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ORIGINAL SCIENTIFIC REPORT

Cytokine Response in the Pleural Fluid and Blood in Minimally Invasive and Open Esophagectomy

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Abstract

Background Transthoracic esophagectomy for cancer triggers a massive inflammatory reaction. The data whether a minimally invasive esophagectomy (MIE) leads to less pronounced inflammatory response compared to open right-sided transthoracic esophagectomy (OE) are scarce. The aim of this study was to evaluate the extent of the inflammatory reaction, represented by levels of the pro-inflammatory interleukins IL-6 and IL-8, the anti-inflammatory IL-1 RA and the chemokines CINC-1 and MCP-1 in the right pleural fluid and the blood from patients undergoing standard OE or MIE.

Methods Pleural drainage fluid and blood was collected at five different time points during the first 72 h following surgery, and the concentrations of IL-6, IL-8, IL-1 RA, CINC-1 and MCP-1 were analyzed using enzyme-linked immune-sorbent assays in 24 patients undergoing MIE or OE.

Results The groups were matched for cancer stage and comorbidities. Pro- and anti-inflammatory mediator levels in the pleural fluid were markedly increased at the end of surgery and on postoperative days 1–3. The pleural inflammatory response of all cyto- and chemokines was lower in the MIE group, reaching significance at some time points. Cyto- and chemokine response levels measured in the blood were overall lower compared to those in the pleural fluid. The chemokines CINC-1 and MCP-1 reacted less pronounced or not at all. Preoperative pulmonary comorbidity, postoperative pulmonary morbidity and length of surgery were associated with an increased reaction in selected mediators.

Conclusions The minimally invasive technique attenuates the inflammatory response, especially locally in the thoracic compartment. Length of procedure, preoperative pulmonary comorbidity and postoperative pulmonary complications are mirrored in an increase in individual inflammatory markers in the pleural fluid. The value of the chemokines CINC-1 and MCP-1 as markers of inflammation in the setting of esophagectomy is unclear.

Introduction

Surgery for esophageal cancer is a highly invasive procedure associated with a substantial risk of adverse outcomes. Pulmonary complications occur in up to 60% and mortality in up to 5%, respectively [1–3]. Open right-sided transthoracic esophagectomy (OE) with one-lung ventilation is a standard surgical option for curative treatment of localized esophageal cancer (abdomino-thoracic or thoraco-abdomino-cervical). Minimally invasive

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esophagectomy (MIE) reduces trauma related to open surgical access and thus improves postoperative outcome. MIE appears to be a feasible and safe option for treating esophageal cancer, but the short- and long-term benefits remain controversial [4].

Esophagectomy triggers a massive local and systemic inflammatory response, with increased secretion of various pro- and anti-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1 receptor antagonist (IL-1RA) and the chemokines monocyte chemotactic protein-1 (MCP-1) and cytokine-induced neutrophil chemoattractant-1 (CINC-1) [5–7]. IL-6 plays a pivotal role in the pro-inflammatory response to injury or infection. It induces acute phase reactants and triggers immunoglobulin synthesis, activation of T cells, pyrogenic action and platelet proliferation [8]. IL-8 acts also as a pro-inflammatory and neutrophil attractant cytokine which induces the re-arrangement of the cytoskeleton, changes in intracellular calcium levels, activation of integrins and exocytosis of granule proteins [9]. CINC-1 is a member of the α-chemokines and has been shown to play an important role in the inflammatory response. It is an acute phase protein with a highly potent ability to recruit neutrophils [10]. IL-1RA is an anti-inflammatory cytokine that plays a role in counterbalancing the inflammatory response. IL-1RA is produced by monocytes and macrophages. An inadequate local IL-1RA synthesis in the lung may predispose severe acute lung injury and result in excess lethality in ARDS [8]. MCP-1 is a member of β-chemokines and a protein which has pro-angiogenic effects. It is a chemoattractant for monocytes, macrophages, eosinophils and lymphocytes that is produced by endothelial cells, epithelial cells, smooth muscle cells, fibroblasts and monocytes [11].

Increased cytokine levels are associated with the systemic inflammatory response syndrome (SIRS) [12–14]. The SIRS affects all organs, and its biochemical components involve pro- and anti-inflammatory properties. Furthermore, it has been suggested that cancer surgery upsets the equilibrium of the immune system, thereby promoting micro-metastatic disease by the growth of dormant micrometastasis, and this compromises long-term oncological outcome [15, 16]. Consequently, extensive surgical trauma may not only increase perioperative adverse effects, but might also adversely impact oncologic survival rates [17, 18].

Previously, our group has shown that an inflammatory response occurs early following open transthoracic esophagectomy and lung surgery, with a complex pattern of pro- and anti-inflammatory cytokines in both the ventilated left and collapsed right lung as well as in the blood [10, 19]. MIE may reduce the inflammatory response and attenuate SIRS, thus improving perioperative and long-term outcomes of esophageal cancer patients. Currently, data comparing open versus MIE regarding the inflammatory response are scarce. The aim of this study was to analyze the inflammatory reaction, represented by levels of pro- and anti-inflammatory cytokines (IL-6, IL-8, IL-1RA, CINC-1 and MCP-1) in the blood and the right pleural fluid in patients undergoing Ivor Lewis OE or MIE.

Methods

Between July 2008 and June 2010, all patients undergoing open or minimally invasive esophagectomy for cancer at the Flinders Medical Centre, Adelaide, South Australia, were assessed for eligibility to be included in this prospective trial. Informed consent was obtained, and the trial was approved by the Flinders Clinical Research Ethics Committee.

Perioperative assessment

All patients underwent preoperative staging with endoscopy, biopsy, abdomino-thoracic computed tomography, endoscopic ultrasound and positron emission tomography. Clinical examination, spirometry and echocardiography were performed in order to assess operative fitness. Patients with locally advanced tumors were considered for neoadjuvant combined chemo- and radiotherapy. Patients with early stage tumors (T1 N0 or T2 N0) underwent surgery without pre-treatment. Neoadjuvant treatment consisted of two courses of 5-fluorouracil and cisplatin in combination with 45 Gray of radiotherapy. Surgery was performed 4–8 weeks after neoadjuvant treatment.

Surgery

The patients were allocated either to an abdomino-thoracic (Ivor-Lewis) or to a thoraco-abdomino-cervical esophagectomy in the open-surgery group or to a thoracoscopic-assisted or total minimally invasive (thoraco-laparoscopic) esophagectomy in the minimally invasive surgery group. The allocation was not randomized, but followed the individual surgeon's preference for one or the other technique. The different surgical techniques have been described in detail previously [20]. In brief, patients undergoing MIE were initially positioned prone for thoracoscopy, the right lung was deflated and three ports were used. The first step entailed esophageal mobilization and the division of the Azygos vein. Patients were then positioned in supine position with the head turned toward the right side. The abdominal part was either performed with a hand-assisted laparoscopic technique with an 8 cm transverse upper abdominal incision for the hand-port (total

minimally invasive) or a 20–25 cm upper midline incision (thoracoscopically assisted), depending on the individual surgeon's preference. With both of these techniques, the stomach was mobilized and the right gastric and gastro-epiploic arteries preserved. The left gastric artery was divided at its origin, and an en-bloc lymphadenectomy was performed. The third step included a separate neck incision on the left side and mobilization of the cervical esophagus. After division of the esophagus, the whole specimen was delivered to the abdomen. The gastric tube was then fashioned using linear staplers, and a pyloromyotomy performed. The stomach was then pulled up to the neck, and a cervical anastomosis was performed with interrupted single layer of absorbable sutures. A feeding jejunostomy was routinely placed.

For the OE, a midline laparotomy and right-sided posterolateral thoracotomy were used for the access to the esophagus (classic Ivor Lewis technique). The abdominal phase was conducted first before repositioning in the lateral position for the thoracic phase. Anastomosis was performed in the chest in the posterior mediastinum using interrupted single-layer absorbable sutures. In one open surgical case, a three-stage thoraco-abdomino-cervical approach was used and the anastomosis performed in the neck using the same technique as for the minimally invasive approach.

In both MIE and OE, the lymph nodes adjacent to the esophagus, to the base of the left gastric artery and below the tracheal bifurcation, were dissected.

Analysis of pleural fluid and peripheral blood samples

Blood and pleural fluid samples were obtained during and following either open or minimally invasive esophagectomy. Blood specimens were collected from intravenous or arterial lines that were routinely in place.

Pleural fluid was collected from the right thoracic cavity at time of surgery by the operating surgeon, and postoperatively from the routinely placed thoracic drains. The samples were obtained at the beginning of the thoracoscopic phase or after thoracotomy, before closure of the thorax and on postoperative days one, two and three. The intraoperative collection entailed introducing 100 ml of saline into the thoracic cavity, and then aspirating 20 ml of fluid 4 min later. Postoperative collection was achieved by aspirating 20 ml of fluid from the dorsal chest drain tube. The collection of the samples was performed in a standardized way by two of the investigators.

All blood samples, including white blood count (WBC) and C-reactive protein (CRP), were obtained using a 10-ml plastic vacutainer tube at the induction of anesthesia, at the end of the operation and between 8 and 10 h on postoperative days one, two and three.

The fluid and blood samples were immediately centrifuged at 2000 rpm, separated into small Eppendorf tubes and stored at − 80°C. The cytokine and chemokine analyses were performed after all samples were obtained.

Concentrations of IL-6, IL-8, IL-1RA, CINC-1 and MCP-1 in the blood and the collected pleural fluid were analyzed using enzyme-linked immune-sorbent assays (ELISA, R & D Systems, Minneapolis, MN, USA).

Statistical analysis

Comparison of data between the two subject groups was undertaken using the x^2 test for categorical data, and the Student's t test or Mann–Whitney U test for continuous data. Correlation analysis was performed by Pearson's correlation coefficient analysis. Wilcoxon rank sum test was used for the analysis of differences in median levels. The multivariate analysis was performed by multivariable linear generalized estimating equation models. Data are presented as mean with standard deviation (SD) or median with interquartile range (IQR) as appropriate. Statistical significance for each model was set at $p < 0.05$. Statistical analyses were performed with MedCalc® Software version 9 for Windows.

Results

Descriptive data

Twenty-four patients were included in this study, 12 in each group. There were nine male patients in each group, with a mean age and a body mass index of 61.1 years (SD 10.2 years) and 27.7 kg/m^2 (SD 5.7) in the OE group and 64.2 years (SD 9.1 years) and 28.1 kg/m^2 (SD 3.5 kg/m^2) in the MIE group, respectively. Mean cardiac ejection fraction, determined by preoperative echocardiography, and pulmonary function tests, reflected by mean forced expiratory volume (FEV1), was 66% (SD 7.2) and 66% (SD 15.7) in the open group and 66% (SD 8.1) and 77% (SD 7.8) in the MIE group, respectively. One patient who had neoadjuvant chemoradiotherapy had no residual tumor identified in the resected esophagus, and two patients had ulcerated Barrett's esophagus and high-grade dysplasia without invasive carcinoma in the resection specimen. Detailed data describing the two groups are summarized in Table 1. Overall, baseline characteristics for both groups were similar.

Table 1 Preoperative treatment and comorbidities

Variables	MIE	OE
Number of subjects	12	12
Neoadjuvant chemoradiotherapy	7	10
Overall comorbidity	3	7
Cardiac	0	1
Respiratory	2	3
Renal	0	1
Diabetes	1	2
UICC stage (based on resected specimen)		
0	1	2
I	3	1
IA	0	2
II	0	1
IIA	1	2
IIB	3	2
III	4	2

Postoperative morbidity

Intra- and postoperative outcomes are summarized in Table 2. Three patients developed postoperative anastomotic leakage; two were treated conservatively, and one patient underwent reoperation to suture the leak and wash out the pleural cavity. One patient experienced intraoperative splenic injury demanding splenectomy. In addition, two patients had recurrent laryngeal nerve injury and one suffered from delayed gastric emptying. In total, six patients had respiratory complications with two of them requiring drainage of an effusion, and four had postoperative pneumonia with one requiring early re-intubation. No patients died.

Pleural fluid cytokine response assay

There was a substantial increase in all pro- and anti-inflammatory cytokine and chemokine levels at the end of surgery and in the postoperative phase (Table 3). The highest levels were measured on postoperative day 1, and decreased thereafter.

The pro-inflammatory response of both IL-6 and IL-8 was lower in the MIE group, but differed across the time course. IL-6 showed lower levels at the beginning and at the end of surgery in the MIE group, reaching statistically significant lower levels in the latter. On days one to three, the levels were similar. IL-8 had similar levels during the operation, with higher levels on days 1 to 3.

The anti-inflammatory response of IL-1RA showed statistically significant lower levels in the MIE group at the end of the surgery. In addition, response levels were lower

Table 2 Intraoperative and postoperative outcome

Variables	MIE	OE
Duration of surgery in minutes (mean) (SD)	231 (±48)	305 (±82)
Blood loss in milliliters (mean) (SD)	241 (±97)	252 (±125)
Patients requiring red-blood-cell transfusion	0	0
Overall surgical morbidity		
Yes	3	4
No	9	8
Anastomotic leak		
Yes	1	2
No	11	10
Chyle leak		
Yes	0	0
No	12	12
Reoperation		
Yes	1	0
No	11	12
Pulmonary morbidity	4	4
ICU stay (mean) (SD)	2.2 (±0.9)	2.3 (±1.7)
Hospital stay (mean) (SD)	13.5 (±1.5)	14.2 (±2.8)
In-hospital death	0	0

Table 3 Comparison of cytokine levels between minimally invasive (MIE) and open esophagectomy (OE) in the pleural fluid

	MIE	OE	*P* value
IL-6 (pg/ml) (*mean*) (*SD*)			
At thoracotomy	68 (±63)	2212 (±4959)	0.16
End of surgery	203 (±304)	9391 (±13,846)	0.03
Day 1	92,476 (±85,048)	86,338 (±94,515)	0.87
Day 2	68,325 (±73,229)	72,185 (±92,513)	0.91
Day 3	29,943 (±33,760)	38,920 (±51,458)	0.61
IL-8 (pg/ml) (*median*) (*IQR*)			
At thoracotomy	161 (108–84)	153 (84–197)	0.92
End of surgery	157 (91–170)	91 (91–168)	0.64
Day 1	1395 (980–2223)	3387 (2515–9832)	<0.01
Day 2	479 (159–1493)	3743 (1782–9201)	<0.01
Day 3	1366 (336–3558)	2918 (631–4885)	0.27
IL-1RA (pg/ml) (*median*) (*IQR*)			
At thoracotomy	480 (30–682)	350 (81–1184)	0.62
End of surgery	578 (49–965)	2158 (855–10,903)	<0.01
Day 1	21,568 (7763–36,334)	21,210 (5652–50,419)	1.00
Day 2	15,772 (8728–50,413)	20,175 (10,070–50,872)	0.73
Day 3	20,426 (16,074–32,705)	24,553 (17,811–34,846)	0.56
CINC-1 (pg/ml) (*median*) (*IQR*)			
At thoracotomy	73 (52–94)	146 (67–159)	0.13
End of surgery	70 (56–98)	150 (71–412)	0.02
Day 1	150 (99–254)	134 (81–665)	0.90
Day 2	100 (74–123)	278 (86–492)	0.11
Day 3	165 (76–318)	156 (71–386)	0.98
MCP 1 (pg/ml) (*median*) (*IQR*)			
At thoracotomy	48 (0–142)	875 (532–2813)	<0.01
End of surgery	2260 (204–4335)	4825 (3546–30,870)	0.03
Day 1	59,610 (29,112–67,706)	59,542 (18,147–110,768)	0.64
Day 2	46,536 (11,453–84,943)	44,461 (28,726–108,371)	0.49
Day 3	44,283 (9945–129,798)	25,495 (16,438–165,847)	0.95

on postoperative days 2 and 3 without reaching statistical significance.

The MCP-1 and CINC-1 response levels in the pleural fluid were lower at the beginning and at the end of the surgery in the MIE group, with MCP-1 reaching statistical significance. Overall, CINC-1 levels increased only discreetly over time.

Blood cytokine response, WBC, CRP

The levels of all markers increased in the blood over time but were lower compared to the pleural fluid response. In the MIE group, pro-inflammatory IL-6 showed significantly lower and the anti-inflammatory IL-1RA higher levels, respectively, at the end of surgery. The comparison of the other cyto- and chemokines, WBC and CRP did not differ between the groups. Response levels for WBC, CRP, chemo- and cytokines as measured in the blood for MIE and OE are summarized in Tables 4 and 5.

Factors affecting cytokine levels

Using Wilcoxon rank sum test for the analysis of differences in median cytokine levels, we found significantly higher pleural fluid IL-6 levels ($p = 0.03$) in patients with postoperative pulmonary morbidity on POD 3. The other cyto- and chemokines showed no such association. Furthermore, preoperative pulmonary comorbidity was associated with an increase in IL-8 ($p < 0.01$), IL-1RA ($p < 0.01$) and CINC-1 ($p < 0.01$).

The length of surgery correlated to an increased level of all cyto- and chemokines (IL-6, $p = 0.01$; IL-8, $p = 0.02$;

Table 4 Comparison of cytokine levels between minimally invasive (MIE) and open esophagectomy (OE) in the blood

	MIE	OE	*P*-value
IL-6 (pg/ml) (*mean*) (*SD*)			
At intubation	8 (±8)	8 (±4)	0.99
End of surgery	45 (±28)	128 (±109)	<0.01
Day 1	65 (±65)	68 (±67)	0.91
Day 2	87 (±110)	48 (±41)	0.26
Day 3	31 (±26.4)	22 (±12)	0.31
IL-8 (pg/ml) (*mean*) (*SD*)			
At intubation	127 (±69)	163 (±62)	0.19
End of surgery	119 (±62)	130 (±58)	0.68
Day 1	119 (±65)	145 (±60)	0.32
Day 2	107 (±60)	150 (±62)	0.10
Day 3	101 (±57)	155 (±49)	0.02
IL-1RA (pg/ml) (*median*) (*IQR*)			
At intubation	68 (20–184)	255 (55–625)	0.27
End of surgery	1170 (528–3363)	11,777 (8099–14,514)	<0.01
Day 1	120 (17–379)	52 (222–897)	0.16
Day 2	420 (289–897)	388 (284–940)	0.68
Day 3	530 (231–272)	467 (272–688)	0.81
CINC-1 (pg/ml) (*mean*) (*SD*)			
At intubation	115 (±144)	102 (±90)	0.79
End of surgery	119 (±157)	144 (±199)	0.73
Day 1	90 (±81)	98 (±85)	0.83
Day 2	98 (±89)	87 (±53)	0.73
Day 3	113 (±121)	98 (±71)	0.70
MCP 1 (pg/ml) (*mean*) (*SD*)			
At Intubation	295 (±199)	205 (±205)	0.30
End of surgery	334 (±218)	694 (±751)	0.12
Day 1	518 (±867)	252 (±330)	0.32
Day 2	608 (±851)	255 (±295)	0.18
Day 3	375 (±252)	183 (±172)	0.05

IL-1RA, $p = 0.04$; CINC-1, $p = 0.02$; MCP-1, $p = 0.03$) at the end of surgery in the pleural fluid, but not in the blood. Additionally, the multivariable models showed that this effect is prolonged and still detectable on POD 1–3 in IL-8 ($p = 0.01$), IL-1RA ($p = 0.03$) and CINC-1 ($p = 0.02$) levels, respectively. Age ($p = 0.09$) and male sex ($p < 0.001$) were only significantly associated with decreases in MCP-1 levels, but not with the course of the other cytokines.

Discussion

The present study demonstrates an attenuated inflammatory reaction in minimally invasive esophagectomy for cancer or high-grade dysplasia in comparison with the standard open procedure. Both pro- and anti-inflammatory cytokines were affected. The release of IL-6, IL-8 and IL-1RA in the pleural fluid and in the blood was lower in MIE, suggesting that the minimally invasive approach reduces the surgical stress response. However, the time course differed for each of these substances. Concerning the two measured chemokines CINC-1 and MCP-1, higher levels at the end of the surgery in the pleural fluid but no significant differences in the blood were found.

The postoperative course of IL-6 and IL-8 in our study is consistent with previous investigations [21]. As a response to the tissue trauma, both cytokines peak in the early postoperative period and decrease thereafter. This response is more pronounced locally, i.e., in the thoracic compartment compared to the systemic reaction the peripheral blood. The thoracotomy and the one-lung ventilation induce a faster response of IL-6, while IL-8 reacts with some delay.

Considering the substantial postoperative morbidity of MIE and open esophagectomy, the early-reacting IL-6 levels could be of interest for the detection of inflammatory or infectious complications. IL-6 has been described as a valuable marker for postoperative sepsis [11]. In our analysis, we found a significant association of IL-6 and postoperative pulmonary morbidity on postoperative day 3. This is consistent with other reports showing that postoperative infectious complications increase cytokine levels after esophagectomy [22]. Patients with acute lung injury and pneumonia showed higher levels of IL-6 as well as prolonged duration of postoperative SIRS. Early elevation of IL-6 may predict the incidence of postoperative infections [22–24].

The length of surgery seems to play an important role in the systemic inflammatory response. We found a correlation between length of surgery and all cytokine levels in the pleural fluid at the end of surgery. In addition, the multivariable models for the cytokine levels on POD 1–3 showed that the length of surgery is also associated with prolonged increases in IL-8, IL-1RA and CINC-1 levels in the pleural fluid. This demonstrates the substantial influence of prolonged tissue trauma on cytokine levels, a finding consistent with previous reports [22]. Longer operation time reflects longer one-lung ventilation, itself a potent trigger of inflammatory response. In a previous study, measuring cytokine levels in broncho-alveolar lavage fluid in both lungs we were able to show that the inflammatory reaction occurs bilaterally [19]. The higher

Table 5 Comparison of CRP and white-blood-cell-count levels between MIE and OE

	MIE	OE	*P*-value
CRP (mg/L) (*mean*) (*SD*)			
At intubation	3.2 (±4.7)	6.5 (±13.6)	0.43
End of surgery	5 (±4.8)	5 (±3.3)	0.95
Day 1	97 (±35.2)	88.9 (±31.3)	0.54
Day 2	188.3 (±73.8)	179.9 (±66)	0.77
Day 3	202.8 (±94.5)	159.2 (±70.2)	0.21
Day 4	164.3 (±78.8)	121.3 (±63.9)	0.15
Day 5	118.1 (±78.5)	86.4 (±32.7)	0.21
WBC (x 10^9/L) (*mean*) (*SD*)			
At intubation	6.9 (±1.6)	7.8 (±2.1)	0.27
End of surgery	10.3 (±2.5)	11.3 (±4.2)	0.51
Day 1	10.5 (±1.8)	11.1 (±2.9)	0.59
Day 2	10.7 (±2.4)	10.9 (±3.7)	0.89
Day 3	9.2 (±4)	8.5 (±2.5)	0.67
Day 4	7.9 (±3.8)	7.4 (±1.9)	0.72
Day 5	7.1 (±2.9)	8.2 (±2.7)	0.34

oxygen levels required during one-lung ventilation in the ventilated contralateral lung as well as the reperfusion damage in the collapsed lung may be responsible for this finding. Importantly, preoperative pulmonary comorbidity was significantly associated with increases in IL-8, IL-1RA and CINC-1 in the postoperative course. Pre-existing pulmonary comorbidities are known to increase systemic inflammation [25]. However, given the small sample size in our study, these results need to be interpreted with care. Still, our data indicate that the careful selection of patients and the optimizing of the pulmonary function may reduce postoperative inflammatory-caused morbidity.

The interpretation of the course of chemokines CINC-1 and MCP-1 in the setting of esophagectomy is difficult, and comparable data in the literature are scarce. CINC-1 did not react substantially in the postoperative phase, similar to previous reports [11]. In the peripheral blood, the levels even decreased. MCP-1 increased on POD1, which is in line with other findings [11]. Age and sex are known variables affecting the immune response of human individuals [26, 27]. In our data, age and male gender showed a negative correlation with MCP-1 levels in the postoperative course; however, no such association was found in all other cytokines. Whether the chemokines CINC-1 and MCP-1 may be used as markers of inflammation in this setting is debatable, and further studies are necessary.

In contrast to the pleural fluid, the cytokine levels in the blood did not show a marked elevation. Our group as well as others has shown similar results previously [10, 19, 28, 29]. The major inflammatory reaction occurred in the broncho-alveolar fluid, in the pleural fluid and less extensively in the blood. Thus, cytokine response levels measured in the compartment where the surgery is performed lead to a substantially higher immune response [23, 30]. Three main reasons may be responsible for this finding. First, the thoracic compartment and the esophageal bed tissue include a widespread vascular and lymphatic network with a dense distribution of inflammatory and endothelial cells that play a key role in cytokine response. Damage to the compartment occurs when the esophagus is mobilized and the lymphnode dissection is performed, inducing a much more pronounced regional response. Second, the one-lung ventilation triggers the inflammatory reaction by high oxygen pressures, resulting in the production of radical oxygen species. Furthermore, due to mechanical stress on the alveolar walls barotrauma develops, increasing the inflammatory response [19]. Third, the thoracotomy is a highly invasive type of access, sometimes resulting in rib fractures. In our study, the main difference between the MIE and OE groups was the access route to the thoracic esophagus. Despite the fact that the basic intrathoracic steps were similar, minimally invasive preparation techniques are known to be more gently. Furthermore, a thoracotomy is usually more painful compared to a thoracoscopy, further enhancing the immune response, especially on early postoperative days. Transthoracic esophagectomy is known to produce a more pronounced inflammatory response, mirrored by higher interleukin levels compared to other complex procedures involving only one body compartment such as transhiatal esophagectomy or duodeno-pancreatectomy [31, 32].

The WBC and CRP levels were similar in the open and minimally invasive groups, respectively. Some studies have shown a significantly lower WBC response in laparoscopic approaches for gastric cancers [28, 33, 34]. By contrast, a recently conducted review comparing postoperative inflammatory markers for open versus minimally invasive approaches did not reveal major differences for WBC response, indicating that the WBC is not always dependent on the extent of the procedure [29].

The results of our study need to be interpreted carefully given the modest sample size of 24 patients and some heterogeneity in the study arms. As previously demonstrated, the inflammatory reaction shows inter-individual differences and is especially complex in esophagectomy given the fact that the surgery has impact on more than one body compartment [15]. We used multivariable analyses to control for some of the heterogeneity. However, despite the small sample size, our findings clearly indicate an advantage of minimally invasive esophagectomy on the inflammatory axis.

Furthermore, this study is the first demonstrating cyto- and chemokine response levels over the first 72 h following surgery for MIE versus OE.

In conclusion, the minimally invasive approach attenuates the inflammatory response, especially locally in the thoracic compartment. The value of the chemokines CINC-1 and MCP-1 as markers of inflammation in the setting of esophagectomy is debatable.

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Author's contribution TD contributed to data collection, statistical analysis and drafted the manuscript. UZ contributed to the study design, sample and data collection and revision of the manuscript. DW and BBS were involved in the study design, manuscript content and its revision. AI and DJH were involved in samples and data collection, cytokine analysis, contribution to the manuscript and its revision. All authors read and gave approval to the final manuscript version.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest Drs. Delko, Watson, Beck-Schimmer, Immanuel, Hussey and Zingg have no conflicts of interest or financial ties to disclose in relation to this study.

Ethical approval The study has been performed in accordance with the Declaration of Helsinki. Informed consent was obtained, and the trial was approved by the Flinders Clinical Research Ethics Committee.

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