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ORIGINAL RESEARCH

Mortality Rate in Upper Gastrointestinal Bleeding Associated with Anti-Thrombotic Therapy Before and During Covid-19 Pandemic

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Introduction: During the last few years, a progressive higher proportion of patients have had upper gastrointestinal bleeding (UGIB) related to antithrombotic therapy. The introduction of direct oral anticoagulant (DOAC) and COVID-19 pandemic may change the incidence, mortality, and follow-up, especially in patients at high risk of bleeding.

Patients and Methods: We studied the use of anti-thrombotic therapy (AT) in patients with upper gastrointestinal bleeding for 5 years (January 2017–December 2021) including Covid-19 pandemic period (March 2020–December 2021). We analyzed mortality rate, rebleeding rate and need for transfusion in patients with AT therapy compared with those without AT therapy and risk factors for mortality, and also the incidence of gastrointestinal bleeding in patients admitted for COVID-19 infection.

Results: A total of 824 patients were admitted during Covid-19 pandemic period and 1631 before pandemic period; a total of 426 cases of bleeding were recorded in patients taking antithrombotic therapy and the frequency of antithrombotic therapy in patients with UGIB was higher in pandemic period (24.39% versus 13.8%). Unadjusted mortality was 12.21%, similar with patients with no antithrombotic treatment but age-adjusted mortality was 9.62% (28% lower). The rate of endoscopy was similar but fewer therapeutic procedures were required. Mean Hb level was 10% lower, and more than 60% of patients required blood transfusion.

Conclusion: Mortality was similar compared with patients with no antithrombotic therapy, fewer therapeutic endoscopies were performed and similar rebleeding rate and emergency surgery were noted. Hb level was 10% lower and a higher proportion of patients required blood transfusions. Mortality was higher in DOAC treatment group compared with VKA patients but with no statistical significance. The rate of upper gastrointestinal bleeding in Covid-19 positive hospitalized cases was 0.58%. The mortality risk in multivariate analysis was associated with GB score, with no endoscopy performed, with obscure and variceal bleeding and with LMWH versus VKA therapy.

Keywords: Covid-19, direct oral anticoagulant therapy, acenocoumarol, antithrombotic therapy, upper gastrointestinal bleeding

Introduction

The use of antithrombotic therapy has increased during the last decades because of higher incidence of cardiovascular diseases (with significant anticoagulation and antiplatelet recommendations), as well as the presence of other diseases with thromboembolic risk (the most recent being SARS-Cov2 infection).[1] The medication used includes both antiplatelet agents (aspirin, P2Y12 receptor inhibitors: thienopyridines – ticlopidine, clopidogrel, prasugrel and cyclopentryltriazolepyrimidines – ticagrelor), as well as anticoagulants such as heparin, vitamin K-antagonists and DOAC.[2,3] Long-term anticoagulant medication is recommended for patients with atrial fibrillation[1,4,5] and thromboembolic history, and the

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alternatives are direct oral anticoagulants (DOAC) or vitamin K antagonists (VKA), except for valvular prostheses. Direct oral anticoagulants (DOAC) include factor Xa inhibitors (rivaroxaban, apixaban and edoxaban) and thrombin inhibitors (dabigatran), have been approved for use since 2010 and have been shown to be effective in controlling thromboembolic events. Treatment with DOACs requires no laboratory follow-up and may have fewer drug interactions;[6–8] DOAC prescription increases substantially each year after 2010.[9,10] In patients with coronary heart disease, antiplatelet agents have a significant effect on reducing mortality and therefore, they need to be administered for as long as possible,[1,2] with an association P2Y12 inhibitor with aspirin for 1 year after an acute coronary event[1,11–13] and even two antiplatelet agents and an anticoagulant after ST-elevation myocardial infarction (STEMI).

In all patients receiving antiplatelet or anticoagulant agents, one of the major concerns is about gastrointestinal bleeding (GIB), particularly upper gastrointestinal bleeding (UGIB).[14,15] Most studies focused on cohort data with patients on antiplatelet or/and anticoagulant therapy and estimated the bleeding risk by following the patients on a certain amount of time. There were some differences between randomized controlled trials, where strict criteria may limit the study to restricted categories of subjects and therefore more severe cases or those with high risk of bleeding were excluded, and real-life studies which included all types of patients. The mortality rate is estimated in the short term (in hospital or at most 7 days after onset, and is due to thrombotic complications and hemorrhage) but also in the long term (at least 30 days – mainly due to thromboembolic complications). There are also multiple potential sites for bleeding in case of antithrombotic therapy; at higher risk are intracranial hemorrhage, followed by gastrointestinal bleeding and other causes.

Most studies evaluated global bleeding risk; some studies separated bleeding in major bleeding and non-major bleeding and focused mainly on bleeding risk and not on mortality. In newer introduced DOAC, rivaroxaban and higher doses of dabigatran and edoxaban are associated with higher risk of bleeding compared with warfarin;[16] other studies comparing rivaroxaban and apixaban found less bleeding events for apixaban.[17] Some analyses found an increased risk of GIB with DOAC versus VKA[18,19] but less intracranial hemorrhage.[19] Several meta-analyses are available today; a potential increased risk of GIB was reported in 2013 (OR 1.58) for DOAC[20] and a relative risk of 1.25 was also noted,[21,22] while other meta-analyses showed no difference between DOAC, VKA and low-weight molecular heparin (LMWH) regarding major GIB rate.[23–26] The risk was higher for rivaroxaban, intermediate for dabigatran and lower for apixaban and edoxaban.[21,22,27,28] A meta-analysis of 8 cohort studies which included 1442 patients with gastrointestinal hemorrhage among the 10,713 patients using rivaroxaban and 106,626 patients using dabigatran found a higher risk for dabigatran compared with VKA and similar risk for rivaroxaban.[29]

Several studies have estimated specific mortality in gastrointestinal bleeding associated with the type of antithrombotic therapy,[30–36] with a higher mortality for VKA as compared with DOAC in some studies[30,31] and similar mortality in others;[32,33,36] only some studies have evaluated the mortality risk for patients with gastrointestinal bleeding on anticoagulant versus antiplatelet therapy. There is heterogeneity of the studies related to monotherapy, dual or triple therapy with different doses, and because of many confounding factors (age, indication for therapy, gastro protective or gastric harmful drugs use, comorbidities or H. pylori infection). As a result of relative recent introduction, a progressively greater use of DOAC can be expected and more studies aiming at assessing the prevalence and mortality of UGIB associated with DOAC are needed. Few studies have assessed the risk factors for mortality in UGIB associated with antithrombotic therapy and a better understanding of predictive risk factors for mortality can be useful to prevent deaths in UGIB associated with antithrombotic treatment.

SARS-CoV-2 infection outbreak has appeared during the last days of 2019 and has dramatically expanded worldwide, being declared an official pandemic by WHO in March 2020; clinical manifestations range from an asymptomatic course or mild flu-like syndrome to severe viral pneumonia with respiratory failure.[37–39] The treatment of patients included glucocorticoids, anticoagulants, monoclonal antibodies, antivirals, symptomatic treatments. Because of thrombosis risk in severe forms of COVID-19 the administration of anticoagulants was implemented in potentially severe cases, which can result in an increased risk of upper gastrointestinal bleeding in these patients.[40] Many patients who are admitted to emergency departments with upper gastrointestinal bleeding have also cardiovascular comorbidities being on anticoagulation or antiplatelet treatment at home; due to the pandemic context, it was no longer monitored, and some patients had upper gastrointestinal bleeding due to overdose.

Materials and Methods

The purpose of the study was to assess the mortality rate and risk factors for mortality in UGIB for patients with AT therapy during pandemic and pre-pandemic period, respectively, the proportion of patients with UGIB associated with AT therapy, the type of AT therapy and changes during pandemic period compared with prepandemic period.

We performed a retrospective study in patients admitted with upper gastrointestinal bleeding in the Emergency Clinical County Hospital of Craiova during the 22 months of pandemic period (March 2020-December 2021) and three years before pandemic (2017–2019). Two groups of patients were included: first group has included all patients admitted for UGIB in our hospital, and second group has included patients admitted with COVID-19 infection without bleeding in our hospital. During the pandemic period, our hospital has admitted mainly COVID-positive patients who also had other pathologies and were tested positive on presentation in emergency department or confirmed later during hospitalization with infection, and also patients with severe forms of COVID infection admitted to the intensive care unit for non-invasive or invasive ventilation. All those patients were treated with LMWH and corticosteroids, which can increase the risk of gastrointestinal bleeding, altogether with hypoxemia in severe cases.

The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all admitted patients and an approval by Local Ethics Committee of the Emergency Clinical County Hospital of Craiova was also obtained. Patients aged below 16 years and those who denied consent for data usage were excluded from the study. We recorded demographic data (age, gender, residence), use of antithrombotic therapy (categorized as AP-antiplatelet therapy, VKA-vitamin K antagonists, VKA+AP- VKA plus antiplatelet therapy, DOAC-direct oral anticoagulants, LMWH-low molecular weight heparin and NO AT-patients with no anticoagulant or antiplatelet therapy), clinical parameters (impaired level of consciousness, onset with syncope or melena, systolic blood pressure and pulse, comorbidities, general condition in all cases) and biological parameters (Hb, creatinine, blood urea nitrogen, albumin, INR, total bilirubin in cirrhotic patients), the result of endoscopic evaluation and the need for endoscopic treatment. We also calculated pre-endoscopic and post-endoscopic bleeding scores (Rockall, Glasgow-Blatchford, Baylor, Cedars-Sinai, AIM65, T-score)[41] in non-variceal bleeding and Child-Pugh in variceal bleeding.

The evaluation of patients for COVID-19 infection during pandemic period (March 2020-December 2021) was based by epidemiologic triage, by pulmonary X-Ray and by PCR testing in case of suspected cases; after the introduction of rapid antigen testing all patients were evaluated before admission. Most patients were examined by endoscopy in the first 24 hours; cases with suspicion of COVID-19 infection were managed conservatively, if possible; cases with hemodynamic instability or those with ongoing bleeding, if positive or suspected for Covid-19 infection, were evaluated by emergency endoscopy in specially designated endoscopy rooms.

The assessed outcomes were the rate of in-hospital mortality, the rate of rebleeding, and the need for transfusion and for surgery. The analyzed risk factors were age, the proportion of variceal bleeding and the proportion of cirrhotic patients, the severity of bleeding (prognostic scores for non-variceal bleeding, and Child score for variceal bleeding), and the presence of Covid-19 infection. Three types of correlations between AT and UGIB were noted: related, not-related, and unknown.

Statistical data were analyzed and provided using Graph Pad Prism 9.2.0 (Graph Pad Software, San Diego, CA, USA). Continuous variables were compared using Mann–Whitney test, if they were not found to have a normal (Gaussian) distribution after a test distribution with Kolmogorov–Smirnov normality test, while for categorical variables Chi-square test or Fisher were used. To have a global image of the influence of the analyzed factors on survivability, we produced a multivariable logistic regression model.

Results

General Characteristics of AT versus No at Group

During the studied period, 824 patients were admitted during Covid-19 pandemic period and 1631 before pandemic; a total of 426 cases using AT therapy were recorded from patients with upper gastrointestinal bleeding (17.35%) Table 1.

Table 1 Comparative Characteristics of AT and No at Group

	AT Group (N=426)	No AT (N=2029)	P-value
Sex M/F (%M)	266/160 (62.4%)	1351/678 (66.6%)	0.1014
Age 18–59 years 60–79 years >80 years	 9.15 62.68 28.17	 42.98 47.71 9.31	 *<0.0001*
Endoscopy %Yes %<24h %Therapeutic	 85.68 78.08 12.21	 85.76 83.51 21.14	 0.9676 *0.0134* *<0.0001*
Variceal/non-variceal	13/379	507/1244	*<0.0001*
Cirrhosis (%)	24 (5.63)	748 (36.87)	*<0.0001*
Rebleeding	3.99	4.53	0.6207
Hospital days	7.80	7.09	*0.0209*
Emergency surgery	0.23	0.79	0.2380
Blood transfusion (%)	61.74	43.81	*<0.0001*
Mortality (%)	12.21	13.41	0.5064
Covid-19 Positive/Negative	16/116	17/344	*0.0346*

Note: P-values statistically significant (<0.05) were marked with italic font.
Abbreviation: AT, anti-thrombotic therapy.

UGIB During Pandemic and Pre-Pandemic Period

The proportion of UGIB associated with AT therapy was almost double during pandemic period (24.39%) than before pandemic (13.8%), OR 2.02, 95% CI 1.63–2.49, P < 0.0001. More patients have used antiplatelet therapy (OR 2.17, 95% CI 1.53–3.08, P < 0.0001), DOAC (OR 7.56, 95% CI 3.27–17.49, P < 0.0001) and LMWH (OR 4.23, 95% CI 2.05–8.71, P = 0.0001) Table 2.

Table 2 Percentage of the Type of AT Therapy During Pre-Pandemic and Pandemic Period

	Pandemic (%)	Before Pandemic (%)	P-value
AP only	8.25	3.99	*<0.0001*
VKA only	9.47	8.28	0.3234
VKA+AP	0.73	0.43	0.3407
DOAC	3.16	0.43	*<0.0001*
LMWH	2.79	0.67	*0.0001*
NO AT therapy	75.61	86.76	*<0.0001*

Note: P-values statistically significant (<0.05) were marked with italic font.
Abbreviations: AT, anti-thrombotic therapy; AP, antiplatelet therapy; VKA, vitamin K antagonists; DOAC, direct Oral Anticoagulants; LMWH, Low Molecular Weight Heparin.

We also analyzed the rate of upper gastrointestinal bleeding in patients admitted for other pathologies and COVID-19 infection in our hospital. During the pandemic period, our hospital has admitted mainly COVID-positive patients who also had other pathologies and were tested positive on presentation in emergency department or confirmed later during hospitalization with infection. Another group of patients were admitted to the intensive care unit with severe forms of COVID infection which required non-invasive or invasive ventilation. All those patients were treated with LMWH and corticosteroids, which can increase the risk of gastrointestinal bleeding, altogether with hypoxemia in severe cases. Of the 1881 patients with COVID-19 infection, only 11 patients (0.58%) had UGIB, all being on treatment with LMWH, while in the literature the rate of bleeding has been estimated between 0.4% and 13%.[37,39]

Mortality and Rebleeding Rate Related to the Type of Anti-Thrombotic Therapy

From 426 cases with UGIB while on AT therapy, 133 had AP treatment (cardiologic aspirin, clopidogrel or both), 213 had acenocoumarol, 13 had both acenocoumarol and AP therapy, 33 were on DOACs (24 cases with apixaban, 6 cases with rivaroxaban, 2 cases with dabigatran, and one with edoxaban), and 34 had LMWH. The mortality rate for DOAC patients was 15.15%, higher than for patients taking VKA, P = 0.4126, and 9.77%, OR 1.65, P = 0.38) but lower than for patients with LMWH (32.35%, P = 0.92) Table 3.

The percentage of variceal bleeding was higher for DOAC than for AP and VKA users (OR = 9.93, P = 0.001, and OR = 5.73, P = 0.0125, respectively). The percentage of patients with no endoscopy and of therapeutic endoscopy was similar between subgroups (no significant statistical difference) Table 4.

The percentage of blood transfusions was higher for DOAC (72.73%) and LMWH (73.53%) and lower for the association VKA+other (46.15%), but with no statistical significance (P = 0.1687). The lowest mean Hb and the highest mean blood units required were noted for patients taking VKA associated with anti-platelet therapies (7.27 g%, 3.67 units), although no statistical significance was noted. Patients with DOAC were much older (75.6 years) than patients with no AT therapy (61 years).

Table 3 Mortality and Rebleeding Rates Related to the Type of AT Therapy

	Mortality Rate (%)	Rebleeding Rate (%)
-AP	9.77	4.51
-VKA	10.33	4.69
-VKA+AP	7.69	0.00
-DOAC	15.15	0.00
-LMWH	32.35	2.94

Table 4 Percentage of Variceal/Non-Variceal Bleeding, Cirrhosis and Endoscopy Related to the Type of AT

	%Variceal	%Cirrhosis	%Non-Variceal	%No ED	%Therapeutic ED
-AP	3.01	8.27	84.96	11.28	12.78
-VKA	2.35	4.23	93.43	16.90	10.80
-VKA+other	0.00	0.00	92.31	15.38	23.08
-DOAC	12.12	6.06	84.85	15.15	15.15
-LMWH	0.00	5.88	94.12	14.71	11.76

Abbreviation: ED, endoscopy.

Risk Factors for Mortality in Patients with AT Therapy

Age

We have analyzed age-adjusted mortality in patients with antithrombotic therapy because patients using anti-thrombotic therapy are generally older than those with upper gastrointestinal bleeding and no anti-thrombotic therapy. We separate patients in three age groups (18–59 years, 60–79 and above 80 years) and calculate specific mortality in every age group for the pandemic and pre-pandemic period, respectively, Table 5. Age adjusted mortality was 28% lower in patients with AT therapy (OR 0.69, 95% CI 0.49–0.97, P = 0.0343).

NSAID Use

We have analyzed the role of association between AT therapy and NSAID consumption regarding mortality in upper gastrointestinal bleeding. NSAID use was not associated with a higher frequency of upper gastrointestinal bleeding in AT group compared with those with no AT treatment (p = 0.2715, OR 0.83). However, in patients taking NSAID, the mortality was 3-fold higher in patients (9.3%) taking AT therapy compared with those with no anti-thrombotic treatment (2.47%, OR = 3.69, 95% CI 1–13.58, P = 0.0491).

Endoscopy

We assessed the correlation between in-hospital mortality and Forrest score, stratified as I (active bleeding), IIa (visible vessel), IIb (adherent clot) and IIc+III (haematin spot and no stigmata, which requires no endoscopic therapy). Less active bleeding lesions (Forrest Ia and Ib) were found in AT therapy patients (7.91%) than in those without AT therapy (11.73%, OR = 0.632, 95% CI 0.432–0924, p = 0.0179) and no significant difference regarding mortality was seen between active bleeding, high risk and low risk/no stigmata of bleeding cases, which suggested that other factors may be implied. However, patients with no endoscopy had an almost 10-fold higher in-hospital mortality than those with endoscopy (43.6 versus 4.4%, OR 16.7786, 95% CI 8.2544 to 34.1054, P < 0.0001). Patients with no endoscopy performed are a heterogeneous group which include those with severe comorbidities and contraindications, those dead shortly after emergency room admission and those who refused consent for the procedure.

Covid-19 Infection

We have analyzed the mortality risk for patients taking AT therapy in relation with Covid-19 status (positive versus negative). In patients admitted for UGIB while on AT therapy and who have Covid-19 infection mortality rate was 62.5% compared with 15.52% in Covid-19 negative patients (OR 9.07, 95% CI 2.93–28.09, P < 0.0001). Thus, the presence of Covid-19 infection was associated with a higher risk of death in UGIB patients already on AT therapy.

Prognosis Scores

We compared mean scores of UGIB for patients with no AT therapy with those with AT therapy and by type of AT treatment (Table 6). For all scores except Cedars-Sinai, patients with AT therapy had superior values of mean scores, which reflect more severe cases with significant comorbidities. Patients with VKA and DOAC had higher mean scores than those with anti-thrombotic therapy or LMWH.

The mean HAS-BLED score was lower and Charlson comorbidity index was higher in patients with upper gastrointestinal bleeding and AT therapy compared with those without AT therapy (1.91 versus 2.25, P < 0.0001, and 4.5 versus 3.59, P < 0.0001, respectively).

Table 5 Age Adjusted Mortality in AT Therapy Group

Age Group	Mortality AT	Mortality No AT
18–59	5.13	11.81
60–79	13.11	14.67
>80	12.50	14.29
Age-adjusted mortality	9.62	13.41

Table 6 Mean Value of Bleeding Prognostic Scores in AT and No at Therapy Groups

Score	No AT	AT	P-value	AP	VKA Only	DOAC	LMWH
GBS	10.33	11.91	*<0.0001*	11.24	12.41	12.09	11.06
Rock pre	2.96	3.76	*<0.0001*	3.48	3.93	3.79	3.94
CS	3.94	4.07	0.43	3.78	4.06	4.57	4.67
BBS pre	7.81	11.31	*<0.0001*	10.49	11.65	12.27	11.29
BBS full	8.75	11.8	*<0.0001*	11.02	12.01	12.86	11.79
AIM65	1.21	1.77	*<0.0001*	1.35	1.98	1.87	2.33
T-score	11.19	11.66	*0.0001*	11.64	11.75	11.76	10.59
Rock full	4.45	4.91	*0.0002*	4.74	4.95	4.966	5.66
mBG	8.21	9.69	*<0.0001*	9.24	10.07	9.82	8.76

Note: P-values statistically significant (<0.05) were marked with italic font.
Abbreviations: GBS, Glasgow-Blatchford score; Rock pre, pre-endoscopic Rockall score; CS, Cedar-Sinai score; BBS pre, pre-endoscopic Baylor bleeding score; BBS full, Baylor bleeding score after endoscopy; Rock full, Rockall score after endoscopy; mBG, modified Glasgow-Blatchford score.

We have analyzed the mortality risk for patients taking AT therapy stratified by age, variceal versus non variceal bleeding, ulcer versus other non-variceal causes, no endoscopy versus endoscopy, therapeutic versus diagnostic endoscopy, cirrhosis, non-variceal bleeding in cirrhosis versus patients without cirrhosis, Hb level, NSAID and alcohol consumption. We found a significant risk for mortality in association with no endoscopy performed (OR 10.8, 95% CI 5.64–20.65, P < 0.0001), cirrhosis (OR 5.01, 95% CI 2.07–12.14, P = 0.0004), cirrhosis in non-variceal bleeding (OR 6, 95% CI 1.86–19.34). Variceal bleeding has been associated with a higher, but not significant statistic risk compared with non-variceal bleeding (OR 2.58, 95% CI 0.6816–9.7661, P = 0.1628). We cannot have sufficient data regarding smoking habit and proton pump inhibitor consumption before UGIB.

Multivariate Analysis

Analyzing the relationship between patient death and some of the variables recorded, we obtained the following significant results (Tables 7–10).

Table 7 Analysis of the Qualitative Variables That Influence Survival

Variable	Deceased	Alive	p Chi Square
CIRRHOSIS-NO	8.62%	91.38%	*< 0.0001*
CIRRHOSIS-YES	23.19%	76.81%	
NON-VARICEAL	7.43%	92.57%	*< 0.0001*
OBSCURE	12.84%	87.16%	
VARICEAL	21.92%	78.08%	
UNKNOWN	37.88%	62.12%	
ENDO-NO	44.00%	56.00%	*< 0.0001*
ENDO-YES	8.08%	91.92%	

(*Continued*)

Table 7 (Continued).

Variable	Deceased	Alive	p Chi Square
ENDO TREATMENT - NO	6.96%	93.04%	*< 0.0001*
ENDO TREATMENT - YES	11.85%	88.15%	
AT-NO	13.41%	86.59%	0.506
AT-YES	12.21%	87.79%	
AT-NO	13.41%	86.59%	*0.0137*
AP	9.77%	90.23%	
VKA	10.33%	89.67%	
VKA+AP	7.69%	92.31%	
DOAC	15.15%	84.85%	
LMWH	32.35%	67.65%	
REBLEEDING-YES	32.11%	67.89%	*< 0.0001*
REBLEEDING -NO	12.32%	87.68%	

Note: P-values statistically significant (<0.05) were marked with italic font.

Table 8 Goodness of Fit of the Proposed Logistic Model

from \ to	Alive	Deceased	Total	% Correct
Alive	1901	46	1947	97.64%
Deceased	173	91	264	34.47%
Total	2074	137	2211	90.09%

Table 9 Statistical Significance of the Fit of the Model

Statistic	DF	Chi-Square	Pr > Chi²
−2 Log (Likelihood)	14	475.1157	*< 0.0001*
Wald	14	328.0222	*< 0.0001*

Note: P-values statistically significant (<0.05) were marked with italic font.

Table 10 Statistical Significance of the Influence of Each Variable Used as Predictor in the Model

Source	DF	Chi-Square (Wald)	p Wald	Chi-Square (Log R)	p Log R
GB score	1	61.38369	*< 0.0001*	66.1406	*< 0.0001*
REBLEEDING	1	34.81856	*< 0.0001*	29.61588	*< 0.0001*
ENDO TREATMENT	2	140.4925	*< 0.0001*	139.6595	*< 0.0001*
Type of Hemorrhage	3	43.31831	*< 0.0001*	44.15466	*< 0.0001*
Type of AT	5	14.96384	*0.0105*	15.29827	*0.0092*

Note: P-values statistically significant (<0.05) were marked with italic font.

Next, we tried to create a multivariable logistic model for estimating survival based on the values of variables identified as having a statistically significant impact on it. We decided to use only the variables Endoscopy, Endoscopic treatment, Type of hemorrhage and Type of antithrombotic therapy in the subsequent statistical analysis. Covid-19 infection was not considered in multivariate analysis because it was present only during pandemic period and therefore it can distort the final results. Out of 2455 patients, we had records for all variables for 2211 of them, on which we performed multivariable logistic analysis.

The proposed model has a correct survival estimation rate of 97.64% and a death estimation rate of 34.47%. From a statistical point of view, this model is statistically significant, with both the Wald test and the likelihood ratio test having highly significant values.

Analyzing the importance of each variable in the generated model, we found that GB score, rebleeding, endoscopic examination and treatment, type of antithrombotic therapy and type of hemorrhage (variceal, non-variceal, obscure, unknown) have a significant influence.

To further detail the model, we present the values of the coefficients used for each numerical variable, respectively, for each category of the qualitative, nominal variables, with the 95% confidence interval, as well as the statistical significance of those values. Negative values of the coefficients represent a decrease in the death probability, and a p-value lower than 0.05 represent a significant change over the base category (no rebleeding, no AT therapy, no endoscopy performed, variceal bleeding) Table 11.

Table 11 Coefficient Values and P-value for Qualitative Variables That Influence Survival

Source	Equation Coefficient Value*	Standard Error	95% CI Lower Bound	95% CI Upper Bound	Wald Chi²	P Wald Chi²
Intercept	−4.956	0.808	−6.539	−3.372	37.614	*< 0.0001*
GB score	**0.233**	0.030	0.175	0.291	61.384	*< 0.0001*
REBLEEDING-NO	0.000	0.000				
REBLEEDING-YES	**1.629**	0.276	1.088	2.171	34.819	*< 0.0001*
Endo Treatment-NA	0.000	0.000				
Endo Treatment -No	**−2.583**	0.236	−3.047	−2.120	119.408	*< 0.0001*
Endo Treatment -Yes	**−2.763**	0.271	−3.293	−2.232	104.283	*< 0.0001*
Type of Hemorrhage						
-NON-VARICEAL	0.000	0.000				
-UNKNOWN	0.297	0.284	−0.260	0.854	1.093	0.296
-OBSCURE	**1.232**	0.373	0.500	1.964	10.888	*0.001*
-VARICEAL	**1.259**	0.208	0.850	1.667	36.512	*< 0.0001*
Type of AT						
-VKA	0.000	0.000				
-AP	0.413	0.453	−0.475	1.302	0.833	0.362
-VKA+AP	−13.340	1590.086	−3129.851	3103.171	0.000	0.993
-DOAC	0.973	0.639	−0.280	2.226	2.316	0.128
-LMWH	**2.587**	0.698	1.219	3.955	13.741	*0.000*
-NO AT	**0.656**	0.327	0.016	1.297	4.035	*0.045*

Notes: *Positive coefficients signify an increase in death risk, negative coefficients signify a decrease, and significant values are marked with bold font. P-values statistically significant (<0.05) were marked with italic font.

By multivariate analysis, we noted that the mortality risk was associated with GB score (0.233 Coefficient value), rebleeding (1.629 Coefficient value), obscure bleeding and variceal bleeding as compared with non-variceal bleeding (1.232 and 1.259 Coefficient value, respectively), for NO ENDOSCOPY compared with both ENDO NO TREATMENT (2.583) and ENDO TREATMENT (2.763) respectively, and LMWH and no AT therapy as compared with VKA therapy (2.587 and 0.656 Coefficient value, respectively).

Discussions

The use of anti-thrombotic therapy has represented an important etiological factor for UGIB (17.35% of all cases, higher in pandemic-24.39%). During the pandemic period, more patients used DOAC, anti-platelet therapy and LMWH. The percentage of DOAC users in UGIB remained relatively small (3.16% from all UGIB in pandemic period and 12.96% from AT-related UGIB).

Patients with AT therapy were much older than those without treatment (72.4 versus 61 years, $P < 0.0001$); gender distribution is similar. Age was an important risk factor for mortality in patients with UGIB while on anti-thrombotic therapy; in our study age-related mortality was 28% lower in patients with AT therapy than in those without AT treatment. Fewer variceal bleeding cases and fewer patients with cirrhosis were noted in anti-thrombotic treatment group, compared with patients without AT therapy. The rate of endoscopy was similar, but 5% fewer patients have performed endoscopy during the first 24 hours and therapeutic endoscopy was necessary in fewer cases with AT therapy (12.21% versus 21.14%, OR = 0.52, 95% CI 0.3807 to 0.7063, $P < 0.0001$); in 23% of cases no endoscopic lesion was found and active bleeding lesions (Forrest Ia and Ib) were found less frequently in AT therapy patients (7.91%) as compared to patients without AT therapy (12.02%, OR = 0.65, 95% CI 0.4418 to 0.9458, $P = 0.01246$). Lack of endoscopy represents a major risk factor for mortality (almost 10-fold higher compared with cases with endoscopy performed, regardless of endoscopic therapy being performed or not). Mean hospital days was 10% higher in patients with AT therapy and the percentage of patients who needed transfusions was higher; rebleeding rate and emergency surgery were similar. It is possible that significantly older age for patients with AT therapy and cardiovascular comorbidities to generate the difference because older patients and those with cardiovascular diseases have a poor tolerance for low Hb levels. The mean Hb level for patients taking AT therapy was 10% lower (8 versus 8.78, $P < 0.0001$), which could also have contributed to the increased need for blood transfusion. Mean blood units for AT therapy were similar between the two groups (3.43 versus 3.33, $P = 0.33$); patients taking DOAC and LMWH therapy have the highest rate of blood transfusion (72.73% and 73.53%, respectively).

Most prognostic scores were higher in patients with AT treatment, which reflect significantly more patients with comorbidities.

Covid-19 pandemic may be associated with an increased prevalence of UGIB: mechanisms rarely included a direct gastrointestinal inflammation and mucosal injury and more often indirect factors such as use of AT, corticosteroids and NSAID therapy, hypoxemia and increased stress in severe cases.[37–39] During the pandemic period, the percentage of UGIB in patients admitted for Covid-19 was small (0.58%); 39 cases positive for Covid-19 infection were admitted for UGIB (7.81%), from which 16 had AT therapy before admission and 5 had NSAID therapy. In 10 cases antithrombotic therapy was recommended for other indications than Covid-19 infection and in 6 cases anticoagulant therapy was recommended because of Covid-19 infection. Other 5 patients with past Covid-19 infection (but less than 180 days) were admitted with UGIB, from which 3 had AT therapy, 2 for other concomitant indications and one for post-Covid respiratory failure. Considering that in 6 cases from 201 UGIB associated with AT therapy were related to anticoagulant therapy for Covid-19 infection, the increase of UGIB induced by AT therapy Covid-19-related was 3.07% in our study. Only 2 patients had hypoxemia before UGIB and 5 patients had NSAID therapy. The impact of pandemic toward more bleeding associated with antithrombotic therapy seems not related to less control of medication, because only 14.3% of patients treated with VKA had an INR value above 3.5 during pandemic, compared with 38% of patients during 2017–2019 (OR = 0.27, $P < 0.0001$). We can conclude that most of the increased prevalence of UGIB associated with AT therapy in pandemic period was therefore not related to the Covid-19 infection and lack of control of medication but more probably to the increased use of AT therapy in cardiovascular or cerebro-vascular diseases.

Mortality rate in patients with UGIB while taking AT therapy was 12.21%, similar to patients without AT therapy (13.41%, OR 0.90, 95% CI 0.65 to 1.23, P = 0.5064). Age-adjusted mortality was 9.62% in AT therapy compared with 13.41% in patients without AT therapy (OR 0.6879, 95% CI 0.6879, P = 0.0343), which suggested age was an important risk factor for mortality in AT therapy group. In univariate analysis the risk factors for a higher mortality were the absence of endoscopy, cirrhosis, and non-variceal bleeding in cirrhosis, while variceal bleeding has been associated with a higher, but not statistically significant risk. The presence of Covid-19 infection was also a powerful risk factor for mortality (OR 9.07, P < 0.0001). In multivariate analysis, the main risk factors for mortality were GB score, rebleeding, obscure bleeding and variceal bleeding as compared with non-variceal bleeding, lack of endoscopy compared with endoscopy performed (regardless of endoscopic therapy being performed or not) and use of LMWH.

In our study the mortality rate in patients taking DOAC (15.5%) was higher than in those taking VKA antagonists (10.33%) and those taking antiplatelet therapy (9.77%), but without statistical significance; a possible explanation for lack of statistical significance may be related to the small number of patients with DOAC treatment (33 cases). More cases of variceal bleeding have been noted in DOAC group compared with both VKA and AP therapy groups. Compared to warfarin, rivaroxaban and dabigatran are correlated with a 30% increase in gastrointestinal bleeding;[42] older patients (>75 years old) using rivaroxaban have higher risk of severe gastrointestinal bleeding (3-fold or 4.5-fold) and those using dabigatran have an increased rate of gastrointestinal bleeding than patients on warfarin.[43] Some studies or meta-analyses which include all bleeding reported a case fatality of 6.1% for DOAC and 10.4% for VKA,[31] 9.8% for DOAC versus 15.2% for VKA,[38] 7.57% for DOAC and 11.04% for warfarin in a meta-analysis of 13 randomized trials[44] (with the difference mainly due to a decrease in intracranial bleeding for DOAC) and 8.3% for VKA and 9.7% for DOAC in another meta-analysis of 27 studies and nearly 10,000 patients.[34] Several studies including only GIB showed that 7.1% of DOAC patients and 8.7% of warfarin patients died from 284 patients,[32] 16.1% at 6 weeks in VKA group versus 7.8% in DOAC group (P < 0.01, 475 patients with UGIB) but more patients in VKA group had cirrhosis (13.1 versus 4.3, P = 0.001) and kidney failure (38.6 versus 19.2%, P < 0.0001).[30] In a study including 61 patients treated with DOAC and 123 treated with warfarin no difference of mortality was noted,[33] while in a large, national seven-year study of over 40,000GIB patients, 5774 (14.1%) patients received an oral anticoagulant therapy; unadjusted in-hospital mortality was 7.5% for DOAC (7.2% for dabigatran, 6.4% for rivaroxaban, 10.1% for apixaban) and 6.5% for warfarin; and after adjustment for demographic and clinical characteristics, no significant difference was seen between DOAC and VKA users (adjusted OR 0.97), but only 38.6% had UGIB in DOAC group and 50.4% in VKA group.[36] In another study, one month mortality for GIB was 11% in patients with DOAC treatment.[35] The possible explanations for differences regarding mortality between DOAC and VKA may include differences between comorbidities, proportion of variceal bleeding and cirrhosis and also among the types of DOAC.

In VKA users, excessive anticoagulation with warfarin is most often the cause of gastrointestinal bleeding and the INR value > 3.5 was correlated with the highest mortality,[45] but in our study INR value >3.5 was not associated with mortality (P = 0.2747). For DOAC, major gastrointestinal bleeding risk was related in a study to concurrent use of gastro toxic drugs, other comorbidities, age, and high HAS-BLED score.[46] In our study, the mortality in patients with anticoagulant therapy (DOAC or VKA antagonists) was similar to mortality in patients with anti-platelet therapy (10.98 versus 9.77%, OR = 1.1380, 95% CI 0.5662 to 2.2874 P = 0.7166) while in a published study patients with anticoagulant treatment have a higher risk of death and rebleeding.[47]

In our multivariate model, increased mortality risk was associated with increased GB score (Coefficient value 0.233), rebleeding (Coefficient value 1.629), obscure and variceal bleeding (Coefficient value 1.232 and 1.259, respectively) and use of LMWH (Coefficient value 2.587) while diagnostic and therapeutic endoscopy were inversely correlated with mortality risk (Coefficient value −2.583 and −2.763, respectively). Compared with VKA use, DOAC treatment was not a risk factor for mortality.

There are some limitations of this study. The number of cases treated with DOAC was small (33 cases), although the proportion has increased during the pandemic period, and an analysis of risk factors for mortality was therefore not possible. A small proportion of cases have not been completely investigated in order to make calculations for all prognostic scores, and in 14.3% of cases endoscopy was not performed, so post-endoscopic scores were not available.

Co-therapy with proton pump inhibitors prior to UGIB was not analyzed during the study. Further studies including large number of patients using DOAC and also with a better evaluation other risk factors including gastro-toxic and gastro-protective drugs may be necessary.

Conclusions

17.35% of patients with upper gastrointestinal bleeding have used AT therapy; the percentage was almost twice higher during the pandemic period than before pandemic. Mortality rate was 12.21%, similar to patients without AT therapy. Patients with AT therapy were 11 years older, had more comorbidities and higher average prognostic scores, and had a 10% lower Hb level, a higher percentage of blood transfusions, a smaller percentage of variceal bleeding and cirrhosis, and similar rate of endoscopy. The rate of therapeutic endoscopy was lower in patients taking anti-thrombotic therapy, 34% fewer patients had active bleeding at endoscopy and 23% of cases had no lesion at endoscopy. Mortality rate of DOAC was superior compared to VKA therapy, but without statistical significance, and only 7.75% of patients with upper gastrointestinal bleeding and AT therapy were on treatment with DOAC. 0.58% of patients admitted for COVID-19 infection and in treatment with LMWH had UGIB. The mortality risk in multivariate analysis was associated with GB score, with no endoscopy performed, with obscure and variceal bleeding as compared with non-variceal bleeding and with LMWH and NO AT therapy versus VKA therapy.

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Disclosure

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