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Serum Biomarkers IL-8 and Sp-D for Pulmonary Damage Assessment After One Lung Ventilation (OLV) Cardio-Thoracic Surgery: Insights into OLV Physiology Changes and Ventilator Parameters

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ABSTRACT

Background: Cardio-thoracic surgeries often necessitate the use of one lung ventilation (OLV) to enhance surgical access and visualization. While OLV is standard in these procedures, it poses risks of pulmonary damage due to complex pathophysiological changes, including shunting, ventilation-perfusion mismatch, and reperfusion injury. Monitoring ventilator parameters during thoracic surgery, such as end-tidal carbon dioxide, peak airway pressure, and mechanical power, can provide insights into lung damage. Identifying serum biomarkers, such as IL-8 and surfactant protein D (SP-D), is crucial for early detection of pulmonary damage. IL-8, a pro-inflammatory cytokine, and SP-D, a collectin protein, are potential markers for assessing lung injury.
Aim: This study aims to analyze the relationship between OLV procedures and the inflammatory response of IL-8 and serum SP-D levels as lung damage biomarkers in patients undergoing thoracic surgery.
Material and Methods: Twenty-eight patients underwent thoracic surgery with one lung ventilation from July to September 2023. All patients were subjected to lung-protective ventilation (LPV) with a tidal volume (VT) of 7 ml/kg predicted body weight (PBW) during two-lung ventilation (TLV) and 5 ml/kg PBW during OLV, with a positive end-expiratory pressure (PEEP) of 5-10 cmH2O. IL-8 and SP-D levels were assessed after intubation (T0), 2 hours after OLV (T1), and 24 hours after surgery (T2). Values for peak pressure, driving pressure, mechanical power and OLV duration were recorded during surgery.
Results: Among the 28 patients, 25 subjects (89%) had comorbidities, with lung tumor (11) and tuberculosis (TB) (9) being the most common. Comparative analysis showed differences in IL-8 and SP-D levels during TLV and 2 hours of OLV (P: 0.018 and P: 0.033), with IL-8 and SP-D levels increasing during OLV. IL-8 levels changed from 70.9 (8.9-233.10) to 75.1 (27.4-243.30) ng/L, and SP-D levels changed from 115.9 (35.8-333.2) to 131.1 (64.3-339.3) ng/ml. However, there was no correlation between driving pressure, mechanical power, compliance, OLV duration, and IL-8 and SP-D levels during OLV (P>0.05).
Conclusion: IL-8 and SP-D levels increase during OLV in thoracic surgical procedures. The implementation of LPV during OLV can reduce airway pressure during OLV and decrease the release of IL-8 levels even in the post-operative period.

Keywords: Biomarkers of Lung Injury, One Lung Ventilation, Thoracic Surgery

1. Introduction

Cardio-thoracic surgeries, including major and minor lung resection procedures, often require one lung ventilation (OLV) procedure (Durkin et al., 2021). OLV procedure selectively perform ventilation on only one lung while collapsing the other lung, for providing better surgical access and visualization (Ashok & Francis, 2018). While OLV has become a standard practice in these surgeries, it can lead to pulmonary damage due to the complex pathophysiological changes that occur during this procedure (Bender et al., 2018).

Changes in lung physiology during OLV can cause several disturbances in lung homeostasis and lead to pulmonary damage through various mechanism (Bussières & Marques, 2023). Shunting which occurs when blood flow is diverted from the collapsed lung to the single ventilated lung can cause maldistribution of blood supply, oxygen, and nutrients (Durkin et al., 2021). This redistribution of blood may expose the unventilated lung to excessive perfusion and potential lung injury through volume overload mechanisms that contribute to epithelial injury and accumulation of inflammatory mediators (Bussières & Marques, 2023). Another pathophysiological change observed during OLV is the mismatch between ventilation and perfusion. The collapsed lung receives little to no ventilation, while the ventilated lung continues to receive normal blood flow. This ventilation-perfusion mismatch further compromises gas exchange and can contribute to pulmonary damage (Zhang et al., 2023). Additionally, reperfusion injury can occur when the collapsed lung is re-ventilated after surgery. Reintroducing oxygen to a previously collapsed lung can trigger an inflammatory response, leading to oxidative stress and tissue damage (Pan et al., 2018).

During thoracic surgery, there are several parameters that can be monitored and regulated regarding the settings of the lung ventilator to deliver air supply to the lungs, including end-tidal carbon dioxide (EtCO2), peak airway pressure (Ppeak), mechanical power (MP), static compliance (Cstat), fraction of inspired oxygen (FiO2), and driving pressure (DP), the analysis of these parameters and the evaluation of lung damage and associated biomarkers may provide new insights for OLV in the field of lung damage-related parameters (Proudfoot et al., 2011).

Identifying reliable serum biomarkers for the early detection and monitoring of pulmonary damage is crucial for early detection and intervention (Bruinooge et al., 2022). Two potential biomarkers that have been studied are IL-8 and sulfactant protein D (SP-D) (Gaunsbaek et al., 2013). IL-8 is a pro-inflammatory cytokine that plays a significant role in neutrophil recruitment and activation during inflammation (Y. Yang et al., 2020). Elevated levels of IL-8 with neutrophil hyperactivation have been observed in various inflammatory lung diseases, including acute respiratory distress syndrome (ARDS) that associated with disease severity and pulmonary damage (Cesta et al., 2022).

IL-8 can be detected in serum as a systemic inflammation markers and may serve as a potential biomarker for the early detection of lung damage following cardio-thoracic surgeries with OLV procedures (Breunig et al., 2011). SP-D, a collectin protein primarily produced by alveolar type II cells in the lungs, is involved in the innate immune response and surfactant function (Carreto-Binaghi et al., 2016). Moreover, it has also reported that SP-D exhibit protective activity towards lung injury and inflammation (Elmore Alyssa et al, 2023). Studies have shown that decreased serum levels of SP-D are associated with pulmonary damage as the alveolar damage could cause extravasation of various proteins from alveolus to the systemic circulation, making it a potential diagnostic marker for assessing pulmonary complications after cardio-thoracic surgeries with OLV procedures (Imtiazul et al., 2019). Early detection of lung injury could help clinicians monitor patient's condition and provide a prompt treatment to decrease further morbidity.

This research aims to evaluate IL-8 and SP-D potential as serum biomarkers for pulmonary damage after cardio-thoracic surgeries, with OLV procedures and assess the potential clinical applications of these biomarkers in pulmonary complications early detection.

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2. Methodology

a. Study Design

This study aimed to investigate the potential of IL-8 and SP-D as serum biomarkers to assess pulmonary damage following cardio-thoracic surgery, in patient undergoing lung resections performed with one lung ventilation (OLV) procedure for 2 hours. The study design involved a prospective observational study conducted at Dr Soetomo Hospital Surabaya between July 2023 and September 2023.

b. Participants

This study involved 30 patients who underwent thoracotomy and video-assisted thoracic surgery (VATS) performed with OLV, however 2 patients were excluded from the study due to the deterioration of clinical state and desaturation during surgery. Participants were selected based on inclusion criteria of being older than 18 years old, patient with American Society of Anesthesiologists Physical Status (PS ASA) II-III (Horvath et al., 2021), absence of pre-existing lung diseases, and consent to participate in the study), and exclusion criteria of comorbidity (immune system disorder, congestive heart failure, hemodynamic instability during surgery, severe renal impairment, and COPD), pregnancy, and the history of previous pulmonary lobectomy.

c. Patient Data Collection

Patient profile was retrieved from medical record, anamnesis, and physical examination, whereas serum specimen was collected with three time points before initiation of OLV (T0), 2 hours post-OLV (T1), and 24 hours post-surgery (T2). Patient characteristic data including age, sex, body mass index, comorbid, diagnosis, medical history, PS-ASA category, and baseline pulmonary function tests was obtained. Intraoperative data consisted of surgery type, surgery duration, OLV duration, anaesthesia, compliant stasis, driving pressure, mechanical power and intraoperative complications (Li et al., 2022).

d. Serum Biomarker Analysis

IL-8 and SP-D was measured using ELISA from serum specimens separated from venepuncture blood specimen using serum separator tube. Blood samples were collected from each participant at different time points, including pre-OLV as baseline (T0), 2 hours post-OLV (T1), and 24 hours postoperative (T2). Serum IL-8 and SP-D levels were measured using ELISA Kit, following the protocol provided. IL-8 and SP-D levels were measured using an ELISA reader, and absorbance of each ELISA reaction was plotted to standard curve to obtain serum concentration of IL-8 and SP-D (Ishikawa et al., 2015).

e. Statistical Analysis

Descriptive statistics were used to summarize the patient characteristics whereas SPSS 24.0 assisted data analysis was performed to assess data normality (Shapiro-Wilk) before proceeded to comparative and correlation study. The ANOVA test was used to compare parameters between groups with normal distribution and Friedman test was used to analyse non-normally distributed data. Spearman and Pearson correlation analysis was performed to assess correlation of lung function parameters, IL-8 and SP-D. Statistical significance was set at $p < 0.05$ (Mishra et al., 2019).

f. Ethical Clearance

Institutional review board of Dr Soetomo Ethical Committee approval was obtained prior to the commencement of the study (Ethical clearance Number.0695/KEPK/VI/2023). Informed consent was obtained from the entire participants before their participation in the study.

3. Results and Discussion

a. Respondent Characteristic

The study subjects were patients who underwent thoracotomy and video-assisted thoracic surgery (VATS) with one lung ventilation (OLV) approach and met the inclusion and exclusion criteria. The study was conducted in the thoracic surgery operating room of the integrated central surgical building of Dr. Soetomo Hospital Surabaya in July 2023 to September 2023. The number of patients who participated in the study was 28 people, namely the proportion of male subjects as many as 21 (75%) and female as many as 7 (25%) with an average subject age of 42.89 years. A total of 25 subjects (89%) had comorbidities, the most comorbidity was lung tumors (Cesta et al., 2022) followed by pulmonary TB (Gaunsbaek et al., 2013). All subjects were measured for hemodynamics, ventilation and oxygenation parameters, ventilator settings and airway pressure. Blood collection for measurement of IL 8 and SP-D levels was done three times, first before OLV, second 2 hours after OLV and finally 24 hours postoperatively.

Table 1. Demographic Characteristics Data of Patients Undergoing OLV

VARIABLE	SAMPLE (N = 28)	NORMALITY
Age, years mean (SD)	42,89 (15,9)	0.130
Body Mass Index, kg/m^2, mean (SD)	20,84 (3,08)	0.700
Duration of surgery, minutes, mean (SD)	227.25 (58.56)	0.293
OLV duration, minutes median (IQR)	226.5 (120 – 225,0)	0,018
Gender n (%) Male Female	 21 (75%) 7 (25%)	
Comorbidities n (%) Lung tumor Pulmonary TB Hypertension DM Pleural effusion None	 11 (39,3%) 9 (32,1%) 2 (7,1%) 1 (3,6%) 2 (7,1%) 3 (10,7%)	
Diagnosis n (%) Pneumothorax Empyema Lung Tumor Other	 7 (25%) 4 (14,3%) 13 (46,4%) 4 (14,3%)	
PS ASA n (%) II (two) III (three)	 11 (39,3%) 17 (60,7%)	
Surgery method n (%) Thoracotomy VATS	 19 (67,9%) 9 (32,1%)	
Pain management n (%) Epidural SAP block Intravenous	 18 (64,3%) 8 (28,6%) 2 (7,1%)	

Normality test with Shapiro-wilk

A national population-based cohort study in Taiwan revealed similar results, with a higher proportion of male patients undergoing surgery with one-lung ventilation (OLV). The mean age of the subjects in this study was 43 years, indicating a relatively young and productive age group, and the mean BMI was within the normoweight range (20.8 kg/m2). It is noteworthy that cytokine concentrations tend to increase with age, particularly for IL-6, IL-8, IL-2, IFN-γ, and TNF-α. Moreover, elevated concentrations of IL-6, TNF-α, IL-10, and IFN-γ have been associated with overweight and obesity (BMI above 25) (Koelman et al., 2019).

The most prevalent diagnosis among the subjects was lung tumor (46.4%), aligning with Global Burden of Cancer (GLOBOCAN) 2020 data, which ranks lung cancer as the 3rd most common cancer (11.4%) and the most prevalent in men. Lung cancer is also the leading condition treated by thoracic surgeons in America (Byrd et al., 2022). Pulmonary tuberculosis (TB) was the next most common comorbidity (32%) after lung tumors. Notably, Indonesia has a high prevalence of pulmonary TB, the national data reporting an incidence of 321 cases per 100,000 population. Considering innate and adaptive immunity, pro- and anti-inflammatory cytokines play a significant role in immune cell differentiation, inflammation, angiogenesis, tumorigenesis, atherosclerosis, cancer, and aging (Liu et al., 2021).

In the study, the duration of surgery exhibited a normal distribution with a mean of 227 minutes, while the OLV duration had an abnormal distribution with a median value of 226.5 minutes (70.0 - 225.0). Thoracotomy was performed more frequently than video-assisted thoracoscopic surgery (VATS) (19/9 patients). The Lin et al study also yielded similar results in the duration of operating time (230 minutes), but the OLV technique duration was shorter at 142 minutes in the protective ventilation group. The primary postoperative pain management method was epidural regional anesthesia, recognizing that pain is one of the factors contributing to an increase in inflammatory mediators (Liu et al., 2021).

b. Difference in IL-8 and SP-D levels at different time course (T0, T1 and T2)

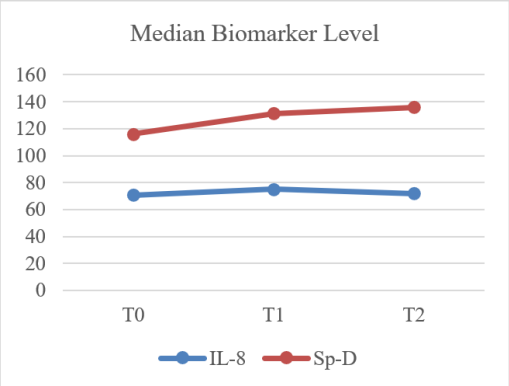

Figure 1. Graph of median IL-8 and SP-D levels at T0, T1 and T2

Differences in serum levels of IL-8 and SP-D in subjects were assessed before one-lung ventilation (OLV) (T0), two hours after OLV (T1), and 24 hours postoperatively (T2), as illustrated in Table 2. Since IL-8 and SP-D levels exhibited an abnormal distribution, the results are presented using the median (Figure 1).

Table 2. IL-8 levels at T0, T1 and T2

Parameter	**T0 median (min-max)**	**T1 median (min-max)**	**T2 median (min-max)**
IL-8 ng/L	70.9 (8,9- 233.10)	75.1[a] (27,4- 243.30)	71.35[b] (21-230)
SP-D ng/ml	115,9 (35.8-333.2)	131,1[a] (64,3 – 339,3)	135,8[b] (43.2-385,8)

Wilcoxon signed rank test, aT0 vs T1: $p < 0.05$, bT0 vs T2: $p > 0.05$ and T1 vs T2: $p > 0.05$.

This study employed the Wilcoxon signed-rank test to evaluate differences in IL-8 levels at various measurement times (Table 2), obtaining a p-value of 0.033 for T0 compared to T1, a p-value of 0.084 for T0 compared to T2, and a p-value of 0.633 for T1 compared to T2. These results indicate a significant difference in IL-8 levels between the T0 and T1 measurement times. Similar findings were observed for the difference in SP-D levels, revealing a significant distinction at the measurement time of T0 and T1 with a p-value of 0.018. However, no meaningful results were obtained at the time of measurement for T0 compared to T2 (p-value = 0.212) and T1 compared to T2 (p-value = 0.699).

Initial measurements revealed that SP-D levels were influenced by age, with higher age corresponding to elevated SP-D levels. A similar trend was observed in IL-8 levels, which tended to increase with age. These findings align with Koelman's study, where cytokine concentrations, including IL-6, IL-8, IL-2, IFN-γ, and TNF-α, increased with age, showing no significant association with metabolic phenotypes (Koelman et al., 2019). Aging is characterized by systemic chronic inflammation, cellular aging, immune system aging, organ dysfunction, and age-related diseases. The cytokine increase serves as a positive response to maintain homeostatic stability; however, as age advances, imbalances arise, leading to a 2- to 4-fold increase in cytokine responses mediated by the chronically activated innate immune system (Li et al., 2022).

The second measurement indicated an increase in IL-8 and SP-D levels 2 hours after one-lung ventilation (OLV), likely due to changes in perfusion/ventilation ratios in the non-dependent lungs. The automatic compensatory response and hypoxia trigger pulmonary vasoconstriction (HPV), redirecting pulmonary capillary blood flow to areas with high oxygen to optimize gas exchange. OLV activated the inflammatory response with the release of inflammatory mediators, predominantly occurring in the dependent lung (Fiorelli et al., 2018). This study utilized IL-8 and SP-D as inflammatory biomarkers reflecting lung injury, and there was an increase in measurements 2 hours post-OLV. Statistical analysis was then conducted to assess the significance of cytokine changes at each examination time, revealing a significant difference in IL-8 levels between T0 and T1 (P = 0.03), but no significant differences between T0 and T2 (P = 0.084) and T1 and T2 (P = 0.633). The study demonstrated that employing protective methods during surgery, such as setting OLV tidal volume at 5 mL/kg PBW, effectively reduced airway pressure and resistance, increased pulmonary compliance, and mitigate proinflammatory released and inflammatory responses. These findings support the successful implementation of protective measures during surgery.

In the third measurement, conducted 24 hours after surgery, there was a decrease in the levels of both cytokines. Previous research by Lin, which assessed the difference in IL-8 and IL-6 levels between protective ventilation and conventional ventilation groups, yielded different results. In Lin's study, there was an increase in the levels of both inflammatory cytokines at 2 hours and 24 hours after one-lung ventilation (OLV) in both groups (Lin et al., 2008). It is important to note that, in addition to protective mechanisms, various factors can influence the increase in inflammatory mediators, as previously discussed. IL-8 is recognized as a potent chemoattractant, specifically for neutrophils. Some cells in the pleural cavity release IL-8, and this chemokine plays a crucial role in neutrophil migration and activation. IL-8 is a proinflammatory cytokine with elevated plasma and bronchoalveolar lavage fluid (BALF) levels early in acute lung injury (ALI). Ventilation using low tidal volumes is associated with a more rapid decline in IL-8 levels (Bhargava & Wendt, 2012).

The air-blood barrier, which separates air and blood, comprises three main layers: the alveolar epithelium, the interstitial space (including the basement membrane), and the blood vessels (including the endothelium). SP-D serves as a specific marker for alveolar, bronchial, and endothelial damage in the lung. Produced by type II pneumocytes, SP-D is secreted into the surfactant layer of the alveoli. When the alveolar air-blood barrier is compromised, SP-D enters the circulation and can be detected in plasma. The loss of air-blood barrier integrity leads to intravascular leakage of secreted pulmonary proteins into the surrounding environment and the influx of edema into the interstitium and air spaces. Lung injury and inflammation impact the secretion of surfactant proteins from lung epithelial cells into the

bloodstream (Murray et al., 2019).

The detection of such proteins at high concentrations in plasma or serum may indicate abnormalities in the lung epithelial/air-blood barrier. The SP-D concentration gradient allows SP-D, synthesized in the respiratory tract, to leak into the bloodstream in cases of acute and chronic lung injury (Sorensen, 2018). Recombinant SP-D significantly downregulates the mRNA levels of pro-inflammatory mediators such as TNF-α, interleukin-1 (IL-1), IL-6, and IL-8. In a lung injury model induced by LPS and lipoteichoic acid (LTA) treatment, intratracheal administration of recombinant SP-D prevented the manifestation of lung inflammation, including neutrophil infiltrates. Recombinant SP-D also reduced neutrophil counts and neutrophil elastase activity in BALF and lung tissue (Elmore Alyssa et al, 2023). This may elucidate why SP-D levels persist in the blood while IL-8 levels tend to decrease in acute lung injury.

c. Comparison of respiration variables during TLV and OLV

This study evaluated the values of EtCO2, Ppeak, Cstat, FiO2, driving pressure, and mechanical power as respiratory variables during surgery. The statistical analysis revealed a significant difference in the values of Cstat ($p = 0.001$) and FiO2 ($p = 0.005$) before and after one-lung ventilation (OLV) (Table 3). During OLV, lung protective ventilation (LPV) was implemented with a tidal volume (TV) of 5 ml/kg predicted body weight (PBW), resulting in a decrease in the value of Cstat compared to two-lung ventilation (TLV) [31.2 (11.3 - 56.25) and 24.6 (10.8 - 34.4)]. It's worth noting that some samples in this study exhibited poor dependent lung compliances, leading to Cstat < 20 ml/cmH2O with a high driving pressure when OLV was performed.

Table 3. Comparison of respiration variables during the duration of surgery

Variable	TLV	OLV	*p* Value
$EtCO_2$ mmHg	36,3 (3,2)	36,4 (4,9)	0,101[a]
Ppeak cmH_2O	23,8 (4,2)	25,6 (3,8)	0,557[a]
MP J/min	12,1 (2,84)	11,2 (2,29)	0,176[a]
Cstat ml/cmH_2O	31,2 (11,3 – 56,25)	24,6 (10,8 – 34,4)	0,001[b]
FiO2 %	50 (30-80)	60 (35-100)	0,005[b]
DP cmH_2O	13 (8 – 23)	13 (9-23)	0,419[b]

a: Independent T test, b: Mann-whitney U

When lung volume exceeds Functional Residual Capacity (FRC), pulmonary vascular resistance (PVR) increases linearly with lung volume. Tidal volume also affects lung tension. Xie et al. have noted that the presence of critical conditions, such as a driving pressure >15 cmH2O and low compliance, actually reflects the patient's state. Tidal volume should be adjusted based on individual respiratory strain and compliance. In ARDS patients, respiratory system compliances are closely linked to tidal volume, lung tension, and driving pressure. In ARDS, the small lungs are not rigid; this condition is analogous to a "baby lung." In patients with low respiratory system compliance, an increase in tidal volume is more likely to cause lung injury. Thus, it is more reasonable to target tidal volume based on decreasing driving pressure (Hidayati et al., 2021).

There were differences in FiO2 values during Two-Lung Ventilation (TLV) and One-Lung Ventilation (OLV) with a mean of 50% (30-80%) vs. 60% (35-100%). This discrepancy was due to the prevalence of atelectasis in ventilated lungs during OLV. Atelectasis predisposes patients to lung injury due to compromised compliance and deteriorating lung oxygenation, necessitating greater ventilatory pressure and increased FiO2 (Durkin et al., 2021). During OLV, the collapsed lung continues to be perfused in the absence of ventilation, leading to increased intrapulmonary shunts (20-30%) and ventilation/perfusion mismatch (V/Q mismatch). Additionally, the lateral decubitus position results in the mixing of

unoxygenated blood with oxygenated blood from the dependent lung, widening the (A-a) O2 gradient and causing hypoxemia (5%-10%) (Végh et al., 2013).

In this study, a low tidal volume was used during OLV, and alveoli opening was maintained with a Positive End-Expiratory Pressure (PEEP) of 5 cmH2O. Low tidal volume can lead to atelectasis, premature alveolar closure, or other complications, especially during open chest surgery and when patients are placed in the lateral position. PEEP has been reported to be effective in preventing alveolar collapse and atelectasis, maintaining alveoli open at the end of respiration and allowing the reopening of collapsed alveoli (Lin et al., 2008). Lung protective ventilation was applied in this study, and the driving pressure did not differ during TLV and OLV, with a median of 13 (8-23) and 13 (9-23) cmH2O (P=0.419). This differs from the study by Blank et al., who observed driving pressure during TLV as 13.9 (5.0) and during OLV as 17.5 (5.7) cmH2O. The difference is attributed to patients receiving tidal volumes exceeding 5, 6, 7, and 8 ml/kg PBW (73.3, 43.3, 18.8, and 7.2%, respectively). Driving pressure was found to be a risk factor for the development of secondary outcomes (OR, 1.034; 97.5% CI, 1.001 to 1.068), with each 1 cmH2O increase associated with a 3.4% rise in the risk of postoperative complications and morbidity (Blank et al., 2016).

The applicability of LPV is also reflected in the Mechanical Power (MP) values, which did not differ between the TLV and OLV periods, with means of 12.1 (2.84) and 11.2 (2.29) J/min (P = 0.176). Clinical observational data on ARDS show that respiratory system energy values greater than 17 J/min are associated with more frequent adverse events (Serpa Neto et al., 2018). During OLV, the incidence of hypoxemia results mainly from the formation of atelectasis in the dependent lung, which increases intrapulmonary shunt and alveolar dead space. Atelectasis can also lead to cyclic collapse and reopening of lung areas, termed atelektrauma. Furthermore, in the presence of atelectasis, tidal volume is distributed across the reduced lung volume, possibly resulting in lung zone hyperdistension or volutrauma. Atelektrauma and volutrauma may increase the energy transfer per time from the ventilator to the lungs (mechanical power), potentially causing ventilator-induced lung injury (VILI) (Wittenstein et al., 2020).

d. Relationship of respiration variables with IL-8 and Sp-D levels during OLV

Analysis was conducted to assess the relationship of respiration variables (Ppeak, driving pressure, mechanical power and number of recruits during OLV) with IL-8 and SP-D levels 2 hours after OLV (T1). From the results of the analysis, there was no correlation between all respiration variables and IL-8 and SP-D levels during the 2-hour OLV (table 4). This is due to the use of LPV during OLV.

Table 4. Relationship between respiration parameters with IL-8 and SP-D levels

Respiration parameters	IL-8 T1	Sp-D T1
Ppeak	0,915[b]	0,545[b]
DP	0,918[a]	0,136[a]
MP	0,392[b]	0,085[b]
Recruitment Maneuvers	0,185[a]	0,998[a]

a: Spearman correlation test, b: Pearson correlation test

Similar results were demonstrated in a study by Yang in thoracoscopic-laparoscopic esophagectomy (TLE) patients. Patients were divided into an intervention group using LPVS and a control group using conventional methods. Measurements were taken to observe respiratory mechanics index, arterial blood gas index, and inflammatory factors at T1 (10 minutes after tracheal intubation), T2 (60 minutes after one-lung ventilation), T3 (end of TLE), and T4 (24 hours after TLE). The results showed that for IL-6, IL8, TNFα, and CRP, the increase from T1 to T2, T3, and T4 was lower in the intervention than the control group, with a higher incidence of pulmonary complications in the control group. LPVS can reduce the increase in respiratory mechanics index, improve oxygenation, and attenuate the

inflammatory response in TLE, which may be helpful in reducing the incidence of pulmonary complications after esophagectomy (L.-X. Yang et al., 2018).

Respiratory compliances are used to measure the size of the expanding lung (change in lung volume), which depends on lung tissue elasticity, elastic force surface tension, surfactant, lung volume, and age. One of the diseases with impaired compliance is chronic obstructive respiratory disease (COPD), in which lung tissue damage occurs, so respiratory compliance increases, causing the lungs to be in a hyperinflated state. Research by Airlangga et al. (2022) found that an increase in SP-D levels was directly proportional to a decrease in compliance in COVID-19 patients (Airlangga et al., 2022). However, in this study, there was no correlation between compliance and SP-D levels because the compliance of the dependent lung during TLV and OLV allows the lung to expand properly in accordance with changes in the volume provided. This is different from COVID-19 patients who have damage to both lungs so that compliance decreases based on the degree of lung damage.

e. Relationship between OLV duration and duration of surgery with changes in IL-8 and SP-D levels

The variables of OLV duration and duration of surgery were associated with changes in IL-8 and SP-D levels during OLV up to 24 hours postoperatively. The results of statistical analysis using the Spearman test showed no relationship between the duration of OLV and the duration of surgery with changes in IL-8 and SP-D levels during OLV up to 24 hours postoperatively with a p-value > 0.05 (Table 5). The duration of OLV in this study had a median value of 226.5 minutes (70.0 - 225.0). In this study, there was also no association between the method of surgery and IL-8 and SP-D levels. This result may be explained by the fact that the increase in cytokines during OLV can be maintained by the application of protective ventilation methods. This was considered effective enough to maintain oxygenation without posing a significant risk of lung damage during OLV. Inflammatory mediators begin to increase after one hour of OLV use. The duration of OLV is one of the main factors that determine the pulmonary inflammatory response, and the pulmonary inflammatory response correlates with the duration of OLV, as obtained in several studies.

Table 5. Relationship between OLV duration and duration of surgery with changes in IL-8 and Sp-D levels

Variable	Δ IL-8 (T0-T2)	Δ IL-8 (T1-T2)	Δ Sp-D (T0-T2)	Δ Sp-D (T1-T2)
OLV Duration	0,706	0,825	0,228	0,237
Duration of Surgery	0,615	0,747	0,554	0,275

Spearman correlation test

In Fiorelli's study, the average duration of OLV was 64.44 ± 21.68 minutes, indicating that the level of Bronchoalveolar Lavage (BAL) cytokines after surgery did not show a significant increase post-OLV. This can be explained by the short duration of OLV (64.44 ± 21.68 minutes), which may account for the absence of inflammatory mediator production in this experiment (Fiorelli et al., 2018). In the study by Komatsu in 2012, IL-8 levels were measured at four time points: after the induction of anesthesia, 30 minutes after OLV began (point 2), just before resuming TLV (point 3), and 30 minutes after TLV (point 4). These measurements were associated with clinical factors such as the duration of anesthesia, surgery, and OLV. The results demonstrated a significant correlation between IL-8 levels in the epithelial lining fluid (ELF) just before TLV and the duration of OLV. IL-8 levels, both in plasma and ELF, were highest just before TLV. The duration of OLV in this study was 213±45 minutes. These findings suggest that surgical stimuli or anesthetic procedures may be responsible for stimulating IL-8 production (Komatsu et al., 2012).

f. Study Limitations

This study had several limitations, including the single-center design and relatively small sample size with specific morbidity. The generalizability of the findings may be limited to similar patient populations and surgical settings. Additionally, the measurement of IL-8 and SP-D levels as serum biomarkers may be influenced by various factors, such as sample processing and storage conditions, which could introduce variability in the results.

4. Conclusion

According to the findings and analysis presented, it was evident that there exist variances in the levels of IL-8 and SP-D between the two lung ventilation (TLV) period and the period of 2 hours following one lung ventilation (OLV). However, no significant correlation was observed between static compliance, driving pressure, and mechanical power with IL-8 and SP-D levels during the OLV period. The implementation of lung-protective ventilation (LPV) during OLV did not result in an elevation of lung damage biomarkers

(IL-8) until the postoperative period.

To further investigate this matter, it is suggested that future research should focus on measuring biomarkers of lung damage using samples of bronchoalveolar lavage fluid (BALF) obtained from both the dependent and non-dependent lung. Additionally, employing a larger sample size and utilizing a more homogeneous sample with a consistent type of diagnosis and surgery would enhance the validity of the study. Notably, this study identified an increase in SP-D levels 24 hours after the operation, indicating the need for further investigation to evaluate postoperative pulmonary complications following OLV.

5. Authors' Contribution

NR: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. PSA, BPS, KHS, PS & M: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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