Original Article

Inflammatory cytokines in robot-assisted thoracic surgery versus video-assisted thoracic surgery

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Background: Cytokines play a crucial role in the inflammatory response and are essential modulators of injury repair mechanisms. While minimally invasive operations have been shown to induce lower levels of cytokines compared to open thoracotomy, the inflammatory cytokine profile difference between video-assisted (VATS) and robotic-assisted thoracic surgery (RATS) techniques has yet to be elucidated.

Methods: In this prospective observational study of 45 patients undergoing RATS (n=30) or VATS (n=15) lung resection for malignancy, plasma levels of interleukin (IL)-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, vascular endothelial growth factor (VEGF), interferon (IFN)-γ, tumor necrosis factor (TNF)-α, monocyte chemo-attractant protein (MCP)-1, and endothelial growth factor (EGF) were measured before and after surgery via immunoassay.

Results: Levels of IL-6 and MCP-1 were significantly higher in patients undergoing VATS than in patients undergoing RATS (P<0.001 and P=0.005, respectively) 2 hours following surgery. MCP-1 levels were also found to be significantly higher in the VATS group (P<0.001) 24 hours following surgery. IL-1α, IL-1β, IL-2, IL-4, IL-8, IL-10, IFN-γ, TNF-α, and EGF levels were not significantly different at any time-point comparing VATS to RATS.

Conclusions: The VATS approach is associated with a more robust pro-inflammatory cytokine response through the upregulation of MCP-1 and IL-6 when compared to the RATS approach in patients undergoing anatomic lung resection. Further studies are necessary to validate the clinical significance of this finding.

Keywords: Non-small cell lung cancer (NSCLC); robotic-assisted thoracic surgery (RATS); video-assisted thoracic surgery (VATS); inflammatory cytokines

Introduction

Minimally invasive thoracic surgery has been shown to be associated with reduced morbidity, mortality, blood loss, hospital length of stay, and patient pain scores when compared to open thoracotomy (1-3). Recently, robot-assisted thoracic surgery has established its role in the management of patients needing lung resection, and is viewed by many surgeons as the preferred approach to lung resection over video-assisted thoracic surgery (VATS). Each of these approaches has its advantages and disadvantages,

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in terms of clinical outcomes and cost (4-10). Several early studies have suggested that the VATS approach is associated with lesser release of cytokines and pro-inflammatory mediators, and that may be responsible for many of the benefits of minimally invasive thoracic surgery over open thoracotomy (11-13). It is plausible, that as a minimally invasive approach, the robotic approach would also have lower cytokine and pro-inflammatory mediator release.

However, it is unknown whether the robot-assisted technique is associated with similar or lower pro-inflammatory mediator release compared to VATS. Despite numerous studies comparing the link between perioperative systemic inflammation and morbidity and mortality in VATS versus open thoracotomy, the same comparison has seldom been studied between VATS and the robotic approach (11-13). The more precise dissection afforded by the improved 3-dimensional visualization with the robot may be associated with less tissue trauma and less cytokine release. Similarly, it has been argued that the robotic-assisted thoracic surgery (RATS) approach is associated with a more complete lymphadenectomy and thus potentially reduced oncologic burden, which may not only be associated with a lesser inflammatory state, but also a reduced recurrence rate, however, data regarding this phenomenon is not yet conclusive (4,14-20).

In this context, we conducted a prospective, observational study to assess the overall inflammatory state of patients undergoing VATS or robot-assisted lung resections for suspected or known non-small cell lung cancer (NSCLC) by comparing levels of various interleukins, cytokines, and growth factors. We hypothesized that the robot-assisted approach is associated with less inflammation. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1820/rc).

Methods

Patient population and inclusion criteria

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Loyola University Medical Center (No. 211663) and informed consent was taken from all individual participants, scheduled to undergo elective lung resection via VATS or robot-assisted techniques. Subjects were recruited between 6/2017–5/2018, and 9/2020–1/2021 at the Loyola University Medical Center, Maywood, IL, USA for this prospective, observational, single-center study. No patients were recruited between 6/2018–9/2020 due to logistical limitations and the coronavirus pandemic. Patients were required to meet the following eligibility criteria: (I) 40+ years old due to a lack of established previous studies detailing the clinic-pathological features and outcomes associated with a younger population; (II) undergoing elective RATS or VATS lung resection for known or suspected NSCLC; and (III) operation to be done by one of two surgeons to reduce operator variability.

Standardized operative techniques, such as incisions and port placements, were implemented for each group as with minimal intragroup operative course heterogeneity. Per convention, CO_2 insufflation was used in the robotic approach but not in VATS. To a similar effect, bipolar electrocautery was often used in the robotic cohort but less often in the VATS cohort. The conduct of the operation was similar in each group between patients. Furthermore, all patients underwent a systematic mediastinal and hilar lymph node dissection.

Independent variables

Clinical and demographic data collected included patient age, sex, comorbid conditions, surgical indication, surgical extent, duration of operation, hospital length of stay, and chest tube duration.

Main exposure variable

The surgical approach, VATS or robotic, was the main exposure variable. Surgical approach utilized was based on surgeon preference. Both surgeons were fully proficient in VATS and robotic, thus a learning curve bias was avoided. All operations were performed at one hospital with similar preoperative, intraoperative and postoperative care pathways and protocols.

Blood sample processing

Patient blood samples were collected at three time-points: pre-operatively and 2 and 24 hours following operation completion. Arterial blood samples were drawn directly into sodium citrate tubes and processed immediately via 3000xg centrifugation at +4 ℃ for 30 minutes with obtained plasma aliquoted for preservation at –80 ℃. Immunoassay measurements of interleukin (IL)-1α, IL-1β, IL-2, IL-4,

IL-6, IL-8, IL-10, IFN-γ, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), monocyte chemo-attractant protein-1 (MCP-1), and endothelial growth factor (EGF) levels were conducted on the Cytokine Biochip Array I using the Evidence Investigator instrumentation from Randox Laboratories (Kearneysville, WV, USA).

Statistical analysis

Clinical and demographic data were collected and analyzed using chi-squared test for categorical variables and two-way analysis of variance for continuous variables as appropriate in order to assess the interaction between both RATS and VATS with lung resection. Bonferroni and Sidak correction were used for multiple comparisons. Data are reported in mean, median, standard deviation (SD), and standard error of the mean (SEM) as appropriate. Patients with missing data were excluded from analysis.

All statistical tests were performed using GraphPad Prism version 8.4.3. All tests were two-sided with alpha set at 0.05.

Results

Patient demographics

This study enrolled 45 patients undergoing minimally invasive anatomic lung resection. Of those, 30 (66.67%) underwent robotic lung resection and 15 (33.33%) underwent VATS anatomic lung resection. Patients were similar in their age, sex, and various other demographic measurements, as shown in *Table 1*. A statistically significant difference was found in employment status between VATS and robot-assisted, however, this is likely due to the cohorts' mean ages centering around the US retirement age. No differences were observed in regard to operation, histology, or tumor staging, as shown in *Table 2*.

Plasma cytokine level differences

Two patients from each cohort had missing or incomplete cytokine data, leaving 30 and 15 patients in the robot-assisted and VATS cohorts, respectively.

Pre-operative levels of all cytokines measured were similar between the robotic and VATS cohorts, as shown in *Table 3* and *Figure 1A*.

Two-hour post-operative levels of IL-6 and MCP-1 were significantly higher in patients undergoing VATS than in patients undergoing robot-assisted. IL-6 demonstrated the most marked difference between the groups (P=0.001, median =100.88 *vs.* 41.13 pg/mL, respectively). The difference in MCP-1 levels between VATS and robot-assisted was significant but less robust (P=0.0051, 135.90 *vs.* 96.90 pg/mL, respectively). Group mean values are shown in *Table 4* and *Figure 1B* (P<0.001 IL-6; P=0.005 MCP-1).

Twenty-four-hour post-operative levels of MCP-1 were significantly higher in patients undergoing VATS than in patients undergoing robotic (P=0.001), as shown in *Table 5* and *Figure 1C*.

Table 1 Demographic data

Variables	VATS, n or mean ± SD	RATS, n or mean ± SD	SE of diff.	95% CI of diff.	Adjusted P value
Sex, male/female	9/6	9/21			0.053
Race					0.448
White	14	24			
Black	0	4			
Asian	0	1			
Hispanic	1	1			
Housing status					0.382
With family/friends	15	25			
Independent	0	4			
Structured/assisted	0	1			
Homeless	0	0			

Table 1 (*continued*)

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Variables	VATS, n or mean ± SD	RATS, n or mean ± SD	SE of diff.	95% CI of diff.	Adjusted P value
Employment status					0.019
Retired	9	25			
Employed	5	1			
Unemployed	1	4			
Disabled	0	0			
Age at surgery (years)	66.4±8.6	70±8.6	2.16	−11.70 to 4.51	>0.99
Surgery time (min)	181.3±56.9	168.1±40.1	14.28	−40.46 to 66.85	>0.99
Weight (kg)	77.38±16.89	76.1±17.8	4.93	−17.27 to 19.8	>0.99
Length of stay (days)	4.1±1.7	3.9±3.1	0.792	−2.73 to 3.22	>0.99
POD chest tube removal	3.2±1.9	2.7±3.5	0.74	−2.27 to 3.31	>0.99
PACU medication (morphine eq)	227.2±230.6	204.1±163	72.14	−247.9 to 294.1	>0.99
Post-op day 0					
Post-op pain day 0	3.9±2.2	4.6±2	0.76	−3.56 to 2.16	>0.99
Narcotic day 0 (morphine eq)	16.7±17.5	45.4±85	23.54	−117.1 to 59.73	>0.99
Acetaminophen day 0 (mg)	952.9±681.3	1,055±633.4	227.3	−956.2 to 751.2	>0.99
Post-op day 1					
Post-op pain day 1	2.7±1.6	3.2±2	0.62	−2.85 to 1.81	>0.99
Narcotic day 1 (morphine eq)	29.1±38.1	33.9±24.8	7.6	−33.70 to 24.13	>0.99
Aspirin day 1 (mg)	9.5±26.9	7.6±24	7.4	−25.85 to 29.72	>0.99
Acetaminophen day 1 (mg)	1,912±994.3	2,082±728.4	307.9	−1,327 to 986.2	>0.99
Post-op day 2					
Post-op pain day 2	2.5±1.5	2.6±2.3	0.7	−2.86 to 2.56	>0.99
Narcotic day 2 (morphine eq)	19.5±15.5	18.5±19.2	6.31	−23.36 to 25.42	>0.99
Aspirin day 2 (mg)	9.5±26.9	8.7±25.5	8.13	−30.54 to 32.24	>0.99
Acetaminophen day 2 (mg)	1,835±1,102	1,679±950.7	353.7	−1,210 to 1,522	>0.99
Post-op day 3					
Post-op pain day 3	2.2±1.2	2.6±2.6	0.89	−4.36 to 3.50	>0.99
Narcotic day 3 (morphine eq)	16.1±13.7	21.8±24.8	7.93	−40.56 to 29.21	>0.99
Aspirin day 3 (mg)	10.8±28.5	5.4±20.9	11.89	−46.92 to 57.72	>0.99
Acetaminophen day 3 (mg)	1,517±948.9	2,011±994.4	397.7	−2,243 to 1,255	>0.99
Cumulative admission totals					
Narcotic (morphine eq)	306.6±253.5	309.3±234.1	86.77	−328.6 to 323.3	>0.99
Aspirin (mg)	28.6±80.7	17.7±57.2	22.12	−72.23 to 93.97	>0.99
Acetaminophen (mg)	6,038±3,052	5,717±2,639	986.1	−3,383 to 4,025	>0.99

VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery; SD, standard deviation; SE, standard error; CI, confidence interval; POD, post-operative day; PACU, post-anesthesia care unit.

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Table 2 Operative and pathological data

Variables	VATS, n (%)	RATS, n (%)	Adjusted P value
Operation			0.522
Lobectomy	7 (46.7)	15 (50.0)	
Wedge resection	3 (20.0)	4 (13.3)	
Segmentectomy	0	4 (13.3)	
Combination	5 (33.3)	7 (23.3)	
Final pathology			0.558
Primary	13 (86.7)	25 (83.3)	
Metastasis	2 (13.3)	2 (6.7)	
Other	0	3 (10.0)	

VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

Table 3 VATS *vs.* RATS serum cytokine levels pre-operatively

Cytokine	VATS median	RATS median	VATS mean	RATS mean	Mean difference 0 hour	Mean difference 95% CI	Adjusted P value	VATS SEM	RATS SEM
IL-2	0.72	0.76	0.908	0.867	0.041	−15.51 to 15.59	>0.99	0.378	0.229
IL-4	1.56	1.51	2.421	1.513	0.907	−14.64 to 16.46	>0.99	0.865	0.102
IL-6	1.69	1.84	5.283	2.748	2.535	−13.02 to 18.09	>0.99	2.529	0.456
IL-8	4.15	4.03	9.288	4.457	4.831	−10.72 to 20.38	0.99	3.635	0.495
IL-10	0.49	0.46	2.476	0.617	1.859	−13.69 to 17.41	>0.99	1.916	0.122
VEGF	14.79	11.69	21.26	16.58	4.673	−10.88 to 20.22	0.99	6.001	3.172
IFNG	0.27	0.31	0.242	0.723	−0.481	−16.03 to 15.07	>0.99	0.042	0.291
TNFA	1.51	1.46	1.501	1.652	−0.151	−15.70 to 15.40	>0.99	0.217	0.227
IL-1A	0.12	0.13	0.123	0.421	−0.299	−15.85 to 15.25	>0.99	0.03	0.22
IL-1B	1.05	1.25	1.731	9.457	−7.727	−23.28 to 7.824	0.866	0.757	5.387
MCP-1	104.24	87.6	107.1	104.4	2.656	−12.90 to 18.21	>0.99	9.58	10.07
EGF	2.61	2.65	4.044	5.653	−1.61	−17.16 to 13.94	>0.99	0.887	8.602

VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery; CI, confidence interval; SEM, standard error of the mean; IL, interleukin; VEGF, vascular endothelial growth factor; IFNG, interferon-γ; TNFA, tumor necrosis factor-α; MCP-1, monocyte chemo-attractant protein-1; EGF, endothelial growth factor.

Clinical outcomes

Assessment of patient demographics, such as population composition and postoperative treatment, showed no statistical difference. The final pathological examination revealed 13 and 25 primary lung cancers in VATS and RATS, respectively, with two patients having undergone a resection for metastasis in each group. Pathology of the remaining three patients in the robotic-assisted group demonstrated inflammatory granulomatous tumors.

Additionally, there was no observed difference in clinical outcomes such as arrhythmias, cardiopulmonary arrests, and prolonged air leaks, as shown in *Table 6*.

Discussion

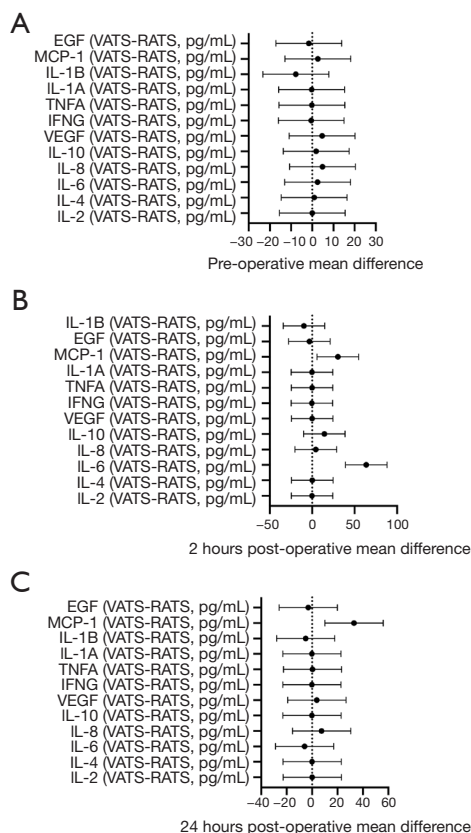The implementation of robot-assisted thoracic surgery for

Figure 1 Mean values of inflammatory cytokines 95% confidence interval error bars. Pre-operatively, no cytokine level was significantly different comparing patients undergoing the VATS and RATS procedures (A). At 2 hours post-surgery, IL-6 and MCP-1 levels were significantly elevated in patients undergoing the VATS procedure in comparison to those undergoing the RATS procedure (B). At 24 hours post-surgery, the level of MCP-1 was significantly elevated in patients undergoing the VATS procedure in comparison to those undergoing the RATS procedure (C). EGF, endothelial growth factor; MCP-1, monocyte chemo-attractant protein-1; IL, interleukin; TNFA, tumor necrosis factor-α; IFNG, interferon-γ; VEGF, vascular endothelial growth factor; VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

the treatment of NSCLC has dramatically increased over the last decade. However, widespread debate regarding its overall efficacy when compared to VATS continues (9,10). In this prospective clinical study, we attempted to address this debate via measurement of blood plasma inflammatory markers in conjunction with patient outcomes in hopes of elucidating the true difference between VATS and RATS in patients undergoing minimally invasive surgery (MIS)

lung resection for the treatment of NSCLC. Through the use of sample-matched cytokine measurement data, the current study functions to contribute a linking factor between clinical observations and basic sciences that more homogeneously explores the true variation between the two MIS techniques. Although numerous previous studies have compared VATS to robot-assisted, none were found that included inflammatory biomarker profiling as conducted in the current study (7,14). Additionally, by limiting our study to a single center with no variation in surgeon, we more aptly limited biases and secondary effects as post-matching was free of strong contributors such as MIS learning curves, hospital protocols, surgeon-to-surgeon variability, and surgical team dynamics.

In terms of design and control, our study seemed to have benefited from surgeon consistency as, unlike the majority of previous studies, we had no difference in operation time between VATS and robotic (3,21-25). Additionally, while select previous studies presented statistically significant inter-cohort age differences, we found no difference between our robotic and VATS cohorts (13,26). Thus, we were able to more adequately isolate surgical approach as our exposure variable.

Our results suggest VATS induces a more pronounced inflammatory response than robot-assisted, as demonstrated by measurements of pro-inflammatory cytokines IL-6 and MCP-1 (27,28). These particular findings suggest a greater degree of surgical trauma-induced systemic inflammation as the VATS elevated cytokines have all been strongly associated with thoracic surgery trauma (11-13). Indeed, elevated of pro-inflammatory cytokines, such as IL-6, have been extensively correlated with the degree of cutaneous trauma and subsequently elicited systemic inflammation throughout the repair process (29-32). Thus, the implication of a more pronounced degree of systemic inflammation in the VATS cohort carries a variety of potential clinical manifestations in the peri-operative period such as respiratory failure, renal dysfunction, coagulopathies, and liver dysfunction, however, further studies must be conducted to determine clinical manifestation thresholds (33,34).

Due to prolonged involvement of the immune system in the wound repair processes, our findings may have further time-based implications as the specific elevated inflammatory response observed in VATS patients can lead to dysregulation and reduced efficacy of the immune system (35,36). For example, elevated levels of IL-6, although pro-inflammatory and classically implicated in the production of a robust immune response, can lead to an

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Table 4 VATS *vs.* RATS serum cytokine levels 2 hours post-operatively

Cytokine	VATS median	RATS median	VATS mean	RATS mean	Mean difference 2 hours	Mean difference 95% CI	Adjusted P value	VATS SEM	RATS SEM
IL-2	0.00	0.73	0.827	0.974	−0.147	−24.67 to 24.37	>0.99	0.389	0.329
IL-4	1.68	1.50	1.638	1.526	0.113	−24.41 to 24.63	>0.99	0.083	0.077
IL-6	100.88	41.13	119	55.2	63.79	39.27 to 88.31	<0.001	16.27	10.61
IL-8	10.25	6.70	11.76	7.492	4.272	−20.25 to 28.79	>0.99	2.951	1.074
IL-10	12.79	7.89	29.82	15.49	14.33	−10.19 to 38.85	0.694	12.67	3.18
VEGF	13.02	9.54	14.58	14.56	0.023	−24.50 to 24.54	>0.99	1.767	3.145
IFNG	0.17	0.18	0.149	0.473	−0.324	−24.84 to 24.20	>0.99	0.037	0.19
TNFA	1.08	1.19	1.202	1.298	−0.096	−24.62 to 24.42	>0.99	0.183	0.204
IL-1A	0.14	0.12	0.153	0.345	−0.191	−24.71 to 24.33	>0.99	0.0423	0.197
IL-1B	0.65	1.20	1.555	11.27	−9.715	−34.24 to 14.81	0.971	0.902	6.568
MCP-1	135.93	96.90	133.8	103.5	30.28	5.763 to 54.80	0.005	14.41	10.37
EGF	0.96	1.49	0.973	4.273	−3.3	−27.82 to 21.22	>0.99	0.211	1.578

VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery; CI, confidence interval; SEM, standard error of the mean; IL, interleukin; VEGF, vascular endothelial growth factor; IFNG, interferon-γ; TNFA, tumor necrosis factor-α; MCP-1, monocyte chemo-attractant protein-1; EGF, endothelial growth factor.

Table 5 VATS *vs.* RATS serum cytokine levels 24 hours post-operatively

Cytokine	VATS median	RATS median	VATS mean	RATS mean	Mean difference 24 hours	Mean difference 95% CI	Adjusted P value	VATS SEM	RATS SEM
IL-2	0.84	0.81	1.029	0.905	0.124	−22.78 to 23.03	0.358	0.162	0.046
IL-4	1.45	1.55	1.478	1.502	−0.024	−22.93 to 22.88	0.08	0.077	0.012
IL-6	44.96	38.33	39.97	45.89	−5.921	−28.83 to 16.99	7.094	6.574	1.038
IL-8	6.64	4.52	13.220	5.724	7.498	−15.41 to 30.40	4.732	0.683	0.577
IL-10	0.78	0.78	0.901	1.049	−0.147	−23.05 to 22.76	0.157	0.165	0.024
VEGF	17.47	12.33	19.61	15.89	3.72	−19.19 to 26.63	3.596	3.265	0.523
IFNG	0.18	0.23	0.139	0.325	−0.185	−23.09 to 22.72	0.041	0.081	0.009
TNFA	1.44	1.41	1.659	1.37	0.289	−22.62 to 23.20	0.2	0.136	0.027
IL-1A	0.11	0.12	0.116	0.273	−0.157	−23.06 to 22.75	0.035	0.149	0.014
IL-1B	1.00	1.81	2.83	7.894	−5.064	−27.97 to 17.84	1.826	2.53	0.315
MCP-1	164.29	131.83	169.8	136.9	32.97	10.06 to 55.88	18.21	14.2	2.54
EGF	1.23	2.35	1.556	4.643	−3.087	−25.99 to 19.82	0.338	1.188	0.113

VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery; CI, confidence interval; SEM, standard error of the mean; IL, interleukin; VEGF, vascular endothelial growth factor; IFNG, interferon-γ; TNFA, tumor necrosis factor-α; MCP-1, monocyte chemo-attractant protein-1; EGF, endothelial growth factor.

Table 6 VATS *vs.* RATS clinical outcomes presented

Variables	Total (n=49)	VATS (n=17)	RATS (n=32)	P value
Anemia	1 (2%)		1 (3%)	>0.99
Arrhythmia	1 (2%)		1 (3%)	>0.99
Cardiopulmonary arrest	1 (2%)	1 (6%)		0.354
Hyponatremia	1 (2%)	1 (6%)		0.354
Metabolic encephalopathy	1 (2%)		1 (3%)	>0.99
Multifocal ischemic infarct	1 (2%)	1 (6%)		0.333
Pneumothorax	3 (6%)	1 (6%)	2 (6%)	>0.99
Pneumomediastinum	1 (2%)		1 (3%)	>0.99
Prolonged air leak	3 (6%)	2 (12%)	1 (3%)	0.273
Total	13 (26%)	6 (36%)	7 (22%)	0.331

VATS, video-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

immunosuppressed state by inhibiting pro-inflammatory IL-1β and TNF-α, both of which play crucial roles in the immuno-competent host response to infection and injury (37,38). Indeed, as TNF-α and IL-1β play pivotal roles in initiating the pro-inflammatory cytokine cascade and mobilizing cells of the immune system, both are rapidly released in substantial quantities following trauma (37,38). Thus, as inducers and predecessors of IL-6 in the cytokine cascade, it would be logical to expect TNF-α and IL-1β levels to rise in conjunction with IL-6 in accordance with the classic cytokine cascade pathway (39,40). However, as depicted data at the 2-hour post-surgery, the lack in statistically significant changes in TNF-α and IL-1β supports the possibility of an IL-6-induced immunosuppressed state and predisposition to infection, as corroborated by previous works (35,39,40). Additional kinetic studies are needed to further validate this notion.

In eliciting elevated MCP-1 levels, VATS also produces potentially negative outcomes as increased MCP-1 levels have been associated with acute kidney injury and increased mortality following thoracic surgery (41). Indeed, in a study of 972 patients, Moledina *et al.* found MCP-1 levels >196 pg/mL to be associated with significantly increased mortality risk (HR =1.95, 95% CI: 1.09–3.49) (41). In the current study, a significantly larger fraction of VATS patients had MCP-1 levels >196 ng/mL at 24 hours (35.7% *vs.* 10.3%, P=0.045, χ^2=4.013). Similarly, Kremen *et al.* demonstrated increased MCP-1 levels in the post-operative period following thoracic surgery to be implicated in contributing to post-operative insulin resistance

(P<0.05) (42). Hoogeveen *et al.* demonstrated elevated MCP-1 levels to be an independent factor significantly associated with coronary disease (HR =1.86, 95% CI: 1.36–2.54) (43). Notwithstanding the aforementioned findings, limited population size (N=15) of the Kremen *et al.* study and inadequate homogeneity amongst the cohort studied by Hoogeveen *et al.* necessitate more robust studies to more adequately corroborate our findings (42,43).

This study has several limitations. First, this is a single center observational study and is limited by its sample size and imbalanced patient treatment allocation, as such the results may not be generalizable. However, due to the fact that consistent differences were found in cytokine levels despite similar patient cohorts, we believe the results are meaningful. Second, cytokine levels were only measured up to 24 hours post-operation and, as such, we do not have data beyond this timeframe. However, the cytokine levels during first postoperative day are most likely to yield information that pertains to the specific approach used, rather than other postoperative events that may occur which could confound the results. Notwithstanding these limitations, we believe the results are relevant and provide further areas for future studies.

Conclusions

In conclusion, in this single-center, prospective, observational study this study demonstrated that the VATS approach is associated with a more robust pro-inflammatory cytokine response through the upregulation of MCP-1 and

IL-6 when compared to the robotic approach in patients undergoing anatomic lung resection. Further studies are necessary in order to determine whether our findings translate to clinically meaningful outcomes.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1820/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1820/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Loyola University Medical Center (No. 211663) and informed consent was taken from all individual participants.

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