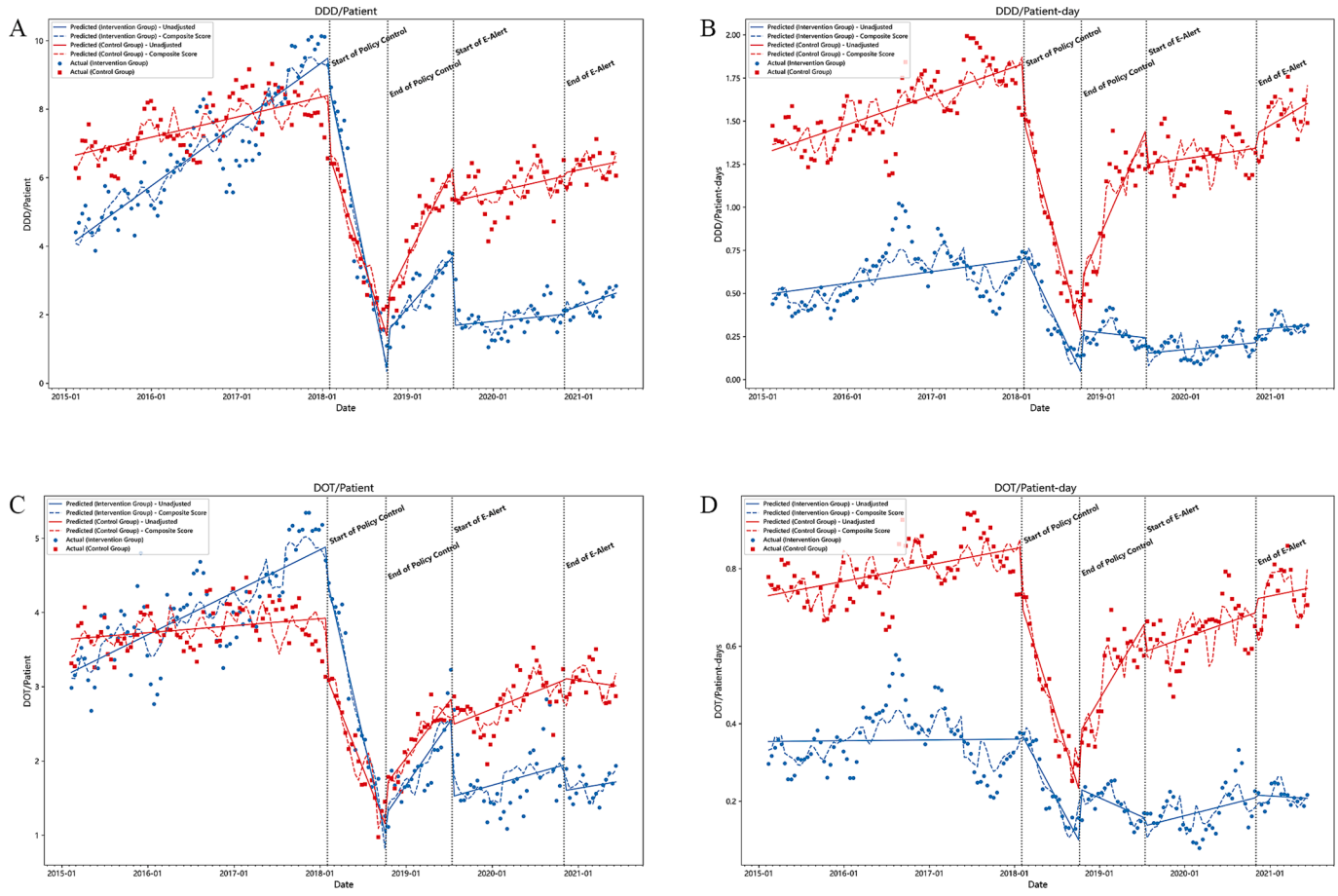

Fig. 2. Title: Interrupted Time Series Analysis of DDD and DOT Trends Per Patient and Per Bed-Day in Intervention and Control Groups Legends: Observed data (circles: intervention; squares: control) with predicted trends from unadjusted (solid lines) and composite score (dashed lines) models. Vertical lines mark policy control and alert intervention periods. Panel A: DDD/Patient; Panel B: DDD/Patient-Day; Panel C: DOT/Patient; Panel D: DOT/Patient-Day.

Table 4
Interrupted time series analysis of E-alert impact on PPI Use quality: level and trend changes following implementation and cancellation.

Indicators	Level Change (E-alert Implementation)			Trend Change (E-alert Implementation)			Level Change (E-alert Cancellation)			Trend Change (E-alert Cancellation)		
	OR	**95 % CI**	**p**	**OR**	**95 % CI**	**p**	**OR**	**95 % CI**	**p**	**OR**	**95 % CI**	**p**
Total Prescription Rate	0.710	(0.570, 0.884)	**0.002**	1.002	(1.0, 1.003)	**0.006**	0.944	(0.703, 1.27)	0.704	1.000	(0.997, 1.002)	0.622
IV Prescription Rate	0.690	(0.514, 0.926)	**0.013**	0.998	(0.996, 1.00)	**0.026**	1.20	(0.855, 1.68)	0.293	1.002	(1.000, 1.004)	0.105
Oral Prescription Rate	1.47	(0.246, 8.72)	0.674	1.05	(1.03, 1.07)	**< 0.001**	0.003	(0.0, 0.046)	**< 0.001**	0.993	(0.981, 1.004)	0.228
IV DDD Proportion	0.526	(0.072, 3.85)	0.527	0.943	(0.928, 0.959)	**< 0.001**	110	(7.50, 1626)	**0.001**	1.010	(0.997, 1.023)	0.122
Proportion of Orders Needing Alerts	0.519	(0.342, 0.790)	**0.002**	1.004	(1.002, 1.006)	**< 0.001**	3.56	(1.96, 6.50)	**< 0.001**	0.998	(0.994, 1.001)	0.24
Proportion of Cumulative DDD > 1	0.243	(0.151, 0.391)	**< 0.001**	1.004	(1.002, 1.007)	**0.001**	2.98	(1.77, 5.00)	**< 0.001**	1.000	(0.997, 1.00)	0.844
Proportion of Single Order DDD > 1	0.221	(0.135, 0.362)	**< 0.001**	1.004	(1.002, 1.007)	**0.002**	3.94	(2.16, 7.16)	**< 0.001**	0.997	(0.994, 1.000)	0.09

Caption: This table shows the immediate level changes and trend changes in PPI use quality indicators following the implementation and cancellation of electronic alerts. Statistically significant changes ($p < 0.05$) are highlighted in bold.
OR: Odds Ratio; 95 % CI: 95 % Confidence Interval. Level Change: immediate change in the outcome following the e-alert implementation intervention or cancellation; Trend Change: change in the slope of the outcome over time following the e-alert implementation intervention or cancellation.. Statistically significant results ($p < 0.05$) are in bold. IV: Intravenous; DDD: Defined Daily Dose.

patient-day outcomes. After adjusting for patient-days, analysis revealed no significant level changes but significant increasing trends in both DDD/patient-day and DOT/patient-day during alert implementation, primarily driven by oral use. Following alert cancellation, most indicators remained unchanged except for a decreasing trend in Oral DOT/patient-day. Detailed results are provided in Supplementary Table 6.

3.4.3. Analysis excluding policy control variables

We conducted analyses modeling only three time periods: pre-alert implementation, during alert implementation, and post-alert cancellation, while excluding the policy control period data. Results remained consistent with our primary findings. Supplementary Table 7.

3.5. Impacts on clinical outcomes

Analysis of gastrointestinal bleeding and *Clostridium difficile* infections in the intervention group revealed no recorded incidents during pre-intervention, intervention, and post-intervention periods.

4. Discussion

Our study demonstrates the effectiveness of an advisory, risk-based, context-aware electronic alert system – in optimizing PPI prescribing behaviors in a surgery department. The alert significantly reduced PPI consumption. We observed substantial decreases in DDD/patient, DOT/patient and PPI prescription rates—primarily by decreasing intravenous administration—along with improved prescribing quality evidenced by reductions in proportions of high-dose orders and alert-triggering orders. These findings suggest that the alert not only reduced overall PPI exposure but also promoted more judicious use, potentially facilitating a shift towards oral administration. Additionally, while patient-level metrics (DDD/patient and DOT/patient) showed significant immediate decreases, similar changes were not observed at the patient-day level. This discrepancy may be attributed to the alert's concurrent effect on reducing patient-days.

The persistence of intervention effects after the alert cancellation is noteworthy. Most PPI consumption metrics, including DDD per patient and DOT per patient, showed no significant changes after the e-alert system was discontinued, suggesting that the intervention fostered enduring improvements in overall PPI consumption. However, we observed a significant immediate rebound effect upon alert cancellation for several prescribing quality indicators, including a decreased oral prescription rate, an increased proportion of IV administration in DDD, and higher proportions of alert-triggering and high-dose orders. These changes may indicate a partial reversion to pre-intervention prescribing behaviors, particularly a preference for intravenous administration. Despite these rebounds, these indicators remained significantly improved compared to the pre-intervention baseline (Supplementary Fig. 2), indicating that prescribing quality did not fully regress to original patterns. Additionally, there was no significant trend toward further deterioration for these metrics during the observed post-cancellation period, suggesting stabilization at this new, albeit suboptimal, level. These findings suggest a differential sustainability pattern: while volume-related prescribing behaviors demonstrated more durable changes, certain aspects of prescribing quality may benefit from ongoing reinforcement. Overall, the intervention achieved both the formation of new habits and increased awareness of appropriate PPI use, though certain prescribing practices may require ongoing support or periodic reinforcement to sustain optimal quality.

Our findings contribute to the literature on PPI stewardship in surgical settings. Previous de-implementation programs often relied on pharmacist-led interventions with educational programs, alerts or audit [12], while such methods have shown efficacy, they can be resource-intensive and may contribute to challenges like alert fatigue, potentially affecting long-term sustainability [13,14]. Our alert system provides context-specific guidance, intervening only when necessary. It likely influenced surgeons' behavior by raising awareness, providing immediate feedback, and facilitating reflective practice at the time of prescription. Also, this approach offers a more scalable and sustainable solution, ideally suited for fast-paced environments such as surgical departments. This aligns with the findings of Herzig et al. [5], who demonstrated that a simple, conditioned alert, triggered only for specific prescribing scenarios, significantly reduced inappropriate medication use. Our results suggest that effective stewardship may not necessarily require intensive oversight, as discussed by Musuuza et al. [8] and McDonald et al. [15]. Also, our alert system's repeated, timely prompts function as continuous education, potentially better than the simple educational program by Lazaridis et al. [16]. Although our study demonstrates that improvements can persist after alert cancellation, the intermittent activation of the alerts post-cancellation hinders the assessment of long-term effects. The issue of short post-intervention periods is common in the literature [17], where occasional rebounds in previous practices are also noted [18].

Our study's strengths include the use of an interrupted time series analysis with a control group, enhancing causal inferences, and the employment of multiple outcome measures for a comprehensive assessment. However, our study has limitations. The retrospective design introduces potential selection bias and unmeasured confounding, such as differences in patient characteristics or clinical practices between departments, and may not fully capture real-time clinical complexities.. Our data collection did not account for abandoned PPI orders after alerts, leaving this "silent" deterrent effect unquantified; similarly, potential alert fatigue among clinicians, which could diminish alert effectiveness over time, was not assessed. The short intervention and follow-up period were due to administrative changes, constraining long-term sustainability assessment. Furthermore, the complex relationship between patient-days and our primary outcomes poses analytical challenges. The apparent lack of effect on DDD/patient-day and DOT/patient-day may reflect concurrent changes in patient-days rather than absence of impact on PPI use. Including patient-days as a covariate could introduce multicollinearity and over-adjustment, potentially underestimating the intervention's effect. Although we assessed key outcomes, gastrointestinal bleeding and C. difficile infection, other potential adverse events like nutritional deficiencies were not evaluated, slightly limiting a comprehensive assessment of the intervention's real-world impact. These limitations underscore the need for prospective studies that incorporate real-time alert data collection and capture abandoned orders. A longer, stable follow-up period would provide more robust evidence of the intervention's long-term impact.

5. Conclusions

This study demonstrates that a risk-based, advisory alert system effectively optimizes PPI prescribing behaviors in a surgical context, leading to significant reductions in PPI use and improved prescribing quality. The differential persistence of intervention effects after alert cancellation, with stability in PPI consumption metrics despite partial rebounds in quality indicators, suggests a certain degree of sustainability in the improved prescribing behaviors. These findings support the use of non-intrusive, context-specific health IT interventions in clinical practice. Future research should refine these strategies, incorporate real-time data collection, and assess long-term impacts on clinical outcomes to advance effective implementation in diverse healthcare settings.

Declarations

Ethics approval and consent to participate

The alert system was implemented by the hospital's administration after consulting the ethics committee. Its advisory nature and the lack of patient or physician-specific data collection meant that individual informed consent was not required. This retrospective study was approved by the Institutional Review Board. Informed consent was waived due to the retrospective nature of the study and the use of de-identified data.

Data Sharing Statement

The datasets of this study are available from the corresponding author on reasonable request.

Declaration of generative AI in scientific writing

The English language editing of this manuscript was assisted by OpenAI's language model (ChatGPT, version 4.0), a machine learning-based tool developed by OpenAI. The tool was used to refine the text

for clarity, coherence, and academic tone.

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CRediT authorship contribution statement

Dan Luo: Writing – original draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Xiaolan Ye:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Hongying Zhao:** Validation, Formal analysis. **Bin Yao:** Formal analysis, Data curation. **Wentong Liu:** Data curation. **Xiaobo Xu:** Writing – review & editing, Visualization, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijmedinf.2025.105960.

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