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# Risk factors for gastrointestinal complications during glucocorticoid therapy in internal medicine inpatients: a real-world retrospective analysis

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## Abstract

**Background** The risk factors for gastrointestinal complications during glucocorticoid therapy in internal medicine inpatients are rarely reported. This study aimed to investigate the risk factors for gastrointestinal complications in internal medicine patients using glucocorticoids.

**Methods** Internal medicine inpatients receiving glucocorticoid therapy from February 2023 to September 2023 were included. Gastrointestinal complications were identified by careful review of the electronic medical records of these patients. The risk factors for gastrointestinal complications during glucocorticoid therapy were analyzed by univariable and multivariable logistic regression. Receiver operating characteristic (ROC) curve with Youden's index was used to determine the best cutoff point of the identified continuous variables.

**Results** Of the 960 inpatients included, 88 had gastrointestinal complications, with the most common complications including 27 (30.7%) with abdominal discomfort, 26 (29.5%) with acid regurgitation and heartburn, and 14 (15.9%) with asymptomatic positive fecal occult blood. Multiple logistic regression analysis showed that age ≥ 65 years [OR = 2.014, 95% CI (1.096, 3.703), $p = 0.024$], history of gastroesophageal reflux disease (GERD) [OR = 1.810, 95% CI (1.009, 3.250), $p = 0.047$], history of peptic ulcer (PU) [OR = 5.636, 95% CI (1.505, 21.102), $p = 0.010$], maximum dose of glucocorticoids [OR = 1.003, 95% CI (1.001, 1.004), $p = 0.001$], and nonsteroidal anti-inflammatory drugs (NSAIDs) [OR = 2.788, 95% CI (1.023, 7.597), $p = 0.045$] were associated with more gastrointestinal complications during glucocorticoid therapy in internal medicine inpatients. ROC curve analysis revealed that when the maximum dose of glucocorticoids was greater than 160 mg, gastrointestinal complications were more likely to occur.

**Conclusions** The study shows that age ≥ 65 years, history of GERD, history of PU, maximum dose of glucocorticoids, and NSAIDs are associated with more gastrointestinal complications during glucocorticoid therapy in internal medicine inpatients. Multidisciplinary teams, including physicians, pharmacists, and nurses, should consider increased monitoring to inpatients with high-risk factors.

**Keywords** Glucocorticoids, Gastrointestinal complications, Risk factors

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## Introduction

Since Dr. Hench first successfully applied cortisone acetate to treat rheumatoid arthritis in 1948, glucocorticoids have been widely used in clinical practice and have become an important means of treating various diseases [1, 2]. However, glucocorticoids are a double-edged sword, which can bring many side effects while treating diseases, among which gastrointestinal complications are one of them [3, 4]. There are many gastrointestinal complications related to glucocorticoids, ranging from mild cases such as gastric upset, vomiting, and dyspepsia to severe cases such as visceral perforation, pancreatitis, and gastrointestinal bleeding [4–6]. From a pathophysiologic perspective, glucocorticoids can increase the secretion of gastric acid and pepsin, reduce the secretion of gastric mucus, weaken the resistance of gastrointestinal mucosa, induce or exacerbate gastric and duodenal ulcers, and further cause gastrointestinal bleeding or perforation. Corticosteroids can also inhibit epithelial cell regeneration and granulation tissue formation, slowing down ulcer repair and thus inhibiting ulcer recovery. In addition, glucocorticoids reduce the synthesis of arachidonic acid and subsequently decrease prostaglandins in the body by inhibiting phospholipase A2 [7–9].

The relationship between gastrointestinal complications and glucocorticoids is currently controversial [8, 10–13], but the incidence of gastrointestinal complications is significantly increased when some risk factors are present, such as a 4-fold increase in the risk of peptic ulcer when glucocorticoids are combined with nonsteroidal anti-inflammatory drugs (NSAIDs) [14]. However, in addition to the well-known combination of NSAIDs, the risk factors for gastrointestinal complications during glucocorticoid therapy in internal medicine inpatients, such as glucocorticoid dose, duration of treatment, and other combinations of medications, are rarely and incomprehensively reported. Luo et al. discovered that old age, smoking and the use of nonspecific cyclooxygenase inhibitors are risk factors for peptic ulcer disease in autoimmune disease patients using glucocorticoids [7]. Other studies have reported more on the relationship between glucocorticoids and gastrointestinal complications [10, 11, 15–17].

Therefore, we attempted to identify and refine the risk factors for gastrointestinal complications in internal medicine patients using glucocorticoids. This study will help to raise awareness among internal medicine physicians about the risk factors for gastrointestinal complications during glucocorticoid therapy and also provide support for avoiding gastrointestinal complications.

## Methods

### Setting and study design

This retrospective study was conducted in the Beijing Tongren Hospital affiliated with Capital Medical University, a 1759-bed tertiary care, teaching, and research institution. Patients receiving glucocorticoids during hospitalization in the department of neurology, rheumatology, endocrinology, and nephrology from February 2023 to September 2023 were included. Patients with current gastrointestinal diseases such as gastrointestinal hemorrhage, peptic ulcer (PU), and gastroesophageal reflux disease (GERD) were excluded. Patients with positive fecal occult blood tests upon admission were excluded. Patients with incomplete data were also excluded. Electronic medical records of these patients during their use of glucocorticoids were carefully reviewed for symptoms and signs suggestive of gastrointestinal complications. The review was carried out independently by two clinical pharmacists and reviewed by each other to avoid information omission. In the study, gastrointestinal complications were defined as heartburn, acid regurgitation, gastric upset, positive fecal occult blood, GERD, PU, gastrointestinal hemorrhage, and so on. This study was performed in accordance with the Declaration of Helsinki and approved by the Beijing Tongren Hospital Ethics Committee (NO. TREC2024-KY065). Patients were exempt from informed consent.

### Data collection

The following information from the electronic medical records of Beijing Tongren Hospital was collected: demographics (age and gender), smoking and drinking habits, body mass index (BMI), serum creatinine, international normalized ratio (INR), platelet count, concomitant diseases, number of concomitant diseases, length of hospital stay, types of medications used, glucocorticoids (maximum dose, total dose, dosage form, duration), gastrointestinal complications.

### Statistical analysis

Patients were divided into positive and negative groups based on whether gastrointestinal complications occurred. A descriptive analysis was performed on the patient's demographics, smoking and drinking habits, BMI, serum creatinine, INR, platelet count, concomitant diseases, number of comorbidities, length of hospital stay, types of medications used, glucocorticoids (maximum dose, total dose, dosage form, duration). For continuous variables, the Student's t-test or the Mann-Whitney U test was used to compare the two groups. The Student's t-test for continuous variables was.

used to compare means between groups when continuous variables conformed to the homogeneity of variance and normal distribution. Otherwise, the Mann-Whitney

U test was used, represented by medians and interquartile ranges (IQRs) (25–75th percentiles). Categorical variables were described by frequencies and percentages, and between-group differences were analyzed using the Chi-square test and Fisher's exact test if necessary. Variance inflation factor (VIF) values were calculated to measure the degree of multicollinearity among the variables that were significant in the univariate analysis ($p < 0.1$). A VIF of >10 was considered indicative of multicollinearity and excluded from the logistic regression analysis. Based on the univariate analysis and VIF values, significant variables ($p < 0.1$) were included in the multiple logistic regression analysis to identify risk factors for gastrointestinal complications in internal medicine patients using glucocorticoids [18]. Receiver operating characteristic (ROC) curve with Youden's index was used to determine the best cutoff point of the identified continuous variables. All statistical analyses were carried out using SPSS (Version 26.0). P values < 0.05 were considered statistically significant.

## Results

### Patient characteristics

During the study period, a total of 960 patients were finally included in our study. The median age of the patients was 52.0 (40.0, 60.0) years and the majority (54.2%) were female. The number of these patients admitted to the department of neurology, rheumatology, endocrinology, and nephrology were 475 (49.4%), 352 (36.7%), 112 (11.7%), and 21 (2.2%) respectively.

### The risk factors for gastrointestinal complications during glucocorticoid therapy

Among the 960 patients included, 88 (9.2%) cases had gastrointestinal complications. The most common gastrointestinal complications were abdominal discomfort (30.7%), acid regurgitation and heartburn (29.5%), as well as asymptomatic positive fecal occult blood (15.9%). In univariate analysis, 11 factors were significantly associated with gastrointestinal complications ($p < 0.05$): age, history of GERD, history of PU, length of hospital stay, number of concomitant diseases, glucocorticoid dosage form, maximum dose of glucocorticoids, total dose of glucocorticoids, NSAIDs, immunosuppressants, and bisphosphonates (Table 1). The results of multicollinearity analysis showed that VIF values of 11 factors were less than 10. In multiple logistic regression analysis, age ≥ 65 years, history of GERD, history of PU, maximum dose of glucocorticoids, and NSAIDs were associated with more gastrointestinal complications ($p < 0.05$) (Table 2).

### The ROC curve of maximum dose of glucocorticoids for predicting gastrointestinal complications

The area under the ROC curve (AUC) of the maximum dose of glucocorticoid was 0.593, with a cut-off of 160 mg determined by Youden's index (Fig. 1; Table 3).

## Discussion

Most of the previous literature reported on the risks of glucocorticoids in relation to gastrointestinal bleeding or gastrointestinal ulcers [8, 10, 11, 15–17]. In fact, the incidence rates of these two risks are rather low. Moreover, with the widespread preventive use of acid suppressants in clinical practice, these risks have been further reduced [19]. Our study has also confirmed this, and no gastrointestinal ulcers or gastrointestinal bleeding were found in our study. The incidence rate of gastrointestinal complications during glucocorticoid treatment in our study was 9.2%, which was higher than in a previous study [20]. The previous study used the General Practice Research Database from the United Kingdom, whereas our study population was single-hospital internal medicine inpatients. In addition, the outcome of our study was gastrointestinal complications, while the outcome of the previous study was upper gastrointestinal complications, limited to bleeding, perforation, or ulcers in the stomach or duodenum. However, our results have led us to think deeply. Firstly, since our result is based on electronic medical records of Beijing Tongren Hospital, we believe that the actual incidence of gastrointestinal complications may be higher due to potential underreporting in medical records. Secondly, why is the incidence rate of gastrointestinal complications still so high despite the extensive preventive use of acid suppressants in clinical practice? Of course, we must admit that serious gastrointestinal complications such as gastrointestinal bleeding did not occur in our study. Our previous study found that patients taking glucocorticoids, who had a history of PU or were in combination with NSAIDs, were not given PPIs that are more effective in inhibiting acid [19]. In fact, there is still a lack of guidelines on how to prophylactic use acid suppressants in internal medicine inpatients receiving glucocorticoids, which has led to the occurrence of the above results to some extent [19].

This is the first study to explore the risk factors of gastrointestinal complications in internal medicine inpatients receiving glucocorticoid therapy, which is one of the biggest highlights of our research. Age ≥ 65 years, history of GERD, history of PU, and NSAIDs were associated with more gastrointestinal complications during glucocorticoid therapy in our study. These factors are known risk factors for gastrointestinal injury and bleeding, which are mentioned in many studies or guidelines [21, 22]. To our surprise, antiplatelet agents and anticoagulants were not associated with more gastrointestinal

**Table 1** Patient demographic and clinical characteristics

| Variable | Positive group ($n=88$) | Negative group ($n=872$) | *P* |
|---|---|---|---|
| Age (years), n (%) | | | 0.011* |
| <65 | 65 (73.9) | 736 (84.4) | |
| ≥65 | 23 (26.1) | 136 (15.6) | |
| Gender, n (%) | | | 0.881 |
| Male | 41 (46.6) | 399 (45.8) | |
| Female | 47 (53.4) | 473 (54.2) | |
| BMI ($kg/m^2$), (IQR) | 25.3 (22.9,27.5) | 25.2 (23.0,27.3) | 0.995 |
| Smoke, currently, n (%) | 12 (13.6) | 157 (18.0) | 0.305 |
| Alcohol, currently, n (%) | 15 (17.0) | 120 (13.8) | 0.398 |
| History of GERD, n (%) | 22 (25.0) | 138 (15.8) | 0.028* |
| History of PU, n (%) | 4 (4.5) | 8 (0.9) | 0.016* |
| Serum creatinine (umol/L), (IQR) | 62.0 (52.5,70.8) | 63.0 (53.0,74.0) | 0.178 |
| INR, (IQR) | 0.99 (0.94,1.05) | 0.98 (0.93,1.02) | 0.152 |
| Platelet count ($10^9$/L), (IQR) | 227.0 (186.8,276.8) | 222.0 (187.0,267.0) | 0.309 |
| Length of hospital stay (days), (IQR) | 11.5 (8.0,16.0) | 10.0 (7.0,14.0) | 0.002* |
| Number of concomitant diseases, (IQR) | 9.0 (4.3,14.0) | 8.0 (4.0,12.0) | 0.031* |
| Concomitant diseases, n (%) | | | |
| Diabetes | 25 (28.4) | 190 (21.8) | 0.156 |
| Coronary heart disease | 4 (4.5) | 42 (4.8) | 1.000 |
| Cerebral infarction | 7 (8.0) | 47 (5.4) | 0.452 |
| Atrial fibrillation | 1 (1.1) | 10 (1.1) | 1.000 |
| Hypertension | 29 (33.0) | 299 (34.3) | 0.801 |
| Liver dysfunction | 16 (18.2) | 98 (11.2) | 0.055 |
| First use of glucocorticoids, n (%) | 41 (46.6) | 376 (43.1) | 0.531 |
| Glucocorticoid dosage form, n (%) | | | 0.034* |
| Oral | 22 (25.0) | 317 (36.4) | |
| Injectable | 66 (75.0) | 555 (63.6) | |
| Acid suppressants, n (%) | | | 0.989 |
| PPIs | 24 (27.3) | 234 (26.8) | |
| $H_2R$ | 61 (69.3) | 606 (69.5) | |
| Other | 3 (3.4) | 32 (3.7) | |
| Maximum dose of Glucocorticoids[a], (IQR) | 500 (65.0,1000.0) | 80 (28.0,500.0) | 0.003* |
| Total dose of glucocorticoids[a], (IQR) | 1588 (320.0,3000.0) | 500 (186.0,1940.0) | 0.007* |
| Duration of glucocorticoid therapy, (IQR) | 7 (5.0,9.0) | 7 (6.0,10.0) | 0.109 |
| Concomitant medications, n (%) | | | |
| Antiplatelet agents | 15 (17.0) | 120 (13.8) | 0.398 |
| Anticoagulants | 3 (3.4) | 15 (1.7) | 0.483 |
| NSAIDs | 6 (6.8) | 21 (2.4) | 0.041* |
| Immunosuppressants | 30 (34.1) | 399 (45.8) | 0.036* |
| Anti-infective drugs | 19 (21.6) | 136 (15.6) | 0.145 |
| Selective serotonin reuptake inhibitors (SSRIs) | 2 (2.3) | 24 (2.8) | 1.000 |
| Blood-activating drugs | 18 (20.5) | 141 (16.2) | 0.303 |
| Bisphosphonates | 20 (22.7) | 109 (12.5) | 0.007* |
| Antiepileptic drugs | 1 (1.1) | 17 (1.9) | 0.902 |
| Lumbrokinase | 3 (3.4) | 15 (1.7) | 0.483 |
| Betahistine | 0 (0.0) | 16 (1.8) | 0.398 |

*PPIs* proton pump inhibitors, *BMI* body mass index, *GERD* gastroesophageal reflux disease, *PU* peptic ulcer, *INR* international normalized ratio, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SSRIs* selective serotonin reuptake inhibitors, *IQR* interquartile range

[a]Glucocorticoid dose measured by methylprednisolone

*$p<0.05$

**Table 2** Multiple logistic regression analysis of factors associated with more gastrointestinal complications

| Variable | Adjusted OR (95% CI) | *P* |
|---|---|---|
| Age (years) | 2.014 (1.096–3.703) | 0.024* |
| Gender | 1.195 (0.745–1.915) | 0.460 |
| History of GERD | 1.810 (1.009–3.250) | 0.047* |
| History of PU | 5.636 (1.505–21.102) | 0.010* |
| Liver dysfunction | 1.762 (0.951–3.262) | 0.072 |
| Number of concomitant diseases | 1.032 (0.987–1.080) | 0.170 |
| Glucocorticoid dosage form | 0.916 (0.446–1.883) | 0.812 |
| Maximum dose of Glucocorticoids[a] | 1.003 (1.001–1.004) | 0.001* |
| Total dose of glucocorticoids[a] | 1.000 (0.999-1.000) | 0.043 |
| Length of hospital stay (days) | 1.046 (0.999–1.096) | 0.057 |
| Antiplatelet agents | 1.110 (0.550–2.241) | 0.771 |
| Immunosuppressants | 0.605 (0.361–1.015) | 0.057 |
| Bisphosphonates | 1.621 (0.897–2.928) | 0.110 |
| Anticoagulants | 1.052 (0.260–4.256) | 0.943 |
| NSAIDs | 2.788 (1.023–7.597) | 0.045* |

*PPIs* proton pump inhibitors, *GERD* gastroesophageal reflux disease, *PU* peptic ulcer, *NSAIDs* nonsteroidal anti-inflammatory drugs, *OR* odds ratio

[a]Glucocorticoid dose measured by methylprednisolone

*$p < 0.05$

complications during glucocorticoid therapy. From a pharmacological perspective, antiplatelet agents such as aspirin mainly cause gastrointestinal mucosal injury by inhibiting COX-1-mediated prostaglandin synthesis and local stimulation, leading to gastrointestinal complications such as mucosal erosion, ulcers and bleeding [23]. $P2Y_{12}$ receptor antagonists can inhibit the release of platelet-derived growth factor and platelet-derived vascular endothelial growth factor, impede the formation of new blood vessels, delay mucosal repair and may exacerbate gastrointestinal mucosal injury [24]. Randomized, double-blind controlled animal trials showed a significant increase in gastrointestinal bleeding scores in dogs given aspirin and prednisone compared to prednisone alone, but no difference in clopidogrel combined with prednisone [25, 26]. Similar population-based studies have not been reported yet. The mechanisms by which different anticoagulants cause gastrointestinal injury or bleeding are also different. Compared with warfarin, novel oral anticoagulants are associated with more gastrointestinal bleeding [27, 28]. A nested case-control study showed

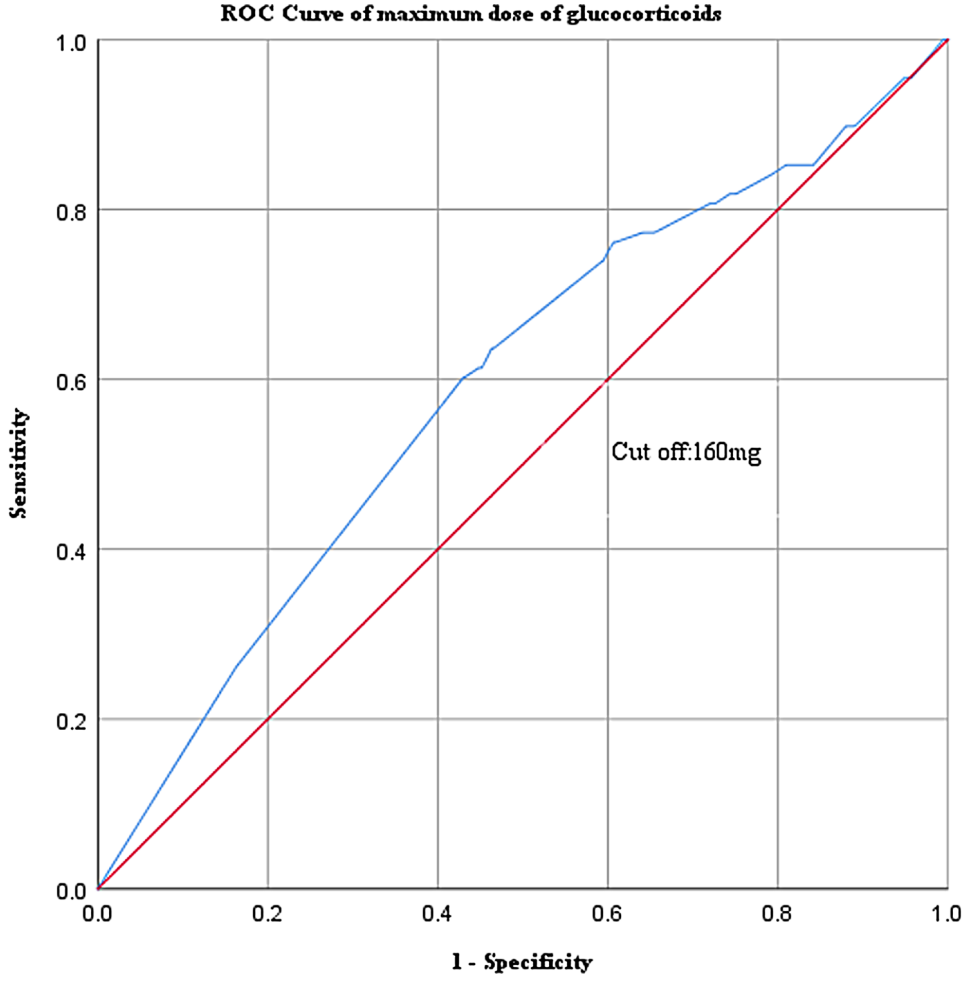


**Fig. 1** ROC curve of maximum dose of glucocorticoids

**Table 3** ROC curve of maximum dose of glucocorticoids

| Variable | AUC (95% CI) | *P* | Sensitivity (%) | Specificity (%) | Cut off (mg) | Youden Index |
|---|---|---|---|---|---|---|
| Maximum dose of Glucocorticoids[a] | 0.593 (0.530–0.657) | 0.004 | 63.6 | 53.7 | 160 | 0.173 |

*AUC* the area under the ROC curve

[a]Glucocorticoid dose measured by methylprednisolone

that non-vitamin K oral anticoagulants combined with glucocorticoids increased the risk of gastrointestinal bleeding compared with non-vitamin K oral anticoagulants alone [29]. The following points may explain our different results. Firstly, we did not subdivide the types of antiplatelet agents or anticoagulants, as well as their usage, dosage and dosage form. Secondly, the sample size of those using antiplatelet agents or anticoagulants was relatively small. Thirdly, the outcome of our study was gastrointestinal complications, including both severe complications such as gastrointestinal bleeding, and mild complications such as heartburn, which is different from previous studies. Finally, as mentioned above, there may be inappropriate situations in the clinical use of acid suppressants due to the lack of guidelines for clinical rational prophylactic use of acid suppressants.

Our study showed that maximum dose of glucocorticoids was associated with more gastrointestinal complications. Further, ROC curve analysis revealed that when the maximum dose of glucocorticoids was greater than 160 mg, gastrointestinal complications was more likely to occur, which is another highlight of this study. Currently, there is still controversy regarding the impact of the dose of glucocorticoids on gastrointestinal complications. A system review based on 71 controlled clinical trials showed that the incidence of gastrointestinal ulcers was directly related to the dose of glucocorticoids [30]. Hernández-Díaz S and Rodríguez LA also found that high-dose glucocorticoids were more likely to cause gastrointestinal complications than low-dose ones [20]. A retrospective study found that high-dose glucocorticoids (higher than 20 mg, measured by prednisolone), but not low-dose, was an independent risk factor for rebleeding after endoscopic hemostasis for peptic ulcer bleeding [31]. However, two Cochrane meta-analyses showed there was no relationship between different doses of glucocorticoids and gastrointestinal bleeding [12, 13]. Differences in the study population, sample size, and the definition of gastrointestinal complications may affect the outcomes. It should be noted that the ROC curve AUC value (0.593) suggests modest predictive accuracy for these risk factors. The single center and limited sample size may be partially responsible for this result. Multiple logistic regression analysis showed that the total dose of glucocorticoids was associated with fewer gastrointestinal complications, but the OR value was close to 1, suggesting a very weak correlation. Therefore, we interpreted this result cautiously, and further research is needed to clarify it in the future. In our study, the duration of glucocorticoid therapy was not identified as a risk factor for increased gastrointestinal complications. A population-based case-crossover study showed that short-term (7–28 days) use of glucocorticoids was significantly associated with gastrointestinal ulcer bleeding [32]. Conn HO found that the incidence of gastrointestinal ulcers in glucocorticoid treatment > 30 days was significantly higher than that in treatment ≤ 30 days [33], but in his subsequent research, he found that in four different courses of < 1 month, 1–3 months, 4–12 months, > 12 months, the risk of gastrointestinal ulcers in the glucocorticoid treatment group and the control group was similar [11]. In our study, the median duration of glucocorticoid use in both the positive group and the negative group was quite short, only 7 days. Moreover, our study focused on internal medicine inpatients, which might be the reason why our results differed from those of other studies. Based on our results, when the total dose of glucocorticoids is fixed, maintenance treatment with the lowest effective dose seems to be safer in terms of gastrointestinal complications than short-term high-dose shock treatment.

To our surprise, there was no difference in the incidence of gastrointestinal complications regardless of which type of acid suppressant was used. On the one hand, due to the lack of guidelines to guide physicians on rational prophylactic use of acid suppressants, there are some cases of irrational prophylactic use of acid suppressants in clinics [19]. On the other hand, although proton pump inhibitors have a stronger effect on acid inhibition than $H_2$ receptor antagonists from a pharmacological perspective [34], there is currently a lack of evidence to compare different acid suppressants on the prevention of glucocorticoid-related gastrointestinal complications in internal medicine patients. In the guiding principles for the clinical application of glucocorticoids in China (2023 edition), it is only recommended to use gastric mucosal protective agents or acid suppressants when using high-dose glucocorticoids [35].

Our study has the following limitations. First, this was a retrospective, single-center study. However, we believe our result is representative based on our hospital scale. Second, the discovery of gastrointestinal complications is based on the records in the hospital's electronic medical record system, so there may be cases where the physician does not record them, but we believe this is rare based on

the physician's professionalism. Third, due to the variety of the diseases treated with glucocorticoids that cannot be classified and analyzed, we did not consider the factor of the diseases treated with glucocorticoids, which may itself be a significant risk factor for gastrointestinal complications. In order to minimize bias due to the diseases treated with glucocorticoids as much as possible, we have restricted the inclusion of patients, excluding those with underlying gastrointestinal diseases. Fourth, our study mainly included internal medicine departments such as neurology, rheumatology, and nephrology that use glucocorticoids more frequently, which may not be suitable for surgery and other departments. Finally, we did not assess the incidence of gastrointestinal complications after discharge, which we will continue to explore in the future.

## Conclusion

Our research reveals that age ≥ 65 years, history of GERD, history of PU, maximum dose of glucocorticoids, and NSAIDs are associated with more gastrointestinal complications during glucocorticoid therapy in internal medicine inpatients. Therefore, in view of these conditions, physicians, pharmacists and nurses may benefit from increased monitoring to prevent the occurrence of gastrointestinal complications.

### Author contributions

PPL, GYL and JWW designed the study. PPL, GYL and QLY collected the study data. PPL and KC performed the statistical analysis. PPL wrote the main manuscript. PPL and JWW revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and approved by the Beijing Tongren Hospital Ethics Committee (NO. TREC2024-KY065). Patients were exempt from informed consent.

### Consent for publication

Not applicable.

### Statement

All methods were carried out in accordance with relevant guidelines and regulations.

### Competing interests

The authors declare no competing interests.

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