



The Potential CC16 (Clara Cell Protein 16) as Biomarkers of Lung Damage in COVID-19 Survivors: Literature Review

Fika Tri Anggraini

Universitas Andalas

Email correspondensi: fikatrianggraini@med.unand.ac.id

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Abstract

CC16 or Clara cell secretory protein-16 is a protein produced from the secretion of respiratory epithelial club cells, especially in the lungs. CC16 in several studies has anti-inflammatory effects and plays an important role in potential biomarkers and pathogenesis of chronic lung damage. One of the main respiratory diseases that attacks the lungs is COVID-19 (Coronavirus disease 2019). COVID-19 survivors had significantly decreased serum CC16 levels. The purpose of this review is to draw conclusions based on findings based on research results on the potential of CC16 as a biomarker of lung damage in COVID-19 survivors. This research used a literature review of research published from 2019-2023 in electronic media, such as ProQuest, Science Direct, CINAHL, and Pubmed. The number of Randomized controlled trials (RCTs) research articles obtained was seven articles that met the criteria. The research subjects of the study involved COVID-19 survivors. The keywords used Clara cell secretory protein-16 (CC16), a biomarker of lung damage, and COVID-19 survivor. They revealed that serum CC16 levels were found to be a potential damage or biomarker of lung disease in COVID-19 survivors. This review concluded that CC16's structure and the possible formation of mechanisms molecular and cellular can inhibit inflammation and in clinical applications are thought to be potential biomarkers and therapeutic targets of respiratory disease or chronic lung damage. Future research is required to investigate this hemoprotein in the circulation of COVID-19 survivors.

Keywords: *Biomarker, CC16, COVID-19 survivors, Clara cell protein-16*

INTRODUCTION

or called by the name of CC10 is the result of secretion from epithelial clara cells of the respiratory tract, CCSP (clara cell secretory protein), urine protein-1, uterine globin, and human protein-1. CC16 is especially in the lungs, respiratory tract, blood, and other parts of the body (Rohmann et al., 2022; Wang et al., 2021). CC16 has been widely studied for its anti-inflammatory effects and plays an important role in providing potential biomarkers or pathogenesis of chronic lung or respiratory diseases and may be a therapeutic target for chronic airway diseases (Pourmanaf et al., 2020; Rong et al., 2020). The structure of CC16 investigated was originally possible in clinical applications to be a potential biomarker and molecular and cellular mechanisms that can inhibit inflammation and therapeutic targets of chronic respiratory disease.

Biomarkers do not have a universal definition but are understood as biomolecules arising from a physiological or pathological process. An ideal biomarker is one that cannot be detected or has low levels in non-inflammatory states and will increase in inflammatory states, which will further decrease when the inflammatory process subsides (Fazal, 2021; Kaur et al., 2020; Zhang et al., 2020). Respiratory biomarkers are a means that is easy and simple to use as specimen testing in diagnostic support laboratories. Besides, respiratory biomarkers are used in diagnosing various respiratory diseases of the lungs, including chronic obstructive pulmonary disease (COPD), lung cancer, asthma, as well as other lung diseases, including COVID-19 patients (Almuntashiri et al., 2020; Cui et al., 2022).

After someone is infected with COVID-19, periodic checks need to be performed to determine if COVID-19 survivors have pulmonary fibrosis and chronic lung damage. This condition will make the lungs stiffer, so patients will complain of difficulty breathing (Sibila et al., 2022; Vlachou et al., 2021).

The results of monitoring and research conducted by various institutions found that about one in three COVID-19 survivors risk suffering long-term lung damage (Andreeva, et al., 2021). This is also corroborated as revealed by the National Health Service (NHS), which states that around 30% of patients who have experienced COVID-19 before have lung damage (McKay et al., 2021; Wymant et al., 2021).

Based on the background of the above problems, the researchers found out whether CC16 proved become the potential for biomarkers or lung damage in COVID-19 survivors.

METHODS

The method used a literature review of research results from 2019-2023, which have been published in international electronic media. The search international journal articles used ProQuest, Science direct, CINAHL, and Pubmed with keywords: CC16, Clara cell protein-16, biomarker, lung damage, COVID-19 survivor. The researchers select literature and reviews according to the subject matter. The subjects of the study involved COVID-19 survivors. The literature sources used come from Google scholar, Pubmed, Medline, Ebsco, Hindawi and Cochrane published within the last 10 years. After searching for keywords, then selection was carried out and selected literature with a literature review method regarding the provision of stem cell therapy in the treatment of keloids and obtained 643 articles identified through the five databases mentioned in the methodology and screened based on title. The full-text articles that have been reviewed for eligibility amounted to 20 articles. Writing begins with a review

of the content of each piece of literature that has been read that meets the criteria. The discussion was arranged in an organized format ranging.

RESULTS

After selection on inclusion and exclusion criteria, six articles were selected in the literature review contained in Figure 1. The results of the analysis and synthesis of six journal articles are in Table 1. as follows:

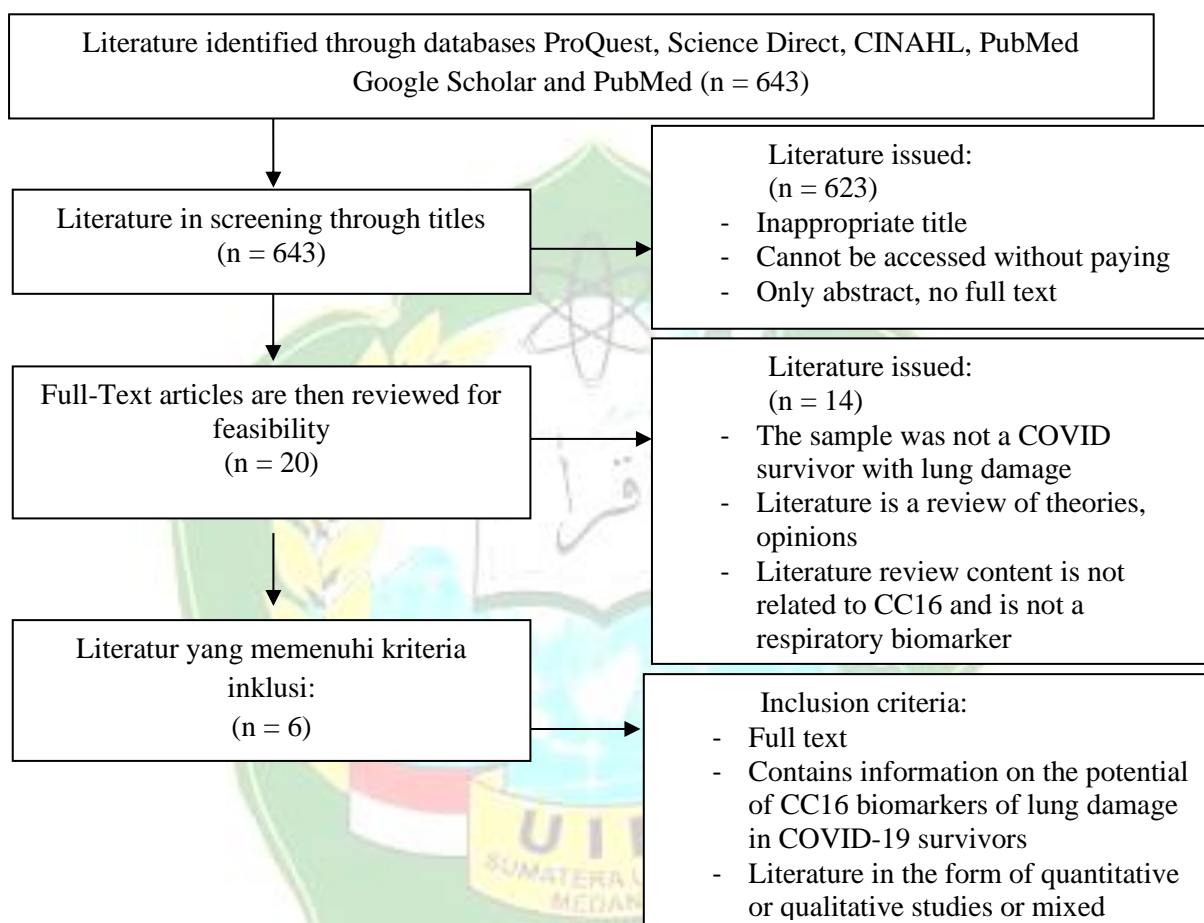


Figure 1. Literature Selection Process Flow Diagram

Table 1. Results of Journal Analysis and Synthesis

No	Title and Author	Research Methods	Result
1.	Host Protein Biomarkers Predicting Severity of Lung Damage due to COVID-19 (Kerschbaumer et al., 2021)	A prospective single-centre cross-sectional study was conducted of 34 adult patients with respiratory symptoms through PCR examination and confirmed COVID-19 treated at Montefiore Medical Center in the Bronx, New York.	These results suggest that host proteins have additional predictive score values as the degree of lung damage and severity due to COVID-19 at the time of the hospital presentation.
2.	Biomarkers of air-blood barrier damage in COVID-19 (Khadzhieva et al., 2021)	A retrospective cohort of 109 patients diagnosed with COVID-19 was conducted. The study consisted of two groups. The first group (1) consisted of victims discharged from the ICU (n = 90). The second group (2) included patients who did not survive (n = 19).	The results were related to levels of SP-D, SP-A, and CC16 in laboratory, blood serum, and clinical data examined by taking into account the estimated sick days at the time of bio-material collection. COVID-19 patients who did not survive had higher levels of SP-A (from day one to day 10, from symptom onset) and lower levels of CC16 (from day 11 to day 20 of symptom onset) compared to those who survived and ICU-discharged. No significant difference in SP-D levels was found between the groups. In conclusion, according to the results of the study, SP-A surfactant protein and Club CC16 cell protein were associated with increased COVID-19 mortality.
3.	Brief Research Report: Serum Clara cell 16 kDa protein levels are increased in patients hospitalized for severe SARS-CoV-2 or sepsis infection (Rohmann et al., 2022)	Using a case-control study design, patients hospitalized for or non-pulmonary sepsis infection or severe SARS-CoV-2 were compared with age- and sex-matched healthy human subjects. Serum CC16 concentrations were measured by ELISA and assessed in two	The results showed that serum CC16 levels were inversely proportional to platelet count in severe SARS-CoV-2 infection and positively correlated with disease duration. In addition, serum CC16 levels rose significantly in both types of infection (sepsis and SARS-CoV-2) in sepsis patients by 35.37 ± 28.10 ng/ml vs. healthy controls of 15.25 ± 7.51 ng/ml, $p = 0.032$. SARS-CoV-2 patients of 96.22 ± 129.01 ng/ml vs. healthy

- types of severe infections.
4. The relationship between the expression of serum IL-18 mRNA, CC16, and sTREM-1 and the severity and prognosis of ventilator-associated pneumonia in elderly patients (Wang et al., 2021)
- The patients were divided into a VAP group (n=75) and a non-VAP group (n=110). According to the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score, patients with VAP are divided into low-risk, medium-risk, and high-risk groups. According to the results of 28 days, patients were divided into a survival group and a death group. Serum levels of IL-18, CC16, and sTREM-1 were detected, and their values in VAP prediction and prognosis were analyzed using the receiver operating characteristic curve (ROC).
- controls of 14.05 ± 7.48 ng/ml, with $p_v = 0.022$ but no clear difference between infection with and without pulmonary focus ($p_v = 0.089$). Serum IL-18 and sTREM-1 levels in the VAP group were higher than in the non-VAP group, while CC16 levels in the VAP group were lower than in the non-VAP group ($p_v < 0.05$). CC16 levels increased sequentially ($p_v < 0.05$), while serum IL-1 and serum IL-18 levels fell sequentially from the high-risk group to the medium-risk group to the low-risk group. The results of the analysis of the ROC curve showed that the Youden index and AUC of the combined diagnosis of VAP with serum IL-18 mRNA, sTREM-1, and CC16 were 0.710 and 0.930 which were higher than those of a single diagnosis ($p_v < 0.05$). CC16 levels were higher than in the mortality group and serum IL-18 sTREM-1 and mRNA values in the survival group were lower than in the death group ($p_v < 0.05$). ROC curve analysis showed that the Youden index and AUC of combined diagnosis with serum IL-18 mRNA, sTREM-1, and CC16 were 0.506 and 0.731 which were higher than that of a single diagnosis ($p_v < 0.05$).
5. Clinical significance of CC16 and IL-12 in bronchoalveolar lavage fluid from various stages of silicosis (Zhang et al., 2020)
- The sandwich double-antibody enzyme-linked immunosorbent assay (ELISA) method was used to determine IL-12 and CC16 in BALF levels of 79 patients with silicosis of various stages. Correlation analysis was performed between IL-12 and CC16 levels, cytological counts in patients with silicosis at various stages, and pulmonary function.
- There were no significant differences in the cell count, BALF recovery volume, lymphocytes in the alveolar lavage fluid, and percentage of macrophages of patients with silicosis in different stages ($p_v > 0.05$). The percentage values of neutrophils in the first stage and the second stage were statistically significantly higher than in the control group ($p_v < 0.05$). CC16 at BALF levels in the stage one and two silicosis groups was lower than

6. The decreased serum concentration of CC16 is associated with the severity of chronic obstructive pulmonary disease and contributes to the diagnosis and assessment of the disease (Rong et al., 2020)

The correlation between serum CC16 concentration and clinical parameters was analyzed by linear correlation analysis and multiple linear regression analysis. The sensitivity and specificity of serum CC16 for differential diagnosis of COPD are determined by the receiver carrier characteristic (ROC) curve.

in the stage three silicosis group and the control group with statistically significant differences ($p < 0.05$), while CC16 levels in the stage two silicosis group were higher than in the stage one group ($p < 0.01$).

IL-12 levels in the second and third-stage silicosis groups were higher than in the stage one silicosis group ($p < 0.01$), and control group IL-12 levels were higher ($p < 0.01$). With increasing duration of dust exposure, IL-12 and CC16 levels decreased and showed positive correlation results between these indices (correlation coefficient $r = 0.559$, $p < 0.01$).

Furthermore, IL-12 levels were negatively correlated with FEV1 and VC max ($r = -0.250$, -0.483 ; both $p < 0.05$), and CC16 silicosis patient levels were positively correlated with FEV1/FVC and VCmax ($r = 0.242$, 0.257 ; both $p < 0.05$).

The decrease of serum CC16 concentrations in COPD patients was more stable compared to the healthy control group ($p < 0.05$). Decreased serum CC16 was negatively associated with smoking ($p < 0.05$), GOLD assessment ($p < 0.005$), mMRC score ($p < 0.05$), and patient's medical history ($p < 0.05$), but the results were positively correlated with lung function ($p < 0.05$). Smoking history, COPD assessment, FEV1/FVC, and mMRC score all affected CC16 concentrations ($p < 0.05$). The occurrence of decreased levels of CC16 is an independent risk factor in the process of decreased lung function. The sensitivity and specificity of serum CC16 for identifying COPD reached 65,3% and 75%.

DISCUSSION

Coronavirus 2019 (COVID-19) is one of the pathogens whose target organs are mainly in the respiratory system. The lungs are the organs in the respiratory system that play the most role and have persistent and prolonged effects post-COVID-19. The upper and lower respiratory tracts are the main pathways of entry of SARS-CoV-2 into the body that cause diseases such as acute endothelin (ET) and lung damage, upper respiratory tract infections, pulmonary fibrosis, thromboembolism, and pneumonia in the long term, it can also reduce the quality of life. COVID-19 survivors are crucial to know whether the lungs, after being infected with COVID-19, develop fibrosis, lose their lung function, or recover well (Iqbal et al., 2022; Sibila et al., 2022).

Clara cells are club cells or secretory epithelial cells that are not ciliated, located along the bronchioles, and these cells differ in morphology and the secretion of the product compared to cells that secrete serous and mucus. The first time these cells were known as a different cell type in the bronchioles morphologically and histochemically. Max Clara, in 1937, described the contents of the same cell discovered by Kolliker in the human lung, and this was named "Clara Cell". He found granules on the cells that indicated exocrine cell types (Cui et al., 2022; Xu & Song, 2017). The granules on Clara's cells contain proteins that distinguish them from mucous secretory cells (Andreeva, Pokhasnikova, et al., 2021).

The product secreted by Clara cells (CCSP/Clara cell secretory protein) is known as CC16 or CC10, which is a source of protein secreted by epithelial club/ clara cells of the respiratory tract, forms a kind of rod-like cell without cilia and produces mucus secretion, which is in the nasal cavity into the respiratory epithelium of the respiratory tract bronchioles (Kerschbaumer et al., 2021; Liu et al., 2021).

CC16 in the circulatory system both in pathological and normal conditions can be detected easily (Hause et al., 2021; Ujiie et al., 2021). This protein has a protective effect on the respiratory inflammatory response by modulating the activity of tumor necrosis factor- α (TNF- α), interferon- γ , and phospholipase A2 (Miyama et al., 2021; Wong et al., 2021).

The main function of Clara cell secretory protein-16 (CC16) in the respiratory system is to protect the bronchiole epithelium as well as a progenitor cell when bronchiole epithelium damage occurs. CC16 has the ability to differentiate into Clara cells and ciliated respiratory epithelial cells, making it a stem cell. The isolated CC16 is then implanted in the damaged trachea; then the epithelial restoration value is evaluated. It turns out that there is a normal

development of damaged cells, so it is evidence that CC16 has a role as a progenitor cell in damaged respiratory epithelium (Combes et al., 2019; Sibila Vidal et al., 2021).

Similar studies were also conducted by inducing epithelial damage in the respiratory tract, where CC16 causes epithelial healing including ciliated epithelial cells. This is due to the CC16's ability migration to damaged tissues or cells. Besides, the CC16 mechanism migrates to injured lung tissue (Eklund et al., 2021; Liu et al., 2021; Méndez et al., 2019).

CC16 has been studied and researched as a potential biomarker for injury in most lung and epithelial lung diseases, including COPD, idiopathic pulmonary fibrosis, pneumonia, asthma, ARDS, sarcoidosis, and COVID-19 (Rong et al., 2020; Wang et al., 2021; Almutashiri et al., 2020). Chronic lung disease involves lung remodelling, including changes in the material in the respiratory epithelium, subepithelial fibrosis, increased thickening of the basement membrane, and smooth muscle hypertrophy. Characteristic pathological changes in the epithelium of the respiratory tract terin integrated at the initiation and progression of COPD. Most COPD and asthma studies measuring CC16 protein levels in serum have shown that the intervention group had lower serum CC16 levels compared to the control group. In contrast to serum CC16 levels in most patients with ARDS, sarcoidosis, and pulmonary fibrosis the results were higher (Almutashiri et al., 2020; Hasegawa et al., 2011).

Patients infected with the COVID-19 virus have diffuse alveolar damage. Circulating levels of CC16 protein in serum were significantly reduced in COVID-19 survivors and patients compared to healthy controls and CC16 mRNA levels decreased dramatically in the lungs of COVID-19 patients and COVID-19 survivors (Almutashiri et al., 2021; Iqbal et al., 2022; Kerschbaumer et al., 2021). CC16 also reported in previous research that in injury remodeling, Clara's cells could migrate and restore injured alveoli in the lungs and were involved in repairing active wounds after alveolar injuries and repairing damaged lung epithelium (Almutashiri et al., 2021; Cui et al., 2022; Khadzhieva et al., 2021; Vlachou et al., 2021).

CONCLUSIONS

This review aims to systematically evaluate the relevant evidence on the potential of CC16, a biomarker of lung damage in COVID-19 survivors. CC16 has been shown to have the potential as a biomarker for lung epithelial damage in most lung diseases. COVID-19 survivors are at risk of suffering long-term damage, with approximately 30% of patients experiencing lung damage. The results revealed that serum CC16 (Clara Cell Protein 16) levels can indicate

severity of respiratory disease manifestations and serves as a potential biomarker in COVID-19-related lung organ injury. This review concluded that the structure of the CC16 protein allows cellular and molecular mechanisms to inhibit inflammation and the application of clinical applications is reviewed as potential biomarkers and therapeutic targets of respiratory disease or chronic lung damage. Future research is required to investigate this hemoprotein in the circulation of COVID-19 survivors.

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