

STUDY PROTOCOL

NCT number:

**NCT04773080**

TITLE:

**Incidence, risk factors and consequences of acute kidney injury in patients  
undergoing esophageal cancer surgery: a historical cohort**

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## **ABBREVIATIONS**

AKI acute kidney injury

SCr serum creatinine

AKD Acute kidney disease

## INTRODUCTION

Surgery alone, or in combination with neoadjuvant chemoradiation therapy, is still considered to be the cornerstone treatment for locally advanced esophageal cancer <sup>1</sup>. Esophagectomy serves as an exemplar of major operative trauma, with well-known risk of pulmonary, cardiac, anastomotic, and septic complications and the presence of postoperative complications after esophagectomies for cancer is associated with a reduced long-term survival <sup>2</sup>. There is a paucity in the literature regarding postoperative renal outcomes after esophageal surgery, with a wide range of incidence.

McCulloch et al <sup>2</sup> reported in 2003 the results of the British ASCOT prospective database collecting data from 955 patients (ASA score of 3-4 in 25%), of whom 229 underwent esophageal surgery. They found an incidence of renal complications of 3.5%, but no definition of renal complication was present in the study.

Lee et al <sup>3</sup> in 2014 investigated retrospectively 595 patients underwent esophageal surgery for cancer in South Korea. AKI according AKIN criteria was found in 35.3% of the population with a mean age of 62 years and mainly ASA score 2 (91.8%). AKI was also associated with longer hospital stay.

Moore et al <sup>4</sup> compared in a retrospective analysis of 150 patients underwent complex or non-complex esophageal reconstruction in 2016, reporting an incidence of renal insufficiency in 1.3% of the entire population, without reference of any diagnostic criteria.

In 2017 Konda et al <sup>5</sup> performed a retrospective study on 897 patients with a mean age of 61 years and mainly ASA 3 (83.6%) in USA, of whom 11.9% fulfilled the AKIN criteria for AKI.

Wang et al <sup>6</sup> showed in a Chinese retrospective case-control study published in 2017 a very low incidence of AKI according RIFLE criteria (2.4%) in a population of 2094 patients with a median age of 62 years and with ASA score of 2 in 84% of the patients.

The most recent study by Murphy et al <sup>7</sup> published in 2020 on 1135 patients with a mean age of 64 years underwent esophageal cancer surgery in three high-volume centers in Ireland showed an incidence of AKI (defined by AKIN criteria) of 18.3%, associated with atrial fibrillation and longer hospital stay.

## **AIM OF THE STUDY**

The aim of this study is to evaluate the incidence of postoperative AKI in patients undergoing elective esophageal cancer surgery. Secondary, we will assess the progression of the acute injury and the association with adverse pulmonary, cardiac, anastomotic, and septic events, as well as mortality. We will also identify risk factors associated with AKI occurrence.

## **STUDY DESIGN**

Retrospective study

## **METHODS**

### **STUDY SETTING, POPULATION**

All patients underwent elective esophagectomy at the Ospedale-Università di Padova

### **PATIENT SELECTION CRITERIA**

#### **INCLUSION CRITERIA**

- Elective esophagectomy

#### **EXCLUSION CRITERIA**

- Age < 18 years;
- End-stage renal disease
- Missing data for AKI definition (serum creatinine or urine output)
- Second surgery (for patients having multiple surgeries performed during a 30-day period, only the first in each period was included)

## **SAMPLE SIZE**

Our sample size will be determined to help ensure stability around the point estimates in the final multivariable model. To avoid overfitting our final outcome model, no more than 8 outcome events will be required per covariate of interest. Thus, to fit a model with 8 covariates, we will require approximately 64 outcome events. We will estimate the sample size after a pilot study on 100 patients.

## **PRIMARY ENDPOINTS**

- To evaluate the incidence of postoperative AKI according to KDIGO criteria within 48 hours after surgery

## **SECONDARY ENDPOINTS**

- Distinction between transient and persistent AKI
- Occurrence of recovery or progression at 7 days, 30 days and 3 months
- Association between AKI and pulmonary complications, major adverse cardiovascular events, anastomotic or septic complications, or death.
- Identify risk factors associated with AKI occurrence.

## **STATISTICAL ANALYSIS**

The statistical analysis will be conducted with the help of Spss software.

Continuous variables are presented through descriptive statistics, including mean, median, variance, minimum and maximum value. Categorical variables are described by the absolute frequencies and percentages.

Data will be examined by T-test or one-way ANOVA (normally distributed variable), Mann-Whitney U test, Kruskal-Wallis one way analysis test (not normally distributed variables), Pearson or Mc Nemar's chi-square test (categorical variables) will be used to evaluate the difference across non-AKI group versus AKI group according to KDIGO criteria or each type of AKI. Two-sided p-values of less than 0,05 were accepted as statistically significant.

Logistic regression analysis will used to build a model of covariates associated with development of AKI and risk of AKI. Likelihood ratio (LR) test statistic, Hosmer-Lemeshow (HL) statistic will used

for assessing goodness of fit (GOF) in the regression models. A discriminatory performance [DP] assessment of the binary logistic model will be performed by classification/diagnostic table, ROC and area under the curve (AUC).

## **DATA COLLECTION**

A team properly instructed will collect patient's data, which will be filled in a CRF (Case Report Form). An electronic copy of CRF will be retained in Microsoft Excel format.

All collected data will be identified and stored in such a way as to protect patient confidentiality. The staff involved in the collection and management of data will not use or disseminate such information for purposes other than those provided for the realization of the study.

All data will be collected and processed in a completely anonymous way, in compliance with the guarantee terms of privacy and as approved by Comitato Etico per la Sperimentazione Clinica della Provincia di Padova.

### **Assessment of renal function**

“Acute kidney injury” (AKI) is defined as an increase in serum creatinine (SCr) by  $\geq 0.3$  mg/dL within 48 h the baseline value (as determined by all available SCr values from hospital and outpatient medical records within the previous 90 days) or urine output  $< 0.5$  mL/kg/h for 6 h<sup>8</sup>. For those who do not have available baseline SCr levels, expand the screening criteria to an increase or decrease in SCr by 0.3 mg/dl during hospital stay. Second, these suspected AKI were reviewed on a case-by-case basis to confirm the diagnosis. Positive fluid balance and hemodilution are considered in the diagnosis and staging of AKI using the following formula<sup>9</sup>:

Adjusted SCr level = SCr  $\times$  correction factor

where the correction factor = (weight (kg) upon hospital admission  $\times$  0.6 +  $\Sigma$  (daily cumulative fluid balance (L)))/hospital admission weight  $\times$  0.6

The estimated glomerular filtration rate is determined using SCr<sup>10</sup>. Chronic Kidney Disease-Epidemiology Collaboration equations.

Persistent acute kidney injury (AKI) is defined by the continuance of AKI by serum creatinine or urine output criteria (according KDIGO criteria) beyond 48 h from AKI onset<sup>11</sup>. Complete reversal of AKI by KDIGO criteria within 48 h of AKI onset is defined transient AKI<sup>11</sup>.

Acute kidney disease (AKD) is defined as a condition wherein criteria for AKI stage 1 or greater persists  $\geq 7$  days after surgery.

### **Assessment of complications and mortality**

Postoperative pulmonary complications were identified and categorized based on European Perioperative Clinical Outcome (EPCO) definitions from the ESA-ESICM joint taskforce on perioperative outcome measures<sup>12</sup>. These include respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, aspiration pneumonitis.

Major adverse cardiac and cerebrovascular events (MACCE) was a composite outcome of non-fatal cardiac arrest, acute myocardial infarction, congestive heart failure, new cardiac arrhythmia, angina, ischemic stroke<sup>12</sup>.

Sepsis was defined according Sepsis-3 definition<sup>13</sup>.

We performed separate analyses of complications apparently related to surgical technique (for instance, anastomotic leakage, fistula, abscess, hemorrhage) and medical complications, i.e. pulmonary, cardiovascular (acute myocardial infarction, atrial fibrillation, cardiogenic shock) and septic.

All complications were evaluated 30 days after surgery.

Mortality in hospital after resection of esophageal cancer was defined as any death during the admission when the operation was performed. This was more reliably quantified than 30-day mortality.



## **ETHIC AND SCIENTIFIC DISSEMINATION POLICY**

### **Patient Information/Informed Consent**

As a retrospective analysis, we would base normative n. 9/2014 (“in merito al trattamento dei dati personali effettuato per scopi di ricerca scientifica dell’11 dicembre 2014”).

After completion of the study, the data will be reported at scientific meetings and/or submitted and published in a scientific journal, regardless of the outcome. In these cases, a publication committee will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues.

### **BUDGET OF THE STUDY**

The present study is NO PROFIT.

# CASE REPORT FORM

## Retrospective study on AKI incidence after esophageal cancer surgery

PATIENT ID

### Inclusion criteria:

- elective esophageal cancer patients

### Exclusion criteria:

- Age < 18 years.
- ongoing KRT or ESRD.
- Missing data for AKI criteria (serum creatinine and urine output).
- Second surgery.

### PREOPERATIVE EVALUATION:

Gender  M  F  
Age \_\_\_\_\_ Birthday \_\_\_\_\_  
Weight \_\_\_\_\_ kg Height \_\_\_\_\_ m  
Surgery date \_\_\_\_\_

### COMORBIDITIES:

- COPD Gold class \_\_\_\_
- Interstitial Lung Disease
- pulmonary hypertension
- asthma
- active smokers
- dyspnea
- stroke/TIA
- coronary artery disease
- DM
- hypertension with medication
- active solid organ neoplasm
- hematologic neoplasm
- disseminated cancer
- alcohol use disorder
- dementia
- congestive heart failure in 30 days prior to surgery
- dialysis
- ascites within 30 days prior to surgery
- systemic sepsis within 48 hours prior to surgery
- ventilator dependent

ASA class \_\_\_\_\_

Functional status: Karnofsky \_\_\_\_\_ ECOG \_\_\_\_\_

Weight loss within the last 3 months \_\_\_\_\_

**PREOPERATIVE MEDICATION:**

- Statins
- ACE-inhibitors
- Sartans
- beta-blockers
- PPI
- steroid use in chronic
- NSAIDs
- insulin
- CT
- RT

\_\_\_\_\_

**PREOPERATIVE LABORATORY TESTS**

Hb \_\_\_\_\_ MCV \_\_\_\_\_ Alb \_\_\_\_\_  
sCr \_\_\_\_\_ eGFR \_\_\_\_\_ urea \_\_\_\_\_  
BNP \_\_\_\_\_ Trop \_\_\_\_\_

**CARDIOVASCULAR TESTS**

- AF at EKG
- FE <45%
- carotid stenosis

**RESPIRATORY TESTS**

FEV1 \_\_\_\_\_ FVC \_\_\_\_\_ DLCO \_\_\_\_\_

**INTRAOP DATA**

Type of surgery:  thoracoscopy  thoracotomy  vls  lpt  cervico

Type of anesthesia:

inhaled  TIVA  epidural+inhaled  epidural+TIVA  
 Lidocaine \_\_\_\_mg  Magnesium\_\_\_\_\_mg  Dexamethasone \_\_\_\_\_mg  
 Ranitidine\_\_\_\_\_mg  PPI \_\_\_\_\_mg

NMB:  rocuronium  cisatracurium

NMB reversal:  neostigmine  sugammadex

Duration of anesthesia: \_\_\_\_\_ h

Type of ventilation:  OLV  TLV max FiO2\_\_\_\_\_ min SpO2\_\_\_\_\_

Hemodynamics:

IABP min SBP\_\_\_\_\_mmHg

fluids:  crystalloids\_\_\_\_\_ml  colloids\_\_\_\_\_ml  
 blood\_\_\_\_\_ml

blood loss\_\_\_\_\_ml end\_surgery Hb\_\_\_\_\_ end\_surgery lactate\_\_\_\_\_

use of vasopressors  max dose\_\_\_\_\_

use of inotropes  max dose\_\_\_\_\_

arrhythmia during surgery  use of antiarrhythmics

Diuresis: total \_\_\_\_\_ml  use of diuretics: \_\_\_\_\_ dose\_\_\_\_\_

End-surgery medication:  NSAIDs

Extubation at the end of surgery  PACU  ICU

**POSTOP :**

	6h	12h	24h	48h	72h	4d	5d	6d	7d	ICU discharge	H discharge	30d	1y
sCr													
eGFR													
urea													
Troponin													
BNP													
Hb													
NGAL													
diuresis													
Fluids in													
drainages													
diuretics													
vasopressors													
inotropes													

\*NA if not present in the medical records

**Outcomes:**

need for RRT: \_\_\_\_\_days

MACCE within 30 days:  AMI

congestive heart failure

non-fatal cardiac arrest

new cardiac arrhythmia

angina

stroke

pulmonary complications within 30 days:  respiratory infection at \_\_\_\_day (i.e. patients has received antibiotics for a suspected respiratory infection + one of the following: new or changed sputum, new or changed opacities, fever, wbc >12000)

respiratory failure at \_\_\_\_day (PaO<sub>2</sub> < 60 mmHg at room air, a P/F < 300 mmHg or SpO<sub>2</sub> <90% requiring oxygen therapy)

pleural effusion at \_\_\_\_day

atelectasis at \_\_\_\_day

pneumothorax at \_\_\_\_day

bronchospasm at \_\_\_\_day (bronchodilators treatment for new expiratory wheezing)

aspiration pneumonitis at \_\_\_\_day

length of CMV \_\_\_\_h

need for NIV in \_\_\_\_\_h

surgical complications within 30 days:  fistula       hemorrhage       abscess

**Clavien-Dingo grading of complications:**

I: any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological interventions. Permitted therapeutic interventions include: drugs such anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. Also included wound infections opened at the bedside

- II: drugs other than grade I
- III: requiring surgical, endoscopic, or radiological interventions
  - IIIa: not under general anesthesia
  - IIIb: under general anesthesia
- IV: life-threatening complication (including CNS complications) requiring critical care
  - IVa: single-organ dysfunction (including KRT)
  - IV b: multi-organ dysfunction
- V: death of a patient

Day of ICU discharge: \_\_\_\_\_

Alive

Dead

Day of H discharge: \_\_\_\_\_

Alive

Dead

Death at 30 days after surgery

readmission \_\_\_\_\_ (date)

second surgery



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