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HUMAN CLINICAL ARTICLE

STEM CELLS TRANSLATIONAL MEDICINE

Umbilical cord mesenchymal stromal cells as critical COVID-19 adjuvant therapy: A randomized controlled trial

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Abstract

One of the main causes of acute respiratory distress syndrome in coronavirus disease 2019 (COVID-19) is cytokine storm, although the exact cause is still unknown. Umbilical cord mesenchymal stromal cells (UC-MSCs) influence proinflammatory T-helper 2 (Th_2) cells to shift to an anti-inflammatory agent. To investigate efficacy of UC-MSC administration as adjuvant therapy in critically ill patients with COVID-19, we conducted a double-blind, multicentered, randomized controlled trial at four COVID-19 referral hospitals in Jakarta, Indonesia. This study included 40 randomly allocated critically ill patients with COVID-19; 20 patients received an intravenous infusion of 1×10^6/kg body weight UC-MSCs in 100 ml saline (0.9%) solution (SS) and 20 patients received 100 ml 0.9% SS as the control group. All patients received standard therapy. The primary outcome was measured by survival rate and/or length of ventilator usage. The secondary outcome was measured by clinical and laboratory improvement, with serious adverse events. Our study showed the survival rate in the UC-MSCs group was 2.5 times higher than that in the control group ($P = .047$), which is 10 patients and 4 patients in the UC-MSCs and control groups, respectively. In patients with comorbidities, UC-MSC administration increased the survival rate by 4.5 times compared with controls. The length of stay in the intensive care unit and ventilator usage were not statistically significant, and no adverse events were reported. The application of infusion UC-MSCs significantly decreased interleukin 6 in the recovered patients ($P = .023$). Therefore, application of intravenous UC-MSCs as adjuvant treatment for critically ill patients with COVID-19 increases the survival rate by modulating the immune system toward an anti-inflammatory state.

KEYWORDS

adjuvants, cord stem cell transplantation, COVID-19, cytokine release syndrome, immunology, mesenchymal stromal cells

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Lessons learned

Application of intravenous umbilical cord mesenchymal stromal cell infusion as an adjuvant treatment for critically ill patients with COVID-19 increases the survival rate by modulating the immune system toward an anti-inflammatory state.

Significance statement

There are some unfortunate patients with COVID-19 who are not responsive to all the combination treatment given. Therefore, this study exclusively involved intubated critically ill patients with COVID-19 in the intensive care unit. In contrast to existing studies, this study used regular umbilical cord mesenchymal stem cells without a special manipulation procedure that was directed at achieving angiotensin converting enzyme-2 (ACE 2)-negative mesenchymal stem cell. The results showed that the survival rate in those receiving umbilical cord mesenchymal stromal cells was 2.5 times higher than that in the control group.

1 | INTRODUCTION

Patients with COVID-19 are increasing around the world, with more than 61.8 million cumulative cases and 1.4 million deaths globally. In November 2020, a referral hospital's data in Jakarta showed that intensive care unit (ICU) occupancy had increased from 60% to 80%. Moreover, the mortality rate of critically ill patients with COVID-19-related pneumonia in the ICU was as high as 87% in a top referral COVID-19 hospital (Persahabatan Central Hospital, Jakarta, Indonesia); this situation necessitated that clinicians fashion a breakthrough therapy to increase the survival of patients in the ICU.

The current management of COVID-19 serves as an empiric and supportive therapy, as the curative regiment has yet to be found. Unfortunately, some patients are not responsive despite all the combination treatments given. There is still very limited research about the new potential therapeutic agents for treating critically ill patients with COVID-19.[1,2]

Acute respiratory distress syndrome (ARDS) is the leading cause of death in patients with COVID-19, and one of the main causes of ARDS in SARS-CoV-2 infection is cytokine storm, although this topic is still a matter of controversy.[3] In interactions with dendritic cells, mesenchymal stromal cells (MSCs) cause proinflammatory Th_2 cells to shift to anti-inflammatory Th_2 cells, including changes in cytokine profiles toward anti-inflammatory. Human umbilical cord mesenchymal stromal cells (hUC-MSCs) have a high proliferative capacity for sustaining paracrine effects and low risk of body rejection due to absent Human Leukocyte Antigen (HLA) expression.[4,5]

Clinical trials in China have shown that patients with COVID-19-related pneumonia treated with UC-MSCs were more likely to survive and have a faster recovery than patients without MSC therapy.[6-8]

In contrast to existing studies, our study exclusively involved intubated critically ill patients with COVID-19 in the ICU and used naïve umbilical cord mesenchymal stromal cells that were processed using the simple multiple harvest explant procedure methods without a special manipulation procedure that was directed at achieving ACE-2 negative MSCs. Therefore, this study aims to investigate whether administration of allogenic UC-MSCs as adjuvant therapy for critically ill patients with COVID-19 who are unresponsive to conventional supportive treatment can improve the survival rate of critically ill patients with COVID-19-related pneumonia in Indonesia.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a multicentered, double-blind, randomized clinical trial, conducted between May 1 and October 10, 2020, at four COVID-19 referral hospitals in Jakarta (Sulianti Saroso Infection Disease Hospital, Persahabatan Central General Hospital, Cipto Mangunkusumo National Central General Hospital, and Universitas Indonesia Hospital).

2.2 | Participants

Subjects in this study were selected using stratified random sampling and randomized using a computerized random number generator. A total of 40 subjects were included, with 20 in the control group and 20 in the experimental group. The number of subjects from this study was determined based on references to previous studies. This is a double-blinded study. Neither the subjects nor the care providers and those assessing the outcomes were aware of the treatment assignment. This is achieved by making the packaging of MSCs and the placebo in an identical way. All patient allocations were determined from a third party that was unrelated to clinical decision-making or data collection. Critically ill patients with COVID-19-related pneumonia were defined as those who were intubated with severe pneumonia clinically and radiologically, confirmed by a positive result in Reverse Transcription - Polymerase Chain Reaction (RT-PCR) swab from nasopharyngeal or bronchoalveolar lavage. The criteria of critical patients included the following: (a) respiratory failure that progressed into ARDS, defined as the partial pressure of oxygen in arterial blood (PaO_2)/the fraction of inspired oxygen (FiO_2) lower than 300 mmHg

and supported by mechanical ventilation; (b) shock, such as septic shock (persistent hypotension following fluid resuscitation and requiring vasopressor to maintain mean arterial pressure of ≥65 mmHg and serum lactate of >2 mmol/L); (c) multiple organ failure and monitored in the ICU.

2.3 | Inclusion criteria

In this study, inclusion criteria for the participant were (a) age 18-95 years, (b) critically ill patients with RT-PCR-confirmed COVID-19 obtained from a nasopharyngeal swab or bronchoalveolar lavage if intubated, (c) leukopenia and lymphopenia in peripheral blood and differential count, (d) presenting with pneumonia on chest x-ray and/or ground-glass opacity on thorax computed tomography (CT) scan, and (e) signed informed consent by subjects or family members.

2.4 | Exclusion criteria

Exclusion criteria in this study were (a) any history of malignancy, (b) pregnant or showed a positive pregnancy test, and (c) any history of or currently taking part in another clinical trial in the last 3 months.

2.5 | Standard protocol approvals, registrations, and patient consents

The study was approved by the ethics board of the Faculty of Medicine Universitas Indonesia (KET-A36/UN2.F1/ETIK/PPM.00.02/2020) (Supplemental Data S1). Written informed consent was obtained from family members because of the patients' poor general condition (Supplemental Data S2). The clinical trial was registered at ClinicalTrials.gov (NCT04457609, https://clinicaltrials.gov/ct2/show/NCT04457609). The timeline of the study can be observed in Figure 1.

2.6 | MSC collection, preparation, and administration

2.6.1 | Umbilical cord material collection and preparation

The MSCs were harvested from human umbilical cord produced by Stem Cells Medical Technology Integrated Service Installation, Cipto Mangunkusumo Central National General Hospital, Faculty of Medicine Universitas Indonesia. MSCs were cultured and harvested from passage 5 or 6 to ensure the best quality of the cells. Positive expression of CD90 and CD73 (>95%) and negative expression of CD34 (<2%) were found on cells acquired starting from passage 3, signifying the presence of MSCs. Our previous study showed that senescence is observed after passage 10 and viability is observed until passage 18 for UC-MSCs.[9]

2.6.2 | Administration

After baseline assessments were done, subjects admitted to the study were given a single intravenous infusion of 1×10^6/kg body weight UC-MSCs in 100 ml saline (0.9%) solution for the experimental group or with placebo (100 ml saline [0.9%] solution) for the control group on day 8 (ranged from day 2-30) of treatment in the ICU.

2.7 | Study assessment

Baseline parameters including routine blood count, differential count, C-Reactive Protein (CRP), D-dimer, fibrinogen, and procalcitonin, and specific markers, including vascular endothelial growth factor (VEGF), ferritin, cytokine IL-6, IL-10, flow cytometry leukemia inhibitory factor (LIF), and lymphocyte subpopulation CX-CR3 CD4, CD8, and CD56, were assessed before the application was done. During 15 days of observation, laboratory evaluations were conducted on day 0 and day 1 and then once every 3 days for routine laboratory examination whereas specific markers were evaluated on day 0 and day 7 only. Adverse events (AEs) were closely observed in the MSCs group.

2.8 | Outcome measurements

The primary outcome is assessed by mortality rate and length of ventilator usage. We measured the onset of intubation, which was defined by the length of ventilator usage during the patient's care. The period of intubation until the application of allogeneic UC-MSCs was defined by the period of the patient still needing mechanical ventilation after being given intervention. Secondary outcomes were measured by (a) length of stay in the ICU; (b) improvement in the routine laboratory value, including routine blood count, differential count, CRP, D-dimer, fibrinogen, and procalcitonin; (c) improvement in biomarker laboratory value of cytokines and lymphocyte subpopulation (VEGF, ferritin, IL-6, LIF, CX-CR3 CD4, CD8, CD56 cell); and (d) AE or serious AE (SAE).

2.9 | Statistical analysis

Descriptive statistics were used to describe demographic and parameter characteristics, including mean, SD, frequencies, and percentages. The rate of change in laboratory value was calculated for each parameter and compared between the control and experiment groups using the Mann-Whitney-U test. Internal analysis of the experiment group was done in patients treated with MSCs, comparing the value before and after treatment using the Wilcoxon signed-rank test. P values <.05 were considered statistically significant. The survival analysis

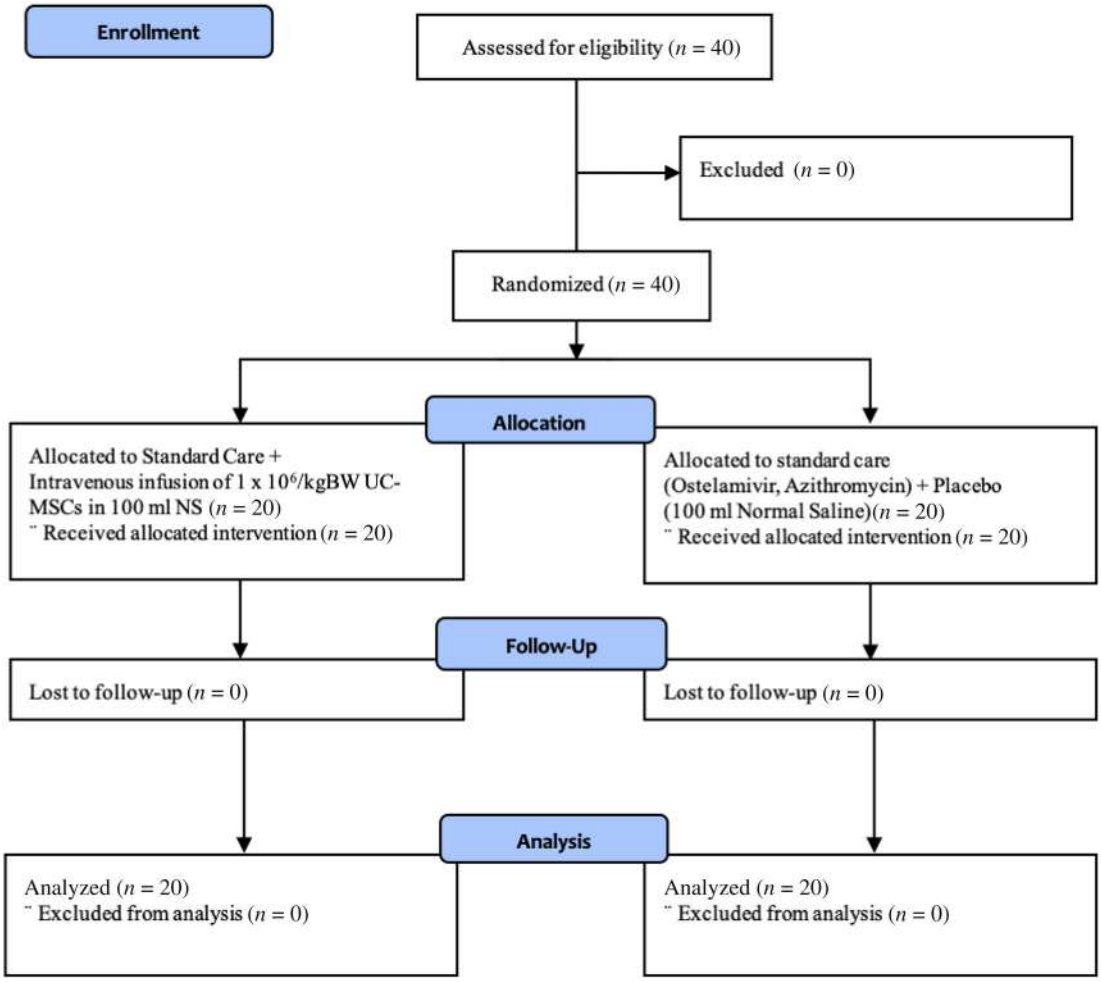

FIGURE 1 Timeline of the study. Standard of care consists of therapy given in accordance to the guidelines, namely, azithromycin 500 mg and oseltamivir 75 mg, which is given tailored to the patient's need and the attending's discretion and clinical judgment. BW, body weight; NS, normal saline; UC-MSCs, umbilical cord mesenchymal stromal cells

was assessed using Cox regression. The analysis was performed using SPSS ver. 25 (IBM, Armonk, NY).

3 | RESULTS

A total of 40 critically ill patients with COVID-19-related pneumonia were included. No patients were excluded or dropped out of the trial. The baseline characteristics of the 40 patients are summarized in Table 1.

3.1 | Primary outcome

Of the 40 subjects, males (75%) were significantly affected compared with females ($P = .049$). The mortality rate was 65% ($n = 26$) and the survival rate was 35% ($n = 14$), in which 71.4% ($n = 10$) of the recovered group were from the MSCs group and 28.6% ($n = 4$) were from the control group. Thus, the survival rate in the MSCs group was 2.5 times higher than that in the control group ($P = .047$). When only analyzing patients with comorbidities, our study showed that UC-MSC administration increased the survival rate by 4.5 times compared with controls, which is nine patients and two patients in the MSCs and control group, respectively. The outcome of the subjects is described in Table 2.

There were 19 subjects (47.5%) who had >2 comorbidities. These subjects had a higher mortality rate than those with <2 comorbidities (79.17% died). The majority of those with >2 comorbidities who recovered came from the MSCs group, with a 4:1 ratio to the control group. Furthermore, there was a significant difference between the subject outcome and the number of comorbidities ($P = .023$). In the distribution of comorbidities among subjects who died, 65% of subjects had diabetes mellitus, 46.15% had hypertension, 26.93% had chronic kidney disease, 15.38% had coronary artery disease, 7.69% had congestive heart failure, and 7.69% had tuberculosis. Three (21.4%) of the 14 patients who survived and 17 (65.3%) of the 26 patients who died had diabetes as a comorbidity. Further experiments to diagnose endothelitis were not performed in this study.

There is no significant difference between both groups regarding the period of intubation and the period from intubation until application. The mean period of intubation is 15.69 ± 10.37 days for the MSCs group and 16.63 ± 5.4 days for the control group, whereas the mean period from intubation until the application is 9.23 ± 6.89 days for the MSCs group and 8.63 ± 2.44 days for the control group.

TABLE 1 Demographic background of subjects

	Control group (*n*)	MSCs group (*n*)	*P* value
Subjects	20	20	
Age, yr			>.05
<40	3	4	
40-60	7	8	
>60	10	8	
Sex			.642
Male	15	15	
Female	5	5	
Comorbidities, *n*			.122
0–1	7	9	
≥2	13	11	

Abbreviation: MSCs, mesenchymal stromal cells.

The illustration of the day of survival using Kaplan-Meier is shown in Figure 2, and it shows a longer survival time for the MSCs group. Further analysis was performed to see the contribution of age, treatment group, and the number of comorbidities to the time of death. Although none of these factors affected death significantly, it shows that MSCs contribute to the improvement of the subjects compared with placebo. Both age and comorbidities positively contribute to early time of death for the subjects.

3.2 | Secondary outcomes

3.2.1 | Length of stay

The length of stay in the ICU was longer for the MSCs group (12.23 + 8.86 days) compared to the control group (10.44 + 7.37 days) with no statistically significant difference.

3.2.2 | Improvement in biomarker laboratory values of organ functions

After comparing the change of every laboratory parameter of the MSCs group and the control group, statistical analysis showed that

TABLE 2 The outcome of the subjects

	Recovered (*n*)		Died (*n*)		
Characteristics	MSC	Control	MSC	Control	*P* value
Subjects	10	4	10	16	.047
Age, yr					.062
<40	4	1	0	1	
40–60	3	2	4	8	
>60	3	1	6	7	
Sex					.492
Male	7	4	8	16	
Female	3	1	2	4	
Comorbidities, *n*					.023
0–1	6	3	3	4	
≥2	4	1	7	12	
Types of comorbidities					
Diabetes mellitus	1	2	7	10	
Hypertension	3	1	3	9	
Chronic kidney disease	0	0	2	5	
Coronary arterial disease	0	1	2	2	
Congestive heart failure	0	0	1	1	
Tuberculosis	0	0	1	1	
Others[a]	7	0	3	6	

Abbreviations: MSC, mesenchymal stromal cell.

[a]Other comorbidities include gastric perforation, pleural effusion, multiple rib fractures, obesity, hypercoagulation, and lung contusion in the Recovered group and icterus, stroke infarction, Disseminated Intravascular Coagulation (DIC), atrial fibrillation, obesity, acute kidney injury, myocardial infarction, and hypertensive heart disease in the Died group.

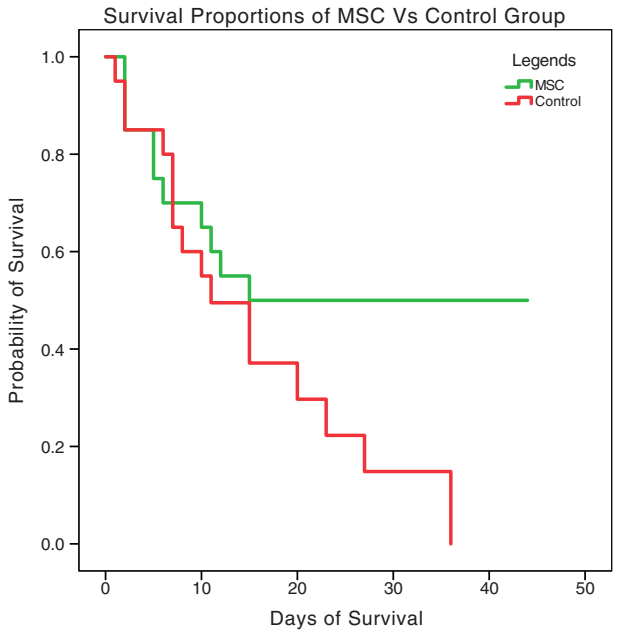

FIGURE 2 Kaplan-Meier diagram of the time from intervention (administration of umbilical cord MSCs or placebo) to death or improvement. MSC, mesenchymal stromal cell

there were no significant differences in the complete blood count (hemoglobin, hematocrit, leukocyte, lymphocyte, and thrombocyte between the MSCs group and the control group with *P* value, respectively: .630; .782; .423; .414; .295).

There was no significant difference between D-dimer and fibrinogen in the MSCs group vs the control group (*P* value, respectively: .233; .979). Inflammatory markers, namely, procalcitonin, and CRP were not significantly different between the MSCs group and the control group (*P* value, respectively: .212; .827; .707).

Ten subjects (62.5%) in the control group had a reduced value of IL-10, whereas most of the subjects in the MSCs group showed an increased IL-10 value on the seventh day after MSC application with no significant difference between groups ($P = .661$). However, an increased value from day 0 to day 7 was observed, from an average 3.26 pg/ml to 4.70 pg/ml in the MSCs group. There was a decreased trend in IL-6 after MSC application; in contrast, an increasing trend was observed in the control group. The application of infusion UC-MSCs significantly decreased IL-6 in the recovered patients ($P = .023$). The trend of cytokine analysis is shown in Figure 3.

VEGF also showed an increasing trend in the MSCs group, compared with a decreased trend in the control group on day 7, but there was no significant difference ($P = .826$). A significant increase in LIF value was also observed in subjects receiving MSC application ($P = .002$). Ferritin was also reduced in the MSCs group but increased in the control group, however, the difference was not statistically significant ($P = .861$). Details of the cytokine analysis are presented in Table 3.

3.2.3 | Flow cytometry analysis of lymphocyte subpopulations

We examined lymphocyte subpopulations (Supplemental Figure 1), namely, CD4-CXCR3, CD8-CXCR3, and CD56-CXCR3 (Supplemental Figure 2). We found that MSCs were better in suppressing the population of CD8-CXCR3 and CD56-CXCR3 among critically ill subjects, but no significant difference between groups was detected ($P = .061$). CD4-CXCR3 analysis revealed that there was also no significant difference between the MSCs and control group during the baseline and day 7 evaluation (*P* value, respectively: .064; .745) (Supplemental Table 1).

3.2.4 | AE or SAE within treatment care period

The intravenous infusion of MSCs was found to be safe and well tolerated with no life-threatening complications or acute allergic reactions during the administration. The critically ill patients with severe COVID-19 showed no immediate deaths or acute anaphylactic shock after MSC application.

4 | DISCUSSION

This study showed that the combined application of mesenchymal stromal cells and standard regimen improved survival rates for the critically ill patients with COVID-19. Of the recovered subjects, 10 (71.4%) came from the MSCs group and 4 (28.6%) from the control group. For instance, 50% of subjects with COVID-19 from the MSCs group showed recovery, whereas only 20% of subjects in the control group recovered. A previous pilot study of modified ACE-2-negative MSC application by Leng et al. showed improvement in seven patients with COVID-19 with varying grades from moderate to a critical degree.[6] In contrast, our study specified the UC-MSC application for critically ill patients with COVID-19, and we used a naïve umbilical cordmesenchymal stromal cells without special manipulation procedure that was directed at achieving ACE-2-negative MSC. Using a similar dose and route of administration, our results are consistent with existing reports that administering UC-MSCs as adjuvant therapy is efficient in treating critically ill patients with COVID-19.

Endothelial dysfunction has been identified as an important factor in the manifestation of vascular abnormalities in critical COVID-19 cases with thrombosis and coagulation manifestation.[10] Besides the intimate proximity between alveolar epithelial cells and endothelial cells, which facilitate efficient oxygen exchange, endothelial cells also express ACE-2. SARS-CoV-2 can be found in endothelial cells not only in the lungs but also in various other organs. Of 26 patients who died in this study, 17 (65.3%) of them had diabetes as a comorbidity. These findings are in line with several meta-analyses that support that diabetes mellitus increases the mortality rate in COVID-19 cases.[11,12] Endothelial dysfunction occurs in patients with diabetes because of oxidative stress processes and chronic inflammation. With endothelial conditions that are already compromised by this process, it cannot be denied that endothelial dysfunction will worsen with COVID-19, particularly in older patients.[13]

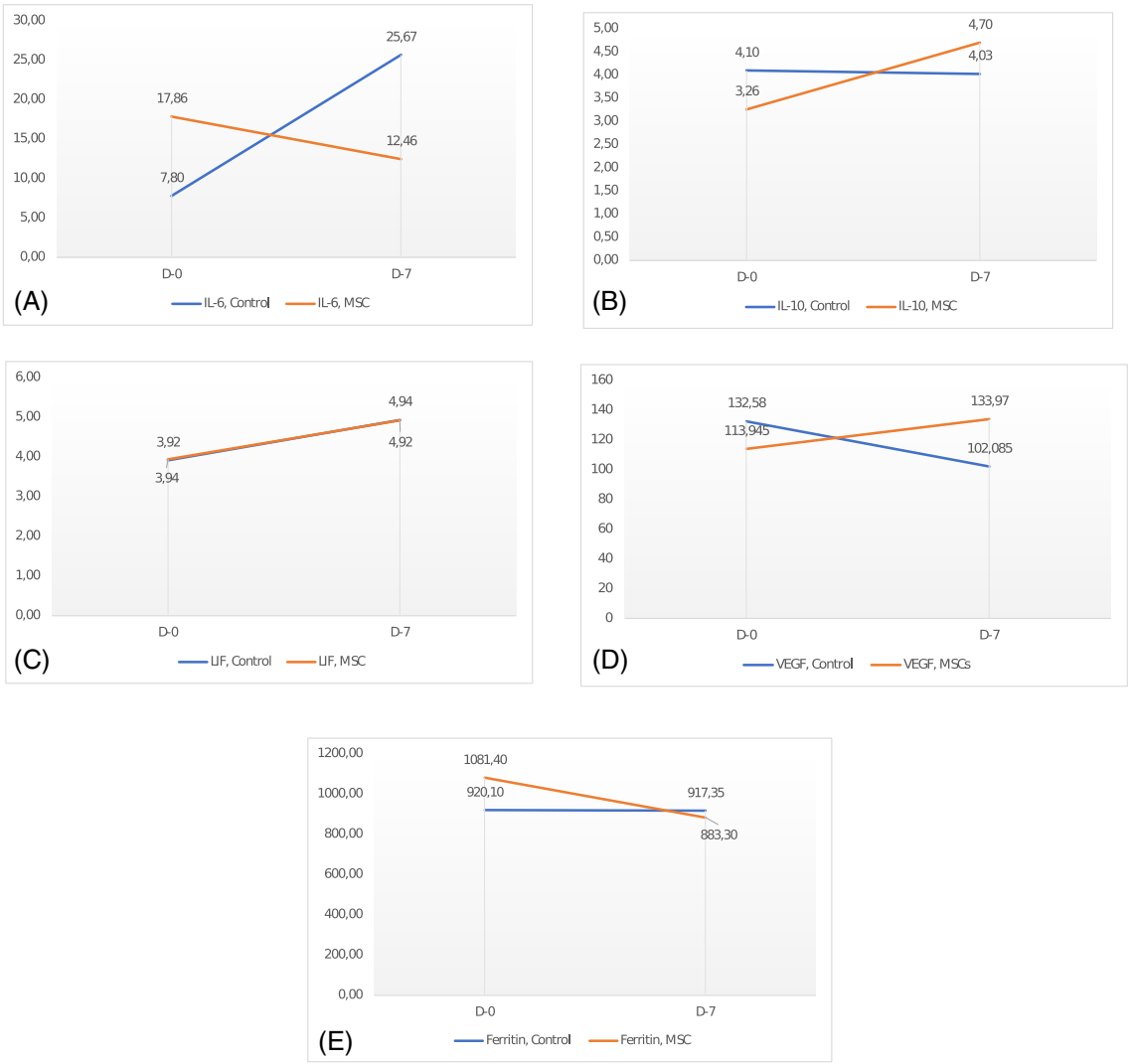

FIGURE 3 Trend of IL-6 (A), IL-10 (B), LIF (C), VEGF (D), and ferritin (E) in the MSCs group vs the control group with the interval of 7 days. D-0: Day 0 (before application), D-7: Day 7 (7 days following the application); IL, interleukin; LIF, Leukemia Inhibitory Factor; MSC, mesenchymal stromal cell; VEGF, vascular endothelial growth factor

TABLE 3 Analysis of cytokine before and after UC-MSC application

Cytokine	*P* value (before application in total subjects)	*P* value (7 days after application in total subjects)	*P* value (7 days after application in subjects who recovered)	*P* value (7 days after application in subjects who died)
IL-6	.11	.469	.023	.312
VEGF	.646	.826	.888	.665
Ferritin	.372	.861	.48	.47
IL-10	.285	.826	.229	.348
LIF	.524	.843	.620	.613

Notes: The analysis was carried out to find the difference between the MSCs and control groups using bivariate analysis via a Mann-Whitney U test. Values were obtained using an Analysis of Covariance (ANCOVA) test with preapplication value as a covariate.
Abbreviations: IL, interleukin; LIF, Leukemia inhibitory factor; UC-MSC, umbilical cord mesenchymal stromal cell; VEGF, vascular endothelial growth factor.

Critically ill patients with COVID-19 often have high systemic procoagulants and are at risk of Disseminated Intravascular Coagulation (DIC) and thromboembolism. Tang et al. stated that 71% of patients who died of critical-grade COVID-19 met the diagnostic criteria for DIC.[14] Administration of MSCs via the intravenous route is controversial because MSCs with high levels of tissue factor (TF)/CD142 have a high risk of causing a patient to fall into a hypercoagulation state.[15]

Adipose tissue-derived MSCs are the MSC source that expresses TF/CD142 the most, and Perlee et al. showed an increase in

thrombin-antithrombin-complex and D-dimer after administration of 4×10^6 cells/kg body weight AT-MSCs; thus, an application dose less than 4×10^6 cells/kg body weight is recommended.[16] Not analyzing the TF/CD142, we used UC-MSCs with 1×10^6/kg body weight dose. Supported with no significant differences in the D-dimer between two groups at baseline and after application, the use of MSCs in this study is not associated with hypercoagulation.[17]

Our study revealed that there was a decreased trend of IL-6 in the MSCs group and an increasing trend of IL-10 with no significant difference. Zheng et al. and Meng et al. also showed a decreasing trend of IL-6 after MSC application for moderate to severe COVID-19 with no statistically significant value.[18,19] Consistently, Leng et al. reported an increase of IL-10 in the MSCs group compared with the placebo group with a significant value ($P < .05$).

Having the ability to secrete paracrine factors that suppress IL-6 serum level, MSCs evoked the tolerance state by which proinflammatory cytokine subsides.[20] Indeed, our result showed IL-10 increment on day 7 after MSC application in comparison to baseline. Released by MSCs, IL-10 activated T-lymphocyte suppressor or regulator and also play roles in the healing of the organ tissue.[21-24]

Increased expression of LIF in our study was shown in 80% of recovered patients who were treated with MSCs. Similarly, Leng et al. also reported 10× RNA analysis of transplanted MSCs, which was highly expressed in LIF. As one of the cytokine family that is still less explored for use in lung injury in COVID-19, LIF possesses the capability to repair and regenerate through stem cell niches of type II alveolar epithelial cells.[6,25] LIF also plays a role in controlling excessive inflammatory cascade, in which the increase has an inhibitory effect on overactive T-lymphocyte populations CXCR3+CD4+, CX-CR3+CD8+, and CX-CR+CD56 cells that play roles in cytokine storms.[26,27]

We found that there was a suppression of the population of CD8-CXCR3 and CD56-CXCR3 after the MSC application. A decrease in the population of these immune cells in the peripheral blood circulation indicates a subsidence of cytokine storms and progression toward clinical improvement.[28,29] However, our analysis did not show a suppression of the population of CD4-CXCR3, but the increment in the MSCs group on day 7 is showing a flatter trend when compared with the control group. The increment pattern of CD4-CXCR3 after MSC application indicates the proliferation of these Th1 populations. MSCs have been indicated to regulate the balance between proinflammatory (Th1) and anti-inflammatory(Th_2), and a shift toward Th_2 phenotype is the target of MSC application.[30-32]

We also studied VEGF, an angiogenic factor that is essential in the recovery of the damaged lung. Whereas VEGF tended to go down in the control group, MSCs gave a boost to increase VEGF in the circulation so that regeneration of capillary at the lung could occur.[23] Similarly, Leng et al. also demonstrated the same result where VEGF is increased significantly after the application of MSCs ($P = .0556$). MSCs are well known to secrete keratinocyte growth factor, VEGF, and hepatocyte growth factor, which play a role in regenerating lung type II alveolar cells, preventing apoptosis of pulmonary capillary endothelial cells, and improving air–alveolar barrier repair in ARDS.[33] Thus, MSCs act not only as an immunomodulator but also to regenerate and to repair the damaged lung tissue in COVID-19 pneumonia.[5] As evidenced by Shu et al. in their study, it was proved that administering MSCs to patients with critical-grade COVID-19 gave better results in terms of Computed Tomography (CT) scores, the number of lobes involved, and the ground-glass opacity image, which represented a reduced lung inflammation.[7]

This study has several limitations. First, the limited subject in this study hold up to acquire a statistically significant result. Second, we did not perform further supplementary tests to check for endotheliitis. Another limitation is that we did not apply exact criteria about how long the critically ill patient with COVID-19 had been treated in the ICU.

5 | CONCLUSION

Application of intravenous infusion MSCs as an adjuvant treatment for critically ill patients with COVID-19 increases the survival rate by modulating the immune system toward an anti-inflammatory state.

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CONFLICT OF INTEREST

D.A. declared institutional funding from Ministry of Research, Technology and Higher Education, Indonesia. The other authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

I.H.D.: conception and design, provision of study material, data analysis and interpretation, manuscript writing, final approval of manuscript; D.A., A.S., E.B., T.D., P.A.S.: conception and design, provision of patients, collection of data, manuscript writing; N.M.: conception and design, administrative support, collection of data; R.D.A. and I.K.L.: provision of study material, data analysis and interpretation, manuscript writing, final approval of manuscript; T. Kispa, F.M., N.N., E.L.: provision of study material, data interpretation; T. Kurniawati and A.M.T.L.: conception and design, administrative support; D.R.: conception and design, administrative support, assembly of data, data analysis, manuscript writing.

DATA AVAILABILITY STATEMENT

The data contained in this study will be accessible with the publication of this article. Data can be accessed by other researchers who is doing

a related research has received permission to request data. Data can be requested by directly emailing the corrseponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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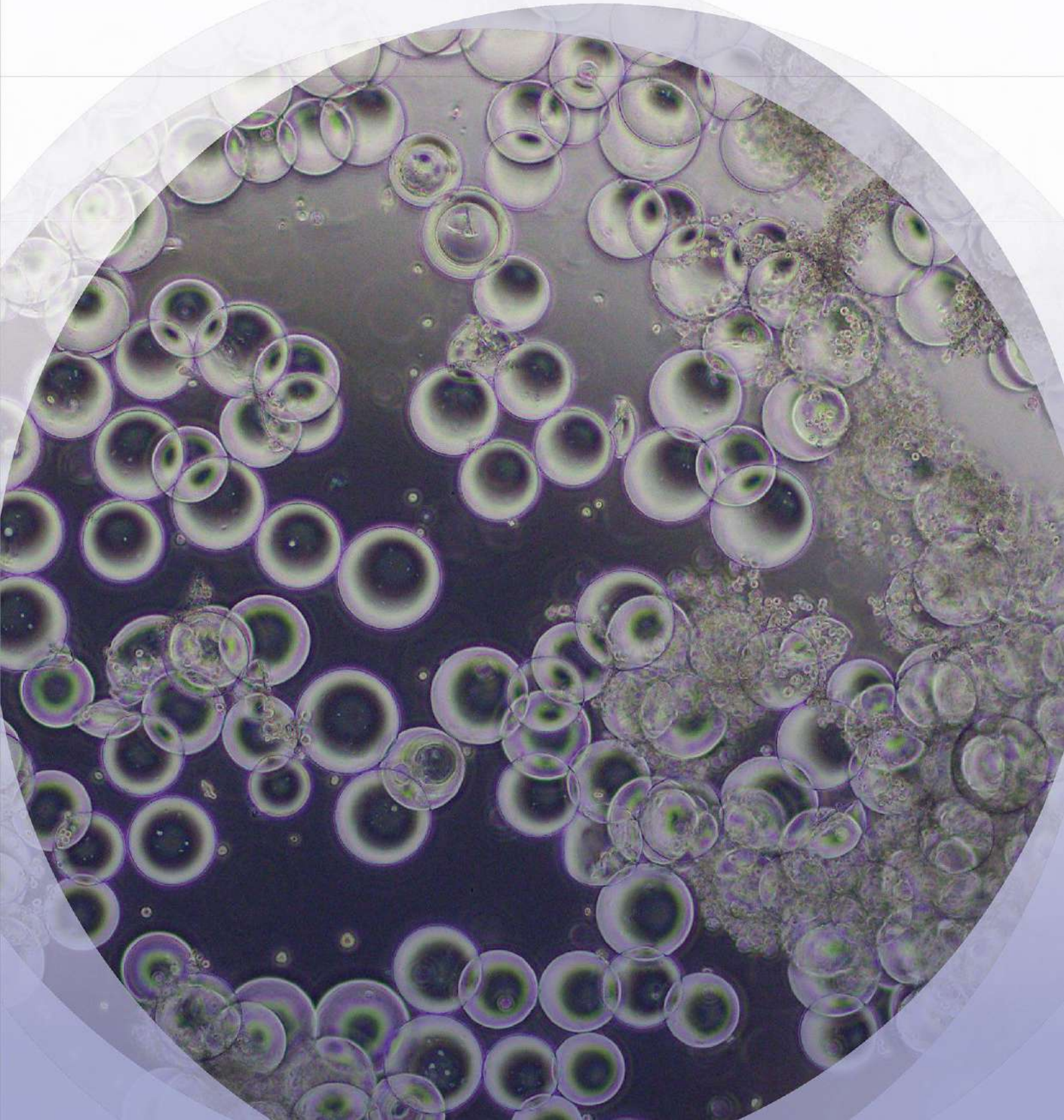

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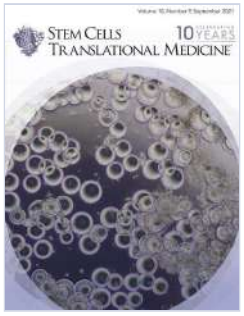

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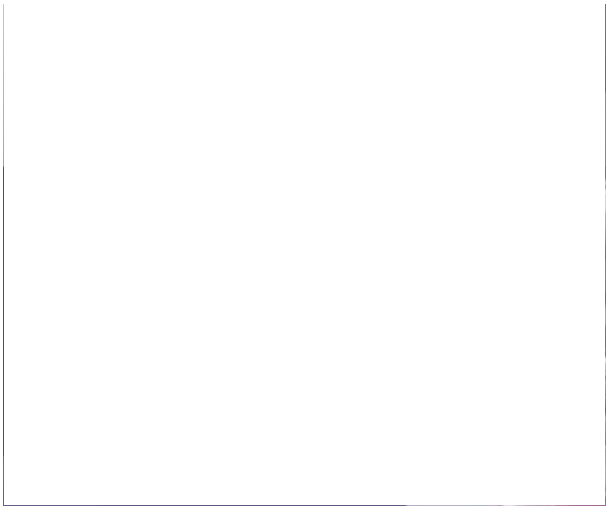

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STEM CELLS Translational Medicine® is a monthly, peer-reviewed, largely online, open access journal. *STEM CELLS Translational Medicine* works to advance the utilization of cells for clinical therapy. By bridging stem cell molecular and biological research and helping speed translations of emerging lab discoveries into clinical trials, the journal will help move applications of these critical investigations closer to accepted best patient practices and ultimately improve outcomes.

The journal encourages original research articles and concise reviews describing laboratory investigations of stem cells, including their characterization and manipulation, and the translation of their clinical aspects from the bench to patient care. *STEM CELLS Translational Medicine* covers all aspects of translational cell studies, including bench research, first-in-human case studies, and relevant clinical trials.

Scope

STEM CELLS Translational Medicine covers:

Human Clinical Articles

- First-in-human case studies
- Phase I/II clinical trials
- Negative clinical results

Cell-Based Drug Development, Screening, and Toxicology

- Derivation, characterization, and differentiation for clinical use
- In vivo models

- In vitro models
- Throughput systems

Cord Blood

- Umbilical cord blood and tissue-based therapies
- Accessory cell populations
- Ex-vivo expansion strategies
- Engineering and manufacturing of cord blood immune cells
- Modulation of endogenous cell and tissue repair
- Cord blood and cord tissue banking
- Malignant and non-malignant disease treated by cord blood transplantation
- Cord blood and cord tissue in regenerative medicine

Enabling Technologies for Cell-Based Clinical Translation

- Cell tracking
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Fetal and Neonatal Stem Cells

- Derivation, characterization, and differentiation for clinical use with in vivo validation
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- Phase I/II clinical trials
- Negative clinical results

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- Cell-based potency/storage
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Pluripotent Stem Cells

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- First-in-human case studies
- Phase I/II clinical trials
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Standards, Protocols, Policies, and Regulations for Cell-Based Therapies

- Cell standards
- Intellectual property relevant to clinical translation

- Cell toxicology/tumorigenesis and other assays
- Regulations for clinical trials

Stem Cells and Cancer

- Characterization
- Therapeutic targets
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- Translational preclinical studies
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Tissue Engineering and Regenerative Medicine

- Applications for cell-based strategies in pathological in vivo conditions
- Tissue engineering
- Medical device and artificial organ development
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- Clinical applications
- First-in-human case studies
- Phase I/II clinical trials
- Negative clinical results

Tissue-Specific Progenitor and Stem Cells

- Derivation, characterization, and differentiation for clinical use with in vivo validation
- Cell banking
- Therapeutic potential
- Animal models
- Translational preclinical studies
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- First-in-human case studies
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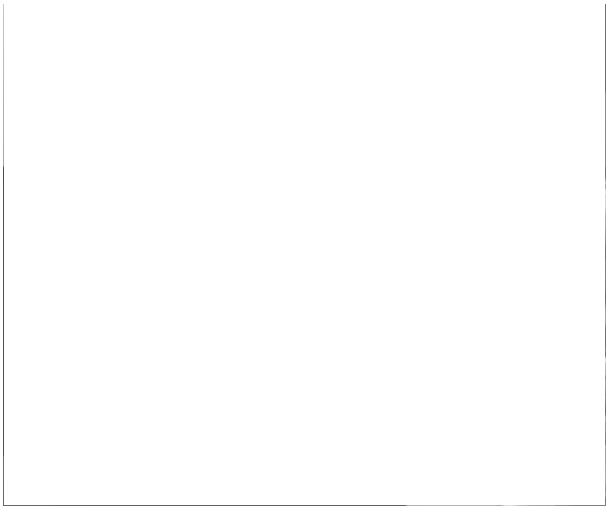

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KETERANGAN LOLOS KAJI ETIK
ETHICAL APPROVAL

Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Indonesia dalam upaya melindungi hak asasi dan kesejahteraan subjek penelitian kedokteran, telah mengkaji dengan teliti protokol penelitian yang berjudul:

The Ethics Committee of the Faculty of Medicine, University of Indonesia, with regards of the Protection of human rights and welfare in medical research, has carefully reviewed the research entitled:

"Penggunaan Sel Punca Mesenkimal Asal Tali Pusat sebagai Terapi Pasien dengan COVID-19 Pneumonia Derajat Kritis"

Protocol Number	: **20-04-0442**
Peneliti Utama *Principal Investigator*	: **Prof. Dr. dr. Ismail HD, Sp.OT(K)**
Nama Institusi *Name of the Institution*	: **UPT Teknologi Kedokteran Sel Punca RSCM**
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Tanggal Persetujuan *Date of Approval*	: 27 APR 2020 ***(valid for one year beginning from the date of approval)***
Dokumen Disetujui *Document Approved*	: **Proposal Penelitian, Version 01 tanggal 06 April 2020** **Lembar Informasi untuk Calon Subjek, Version 01 tanggal 06 April 2020**

dan telah menyetujui protokol berikut dokumen terlampir.
and approves the above mentioned protocol including the attached document.

Ditetapkan di : Jakarta
Specified in

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Prof. dr. Rita Sita Sitorus, Ph.D., Sp.M(K)

** Peneliti berkewajiban
1. Menjaga kerahasiaan identitas subjek penelitian.
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   b. Penelitian berhenti ditengah jalan
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6. Cantumkan nomor protokol ID pada setiap komunikasi dengan KEPK FKUI-RSCM

Semua prosedur persetujuan dilakukan sesuai dengan standar ICH-GCP.
All procedure of Ethical Approval are performed in accordance with ICH-GCP standard procedure.

Progress Penelitian Uji Klinis

“Penggunaan Sel Punca Mesenkimal Asal Tali Pusat sebagai Terapi Pasien dengan Covid-19 Pneumonia Derajat Kritis”

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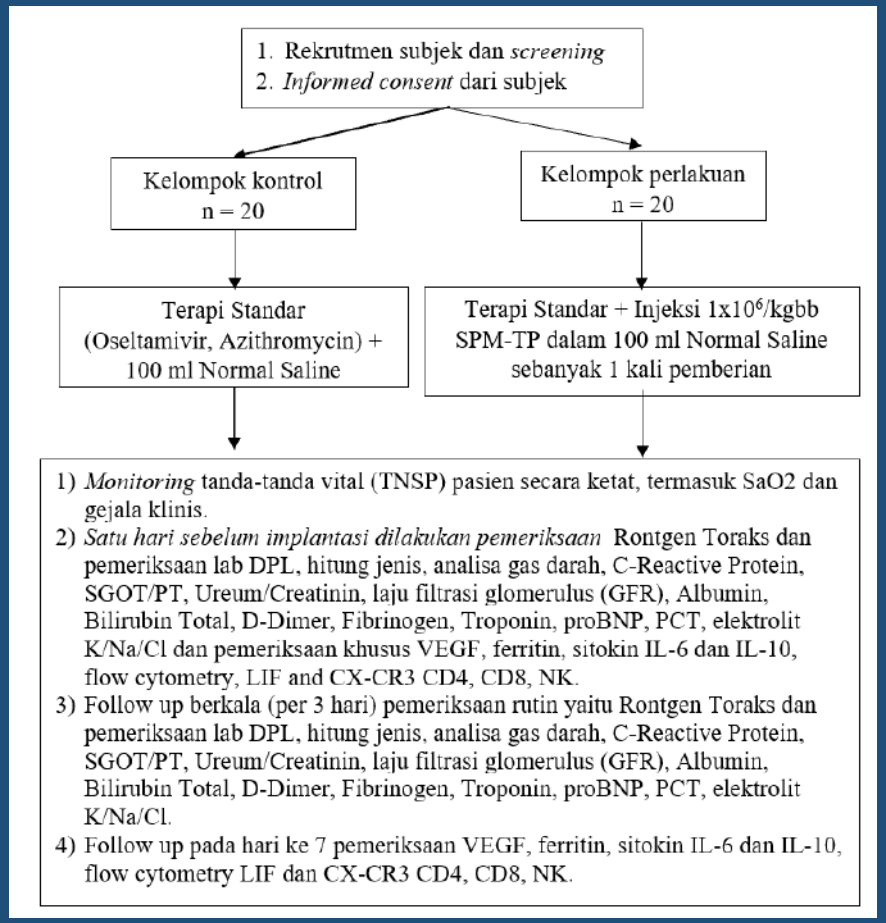

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Kriteria Inklusi :

- Pria atau wanita berusia 18 hingga 95 tahun
- Terdiagnosis dengan Pneumonia COVID-19 yang terkonfirmasi dengan pemeriksaan RT-PCR sampel dari swab nasofaring dan/atau *bronchoaveolar lavage* pada pasien terintubasi, dengan derajat kritis
- Ditemukan leukopenia dan limfopeni pada pemeriksaan darah
- Adanya bukti perubahan foto toraks dengan gambaran pneumonia dan/atau CT-Scan toraks dengan gambaran *ground glass opacity*
- Jika pasien pernah mengikuti uji klinis lain untuk terapi Covid-19 dan jatuh dalam kondisi kritis, pasien telah melewati *washout period* untuk obat-obatan/regimen terapi yang sedang diujikan.
- Bersedia mengikuti penelitian dan menandatangani *informed consent* oleh subyek atau anggota keluarga.

Kriteria Derajat Kritis :

(1) gagal napas yang memerlukan ventilasi mekanik,
(2) mengalami syok,
(3) gejala juga muncul disertai dengan gagal organ lainnya, pasien membutuhkan monitoring dan perawatan di ICU.

Kriteria Ekslusi :

- Memiliki riwayat keganasan
- Wanita hamil atau uji kehamilan positif

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PARAMETER/OUTCOME

Outcome Primer

Angka mortalitas dan/atau lama penggunaan ventilator

Outcome Sekunder

1) Perbaikan outcome klinik (saturasi oksigen, suhu, laju, respirasi, hemodinamik)
2) Lama perawatan di ICU
3) Perbaikan nilai laboratorium biomarker fungsi organ (hemodinamik, paru, ginjal, liver) dan kadar sitokin (VEGF, Ferritin, IL-6, Leukemia Inhibiting Factor, CXCR3+ CD4+, CXCR3+ CD8+, CXCR3+ NK Cell)
4) Perbaikan gambaran paru secara radiologis yang dibuktikan dengan X-Ray Thorax dan /atau CT-Scan Thorax
5) Waktu untuk konversi hasil swab PCR dari positif menjadi negatif dalam 15 hari pengamatan
6) Kejadian *Adverse Event* (AE) atau *Serious Adverse Event* (SAE) selama masa perawatan

RSUP PERSAHABATAN
KOMITE ETIK PENELITIAN KESEHATAN

KETERANGAN LOLOS UJI ETIK
ETHICAL CLEARANCE

"APLIKASI SEL PUNCA MESENKIM ASAL TALI PUSAT SEBAGAI TERAPI ADJUVAN PADA PASIEN PNEUMONIA COVID-19 KRITIS"

UNIVERSITAS INDONESIA
FAKULTAS KEDOKTERAN

KETERANGAN LOLOS KAJI ETIK
ETHICAL APPROVAL

"Penggunaan Sel Punca Mesenkimal Asal Tali Pusat sebagai Terapi Pasien dengan COVID-19 Pneumonia Derajat Kritis"

Protocol Number : 20-04-0442

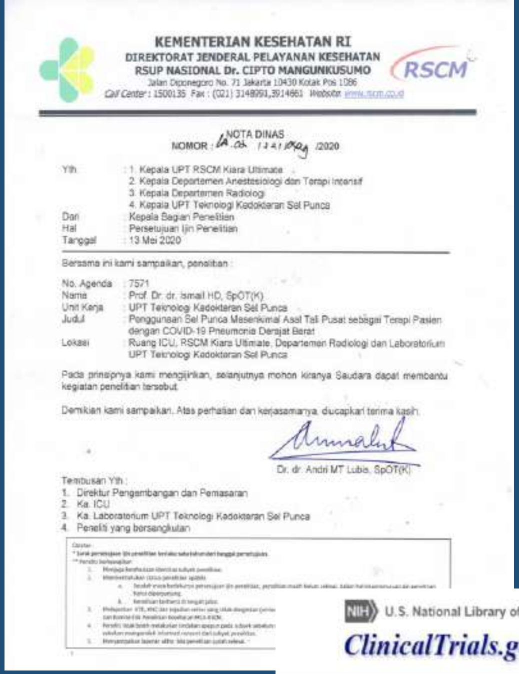
Peneliti Utama / *Principal Investigator* : Prof. Dr. dr. Ismail HD, Sp.OT(K)

Nama Institusi / *Name of the Institution* : UPT Teknologi Kedokteran Sel Punca RSCM

Lokasi Penelitian / *Site* :
1. RSUPN Dr. Cipto Mangunkusumo
2. RS Pusat Infeksi Sulianti Saroso
3. RSUP Persahabatan
4. RS Universitas Indonesia
5. RSUD Dr. Soetomo – Surabaya
6. RS Universitas Airlangga - Surabaya

Tanggal Persetujuan / *Date of Approval* : 2 7 APR 2020

Prof. dr. Rita Sita Sitorus, Ph.D., Sp.M(K)



KEMENTERIAN KESEHATAN RI
DIREKTORAT JENDERAL PELAYANAN KESEHATAN
RSUP NASIONAL Dr. CIPTO MANGUNKUSUMO

NOTA DINAS

Yth : 1. Kepala UPT RSCM Kiara Ultimate
2. Kepala Departemen Anestesiologi dan Terapi Intensif
3. Kepala Departemen Radiologi
4. Kepala UPT Teknologi Kedokteran Sel Punca

Dari : Kepala Bagian Penelitian
Hal : Persetujuan Ijin Penelitian
Tanggal : 13 Mei 2020

Bersama ini kami sampaikan, penelitian :

No. Agenda : 7571
Nama : Prof. Dr. dr. Ismail HD, SpOT(K)
Unit Kerja : UPT Teknologi Kedokteran Sel Punca
Judul : Penggunaan Sel Punca Mesenkimal Asal Tali Pusat sebagai Terapi Pasien dengan COVID-19 Pneumonia Derajat Berat
Lokasi : Ruang ICU, RSCM Kiara Ultimate, Departemen Radiologi dan Laboratorium UPT Teknologi Kedokteran Sel Punca

Pada prinsipnya kami mengijinkan, selanjutnya mohon kiranya Saudara dapat membantu kegiatan penelitian tersebut.

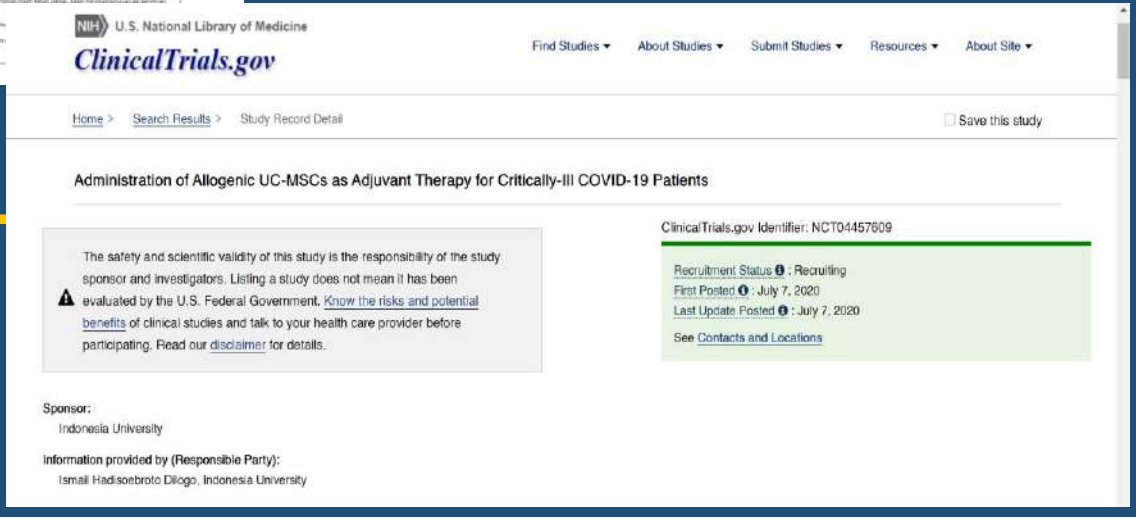
Demikian kami sampaikan. Atas perhatian dan kerjasamanya, diucapkan terima kasih.

Dr. dr. Andri MT Lubis, SpOT(K)

Tembusan Yth :
1. Direktur Pengembangan dan Pemasaran
2. Ka. ICU
3. Ka. Laboratorium UPT Teknologi Kedokteran Sel Punca
4. Peneliti yang bersangkutan

REGISTRASI KE CLINICALTRIAL.GOV

LULUS KAJI ETIK & IJIN LOKASI PENELITIAN



U.S. National Library of Medicine
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Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients
The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.
ClinicalTrials.gov Identifier: NCT04457609
Recruitment Status : Recruiting
First Posted : July 7, 2020
Last Update Posted : July 7, 2020
See Contacts and Locations
Sponsor:
Indonesia University
Information provided by (Responsible Party):
Ismail Hadisoebroto Dilogo, Indonesia University

KESEHATAN UNTUK BANGSA
MEMBANGUN SDM INDONESIA UNGGUL

Progress & Rekruitmen Pasien

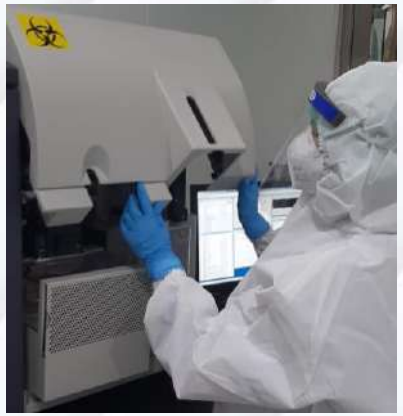
Ruang perawatan:
ICU

Asal rumah sakit: RSCM, RSUP Persahabatan, RSPI Sulianti Saroso, RSUI

Jumlah subjek hingga saat ini (12 Agustus 2020) : 32 orang

Implantasi Pasien #1: 20 Mei 2020
Implantasi Pasien #2: 27 Mei 2020
Implantasi Pasien #3: 8 Juni 2020
Implantasi Pasien #4: 12 Juni 2020
Implantasi Pasien #5, #6: 15 Juni 2020
Implantasi Pasien #7: 18 Juni 2020
Implantasi Pasien #8: 26 Juni 2020
Implantasi Pasien #9, 10, 11: 3 Juli 2020
Implantasi Pasien #12, #13: 07 Juli 2020
Implantasi Pasien #14: 13 Juli 2020
Implantasi Pasien #15: 14 Juli 2020
Implantasi Pasien #16, 17: 20 Juli 2020
Implantasi Pasien #18, 19, 20: 21 Juli 2020
Implantasi Pasien #21-24: 28 Juli 2020
Implantasi Pasien #25-28: 3 Agustus 2020
Implantasi Pasien #29: 4 Agustus 2020
Implantasi Pasien #30-32: 10 Agustus 2020

Produksi Sel Punca Mesenkimal:
UPT TK Sel Punca RSCM-FKUI-KF



Pemeriksaan Laboratorium:
Klaster SCTE IMERI dan Lab Terpadu FKUI

Progress Uji Klinis

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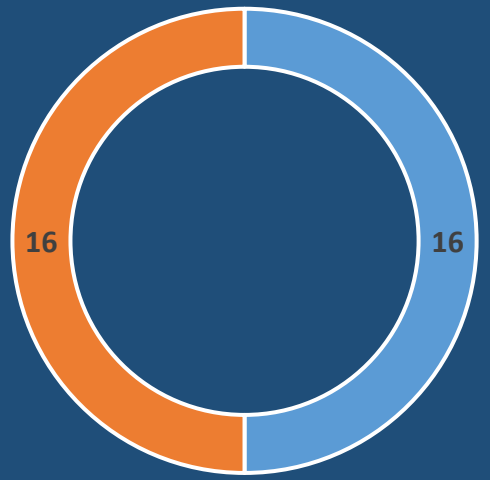
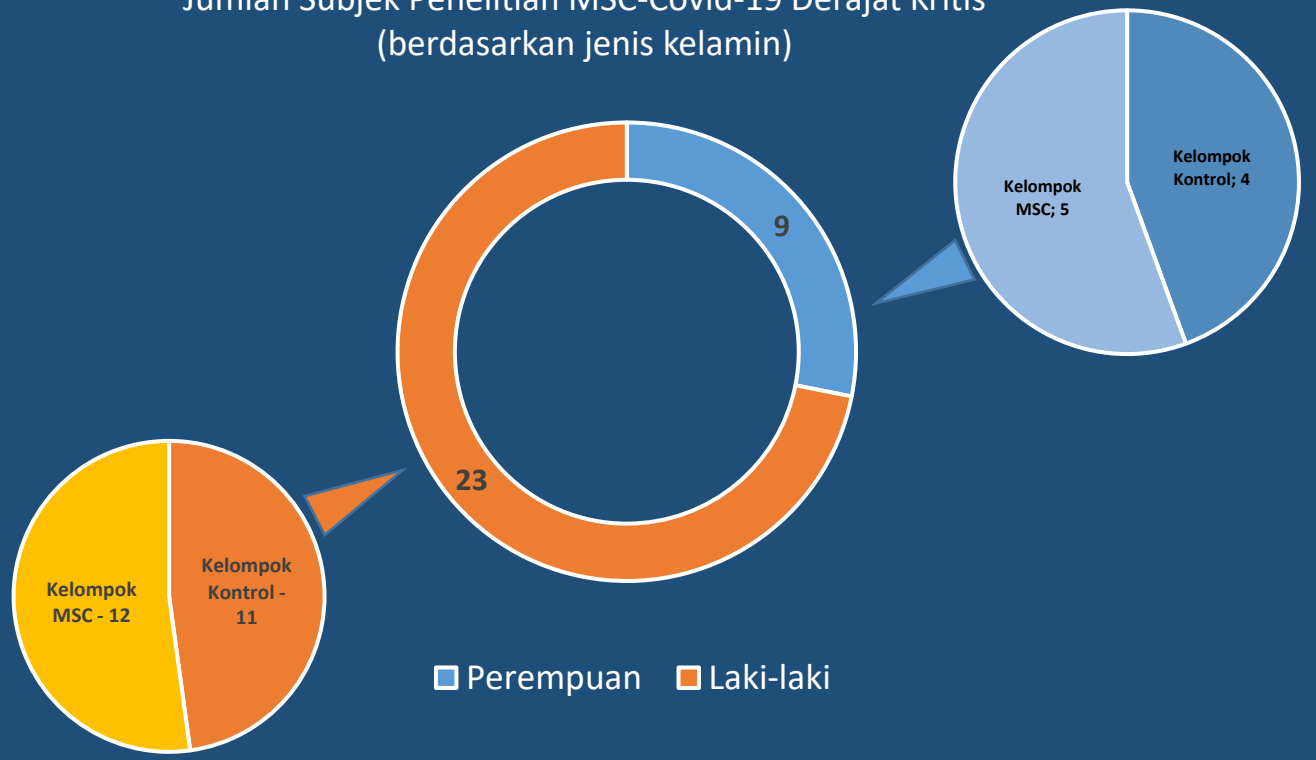
Best Practice & Lesson learn

Jumlah Subjek Penelitian MSC-Covid-19 Derajat Kritis
(berdasarkan kelompok)



Jumlah Subjek Penelitian MSC-Covid-19 Derajat Kritis
(berdasarkan jenis kelamin)



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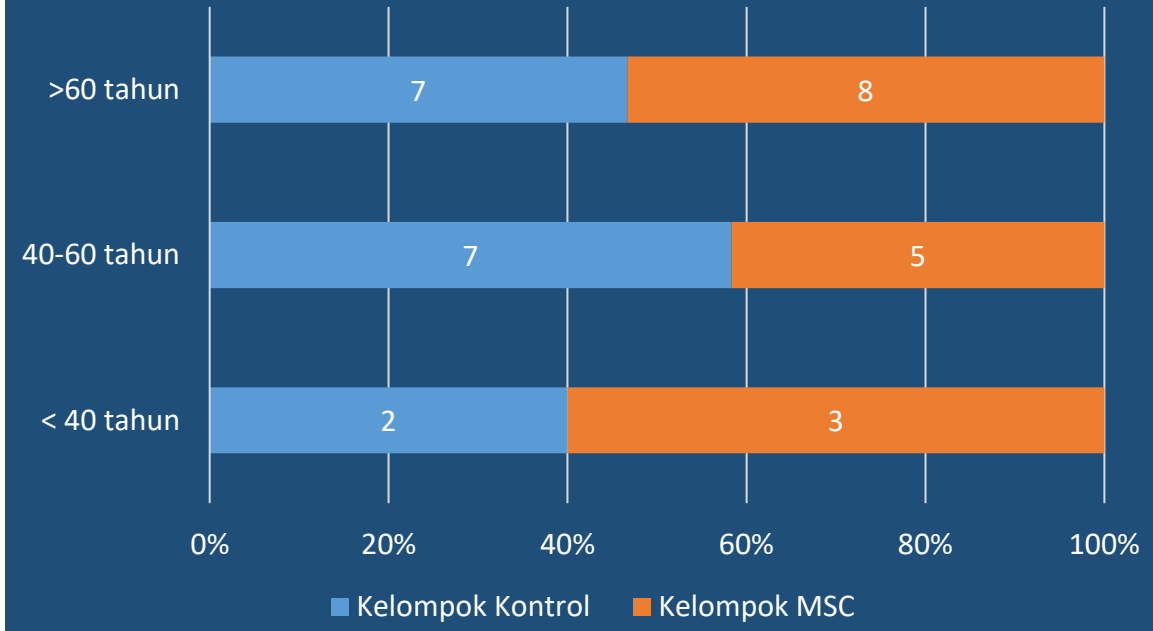
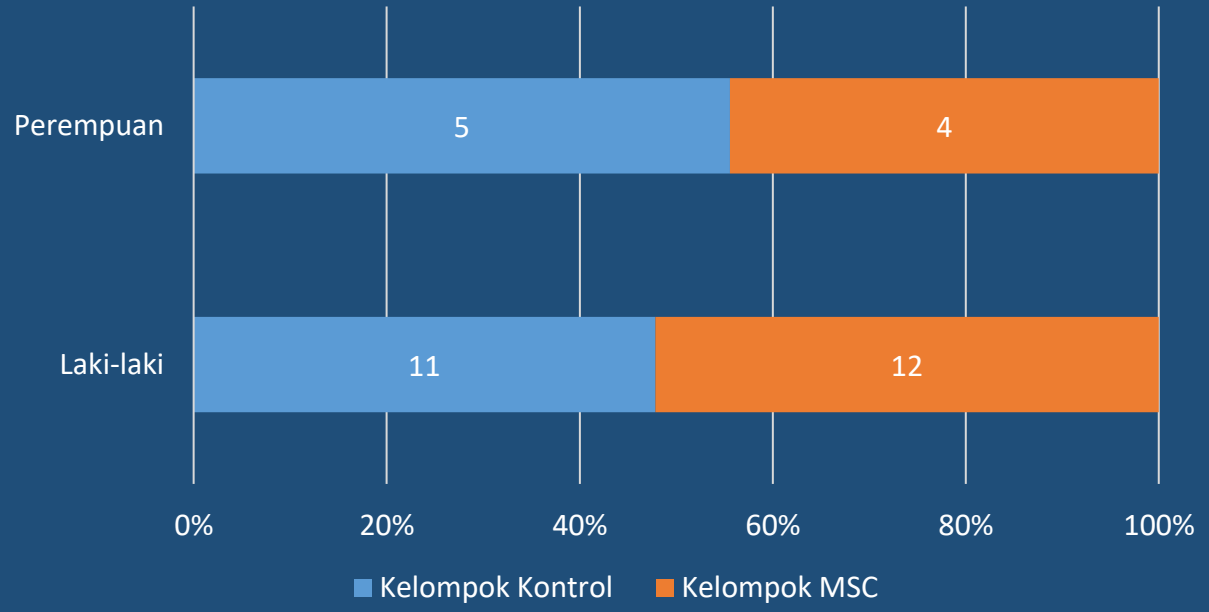
Sebaran Usia pada setiap Kelompok Penelitian



Sebaran Jenis Kelamin pada setiap Kelompok Penelitian



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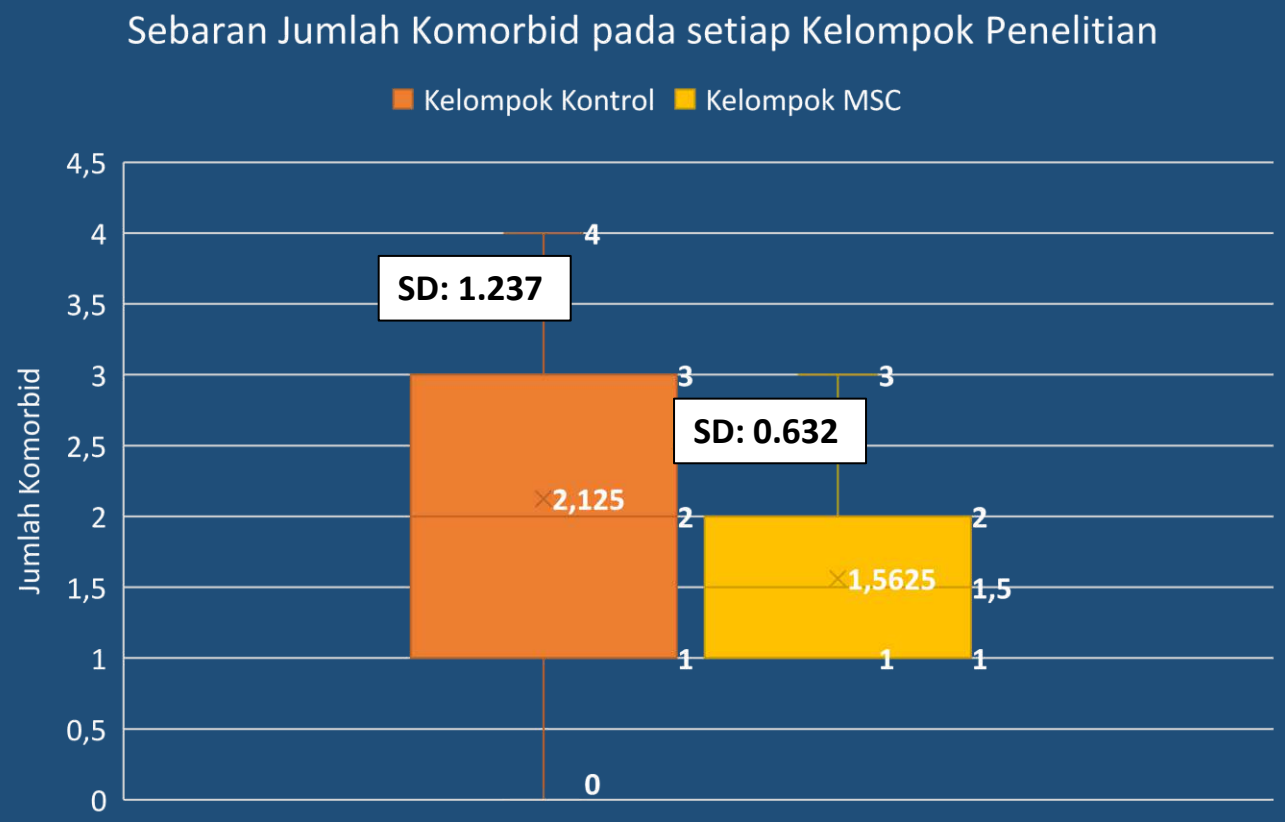

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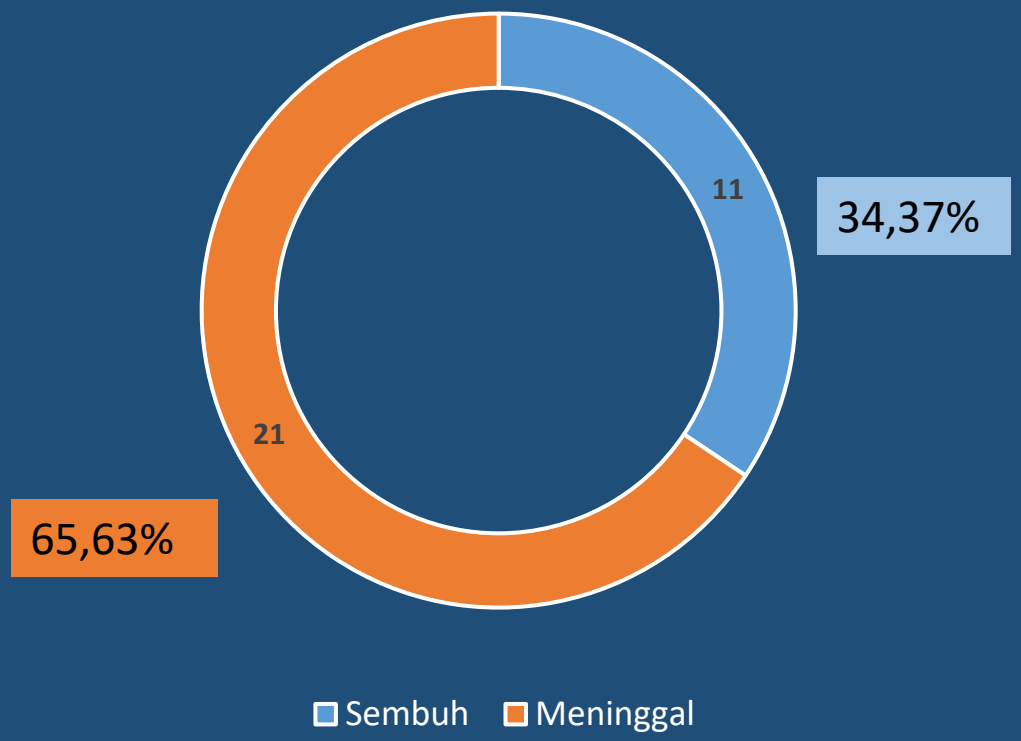
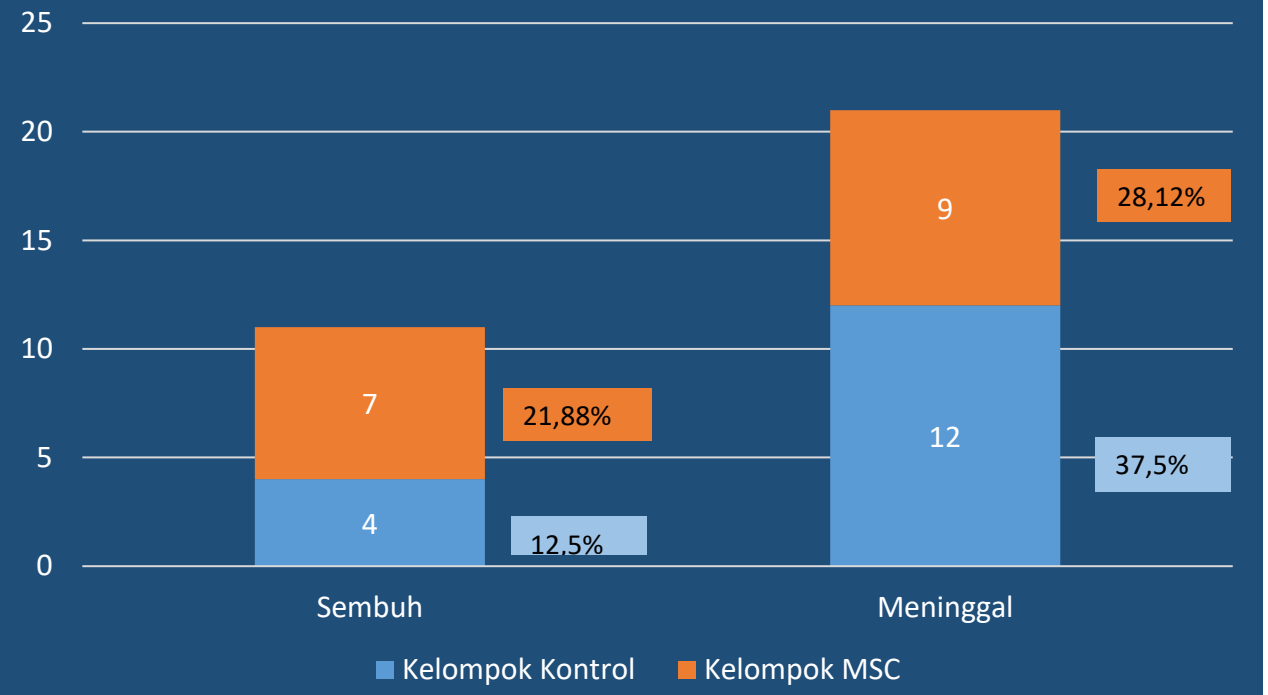
Sebaran outcome subjek penelitian MSC-Covid-19 Derajat Kritis



Outcome Pasien Berdasarkan Kelompok Penelitian



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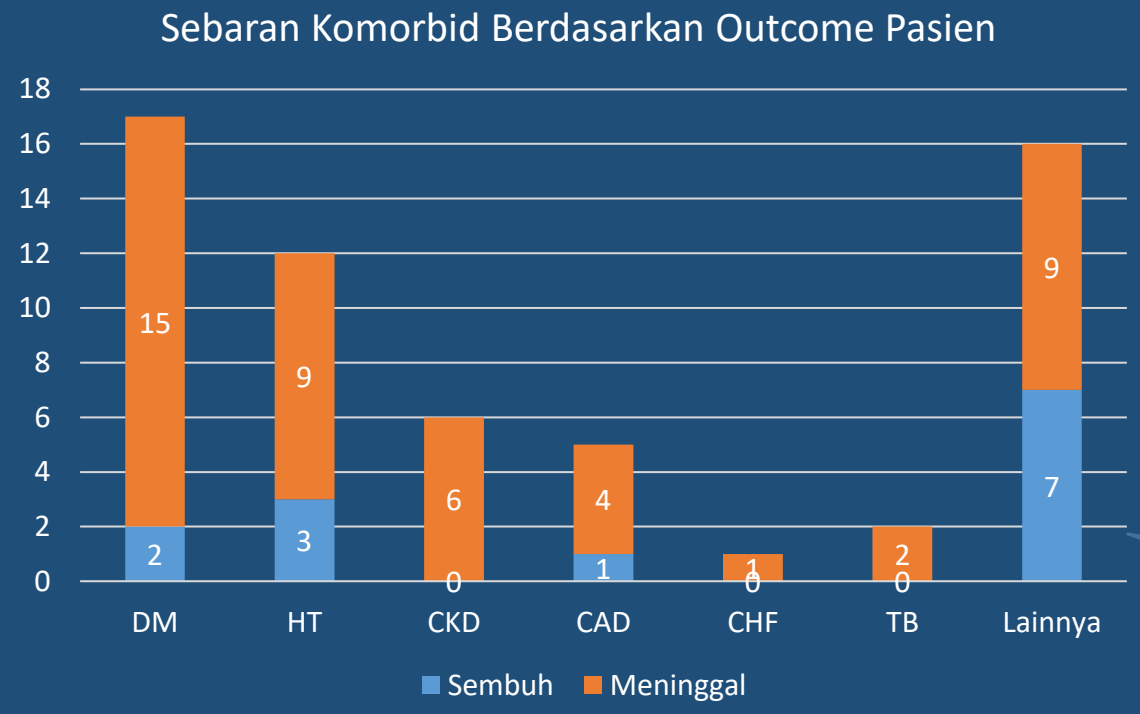

Ikterus
Hiperkoagulasi
Stroke infark
DIC
AF
Obesitas
AKI

Perforasi Gaster
Efusi Pleura
Multiple fracture of the rib
Obesitas
Hiperkoagulasi
Hematotoraks
Kontusio paru

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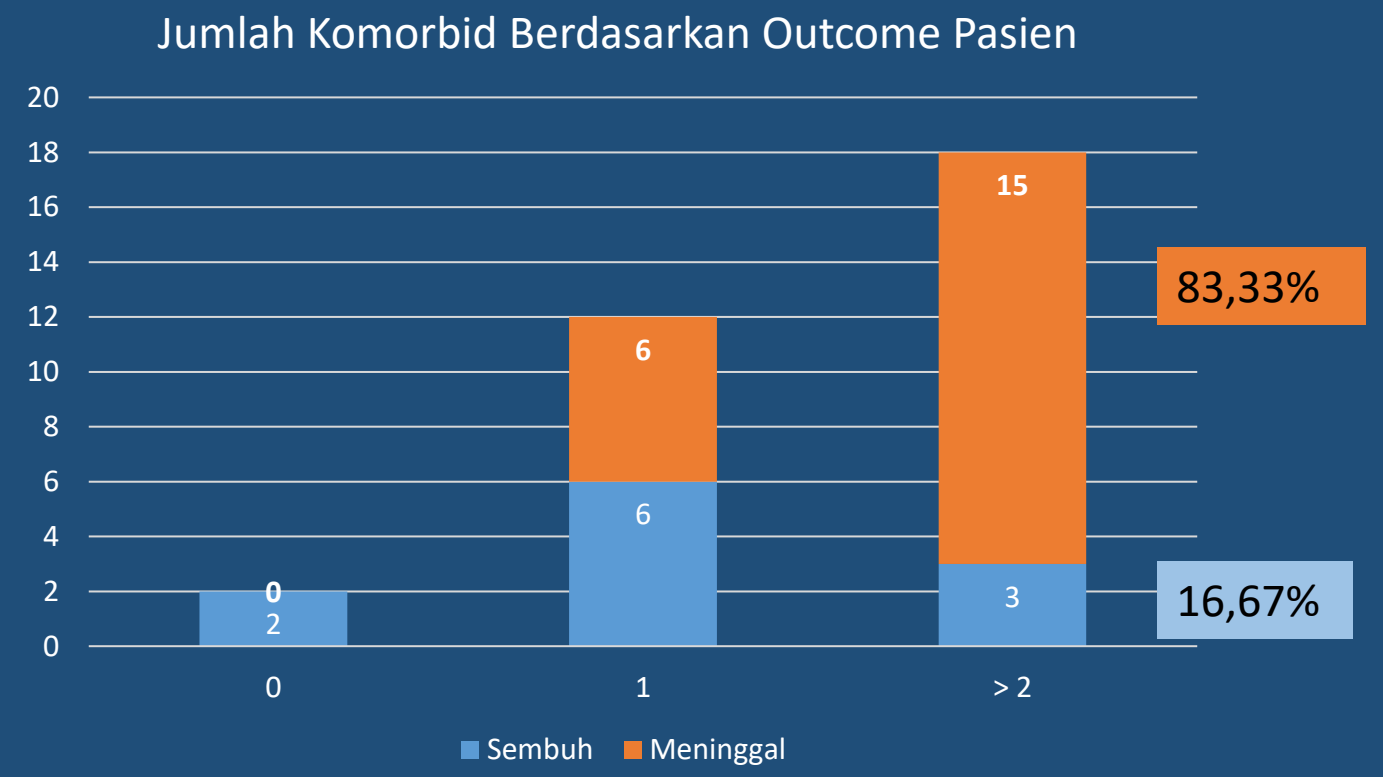

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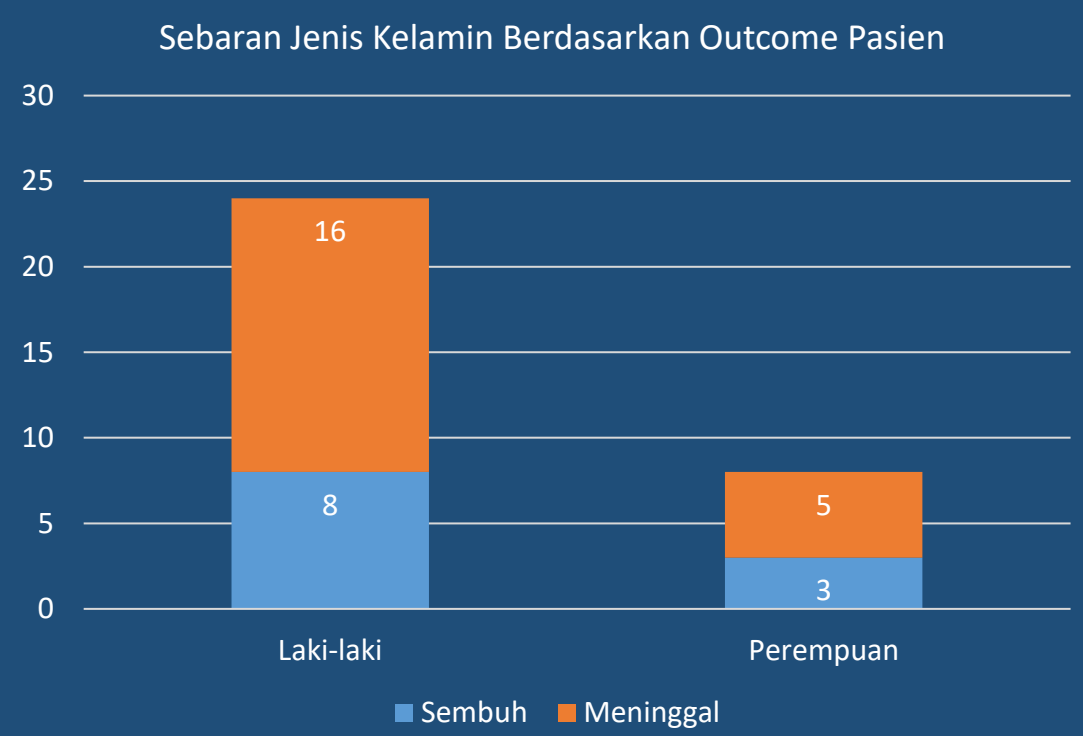

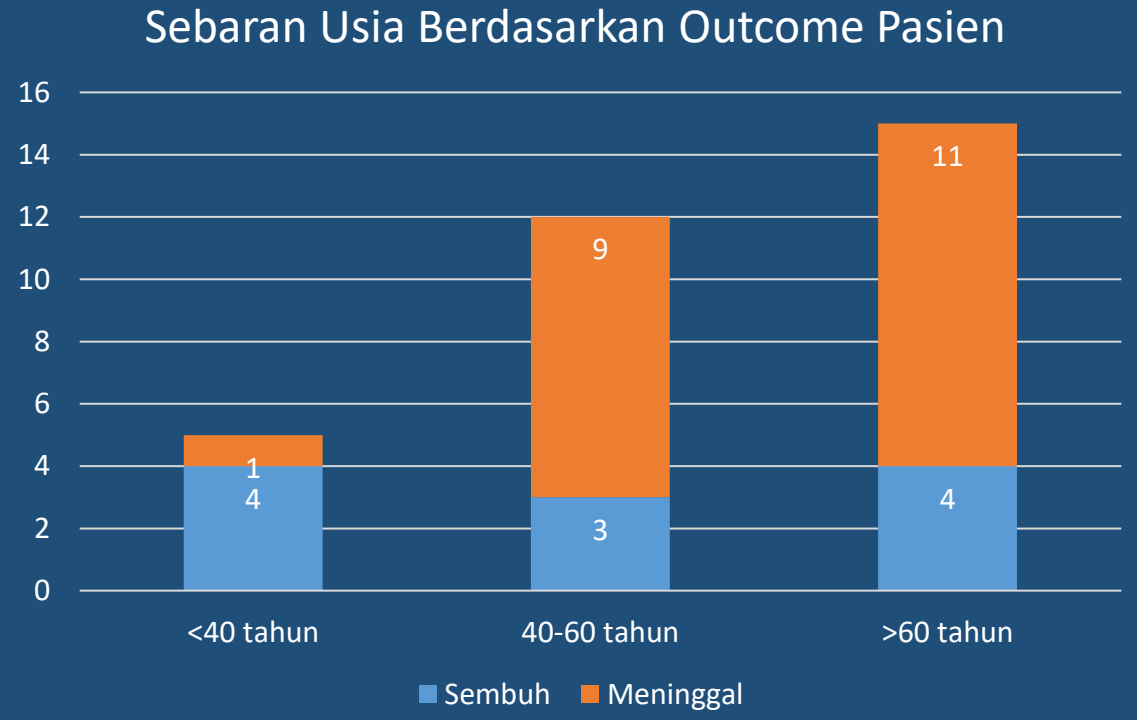

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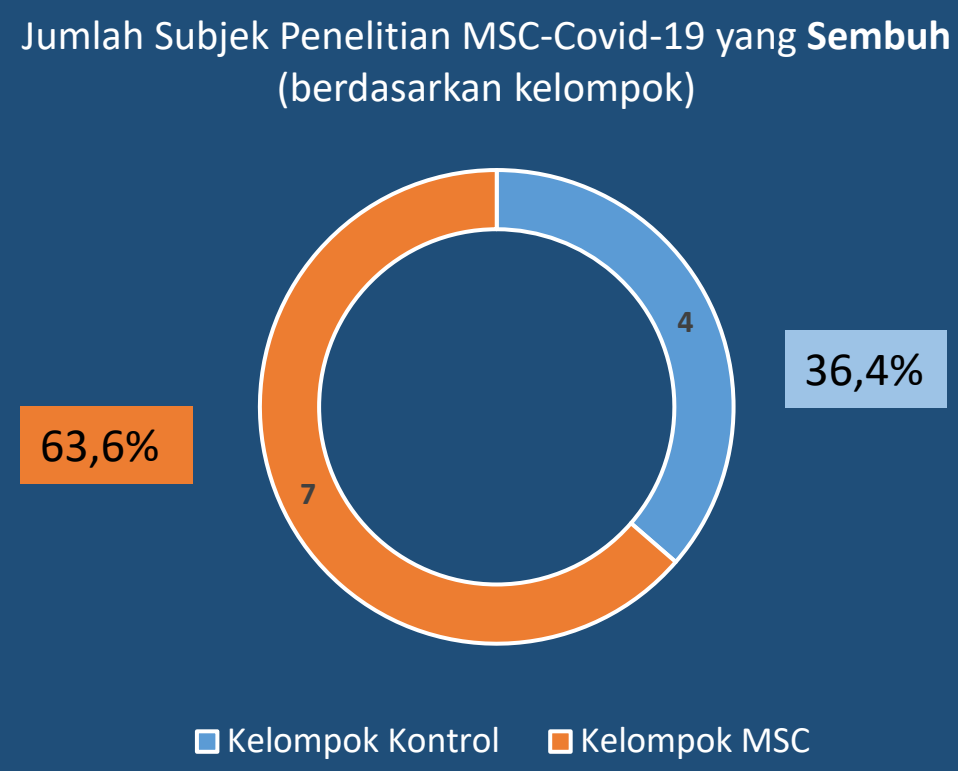

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Best Practice & Lesson learn

Di antara 21 subjek yang meninggal, subjek ini memiliki > 2 komorbid

Pasien yang meninggal memiliki peningkatan D-Dimer dan Fibrinogen → menandakan adanya hiperkoagulasi

Pasien yang memiliki kondisi di atas disertai dengan komorbid CAD memiliki morbiditas yang lebih tinggi, sedangkan pasien dengan kondisi di atas tanpa komorbid CAD memiliki mortalitas yang lebih rendah

Pada echocardiografi pasien pre-implantasi yang meninggal, menunjukkan EF yang menurun

No	Inisial	Jenis Kelamin	Umur	Tanggal Implantasi	Asal RS	Jumlah Sel	Rute	Komorbid	Status
1	EFi	Perempuan	38	20/05/2020	RSCM	60 jt (10 cc NaCl) TK - UC	Intravena	Perforasi gaster, efusi pleura	Sembuh
2	Rah	Laki-Laki	62	27/05/2020	RSCM	60 jt (10 cc NaCl) TK - UC	Intravena	Multiple fracture of the rib	Sembuh
3	ESu	Laki-Laki	75	08/06/2020	RSCM	Kontrol	Intravena	DM, CKD, HT	Meninggal H20 post implantasi
4	Bay	Perempuan	52	12/06/2020	RSP	Kontrol	Intravena	-	Sembuh
5	Sar	Perempuan	61	15/06/2020	RSP	60 jt (10 cc NaCl) TK - UC	Intravena	DM, CAD	Meninggal H5 post implantasi
6	Pul	Laki-Laki	69	15/06/2020	RSPI	Kontrol	Intravena	-	Sembuh
7	Nop	Laki-Laki	28	18/06/2020	RSUI	100 jt (10 cc NaCl) TK - UC	Intravena	Obese	Sembuh
8	ABa	Laki-Laki	65	26/06/2020	RSP	68 jt (10 cc NaCl) TK - UC	Intravena	DM Tipe II, Stroke Infark, CKD	Meninggal H11 post implantasi
9	MNa	Laki-Laki	79	03/07/2020	RSCM	50 jt (10 cc NaCl) TK - UC	Intravena	CHF, AF	Meninggal H6 post implantasi
10	Pur	Perempuan	55	03/07/2020	RSCM	Kontrol	Intravena	CKD	Meninggal H6 post implantasi
11	Sya	Laki-Laki	66	03/07/2020	RSPI	70 jt (10 cc NaCl) TK - UC	Intravena	HT	Meninggal H10 post implantasi
12	Sul	Perempuan	48	07/07/2020	RSP	Kontrol	Intravena	HT	Meninggal H36 post implantasi
13	TSi	Perempuan	60	07/07/2020	RSP	70 jt (10 cc NaCl) TK - UC	Intravena	DM, CAD	Meninggal H2 post implantasi
14	BLe	Laki-Laki	42	13/07/2020	RSP	80 jt (10 cc NaCl) TK - UC	Intravena	DM, HT	Meninggal H12 post implantasi
15	Emm	Perempuan	69	14/07/2020	RSPI	80 jt (10 cc NaCl) TK - UC	Intravena	HT	Sembuh
16	HLe	Laki-Laki	31	20/07/2020	RSUI	Kontrol	Intravena	DM	Sembuh

Best Practice & Lesson learn

Di antara 21 subjek yang meninggal, subjek ini memiliki > 2 komorbid

Pasien yang meninggal memiliki peningkatan D-Dimer dan Fibrinogen → menandakan adanya hiperkoagulasi

Pasien yang memiliki kondisi di atas disertai dengan komorbid CAD memiliki morbiditas yang lebih tinggi, sedangkan pasien dengan kondisi di atas tanpa komorbid CAD memiliki mortalitas yang lebih rendah

Pada echocardiografi pasien pre-implantasi yang meninggal, menunjukkan EF yang menurun

17	USa	Laki-Laki	42	20/07/2020	RSUI	75 jt (10 cc NaCl) TK - UC	Intravena	Hiperkoagulasi	Sembuh
18	SBa	Laki-Laki	74	21/07/2020	RSPI	65 jt (10 cc NaCl) TK - UC	Intravena	DM, TB	Meninggal H2 post implantasi
19	ERo	Perempuan	57	21/07/2020	RSP	Kontrol	Intravena	DM, AKI, DIC, TB	Meninggal H2 post implantasi
20	MAS	Laki-Laki	48	21/07/2020	RSP	Kontrol	Intravena	HT, DM, DIC, Hiperkoagulasi	Meninggal H10 post implantasi
21	Dar	Laki-Laki	64	28/07/2020	RSP	Kontrol	Intravena	DM Tipe 2, CAD	Meninggal H27 post implantasi
22	KJT	Laki-Laki	66	28/07/2020	RSP	60 jt (10 cc NaCl) TK-UC	Intravena	HT gr II	Sembuh
23	Roj	Laki-Laki	62	28/07/2020	RSCM	Kontrol	Intravena	AKI dd CKD, HT	Meninggal H11 post implantasi
24	Pet	Laki-Laki	38	28/07/2020	RSCM	Kontrol	Intravena	CKD on HD, CVD, CHF	Meninggal H2 post implantasi
25	NAA	Laki-Laki	56	03/08/2020	RSUI	Kontrol	Intravena	CAD, Obesitas	Meninggal H7 post implantasi
26	Jon	Laki-Laki	54	03/08/2020	RSPI	Kontrol	Intravena	HT, DM, CAD	Sembuh
27	Agu	Laki-Laki	51	03/08/2020	RSPI	67 jt (10 cc NaCl) TK-UC	Intravena	DM Tipe II	Meninggal H2 post implantasi
28	Mul	Perempuan	82	03/08/2020	RSPI	Kontrol	Intravena	DM Tipe II, HT	Meninggal H23 post implantasi
29	DKr	Laki-Laki	42	04/08/2020	RSPI	80 jt (10 cc NaCl) TK-UC	Intravena	DM Tipe II	Meninggal H15 post implantasi
30	MRi	Laki-Laki	30	10/08/2020	RSCM	94 jt (10 cc NaCl) TK-UC	Intravena	Hematothorax, Kontusio paru	Sembuh
31	Ish	Laki-Laki	65	10/08/2020	RSCM	Kontrol	Intravena	DM Tipe II, CKD on HD, ikterus	Meninggal H1 post implantasi
32	Muk	Laki-Laki	75	10/08/2020	RSCM	Kontrol	Intravena	DM tipe II, HT	Meninggal H15 post implantasi

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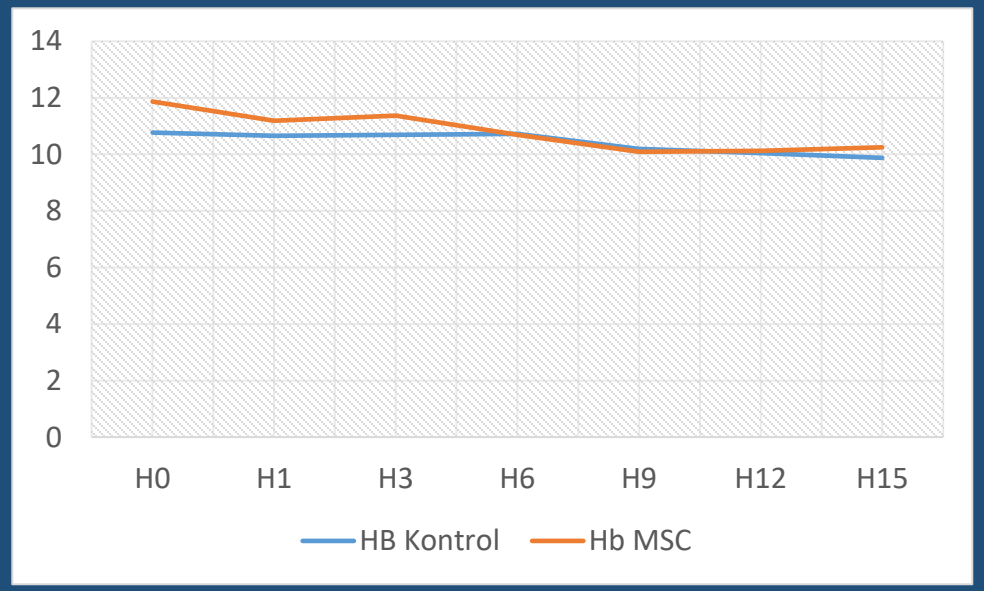
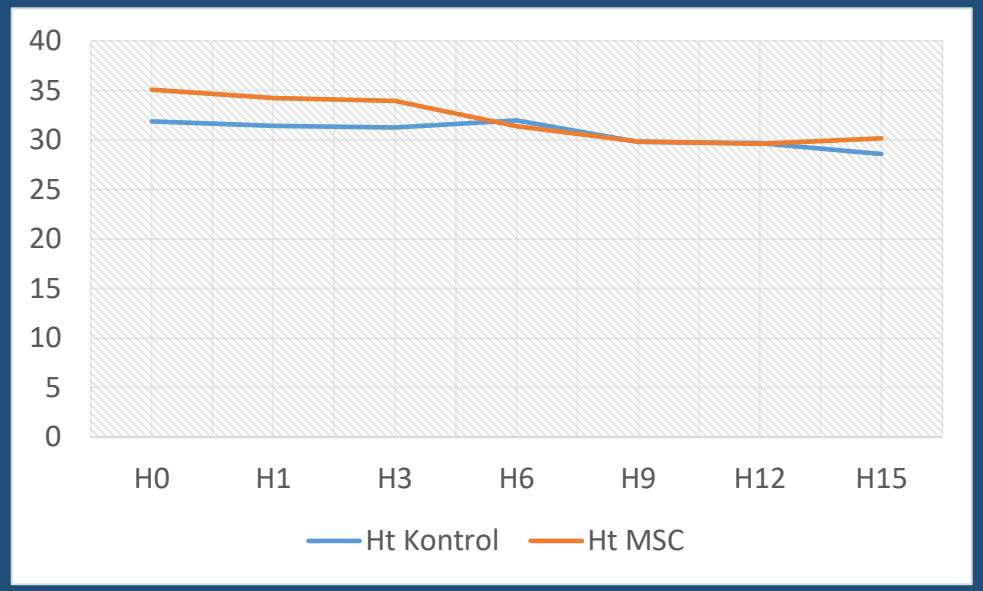
Trend Hb Pada Kelompok Kontrol vs Kelompok MSC



Trend Hematokrit Pada Kelompok Kontrol vs Kelompok MSC



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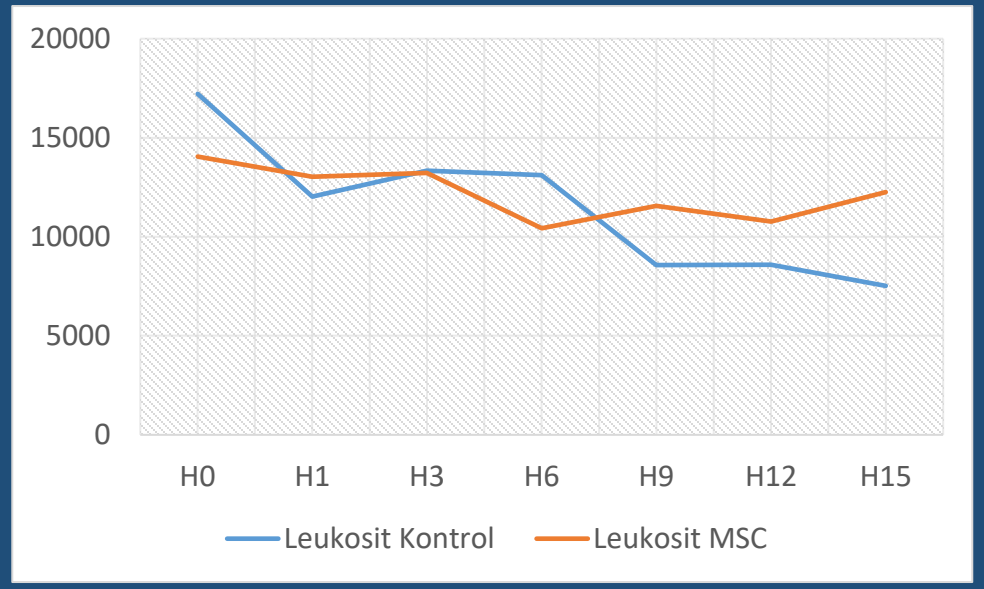
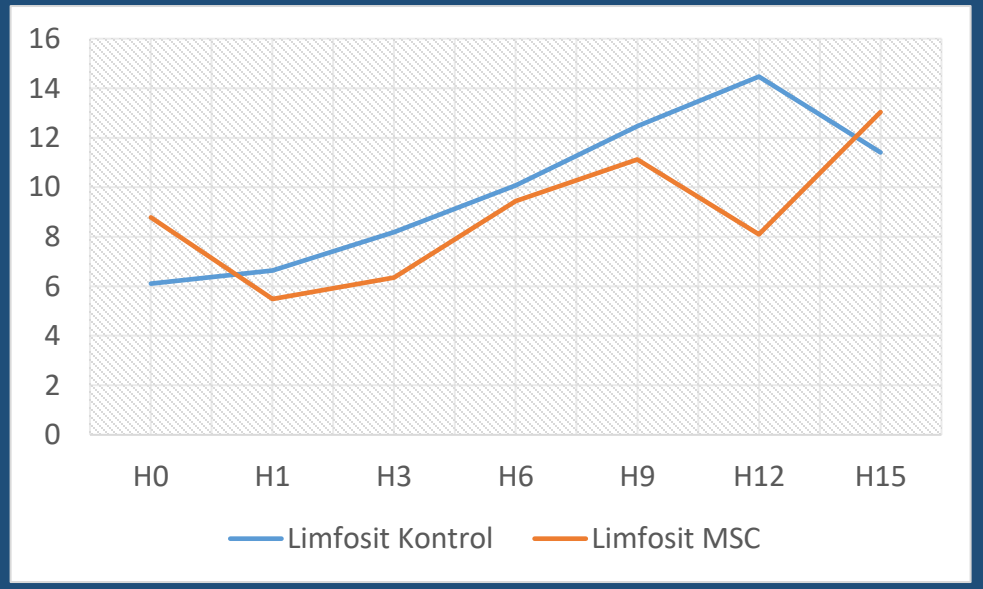
Trend Leukosit Pada Kelompok Kontrol vs Kelompok MSC



Trend Limfosit Pada Kelompok Kontrol vs Kelompok MSC



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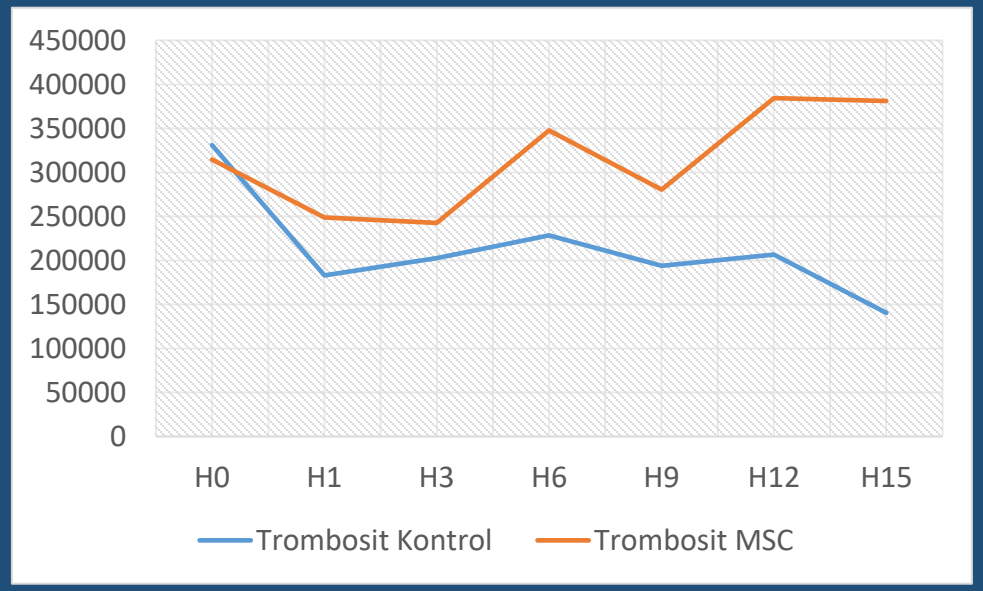
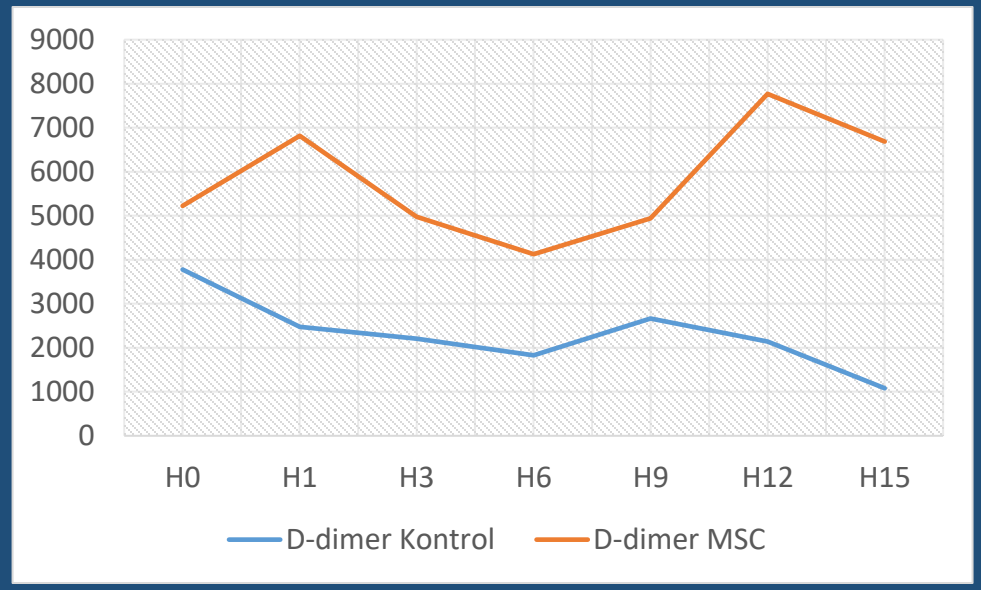
Trend Trombosit Pada Kelompok Kontrol vs Kelompok MSC



Trend D-dimer Pada Kelompok Kontrol vs Kelompok MSC



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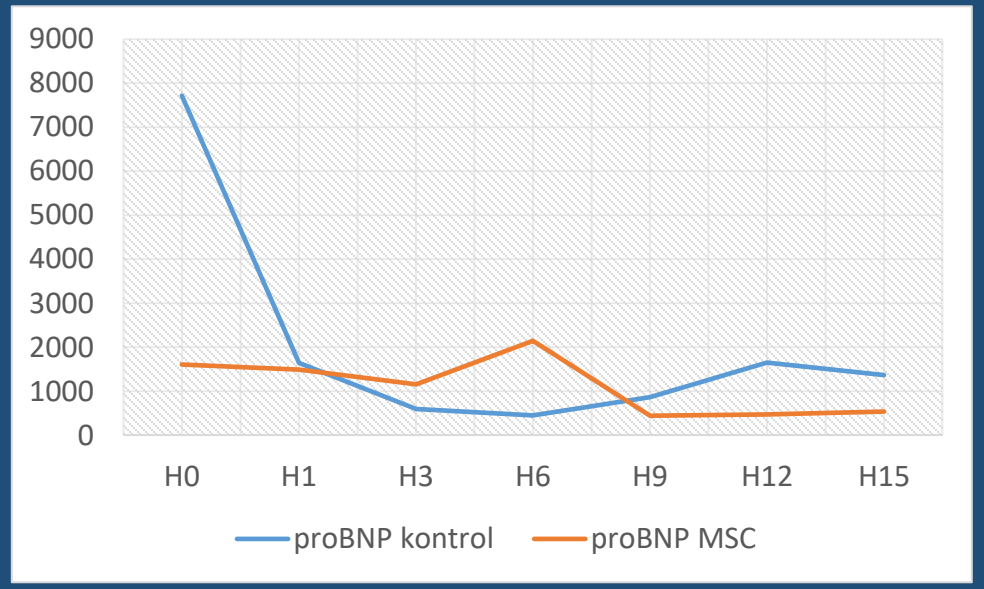
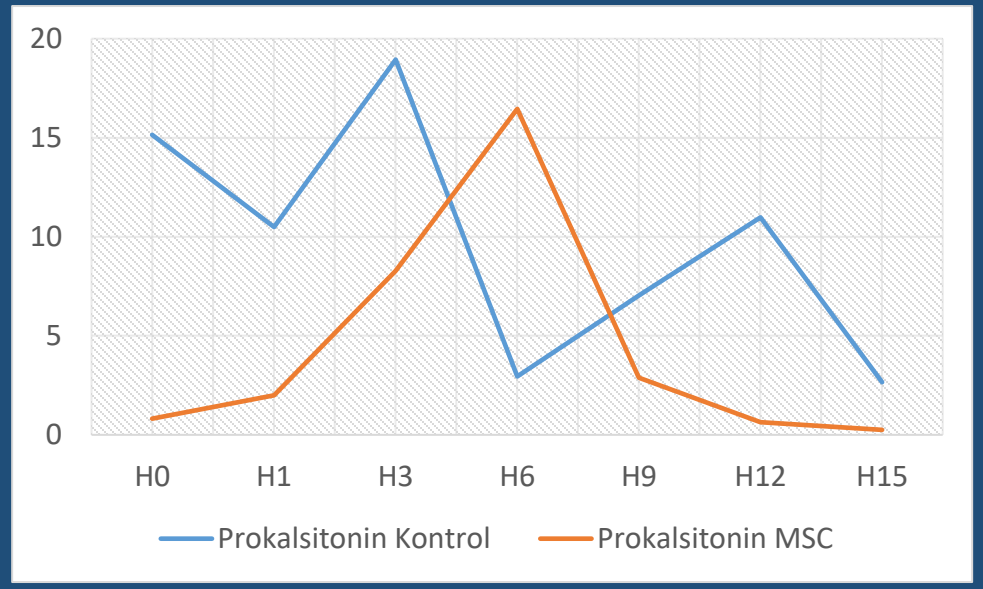
Trend proBNP Pada Kelompok Kontrol vs Kelompok MSC



Trend Prokalsitonin Pada Kelompok Kontrol vs Kelompok MSC



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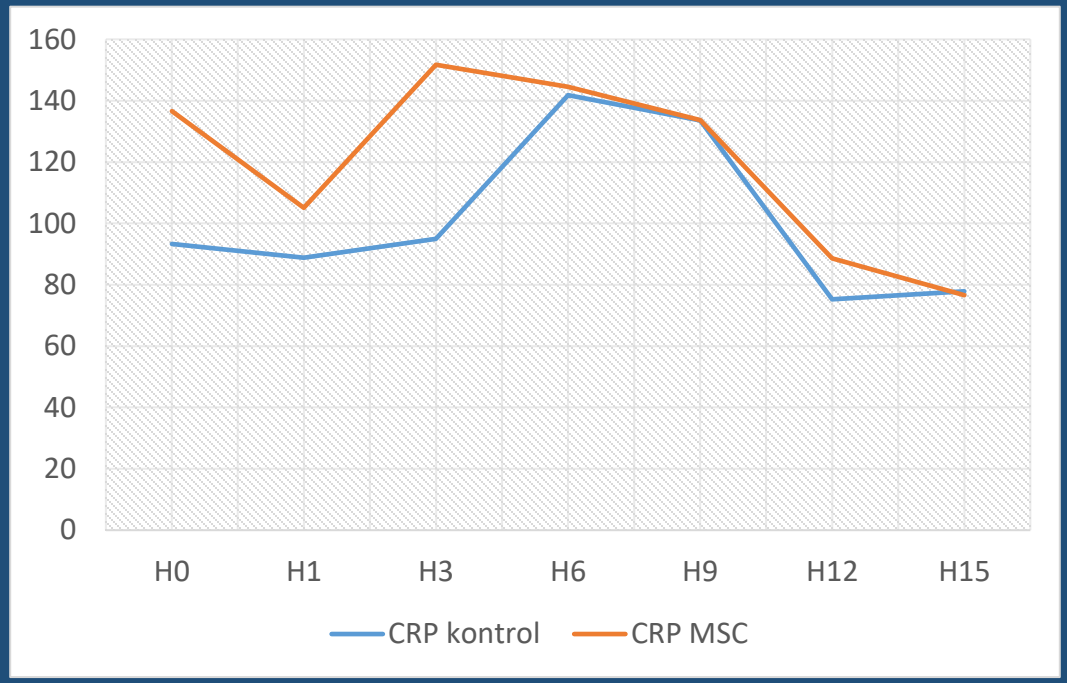
Trend CRP Pada Kelompok Kontrol vs Kelompok MSC



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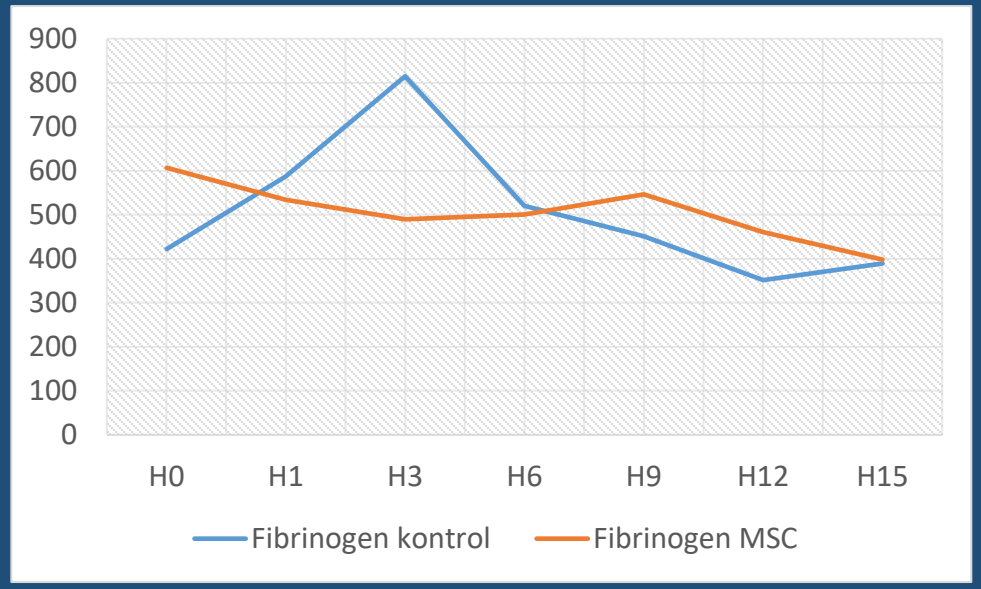
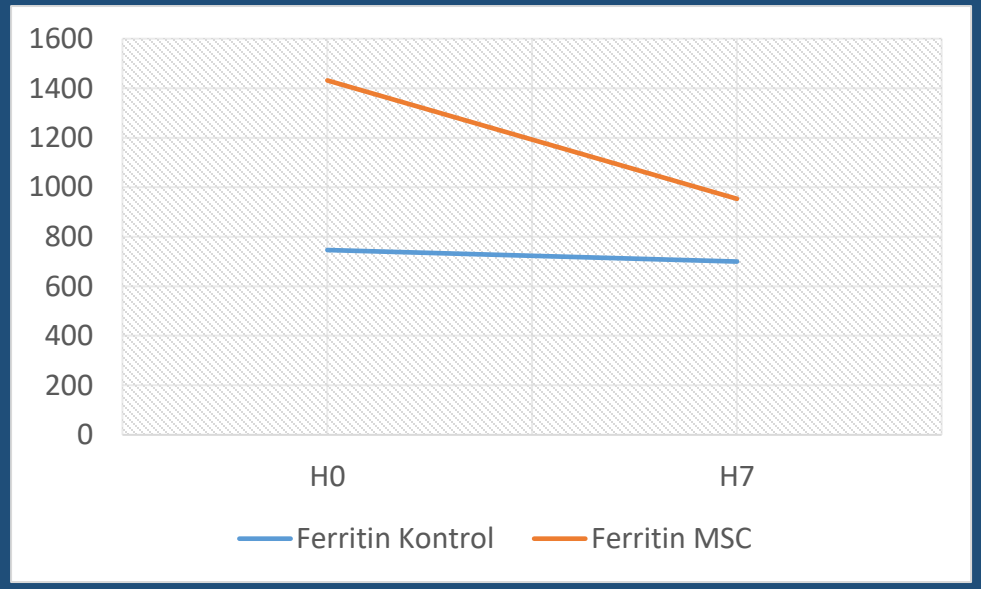
Trend Fibrinogen Pada Kelompok Kontrol vs Kelompok MSC



Trend Ferritin Pada Kelompok Kontrol vs Kelompok MSC



Mean Ferritin Kelompok Kontrol: H0 746,39 ; H7 699,96
Mean Ferritin Kelompok MSC: H0 1431,28 ; H7 952,72

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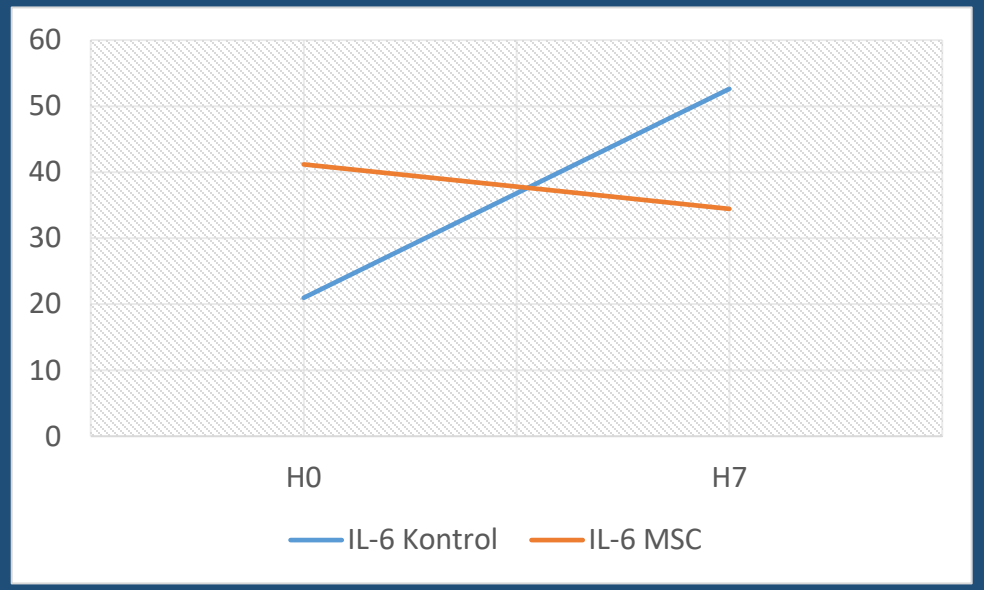
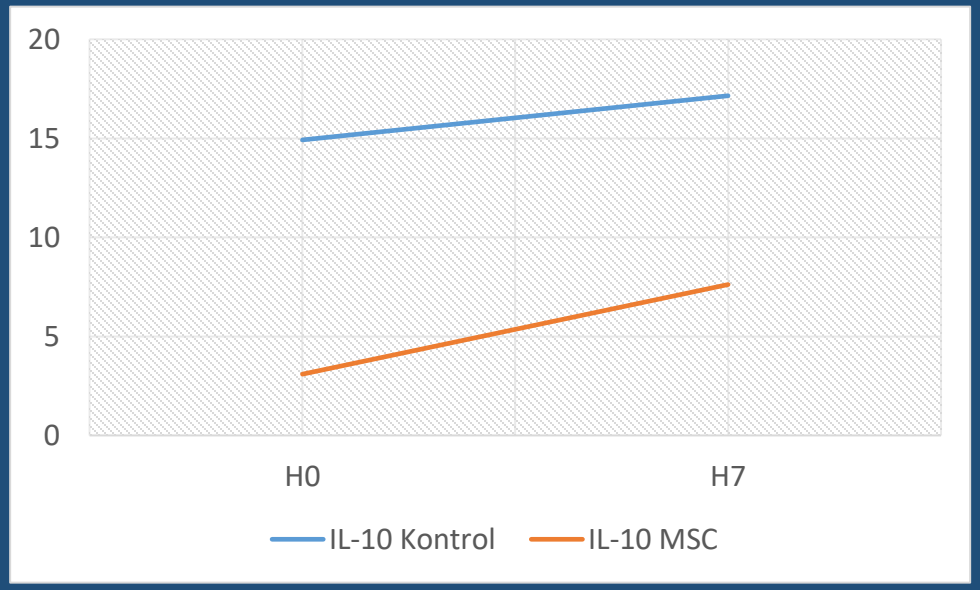
Trend IL-6 Pada Kelompok Kontrol vs Kelompok MSC



Mean IL-6 Kelompok Kontrol: H0 20,98 ; H7 52,61
Mean IL-6 Kelompok MSC: H0 41,2 ; H7 34,45

Trend IL-10 Pada Kelompok Kontrol vs Kelompok MSC



Mean IL-10 Kelompok Kontrol: H0 14,93 ; H7 17,16
Mean IL-10 Kelompok MSC: H0 3,09 ; H7 7,62

KESEHATAN UNTUK BANGSA
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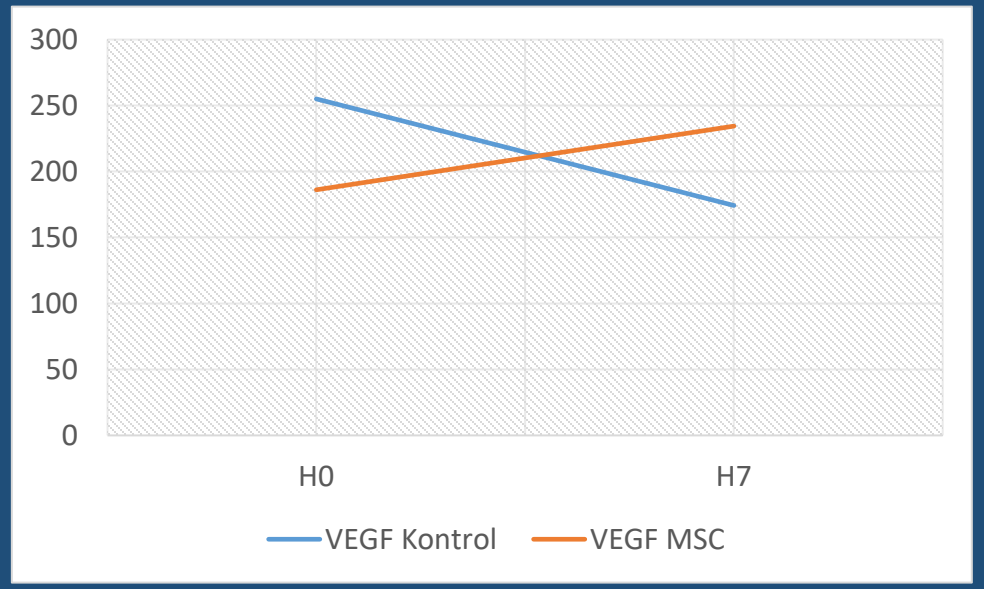
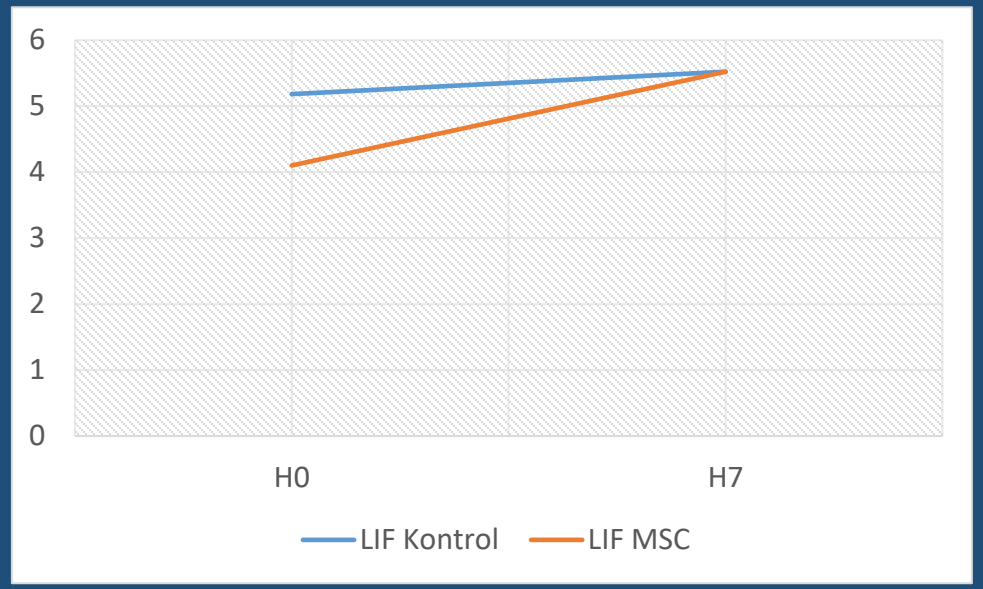
Best Practice & Lesson learn

Trend VEGF Pada Kelompok Kontrol vs Kelompok MSC



Mean VEGF Kelompok Kontrol: H0 254,96 ; H7 186,16
Mean VEGF Kelompok MSC: H0 174,13 ; H7 234,25

Trend LIF Pada Kelompok Kontrol vs Kelompok MSC



Mean LIF Kelompok Kontrol: H0 5,18 ; H7 5,52
Mean LIF Kelompok MSC: H0 4,10 ; H7 5,52

KESEHATAN UNTUK BANGSA
MEMBANGUN SDM INDONESIA UNGGUL

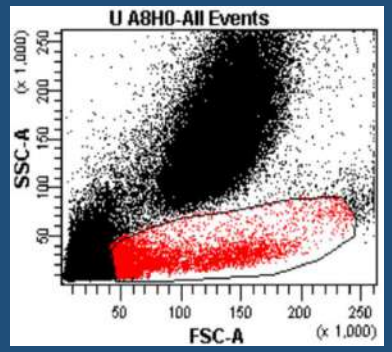
Hasil flow cytometry MSC trial for critical COVID-19

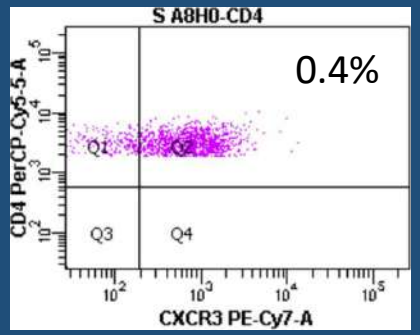
- Populasi limfosit yang berperan dalam badai sitokin
  - CD4-CXCR3
  - CD8-CXCR3
  - CD56-CXCR3

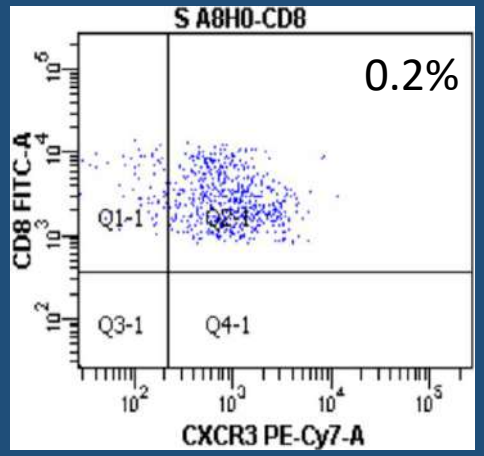
Best Practice & Lesson learn

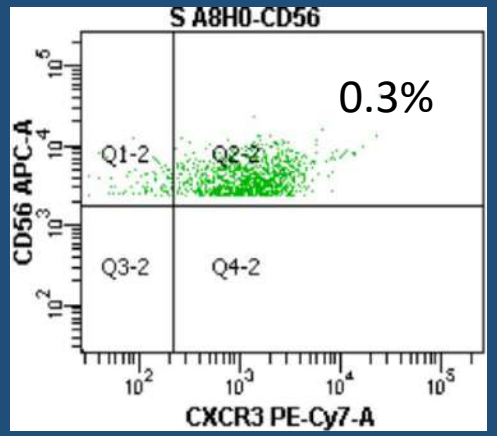
Flow cytometry representatif H-0 (Baseline)

- MSC

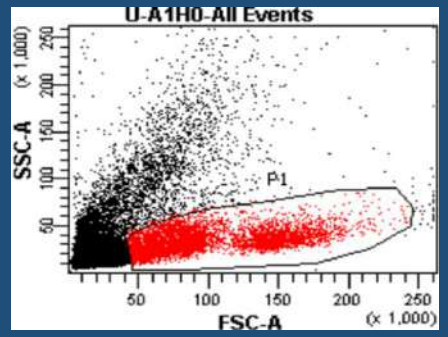


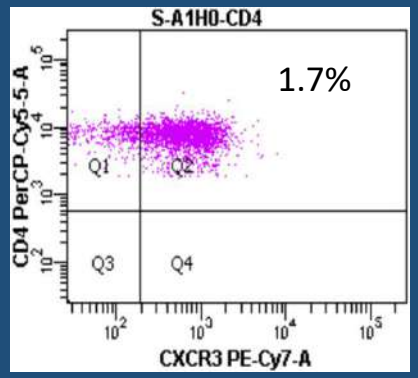


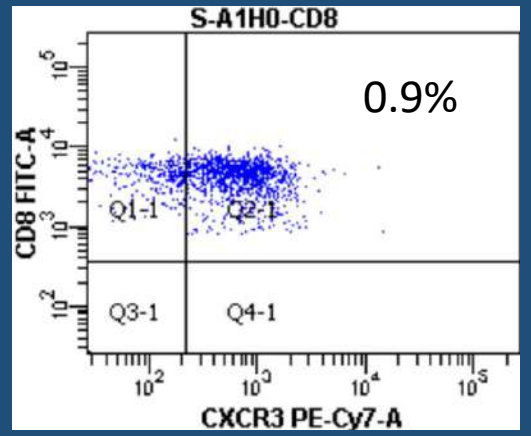


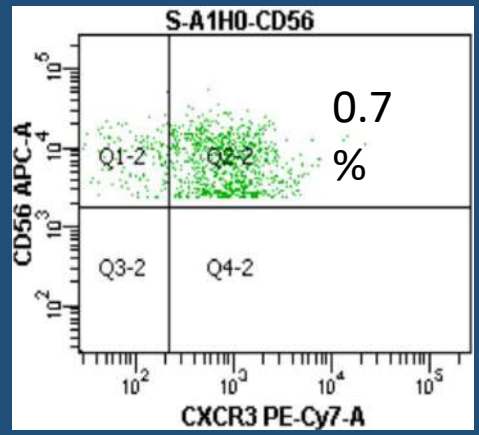


- Kontrol







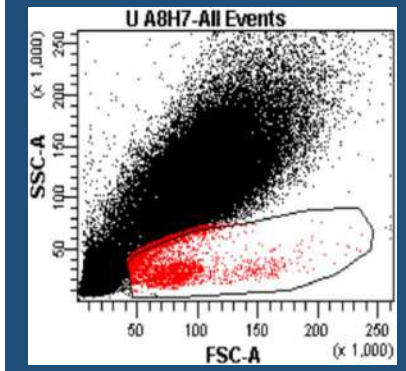


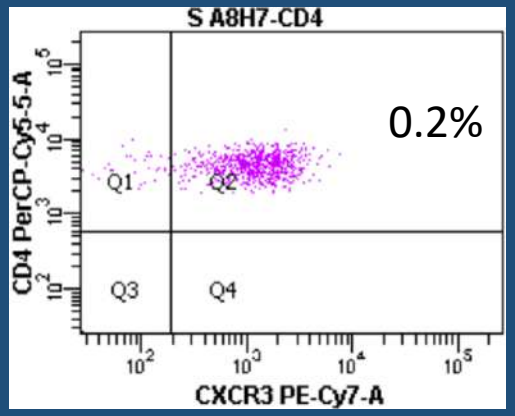
KESEHATAN UNTUK BANGSA
MEMBANGUN SDM INDONESIA UNGGUL

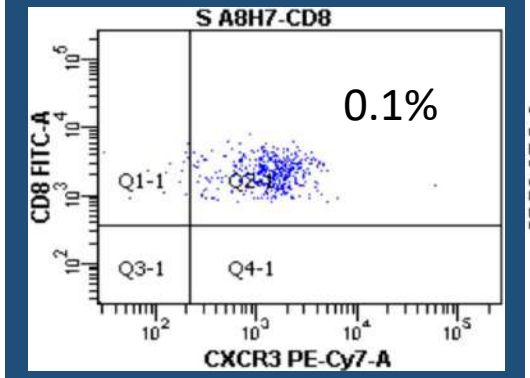
Best Practice & Lesson learn

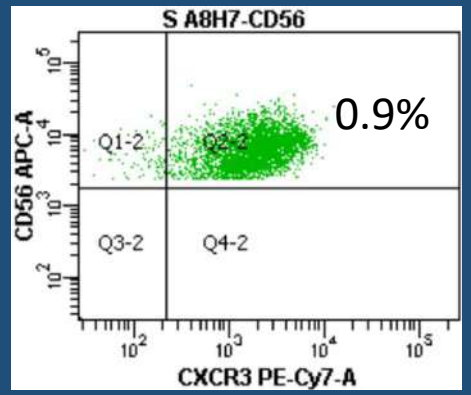
Flow cytometry representatif H-7

- MSC

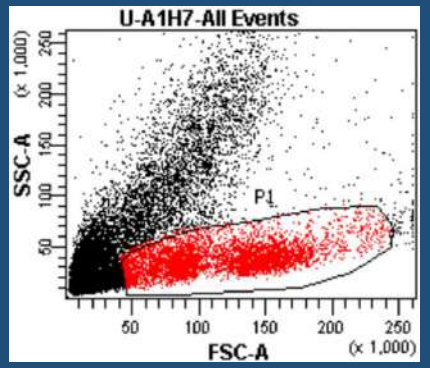


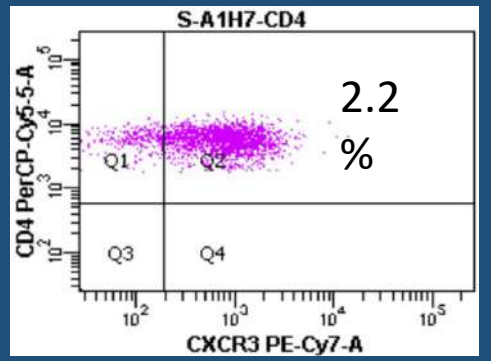


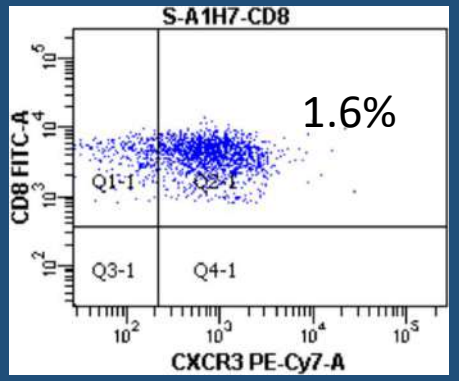


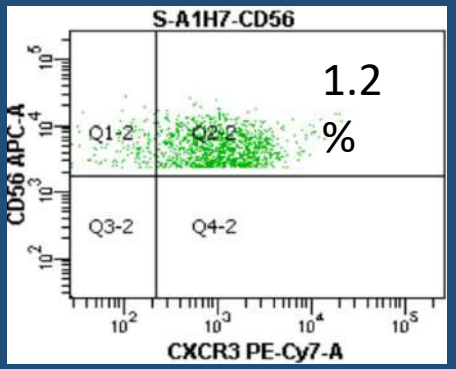


- Kontrol









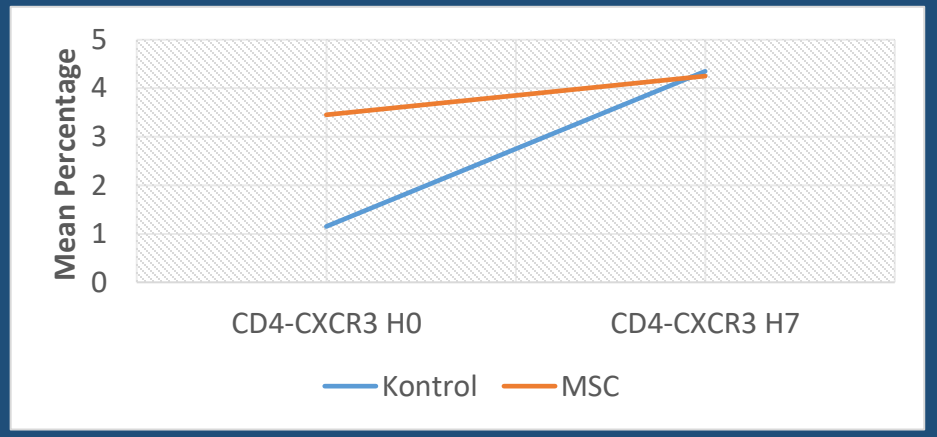
KESEHATAN UNTUK BANGSA
MEMBANGUN SDM INDONESIA UNGGUL

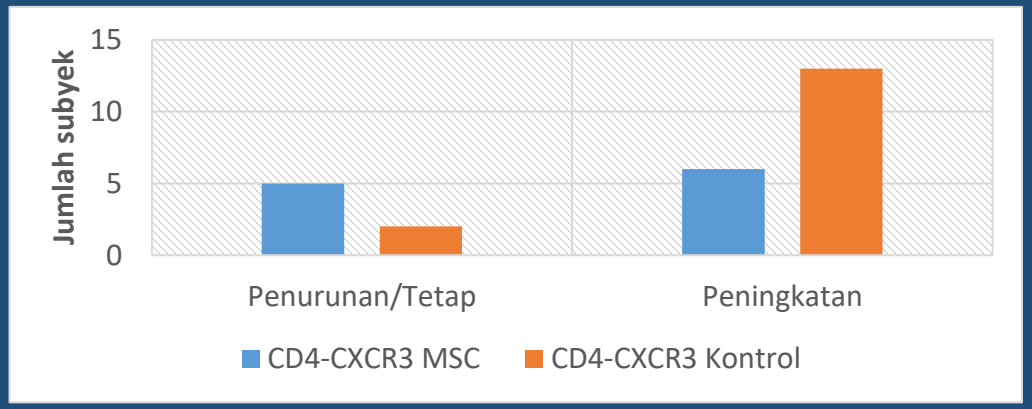
Best Practice & Lesson learn

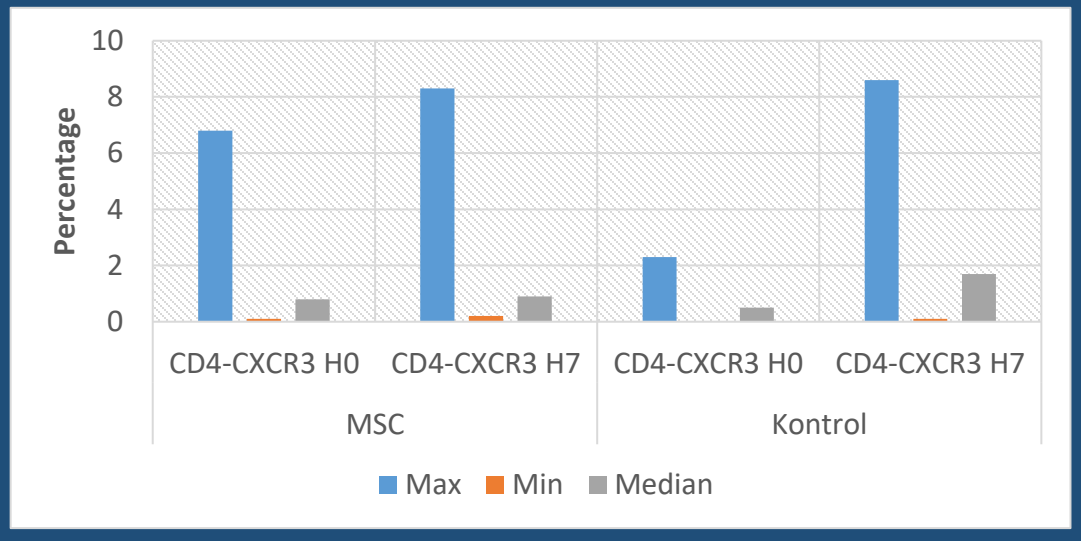
Populasi CD4-CXCR3

Nilai Min, Median, Max kelompok MSC pada hari-7 dibandingkan baseline (h0) peningkatannya tidak sedrastis kelompok control

Lebih banyak jumlah subyek yang menurun atau tetap persentase populasi CD4-CXCR3 dengan MSC dibandingkan kontrol





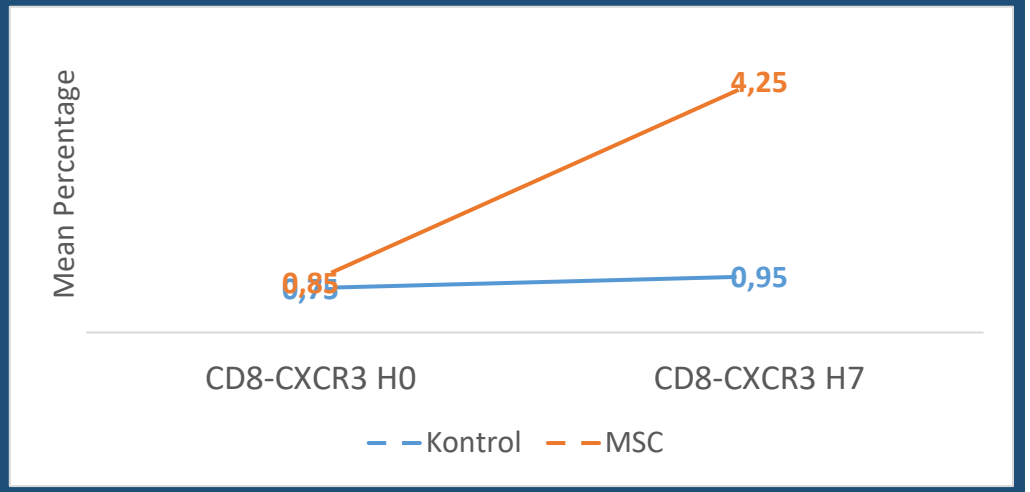


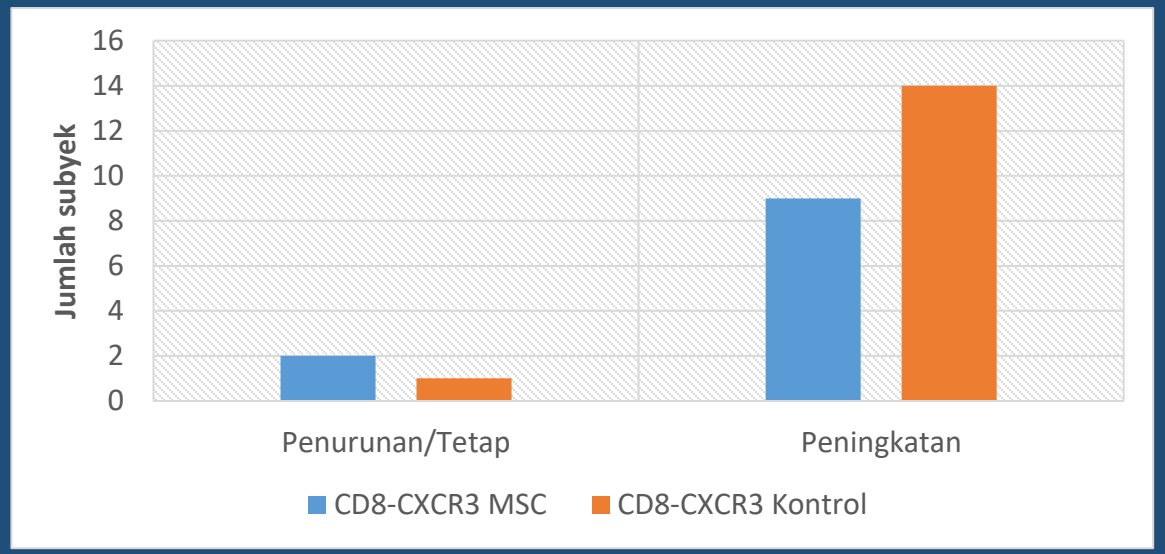
KESEHATAN UNTUK BANGSA
MEMBANGUN SDM INDONESIA UNGGUL

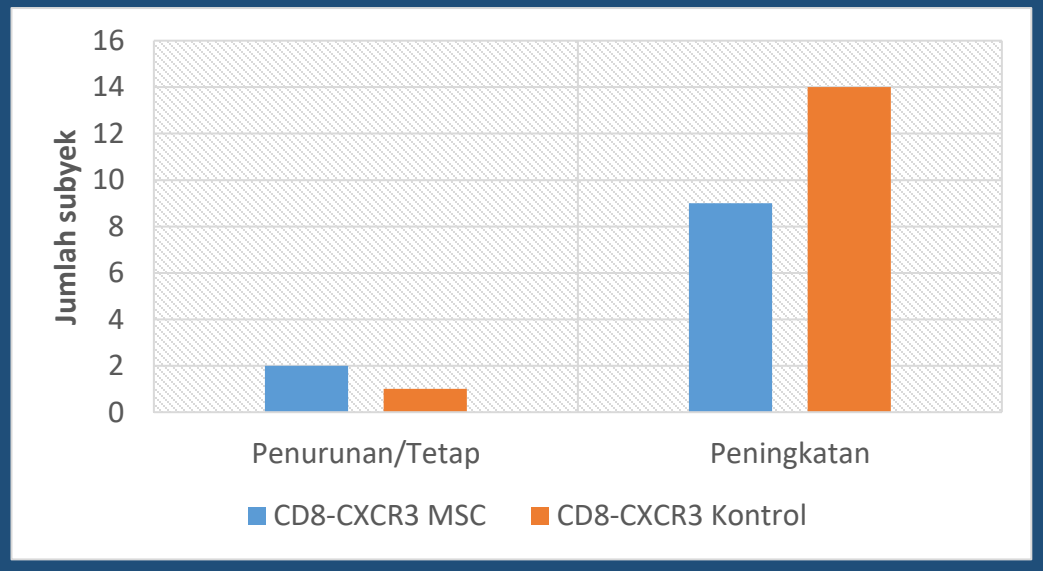
Best Practice & Lesson learn

Populasi CD8-CXCR3

Pola yang serupa untuk CD8-CXCR3
MSC > Kontrol dalam menekan peningkatan persentase populasi CD8-CXCR3





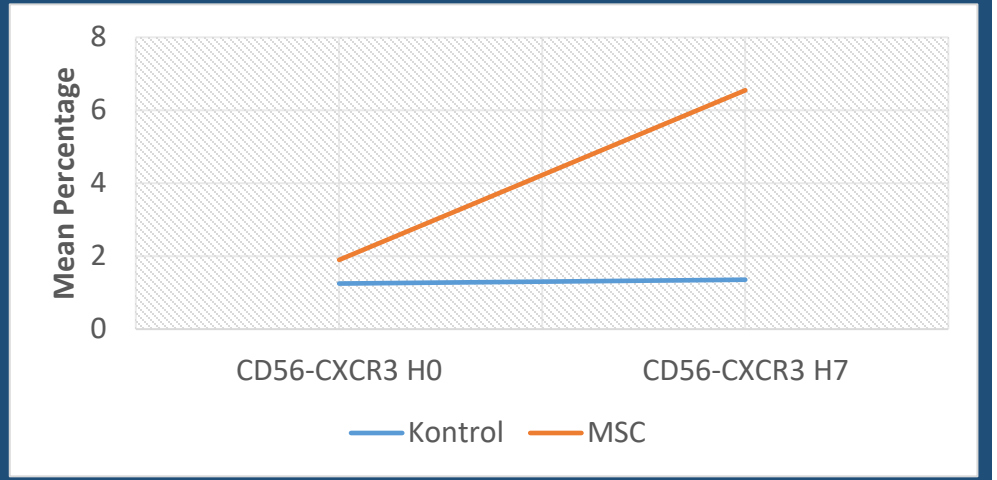


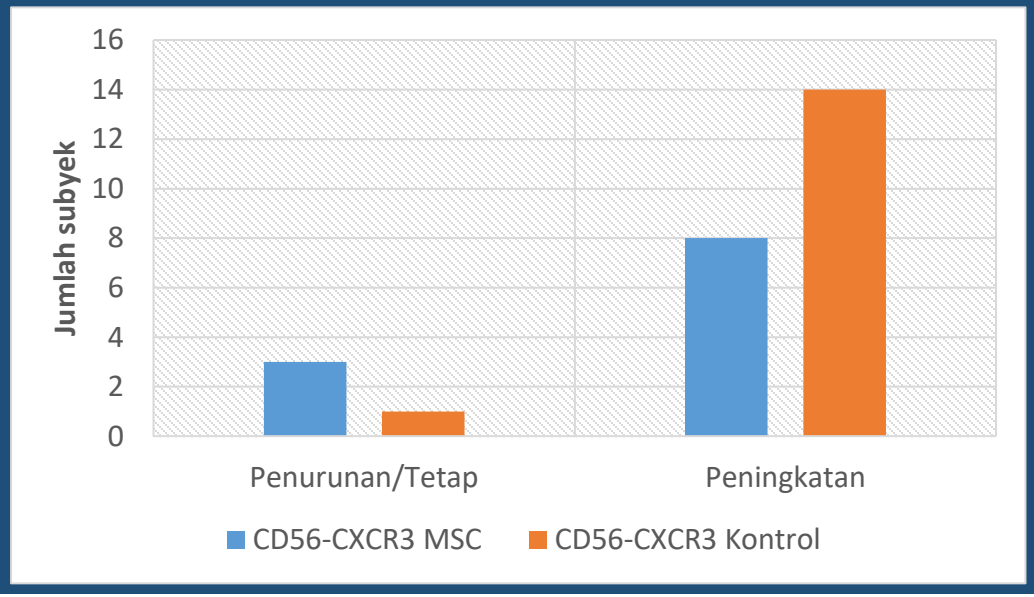
KESEHATAN UNTUK BANGSA
MEMBANGUN SDM INDONESIA UNGGUL

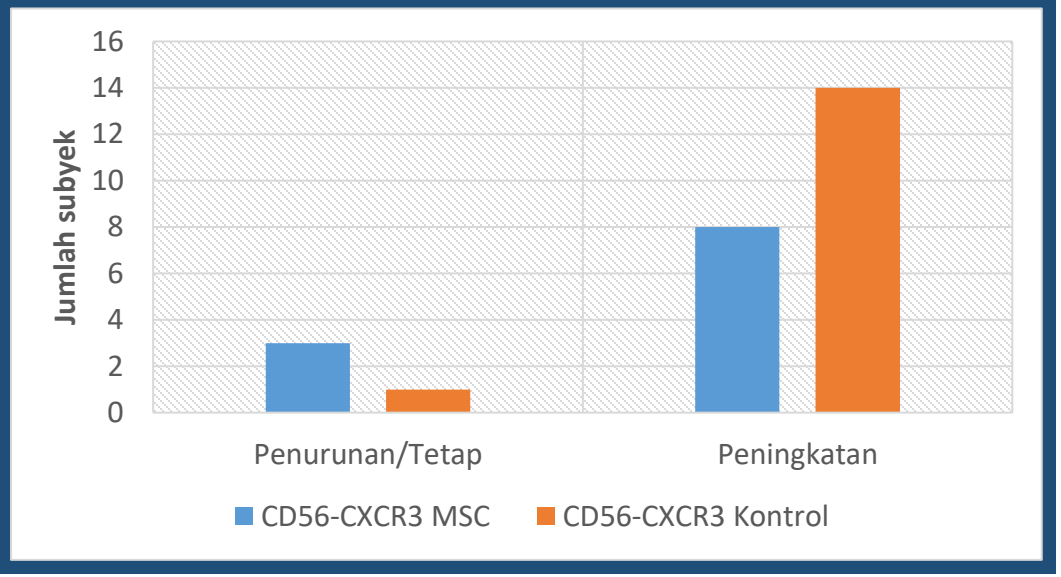
Best Practice & Lesson learn

Populasi CD56-CXCR3

CD56-CXCR3 adalah populasi sel NK
MSC > Kontrol dalam menekan peningkatan persentase populasi CD56-CXCR3







KESEHATAN UNTUK BANGSA
MEMBANGUN SDM INDONESIA UNGGUL

Challenge

- Pasien dengan derajat kritis sering kali disertai komorbid.

Solution

- Kolaborasi yang optimal dengan masing-masing spesialis dan subspesialis
- Konsultan intensive care- Tim paru-penyakit dalam : jantung kardiovaskuler- hematologi-endokrin metabolic-nefrologi-tim bedah-rehabilitasi medis-gizi- psikiatri dan interdisiplin lain yang berhubungan dengan ko morbid pasien

Kendala

1. Uji Klinis sudah dilakukan multi center, namun krn ada beberapa penelitian lain terkait C-19 ini, maka Uji Klinis ini sangat ketat dalam memilih pasien untuk masuk dalam kriteria Inklusi
2. Kondisi Pasien yg termasuk dalam derajat kritis, kemungkinan lebih 80% meninggal
3. Pasien yg masuk dalam kriteria inklusi sebagian besar memiliki Kormobid yg dapat memperburuk keadaan pasien dengan cepat
4. Keterbatasan dana untuk melakukan uji klinis ini sehingga jumlah –n subjek terbatas

Upaya yg dilakukan

1. Selektif dan sesegera mungkin untuk melakukan implantasi sel punca sebelum pasien mengalami perburukan
2. Memperluas kriteria inklusi, yaitu pada pasien derajat sedang-berat → Uji Klinis ini dilakukan oleh dr Erlina Burhan , Sp.P (K) di RSP Persahabatan

Uji Klinis pada pasien C-19 ini akan dikembangkan pada :

- Derajat Sedang – Berat
- Menggunakan Sekretome/metabolit→ Prof Murdani

KESEHATAN UNTUK BANGSA
MEMBANGUN SDM INDONESIA UNGGUL

Perkembangan Pasien #1 (Ny. EFi, 38 thn - RSCM)

- OS mengeluhkan nyeri perut memberat sejak 4 hari SMRS, disertai mual muntah warna kuning, dan nyeri menelan, tidak ada kentut. Dirujuk dari RSUD Tebet dengan diagnosis Peritonitis, ileus paralitik, syok hipovolemik dd syok sepsis, kolelitiasis dd pankreatitis akut, mioma uteri, efusi pleura bilateral
- Dirawat di RSCM sejak 19/04/2020, dilakukan operasi laparotomi perforasi gaster tanggal 20/04/2020, dilakukan relaparotomy ec peritonitis umum tanggal 29/04/2020. Karena pasien terpasang WSD dan keluar darah, pasien dilakukan video assisted thoracoscopy pada tanggal 22/05/2020

- **Comorbid** : perforasi gaster, efusi pleura

Perkembangan Pasien #1 (Ny. EFi, 38 thn - RSCM)

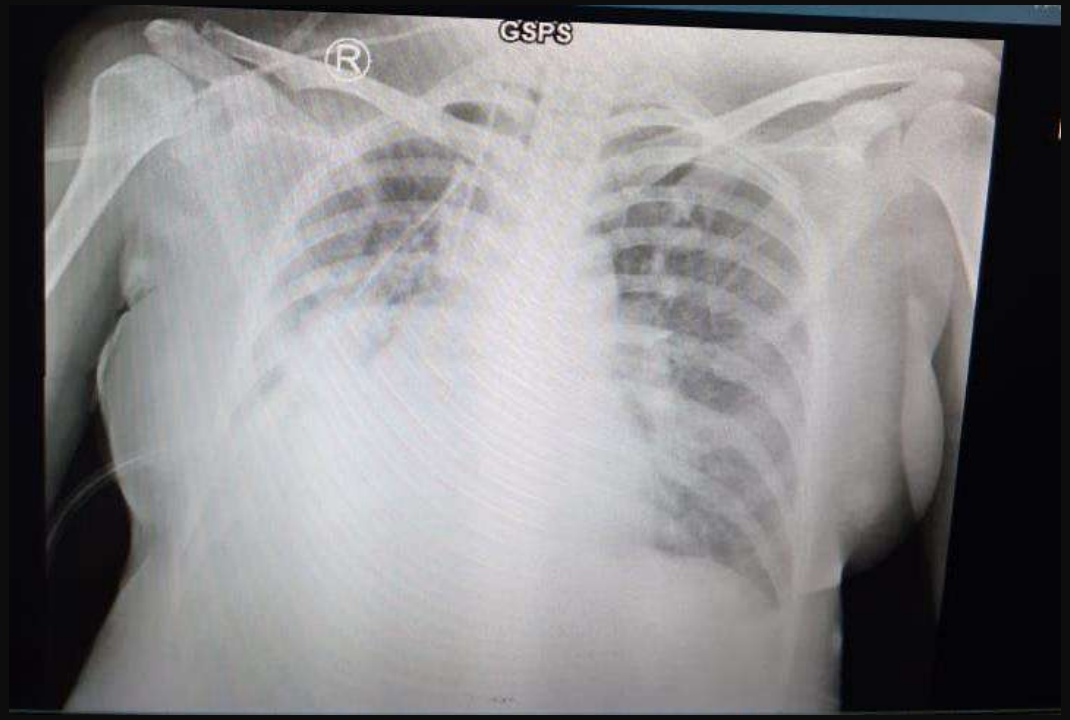
Parameter	Baseline (20/05/2020)	H15 Pasca Implantasi (04/06/2020)
Klinis		
Sesak	Ada	Tidak Ada
Batuk	Tidak Ada	Tidak Ada
Dahak	Tidak Ada	Tidak Ada
Demam	Tidak Ada	Tidak Ada
Intubasi	Ada	Tidak Ada (terekstubasi pada hari ke-13)
Tanda Vital		
Tekanan Darah (mmHg)	SBP: 123-132; DBP: 64-75	151/92
Nadi (x/menit)	122-128	92
Suhu (^{o}C)	37.4	17
Laju Pernapasan (x/menit)	26-33	20-22
Saturasi Oksigen (%)	100%	100% on nasal canule 3 lpm

Perkembangan Pasien #1 (Ny. EFi, 38 thn - RSCM)

Parameter	Baseline (20/05/2020)	H15 Pasca Implantasi (04/06/2020)	Parameter	Baseline (20/05/2020)	H15 Pasca Implantasi (04/06/2020)
	Laboratorium		Fibrinogen	319	201.9
DPL (Hb/Ht/L/T)	8.7/26.3/15.990/130.000	10.1/29.9/20.220/531.000	Troponin	0.17	0.06
Hitung Jenis (B/E/N/L/M)	0.6/0.3/78.9/10.1/10.1	0.5/0.0/86.1/9.3/41	ProBNP	1,483	615.9
Analisa Gas Darah	7.45/42.1/132.7/29.5/5.6/98.9	7.49/37.2/65.7/5.7/28.5/94.1	**Sitokin**		
CRP	82.4	19.1	VEGF	On process	
SGOT/SGPT	65/45	61/64	Ferritin	On process	
Ureum/Kreatinin	11.1/0.3	42.6/0.2	IL-6	On process	
Elektrolit (Na/K/Cl)	138/3.7/104.6	134/3.8/98.3	LIF	On process	
Pro-Calcitonin	0.69	0.08	CXCR3 CD4	On process	
Albumin	2.33	2.94	CXCR3 CD8	On process	
Bilirubin total	0.99	0.56	CXCR3 Sel NK	On process	
D-Dimer	6600	8130			

Perkembangan Pasien #1 (Ny. EFi, 38 thn - RSCM)

- Radiologis

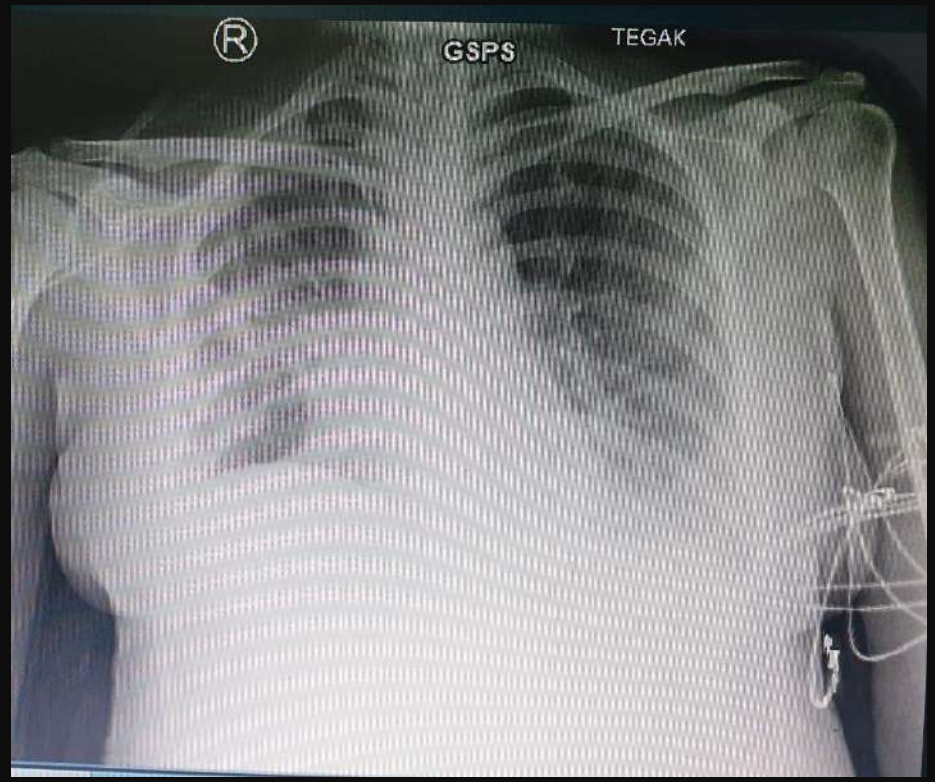


Ro Thorax (20/05/2020)

- Efusi pleura kanan tampak berkurang
- Efusi pleura kiri, stqa
- Konsolidasi di lapang baru kanan (sulit dibandingkan karena sebelumnya tertutup efusi)
- ETT dengan tip distal sekitar 5,5 cm di atas carina
- Posisi tip CVC di proyeksi vena cava superior
- Tidak tampak pneumotoraks, pneumomediastinum maupun emfisema subkutis

Perkembangan Pasien #1 (Ny. EFi, 38 thn - RSCM)

- Radiologis



Ro Thorax (05/06/2020)

- Dibandingkan dengan radiografi toraks tanggal 4 Juni 2020: infiltrat paru kanan berkurang, infiltrat di parakardial kiri relative stqa, suspek efusi pleura bilateral
- Posisi tip CVC relatif stqa

Perkembangan Pasien #1:
Ny. EFi, 38 thn (ICU IGD - RSCM)

12 Juni 2020
Pasien **KRS pada hari ke 23 setelah** implantasi

Pasien sudah diekstubasi dan menjalani program rehabilitasi dengan tim Rehabilitasi Medik

Perkembangan Pasien #2 (Tn. Rah, 62 tahun - RSCM)

Pengkajian Awal Masuk (masuk IGD 23/05/2020)

- OS mengeluhkan sesak napas sejak 2 minggu SMRS, OS sulit berkomunikasi karena sesak yang berat. OS tinggal di daerah Pasar Senen, sempat berobat ke klinik dan diberi obat, namun keluhan sesak tidak membaik. OS memiliki riwayat asma.
- Diperiksa rapid test tgl 24/05/2020, hasil: IgM reaktif

- **Comorbid** : -

Perkembangan Pasien #2 (Tn. Rah, 62 tahun - RSCM)

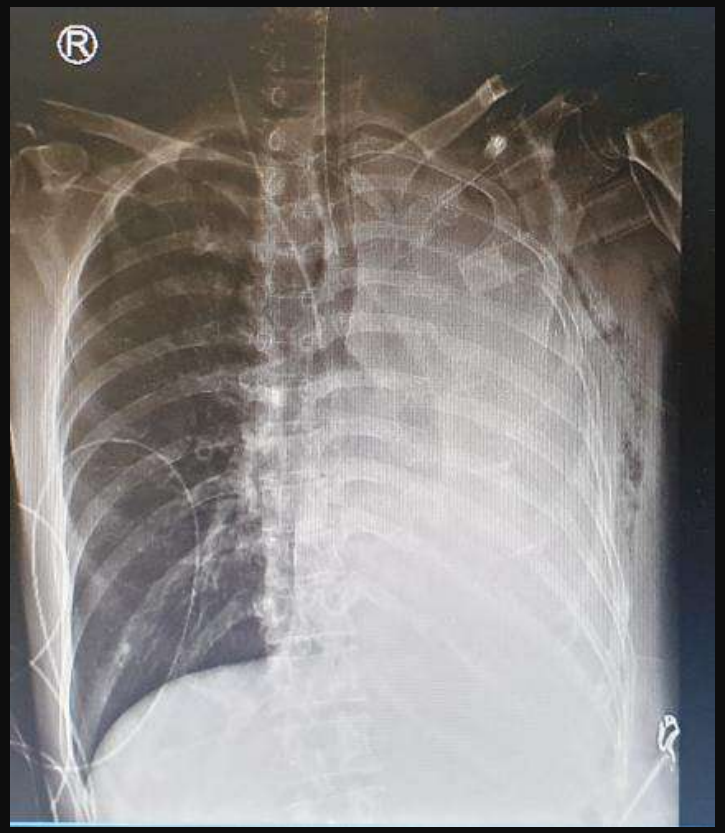
Parameter	Baseline (27/05/2020)	H10 Pasca Implantasi (06/06/2020)
Klinis		
Sesak	Ada	Tidak Ada
Batuk	Tidak Ada	Tidak Ada
Dahak	Ada	Tidak Ada
Demam	Tidak Ada	Tidak Ada
Intubasi	Ada	Tidak Ada (terekstubasi pada hari ke-2 post implantasi)
Tanda Vital		
Tekanan Darah (mmHg)	134/71	139/80
Nadi (x/menit)	106	107
Suhu (^oC)	36.6	36.4
Laju Pernapasan (x/menit)	18	23
Saturasi Oksigen (%)	100% on PSIMV 14/12/7/40	100%

Perkembangan Pasien #2 (Tn. Rah, 62 tahun - RSCM)

Parameter	Baseline (27/05/2020)	H15 Pasca Implantasi (11/06/2020)	Parameter	Baseline (27/05/2020)	H9 Pasca Implantasi (11/06/2020)
Laboratorium			D-Dimer	1850	1510
DPL (Hb/Ht/L/T)	9.5/27.3/12.720/167.000	8.6/24/14,240/489.000	Fibrinogen	449.2	203.4
Hitung Jenis (B/E/N/L/M)	0.3/0.0/90.3/4.1/5.3	0.1/0.5/90.8/3.7/5.2	Troponin	0.28	0.02
Analisa Gas Darah	7.467/45.4/219.5/9.3/33.10/34.5/97.3%	7.52/46.9/100.2/15.1/38.6/38.7/74.4	ProBNP	1223	403
CRP	40.3	1.1	**Sitokin**		
SGOT/SGPT	42/15	19/18	VEGF	On process	
Ureum/Kreatinin	19.8/0.5	31.3/0.4	Ferritin	On process	
Laju Filtrasi Glomerulus	116.1	127.3	IL-6	On process	
Elektrolit (Na/K/Cl)	124/4.2/93.3	136/3.9/99.2	LIF	On process	
Pro-Calcitonin	1.25	0.02	CXCR3 CD4	On process	
Albumin	3.12	3.41	CXCR3 CD8	On process	
Bilirubin total	0.76	1.08	CXCR3 Sel NK	On process	

Perkembangan Pasien #2 (Tn. Rah, 62 thn - RSCM)

- Radiologis

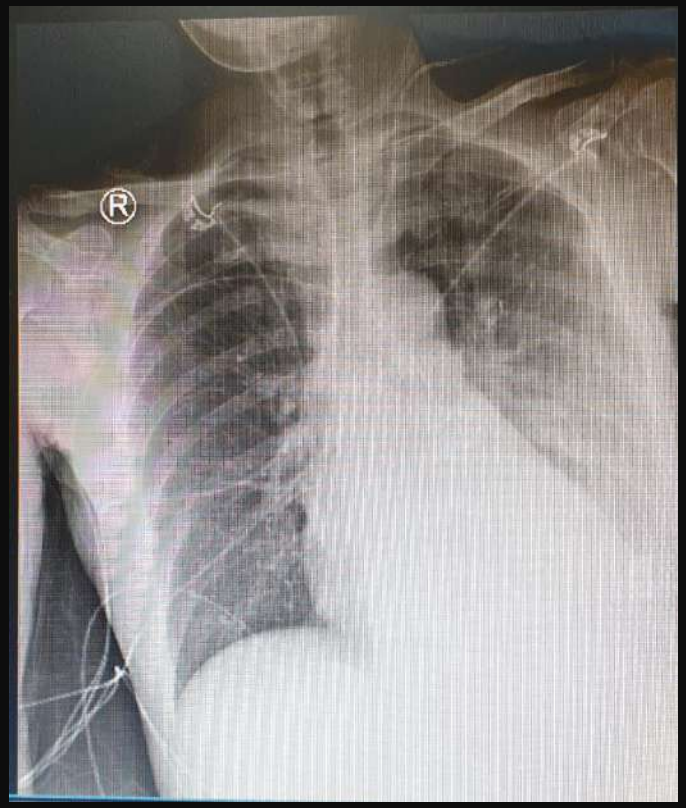


<u>Rontgen Thorax (26 Mei 2020)</u>

- Dibandingkan dengan radiografi toraks tanggal 23 Mei 2020, saat ini:
  - Sugestif gambaran atelectasis paru kiri
  - Multipel fraktur komplit segmental pada costae 4-9 posterior dan lateral kiri, stqa
  - CVC di proyeksi vena cava superior
  - ETT dengan tip sekitar 4.9 cm di atas carina
  - Soft tissue swelling disertai emfisema subkutis regio colli bilateral dan dinding dada lateral kiri
  - Tidak tampang gambaran pneumotoraks maupun pneumomediastinum

Perkembangan Pasien #2 (Tn. Rah, 62 thn - RSCM)

- Radiologis



Rontgen Thorax (30 Mei 2020)

- Dibandingkan dengan radiografi toraks tanggal 29 Mei 2020, saat ini:
  - Efusi pleura kiri
  - Multiple fraktur komplit segmental pada costae 4-8 posterior dan lateral kiri
  - CVC dengan tip distal pada proyeksi vena kava superior
  - Opasitas berbatas tegas kecil di lapangan bawah paru kangan, dd/ kalsifikasi, nodul paru

Perkembangan Pasien #2 (Tn. Rah, 62 thn - RSCM)

Pasien sudah ekstubasi dan sudah latihan makan lunak

12 Juni 2020
Pasien **KRS pada hari ke 23 setelah** implantasi

Perkembangan Pasien #8 (Tn. ABa, 65 y.o. - RSP)

- Pasien rujukan dari Rumah Sakit Gadung Pluit (Belum sempat rawat inap) dengan keluhan sesak susp COVID-19, sesak memberat sejak 1 hari sebelum masuk rumah sakit. Mengeluhkan batuk tanpa dahak dan juga demam sejak 1 minggu sebelum masuk rumah sakit, pasien datang ke IGD dengan keadaan penurunan keasadaran

APACHE II Score : Angka kematian 40%

- **Komorbid : Syok sepsis, DM Tipe II, CAD (EF 39%), Cerebrovaskular Disease (Stroke lacunar infark)**

Perkembangan Pasien #8 (Tn. ABa, 65 y.o. - RSP)

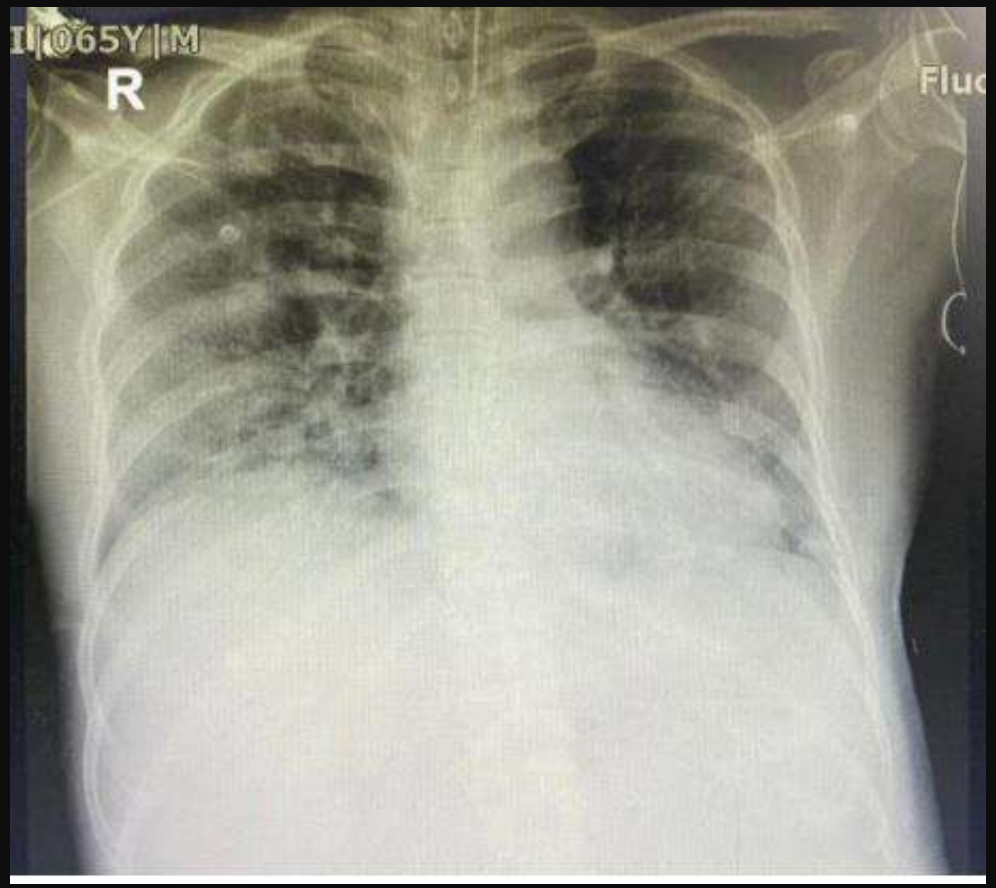
Parameter	Baseline (26/06/2020)	D6 Pasca Implantasi (02/07/2020)
Manifestasi Klinis		
Sesak	Ada	Ada
Batuk	Ada	Tidak ada
Dahak	Ada	Ada
Demam	Tidak ada	Tidak Ada
Intubasi	Ada	Ada
Tanda Vital		
Tekanan Darah(mmHg)	119/76	92/46
Nadi (x/min)	102	119
Suhu (^oC)	36.5	37.7
Laju Pernapasan (x/min)	24	26
Saturasi O2 (%)	92% on ventilator, FiO2: 70%, PEEP: 10, Tins:1.2, TV: 480, Mode : A/C	88% on ventilator, FiO2 : 100%, PEEP:10, Tins: 1, TV:460, Mode: VC/AC

Perkembangan Pasien #8 (Tn. ABa, 65 y.o. - RSP)

Parameter	Baseline (26/06/2020)	D6 Pasca Implantasi (02/07/2020)	Parameter	Baseline (26/06/2020)	D6 Pasca Implantasi (02/07/2020)
Laboratorium			Fibrinogen	541	404.8
DPL (Hb/Ht/L/T)	13.3/39.8/10.730/286.000	10/31/2.070/32.000	Troponin	58	219.2
Hitung Jenis (B/E/N/L/M)	0.2/0/95.8/2.1/1.9	0.5/0/84/11.6/3.9	ProBNP	799.6	10,866
Analisa Gas Darah	7.396/40.8/79.8/25.3/95.9/0.2	7.044/67.5/45.8/18.6/59.3/-12.2	**Sitokin**		
CRP	74	305.5	VEGF	On process	
SGOT/SGPT	24/37	20/21	Ferritin	On process	
Ureum/Kreatinin	136/1	339/1.1	IL-6	On process	
Elektrolit (Na/K/Cl)	138/4/97	138/4.7/109	LIF	On process	
Pro-Calcitonin	1.68	93.96	CXCR3 CD4	On process	
Albumin	2.6	1.08	CXCR3 CD8	On process	
Bilirubin total	0.5	1.08	CXCR3 Sel NK	On process	
D-Dimer	1560	1130			

Perkembangan Pasien #8 (Tn. ABa, 65 y.o.- RSP)

- Radiologis

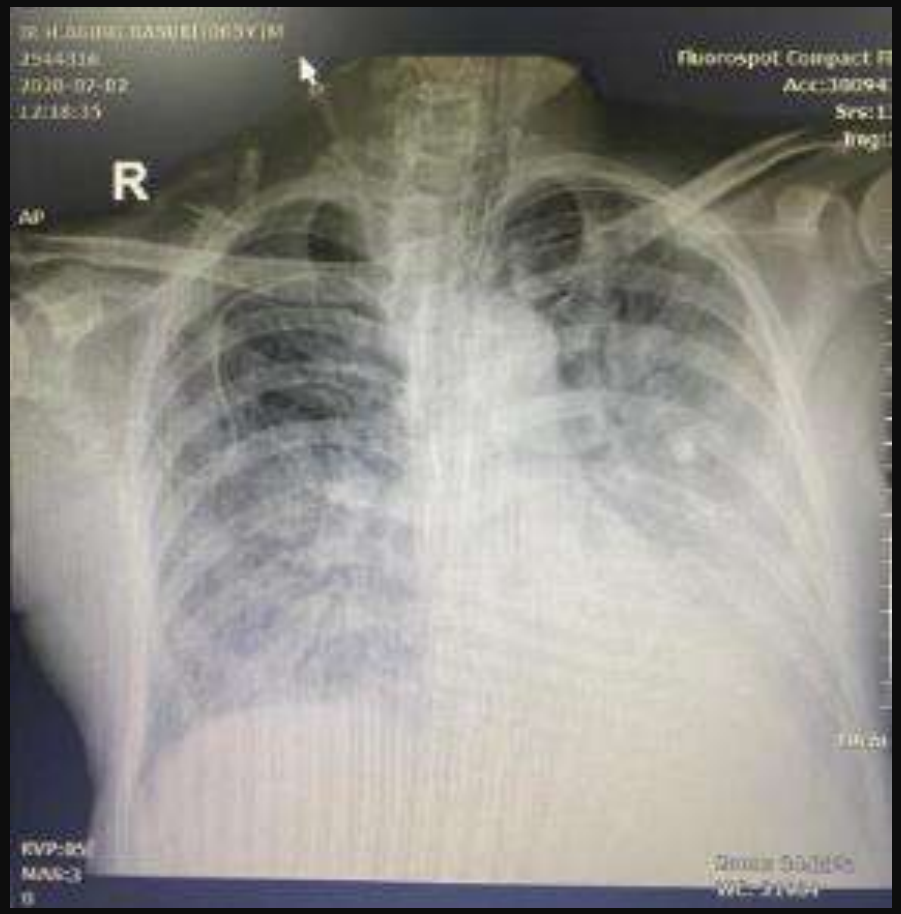


Radiografi Toraks (26 June 2020)

- Bilateral pneumonia, tipikal Covid pneumonia
- Terpasang ETT di saluran nafas/trachea

Perkembangan Pasien #8 (Tn. ABa, 65 y.o.- RSP)

- Radiologis



Radiografi Toraks (2 Juli 2020)

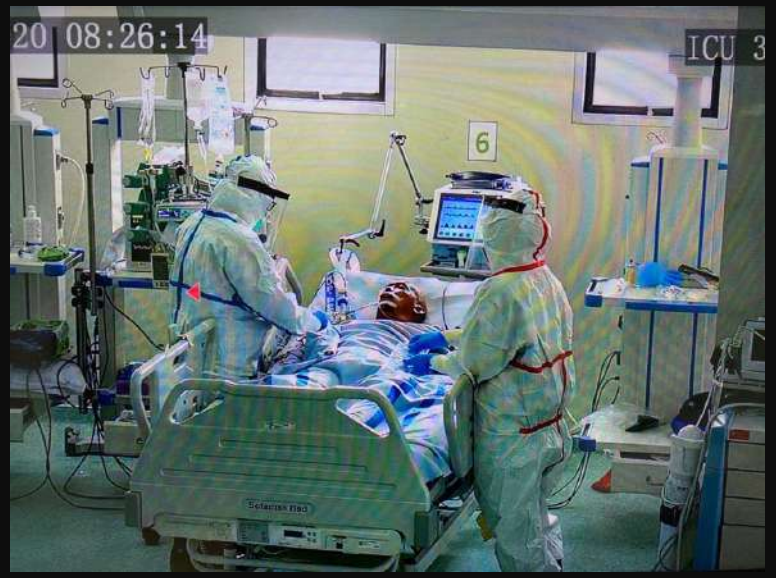
- Dibanding ro. thorax sebelumnya infiltrat paru kiri terlihat bertambah.

Kesimpulan : dibanding rontgen sebelumnya tampak perburukan infiltrat paru kiri

Perkembangan Pasien #8: Tn. ABa, 65 thn (ICU - RSP)

2 Juli 2020
Pasien **meninggal di ICU pada hari ke 7 setelah** implantasi.
Dengan *Cause of death* : Syok sepsis

H-0 Pre-implantasi stem cell



H-1 Post-implantasi stem cell

H-6 Post implantasi stem cell, pasien mengalami perburukan

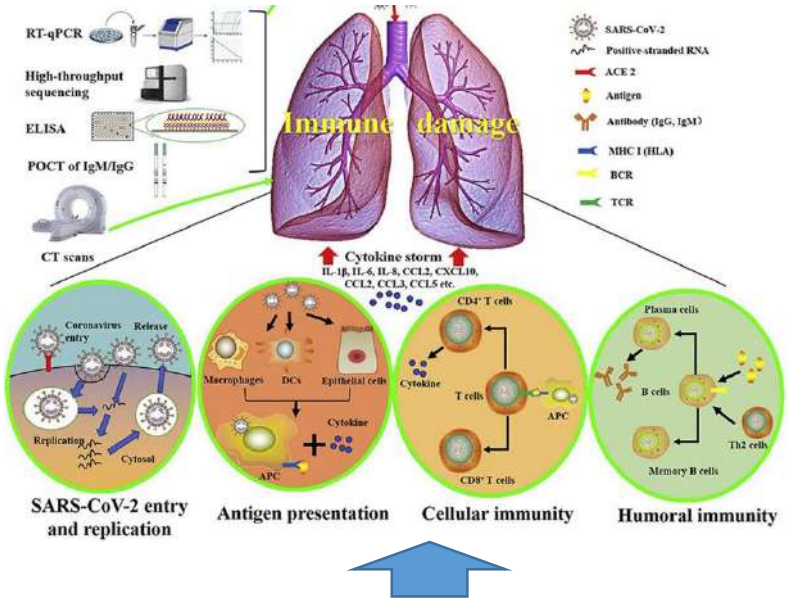
- Angka mortalitas subyek covid19 derajat kritis adalah 65, 63%, dengan angka kesembuhan sebesar 34, 37 persen :
  - 63,6% dari kelompok MSC sedangkan kelompok kontrol 36,4%
- Untuk subyek yang mempunyai ko morbid dua atau lebih:
  - 83,3 persen meninggal
  - Yang sembuh lebih banyak di kelompok MSC dengan rasio 2:1
- 50 persen yang sembuh dari kelompok kontrol tidak memiliki ko morbid

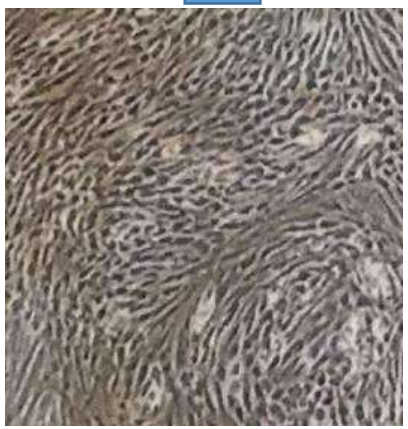
- Kelompok MSC memberikan kesembuhan yang lebih baik dibandingkan kelompok kontrol (63,6 persen dibandingkan 36,4 persen), khusus nya pada subyek yang jumlah komorbidnya kurang dari dua) melalui mekanisme :
- Penurunan pro inflamasi IL-6 dan ferritin
- Peningkatan faktor anti inflamasi dan regenerasi jaringan
  - IL-10
  - LIF
  - Pro BNP
  - VEGF

Populasi limfosit yang berperan dalam badai sitokin

- Perlakuan MSC menurunkan atau mempertahankan populasi limfosit yang berperan dalam badai sitokin dibandingkan kontrol
- Lebih sering ditemukan peningkatan persentase populasi limfosit yang berperan dalam badai sitokin pada kelompok kontrol

MENOLONG
MEMBERIKAN YANG TERBAIK





Webinar IMERI untuk sosialisasi pemanfaatan UC MSC sebagai adjuvant C19 terdapat di link kanal youtube berikut: https://www.youtube.com/watch?v=FnlFnKD6GwY

Link ke clinical trials.gov (ID study NCT04457609)
https://clinicaltrials.gov/study/NCT04457609?lat=-6.382411&lng=106.8292109&locStr=Current%20Location&distance=50&cond=covid%2019%20critically%20ill&intr=Stem%20Cell&rank=1

dr.Radiana D Antarianto,Mbiomed,PhD

- Lektor Departemen Histologi Fakultas Kedokteran Universitas Indonesia (2008-…)
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- Koordinator Lab Kultur, Klaster riset Stem Cell and Tissue Engineering, IMERI UI (2017-….)
- Pendidikan:
  - PhD Regenerative Science, Hannover Biomedical Research School, Germany (2010-2014)
  - Mbiomed, Program Magister Ilmu Biomedik, Fakultas Kedokteran Universitas Indonesia (2006-2008)
  - Dokter, Fakultas Kedokteran Universitas Indonesia (1998-2004)
- Training:
  - Tissue Engineering Training, National University of Singapore Tissue Engineering Program (2014)
- Scopus Author ID: 57190862806
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- Google Scholar ID: Radiana Dhewayani Antarianto, MD, Mbiomed, PhD

Stem cells as imunomodulator and anti-inflammation: MSC for Critical Pneumonia CoVid19 adiuvant therapy

dr. Radiana D Antarianto, Mbiomed, PhD[1,2,3]*

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Topics

- Stem cell introduction
- Stem cells: classification based on eliciting immune response
- MSC as immunomodulatory stem cells
- MSC for critical CoVid 19 : stem cell based approach
- MSC for critical severe pneumonia CoVid19 in Indonesia

Stem cell introduction

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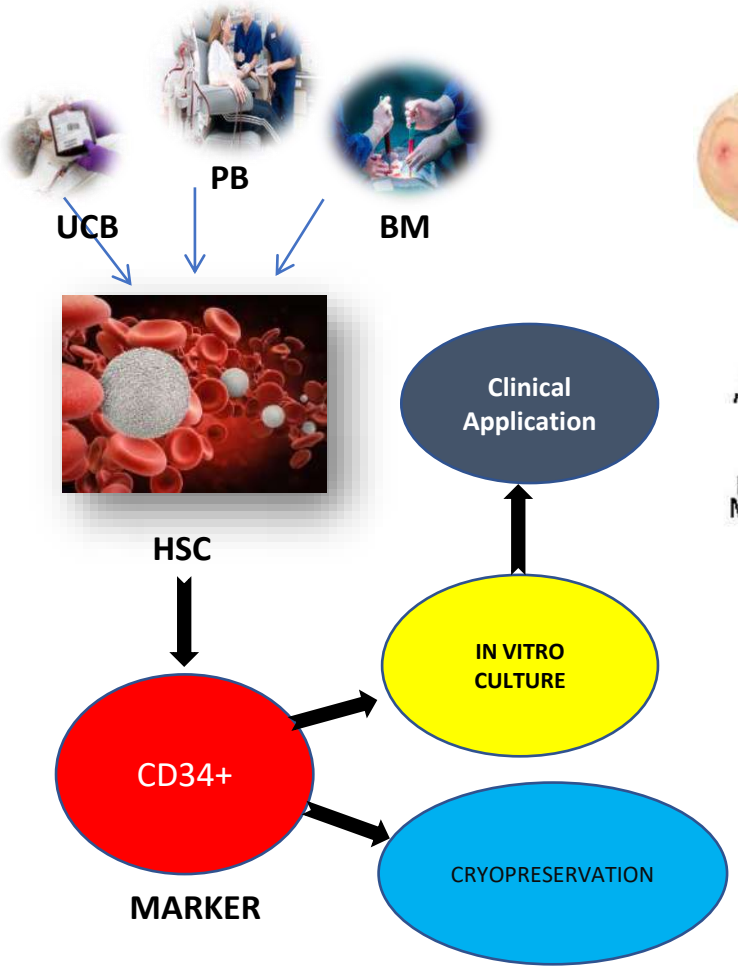
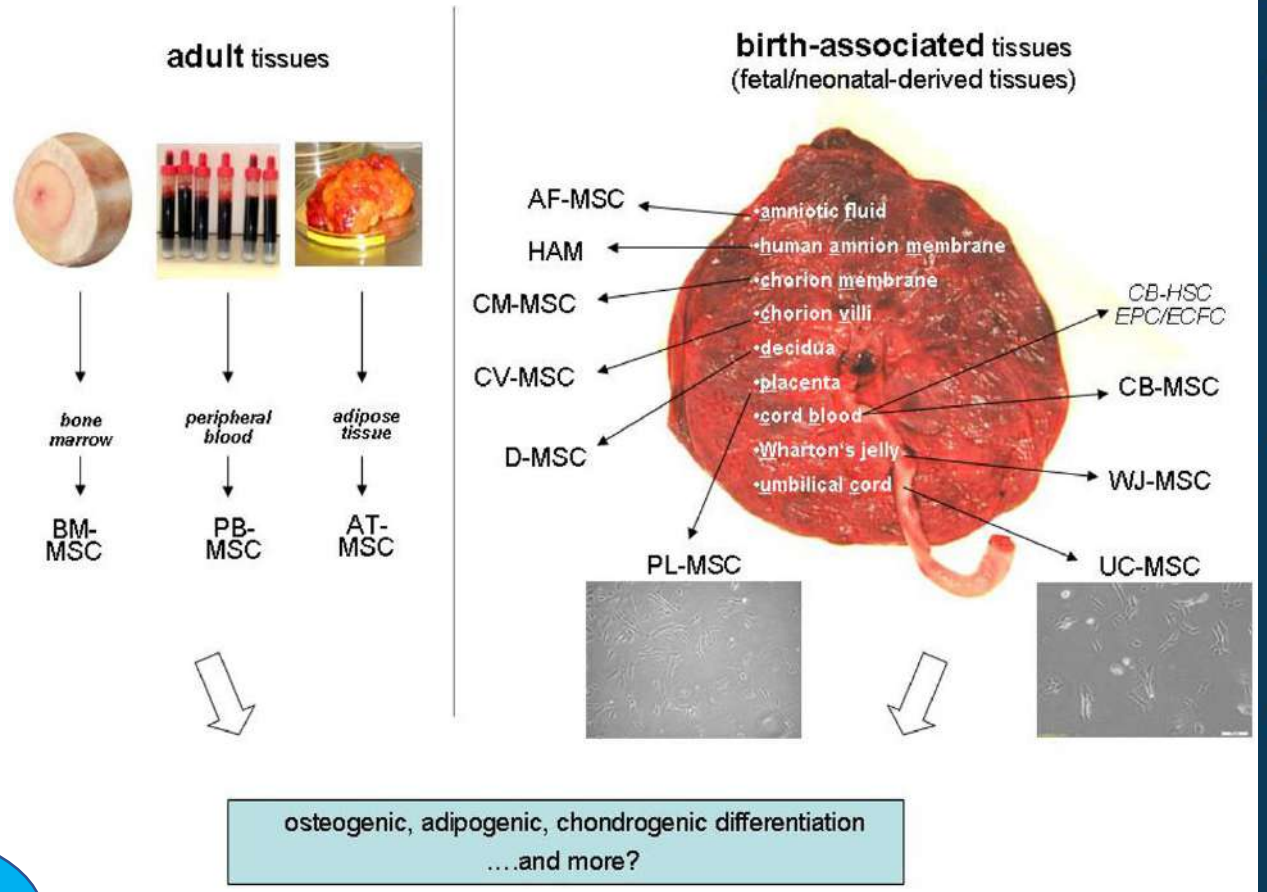
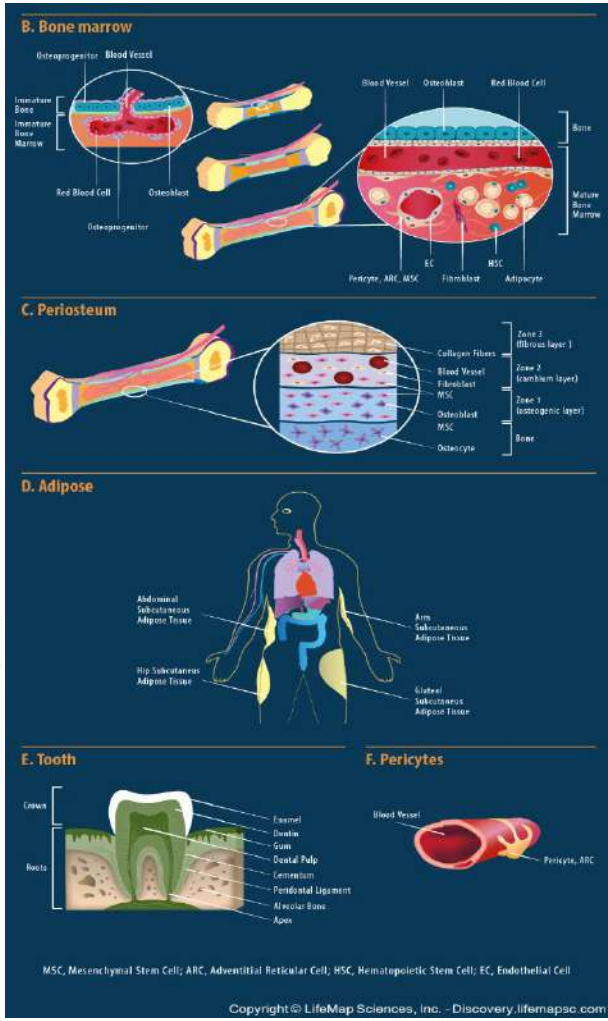






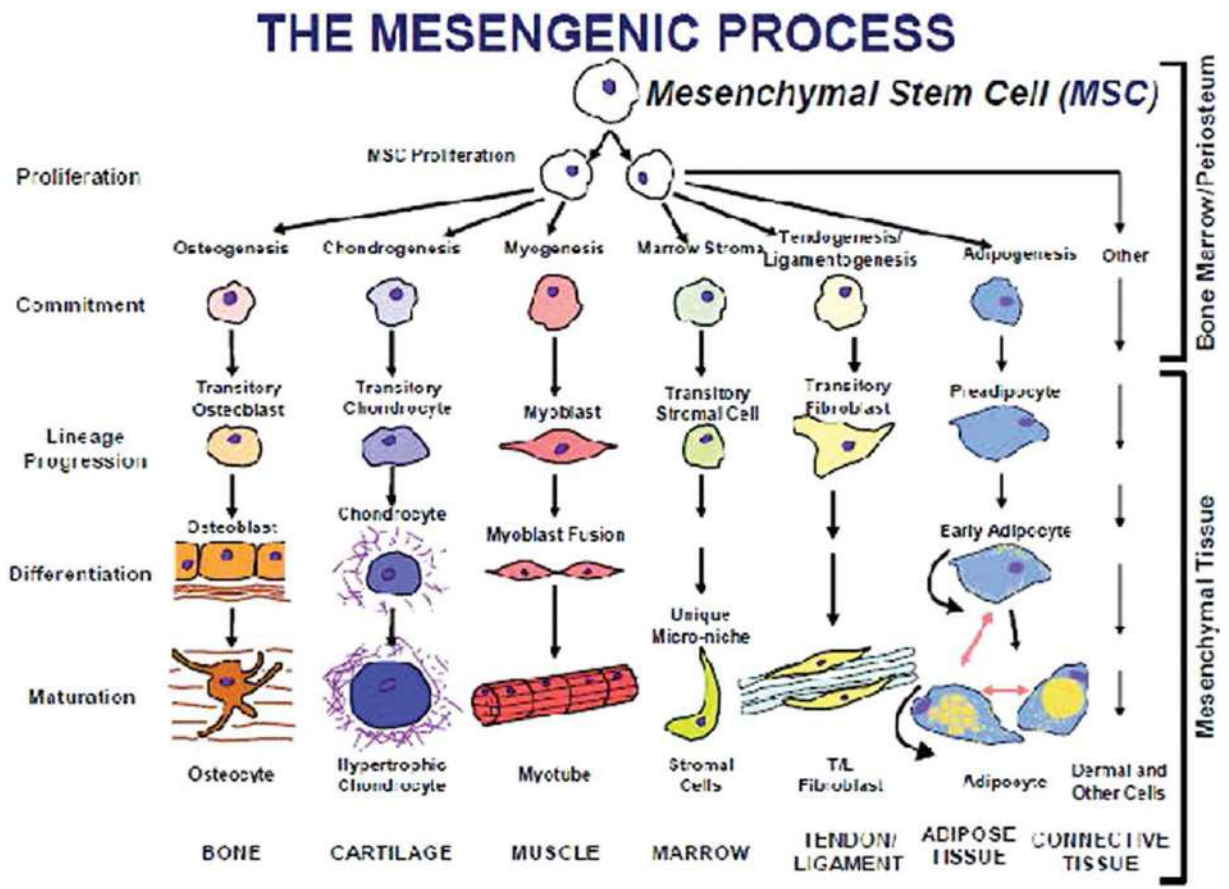
Hass et al. Cell Communication and Signaling 2011, 9:12
LifeMap Sciences, Inc

Classification of stem cells on eliciting immune response

Parameters	ESC/iPSC	HSC	MSC	Progenitor cells
Major antigens: - HLA class I - HLA class II - ABO antigens	 Low to absence Low to absence None	 ++ (donor specific) ++(donor specific) None	 +, sHLA-G5 (-) surface None	 ++ ++ Erythrocyte lineage +
Interaction with T cells (allo/xenogeneic)	Infiltrates (+) in transplanted derived cells	Rejection (++) HLA mismatch	Th1→Th2 (anti-inflammatory) Tregs↑	Th1>> CD8
Interaction with B cells (allo/xenogeneic)	Infiltrates (+) in transplanted derived cells	Rejection (++)	Plasma cells ↓ B Regs↑	Plasma cells >>
Interaction with NK cells (allo/xenogeneic)	NR	Rejection (++)	Inhibit NK cell activity	↑NK cells activity
Interaction with monocyte (allo/xenogeneic)	NR	Rejection (++)	M1→M2(anti-inflammatory)	M1>>
Interaction with DCs (allo/xenogeneic)	NR	Rejection (++)	Inhibit DC differentiation ↑Tolerogenic DCs	Activated DCs
Teratoma formation (NOD SCID mouse)	+++	(-)	(-)	(-)

About MSC

- 1988: bone marrow and peri-osteal tissue culture → differentiate into mesodermal lineage cells
- Characteristics of MSC (in vitro): culture plastic adherence, long term culture, indefinite proliferation, multy-lineage differentiation potency
- MSC:
  - Mesenchymal stem cells
  - Marrow stromal cells
  - Multipotent stromal cells
  - Mesodermal stem cells
  - Mesenchymal stromal cells
  - Medicinal signaling cells



Caplan AI. Stem cells Translational Medicine 2017

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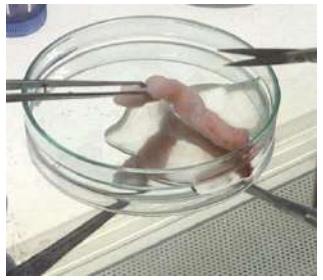
INOVASI UI-CM SYSTEM: STEM CELL TECHNOLOGY & PROCESSING




Adult SC
Umbilical Cord
Adipose (lipoaspirate)
Bone Marrow

Simple method of Isolation

Propagation

Cryopreservation

Preparation MSCs for implantation, MSCs combined with Hydroxyappatite granules (scaffold), BMP-2 (growth factor) now ➡ secretome

Implantation

Stem cell clinical trial for Critical Severe Pneumonia CoVid19

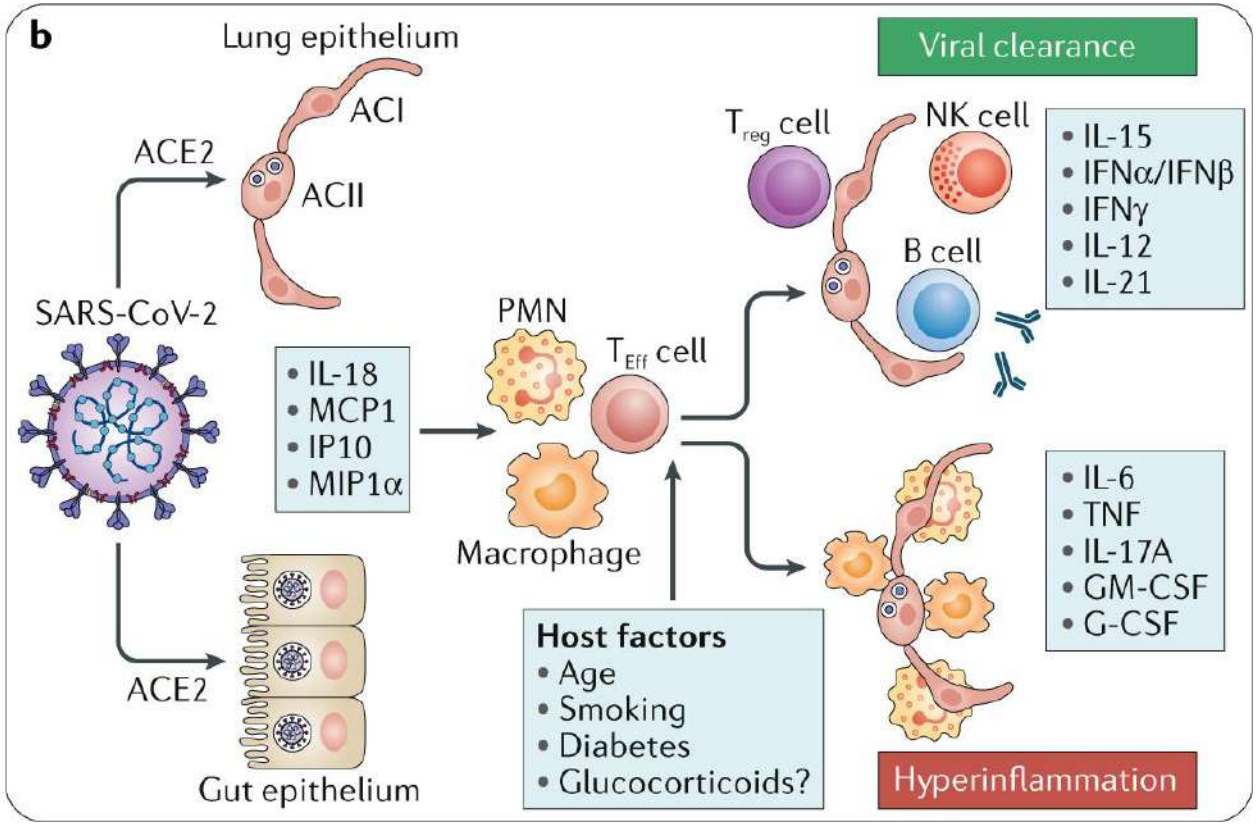
Sel Punca			
Mesenchymal stem cells-derived exosoms	$2.0*10^8$ pada hari ke-1 s.d hari ke-5	N.A.	30
Pulp mesenchymal stem cells	Dosis (?) Diberikan pada hari ke-1, hari ke-3, dan hari ke-7	Terapi standar	24
Mesenchymal Steam Cells (MSc)	Tiga kali ($4.0*10^7$) pada hari 0, hari ke-3, dan hari ke-6	Plasebo	90
Tatalaksana konvensional + *Mesenchymal Steam Cells* (MSc)	Tiga kali ($4.0*10^7$) pada hari 0, hari ke-3, dan hari ke-6	Tatalaksana konvensional	60
Tatalaksana konvensional + *Mesenchymal Steam Cells* (MSc)	Tiga kali ($3.0*10^7$) pada hari 0, hari ke-3, dan hari ke-6	Tatalaksana konvensional	20
Tatalaksana konvensional + *NestCell®*	Tiga kali ($1.0*10^6$) pada hari 1, hari ke-3, dan hari ke-7	Terapi konvensional	6
Terapi konvensional + *stem cell educator*	?	Terapi konvensional	20
Terapi konvensional + UC-MSCs	$0.5*10^6$/kgBB pada hari ke-1, hari ke-3, hari ke-5, dan hari ke-7	Terapi konvensional	48
Umbilical Cord-derived Mesenchymal Stem Cells (UC-MSCs)	$3.3*10^7$ pada hari ke-1, hari ke-3, hari ke-5, dan hari ke-7.	Terapi standar	10
Wharton's Jelly Mesenchymal Stem Cells (WJ-MSc)	Tiga kali ($1*10^6$/kgBB) pada tiga hari yang berbeda.	Plasebo	5

Jurnal Penyakit Dalam Indonesia | Vol. 7, No. 1 | Maret 2020 |

Adityo Susilo, C. Martin Rumende, Ceva W Pitoyo, Widayat Djoko Santoso, Mira Yulianti, Herikurniawan, Robert Sinto, Gurmeet Singh, Leonard Nainggolan, Erni J Nelwan, Lie Khie Chen, Alvina Widhani, Edwin Wijaya, Bramantya Wicaksana, Maradewi Maksum, Firda Annisa, Chyntia OM Jasirwan, Evy Yunihastuti

Cytokine storm as target in Critical Severe CoVid 19 therapy

- Induces lymphocytopenia → CD4+ T cell subset (effector, memory and regulatory T cells)
- Cytokine storm CoVid 19 ~ secondary haemophagocytic lymphohistiocytosis(sHLH) or MAS (Macrophage Activation Syndrome-like)→ a hyperinflammatory state triggered by viral infection



Schett G, Sticherling M, Neurath MF. Nat Rev Immunol 2020

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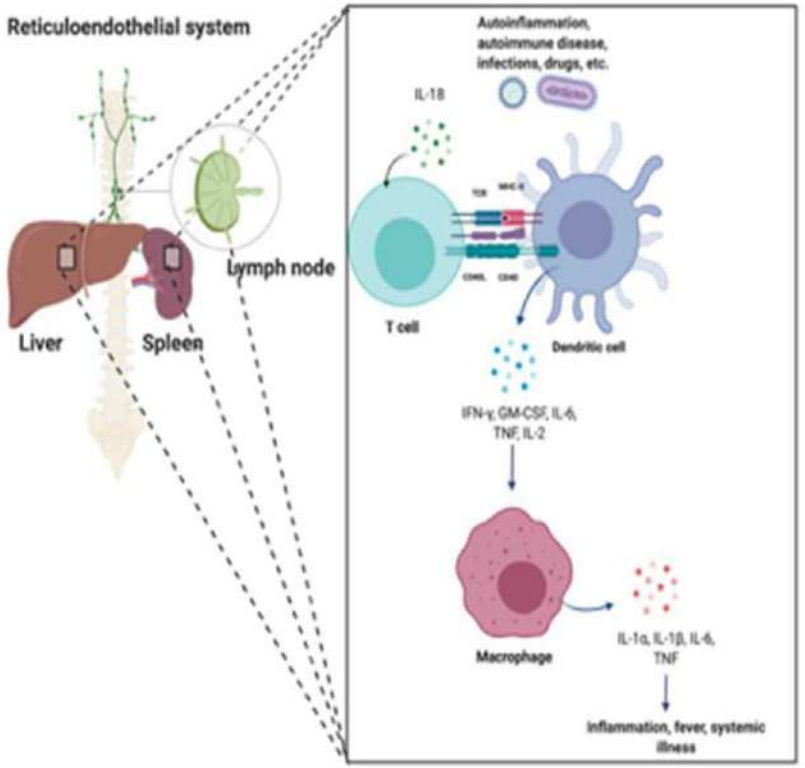
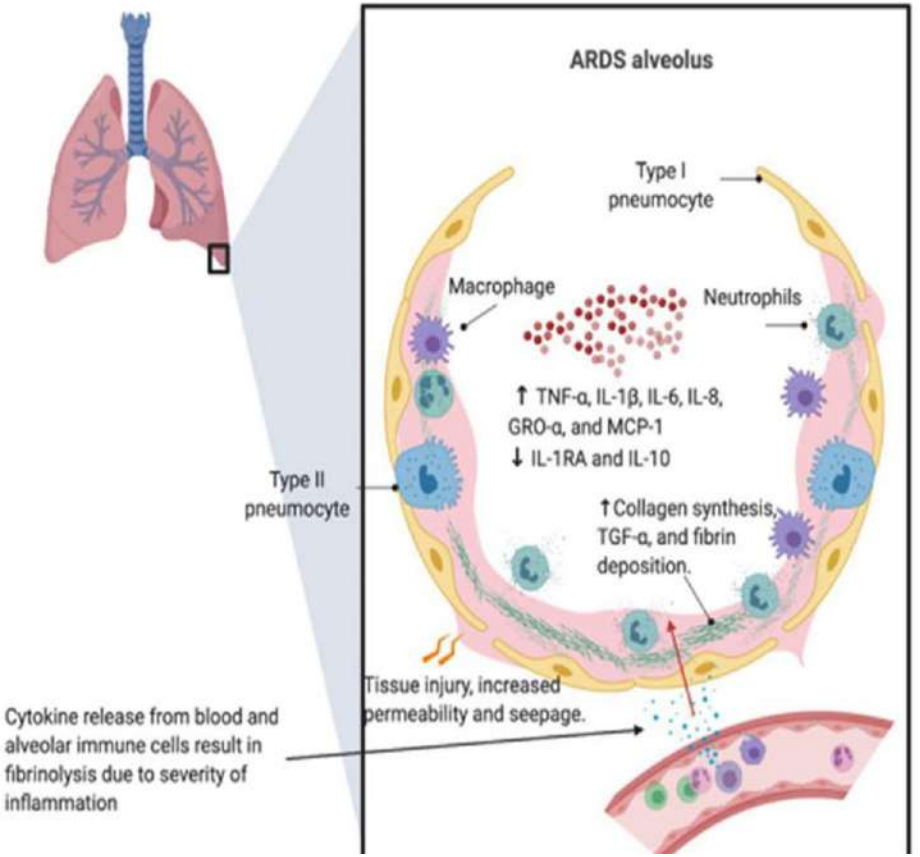
sHLH / MAS in Covid 19

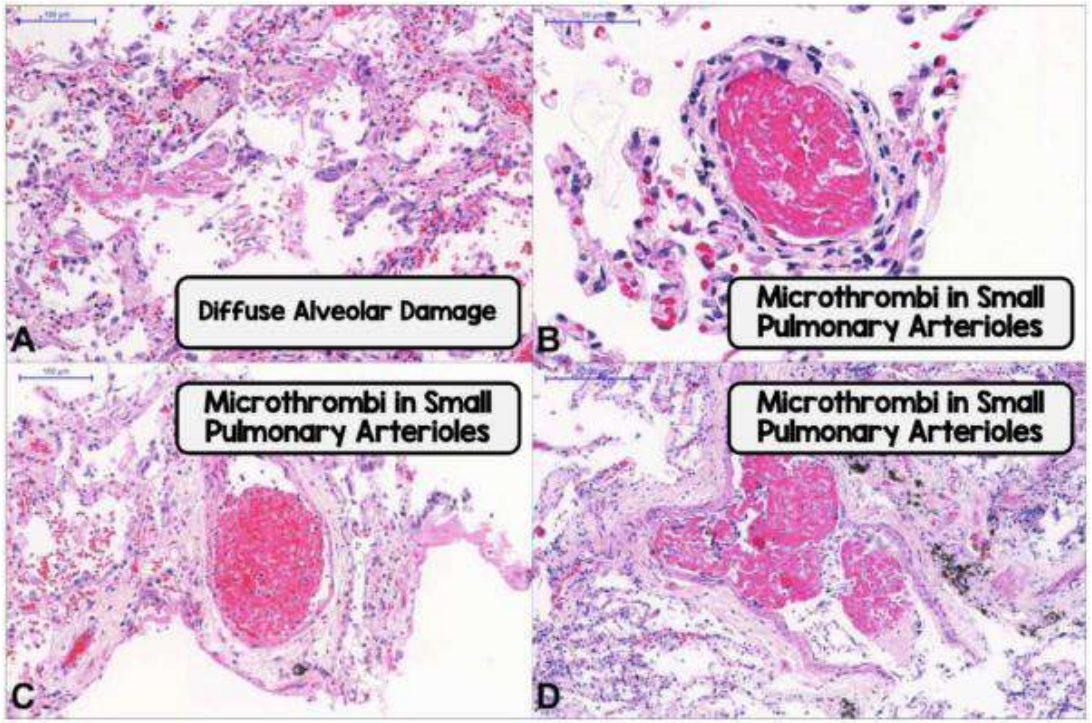




- Classic MAS/sHLH picture >> outside the lungs → fevers, adenopathy, hepatosplenomegaly (high CRP and hyperferitinemia), anaemia, lymphocytopenias, liver function derangement and the activation of intravascular coagulation cascades → 2nd to inflammation→ hypercytokinaemia
- A cytokine profile (~ MAS/sHLH) in COVID-19 patients→ increased IL-1β, IL-2, IL-6, IL-17, IL-8, TNF-α and CCL2. Virally induced hyper-inflammatory pulmonary immunopathology to the adjacent microcirculation with extensive secondary fibrinolytic activation → elevated D-dimer. Severe local vascular dysfunction : micro-thrombosis and haemorrhage → pulmonary intravascular coagulopathy (PIC)

Dennis McGonagle, et al., Autoimmunity Reviews 2020

Histopathology findings of Pulmonary Thrombotic Phenomena in Severe COVID-19



Dolhnikoff M et al. J Thromb Hemostasis 2020

- 10 fatal cases in Sao Paolo, Brazil
- >>> epithelial viral cytopathic effects ➔ alveolar and small airway epithelium
- Variable number of small fibrinous thrombi ➔ small pulmonary arterioles in areas of damaged and preserved lung parenchyma (8/10 cases)
- Endothelial tumefaction (swelling) + >>>pulmonary megakaryocytes ➔ pulmonary capillaries (activation of coagulation cascade)
- Few and small foci of alveolar hemorrhage and pulmonary infarctions
- Hypercoagulative state → pulmonary microthrombi

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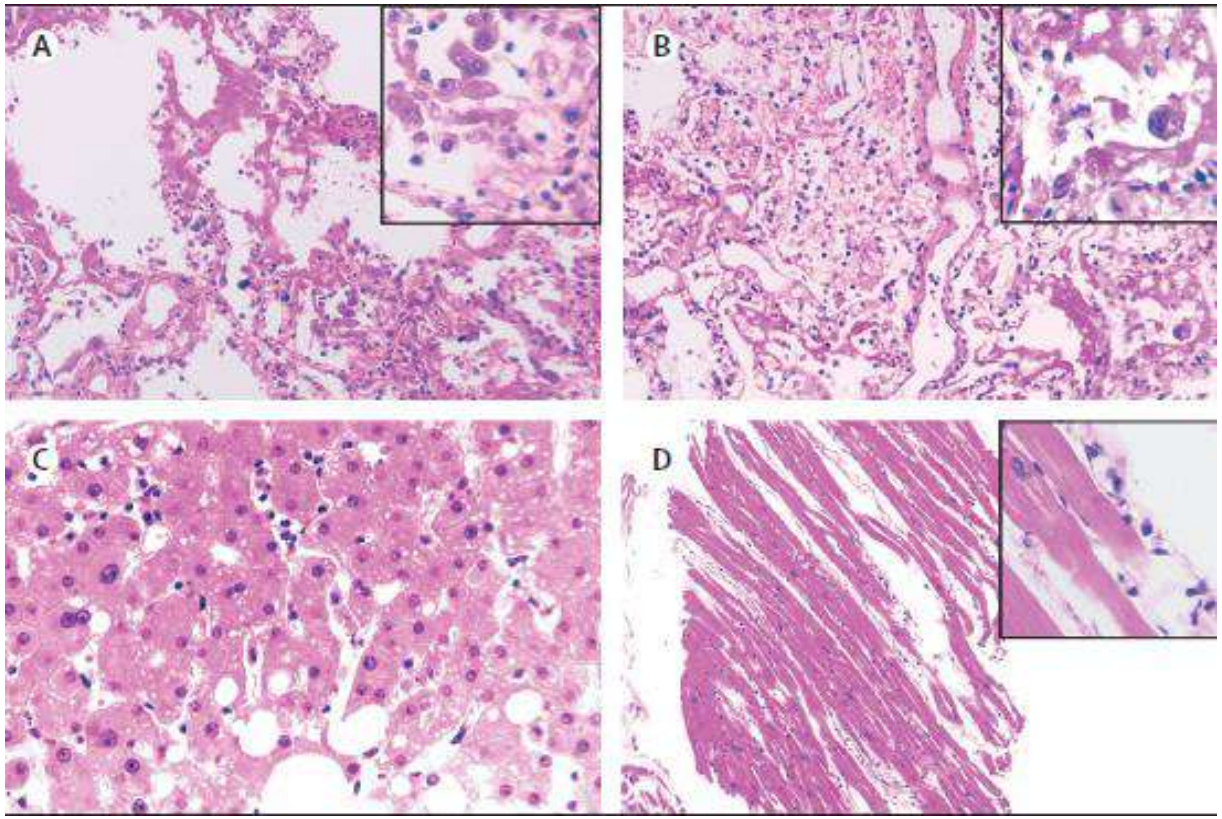
Histopathology findings of ARDS and associated organ damage in CoVid19

- Desquamation of pneumocyte and hyaline membrane formation, infiltrates of mononuclear cells (>> lymphocyte) → ARDS (A)
- Pulmonary edema and hyaline membrane formation, infiltrates of mononuclear cells (>> lymphocyte) → ARDS (B)
- Viral cytopathic effect → multinucleated syncytial cells w/ atypical large pneumocyte, viral inclusion (-)
- Liver (C) : moderate microvesicular steatosis, mild lobular and portal activity
- Heart (D):Interstitial mononuclear infiltrates, substantial damage (-)



Xu Z et al. Lancet Respir Med 2020

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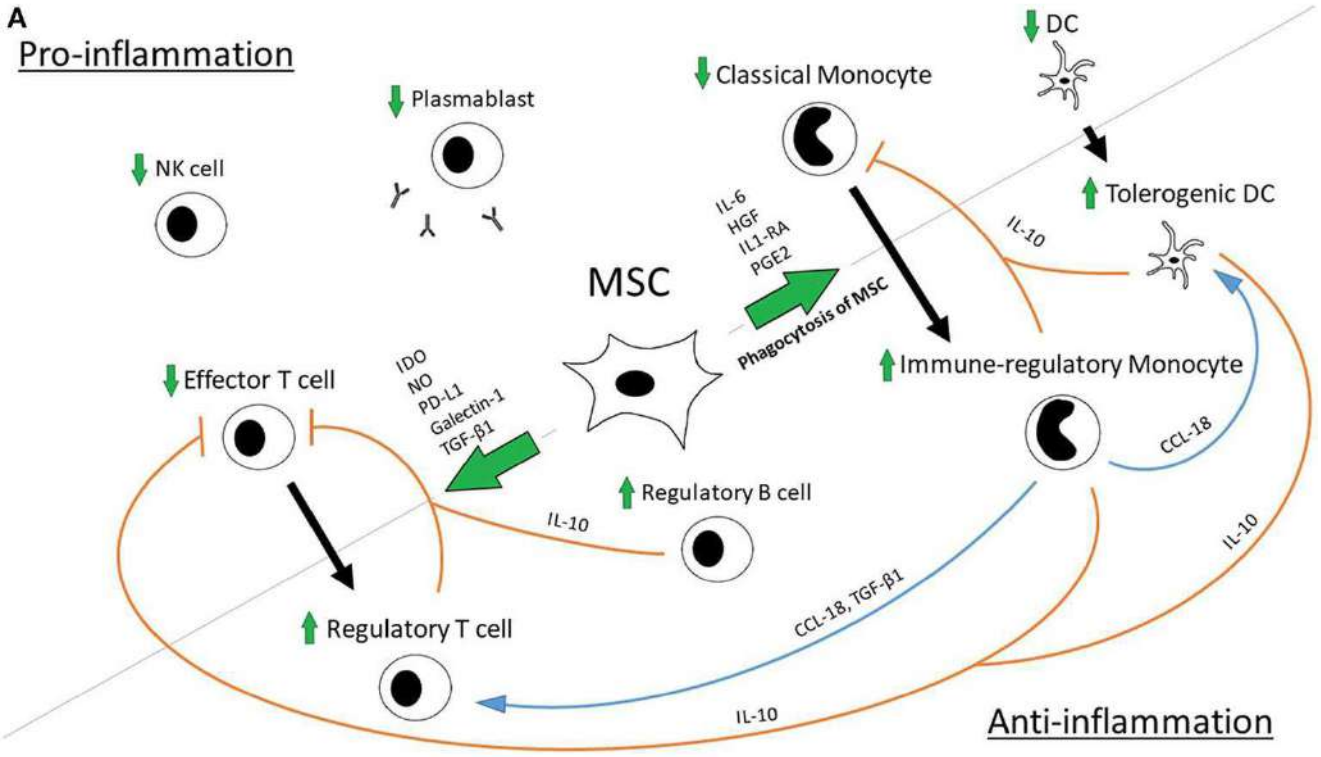
MSC immunomodulatory capacity



- MSCs IL-1RA = M1 → M2 (↑IL-10)
  - Inhibit differentiation of DCs
  - Induced tolerogenic DCs (↑IL-10)
  - Positive feedback loop X M1
  - ↑ HLA class II, CD45R, CD11b monocyte → suppressed effector T cells
  - Induced differentiation/ shift to Th2
- +MSCs HGF + MSCs IL-6= ↓IL-12p70, TNF-a, and IL-17 ~ inhibit differentiation of Th1& Th17 (also neutrophil)
- M2 CCL-18+TGF-β=induced Tregs
- M2 CCL-18=differentiation of DCs into tolerogenic DCs
- Tregs X effector T cells
- Direct interaction MSC : ↓plasmablast and ↑ Bregs
- MSCs PGE2, IDO, TGF-b1, IL-6, NO = inhibit NK cell

Weiss ARR and Dahlke MH. Front Immunol 2019

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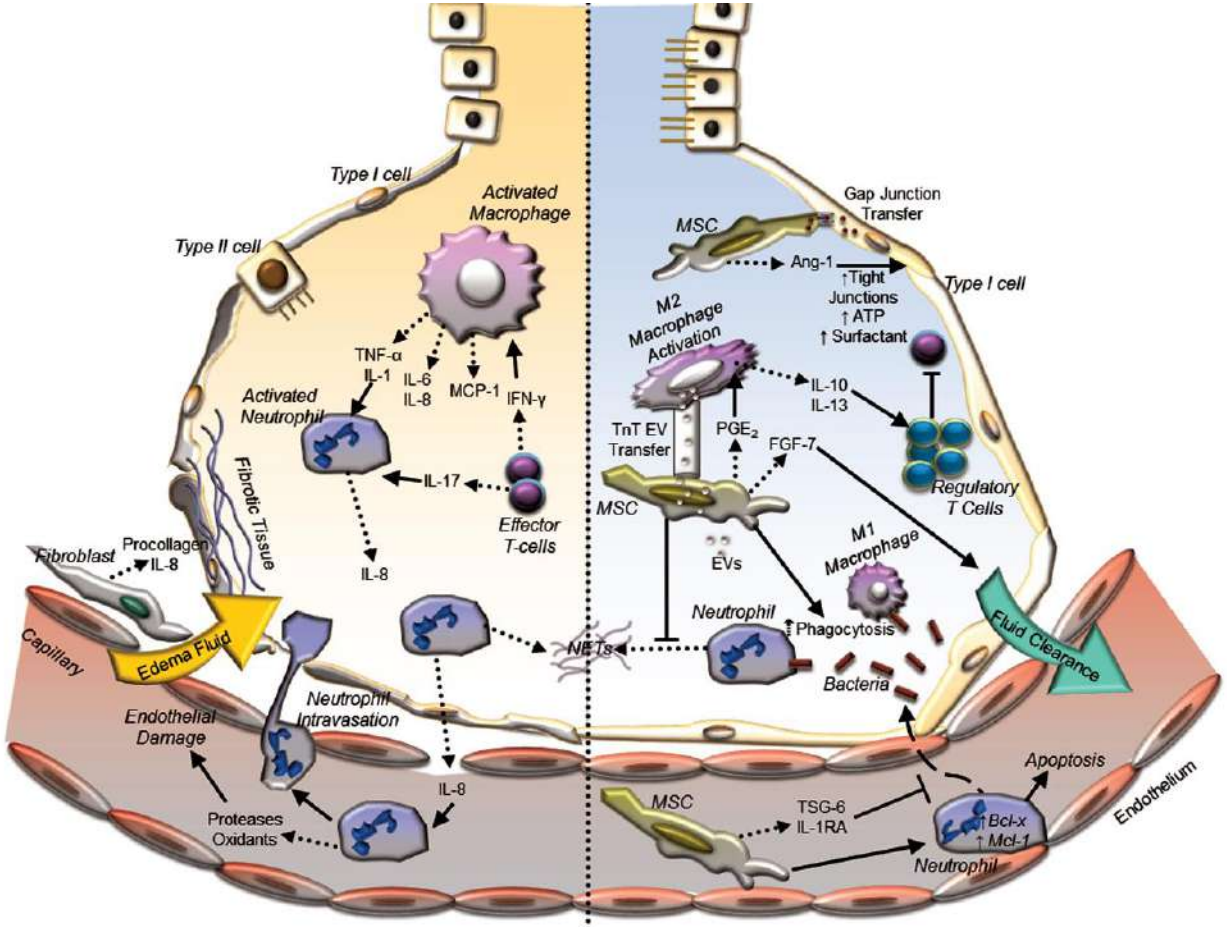
MSC mechanism of action in ARDS (non viral)



Horie S, Gonzales HE, Caffey JG, Masterson CH. J Thorac Dis 2018
Hupert LA, Liu KD, Matthay MA. Transfusion 2019

- MSCs >< neutrophil trafficking : pulmonary capillary ↔ alveolar space
- MSCs >< pro-inflammatory neutrophils, formation of NETs (neutrophil extracellular traps) → << damage alveolar epithelial cells & capillary endothelial cells
- HGF, KGF → ↓ apoptosis of alveolar epithelial cells, protection of endothelial cells (+Ang-1)
- MSC transfer of mitochondria : ↑ pneumocyte bioenergetics (↑ATP)
- FGF-7 = ↑ Transepithelial fluid transport → epithelial apical sodium chanel transporter
- MSCs = ↑ phagocytic capacity M1 → clearance of bacteria.
- MSCs→anti-inflammatory environment, resolution of ARDS, recovery of function, and alveolar tissue repair (interstisial, epithelial lining, endothelial capillary)

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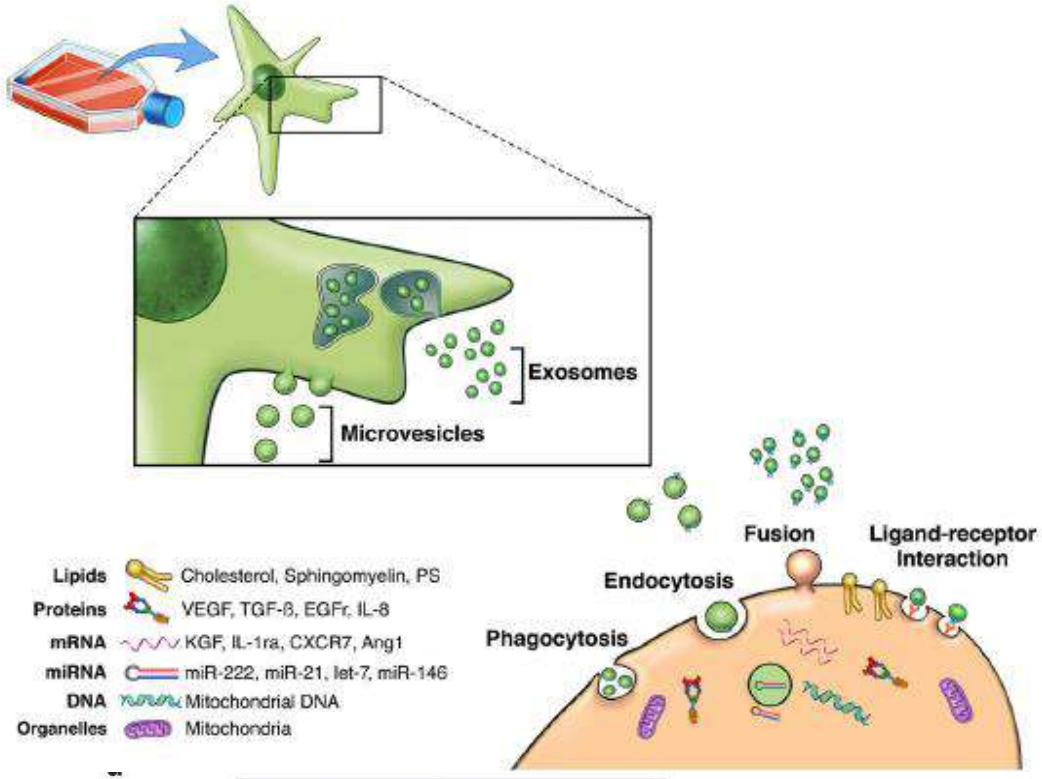
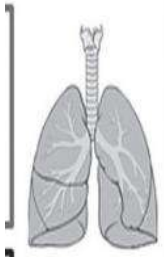
MSCs Secretome (+EVs) in Acute Lung Injury

Table 1 Bioactive factors secreted by MSCs directly in CM or via EVs

Angiogenesis	Anti-apoptosis	Anti-fibrosis	Anti-oxidation	Chemo-attraction	Immuno- modulation	Proliferatio
Ang1	FGF	Ang-1	HO-1	CCLs	HO-1	FGF
FGF	GM-CSF	FGF	IL-1β	CXCLs	IDO	HGF
HGF	HGF	HGF	STC-1	G-CSF	IL-1ra	IGF-1
IGF-1	IGF-1	KGF		LIF	IL-6	KGF
IL-6	IL-6	MMPs		M-CSF	IL-10	PDGF
MCP-1	STC-1	TIMP-1		MCP-1	LIF	VEGF
PDGF				SDF-1	PGE2	
VEGF					STC-1	
					TGF-β	
					TSG-6	

Ang-1 – angiopoietin 1, *CCL* – chemokine ligand, *CXCL* – chemokine (C-X-C motif) ligand, *FGF* – fibroblast growth factor, *GM-CSF* – granulocyte monocyte colony stimulating factor, *HGF* – hepatocyte growth factor, *HO-1* – hemeoxygenase 1, *IDO* – indoleamine 2,3-dioxygenase, *IGF-1* – insulin like growth factor 1, *IL* – interleukin, *IL-1ra* – IL-1 receptor antagonist, *KGF* – keratinocyte growth factor, *LIF* – leukemia inhibitory factor, *LL-37* – human cathelicidin, *MMP* – metalloproteinase, *MCP-1* – monocyte chemoattractant protein 1, *PDGF* – platelet derived growth factor, *PGE2* – prostaglandin E2, *SDF-1* – stem cell-derived facto 1, *STC-1* – stanniocalcin 1, *TIMP-1* – tissue inhibitor of metalloproteinase 1, *TGF-β* – transforming growth factor beta, *TSG-6* – tumor necrosis factor-stimulated gen 6, *VEGF* – vascular endothelial growth factor





Lung injury
1. Reduce lung edema (86, 89)
2. Reduce inflammation (86)
3. Improve pulmonary hypertension (90)
4. Improve ventricular hypertrophy (90)
5. Improve lung vascular remodelling (90)

Marker
1. miR-204 (90)
2. miR-17 targets STAT3 (90)
3. keratinocyte growth factor (86)

Mohammadipoor A, Antebi B, Batchinsky AI. Respir Res 2018
Rani S et al. Mol Ther 2015

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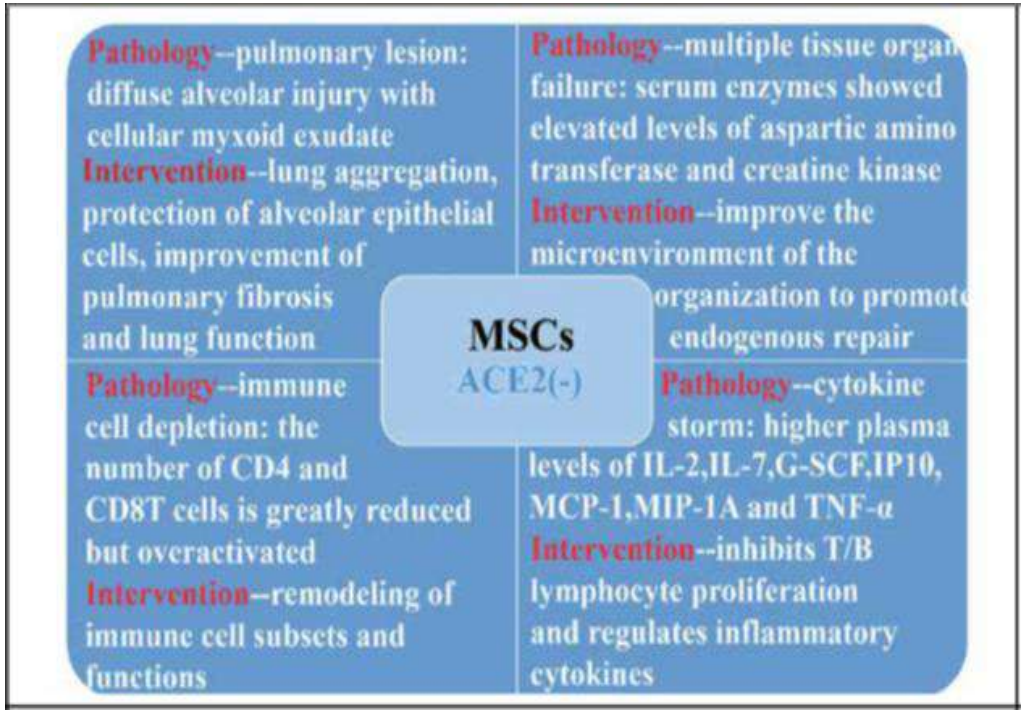
MSCs mechanism of action in CoVid19 infection



- Flow cytometry : ↓$CXCR3^+$ $CD4^+$, $CD8^+$, NK^+ → ↓ hyperinflammation
- RNA seq analysis → MSCs recovered in peripheral blood of CoVid19 patients post MSC transplantation
  - LIF >>> =indispensable factor in ARDS/ALI resolution, ↑ Tregs, ↓Th17, protection of alveolar epithelial cells
  - IL-10 >> → immunomodulation

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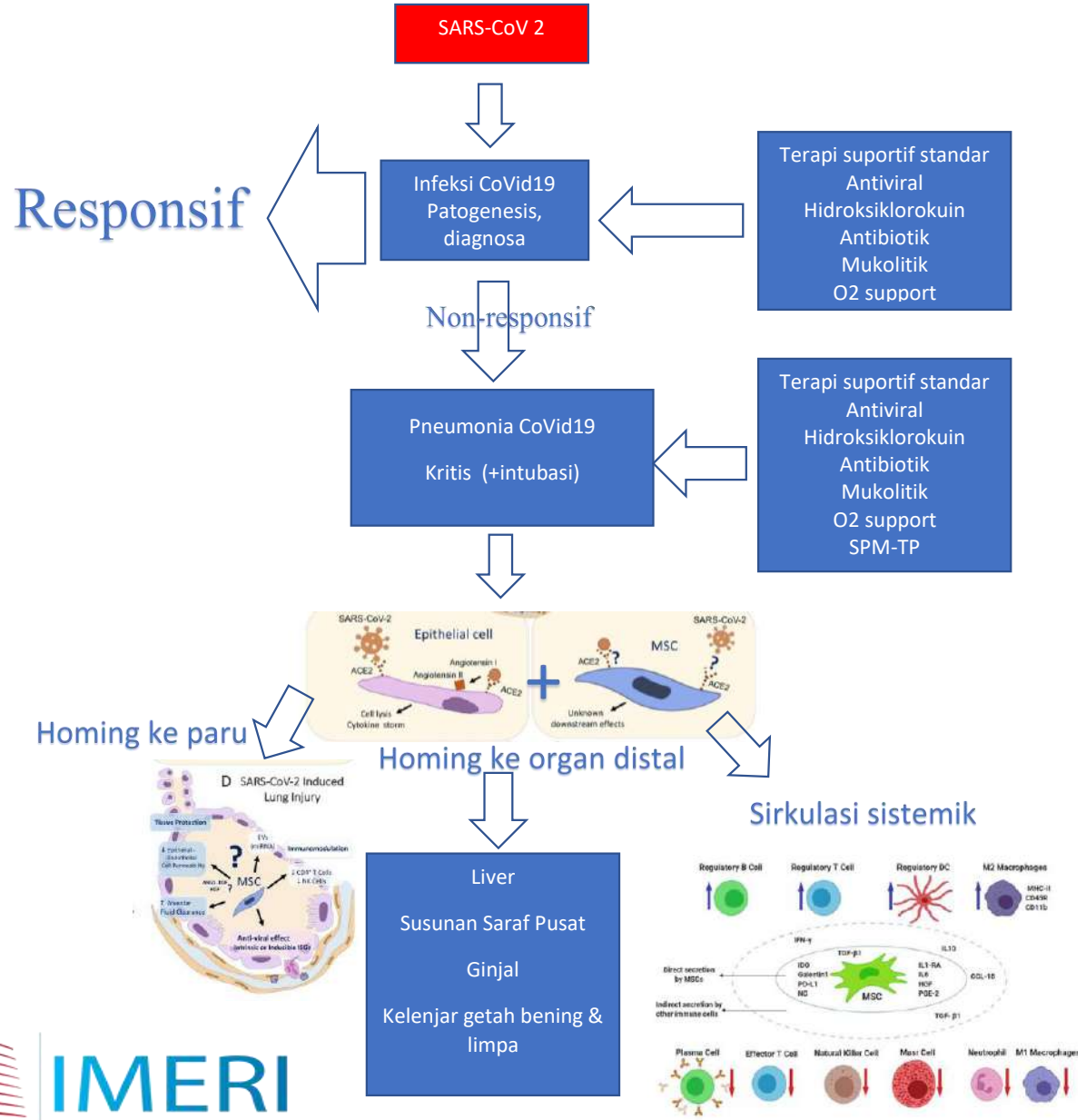
Metcalfe SM. Med Drug Disc 2020
Khoury M, Cuenca J, Cruz FF, et al. Eur Respir J 2020
Jones MR, Kwon CY, Allen E, Quinton LJ, Mizgerd JP, Hilliard KL. J Immunol 2012
Jones MR, Kwon CY, Allen E, Quinton LJ, Mizgerd JP, Hilliard KL. Exp Cell Res 2011

MSC for CoVid 19 in Indonesia



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Thank you

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