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GENE EXPRESSION DATA ANALYSIS SUGGESTS MALE GERM CELL ASSOCIATED KINASE (MAK) MAY BE ASSOCIATED WITH COVID-19 SEVERITY IN MEN VIA INTERFERON SIGNALING

Irandi Putra Pratomo[1], Aryo Tedjo[2*]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Universitas Indonesia Hospital, Depok, Indonesia;
[2*]Bioinformatics Core Facilities, Indonesian Medical Education and Research Institute-Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[3]Department of Medical Chemistry, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

Corresponding E-mail: [2]aryo.tedjo@ui.ac.id

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ABSTRACT:

Introduction: Coronavirus Disease 2019 (COVID-19) and prostate cancer are known to have the same comorbidities. Prostate cancer patients are also known to have a mortality risk and hospitalization risk in COVID-19. Lately, co-expression between the androgen receptor and the viral entry receptor TMPRSS2 has been reported. Activation of the androgen receptor pathway may be associated with the severity of COVID19 patients. Method: The microarray data were taken from the GEO database (GSE 164805 and GPL26963 platform). Dataset creation and gene expression analysis were performed using Orange Data-mining version 3.30 Protein-Protein interaction (PPi) analysis was performed using STRING database with a confidence score >0.4. Result: The means of MAK expression was distinguishable between a combined group of healthy controls (HC) and mild COVID-19 and severe COVID-19 ($p \leq 0.01$). There was no significant difference in the number of androgen receptors (AR) between mild and severe COVID-19 and HC ($p=0.187$). The expression of interferon related genes (IFNAR1, IFI6, TMPRSS2, IFIT1, and IFIT3) were shown to be different between mild and severe COVID-19 and HC. The PPi results showed a significant difference in STAT5A expression between mild and severe COVID-19 and HC ($p \leq 0.01$). Conclusion: MAK and other genes/proteins that affect AR activity and signaling were shown to be the potential targets for therapy for SARS-CoV-2 infection.

Keyword : Coronavirus Disease 2019 (COVID19), Prostate Cancer, Gene analysis, Machine Learning, Protein-Protein Interaction (PPi)

1. INTRODUCTION

Recently, a meta-analysis study performed by Peckham et al. (2020) showed that gender was also a risk factor in Coronavirus Disease 2019 (COVID-19). Male have almost three times the chance of requiring an intensive care unit (ICU) admission than women [1]. However, the reason remain unclear. One theory that might explain that men are more susceptible to the disease is sexual hormones due to modulation of the X chromosome. Androgen can suppress the immune system, whereas estrogen increases the immune response. The sexual hormones can also modulate cytokine productions by several cell effectors [2]. furthermore, the activity of androgens and their receptors increases the transmembrane serine protease 2 (TMPRSS2) expression caused by androgens and androgen receptors (AR), leading to exacerbate a severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections. The results of the study by Leach et al. (2021) are one of the studies that support the theory that the antiandrogen enzalutamide, a drug that is well tolerated and widely used in advanced prostate cancer, can reduce the expression of TMPRSS2 in human and mouse lung cells [3]. The study also showed significant co-expression of AR and TMPRSS2 in A549 lung cells infected with SARS-CoV-2. However, several studies showed that androgen depletion therapy cannot increase the protective effect against SARS-CoV-2 infection by reducing the production of TMPRSS2 , nor for use as a therapy for COVID-19 patients [3].

Prostate cancer is known to have comorbidities similar to COVID-19, namely old age, diabetes, hypertension, obesity, smoking habits and racial differences, thereby increasing the number of patients hospitalized, ICU care, intubation, and mortality is one of the risk factors for severity and death due to COVID-19. One such study is a retrospective study of 286,609 patients who underwent testing for COVID-19 in the Mount Sinai Hospital system from March 2020 to December 2020 [4]. In this study, it was shown that patients with prostate cancer have a higher susceptibility to COVID-19-associated pathogenesis, which results in higher mortality and hospitalization rates. Hospitalization and mortality rates were higher in prostate cancer patients with COVID-19 when compared to COVID-19 patients with non-prostate genitourinary (GU) malignancies and breast cancer. The pathophysiology of prostate cancer is caused by an imbalance between prostate cell proliferation and apoptosis, which is influenced by AR. Androgen receptors are regulated by two main ligands, namely testosterone and dihydrotestosterone (DHT), the most potent intrinsic androgen hormone and has an affinity ten times higher than testosterone. The binding of DHT to the androgen receptor will increase the phosphorylation of serine residues. Research by Ma et al (2006) showed that Male germ cell-associated kinase (MAK), a serine/threonine-protein kinase, physically associates with AR, and increases the transactivation potential of AR in an androgen and kinase-dependent manner synergizes with co-activators Steroid Receptor Coactivator-3 (ACTR) [5]. In this study, it was also shown that knock-down or mutation in MAK was shown to cause a decrease in AR transactivation ability and inhibit AR signaling. The study then concluded that endogenous MAK plays a general role as an AR activator in prostate tissue.

One of the main features of COVID-19 is hyper-inflammation that is observed in several patients, especially those with severe disease [6]. Several studies suggested that inflammatory mediators play a role in the pathogenesis of the disease. Huang et al (2021), in their research, stated that several cytokines/chemokines such as Interleukin-6 (IL-6), Carcinoembryonic Antigen (CEA), and Tumor Necrosis Factor- α (TNF-α) in bronchoalveolar fluid (BALF) as excellent biomarkers to monitor or predict the development of COVID-19 and the results are positively correlated with their levels in peripheral blood [7]. Moreover, Several SARS-CoV-2 proteins, including open reading frame 3b (ORF3b), ORF6, ORF7, ORF8, and nucleocapsid (N) proteins, can inhibit the production of interferon (IFN) types I and II (IFN-I and -II) which is the body's natural anti-virus. The results of protein-protein interaction (PPi) analysis using

principal component analysis (PCA) and ClusterONE by the authors also show that inflammatory mediators such as IL6 and interferon mediators such as IRF7, IRF3, IFNAR1, IFIT3, IFIT1, IFI6 are important proteins associated with COVID-19 [8]. Thus, the combination of hyperinflammation, and lack of IFN response to SARS-CoV-2 in the early stages of infection, is thought to strongly contribute to the rapid disease progression in COVID-19 patients [9].

Although the important role of TMPRSS2 has been known as the entry of SARS-CoV-2 into host cells, so far, it has not been discussed how the expression of MAK, AR, and TMPRSS2 is related during viral infection. Knowledge of changes in the expression of these three genes in COVID-19 patients may be able to clarify several things. The main key may explain how prostate cancer could increase the risk of severity and mortality in COVID-19 patients. Furthermore, it may also explain why there is an increase in severity in male COVID-19 patients. For this reason, the study was performed to analyze gene expression profile data taken from the Gene Expression Omnibus (GEO) database to see changes in the expression of the three genes. This study also carried out an analysis of the expression profile of inflammation-related genes and IFN responses such as IL6, IRF7, IRF3, IFNAR1, IFIT3, IFIT1, IFI6. Furthermore, we performed PPi analysis to the revealed relationship between viral entry mediated by MAK, AR, and TMPRSS2, with inflammatory mediators and the interferon response. Thus, the relationship between viral entry, inflammation, and IFN response to the severity of COVID-19 patients can be explained.

2. METHOD

MicroArray Dataset Analysis.

Microarray data was collected from data that referred to Zhang et al. (2021). The data showed whole peripheral blood mononuclear cell (PBMC) genomic transcriptomes from severe and mild COVID-19 patients, as well as healthy controls (HC) retrieved from the GEO database (GSE 164805 and GPL26963 platform). In these data, all severe patients were male and aged over 50 (52-73) years old [10].

Dataset Analysis Using Orange Data mining .

The dataset was compiled by collecting the protein-coding expression values from the results of the PBMC microarray in each of 5 severe, mild, and HC. The datasets were then analyzed, especially to see differences in the expression of MAK, AR, TMPRSS2, IL6, IRF7, IFNAR1, IFIT3, IFIT1, IFI6 from the three groups. Dataset creation and gene expression analysis were performed using Orange Data-mining version 3.30

PPi analysis using STRING.

Protein-Protein Interaction analysis of the altered expression of MAK, AR, TMPRSS2, IL6, IRF7, IFNAR1, IFIT3, IFIT1, IFI6 in severe COVID-19 patients was performed using the STRING database. PPi analysis between the expression of these genes and the genes resulting from enrichment was carried out with a confidence score >0.4. The type of interaction, the confidence score, and the type of change in expression (upregulation or downregulation) were recorded and arranged in tabular form [11].

3. RESULTS

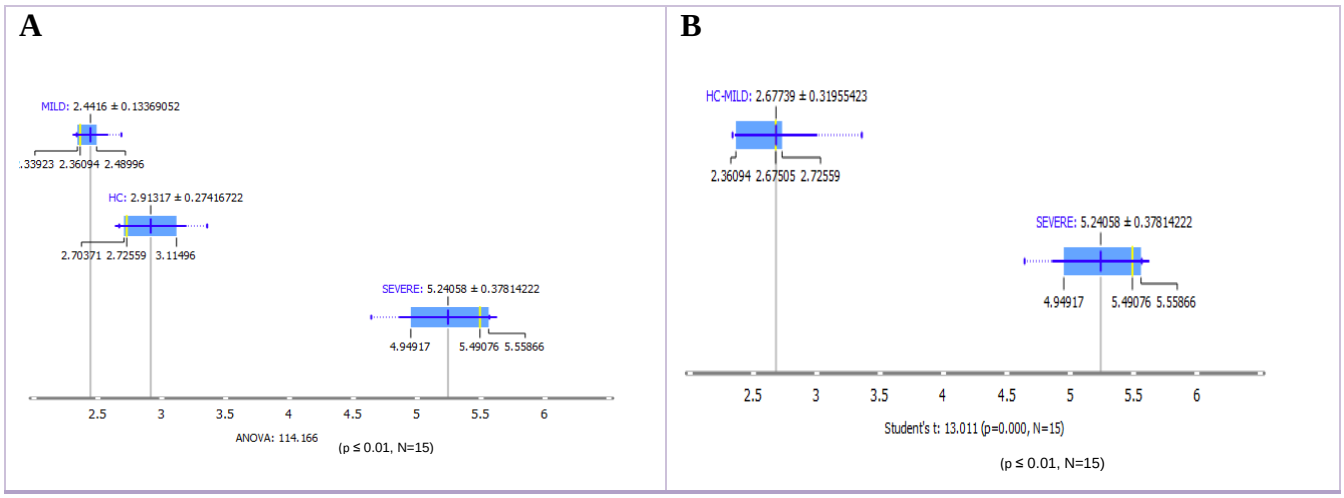
Relationship between MAK, AR and TMPRSS expression and the COVID19 severity

The dataset collected from the GEO database and referring to the research results of Zhang et al. (2021) consisted of about 18,885 protein coding gene expressions [12]. The ranking results using Orange Data-mining version 3.30 of several genes based on ANOVA-Score can be seen in Table 1.

Table 1. 20 Genes with the highest ANOVA-Score

GENE ID	ANOVA-Score	GENE ID	ANOVA-Score
TMEM252	546.266	TULP2	131.516
KCNJ2	166.697	SLC25A2	124.728
MAK	163.986	FZR1	121.971
FIS1	158.915	ZBTB14	119.633
VSIG8	157.624	SPINK8	116.674
KRT2	156.768	TMEM154	115.535
PGP	156.434	CDRT15L2	113.300
TIGD3	138.819	CREB3L2	109.625
MYADM	135.004	ELMO2	107.659
EDN1	134.335	IL18RAP	107.131

In Table 1, ANOVA score showed that MAK was in the top three genes with the highest score. Since ANOVA-Score indicates a high variance of the data, it was possible to distinguish the MAK expression data between the three groups. Therefore, we performed the Box-plot analysis using Orange Data-mining version 3.30 afterwards. The mean MAK expression of the three groups was shown in Figure 1A and 1B.Figure 1A showed no significant difference between the mean MAK expression in the HC and mild COVID-19. However, in Figure 1B, the data showed that MAK expression was able to be distinguished by comparing means between two groups (mild COVID-19 and HC respectively) to severe COVID-19 ($p \leq 0.01$). The average expression of AR and TMPRSS2 was shown in Figures 1C and 1D. In Figure 1C, it is shown that there was no significant difference in AR expression between the three groups ($p=0.187$). It indicated no significant difference in the number of AR between mild and severe COVID-19 and HC. For TMPRSS2 expression, a significant difference between COVID-19 patients and HC ($p \leq 0.01$) was shown in Figure 1D. However, there was no significant difference in TMPRSS2 expression between mild and severe COVID-19. Relationship between MAK, AR, and several interferon-related signaling expressions Furthermore, we examined the association between MAK expression with IL6, IRF7, IFNAR1, IFIT3, IFIT1, IFI6 and expressions in mild and severe COVID-19 and HC as presented in Table 2. which describes the difference in the mean value of gene expression for each group. The p-value indicating a significant difference in the mean gene expression value for each group was set at 0.05.



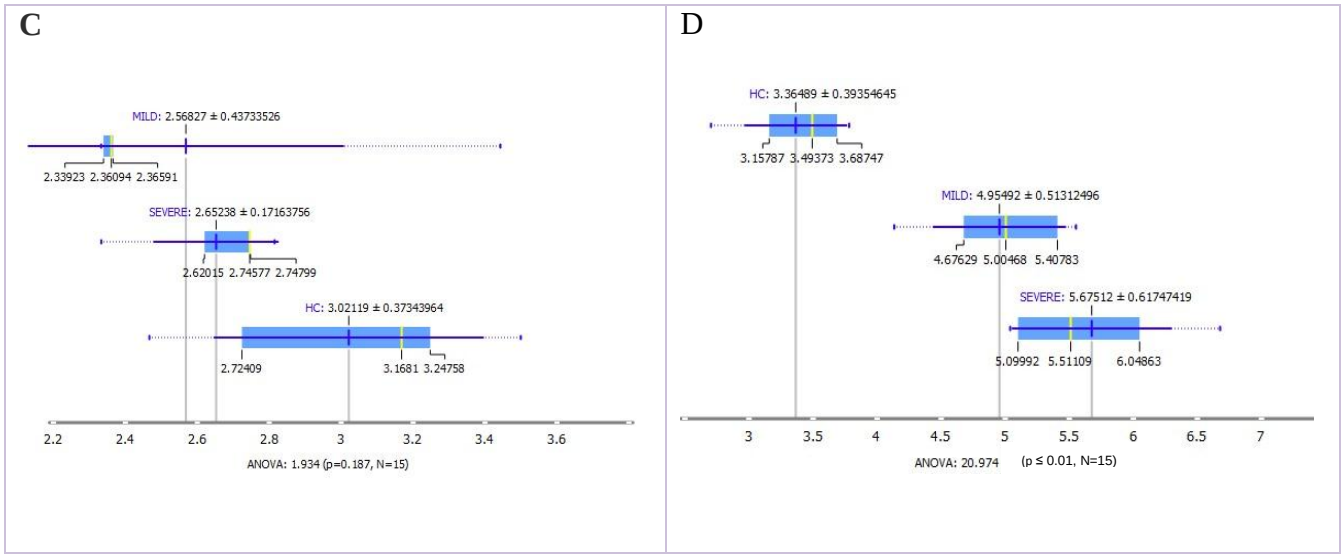


Figure 1. Mean Comparison of of MAK, AR, and TMPRSS2 expression in PBMC of mild and severe COVID-19 and Healthy Control (HC).

Mean comparison of MAK expression between mild, severe COVID-19 and HC (A), mean comparison of MAK expression between combination of mild COVID19 with HC and severe COVID-19 (B) mean comparison of AR expression between mild, severe COVID19 and HC. (C) mean comparison of TMPRSS2 expression between mild and severe COVID-19 and HC (D) Table 2 showed nine genes and their expression profiles. The expression of MAK and IRF7 had significant difference in severe COVID-19 compared to mild COVID-19 and HC. However, for MAK, there was no significant difference in expression between mild COVID-19 and HC. For the expression of the IFNAR1, IFI6, TMPRSS2, IFIT1, and IFIT3 genes, it was shown that there were differences in expression between mild and severe COVID-19 and HC. It showed that the gene expression was different between mild and severe COVID-19 and HC, however, the difference between COVID-19 severities was not determined. There were no significant differences in AR and IL6 expression in PBMC with mild and severe COVID-19, and HC.

Table 2. Average Expression Value of MAK, AR, TMPRSS2, and Related Genes to Inflammation and Interferon Response

ID GENE	HC Mean (N=5)	MILD Mean (N=5)	SEVERE Mean (N=5)	P value	Gene regulation in Patient (up/down regulated)
MAK	2.913 ± 0.274*	2.441 ± 0.133*	9.660 ± 0.305	≤ 0.01	Up
IFNAR1	6.963 ± 0.313	8.961 + 0.282*	10.461 ± 0.505*	≤ 0.01	Up
IFI6	7.739 ± 0.228	10.569 ± 0.739*	10.461 ± 0.505*	≤ 0.01	Up
IRF3	9.699 ± 0.762	8.074 ± 0.288*	7.713 ± 0.274*	≤ 0.01	Down

IRF7	6.886 ± 0.481	5.796 ± 0.102	4.985 ± 0.376	≤ 0.01	Down
TMPRSS2	3.364 ± 0.343	4.954 ± 0.513*	5.675 ± 0.617*	≤ 0.01	Up
IFIT1	3.373 ± 0.247	5.743 ± 0.565*	5.214 ± 0.752*	≤ 0.01	Up
IFIT3	2.894 ± 0.286	4.387 ± 0.969*	4.699 ± 0.769*	≤ 0.01	Up
AR	3.021 ± 0.373*	2.568 ± 0.437*	2.652 ± 0.171*	0.187	Down
IFNG	11.731 ± 1.069*	9.729 ± 0.709*	8.273 ± 1.088	≤ 0.01	Down

Note: the mean marked with an asterisk has not insignificant difference in value PPi analysis showed the relationship of a MAK, AR, and TMPRSS2 and Interferon Response via STAT5A. We tried to analyze which proteins may connect the MAK, AR, and TMPRSS2 to the inflammatory mediator by performing PPi analysis using STRING. The results of the PPi analysis of the nine genes was shown in Figure 2. The figure showed that there was a relationship between the interferon response represented by the gene expression group (IRF7, IFNAR1, IFIT3, IFIT1, IFI6) and the gene/protein expression group TMPRSS2, AR, and MAK which play a role in virus entry. The STAT5A expression was shown linking the two groups. The comparison of the mean STAT5A expression in mild, severe, and HC was shown in Figure 3. In Figure 3, we showed that there was a significant difference in STAT5A expression between mild and severe COVID-19 and HC ($p \leq 0.01$). This suggested that down-regulation of STAT5A plays a role in the virus entry process up to the occurrence of an anti-viral response by interferon. Gene's potency to predict the severity of COVID 19 with Machine Learning. The prediction model for COVID-19 severity from genes expression between mild and severe COVID-19 and HC was carried out using Support Vector Machine (SVM). The expression of the analyzed genes was as listed in table 2 with significantly different expressions ($p<0.05$), and included in the 20 important proteins based on our previous study.(8) These genes were IFNAR1, IRF3, IRF7, IFI6, IFIT1, and IFIT3. Next, we selected several genes that had significant differences in table 2 ($p \leq 0.01$) with the mean value in the severe group that higher than HC and mild. Based on these criteria, three genes were obtained: IFNAR1, IRF3, and IRF7. If MAK is included in the criteria along with IFNAR1, IRF3, and IRF, then results were increased to 100 %. In the table 3, we summarized genes that have potency to predict severity of COVID-19.

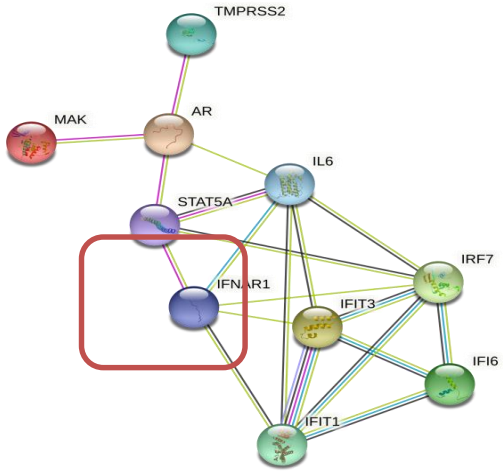


Figure2. Protein-protein interaction (PPi) between groups of genes related to interferon responses (IRF7, IFNAR1, IFIT3, IFIT1, IFI6) and TMPRSS2, AR, and MAK that play a role in virus entry

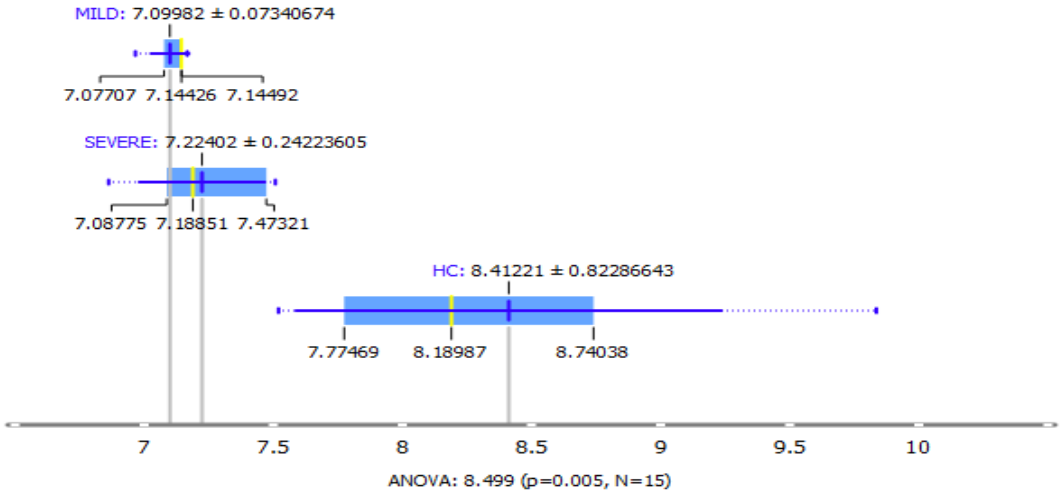


Figure 3. Comparison of the mean STAT5A expression in PBMC samples of COVID-19 patients with mild and severe COVID-19 and HC. ($p \leq 0.01$, N=15)

Table 3. Prediction models of Interferon related genes and MAK to distinguished mild and severe COVID-19 and Healthy Control (HC) was evaluated using Support Vector Machine (SVM) analysis using Orange Data Mining.

		Predicted value								
		Genes Expression : IFNAR1, IRF3, IRF7, IFI6, IFIT1, and IFIT3			**Genes Expression :** IFNAR1, IRF3, and IRF7			**Genes Expression :** MAK, IFNAR1, IRF3, and IRF7		
		HC	**Mild**	**Severe**	**HC**	**Mild**	**Severe**	**HC**	**Mild**	**Severe**
Actual value	**HC**	**100 %**	0%	0%	**100 %**	0%	0%	**100 %**	0%	0%
	Mild	0%	**20 %**	80%	0%	**100 %**	0%	0%	**100 %**	0%

	Severe	0	40%	**60%**	0	20%	**80%**	0	0%	**100%**
Total samples		5	3	7	5	6	4	5	5	5

4. DISCUSSION

The role of AR activation in increasing TMPRSS2 expression has been demonstrated by Leach et al (2021).(3) However, whether the AR activation occurs in lung cells or is carried out by MAK as it occurs in prostate tissue was not clearly understood. The gene expression analysis showed that MAK expression had a significant increase in severe patients compared to mild patients and healthy people (Figure 1B). This suggested a significant increase in AR phosphorylation by serine/threonine protein kinase MAK in severe patients. In a study by Zhang et al (2021) whose gene expression data were used in this study, information was obtained that subjects with active cancer were excluded from healthy donors [10]. There was no information obtained whether subjects with active cancer were excluded from the COVID-19 patient group. However, if we assumed that all subjects with active cancer (including prostate cancer) were excluded, it can be concluded that the increase in MAK phosphorylation activity occured at the AR in lung cells of COVID-19 patients. The changes of gene expression in COVID19 were summarized in Table 4. AR activation in prostate tissue will disrupt the balance of cell proliferation and apoptosis, especially in people who have high amounts of androgen hormones. Although the activation of AR by MAK in lung cells was still unclear, based on the explanation above, it is necessary to consider COVID-19 patients with high MAK expression in their PBMCs or people with a history of prostate cancer to experience a worsening condition which required ICU admission. Furthermore, consider COVID-19 patients with high DHT and have sensitive/active AR, such as characteristic with significant androgenetic alopecia (AA) was also important. Androgenetic alopecia is a hyperandrogen condition associated with scalp hair loss and baldness. The study of Goren et al (2021) stated that among 41 men hospitalized with COVID-19, 71% (29 patients) experienced significant androgenetic AA alopecia in the first exon of the androgen receptor gene that is associated with higher rates of COVID-19 morbidity and mortality [21].

Table 4. Changes of Gene Expression in COVID-19

Gene ID	Gene Regulation	Not significant changes	Significant changes	Functions
MAK	Up	HC-mild	Severe	Plays a role in AR transcriptional co-activation [13].
AR	Down	HC-mild-Severe	--	Activated AR increased TMPRSS2 expression. AR protein and STAT5A/B protein reciprocally synergize [14]
TMPRSS2	Up	Mild-severe	HC	This gene was demonstrated to be up-regulated by androgenic hormones in prostate cancer cells and down-regulated in androgen-independent prostate cancer tissue. This protein also facilitates entry of viruses into host cells by

				proteolytically cleaving and activating viral envelope glycoproteins. Viruses found to use this protein for cell entry include Influenza virus and the human coronaviruses [13]
STAT5A	Down	Mild-severe	HC	Inhibition of IL-2/IL-2R causes a decrease in lymphocytes via JAK1-STAT5 in critically ill patients with COVID-19 pneumonia [15].
IFNAR1	Up	Mild-severe	HC	Interferon alpha/beta receptors. Interaction of IFN-α with IFNAR activates the JAK1-STAT5 signaling pathway [16]
IFI6	Up	Mild-severe	HC	Has an antiviral activity towards hepatitis C virus/HCV by inhibiting the EGFR signaling pathway, which activation is required for entry of the virus into cells [17]
IRF7	Down	--	HC-mild-Severe	Activating the IFN-beta (IFNB) and IFN-alpha (IFNA) genes. RNA viruses belong to the coronaviridae. Induces host translational arrest and thereby prevents infected cells from synthesizing new peptides and proteins, including IFN-stimulated IRF and STAT. Viruses can also upregulate certain miRNAs to adjust the expression of factors involved in IRF and STAT activation [18].
IFIT1	Up	Mild-severe	HC	Interferon-induced proteins with tetratricopeptide repeats (IFITs) are innate immune effector molecules that are thought to confer antiviral defence through disruption of protein–protein interactions in the host translation-initiation machinery. However, it was recently discovered that IFITs can directly recognize viral RNA bearing a 5′-triphosphate group (PPP-RNA), which is a molecular signature that distinguishes it from host RNA [8]
IFIT3	Up	Mild-severe	HC	Interferon-induced proteins with tetratricopeptide repeats (IFITs) are innate immune effector molecules that are thought to confer antiviral

				defence through disruption of protein–protein interactions in the host translation-initiation machinery. However, it was recently discovered that IFITs can directly recognize viral RNA bearing a 5′-triphosphate group (PPP-RNA), which is a molecular signature that distinguishes it from host RNA [19]
IL6	Up	HC-mild-Severe	--	Interleukin-6 (IL-6), known as an inflammatory cytokine, can be involved in many innate and adaptive immune responses. IL-6, along with some other inflammatory cytokines, including IL-1 beta (β), IL-8, and tumor necrosis factor-alpha (TNF-α), as well as inflammatory chemokines, can significantly contribute to, fever, lymphopenia, coagulation, lung injury, and multi-organ failure (MOF) [20]

Increased MAK expression in severe patients indicates AR activation. However, the analysis of AR expression carried out in this study shown no significant differences between mild and severe COVID-19 and HC. This suggested that the role in increasing the expression of TMPRSS2 is the AR activation. There was an increase in TMPRSS2 in PBMC samples of mild and severe COVID-19 compared to HC. However, the increase in TMPRSS2 expression did not depend on the amount of AR present in the tissue. This result is different from the study by Leach et al (2021) which stated a significant co-expression of AR and TMPRSS2 in A549 lung cells infected with SARS-CoV-2 [3]. The results of gene expression analysis in this study also showed that there was no co-expression between MAK and AR, respectively. A previous study by Ma et al (2006) stated that the interaction between MAK and AR occurred physically (binding) where MAK and AR experience co-precipitation after being given DHT [5]. This study at least confirmed that the interaction between MAK and AR occurred physically and not by co-expression.

Based on the PPi analysis in Figure 2 and Table 2, it can be seen that only IRF7 of the gene group associated with the interferon response gave a significant difference between mild, severe, and HC. However, the other genes in the interferon response group that were analyzed for their expression all showed differences in COVID-19 patients compared to HC. It was just that the difference in expression is not significant in mild and severe patients. Apart from being significantly different, IRF7 expression was down-regulated. IRF7 plays a role in activating the IFNA and IFNB genes. Interferon is a natural protein produced by the body in response to the body against harmful compounds, such as viruses, bacteria, or cancer. The down-regulation of IRF7 expression observed in PBMCs of COVID-19 patients appears to affect interferon production and is thought to be an important factor in the severity of COVID-19 patients.

PPi analysis also showed that there was a relationship between gene expression groups involved in virus entry (MAK, AR, and TMPRSS2) and gene groups involved in interferon responses (IRF7, IFNAR1, IFIT3, IFIT1, IFI6). As shown in Figure 2, the relationship between

the two gene groups seems to be linked by the role of activated AR. Although AR expression cannot be used as a biomarker as previously described, COVID-19 therapeutic agents can be directed at AR targets and other genes/proteins that affect their signaling activity or function. This includes making the MAK gene/protein.

In this study, we tried to determine the genes capable of predicting the severity of COVID 19 by using SVM analysis. First, according to our previous study, we found IFNAR1, IRF3, IRF7, IFI6, IFIT1, and IFIT3 were the best of candidates [8]. We then followed this by analyzed genes expression in severe, mild, and HC. The SVM was shown in the table 3. The data was shown that 80% of severe patients could be predicted or distinguished from mild patients. Furthermore, we tried to investigate genes that significant from the table 2, wtih average of mean higher in severe than mild and HC. We choosed IFNAR1, IRF7, and IRF3 and tried to predicted by included MAK in the result as shown in table 3. This shown that MAK was able to increase sensitivity to predict severity in COVID-19. Combination of MAK, IFNAR1, IRF3, and IRF7 were able to completely distinguished mild and severe COVID-19, and HC.

Moreover, in the data set used in this study, it is also shown that the expression of Interferon Gamma (IFNg) was down-regulated as can be seen in table 2. IFNG was known to be one of the factors associated with the severity of COVID19. research by Hu et al. (2020) showed that decreased circulating IFNG expression was associated with the severity of COVID19 patients. In this study, it was found that IFNG is one of the risk factors associated with pulmonary fibrosis [22]. In line with the study by Laarhoven et al. (2021) administering IFNG is one of the modalities of adjuvant therapy in the treatment of COVID-19 patients who have an impaired immune system [23]

5. CONCLUSION

The absence of co-expression of AR and TMPRSS in COVID-19 patients suggests that expression of TMPRSS2 does not depend on the number of ARs but rather on the number of activated ARs. This was confirmed by a significant increase in MAK expression in severe COVID-19 compared to mild COVID-19 and HC. Based on PPi analysis, MAK is associated with interferon signaling as evidenced by changes in gene expression related to interferon signaling. Thus MAK serine/threonine-protein kinase has the potential to be used as a biomarker of COVID-19 severity and a therapy target, especially in male patients.

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