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A longitudinal study of endoscopic naso-leakage negative pressure drainage for anastomotic leak after esophagectomy

Xin-Yang Liu[1,2†], Meng-Jiang He[1,2†], Yan-Bo Liu[1,2], Hao Yin[3], Li-Jie Tan[3], Ping-Hong Zhou[1,2*] and Miao Lin[3*]

Abstract

Background and aims Postoperative anastomotic leak is a threatening complication after esophagectomy. This study aims to evaluate the efficacy of endoscopic naso-leakage negative pressure drainage for anastomotic leak by longitudinal analyses, so as to focus on the intra-individual changes associated with the drainage in the disease course and to minimize the between-subject variations.

Methods We conducted a retrospective longitudinal study. We hypothesize that maximum temperature (Tmax), maximum heart rate (HRmax), White blood cell count (WBC), and C reactive protein (CRP) had a two-piece linear spline growth curve with a notch at the time of drainage. Linear mixed-effects regressions were used to test the hypothesis of whether endoscopic naso-leakage negative pressure drainage changed the pattern of development of these clinical parameters with time.

Results Thirty patients were included, among which 83.3% were male, with a median age of 77 years. The median postoperative time to drainage was 16.5 days (range 6-66). Observations for Tmax, HRmax, WBC, CRP and PCT were 1366, 1372, 394, 296 and 290, respectively. After adjusting for age, sex, and body mass index, Tmax, HRmax, WBC and CRP showed similar pattern. There was no significant change over time before naso-leakage negative pressure drainage, while the four parameters all decreased significantly over time after naso-leakage negative pressure drainage.

Conclusions The slope over time of Tmax, HRmax, WBC and CRP changed significantly after naso-leakage negative pressure drainage. Naso-leakage negative pressure drainage brought gradual decrease of these inflammatory parameters and could serve as a promising management for postoperative anastomotic leak after esophagectomy.

Keywords Anastomotic leak, Endoscopic drainage, Longitudinal study, Esophagectomy

†Xin-Yang Liu and Meng-Jiang He shared co-first authorship.

*Correspondence:
Ping-Hong Zhou
pinghong.zhou@zs-hospital.sh.cn
Miao Lin
linmiao@fudan.edu.cn
[1] Endoscopy Center and Endoscopy Research Institute, Zhongshan Hospital, Fudan University, Shanghai, China
[2] Shanghai Collaborative Innovation Center of Endoscopy, Shanghai, China
[3] Department of Thoracic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China

Introduction

Esophagectomy is the primary choice for patients with resectable esophageal cancer. Despite the advances in surgical techniques, esophagectomy remains a challenging and difficult surgical procedure, associated with significant morbidity and mortality. Postoperative anastomotic leak is one of the most common and threatening complications, in which subsequent mediastinal abscess can easily lead to cardio-respiratory failure, sepsis, vascular erosion and esophago-bronchial fistula. The reported incidence of postoperative anastomotic leak is higher than 10% [1, 2] according to previous reports. Location of anastomosis seems to affect leak rate after esophagectomy. Cervical anastomosis results in higher leak rate than intrathoracic anastomosis [3]. Presentation ranges from clinical silence to overwhelming sepsis and death, and clinical outcomes mainly depend on the extent of contamination and time interval to diagnosis [4]. This complication lays a substantial impact on length of hospitalization, subsequent stricture formation, quality of life, and results in a 90-day perioperative mortality rate of around 3% [1, 5–7].

The traditional treatment of anastomotic leak described in the literature includes surgical exploration and conservative management consisting of strict nil per oral, antibiotics and chest drainage. Esophageal stents showed certain effectiveness as a minimally invasive treatment option, but with non-negligible problems such as possible inadequate drainage of necrotic tissue, high migration rates of the stents., and enlargement of the leak [8–10].

With the accumulation of experience in managing anastomotic leakage, adequate drainage of necrotic tissues has gradually become the consensus. Chest tube is placed during operation to assure effective drainage, but sometimes cannot get sufficient drainage, especially in the mediastinum and top of the chest. Recently, endoscopic naso-leakage negative pressure drainage has become a promising choice in addition to chest drainage and other conservative therapies. Several preliminary studies, including case series or retrospective cohort studies, have proposed the safety and efficacy in facilitating the recovery of anastomosis leakage [11–14]. However, selection bias and potential confounding may influence the results. Therefore, this study aims to evaluate the role of endoscopic naso-leakage negative pressure drainage for anastomotic leak by longitudinal analyses with repeated measures data collected on individuals over time, so as to focus on the intra-individual changes associated with the drainage in the disease course and to minimize the between-subject variations.

Materials and methods

Patients

We conducted a retrospective longitudinal study. The inclusion criteria were as follows: (1) patients were diagnosed with anastomotic leak after esophagectomy for esophageal cancer in Zhongshan Hospital Fudan University, from 2018 to 2021; (2) anastomotic leak was confirmed by CT scan together with endoscopy; (3) anastomotic leak was treated with endoscopic naso-leakage negative pressure drainage. A transdermal chest tube that was intubated intraoperative routinely during esophagectomy was then used for chest drainage. Besides chest drainage, all patients received a routine conservative therapy, including strict nil per oral, intravenous antibiotics, intravenous or enteral nutrition. Specifically, enteral nutrition was priorities unless otherwise contraindicated. Intravenous nutrition was prescribed to patients without indwelling of enteral nutrition tube or intolerant of enteral nutrition solution, or with impaired intestinal function (e.g. patients undergoing same term intestinal surgery). The placement of naso-leakage negative pressure drainage was evaluated by Multi-Disciplinary Team discussion. This study was approved by the institutional review board of Zhongshan Hospital Fudan University (B2022-069).

Endoscopic naso-leakage negative pressure drainage

An ultra-slim gastroscope was inserted through nasal cavity to the anastomosis. The location and diameter of the leak was carefully evaluated. A leak with a diameter of larger than 5 mm through which the ultra-slim gastroscope could pass was considered suitable for endoscopic naso-leakage negative pressure drainage. In these selected patients, the ultra-slim gastroscope was advanced to the bottom of the vomica with repeated rinse and suction. Then, a hydrophilic polymer-coated 0.035- to 0.038-inch guidewire was inserted through the channel to the bottom of the vomica. After withdraw of the endoscope, the guidewire was used to advance the drainage tube into the vomica. Confirmation of the adequate placement was immediately performed for endoscopic check through the oral cavity, and after that the guide wire was removed. Finally, the drainage tube was connected to a negative pressure drainage device. Rinse with normal saline through the naso-leakage drainage tube was performed when necessary.

Decision to withdraw the drainage tube was determined according to the patients' vital sighs, lab results, CT scan as well as the volume and characteristics of the drainage fluid, on a case-by-case basis. The drainage tube was withdrawn gradually about 3-4 cm per 4-5 days to ensure complete drainage of the residual necrosis. Caution should be taken not to entangle the drainage tuve with the naso-jejunal tube (if one presented). Chest and abdominal X-ray examination should be routinely performed every time the drainage tube was withdrawn. After complete removal of the drainage tube, gastroscopy was performed again to confirm the healing of leakage.

Patient characteristics and longitudinal parameters

The demographics and clinical characters were extracted from medical records. Demographics included age, sex, height and weight. Baseline characteristics consisted of type of surgery, tumor location, cancer stage, time interval from surgery to drainage, as well as clinical outcome.

The following parameters were repeated measures data collected longitudinally on individuals over time. Among them, maximum temperature (Tmax) and maximum heart rate (HRmax) were collected on a daily basis. White blood cell count (WBC), C reactive protein (CRP), procalcitonin (PCT) and volume of drainage were measured repeated by different intervals, so the results were recorded together with the sets of time for measurements.

Statistical analyses

The demographics and baseline clinical characters were described using median with interquartile ranges for continuous variables and count with percentages for categorical variables. Trend of longitudinally measured parameters were visualized by line plots. Number of measurements per subject for each parameter was calculated. We hypothesize that maximum temperature (Tmax), maximum heart rate (HRmax), White blood cell count (WBC), C reactive protein (CRP) and procalcitonin (PCT) changed linearly with time, but with different slopes before and after the initiation of endoscopic naso-leakage negative pressure drainage. In other words, we assumed that each subject had a two-piece linear spline growth curve with a notch at the time of drainage. Graphical representation of the research hypothesis and the modelling approach is shown schematically in Fig. 1. Linear mixed-effects regressions were used to test the hypothesis of whether endoscopic naso-leakage negative pressure drainage changed the pattern of development of these clinical parameters with time [15]. Tmax, HRmax, WBC, CRP and PCT were used as separate outcomes in each of the regression models. Covariates included in the model consisted of age, sex, body mass index, time to drainage for measurements before drainage, and time from drainage for measurements after drainage. The model was formulated as follows: $Y_{ij} = \beta_0 + \beta_1 t_{ij}\delta_{ij} + \beta_2 t_{ij}(1\text{-}\delta_{ij}) + \beta_3 Age + \beta_4 Sex + \beta_5 BMI + b_{0i} + b_{1i} t_{ij}\delta_{ij} + b_{2i} t_{ij}(1\text{-}\delta_{ij}) + e_{ij}$, where $\delta_{ij} = 0$ for the time before drainage $t_{ij} <= 0$ and $\delta_{ij} = 1$ for the time after drainage $t_{ij} > 0$. This model was used for calculation of slopes of the four parameters before and after drainage. A second model with interaction terms of time*drainage instead of pre- and post-drainage time was also used to test the significance of difference in slopes before and after drainage. In our model, baseline variables (age, sex, body mass index) were included as fixed effect variables, and the pre- and post-event times were included as random effect variables. A *P* value of < 0.05 was considered statistically significant. All statistical analyses were carried out by Stata 14.0.

Results

Characteristics of included patients

Thirty patients were included, among which 83.3% were male, with a median age of 77 years (interquartile range, IQR, 70-85 years). Tumors were located in the middle (60%) or lower (40%) esophagus. Most patients presented with normal body mass index (BMI). The majority of the patients received minimally invasive Ivor Lewis esophagectomy (80%). Stages varied from T1 to T3 and N0 to N3. The median postoperative time to drainage was 16.5 days (IQR 14-22 days), and the median time from drainage to discharge was 15 days (IQR 7-27 days).

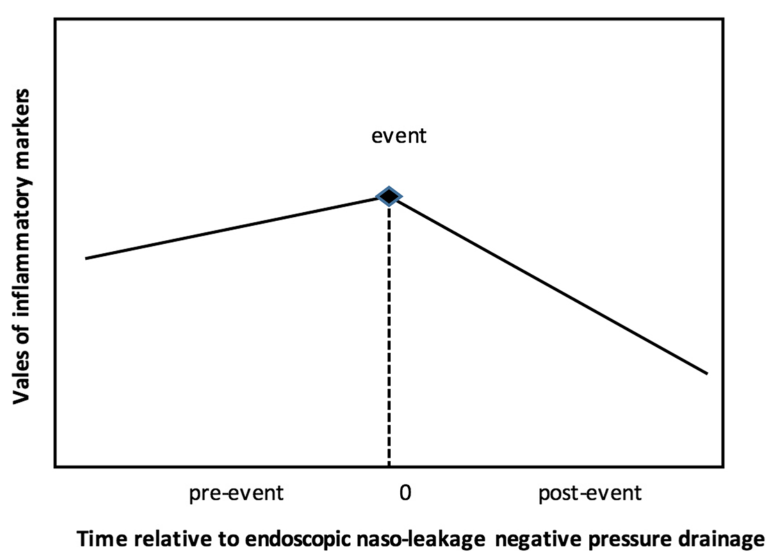

Fig. 1 Graphical representation of the research hypothesis and modelling approach. The piecewise model assigns a pre-event slope β1 and a post-event β2 separated by naso-leakage negative pressure drainage

20% patients (6/30) were discharged with oral intake, 76.67% patients (23/30) were discharged without oral intake, and only one of the 30 patients (3.33%) was discharged against medical advice (Table 1).

The patient discharged against medical advice was a 64-year-old gentlemen who underwent minimally invasive mckeown esophagectomy for esophageal cancer in the lower third of the esophagus. The pathological diagnosis was T1b squamous cancer carcinoma. Anastomotic leak was detected on post-operative day (POD) 8, and endoscopic naso-leakage negative pressure drainage was performed on POD 11. The patient was discharged against medical advice 15 days after drainage because of long hospitalization.

Characteristics of longitudinal parameters

The cumulated day count before naso-leakage negative pressure drainage was 600 days and was 774 days after drainage. Observations for Tmax, HRmax, WBC, CRP and PCT were 1366, 1372, 394, 296, and 290, respectively. Observations for these parameters before and after drainage were presented in Table 2. Tmax and HRmax were available on a daily basis. WBC was measured on averagely every 2.86 days before drainage and 4.3 days after drainage. Meanwhile, the average time interval for CRP measurement was 3.64 days before drainage and 5.91 days after drainage, respectively. For PCT, the numbers were 3.77 and 5.91, respectively. These parameters also presented higher variations before drainage than those after drainage.

Role of naso-leakage negative pressure drainage in decreasing inflammatory parameters

Although the mean Tmax, HRmax, WBC, CRP and PCT before drainage were all shown to be higher than those after drainage, the measurements were repeatedly collected and were not independent from each other, and therefore a t test based on independent observations was not appropriate for testing the difference before and after drainage. In order to focus on the intra-individual

Table 1 Baseline characteristics of included patients

	Number/Median	Percentage/IQR
Age	77	70–85
Sex		
Male	25	83.33%
Female	5	16.67%
BMI	23.31	21.23–23.44
Tumor location		
Middle esophagus	18	60.00%
Lower esophagus	12	40.00%
Surgery		
Minimally invasive mckeown esophagectomy	24	80.00%
mckeown esophagectomy	1	3.33%
Left Thoracic Approach Esophagectomy	2	6.66%
ivor lewis esophagectomy	2	6.66%
Minimally invasive ivor lewis esophagectomy	1	3.33%
T		
1	11	36.67%
2	8	26.67%
3	11	36.67%
N		
0	23	76.67%
1	6	20.00%
3	1	3.33%
POD of drainage	16.5	14–22
Day from drainage to discharge	15	7–27
Outcome		
Discharge with oral intake	6	20.00%
Discharge without oral intake	23	76.67%
Discharge against medical advice	1	3.33%

Table 2 Characteristics of repeatedly measured parameters before and after naso-leakage negative pressure drainage

Parameter	Before naso-leakage negative pressure drainage		After naso-leakage negative pressure drainage	
	No. of measurements	Mean ± SD	No. of measurements (median, IQR)	Mean ± SD
Tmax (℃)	595	37.24 ± 0.77	771	36.87 ± 0.65
HRmax (bpm)	599	90.83 ± 15.66	773	86.01 ± 12.95
WBC (*10^9/L)	210	10.65 ± 5.36	184	7.93 ± 3.32
CRP (mg/L)	165	112.14 ± 92.21	131	64.50 ± 61.37
PCT (μg/L)	159	0.91 ± 1.85	131	0.22 ± 0.41
Volume (mL)	-	-	628	43.39 ± 107.67

changes associated with the drainage in the disease course and to minimize the between-subject variations, linear mixed-effects regressions were used to test the hypothesis of whether endoscopic naso-leakage negative pressure drainage changed the pattern of development of these clinical parameters with time.

After adjusting for age, sex and BMI, Tmax showed different pattern over time before and after naso-leakage negative pressure drainage (Figs. 2 and 3). There was an insignificant increase of 0.002℃ per day before drainage ($P = 0.837$) and a significant decrease of 0.025℃ per day after drainage ($P < 0.001$). The estimated slope after drainage (-0.025) did not fall into the confidence interval of the slope before drainage (-0.019, 0.015), suggesting significant difference between the slopes before and after drainage (Table 3). Test of interaction term of drainage with time also confirmed the difference ($P < 0.001$).

HRmax, WBC and CRP showed similar pattern. There was no significant change over time before naso-leakage negative pressure drainage, with slight increase or decrease, while the three parameters all decreased significantly over time after naso-leakage negative pressure drainage (Figs. 2 and 3). The rates of decrease were 0.385 bpm per day for HRmax, 0.135*10^9/L per day for WBC, and 3.079 mg/L per day for CRP, respectively, all with P values < 0.001. For these parameters, the point estimate of the slopes after drainage were all smaller than the lower boundary of the confidence interval of the slopes before drainage, and the interaction terms of drainage with time were all significant ($P < 0.001$), suggesting significant difference between the slopes before and after drainage for each parameter.

The change of PCT is different from the above mentioned four parameters (Figs. 2 and 3). Before drainage, there was a significant decrease of 0.059 μg/L per day ($P = 0.014$). However, the decrease became smoother (0.010 μg/L per day) and insignificant ($P = 0.286$) after drainage. The point estimate slope after drainage (-0.010) was higher than the upper boundary of the confidence interval of the slope before drainage (-0.012), and the interaction term of drainage with time was statistically significant ($P = 0.013$), suggesting significant difference between the slopes before and after drainage.

Discussion

Adequate drainage is the vital management for leakage. However, traditional management for anastomotic leak after esophagectomy sometimes fails to achieve satisfactory drainage due to the anatomical complexity. How to achieve better drainage with less invasiveness remains a clinical challenge.

Endoscopic naso-leakage negative pressure drainage has been proposed as a minimally invasive choice in addition to chest drainage and other conservative therapies. A trans-nasal drainage tube is placed into the abscess cavity without additional incision.

Shuto et al. [12] summarized 50 patients with this novel method, none of the naso-esophageal extraluminal drainage cases required re-intervention or reoperation and all experienced complete cure during hospitalization. Guo et al. [11] compared 23 patients with endoscope-assisted mediastinal drainage therapy and the other 28 patients with endoscope-assisted biomedical fibrin glue occlusion, and drainage was significantly associated with reduced postoperative hospitalization. Zhang et al. [14] analyzed 38 treated by conventional chest drainage and 29 patients with endoscopic naso-leakage negative pressure drainage with or without chest drainage. Endoscopic naso-leakage negative pressure drainage was associated with a reduced mortality and a shorter healing course. These studies provided promising evidence of the safety and efficacy in facilitating the recovery of anastomosis leakage. This novel treatment was introduced in highly selected patients, with unneglectable selection bias and potential confounding. What's more, these studies mainly focus on between-subject variations rather than intra-individual changes as a result of the intervention. Therefore, we adopted longitudinal analyses so as to focus on

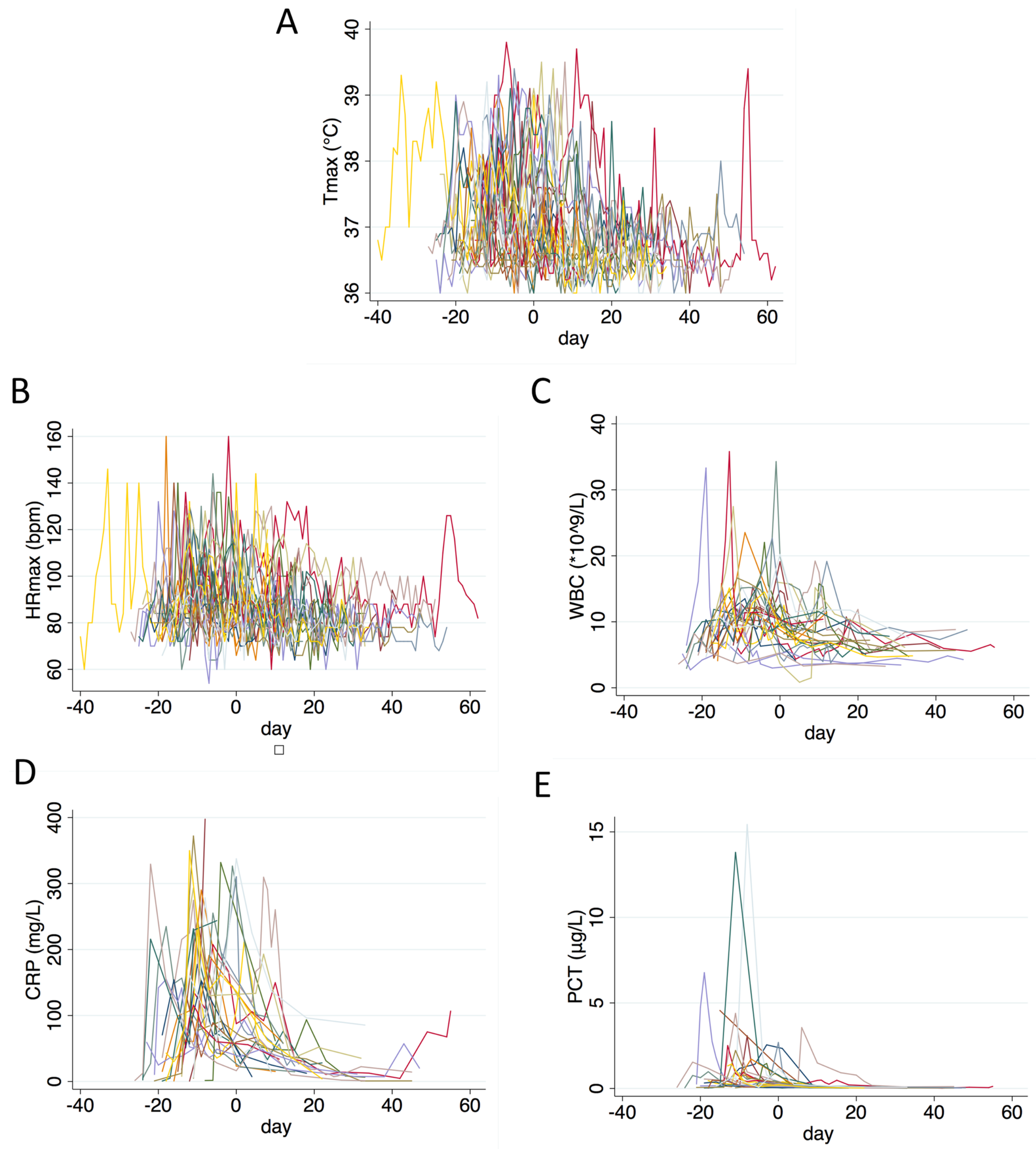

Fig. 2 Line plots of inflammatory markers in each patient. **A** Tmax; **B** HRmax; **C** WBC; **D** CRP; **E** PCT

the intra-individual changes associated with the drainage in the disease course and to minimize the between-subject variations.

Our results suggested that after adjusting for age, sex and body mass index, Tmax, HRmax, WBC and CRP showed similar pattern. There was no significant change over time before naso-leakage negative pressure drainage, while the four parameters all decreased significantly over time after naso-leakage negative pressure drainage. The difference of development of these inflammatory markers before and after endoscopic naso-leakage negative pressure drainage further added to the evidence proving

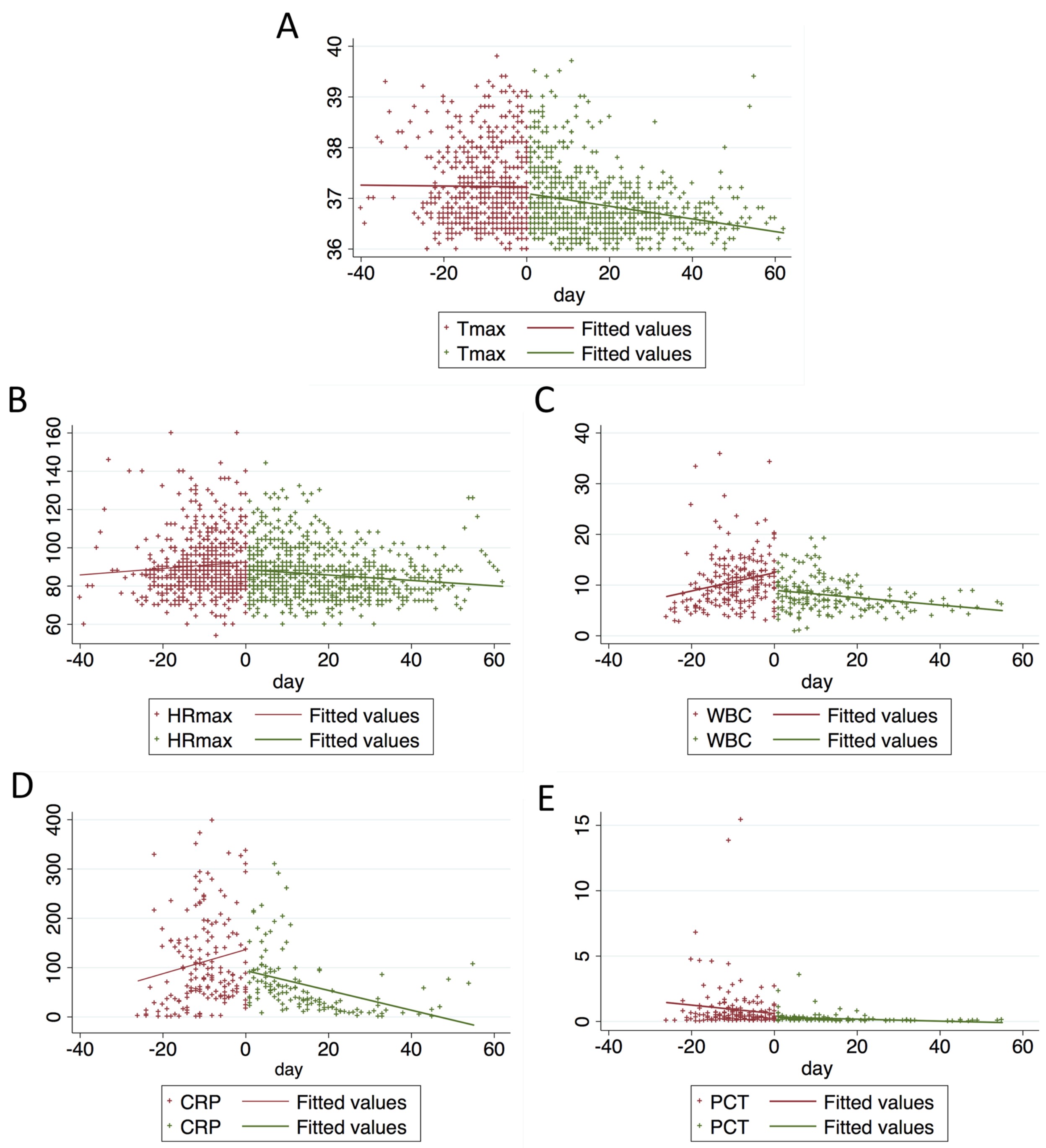

Fig. 3 Dot plots with fitted lines of inflammatory markers before and after naso-leakage negative pressure drainage. **A** Tmax; **B** HRmax; **C** WBC; **D** CRP; **E** PCT

the safety and efficacy of this method. In the 30 patients included, only one patient was discharged against medical advice. Nevertheless, all inflammatory markers of this patient improved after endoscopic intervention based on available medical records.

One interesting finding is that PCT showed different change pattern compared with other inflammatory indicators. It was previously reported that in patients with anastomotic leak after colonrectomy, serum procalcitonin, was not sensitive enough to detect the anastomotic leak early [16] and did not seem to increase

Table 3 Patterns of change over time of longitudinal parameters before and after naso-leakage negative pressure drainage

Parameter	Before naso-leakage negative pressure drainage		After naso-leakage negative pressure drainage	
	Slope (95%CI)	*P*	Slope (95%CI)	*P*
Tmax (℃)	0.002 (-0.019, 0.015)	0.837	-0.025 (-0.034, -0.017)	< 0.001
HRmax (bpm)	-0.048 (-0.382, 0.287)	0.780	-0.385 (-0.550, -0.220)	< 0.001
WBC (*10^9/L)	0.021 (-0.112, 0.153)	0.761	-0.135 (-0.205, -0.065)	< 0.001
CRP (mg/L)	0.613 (-1.177, 2.403)	0.502	-3.079 (-4.453, -1.706)	< 0.001
PCT (μg/L)	-0.059 (-0.107, -0.012)	0.014	-0.010 (-0.029, 0.009)	0.286

the diagnostic accuracy [17]. However, in postoperative anastomotic leak after esophagectomy, there is limited evidence on the sensitivity of markers for inflammation. Marked elevation of PCT was only observed in certain patients in our study, and further interpretation of its prediction value is still needed in the future.

The limitations should be addressed when interpreting the results. First, the anastomotic leak after esophagectomy in this study was only for esophageal cancer, and the majority cases received minimally invasive mckeown esophagectomy, which may limit the generalization of our conclusions to other types of surgeries. Second, standard protocol for management of anastomotic leak after esophagectomy was lacking, especially for the management after placement of naso-leakage negative pressure drainage. Third, indicators of respiratory function which may also reflect inflammatory status, were not available in this cohort. Fourth, the retrospective design of this study may lead to potential bias, and prospective validation is warranted.

Conclusions

The slope over time of Tmax, HRmax, WBC and CRP changed significantly after endoscopic naso-leakage negative pressure drainage. Endoscopic naso-leakage negative pressure drainage brought gradual decrease of these inflammatory parameters and could serve as a promising management for postoperative anastomotic leak after esophagectomy.

Authors' contributions

Planning and conducting the study: Miao Lin, Ping-Hong Zhou. Collecting data: Miao Lin, Xin-Yang Liu, Meng-Jiang He, Yan-Bo Liu. Analyzing and interpreting data: Xin-Yang Liu, Meng-Jiang He. Draftingmanuscript: Xin-Yang Liu, Miao Lin, Ping-Hong Zhou. Administrative support: Li-Jie Tan, Ping-Hong Zhou. Final approval of manuscript: all authors.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Zhongshan Hospital Fudan University (B2022-069).

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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