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## The potential role of exosome on cytokine storm and treatment of severe COVID-19 infection



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### ABSTRACT

The symptoms of COVID-19 varies from mild to severe. The risk of severe infection occurs about 10% of cases, while the risk of death occurs about 0-14.6% of cases. One of the suspected pathophysiology in cases of severe infection and death of COVID-19 is due to cytokine storms. Exosome plays a vital role in the pathogenesis of several diseases, including severe disease such as sepsis due to cytokine storm. Exosome has been proven as a

nanomaterial carrier that can tackle cytokine storm in the treatment of severe COVID-19 infection. Several studies have been conducted for this purpose, and its clinical application continually increases. This review will explore the role of exosomes in cytokine storms that occur in patients with COVID-19 and seek the opportunity to use exosomes in their management

**Keywords:** COVID-19, cytokine storm, exosome, treatment, severe case

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### INTRODUCTION

COVID-19 was declared as a pandemic by the WHO since February 2020. Recently, COVID-19 has infected more than 200 countries in the world.<sup>1</sup> Symptoms of COVID-19 infection vary from mild to severe. Mild symptoms can include sore throat, runny nose, and mild fever. Severe symptoms are characterized by high fever, shortness of breath, and acute respiratory distress syndrome that can even cause death.<sup>2</sup>

The severe infection risk occurs about 10% of cases, while the risk of death occurs in about 0-14.6% of cases.<sup>2</sup> Yang et al. (2020) reported 52 (7%) critical cases of 710 confirmed pneumonia cases of SARS-Cov-2 and found 32 (4.5%) cases of death in the group. As of June 7, 2020, from 3.1 million active cases, 53,000 patients were treated in critical condition (1.7%). While death has reached more than 400 thousand people from 6.9 million cases (5.8%).<sup>3</sup>

One of the suspected pathophysiology in cases of severe infection and death of COVID-19 is due to cytokine storms, where this condition causes excessive release of cytokines from the patient's body, such as interleukins, GMCS-F, TNF- $\alpha$ . Ultimately, the cytokine storm can cause the failure of various organs to maintain the immune system, thus leading to mortality.<sup>4</sup>

Exosomes are membrane-bound extracellular

vesicles measuring 30-100 nm. Exosomes carry various molecules that have implications for inter-cell communication to play a role in the pathogenesis of many diseases and infections. Exosomes generally contain proteins, fats, nucleic acids, and various other materials. At present, there were 4,563 proteins, 194 types of fat, 1,639 mRNA and 764 micro RNA, and non-coding RNA (ncRNA), as well as mtDNA, ssDNA, and dsDNA that have been identified in exosomes.<sup>5,6</sup> Exosomes play a role in cell material transport from one cell to another cell. From normal cells to normal cells, from unhealthy cells to normal cells, or vice versa from normal cells to unhealthy cells. The analogy of an exosome is a truck carrying material that can move the material to another place.

In cases of severe infections such as sepsis cardiomyopathy, the exosomes released by platelets (platelet-derived exosomes), were found higher in numbers compared to healthy people.<sup>7</sup> The exosomes obtained from sepsis-induced rats demonstrated roles in proinflammation and in triggering cytokine overproduction.<sup>8</sup>

COVID-19 management is currently carried out by various methods. In cases of severe COVID-19 infection, the choice can be in the form of steroids, intravenous immunoglobulin, selective cytokine blockade, and the treatment of Janus kinase (JAK).<sup>9</sup> Several studies have reported that exosome has potentials in the management of various diseases,

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including sepsis. Essandoh et al. (2015) found that blocking exosomes can reduce inflammation induced by sepsis and cardiac dysfunction.<sup>8</sup>

Based on this, it is interesting to explore the role of exosomes in cytokine storms that occur in patients with COVID-19 and seek the opportunity to use exosomes in their management.

## SEVERE INFECTION COVID-19

Severe infections in COVID-19 mainly show symptoms of fever in 80% of cases and dry cough in 51.7% of 60 patients. More than half (51.7%) of patients with severe infections have preexisting diseases such as hypertension, diabetes, autoimmune diseases, strokes, and pregnant woman. Based on laboratory tests, decreased levels of procalcitonin were frequently found (88.3%). It is also followed by an increase in lactate dehydrogenase and lymphopenia, respectively 80% and 63.3%. Based on the results of a chest CT scan, all patients with severe infection with COVID-19 had pneumonia with the main feature of patchy bilateral shadows (85%).<sup>10</sup>

According to Zhao et al. (2020), lymphopenia is a marker of severe infections with poor treatment results.<sup>11</sup> However, based on the results of the study of Zhu et al., lymphopenia did not affect the increased risk of death of patients with severe infections.<sup>12</sup>

A meta-analysis conducted by Lippi et al. (2020) found that patients with lower platelets were more at risk of suffering from more severe COVID-19. This condition is evident from the significant differences between the platelets of patients with severe infections compared to patients with mild symptoms.<sup>13</sup> Zhu et al. (2020) found that in patients with severe infections COVID-19 who died had significantly lower platelet rates than those who survived.<sup>12</sup>

Analysis of 102 patients with severe COVID-19 infections showed that the liver, kidneys, and heart were affected. In the liver, there is an increase in the Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) enzymes. When compared, the two enzymes among patients who survived and died found that AST was significantly different, while ALT did not show a significant difference. Kidney function represented by blood urea nitrogen and creatinine showed a considerable increase in patients with severe infections. Likewise, the examination of heart function defined by CK-MB and CK also showed an increase. Furthermore, the ratio of the two enzymes in patients who survived and died was significantly different.<sup>12</sup>

Based on RNA sequencing research and viral track analysis of 3 mild cases and six severe cases in

which there were about 50,615 cells analyzed using the MetaCell algorithm, then subsequently were divided into three pathways into myeloid, lymphoid, and epithelial cells. Some significant differences were found between mildly and severely infected patients, including alveolar macrophages and pDC, enriched in the myeloid compartment in mild patients. In contrast, in severe patients, myeloid cells were affected by a patient-specific diversity associated with the accumulation of neutrophils, FCN1 + monocytes, and monocyte-derived SPP1 + macrophages. NK cells and CCR7 + CD4 + T cells also increase in severe cases, whereas activated ZNF683<sup>hi</sup> CD8 + cytotoxic T cells are found in mild cases. With differential gene expression analysis, in cases of severe infections, found CD4 + T cells that have a more naïve phenotype, expressing IL7R, CCR7, S1PR1, and higher LTB. The most surprising thing found was the sign of inflammation and perturbed immune response in cases of severe infection.<sup>14</sup>

In severe COVID-19 infections, ARDS is the most common condition. In ARDS caused by severe community-acquired pneumonia (SCAP), ten exosomal subsets of miRNA were found, among others, miR-146a, miR-126, and miR-155 had significantly increased. Based on these studies, it was also found that only miR-126 can potentially predict mortality on the 28th day (OR = 1,002, P = 0.024).<sup>16</sup> In the case of ARDS, there can also be a decrease in miRNA-425, which can lead to an increase in cell apoptosis, which results in widespread lung tissue damage.<sup>15</sup>

## CYTOKINE STORM

Cytokines are small and short-lived proteins. Many different cell types secrete them. Cytokines provide communication between cells and play a crucial role in modulating the innate and adaptive immune response. There are several types of cytokines includes interferons, interleukins, chemokines, mesenchymal growth factors, tumor necrosis factor family, and adipokines.<sup>16</sup>

Normally the body needs moderate amounts of cytokines; however, when cytokines were overproduced, the immune system starts causing damage to the patient. This increased immune response does not occur in all patients with severe infections. This condition is caused by increased pro-inflammatory activity in patients infected with severe human coronavirus (HCoV).<sup>17</sup>

Cytokine and chemokine levels were found to be higher in patients with more severe infections, which leads to the attraction of other inflammatory cells such as neutrophils and monocytes, which eventually resulted in excessive infiltration of

inflammatory cells to the lungs, which in turn caused damage to the lungs. Cytokines (such as IFN- $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-18) play a role in the pathogenesis of clinical symptoms in COVID-19. The signs were fever, hematopoietic function disorder, disseminated intravascular coagulation (DIC), decreased serum protein, debilitating, liver damage, acute kidney injury, anemia, and acute-phase protein.<sup>18</sup>

Cytokine storm is an event where the excessive release of pro-inflammatory cytokine can be triggered by various factors, including infection by a virus. If the incoming virus is new (there is no memory in the immune system) and the pathogenic power is high, then the release of cytokines tends to be out of control. This condition occurs when large numbers of white blood cells are activated and release inflammatory cytokines, which activate even more white blood cell involvement.<sup>17</sup>

When someone who has the potential for cytokine release is then infected with the virus that causes COVID-19, the cytokine release seems triggered and awakened. That cytokine release will result in an uncontrolled release of cytokines or cytokine storms. Cytokine storms create inflammation, which weakens the blood vessels in the lungs and causes fluid to seep into the alveoli, flooding the blood vessels and eventually creating systemic problems in many organs, which can cause damage to all organs.<sup>4</sup>

When a cytokine storm in the lungs occurs, the lungs will be filled with fluid and immune cells, such as macrophage, which can eventually cause airway obstruction. This condition will cause shortness of breath and can even cause death.<sup>4</sup>

In the COVID-19 case, the occurrence of non-lung organ failures such as in the liver and kidneys can be caused by this cytokine storm, even when there is no lung damage. However, the cytokine storm is most often associated with the onset of ARDS. Furthermore, cytokine storms can cause multi-organ dysfunction (MOD). This situation can lead to death.<sup>4,18</sup>

One hypothesis is that free DNA causes cytokine storms. Free DNA in COVID-19 patients can be released by infected lung cells, lymphocytes, and various other immune cells. This free DNA will enter the circulation system and stimulate the release of large amounts of cytokines. Moreover, this condition will then cause a cytokine storm.<sup>19</sup>

An immunologist from Japan proposed a possible molecular mechanism that causes a massive release of pro-inflammatory cytokines (cytokine storm), which leads to the ARDS in COVID-19 patients. Their suggestions were based on recent findings that explain how SARS-CoV-2 enters the human cells.

They explain pro-inflammatory cytokine release via the associated angiotensin II pathway.<sup>20</sup>

A cytokine profile on hiper-inflammatory syndrome was associated with COVID-19 severity. The more severe cases were characterized by increased interleukin IL-2, IL-7, granulocyte-colony stimulating factor, interferon- $\gamma$  inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- $\alpha$ , and tumor necrosis factor- $\alpha$ .<sup>21</sup>

Sun et al. (2020) scheme the relationship between cytokine and clinical features of COVID-19 patients. In these publications, IFN $\gamma$  can cause fever, impaired hematopoietic function, DIC, and a decrease in serum protein. TNF can cause symptoms such as that from IFN $\gamma$ , coupled with debilitating, hyperlipidemia and liver damage. IL-1 $\beta$  can cause fever and acute-phase protein. IL-6 can trigger a fever, acute kidney damage, anemia, and acute-phase protein. IL-8 can trigger liver damage.<sup>18</sup> IL 17A has the potential to stimulate the occurrence of a pro-thrombotic state in the vascular system. Furthermore, this increase in cytokine levels supports the formation of platelet aggregation at the site of vascular injury.<sup>22</sup>

## POTENTIAL ROLE OF EXOSOME IN CYTOKINE STORM

Several published studies show that cytokine storms occurring in sepsis cases show an increased concentration of exosomes.<sup>7,23</sup> In severe cases of COVID-19, sepsis can occur. This condition is the same as in acute respiratory distress syndrome (ARDS) caused by other coronaviruses such as SARS and MERS, where the development of cytokine storms is a sign of disease severity.<sup>18</sup>

In experimental studies with exosome cytokines extraction from sepsis mice animal models, there were increase pro-inflammatory cytokines IL-1 $\beta$ , IL-2, IL-6, and TNF- $\alpha$ . In the advanced stages, all proinflammation of cytokines experienced a rise, including IL-12, IL-15, IL-17, and IFN- $\gamma$ . Exosome took from sepsis mice also results in increased differentiation of Th1 and Th2 cells.<sup>24</sup>

In septic shock, the exosome isolated from the patient's serum was significantly different from the healthy person, both at hospital admission and seven days after treatment. There were 28 miRNAs found in sepsis patients on day 0 and day 7, including has-miR-122-5p, has-miR-125b-5p, and has-miR-126a. This modulation pathway by exosomal micro RNA is mainly related to inflammatory and immune responses. In this report, it is also shown the mRNA contained in the exosome of sepsis patients is associated with an inflammatory reaction. This condition is indicated

by inflammatory genes only found in sepsis patients, whereas in normal people, no expression is found. There are 84 mRNAs associated with antioxidant defense and oxidative stress in normal people and sepsis patients. Still, in sepsis patients, there is an increase in mRNA for myeloperoxidase (MPO) and oxidative stress response gene Fork-head box protein M1 (FOXM1).<sup>23</sup>

Platelet-derived exosomes from septic patients could have induced myocardial dysfunction by previous *in vivo* exposure to lipopolysaccharide. The generation of nitrate oxide by septic exosomes and the increased myocardial nitrate content after incubation with exosomes from septic patients suggests a nitrate oxide-dependent mechanism that might contribute to myocardial dysfunction of sepsis. [25] That might explain the occurrence of heart damage in severe cases of COVID-19.

According to the explanation above, there are several pathways the exosome can contribute to the development of cytokine storm. The relation between the exosome and cytokine storm is shown in Figure 1.

## MANAGEMENT OF SEVERE CASES OF COVID-19

Several guidelines for the management of COVID-19 have been released, both in mild and severe COVID-19 infections. The management in severe infections cases was ranging from the use of anti-malaria such as chloroquine, anti-bacteria such

as azithromycin, anti-viruses such as remdesivir, plasma convalescence, and others.<sup>4,17,18,26</sup>

The basic principle in the management of severe COVID-19 infection is supportive therapy to overcome complications that may arise, such as pneumonia, ARDS, sepsis, septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization, including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy.<sup>27</sup> Oxygen must be administered immediately through a nasal cannula, or high-flow oxygen.<sup>26</sup>

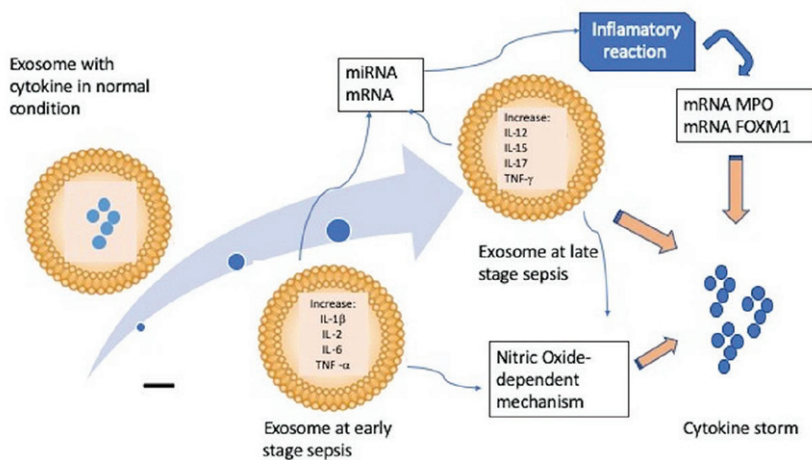
Management to cope with cytokine storms in cases of COVID-19 infection is essential, given the effects that can result in death. Immune-based therapy to deal with cytokine storms is still limited. The ongoing investigations for COVID-19 management include understanding the roles of convalescent plasma, intravenous immunoglobulin, IL-1, IL-6 inhibitors, Interferon, and Janus kinase inhibitors. [26] Hirano et al. (2020) proposed a possible therapeutic target of inflammatory cytokine via the IL-6- STAT3 axis.<sup>20</sup>

The use of remdesivir for severe cases of COVID-19 showed quite encouraging results, where there was clinical improvement in 36 of 53 cases (68%).<sup>28</sup> National Institute of Health recommends remdesivir for the treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO).<sup>26</sup>

The use of anti-inflammatory dexamethasone in COVID-19 patients is recommended by Theohadires and Conti (2020), however, only for intubated patients, and even then for a short time. That is because dexamethasone suppresses inflammatory reactions, and subsequently suppresses the immune system needed to prevent further damage due to COVID-19.<sup>29</sup>

## POTENTIAL ROLE OF EXOSOME IN CRITICAL COVID-19 CASES

Since it is understood that exosomes can carry various cellular materials, especially nanoparticles. There is a possibility of exosomes used as transporters by inserting a material to prevent or treat various diseases. The exosome has the right character for this purpose, due to the size and surface charge suitable for nanocarriers in complex physiological environments. The size of nanoparticles used in systematic delivery determines their blood circulation in two ways. First, it should be large enough to avoid rapid renal clearance, and second, it should be small enough to evade reticuloendothelial system uptake. Its surface



**Figure 1.** The role of exosome in cytokine storm development. The incidence of cytokine storm is influenced by the presence of mRNA associated with inflammatory reactions such as MPO mRNA and FOXM1 mRNA. In addition, the nitric oxide dependent mechanism which is influenced by exosome at early and late stage sepsis will modulate the occurrence of cytokine storm.



charge is a crucial factor in determining the colloidal stability of nanoparticles and their interactions with biological systems. Besides, exosomes also have a double membrane structure that makes them possible to compartmentalize and solubilize both hydrophilic and hydrophobic materials.<sup>30</sup>

There have been many studies that prove exosome can carry various drugs such as curcumin, doxorubicin, paclitaxel, and even miRNA. This endogenous transport system can increase the solubility and pharmacokinetics of the drug so that its effectiveness has increased. In addition, exosomes are intrinsic materials that are biocompatible, biodegradable, and non-immunogenic.<sup>30</sup>

Research at Massachusetts University has proven that exosomes produced by B cells (exosome-derived B cells) can be inserted with artificial miRNA-155. In this study, it can also be proven that mi-RNA-155 inserted into the exosome can be transported to the target cell, which is the hepatocyte cell. Therefore, the exosome can be used to transport particular cellular material towards the specified target organ.<sup>31</sup>

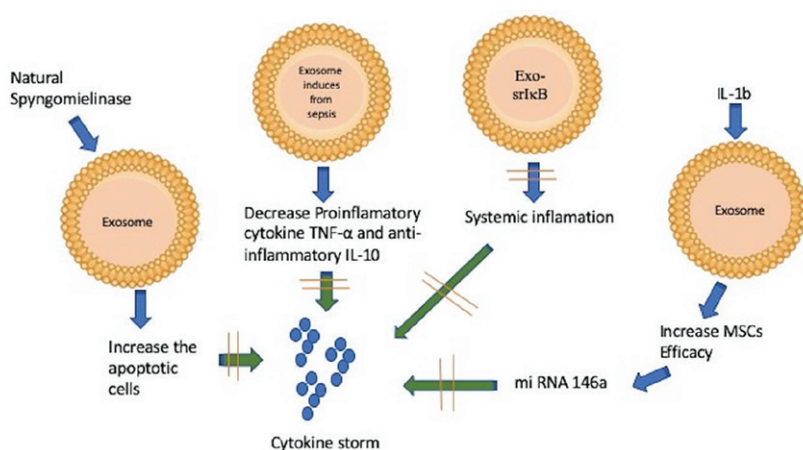
In an in-vivo study, the results show that natural sphingomyelinase (GW4869) can inhibit exosomes that produce excessive cytokine (cytokine storm). Moreover, exosome in sepsis animal model experiments shows an increase in phagocytosis of apoptotic cells and significantly reduces death.<sup>32</sup> Exosomes derived from sepsis-induced rats can prevent the occurrence of sepsis in other mice. This condition can show the potential of injected exosome can decrease the immune response and

tissue injury, represented by a decreased level of pro-inflammatory cytokines TNF- $\alpha$  and anti-inflammatory IL-10.<sup>24</sup>

Other studies using an intraperitoneal injection of purified srIkB-loaded exosomes (Exo- srIkB) attenuates mortality and systemic inflammation in septic mouse models.<sup>33</sup> Song et al. (2017) found IL-1b pretreatment enhanced mesenchymal stem cells (MSC)-induced alternative macrophage polarization. IL-1b pretreatment improved the therapeutic efficacy of MSCs on sepsis. Finally, the author concluded that IL-1b-mediated up-regulation of miR-146a in exosomes plays an essential role in the protective effects of bMSCs. MiR-146a is known as an anti-inflammatory miRNA that plays an essential role in inflammatory disorders.<sup>34</sup> According to the review of Tsuchiya et al. (2020), the exosomes produced by MSC can be utilized as a preventative agent in the treatment of severe infections and COVID-19. This is based on published studies that have shown therapeutic benefits in ARDS cases triggered by other coronaviruses. Furthermore, there are currently also 33 ongoing clinical trials for the use of MSC exosome in the treatment of various diseases, but for COVID-19 alone, no one has done the research.<sup>35</sup>

Wu et al. (2016) from the review shows that exosomes are an alternative treatment in sepsis cases. However, based on the results of the analysis, the current publications are mostly animal studies. Therefore, further research for its application in humans is needed.<sup>36</sup>

The pathogenesis of severe COVID-19 infection was strongly related to the cytokine storm. The basis of treatment should be based on this theory. There was the potential role of exosome in the treatment of severe COVID-19. The potential role of exosome through the cytokine storm inhibition is described as Figure 2.



**Figure 2.** The potential role of exosome on inhibition of cytokine storm. This figure shows the potential of the exosome in several studies regarding its role in inhibiting the cytokine storm process. These studies demonstrate a pathway of cytokine storm inhibition whereby the exosome is able to decrease systemic inflammation by increasing cell apoptosis and decreasing proinflammatory cytokines (TNF- and IL-10). In addition, the exosome is able to mediate regulation of miR-146a via MSC.

## CONCLUSION

Exosome has the potential for the management of COVID-19 infection, especially in the incidence of sepsis through the emergence of cytokine storms. For the management of severe COVID-19 infection, exosome can be used, but further research is still needed for its use in humans.

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## AUTHOR CONTRIBUTION

All authors have contributed to all processes in this research, including preparation, data gathering, and analysis, drafting, and approval for publication of this manuscript.

## DISCLOSURE

The authors declare that they have no conflict of interest regarding the publication of the current review

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