Original Research Article

A case-control study on the risk of UGIB in patients taking NSAIDs in Mashhad, Iran

ABSTRACT

Introduction: Gastrointestinal bleeding is one of the most common causes of patient admissions at emergency wards. Despite considering NSAIDs, aspirin and Helicobacter pylori as the leading causes, mortality from GI bleeding is still high. So pattern of NSAID consumption and related conditions may help in preventative behavior.

Methods: This case-control study was conducted on 300 patients. Patients were divided into two groups: with and without gastrointestinal bleeding. Patient's information was extracted using their hospital records and the data eventually was statistically analyzed.

Results: The results of this study showed no significant difference between the two groups in terms of age, gender, marital status, distribution of weight, and education level (P>0.05).The frequency of NSAIDs use was significantly higher in patients with gastrointestinal bleeding (P = 0.016) with the most NSAID use as Aspirin(32.66%). The prevalence of smoking, using drugs and alcohol consumption was significantly higher in the study group (P <0.05).

Conclusion: A history of consuming NSAIDs increases the risk of GI bleeding. The frequency of cigarette, drug, and alcohol consumption in the case study group was significantly higher than that of the control group.

Keywords: Gastrointestinal bleeding, Nonsteroidal anti-inflammatory drugs, aspirin

Introduction:

Gastrointestinal (GI) bleeding is the most common reason for acute hospitalization of patients in gastroenterology wards(1). Different studies have evaluated the implemented cost of GI bleeding on both patients and the health care system, in addition to its impact on mortality and morbidity rates.These studies have concluded that GI bleeding, in fact, incurs higher patient and system costs and raises mortality and morbidity

rates(2, 3).Several factors have been propounded as etiologic factors behind GI bleeding, among which H.pylori, Non-Steroid Anti-Inflammatory Drugs (NSAIDs), and aspirin have been deemed as the most significant, especially in upper GI bleeding(4). Different epidemiologic studies have suggested that a combination of several different NSAIDs,or a high dose of any one of these drugs, can increase the risk of GI bleeding up to seven and nine fold respectively(5). These results emphasizenot only the importance of NSAIDs but alsotheir sensible usage. Recently, due to the increased prevalence of arthritic diseases and osteoarthritis, the use of NSAIDs has grown. The prescription of multiple NSAIDs to patients by different physicians in various fields has led tothe increased simultaneousconsumption of several NSAIDs. This raises the risk of GI bleeding and other NSAID side effects, especially among the older population.

In a study on Northeast of Iran Zeinali et al showed that about 20% of all prescriptions included at least one NSAID drugs in comparison with 12.1% in USA (6).In consideration of the rising usage of NSAIDs, it is imperative to study the correlation between the use of NSAIDs and upper GI bleeding. Although this relationship is now mentioned in textbooks, there has not yet been any relatedstudy conducted in Mashhad, Iranto explorethe high prevalence of NSAID consumption, this

despite numerous warnings aboutthe side effects following the unbridled use of these drugs. Furthermore, since accurate statistics about NSAID side effects are critical for future prophylaxis recommendations, it appears beneficial to conducta study on the correlation between upper GI bleeding and NSAID consumption (6).

Method and Materials:

The present case control study was conducted in several steps. These steps were performed simultaneously and by only one researcher in order to reduceany possible risk of error. The steps were designed as a checklist for utilizationin the present study, by which samples were chosen, data extracted and collected, and statistical calculations made.

Checklist Design:

The checklist was designed as two forms. The first form was intended for patients hospitalized at the emergency ward of Qaem Hospital due to upper GI bleeding and who had undergone diagnostic and therapeutic measures.This checklist included identification code, gender, age, weight, educational level, occupation, marital status, and residence. Also listed was any history of digestive diseases, GI bleeding, non-digestive diseases,smoking, alcohol consumption, drug abuse,and medications. In addition, the following information was provided:endoscopy results,

primary hemoglobin, primary platelet, primary PT, INR, and the possible need for a blood transfusion.

The second form was designed for patients hospitalized at Khatam-al_Anbia Hospital of Ophthalmology with a chief complaint and reason for hospitalization that was unrelated to GI bleeding (control group). This checklist included the following: identification code, gender, age, weight, educational level, occupation, marital status, and residence.Also listed was any history ofdigestive diseases, GI bleeding, non-digestive diseases, smoking, alcohol consumption, drug abuse. All the patients were asked for NSAID use (continuously or based on need).

Selection of Cases and Control Samples:

The method of sampling in the currentstudy was simple nonrandomized. Two groups were studied. The first group (case group) consisted of patients hospitalized for gastrointestinal bleeding according to clinical manifestation and/or diagnostic endoscopic examinationat the emergency ward of Qaem Hospital. The second group (control group) was made up of patients hospitalized at Khatam-al_Anbia Hospital of Ophthalmology due to a chief complaint and reason for hospitalization unrelated to gastrointestinal bleeding.

Data Extraction and Collection:

In this step of the present study, required data were collected and registered onto the appropriate checklist. The case study group data were collected from the patients' hospital files. The control group data was obtained by conducting direct interviews and also by accessing the patients' previous files. To accomplish this, at Khatam-al Anbia Hospital, the researcher first explained the study and its purpose to the patients and obtained their consent before reviewing files or interviewing.

Statistical Calculations:

First, the data were input into SPSS ver.16 software. The mean and Interquartile rangewere utilized to describe the quantitative data indexes. Frequency and frequency percentage served as the indexes for explaining qualitative data. In order to compare qualitative variables in the case study and control groups, the Chi-squared test or exact fisher test were utilized. If the data had a normal distribution, the independent t-test compared the quantitative data from the two groups; otherwise, its nonparametric equivalent (Mann-Whiteny) performed this comparison. The confidence interval and the level of significance were deemed as 95% and 0.05% respectively.

Results:

The present work studied a total number of 300 patients aged above 35. Patients were dividedinto two groups: 1)those suffering from upper GI

bleeding (case study) and 2) those without GI bleeding (control group). The mean age of the patients was 45.81±21.28 years (in the range of 40 to 87 years).

The patient demographics of the two groups are compared in Table 1 and 2. Statistical tests showed no significant difference between the two groups in terms of age, gender, marital status, distribution of weight, and education level (P>0.05). In regard to residence, the results indicated a significant difference between that of the case study and the control group(p=0.002).

Table 1: Comparison of Mean and Interquartile Range of demographic variables

Variable Group		**Case Study Group (with GI bleeding) (IQR) Median (150n=)**	**Control Group (without GI bleeding) Median (IQR)(150n=)**	**P-value**
*§*Age		(65-47) 59	(65-45) 54	0.116
Gender	male	88 (58.6%)	84 (56%)	0.726
	female	62 (41.3%)	66 (44%)	
Weight (kg)	< 50	25 (16.6%)	31 (20.7%)	0.615
	50 -70	81 (54%)	74 (49.3%)	
	>70	44 (29.4%)	45 (30%)	

123 *§:* Mann-Whitney statistical test

124

125 **Table 2:** Comparison of Qualitative demographic Variable Frequency

Variable Group		Case Study Group Frequency& Frequency Percentage	Control Group Frequency & Frequency Percentage	*P-value
Marital Status	single	45 (28.7%)	40 (26.7%)	0.796
	married	105 (71.3%)	110 (73.3%)	
Educational Level	illiterate	12 (8%)	12 (8%)	0.107
	only reading & writing	36 (24%)	20 (13.3%)	
	up to elementary school	32 (21.3%)	36 (24%)	
	high school diploma	53 (35.3%)	51 (34%)	
	associate degree	13 (8.7%)	25 (16.7%)	
	Bachelor degree&higher	4 (2.7%)	6 (4%)	

Residence	city	94 (62.7%)	124 (82.7%)	0.002
	village	56 (37.3%)	26 (17.3%)	

*: Chi-Square statistical test

Figure-1compares the two groups' frequency of cigarette and alcohol consumption and drug abuse.

Figure 1: Comparison of the Consumption of Cigarettes, Drugs, and Alcohol

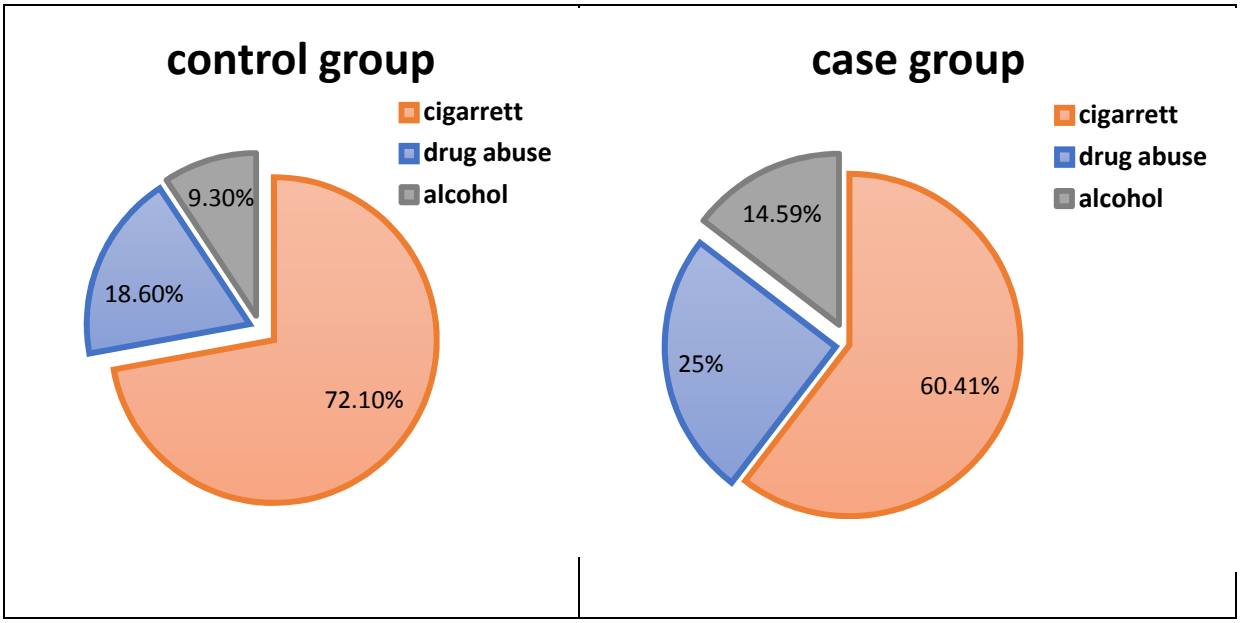


Table 3 provides the frequency of NSAID consumption inthe two groups. As indicated, NSAID consumption in patients with GI bleeding was significantly higher compared to those not suffering from this condition (p=0.022).Furthermore, the comparison among the types of NSAID consumed by patients of the two groups showed a significant difference

in regard to type(p<0.001). The most commonlyused NSAID in the case study group was aspirin 80 mg per day, either as an ongoing consumption or at least for a past period of time.In fact, except for sixpatients, all subjects in the control group using NSAIDs were taking aspirin. After aspirin, the most common NSAID in the case study group was ibuprofen. However, in the control group, there was greater consumption of ibuprofen followed by aspirin and diclofenac respectively. In both study groups, other NSAIDs, such as indomethacin and naproxen,were less commonly used.

Table 3: Comparison of the frequency of NSAID consumption and its subtypes

		control	case	p-value
NSAID Consumption	yes	35 (23.4%)	55 (36%)	0.022**
	no	115 (76.6%)	95 (64%)	
Type of NSAID	Aspirin	13 (8.7%)	49 (32.66%)	*<0.001
	Ibuprofen	14 (9.3%)	5 (3.34%)	
	Diclofenac	7 (4.7%)	0 (0%)	
	Indomethacin	0 (0%)	1 (0.7%)	

	Naproxen	1 (0.7%)	0 (0%)
	others	0(0%)	0(0)%)

*: Chi-Square statistical test
**: Fisher Exact statistical test

The frequency of other medications taken by patients is presented in figure 2. A significant difference inthetype of drugs taken is evident between the two groups (p=0.035). In the case study group, the most common were corticosteroids (15.3%), Warfarin (14%), and Plavix (13.3%). However, in the control group, the most prevalent drugs were SSRIs[1] (10.6%), Plavix (4%), and corticosteroids (4%). In both groups, the consumption of Heparin was less than any other of the drugs.

[1] Specific Serotonin Receptor Inhibitors

Figure 2: Comparison of the Frequency of Other Drug Consumption

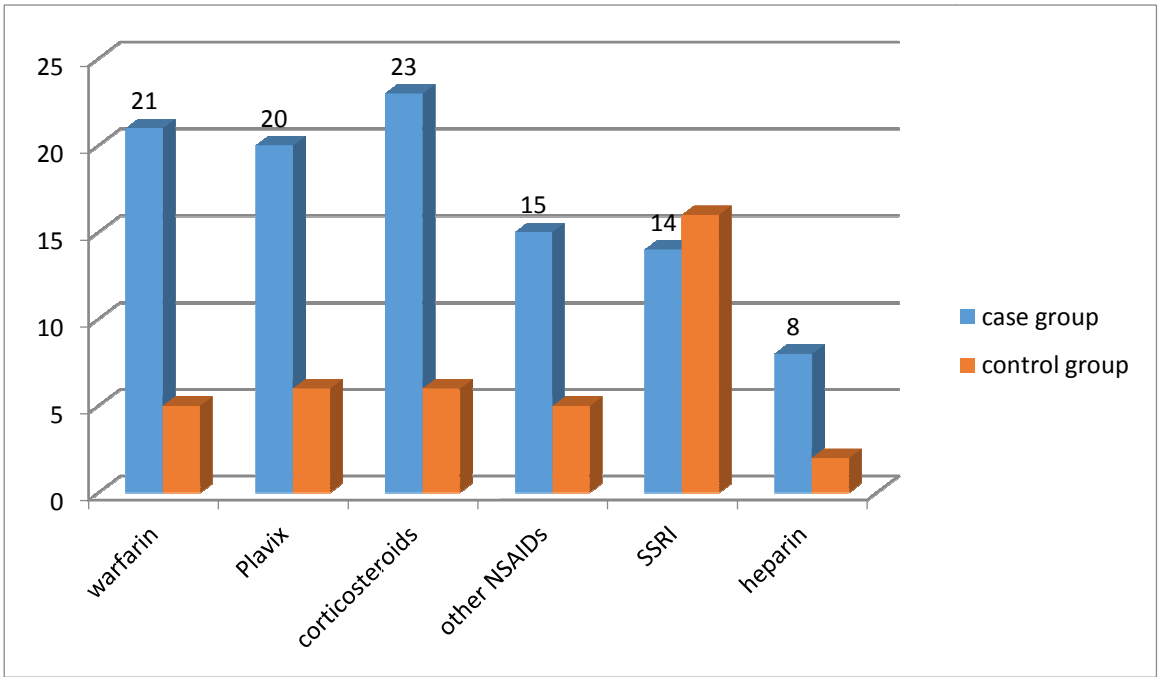
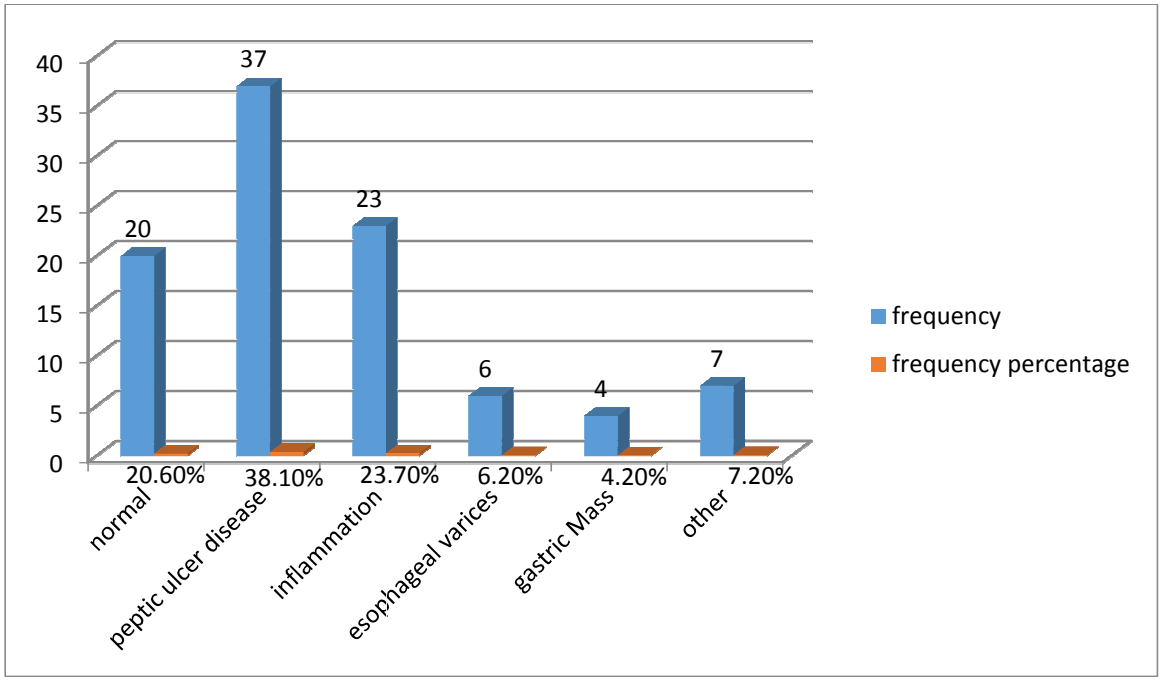


Figure 3 provides patient endoscopy results. As seen, out of 150 patients with GI bleeding, 97 had undergone anendoscopy while the other 53 patients had not because ofvarious reasons, such as patient unwillingness or medical conditions. The most common pathologic finding following endoscopy was ulcers (38.1%), while a mass was the least commonly observed pathology (4.2%). In 20.6 % of the patients, the endoscopy results were normal.

Figure 3: Frequency of Endoscopic Findings in Patients with Upper GI Bleeding



The logistic regression test was employed to assess the extent of the studied variables' prediction effect on GI bleeding. As seen, in a comparison between the case study and the control group, cigarette use, alcohol consumption, and, finally, a history of NSAID consumption can lead to an increased risk of upper GI bleeding incidence with an OR of 1.81, 4.241, and 1.838 respectively.

From these variables, drug abuse, gender, and age did not have any effect onraising or lowering the risk of upper GI bleeding incidence. Table 4 lists the results for each studied variable.

Table 4: Evaluating the Predictive Effect of Variables under Study on the Establishment of GI Bleeding

Variable	CI 95% for OR (lower-upper)	Odds Ratio(OR)	P-value**

Age	0.942-1.004	0.965	0.175
Gender*	0.634-1.664	1.029	0.92
Cigarette	1.071-3.151	1.838	0.024
Drug abuse	0.941-5.459	2.72	0.06
Alcohol Use	1.415-13.29	4.241	0.02
NSAID Use	1.076-3.067	1.812	0.021

*risk of males compared to females

Logistic regression test**

Discussion

In the present study, statistical tests revealed that there was no significant difference between the two groups in regard to gender frequency, age, marital status, weight group frequency, and educational level. The study revealed that patients in the case group more frequently lived in urban areas, a finding that had barelybeen investigatedpreviously.For instance, the Button et al. study conducted in2010 showed that ahigher number of patients with upper GI bleeding lived in urban areas(7). Likewise, in the 2012 study by Whiskey et al., the prevalence of variceal and non-variceal upper GI bleeding was reported to be greateramong the urban population(8).Yet, these two above mentioned studies did not further explore the possible reasons behind their findings. In any case, it seems that the stronger presence of

risk factors for upper GI bleeding in urban areas has led to a greater number of patients in these areas.

The present research suggest that the prevalence of cigarette smoking, alcohol consumption, and drug abuse was significantly higher in the case study group when compared to the control group. These findings have also been reported in other similar studies. For example, the Crooks et al. 2013 study found thatcigarette use (whether active or passive) and alcohol consumption increased the risk of upper GI bleeding.The study also reported that the risk of bleeding incidence grew following a rise in alcohol consumption (9). Another US study in 2016 revealed that drinking more than 30 gr of alcohol per day or more than 5 times per week was deemed to be an independent risk factor increasing the incidence of GI bleeding. The study also suggested that cigarette use is not related to GI bleeding (10). Alcohol related mucosal damage can be caused by a rise in the production of oxygen-free radical species, a fall in the level of prostaglandins, and also the release of mucosal leukotrienes(11, 12).

As for cigarette smoking and upper GI bleeding, different results have been reported by various studies. This factor requires larger population size for evaluation. Similar to the current work, some researchers have propounded cigarettes as a risk factor for GI bleeding, while some others have not(10, 13, 14).

In the present study's comparison of NSAID consumption between the case study and control group, there was a significant difference in the type of NSAID used. Except for six patients, all of the case study patients had used NSAIDs,of which aspirin was the most commonly consumed followed by ibuprofen.Patients in the control group, however, had comparatively higher ibuprofen consumption,with aspirin being the second most common drug consumed. Aspirin was used at a dose of 80 mg per day in both groups and unfortunately the dose of NSAIDs were not available which was the limitation of the present study. After aspirin, the control group used Diclofenac at a higher rate than that of the case study patients. Both groups had a lower consumption of other types of NSAIDs, such as indomethacin and naproxen. In conclusion, the present study generally associates aspirin consumption with greater GI bleeding. This finding has also been noted in several previous studies. For example, the 2012 review article by Castellsague et al. concluded that Ibuprofen, the most commonly used drug in the control group, is the safest NSAID from the aspect of upper GI bleeding(15). Also, in their 2012 study, De Abajo et al. investigated the relation of NSAIDs and other drug consumption with upper GI bleeding. It was revealed that aspirin poses a higher risk of upper GI disease than the consumption of other drugs(16).These results are in accordance with the present work's findings.

Another result of the present study addresses the frequency of other drug consumption by the patients of the two groups. In both the case study and the control group, a large spectrum of drugs were taken by patients, out of which the current work attempted to discern which are closer related to upper GI bleeding. The findings show a significant difference in the amount of drugs consumed by the two groups. Among the cases study subjects, the most common were corticosteroids (15.3%), Warfarin (14%), and Clopidogrel(13.3%). However, the most prevalent medications for control group subjects were SSRIs (10.6%), clopidogrel (4%), and corticosteroids (4%). In general, the drug consumption in the case study group was significantly higher. In both groups, Heparin was the least used. Previous studies have also investigated the correlation between the use of various drugs and upper GI bleeding. For instance, the 2014 review by Narum et al. finally concluded that corticosteroids use is associated with an increased risk of upper GI bleeding and gastric ulcers(17). As mentioned in the present study, using these drugs in the case study group was more than in the control group. Regarding Warfarin and Clopidogrel and their relation to upper GI bleeding, previously conducted studies concur with thecurrentpaper's findings. In 2013, De Abajo et al. concluded that Clopidogrel consumption can heighten the risk of upper GI bleeding in comparison to healthy individuals(16). The subjects in the present

paper's case study group also took more multiple NSAIDs than did the control group. Previous studies have stressed that the consumption of multiple NSAIDs increase the risk of upper GI bleeding. After exploring the risk factor of upper GI bleeding in their 2010 research, Scarpiganto and Hunt concluded that taking multiple NSAIDs or anticoagulant drugs, such as Warfarin and corticosteroids, all can increase the risk of gastric bleedings,a finding with which the present paper is in accordance(18).

The current paper's other results deal with patient endoscopies. 97 patients with GI bleeding underwent endoscopy while the other 53 patients did not for reasons such as medical issues orunwillingness to consent to the procedure. The most common pathologic finding was ulcers. In the 2011Hearnshaw et al. study of 6,750 patients with upper GI bleeding, the most commonly observed pathology was ulcers (19),findings similar to those of the current research.

Conclusion:

The results of the present study indicate that greater consumption of NSAIDs in patients with upper GI bleeding is significantly higher in comparison with patients not suffering from this condition. Aspirin and Ibuprofen were the most two common drugs used. Moreover,a history of consuming NSAIDs increases a patient's risk of acquiring GI bleeding. Concurrent consumption of corticosteroids, Warfarin and clopidogrel increased the risk of GI bleeding in case group. Likewise, the frequency

of cigarette, drug, and alcohol consumption in the case study group was significantly higher than that of the control group,thus signifying that variables, such as alcohol and cigarettes, increase the risk of GI bleeding in patients.

We suggest to consider the factors that increase the risk of upper GI bleeding in patients with NSAID use and prescribe prophylaxis to high risk patients.

Ethical Approval Disclaimer:

This research was approved at ethical committee of Mashhad University of Medical Sciences with ethical code:922817

Consent Disclaimer:

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

References:

1. Williams JG, Roberts SE, Ali MF, Cheung WY, Cohen DR, Demery G, et al. Gastroenterology services in the UK. The burden of disease, and the organisation and delivery of services for gastrointestinal and liver disorders: a review of the evidence. Gut. 2007;56 Suppl 1:1-113.
2. Peery AF, Crockett SD, Barritt AS, Dellon ES, Eluri S, Gangarosa LM, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology. 2015;149(7):1731-41.e3.
3. Abougergi MS, Travis AC, Saltzman JR. The in-hospital mortality rate for upper GI hemorrhage has decreased over 2 decades in the United States: a nationwide analysis. Gastrointestinal endoscopy. 2015;81(4):882-8.e1.
4. Yeomans ND. The ulcer sleuths: The search for the cause of peptic ulcers. Journal of gastroenterology and hepatology. 2011;26 Suppl 1:35-41.
5. Grosser T, Smyth E, FitzGerald G. Anti-inflammatory, Antipyretic, and Analgesic Agents. In: Brunton L, Chabner B, Knollmann B, editors. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill 2011. p. 959-1005.

6. Zeinali M, Tabeshpour J, Maziar SV, Taherzadeh Z, Zirak MR, Sent D, et al. Prescription pattern analysis of nonsteroidal anti-inflammatory drugs in the northeastern iranian population. Journal of Research in Pharmacy Practice. 2017;6(4):206.
7. Button LA, Roberts SE, Evans PA, Goldacre MJ, Akbari A, Dsilva R, et al. Hospitalized incidence and case fatality for upper gastrointestinal bleeding from 1999 to 2007: a record linkage study. Alimentary pharmacology & therapeutics. 2011;33(1):64-76.
8. Wysocki JD, Srivastav S, Winstead NS. A nationwide analysis of risk factors for mortality and time to endoscopy in upper gastrointestinal haemorrhage. Alimentary pharmacology & therapeutics. 2012;36(1):30-6.
9. Crooks CJ, West J, Card TR. Comorbidities affect risk of nonvariceal upper gastrointestinal bleeding. Gastroenterology. 2013;144(7):1384-93, 93.e1-2; quiz e18-9.
10. Strate LL, Singh P, Boylan MR, Piawah S, Cao Y, Chan AT. A Prospective Study of Alcohol Consumption and Smoking and the Risk of Major Gastrointestinal Bleeding in Men. PloS one. 2016;11(11):e0165278.
11. Tarnawski A, Hollander D, Stachura J, Klimczyk B, Mach T, Bogdal J. Alcohol injury to the normal human gastric mucosa: endoscopic, histologic and functional assessment. Clinical and investigative medicine Medecine clinique et experimentale. 1987;10(3):259-63.
12. Oates PJ, Hakkinen JP. Studies on the mechanism of ethanol-induced gastric damage in rats. Gastroenterology. 1988;94(1):10-21.
13. Udd M, Miettinen P, Palmu A, Heikkinen M, Janatuinen E, Pasanen P, et al. Analysis of the risk factors and their combinations in acute gastroduodenal ulcer bleeding: a case-control study. Scandinavian journal of gastroenterology. 2007;42(12):1395-403.
14. Yamada A, Sugimoto T, Kondo S, Ohta M, Watabe H, Maeda S, et al. Assessment of the risk factors for colonic diverticular hemorrhage. Diseases of the colon and rectum. 2008;51(1):116-20.
15. Castellsague J, Riera-Guardia N, Calingaert B, Varas-Lorenzo C, Fourrier-Reglat A, Nicotra F, et al. Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). Drug safety. 2012;35(12):1127-46.
16. de Abajo FJ, Gil MJ, Bryant V, Timoner J, Oliva B, Garcia-Rodriguez LA. Upper gastrointestinal bleeding associated with NSAIDs, other drugs and interactions: a nested case-control study in a new general practice database. European journal of clinical pharmacology. 2013;69(3):691-701.
17. Narum S, Westergren T, Klemp M. Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ open. 2014;4(5):e004587.
18. Scarpignato C, Hunt RH. Nonsteroidal antiinflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis, and prevention. Gastroenterology clinics of North America. 2010;39(3):433-64.
19. Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut. 2011;60(10):1327-35.