

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

30 rates(2, 3).Several factors have been propounded as etiologic factors
31 behind GI bleeding, among which H.pylori, Non-Steroid Anti-
32 Inflammatory Drugs (NSAIDs), and aspirin have been deemed as the
33 most significant, especially in upper GI bleeding(4). Different
34 epidemiologic studies have suggested that a combination of several
35 different NSAIDs,or a high dose of any one of these drugs, can increase
36 the risk of GI bleeding up to seven and nine fold respectively(5). These
37 results emphasize not only the importance of NSAIDs but also their
38 sensible usage. Recently, due to the increased prevalence of arthritic
39 diseases and osteoarthritis, the use of NSAIDs has grown. The
40 prescription of multiple NSAIDs to patients by different physicians in
41 various fields has led to the increased simultaneous consumption of
42 several NSAIDs. This raises the risk of GI bleeding and other NSAID
43 side effects, especially among the older population.

44 In a study on Northeast of Iran Zeinali et al showed that about 20%
45 of all prescriptions included at least one NSAID drugs in comparison with
46 12.1% in USA (6).In consideration of the rising usage of NSAIDs, it is
47 imperative to study the correlation between the use of NSAIDs and
48 upper GI bleeding. Although this relationship is now mentioned in
49 textbooks, there has not yet been any related study conducted in
50 Mashhad, Iran to explore the high prevalence of NSAID consumption, this

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

56 **Method and Materials:**

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

62 Checklist Design:

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

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

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

81 Selection of Cases and Control Samples:

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

90 Data Extraction and Collection:

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

98 Statistical Calculations:

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

109 **Results:**

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

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

115 The patient demographicsofthe two groups are compared in **Table 1 and**
 116 **2**. Statistical tests showed no significant difference between the two
 117 groups in terms of age, gender, marital status, distribution of weight, and
 118 education level ($P > 0.05$). In regard to residence, the resultsindicated a
 119 significant difference between that of the case study and the control
 120 group($p = 0.002$).

121 **Table 1:** Comparisonof Mean and Interquartile Range

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%)	

122 §: Mann-Whitney statistical test

Table 2: Comparison of Qualitative 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%)	
	city	94 (62.7%)	124 (82.7%)	

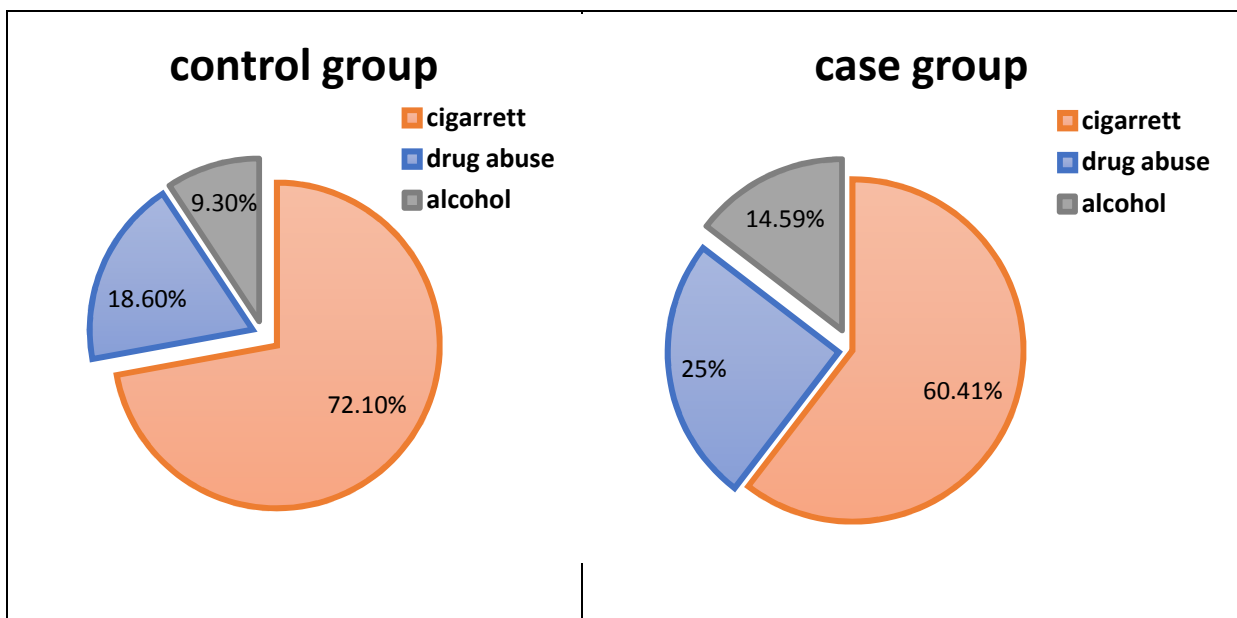
Residence	village	56 (37.3%)	26 (17.3%)	
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126 *: Chi-Square statistical test

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

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



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132 **Table 3** provides the frequency of NSAID consumption in the two groups.

133 As indicated, NSAID consumption in patients with GI bleeding was
 134 significantly higher compared to those not suffering from this condition
 135 ($p=0.016$). Furthermore, the comparison among the types of NSAID
 136 consumed by patients of the two groups showed a significant difference
 137 in regard to type ($p<0.001$). The most commonly used NSAID in the case

138 study group was aspirin, either as an ongoing consumption or at least for
 139 a past period of time. In fact, except for six patients, all subjects in the
 140 control group using NSAIDs were taking aspirin. After aspirin, the most
 141 common NSAID in the case study group was ibuprofen. However, in the
 142 control group, there was greater consumption of ibuprofen followed by
 143 aspirin and diclofenac respectively. In both study groups, other NSAIDs,
 144 such as indomethacin and naproxen, were less commonly used.

145 **Table 3:** Comparison of the frequency of NSAID consumption and its
 146 subtypes
 147

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 (3.9%)	5 (34.3%)	
	Diclofenac	7 (7.4%)	0 (0%)	
	Indomethacin	0 (0%)	1 (7.0%)	
	Naproxen	1 (7.0%)	0 (0%)	
	yes			

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 149 *: Chi-Square statistical test

150 **: Fisher Exact statistical test

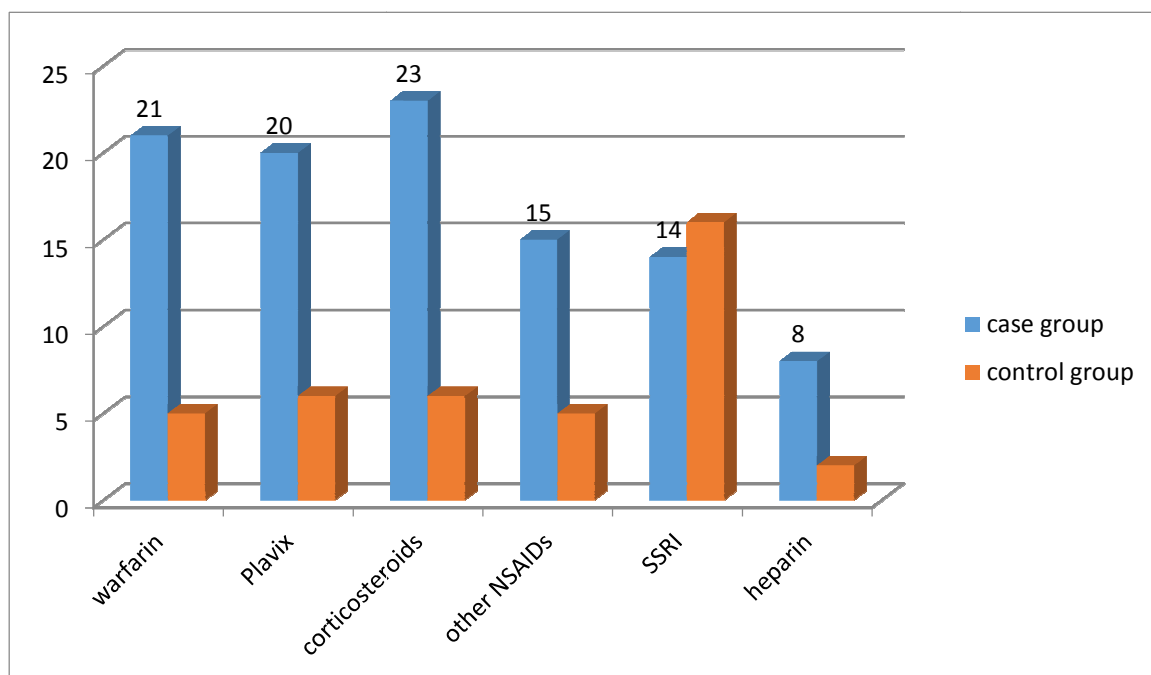
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152 The frequency of other medications taken by patients is presented in
153 figure 2. A significant difference in the type of drugs taken is evident
154 between the two groups ($p=0.035$). In the case study group, the most
155 common were corticosteroids (15.3%), Warfarin (14%), and Plavix
156 (13.3%). However, in the control group, the most prevalent drugs were
157 SSRIs (10.6%), Plavix (4%), and corticosteroids (4%). In both groups,
158 the consumption of Heparin was less than any other of the drugs.

159 **Figure 2: Comparison of the Frequency of Other Drug Consumption**

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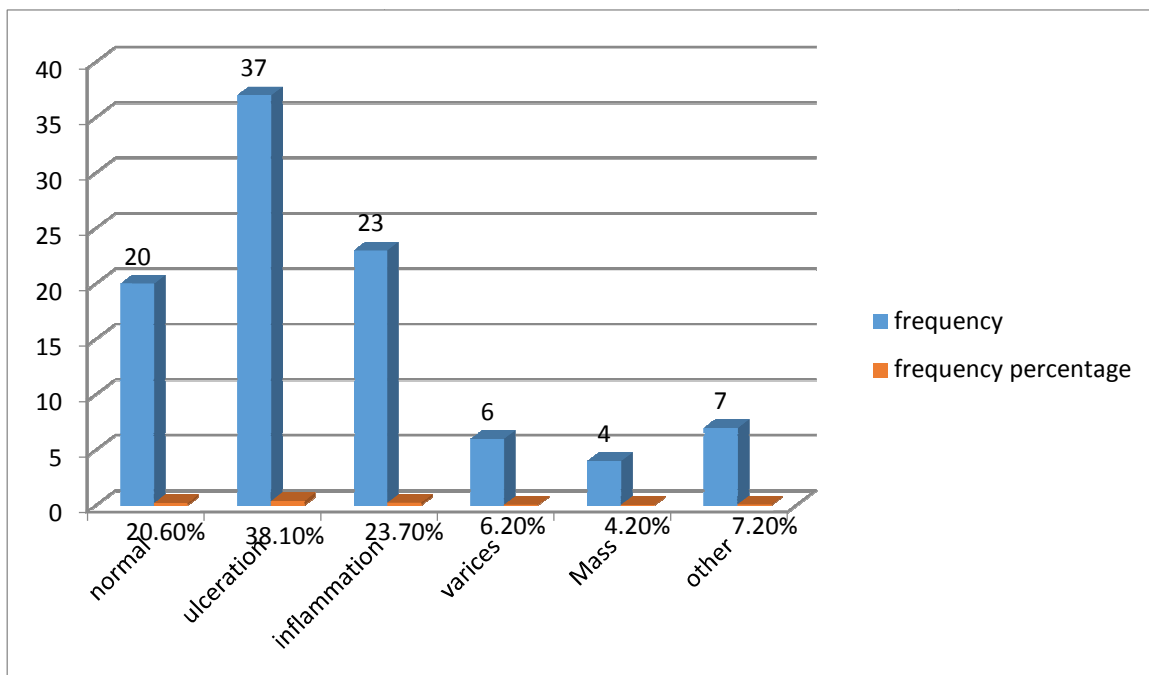
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165 Figure 3 provides patient endoscopy results. As seen, out of 150
166 patients with GI bleeding, 97 had undergone an endoscopy while the
167 other 53 patients had not because of various reasons, such as patient
168 unwillingness or medical conditions.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

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



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177 The logistic regression test was employed to assess the extent of the
178 studied variables' prediction effect on GI bleeding. As seen, in a
179 comparison between the case study and the control group, cigarette

180 use, alcohol consumption, and, finally, a history of NSAID consumption
181 can lead to an increased risk of upper GI bleeding incidence with an OR
182 of 1.81, 4.241, and 1.838 respectively.

183 From these variables, drug abuse, gender, and age did not have any
184 effect on raising or lowering the risk of upper GI bleeding incidence.

185 **Table 4** lists the results for each studied variable.

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

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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 Use	1.071-3.151	1.838	0.024
Drug Abuse	0.941-5.459	2.72	0.06
Alcohol Use	1.415-13.29	4.421	0.02
	1.076-3.067	1.812	0.021

*risk of males compared to females

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Logistic regression test**

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Discussion

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192 In the present study, statistical tests revealed that there was no
193 significant difference between the two groups in regard to gender
194 frequency, age, marital status, weight group frequency, and educational

195 level. The study revealed that patients in the case group more frequently
196 lived in urban areas, a finding that had barely been
197 investigated previously. For instance, the Button et al. study conducted
198 in 2010 showed that a higher number of patients with upper GI bleeding
199 lived in urban areas (7). Likewise, in the 2012 study by Whiskey et al.,
200 the prevalence of variceal and non-variceal upper GI bleeding was
201 reported to be greater among the urban population (8). Yet, these two
202 above mentioned studies did not further explore the possible reasons
203 behind their findings. In any case, it seems that the stronger presence of
204 risk factors for upper GI bleeding in urban areas has led to a greater
205 number of patients in these areas.

206 The present research suggest that the prevalence of cigarette smoking,
207 alcohol consumption, and drug abuse was significantly higher in the
208 case study group when compared to the control group. These findings
209 have also been reported in other similar studies. For example, the
210 Crooks et al. 2013 study found that cigarette use (whether active or
211 passive) and alcohol consumption increased the risk of upper GI
212 bleeding. The study also reported that the risk of bleeding incidence grew
213 following a rise in alcohol consumption (9). Another US study in 2016
214 revealed that drinking more than 30 gr of alcohol per day or more than 5
215 times per week was deemed to be an independent risk factor increasing
216 the incidence of GI bleeding. The study also suggested that cigarette

217 use is not related to GI bleeding (10). Alcohol related mucosal damage
218 can be caused by a rise in the production of oxygen-free radical species,
219 a fall in the level of prostaglandins, and also the release of mucosal
220 leukotrienes(11, 12).

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

226 In the present study's comparison of NSAID consumption between the
227 case study and control group, there was a significant difference in the
228 type of NSAID used. Except for six patients, all of the case study
229 patients had used NSAIDs,of which aspirin was the most commonly
230 consumed followed by ibuprofen.Patients in the control group, however,
231 had comparatively higher ibuprofen consumption,with aspirin being the
232 second most common drug consumed. Aspirin was used at a dose of 80
233 mg per day in both groups and unfortunately the dose of NSAIDs were
234 not available which was the limitation of the present study. After aspirin,
235 the control group used Diclofenac at a higher rate than that of the case
236 study patients. Both groups had a lower consumption of other types of
237 NSAIDs, such as indomethacin and naproxen. In conclusion, the present
238 study generally associates aspirin consumption with greater GI bleeding.

239 This finding has also been noted in several previous studies. For
240 example, the 2012 review article by Castellsague et al. concluded that
241 Ibuprofen, the most commonly used drug in the control group, is the
242 safest NSAID from the aspect of upper GI bleeding(15). Also, in their
243 2012 study, De Abajo et al. investigated the relation of NSAIDs and
244 other drug consumption with upper GI bleeding. It was revealed that
245 aspirin poses a higher risk of upper GI disease than the consumption of
246 other drugs(16).These results are in accordance with the present work's
247 findings.

248 Another result of the present study addresses the frequency of other
249 drug consumption by the patients of the two groups. In both the case
250 study and the control group, a large spectrum of drugs were taken by
251 patients, out of which the current work attempted to discern which are
252 closer related to upper GI bleeding. The findings show a significant
253 difference in the amount of drugs consumed by the two groups. Among
254 the cases study subjects, the most common were corticosteroids
255 (15.3%), Warfarin (14%), and Clopidogrel(13.3%). However, the most
256 prevalent medications for control group subjects were SSRIs (10.6%),
257 clopidogrel (4%), and corticosteroids (4%). In general, the drug
258 consumption in the case study group was significantly higher. In both
259 groups, Heparin was the least used. Previous studies have also
260 investigated the correlation between the use of various drugs and upper

261 GI bleeding. For instance, the 2014 review by Narum et al. finally
262 concluded that corticosteroids use is associated with an increased risk of
263 upper GI bleeding and gastric ulcers(17). As mentioned in the present
264 study, using these drugs in the case study group was more than in the
265 control group. Regarding Warfarin and Clopidogrel and their relation to
266 upper GI bleeding, previously conducted studies concur with
267 thecurrentpaper's findings. In 2013, De Abajo et al. concluded that
268 Clopidogrel consumption can heighten the risk of upper GI bleeding in
269 comparison to healthy individuals(16). The subjects in the present
270 paper's case study group also took more multiple NSAIDs than did the
271 control group. Previous studies have stressed that the consumption of
272 multiple NSAIDs increase the risk of upper GI bleeding. After exploring
273 the risk factor of upper GI bleeding in their 2010 research, Scarpiganto
274 and Hunt concluded that taking multiple NSAIDs or anticoagulant drugs,
275 such as Warfarin and corticosteroids, all can increase the risk of gastric
276 bleedings,a finding with which the present paper is in accordance(18).

277 The current paper's other results deal with patient endoscopies. 97
278 patients with GI bleeding underwent endoscopy while the other 53
279 patients did not for reasons such as medical issues orunwillingness to
280 consent to the procedure. The most common pathologic finding was
281 ulcers. In the 2011Hearnshaw et al. study of 6,750 patients with upper

282 GI bleeding, the most commonly observed pathology was ulcers
283 (19), findings similar to those of the current research.

284 **Conclusion:**

285 The results of the present study indicate that greater consumption of
286 NSAIDs in patients with upper GI bleeding is significantly higher in
287 comparison with patients not suffering from this condition. Aspirin and
288 Ibuprofen were the most two common drugs used. Moreover, a history of
289 consuming NSAIDs increases a patient's risk of acquiring GI bleeding.

290 Concurrent consumption of corticosteroids, Warfarin and clopidogrel
291 increased the risk of GI bleeding in case group. Likewise, the frequency
292 of cigarette, drug, and alcohol consumption in the case study group was
293 significantly higher than that of the control group, thus signifying that
294 variables, such as alcohol and cigarettes, increase the risk of GI
295 bleeding in patients.

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

299 **Ethical Approval Disclaimer:**

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

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303 **Consent Disclaimer:**

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

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