Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Sep 10; 10(B):2208-2214.
https://doi.org/10.3889/oamjms.2022.10591
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Intensive Care*

Contributing Factors to Increased Left Ventricular End-Diastolic Volume in COVID-19 ICU Patients in Sanglah Hospital: A Study on Galectin-3

Marilaeta Cindryani Lolobali[1]*, I. M. G. Widnyana[2], Ni Made Ayu Wulansari[3], Ida Bagus Rangga Wibhuti[3], Made Wiryana[2], Rudyanto Sedono[1], Aldy Heriwardito[1]

[1]Department of Anesthesiology and Intensive Care, Universitas Indonesia, Rumah Sakit Cipto Mangunkusumo, Jakarta, Indonesia; [2]Department of Anesthesiology and Intensive Care, Udayana University, Sanglah Hospital, Denpasar, Indonesia; [3]Department of Cardiology and Vascular, Udayana University, Sanglah Hospital, Denpasar, Indonesia

Edited by: Mirko Spiroski
Citation: Lolobali MC, Widnyana IMG, Wulansari NMA, Wibhuti IBR, Wiryana M, Sedono R, Heriwardito A. Contributing Factors to Increased Left Ventricular End-Diastolic Volume in COVID-19 ICU Patients in Sanglah Hospital: A Study on Galectin-3. OpenAccessMacedJMedSci.2022Sep10;10(B):2208-2214. https://doi.org/10.3889/oamjms.2022.10591
Keywords: Factors; Increased LVEDV; ICU; COVID-19; Galectin-3
***Correspondence:** Marilaeta Cindryani Lolobali, Department of Anesthesiology and Intensive Care, Universitas Indonesia–Rumah Sakit Cipto Mangunkusumo, Jakarta, Indonesia. E-mail: onkhenk@yahoo.com
Received: 02-Jul-2022
Revised: 14-Aug-2022
Accepted: 31-Aug-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Coronavirus disease 2019 (COVID-19) is a respiratory disease that has become the largest pandemic and also could put the heart at risk of dysfunction. Galectin-3 is involved in the inflammatory process that continues with remodeling and eventually fibrosis. Using galectin-3 examination, we could predict the possible worsening of heart function and evaluate data on influencing factors for increased left ventricular end-diastolic volume (LVEDV) which could later progress to heart failure.

METHODS: This is an observational prospective analytic study in the COVID-19 ICU of Sanglah Hospital, Bali, Indonesia. The study was conducted from June to October 2021. All research subjects had their blood samples taken for galectin-3 levels examination using enzyme-linked immunosorbent assay (ELISA). Subjects were also evaluated for left ventricular end-diastolic volume (LVEDV) with echocardiography, SOFA scores, and troponin I levels. Subjects were treated with COVID-19 standard protocol established by the Ministry of Health. After 72 h post-admission, subjects were re-examined for galectin-3 levels and LVEDV. Data were analyzed using STATA™.

RESULTS: A total of 45 research subjects were analyzed. Bivariate analysis of the difference of galectin-3 and LVEDV was shown to be insignificant (r = 0.08), no correlation was found between galectin-3 level and LVEDV on ICU admission (r = 0.191), and no correlation found between galectin-3 level and LVEDV after 72 h of hospitalization (r=0.197). Multivariate analysis also showed that none of the variables, namely, difference of galectin-3 level, age, gender, troponin I, SOFA, and Charlson scores had statistically significant correlation with LVEDV ($p < 0.05$).

CONCLUSION: No significant correlation was found between galectin-3 level and an increase in LVEDV.

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease that has become the largest pandemic in the last decade and the mortality rate continues to increase, while valid management has not shown consistent results. Epidemiological data from the World Health Organization (WHO) on December 26, 2020, recorded that there were more than 78 million cumulative cases and 1.7 million cumulative deaths due to COVID-19 globally [1]. In Indonesia, as of December 26, 2020, there were 706,837 cumulative confirmed cases and 20,994 cumulative deaths from COVID-19 [2]. The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause severe pneumonia which develops into acute respiratory distress syndrome which can lead to death [3]. In addition to acute respiratory failure syndrome and thrombosis, the risk of dysfunction of important organs such as the heart is also experienced by patients who contracted COVID-19. Advances in research and technology within the past 20 years have led to many markers at the microcellular level that appears during exposure to injury that disrupt the body's physiology. Some biomarkers appear to provide significant results and are in accordance with theoretical basis. Galectin-3 is often expressed by inflammatory cells, namely, macrophages. Its involvement is thought to be related to the inflammatory process that continues with remodeling and eventually fibrosis of organs such as the heart, brain, and kidneys. Galectin-3 is thought to mediate macrophage activation triggered by IL4 and then the IL4/IL13 macrophage complex formed will stimulate matrix production and multiple fibrosis. This concept is called the Gal-3-macrophage-fibroblast axis. As it is known that COVID-19 infection will have an impact on excessive inflammatory reactions from the whole body, this in turn, will certainly facilitate the fibrosis due to activation of the axis. Failure or

dysfunction of the heart that occurs is not only caused by the pro-inflammatory activation but also from the overactivation of the sympathetic nerves, failure of the respiratory system which also causes heart failure due to heart-lung interaction, and the possibility of direct infection or necrosis of the myocytes. The inflammatory process due to the induction of the galectin-3-monocyte-macrophage axis, which continues in this remodeling, causes a decrease in cardiac contractility which is characterized by an increase in end-diastolic volume in the left ventricle due to the inability of the heart muscle to contract to pump blood throughout the body.

A Chinese study conducted by Guo *et al*. in March 2020 reported that out of 187 patients with COVID-19 treated in their institutions, 52 of them (27.8%) had myocardial injury confirmed by elevated troponin T levels. Moreover, mortality was found to be very high in patients with high levels of troponin T [4].

On the other hand, the association between SOFA scores and biomarkers such as galectin-3 has not been studied much. However, a 2017 study by Hanah Kim and colleagues explained that procalcitonin, presepsin, and sST2 together with galectin-3 as a multimarker were examined overall, providing better predictive results for 30-day mortality than SOFA scores alone in septic patients [area under the curves (95) %CI), 0.769 (0.695–0.833) vs. 0.615 (0.535–0.692)]. However, its continued potential in COVID-19 patients is unknown [5].

By testing galectin-3, data on the influencing factors of increased left ventricular end-diastolic volume (LVEDV) in COVID-19 patients treated in the ICU could be obtained.

Methods

This research was an observational prospective analytic study in the COVID-19 ICU of Sanglah Hospital, conducted from June to December 2021 after obtaining approval from the Research Ethics Committee. Patients were provided with a full description of the study and signed a written consent to participate in the study. Inclusion criteria included patients aged 18–65 years old, confirmed COVID-19 with positive RT-PCR, and agreed to be included in the study. Exclusion criteria were patients with comorbidities (e.g., pregnant and breastfeeding) and did not agree to be included in the study. The dropout criteria in this study were patients with incomplete panel data. General characteristics of research subjects were recorded according to the research data form including age, gender, and comorbid scores based on the Charlson score. The research subjects had their blood samples taken for galectin-3 levels evaluation at the Clinical Pathology Laboratory of Sanglah Hospital using enzyme-linked immunosorbent assay (ELISA). They were also evaluated for their left ventricular end-diastolic volume (LVEDV) with echocardiography performed by a cardiologist. Research subjects were also examined for SOFA scores and levels of troponin I. Subjects received standard COVID-19 therapy in accordance with the standard protocol established by the Indonesian Ministry of Health. After 72 h post-ICU admission, subjects underwent re-examination of galectin-3 levels and LVEDV.

The data were analyzed using appropriate statistical tests using the STATA software. Basic characteristics were presented according to the specified variable types, and analyzed data were presented in the form of tables and graphs accompanied by narration. Statistical analyses were divided into descriptive analysis to assess the distribution of subjects' characteristics and correlation analysis to analyze the relationship between galectin-3 levels with changes in LVEDV. To assess the relationship between galectin-3 levels and LVEDV while taking into account SOFA scores, comorbidities, and troponin I levels, multiple linear regression analysis was performed.

Results

Table 1 shows that the mean age of the research subjects is 50.44 years with the youngest being 21 years old and the oldest 65 years old. The 45 subjects consisted of 25 men (55.60%) and 20 women (44.40%). Table 1 shows that the average level of galectin-3 on admission to the COVID-19 ICU was 100.27 ± 10.99 ng/ml while the average level of galectin-3 after 72 h of treatment was 106.69 ± 13.80 ng/ml. The mean difference in galectin-3 levels after 72 h of hospitalization and admission to the ICU was 6.42 ± 7.97 ng/ml. The mean LVEDV at the time of admission to the COVID-19 ICU was 79.84 ± 4.96 ml, while the average LVEDV after 72 h of treatment was 80.88 ± 5.48 ml. The mean difference in LVEDV after 72 h of admission to ICU admission was 1.03 ± 5.53 ml. The mean SOFA score at the time of admission to the

Table 1: Characteristics of subjects

Characteristics	Outcome (n=45)
Age, (mean ± SD) years	50.44 ± 1.99
Gender, n (%)	
Male	25 (55.60)
Female	20 (44.40)
Galectin-3 level, (mean ± SD)	
Upon Admission (mean ± SD) ng/ml	100.27 ± 10.99
72 h post-admission (mean ± SD) ng/ml	106.69 ± 13.80
Delta (mean ± SD) ng/ml	6.42 ± 7.97
LVEDV, (mean ± SD)	
Upon admission (mean ± SD) ml	79.84 ± 4.9628
72 h postadmission (mean ± SD) ml	80.88 ± 5.48
Delta (mean ± SD) ml	1.03 ± 5.53
Troponin I level, (median) ng/ml	82.7
SOFA score, (mean ± SD)	
Upon admission (mean ± SD)	9.51 ± 2.98
72 h postadmission (mean ± SD)	10.55 ± 3.52
Delta (mean ± SD) ng/ml	1.04 ± 2.27
Charlson score, (mean ± SD)	1.88 ± 1.51

SD: Standard deviation, LVEDV: Left ventricular end-diastolic volume.

Table 2: Spearman correlations between independent and dependent variables

Independent variables	Dependent variables	R
Galectin-3 upon admission	LVEDV upon admission	0.191
Galectin-3 72 h postadmission	LVEDV 72 h postadmission	0.197
Delta Galectin-3	Delta LVEDV	0.08

LVEDV: Left ventricular end-diastolic volume.

COVID-19 ICU was 9.51 ± 2.98, while after 72 hours of treatment, it was 10.55 ± 3.52, with a difference of 1.04 ± 2.27. The median troponin I level was 82.7 ng/ml. Meanwhile, Charlson's mean score was 1.88 ± 1.51. Table 2 summarizes the results of the independent and dependent variables analysis. A normality test revealed that our data were distributed non-normally, thus non-parametric analysis was performed. Spearman correlation test on the difference between galectin-3 and LVEDV revealed no significant correlation (r = 0.08), and the correlation test between galectin-3 and LVEDV on ICU admission also revealed no significant correlation (r = 0.191). Moreover, no significant correlation was also found between galectin-3 levels and LVEDV after 72 h of hospitalization (r = 0.197). Multivariate analysis of the effect of independent variables, namely, the difference between galectin-3 levels, age, sex, troponin I, SOFA, and Charlson scores, on the LVEDV variable, as shown in Table 3, showed that none of the independent variables had statistically significant correlation with LVEDV ($p < 0.05$).

Table 3: Multivariate regression analysis

Variables	Regression coefficient (B)	SE	CI 95%		p
			Lower	Upper	
Delta Galectin-3	0.034	0.117	−0.214	0.261	0.843
Age	0.000	0.490	−0.994	0.993	0.999
Gender	0.090	12.443	−18.502	31.921	0.593
Troponin I	0.034	0.000	0.000	0.000	0.842
SOFA score 72 h postadmission	0.024	1.937	−4.179	3.671	0.896
CHARLSON score	0.178	4.643	−5.025	13.792	0.351

SE: Standard error, CI: Confidence interval.

Discussion

At the start of the study, the authors calculated the sample size required to generate a statistically representative sample, namely, 38 subjects plus a 10% dropout correction to a total of 42 subjects. However, at the end of the study, 45 subjects were obtained and all of them could be analyzed which are summarized in Figure 1.

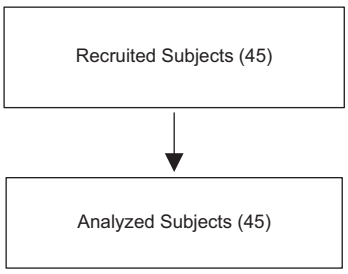

Figure 1: Research flow

Based on data dated August 4, 2021, from the Ministry of Health, the proportion of deaths due to COVID-19 infection by age is around 2.8% for ages 19−30 years, 12.7% for 31−45 years, 36.7% for 46-59 years, and 46.7% for over 60 years. The research subjects all fall into the aforementioned categories where the mean age of the research subjects is 50.44 with the youngest age being 21 years and the oldest being 65 years (Table 1). Based on data from the Ministry of Health until January 2021, positive COVID-19 cases in Indonesia are dominated by women. The proportion is 50.4% compared to 49.6% in men, which if further detailed, the percentage of women in active cases is 52.3% and 50.2% in cured cases. However, the comparison is different in the case of deaths. The proportion of men is greater than women, with 56.3% and 43.7%, respectively [6]. This study found that there were 25 male subjects with COVID-19 (55.60%) and 20 females (44.40%). Considering that all study subjects died at the end of their treatment, the proportion of mortality in this study was in accordance with the Ministry of Health data, where the proportion of males was greater than that of females. In a previous study on critically ill patients, Needham *et al*. have validated the use of the Charlson index (AUC 0.67) [7]. The comorbidity index is shown to be able to identify patients who require high medical costs [7]. On the other hand, Stavem *et al*. also showed that the Charlson index was valid in predicting the 30-day and 1-year mortality of ICU patients [8]. A recent Korean study by Kim *et al*. in 2021 reported that the Charlson comorbidity index with age adjustment was an independent risk factor for death in COVID-19 infection, as analyzed using a multivariate Cox proportional analysis. The study reported a 28.5% mortality rate in those with index value of 5, followed by 4.9% in those with index value of 3−4, 0.6% in those with index value of 1-2, and 0.1% in those with index value of 0.28. The Charlson comorbidity score was 1.88 ± 1.51, not as high as the index reported in Korea. A 2020 Indonesian meta-analysis by Kuswardhani *et al*. was in line with the Korean study, where they reported a Charlson comorbidity index of 1-2 and 3, which were prognostically associated with mortality and poor outcome. Each increase in the index score increases the risk of mortality by 16% [9]. Meanwhile, in this study, the mean Charlson comorbidity score was 1.88 ± 1.51. When compared with the results of the Korean study, the mortality rate in this study would naturally range from 0.6 to 4.9%. However, considering the outcome of all research subjects experiencing mortality, the results of the meta-analysis of Kuswardhani *et al*. seem more able to explain what happened in this study, because according to the average index obtained, the risk of mortality can range from 32 to 48%. This study found that the average SOFA score at the time of admission to the COVID-19 ICU was 9.51 ± 2.98, while after 72 h of treatment, it was 10.55 ± 3.52, with a difference of 1.04 ± 2.27. Medam *et al*. in a cohort study of risk factors for mortality in patients with septic shock found

that having a SOFA score above 12 was an independent factor for mortality with an OR of 6.8 (95% CI 1.3−37; p = 0.02518). In a Chinese retrospective observational study in 2021 by Yang *et al*. on 117 COVID-19 patients, it was found that high SOFA scores, age and hypertension were associated with severe COVID-19. The median SOFA in their patients was 2 (IQR, 1–3). Patients with severe COVID-19 scored higher than those with mild COVID-19 (3 [IQR, 2–4] vs. 1 [IQR, 0–1]; p <.001). It is also reported that SOFA can identify severity with an odds ratio of 5.851 (95% CI: 3.044–11,245; p < 0.001). The area under the ROC curve (AUC) was also used to evaluate the diagnostic accuracy of SOFA in COVID-19 prediction, the cutoff value = 2; AUC = 0.908 [95% CI: 0.857–0.960]; sensitivity: 85.20%; specificity: 80.40%) and the mortality risk (cutoff value = 5; AUC = 0.995 [95% CI: 0.985–1,000]; sensitivity: 100.00%; specificity: 95.40%) [10].

The above results were refuted by a study by Raschke *et al*. in 2021 where in their rebuttal, it was found that the SOFA score is less accurate in determining mortality due to COVID-19. They obtained results where the median SOFA score was 6 (interquartile range, 4−8), the sub-scores were 0 to 1 in 72.1% of patients with renal impairment, 78.5% for central nervous system disorders, 94.2% for coagulation, 95.1% for cardiovascular systems, and 96.5% for hepatobiliary disorders. Four hundred of the patients died or went into palliative care (59.3%). The AUROC SOFA value was 0.59 (95% CI, 0.55−0.63) and the value for age was 0.66 (95% CI, 0.62−0.70) (p= 0.02) [11]. Similar results were obtained in this study where the SOFA score was 9.51 ± 2.98, while after 72 h of treatment, it was 10.55 ± 3.52, with a 1.04 ± 2.27 difference. This value differed from other studies. This study also found that the average level of galectin-3 at the time of admission to the COVID-19 ICU was 100.27 ± 10.99 ng/ml while the average level of galectin-3 after 72 hours of treatment was 106.69 ± 13.80 ng/ml. The mean difference in galectin-3 levels after 72 hours of hospitalization and admission to the ICU was 6.42 ± 7.97 ng/ml. A study by Portacci *et al*. in 2021 found that of 156 recruited patients, patients with galectin-3 above 35.3 ng/ml had an increased risk of mortality, intensive care, and severe acute respiratory failure syndrome [12]. While the study from Kusnierz-Cabala also in 2021 reported that galectin-3 was significantly increased in patients with pneumonia, especially those treated in the intensive care unit. Positive correlations were found between galectin-3 and inflammatory markers such as interleukin-6, C-reactive protein, ferritin, pentraxin-3, and endothelial injury markers such as soluble FMS-like tyrosine kinase-1 [13]. It was also found that the median level of troponin I was 82.7 ng/ml. A meta-analysis study conducted by Wibowo *et al*. in 2021 found that there was an increase of troponin in 31% (23−38%) of patients. Increased troponin was strongly associated with mortality [odds ratio (OR) 4.75, 95% CI 4.07-5.53; p < 0.001; I2 = 19.9%]. The association between increased troponin and mortality had a sensitivity of 0.55 (0.44−0.66), specificity of 0.80 (0.71−0.86), positive likelihood ratio of 2.7 (2.2−3.3), negative likelihood ratio 0.56 (0.49−0.65), diagnosis odds ratio 5 (4−5), and the area under the curve was 0.73 (0.69−0.77). The mortality probability was 45% in patients with elevated troponin and 14% in patients without elevated troponin. However, this study did not explain in detail the type of troponin used, because all types of troponins were included in the meta-analysis [14]. There was a study specifically examining troponin I and COVID-19 infection conducted by Abbasi *et al*. in 2020. This retrospective cohort study found that patients with elevated troponin I in the first 24 h of hospitalization had a higher risk of mortality (52% vs. 10%, p < 0.0001). Troponin I levels in the first 24 h of treatment had a negative predictive value of 89.7% and a positive predictive value of 51.9% for mortality [15]. The present study found that the mean LVEDV when admitted to the COVID-19 ICU was 79.84 ± 4.96 ml while the mean LVEDV after 72 h of treatment was 80.88 ± 5.48 ml. The mean difference in LVEDV after 72 h of admission to ICU admission was 1.03 ± 5.53 ml. No studies have examined LVEDV in patients with COVID-19 infection, but several studies have made observations on echocardiographic parameters. Based on a study conducted by Silverio *et al*. in 2021, after performing TTE (transthoracic echocardiography) in 226 patients, the results of a multivariate analysis showed that left ventricular ejection fraction (LVEF, p <.001), tricuspid annular plane systolic excursion (TAPSE, p < 0.001), and ARDS (p < 0.001) were independent factors related to mortality. Another analysis of several risk factors found a significantly higher risk of mortality in patients with ARDS than those without (HR: 7.66; CI: 3.95−14.8), patients with TAPSE 17 mm and >17 mm (HR: 5.08; CI: 3.15−8.19), and patients with LVEF 50% versus those >50% (HR: 4.06; CI: 2.50−6.59) [16]. The results of the Spearman correlation test in this study on the difference between galectin-3 and LVEDV revealed a non-significant correlation (r = 0.08). Similarly, the correlation between galectin-3 levels and LVEDV on ICU admission and the correlation between galectin-3 and LVEDV after 72 h of admission were not statistically significant (r = 0.191 and 0.197, respectively. These results are certainly surprising for the authors because based on several literatures discussing the role of these biomarkers in cardiovascular disorders, these biomarkers provide promising potential supported by a sound theoretical basis. To date, there has been no publication of literature on galectin-3 and COVID-19 infection with statistically non-significant results. The recent studies are only preliminary or retrospective studies on patients in the range of hundreds and these parameters have not been analyzed in a larger number of subjects. Because COVID-19 disease is a new disease, it is understandable that studies tend to yield non-significant results. The

same goes for studies in other diseases related to galectin-3 as well. Following a search of several other studies, Felker *et al*. in a 2011 double-blind randomized clinical trial of HF-ACTION in 895 chronic heart failure patients found that in a simple one-way analysis without adjustment, there was indeed a significant association between increased galectin-3 and hospital discharge rate (unadjusted hazard ratio, 1.14 per 3 ng/mL increase in galectin-3; $p < 0.0001$). However, after being included in a multivariate model, the effect was reduced due to the presence of another predictor, namely NTproBNP [17]. Therefore, it is highly probable that there may be an influence from other factors in relation to LVEDV, for example, the presence of an intermediate variable or other contributing factors that contribute to a greater risk which also affect the value of existing galectin-3. It is possible that this variable is present in the inflammatory pathophysiology of the Gal-macrophage-fibroblast axis but no method for its extraction or measurement has been found. As a result of not finding a significant relationship between the independent variables, namely, galectin-3 and LVEDV, the authors attempted to investigate the relationship between each variable studied in this study and LVEDV through regression analysis. The results of multivariate analysis of the effect of the independent variables, namely, delta Galectin-3, age, gender, troponin I, SOFA, and Charlson scores on the LVEDV variable revealed that none of the variables had statistically significant effect ($p < 0.05$) on LVEDV. This might be due to the influence of intermediate variables or other contributing factors resulting in a greater risk which also affects the existing galectin-3 value. The results of this study differ from those obtained by Portacci, *et al*. and Kusnierz-Cabala [12], [13] where they recommend the potential use of galectin-3 as a prognostic marker for the assessment of mortality and severity in COVID-19 infection. It is possible that the small number of patients in this study as compared to other studies was one of the reasons why the proposed hypothesis was not proven. Another reason is because of the novelty of the COVID-19 disease, where the latest published studies in 2020−2021 are only preliminary and retrospective studies whose degree of significance was not relatively strong. Therefore, it is understandable that this study actually obtained non-significant results when presented with prospective real patients. The study by Raschke *et al*. [11] also suggested the selection of a new disease severity scoring system other than SOFA for COVID-19. This was due to the fact that the SOFA score actually gave indeterminate results, especially for patients with certain organ system failure due to COVID infection [18]. Hence, this might lead to unsatisfactory results in this study. A quite significant finding in this study was the average mortality of research subjects on the 5th day of treatment, which occurred just after the observation day of the study. The mortality of research subjects was 100%. This finding is in contrast to the results of an increase in LVEDV which was only about 1.03 ± 5.53 ml after 72 hours of being hospitalized in the COVID-19 ICU. The results of these measurements are still in accordance with the normal LVEDV range that has been suggested in a 2006 study by Clay *et al*., which is about 62−120 ml for men and 58−103 ml for women [19]. The volume difference is not enough to cause left ventricular failure resulting in circulatory failure and eventual death. On the other hand, the observation period of only 72 h adjusted for the half-life of the biomarkers galectin-3 and troponin I seemed to be insufficient to describe the observations of increased LVEDV and the co-occurrence of death on the 5th day. Hence, this could be the cause of the discrepancy between the results of observations and the outcome of death. In addition, the mean TAPSE screening value in 45 study subjects was 23 mm which was still within the normal range, so that within the 72-h subject observation range, there was no suspicion of the right heart failure, although other causes have not been determined. There are several reasons that can explain the non-statistically significant results of this study. The first is the possibility of hypoxemia which is usually termed silent hypoxemia where there is a risk of desaturation and failure of oxygen uptake to body tissues but is not accompanied by appropriate clinical appearance due to reflex blunting of the respiratory center in the brain due to infection with the SARS-CoV-2 virus. In a recent 2022 literature review conducted by Ribeiro *et al*., silent hypoxemia was found to have a highly variable prevalence ranging from 3 to 56.5% according to a review of eight prospective and retrospective single-site and multicenter mixed studies. Clinically, the appearance of the subjects of this study also showed a stable condition during surveillance, but after the observation period, their condition worsened and they eventually died, which is in stark contrast to the clinical appearance [20]. This study was conducted during the third wave of the pandemic which was most feared by far because of the delta variant of the SARS-CoV-2 virus. Its strong virulence is caused by the P681R mutation in the S protein of the virus, facilitates the cleavage of the protein which results in more pathogenicity. This may also have caused the condition of the study subjects to worsen despite efforts to provide the best therapy during the pandemic. However, in determining its future as one of the prognostic benchmarks, it should be confirmed with other more specific markers. In addition, the potential extracellular function of galectin-3 as a marker of inflammation and cell-to-cell contact needs to be further demonstrated in humans. Many animal studies have shed light on galectin-3 as a marker of myocardial dysfunction and heart failure, but in human cohorts, the use of these markers has not been able to explain the degree, cause, and risk in the future, so future studies remain needed [21].

In accordance with the pathophysiology of heart failure [22], [23], [24] there will be hemodynamic consequences in the form of decreased cardiac

output, increased LVEDP (left ventricular end-diastolic pressure), peripheral vasoconstriction, sodium and water retention, and decreased oxygen delivery to tissues. However, there is another effect on the acquired increase in LVEDV in the subjects, leading to a sudden increase in LVEDP which immediately resulted in a severe decrease in oxygen delivery to tissues and ultimately death. Due to the involvement of the heart-lung interaction in COVID-19 patients, especially coupled with the use of mechanical ventilation, the risk of increased intrathoracic pressure may affect the increase in LVEDP. The LVEDP can also be more thoroughly examined with more invasive methods such as the insertion of a Swan-Ganz catheter, which was not performed in this study. The authors recommend that further research be conducted regarding the findings and weaknesses of this study, especially on the effect on mechanical ventilation and interactions with the right heart in COVID-19 patients. In addition, it is also necessary to consider whether these results were influenced by the small number of samples, the time of sampling, and observation which was only 72 h, and the fact that this is a single-center study.

Conclusion

This study found no correlation between increased expression of galectin-3 and increased LVEDV. There was also no correlation between increased galectin-3 expression and SOFA score in COVID-19 patients. No correlation was observed between increased expression of galectin-3 and comorbidities as represented by the Charlson score in COVID-19 patients. Multivariate analysis on the effect of delta galectin-3, age, sex, and troponin I on LVEDV indicated that none of those variables had statistically significant correlation ($p < 0.05$) with LVEDV.

References

1. World Health Organization. COVID-19 Weekly Epidemiological Update. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20201020-weekly-epi-update-10.pdf [Last accessed on 2020 Oct 20].
2. World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report-30. Available from: https://www.who.int/docs/default-source/searo/indonesia/covid19/external-situation-report-30-21october2020.pdf?sfvrsn=9d689952_2 [Last accessed on 2020 Dec 27].
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395(10223):507-13. https://doi.org/10.1016/S0140-6736(20)30211-7
   PMid:32007143
4. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al*. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811-8. https://doi.org/10.1001/jamacardio.2020.1017
   PMid:32219356
5. Kim H, Hur M, Moon H, Yun Y, di Somma S. Multi-marker approach using procalcitonin, presepsin, galectin-3, and soluble suppression of tumorigenicity 2 for the prediction of mortality in sepsis. Ann Intensive Care. 2017;7(1):27. https://doi.org/10.1186/s13613-017-0252-y
   PMid:28271449
6. Kementerian Kesehatan (Kemenkes). Kasus COVID-19 Indonesia Didominasi Perempuan; 2021. Available from: https://databoks.katadata.co.id/datapublish/2021/01/23/kasus-covid-19-indonesia-didominasi-perempuan [Last accessed on 2021 Jan 21].
7. Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: A perspective on risk adjustment in critical care research. J Crit Care. 2005;20(1):12-9. https://doi.org/10.1016/j.jcrc.2004.09.007
   PMid:16015512
8. Stavem K, Hoel H, Skjaker SA, Haagensen R. Charlson comorbidity index derived from chart review or administrative data: Agreement and prediction of mortality in intensive care patients. Clin Epidemiol. 2017;9:311-20. https://doi.org/10.2147/CLEP.S133624
   PMid:28652813
9. Kuswardhani RA, Henrina J, Pranata R, Lim MA, Lawrensia S, Suastika K. Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Metab Syndr. 2020;14(6):2103-9. https://doi.org/10.1016/j.dsx.2020.10.022
   PMid:33161221
10. Yang Z, Hu Q, Huang F, Xiong S, Sun Y. The prognostic value of the SOFA score in patients with COVID-19: A retrospective, observational study. Medicine (Baltimore). 2021;100(32):e26900. https://doi.org/10.1097/MD.0000000000026900
    PMid:34397917
11. Raschke RA, Agarwal S, Rangan P, Heise CW, Curry SC. Discriminant accuracy of the SOFA score for determining the probable mortality of patients with COVID-19 pneumonia requiring mechanical ventilation. JAMA. 2021;325(14):1469-70. https://doi.org/10.1001/jama.2021.1545
    PMid:33595630
12. Portacci A, Diaferia F, Santomasi C, Dragonieri S, Boniello E, Di Serio F, *et al*. Galectin-3 as prognostic biomarker in patients with COVID-19 acute respiratory failure. Respir Med. 2021;187:106556. https://doi.org/10.1016/j.rmed.2021.106556
    PMid:34375925
13. Kusnierz-Cabala B, Maziarz B, Dumnicka P, Dembiński M, Kapusta M, Bociąga-Jasik M, *et al*. Diagnostic significance of serum galectin-3 in hospitalized patients with COVID-19-a preliminary study. Biomolecules. 2021;11(8):1136. https://doi.org/10.3390/biom11081136
    PMid:34439802
14. Wibowo A, Pranata R, Akbar MR, Purnomowati A, Martha JW. Prognostic performance of troponin in COVID-19: A diagnostic meta-analysis and meta-regression. Int J Infect Dis. 2021;105:312-8. https://doi.org/10.1016/j.ijid.2021.02.113
    PMid:33667694
15. Al Abbasi B, Torres P, Ramos-Tuarez F, Dewaswala N, Abdallah A, Chen K, *et al*. Cardiac troponin-I and COVID-19: A prognostic tool for in-hospital mortality. Cardiol Res. 2020;11(6):398-404.

https://doi.org/10.14740/cr1159

PMid:33224386

16. Silverio A, di Maio M, Scudiero F, Russo V, Esposito L, Attena E, *et al*. Clinical conditions and echocardiographic parameters associated with mortality in COVID-19. Eur J Clin Invest. 2021;51(12):e.13638. https://doi.org/10.1111/eci.13638

    PMid:34287861

17. Felker GM, Fiuzat M, Shaw LK, Clare R, Whellan DJ, Bettari L, *et al*. Galectin-3 in ambulatory patients with heart failure: Results from the HF-action study. Circ Heart Fail. 2012;5(1):72-8. https://doi.org/10.1161/CIRCHEARTFAILURE.111.963637

    PMid:22016505

18. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315(8):801-10. https://doi.org/10.1001/jama.2016.0287

    PMid:26903338

19. Clay S, Alfakih K, Radjenovic A, Jones T, Ridgway JP, Sinvananthan MU. Normal range of human left ventricular volumes and mass using steady state free precession MRI in the radial long axis orientation. MAGMA. 2006;19(1):41-5. https://doi.org/10.1007/s10334-005-0025-8

    PMid: 16477435

20. Ribeiro A, Mendonca M, Sousa CS, Barbosa MT, Morais-Almeida M. Prevalence, presentation and outcomes of silent hypoxemia in COVID-19. Clin Med Insights Circ Respir Pulm Med. 2022;16:1-5. https://doi.org/10.1177/11795484221082761

    PMid:35221741

21. Hara A, Niwa M, Noguchi K, Kanayama T, Niwa A, Matsuo M, *et al*. Galectin-3 as next-generation biomarker for detecting early stage of various disease. Biomolecules. 2020;10(3):389. https://doi.org/10.3390/biom10030389

    PMid:32138174

22. Siswanto BB, Hersunarti N, Erwinanto, Barack R, Pratikto RS, Nauli SE, *et al*. Pedoman Tatalaksana Gagal Jantung. Indonesia: Perhimpunan Dokter Spesialis Kardiovaskular Indonesia-Perkki; 2015. p. 1-56.

23. Pramana IM. Tatalaksana gagal jantung perioperatif. JAI. 2014;1(3):63-71.

24. Astuti DP. Tinjauan Pustaka: Gagal Jantung. Fakultas Kedokteran Universitas Udayana; 2017. p.1-18.