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Upper gastrointestinal bleeding in mechanically ventilated patients in medical ICU: A single-center study

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Running Head: gastrointestinal bleeding in ventilated patients

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Abstract**Aims**

Upper Gastrointestinal bleeding (UGIB) in critically ill patients under mechanical ventilation (MV) is a significant cause of morbidity and mortality. Therefore, it aimed to study the incidence, predictors, and etiology of UGIB in critically ill patients under MV.

Patients and Methods

Three hundred and sixty critically ill patients were managed by mechanical ventilation. The patients were evaluated by complete clinical examination, APACHE II score, liver and kidney function tests, and abdominal ultrasound. In addition, upper gastrointestinal endoscopy was done for survived patients with UGIB during MV after weaning with a stable clinical condition for at least 48 hours.

Results

41 patients (11.4 %) had UGIB; 15 patients (36.6%) survived and death occurred in 26 (63.4%). Upper endoscopy revealed large ulcers > 2 cm in the gastric antrum (n=1), multiple antral ulcers (n=2), large >2cm corporeal gastric ulcers (n=2) [all were Forrest Ib with oozing surface], bleeding small duodenal bulb ulcers < 2cm (n=1) [Forrest Ia with spurting], small ulcers in the lower esophagus with lower end esophagitis (n=2), black esophagus (n=1), ulcer on top of grade III oesophageal varices (n=2), severe portal hypertensive gastropathy (n=3), candida esophagitis and gastritis (n=1). Logistic regression analysis revealed that the independent variables of UGIB were elevated serum creatinine, APACHE II score >14, peak inspiratory pressure $\geq 30\text{cmH}_2\text{O}$, and prolonged aPTT.

Conclusions

Mechanically ventilated patients had a high risk of upper gastrointestinal bleeding, which the postulated parameters can predict for adequate prophylaxis.

Keywords: Mechanical ventilation, upper gastrointestinal bleeding, Critical ill, endoscopy, peptic ulcer, gastropathy, prophylaxis, sepsis, morbidity, PPI.

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Introduction

In the first 24 hours of ICU admission, gastrointestinal bleeding may reach 50%, with severe bleeding occurring in 6% of cases. The most prevalent cause of UGIB in critically ill patients admitted to the ICU is stress ulcers, which may lead to severe complications with substantial morbidity and death [1].

Pharmacological prophylaxis of UGIB in critically ill ventilated patients may have some benefits. However, this may not be cost-effective and may increase the incidence of ventilation-associated pneumonia [2]. Therefore, the constraints must be considered before considering pharmacological prophylaxis, particularly in managing severe sepsis and septic shock [3].

Mechanical ventilation of patients following surgery or due to multi-organ failure, sepsis, and respiratory failure may be complicated with UGIB due to stress-related mucosal damage, resulting in acute erosive gastritis or duodenitis [4]. Clinically significant UGIB may cause hypotension from hypovolemia, organ failure, and death. In addition, the stress-related insult's severity increases mortality, reaching up to 80% in severe cases [5].

Mechanical ventilation has been identified as one of the most prominent risk factors for UGIB in the ICU [6]. It is the most advanced form of respiratory support and is often complicated by Ventilator-Associated Events (VAEs), which increase morbidity and length of ICU stay [7], and are recognized as persistent worsening of oxygenation for at least 48 hours following initial improvement for two consecutive days [8].

There have been few major observational studies on the Prevalence of UGIB in ICU patients [9]. Therefore, this study assessed the incidence, etiology, and predictors of upper gastrointestinal bleeding in critically ill patients under mechanical ventilation in the medical ICU.

2. Patients and Methods

This observational cross-sectional cohort study was conducted in the Department of Internal Medicine medical ICU unit, Zagazig Faculty of Medicine, a tertiary referral center. Ethical committee approval was obtained (255-2018). In addition, written informed consent was taken from the patient's first-degree relatives to participate in this study.

-Patients

The study included 360 critically ill patients who were admitted to the medical ICU & managed with MV; patients were categorized into two groups:

Group I: consisted of 41 (11.4%) patients with UGIB and then subdivided into two subgroups: *Group IA* included 15 survived patients and *Group I.B.* included 26 deceased patients.

Group II: consisted of 319 patients without UGIB.

The patients with UGIB were followed up until they were stabilized and weaned from MV. Upper G.I. endoscopy was performed at least 48 hours after MV weaning, and they were discharged from the ICU, and then the follow-up was scheduled in the outpatient clinic.

Exclusion criteria: patients who had a history of gastrointestinal bleeding, history of recent gastrointestinal surgery, brain death, or bleeding disorders.

-Methods

All patients underwent a thorough clinical examination, a complete blood count, liver and renal function testing, and a coagulation profile.

Cardiac assessment by ECG and bed-side echocardiography in addition to evaluation and optimization of mechanical ventilation parameters (respiratory rate 12-20, tidal volume 5-15 ml/kg, FIO₂ initially 100%,

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minute ventilation 150-250 ml/kg/min, Peak inspiratory pressure (PIP) 10-20 cm H₂O in normal lungs and 15-25 in diseased lungs, I: E ratio 1:2, PEEP 5-10 cm H₂O, trigger sensitivity - 2 cm H₂O or 2 L/min) ^[10].

- Assessment of severity, patient prognosis, and mortality using acute physiology and chronic health evaluation score (APACHE II) ^[11], measured within 24 hours of admission, with a value from 0 to 71, it included PaO₂ (for FiO₂ ≥ 0.5 or < 0.5, rectal body temperature, mean arterial pressure, blood pH, heart rate, respiratory rate, serum sodium & potassium, creatinine (Double point score for acute renal failure), hematocrit value, white blood cell count, Glasgow Coma Scale, Age (≤ 44 years = 0, 45-54 = 2, 55-64 = 3, 65-74 = 5, ≥ 75 = 6), patients associated co-morbid conditions such as NYHA class IV heart failure, severe respiratory disease, dialysis or immunocompromised states by cancer, immunosuppressants were given 5 points in non-operative or emergency postoperative patients, and 2 points for elective postoperative

-Upper GIT endoscopy was performed using Pentax one channel (EG₂₉₄₀) and dual channel (EG₃₈₀₀) video scopes for patients with UGIB who had survived and were weaned from mechanical ventilation.

-Bleeding from peptic ulcers was evaluated by Forrest (F) classification ^[12]. Esophageal varices were graded according to Modified Paquet classification ^[13].

Gastrointestinal bleeding was recognized as overt or clinically significant bleeding. Overt bleeding means a prominent feature of bleeding without hemodynamic compromise as hematemesis, melena, coffee ground secretions in a nasogastric tube, and hematochezia. Clinically significant UGIB is an overt bleeding with an associated decrease in mean arterial pressure of positive tilt test denoting an orthostatic reduction in systolic pressure > 10 mmHg and simultaneous increase of arterial pulse > 20 beat/min or a significant decrease of H.B. > 2gm that needed transfusion of at least two units of blood within 24 hours of bleeding. Sucralfate and H₂ blockers had done upper gastrointestinal bleeding prophylaxis only to minimize the risk of sepsis and significant morbidity if using stress ulcer prophylaxis with PPIs.

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Statistical analysis

The data were collected, tabulated, and statistically analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software, Ostend, Belgium). Data were tested for normal distribution using the Shapiro Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test (χ^2) and Fisher exact were used to calculate the difference between qualitative variables as indicated. Quantitative data were expressed as mean \pm S.D. (Standard deviation) for parametric, median, and range for non-parametric data. The Independent T-test and Mann-Whitney test were used to calculate the difference between quantitative variables in two groups for parametric and non-parametric variables, respectively.

The relative risk and 95% confidence interval of the significant factors were calculated by multivariate logistic regression analysis using the stepwise method to determine independent risk factors of UGIB with $p < 0.05$ in univariate analysis. All statistical comparisons were two-tailed with a significance level of P-value < 0.05 .

3. Results

Three hundred and sixty critically ill patients were admitted for mechanical ventilatory support due to pneumonia (n=43), septic shock (n=87), respiratory failure (n= 75), chronic obstructive pulmonary disease (n= 56), ischemic heart disease (n= 39), and cerebrovascular stroke (n= 60) (**Table1**).

Table 1. Etiology of critical illness and MV in the studied group.

<i>Admission diagnosis</i>	<i>Frequency</i>	<i>Percent</i>
Pneumonia	43	11.9%
Septic shock	87	24.2%
Respiratory failure	75	20.8%
COPD	56	15.6%
Ischemic heart disease	39	10.8%
Stroke	60	16.7%

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Regarding MV characteristics, mechanical ventilation duration ranged from 2 -20 days with a median volume of 450 ml; median O₂ was 45 %, and median PEEP was 5 cm H₂O (**Table 2**).

Table 2. Mechanical ventilation characteristics of the studied patients.

<i>Variables</i>	<i>The studied patients</i> (N=360)
<i>Duration of ventilation (days): Median, Range</i>	6 (2 – 20)
<i>Volume: Median, Range</i>	450 (250 – 650)
<i>O₂: Median, Range</i>	45 (25 – 100)
<i>PEEP: Median, Range</i>	5 (0 – 15)

Out of 360 critically ill patients on MV, 41 patients (11.4 %) had UGIB; only 15 patients of them had survived (36.6 %), and 26 patients had deceased (63.4%) due to irreversible hypovolemic shock (n=2), Ventilator-Associated Events (VAEs) mainly aspiration (n=3), sepsis (n=8), myocardial infarction (n=4), multi-organ failure (n= 9).

Features of obvious gastrointestinal bleeding were hematemesis, melena, hematochezia, fresh blood revealed in the nasogastric tube (n=41), development of hemorrhagic shock presented with systolic hypotension < 100 mmHg or tachycardia > 100 beats/min, decrease in hematocrit or hemoglobin levels by more than 5% or 2g/dl were evident 10/41 (2.4%) patients [6 patients in the deceased subgroup (n=26) and four patients in the survived subgroup (n=15)].

They were treated with proton pump inhibitors (PPIs) IV infusion at a loading dose of 80 mg, then continuous infusion of 8 mg/h for three days. The hemodynamic variables were evaluated every 6 hours. Hemoglobin and hematocrit values were considered daily, and blood transfusion was commenced if the hemoglobin decreased at least 2 gm or below 7 gm/dl with documented signs of shock.

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At least 48 hours were dedicated to watch for signs of stability after weaning from MV then, upper endoscopy was allowed which had revealed large ulcers > 2 cm in the gastric antrum (n=1, 6.7%), multiple antral ulcers (n=2, 13.3%), large >2cm corporeal gastric ulcers (n=2, 13.3%) [all were Forrest Ib with oozing surface], bleeding small duodenal bulb ulcers < 2cm (n=1, 6.7%) [Forrest Ia with spurting], small ulcers in the lower esophagus with lower end esophagitis (n=2, 13.3%), black esophagus (n=1, 6.7%), ulcer on top of grade III esophageal varices (n=2, 13.3%), severe portal hypertensive gastropathy (n=3, 20%), candida esophagitis and gastritis (n=1, 6.7%) (**Fig 1**).

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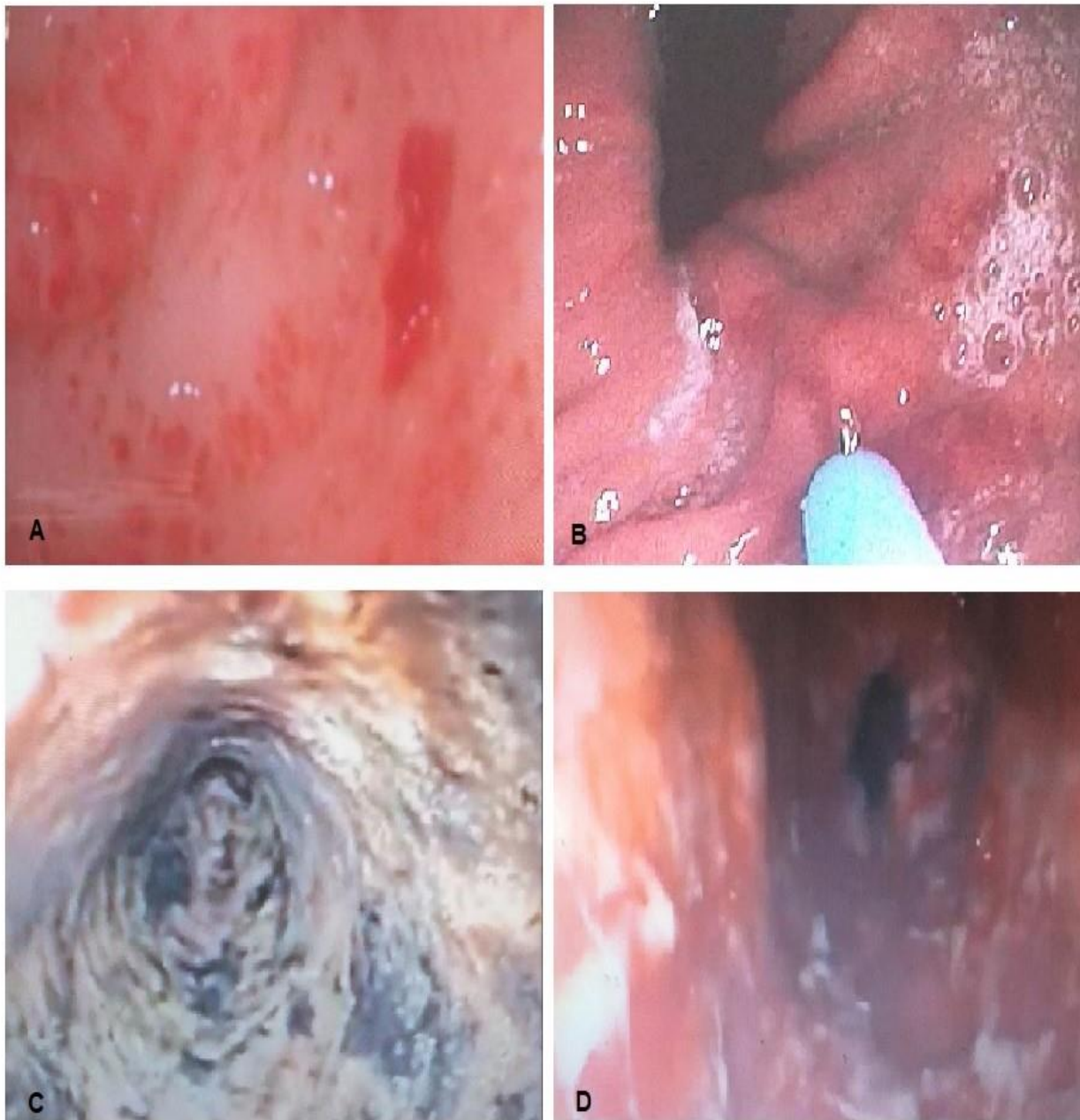


Fig 1: Causes of upper GIT bleeding in mechanically ventilated patients A: gastric ulcer B: Portal hypertensive gastropathy C: Black esophagus with a blackish necrotic surface. D: candida esophagitis with whitish membranes and superficial ulcers.

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There was a significant difference between group I and group II regarding ICU length of stay, MV duration, peak inspiratory pressure, total and direct bilirubin, serum creatinine, AST being indirect markers of sepsis and morbidity, albumin due to mucosal protein loss from ulcers, P.T., aPTT, INR due to organ dysfunction, sepsis and prolonged antibiotic use and APACHE II score >14 (**Table 3**).

Table 3: Comparison between the studied patients' groups regarding demographic, laboratory, and ventilatory parameters

Variable	Group I (UGIB) (N=41, 11.4%)	Group II (Non-UGIB) (N=319, 63.4%)	t-test	P
Age (years)	56.14 ± 17.41	44.67 ± 16.90	1.10	0.340
Sex	Male	192 (60.18%)	Chi-square test (X ²) 1.920	0.084
	Female	127(39.82%)		
Hemoglobin (g/dl)	9.8 ± 2.45	10.74 ± 2.53	0.255	0.817
Hematocrit	27.75 ± 8.40	28.63 ± 7.48	0.179	0.868
Platelets (10 ³ /μL)	196.25 ± 72.78	217.36 ± 104.45	1.53	0.199
Total Bilirubin	1.989 ± 0.992	0.891 ± 0.785	8.12	0.0001
Direct Bilirubin	0.387 ± 0.314	0.512 ± 0.314	2.23	0.026
AST IU/L (mean ±SEM)	669.16 ± 33.4	115.5 ± 31.1	6.3	0.0001
ALT IU/L(mean ±SEM)	222.32 ± 31.4	105.9 ± 25.7	1.59	0.1124
Albumin gm/dl	2.49 ± 0.91	2.98 ± 0.84	3.48	0.0006
Creatinine mg/dl	1.98 ± 0.92	1.15±0.30	2.632	0.001
INR	1.95 ± 1.23	1.11 ± 0.32	9.9	0.0001
aPTT (sec)	51.29 ± 23.68	27.02 ± 14.56	8.9	0.0001
PT (sec)	31.84 ± 13.12	20.46 ± 15.74	4.4	0.001
PH	7.3 ± 0.186	7.34 ± 0.116	1.86	0.06
Length of ICU stay (days) Median (Range)	13 (3 – 20)	9 (2 – 14)	3.69	0.009
APACHE II score	26.92 ± 7.91	23.52 ± 3.44	4.96	0.0001

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MV duration (days)	12.42 ± 2.69	8.36 ± 2.98	2.136	0.001
Peak Inspiratory Pressure ≥ 30cm H2O	37(32.1)	23(17.5)	8.3	0.0001
FiO ≥ 60%	42(37.18)	47(35.91)	0.256	0.524
PEEP ≥ 10cm H2O	19(16.1)	23 (16.54)	0.48	0.39

Multiple logistic regression analysis revealed that the independent risk factors for predicting upper gastrointestinal bleeding in critically ventilated patients were elevated serum creatinine, APACHE II score >14, peak inspiratory pressure ≥ 30cmH₂O, and prolonged aPTT (**Table 4**).

Table 4: Multivariate logistic regression of potential independent risk factors for UGIB.

Variables	B	S.E.	Sig.	OR	95% Confidence Interval for OR	
					Lower Bound	Upper Bound
APACHE II score	0.580	0.129	0.025	0.092	2.320	5.361
Prolonged APTT	0.183	0.004	0.039	0.003	2.010	11.005
Creatinine	0.989	0.076	0.009	0.247	1.091	2.376
ICU stay in days	0.320	0.019	0.098	0.050	1.014	3.090
MV duration in days	0.889	0.024	0.001	0.119	1.088	4.138
Peak Inspiratory Pressure ≥ 30cm H2O	0.187	0.365	0.001	0.480	2.102	10.003

The mortality rate among all critically ill ventilated patients was 27.2% (98/360 patients), while in UGIB patients was 63.4% (26 patients out of 41 patients), and that was statistically highly significant ($\chi^2 = 26.18$, $P < 0.0001$).

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Discussion

Gastrointestinal bleeding in critically ill patients can be attributed to stress ulceration of gastrointestinal mucosa, oxidative stress, hypoxemia, and altered splanchnic circulation, all impairing mucosal defensive mechanisms ^[14]. In addition to the burden of the underlying diseases, many vital drugs given to critically ill patients can induce bleeding, such as antiplatelet agents, anticoagulants, and corticosteroids ^[15].

Mechanical ventilation and coagulopathy were significant variables for G.I. bleeding in ICU, so; prophylaxis and correction of general condition were needed ^[16]. The proper time of practical endoscopy depends on the clinical situation, hemodynamic state, and presence of significant and life-threatening GIB ^[17].

In the current study, 41 patients (11.4 %) had UGIB, and only 15 survived. earlier reports of the incidence of UGIB in ICU by Chu et al. ^[18] showed a higher incidence of gastrointestinal bleeding if mechanical ventilation exceeded 48 hours (6.7%) with significant life-threatening bleeding had occurred in 3.3%. The length of ICU stay attributable to clinically substantial bleeding should exceed 4-8 days, as documented previously ^[19]; in the current study, clinically significant UGIB was observed in 2.4% of patients (6 patients in the deceased subgroup and four patients in the survived subgroup).

In the current study, the patients with UGIB were significantly older compared to non-UGIB patients, while no significant difference was found between the two groups regarding sex. It was noted that ICU stay and MV duration were significantly longer in UGIB patients than in those without UGIB, which was supported by previous studies ^[18, 20]. The mortality rate was higher in UGIB patients (63.4%) vs. non-UGIB patients (22.6%). This could be explained by the fact that UGIB in critically ill patients enhances the occurrence

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of sepsis, decrease blood flow to vital organs such as the brain and heart, and accentuates organ dysfunction.

Most patients in the current study had respiratory failure and Septic shock, which required mechanical ventilatory support. This study's significant risk factors of upper gastrointestinal bleeding in ICU patients could be attributed to shock, drugs (catecholamines, muscle relaxants), and impaired gastrointestinal motility, mainly due to electrolyte disturbance. These are consistent with previous studies [21, 22].

We found that length of stay in the ICU and longer MV duration was associated with an increased risk of UGIB in both univariate and multivariate analyses. More extended ICU stays can predict the severity of illness and thus increase the risk of UGIB. In patients with acute disease, repeated bouts of hypotension and hypoperfusion with subsequent multi-organ ischemia could accentuate the occurrence of UGIBs in high-risk patients.

Common medications used in intensive care units (ICUs) have been implicated as contributing to UGIB; opiates and sedatives for intubated patients are associated with decreases in gut motility and venous return, as are vasopressor agents and were used routinely in our patients [23].

Vartic et al. and Faisy et al. [24, 25] reported that age, organ failure, mechanical ventilation duration, and length of ICU stay were risk factors for UGIB, and Prophylactic measures resulted in a 50% decrease in UGIB in ICU.

In this study, elevated serum creatinine was an independent risk factor of UGIB in critically ill ventilated patients, as patients with significant kidney injury have qualitative platelet defects, predisposing them to bleed, and represented an independent risk factor identified by multivariate analysis. The mechanisms by which renal failure predisposed to bleeding were likely multifactorial and included gastric erosions and impaired perfusion of the gastric mucosa [26, 27].

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The peak inspiratory pressure $\geq 30\text{cmH}_2\text{O}$ is an independent risk factor for upper gastrointestinal bleeding in critically ill patients receiving MV. The mechanism underlying upper gastrointestinal bleeding was likely associated with high pressure and impaired venous return resulting in reduced cardiac output and impaired tissue perfusion with mucosal ischemia [28].

Prolonged PTT is an independent risk factor for upper gastrointestinal bleeding in critically ill ventilated patients, significantly if associated with thrombocytopenia or if heparin was used. This was in agreement with Lauzier et al. [29]. Also, an APACHE II score >14 is an independent risk factor for upper gastrointestinal bleeding in critically ill patients receiving mechanical ventilation, even though APACHE II may have limitations and fail to predict the prognosis of some patients without G.I. bleeding [30].

The limitation of this study was that it was a single-center study, and the impact of the pattern of MV on the frequency of UGIB was not studied.

Finally, the current study found a high rate of upper gastrointestinal bleeding in critically ill patients exposed to MV. Elevated serum creatinine, ICU length of stay, peak inspiratory pressure $30\text{cm H}_2\text{O}$, APACHE II score >14 , and prolonged aPTT were all associated with UGIB and patients. In addition, they developed UGIB in the ICU while on MV and had a higher death rate.

Footnotes.

Peer- Reviewers: Mohamed Bassuny (professor of internal medicine), Amany Mohammed Abdallah professor of community medicine).

Ethical committee approval:(255-2018)

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Declaration of competing interest

There are no conflicts of interest related to this study.

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