



Clinical Outcomes of Non-variceal Upper Gastrointestinal Bleeding and its Relation to Aspirin and Anticoagulants

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Abstract

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BACKGROUND: Non-variceal upper gastrointestinal bleeding (NVUGIB) is a life-threatening emergency that requires an urgent management. Antiplatelet (e.g., aspirin) and anticoagulant drugs are widely chronically used in various cardiac and coronary artery diseases. These drugs increase the risk of NVUGIB as they may cause ulceration of the upper gastrointestinal (GI) mucosa directly or may cause bleeding or rebleeding. The management of NVUGIB is complicated as the risk between GI bleeding episodes and cardiovascular attacks needs to be well managed.

AIM: The aim of this study is to determine the impact of antiplatelets (aspirin) and anticoagulants use on the morbidity, mortality, and clinical outcomes in patients presented with non-variceal GI bleeding.

PATIENTS AND METHODS: A total of 105 patients presented with melena and/or hematemesis and diagnosed by upper GI endoscopy were enrolled in a prospective cohort study. Patients were sub-grouped according to their use of antiplatelets, anticoagulants, or none (controls). Patients were excluded if they had portal hypertension or nonsteroidal anti-inflammatory drugs (NSAIDs) use and divided into five groups: Group I – patients who had not taken anticoagulants and antiplatelet; Group II – patients on heparin, warfarin, and LMWH only; Group III – patients on aspirin only; Group IV – patients on clopidogrel and ticlopidine with or without aspirin; and Group V – patients on combined anticoagulants and antiplatelet. All patients were subjected to clinical, laboratory (complete blood count, liver function tests, renal function tests, prothrombin time, and partial thromboplastin time), and endoscopic investigations. Clinical details were reported including admission, blood transfusion, rebleeding, and mortality.

RESULTS: Full medical history revealed that 43 patients were diabetic, 45 patients were cardiac, and 67 patients were hypertensive. Regarding the history of analgesic drug intake, 38 patients used NSAIDs and 29 of them used non-selective NSAIDs and 8 patients used selective NSAIDs. There were non-significant differences among the studied groups with NVUGIB regarding sex, hematemesis only presentation, melena only presentation, liver function tests, and endoscopic findings. On the other hand, there were statistically significant differences between the studied groups with NVUGIB regarding increasing age, NSAIDs use whatever selective or non-selective, decrease level of HB, WBCs, serum albumin, bleeding profile, kidney function tests, clinical presentation in the form of hematemesis and melena, need for blood transfusion, history of associated diseases, especially being cardiac patients, rebleeding after 6 and 12 months, and mortality.

CONCLUSION: Aspirin intake may be associated with less favorable clinical outcomes in patients with NVUGIB, while combined anticoagulants and antiplatelets seem to be associated with the worse outcomes.

Introduction

Non-variceal upper gastrointestinal bleeding (NVUGIB) is a critical clinical condition that requires an urgent management [1], [2]. It remains a clinically important due to the increase in the proportion of elderly population, use of nonsteroidal anti-inflammatory drugs (NSAIDs) [3].

The incidence of upper gastrointestinal bleeding (UGIB) is 2-fold greater in males than in females, in all age groups; however, the death rate is similar in both sexes [4].

The initial laboratory tests include a blood count, international normalized ratio, partial thromboplastin time, electrolytes, creatinine, and blood typing in case transfusion is necessary [5].

Management of NVUGIB (Figure 1) [6]

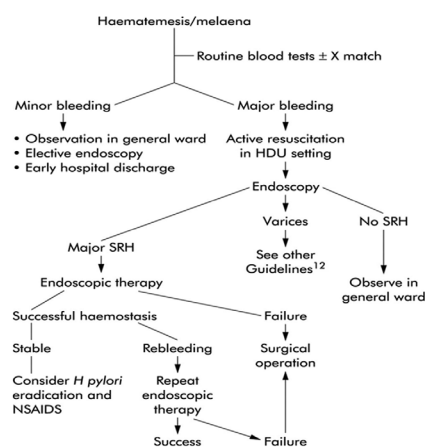


Figure 1: Algorithm for the management of acute gastrointestinal hemorrhage. HDU: High dependency unit, NSAIDs: Nonsteroidal anti-inflammatory drugs, SRH: Stigmata of recent hemorrhage (NICE Clinical Guideline, 2015) [6]

Resuscitation

The first priority is to correct fluid losses and restore blood pressure. Thus, intravenous (IV) access is a must [7].

Blood transfusion

The timing and amount of blood transfusions are valuable. It is accepted that patients with a hemoglobin level of ≤ 7 g/dL should receive a transfusion, whereas it is rarely indicated in patients with a hemoglobin level of ≥ 10 g/dL [8].

Pre-endoscopic care

Recent consensus suggests that nasogastric lavage is not helpful for diagnosis, prognosis [9], [10]. Pre-endoscopic use of proton-pump inhibitors (PPIs) is highly important [11].

Endoscopy

It is the principle diagnostic tool in UGIB and hemostatic therapy. While diagnostic endoscopy in clinically stable patients without relevant comorbidity is safe, complications may occur [9].

There are various endoscopic techniques: injection with epinephrine; clip application; thermocoagulation, argon plasma coagulation or injection with alcohol; fibrin; or thrombin glue [12].

The combination of epinephrine injection with one of the above-mentioned therapies significantly reduces rebleeding, need for surgery, and mortality [13].

Second look endoscopy has to be outweighed with potential risks [8]. On the contrary, another cost-effectiveness study [14] found endoscopy is more effective and less expensive.

The highest risk for rebleeding in patients treated with a combination of endoscopic and PPI therapy is within the first 72 h after the initial bleeding episode [15,16].

Medical therapy after endoscopy

IV bolus followed by infusion of high-dose PPI reduces recurrent bleeding, need for repeated endoscopy, surgery, and blood transfusion [17], [18]. However, in patients with lower risk standard, PPI therapy (e.g., oral PPI once daily) is enough [19].

Other considerations

Surgery offers a better chance to secure hemostasis [20]. Angiographic embolization should be considered as an alternative to surgery [21].

Helicobacter pylori

The successful eradication of an associated *H. pylori* infection lowers the risk of reappearance of an ulcer in the 1st year after hemorrhage to $<5\%$ [22].

It is well known that *H. pylori* testing might reveal false-negative results in the setting of an acute bleeding episode [23].

NSAID use

In patients with NSAID-associated bleeding ulcers, the need for NSAIDs should be carefully assessed. In patients who must continue on NSAIDs, a cyclooxygenase-2 selective NSAID plus PPI offers the best available upper gastrointestinal (GI) protection [24], [25], [26].

NVUGIB and antiplatelet and antithrombotic

Nowadays, many patients receive chronic antithrombotic therapy for various cardiac diseases (Figure 2) [27].

Nonvariceal bleeding (80%)	Portal hypertensive bleeding (20%)
Peptic ulcer disease (30-50)	Gastroesophageal varices (>90)
Mallory-Weiss tears (15-20)	Hypertensive portal gastropathy (<5)
Gastritis or duodenitis (10-15)	Isolated gastric varices (rare)
Esophagitis (5-10)	
Arteriovenous malformations (5)	
Tumors (2)	
Others (5)	

Adapted from Ferguson CB, Mitchell RM. Nonvariceal upper gastrointestinal bleeding: Standard and new treatment. *Gastroenterol Clin North Am* 2005;34:607-21. GI:Gastrointestinal

Figure 2: Causes of non-variceal upper gastrointestinal bleeding

The relative risk for UGIB increases up to 10% in patients treated with these therapies [28], [29], [30]. This complication puts affected patients into an acutely life-threatening situation because the mortality from UGIB ranges from 1% to 13% [31], [32], [33]. Therefore, therapy with ASA or clopidogrel in patients with cardiovascular risk factors should be restarted as soon as possible [8].

Anticoagulant therapy has historically consisted of heparins for the treatment of acute thrombosis and Vitamin K antagonists (VKA) for long-term treatment [34].

VKAs are indicated in patients with atrial fibrillation, thromboembolic venous disease, or a mechanical heart valve, while, recently, the novel oral anticoagulants, such as dabigatran, rivaroxaban, and apixaban, have been used in non-valvular atrial fibrillation and venous thromboembolism [35].

The indications of antiplatelet drugs use are in the management of thrombotic diseases include stroke, acute myocardial infarction, acute coronary syndrome, and angina [36].

Clopidogrel requires cytochrome P450 isoenzyme CYP2C19 to be converted to its active metabolite [37]. PPI and clopidogrel compete for the same cytochrome P450 isoenzyme [38], [39], [40], [41], [42], but other studies did not reveal an increase in cardiovascular events [42], [43].

In the current study, we aim to determine the impact of antiplatelets and anticoagulants on the morbidity, mortality, and clinical outcomes in patients presented with non-variceal GI bleeding.

Patients and Method

This study included 105 patients admitted in Ain Shams University Hospitals and Ahmed Maher Teaching Hospital whom presented with hematemesis and/or melena and diagnosed by upper GI endoscopy and divided into five groups according to the drug intake.

Group I: Patients who had not taken anticoagulants and antiplatelet.

Group II: Patients on anticoagulants (heparin, warfarin, and low-molecular-weight heparin [LMWH] only).

Group III: Patients on aspirin only.

Group IV: Patients on clopidogrel and ticlopidine with or without aspirin.

Group V: Patients on combined anticoagulants and antiplatelet.

Patients were excluded if there were other causes of UGIB (esophageal varices, portal hypertensive gastropathy, and gastric varices if the bleeding source was gastric cancer, if bleeding was associated with endoscopic procedures such as endoscopic mucosal resection, or if bleeding occurred in the lower GI tract).

Methods

A written consent was taken from all participants and oral explanation of the whole procedure, in which they will be involved in. A full history taking including age-associated medical conditions as diabetes mellitus, cardiac, hypertension, gender, history of drug intake (NSAID) and antithrombotic drugs, and history of any inserted cardiac prostheses that might be a causal relationship to the hemorrhage (coronary stents and platelet aggregation inhibitors, cardiac valvular prostheses and anticoagulants, and aortic prostheses with the risk of an aortointestinal fistula). Full examination and full laboratories were done, including complete blood count, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], serum albumin, and total and direct bilirubin), renal function tests (serum creatinine and blood urea), and prothrombin time and partial thromboplastin time. Upper endoscopy was done by expert (one expert in each hospital to decrease the bias) endoscopists using fiber-optic endoscopy after good sterilization. Initial assessment and resuscitation according to the amount of bleeding

(mild-moderate-massive), urgently or within 24–48 h (all patients were intravenously administered PPIs) was performed. Then, follow-up of our studied patients for rebleeding and mortality after 6 and 12 months after discharge from the hospital was done.

Statistical analysis

The collected data were tabulated and statistically analyzed using SPSS software (Statistical Package for the Social Sciences, version 16, SPSS Inc., Chicago, IL, USA). For quantitative data, the range, mean, and standard deviation were calculated. For qualitative data, the comparison between two groups was done by Chi-square test. For comparison between more than two means of data, F value of ANOVA test was calculated. Significance was at $p < 0.05$ for the results of the tests of significance.

Results

The study included 105 patients who were divided into five groups: Group I: Thirty patients (14 men [46.6%] and 16 women [53.3%]) who had not taken anticoagulants and antiplatelet, their mean age of 44.56 ± 7.63 . Group II: Twenty patients on heparin, warfarin, and LMWH only. They were 8 males (40%) and 12 females (60%) with their mean age of 45.72 ± 6.84 . Group III: Twenty-five patients on aspirin only who were 12 men (48%) and 13 women (52%) with a mean age of 53.50 ± 5.39 . Group IV: Fifteen patients (9 men [60%] and 6 men [40%]) on clopidogrel and ticlopidine with or without aspirin with a mean age of 55.19 ± 6.47 . Group V: Fifteen patients 10 male (66.6%) and 5 female (33.3%) who were on combined anticoagulants and antiplatelet with their mean age of 56.46 ± 7.35 (Table 1).

Table 1: Demographic findings of the studied patients

Group number	I (30)	II (20)	III (25)	IV (15)	V (15)	p value
Age (mean±SD)	44.56±7.63	45.72±6.84	53.50±5.39	55.19±6.47	56.46±7.35	0.000
Sex						
Male n (%)	14 (46.66%)	8 (40%)	12 (48%)	9 (60%)	10 (66.66%)	0.519
Female n (%)	16 (53.33%)	12 (60%)	13 (52%)	6 (40%)	5 (33.33%)	

SD: Standard deviation.

The study revealed that the sex among the studied groups was not statistically significant ($p = 0.519$). Age of the patients was statistically significant ($p = 0.000$), as shown in Table 1.

According to the laboratory profile of the studied patient groups, all were statistically significant except for ALT, AST, PLT, and total bilirubin which were statistically insignificant, as shown in Table 2.

Table 2: Biochemical results of our studied patients

Group (n)	I (30)	II (20)	III (25)	IV (15)	V (15)	p value
Hgb	10.83±1.32	8.43±1.54	9.67±1.46	8.26±0.74	8.65±1.63	0.000
WBCs	7.25±1.53	7.38±1.56	8.45±1.24	8.16±1.37	8.84±1.74	0.002
PLT	194.75±83.56	185.54±74.33	188.52±72.23	198.87±63.59	233.82±75.93	0.364
PT	12±0.09	12.14±0.35	12.10±0.21	12.25±0.47	12.34±0.36	0.004
PTT	30.41±2.65	33.65±3.71	32.26±4.42	35.25±3.86	35.55±4.52	0.000
INR	1.00±0.12	1.14±0.14	1.12±0.13	1.21±0.05	1.23±0.07	0.000
ALT	22.0±5.76	24.00±7.36	23.0±8.39	25.0±8.85	25.0±9.88	0.667
AST	30.0±6.67	33.0±6.38	32.0±7.27	33.0±6.53	34.0±7.46	0.342
T. bil.	0.84±0.23	1.21±0.67	0.86±0.43	0.89±0.75	1.02±0.13	0.068
D. bil.	0.17±0.06	0.33±0.18	0.18±0.15	0.27±0.23	0.48±0.25	0.000
S. alb.	4.23±0.44	3.84±0.35	4.12±0.51	3.86±0.52	3.92±0.65	0.027
S. cr.	0.8±0.10	0.9±0.14	0.87±0.12	0.92±0.11	0.98±0.12	0.000
Bl. urea	26.52±5.41	30.0±6.82	28.6±4.71	32.45±5.83	31.36±5.78	0.008

Hgb: Hemoglobin, WBCs: White blood cells, Plt: Platelet, PT: Prothrombin level, PTT: Partial thromboplastin time, INR: International normalized ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, T. bil.: Total bilirubin, D. bil.: Direct bilirubin, S. alb.: Serum albumin, S. cr.: Serum creatinine, Bl. urea: Blood urea.

Table 3: History of other associated diseases

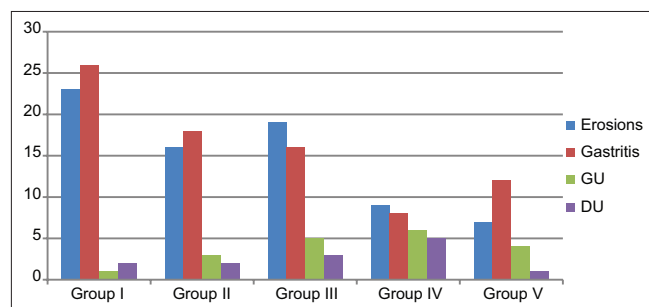
Group (n)	I (30)	II (20)	III (25)	IV (15)	V (15)	p value
DM	n 3	12	8	9	11	0.0276
	% 10	60	32	60	73.33	
HTN	n 6	16	17	13	15	0.037
	% 20	80	68	86.66	100	
Cardiac	n 3	4	8	15	15	0.000
	% 10	20	32	100	100	

DM: Diabetes mellitus, HTN: Hypertension.

Regarding the medical history of the patients, being diabetic or hypertensive or cardiac patient was statistically significant (Table 3).

Our studied patients were presented by NVUGIB, which was either in the form of hematemesis or melena or both together and was the statistically significant symptom ($p = 0.011$) as shown in Table 4.

Regarding the management of NVUGIB, UGI endoscopy had been performed and the results of the endoscopy are shown in Figure 3 and Table 5, which showed no statistical significance.

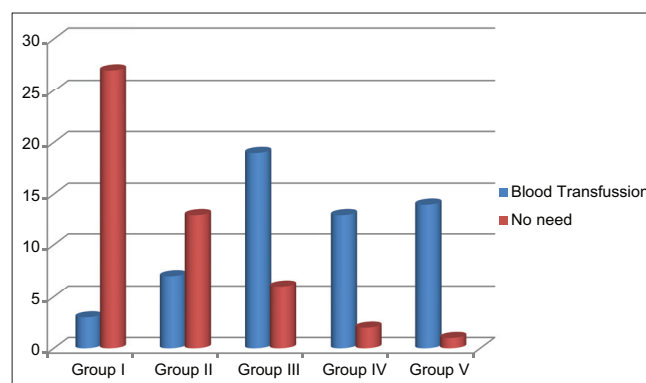
**Figure 3: Upper gastrointestinal endoscopic findings of our studied patients**

According to the management of UGIB, the need for blood transfusion was statistically significant when compared to the studied groups (no need to blood transfusion among the studied groups, $p = 0.001$

Table 4: Presenting bleeding symptoms

Group		I (30)	II (20)	III (25)	IV (15)	V (15)	χ^2	p value	χ^2	p value
Hematemesis	n	22	11	17	6	5	2.756	0.599	21.412	0.044
	%	73.33	55	68	40	33.33				
Melena	n	7	4	6	3	2	0.535	0.970		
	%	23.33	20	24	20	13.33				
Hematemesis and melena	n	1	5	2	6	8	13.03	0.011		
	%	3.33	25	8	40	53.33				

and the need to blood transfusion among the studied groups, $p = 0.003$), as shown in Table 6 and Figure 4.

**Figure 4: Need for blood transfusion in the management of our studied groups**

Then, we followed up our studied patients after 6 and 12 months after the first attack of NVUGIB and the discharge from the hospital. We followed up the rebleeding episodes and occurrence of mortality while using their medications, we noticed statistically significant values among the studied patients' groups, as illustrated in Table 7.

Discussion

GI bleeding is a serious problem, especially in the elderly and/or multimorbid patients. On the one hand, any anticoagulant and antiplatelet treatment should be discontinued to help stopping the acute bleeding. On the other hand, discontinuing this type of therapy can significantly increase the risk for cardiovascular or cerebrovascular complications due to the underlying disease [44].

Table 5: UGI endoscopic findings of our studied patients

Group number	I (30)	II (20)	III (25)	IV (15)	V (15)	χ^2	p value
Esophageal erosions	23	16	19	9	7	1.265	0.867
Gastritis	26	18	16	8	12	1.479	0.830
GU	1	3	5	6	4	6.952	0.138
DU	2	2	3	5	1	5.188	0.268

GU: Gastric ulcer, DU: Duodenal ulcer.

Monotherapy with antiplatelet agents or anticoagulants is associated with an increasing risk of UGIB [45]. Therefore, these medications in patients with UGIB should be discontinued for days, even weeks, and during and after bleeding episode [46].

Table 6: Need for blood transfusion in the management of NVUGIB

Group number	I (30)	II (20)	III (25)	IV (15)	V (15)	χ^2	p value	χ^2	p value
No need	27	13	6	2	1	17.419	0.001	46.835	0
%	90	65	24	13.33	6.66				
Need	3	7	19	13	14	15.906	0.003		
%	10	35	76	86.66	93.33				

NVUGIB: Non-variceal upper gastrointestinal bleeding.

Although the continuation of low-dose aspirin will increase the risk of rebleeding, it has been reported to be able to reduce all causes of mortality rate in a small sample of patients [47].

Table 7: Rebleeding and mortality after 6 months and 12 months

Group	I (30)	II (20)	III (25)	IV (15)	V (15)	p value
Rebleeding after 6 months						
Yes	1	3	4	5	5	0.046
No	29	17	21	10	10	
Mortality after 6 months						
Yes	0	1	0	1	3	0.032
No	30	19	25	14	12	
Rebleeding after 12 months						
Yes	1	3	2	4	6	0.046
No	29	17	22	11	9	
Mortality after 12 months						
Yes	0	1	0	1	4	0.032
No	30	19	25	14	11	

The current evidence on the effects of aspirin or anticoagulants on the clinical outcomes of patients with UGIB is controversial, as Sung *et al.* [47] have reported that aspirin decreases the mortality of patients while Ortiz *et al.* [48] have suggested that these drugs have no effects. Similarly, conflicting results on the effects of anticoagulants such as warfarin have been reported [49].

In this study, we aimed to determine the impact of antiplatelets (aspirin) and anticoagulants on the clinical outcomes of 105 patients (53 males and 52 females) aged 36–62 years. Forty-three were diabetic patients, 45 patients were cardiac, and 67 patients were hypertensive; 38 patients used NSAIDs and 29 of them used non-selective NSAIDs and 8 patients used selective NSAIDs who were hospitalized due to NVUGIB and followed up after 6 and 12 months for rebleeding attacks and mortality outcomes.

Statistically significant differences were found among the studied patients regarding age, history of associated disease (especially, cardiac), use of analgesics, clinical presentation of NVUGIB (both hematemesis and melena presenting together), HB, WBCs, bleeding profile, kidney function, serum albumin, need for blood transfusion, rebleeding after 6 and 12 months, and mortality, these results are in conformity with Hearnshaw *et al.* [50] and Modaber *et al.* [51].

Aging and comorbidities are known predictors of mortality and adverse clinical outcomes [46]. The mortality rate in elderly patients with NVUGIB is increased and the reason is unclear, it may be due to that elderly patients are more prone to have complex comorbidities and be more susceptible to physiological changes associated with acute bleeding episodes than younger patients. Therefore, more careful follow-up with intensive monitoring is needed in this population group following bleeding events.

In our study, we noticed that the patient group on aspirin only had a less mortality and rebleeding events were lower than in other patient groups. Similar protective effects of aspirin against UGIB-related deaths, besides, its cardiovascular benefits had been reported by Sung *et al.* [47] Wehbeh *et al.* [52], and Souk *et al.* [53] and also in a study that included both peptic and non-peptic ulcer patients [49].

On the contrary, Ahsberg *et al.* [54] have reported non-statistically significant association between aspirin use and mortality although those taking NSAIDs were included. In addition, recently, Luo *et al.* [55] found that the use of aspirin increases the risk of 1st time NVUGIB in general population after adjusting for age, gender, *H. pylori* infection, underlying comorbidities, and concomitant use of certain medications. Moreover, Taha *et al.* [56] noticed that a low-dose aspirin intake is associated with longer hospital stays and increased requirements of blood transfusion, but the study included those with variceal bleeding. However, Taha *et al.* [57] stated that in NVUGIB, the antiplatelet and anticoagulant activities are associated with older age and greater need for admission, transfusion, and rebleeding. The outcomes were more in users of anticoagulants even after adjustment for age, sex, and endoscopy, but with an insignificant effect on mortality.

Aspirin use was a predictor for short length of hospital stay in our study, which is consistent with a better overall outcome for those patients. This is different from what has been reported, which might be due to varied study designs [47] or the patients included in the study (both peptic ulcer disease [PUD] and non-PUD-related UGIB) [48].

On the other hand, Lanis *et al.* [49] observed that anticoagulants use to increase the requirements for blood transfusion and are associated with a longer hospital stay. Marmo *et al.* [4] showed that heparin, but not warfarin, increases mortality risk.

In our studied patients groups, we noticed that the most common cause of NVUGIB by endoscopy was gastritis followed by esophageal erosions then GU, but all with no statistically significant difference. This was not in agreement with Telaku *et al.* [58] who stated that the most common cause of NVUGIB was peptic ulcer.

Rebleeding is a predictor of mortality [50]. Rubin *et al.* [59] have suggested that the risk of rebleeding is not affected by antithrombotic. However, aspirin continuation seems to be associated with its increased risk of rebleeding.

Non-bleeding related causes accounted for most deaths, which is in accordance with Wong *et al.* [60] who concluded that the number of patients who died of acute renal failure in their study was high enough to be considered as an independent risk factor of death [60], while we considered as a part of multiorgan failure.

Malignancies were also responsible for the non-bleeding-related deaths which were observed during follow-up periods. That was in agreement with the results of Marmo *et al.* [61], while cardiovascular causes were high [61].

Conclusion

Our study suggested that aspirin intake may be associated with less favorable clinical outcomes in UGIB, while combined anticoagulants and antiplatelet seem to be associated with worse clinical outcomes.

Recommendations

- Study a larger scale of patients in many centers to decrease the bias.
- Patients on low-dose ASA should be tested for *H. pylori*.
- A discussion and ultimately a consensus among gastroenterologists and cardiologists with respect to the benefit-risk ratios are desirable.
- Adding a questionnaire to assess the quality of life before and after being admitted and endoscopically and medically managed during the episode of NVUGIB.

Limitations

Our study has some limitations and pitfalls:

- The small number of studied patients as we selected the patients with an emergency presentation (hematemesis and/or melena) and need to follow them up for a long time, which can be avoided if the study was retrospective.
- *H. pylori* analysis for the studied patients with NVUGIB which was not performed.
- Lack of endoscopic scoring system.

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