Study Protocol

Effect on post-operative pulmonary complications frequency of high flow nasal oxygen versus standard oxygen therapy in patients undergoing esophagectomy for cancer: study protocol for a randomized controlled trial—OSSIGENA study

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Background: Postoperative pulmonary complications (PPCs) remain a challenge after esophagectomy. Despite improvement in surgical and anesthesiological management, PPCs are reported in as many as 40% of patients. The main aim of this study is to investigate whether early application of high-flow nasal cannula (HFNC) after extubation will provide benefit in terms of reduced PPC frequency compared to standard

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oxygen therapy.

Methods: Patients aged 18–85 years undergoing esophagectomy for cancer treatment with radical intent, excluding those with American Society of Anesthesiologists (ASA) score >3 and severe systemic comorbidity (cardiac, pulmonary, renal or hepatic disease) will be randomized at the end of surgery to receive HFNC or standard oxygen therapy (Venturi mask or nasal goggles) after early extubation (within 12 hours after the end of surgery) for 48 hours. The main postoperative goals are to obtain SpO_2 ≥94% and adequate pain control. Oxygen therapy after 48 hours will be stopped unless the physician deems it necessary. In case of respiratory clinical worsening, patients will be supported with the most appropriate tool (noninvasive ventilation or invasive mechanical ventilation). Pulmonary [pneumonia, pleural effusion, pneumothorax, atelectasis, acute respiratory distress syndrome (ARDS), tracheo-bronchial injury, air leak, reintubation, and/or respiratory failure] complications will be recorded as main outcome. Secondary outcomes, including cardiovascular, surgical, renal and infective complications will also be recorded. The primary analysis will be carried out on 320 patients (160 per group) and performed on an intention-to-treat (ITT) basis, including all participants randomized into the treatment groups, regardless of protocol adherence. The primary outcome, the PPC rate, will be compared between the two treatment groups using a chi-square test for categorical data, or Fisher's exact test will be used if the assumptions for the chi-square test are not met.

Discussion: Recent evidence demonstrated that early application of HFNC improved the respiratory rate oxygenation index (ROX index) after esophagectomy but did not reduce PPCs. This randomized controlled multicenter trial aims to assess the potential effect of the application of HFNC versus standard oxygen over PPCs in patients undergoing esophagectomy.

Trial Registration: This study is registered at clinicaltrial.gov NCT05718284, dated 30 January 2023.

Keywords: Esophagectomy; postoperative pulmonary complications (PPCs); high-flow nasal cannula (HFNC); outcome; perioperative medicine

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Introduction

Esophageal cancer is the sixth leading cause of cancer-related death worldwide, with an estimated 540,000 deaths (1).

According to the Global Cancer Observatory, by the end of 2040, there will be nearly 1 million new diagnoses of esophageal cancer worldwide (2).

Esophagectomy is still the only curative treatment. Despite improvements in surgical and anesthesiological perioperative management, esophagectomy still carries a high risk of postoperative complications, which are reportedly as great as 50% (3,4). Postoperative pulmonary complications (PPCs) are particularly frequent, and according to the literature, they affect 40% of patients (5).

PPCs comprehend different entities, with pneumonia being the most common with an overall incidence rate of 15% (6); however, pleural effusion, atelectasis and pneumothorax are reported in a non-negligible frequency rate (7).

Some pre- and intra-operative factors have been demonstrated to reduce PPCs' incidence rate (8). However, postoperative options have not received adequate consideration.

Despite pathophysiology being extremely complex, it seems that postoperative atelectasis might relate to PPCs' onset, especially for pneumonia and acute respiratory failure requiring oxygen supplementation (9).

Some noninvasive respiratory support (NIRS) options are available to overcome these complications (10). However, efficacy, tolerance and NIRS ease of use should always be taken into consideration for the success of the treatment (11).

Noninvasive preventive ventilation (NIV) has been proposed to reduce PPC after extubation, but its role is still being debated raising concerns about possible interference with surgical anastomosis (8).

High-flow nasal cannula (HFNC) has been developed within acute respiratory failure treatment in critical care settings, but evidence also supports its use for prevention of PPCs (12,13).

In the specific setting of esophagectomy, only small observational studies have assessed this aspect, albeit with promising results (14,15).

As a consequence, the primary aim of this multicenter randomized controlled trial is to evaluate whether early HFNC application after extubation in patients undergoing esophagectomy will reduce PPCs compared to standard oxygen therapy (Venturi mask or nasal googles).

Secondary aims explore whether any difference in cardiovascular, surgical, renal or infective complications will be recorded within the two treatment groups. Finally, we will test if serum biomarkers, i.e., cardiac troponin and NT-pro brain natriuretic peptide (NT-proBNP) have sufficient sensitivity to predict the onset of postoperative complications. We present this article in accordance with the SPIRIT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-575/rc).

Methods

This study was approved by the Ethics Committee of Friuli Venezia Giulia Region (CEUR-FVG), the coordinating center, with the identification number 16941 dated 28 February 2023. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was also registered at clinicaltrials.gov, identifier NCT05718284 (https://clinicaltrials.gov/study/NCT05718284), dated 30 January 2023. Ad hoc insurance has been activated for the study (Lloyd's Insurance Company S.A., # A1202352299-LB).

Study design and patients

OSSIGENA is an Italian multicenter randomized controlled trial. Patients will be recruited in high-volume centers for esophageal cancer surgery. Centers have been previously identified through inspection of the website (https://pne.agenas.it/home) of the Italian National Agency for Regional Healthcare Systems, which provides official data about health-care volume and outcomes of Italian hospitals for every single illness (16).

High-volume centers have been defined as surgery units that perform ≥20 esophagectomies per year (17).

Patients will be recruited in the 12 participating centers after each one has received approval from their institution's ethics committee before the enrollment of the first patient.

Inclusion criteria

Inclusion criteria are age 18–85 years; esophagectomy to remove esophageal cancer with radical intent (R0); open-mininvasive or robotic surgery; extubation in operating room or within 12 hours after the end of surgery; and self-reported metabolic equivalents (METs) ≥4.

Exclusion criteria

Exclusion criteria are American Society of Anesthesiologists (ASA) score >3; chronic obstructive pulmonary disease (COPD) stage ≥ III according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification; diffusing capacity of the lungs for carbon monoxide (DLCO) <50%; forced expiratory volume in the first second (FEV1) <50% predicted value for population reference; previous lung resection surgery; severe cardiac disease [ejection fraction (EF) ≤30%, New York Heart Association (NYHA) >2, implantable cardioverter defibrillator (ICD), pulmonary hypertension]; body mass index (BMI) ≤17 or ≥35 kg/m^2; CKD with estimated glomerular filtration rate (eGFR) <50 mL/min; combined with other type of surgery (example: laryngectomy); recent deep vein thrombosis (in the last month), and/or invasive mechanical ventilation >24 hours after surgery for respiratory or other problems (according to the clinical judgment of the physician).

Patient consent and data protection

Patients will receive information about the study, and written consent will be requested before surgery. If the patient is unable to write their signature, verbal consent will be requested in the presence of two witnesses. Patient data will be processed according to the Declaration of Helsinki and the European Privacy Regulation 2016/679 for General Data Protection Regulation (GDPR). Each center is provided with an identical case report form (CRF). A principal investigator (PI) will be responsible for each participating center's data collection, ensuring proper concealment of each patient's identity on the linked CRF and for storing links between sensitive data and patient univocal codes under password protection. In case of any difficulties or problems, each PI will be able to communicate with the study's other PIs. Two

independent investigators will perform data management activities on the database and check for abnormalities and inconsistencies. The study will be reported according to the CONSORT checklist for reporting parallel group randomized trials.

Outcomes

The primary outcome of this trial is to assess the efficacy of early HFNC oxygen therapy in reducing PPCs after esophagectomy compared to standard oxygen therapy delivered via a Venturi mask or nasal cannula. PPCs will be defined according to standardized criteria, which may include, but are not limited to, pneumonia, atelectasis, bronchospasm, respiratory failure, and the need for re-intubation.

The secondary outcomes of the study are focused on evaluating differences in the complication rates across four key areas between the two groups:

(I) Cardiovascular complications: arrhythmias, myocardial infarction, heart failure or any other cardiovascular event rate occurred postoperatively;
(II) Surgical complications: anastomotic leakage, wound infection or any other surgical site complication rate;
(III) Renal complications: acute kidney injury or failure rate, as measured by changes in serum creatinine or urine output; and
(IV) Infective complications: sepsis, urinary tract infections or any other hospital-acquired infections rate.

As exploratory outcomes, the study will evaluate the sensitivity of serum biomarkers, specifically sensitive cardiac troponin, and NT-proBNP in predicting the onset of postoperative complications. These biomarkers will be measured pre-operatively and at defined intervals postoperatively (once a day for the first 3 postoperative days) to assess their association with the actual occurrence of complications.

Endpoints

The primary endpoint is the PPC reduction defined by a statistically significant lower rate of PPCs in the HFNC group compared to the standard oxygen therapy group.

Secondary endpoints are:

- the difference in complication rates, defined by comparing the rate of cardiovascular, surgical, renal and infective complications between the two groups; and
- the difference in biomarker predictive value defined by the ability of pre-operative and postoperative levels of sensitive cardiac troponin and NT-proBNP to accurately predict the occurrence of postoperative complications.

Randomization

After informed written consent is obtained, at the end of surgery, each patient will be assigned to intervention or standard oxygen treatment.

Block randomization derived in a central computerized system through http://www.randomization.com will be managed by the PI of the study (C.D.). The enrollment ratio will be 1:1 and will be competitive among participating centers.

Peri-operative anesthesiological management

All patients scheduled for esophagectomy will be evaluated before surgery according to ESC guidelines (18) and following the internal protocol in use at each participating center.

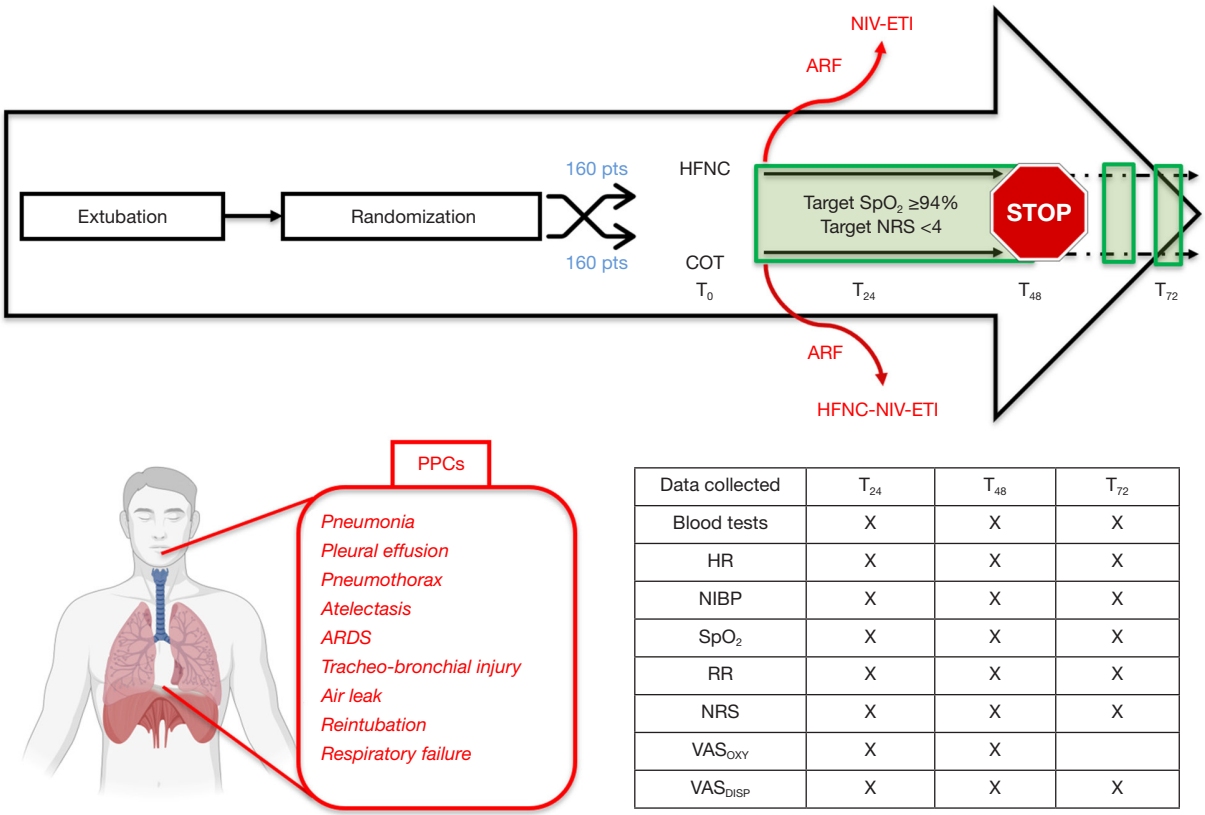
Standard [electrocardiogram (EKG), peripheral saturation of oxygen (SpO_2), neuromuscular transmission, end tidal CO_2 ($ETCO_2$)] plus invasive arterial monitoring, urinary catheter and internal temperature probe will be adopted for every patient.

Intraoperative protective mechanical ventilation with tidal volume (V_T) of 6–8 mL/kg of predicted body weight (PBW) [calculated according to acute respiratory distress syndrome (ARDS) network formula (19)] and positive end expiratory pressure (PEEP) 5 cmH_2O during two-lung ventilation will be adopted. In case of one-lung ventilation, V_T will be reduced to ≤5 mL/kg of PBW. Lung recruiting maneuvers can be performed if the anesthesiologist deems them necessary. In any case, the anesthesiologist in charge will be free to modify ventilatory parameters as needed.

Hemodynamic monitoring will not be protocolized. However, fluid therapy should be targeted to reach zero fluid balance at the end of surgery, or it will be goal-directed if cardiac output monitoring is available. The maximum amount of fluid infusion allowed will be ≤10 mL/kg/h.

Intraoperative transfusion will take place when Hb ≤7 g/dL, unless there is a history of coronary artery disease or signs of inadequate organ perfusion (lactates >2 mmol/L, central saturation of oxygen ($ScVO_2$) <70% or urinary output ≤0.5 mL/kg/h), when higher Hb targets should be considered.

Depth of anesthesia will be monitored and tailored



Data collected	T_{24}	T_{48}	T_{72}
Blood tests	X	X	X
HR	X	X	X
NIBP	X	X	X
SpO_2	X	X	X
RR	X	X	X
NRS	X	X	X
VAS_{OXY}	X	X	
VAS_{DISP}	X	X	X

Figure 1 Study timeline. After extubation that will be performed within 12 hours after the end of surgery, patients will be randomized (T_0) to receive HFNC or COT for the following 48 hours. The primary oxygenation target will be to maintain SpO_2 ≥94% with the lowest FiO_2 possible. After this period (T_{48}), treatment will be stopped unless the physician deems it necessary. In case of clinical signs of respiratory worsening (ARF) during the period T_0–T_{48}, irrespective of the treatment assigned, patients will be treated with noninvasive or invasive respiratory support per the physician's decision. Similarly, patients randomized to COT will be allowed to receive HFNC if increased NIRS is necessary. The main PPCs recorded within the first 30 days after surgery will be pneumonia, pleural effusion, pneumothorax, atelectasis, ARDS, tracheo-bronchial injury, air leak, reintubation and respiratory failure. After the initiation of oxygen treatment, for 72 hours, all parameters shown in the table in the lower right part of the figure will also be collected. Figure made with biorender.com. HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; ARF, acute respiratory failure; NIV, noninvasive ventilation; ETI, endotracheal intubation; NRS, numerical rating scale for pain; HR, heart rate; NIBP, noninvasive blood pressure; RR, respiratory rate; VAS_{OXY}, visual analogue scale for the tolerance of the oxygen treatment delivered; PPC, postoperative pulmonary complication; NIRS, noninvasive respiratory support; VAS_{DISP}, visual analogue numeric scale for dyspnea.

according to the available monitoring tools at each participating center.

Postoperative analgesia should provide numeric rating scale (NRS) <4.

Postoperative oxygen supplementation treatment protocol

According to randomization, patients will receive HFNC or conventional oxygen therapy (COT) as shown in *Figure 1*.

Intervention group—HFNC group

In the intervention group, HFNC (Optiflow™ Nasal High Flow, AIRVO2 Fisher & Paykel HealthCare Ltd., Auckland, New Zealand) will be applied immediately after extubation with the following setting: gas flow will be initially set at 50 or 60 L/min if body weight is <80 or ≥80 kg, respectively. The initial temperature will be set at 37 ℃, while the lowest fraction of inspired oxygen (FiO_2) to reach SpO_2 ≥94% will be used.

In case of intolerance, set parameters will be modified to cope with the patient's comfort.

The nasal cannula will be of adequate size considering the dimensions of the patient.

COT group

The control group will receive oxygen supplementation with Venturi mask or nasal goggles with the minimum FiO_2 to reach SpO_2 ≥94%.

Both treatments (HFNC and COT) will last 48 hours after extubation, and then they will be stopped unless they are deemed clinically necessary per the physician's evaluation.

Any interruption of oxygen supplementation required during the 48 hours after extubation should be reduced to the minimum time possible.

If clinically necessary according to the physician's judgment in case of acute respiratory failure (as described further on), patients in the control oxygen group will be allowed to receive HFNC as long as necessary. Moreover, in both groups, NIRS or endotracheal intubation will be allowed in the same case or other life-threating complications if the ongoing treatment will be insufficient to treat the acute illness (see *Figure 1*). This event will be recorded as appropriate in CRF.

Data collected for the analysis

Preoperative data collected will be age, sex, weight, height, BMI, American Society of Anesthesiologists score (ASA) class status, any cardiovascular-pulmonary-liver-renal or endocrinological comorbidity, Charlson Comorbidity Index (CCI), ARISCAT score (20), neoadjuvant chemo and/or radiotherapy, type and site of tumor, lung function test (spirometry), reported METs, hemoglobin (Hb) and creatinine.

Intraoperative data are type of anesthesia [totally intravenous (TIVA) or inhalatory (INA)], use of vasoactive drugs (norepinephrine-epinephrine-dopamine-dobutamine), complete ventilatory parameters [V_T, PEEP, driving pressure (DP), respiratory rate (RR)], fluid balance (cumulative), and type of postoperative analgesia (locoregional analgesia, intravenous, other).

Some surgical data will be also recorded, such as type of surgery (open-mininvasive or robotic), duration of surgical procedures and blood loss.

Postoperative data will include blood gas analysis (pH, PaO_2, $PaCO_2$, HCO_3^-, PaO_2/FiO_2), hemochrome, cardiac troponin and NT-proBNP, C-reactive protein (CRP), procalcitonin (PCT), serum creatinine and blood urea nitrogen (BUN). These tests will be sampled once a day for the first 3 postoperative days.

Moreover, 4 times a day for the first 3 postoperative days, heart rate (HR), noninvasive blood pressure (NIBP), SpO_2, RR, temperature, and pain (with NRS) and visual analogue numeric scale for dyspnea (VAS_{DYSP}) [from 0 (no dyspnea) to 10 (the worst dyspnea ever)] will be collected.

Each day at least once a day for the first 48 hours after extubation, oxygen supplementation parameters will be registered, including HFNC tolerance according to the VAS scale (VAS_{OXY}) (from 0 to 10, 0 completely tolerated, 10 not tolerable).

Finally, survival will be assessed at 30 days after surgery.

All data will be collected in dedicated Excel (Microsoft Windows) sheets ad hoc prepared by PI (C.D.). Each single center will receive the Excel file where anonymized data will be recorded and shared with PI.

Postoperative complications

All the following postoperative complications partially modified from "International Consensus on Standardization of Data Collection for Complications Associated with Esophagectomy" (21) and "Postoperative Pulmonary Complications" (22) that appeared within 30 days after surgery will be considered for the final analysis.

- Pulmonary:
  - (I) Pneumonia (defined as lung opacity at chest X-ray; plus at least 1 from fever >38 ℃ without any other plausible cause, WBC <4,000 or >12,000/mm^3, mental alteration in patients >70 years old without any other cause; plus at least 2 from new onset purulent sputum, increasing bronchial secretions, new onset or increasing cough, dyspnea, tachypnoea, decreasing SpO_2 or lung crackles);
  - (II) Pleural effusion: chest X-ray with obliteration of costophrenic angle blunting or ultrasound findings suggesting free fluid within the pleural space;
  - (III) Pneumothorax: air in chest cavity diagnosed with chest X-ray or CT scan;
  - (IV) Atelectasis: lung opacity with/without mediastinal shift, with contralateral signs of hyperinflation diagnosed with chest X-ray or CT scan, with/without need for bronchoscopy;

(V) ARDS: ARDS according to Berlin definition (23);
(VI) Tracheobronchial injury: bronchoscopic evaluation or CT scan suggesting discontinuity within the bronchial tree;
(VII) Air leak: continuous air leak within the chest drainage lasting for >72 h;
(VIII) Reintubation: need for reintubation; and/or
(IX) Respiratory failure: oxygen supplementation required to maintain SpO_2 ≥94% with dyspnea, tachypnoea, without signs of pneumonia.

❖ Cardiovascular:
(I) Cardiac arrest;
(II) Acute myocardial infarction;
(III) New onset arrythmia requiring cardiological consultation;
(IV) Acute heart failure;
(V) Pericarditis;
(VI) Pulmonary embolism at computed tomography (CT) scan;
(VII) Deep vein thrombosis; and/or
(VIII) Stroke, either ischemic or hemorrhagic.

❖ Surgical:
(I) Anastomotic leak;
(II) Chylothorax;
(III) Conduit necrosis;
(IV) Dysphagia;
(V) Delayed emptying; and/or
(VI) Reoperation needs.

❖ Renal:
(I) Acute kidney failure [Kidney Disease: Improving Global Outcomes (KDIGO) criteria (24)]; and/or
(II) Need for hemodialysis or continuous renal replacement therapy (CRRT).

❖ Infective:
(I) Surgical site infection, bloodstream infection, catheter-related bloodstream infections (CRBIs), urinary tract infection (UTI), septic shock.

For both groups, treatment failure, i.e., the need to increase the intensity of respiratory support as shown in *Figure 1*, will be recorded.

Statistical analysis

For continuous variables, the data will be described using the median and the interquartile range (IQR). Categorical variables, such as the gender of participants or the presence of specific clinical conditions, will be described using absolute frequencies and percentages. For the analysis of continuous variables, the Wilcoxon test will be used. For categorical variables, the chi-square test or Fisher's exact test, whichever is appropriate, will be employed.

The primary outcome, the PPCs rate, will be compared between the two treatment groups (early HFNC application *vs.* standard oxygen therapy). This comparison will be conducted using a chi-square test for categorical data. If the assumptions for the chi-square test are not met (e.g., small expected cell counts), Fisher's exact test will be used as an alternative. The primary analysis will be performed on an intention-to-treat (ITT) basis, including all participants being randomized into the treatment groups, regardless of protocol adherence.

Secondary outcomes include differences in cardiovascular, surgical, renal or infective complications between the two groups. Each of these outcomes will be analyzed separately: similarly to the primary outcome, the rate of these complications will be compared using chi-square or Fisher's exact tests, as appropriate.

To evaluate the sensitivity of biomarkers (cardiac troponin and BNP) in predicting postoperative complications, receiver operating characteristic (ROC) curves will be used. The area under the curve (AUC) will provide a measure of the biomarkers' ability to discriminate between patients with and without complications. Optimal cutoff values will be determined based on the Youden index.

The statistical analyses will be conducted with R (R Core Team 2015) (25).

Power analysis

From the available data, the PPCs' frequency rate after esophagectomy is 20–40% (26). Considering PPCs' frequency of 25% (3) and expecting their absolute reduction of 12.5% [prudential reduction as show in Xia *et al.*'s study (15)], the sample size required to compare two independent proportions with the chi-square test with α=0.05 and β=0.20, with an enrollment ratio of 1:1, is 152 patients per group. Expecting a drop-out rate of near 5%, 160 patients per group will be required to test the null hypothesis.

Discussion

PPCs represent a major problem after esophagectomy (27). Their onset is associated with adverse outcomes, including longer hospital stay and increased risk of death (28,29).

Evidence supports early application of noninvasive ventilation after extubation in some clinical settings such as

cardiac, lung resection or major abdominal surgery (12,13).

Scarce evidence exists in the specific setting of esophagectomy. A recent observational study demonstrated that early HNFC application was associated with a better respiratory rate oxygenation (ROX) index in the first 24 hours than in the standard oxygen group, especially by reduction of RR (14). This is an important aspect to consider since it probably allows the performance of respiratory physiotherapy early after surgery, with all the potential consecutive benefits.

In fact, a recent meta-analysis demonstrated that postoperative rehabilitation resulted in a lower incidence of pneumonia, a shorter length of hospital stay (LOS_{HOSP}) and better health-related quality of life scores for dyspnea and physical functioning (26).

Moreover, in our study, we noted that in the HFNC group, there was a decreased frequency of postoperative acute respiratory failure, although it was not statistically significant (P=0.07).

We should consider that the trial was not adequately powered and was not randomized, so some biases could have been present. However, we did not demonstrate any reduction in the frequency of either overall postoperative or pulmonary complications.

In this regard, our study contrasts with the findings of Xia *et al.*, who found that application of HFNC after extubation reduced hypoxemia, incidence of clinical PPC and anastomotic leakage and was associated with shorter stays in hospital (15).

In more detail, HFNC compared to COT reduced lung volume loss caused by pneumothorax, atelectasis and pulmonary consolidation as demonstrated with CT scan imaging.

From a pathophysiological point of view, these findings are expected since HFNC provides positive airway pressure and increased anatomical dead-space washout, with clinical improvement of oxygenation, reduction of breathing effort and, finally, ameliorating respiratory mechanics with optimization of the patient's comfort (30). Many effects of HFNC are flow-dependent (31). However, high gas flow is better tolerated by hypoxemic patients since they feel the beneficial effect compared to the ones without respiratory failure, in whom lower flows could be required to accommodate the patient's tolerability. Probably for this reason, we were not able to demonstrate that HFNC reduced atelectasis investigated with radiological atelectasis score (32). In fact, in our previous study, mean gas flow was 47±6 L/min, but only 65% of patients tolerated the prescribed gas flow, while 35% required flow reduction due to discomfort (14). In addition, we should highlight that the RAS score has its intrinsic limits such as low specificity for atelectasis.

Early recognition of postoperative complication is of fundamental importance to begin proper treatment without any delay.

There has been considerable debate about the predictive capacity of some serum biomarkers such as troponin and natriuretic peptides (NPs) (33).

A recently published work containing a sub-analysis of the MET-repair study, however, demonstrated that pre-operative evaluation of NPs did not add benefit to the classical predictive scores for cardiac events such as ASA score and Gupta Perioperative Risk for Myocardial Infarction or Cardiac Arrest (MICA) score (34).

On the other hand, increased postoperative NPs and high-sensitive cardiac troponin are independently associated with adverse cardiac events in major abdominal surgery (35).

For this reason, we will evaluate whether early postoperative increase in NPs or cardiac troponin should help identify patients at risk of worsening before it becomes clinically relevant.

Our study protocol has some limitations: firstly, esophagectomies will be performed by different surgical teams with different level of expertise. However, we decided to include only high-volume centers to reduce this bias. Second, perioperative management is prone to considerable variability from center to center, such as postoperative ward admission type and level of intensity [intensive care unit (ICU) versus surgical ward]. But this is a practical study, and it is impossible to protocolize every single action for this population simply because human, technology and economic resources vary from one center to another. Finally, we did not consider a standardized prehabilitation program before surgery for this group of patients. However, this was not the aim of the study.

The study is currently in the enrollment phase. Esophageal surgery for cancer is increasing, but it is still subject to high rates of postoperative complications, with PPCs being the most represented. We will try to explore a possible PPCs reduction by early application of HFNC after esophagectomy.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by Ethics Committee of Friuli Venezia Giulia Region (CEUR-FVG), the coordinating center, with the identification number 16941 dated 28 February 2023. Patients will receive information about the study, and written consent will be requested. In the case that the patient is unable to write his signature, verbal consent will be asked in the presence of two testimonies. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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