Original Article
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Characteristics of Patients with Nonvariceal Upper Gastrointestinal Bleeding - Are We Underestimating Gastroprotection during NSAIDs Therapy?

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Abstract

Objective. The aim of our study was to determine the etiological factors, treatment and outcome of patients with non-variceal bleeding from upper gastrointestinal tract. **Materials and Methods.** This study enrolled 200 patients admitted to Sarajevo University Clinical Center with signs and symptoms of upper gastrointestinal bleeding, from January 2019 to July 2020. All patients had undergone gastroscopy, confirming the cause of gastrointestinal bleeding. Clinical and laboratory data were collected retrospectively, including previous non-steroid antiinflammatory drugs (NSAIDs) and anticoagulant therapy, comorbidities, risk factors, as well as endoscopic findings, laboratory findings, treatment and clinical follow-up. **Results.** The majority of patients were men (59%) with an average age of 53±6 years. Duodenal and gastric ulcers were the most common cause, followed by other etiologies. In our study, previous NSAIDs therapy had been registered in 29.5% of patients, anticoagulants in 8%, and proton pump inhibitors (PPI) in 2.9% of patients. Endoscopic intervention was required in 34% of patients. The need for transfusion occurred in 44.5% of cases. Rebleeding during hospitalization was observed in 7.5% of patients, mortality in 1.5% and surgery in 3% of patients. **Conclusion.** The patients admitted to our hospital with symptoms of acute nonvariceal upper gastrointestinal bleeding were elderly, predominantly males, with significant comorbidities and a higher incidence of NSAID use. Gastroprotection is underutilized during NSAID treatment in patients with other coexisting risk factors,with a low rate of concomitant use of PPI during NSAIDs therapy. Endoscopic therapy, together with PPI, significantly reduces rebleeding rates, mortality and the number of emergency surgical interventions.

Key Words: Mortality ▪ Transfusion ▪ Forrest Classification.

Introduction

Upper gastrointestinal bleeding can be a life-threatening condition and requires careful evaluation from admission to the emergency center. Epidemiological data are important to gain an insight into the actual healthcare problem. The outcome of patients with upper gastrointestinal bleeding depends on the adequate assessment of patients with a high risk of mortality and rebleeding requiring immediate intervention, and those at low risk who can be safely discharged as outpatients (1, 2).

Petpic ulcer bleeding is the most common cause of non-variceal upper gastrointestinal bleeding, responsible for about 50% of all cases, followed by oesophagitis and erosive disease. Rebleeding occurs in 7-16% of cases, despite endoscopic therapy. Mortality ranges between 3 and 14%, increasing with age and in patients with significant comorbidities (3).

One of the main risk factors for peptic ulcer bleeding is non-steroid anti-inflammatory drugs (NSAIDs) use. The remaining risk factors include: Helicobacter pylori infection, age >65 years, past history of gastrointestinal ulcers, multiple-drug combination therapy, and comorbidities, such as cardiovascular disease and nephropathy. Cyclooxygenase-2 (COX-2) selective inhibitors

have an advantage over non-selective NSAIDs. In patients using NSAIDs, who are at risk for gastrointestinal bleeding, protective drugs are used in a small percentage of patients. Recommendations for prevention and treatment of non-steroidal anti-inflammatory drug-induced gastrointestinal ulcers include evaluation of gastrointestinal and cardiovascular function before using NSAIDs, as well as using PPI as the first choice of therapy for the prevention and treatment of these injuries. A high-dose of PPI in patients using NSAIDs effectively prevents rebleeding, and reduces the possibility of surgery and mortality rate (4, 5).

The aim of our study was to determine the etiological factors, treatment and outcome of patients with non-variceal bleeding from the upper gastrointestinal tract at the Clinic of Gastroenterohepatology.

Material and Methods

This study enrolled 200 patients admitted to Sarajevo University Clinical Center with signs and symptoms of upper gastrointestinal bleeding, from January 2019 to July 2020. During this period, 260 patients came to the emergency center with suspected gastrointestinal bleeding. Twenty of them had variceal bleeding and 40 had a Glasgow-Blatchford score lower than 3 and normal endoscopic findings, which is why they were not taken into consideration in the study. All the patients underwent emergency gastroscopy within 6 hours from arrival at the emergency center, confirming the cause of non-variceal bleeding from upper gastrointestinal tract. Out of the 200 patients, 183 had a Glasgow-Blatchford score higher than 6 at the time of arrival at the emergency center, which classified them as high-risk patients, and the remaining 17 had a Glasgow-Blatchford score between 4 and 6, placing them in the moderate risk category. The indication for endoscopic intervention was active bleeding from the proximal gastrointestinal tract confirmed by gastroscopy, and the threshold of hemoglobin for transfusion was 80 g/L in a bleeding patient. Clinical and laboratory data were collected retrospectively, including previous NSAIDs and anticoagulant therapy, comorbidities, risk factors, laboratory findings, treatment and clinical follow-up. The rate of rebleeding, surgical treatment and mortality was noted. Exhaustion of endoscopic methods, without successful cessation of bleeding, was an indication for surgical treatment.

Statistical Analysis

The statistical analysis was performed with SPSS version 22, including descriptive statistics, diagrams of associations between the etiology of gastrointestinal bleeding and the need for endoscopic intervention and transfusion, as well as binary logistic regression to evaluate risk factors, comorbidities and drugs used as potential predictors for endoscopic intervention in patients with gastrointestinal bleeding. $P<0.05$ was considered statistically significant.

Results

The majority of patients were men (59%). The average age of the patients was 53±6 years. Duodenal ulcer was verified in 45.5% of patients, gastric ulcer in 32%, neoplasm in 7.5%, anastomosis ulcer in 5.5%, erosions and gastroesophageal reflux disease in 4.5%, Sy Mallory Weiss in 3%, and angiodysplasia in 2% (Figure 1).

In the group of patients with ulcers, 22% of them had Forrest I, 34% Forrest II and 44% Forrest III type of bleeding. In 72% of cases the duodenal ulcer was classified as Forrest III, 14% Forrest II and 14% Forrest I, while the gastric ulcer in 16% of cases was classified as Forrest III, 54% Forrest II and 26% as Forrest I. All patients with Forrest I type bleeding needed endoscopic intervention, and 82% of patients with Forrest II as well. In 59% of patients, gastrointestinal haemorrhage presented as melena, while 21% of patients had melena and haematemesis simultaneously. 42% of patients were hypotensive with systolic blood pressure lower than 100 mm Hg and 30.5% of patients had tachycardia with heart rate above 100 beats per minute.

Previous NSAIDs therapy was registered in 29.5% of patients, anticoagulant use in 8% of patients, while PPI in 2.9% of patients. Comorbidi-

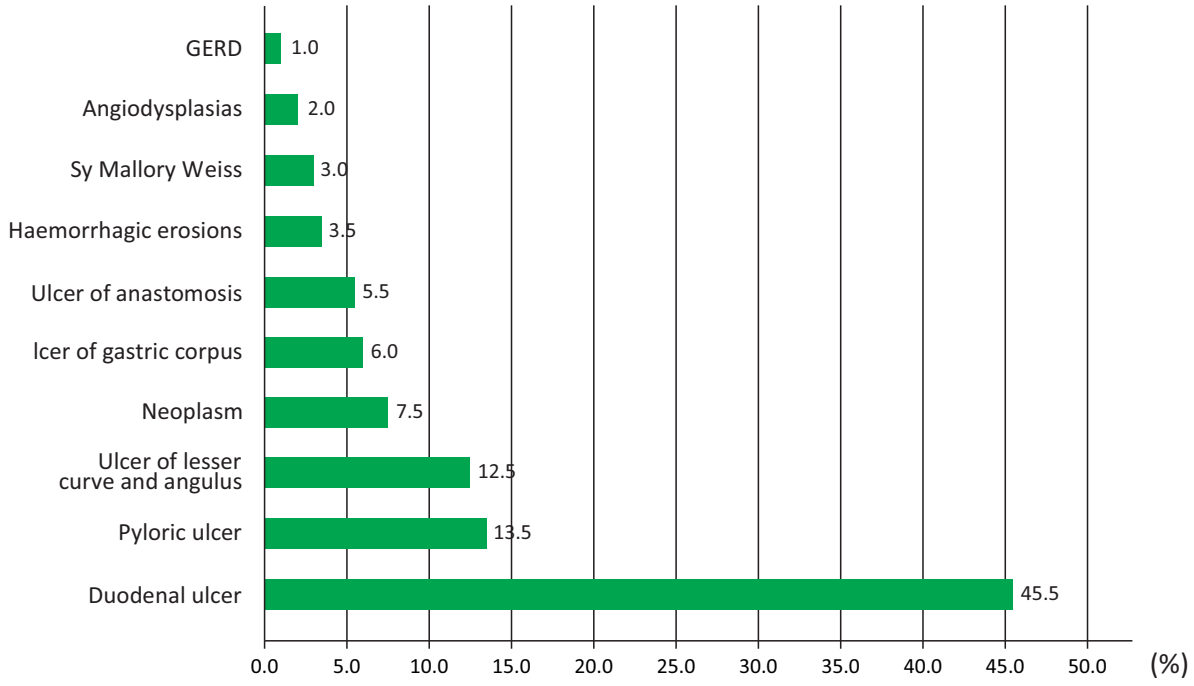
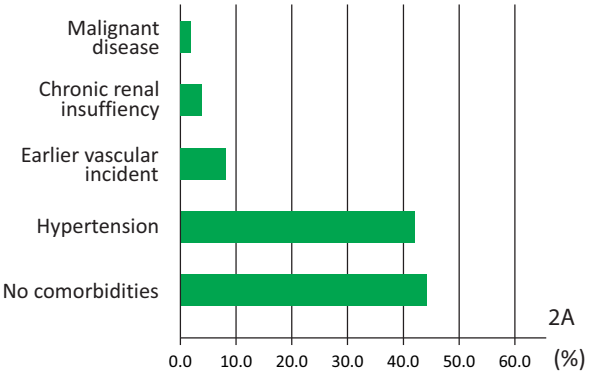


Figure 1. Localization of non-variceal bleeding in upper gastrointestinal tract.

ties were identified in 56% of subjects. An earlier episode of gastrointestinal bleeding within the previous 10 years, requiring endoscopic treatment, was observed in 22% of patients. Smoking was verified in 34% of the patients, alcohol consumption in 15%. Among comorbidities, the majority of patients had hypertension (42% of patients), an earlier vascular incident (8.5%), chronic renal insufficiency (3.5%) and malignant disease (2%). "Earlier vascular incident" refers to cerebrovascular insult, ischemic heart disease and peripheral blood vessel thrombosis, since this population requires the use of anticoagulant therapy. Among NSAIDs, patients most commonly used acetylsalicylic acid in a dosage of 100mg for pre-existing cardiovascular disease, and 400 mg ibuprofen for intermittent back and joint pain. Anticoagulant therapy was administered to patients with a previous vascular incident-acenocoumarol in a dosage of 4 mg, rivaroxaban 20 mg and antiplatelet drug clopidogrel in a dosage of 75 mg. All prescribed medicines were taken for 2 years before the study (Figure 2A and 2B).

Endoscopic intervention was required in 34% of patients, and the remaining patients underwent conservative treatment with PPI parenterally. Among those 34% of patients, in 6% hemostasis was achieved with adrenalin injection, 18% with endoscopic clips and in 10% with both adrenalin and clips. Since in all patients continuous IPP therapy was included within 24 hours after endoscopic treatment, in 6% of cases (12 patients in total) adrenalin injection therapy with continuation of IPP therapy for the next 24 hours proved to be effective. None of these patients had rebleeding. The need for transfusion occurred in 44.5% of cases, with an average of 3.51±2.10 blood doses of 250 ml. In-hospital rebleeding within 48 h of achieved hemostasis was observed in 7% of patients, and those patients required re-endoscopy, there was in-hospital mortality in 3% and surgery was required in 3% of patients. All patients from the rebleeding group had previously undergone endoscopic treatment. The average length of hospitalization was 5±2 days (Figure 3A and 3B).



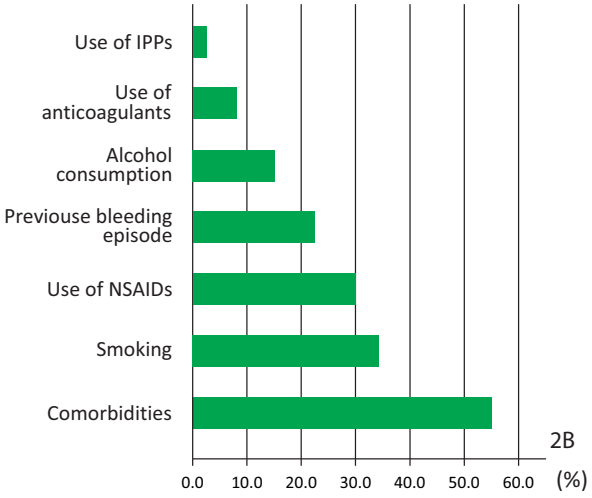
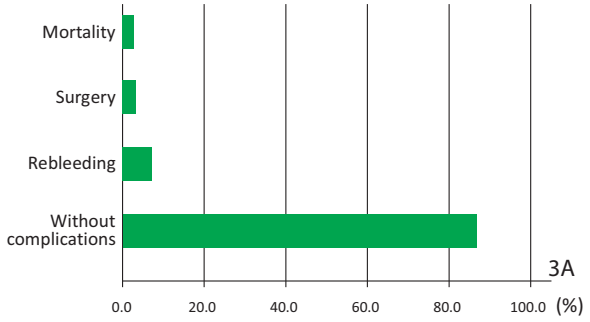


Figure 2A and 2B. Risk factors for gastrointestinal bleeding.



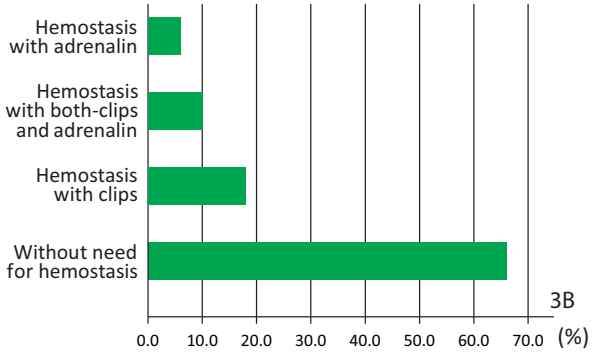


Figure 3A and 3B. Outcomes of gastrointestinal bleeding.

The association between the etiology of gastrointestinal bleeding and the need for endoscopic intervention. Lambda value 0.235, P=0.043 (Figure 4).

The association between the etiology of gastrointestinal bleeding and the need for transfusion. Lambda value 0.427, P<0001 (Figure 5).

Binary logistic regression was performed. There were 11 independent variables considered as predictors of endoscopic intervention and transfusion, as dependent variables. For endoscopic intervention the significance of the model was χ^2 (11,200)=202.30, P<0.001, with R^2 0.636 and 0.881 and percent of accuracy 95.5%, which means that between 63.6% and 88.1% of the variance in the dependent variable is explained by the independent variables and predicted correctly in 95.5% of cases. For transfusion, significance was χ^2 (11.200)=207.86, P<0.001, with R^2 0.646 and 0.865 and 94% accuracy. The significance of each of the independent variables is shown separately in Table 1.

NSAIDs and alcohol showed predictive ability for endoscopic intervention (P<0.001; P=0.037), while for transfusion NSAIDs (P<0.001) and two categories of comorbidities, hypertension and malignant disease, were shown to be statistically significant (P=0.024, P=0.002 respectively).

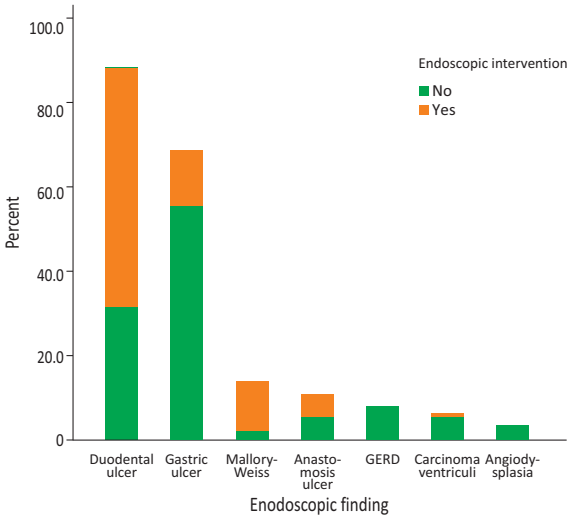


Figure 4. The association between the etiology of gastrointestinal bleeding and the need for endoscopic intervention.

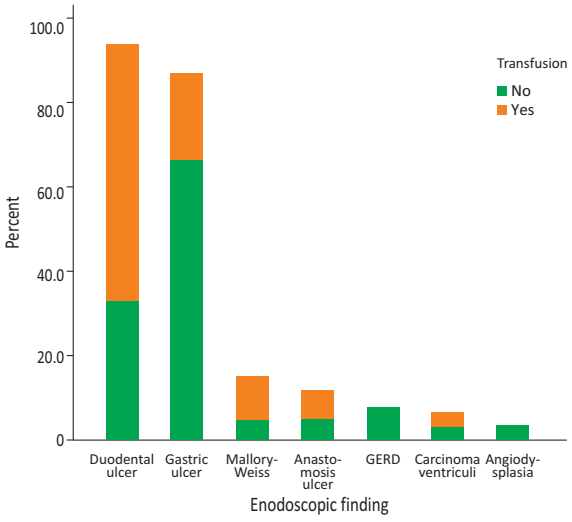


Figure 5. The association between the etiology of gastrointestinal bleeding and the need for transfusion.

Table 1. Predictive Ability of the Independent Variables

Independent variables	Endoscopic intervention			Transfusion		
	B	df	Sig.	B	df	Sig.
Melena	52.433	1	0.997	15.772	1	0.998
Hematemesis	50.272	1	0.997	14.616	1	0.998
NSAIDs	3.588	1	0.000	5.286	1	0.000
Anticoagulants	-17.415	1	0.998	2.044	1	0.220
Hypertension	1.333	1	0.164	2.190	1	0.024
Chronic renal disease	-17.974	1	0.999	1.822	1	0.110
Malignant disease	-17.696	1	0.999	4.125	1	0.002
Earlier vascular incident	-15.183	1	0.997	0.154	1	0.919
Earlier bleeding	-18.441	1	0.999	20.151	1	0.997
Smoking	-0.025	1	0.983	-0.450	1	0.743
Alcohol	2.850	1	0.037	-0.930	1	0.528

df=degrees of freedom; NSAIDs=Nonsteorid anti-inflammatory drugs.

Discussion

The mean age of our patients was between 55-65, with male predominance, in accordance with other studies (6, 7).Upper gastrointestinal bleeding usually presents as melena or hematemesis (8). Our results confirmed this, with 59% of patients presenting with as melena and 21% of patients with melena and haematemesis simultaneously. Ar ecent study showed that the most frequent non-variceal findings on proximal endoscopy were duodenal ulcers, representing about two-thirds of cases, followed by antral gastropathy, gastric ulcers and duodenal/gastric mass, with GERD and Mallory Weiss syndrome much less frequent (9). Our results are in accordance with this study, confirming that duodenal ulcers the leading cause of gastrointestinal bleeding, followed by gastric ulcers, hemorrhagic erosions, neoplasm and GERD. The high percentage of malignant disease verified by emergency gastroscopy in our study is a consequence of the late arrival of patients, as well as

the small percentage of patients taking PPI, despite the presence of risk factors, considering that gastric ulcer is a premalignant condition if not treated in good time.

In the study by Young Joo Yang et al. which enrolled patients with peptic ulcer disease, 31.1% of patients had at least one comorbidity (cardiovascular disease, diabetes, chronic liver disease or cerebrovascular disease). The proportion of medication use was as follows: 11.2% NSAIDs and 7.8% antiulcer medications. About half the patients had alcohol consumption and smoking habits – 47.2% and 55.8% respectively (10). Comparing these results with the results of our study, we notice that a higher percentage of NSAIDs consumption (29.5%) and preexisting comorbidities (56%) are present in our population, without appropriate consumption of antiulcer drugs. On the other hand, a signficantly lower percentage of alcohol and cigarette consumption was registered in our population. Other studies showed slightly higher NSAIDs use (43.7%, 52.4%) and comorbidities present (57.6%, 83%) than in our study, with a higher percentage of gastro-protective drugs as well (13.9%, 14.3%) (6, 7). According to this, gastroprotection was underutilized during NSAIDs treatment in our patients with comorbidities. Increased risk of hemorrhage is NSAIDs dose-dependent (11-13). Although PPI can prevent aspirin-induced upper gastrointestinal bleeding, a clinical dilemma exists about the increased risk of gastric cancer after long-term use of PPI. The study by Cheung KS et al. investigated the potential interaction between aspirin and PPI on gastric cancer development in patients who had eradicated Helicobacter pylori, and perceived that the potentially harmful effects of PPI appeared to be limited to non-aspirin users. Coprescription of PPI is therefore recommended for patients who are at risk of aspirin-induced upper gastrointestinal bleeding (14, 15). Other studies found no evidence that PPI increased the risk of gastric cancer development (16). One of these studies showed that aspirin use for five or more years had positive effects and was associated with a reduction in gastric cancer risk after H pylori eradication (17). Current evidence suggests that short-term use of PPI could be considered effective and safe in adult patients with acid-related disorders. On the other hand, their long-term and often inappropriate use in patients with vulnerability to adverse events and a high risk of drug-interaction, should be avoided (18).

In our study, endoscopic intervention was required in 34% of patients. The need for transfusion occurred in 44.5% of cases, with an average of 3.51±2.10 doses of blood. In the study by Ket SN and al. transfusion was needed in 85% of patients with mainfested upper gastrointestinal bleeding (19). Rebleeding during hospitalization was observed in 7% of patients, surgical intervention in 3% and mortality in 3% of patients. The average length of hospitalization was 5±2 days. Other studies reported a rebleeding rate of 10% and 5.4% of patients, and mortality in 5.7% and 4% patients, respectively. Transfusions were needed in 43.9% patients, with an average length of hospital stay of 9.29+5.58 days (6, 7). Although a recent study showed that endoscopy performed within 6 hours after gastroenterological consultation was not associated with a lower 30-day mortality than endoscopy performed between 6 and 24 hours after consultation, our study showed that timely endoscopic intervention within 6 hours from admission enabled success in 94% of cases, reducing the need for surgery to 3% and rebleeding rate to 7% (20). The transfusion rate and length of hospital stay were lower in our study compared to other published ones.

Our results showed that knowing the etiology of bleeding improves our ability to predict the need for endoscopic intervention by 23.5% and a moderate correlation was found between the two variables. On the other hand, knowing the etiology of bleeding improves our ability to predict the need for transfusion by 42.7%, which is considered as a strong relationship between two variables. NSAIDs and alcohol use were good predictors of endoscopic interventions ($P<0.001$; $P=0.037$), while previous NSAIDs use ($P<0.001$), as well as the presence of hypertension and malignant disease ($P=0.024$, $P=0.002$ respectively) were shown to be statistically significant predictors for transfusion use.

Conclusion

Upper gastrointestinal bleeding is a condition requiring immediate medical intervention. The most common cause of upper gastrointestinal bleeding is peptic ulcer disease, with malignant disease also presenting in a high percentage. The patients admitted to our hospital with symptoms of acute nonvariceal upper gastrointestinal bleeding were elderly, predominantly male, with significant comorbidities and a higher incidence of NSAIDs use. Gastroprotection was underutilized during NSAIDs treatment in patients with other coexisting risk factors. Emergency endoscopic therapy together with PPI significantly reduces rebleeding rates, mortality and the number of emergency surgical interventions.

What Is Already Known on This Topic:

Upper gastrointestinal bleeding can be a life-threatening condition and requires careful evaluation from admission to the emergency center. One the other hand, overuse of NSAIDs, the main risk factors for peptic ulcer bleeding, is common in everyday cinical practice. The question that remains is whether gastroprotection with PPI during NSAIDa therapy is considered sufficiently.

What This Study Adds:

Our study provides insight into epidemiological data about upper gastrointestinal bleeding, which is very important for an insight into the actual healthcare problem. Our results showed that gastroprotection is underutilized during NSAIDs treatment in patients with other coexisting risk factors, with a low rate of concomitant use of PPIs during NSAIDs therapy. This is important for the development of guidelines for management of gastrointestinal hemorrhage at the level of primary, secondary and tertiary health care, in order to reduce the incidence of gastrointestinal hemorrhage.

Author's Contributions: Conception and design: NČ, AS and NT; Acquisition, analysis and interpretation of data: NČ, NH, SĆM, SS and IT; Drafting the article: NČ, AS, SĆM, SS, NT and NH; Revising it critically for important intellectual content: NČ, AS, NT, IT; Approved final version of the manuscript: NČ, AS, SĆM, SS, NT, NH and IT.

Conflict of Interest: The authors declare that they have no conflict of interest.

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