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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

How to preserve the native or reconstructed esophagus after perforations or postoperative leaks: A multidisciplinary 15-year experience

Dania Nachira, Giuseppe Calabrese, Alessia Senatore, Valerio Pontecorvi, Khrystyna Kuzmych, Claudia Belletatti, Ivo Boskoski, Elisa Meacci, Alberto Biondi, Federico Raveglia, Vincenzo Bove, Maria Teresa Congedo, Maria Letizia Vita, Gloria Santoro, Leonardo Petracca Ciavarella, Filippo Lococo, Giovanni Punzo, Angelo Trivisonno, Francesco Petrella, Federico Barbaro, Cristiano Spada, Domenico D'Ugo, Ugo Cioffi, Stefano Margaritora

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Abstract

BACKGROUND
Esophageal perforation or postoperative leak after esophageal surgery remain a life-threatening condition. The optimal management strategy is still unclear.

AIM
To determine clinical outcomes and complications of our 15-year experience in the multidisciplinary management of esophageal perforations and anastomotic leaks.

METHODS
A retrospective single-center observational study was performed on 60 patients admitted at our department for esophageal perforations or treated for an anastomotic leak developed after esophageal surgery from January 2008 to December 2023. Clinical outcomes were analyzed, and complications were evaluated to investigate the efficacy and safety of our multidisciplinary management based on the preservation of the native or reconstructed esophagus, when feasible.

RESULTS
Among the whole series of 60 patients, an urgent surgery was required in 8 cases due to a septic state. Fifty-six patients were managed by endoscopic or hybrid treatments, obtaining the resolution of the esophageal leak/perforation without removal of the native or reconstructed esophagus. The mean time to resolution was 54.95 ± 52.64 days, with a median of 35.5 days. No severe complications were recorded. Ten patients out of 56 (17.9%) developed pneumonia that was treated by specific antibiotic therapy, and in 6 cases (10.7%) an atrial fibrillation was recorded. Seven patients (12.5%) developed a stricture within 12 months, requiring one or two endoscopic pneumatic dilations to solve the problem. Mortality was 1.7%.

CONCLUSION
A proper multidisciplinary approach with the choice of the most appropriate treatment can be the key for success in managing esophageal leaks or perforations and preserving the esophagus.

Key Words: Esophageal perforations; Postoperative leak; Endoscopic vacuum-assisted closure therapy; Metal stent; Endoscopic suture; Lateral esophagostomy; Autologous emulsified stromal vascular fraction

Core Tip: This is a retrospective single-center observational study to evaluate our multidisciplinary management of esophageal perforations and anastomotic leaks based on the preservation of the native or reconstructed esophagus when feasible. In our experience, the choice of the most appropriate treatment led to the resolution of the esophageal fistula with low morbidity and mortality and a reasonable mean resolution time. Long-term complications, as strictures, were also low and in line with the literature.

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INTRODUCTION

Esophageal perforation is defined as a full-thickness tear in the esophageal wall due to a trauma or to a sudden increase

of endoluminal pressure, as in spontaneous perforation[1]. Iatrogenic perforation is the most frequent type (59% of all cases), followed by spontaneous perforation (15%) and ingestion of a foreign body or caustic ingestion (12%)[1]. A particular type of "perforation" is the postoperative leak after esophageal resection and reconstruction with gastric conduit, that has a different etiology but a similar clinical presentation and treatment. Indeed, despite the improvements in surgical techniques and staplers, the incidence of postoperative leak is still reported to be quite high, ranging from 5% to 30%[2-4]. In particular, cervical leaks occur in 6.6%-17.2% of cases[5], while the intrathoracic ones are assessed around 2.0%-15.9%. Mortality can be very high if the treatment is delayed, and it can reach 80% for esophageal perforations[6], with lower percentages (17%-35%) for postoperative anastomotic leaks[7].

The therapeutic management of esophageal perforations and leaks is multidisciplinary, involving surgeons, endoscopists, radiologists, and infectious disease specialists. Additionally, in the high-volume centers, lower mortality rates are reached through an optimized management of complications[8] by the different specialists. Early diagnosis (within the first 24 h) is crucial as it reduces the overall mortality, length of in-hospital stay, and surgery[9]. Indeed, surgery or redo surgery (as in case of anastomotic leaks) is burdened by a high mortality rate (over 40%)[10], particularly in fragile and compromised patients. Often it can require the sacrifice of the esophagus with its total removal and second-step reconstruction. Therefore, when feasible, it is mandatory to consider other conservative, endoscopic or hybrid alternatives (endoscopic and surgical) to preserve the esophagus and reduce morbidity and mortality related to the procedures.

However, the optimal management strategy remains unclear. Nowadays, several endoscopic options are available and proven to be safe and effective including through the-scope clips[11-17], over-the-scope clips[18-21], and endoscopic suturing techniques [OverStich™ and Helix device[22-24], self-expanding-metal stents (SEMS)[25-33], endoscopic vacuum-assisted closure therapy (EVAC)[34-40], and local injection of emulsified autologous stromal vascular fraction (tSVFem)[41]]. Surgery may have a role in preserving the organ and reducing mortality through the toilette of pleural cavity and mediastinum in cases of purulent effusion and by the creation of a cervical esophageal mucosa fistula (diverting lateral esophagostomy)[1]. It consists of a proximal esophageal ligation to divert the saliva and to temporarily exclude the esophageal transit promoting the healing.

Here, we reported our 15-year experience in the multidisciplinary management of esophageal perforations and anastomotic leaks at a tertiary center with extensive experience in esophageal surgery. We summarized our empirical algorithm for the management of such a burdensome condition based on esophageal preservation when feasible and indication to esophagectomy or removal of gastric conduit transposed only in cases of esophageal necrosis or complete dehiscence of the esophagogastric anastomosis with septic status. Clinical outcomes were analyzed, and complications were evaluated to investigate the efficacy and safety of our management.

MATERIALS AND METHODS

From January 2008 to December 2023, clinical data of 250 patients who were admitted to our department for esophageal spontaneous or iatrogenic perforations or who had undergone esophageal surgery for benign (middle or distal esophagus diverticula) or malignant diseases were reviewed. Patients who met the inclusion criteria for the study were selected, and clinical data were analyzed. The inclusion criteria were: Spontaneous or iatrogenic perforations of the esophagus (located under the upper esophageal sphincter up to the cardia included) and esophageal leaks after esophagogastric anastomosis (cervical in McKeown esophagectomy or intrathoracic in Ivor-Lewis esophagectomy). The exclusion criteria were: Perforations after caustic injection, perforations on advanced esophageal cancer, or perforations of the pharynx and upper esophageal sphincter.

Diagnosis and management

If there was a clinical suspicion of perforation or leak, an instrumental diagnosis confirmation was mandatory. In cases of esophageal perforation, the symptoms varied according to the location (cervical or intrathoracic) as well as the extension and the time of onset[1,42]. The most frequent symptoms of cervical perforations were: Dysphagia, sialorrhea; odynophagia; and subcutaneous emphysema[43,44]. The most frequent symptoms of intrathoracic perforations were: Chest pain usually extending to the neck and shoulders; dyspnea; dysphagia; pneumothorax; and pneumomediastinum. Later symptoms were: Fever; tachycardia; pleural effusion; respiratory disorders; and signs of septic shock[45]. The symptomatology was quite similar for cervical and thoracic postoperative leakages, and the presence of a surgical drain facilitated the diagnosis due to purulent or enteric material output or air leak. In all cases, it was mandatory to drain/divert or prevent the saliva (in the esophageal perforations) or the gastric juice (in the postoperative leaks) from collecting in the mediastinum or pleural cavity developing into an abscess or empyema and causing a septic state.

A chest X-ray with water-soluble contrast medium (Gastrografin®[1]) was performed, or computed tomography scan with Gastrografin® taken per os was conducted to more accurately evaluate the size of the esophageal tear and the extension of the leakage into the mediastinum (with mediastinal abscesses) or pleural cavity (pleural effusion). According to this radiological criterion, the esophageal leakages can be classified into esophago-mediastinal or esophago-pleural fistula[46].

Esophagoscopy was performed to evaluate and measure the extension of the defect in the esophageal wall or in the anastomosis (not always feasible through the computed tomography scan) and the status of the esophageal conduit to exclude necrosis. However, its role in non-penetrating perforation is still debated due to the risk of exacerbating mucosal tears and contaminating the mediastinum[1]. Following confirmation of diagnosis, a regimen of fasting per os was prescribed, along with parenteral/enteral (through nasogastric tube or jejunostomy) nutrition and broad-spectrum antibiotic and antifungal therapy. A subsequent targeted antibiotic therapy was prescribed by our infectious disease

specialists after obtaining culture tests from any drained mediastinal or pleural collections or from blood cultures in septic patients.

In all cases of early diagnosis, in patients with stable clinical conditions and absence of esophageal necrosis/complete anastomosis dehiscence (type 3 Esophageal Complications Consensus Group classification[47]), the perforation/leak was managed as in Figure 1, using one of the following endoscopic, hybrid, or surgical approaches to preserve the esophagus.

Four-side hole nasogastric tube: With an intermitted suction (applied vacuum of 125 mmHg) to keep clean the esophageal zone of tear. This technique is used for very small perforations or leaks (mean diameter < 3-4 mm).

Through the-scope clips: They are indicated for small perforations and tears measuring from a few millimeters to 1 cm, and they are applied according to the so called "zipper technique" from the distal to the proximal part of the defect[11-17].

Over-the-scope clips: They were devolved to manage endoscopically larger full-thickness defects (between 1 and 2 cm) [18-21].

SEMS: They are largely used for perforations larger than 20 mm and not treatable by clips[25-33]. Fully covered SEMS were developed to allow the diversion of enteral content and restart nutrition. They also allow their removal preventing tissue ingrowth. However, a higher risk of migration is reported for such stents[27]. Partially-covered SEMS were developed to prevent this adverse event. In our experience either fully covered SEMS (fixed to the esophageal wall by endoscopic stiches) and partially-covered SEMS were used.

Endoscopic suturing: OverStich™ (Apollo Endosurgery, Austin, TX, United States) for suturing defects from 2 to 5 cm [22-24] and Helix device (Apollo Endosurgery, Austin, TX, United States) to approximate esophageal tissue allowing a full-thickness suture. Endoscopic suturing can be also used to fix the SEMS to the esophageal wall, preventing migration.

Endoscopic double-pigtail catheter (EDPC): It can be used to manage defects smaller than 1-2 cm of cardia or gastric wall after bariatric surgery[48]. It is useful in cases of fluid collection in the mediastinum or pleural cavity (esophago-mediastinal or esophago-pleural fistula) because it allows an internal drainage of the fluid into the digestive tract, without the need of a surgical drain.

EVAC: It is a polyurethane sponge that can be molded based on the perforation shape. In cases of defects without extraluminal cavity, it can be placed directly in the esophageal lumen or in the cavity[34-40]. More than one sponge can be used to obliterate the cavity. The main advantage of EVAC is the possibility to manage perforations/leaks with the surrounding fluid collection (esophago-mediastinal or esophago-pleural fistula) due to the continuous wound cleaning and granulation promotion provided by suction (generated by a vacuum pump of 125 mmHg).

tSVFem injection: This is a very recent method developed by our group[41] to promote wound healing of the esophageal wall through the endoscopic injection of 3-4 mL of autologous tSVFem in the submucosa of fistula borders. It can be used to manage defects smaller than 10 mm. For larger defects, endoscopic suture is performed before the tSVFem injection to accost the margins.

Lateral esophagostomy: Esophageal fistula[49] fixes the esophageal mucosa of the surgical fistula borders on the skin with 3/0 vicryl stiches. A proximal esophageal ligation with silk lace 0 or 1 was performed 2-3 cm distally to the created esophagostomy, over the jugular level, to divert the saliva and to temporarily exclude the esophageal transit. This technique prevents the need for a second step esophageal reconstruction. In fact, 4-6 months later, the silk lace can be removed and an esophagoscopy/esophagography performed to verify esophageal perforation or leak complete has completely healed. Therefore, the cutaneous fistula can be closed. In general, for subcentimetric perforations and leaks, the four-side hole nasogastric tube, endoscopic suturing (in cases of vital esophageal tissue), and EDPC were adopted, while using EVAC and SEMS are used for larger defects.

Since 2020, EVAC has nearly completely replaced the use of SEMS in our center in treating esophageal perforations/leaks with a median diameter of 20 mm. This procedure has the added benefit of treating esophago-mediastinal or esophago-pleural fistula without the need for a surgical drain or toilette (Figure 2). Since 2019, the endoscopic injection of tSVFem in the fistula borders was used for non-approachable lesions or lesions non-responsive to standard treatments at our center[41], reserving the diverting lateral esophagostomy for cases with larger esophageal defects or septic status.

In the presence of a concomitant pleural effusion, a large bore chest (24-28 Fr) drain was placed to drain the pleural cavity. In cases of pleural empyema (esophago-pleural fistula), mediastinal abscess, or fluid collection (esophago-mediastinal fistula), a surgical toilette was performed (if not drained by EVAC or EDPC), leaving in place chest tubes until the resolution of the clinical-radiological condition. Since 2016, the surgical toilette was performed by the Uniportal-VATS approach, with a single 4 cm incision in the fifth/sixth intercostal space on the middle axillary line[50], improving postoperative recovery compared to traditional thoracotomy.

Excluding the cases treated by SEMS or side esophagostomy (where radiological and endoscopic checks were performed after a mean period of 2-3 months and 4-5 months, respectively), all other patients underwent a gastroscopy or a gastrography about 7-10 days after the first treatment. In cases of EVAC treatment, an operative gastroscopy was performed 4-5 days later to check the local situation and change the sponge if a redo was necessary.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, with median and interquartile range for those with right skewness. Categorical variables were described with absolute frequencies and percentage (%). The

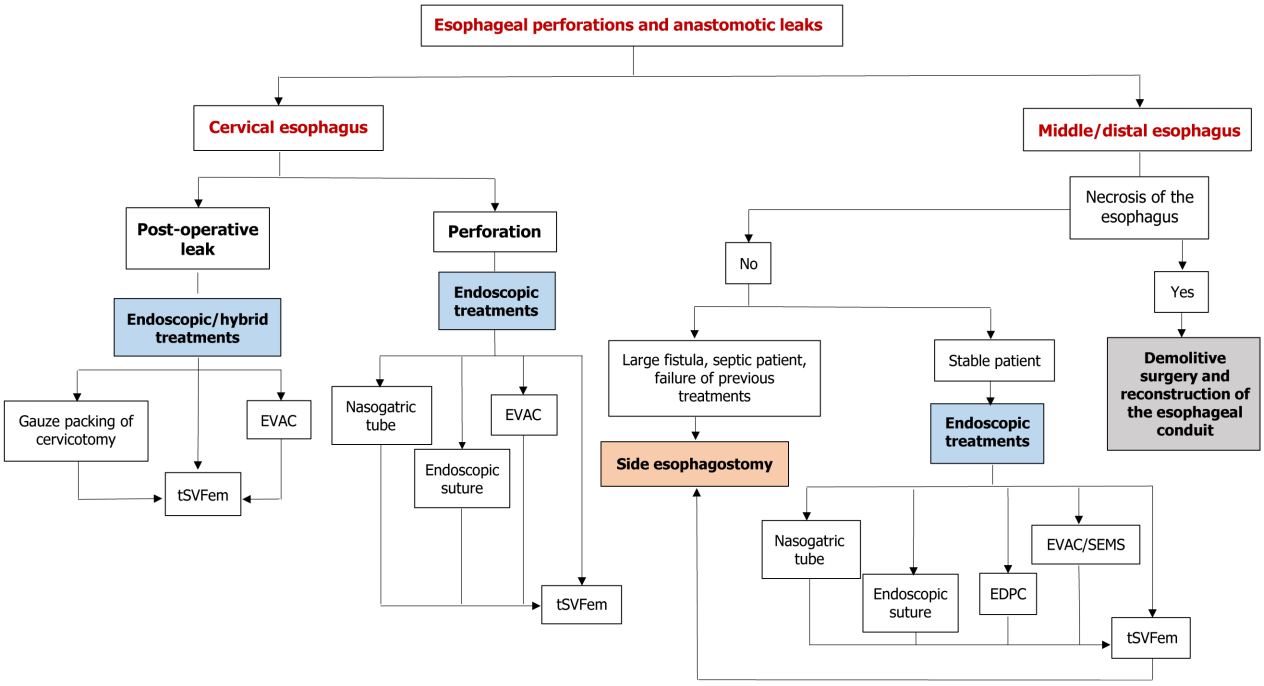

Figure 1 Flowchart summarizing our multidisciplinary endoscopic, hybrid (endoscopic + surgical) or surgical management of esophageal perforations and postoperative leaks. EDPC: Endoscopic double-pigtail catheter; EVAC: Endoscopic vacuum-assisted closure therapy; SEMS: Self-expanding-metal stent; tSVFem: Emulsified autologous stromal vascular fraction.

Kolmogorov-Smirnov test was used to evaluate normal distribution of data. Categorical variables were compared by a χ^2 test. The Student's *t* test was used to compare means between two continuous variables if normally distributed or by Mann-Whitney *U* test if not normal. A *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 25.00 (Armonk, NY, United States).

RESULTS

Sixty patients who met the inclusion criteria were identified in the study period (Figure 3). In 59 cases, a multidisciplinary conservative/endoscopic or hybrid (endoscopic and surgical) management was attempted for the esophageal perforation/anastomotic leak as first treatment. In 1 case (a large spontaneous perforation of the distal esophagus in a patient with Boerhaave syndrome), the septic status of the patient, due to immediate circumferential necrosis of the distal esophagus, made the complete esophagectomy mandatory, followed by a second stage reconstruction (after 6 months with a colonic interposition) (Figure 3).

In 56 out of 59 cases (94.9%) managed by a multidisciplinary team through conservative/endoscopic or hybrid (endoscopic and surgical) treatments, a complete resolution of the fistula and the preservation of the native or reconstructed esophagus was obtained (Figure 3). In 3 cases (5.1%, one spontaneous perforation of the distal esophagus, one postoperative leak after Ivor-Lewis esophagectomy, and one esophageal diverticulectomy), it was not possible to preserve the esophagus due to the failure of several previous treatments, with consequent necrosis of the organ in 2 cases, and a complete surgical demolition was necessary with a subsequent reconstruction using a gastric or colonic conduit (Figure 3). One patient (Ivor-Lewis esophagectomy) died after demolitive surgery of the esophagus.

The mean diameter of the defect in the esophageal wall in these 4 cases that underwent demolitive surgery was 20.34 ± 15.58 mm. One patient was affected by diabetes mellitus type II, and the mean age of patients was 51.75 ± 19.55 years (*P* value = 0.459). The main clinical characteristics of the 56 patients successfully managed and including the two groups of esophageal perforations and postoperative anastomotic leaks (Figure 3) were reported in Table 1.

In detail, 12 out of the 56 patients had an esophageal perforation (10 spontaneous due to Boerhaave syndrome or foreign body ingestion and 2 iatrogenic), while 44 had an anastomotic leak after esophageal surgery (16 after McKeown esophagectomy, 25 after Ivor-Lewis, and 3 after middle-esophagus diverticulectomy) (Table 1). Forty-two (75.0%) patients were male, with a mean age of 56.45 ± 12.70 years and a mean body mass index of 23.91 ± 5.37 (Table 1). Perforation was mainly located in the middle esophagus (6 cases, 50%), while the anastomotic leak after esophageal surgery was manly located in the distal esophagus (19 cases, 43.1%) followed by cervical esophagus (16 cases, 36.45). The median diameter of the orifice was 13 (5-30) mm, with no significant difference in the median diameter between the groups of perforations and anastomotic leaks [15 (6-24) *vs* 10 (4-30), *P* value = 0.820]. The mean time between the acute event and the first treatment was 4.5 (2-10) days, including the days that some patients spent in other centers before being transferred to our referral center for management. In many cases (82.1%), the leak/perforation was associated with mediastinal or pleural

Table 1 Clinical characteristics and outcomes of the patients successfully managed by endoscopic/hybrid treatments

Characteristics	Population, *n* = 56 patients	Esophageal perforations, *n* = 12 patients	Anastomotic leaks, *n* = 44 patients
Male sex	42 (75.0)	11 (91.7)	31 (70.5)
Age in years	56.45 ± 12.70	58.13 ± 12.03	57.05 ± 13.09
Cardiovascular disease	12 (21.4)	2 (16.7)	10 (22.7)
DM	13 (23.2)	5 (41.7)	8 (18.2)
BMI	23.91 ± 5.37	25.23 ± 2.98	20.89 ± 10.45
Localization: Cervical	18 (32.2)	2 (16.6)	16 (36.4)
Middle esophagus	15 (26.8)	6 (50.0)	9 (20.5)
Distal esophagus	19 (33.9)	2 (16.7)	19 (43.1)
Cardias	4 (7.1)	2 (16.7)	0
Cause: Spontaneous	10 (17.9)	10 (83.3)	/
Iatrogenic	2 (3.6)	2 (16.7)	/
Post-surgical	44 (78.5)	/	44 (100.0)
Single/multiple orifice of the fistula	53 (94.6)/3 (5.4)	12 (100)	41 (93.2)/3 (6.8)
Size in mm	13 (5-30)	15 (6-24)	10 (4-30)
Mediastinal/pleural fluid collection	46 (82.1)	7 (58.3)	39 (88.6)
Side of pleural collection (right)	41 (73.2)	5 (41.7)	36 (81.8)
Chest tube	28 (50.0)	3 (25.0)	25 (56.8)
Surgical toilette pleural/mediastinal cavity	13 (23.2)	5 (41.7)	8 (18.2)
Time between acute event and treatment in days	4.5 (2-10)	8.5 (1.75-28.50)	4 (2-8.5)
First treatment			
Endoscopic suture	5 (8.9)	1 (8.3)	4 (9.1)
Surgical suture + drainage	3 (5.4)	1 (8.3)	2 (4.5)
SEMS	8 (14.3)	3 (25.0)	5 (11.4)
EVAC	10 (17.9)	2 (16.7)	8 (18.2)
EDPC	2 (3.6)	2 (16.7)	0
tSVFem	4 (7.1)	1 (8.3)	3 (6.8)
Lateral esophagostomy (esophageal fistula)	3 (5.4)	1 (8.3)	2 (4.5)
Gauze packing of cervicotomy	11 (19.6)	1 (8.4)	10 (22.7)
Time between treatments in days	28 (10-61)	26 (8-51)	32 (7-57)
Second treatment			
Endoscopic suture	0	0	0
Surgical suture + drainage	1 (1.8)	0	1 (2.3)
SEMS	7 (12.5)	0	7 (15.9)
EVAC	2 (3.6)	0	2 (4.5)
EDPC	0	0	0
tSVFem	5 (8.9)	2 (16.6)	3 (6.8)
Lateral esophagostomy (esophageal fistula)	7 (12.5)	3 (25.0)	4 (9.1)
Gauze packing of cervicotomy	1 (1.8)	0	1 (2.3)

Four-side hole nasogastric tube + intermitted suction	0	0	0
Fistula size after second treatment in mm	7.04 ± 4.29	4.26 ± 6.45	7.20 ± 4.36
Third treatment			
tSVFem	5 (8.9)	0	5 (11.4)
Time to resolution in days	36 (15-71)	40 (11-150)	35 (15-71)

Data are *n* (%), mean ± standard deviation, or mean (interquartile range). BMI: Body mass index; DM: Diabetes mellitus; EDPC: Endoscopic double-pigtail catheter; EVAC: Endoscopic vacuum-assisted closure therapy; IQR: Interquartile range; SD Standard deviation; SEMS: Self-expanding-metal stent; tSVFem: Emulsified autologous stromal vascular fraction.

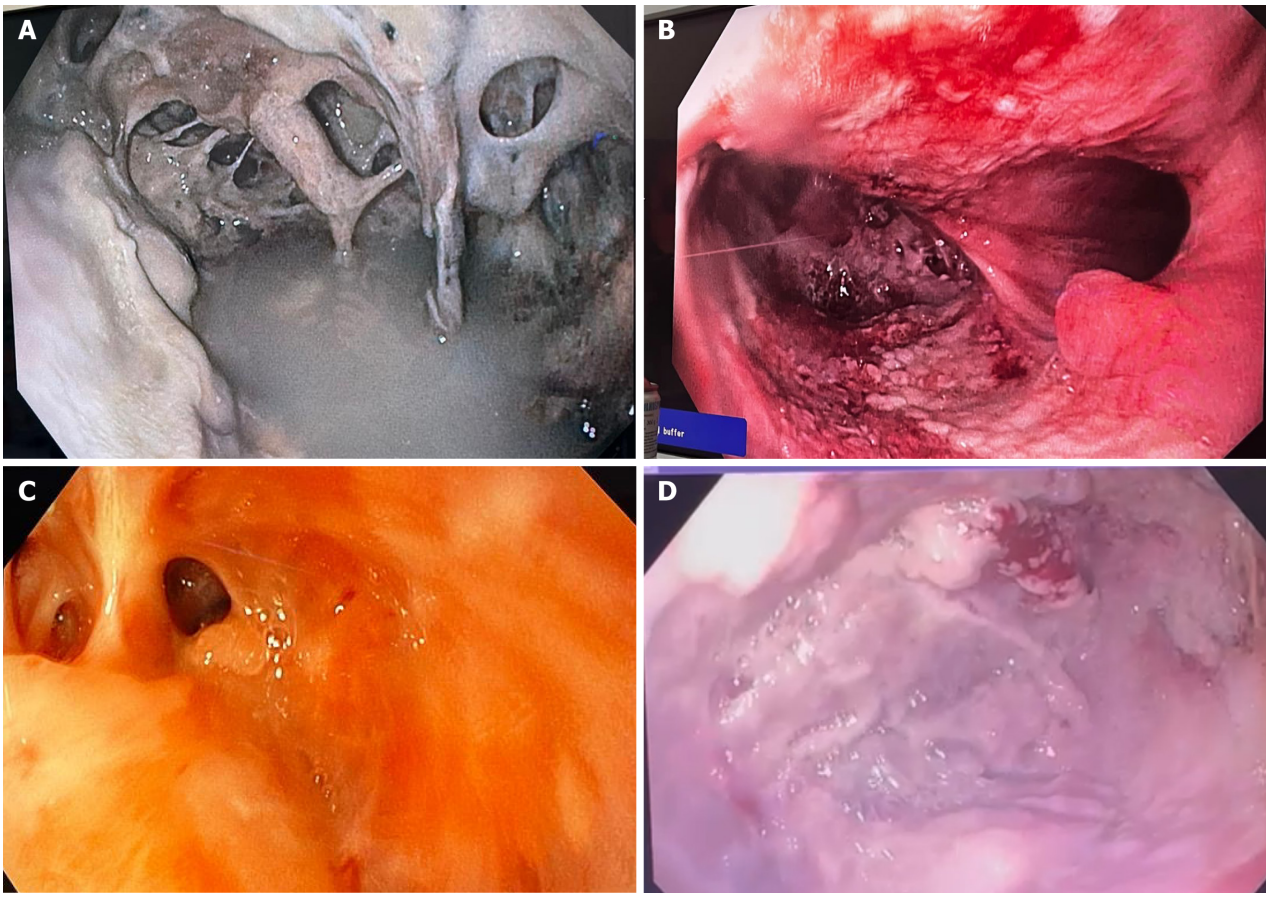

Figure 2 Endoscopic image of anastomotic leak after distal esophagus diverticulatectomy. A: Initial aspect; B and C: After consecutive endoscopic vacuum-assisted closure therapy treatment; D: Complete resolution.

fluid collection, mainly located on right side (73.2% of cases), that required a chest tube in 50% of cases and a surgical pleural/mediastinal toilette in the other 23.2% for corpuscular effusion.

In general, the most used procedures as first treatment for esophageal perforations and leaks of middle/distal esophagus were four-side hole nasogastric tube with intermittent suction [10 (17.8%) cases of anastomotic-leak of middle/distal esophagus], EVAC (16.7% and 18.2%, respectively) and SEMS (25.0% *vs* 11.4%, respectively) in the whole series, while the gauze packing of the cervicotomy was the first treatment used (22.7%) for cervical anastomotic leaks (Table 1 and Figure 1). Table 2 summarized the type of treatment used and the corresponding mean diameter of the fistula treated.

In 23 patients, a second treatment was necessary after a median time of 28 (10-61) days from the first one, as reported in Table 1. Two out of the 23 cases were patients affected by anastomotic leak and treated by EVAC that required the change of the sponge before obtaining complete healing. For all the other cases, SEMS was adopted when feasible as a second treatment in all failures of endoscopic/surgical suture or nasogastric tube for postoperative leaks (7 cases), while tSVFem injection (5 cases) was used for either perforations and postoperative leaks smaller than 1 cm and not solved with previous standard treatments (including SEMS). In 7 patients, a lateral esophagostomy was necessary for a persistent large esophageal defect, without signs of improvement, after a previous treatment.

Table 2 Type of first treatment adopted and corresponding mean diameter of the esophageal fistula

Type of first treatment adopted	Fistula diameter in mm
Endoscopic suture	13.00 ± 9.90
Surgical suture + drainage	12.00 ± 1.53
SEMS	22.00 ± 6.21
EVAC	25.78 ± 20.16
EDPC	2.50 ± 0.59
tSVFem	8.21 ± 4.24
Lateral esophagostomy (esophageal fistula)	32.50 ± 24.74
Cervicotomy + gauze packing	15.00 ± 2.60
Four-side hole nasogastric tube + intermitted suction	3.53 ± 4.56

Data are mean ± standard deviation. EDPC: Endoscopic double-pigtail catheter; EVAC: Endoscopic vacuum-assisted closure therapy; SEMS: Self-expanding-metal stent; tSVFem: Emulsified autologous stromal vascular fraction.

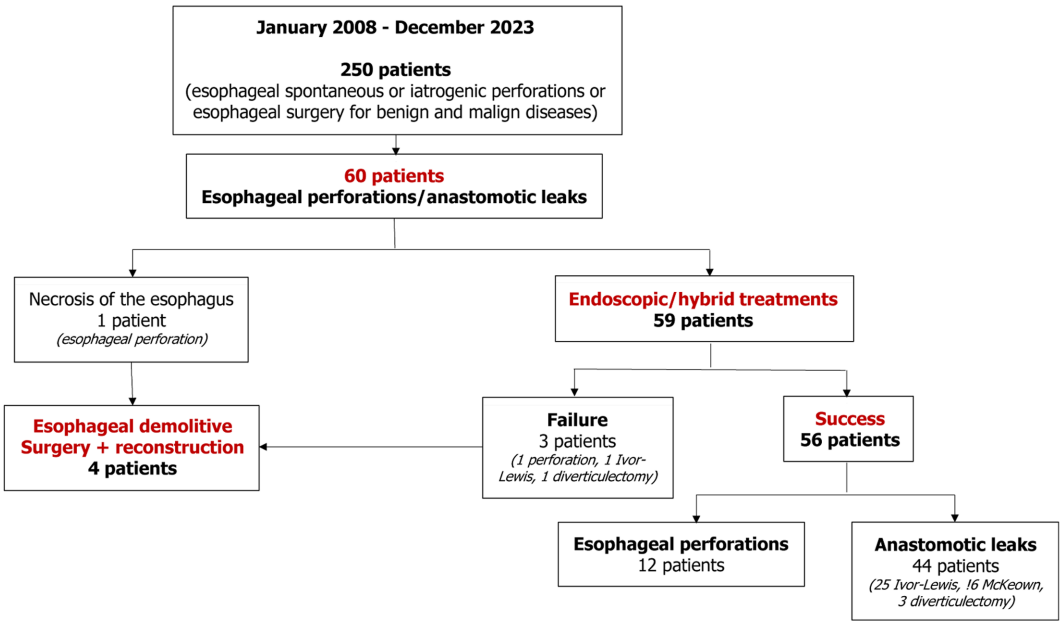

Figure 3 Management of the whole population of the study.

In 5 cases, a third treatment (tSVFem injection) was also needed for obtaining complete healing of the residual millimetric defect after a previous treatment. Figure 4 graphically compares resolution times since the first specified treatment (if the only one) or since the last treatment of the same type (if more than one) per each type of procedure and corresponding median diameter of the esophageal defect. The success rates of endoscopic treatments were: 83.3% for EVAC (10 out of 12 cases treated, as first or second treatment); 78.6% for SEMS (11 out of 14 cases treated, as first or second treatment); 50% for nasogastric tube; and 20% for endoscopic suture alone.

In this series, tSVFem injection was used 14 times in 12 patients. In 2 of them it was necessary to repeat the treatment after about 10 days. Complete healing was obtained in 11 patients out of the 12 treated (success rate: 91.7%). In 1 case, tSVFem failed as rescue treatment after two EVAC procedures (for a large and partially necrotic dehiscence of the esophageal anastomosis), and the patient underwent complete esophagectomy (for a subsequent esophageal necrosis) and reconstruction with colonic conduit.

The diverting lateral esophagostomy (surgical cervical esophageal mucosal fistula) was performed as first treatment in 3 cases (5.4%) due to the septic status of the patients with a large defect of the esophageal wall (median 31 mm) and was associated to a surgical toilette of the mediastinum and pleural cavity. In 7 cases (12.5%), it was performed as a second treatment. In all 10 cases, the complete healing of the esophageal defect was recorded after a median time of 130 (114-164) days.

In the 56 successfully treated patients, the median time to resolution of esophageal leak/perforation was 36 (15-71) days; no significant difference was recorded (*P* value = 0.948) between postoperative leaks and perforations. Among the

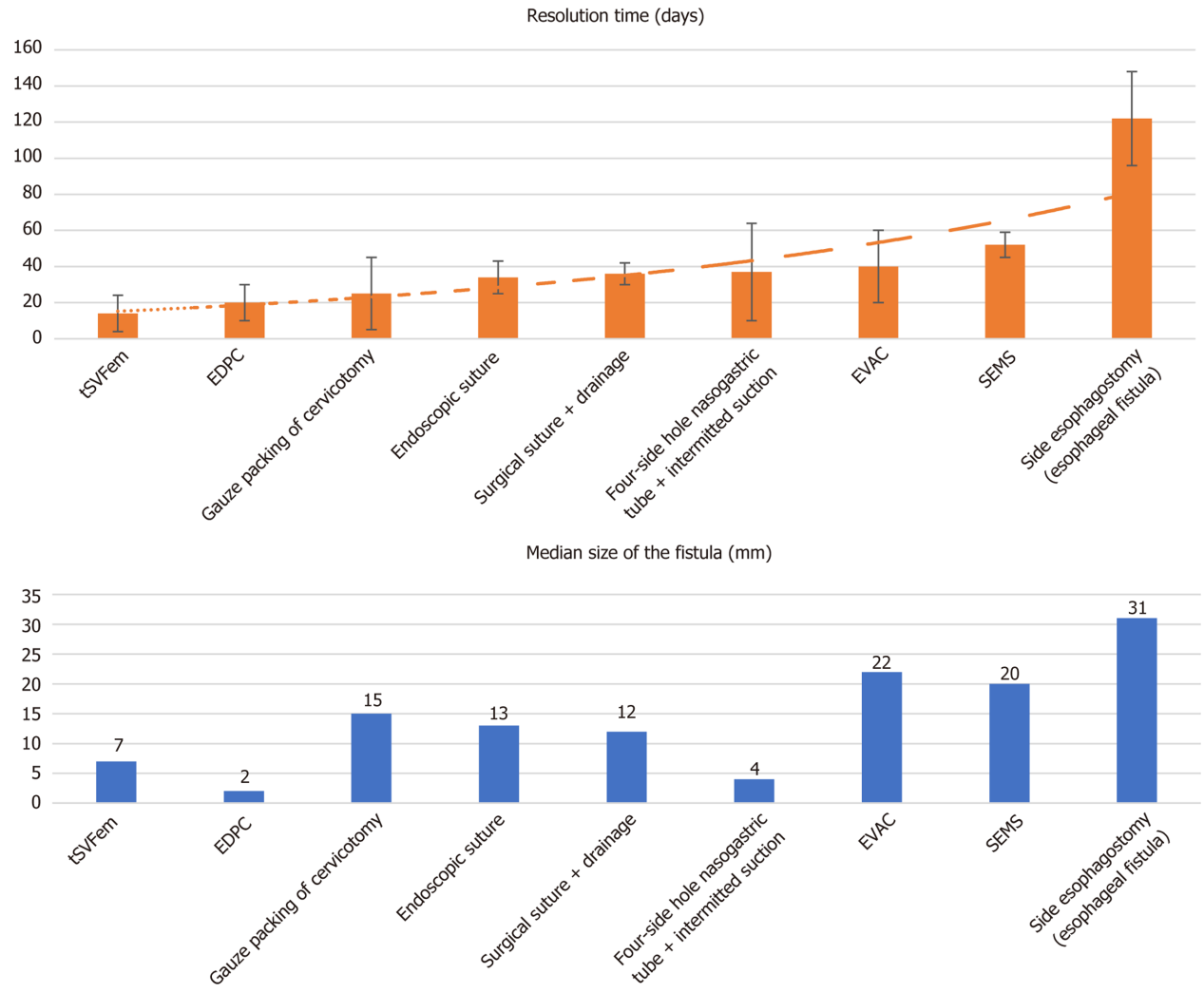

Figure 4 Resolution time and corresponding median diameter of the esophageal fistula per each type of treatment adopted in the study.
EDPC: Endoscopic double-pigtail catheter; EVAC: Endoscopic vacuum-assisted closure therapy; SEMS: Self-expanding-metal stent; tSVFem: Emulsified autologous stromal vascular fraction.

whole series of 60 patients, an urgent surgery was mandatory in 8 cases due to the septic status of the patients. In 4 patients in whom it was not possible to preserve the esophagus, a complete esophagectomy was performed. In the other 4 cases, a lateral esophagostomy and pleural/mediastinal toilette was performed (in 3 patients as first treatment, and in 1 in a second step). No other severe complications, such as bleeding or trachea-esophageal fistula, were recorded. Ten patients out of 56 (17.9%) developed pneumonia treated by specific antibiotic therapy, and in 6 cases (10.7%) cardiovascular diseases, as atrial fibrillation, were recorded. Twenty-five patients (41.6%) were admitted to the intensive care unit (ICU) after treatment, with a median length of stay of 5 days. Then the patients were transferred and managed in a surgical ward.

Seven patients (12.5%) in the group of postoperative leaks developed a stricture within 12 months, requiring one or two endoscopic pneumatic dilations to solve the problem. Two out of the 7 patients belonged to the group of patients subjected to iterative treatments (by EVAC or SEMS). No other complication was recorded in patients who underwent a second or third treatment for the esophageal perforation/leakage. None of the complications recorded correlated with a specific type of treatment adopted. Mortality was 1.7% (1 out of the 4 patients underwent removal of the reconstructed esophagus).

DISCUSSION

In this study, we analyzed our long experience in managing one of the most life-threatening conditions: The esophageal perforation or postoperative leak after esophageal surgery. Our results showed how this dreaded condition can be managed not only by surgery, which has long been considered the standard of care for a long time[51], but also by endoscopic and hybrid treatments that are employed more and more. The main advantage of this type of management used at our center (Figures 1 and 2) was the preservation of the native or the reconstructed esophagus (by gastric conduit) without the necessity to subject the patient to a highly destructive surgery, when feasible. The proper treatment was

chosen based on the patient's clinical condition, location and size of the fistula, and presence of mediastinal/pleural collections.

As stated before, the type of endoscopic treatments varied during the study period. From 2008 to 2019/2020, the main treatments used were four-side hole nasogastric tube + intermittent suction for small fistula (median 4 mm), endoscopic suture for pericentimetric lesions and SEMS for larger ones (median 13-20 mm). After 2019/2020, the use of a nasogastric tube and SEMS was gradually substituted by the EVAC, as reported by other authors[52-54]. Luttikhold *et al*[52] described an 89% success rate in a series of 27 patients with esophageal perforations treated by EVAC in five European centers; 2 patients died and one underwent a complete esophagectomy in Boerhaave syndrome. Our results were comparable in terms of success rate (83.3% *vs* 85%-89% reported in literature[52,55]), but with lower mortality (that was 1.7% in our series). Scognamiglio *et al*[55] reported a higher closure rate of EVAC compared to SEMS (85% *vs* 65%) with a 11.6-day shorter healing time, and the results were in line with our findings (closure rate of EVAC *vs* SEMS: 83.3% *vs* 78.6%, with a heling time of 39.73 ± 19.86 days *vs* 52.33 ± 7.13 days, respectively).

Although EVAC was considered a relatively expensive procedure due to the need for a sponge change[56], operating room, and ICU costs. At the same time, EVAC could avoid the need of surgical toilette of fluid collection in the mediastinal/pleural cavity around the fistula in several cases. Furthermore, as stated by Luttikhold *et al*[52] and confirmed by our data, in high volume centers, the ICU stay has been gradually reduced to 6.3 days (a median of 5 days in our series) for such patients. Intensive monitoring is often not required for EVAC treatment in stable patients. Furthermore, in our opinion, the use of EVAC instead of other previous treatments (as nasogastric tube, endoscopic suture, or SEMS) improved the management of esophageal fistula by speeding up the healing time and by ensuring a good control of local infection through drainage of mediastinal or pleural fluid collection or preventing their onset. This important aspect reduced the necessity of invasive surgical operations for pleural/mediastinal toilette, which could potentially expose compromised patients to potential complications and the need for intensive care and prolonged hospitalization. Therefore, although EVAC is usually considered a more expensive treatment, it is not in reality if all these factors are taken into account.

Moreover, in 2019, a new effective and costless weapon was added to the treatments available at our centers for refractory subcentimetric fistulas: The tSVFem endoscopic injection[41]. This procedure was developed in a clinical trial at our center[41], and it can be easily reproduced and performed at the same time of a gastroscopy, because the process for obtaining tSVFem requires a minimal, easily reproducible mechanical manipulation of autologous adipose tissue without enzymatic digestion. It also showed a high success rate (91.7%) due to the immunomodulatory and tissue regenerative properties of mesenchymal cells contained in the tSVFem, with a mean healing time that was shorter (13.78 ± 10.33 days for fistula with a median diameter of 7 mm). tSVFem injection has no potential complications (being an autologous tissue), and it allowed us to treat complex or tough cases not responsive to standard treatments in a reasonable time (Figure 4) and with low costs in a decisive manner.

However, along the whole 15-year experience, the diverting lateral esophagostomy remained the minimally-invasive surgical procedure of choice to preserve the native or reconstructed esophagus (Ivor-Lewis esophagectomy) in cases of large esophageal wall defects, situations that would require long in-hospital stay for redo treatments, or septic status of the patients. This treatment was characterized by low morbidity and gave the possibility to discharge the patient a few days after surgery (if in stable condition), with complete enteral nutrition *via* jejunostomy. After a median of 104 (96-118) days, the patients were readmitted to remove the silk lace that temporarily closed the esophagus under the lateral cervical esophagostomy, to check the full healing of the distal esophagus by gastroscopy before closing the esophageal stoma (mucosal fistula), and to restore esophageal continuity in 100% of patients.

Overall, our treatment strategy illustrated in the present series (Figure 1) and adopted in the last 15 years at our center gave us the possibility to save the native esophagus in 93.3% of cases, with 1.7% mortality. In particular, the success rate was 85.7% in cases of esophageal perforations (14 cases treated in total) with null mortality. Recently, Triantafyllou *et al* [57] reported a series of 33 patients surgically treated by a T-tube placement in thoracotomy (from 2012 to 2022) after spontaneous perforation of the esophagus in Boerhaave syndrome, with a 24% mortality.

In our experience, the reconstructive esophagus after esophageal surgery was saved in 100% of McKeown (16 cases treated) and 96.2% of Ivor-Lewis (25 out of 26 cases treated) esophagectomies, with a low morbidity and mortality. Only 1 patient after Ivor-Lewis esophagectomy who underwent upfront demolitive surgery of the reconstructed esophageal conduit (due to necrosis), died. The lower success rate and higher mortality recorded in the treatment of fistula after Ivor-Lewis esophagectomy reflects the greater clinical complexity and management difficulties of intrathoracic leakages[2,4,5, 46] compared to cervical ones after McKeown procedures. Indeed, in addition to frequent[5] tensile forces on the anastomotic suture and potentially reduced blood supply of the distal esophagus (after its dissection and mobilization), the intrathoracic anastomotic leakages can be also potentially deadly due to gastric juice spreading in the mediastinum or pleural cavity[46] and the risk of complete necrosis of the reconstructed tube in cases of insufficient blood supply. Nevertheless, our management brought satisfactory results. In general, the multidisciplinary management was pivotal to our experience, involving multiple experts from the diagnosis to the endoscopic/surgical (even iterative) treatments, passing through a constant medical evaluation of the patient for antibiotic, supportive, or intensive care therapies.

In particular, the strategy of choosing continuous and iterative conservative treatments when feasible (with two or three consecutive endoscopic/surgical procedures), instead of upfront demolitive and reconstructive surgery, did not affect morbidity and mortality of our series, with only 2 cases of esophageal strictures recorded among patients who underwent a second treatment (and solved by pneumatic dilation) and no deaths.

Our study had several limitations. It was a retrospective, single center study on a limited series. The types of treatments used varied along the study period and were based mainly on the patient's conditions, conduit vitality, or presence of fluid collections (esophago-mediastinal or esophago-pleural fistula), not strictly on fistula size. And this aspect made difficult the comparison of the different procedures to find the optimal one. However, to the best of our

knowledge, this is the only study reporting a series of esophageal perforation and anastomotic leaks that were successfully managed to preserve the native/reconstructive esophagus using multidisciplinary endoscopic/hybrid or not-demolitive surgical treatments, on a long period (15 years) at a high-volume center, with low morbidity and mortality.

CONCLUSION

A proper multidisciplinary approach that guarantees a prompt diagnosis and the choice of the most suitable and targeted treatment is the key point for the success in managing the patient after an esophageal leak or perforation and in preserving the esophagus.

FOOTNOTES

Author contributions: Nachira D, Calabrese G, Senatore A, Pontecorvi V, Belletatti C, Boskoski I, Biondi A, and Santoro G participated in the conception and design of the study and were involved in the acquisition, analysis, or interpretation of data; Nachira D wrote the manuscript; Nachira D, Boskoski I, Pontecorvi V, and Margaritora S accessed and verified the study data; Kuzmych K edited the English language; Meacci E, Raveglia F, Bove V, Congedo MT, Vita ML, Petracca Ciavarella L, Lococo F, Punzo G, Trivisonno A, Petrella F, Barbaro F, Spada C, D'Ugo D, and Cioffi U were involved in the interpretation of data and verified the study data; All authors critically reviewed and provided final approval of the manuscript, and were responsible for the decision to submit the manuscript for publication. Nachira D and Cioffi U assumed primary responsibility for the communication with the journal during the manuscript submission, peer-review, and publication process, sharing co-corresponding authorship.

Institutional review board statement: This study was evaluated by the Institutional Review Board (IRB) of Catholic University of Sacred Hearth and, as this was a retrospective review for service evaluation (within an audit approved by our Surgical Department). There was no modification in patient care (no prospective randomized study), and we did not need the final ethical approval of our IRB. In this study, the clinical data of 12 patients involved in a prospective trial [Endoscopic injection of Autologous Emulsified stromal vascular fraction (tSVFem) for the treatment of esophageal fistula] were also included and retrospectively reviewed along with the data of the other patients undergone standard treatments. This prospective trial was approved by the Ethical Committee (Università Cattolica del Sacro Cuore, Prot. ID 3127).

Informed consent statement: All study participants provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: Boskoski I is consultant for Apollo Endosurgery, Boston Scientific, Cook Medical, Nitinotes, Erbe Elektromedizin, Pentax Medical, Fractyl Health, and Lecturer for Microteach. All the other authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available. The data presented in this study are available from the corresponding author upon reasonable request.

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