

Factors Affecting Weaning Failure in Critically-Ill Patients Undergoing Emergency Gastrointestinal Surgery

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ABSTRACT

Aim: Mechanical ventilation (MV) is one of the most commonly used treatment modalities in critically ill patients in the intensive care unit (ICU). Prolonged MV is associated with increased morbidity and mortality, and so the prevention of unnecessary prolonged MV and reintubation due to early extubation is of great importance. Although studies to date have studied factors that are predictive of weaning success and failure, there have been very few studies to date examining critical surgical patients requiring MV in the postoperative period. The present study investigated the factors affecting weaning failure in patients undergoing emergency gastrointestinal surgery.

Material and Method: The data of patients who underwent emergency gastrointestinal surgery between August 2016 and January 2019, that required MV for longer than 48 hours postoperatively and that were followed up in the general surgery ICU, was analyzed retrospectively.

Results: Ninety-seven patients with a mean age of 71.8±14.2 years included in study, of which 63 (64.9%) were male and 34 (35.1%) were female. The mean APACHE II score was 25.2±6.7. The main primary disease was gastrointestinal malignancy in 72.1% of the patients and the most common comorbid diseases were hypertension (53.6%) and congestive heart failure (36.1%). The median duration of MV was 9 [2-56] days and the mean length of ICU stay was 18.7±12.2 days. Weaning was started at a median 2 [2-4] days after intubation. The median weaning time was 4 [4-18] days. While 71 (73.2%) of the patients were successfully weaned, 26 (26.8%) experienced weaning failure. Of these patients, 21 (21.6%) experienced simple weaning, 40 (41.2%) experienced prolonged weaning and 36 (37.1%) experienced difficult weaning. The most common causes of weaning difficulty were hypervolemia in 88 (90.7%) patients and postoperative sepsis in 21 (21.6%) patients. Patients who suffered weaning failure had higher lactate levels, a greater need for erythrocyte suspension and vasopressor administration, and a higher rate of sepsis and acute renal failure. The presence of sepsis (OR: 4.034, 95% CI: 1.995-3.450, p= 0.04) was determined as an independent risk factor for weaning failure.

Conclusion: Weaning failure and difficult weaning were found common in critically ill patients undergoing emergency gastrointestinal surgery; and sepsis was found as an independent risk factors for weaning failure. We lack sufficient data on this patient population in our country, and so our findings need to be supported by prospective studies involving larger patient series.

Keywords: Gastrointestinal Surgery, Postoperative Respiratory Failure, Mechanical Ventilation, Weaning

Introduction

Invasive mechanical ventilation (IMV) is one of the most commonly used treatment modalities in critically ill patients with respiratory failure in the intensive care unit (ICU) (1). As a life-saving treatment in patients requiring respiratory support, MV reduces respiratory workload and thereby increases survival and decreases the length of ICU stay by providing oxygenation until the critical illness resolves. Weaning of critically ill patients is of critical importance for the patients in gaining the maximum benefit from MV and

in the avoidance of possible complications related to MV. At this stage, determining the most appropriate time for weaning of patients is required to prevent prolonged MV and extubation failure (2,3). Disconnecting a patient from MV after the resolution of critical illness is defined as “weaning” (4). Weaning and extubation follow each other in clinical practice, but refer to different actions.

Studies to date have investigated factors that could be predictive of weaning failure or success in an attempt to determine predictive indicators

for either of these conditions (5,6). Some such indicators would aid ICU clinicians in establishing a gain and loss relationship while disconnecting the patient from the MV. The majority of studies to date investigating the indicators for successful weaning have focused on critically ill ICU patients with medical conditions, while very few studies have evaluated critically ill patients requiring MV support due to respiratory failure in the postoperative period.

The present study investigated the risk factors associated with weaning failure in patients followed up in the ICU due to the need for MV following emergency gastrointestinal tract (GIT) surgery.

Materials and Method

Study Population

The medical records of patients who were followed up in the General Surgery ICU of Dışkapı Yıldırım Beyazıt Training and Research Hospital following emergency GIT surgery between August 1, 2016 and January 1, 2019 were reviewed retrospectively. The study was approved by the Dışkapı Yıldırım Beyazıt Training and Research Hospital clinical trials ethics committee (Date: 22.07.2018, number: 68/09). The study flow chart determining the inclusion and exclusion criteria of the study population was presented in Figure 1.

Study Inclusion Criteria

1. Aged 18 and over; patients operated within 12 hours of diagnosis
2. Patients who needed MV for at least 48 hours in the ICU

Study Exclusion Criteria

1. Patients undergoing surgery for acute appendicitis
2. Patients who were lost before the start or completion of weaning
3. Pregnant patients
4. Patients with terminal-stage cancer
5. Patients with acute neurological events
6. Patients sustaining acute myocardial damage in the early post-operative period
7. Patients who were re-intubated following a failed extubation attempt due to an upper airway pathology
8. Patients with severe heart failure (Ejection fraction <40%).

The age, gender, ASA (American Society of Anesthesiologists) score, APACHE (Acute Physiology and Chronic Health Evaluation) II score, SOFA (Sequential Organ Failure Assessment) score and the comorbid diseases of the patients were recorded. Perioperative clinical and surgical conditions, subsequent laboratory and clinical values, and MV values and outcomes were examined. The patients were compared after categorizing them into two groups, as successful weaning and weaning failure groups.

Definitions

Successful weaning was defined as the maintenance of effective spontaneous breathing without the need for invasive or non-invasive MV support for longer than 48 hours following extubation, while weaning failure was defined as the need for invasive or non-invasive MV within 48 hours of extubation. All weaning and extubation procedures in the ICU were performed by an ICU specialist in accordance with a defined protocol (Table 1) (7).

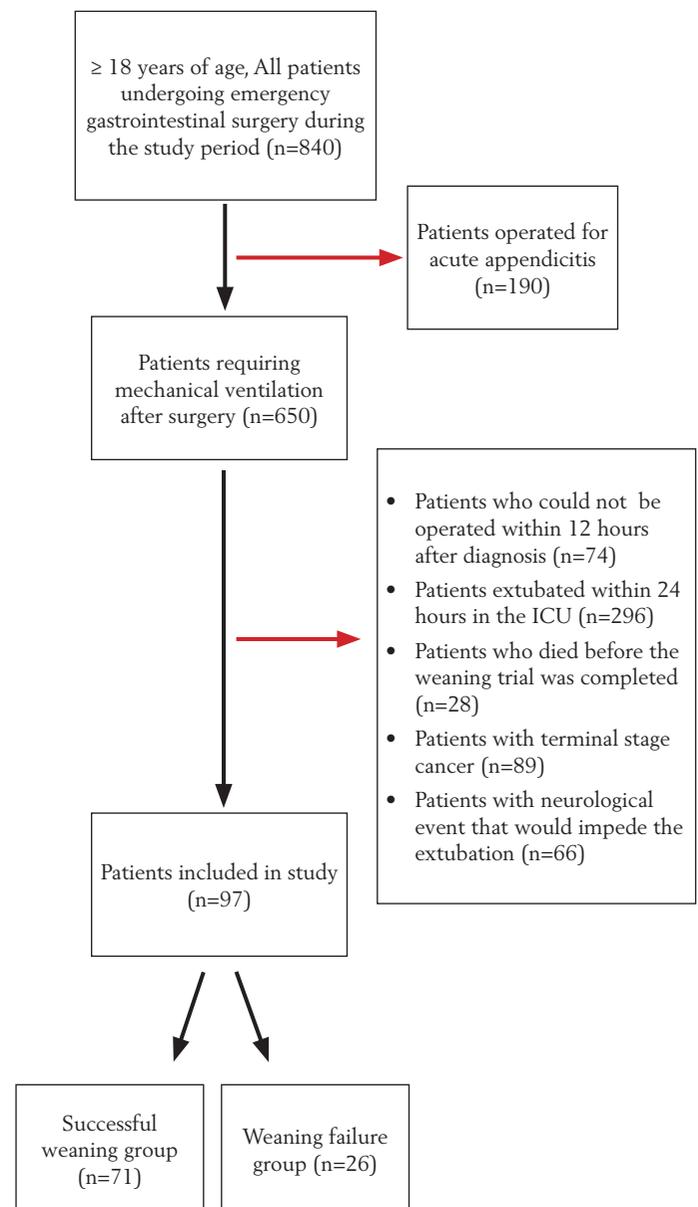


Figure 1. Flow chart for the patients included in the study

Simple weaning was defined as extubation following the first spontaneous breathing trial, difficult weaning was defined as successful extubation following three spontaneous breathing trials within 7 days, and prolonged weaning was defined as more than three spontaneous breathing trials within 7 days or extubation after more than 7 days (8).

Shock was defined as systolic blood pressure below 90 mmHg, despite adequate fluid resuscitation within 24 hours before or after surgery, or the need for vasopressor therapy (noradrenalin and/or dopamine) in order to maintain a mean arterial blood pressure above 65 mmHg.

Acute renal failure and acute kidney injury (AKI) were defined according to the KDIGO 2012 guidelines. The worst serum creatinine or urine output values were taken into consideration (9).

Table 1. Mechanical ventilation weaning protocol**Step 1:**

- A. Reduce FiO_2 <50% to maintain oxygen saturation (SpO_2) >92%
- B. When FiO_2 is <50%, gradually reduce PEEP by 2–3 H_2O increments to 5 cmH_2O

Step 2: Start spontaneous ventilation attempts if the following criteria have been met in a patient meeting the criteria in step 1

- A. Lack of need for vasopressor medications or hemodynamically stable patients when the need for vasopressor medications is less than 5 mcg/min
- B. Presence of spontaneous respiration efforts
- C. Presence of cough reflex upon tracheal aspiration, presence of swallow reflex
- D. Patient receiving no sedation or being awake while receiving minimal sedation
- E. $\text{PaO}_2/\text{FiO}_2$ ratio being above 200 mmHg

Step 3: Spontaneous Breathing Trial: If the patient breathes comfortably for 30–60 minutes with a PEEP of 5 $\text{cm H}_2\text{O}$, PS of 10 $\text{cm H}_2\text{O}$, and FiO_2 of <50% in spontaneous mechanical ventilation mode**Spontaneous Breathing Trial Termination Criteria**

1. Oxygen saturation <90% for 2 minutes
2. Pulse rate >120 bpm or <60 bpm for 2 minutes
3. Systolic blood pressure >180 mmHg or <90 mmHg for 2 minutes
4. Respiratory rate >30 breaths/min for 15 minutes
5. Spontaneous tidal volume <5 ml/IBW
6. Agitation, sweating, anxiety in the patient exceeding >5 min

In case of a failed spontaneous breathing trial, the next trial must be made the following morning during sedation break.

Step 4: Extubation: If spontaneous breathing trial is tolerated for 60 minutes:

1. The patient is connected to the T-tube for 30 minutes.
2. If the patient tolerates the T-tube for 30 minutes, an arterial blood gases analysis is performed and compared with the previous one.
3. A cuff leakage test is performed.
4. The patient is extubated and oxygen support is provided to maintain SpO_2 >92%.
5. An arterial blood gas analysis is performed 30 minutes after extubation.

FiO_2 : Fraction of inspired oxygen, PEEP: Positive end-expiratory pressure, PS: Pressure support, IBW: Ideal body weight (adapted from reference number 7)

Sepsis was defined in accordance with the definition made in the Sepsis 3 meeting held by the European Society of Intensive Care Medicine and the Association of Critical Care (10).

Statistical Analysis

The statistical analysis was performed using SPSS (Version 17.0, SPSS, Inc.) software. Prior to the statistical analysis, a Shapiro-Wilk test was used to test for the normal distribution of data. Continuous variables were expressed as mean \pm standard deviation (25th and 75th percentiles) or median depending on the distribution pattern of the data, and a Student's t-test or Mann-Whitney U test were used in the analysis. Categorical variables were expressed as number and compared using a Chi-square test or a Fisher's exact test. A multivariate logistic regression analysis with backward stepwise selection was used to determine the risk factors for weaning failure.

Results

The study included 97 patients with a mean age of 71.8 ± 14.2 years, of which 63 (64.9%) were male and 34 (35.1%) were female. The mean APACHE (Acute Physiology and Chronic Health Evaluation) II score was 25.2 ± 6.7 . The most common primary disease was gastrointestinal malignancies (72.1%) and the most common comorbid conditions were hypertension (53.6%) and congestive heart failure (36.1%).

Of the 97 patients who required postoperative MV, weaning was successful in 71 (73.2%) and unsuccessful in 26 (26.8%).

The mean age was 72.3 ± 14.6 years in the weaning failure group and 69.4 ± 13.2 years in the successful weaning group ($p=0.045$). There was no significant difference between the two groups in terms of gender distribution, and the number of male patients was higher in both groups. The ASA score [3 (1–4) vs 2 (1–3), $p=0.034$], the APACHE II score [25.3 ± 7.1 vs 23.1 ± 6.5 ; $p=0.008$] and the SOFA score on admission to the ICU [6 (3–8) vs 3 (1–6), $p=0.002$] were all higher in the weaning failure group. Hypertension, coronary artery disease and congestive heart failure were significantly more common in the weaning failure group ($p<0.05$). Strangulation was the most common reason for emergency abdominal surgery in both groups, followed by perforation and mesenteric ischemia. There was no significant difference between the two groups in terms of the type of surgery (laparoscopic vs open). Shock (34.7% vs 26.7%; $p=0.039$), sepsis (73.1% vs 26.8%, $p<0.001$) and acute renal failure (38.1% vs 15.5%; $p<0.001$) were more common in the postoperative period, and the need for vasopressor medications (38.4% vs 19.7%; $p=0.041$) and erythrocyte suspension replacement (65.4% vs 36.8%; $p=0.028$) was higher in the weaning failure group (Table 2).

In terms of laboratory data upon admission to the ICU in the early postoperative period, the white blood cell count, ProBNP, lactate, creatinine and PaCO_2 levels were higher and the albumin levels were lower in the weaning failure group ($p<0.005$) (Table 3).

Weaning was started at day one (0–4) in the successful weaning group and at day 2 (1–5) in the weaning failure group. In the entire study group, the median MV time was 9 [2–56] days

Table 2. Comparison of successful and failed weaning groups

Characteristics	Successful Weaning (n=71, 73.2%)	Weaning Failure (n=26, 26.8%)	p
Age (Mean±SD)	69.4±13.2	72.3±14.6	0.045
Gender (Female/Male)(%)	43 (60.6)/28 (39.4)	20 (76.9)/6 (23.1)	0.073
ASA score (median)[25-75]	2 [1-3]	3 [1-4]	0.034
APACHE II score (Mean±SD)	23.1±6.5	25.3±7.1	0.008
SOFA score on admission (median)[25-75]	3 [1-6]	6 [3-8]	0.002
Comorbidities (n,%)			
Hypertension	34 (47.9)	18 (69.2)	0.043
Coronary artery disease	25 (35.2)	3 (11.5)	0.018
Atrial Fibrillation	11 (15.5)	4 (15.4)	0.631
Congestive Heart Failure	16 (22.5)	19 (73.0)	0.001
Diabetes Mellitus	16 (22.5)	9 (34.6)	0.172
COPD	30 (42.3)	7 (26.9)	0.126
GIT Malignancy	50 (70.4)	20 (76.9)	0.255
Reason for Admission (n,%)			
Perforation	24 (33.8)	9 (34.6)	0.129
Strangulation	30 (42.3)	10 (38.4)	0.413
Mesenteric ischemia	17 (23.9)	7 (20.9)	0.198
Operation Site (n,%)			
Stomach	11 (15.5)	4 (15.4)	0.816
Small bowel	33 (46.5)	12 (46.1)	0.482
Large bowel (colon, rectum)	27 (38.0)	10 (39.5)	0.980
Laparoscopic/Open surgery (n,%)	31 (43.7)/ 40 (56.3)	11 (42.3)/ 15 (57.7)	0.517
Presence of shock prior to surgery (n,%)	5 (7.0)	1 (3.8)	0.488
Shock after surgery (n,%)	15 (26.7)	9 (34.7)	0.039
Cumulative fluid intake in the first 24 hours (ml) (median)[25-75]	2850 [2536-4530]	5460 [3310-7860]	0.002
Presence of sepsis (n,%)	7 (9.9)	11 (42.3)	<0.001
Vasopressor requirement (n,%)	14 (19.7)	10 (38.4)	0.041
Erythrocyte suspension replacement (n,%)	28 (36.8)	17 (65.4)	0.028
Presence of acute renal failure (n,%)	11 (15.5)	8 (38.1)	<0.001

ASA: American Society of Anesthesiologists, APACHE: Acute Physiology and Chronic Health Evaluation, SOFA: Sequential Organ Failure Assessment, COPD: Chronic Obstructive Pulmonary Disease, GIT: Gastrointestinal Tract

Table 3. Laboratory values on admission to the intensive care unit (immediately after surgery)

Laboratory value	Successful weaning (n=71)	Weaning Failure (n=26)	p
White blood cell count (10 ³ /mL)	12.6±3.4	15.5±2.8	0.042
Hb (gr/dL)	11.7±1.2	11.0±1.0	0.664
ProBNP (pg/ml)	2560±1080	3210±1890	0.018
Lactate (mmol/L)	3.7±2.0	6.7±4.2	0.003
BUN (mg/dL)	44.6±27.6	47.2±28.8	0.396
Creatinine (mg/dL)	1.2±0.6	1.8±1.1	0.040
Albumin (gr/ dL)	3.4±0.8	2.6±0.9	0.002
PaO ₂ (mmHg)	70.5±21.7	69.1±17.1	0.080
PaCO ₂ (mmHg)	40.7±9.1	45.7±13.8	0.011
SpO ₂ (%)	91.5±3.1	90.1±5.0	0.098

“The values are presented as mean±standard deviation. Hb: Hemoglobin, BUN: Blood Urea Nitrogen

and the mean length of ICU stay was 18.7 ± 12.2 days. Weaning was started a median 2 days [2-4] after intubation. The mean weaning time was 4 [4-18] days. Of the patients, 21 (21.6%) experienced simple weaning, 36 (37.1%) experienced prolonged weaning and 40 (41.2%) experienced difficult weaning. Successful weaning was more common in the simple weaning group (28.2% vs 3.8%; $p=0.002$) and prolonged weaning was more common in the weaning failure group (32.4% vs 65.4%; $p=0.003$). The most common reasons for difficult weaning were hypervolemia, occurring in 88 patients (90.7%), and postoperative sepsis, occurring in 21 (21.6%) patients (Table 4).

Age (>65 vs ≤ 65 years), APACHE II Score (median >21 vs ≤ 21), congestive heart failure, presence of shock after surgery, cumulative fluid balance in the first 24 hours (>2000 ml vs ≤ 2000 ml), presence of sepsis, erythrocyte suspension replacement and presence of acute renal failure on admission that were found to be significant in the univariate analysis and that showed no relationship with each other were added to the multiple regression model. Age, high APACHE II score, congestive heart failure, presence of shock after surgery, positive fluid balance in the first 24 hours, need for transfusion of erythrocyte suspension and presence of acute renal

failure on admission were not found to be independent risk factors for weaning failure, whereas the presence of sepsis (Odd's ratio 4.034, 95 confidence interval: 1.995-3.450, $p=0.04$) was found to be an independent risk factor for weaning failure.

Discussion

In the present study, difficult weaning and weaning failure were commonly observed among the patients that underwent emergency gastrointestinal surgery. The presence of sepsis was an independent risk factor for weaning failure. To the best of our knowledge, the present study is the first in Turkey to present predictive factors for weaning failure when using a weaning protocol by an ICU specialist among patients who underwent emergency GIT surgery in a general surgery ICU.

Prolonged MV and early weaning that results in the re-intubation in critically ill ICU patients are associated with increased morbidity and mortality (2,3). It is therefore important to determine the existing risk factors in order to increase weaning success. Patients generally maintain spontaneous respiration after awaking from anesthesia in the postoperative period, although patients

Table 4. Reasons for difficulty weaning, duration of weaning, mechanical ventilation, length of intensive care unit stay and length of hospital stay

Characteristics	Successful weaning (n=71)	Failed weaning (n=26)	p
Start of weaning (day) (median)[25-75]	1 [0-4]	2 [1-5]	0.211
Type of weaning (%)			
Simple weaning	20 (28.2)	1 (3.8)	0.002
Difficult weaning	28 (39.4)	8 (30.8)	0.058
Prolonged weaning	23 (32.4)	17 (65.4)	0.003
Reasons for Difficult Weaning (%)			
Hypervolemia	67 (94.4)	21 (80.8)	0.057
Postoperative sepsis (%)	7 (9.9)	11 (42.3)	0.034
Pneumonia (%)	13 (18.3)	6 (23.1)	0.068
Total weaning time (day) (Mean \pm SD)	4.1 \pm 2.4	8.3 \pm 4.8	<0.001
Mechanical Ventilation Time (median)[25-75]	6 [3-11]	10 [6-22]	0.001
Length of ICU Stay (Mean \pm SD)	15.6 \pm 10.8	21.0 \pm 12.5	0.021
Outcome in the ICU (%)			0.008
Discharge/Transfer to Ward	58 (81.7)	16 (57.7)	
Died	13 (18.3)	10 (42.3)	
Length of Hospital Stay (day) (Mean \pm SD)	21.4 \pm 13.4	27.6 \pm 13.3	0.118

Table 5. Results of multiple logistic regression analysis in predicting weaning failure

Characteristic	Adjusted OR	95% CI	p
Age (>65 vs ≤ 65 years)	0.46	0.38-1.18	0.119
APACHE II Score (median >21 vs ≤ 21)	1.65	0.47-1.10	0.092
Congestive Heart Failure (present vs absent)	3.64	1.37-8.6	0.10
Shock after surgery (present vs absent)	1.33	0.97-3.41	0.181
Cumulative fluid balance within the first 24 hours (>2000 ml vs ≤ 2000 ml)	2.92	0.89-11.4	0.068
Erythrocyte suspension replacement (present vs absent)	1.61	0.88-3.13	0.161
Presence of sepsis	4.034	1.995-3.450	0.04
Acute renal failure on admission (present vs absent)	4.48	1.61-14.24	0.58

OR: Odd's ratio, CI: Confidence interval

undergoing emergency surgical procedures may require MV due to hemodynamic instability (i.e. septic shock, hemorrhagic shock), metabolic acidosis, type 3 respiratory failure and hypervolemia. It has been reported that MV support was required in 3–6% of patients admitted to the ICU in the postoperative period, and the rate of failed weaning is reportedly 5–8% in all surgical patients (10–12). That said, it is known that ICU patients requiring prolonged MV in the postoperative period have a higher rate of failed weaning and a higher rate of morbidity and mortality (13,14).

Critically ill patients are generally weaned when the underlying condition has resolved, when gas exchange has reached adequacy and when the hemodynamic status has become stable, and the level of consciousness as well as cough and gag reflexes have become adequate to maintain spontaneous breathing (15,16). The criteria and strategies for successful weaning have not been adequately described for surgical patients to date. The definitions and strategies for weaning were originally described for patients with chronic obstructive pulmonary disease and for those with other respiratory problems (8). The mechanical parameters of breathing and oxygenation do not seem to be adequate to predict weaning success in postoperative surgical patients with normal lung function, although there are an increasing number of studies on this subject.

In a recent study, Li et al. (17) investigated the risk factors for weaning failure in 381 patients undergoing major abdominal surgery. They reported a weaning failure rate of 28% and advanced age, low albumin level, low left ventricular ejection fraction and development of cardiac myocardial damage as a complication of surgery as independent risk factors for weaning failure. The present study made no evaluation of the left ventricular ejection fraction, and no patients with an ejection fraction of less than 40% were included in the study. No acute cardiac events occurred in any patient in the postoperative period.

Early spontaneous breathing trials and early start of weaning have been reported to reduce MV time in patients receiving MV support (18,19). The current guidelines recommend the cessation of daily sedation and the initiation of spontaneous breathing trials. In a study involving 3,327 patients undergoing emergency GIT surgery, Jung et al. (20) reported a need for MV in 387 patients (11.6%) in the postoperative period. In their study, delayed spontaneous breathing trials along with low platelet count and postoperative shock (adjusted OR: 14.152; 95% CI: 6.571–30.483; $p < .001$) were found to be independent risk factors for weaning failure. The median time to start weaning was 1 day in the successful weaning group and day 2 in the weaning failure group in our study. This was attributed to the more severe disease condition in the weaning failure group, in which higher APACHE II, ASA and SOFA scores were recorded.

It is reported that weaning failure is more common among patients recovering from systemic inflammatory response syndrome (SIRS) after abdominal surgery (21). In a study by Amoateng-Adjepong et al. (22), the respiratory rate/tidal volume ratio was found to be higher, the maximum inspiratory pressure was found to be lower and the rate of weaning failure was found to be higher in patients with sepsis and septic shock. Sepsis was more common in the weaning failure group in our study, and sepsis was found to be an independent risk factor for weaning failure.

Fluid replacement is an important part of the treatment of hemodynamic disturbances associated with sepsis and other conditions, although it can be difficult to determine optimal fluid balance in critically ill patients. Studies to date have identified cumulative fluid excess as a factor that increases morbidities in the ICU such as acute renal failure and ICU mortality (23,24). The cumulative fluid amount in the first 24 hours was found to be higher in the weaning failure group in our study, but did not appear to be an independent risk factor for weaning failure.

It is known that induced thoracic hypervolemia increases mechanical respiratory workload and airway pressure, even in normal individuals (25). It is also well known that hypervolemia and volume overload are associated with increased organ dysfunction in critically ill patients, increased weaning time and total time of weaning, as well as an increase in infectious complications and mortality (26). The effects of hypervolemia on the outcomes of critically ill patients have been investigated in medical patients, although there is a paucity of studies in this field. In a study involving 144 patients underwent emergency surgery, Barmparas et al. (26) could find no effect of positive fluid balance on total mortality (11% negative fluid balance vs 15.5% positive fluid balance, $p = 0.422$), but when evaluated together with other accompanying factors, negative fluid balance was found to provide survival benefit by 70% in the first five days of surgery and negative fluid balance on the first day of surgery provided survival benefit, but also reduced infectious complications [95% confidence interval 0.63 (0.45, 0.88); $p = 0.006$ and 0.64 (0.46, 0.90); $p = 0.010$ respectively] (26). In the same study, MV time and length of ICU stay were found to be longer in patients with a positive fluid balance and prolonged MV was found to be an independent risk factor for mortality in of surgical patients.

Our study has some limitations. Firstly, it was conducted in a single center and a single ICU, and the study population was relatively small. Secondly, the potential of missing data in the evaluation of medical records may be increased due to the retrospective study design.

In conclusion, the presence of sepsis in patients undergoing emergency GIT surgery was independent risk factor for weaning failure. It must be kept in mind that the criteria for successful weaning may be different in this patient group than in patients with medical conditions.

AUTHOR CONTRIBUTIONS:

Concept: FY, HK; **Design:** FY, HK; **Supervision:** İOK; **Fundings:** FY, HK; **Materials:** FY; **Data Collection and/or Processing:** FY, HK, İOK; **Analysis and/or Interpretation:** FY; **Literature Search:** FY, HK; **Writing Manuscript:** FY, HK; **Critical Review:** İOK.

Ethics Committee Approval: Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee, July 2019

Informed Consent: Informed consent was obtained from the patient if the patient's consciousness is clear; if it is not clear informed consent was obtained from patient's relatives.

Peer-review: Externally peer-reviewed.

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