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Upper gastrointestinal bleeding during the COVID-19 pandemic; particularities of diagnosis and therapy

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ABSTRACT

SARS-COV 2 recently caused a global pandemic, with the first case being reported in Romania in February 2020. Important restrictive measures were imposed, so that the addressability of patients to medical services decreased. Upper gastrointestinal bleeding had more severe forms of evolution at the time of presentation, which required additional methods of diagnosis and treatment. This is a retrospective study performed on 268 patients, which aims to evaluate the type and effectiveness of different treatment methods for upper gastrointestinal bleeding during the COVID 19 pandemic. Severity assessment was performed by measuring the Rockall score and additional methods of diagnosis. The association of COVID-19 with upper gastrointestinal bleeding can lead to much more severe outcomes for the patient, so treatment must be sustained and fast established. If the initial therapeutic methods fail, the other available therapeutic measures should be introduced progressively and without delay to achieve the best possible outcomes.

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Introduction

Upper gastrointestinal bleeding is one of the most frequent medical emergencies, which requires intensive drug treatment or even surgery. It occurs more frequently in the elderly, who often have associated comorbidities such as cardiovascular, cerebrovascular, pulmonary or renal diseases, which may be decompensated and thus aggravated by untimely or intermittent bleeding [1]. The location of the bleeding is proximal to the duodeno-jejunal angle, the most important sources being represented by the stomach, esophagus, even recent liver trauma or instruments of the common bile duct, when hemobilia can occur [2].

Due to different etiology, treatment and survival rates, upper gastrointestinal bleeding has been divided into bleeding due to variceal and non-varicose causes. Varicose veins are the consequence of increased pressure in the portal system, secondary to mechanical obstruction (destruction of liver architecture by fibrosis) and/or dynamic obstruction (inability of hepatocytes to synthesize nitric oxide) [3].

There are several locations where the porto-systemic anastomosis can be present, the most important that can cause bleeding being at the junction between the esophagus and the stomach. The main factor that causes bleeding is blood pressure in the vascular system, so above a pressure of 10 mmHg in the portal system varices may be present, and above 12 mmHg the risk of variceal rupture and bleeding becomes significant [4].

Regarding the non-variceal etiology, the most important cause is represented by peptic ulcer, which is at the origin of 60-65% of all upper gastrointestinal bleeding [5]. Generally, the main factor for the appearance of peptic disease is the aggression of gastric acid on the protective layer of the mucosa, followed by the erosion of the vessels in the structure of the duodenal/gastric wall [6]. Over time, acid aggression leads to the onset of esophagitis, gastritis

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and/or duodenitis, but which seem to have decreased in frequency due to the introduction of proton pump inhibitors and the eradication of helicobacter pylori through specific antibiotic treatment in many of these patients [7].

Neoplastic pathology can appear both sporadically (in people who have a diet rich in fats and smoked proteins, who are smokers or in the presence of helicobacter pylori) or in people with premalignant conditions (such as stomach surgery) [8,9]. Genetic factors must also be taken into consideration in families that develop a pattern of diffuse pathology under the age of 40, the genes that predispose to the appearance of neoplastic pathology leading to a heterozygous germline mutation in CDH1 [10].

Other rare causes are represented by: gastric or duodenal polyps, Dieulafoy and Mallory-Weis lesions, aorto-duodenal fistulas secondary to an intense atheromatous process at the level of the abdominal aorta, and last but not least, hemobilia [6].

The clinical expression of upper gastrointestinal hemorrhages is represented by hematemesis (exteriorization of fresh blood through vomiting), melanemesis (which is the result of the action of hydrochloric acid on blood with a blackish appearance) and melena (black, shiny, foul-smelling stool) [2].

When the volume of blood is considerable, it can generate an accelerated transit (secondary to intestinal irritation by the blood), the result being a particular clinical expression of red or partially digested blood, eliminated through the stool [11].

In addition to the common manifestations described, upper gastrointestinal bleeding can be expressed by syncope, decompensation of other cardiovascular events, such as acute myocardial infarction or the sudden onset of a stroke.

The gold standard for diagnosing upper gastrointestinal bleeding is upper digestive endoscopy, which can specify the location and severity of the lesion/risk of bleeding. In addition, it can also have a therapeutic effect, leading to the stopping of bleeding by performing minimally invasive methods [12].

The Rockall risk scoring system was developed in 1996, based on several variables: patient age, blood pressure, pulse, presence and severity of associated comorbidities, endoscopic diagnosis (presence or absence of hemorrhagic stigmata). This score is useful to determine the evolution, risk of rebleeding and even death [13-15].

One of the most important factors that can stop upper gastrointestinal bleeding is represented by the increase in gastric and duodenal pH [16]. A pH value above 6 facilitates the aggregation of platelets and enables the activation of the coagulation cascade, thus helping to stop bleeding. This value must be maintained for 1-3 days to be able to lead to stopping the bleeding [17]. Regarding the healing of the ulcer that was the source of the bleeding, this is achieved by maintaining the pH at values above 3 for about 10 days [18]. This therapeutic goal can be achieved by administering proton pump inhibitors or histamine H2 receptor inhibitors [19].

Other therapeutic methods are represented by minimally invasive treatment, such as the use of the upper gastrointestinal endoscope for perilesional injection of procoagulant substances [20], as well as different types of energy (mechanical, thermal) that can be used to eliminate the vascular fistula [21]. Angioembolization is indicated if endoscopic treatment fails, and when active bleeding can be visualized or there are indirect signs of bleeding such as: pseudoaneurysms, vascular spasm and focal hypervascularity [22]. A variety of materials can be used to induce thrombosis, from autologous blood clot to metal coils and gelatin sponges [23]. If these treatment methods also fail, the last therapeutic resource is represented by surgical treatment, which consists of different procedures (in situ hemostasis or various upper digestive resection procedures) depending on the local lesion and the general condition of the patient [24].

SARS-COV 2 is a betacoronavirus that recently caused a global pandemic and was first identified in Wuhan, China, in the bronchoalveolar lavage of patients with severe pneumonia [25]. The first case of COVID 19 appeared in Romania on February 26, 2020, when successive restrictive measures were imposed at the national level. As a consequence, the addressability of patients to medical services has decreased, thus presenting late to medical institutions, that is with advanced/ complicated forms of the disease. In this context, upper gastrointestinal bleeding took more severe forms of evolution, not only due to late presentation but also due to numerous other factors that had synergistic effects in some patients.

Among these factors should be listed: the use of non-steroidal/ steroidal anti-inflammatory drugs (used to relieve fever or systemic inflammatory syndrome and to stop the progression of fibrosis), the use of systemic anticoagulants to prevent various forms of vascular thrombosis, lifestyle changes (sedentary and fast food consumption, increasing during the pandemic), as well as long hospital stays in intensive care units where patients are predisposed to developing severe forms of stress ulcers [26].

The current study is a retrospective investigation that aims to evaluate the type and effectiveness of different treatment methods for upper gastrointestinal bleeding (depending on their etiology and severity) during the COVID 19 pandemic. For an objective evaluation, the assessment of severity was achieved by measuring the Rockall score, and identifying the best therapy according to the risk class in which the patient was classified.

Materials and Methods

In the present study, the cohort is represented by patients who were admitted to the General Surgery Department of the Pantelimon Emergency Hospital during 01.03.2020-31.03.2022, patients who presented for hematemesis and/or melena as separate or combined symptoms. Patients were identified based on clinical procedure codes. Afterwards, they were classified by performing upper gastrointestinal endoscopy, as an objective diagnostic and possibly therapeutic method. In the case of surgical interventions performed for resected gastric tumors, only patients with hemorrhagic tumors were enrolled in the study, as patients with neoplastic stenosis met the exclusion criteria.

The criteria for inclusion in the study were represented by: the presence of hematemesis, melanemesis and/or melena at presentation, as well as the identification of the source of hemorrhage by endoscopic methods or by direct intraoperative visualization. The exclusion criteria are represented by variceal etiology, portal hypertension, or patients who did not agree to participate in the study. All patients included in the study received consent forms to participate in the study.

Results

Following the application of the inclusion and exclusion criteria, 268 patients were enrolled in the study. There were 59.3% men and 40.7% women, aged between 26 and 97 years (the average being 68.87), while 67.31% of the patients came from an urban environment.

Regarding the etiology of upper digestive hemorrhages, the most common cause was represented by peptic etiology in 67.53% of cases. The presence of infection with the SARS-COV 2 virus was identified in 8.95% of patients.

The Rockall score calculated for the patients enrolled in the study had values between 0 and 10 (with an average of 4.91), most of them having values close to 4 and representing 17.2% of all patients.

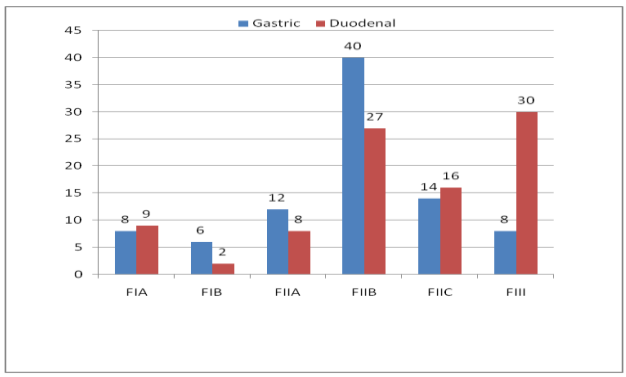

Figure 1. Active bleeding distribution between stomach and duodenum

In the case of peptic ulcer, active bleeding (during endoscopic or intraoperative examination) was identified in 13.81% of patients, with a comparable distribution between stomach and duodenum (49.18% vs 50.82%). The rest of the patients were either with hemorrhagic stigmata or without active bleeding at the time of examination (Figure 1).

The presence of the SARS-COV 2 virus was identified in 8 patients with duodenal ulcer and in 3 with gastric ulcer, and active bleeding was found in 7 of these patients.

The Rockall score according to location was between 0-10 for the duodenum and 1-10 for the stomach; in both subgroups, most patients were distributed around a score of 6. In the case of active bleeding, above average results were usually obtained.

Comorbidities associated with upper gastrointestinal bleeding were represented by hypertension in 52.98% of cases, followed by type II diabetes in 16.04% and congestive heart failure in 11.94% of cases. In the peptic etiology, other associated pathologies were also identified, such as: acute pyelonephritis, hemorrhagic stroke in patients admitted to intensive care, some of them with fatal evolution.

Hemorrhagic gastric tumors represent 13.86% of all cases of upper digestive hemorrhages, being more frequent in men (25 out of 37 cases, with an average age of 67.97 years), of which those located at the antral level were predominant (in 18 out of 37 cases) (Figure 2). In most cases, the malignant pathology was associated with general cardiovascular diseases (hypertension, ischemic coronary disease, atrial fibrillation) but also rare diseases such as Williams-Beuren syndrome (a 27-year-old patient with a gastric tumor placed at the level of the fornix).

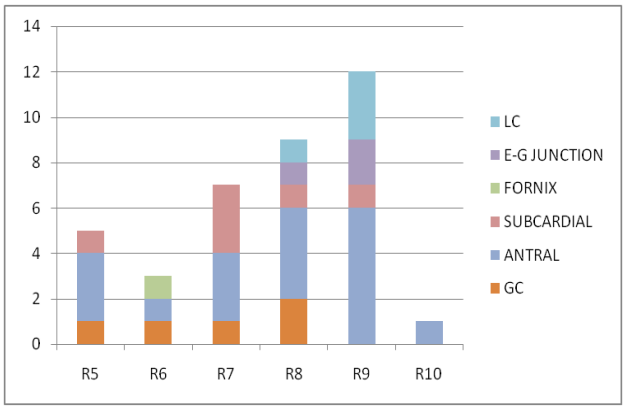

Figure 2. Placement of hemorrhagic gastric tumors

The association between 2 distinct neoplastic pathologies was seen (in the form of synchronous cancer) in 3 patients, 2 of whom had cephalic pancreatic cancer and gastric cancer, and 1 patient had a gastric tumor associated with a left adrenal gland cancer.

Regarding COVID 19, 8 patients presented with hemorrhagic gastric tumors. The Rockall score of the patients with malignant pathology was between 5 and 10, the majority having a score of 9.

Other etiologies of upper gastrointestinal bleeding were represented by hemorrhagic gastritis (10.07%), esophagitis

(5.97%) and other rare causes including strangulated transhiatal gastric hernia with active bleeding (2 cases), 2 cases of gastric polyps, 1 duodenal polyp, 1 case of Mallory-Weiss syndrome and 1 case of duodenal angiodysplasia.

Esophagitis occurred in equal proportion (8 cases) in both men and women, most of them being overweight/ obese and with associated cardiovascular problems.

Hemorrhagic gastritis occurred especially in men in 16 out of 27 cases, most patients presenting a pathology with comorbidities requiring chronic anticoagulant treatment. Seven of 27 patients were on such therapy at the time of evaluation for atrial fibrillation/recent acute myocardial infarction or ischemic stroke, while 5 patients were positive after PCR testing for SARS-COV 2. The Rockall score of these patients was between 0 and 8, most having values of 4.

The treatment administered to patients enrolled in the study was represented by drug therapy (in 79.9% of cases), treatment by minimally invasive methods (6.7% of patients) and surgical treatment in patients who did not respond to conservative treatment methods or minimally invasive procedures (in 13.4% of cases).

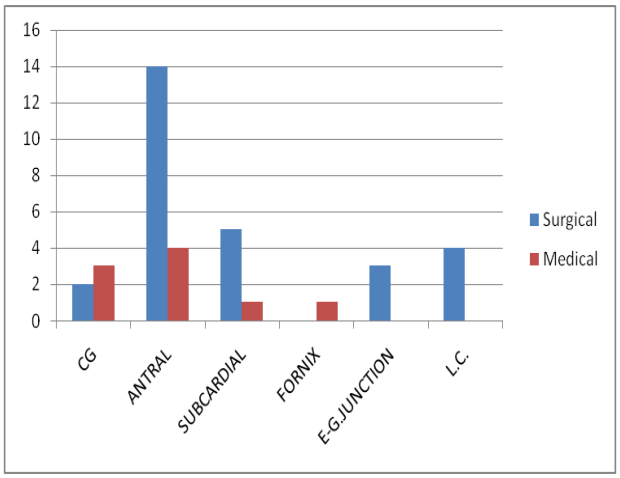

Figure 3. The method of treatment established

Regarding peptic etiology, 96.79% of patients without active bleeding were treated with proton pump inhibitors, while 3.22% were treated by endoscopic methods. For comparison, in the case of hemorrhagic peptic ulcer, 7 patients had an indication for surgical intervention, 12 patients needed minimally invasive intervention when medical treatment failed and 6 patients only benefited from proton pump inhibitors, treatment under which the bleeding ceased.

The malignant pathology of the stomach was treated by both surgical treatment and drug treatment to stop the bleeding. For 27 out of 37 cases the surgical treatment was used, and for the rest conservative treatment proved effective.

For the other causes of upper digestive bleeding, drug therapy was used in 48 of the 50 patients. One case was treated by endoscopy (for duodenal polyp which was removed) and another case was treated surgically for a strangulated diaphragmatic hernia.

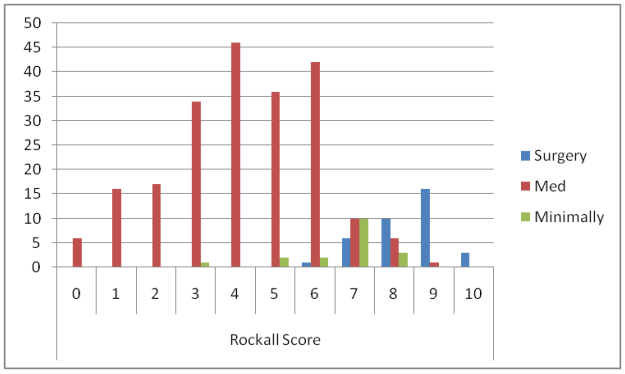

Figure 4. The Rockall Score

Discussion

Severe Acute Respiratory Syndrome Coronavirus 2 caused a global pandemic that had a huge impact on the economy and the medical system, due to severe forms of the disease and prolonged hospitalizations. The classic symptomatology consists of the appearance of cough, fever, myalgia, but also gastrointestinal symptoms such as: diarrhea, vomiting and hematemesis or melena, symptoms that are specific to bleeding from the digestive tract [27.28].

This variable symptomatology is due to the distribution of ACE II receptors on the mucous membranes of the respiratory and digestive tracts [29,30]. By binding the viral S protein to this receptor, the integration of the virus in the enterocyte/pneumocyte takes place [31,32]

Upper digestive hemorrhage externalized by melena or hematemesis can occur in COVID 19 through a direct mechanism, which is generated by the inflammatory response caused by the integration of the virus into cells. An indirect mechanism is also described, represented by the ACE II receptor [33] which has a vasoconstrictive and pro-inflammatory effect and which can lead to necrosis and degeneration of the mucosa, thus causing ulceration and bleeding [34].

As an infection that affects the respiratory tract in patients who develop respiratory failure and hypoxemia, mechanical ventilation is required. Associated with ventilation, opioid and sedative medication is necessary, which leads to a decrease in digestive motility and a decrease in preload [35-37].

Regarding the therapeutic approach of patients with COVID 19, it is complex and involves the administration of several classes of drugs. Depending on the symptoms/general condition, antiviral treatment with Remdesivir, immunomodulatory treatment based on corticosteroids or Tocilizumab (which inhibits the release of cytokines with the triggering of the systemic inflammatory response, but which can affect the mucous membranes and cause bleeding) can be administered. In

addition, nonsteroidal anti-inflammatory drugs can be administered to lower body temperature and also for the prophylaxis of deep vein thrombosis and pulmonary thromboembolism [38].

Severe forms of COVID 19 can be associated with acute respiratory distress syndrome (ARDS), with a massive and uncontrollable release of cytokines such as IL-6, IL-8 and TNF alpha, which can cause activation of the coagulation cascade [39]. Other proinflammatory responses, such as hyaline membrane formation in alveoli in the acute stage, followed by interstitial widening and edema, and then fibroblast proliferation in the organizing stage, are also commonly encountered [40,41].

Dexamethasone is a synthetic corticoid that has anti-inflammatory and immunosuppressive action. Its short-term administration (3-5 days) can reduce the systemic inflammatory response by decreasing the plasma concentration of pro-inflammatory cytokines and thus ameliorating the localized lung lesions associated with COVID 19. All these therapeutic benefits are obtained at the cost of decreasing the immunity mediated by T lymphocytes and by decreasing the activity of macrophages, being therefore recommended only in severe cases due to the association of an increased risk of bacterial infections [42]. Adverse effects of dexamethasone include an increased occurrence of perforated or bleeding ulcers, administration of the drug to intubated or hospitalized patients may result in a 40% higher bleeding rate [43,44].

Another complication of severe disease COVID 19 is the onset of sepsis (either of viral or bacterial origin) due to prolonged mechanical ventilation. The consequence is disseminated intravascular coagulation, initially causing microthrombosis that can be located in the digestive mucosa and have the appearance of ischemia. Due to the consumption of coagulation factors, diffuse bleeding from the tissues and mucous membranes may occur later [45]. Thus, infection with the SARS-COV 2 virus causes a procoagulant status, which means that prevention of thrombosis is mandatory. This can be achieved by administering low molecular weight heparin (LMWH), or with oral anticoagulants such as dicoumarins or new oral anticoagulants (NOACs). Their risk of inducing gastro-intestinal bleeding is much higher, while the administration of prophylactic treatment with proton pump inhibitors does not necessarily reduce the occurrence and recurrence of upper gastrointestinal bleeding [46,47].

The general risk factors for the occurrence of gastrointestinal bleeding in association with anticoagulant treatment are advanced age, history of gastrointestinal bleeding, association with antiplatelet treatment and chronic kidney disease, factors that are relatively common in patients with COVID 19 [48-50].

The therapeutic approach to upper gastrointestinal bleeding includes treatment with proton pump inhibitors, endoscopic treatment and surgical therapy. With the emergence of the infection with COVID 19 the number of upper digestive endoscopies decreased (secondary to a reduced presentation of patients in medical units), but presenting a much more severe symptomatology. In addition, the number of hemodynamically unstable patients at presentation was higher than in the pre-pandemic period, resulting in a lower success rate of conservative medical therapy [26]. In the first 24 hours after presentation, it is necessary to perform an upper digestive endoscopy; before this is done, resuscitation and hemodynamic rebalancing of the patients is carried out. Performing such an intervention on a patient with COVID 19 can cause aerosols that can infect the medical staff participating in performing it, and can affect the lungs of ventilated patients [51,52]. Consequently, the European Society of Gastroenterology maintains that endoscopy should only be performed when absolutely necessary [53]. Cavaliere et al. proposed endoscopy when the patient does not respond to conservative treatment, as well as in cases of treatment with proton pump inhibitors and blood transfusions [54].

An alternative to upper gastrointestinal endoscopy in locating and evaluating bleeding is endocapsular examination. This allows stratification of the risk of bleeding and the need for interventional endoscopy or emergency surgery, limiting the degree of exposure/contamination of staff [55,56], and without a statistically significant difference between diagnostic endoscopy and enterocapsule in identifying the source of bleeding.

The advantages of the diagnostic enterocapsule are represented by the lower risk of staff contamination (for endoscopy it is necessary to have a gastroenterologist, technician, anesthesiologist, nurse, etc.). In addition, it is not necessary for the patient to be sedated/mechanically ventilated, while the effectiveness of the two methods seems to be comparable. The video capsule can be replaced and cleaned quickly without the risk of contamination [57].

The main inconvenience of the enterocapsule is represented by its degree of passivity, being only a diagnostic element. Subsequent guidance of patients requiring surgical or endoscopic intervention and adequate peristalsis of the digestive tube are necessary to complete the diagnosis [58,59]. Due to these shortcomings, the number of endoscopies performed during the pandemic in India has decreased. Most of the patients who were admitted were diagnosed with either gastric ulcer or duodenal peptic ulcer.

Interventional endoscopic treatment had a success rate of 98.8%, with a rebleeding rate of 6.7% at 28 days, and the infection rate of the patients combined with the staff who performed the endoscopy did not exceed 1%. Thus, although initially performed only in selected cases, the endoscopic treatment seems to be effective and safe, the rates of infection with COVID 19 being low [60].

In the present study, the curative attitude had 3 components. Drug treatment represented by proton pump inhibitors (Pantoprazole/ Omeprazole, 40mg), in continuous infusion 200mg diluted in 50ml saline with an administration rate of 2ml/hour. Endoscopic treatment, with adrenaline injection diluted 1:10000 in serum, electrocoagulation/ electroresection, application of hemostatic clips or combinations of the above two methods. Finally, the surgical treatment represented by gastrotomy/pylorotomy with bleeding control or distal resections with Billroth anastomosis was performed.

Regarding the malignant pathology, subtotal/total resections were performed depending on the location of the tumor, with the restoration of digestive continuity through several types of anastomoses: Bilorth II, Hofmeister-Finsterer, Roux-en-Y anastomosis, etc. [61,62]

For patients who had positive PCR tests for SARS-COV 2 infection and signs of upper gastrointestinal bleeding, the treatment was represented by Remdesivir 200mg on the first day, then 100 mg/day for the next 7 days, Dexamethasone 8 mg 2 times a day in cases with ARDS criteria and proton pump inhibitors in continuous infusion. Administration of anticoagulant treatment was initiated after 8 hours in cases where there were no signs of active bleeding. If the hemoglobin value decreased by 2 g in 24 hours without blood administration, or by 1 g after the administration of more than one unit of blood, therapeutic upper digestive endoscopy was performed. If the COVID 19 test was positive and the patient hemodynamically unstable secondary to bleeding, the treatment was surgical, under antisecretory treatment in continuous infusion, then antiviral treatment was administered and after 8 hours anticoagulant therapy.

Following the statistical analysis, we found that patients with Rockall scores of up to 6 points benefited (regardless of etiology) from the administration of drug treatment. At higher score values, surgical and endoscopic treatment are required, so that the higher the Rockall score, the higher the probability of a minimally invasive or invasive treatment, with a strong statistical significance in the study group ($p<0.001$).

Patients who presented with upper gastrointestinal bleeding and specific symptoms of COVID 19 underwent endoscopic and surgical treatment in a higher proportion than the uninfected population for the same pathology, their Rockall scores being 1 point higher than the standard population. In 5 out of 24 cases the associated pathologies generated hemodynamic instability at the time of hospitalization in the general surgery department, requiring emergency surgical intervention including tracheostomy [63,64], and 3 out of 5 patients had a fatal outcome after the first 24 hours.

The main limitation of the study was represented by the fact that it was a retrospective investigation. Although the conclusions reached are statistically relevant, how the severity of upper gastrointestinal bleeding is influenced by the presence or absence of SARS-COV 2 infection still remains to be further investigated [65]. A possible explanation could be represented by the prothrombotic and ischemic state of the infection, which can affect the protective barrier of the cavitary viscera with the appearance of secondary ulcers.

Another explanation can be given by the effect of drugs on the integrity of the stomach/duodenum. During the pandemic, the consumption of medicinal substances increased by the administration of non-steroidal anti-inflammatory drugs used to treat cold symptoms, or by the administration of other substances with the intention of increasing the survival rate of patients. Colchicine was used in the first months of the pandemic, a large dose of it being known to produce gastritis and upper gastrointestinal bleeding [66]. Tocilizumab has been introduced into therapy to reduce the systemic inflammatory response by inhibiting the action of IL-6, but has numerous side effects such as bleeding, nausea, vomiting and ulceration [67].

Conclusions

In conclusion, the Rockall score used in the assessment of the severity of gastrointestinal bleeding can predict quite well the type of treatment required for each patient. The association of COVID-19 with upper gastrointestinal bleeding may lead to a poorer therapeutic outcome, so treatment should be sustained. In case of initial therapeutic failure, other available therapeutic measures should be rapidly introduced to achieve the best possible outcome.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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