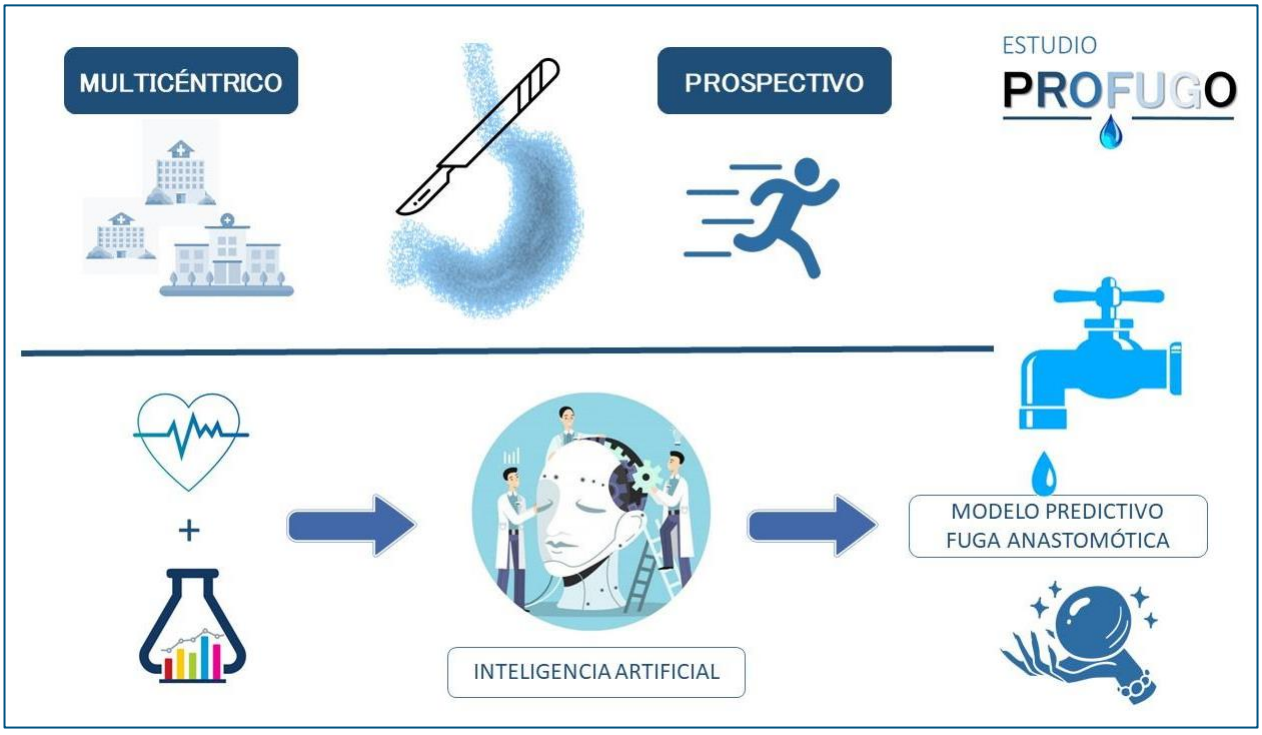
ESTUDIO PROFUGO

Predictive model for early diagnosis of anastomotic leak after esophagectomy and gastrectomy

SUMMARY

In esophagogastric surgery, the appearance of a leak at the level of the anastomosis is the most feared complication with important repercussions for both the patient and his disease. There are many risk factors that are related to its appearance and that makes it difficult to prevent its appearance. Making an early diagnosis of it is important for optimal management and resolution and therefore, different studies have investigated the usefulness of the use of markers, both pre and postoperative, to predict possible postoperative complications such as anastomotic leak. Due to the importance of early diagnosis and management of possible complications after esophagogastric surgery, it is mandatory to research and create predictive models that identify patients with a high risk of suffering complications, in order to be able to act accordingly. indicating the complementary examinations that are considered adequate to obtain an early diagnosis.

The PROFUGO study (PRedictive Model for the Early Diagnosis of Anastomotic LEAK after esophagectomy and gastrectomy) is proposed as a prospective and multicenter study at the national level that aims to develop, with the help of artificial intelligence methods, a tool and predictive model that allows identifying cases with a high risk of anastomotic leak and/or major complications through the analysis of different clinical and analytical variables collected during the postoperative period of patients undergoing esophagectomy or gastrectomy.



INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer death worldwide, with an incidence that has been increasing in recent years. Surgery is the mainstay of curative therapy for fit patients with the ability to tolerate extensive surgical procedures. Postoperative morbidity associated with esophagectomy is high (around 60%) (1), pulmonary complications occur in 20-50% of patients, and anastomotic leak (AF) has a variable incidence depending on the series (0- 34%) (1, 2) with an associated mortality of 5-36% (3). Regarding gastric cancer, it represents the fifth most common and the second most frequent cause of death from cancer worldwide, with a rate of postoperative complications close to 40-50% (4).

Among the postoperative complications, AF is the most feared, presenting a high mortality rate. This complication is not only associated with a longer hospital stay and increased costs, but also with a worse prognosis of the disease and the patient's quality of life (5). The variability in the rate of AF in the literature is due to the lack of a precise definition that is generally accepted by all groups, as well as the need to establish a reliable and unanimous diagnostic method. In addition to possible technical failures, there are many potential risk factors that may be related to the appearance of this complication. Thus, patients with this type of pathology and due to factors such as accelerated metabolism and decreased intake present a high risk of malnutrition, hypoproteinemia and systemic inflammation, which can alter collagen synthesis, reduce tensile strength in the anastomosis, facilitate poor tissue healing and induce anastomotic dehiscence.

The diagnosis of AF, as well as that of other complications, is often made when the patient is symptomatic, requiring immediate and perhaps more aggressive intervention than if an earlier diagnosis had been made. Treatment is generally decided based on the size of the leak, the degree of local contamination, and the associated severity status of the patient. Thus, early diagnosis of AF by clinical, radiological and/or endoscopy is essential to provide immediate treatment through antibiotic therapy, placement of a feeding tube, application of endoscopic therapies, percutaneous drainage of collections, etc., possibly reducing the rate surgical review. For all these reasons, early prediction, diagnosis and treatment of possible major complications (Clavien-Dindo greater than 3), especially AF, are essential to improve the results and prognosis of the disease (6).

Different studies have investigated the usefulness of the use of markers, both pre and postoperative, to predict possible postoperative complications. Recent studies have evaluated different markers in early postoperative stages as predictors of AF and other major complications. These include C-reactive protein (CRP) (7), white blood cell count (RGB) (8), serum albumin (9), tumor necrosis factor α (TNF α), interleukins 1 and 6, the CRP- albumin (CAR) (10-13), modified Glasgow Prognostic Score (mGPS), platelet/lymphocyte ratio and neutrophil/lymphocyte ratio (4) among others.

After carrying out a thorough bibliographic search, the small number of quality prospective studies in this area has been observed, most of them being retrospective or systematic reviews of retrospective studies.

CRP is one of the most studied inflammatory markers related to AF. It is mainly synthesized in the liver in response to proinflammatory cytokines, as an acute phase response protein, and its levels correlate with the severity of inflammation (14). CRP levels increase after surgery and commonly peak after 48 hours (15,16), subsequently decreasing in patients with an uncomplicated postoperative course. Therefore, CRP is especially valuable as a negative test, and a normal or falling CRP level on the third and fifth postoperative days (POD) can help predict which patients are not likely to develop AF (17). Although several prospective

studies and meta-analyses have shown that CRP is a useful marker of AF after colorectal surgery, the role of this marker in esophagogastric surgery is less well studied and established (18). In the study carried out by Aiolfi et al (19) it is concluded that postoperative CRP values can be useful to rule out rather than diagnose AF after elective esophagectomy. Thus, in the context of an enhanced recovery protocol, CRP could be used for early initiation and progression of oral diet and safe hospital discharge.

Liesenfeld et al (20) in a retrospective study of 233 patients, observed a less marked decrease in RGB after the 2nd POD in patients with AF, in addition to optimal diagnostic accuracy on the fourth postoperative day with a cut-off value of 8/ nl, which is within the normal RGB range. It was also found that CRP is an accurate negative predictive marker: for CRP levels below 155 mg/l from the 3rd to the 7th DPO, the negative predictive value for the absence of a leak was greater than 80%. The best precision for CRP was on the 4th DPO, with a cut-off value of 145 mg/l.

Serum albumin has been used as a simple nutritional marker to predict postoperative complications in various gastrointestinal surgeries (21).

In 2011, Noble and Underwood (22) developed the NUn score, through a retrospective study of 258 patients, calculated from the individual values of CRP, RGB and albumin on the 4th POD in patients who underwent esophagogastric resection with esophageal anastomosis. This score has a sensitivity greater than 95% when its value is greater than 10 and a specificity of 49%, as well as a high diagnostic precision for AF, which allows predicting, according to its values, the risk of appearance in asymptomatic patients, allowing personalized investigation and early intervention to prevent the development of significant morbidity and mortality. The NUn score was compared with other markers such as albumin, CRP, and RGB, and showed greater diagnostic accuracy, sensitivity, specificity, and statistical significance in predicting AF. In the retrospective study carried out by Brunded et al (23) of 382 patients, it was found that the NUn score is the best predictor of major complications, even greater than the CRP evaluated individually in patients undergoing esophagectomy.

Peritoneal levels of IL-6 and TNFα were significantly higher in patients with colorectal anastomosis leak compared to patients without leak in some studies and may contribute to their early detection (18), having found that increased levels Serum IL-6 is a predictor of AF in gastrointestinal surgery (24).

In the retrospective study of 330 patients carried out by Yansen et al (25), the neutrophil-lymphocyte ratio (NLR) was used as a biochemical marker. The incidence of AF was 16%, 47.2% of them being treated by surgery. An increasing trend in RLN was significantly associated with the need for surgical intervention, with the mean leak diagnosis time being 7 days and 49.1% being grade III AF. An NLR cut-off value of 10 at the 3rd POD had 74.5% sensitivity, 58% specificity, 25% positive predictive value, and a value of less than 10 had 92.4% negative predictive value for leaks. The results of this study concluded that the value of NLR is more relevant in its negative predictive values and helps in making postoperative decisions with more confidence. On the contrary, an increasing trend of RLN between 1st and 3rd DPO is an independent factor of AF that should be alerted to its suspicion.

Findlay et al (26) developed a prospective study of 326 patients where it was concluded that the use of elevated inflammatory markers is more useful in diagnosis than in prediction, therefore, these parameters do not seem to be very useful for diagnosis and management. early AF. Similar conclusions were obtained in the work published by Liesenfeld et al (20) where the CRP, RGB and NU scores are not recommended as independent markers for the prediction of AF after transthoracic esophageal resection. Another retrospective study by Sugimoto et al (13) of 295 patients analyzed preparatory inflammatory and nutritional markers and studied their relationship with the appearance of postoperative AF in esophageal cancer. The study compared the predictive capacity of preoperative CAR, nutritional prognostic index (PNI), and mGPS for AF, and identified that an elevated value of preoperative CAR (≥0.0139), but not PNI or mGPS, is a useful indicator for predict the occurrence of AF after esophagectomy. The results of their study suggest that preoperative CAR is a promising predictive marker of AF.

For all these reasons, the evidence on the usefulness of different markers for early prediction of AF and/or major complications after esophagogastric resection surgery is still limited, and quality prospective studies with an adequate sample size are needed to be able to draw more accurate conclusions. .

On the other hand, due to the importance of early diagnosis and management of possible complications after esophagogastric surgery, it is mandatory to research and create predictive models that identify patients with a high risk of suffering complications, in order to be able to Act accordingly, indicating the complementary examinations that are considered appropriate to obtain an early diagnosis, thus avoiding further deterioration of the patient and a possible septic situation in more advanced states. For this purpose, this study has been designed to try to create a predictive model that allows identifying patients with a high risk of anastomotic leak and/or major complication during the postoperative period of esophagogastric tumor resection surgery, through the analysis of different clinical variables and analytics collected in the postoperative period.

HYPOTHESIS

The appearance of AF in esophagogastric surgery is one of the most serious complications and marks the postoperative course and prognosis of the disease. One of the most important pillars in the management of AF is its early diagnosis, there is a gap in the literature on the role of inflammatory biomarkers in its prediction and an urgent need to identify and develop predictive tools for this purpose.

Thus, the early identification of patients at high risk of the appearance of AF and/or major complications after esophagogastric surgery through the daily postoperative study of objective clinical variables and analytical markers would allow an earlier diagnosis and more appropriate treatment of said situation, thus avoiding a greater deterioration of the patient and a possible septic situation in more advanced states that compromise their clinical evolution and the prognosis of their disease.

OBJECTIVES

Based on the hypothesis of the study, the main and secondary objectives of this study are established:

- Main goal:

*Design a predictive model based on clinical and analytical variables that allow identifying patients with a high risk of anastomotic leak (main variable) during the postoperative period of esophagogastric surgery.

- Secondary objectives:

* Design a predictive model based on clinical and analytical variables that allow identifying patients at high risk of other major complications (Clavien-Dindo greater than 3) during the postoperative period of esophagogastric surgery.
* Individually describe the postoperative evolution of the clinical and analytical parameters studied in patients without major complications or AF and those who did suffer from any of them.
* Describe the complications and types of AF diagnosed in the study.
* Assess the day AF was diagnosed and the treatment used for its possible resolution.
* Assess the day AF was diagnosed and hospital stay.
* Compare the preoperative Glasgow prognostic score (mGPS) and the biochemical value of inflammatory markers (CRP, Interleukin 6 (IL-6) and procalcitonin) and the appearance of AF.
* Assess the AF resolution capacity of each technique used.

MATHERIAL AND METHODS

The methodological properties of the study are described below:

1.- Type of design

Prospective and multicenter study that aims to develop, with the help of artificial intelligence methods, a tool and predictive model that allows identifying cases with a high risk of anastomotic leak and/or major complications through the analysis of different clinical and analytical variables collected during the postoperative period. of patients undergoing esophagectomy or gastrectomy.

2.- Study population

Patients diagnosed with neoplasia of the esophagus or stomach with an indication for oncological surgery with curative intent in any of the centers participating in the study.

3.- Inclusion and exclusion criteria

Patients with a surgical indication and curative intent due to esophagogastric neoplasia who do not meet exclusion criteria and recruited by hospitals nationwide that decide to participate in the study will be included.

The study exclusion criteria are:

- Patients under 18 or over 85 years
- Patients with chronic infections
- Patients with synchronous tumors in other locations
- Patients with autoimmune disease
- Patients who die in the operating room
- Patients who do not sign the informed consent to participate in the study
- Patients in clinical stage IVB
- Surgical resection R2 (there are macroscopic remains of the tumor in the surgical field after performing the resection of the surgical piece)
- Combined intraoperative resection of other organs
- Surgeries without anastomosis

In addition, the following situations are considered criteria for abandonment or withdrawal of the patient from the study:

- Revocation of the informed consent expressed by the patient at any time during the study.
- Patient loss during study follow-up
- Incorrect data collection according to the indications provided

4.- Sample size

The purpose of the study is to recruit as many patients as possible from all national centers who wish to participate.

For an alpha error of 5% (95% confidence) with a precision of 3% and estimating a number of patients with major complications (including AF) around 30%, the calculation of the sample size yields a total of 847 patients. However, the final sample size may be smaller depending on the proportion of complications detected and the statistical and artificial intelligence models to create the predictive model will be adapted to the event rate provided by the recruited sample.

5.- Recruitment

All patients who meet the inclusion and exclusion criteria will be offered preoperative participation in this study. Once the information has been understood (Annex 1) and the written informed consent (Annex 2) has been signed, each patient will be assigned a code that will be used to anonymously manage any of their information obtained during the study. Thus, the confidentiality of the data belonging to all the patients included in the study will be guaranteed at all times from the moment of recruitment.

6.- Intervention

The patient will undergo the indicated surgical intervention depending on whether it is an esophageal or gastric neoplasm, with curative intent with or without prior neoadjuvant treatment. Surgical intervention and postoperative care will be carried out in each of the centers of the national territory that commit to participate according to their usual clinical practice. Thus, the perioperative management and care protocol will be that of each center without the need to apply exceptional measures (beyond the control of the clinical and analytical variables of this study) or a homogeneous protocol in all the participating centers.

The analysis and control of the preoperative clinical variables must be carried out the day before or the same day of the surgical intervention prior to it.

7.- Follow up

The patient will be monitored during the first 90 postoperative days, compiling all the specific variables of this study and the possible complications and mortality that occurred in this period.

During the immediate postoperative period, apart from the care applied routinely in each center, patients should be evaluated daily and the clinical and laboratory variables specified later should be collected on days 1, 2, 3, 4 and 6 postoperatively. In the same way, in this postoperative course, the possible complications that appeared during the hospital stay will be compiled.

Subsequently, if the patient is discharged from the hospital, a follow-up will be carried out in the outpatient consultations at 30 and 90 days to evaluate the possible complications that appear in this period and other variables studied will be completed.

8.- Database and study variables

The variables collected throughout the study protocol will be collected on the following dates of assistance, care, control and follow-up of the patient.

8.1.- FORMAT and ACCESS to the DATABASE

A database included in the REDCAP of the AEC has been designed to collect the different variables included in this study.

For access to said database, the passwords will be provided to each participating center.

8.2.- PARTS of the DATABASE

After opening the REDCAP application of the AEC, you can access the data set and the different variables to be collected at each moment of the care process and which will be described in more detail below:

The main outcome variable of the study is ANASTOMOTIC LEAKAGE, a categorical variable divided into the following categories, according to the consensus definitions of the Consensus Group on Complications of Esophagectomy (ECCG) (27), which in this study will be applicable both to fistulas occurred after esophagectomy and after gastrectomy:

- NO: If this complication did not occur.
- I: Defect that does not require specific treatment or that can be treated medically or with diet modification
- II: Defect that requires some intervention, but not surgical, such as: drainage by interventional radiology, prosthesis placement, opening of the wound at the bedside, compression or wound healing.
- III: Defect requiring surgical intervention

In relation to this variable, the following data are also included in the study:

- DAY Dx LEAK (DAY of DIAGNOSIS OF THE ANASTOMOTIC LEAK: ordinal variable that shows the number of the postoperative day on which the diagnosis of the anastomotic leak occurred.

- EDA Dx LEAK (LEAK DIAGNOSIS THROUGH ENDOSCOPY): Dichotomous variable: YES/NO.

- CAT Dx LEAK (DIAGNOSIS OF LEAK BY CAT): Dichotomous variable: YES/NO.

The rest of the variables collected in this study are:

8.2.1.- GENERAL DATA

- AGE: continuous variable expressed in completed years.

- SEX: dichotomous variable: MAN / WOMAN.

- WEIGHT: continuous variable expressed in Kg.

- BMI (Body Mass Index): continuous variable expressed in Kg/m2.

- HIST TYPE (Histological type): Categorical variable divided into the following categories:

SQUAMOUS: squamous cell carcinoma

ADENO: Adenocarcinoma

INTESTINAL ADENOCA: Intestinal adenocarcinoma

DIFFUSE ADENOCA: Diffuse adenocarcinoma

OTHERS: Others

- LOCATION: Categorical variable divided into the following categories:

CERVICAL ESOPHAGUS: Cervical esophagus

SUP THORACIC ESOPHAGUS: Upper thoracic esophagus

THORACID ESOPHAGUS MED: Middle thoracic esophagus

LOWER THORACIC ESOPHAGUS: Lower thoracic esophagus

CARDIA: Cardia – esophagogastric junction

FUNDUS: Gastric fundus

BODY: Gastric body

ANTHRUM-PYLORUS: Antrum and/or pylorus

- NEOADJUVANCE: Categorical variable divided into the following categories:

NO: No neoadjuvant

CT: Chemotherapy

QT+RT: Chemotherapy + Radiotherapy

RT: Radiotherapy

- cTNM TUMOR STAGING (includes cT, cN and cM variables), according to the 8th TNM classification.

ESOPHAEAL CANCER

Category T

Tx Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis High-grade dysplasia defined as the presence of malignant cells confined to the epithelium by the basement membrane

T1 Tumor invades lamina propria, muscularis mucosae, or submucosa

T1a Tumor invades the lamina propria or muscularis mucosae

T1b Tumor invades submucosa

T2 Tumor invades the muscularis propria

T3 Tumor invades adventitia

T4 Tumor invades neighboring structures

T4a Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum

T4b Tumor invades other structures such as aorta, vertebrae, or airway

Category N

N- No regional lymph node metastasis

N+ Metastasis in 7 or more regional lymph nodes

Category M

M0 No distant metastasis

M1 Distant metastasis

GASTRIC CANCER

Category T
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Tumor in situ
T1 Tumor invades mucosa or submucosa
T1a Tumor invades mucosa
T1b Tumor invades submucosa
T2 Tumor invades the muscularis propria
T3 Tumor invades the subserosa
T4 Tumor invades serosa or neighboring structures
T4a Tumor invades serosa
T4b Tumor invades neighboring structures
Category N
N- No regional lymph node metastasis
N+ Metastasis in 7 or more regional lymph nodes
Category M
M0 No distant metastasis
M1 Distant metastasis

- ECOG (ECOG functional classification): Categorical variable divided into the following categories:
- 0: Asymptomatic. Fully active.
- 1: Restriction of intense activity. Capable of ordinary work.
- 2: Ambulatory and capable of self-care. Inability to work. Up more than 50% of the time awake.
- 3: Capable of some self-care. Life bed-chair more than 50% of the time awake.
- 4: Total disability. Chair-bed 100% of the time awake
- 5: Dead

- ASA (ASA Classification): Categorical variable divided into: 1, 2, 3 and 4.

- DM (Diabetes Mellitus): Dichotomous variable: YES/NO.

- AHT (Arterial hypertension): Dichotomous variable: YES/NO.

- HEART DISEASE: Heart failure or ischemic heart disease. Dichotomous variable: YES/NO.

- NEPHROPATHY: Chronic renal failure. Dichotomous variable: YES/NO.

- SMOKER: Dichotomous variable: YES/NO.

- PNEUMOPATHY: Chronic obstructive pulmonary disease or Emphysema. Dichotomous variable: YES/NO.

- CEREBRAL VASC DISEASE (Cerebral Vascular Disease): Dichotomous variable: YES/NO.

- ENF ARTER PERIF (Peripheral arterial disease): Dichotomous variable: YES/NO.

- DEMENTIA: Dichotomous variable: YES/NO.

- STEROIDS: Taking corticoid medication. Dichotomous variable: YES/NO.

- OTHER AP (PERSONAL BACKGROUND): write the most relevant

- CONDITIONING (CONDITIONING OF GASTRIC PLASTY): Dichotomous variable: YES/NO.

- DATE CIR (DATE OF INTERVENTION): in day/month/year format

- TYPE OF SURGERY: Categorical variable divided into the following categories:

IVOR LEWIS ESOPHAGECTOMY: 2-stage esophagectomy
MCKEOWN ESOPHAGECTOMY: 3-stage esophagectomy
TRANSHIATAL ESOPHAGECTOMY: 2-stage transhiatal esophagectomy
TOTAL ESOPHAGOSGASTRECTOMY: Total esophagogastrectomy
SUBTOTAL GASTRECTOMY: Subtotal gastrectomy
TOTAL GASTRECTOMY: Total gastrectomy
POLAR SUPERIOR GASTRECTOMY: Polar superior gastrectomy
EXTENDED TOTAL GASTRECTOMY: Extended total gastrectomy
OTHERS: Others

- APPROACH (SURGICAL APPROACH): Categorical variable divided into the following categories:
TOTAL ROBOT Total Robotic Approach
HYBRID Combined approach to abdomen and thorax: open + robot, open + MIS, MIS + robot
MIS TOTAL Laparoscopy and thoracoscopy approach (+/- cervicotomy)
FULL OPEN Full open approach

- BLOOD LOSS (ESTIMATED INTRAOPERATIVE BLOOD LOSS): Continuous variable expressed in ml.

- PLASTY TYPE: Categorical variable divided into the following categories: STOMACH, COLON, JEJUNUM and OTHERS.

- VIA ASCENT (FROM THE PLASTIA TO MAKE THE ANASTOMOSIS): Categorical variable divided into the following categories: MEDIASTINO, RETROESTERNAL and SUBCUTANEOUS.

- ANASTOMOSIS: Categorical variable divided into the following categories:
- CERVICAL ESOPHAGUS-PLASTY
- INTRATRORACIC ESOPHAGUS-PLASTY
- GASTROJEJUNOSTOMY
- ESOPHAGOGJEJUNOSTOMY

- ANASTOMOSIS TYPE: Categorical variable divided into the following categories:
MANUAL Manual
CIRCULAR MECHANICS Circular mechanics with CEEA (includes Orvil)
MECHANICAL L-L Lateral-lateral mechanics
OTHER Other

- PYLORUS (ACT ON THE PYLORUS): includes the performance of pyloromyotomy, pyloroplasty, endoscopic dilation of the pylorus, injection of botulinum toxin, or any other procedure on the pylorus to facilitate emptying of the plasty. Dichotomous variable: YES/NO.

- ICG (USE OF INTRAOPERATIVE FLUORESCENCE TO EVALUATE THE VASCULARIZATION OF THE PLASTY AND OF THE AREA OF THE ANASTOMOSIS): Dichotomous variable: YES/NO.

- pTNM TUMOR STAGING (includes the variables pT, pN and pM): based on the pathological study of the piece resected in the intervention.

Esophageal and GEJ cancer.

Category T
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis High-grade dysplasia defined as the presence of malignant cells confined to the epithelium by the basement membrane
T1 Tumor invades lamina propria, muscularis mucosae, or submucosa
    T1a Tumor invades the lamina propria or muscularis mucosae
    T1b Tumor invades submucosa
T2 Tumor invades the muscularis propria
T3 Tumor invades adventitia
T4 Tumor invades neighboring structures
    T4a Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum
    T4b Tumor invades other structures such as aorta, vertebrae, or airway
Category N
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1-2 regional lymph nodes
N2 Metastasis in 3-6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes
Category M
M0 No distant metastasis
M1 Distant metastasis

Gastric cancer.

Category T
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Tumor in situ
T1 Tumor invades mucosa or submucosa
    T1a Tumor invades the mucosa
    T1b Tumor invades submucosa
T2 Tumor invades the muscularis propria
T3 Tumor invades subserosa
T4 Tumor invades serosa or neighboring structures
    T4a Tumor invades serosa
    T4b Tumor invades neighboring structures

Category N
N- No regional lymph node metastasis
N1 Metastasis in 1-2 regional lymph nodes
N2 Metastasis in 3-6 regional lymph nodes
N3 Metastasis in 7 or more regional lymph nodes

Category M
M0 No distant metastasis
M1 Distant metastasis

8.2.2.- PREOP (PRE-OPERATIVE) and POST-OPERATIVE DAYS (DAY 1, DAY 2, DAY 3, DAY 4 AND DAY 6)

These boxes include the variables collected PREOPERATIVELY and during the established postoperative days. These variables are:

- HR (HEART RATE): continuous variable expressed in beats per minute.

- RR (RESPIRATORY RATE): continuous variable expressed in breaths per minute.

- Tª (TEMPERATURE): continuous variable expressed in OC.

- VAS (VISUAL ANALOGUE SCALE): Scale used to assess the degree of pain. Ordinal variable from 1 to 10.

- TAS (SYSTOLIC ARTERIAL PRESSURE): continuous variable expressed in mmHg.

- DBP (DIASTOLIC ARTERIAL PRESSURE): continuous variable expressed in mmHg.

- SAT O2 (OXIGEN SATURATION): continuous variable expressed in %.

- DIURESIS (DIARIES VOLUME OF DIURESIS): continuous variable expressed in ml/day.

- LEUKES (LEUKOCYTES): continuous variable expressed in number/µL.

- LYMPHOS (LYMPHOCYTES): continuous variable expressed in number/µL.

- NEUTRAL (NEUTROPHILS): continuous variable expressed in number/µL

- HB (HEMOGLOBIN): continuous variable expressed in g/dL.

- PLATELET (PLATELET): continuous variable expressed in number/µL

- CREATININE (CREATININE): continuous variable expressed in mg/dL.

- PROTEINS (PROTEINS): continuous variable expressed in g/dL.

- ALBUMIN (ALBUMIN): continuous variable expressed in g/dL.

- CRP (C-REACTIVE PROTEIN): continuous variable expressed in mg/L.

- PROCAL (PROCALCITONIN): continuous variable expressed in ng/mL.

- IL 6 (INTERLEUKIN 6): continuous variable expressed in pg/ml.

- QUICK (QUICK INDEX): continuous variable expressed in %.

8.2.3.- RESULTS

- ORAL TOLERANCE BEGINNING DAY: postoperative day number on which the patient begins to tolerate food and/or water orally. Continuous variable expressed in days.

- DISCHARGE DATE (DATE OF INTERVENTION): in day/month/year format

- CLAVIEN DINDO COMPLICATION (CLASSIFICATION OF POSTOPERATIVE COMPLICATIONS ACCORDING TO CLAVIEN-DINDO): Categorical variable divided into the following categories:

- NO COMPLICATION: If this complication did not occur.
- I: Any deviation from the normal postoperative course WITHOUT the need for pharmacological treatment or surgical, endoscopic and radiological interventions Acceptable therapeutic regimens are drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes open wound infections at the patient's bedside.
- II: Requires pharmacological treatment with medications other than those authorized for grade I complications. Blood transfusions and total parenteral nutrition are also included.
- IIIa: Requires surgical, endoscopic or radiological intervention with local anesthesia.
- IIIb: Requires surgical, endoscopic or radiological intervention under general anesthesia.
- IVa: Life-threatening complication (including central nervous system complications: cerebral haemorrhage, cerebral infarction, subarachnoid haemorrhage, but excluding transient ischemic attacks) requiring Intermediate/Intensive Care Unit management. Single organ dysfunction (includes dialysis)
- IVb: Life-threatening complication (including central nervous system complications: cerebral haemorrhage, cerebral infarction, subarachnoid haemorrhage, but excluding transient ischemic attacks) requiring Intermediate/Intensive Care Unit management. Multi-organ dysfunction.
- V: Death of the patient.

- NECROSIS of the PLASTY: Categorical variable divided into the following categories according to the consensus definitions of the Consensus Group on Complications of Esophagectomy (ECCG) (27):
- NO: If this complication did not occur.
- I: Focal necrosis of the graft identified endoscopically, which does NOT require surgical treatment.
- II: Focal necrosis of the graft identified endoscopically, requiring surgical treatment, but not esophageal diversion
- III: Extensive necrosis of the graft, which requires surgical treatment with resection of the graft and esophageal diversion.

- DIA Dx NECROSIS (DAY OF DIAGNOSIS OF PLASTY NECROSIS): ordinal variable that shows the number of the postoperative day on which the diagnosis of plasty necrosis occurred

- EDA Dx NECROSIS (DIAGNOSIS OF PLASTY NECROSIS BY ENDOSCOPY): Dichotomous variable: YES/NO.

- CAT Dx LEAK (DIAGNOSIS OF PLASTY NECROSIS BY CAT): Dichotomous variable: YES/NO.

- CHYLOTHORAX: Categorical variable divided into the following categories according to the consensus definitions of the Consensus Group on Complications of Esophagectomy (ECCG) (27):
- NO: If this complication did not occur.
- Ia: Debit less than 1 liter per day - Treatment: changes in the enteral diet
- Ib: Debt greater than 1 liter per day - Treatment: changes in the enteral diet
- IIa: Debt less than 1 liter per day – Treatment: total parenteral nutrition
- IIb: Debt greater than 1 liter per day – Treatment: total parenteral nutrition
- IIIa: Debit less than 1 liter per day - Treatment: interventional radiology or surgery
- IIIb: Debt greater than 1 liter per day - Treatment: interventional radiology or surgery

- DAY Dx CHYLOTHORAX (DAY of DIAGNOSIS OF CHYLOTHORAX): ordinal variable that shows the number of postoperative day on which the diagnosis of chylothorax occurred.

- RECURRENT INJURY: Categorical variable divided into the following categories according to the consensus definitions of the Esophagectomy Complications Consensus Group (ECCG) (27):
- NO: If this complication did not occur.
- Ia: Transient unilateral lesion that does NOT require treatment (dietary modifications allowed)

- Ib: Transient bilateral lesion that does NOT require treatment (dietary modifications allowed)
- IIa: Unilateral injury that requires scheduled and deferred surgical treatment (such as thyroplasty or medialization procedure)
- IIb: Bilateral lesion that requires scheduled and deferred surgical treatment (such as thyroplasty or medialization procedure)
- IIIa: Unilateral lesion requiring urgent or preferential surgical treatment due to episodes of aspiration or respiratory problems (such as thyroplasty or medialization procedure)
- IIIb: Bilateral lesion requiring urgent or preferential surgical treatment due to episodes of aspiration or respiratory problems (such as thyroplasty or medialization procedure)

- DAY Dx RECURRENT INJURY (DAY of DIAGNOSIS OF THE RECURRENT NERVE INJURY): ordinal variable that shows the postoperative day number on which the diagnosis of the recurrent nerve injury occurred.

- AF (ATRIAL FIBRILLATION): Dichotomous variable: YES/NO.

- DAY Dx AF (DAY of DIAGNOSIS OF ATRIAL FIBRILLATION): ordinal variable that shows the postoperative day number on which the diagnosis of atrial fibrillation occurred.

- RESPIRATORY INFECTION: Dichotomous variable: YES/NO.

- DAY Dx INFECC RESP (DAY of DIAGNOSIS OF RESPIRATORY INFECTION): ordinal variable that shows the number of the postoperative day on which the diagnosis of respiratory infection occurred.

- SURGICAL SITE INFECTION (NOT WOUND): Dichotomous variable: YES/NO.

- DAY Dx SURGICAL SITE INFECTION (DAY OF DIAGNOSIS OF SURGICAL SITE INFECTION): ordinal variable that shows the number of postoperative day on which the diagnosis of surgical site infection occurred, not including wound infection.

- WOUND INFECTION: Dichotomous variable: YES/NO.

- DAY Dx WOUND INFECTION (DAY OF SURGICAL WOUND INFECTION DIAGNOSIS): ordinal variable that shows the postoperative day number on which the diagnosis of wound infection occurred.

- MORTALITY: Dichotomous variable: YES/NO.

- MORTALITY DAY: ordinal variable that shows the postoperative day number on which death occurred.

- CAUSE OF MORTALITY: categorical variable with the following categories:
- Heart problems: including acute myocardial infarction, heart failure, malignant arrhythmias.
- Respiratory problems: which includes pneumological conditions with respiratory failure that cannot be corrected
- Neurological problems: including massive stroke, cerebral edema or brain death.
- hemorrhagic shock
- Sepsis and septic shock
- Tumor progression: defined as progressive deterioration of the patient directly related to the oncological process.
- Other: Free text to write a summary of the cause of the patient's death, if it cannot be included in the previous categories.

- READMISSION: Dichotomous variable: YES/NO.

- READMISSION DAY: ordinal variable that shows the postoperative day number on which the readmission occurred.

- CAUSE OF READMISSION (WRITE): Free text to write in summary the cause of the patient's readmission.

8.2.4.- LEAK TREATMENT

- RESOLUTION (RESOLUTION OF THE LEAK): Achievement of healing or closure of the fistula or dehiscence. Dichotomous variable: YES/NO.

- RESOLUTION DAY: ordinal variable that shows the postoperative day number on which the resolution or closure of the fistula occurred.

- ENDOSCOPY 1: application of some endoscopic treatment for the resolution of AF. Categorical variable divided into the following categories:
- NOT
- CLIPS / SUTURE
- ENDOPROSTHETICS
- ENDOSPONGE
- OTHERS

- ENDOSCOPY 2: application of a second endoscopic treatment for the resolution of AF. Categorical variable divided into the following categories:
- NOT
- CLIPS / SUTURE
- ENDOPROSTHETICS
- ENDOSPONGE
- OTHERS

- SURGERY 1: surgical intervention to try to resolve the AF. Categorical variable divided into the following categories:
- NOT
- WASHING + DRAINAGE
- JEJUNOSTOMY
- CLOSURE +/- COVERAGE FLAP
- EXTERIORIZATION (KERH OR SIMILAR)
- ESOPHAGEAL EXCLUSION
- OTHER

- SURGERY 2: surgical intervention added to the previous one to try to resolve the AF. Categorical variable divided into the following categories:
- NOT
- WASHING + DRAINAGE
- JEJUNOSTOMY
- CLOSURE +/- COVERAGE FLAP
- EXTERIORIZATION OF THE AF (KERH TUBE)
- ESOPHAGEAL EXCLUSION
- OTHER

- SURGERY 3: surgical intervention added to the previous ones to try to resolve the AF. Categorical variable divided into the following categories:
- NOT
- WASHING + DRAINAGE

- JEJUNOSTOMY
- CLOSURE +/- COVERAGE FLAP
- EXTERIORIZATION OF THE AF (KERH TUBE)
- ESOPHAGEAL EXCLUSION
- OTHER

- RX INTERVENTIONISM 1 (INTERVENTIONIST RADIOLOGY): Intervention by Interventional Radiology to try to resolve AF and its associated complications. Categorical variable divided into the following categories:
- NOT
- DRAINAGE
- JEJUNOSTOMY
- ENDOPROSTHESIS
- OTHERS

- RX INTERVENTIONISM 2 (INTERVENTIONIST RADIOLOGY): Interventional Radiology intervention added to the previous one to try to resolve AF and its associated complications. Categorical variable divided into the following categories:
- NOT
- DRAINAGE
- JEJUNOSTOMY
- ENDOPROSTHESIS
- OTHERS

DATA COLLECTION AND ANALYSIS

1.- Data collection

Prior to being included in this study, the patient must have received and understood the information provided about the procedures to be performed. For this, an information sheet will be provided (Annex 1), and the patient must accept and sign the informed consent to voluntarily participate in the study (Annex 2). The selection and inclusion of patients will be carried out by the specialist doctors of each center according to the inclusion and exclusion criteria defined above.

In each center there will be a specialist physician who will be the coordinator or person in charge of updating and updating the database created for the development of this study.

Data collection will take place in four stages:

1.- First stage: collection of the patient identification data and the variables included in the GENERAL and PRE-OPERATIVE DATA section.

2.- Second time: collection of data that refer to the surgical intervention (within the GENERAL DATA section).

3.- Third time: collection of patient data during the postoperative period (within the sections of the different postoperative days and RESULTS)

4.- Fourth time: collection of patient data at 30 and 90 days during follow-up.

It is expected that, in most cases, the main objective can be quantified after the end of the hospital stay and the collection of data from the first, second and third times. The secondary objectives will be completed mostly once the hospital stay is over, completing them after follow-up and the fourth time of data collection.

2.- Data análisis

The statistical study will be carried out with the help of the SPSS® version 23.0 software for Windows, using the MATLAB® programming environment for the preparation of the predictive model based on artificial neural networks (ANN).

In the first place, a descriptive analysis will be carried out, both of the sociodemographic and clinical variables, as well as of the analytics and the results of the study.

To describe the quantitative variables that follow a normal distribution, the mean and standard deviation will be used, and the median and interquartile range for those that do not follow a normal distribution, as well as histograms with normality curves for their graphical description.

For the qualitative variables, frequencies and percentages will be used, using bar graphs and/or sectors for the graphic description of those with greater relevance.

A univariate study will be performed to relate the variables studied with the appearance of AF and major postoperative complications. For this, different tests will be used depending on the variable to be studied:

a) Normal categorical variables: Chi-square test or Fisher's exact test.

b) Normal continuous variables: Student's t-test.

c) Non-normal continuous variables: Mann-Whitney U test.

In the results obtained from the univariate study, those variables that show a $p < 0.1$ after the application of the corresponding tests will be considered as related or candidates to predict AF or major

complications. This value will be considered more conservative, different from the conventionally accepted value of 0.05, with the intention of not ruling out potential variables that could have some influence on the results of the study.

Once the univariate study has been completed, a multivariate study will be carried out, using the logistic regression (RL) method. To do this, a recoding of the variables will be carried out, transforming the categorical variables into dummy variables. It will be verified that the variance inflation factor (VIF) is less than 2 in all cases, thus ruling out important problems of collinearity between the variables.

On the other hand, a predictive model based on artificial neural networks (ANN) will also be developed, using a Multilayer Perceptron, a multilayer neural network of forward connections, without recurrent connections and supervised learning.

In addition, once the model has been designed, an application for mobile devices and/or a web page will be created to prospectively introduce new data on developing cases, in order to obtain predictive information on the possibility of developing AF or a major postoperative complication in each case. in particular, thus being able to help the clinician in decision-making during the postoperative control of these patients.

STAGES OF DEVELOPMENT AND DISTRIBUTION OF TASKS

The project will be developed at a national level and all the centers that wish to include patients who meet the recommended inclusion and exclusion criteria will participate in it and will follow the following stages of development:

1.- Idea and creation of the project

This project has been developed jointly by members of the General Surgery and Digestive System Services of the La Fe University and Polytechnic Hospital in Valencia and the Juan Ramón Jiménez Hospital in Huelva.

2.- Presentation of the project

The project will be presented to the Spanish Association of Surgeons, Esophagogastric Surgery section of the same and to all the Spanish centers that are candidates to participate through the cover letter that is attached in the Annexes section (Annex 3).

3.- -Duration of the study

It is estimated that the approximate total duration of the study will be 2 years, in which each center will carry out the recruitment of patients and their postoperative follow-up for 90 days. In each center, patients who meet the inclusion and exclusion criteria consecutively and for one year will be included. The coordinators of each hospital center must inform the general coordinators of the study of the date of inclusion of the first patient in the study, as well as any problem that occurred in the incorporation of cases and data collection.

4.- Distribution of tasks

The different tasks to be carried out during the study will be distributed as follows:

4.1.- The coordinators of the study will be Rocío Pérez Quintero and Marcos Bruna Esteban and they will be in charge of coordinating with the hospitals involved. These features include:
4.1.1.- Publicity and dissemination of the project
4.1.2.- Sending the necessary documents to carry out the study:
—> Invitation letter
—> Explanatory document of the research project
—> Database to complete
—> Instructions for filling the database and definition of variables
—> Approval of the project by the Research and Ethics Committee of one of the centers included in it.
—> Informative document and informed consent for the inclusion of patients in the study.
4.1.3.- Contact with those responsible for the study at each hospital, in order to resolve possible doubts and to control and monitor the data entered.
4.1.4.- Reception, grouping, revision and homogenization of the data collected, performing the calculations of the necessary variables and processing the information for analysis and obtaining results.
4.1.5.- Periodic information to the participating centers on the status of the study, number of cases collected, etc.

4.2.- Those responsible for the study in each center

The inclusion of patient data in the study database will be carried out by those responsible for the study in each center and the professionals they consider appropriate to help them. Each person in charge at each center will be in charge of presenting the project and obtaining authorization from the Research and Ethics Committee of their hospital to be able to carry it out. Once submitted and approved, each hospital must collect data according to the established instructions, obtaining the informed consent of all patients in the study, which must be stored safely.

4.3.- Responsible for the statistical study and creation of the predictive model and application for mobile devices
The work of the descriptive and analytical statistical study of the series, as well as the creation of the predictive models and the development of the application for mobile devices and/or web for the application of the predictive model will be carried out by members of the Intelligent Data Analysis Laboratory. of the Department of Electronic Engineering of the Higher Technical School of Engineering of the University of Valencia.

5.-Schedule:
The schedule of the study is presented schematically below:
5.1.- Conceptual or theoretical phase: choice of topic, literature review, goal setting, hypothesis development: 1 month (November 2021).

5.2.- Design phase: choice of design and choice of variables, development of database and schedule: 1 month (December 2021).

5.3.- Evaluation, approval and authorization of the study by the Research and Ethics Committee of one of the collaborating centers (January 2022).

5.4.- Dissemination and adhesion phase: presentation and dissemination of the project to the Spanish Association of Surgeons, the Esophagogastric Surgery Section and all the centers that wish to collaborate in it (January 2022). The centers may gradually join the study until June 2022.

5.5.- Empirical phase: recruitment and collection of patient data, surgical intervention, results and follow-up. In each center, the data of consecutively operated patients during the period of 1 year from the inclusion of the first case will be collected. Access to the medical records of participating patients will only be allowed to researchers at each center. The data will be collected in each of the participating hospitals and the custody of the same will be the responsibility of the main coordinator or person in charge in each center, who will be in charge of guaranteeing that no identifying data of the patients is transmitted. The data will be encrypted by generating a unique code that will be the only one that will be sent to the central coordination team.

5.6.- Interpretive phase: once the recruitment period for all the centers has closed, the data will be analyzed, the results discussed and compared with other studies. The predictive model described and reason for the study will be created. The estimated duration of this phase will be 3 months.

5.7.- Communicative phase or dissemination of results. Communication of the results to all the participating centers and writing and preparation of scientific articles and communications to congresses (national and international scope). All those responsible for each center will appear as co-authors in all the works and communications published, establishing the order of appearance in them based on the number of cases included in the study. The estimated time for the preparation of this material will be approximately 1 month.

5.8.- Creation and dissemination of the predictive tool. Creation of an application for mobile devices and/or web page where the data of new cases can be entered prospectively, obtaining the prediction of a possible AF or major postoperative complication in each new patient. The estimated time for the creation of this tool will be approximately 3-4 months. Once it has been created and its correct functioning has been tested, it will be disseminated. With the new data entered, an evaluation of the effectiveness and profitability of the model will be carried out, which will supposedly improve with the introduction of more data.

5.9.- Development of sub-studies: once the previous stages have been completed, different sub-studies proposed by the project collaborators will be developed. The collaborator or collaborators who have

proposed the sub-study will be the coordinator and responsible for it, appearing as the first or first signatories in the communications and publications that arise from its realization.

LIMITATIONS OF THE STUDY

Despite the prospective design of the study, there are certain limitations to take into account during its development and analysis of results. Among them, the following stand out:

1.- Possible existence of confounding variables that have not been taken into account in the study approach, that are unknown or not measurable or suitable for collecting and that influence the results.

To solve this possible limitation, an extensive bibliographic search has been carried out and all the easily accessible variables that can influence the result in a global way have been included.

2.- Possible limitations in the collection of information. Being a multicenter study that includes the collection of a large number of variables, there is the possibility of a partial collection of all the information required in each included case.

To reduce this limitation, the collection of information is proposed in the most objective way possible, filling in all the variables proposed to be studied and carrying out periodic supervision and evaluation of the quality and quantity of the data entered in each center. Once all the data has been collected and added to the database according to the instructions described, the database will be sent to the study coordinators, who will evaluate its content and review again the quality and quantity of the data entered, being able to notice errors that require a correction by the researchers responsible for each center.

3.- Another possible limitation of the study is the low incidence of the pathology studied in our environment, which requires a long period of time to achieve an optimal sample size.

As a solution to this limitation, a multicenter study has been proposed, trying to achieve the greatest possible collaboration and participation of all the centers at the national level, in order to achieve an adequate sample size in the expected data collection time. .

4.- Another possible limitation of the study could be the differences in the surgical technique and the specific perioperative management protocols of each center, which, being different and particular in each one of them, would facilitate a wide variability in the management of the cases. However, the purpose of the study is to create a predictive model that is universal and based on objective clinical and analytical variables, in order to obviate these differences between centers and with the ability to be applied in each of them with the same effectiveness.

ETHICAL AND LEGAL ASPECTS

This study will be carried out under the following ethical considerations and based on current legal regulations.

1.- Ethical considerations

The nature and prospective and observational nature of the study do not imply the application of techniques or procedures that are not contemplated in the current Clinical Practice Guidelines, recommendations endorsed by scientific societies and consensus of experts accepted and used routinely and globally regarding clinical management. (diagnosis and therapeutic) of these patients.

2.- Regulations and medical-legal aspects

During all the analytical stages of the study, the data collected will be used anonymously in accordance with current regulations on confidentiality and data protection, guaranteeing the protection of personal data according to Regulation (EU) No. 2016/679 of the European Parliament and of the Council of April 27, 2016 on Data Protection (RGPD) (28), maintaining professional secrecy at all times regarding the data of the patients included in the study, which will be scrupulously handled.

This study will be carried out following the current regulatory requirements, respecting the codes and standards of good clinical practice and guaranteeing the rights of patients, as well as the basic ethical principles (Declaration of Helsinki approved by the World Medical Assembly in its Fortaleza version in 2013 (29) and the Oviedo Convention of 1997) (30). The rights, safety, and welfare of study patients will take precedence over the interests of science.

Thus, each patient included in the study must previously grant her consent by signing a specific informed consent prepared for this purpose. The legal representative will give their informed consent in the event that the patient is not legally competent.

The collection of patient data will be methodical and exhaustive. The data of each patient will be codified, anonymized, included and managed in the database designed for it. Once the study has been completed, the data will be kept on file for the maximum legally established time (15 years) to ensure possible audits and controls. After this period, they will be deleted.

Biological samples will not be obtained for this study, although data derived from routine blood tests and other healthcare diagnostic tests and used in routine clinical practice recorded in your medical record will be collected.

The study will begin once this project is evaluated, approved and authorized by the Research and Ethics Committee of the different participating hospitals.

3.- Insurance

Due to the characteristics and design of the study, insurance coverage is not considered necessary.

CONFLICT OF INTERESTS

The researchers assure that there is no type of conflict of interest that could compromise the validity of the results.

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ANEXOS

Anexo 1.- Documento de información para el paciente

DOCUMENTO DE INFORMACIÓN PARA EL PARTICIPANTE

Centro: **Fecha:**	**DATOS PACIENTE** **- Apellidos:** **- Nombre:** **- NHC:**

Título de la investigación: "**ESTUDIO PROFUGO**: Modelo **PR**edictiv**O** para el Diagnóstico Precoz de la **FUG**a anastomótica tras esofaguectomía y gastrectomía"

1. Introducción

Nos dirigimos a usted para invitarle a participar en un proyecto de investigación que estamos realizando en nuestro hospital y en otros centros del territorio nacional y para el cual su participación es importante para obtener el conocimiento que necesitamos, pero antes de tomar una decisión debe:

- Leer este documento entero
- Entender la información que contiene el documento
- Hacer todas las preguntas que considere necesarias
- Consultar con su médico-persona de confianza
- Tomar una decisión meditada
- Firmar el consentimiento informado, si finalmente desea participar.

Si decide participar se le entregará una copia de este documento y del consentimiento firmado. Por favor, consérvelos por si lo necesitara en un futuro.

2. ¿Por qué se le pide participar?

Se le solicita su colaboración al ser mayor de 18 años e ir a ser usted intervenido quirúrgicamente para extirparle la parte enferma, para posteriormente restaurar la continuidad del tubo digestivo en su caso. Sobre el procedimiento quirúrgico recibirá información adecuada y complementaria a esta por parte de su cirujano.

3. ¿Cuál es el objeto de este estudio?

El estudio tiene la intención y el objetivo de evaluar los resultados postoperatorios e intentar establecer un modelo predictivo para el diagnóstico precoz de la fuga o fístula anastomótica tras la cirugía de resección del estómago y esófago basado en datos analíticos y clínicos. Con ello se pretende establecer un modelo que permita acercarnos al diagnóstico más temprano de esta posible complicación y así poder ofrecer un tratamiento más rápido y efectivo.

4. ¿Qué tengo que hacer si decido participar?

Recuerde que su participación es voluntaria y si decide no participar esto no afectará a su asistencia o a su relación con el investigador y su equipo.
Si decide participar y como se le ha informado, se evaluarán a diario sus constantes y situación clínica según la asistencia clínica habitual y se extraerán analíticas sanguíneas similares a las que se le realizarían si no participa en este estudio.

5. ¿Qué riesgos o molestias supone?

Como se le comentaba antes, en este estudio se pretende evaluar los resultados postoperatorios e intentar establecer un modelo predictivo para el diagnóstico precoz de la fuga o fístula anastomótica tras la cirugía de resección del estómago y esófago basado en datos analíticos y clínicos. Con ello se pretende establecer un modelo que permita acercarnos al diagnóstico más temprano de esta posible complicación y así poder ofrecer un tratamiento más rápido y efectivo.

Para ello, se evaluarán a diario sus constantes y situación clínica según la asistencia clínica habitual y se extraerán analíticas sanguíneas similares a las que se le realizarían si no participa en este estudio en las que se determinarán diferentes valores en relación a la inflamación e infección usados rutinariamente en la práctica clínica habitual.

Riesgo de la extracción de sangre: Se extraerá sangre a través de una aguja insertada en una de las venas de su brazo. Este procedimiento conlleva una serie de riesgos asociados, entre los que se encuentran los siguientes: dolor, hematoma, enrojecimiento, hemorragia, infección y desmayos. Sin embargo, estos riesgos asociados a la extracción de la muestra no son más que los asociados a la extracción de una muestra de sangre con motivo de un análisis rutinario

6. ¿Obtendré algún beneficio por mi participación?

Al tratarse de un estudio de investigación orientado a generar conocimiento es probable que no obtenga ningún beneficio por su participación si bien usted contribuirá al avance del conocimiento y al beneficio social.

Usted no recibirá ninguna compensación económica por su participación.

7. ¿Cómo se van a gestionar mis datos personales?

Toda la información recogida se tratará conforme a lo establecido en la Ley Orgánica 15/99, de protección de datos de carácter personal. En la base de datos del estudio no se incluirán datos personales: ni su nombre, ni su nº de historia clínica ni ningún dato que le pueda identificar. Se le identificará por un código que sólo el equipo investigador podrá relacionar con su nombre.

Sólo el equipo investigador tendrá acceso a los datos de su historia clínica y nadie ajeno al centro podrá consultar su historial.

Para ejercer su derecho de acceso, rectificación, cancelación y oposición respecto a sus datos

obtenidos durante el estudio debe ponerse en contacto con el investigador principal.

Las conclusiones del estudio se presentarán en congresos y publicaciones científicas pero se harán siempre con datos agrupados y nunca se divulgará nada que le pueda identificar.

8. ¿Quién financia el estudio?

No existe financiación para la realización de este proyecto.

9. ¿Se me informará de los resultados del estudio?

Usted tiene derecho a conocer los resultados del presente estudio, tanto los resultados generales como los derivados de sus datos específicos. También tiene derecho a no conocer dichos resultados si así lo desea. Por este motivo en el documento de consentimiento informado le preguntaremos qué opción prefiere. En caso de que desee conocer los resultados, el investigador le hará llegar los resultados.

10. ¿Puedo cambiar de opinión?

Tal como se ha señalado, su participación es totalmente voluntaria, puede decidir no participar o retirarse del estudio en cualquier momento sin tener que dar explicaciones y sin que esto repercuta en su atención sanitaria. Basta con que le manifieste su intención al investigador principal del estudio.
Si usted desea retirarse del estudio se eliminarán los datos recogidos y las muestras biológicas no utilizadas en ese momento.

11. ¿Qué pasa si me surge alguna duda durante mi participación?

En caso de duda o para cualquier consulta relacionada con su participación puede ponerse en contacto con el investigador responsable, Dr. _____ en el Servicio de Cirugia General del Hospital _____ en horario de mañanas o por correo electrónico en la dirección**:** _____

Muchas gracias por su atención, si finalmente desea participar le rogamos que firme el documento de consentimiento que se adjunta.

Anexo 2.- Consentimiento informado para participación en el estudio

DOCUMENTO DE CONSENTIMIENTO INFORMADO

Título del PROYECTO: "**ESTUDIO PROFUGO**: Modelo **PR**edictiv**O** para el Diagnóstico Precoz de la **FUG**a anastomótica tras esofaguectomía y gastrectomía"

Yo, ...(nombre y apellidos del participante) con DNI ……..

He leído el documento de información que se me ha entregado.

He podido hacer preguntas sobre el estudio y he recibido suficiente información sobre el mismo.

He hablado con: ..... (nombre del investigador) con DNI…….

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1) cuando quiera
2) sin tener que dar explicaciones
3) sin que esto repercuta en mis cuidados médicos

Comprendo y acepto la ley orgnánica de protección de datos.

Presto libremente mi conformidad para participar en el estudio

Deseo ser informado sobre los resultados del estudio: sí no (marque lo que proceda)

He recibido una copia firmada de este Consentimiento Informado.

Nombre, DNI y firma del Participante: .....
Fecha:.....

He explicado la naturaleza y el propósito del estudio al paciente mencionado

Nombre, DNI y firma del Investigador:……
Fecha:.....

CONSENTIMIENTO INFORMADO DEL REPRESENTANTE LEGAL

Título del proyecto de investigación: "**ESTUDIO PROFUGO**: Modelo **PR**edictiv**O** para el Diagnóstico Precoz de la **FUG**a anastomótica tras esofaguectomía y gastrectomía"

Yo, ……

en calidad de: ……

de: ……

He leído la hoja de información anterior.
He podido hacer preguntas sobre el estudio.
He recibido suficiente información sobre el estudio.

He hablado con ……

Comprendo que la participación es voluntaria.
Comprendo que puede retirarse del estudio:

- Cuando quiera.
- Sin tener que dar explicaciones.
- Sin que esto repercuta en sus cuidados médicos.

Comprendo que este material aparezca en informes y artículos de revista de publicaciones médicas.
Entiendo que:

- Mi nombre no será publicado.
- El material no será utilizado para publicidad o embalaje.
- El material no será utilizado fuera de contexto.

En mi presencia se ha dado a …… …… toda la información pertinente adaptada a su nivel de entendimiento y está de acuerdo en participar.

Y presto mi conformidad con que …….. participe en el estudio.

Firmado: …….. Fecha……..

Anexo 3.- Carta de presentación e invitación a participar en el estudio

Querid@ compañer@;

Como bien sabes la fuga anastomótica en la cirugía esofagogástrica es una de las más temidas complicaciones y, a pesar de los múltiples avances realizados para disminuir su incidencia, ésta aún sigue siendo considerable. Además, su aparición durante el postoperatorio de nuestros pacientes se asocia a un incremento considerable de la mortalidad, estancia hospitalaria y deterioro grave de su estado funcional. Por todo ello, además de las múltiples medidas que aplicamos para prevenir su aparición, es de vital importancia establecer un diagnóstico lo más precoz posible, con el propósito de aplicar un rápido y adecuado tratamiento en cada caso, lo cual disminuye de forma significativa la mortalidad asociada a esta complicación.

Así, con el propósito de crear un modelo predictivo que permita identificar los pacientes con un elevado riesgo de fuga anastomótica durante el postoperatorio de una cirugía esofagogástrica ha nacido el **estudio PROFUGO** (Modelo **PR**edictiv**O** para el Diagnóstico Precoz de la **FUG**a anastomótica tras Esofaguectomía y Gastrectomía). El estudio tiene un diseño **prospectivo y multicéntrico** y pretende, mediante el análisis de diferentes variables clínicas y analíticas recogidas durante el postoperatorio de estos pacientes, elaborar con ayuda de métodos de **inteligencia artificial** una herramienta que permita identificar casos con un elevado riesgo de fuga anastomótica. Con ello, en los pacientes identificados por el modelo con un riesgo elevado, se podría actuar en consecuencia e indicar las exploraciones complementarias que se consideren adecuadas para obtener un diagnóstico precoz, evitando así un mayor deterioro del paciente y una posible situación séptica en estados más avanzados.

Por todo ello, te invitamos a participar en este estudio donde se recogerán de forma prospectiva los datos de los pacientes sometidos a una esofaguectomía o gastrectomía en todos los hospitales españoles que participen en el mismo. Se designará un **responsable en cada centro** colaborador, que será el encargado de mantener la comunicación con los promotores del estudio y cuyo nombre aparecerá reflejado en los proyectos y publicaciones científicas que se desarrollen en consecuencia. Del mismo modo, existe la posibilidad de plantear y desarrollar diferentes **subestudios o subanálisis** con los datos recopilados en base a la evaluación de las propuestas que los miembros colaboradores presenten.

¡¡¡ Esperamos contar con tu ayuda y participación en el estudio PROFUGO!!!

Si deseas más información o inscribirte al proyecto, escríbenos un email a alguna de las direcciones de correo que aparecen a continuación, indicándonos tu interés, tu nombre y apellidos y el centro en el que trabajas.

Rocio Pérez Quintero
roc14589@hotmail.com

Marcos Bruna Esteban
drbruna@comv.es

ESTUDIO PROFUGO