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ORIGINAL ARTICLE

Upper gastrointestinal bleeding in COVID-19 inpatients: Incidence and management in a multicenter experience from Northern Italy

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KEYWORDS
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Abstract
Background: COVID-19 patients have an increased susceptibility to develop thrombotic complications, thus thromboprophylaxis is warranted which may increase risk of upper gastrointestinal bleeding (UGIB). Our aim was to evaluate incidence of UGIB and use of upper GI endoscopy in COVID-19 inpatients.

Abbreviations: COVID 19, coronavirus 2019 disease; GBS, Glasgow Blatchford score; ICU, intensive care unit; LMWH, low molecular weight heparin; UGIB, upper gastrointestinal bleeding.

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Methods: The medical and endoscopic management of UGIB in non-ICU COVID-19 patients has been retrospectively evaluated. Glasgow Blatchford score was calculated at onset of signs of GI bleeding. Timing between onset of signs of GI bleeding and execution, if performed, of upper GI endoscopy was evaluated. Endoscopic characteristics and outcome of patients were evaluated overall or according to the execution or not of an upper GI endoscopy before and after 24 h.
Results: Out of 4871 COVID-19 positive patients, 23 presented signs of UGIB and were included in the study (incidence 0.47%). The majority (78%) were on anticoagulant therapy or thromboprophylaxis. In 11 patients (48%) upper GI endoscopy was performed within 24 h, whereas it was not performed in 5. Peptic ulcer was the most common finding (8/18). Mortality rate was 21.7% for worsening of COVID-19 infection. Mortality and rebleeding were not different between patients having upper GI endoscopy before or after 24 h/not performed. Glasgow Blatchford score was similar between the two groups (13;12—16 vs 12;9—15).
Conclusion: Upper GI bleeding complicated hospital stay in almost 0.5% of COVID-19 patients and peptic ulcer disease is the most common finding. Conservative management could be an option in patients that are at high risk of respiratory complications.

Introduction

Outbreak of the novel severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection, leading to coronavirus 2019 disease (COVID-19) is dramatically growing worldwide and declared an official pandemic by WHO on March 11, 2020 [1]. The first COVID-19 case was detected in Italy on February 20th 2020 and at the time of the writing of the paper more than 230,000 cases were diagnosed with 31,936 deaths.

COVID-19 ranges from an asymptomatic course or mild flu-like syndrome to a severe viral pneumonia with respiratory failure [2,3]. No specific treatment is currently available and different classes of drug have been used in hospitalized patients (i.e. antiviral agents, glucocorticoids, monoclonal antibodies and antimalarial drugs) [4]. Recent evidence suggests that COVID-19 patients have an increased susceptibility to develop venous thromboembolism, which may be a poor prognostic factor [5]. Therefore thromboprophylaxis is formally recognized as a pivotal treatment [6,7]. Risk and incidence of upper gastrointestinal bleeding (UGIB) in COVID-19 patients is unknown, and at the moment only two case series (one without endoscopy data) [8,9] and two case reports are reported in literature [10,11]. Moreover, hospitalized patients frequently have cardiovascular comorbidity and are on antiplatelet or anticoagulant drugs. A proportion of patients with a severe course of the disease are exposed to stress ulcers, like intensive-care unit (ICU) patients [12], and this further increases the risk of UGIB.

Routinely UGIB is managed by endoscopists after clinical stabilization within 24 h, as suggested by International Guidelines [13]. The recent ESGE and ESGENA Position Statement on gastrointestinal (GI) endoscopy and the COVID-19 pandemic [14] includes GI endoscopy in the setting of UGIB within the procedures that should be performed. However, the Authors did not consider the complex clinical scenario in which bleeding complications occur. Risk of desaturation and cardiopulmonary complications needs to be considered in patients with UGIB [15,16]. COVID-19 patients are probably at increased risk of respiratory worsening during endoscopy with the possible need of respiratory support escalation and transferal to ICU department which may be a critical issue during the peak of COVID-19 outbreak for poor availability of ICU beds. Thus timing of endoscopy and medical management are crucial for patients' outcome.

Aim of our study is to retrospectively evaluate incidence, management and outcome of UGIB in COVID-19 patients in non-ICU of tertiary COVID-19 hospitals from Northern Italy.

Material and methods

From March 1st to April 30th, 2020, COVID-19-positive patients with signs of UGIB were retrospectively included in our study from six academic and two non-academic hospitals in Northern Italy (Como, Legnano, Milan ''Ca' Granda'', Milan ''Sacco'', Monza, Novara, Padua and Pavia). Two Centers are also referral for Liver Transplantation (Milan ''Ca' Granda'' and Padua).

Medical history, in particular use of antiplatelet and/or anticoagulant, was acquired.

Patients who had overt signs of acute UGIB (i.e. haematemesis, tarry stool or coffee ground vomitus) with a positive diagnosis of COVID-19 infection (positive real-time PCR obtained with nasopharyngeal swab or bronchoalveolar lavage) were eligible to be included in the study. We excluded patients who were younger than 18 years of age, pregnant, or moribund from terminal course of COVID-19, and those who were already admitted to ICU. We decided to exclude from the study patients admitted to ICU Departments because during COVID-19 outbreak the majority of them were intubated and therefore the management and decision on timing of endoscopy was not influenced by the risk of the procedure or sedation.

Glasgow-Blatchford score (GBS) was calculated at onset of signs of GI bleeding. Time between onset of sign of GI bleeding and upper GI endoscopy was calculated by checking medical records. Type of thromboprophylaxis or anticoagulant therapy if thrombotic events occurred during hospital stay (i.e. deep venous thrombosis and/or pulmonary embolism) were recorded. Severity of COVID-19 pneumonia was classified according to the type of oxygen support (ambient air, low flow oxygen, high flow oxygen, noninvasive positive pressure ventilation).

Upper GI endoscopy, when needed, was performed by experienced endoscopists. Endoscopic bleeding findings were classified accordingly. Gastroduodenal ulcers with

active bleeding or with nonbleeding visible vessels (i.e. Forrest Ia, Ib and IIa), gastroesophageal varices with active or recent stigmata of bleeding and other source of active bleeding were treated by the endoscopists accordingly to guidelines [13,17]. If the endoscopic management was unsuccessful, a radiological or surgical treatment was proposed.

Endoscopic characteristics and outcome of patients were evaluated overall or according to the execution or not of an upper GI endoscopy within and after 24 h. Data are expressed as median with IQ range. Chi-square test with Fisher test and Mann–Whitney test were used when appropriate. The study was approved by the Local Ethics Committee (San Matteo Hospital Foundation) on March 13th, 2020, and all patients provided written informed consent for the anonymized use of their data for research purposes, within the respect of their privacy.

Results

Among 4871 COVID-19-positive patients, we enrolled 23 cases (18 males; 75 years; IQR 64–78) with UGIB in non-ICU

Table 1 Clinical characteristics and biochemical data of COVID-19 positive patients with upper gastrointestinal bleeding. Data expressed as Median (IQR) and as absolute number (percentage).

	All patients ($n = 23$)	Endoscopy ≤ 24 h ($n = 11$)	Endoscopy > 24 h or not performed ($n = 12$)
Age, years	75 (64–78)	72 (64–76)	78 (70–81)
Comorbidity			
Hypertension	16 (70)	7	9
Diabetes mellitus	11 (48)	5	6
Chronic heart disease	9 (39)	3	6
Active oncological disease	3 (13)	3	0
Cirrhosis	2 (9)	2	0
Chronic kidney disease	4 (17)	2	2
Obesity	2 (9)	1	1
Neurological disease	5 (22)	2	3
Antiplatelet therapy	7 (30)	2	5
Low dose aspirin	5 (22)		
Clopidogrel	1 (4)		
Dual antiplatelet therapy	1 (4)		
Anticoagulant therapy	18 (78)	7	11
LMWH qd[a]	8 (35)		
LMWH bid	5 (22)		
Vitamin k antagonist[b]	1 (4)		
DOAC[b]	4 (17)		
Respiratory support			
Ambient air	4 (17)	2	2
Low flow oxygen	3 (13)	2	1
High flow oxygen	8 (35)	5	3
Non-invasive positive pressure	8 (35)	2	6
Biochemical parameters at admission			
C-reactive protein, mg/dl	7.8 (4.4–11)	4.5 (4–6.3)	11 (8.8–16.9)[d]
LDH, mg/dl	320 (278–418)	285 (238–392)	324 (291–418)
D-Dimer[c]	919 (621–2046)	660 (333–2080)	1013 (800–1635)
Hb, g/dl	9 (8.1–10.8)	(7.6–8.9)	10.7 (8.9–12.5)[e]
Signs of upper GI bleeding			
Tarry stools	12 (52)	4	8
Haematemesis	5 (22)	4	1[f]
Coffee ground vomitus	3 (13)	1	2
Severe progressive anemia and dark stool	3 (13)	2	1
Glasgow-Blatchford score	13 (10–16)	13 (12–16)	12 (9–15)

[a] In one patient before admission.
[b] Before admission.
[c] Not available in three patients.
[d] $p = 0.001$ vs endoscopy ≤ 24 h.
[e] $p = 0.03$ vs endoscopy ≤ 24 h.
[f] $p = 0.09$ vs endoscopy ≤ 24 h.
LMWH, low molecular weight heparin; DOAC, direct oral anticoagulant; LDH, lactate dehydrogenase; Hb, Hemoglobin.

Table 2 Endoscopic findings and outcome. Data expressed as absolute number (percentage).

	All patients ($n = 23$)	Endoscopy before 24 h ($n = 11$)	Endoscopy after 24 h or not performed ($n = 12$)
Endoscopic findings[a]			
Gastric or duodenal ulcer	8 (44)	5	3
Erosive or haemorragic gastritis	4 (22)	1	3
GOV1 variceal bleeding	1 (6)	1	0
Mallory-Weiss	2 (11)	1	1
Dieulafoy' lesion	2 (11)	2	0
Normal	1 (6)	1	0
Endoscopic treatment	7 (38)	6	1[b]
Adrenaline injection + clips	6 (33)	5	1
Cyanoacrylate injection	1 (6)	1	0
Rebleeding[a]	3 (17)	2	1
Outcome			
Discharged	18 (78)	9	9
Died	5 (22)	2	3

[a] In 18 patients.
[b] $p = 0.08$ vs endoscopy $\leq$24 h.

Departments (prevalence 0.47%). One Center (Como) did not report any case of upper GI bleeding out of 410 COVID-19 positive patients. Prevalence among Centers was homogeneous being always lower than 1% and ranging from 0.1% to 0.9%.

All 23 patients had a confirmed diagnosis of COVID-19 by nasopharyngeal swab. Clinical characteristics and biochemical data are detailed in Table 1. In particular 15 out of 23 patients (65%) had two or more comorbidities (78% hypertension or chronic heart disease, 48% diabetes and 9% cirrhosis).

Seven patients (30%) were on antiplatelet therapy, and three of them were also taking at home direct oral anticoagulant. A total of 18 patients (78%) were on anticoagulant therapy at the moment of gastrointestinal bleeding (35% on prophylactic therapy and 44% in full dose anticoagulant). Thromboprophylaxis with LMWH qd was started in seven patients during hospital stay. Full dose anticoagulant was started with LMWH bid in five patients because of pulmonary embolism (1), new onset atrial fibrillation (2) and high-risk laboratory features of thrombosis (2).

Sixteen patients (69%) had a severe respiratory involvement of COVID-19 pneumonia (high flow oxygen or non-invasive positive pressure support).

Upper gastrointestinal bleeding

Signs of UGIB appeared in a median time of 4 days (0.6—7) during hospital stay being presence of tarry stool the most common finding (52%). In six out of 23 patients upper GI bleeding was the reason for admission at the Emergency Department with concomitant diagnosis of COVID-19 infection; three of them had at admission a significant respiratory involvement with the necessity of non-invasive positive pressure support (2 patients) or high flow oxygen.

At onset of GI bleeding all but one patient were treated with intravenous bolus of proton pump inhibitor. One patient was treated before endoscopy with vasoactive agent for suspicious of variceal bleeding. GBS at onset of bleeding was 13 (range 10—16).

Upper GI endoscopy was performed in 18 patients. Endoscopic findings and treatments are detailed in Table 2. Peptic

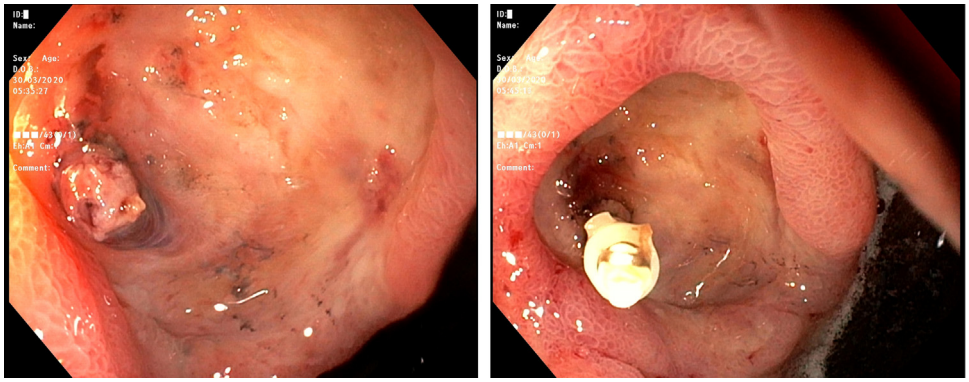

Figure 1 Peptic ulcer with visible vessel (Forrest IIa) on the anterior wall of duodenal bulb (on the left) treated with epinephrine injection and one hemostatic clip, Olympus HX-610-090 (on the right).

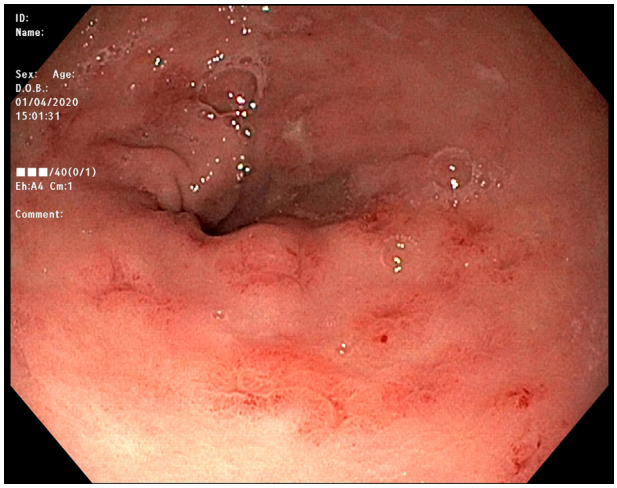

Figure 2 Diffuse antral erosive gastritis with superficial ulcers on the lesser wall.

ulcer (Fig. 1) was the most common finding (44%) followed by erosive (Fig. 2) or haemorragic gastritis (22%). Variceal bleeding from gastroesophageal varices occurred only in one patient. Endoscopic treatment was necessary in six patients (adrenaline injection + clips in 5 and cyanoacrylate injection in one). Three patients presented early rebleeding: two were treated with radiological embolization and one with endoscopic retreatment.

Timing between onset of upper GI bleeding and endoscopy execution

Upper GI endoscopy was performed after a median time of 24 h (2—60 h). In 11 patients (48%) upper GI endoscopy was performed within 24 h and noteworthy four of them had haematemesis. In one patient it was not executed for a severe respiratory worsening that lead to patients' death after 24 h. In the other four patients (three with severe respiratory involvement) conservative treatment with PPI iv, anticoagulant withdrawal and blood transfusions lead to stabilization of hemoglobin values and resolution of bleeding.

Clinical characteristics were similar between the two groups (see Table 1).

Rebleeding rate was not different between patients having upper GI endoscopy within or after 24 h (2/11 vs 1/7 episodes). Need for endoscopic treatment was more common in patients in whom upper GI endoscopy was performed before 24 h (6 vs 1 patients, $p = 0.08$) although GBS score was similar between the two groups (13;12—16 vs 12;9—15, p = NS).

Interestingly, C-reactive protein was higher in the group of patients where upper GI endoscopy was not performed or after 24 h (4.5 mg/dl; 4—6.3 vs 11 mg/dl; 8.8—16.9). As expected, hemoglobin levels were lower in the group where upper GI endoscopy was performed within 24 h (8.3 g/dl; 7.6—8.9 vs 10.7 g/dl; 8.9—12.5, $p = 0.03$).

Outcome

Eighteen patients were discharged. Mortality rate was 21.7% (five patients). All of them have died for worsening of COVID-19 infection, and one of them had a rebleeding that was successfully treated with radiological embolization.

Patients who underwent to upper GI endoscopy before 24 h or after 24 h/not performed have similar mortality rate (2 vs 3 patients).

Discussion

This is the first study, to the best of our knowledge, that evaluated the incidence and the endoscopic characteristics of UGIB in COVID-19 patients. All the Centers came from Regions (six in Lombardy, one in Piedmont and one in Veneto) that had the highest incidence of SARS-CoV-2 outbreak in Italy [18]. We reported an incidence of 0.47% in COVID-19 patients who were admitted in non-ICU Department. Reported incidence in literature of UGIB in hospitalized patients is different among studies and varies in consideration of diagnostic definition, the prophylaxis prescribed, the publication era and type of admission department [19]. It is certainly known that the incidence is higher in critically ill patients admitted to the ICU ranging from 1.5% to 5.5% [20,21] compared to non-critically ill patients in whom the incidence varies from 0.005% [22] to 0.4% [23]; hospital admission incidence for UGIB was reported around 0.3% [24]. Our reported incidence is in line with the rate of patients not admitted to the ICU. However, COVID-19 inpatients need to be considered as a group of critically ill patients. Indeed, in our cohort the majority had at least two comorbidities (78%) and the majority of them had a significant respiratory involvement (69%). Moreover, during COVID-19 outbreak availability of ICU beds was poor and therefore many patients were managed in non-ICU departments although they had many criteria for admission to the ICU. Therefore, incidence of UGIB in COVID-19 patients is not as high as expected, given the significant comorbidity and the widespread of thromboprophylaxis.

Median age in our cohort was 75 years, confirming previously published data showing that UGIB predominantly afflicts elderly patients with comorbidities in a hospital setting [25].

Anticoagulant therapy and thromboprophylaxis are recognized risk factors for upper GI bleeding in hospitalized patients with an OR in a multivariate analysis of 2.6 and 1.7 respectively; the OR increases to 3.2 if anticoagulation is associated with a single antiplatelet agent [26]. In our retrospective study we did not have data about the overall use of anticoagulant therapy or thromboprophylaxis in all COVID-19 patients. However given the progressive evidence on the risk of thrombosis in this category of patients [5], thromboprophylaxis was progressively and early started in COVID-19 patients. Italian agency of drugs inserted on 11th of April enoxaparin as a recommended off-label therapy in patients with acute respiratory failure and/or reduced mobility [27]. This type of management is confirmed in our report where 78% of patients were in anticoagulant therapy or thromboprophylaxis that was started during hospital stay in 48% of them. Although the diffuse use of LMWH, incidence of UGIB remained low.

About endoscopic findings, peptic alterations were the most common finding (44% active ulcers and 22% diffuse erosive or hemorrhagic gastritis) in agreement with a case series. Despite the participation in our study of two referral Centers for liver transplantation and one center being the referral for infectious disease in Milan with a high number of cirrhotic patients in follow up, only one patient developed variceal bleeding from a gastroesophageal varice. It must be remarked that we did not know which is the incidence of COVID-19 infection in cirrhotic patients. Our percentage of endoscopic findings are in line with the ones reported in literature as a cause for non-variceal UGIB [28] and therefore we cannot speculate on a causative effect of COVID-19 on GI bleeding.

One of the aims of our study was to evaluate which was the management of UGIB in this novel systemic disease. We interestingly found that almost half of the enrolled patients (52%) performed the endoscopy after 24 h and five of them were managed conservatively with resolution of bleeding and stabilization of hemoglobin values, except in one case where endoscopy was not performed for a progressive respiratory worsening that lead to patients' death. We compared the two category of patients (endoscopy within 24 h vs endoscopy after 24 h or not performed), and we found similar clinical characteristics in terms of comorbidities, respiratory support and GBS. As expected, we observed a trend toward a higher number of pathologic findings needing endoscopic treatment in the group that performed upper GI endoscopy within 24 h (6 vs 1, $p = 0.08$). However, we found a similar outcome considering mortality and rebleeding rate, although endoscopic treatment is known not to be always associated with a better outcome [29]. We have to point out that the decision to group patients that performed endoscopy after 24 h with those who did not was arbitrary and related to the assumption of a wait-and-see approach.

Noteworthy, c-reactive protein values were higher in patients where endoscopy was performed after 24 h. It is known from the literature that higher c-reactive protein values at admission are associated with worse outcome in COVID-19 patients [30]. Despite this significant difference, patients had a similar outcome. Patients with haematemesis were managed earlier than patients presenting other symptoms (i.e. tarry stool or coffee ground vomitus) as expected and in line with guidelines [13]. The decision to postpone upper GI endoscopy or to not perform was probably related to the significant respiratory involvement (nine out of 12 patients) or to a severe systemic course of COVID-19 disease that reflected higher c-reactive protein values and that lead physicians to avoid additional factors (i.e. sedation, endoscopic procedure) that could worsen respiratory function. Moreover, in Italy during the peak of COVID-19 outbreak there was a complete saturation of ICU beds and therefore there was a trend to manage conservatively all type of complications that could result in transferal to the ICU. This type of conservative management was also described with clinical success by Cavaliere et al. in six COVID-19 patients with UGIB [8].

Our study has also some limitations. First, the retrospective nature of the study could not have included those patients with non-significant UGIB in which endoscopist's evaluation was not requested. Therefore, the rate of UGIB in COVID-19 may be underestimated. However, in our centers endoscopists are usually consulted for minor bleedings and therefore the underestimation is, in our opinion, negligible. Second, the total number of enrolled cases is limited, thus comparative results between the two groups needs to be considered with caution. Moreover predictive analysis of UGIB on mortality or disease worsening was not possible.

Based on our results we propose a simple algorithm (Fig. 3) for the management of UGIB in COVID-19 patients. First, it is crucial patients' support if there are signs of hemodynamic instability with infusion of liquids and hemotransfusion, infusion of PPI and anticoagulant withdrawal. Then it is necessary to stratify respiratory involvement based on type of respiratory support. In a study by Stanley A. et al. need of endoscopic treatment was predicted with a sensitivity of 80% using the GBS with a cut off ≥ 7 [31]. In our study all but one patients have a GBS more than 7 and therefore we did not included GBS for endoscopic risk stratification. In presence of low risk patients that are in ambient air or low flow oxygen support (type 1—2 support), upper GI endoscopy could be performed based on standard guidelines within 24 h. If patients are more critical (high flow or non-invasive positive pressure support) it is important to stratify them according to presence of haematemesis: if there is not haematemesis (i.e. tarry stool with anemia) the patient could be strictly monitored with medical support (PPI iv, blood transfusions and anticoagulant withdrawal). Upper GI endoscopy needs to be considered in case of poor response of medical management.

In conclusion our study shows that the prevalence of UGIB in COVID-19 patients is in line with previous epidemiological studies in non-ICU patients despite the widespread of anticoagulation. Thus thrombotic and other systemic complications remain the main challenge in this group of patients. Conservative management with optimization of medical therapy and delay of endoscopy could be considered in those patients with high risk of worsening respiratory function.

Conflict of interest

None declared.

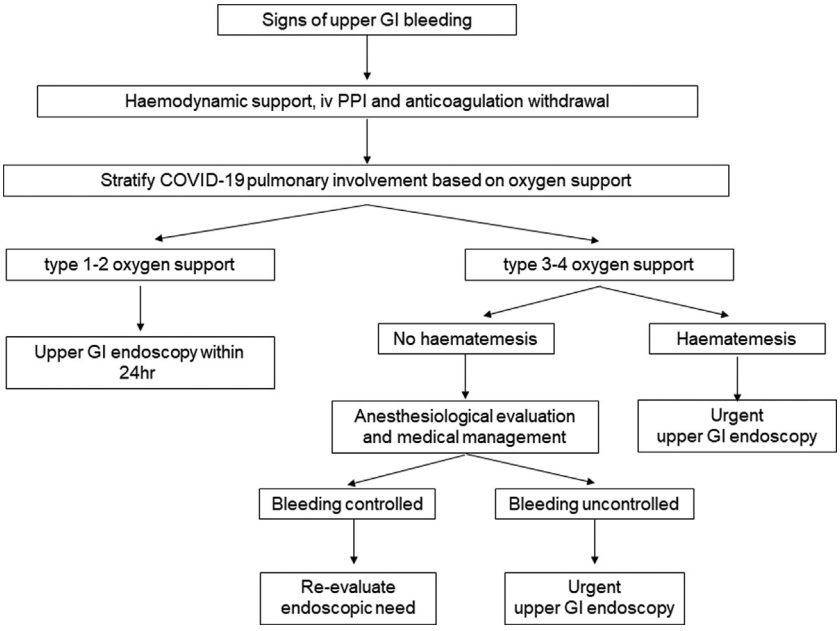

Figure 3 Proposed algorithm for the management of upper gastrointestinal bleeding in COVID-19 positive patients.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.clinre.2020.07.025.

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