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Original Research Article

CORRELATION OF IL-1β LEVEL AND BODY TEMPERATURE TO THE SEVERITY OF ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) AND MORTALITY IN COVID-19 PATIENTS

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ABSTRACT

Introduction: IL-1β and IL-6 are cytokines that have major roles in cytokine storms and endogenous pyrogens. Several studies have also displayed the effectiveness of IL-1β inhibitors in COVID-19 patients in minimizing severity and mortality. **Objective:** This study aims to analyze the correlation between IL-1β and body temperature with ARDS severity and mortality in COVID-19 patients. **Methods**: This is an analytical observational study with a prospective cohort design. A total of 54 patients have met the inclusion criteria from July to September 2020. This study mainly applied the Spearman-Rho, Mann Whitney, free sample T2 test, and Chi-Square test. **Results**: The correlation between body temperature and IL-1β levels in COVID-19 patients with ARDS did not show a statistically significant difference towards mortality and ARDS severity, as shown by the *p*-value > 0.05 in the analysis tests of each of the variables studied. Nonetheless, the occurrence of ARDS ($p = 0.022$), the severity of ARDS ($p = 0.001$), application of mechanical ventilation ($p = 0.00$), secondary infection ($p = 0.00$), and length of stay ($p = 0.042$) were found to be statistically significant towards COVID-19 patients' mortality. **Conclusion**: Body temperature does not correlate with the occurrence of ARDS, the severity of ARDS, mortality, and IL-1β levels. IL-1β levels and transformation in IL-1β levels also do not correlate with mortality as well as the occurrence and severity of ARDS, but the use of mechanical ventilation, secondary infection, and length of stay were correlated with mortality in COVID-19 patients.

Keywords: ARDS; COVID-19; Fever; IL-1β; Mortality; Severity

ABSTRAK

Pendahuluan: IL-1β dan IL-6 merupakan sitokin yang berperan besar dalam badai sitokin dan pirogen endogen. Beberapa penelitian memperlihatkan efektivitas inhibitor IL-1β pada pasien COVID-19 dapat mengurangi keparahan dan kematian. **Tujuan:** Penelitian ini bertujuan untuk mempelajari hubungan kadar IL-1β dan suhu tubuh dengan tingkat keparahan ARDS dan mortalitas pada pasien dengan COVID-19. **Metode**: Penelitian ini merupakan studi observasional analitik dengan desain kohort prospektif. Sejumlah 54 pasien memenuhi kriteria inklusi dan eksklusi dari Juli sampai September 2020. Studi ini menggunakan uji analisis Spearman-Rho, Mann Whitney, uji T2 sampel bebas, dan Chi-Square. **Hasil**: Hubungan suhu tubuh dan kadar IL-1β pada pasien COVID-19 dengan ARDS tidak memiliki kemaknaan secara statistik terhadap mortalitas dan keparahan ARDS. Hal ini terlihat dalam uji analisis pada setiap variabel yang diteliti dimana nilai $p > 0,05$. Meskipun begitu terjadi nya ARDS (p 0,022), tingkat keparahan ARDS (p 0,001), penggunaan ventilasi mekanik (p 0,00), infeksi sekunder (p 0,00) dan lama perawatan (p 0,042) secara statistik bermakna terhadap mortalitas pada pasien COVID-19. **Kesimpulan**: Suhu tubuh tidak berkorelasi terhadap terjadi nya ARDS, tingkat keparahan ARDS, mortalitas, dan kadar IL-1β. Kadar IL-1β dan perubahan kadar IL-1β tidak berkorealsi dengan mortalitas, kejadian dan tingkat keparahan ARDS; tetapi penggunaan ventilasi mekanik, infeksi sekunder dan lama perawatan berkorelasi dengan mortalitas pasien COVID-19.

Kata Kunci: ARDS; COVID-19; Demam; IL-1β; Mortalitas; *Severity*

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INTRODUCTION

At the end of December 2019, several patients in Wuhan China were hospitalized with an initial diagnosis of pneumonia whose cause was still unknown. The patients were linked to a fish market in Wuhan. Then, on February 11, 2020, the WHO determined that the cause of pneumonia cases in Wuhan was a new type of coronavirus, which was later named COVID-19, as it was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (1).

A study of the risk factors associated with the incidence of Acute Respiratory Distress Syndrome (ARDS) and death in patients with COVID-19 stated that high fevers of above 39.0ºC were also associated with the incidence of ARDS. The study also suggested that fever was associated with better outcomes (2). The Infectious Disease Society of America defines a fever as a core body temperature of 38.3ºC or more. High temperatures can provide a protective mechanism effect because pathogens often show optimal replication at temperatures below 37.0ºC, therefore an increase in body temperature by the host can inhibit the reproduction of pathogens. In addition, increased body temperature is associated with increased innate immunity and is associated with microbial and viral destruction. However, temperatures of over 40.0ºC could increase mortality (3). A study showed that in the early stages of ARDS, specifically in the acute phase, fevers are associated with increased survival rates, but it is still unclear whether the beneficial effect of fevers is due to the adequate levels of acute-phase proteins or the fever itself (4).

The interaction between exogenous pyrogens (e.g., microorganisms) or endogenous pyrogens such as interleukin-6 (IL-6), IL-1, tumor necrosis factor (TNF)-α, with organum vasculum in the *lamina terminalis* (OVLT) causes fever production. This is a pro-inflammatory cytokine that is most relevant to the acute phase response process. The pro-inflammatory IL-1 is IL-1α and IL-1β, especially IL-1β (5). IL-1β is never produced by healthy individual cells. In addition to triggering fever in the hypothalamus, IL-1β is secreted by dead cells by the process of pyroptosis (6). Additionally, IL-1β and IL-6 are cytokines that are overproduced and cause hyper inflammation in COVID-19 (7). A 2020 study of cytokine levels in a COVID-19 case showed that IL-1β levels were higher in patients with COVID-19 than in healthy subjects and that it was also higher in COVID-19 patients that were admitted to the ICU than in those without ICU admission (8). Several studies have also shown the effectiveness of IL-1β inhibitors in COVID-19 patients to reduce severity and mortality (9,10).

Conversely, many studies have shown that the role of IL-1β as a pro-inflammatory cytokine in COVID-19 is not significant enough compared to IL-6 or TNF- (11–13). Therefore, this study aims to examine the relationship between IL-1β levels and body temperature with the severity of ARDS and mortality in patients with COVID-19 and whether fevers could provide better outcomes in these patients.

METHODS

This is an analytical observational study with a prospective cohort design. The study's population are COVID-19 patients who were treated in the Special Isolation Room of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The research samples were collected from the population according to several inclusion and exclusion criteria from

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July to September 2020. It was found that 55 patients met the inclusion criteria. However, 1 patient dropped out due to sample errors, so this study used the data of 54 patients. The inclusion criteria in this study were adult patients (above 19 years), patients with clinical symptoms of COVID-19, have tested positive for COVID-19 and confirmed twice by RT-PCR results from nasopharyngeal swab tests, willingness to participate in the study, was receiving treatment according to standard protocol, and met the ARDS criteria based on the Berlin criteria. The exclusion criteria in this study were patients with HIV or other immunocompromised diseases, patients with a history of autoimmune disease or receiving immunosuppressant therapy, patients with malignancy, surgical or perioperative patients, patients who were pregnant, or was in the puerperium period.

Patients who met the inclusion criteria were recorded and a medical history check was conducted regarding the patients' history of fever and the first onset of symptoms. If they had a history of fever, the date of the patient's arrival to the hospital and the number of days of fever was recorded. A thorough physical examination was then performed, the core temperature was measured on arrival with a tympanic membrane thermometer, using infrared Braun Thermoscan 7 IRT 6520. Peripheral blood sampling for IL-1β examination was performed on arrival (H-0 treatment) and was repeated on the 6th day of treatment. The sample was then analyzed by using the CBA technique (Cytometric Bead Array). If there is a history of using antipyretic drugs, then the blood samples and temperature re-measurements were carried out at least 6 hours after the antipyretic drug administration. During treatment, core temperature was measured in the morning (basal temperature) according to the circadian cycle and repeated every shift (3 times a day). Temperature measurement was performed through the ear (tympanic membrane) by inserting a thermometer probe into the ear, making sure that the ear is not covered with cerumen. The otoscope maneuver was conducted, namely pulling the earlobe up and back until the entire ear canal is visible, then the entire thermometer probe is inserted into the ear canal in the direction of the corner of the eye until a sound is heard (5 seconds). The increase in body temperature between when the patient first arrived at the hospital and during treatment was recorded. The condition of secondary infection is evidenced by the examination of culture specimens.

The research was conducted from July 2020 until August 2021. Thus, this research was carried out for approximately one year. The research was conducted in the COVID-19 special treatment room at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, and the Clinical Pathology and Microbiology Laboratory of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

RESULTS AND DISCUSSION

A total of 55 people met the inclusion criteria in this study, but 1 patient was dropped out due to a sampling error. Therefore, the remaining 54 subjects were included in this entire study. In general, the subjects of this study have the characteristics listed in table 1.

Most of the subjects in this study were male patients (34 people or 63%), with an age range of 25 years to 73 years and a median age of 50.5 years. A total of 35 patients had comorbidities (64.8%), with the highest number of comorbidities being hypertension (31.5%) and Diabetes Mellitus (25.9%), obesity (13%), the remaining comorbidities were less than 10%. Most of the patients also

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had a history of fever before entering the hospital (41 people or 75.9%).

Table 1. Demographics and Patient Characteristics.

Variable	N (%)	Median (*Range*)	*Mean* ± SD
Age (years)	54 (100%)	50.5 (25 – 73)	48.93 ± 11.535
Gender			
Male	34 (63%)	-	-
Female	20 (37%)		
Initial SOFA Score	54 (100%)	2.0 (0 – 3)	1.69 ± 0.609
The onset of Symptoms (days)	54 (100%)	7 (1 – 15)	7.13 ± 3.561
ARDS			
Have	37 (68.5%)	-	-
Not have	17 (31.5%)		
Comorbid			
Have	35 (64.8%)	-	-
Not have	19 (35.2%)		
Comorbid Type			
Hypertension	17 (31.5%)	-	-
Diabetes Mellitus	14 (25.9%)		
Obesity	7 (13%)		
Asthma	1 (1.9%)		
Coroner Heart Disease	1 (1.9%)		
COPD	1 (1.9%)		
CVA	1 (1.9%)		
Chronic Hepatitis B	1 (1.9%)		
HBsAg reactive	1 (1.9%)		
BMI (kg/m^2)	54 (100%)	25.71 (20.44 – 48.07)	26.56 ± 9.96
Highest temperature (^{o}C)	54 (100%)	38.15 (36.8 – 39.6)	38.29 ± 0.70
History of Fever			
Have	41 (75.9%)	-	-
Not Have	13 (24.1%)		
Secondary Infection			
Have	20 (37%)	-	-
Not Have	34 (63%)		
Use Mechanical Ventilation			
Have	12 (22.2%)	-	-
Not Have	42 (77.8%)		
Severity level of ARDS			
Mild	6 (11.1%)	-	-
Moderate	21 (38.9%)		
Severe	10 (18.5%)		
Mortality			
Death	10 (18.5%)	-	-
Live	44 (81.5%)		
Length of Stay (days)	54 (100%)	20 (8 – 69)	21.8 ± 13.10
IL-1β (pg/ml)	54 (100%)	2.48 (0.61 – 47.02)	6.49 ± 8.94

*In general, patients have more than 1 comorbidity. Categorical data uses percentages, numerical data uses median and mean ± SD.

The onset of symptoms varied from 1 day to 15 days with a median of 7 days, while the length of stay was 8 to 69 days with a median of 20 days. The Sequential Organ Failure Assessment (SOFA) score taken during the patients' arrival ranged from 0 to 3 with a median of 2. The patient with the lowest BMI recorded was at 20.44 kg/m2 and the highest was 48.7 kg/m2. The patient with the lowest temperature measured was at 36.8^o C and the highest was 39.6^o C. ARDS patients were categorized according to the Berlin criteria as mild, moderate, and severe. Most of the patients came with moderate severity of ARDS at 21 people (38.9%), followed by severe ARDS at 10 people (18.5%) and mild ARDS at 6 people (11.1%). The total number of ARDS patients was 37 people. The lowest

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IL-1β measurement obtained was 0.61 pg/ml and the highest was 47.02 pg/ml.

During treatment, 20 people (37%) had a secondary infection (secondary bacterial infection evidenced by culture results, bleeding, and blood clotting disorders), and other complications, of the 20 patients, 12 (22.2%) used mechanical ventilation, and 10 (18.5%) died. Furthermore, as many as 41 people (75.9%) had clinical symptoms of fever, followed by shortness of breath (68.5%), dry cough (59.3%), and the rest complained of runny noses, nausea, and vomiting, decreased appetite, cough with sputum, anosmia, diarrhea, sore throat, fatigue, abdominal pain, muscle pain, chest pain, headache, loss of consciousness, hemiparesis, and loss of sense of taste.

Table 2. Clinical Signs and Symptoms.

Clinical Symptoms	N (%)
Fever	41 (75.9%)
Shortness of breath	37 (68.5%)
Dry Cough	32 (59.3%)
Rhinorrhea	10 (18.5%)
Nausea and vomiting	7 (13%)
Decreasing of Appetite	7 (13%)
Cough with sputum	9 (16.7%)
Anosmia	6 (11.1%)
Diarrhea	4 (7.4%)
Sore Throat	6 (11.1%)
Fatigue	6 (11.1%)
Stomach ache	3 (5.6%)
Muscle pain	3 (5.6%)
Chest pain	2 (3.7%)
Headache	2 (3.7%)
Loss of consciousness	1 (1.9%)
Hemiparesis	1 (1.9%)
Loss of Taste	1 (1.9%)

* Generally, patients have more than 1 clinical symptom, the assessment was done when the patient arrived at the hospital

Table 3. Analysis of the Relationship between Body Temperature and IL-1β with ARDS

	ARDS	N (%)	Median (*Range*)	*Mean* ± SD	*p*
Body Temperature (°C)	Yes	37 (68.5%)	38.5 (37.0 – 39.6)	38.38 ± 0.67	0.146
	No	17 (31.5%)	38.0 (36.8 – 39.6)	38.08 ± 0.73	
IL-1β (pg/ml)	Yes	37 (68,5%)	2,64 (0,61 – 18,42)	5,12 ± 5,14	0,502
	No	17 (31,5%)	2,32 (1,61 – 47,02)	9,49 ± 13,83	

* Analysis using free sample T2 test, significant if p < 0.05

It was found that ARDS patients had a temperature range of 37.0°C to 39.6°C with a median of 38.5°C, while patients without ARDS had a temperature range of 36.8°C to 39.6°C, with a median of 38.0°C. By using the free sample T2 test, a *p*-value of 0.146 was obtained where the *p*-value of < 0.05 was statistically significant. Therefore, the relationship between body temperature and ARDS was not statistically significant.

Moreover, ARDS patients and those without ARDS did not have a significant difference in IL-1β levels. This can be seen from the median value of IL-1β in ARDS patients of 2.64 pg/ml with a range of 0.61 to 18.42 pg/ml and in patients without ARDS of

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2.32 pg/ml with a range of 1.61 to 47.02 pg/ml. By using the Mann-Whitney comparison test, a *p*-value of 0.502 was obtained where the *p*-value of <0.05 was statistically significant. Therefore, the relationship between IL-1β and ARDS was not statistically significant. The IL-1β recording was conducted within the first 24 hours of treatment if the patient had ARDS on that day and at day 6 if there was ARDS between day 2 and day 6 of treatment.

A study with a retrospective cohort design in China was conducted with a sample of 201 patients with an age range of 21 to 83 years and found that the risk factors for ARDS in COVID-19 patients were old age (> 65 years) and high fever (> 39.0^{o}C). Comorbidities such as hypertension and DM, neutrophilia, lymphocytopenia, increased markers of organ failure (Aspartate Aminotransferase (AST), urea, Lactate dehydrogenase (LDH)), increased inflammatory markers (C-Reactive Protein (CRP), serum ferritin), increased coagulation function indicators (PT and D-Dimer) were also significantly associated with a high risk of developing ARDS. Whereas ARDS patients who experience death tend to be related to old age, other comorbidities such as hypertension, methylprednisolone treatment, use of mechanical ventilation, and use of ECMO. Interestingly, this study was stated that patients that had a high fever, although strongly associated with the risk of developing ARDS, were not associated with death (2).

Fever is common in critically ill patients, especially in patients with ALI/ARDS. ARDS is also a frequent complication of heatstroke. A study of the relationship between temperature and ARDS in experimental rats showed that the increase in ambient temperature indicates the condition of Febrile-Range Hyperthermia (FRH), a condition where an increase in core body temperature is equivalent to 2.0^{o}C can significantly increase the occurrence of ARDS. FRH greatly increases the accumulation of pulmonary PMN cells, endothelial dysfunction, and epithelial trauma. These are the three main signs of ARDS in humans. This study showed that FRH amplifies the expression of the chemokine CXC as the promoter of neutrophil cells. This study also emphasized that the FRH model used was not a regulated fever model, as the rapid increase in core body temperature was a result of the acute phase response. The increasing core body temperature in this study was achieved gradually and steadily and without pro-inflammatory signals or other components of the acute phase response (14).

As is known in the pathophysiology of ARDS, the occurrence of ARDS begins with an exudative phase characterized by damage to the alveolar endothelium, epithelial defenses, and accumulation of protein-rich fluid in the interstitium and alveoli mediated by innate immune cells. Macrophages that reside in the alveoli then secrete pro-inflammatory cytokines such as IL-6, IL-1β, TNF, IL-8, and other pro-inflammatory cytokines, which then result in the recruitment of neutrophils and monocytes or macrophages, as well as the activation of alveolar epithelial cells and other proinflammatory cells. T effector cells promote and sustain the inflammatory process and tissue trauma (15). The same pro-inflammatory cytokines also play a role in the mechanism of fever (TNF, IL-6, IL-1β). Therefore, body temperature does not directly cause ARDS or increase the risk of ARDS but it has the same pro-inflammatory cytokine mechanism as ARDS pathogenesis.

The wide standard deviation value may be caused by the wide jump of IL-1β values or other factors that can affect IL-1β levels and cannot be controlled in this study, such as

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heart failure, angina, low serum Ca^{2+} levels, and dyslipidemia (16).

An observational pilot study on the pro- and anti-inflammatory response to severe COVID-19 with ARDS was conducted with a single-center retrospective study method and involved 39 study subjects. They found that their subject's IL-1β levels were below the reference range in COVID-19 patients. In severe cases with ARDS, the levels of IL-6 and CRP massively increased. However, this study had several limitations as only patients with ARDS were found, so it could not compare between those with ARDS and those without ARDS (17).

Another study regarding the evaluation of alpha defensin, IL1Ra, and IL-18 levels in COVID-19 patients with macrophage activation syndrome (MAS) and ARDS involving 100 study subjects was conducted prospectively and found that alpha defensin levels, IL1Ra, and IL-18 levels in patients with COVID-19 were significantly higher in patients who had MAS and ARDS than patients who did not experience MAS and ARDS. The levels of alpha-defensins, IL1Ra, and IL-18 levels with or without MAS or ARDS were higher than the control group, where this control group consisted of 50 asymptomatic health workers with negative routine PCR tests. The IL1Ra levels and IL-18 levels were higher in patients who died. The limitation of this study was that the patients with MAS and ARDS were older and have more comorbidities (18). Moreover, TNF-, IL-1β, IL-6, and IL-8 levels were found to be elevated in bronchoalveolar lavage fluid (BALF) specimens in ARDS patients, not in blood (19).

IL-1Ra is an antagonist of IL-1 where the IL-1Ra protein can exert an inhibitory effect on IL-1α and IL-1β, but IL-1Ra is a natural inhibitor of IL-1β. However, the study by Kerget et al 2021, could not explain the relationship between IL-1β levels and ARDS in patients with COVID-19 (18).

In this study, a total number of 10 patients died, all of whom were patients with ARDS. The body temperature of ARDS patients who died ranged from 37.0°C to 39.5°C, with a median of 38.45°C. The study used a free sample T2 test, the *p*-value of 0.792 was obtained, where $p < 0.05$ was statistically significant. Therefore, the relationship between body temperature and mortality in ARDS patients was not statistically significant. ARDS in patients was determined on the first day of hospitalization and day 6 of treatment. This was done to determine whether there were patients who experienced a change in condition on day 6, from no ARDS to ARDS, between day 2 to day 6 of treatment. The highest body temperature during treatment was used and the measurements were taken by using tympanic membrane temperature.

Table 4. Analysis of the Relationship between Body Temperature and IL-1β with Mortality in Patients ARDS

		ARDS	N (%)	Median (*Range*)	*Mean* ± SD	*p*
Body Temperature (°C)	Yes					
		Non-Survivor	10 (27%)	38.45 (37.00 - 39.50)	38.34 ± 0.80	0.792
		Survivor	27 (73%)	38.50 (37.20 – 39.60)	38.40 ± 0.63	
	No					
		Non-Survivor	0 (0%)	0	0	
		Survivor	17 (100%)	38.00 (36.80 – 39.60)	38.08 ± 0.73	

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	Yes					
IL-1β (pg/ml)		Non-Survivor	10 (27.02%)	2.07 (1.61 – 12.14)	3.28 ± 3.18	0.441
		Survivor	27 (72.97%)	3.63 (0.61 – 18.42)	5.79 ± 5.60	

* Analysis using free sample T2 test, significant if p < 0.05.

No significant difference in IL-1β levels was found in patients who died and survived, with the median value of IL-1β in patients who died 2.07 pg/ml and ranged from 1.61 to 12.14 pg/ml, while in surviving patients the median was 3.63 pg/ml with a range of 0.61 to 18.42 pg/ml. By using the Mann-Whitney comparison test, a *p*-value of 0.441 was obtained where the *p*-value < 0.05 was statistically significant. Thus, the association of IL-1β with mortality in ARDS patients was not statistically significant. The IL-1β recording was conducted in the first 24 hours of treatment if the patient had ARDS on arrival and day 6 if there was ARDS between day 2 and day 6 of treatment.

A study of fever in the ICU as a predictor of mortality in mechanically ventilated COVID-19 patients was performed using a retrospective cohort method involving 103 patients. The results showed that patients who died had higher peak temperatures during their ICU stay compared to patients who survived. Patients whose highest temperature reached 39.5ºC had a 60% higher risk of death and the patients with a temperature reaching 40.0ºC had a 75% higher risk of death. Patients who experienced fever and were treated to achieve normothermia did not have different outcomes compared to patients who did not receive active therapy to achieve normothermia. Another aspect that was listed in this study was that in patients aged over 65 years, the male sex and patients with acidosis at the start of treatment had a higher mortality rate. Nevertheless, this study had several limitations because it was a retrospective study and there was no uniformity in the method of temperature measurement and temperature management (20).

Fever in COVID-19 begins 1 day after the symptom onset and can last up to 12 days in living patients, and 13 days in patients who die (21). A study regarding the risk factors for ARDS in COVID-19 patients was conducted with a retrospective cohort design in China. The sample was 201 patients with ages from 21 to 83 years and showed that although high fever (>39.0ºC) was strongly associated with the risk of developing ARDS, it was not related to the occurrence of death. As many as 73% of ARDS patients who survived had high fever > 39.0ºC, while only 41.2% of ARDS patients who died had high fever > 39.0ºC (2). ARDS is one of the main complications of COVID-19 that causes death.

A review of the febrile cycle as a potential mechanism to protect the respiratory system in COVID-19 patients stated that a low-grade fever (<38.0ºC) due to infection will stimulate a heat shock response (HSR) and lead to the accumulation of heat shock protein (HSP). Among them is HSP70 which belongs to the chaperone family, which has a protective effect and is known to be more effective in young adults than in old age. Using rats with adenovirus to stimulate the formation of HSP70, it was found that HSP70 can effectively protect against sepsis-induced ARDS by limiting the accumulation of neutrophils in the lung. Fever temperature longer than 2 to 3 hours will not cause an increase in the accumulation of heat-shock protein, it will cause degradation and ineffectiveness and cannot prevent apoptosis. Therefore, it is necessary to immediately maintain the body's temperature for several

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hours at normal temperature conditions (37.0ºC) to restore the effectiveness and ability of cells to produce HSP70 again (22).

A previous study on the inflammatory profile associated with higher mortality in COVID-19 patients that involved 41 patients prospectively showed that plasma IL-1Ra levels and IL-8 levels had a positive correlation with mortality in COVID-19 ARDS patients. However, this study still requires further research (23).

Another study of IL-1β blockade with canakinumab in COVID-19 patients involved 88 patients in a prospective observational cohort design and showed an improvement in the PaO2/FiO2 ratio in 45 patients from the baseline with a median of 160 to 237 on day 7 of canakinumab therapy. Canakinumab is a monoclonal IgG antibody that specifically targets IL-1β. This study's result was a *p*-value < 0.0001, thereby indicating that this form of therapy reduces mortality. The drawbacks of this study were the small sample size and limited follow-up for 1 month. Moreover, the patients in this study also received other therapies such as tocilizumab, hydroxychloroquine, and steroids. Steroids in particular was one of the confounding factors. (9).

Table 5. Analysis of the relationship between body temperature and IL-1β with the severity of ARDS

	Severity Level	N (%)	Median (*Range*)	*Mean* ± SD	*p*
Body Temperature (ºC)	Mild	6 (16.22%)	38.05 (37.70 – 38.80)	38.20 ± 0.48	0.05
	Moderate	21 (56.76%)	38.50 (37.00 – 39.50)	38.34 ± 0.76	
	Severe	10 (27.02%)	38.75 (37.8 – 39.6)	38.60 ± 0.57	
IL-1β (pg/ml)	Mild	6 (16.22%)	3.30 (0.61 – 15.92)	5.14 ± 5.58	0.301
	Moderate	21 (56.76%)	2.81 (1.26 – 18.42)	5.87 ± 5.75	
	Severe	10 (27.02%)	2.05 (1.50 – 12.14)	3.52 ± 3.30	

* Analysis using Spearman-Rho correlation test, it is significant if p < 0.05.

The temperatures of patients with mild ARDS were in the range of 37.7ºC to 38.8ºC with a median of 38.05ºC. The body temperature of patients with moderate ARDS was 37.0ºC to 39.5ºC, with a median of 38.5ºC, and the body temperature of patients with severe ARDS was 37.8ºC to 39.6ºC, with a median of 38.75ºC. By using the Spearman-Rho correlation test, a *p*-value of 0.05 was obtained, where a *p*-value <0.05 was statistically significant. Therefore, the relationship between body temperature and the severity of ARDS was not statistically significant. The body temperature used was the highest body temperature recorded during treatment by the tympanic membrane temperature.

Furthermore, the levels of IL-1β at each level of ARDS severity also showed no significant difference. The median value of IL-1β in patients with mild ARDS was 3.30 pg/ml with a range of 0.61 to 15.92 pg/ml. Moderate ARDS patients had a median IL-1β value of 2.81 pg/ml with a range of 1.26 to 18.42 pg/ml. And patients with severe ARDS had a median of 2.05 pg/ml with a range of 1.50 to 12.14 pg/ml. By using the Spearman Rho correlation test, a *p*-value of 0.301 was obtained where the *p*-value <0.05 was statistically significant. Therefore, the relationship between IL-1β with the severity of ARDS was not statistically significant. The IL-1β levels were recorded in the first 24 hours of treatment if the patient had ARDS on that day and also at day 6.

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A 2015 study of body temperature and mortality in patients with ARDS showed that in the early phase of ARDS, fever was associated with increased survival. For every 1.0^{o}C increase in baseline temperature, mortality will decrease by 15%. This study used secondary analysis of body temperature by using data from the National Heart, Lung and Blood Institute and the ARDS network Fluid and Catheter Treatment Trial. The measurement of body temperature was done through the rectal, tympanic, and axillary temperatures of adult patients who meet the ARDS criteria based on the Berlin criteria for 48 hours or less. Mortality was based on 90 days of observation during treatment. However, this study has some limitations, there was a lack of standardized body temperature measurement methods and a lack of information or data on unit-based protocols for treating hypothermia and fever, which can vary widely (4). However, this study did not analyze the severity of ARDS.

Table 6. Analysis of Changes in IL-1β on Mortality in ARDS Patients

ARDS	N (%)	*p*
Non-Survivor		
Increasing ΔIL-1β	2 (20%)	
Decreasing ΔIL-1β	8 (80%)	
Survivor		
Increasing ΔIL-1β	12 (44.4%)	0.260
Decreasing ΔIL-1β	15 (55.6%)	
No ARDS	**N (%)**	
Survivor		
Increasing ΔIL-1β	8 (47.1%)	
Decreasing ΔIL-1β	9 (52.9%)	

*Analysis using Chi-Square Test, it means if p < 0.05; the difference in IL-1β levels on day zero and day 6

A study on the inflammatory profile associated with higher mortality in COVID-19 patients that involved 41 patients prospectively, showed that plasma IL-1Ra levels and IL-8 levels had a positive correlation with mortality in COVID-19 ARDS patients. However, this study still requires further research (23).The total number of ARDS patients was 37 people, 10 people died, and among the 10 people who died there were 2 people (20%) who experienced an increase in IL-1β and 8 people (80%) who experienced a decrease in IL-1β. There were 27 surviving ARDS patients, of which 12 people (44.4%) had an increase in IL-1β and 15 people (55.6%) experienced a decrease in IL-1β. There were no deaths found in patients who did not have ARDS (17 people). Of these 17 people, 8 people (47.1%) had an increase in IL-1β, and 9 people (52.9%) had a decrease in IL-1β. By using the Chi-Square test, a *p*-value of 0.260 was obtained, where the p-value <0.05 was statistically significant. Therefore, changes in IL-1β levels on mortality in ARDS patients were not statistically significant, so it cannot be concluded whether ARDS patients who survived or died have decreased, increased, or persistent IL-1β levels. The value of IL-1β was obtained from the difference in levels of IL-1β recorded on the first 24 hours of treatment and day 6 of treatment.

A 1995 study of inflammatory cytokines in BAL from ARDS patients, regarding persistent elevations, predicted poor outcomes. The study only showed that in patients who died, the levels of TNF- α, IL-1β, IL-6, and IL-8 were higher on the first day of ARDS than in the living group and increased persistently during treatment, where BAL and plasma samples were taken on the day of

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treatment. During day 1 and every 7 days after treatment, the results indicated a continuous injury process. This study was conducted prospectively and involved 27 consecutive patients with ARDS (24).

Table 7. Analysis of the relationship between body temperature and IL-1β in patients with ARDS

ARDS	N (%)	*p*
Yes	37 (68.51%)	0.161
No	17 (25.92%)	0.310

* Analysis using Spearman-Rho correlation test, it is significant if p < 0.05.

The effect of body temperature on IL-1β in ARDS patients have a p-value of 0.161, while patients without ARDS has a *p*-value of 0.310. This analysis used the Spearman Rho correlation test, where the *p*-value < 0.05 was statistically significant. Therefore, this suggests that the relationship between body temperature and IL-1β in ARDS patients was not statistically significant. The highest temperature recorded was used during the first 6 days of treatment and IL-1β levels were recorded in the first 24 hours of treatment if the patient had ARDS on that day and day 6 if they had ARDS between day 2 and day 6 of treatment. There was no other study about the relationship between body temperature and IL-1β in patients with ARDS in COVID-19 yet.

No statistically significant analysis results were found for each of the specific objectives of this study. Thus, an analysis of patient characteristics on mortality was conducted to determine the variables of patient characteristics that were correlated with mortality.

Table 8. Analysis of Characteristics of Mortality

Variable		Death Frequency N (%)	Live Frequency N (%)	Median (*Range*)	*Mean* ± SD	*p*
Gender						
	Female	4 (40%)	16 (36.4%)			1.00*
	Male	6 (60%)	28 (63.6%)			
ARDS						
	No	0 (0%)	17 (38.6%)			**0.022***
	Yes	10 (100%)	27 (61.4%)			
Age(year)						
	Non-Survivor	10 (18.5%)	-	52 (40 – 73)	53.7 ± 11.43	0.149**
	Survivor	-	44 (81.5%)	50 (25 – 68)	47.8 ± 11.4	
Comorbid						
	Have	8 (80%)	27 (61.4%)			0.465*
	Not Have	2 (20%)	17 (38.6%)			
Fever History						
	Have	8 (80%)	33 (75.0%)			1.00*
	Not Have	2 (20%)	11 (25.0%)			
Comorbidity Type						
	Hypertension	5 (50%)	12 (27.3%)			0.257*
	Diabetes Mellitus	4 (40%)	10 (22.7%)			0.424*
	Obesity	0 (0%)	1 (2.3%)			1.00*
	Asma	2 (20%)	5 (11.4%)			0.601*
	Coroner Heart	0 (0%)	1 (2.3%)			1.00*
Disease		0 (0%)	1 (2.3%)			1.00*
	COPD	1 (10%)	0 (0%)			0.185*

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Variable	Death Frequency N (%)	Live Frequency N (%)	Median (*Range*)	*Mean* ± SD	*p*
CVA	1 (10%)	0 (0%)			0.185*
Chronic Hepatitis B	0 (0%)	1 (2.3%)			1.00*
HBsAg reactive					
Clinical Symptom					
Fever	8 (80%)	33 (75.0%)			1.00*
Shortness of breath	7 (70%)	25 (56.8%)			0.501*
Dry Cough	8 (80%)	29 (65.9%)			0.476*
Rhinorrhea	1 (10%)	5 (11.4%)			1.00*
Nausea and vomiting	2 (20%)	5 (11.4%)			0.601*
Decreasing of Appetite	2 (20%)	4 (9.1%)			0.306*
Cough with sputum	1 (10%)	2 (4.5%)			0.466*
Anosmia	1 (10%)	8 (18.2%)			1.00*
Diarrhea	2 (20%)	8 (18.2%)			1.00*
Sore Throat	0 (0%)	7 (15.9%)			0.325*
Fatigue	0 (0%)	4 (9.1%)			1.00*
Stomachache	0 (0%)	1 (2.3%)			1.00*
Muscle pain	0 (0%)	2 (4.5%)			1.00*
Chest pain	0 (0%)	3 (6.8%)			1.00*
Headache	0 (0%)	6 (13.6%)			0.580*
Loss of consciousness	1 (10%)	1 (2.3%)			0.339*
Hemiparesis	0 (0%)	1 (2.3%)			1.00*
Loss of Taste	1 (10%)	0 (0%)			0.185*
Secondary Infection					
Have	9(90%)	11 (25.0%)			**0.00***
Not Have	1 (10%)	33 (75.0%)			
Use Mechanical Ventilation					
Yes	8 (80%)	4 (9.1%)			**0.00***
No	2 (20%)	40 (90.9%)			
Severity level of ARDS					
Mild	0 (0%)	6 (13.6%)			**0.001***
Moderate	4 (40%)	17 (38.6%)			
Severe	6 (60%)	4 (9.1%)			
Length of Stay (Days)					
Non-Survivor	10 (18.5%)	-	12.5 (11 – 25)	15.2 ± 4.98	**0.042*****
Survivor	-	44 (81.5%)	21 (8 – 69)	23.3 ± 13.9	
Onset of Symptom (Days)					
Non-Survivor	10 (18.5%)	-	8.5 (1 – 14))	8.0 ± 4.4	0.380***
Survivor	-	44 (81.5%)	7.0 (1 – 15)	6.93 ± 3.3	
qSOFA					
Non-Survivor	10 (18.5%)	-	2 (1 – 3)	1.7 ± 0.67	0.949***
Survivor	-	44 (81.5%)	2 (0 – 3)	1.68 ± 0.60	
BMI (kg/m^2)					
Non-Survivor	10 (18.5%)	-	25.74 (21.48 - 48.07)	28.44 ± 8.27	0.722***
Survivor	-	44 (81.5%)	25.34 (20.44 – 39.54)	26.14 ± 3.87	

* Chi-Square test, significant if p < 0.05; ** T-test, significant if p < 0.05; *** Mann-Whitney test, significant if p < 0.05.

In this study, analysis of the patients' characteristics on mortality showed that several factors that had statistical significance. The factors are ARDS conditions with a *p*-value of 0.022 using the Chi-Square test, secondary infection involvement with a *p*-value of 0.00 using the Chi-Square test, patients using ventilation mechanics with a *p*-value of 0.00 using the Chi-Square test, the severity of ARDS with a *p*-value of 0.001 using the Chi-Square test, and the length of stay period with a *p*-value of 0.042 using the Mann-Whitney test. All *p*-values in the analysis test were stated to be statistically

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significant if <0.05. These results showed that patients with ARDS are correlated with mortality with a *p*-value of 0.022, the presence of secondary infection during the treatment period also correlated with mortality with a *p*-value of 0.00, patients using mechanical ventilation correlated with mortality with a *p*-value of 0.00, ARDS severity also correlated with mortality with a *p*-value of 0.001. All results were obtained from conducting the Chi-Square test. Another variable that correlates with mortality is the length of stay. By using the Mann-Whitney test, a *p*-value of 0.042 was obtained with a median value of 12.5 days and a range of 11 to 25 days and a mean ± SD of 15.2 ± 4.98 in patients who died.

These results showed that patients with ARDS, the presence of secondary infection during the treatment period where the secondary infection was proven by specimen culture, patients using mechanical ventilation, and the severity of ARDS, all correlate with mortality.

Secondary infections generally come from secondary bacterial lung infections, followed by the blood and urinary tract. All patients who used mechanical ventilation were at severe to critical severity of COVID-19 when they arrived at the hospital and on average had a severe degree of ARDS. This shows that patients with ARDS, patients with ARDS with extreme severity, secondary infections, and patients that used mechanical ventilation, all have an association with mortality. Another variable that correlates with mortality is the length of treatment. The results suggest that the longer the treatment, the greater patient's survival.

Research on mortality in COVID-19 patients with ARDS and the use of corticosteroids has shown that patients with ARDS have high mortality and require appropriate and aggressive therapy. This study is a meta-analysis, which found that the mortality with the highest ARDS is in China, especially at the beginning of the pandemic, at 69%. In Europe, the countries with the highest ARDS mortality are Poland at 73%, followed by Spain at 40%, and France at 19%, with Germany having the lowest mortality. Globally, the total mortality in COVID-19 patients with ARDS is 39% with or without corticosteroid therapy. This study involved 28 articles that were screened and matched the inclusion and exclusion criteria (25).

Another study of COVID-19 patients with secondary infection showed that the risk of secondary infection increased after receiving invasive mechanical ventilation and intravenous devices, which in turn increased mortality. This study was a retrospective multi-center cohort study and involved 612 patients. Secondary infection was evidenced by clinical symptoms, supportive radiological results, and specimen culture results. Most of the bacteria that were causes of respiratory tract infections were Gram-negative bacteria (26).

Another meta-analysis study of the case fatality rate (CFR) in COVID-19 patients using mechanical ventilation, stated that the overall CFR in patients that used mechanical ventilation reached 45%. Nearly half of the patients that received mechanical ventilation died. The reported CFR was higher in older patients, and was higher at the onset of the pandemic, possibly due to limited ICU resources. This study involved 69 articles after being screened to be according to the inclusion and exclusion criteria (27).

CONCLUSION

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From this study, it can be concluded that body temperature does not correlate with the occurrence of ARDS, the severity of ARDS, as well as mortality, and IL-1β levels. IL-1β levels and transformation in IL-1β levels did not correlate with mortality and the occurrence and severity of ARDS.

The use of mechanical ventilation, secondary infection, and length of stay were correlated with mortality in COVID-19 patients. Further studies are needed with serial IL-1β samples that are taken more frequently during treatment, along with other pro-inflammatory cytokines.

REFERENCES

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;xxx(xxxx):1–4.
2. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;0994:1–10.
3. Walter EJ, Hanna-jumma S, Carraretto M, Forni L. The pathophysiological basis and consequences of fever. Crit Care. 2016;200(20):1–10.
4. Hildy M. Body Temperature and Mortality in Patients with Acute Respiratory Distress Syndrome. Am J Crit Care. 2016;24(1):15–23.
5. Radhi E. Pathogenesis of Fever. Clin Man Fever Child. 2018;53–68.
6. Afonina IS, Mu C. Proteolytic Processing of Interleukin-1 Family Cytokines : Variations on a Common Theme. Imunity. 2015;42:991–1004.
7. Van De Veerdonk FL, Netea MG. Blocking IL-1 to prevent respiratory failure in COVID-19. Crit Care. 2020;24(1):1–6.
8. McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, et al. Characterization of the inflammatory response to severe COVID-19 Illness. Am J Respir Crit Care Med. 2020;202(6):812–21.
9. Landi L, Ravaglia C, Russo E, Cataleta P, Fusari M, Boschi A, et al. Blockage of interleukin-1β with canakinumab in patients with Covid-19. Sci Rep. 2020;10(1):1–9.
10. Cauchois R, Koubi M, Delarbre D, Manet C, Carvelli J, Blasco VB, et al. Erratum: Early IL-1 receptor blockade in severe inflammatory respiratory failure complicating COVID-19 (Proceedings of the National Academy of Sciences of the United States of America (2020) 117 (189510-18953) DOI: 10.1073/pnas.2009017117). Proc Natl Acad Sci U S A. 2020;117(36):22604.
11. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10):1636–43.
12. Merza MY, Hwaiz RA, Hamad BK, Mohammad KA, Hama HA, Karim AY. Analysis of cytokines in SARS-CoV-2 or COVID-19 patients in Erbil city, Kurdistan Region of Iraq. PLoS One. 2021;16(4 April):1–7.
13. Dorgham K, Quentric P, Gokkaya M, Marot S, Parizot C, Sauce D, et al. Distinct cytokine profiles associated with COVID-19 severity and mortality. allergy Clin Immunolgy. 2020;147(January):2098–107.

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** https://doi.org/10.20473/ijar.V4I12022.22-36

14. Tulapurkar ME, Almutairy EA, Shah NG, He J, Purche AC, Shapiro P, et al. Febrile-Range Hyperthermia Modifies Endothelial and Neutrophilic Functions to Promote Extravasation. Am J Respir Cell Mol Biol. 2012;46(6):807–14.
15. Thompson B taylo., Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. N Engl J Med. 2017;377:562–72.
16. Di Iorio A, Ferrucci L, Sparvieri E, Cherubini A, Volpato S, Corsi A, et al. Serum IL-1β levels in health and disease:A population-based study. "The InCHIANTI study." Cytokine. 2003;22(6):198–205.
17. Notz Q, Schmalzing M, Wedekink F, Schlesinger T, Gernert M, Herrmann J, et al. Pro- and Anti-Inflammatory Responses in Severe COVID-19-Induced Acute Respiratory Distress Syndrome—An Observational Pilot Study. Front Immunol. 2020;11(October):1–13.
18. Kerget B, Kerget F, Aksakal A, Aşkın S, Sağlam L, Akgün M. Evaluation of alpha defensin, IL-1 receptor antagonist, and IL-18 levels in COVID-19 patients with macrophage activation syndrome and acute respiratory distress syndrome. J Med Virol. 2021;93(4):2090–8.
19. Fujishima S. Pathophysiology and biomarkers of acute respiratory distress syndrome. J Intensive Care. 2014;2(1):1–6.
20. Choron RL, Butts CA, Bargoud C, Krumrei NJ, Teichman AL, Schroeder ME, et al. Fever in the ICU: A Predictor of Mortality in Mechanically Ventilated COVID-19 Patients. J Intensive Care Med. 2021;36(4):484–93.
21. Huang C, Wang Y, Li X, Ren L, Zhao J, Zhang L, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan , China. Lancet. 2020;6736(20):1–10.
22. Guihur A, Rebeaud ME, Fauvet B, Tiwari S, Weiss YG. Moderate Fever Cycles as a Potential Mechanism to Protect the Respiratory System in COVID-19 Patients. Front Med. 2020;7(September):1–8.
23. Balnis J, Adam AP, Chopra A, Chieng HC, Drake LA, Martino N, et al. Unique inflammatory profile is associated with higher SARS-CoV-2 acute respiratory distress syndrome (ARDS) mortality. Am J Physiol - Regul Integr Comp Physiol. 2021;320(3):250–7.
24. Meduri GU, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS: Plasma IL-1β and IL-6 levels are consistent and efficient predictors of outcome over time. Chest. 1995;107(4):1062–73.
25. Hasan SS, Capstick T, Ahmed R, Kow CS, Mazhar F, Merchant H a., et al. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis. Expert Rev Respir Med. 2020;14(11):1149–63.
26. Zhang H, Zhang Y, Wu J, Li Y, Zhou X, Li X, et al. Risks and features of secondary infections in severe and critical ill COVID-19 patients. Emerg Microbes Infect. 2020;9(1):1958–64.
27. Lim ZJ, Subramaniam A, Reddy MP, Blecher G, Kadam U, Afroz A, et al. Case Fatality Rates for Patients with COVID-19 Requiring Invasive Mechanical Ventilation. Am J Respir Crit Care Med. 2021;203(1):54–66.

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