Cortisol Serum Levels and Correlation with the Level of Depression in Hiv Patients During the Covid-19 Pandemic

Eny Pujiati[1], [5]*, Meidiana Dwidiyanti[2], Muchlis Achsan Udji Sofro[3], Muhammad Hussein Gasem[4]

[1]*Faculty of Medicine, Diponegoro University, Semarang, Indonesia
[2]Nursing Department, Medicine Faculty, Diponegoro University, Indonesia
[3]Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Diponegoro University, Dr. Kariadi Hospital, Semarang
[4]Center for Tropical and Infectious Diseases, Faculty of Medicine, Diponegoro University, Dr. Kariadi Hospital, Semarang.
[5]*ITEKES Cendekia Utama Kudus, Middle Java, Indonesia
*Email: enypujiati886@gmail.com1
mdwidiyanti@gmail.com
muchlis.aus@gmail.com
mhgasem@gmail.com

Abstract

The COVID-19 pandemic leads to serious and has the potential impact on the community's mental health, such as depression among the common people and people living with HIV (PLWH). The negative stress life events occur due to the correlation between biological vulnerability and psychosocial impacts. This correlation leads to depression. In this case, the HPA-axis may involve in pathogenic depression. The same matter goes for the correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic. To analyze the cortisol serum levels and the correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic. The study design was cross-sectional with a consecutive sampling method. The bivariate analysis used Kendall's Tau test since the data were not normally distributed (<0.05). Sixty-two respondents were included in the study. The laboratory analysis showed the cortisol serum level average of 152.03 ng/ml ± 123,237 ng/ml with a minimum value of 26 ng/ml and a maximum value of 336 ng/ml. The average depression level was 34,65 ± 4,9333 with a minimum value of 26 and a maximum value of 44. The results indicated a significant correlation between the cortisol serum levels and the level of depression of HIV patients during COVID-19 ($p < 0.05$; r:0.280). There was a correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic.

Keywords: Cortisol, Depression Level, Hiv Patients During Covid-19 Pandemic

1. Preliminary

The coronavirus 2019, COVID-19, is a disease caused by *Severe Acute Respiratory Syndrome Coronavirus 2*, SARS-CoV2. The COVID-19 spread occurs suddenly and undetected that influences the mortality and morbidity incidents in various countries. Until recently, the virus infected more than 600 million people and caused more than six million deaths in the world (Juruena et al. 2020)(Randolph and Barreiro 2020);(Liu et al. 2020). The *World Health Organization* (WHO) deemed the virus to be a pandemic. The COVID-19 pandemic leads to serious and critical impacts on the community's mental health, such as depression among the common
people and people living with HIV (PLWH) (Guo et al. 2020);(Ryu et al. 2020).

Depression refers to the remnant of the psychological symptoms that commonly happen in PLWH who frequently suffer from depression more than other populations (Perera et al. 2020);(Le et al. 2020). The meta-analysis study reported that HIV-infected people had a higher risk to suffer from depression with [OR= 1,99, 95% (CI): 1,32– 3.0] (Le et al. 2020). Before the COVID-19 pandemic, the prevalence of depressed HIV/AIDS patients ranged from 30-50% compared to the common population.(Rogers et al. 2020);(Vu et al. 2020) The prevalence of depressed people in low, moderate and high-income countries ranged from 12.8-78%.(Uthman et al. 2014) On the other hand, the prevalence of depression in Indonesia was 21.8%. The estimated depressionprevalence among people with HIV/AIDS was 60%.(Peltzer and Pengpid 2018). During the COVID-19 pandemic, depressed HIV/AIDS people had a strong correlation to the increased stressor due to the psychological, social,

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and HIV-agent effect factors in the central neural system, medication compliance, and disease prognosis of HIV/AIDS people (Rivera-Rivera et al. 2016).

The chronic stress on HIV/AIDS people leads to HPA-axis hyperactivity and depressed behaviors along with hippocampal and medial prefrontal cortex (mPFC) disorders.(Herman et al. 2016). The results found that the HPA-axis disorder led to depression(Roubos et al. 2012). The depression due to biopsychosocial and neurotransmitter interaction could influence the pathophysiology in a complex manner (Cole 2008) (Ironson et al. 2015). Depressed patients have higher cortisol serum levels than common people (Nandam et al. 2020). This condition leads to the exaggerated *corticotrophin-releasing hormone*, CRH (Herman et al. 2016) (Joseph and Whirledge 2017). While feeling stress, the cerebral cortex and amygdala receive the signs and send the signs to the hypothalamus. Hypothalamus secretes CRH while the pituitary secretes corticotropin. The corticotropin stimulates the adrenal cortex and increases the steroid hormone contents, including cortisol. Then, the corticotropin secretes the cortisol in the saliva and blood (Herman et al. 2016) (Joseph and Whirledge 2017). Studies reported that chronic hyper-cortisol caused neurogenesis suppression and hippocampus atrophy (Slavich and Irwin 2014). The same matter happened in the cortisol responses toward psychosocial stressors. Some studies found cortisol-hyper activities while the other studies found the hypo-activities of cortisol (Zorn et al. 2017) (Morris and Rao 2013). The psychosocial factor with high BDI II, and high neurohormone, such as cortisol and norepinephrine (NE), significantly influences the growth of infected HIV toward AIDS. This matter increases the CD-4 and viral load(Oladipo, Amoateng, and Kalule-Sabiti 2014). On the other hand, chronic stress develops the function of the maladaptive HPA-axis. However, chronic stress influences decreased immunity function, modifies cardiovascular system regulation, and interrupts the metabolism process.[23] The progressive effects of HIV/AIDS can infect the central nervous system, thereby disrupting the balance of neurotransmitters, accelerating viral replication and suppressing the immune response, which in turn can shorten the period of asymptomatic HIV. This condition, if not treated properly, can reduce quality of life, weaken physical function and therapeutic effects, as well as medical comorbidities in HIV patients so that treatment and care are needed by paying attention to psychological aspects that have an impact on physical factors in HIV patients with depression (Herman et al. 2016)(Oladipo, Amoateng, and Kalule-Sabiti 2014)(Oladipo, Amoateng, and Kalule-Sabiti 2014)(H. A. Kim et al. 2016).

Many advanced countries study the cortisol serum level and saliva of depressed patients (Islam et al. 2018) (Dziurkowska, Wesolowski, and Dziurkowski 2013)(Hardeveld et al. 2014)(Xu et al. 2018). The studies focus on pre-diagnosed depressed patients instead of newly diagnosed depressed patients. The studies compared the cortisol serum level among normal individuals, and individuals with mental illness, and treated patients with some depression episodes. Even though, there are still studies that report results were contrary to the current research's explanation (Hardeveld et al. 2014)(Keating et al. 2013).

The primary focus of studies about cortisol serum level and its correlation with depression level is the role of the HPA-axis as the depression response indicator and as the collateral pathological consequence mediator (Zhao et al. 2017)(Frodl and O'Keane 2013). Depression occurs due to HPA-axis dysregulation that produces various cortisol serum levels. This matter is strongly recommended as the biomarker. (Islam et al. 2018)(Frodl and O'Keane 2013). The linear correlation between cortisol serum level and depression level cannot be estimated. The lack of studies on cortisol levels and the depression level of HIV patients during the COVID-19 pandemic bring clinical significance to be renewed with other clinical and psychosocial interventions. The other opportunities are to promote mental health and HIV management as the primary data for further studies. Thus, this research analyzed the cortisol serum levels and the correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic.

2. Objective

This research analyzed the cortisol serum levels and the correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic. The hypothesis was - there was a correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic.

3. Research and Methods

The researchers promoted this cross-sectional research in the Voluntary Counseling Testing, VCT, of R.A Kartini Regional Hospital, Jepara Regency, Central Java, Indonesia, from January to May 2021. R.A Kartini Regional Hospital is A type-B public hospital with the Satellite Education, Ministerial Decree of the Health Ministry of Republic of Indonesia Number GK.01.07/MENKES/436/2019. The hospital applied a Regional Service Agency-based-Financial Management (PPK BLUD). The hospital had 457 beds and 886 employees.

Population study

The population in this study consisted of all HIV patients with depression. Then, the targeted population consisted of depressed HIV patients with anti-retroviral medication at the VCT clinic service of RA Kartini Regional Hospital, Jepara Regency. The applied sampling technique was the consecutive sampling technique. The researchers took the

sample based on the applied subject selection criteria inclusion and exclusion criteria, within a certain period until the targeted number of subjects achieved. The inclusion criteria were HIV patients with mild-moderate depression, HIV patients with less than a year of diagnosis, HIV patients with ARV therapy, patients aged 18 to 60 years old, and patients with informed consent approval. The exclusion criteria were: patients without informed consent approval, patients with psychiatric comorbidity, and patients with emergency state conditions.

The Instrument and Data Collection Materials

The diagnoses for depressed HIV patients were based on the psychiatric examination at Jepara Regional Hospital, measuring the degree of depression using the Beck Depression Inventory-II scale, and the value of serum cortisol levels was obtained from the GAKI UNDIP laboratory. The instrument for subject characteristics was a questionnaire, consisting of age, sex type, marital status, education, profession, income, family support, and COVID-19 pandemic response. The BDI II scale evaluated 21 depression symptoms with 15 items describing the emotion and attitude change and 6 items describing the somatic symptoms. The scores of 0 to 16 indicated no depression, and scores of 17 to 63 indicated the respondents were depressed. The normal category ranged from 0 to 16, mild depression category with a range of 17 to 30, moderate depression with a range of 31 to 45, and severe depression from 46 to 63. The cortisol serum level measurement applied the enzyme-linked immunosorbent assay / ELISA, with the normal cortisol serum level of ≥50–230 ng/ml. The data collection of depression degrees and respondents' characteristics involved 6 enumerators with a Master of Nursing Education degree. They also had the signed registration letter / STR. The process of taking the patient's blood involved the laboratory staff of RA Kartini Regional Hospital of Jepara Regency. The diagnosis of depression in HIV patients was obtained from the results of a psychiatrist's examination at the Jepara District Hospital, measuring the degree of depression using the Beck Depression Inventory-II scale. The value of serum cortisol levels was obtained from the GAKI UNDIP laboratory.

The Sampling Procedure

The diagnoses of the depressed HIV patients from the psychiatric examination at Jepara Regional Hospital were based on DSM-V diagnostic criteria. The researchers checked of cortisol serum levels with the ELISA method at the GAKI laboratory of UNDIP, the accredited laboratory by the National Accreditation Committee - the National Standardization Agency, as the examiner laboratory based on SNI ISO/IEC 17025:2017. The blood sampling was done by the laboratory officers at R.A Kartini hospital, Jepara. The officers took the venous blood without anticoagulant (EDTA) at 06.30 - 09.00 Indonesian Western Region Time without hemolysis case entailment. The required blood specimen was 3cc. The blood was put in red vacutainers without an anticoagulant (EDTA). Then, the vacutainers were spun with an angular speed of 3000 rpm for 10 minutes to separate the serum and the plasma. The researchers stored the serum in a room with - 20°C at the laboratory of RA Kartini Regional Hospital, Jepara Regency. The laboratory was accredited with SNARS with a predicate of plenary pass. Then, the serum was sent to GAKI UNDIP's laboratory for further examination. In this step, the blood sample with hemolysis was excluded. The researchers examined the cortisol level of the blood with ELISA Kit Catalog Number CO103S. For the depression level, the researchers used the BDI II scale.

Data Management and Statistic Analysis

The applied statistic method was SPSS software version 24. The univariate analysis dealt with the descriptive analysis to describe the whole data. The researchers analyzed the numerical data, such as age and cortisol level, with the analyses of the mean, the standard of deviation, minimum score, and maximum score. On the other hand, the researchers analyzed the categoric data, such as sex type, education, profession, income, marital status, family support, and the COVID-19 pandemic response with frequency distribution. The bivariate analysis used Kendall's Tau test since the data were not normally distributed (<0.05). The researchers promoted computerized examination for all statistical tests.

Ethical Clearance Considerations

The granted ethical clearance of this research came from the Ethical Commission of Health and Medicine Research, Medicine Faculty, Universitas Diponegoro. All subjects received informed consent and agreed with the research by writing their consent.

4. Results

The subject characteristics

The study was conducted from January to May 2022, involving 62 respondents based on the inclusion and exclusion criteria in the VCT service clinic of RA. Kartini Regional Hospital, Jepara.

Table 1 Subject Characteristics (n = 62)					
The characteristics of the respondents	Frequency (N)	Percentage (%)	Mean	SD	Min-Max
Age (years old)					
Late Adolescence	8	12,9			
Early Adulthood	27	43,5			
Late Adulthood	27	43,5			
Sex Types					
Male	24	38,7			
Female	38	61,3			
Education					
Higher	7	11,3			
Lower	55	88,7			
Profession					
Employed	42	67,7			
Unemployed	20	32,3			
Income					
High	0	0 (0)			
Moderate	10	16,1			
Low	52	83,9			
Marital Status					
Married	28	45,2			
Not Married	34	54,8			
Family Support					
Supportive	37	59,7			
Not Supportive	25	40,3			
COVID-19 Pandemic Response					
Normal	0	0			
Mild Psychosomatic	28	45,2			
Moderate Psychosomatic	34	54,8			
Severe Psychosomatic	0	0			
Cortisol Serum Level			152,03	123,24	26 - 336
Depression Level Score			34,65	4,933	26 - 44

Table 1 shows most respondents are female. They were mostly at the early adulthood, 27 (43.5%), late adulthood-27 (43.5%), lower education-55 (88.7%), employed-42 (67.7%), low income-52 (83.9%), Married-34 (54.8%), supportive family support-37 (59.7%), and suffering from moderate psychosomatic-34 (54.8%). On the other hand, the cortisol serum level was 152.03 ng/ml with a mean depression level was 34.65.

Table 2 The Distribution of the Respondents' Depressions based on the Influential Factors					
Variables	Depression Level Score				p-value
	High		Low		
	N	%	N	%	
Age (years old)					0,580
Late Adolescence	7	87,5	1	12,5	
Early Adulthood	19	70,4	8	29,6	
Late Adulthood	21	77,8	6	22,2	
Sex Types					1,000
Male	18	75,0	6	25,0	
Female	29	76,3	9	23,7	
Education					
High	6	85,7	1	14,3	
Low	41	74,5	14	25,5	1,000
Profession					0,532
Employed	33	78,6	9	21,4	
Unemployed	14	70,0	6	30,0	
Income					0,237
High	0	0	0	0	
Moderate	6	60,0	4	40,0	
Low	41	78,8	11	21,2	
Marital Status					0,557
Married	20	71,4	8	28,6	
Not Married	27	79,4	7	20,6	
Family Support					0,763
Supportive	29	78,4	8	21,6	
Not Supportive	18	72,0	7	28,0	
COVID-19 Pandemic Response					0,769
Normal	0	0	0	0	
Mild Psychosomatic	22	78,6	9	21,4	
Moderate Psychosomatic	25	73,5	6	26,5	
Severe Psychosomatic	0	0	0	0	

Table 2 shows no significant correlation between the factors of age, sex types, education, profession,

income, marital status, family support, and COVID-19 pandemic response toward the depression degree of HIV patients during the COVID-19 pandemic ($p > 0.05$).

Table 3 The Correlation between Cortisol Serum Level and the Depression Levels of HIV Patients

Variables	Mean	*p-value*	Correlation Coefficient
Corticol serum levels	152.03	0.002	0.280
Level of depression	34.65		

Table 3 shows the significant correlation between cortisol serum level and the depression level of HIV patients during the COVID-19 pandemic.

5. Discussion

This study showed a significant correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic. Current results were in line with the previously reported studies. The reports found depressed patients suffered from higher increased cortisol levels than the control group(Nandam et al. 2020). The cortisol, as a biomarker of depression, proved the correlation between cortisol serum level and vulnerability toward depression.

The COVID-19 pandemic made people panic and anxious (Haleem, Javaid, and Vaishya 2020). The lifestyle and habits changed dramatically. The pandemic also influenced many life aspects (S. W. Kim and Su 2020). The virus is different from other viruses, such as influenza and other infectious viruses. This specific feature received exaggerated attention from the media. The media informed us that the virus was dangerous and dreadful so people were frightened, stressed, and anxious (S. W. Kim and Su 2020). These matters raised the correlation between the central neural system, endocrine system, and immunity system. The inflammation process occurs as the psychological stress and physical stress respond by releasing the neuropeptide or other inflammatory mediators (Seiler, Fagundes, and Christian 2019).

The correlation between cortisol serum levels and depression due to physical and psychological stress and the fact of exaggerated adrenal activities led to destructive effects on the hippocampus. The correlation also increased the vulnerability to depression (Qin et al. 2015). Both acute and chronic stresses of HIV patients during the COVID-19 pandemic stimulated the hypothalamus to activate the HPA-axis by increasing the production and excretion of corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), and hypothalamic paraventricular nucleus. The AVP and CRH stimulate the pituitary via a venous portal system to produce an adrenocorticotropic hormone, ACTH. The hormone then gets into the blood and activates the adrenal gland to release glucocorticoids, GC, such as cortisol (Herman et al. 2016)(Joseph and Whirledge 2017). Chronic stress influences the depression problem development and increases the cortisol levels. Some of them occur due to the dysregulation of the HPA-axis (Belleau, Treadway, and Pizzagalli 2019)(Ignácio et al. 2019). The collateral endocrine factor release happens due to the stress responses, including dopamine, prolactin, nerve growth factor (NGF), P-substance, and oxytocin (Belleau, Treadway, and Pizzagalli 2019).

The same matter happens in the chronic mild stress model, CMS. The increased corticosterone occurred due to the stress responses and corticosterone synthetic hindrance related to the depressed behavior of CMS.39 Studies on an animal model with the focus of correlation analysis between the stress-induced cortisol levels increase and depression development showed significant correlation (Qin et al. 2015).

The glucocorticoids lead to GC receptor problem in the hippocampus and influences the feedback system of the GC receptor and transcription factor. These matters lead to hyperactivity of the HPA axis and increase inflammation. Glucocorticoids also provide negative feedback on the hypothalamus gland and pituitary gland by hindering the CRH and ACTH synthesis and secretion. Glucocorticoids influence the body, such as improving energy use, improving the cardiovascular activity to respond to flight or fight, and hindering some functions, such as immunity, reproduction, and growth (Herman et al. 2016)(Joseph and Whirledge 2017). Glucocorticoids provide a systemic effect and influence the homeostasis mechanism of metabolism, ion transportation, and the immunity response. During stressful conditions, the HPA-axis and negative feedback are active due to the hindering mechanism of cortisol secretion. This condition leads to lower HPA-axis sensitivity and influences the neuroendocrine circadian rhythm (Herman et al. 2016)(Joseph and Whirledge 2017).

Hypercortisolemia during stress on the HPA-axis lowers the glucocorticoid function. This matter influences the immunity system due to the cortisol secretion stimulation from the adrenal medulla and cortex . The cortisol also influences the non-release adrenalin release from the postganglionic sympathetic nerve terminal in the blood vessel and lymphoid organs. The stress also increases catecholamines that decrease interleukin secretion (IL). They are IL-1 and IL-2 by the macrophage. The stress also decreases antibody formation. Low IL-1 leads to decrease T-helper and lymphocyte that influence the decreased antibody formation and inflamed cellular phagocytosis activity against the infecting bacteria. Thus, the patients would be vulnerable to infection. The systemic effect of glucocorticoids and catecholamines influence the regulation of type 1 and type 2 cytokines. Stress lowers the type 1 cytokine production needed to respond the cellular immunity. The cortisol secretion goes linearly with the mental changes of patients.

However, the cortisol secretion does not go linearly with the body's immunity since cortisol suppresses the synthesis of T-cell protein. Cytokine causes the HPA-axis hyperactivity on depression problems via the negative feedback line of corticosteroid in the HPA-axis.

The increased cortisol secretion leads to interrupted cognitive function, the constant stress exposure against stress disturbs cognition and leads to irreversible changes in the nervous system. The steroid availability on the mineralocorticoid receptors and glucocorticoids, influence the performance of glucocorticosteroids on the central nervous system. The constant exposure to stress interrupts the signal receptors in the amygdala leading to HPA-axis activation. This matter proves the HPA-axis involvement in the pathogenesis of neuropsychiatric problems, including depression.

Studies reported inconsistent findings about cortisol serum levels of depressed patients and the influential factors of antidepressant medication. The result showed no significant correlation between depression and the HPA-axis activity. The studies found no different cortisol serum levels change after the medication with selective serotonin reuptake inhibitor (SSRI) on 16 patients with major depressive disorder, before and after 12 weeks of medication.45 Studies also found no correlation between cortisol levels in the evening during a trip and depression symptoms. Unfortunately, the correlation was not explored properly. The differences happened due to the fact of complex cortisol measurement that could not be controlled due to various factors, such as the sampling time and season variation. The other factors were stress, exercise before sampling, psycho-active compound consumption, medical comorbid, and direct occurrence before sampling. These factors influenced the biological measurement of cortisol. In this research, we controlled the sampling time, coffee intake, alcohol abuse, and smoking within 24 hours before the study visit.

6. Conclusion

The results showed the correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic.

Research Limitation

The limitation was observable in the limited sample size. Studies with a larger sample size are useful to determine more accurate results about the correlation between cortisol serum levels and the depression level of HIV patients during the COVID-19 pandemic

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