

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 Frequency and frequency percentage served as the indexes for
102 explaining qualitative data. In order to compare qualitative variables in
103 the case study and control groups, the Chi-squared test or exact fisher
104 test were utilized. If the data had a normal distribution, the independent
105 t-test compared the quantitative data from the two groups; otherwise, its
106 nonparametric equivalent (Mann-Whiteny) performed this comparison.
107 The confidence interval and the level of significance were deemed as
108 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 demographics of the two groups are compared in **Table 1**
 116 **and 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 results indicated a
 119 significant difference between that of the case study and the control
 120 group ($p = 0.002$).

121 **Table 1:** Comparison of Mean and Interquartile Range of **demographic**
 122 **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%)	

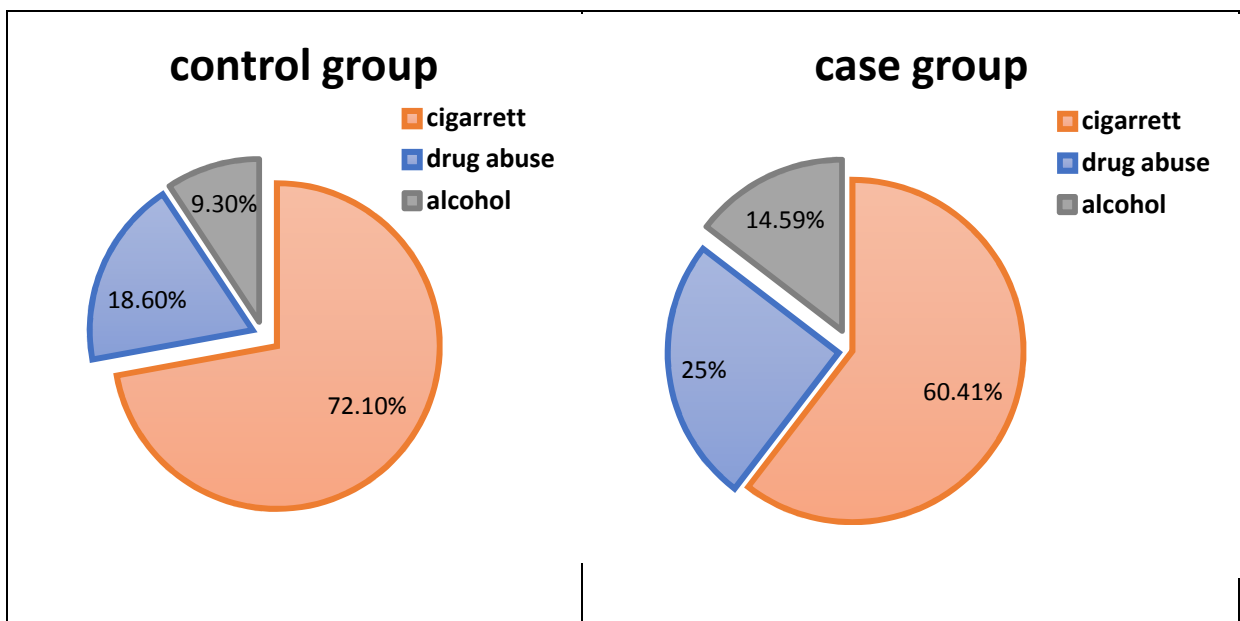
Residence	city	94 (62.7%)	124 (82.7%)	0.002
	village	56 (37.3%)	26 (17.3%)	

126

127 *: Chi-Square statistical test

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

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



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

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

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

147 **Table 3:** Comparison of the frequency of NSAID consumption and its
 148 subtypes
 149

		case	control	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 (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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151 *: Chi-Square statistical test

152 **: Fisher Exact statistical test

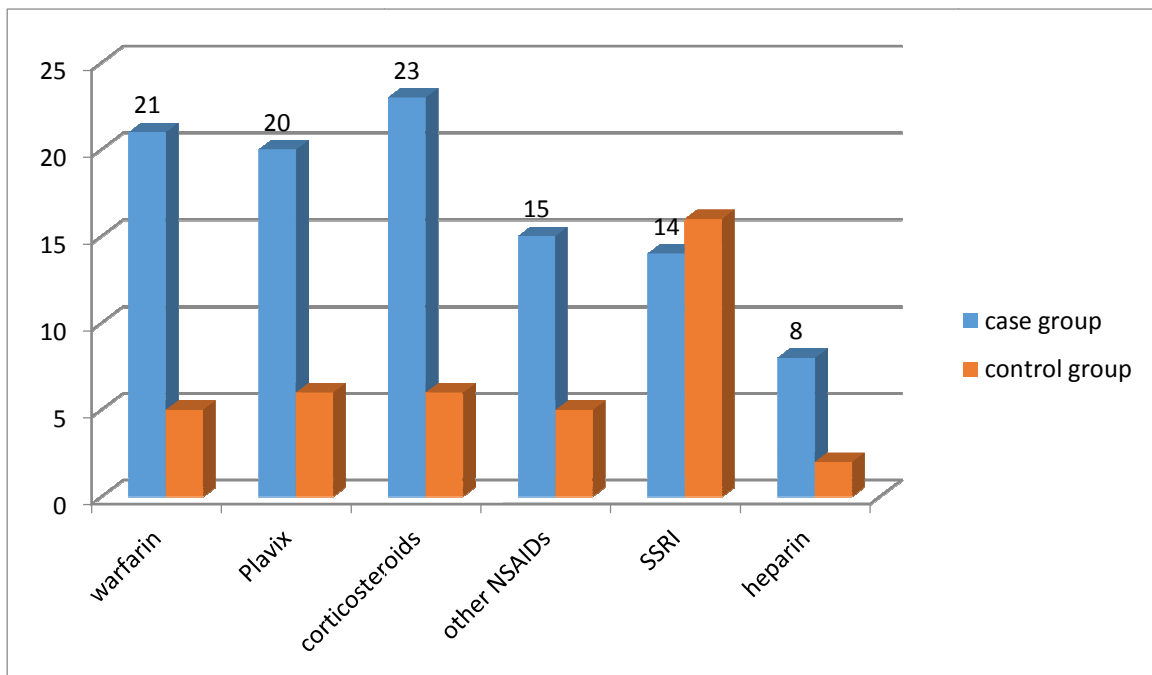
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154 The frequency of other medications taken by patients is presented in
 155 figure 2. A significant difference in the type of drugs taken is evident
 156 between the two groups (p=0.035). In the case study group, the most
 157 common were corticosteroids (15.3%), Warfarin (14%), and Plavix
 158 (13.3%). However, in the control group, the most prevalent drugs were
 159 SSRIs¹ (10.6%), Plavix (4%), and corticosteroids (4%). In both groups,
 160 the consumption of Heparin was less than any other of the drugs.

¹ Specific Serotonin Receptor Inhibitors

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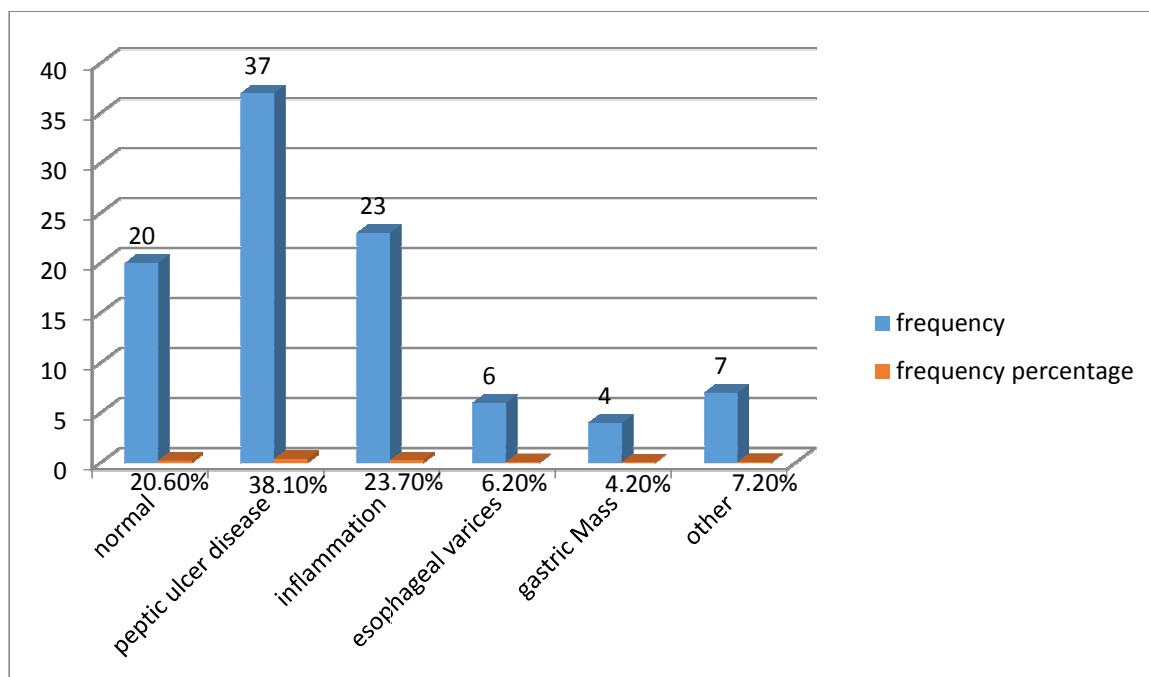
Figure 2: Comparison of the Frequency of Other Drug Consumption



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

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



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

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

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

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

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

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Logistic regression test**

192

Discussion

193

194 In the present study, statistical tests revealed that there was no
195 significant difference between the two groups in regard to gender
196 frequency, age, marital status, weight group frequency, and educational
197 level. The study revealed that patients in the case group more frequently
198 lived in urban areas, a finding that had barely been
199 investigated previously. For instance, the Button et al. study conducted
200 in 2010 showed that a higher number of patients with upper GI bleeding
201 lived in urban areas (7). Likewise, in the 2012 study by Whiskey et al.,
202 the prevalence of variceal and non-variceal upper GI bleeding was
203 reported to be greater among the urban population (8). Yet, these two
204 above mentioned studies did not further explore the possible reasons
205 behind their findings. In any case, it seems that the stronger presence of

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

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

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

228 In the present study's comparison of NSAID consumption between the
229 case study and control group, there was a significant difference in the
230 type of NSAID used. Except for six patients, all of the case study
231 patients had used NSAIDs, of which aspirin was the most commonly
232 consumed followed by ibuprofen. Patients in the control group, however,
233 had comparatively higher ibuprofen consumption, with aspirin being the
234 second most common drug consumed. Aspirin was used at a dose of 80
235 mg per day in both groups and unfortunately the dose of NSAIDs were
236 not available which was the limitation of the present study. After aspirin,
237 the control group used Diclofenac at a higher rate than that of the case
238 study patients. Both groups had a lower consumption of other types of
239 NSAIDs, such as indomethacin and naproxen. In conclusion, the present
240 study generally associates aspirin consumption with greater GI bleeding.
241 This finding has also been noted in several previous studies. For
242 example, the 2012 review article by Castellsague et al. concluded that
243 ibuprofen, the most commonly used drug in the control group, is the
244 safest NSAID from the aspect of upper GI bleeding(15). Also, in their
245 2012 study, De Abajo et al. investigated the relation of NSAIDs and
246 other drug consumption with upper GI bleeding. It was revealed that
247 aspirin poses a higher risk of upper GI disease than the consumption of
248 other drugs(16). These results are in accordance with the present work's
249 findings.

250 Another result of the present study addresses the frequency of other
251 drug consumption by the patients of the two groups. In both the case
252 study and the control group, a large spectrum of drugs were taken by
253 patients, out of which the current work attempted to discern which are
254 closer related to upper GI bleeding. The findings show a significant
255 difference in the amount of drugs consumed by the two groups. Among
256 the cases study subjects, the most common were corticosteroids
257 (15.3%), Warfarin (14%), and Clopidogrel(13.3%). However, the most
258 prevalent medications for control group subjects were SSRIs (10.6%),
259 clopidogrel (4%), and corticosteroids (4%). In general, the drug
260 consumption in the case study group was significantly higher. In both
261 groups, Heparin was the least used. Previous studies have also
262 investigated the correlation between the use of various drugs and upper
263 GI bleeding. For instance, the 2014 review by Narum et al. finally
264 concluded that corticosteroids use is associated with an increased risk of
265 upper GI bleeding and gastric ulcers(17). As mentioned in the present
266 study, using these drugs in the case study group was more than in the
267 control group. Regarding Warfarin and Clopidogrel and their relation to
268 upper GI bleeding, previously conducted studies concur with
269 thecurrentpaper's findings. In 2013, De Abajo et al. concluded that
270 Clopidogrel consumption can heighten the risk of upper GI bleeding in
271 comparison to healthy individuals(16). The subjects in the present

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

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

286 **Conclusion:**

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

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

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

301 **Ethical Approval Disclaimer:**

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

304

305 **Consent Disclaimer:**

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

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