Serum Serotonin, A Good Indicator of Insomnia And Depression In Elderly

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ABSTRACT

Aim: This study aims to investigate whether there is a relationship between serum 5-HT levels and insomnia and depression in the elderly population aged \( \geq 60 \) years.

Methods: Subjects in this retrospective study were 40 elderly people in Pucang-Gading Nursing Home, Semarang, Central Java, Indonesia. 27 elderly people were diagnosed with insomnia. Serum serotonin level were measured in elderly with and without insomnia. Bi-and multi-variate logistic regression were used to evaluate the impact of serotonin to predict insomnia.

Results: The median age of the whole population was 70 years and 90.0% were female. Elderly with serum serotonin level below 35.6ng/mL have 21,600 risk of developing insomnia compare to those with serum serotonin level more than 35.6 ng/mL (\( p = 0.000 \)). In bivariate analysis, low serotonin level was significantly associated with insomnia. In multivariate analysis, serotonin was an independent prognostic factor for insomnia (\( p = 0.001, \ OR = 0.046, 95\%\ CI \)). The AUC for serotonin was 0.846 (95% CI = 0.708 s/d 0.958 p< 0.001).

Conclusions: We identified serum serotonin level predictive to insomnia in elderly.

Key words: serotonin–5-HT–depression–insomnia

1 INTRODUCTION

Insomnia is a common problem in elderly. The overall incidence of insomnia between men and women is the same, but more in men aged 85 years or older. [1] The incidence of insomnia in women is usually 20% to 50% higher than men. [2] The prevalence of insomnia reported in the United States ranges between 30% -60%. [1] Ancoli and Ayalon did research in population of more than 9,000 adults living in communities over 65 years of age, 42% of subjects reported difficulties on initiating and maintaining sleep. [3]

The classification of insomnia consists of transient insomnia (not more than a few nights), acute insomnia (less than 3-4 weeks), and chronic insomnia (more than 3-4 weeks). The diagnosis of primary insomnia is established if the criteria is defined in the International Classification of Sleep Disorders, second edition, (ICSD-2, American Academy of Sleep Medicine). To distinguish the causes of insomnia (primary or comorbid) and its manifestations (difficulty of initiating or maintaining sleep, early waking, or sleep that does not recover), further differentiation can be made by taking into the consideration of the duration of insomnia whether it’s acute or chronic. [4, 5] The classification of insomnia is always clinically based. Classification can be based on the causes, symptoms, and time. The most important instrument in diagnosing insomnia is by interview. [6] Insomnia can occur in 60-80% of patients with depression. Sleep disorders have been reported as symptoms seen in so many depressed patients. [7] The prevalence of all depressive disorders in the elderly is around 10 to 15%, and the prevalence of major depression is around 2% . [2] Symptoms of depression are high and consistent risk factor for insomnia. Insomnia therapy can improve depression. [7] Depression in elderly significantly increases the risk of suicide, due to a decrease in quality of life and functional status. According to the National Vital Statistics report in 1997, people aged 65 and older comprise 13% of the population of the United States, with 19% of suicides. The highest risk groups were men aged \( \geq 85 \) years, with a suicide incidence of 64.9 / 100,000, compared with the overall rate in the United States of 10.6 / 100,000. [2] Sunderajan et al. reported that the most common symptoms is mid-nocturnal insomnia (13.5%). [8] Vashadze’s study showed 85% of the population suffered from sleep disorders, 32% had difficulty falling asleep, 16% with moderate insomnia, 30% with severe depression, 25% of the population with low serotonin (5-hydroxytryptamine / 5-HT) levels, 10% with moderate
5-HT levels, 65% with high 5-HT levels. [9] Previous studies have a broad range of age population. This study aims to investigate whether there is a relationship between serum 5-HT levels and insomnia and depression in the elderly population aged ≥ 60 years.

1.1 The Relationship between Sleep and 5-HT

Humans spend about a third of their lives asleep, but only a few know about sleep. Sleep universal needs of all higher forms of life, including humans, not sleeping has serious physiological consequences. [10] Individuals who learn new assignments have a higher sleep spindle density than the control group. [10–12]

Over the course of a period of sleep, NREM and REM sleep alternate cyclically. The function of alternations between these two types of sleep is not yet understood, but irregular cycling and/or absent sleep stages are associated with sleep disorders. A sleep episode begins with a short period of NREM stage 1 progressing through stage 2, followed by stages 3 and 4 and finally to REM [10, 11].

Tryptophan is one of eight essential amino acids found in food, is an essential substance and is obtained from food or supplements. L-tryptophan functions as a precursor for 5-HT, melatonin and niacin. An adult male needs 3.5 mg / kg / day of tryptophan to maintain nitrogen balance. [13] There are two sources of L-tryptophan: diet and protein tissue. Aging, chronic inflammatory disease, and HIV infection are associated with decreased tryptophan, even in the absence of tryptophan diet deficiency. L-tryptophan is converted to 5-HT, especially in the brain. [14] Tryptophan 5-monooxygenase is needed to convert L-tryptophan to 5-Hydroxytryptophan (5-HTP). [15] Vitamin B6 and dopa-decarboxylase (DDC) are needed to convert 5-HTP to 5-HT, found in the brain, platelets, and along the tract gastrointestinal, [16, 17] The major neurotransmitters involved in many somatic and behavioral functions, including mood behavior, appetite and eating, sleep, anxiety, and endocrine regulation are 5-HT. [14]

The 5-HT system has a facilitation effect on cortisol, adrenocorticotropic hormone (ACTH) hormones and prolactin. [18] Corticotropin-releasing hormone (CRH) is secreted by the hypothalamic paraventricular nucleus (PVN) region and acts on the Corticotropin-releasing hormone receptor in the anterior pituitary which causes the release of adrenocorticotropic hormone (ACTH) into the blood. ACTH works on the adrenal cortex, which produces and releases cortisol into the blood and participates in maintaining whole-body homeostasis. Corticotropin-releasing hormone also activates the locus coeruleus (LC) which utilizes nor-epinephrine (NE) and causes further stimulation of the paraventricular nucleus and subsequently releases corticotropin-releasing hormone. Corticotropin-releasing hormone also stimulates the amygdala, part of the limbic system. Increased levels of norepinephrine and corticotropin-releasing brain hormones have been implicated in sleep disorders, including primary insomnia. Norepinephrine levels have also been shown to directly correlate with corticotropin-releasing hormone levels, an increase in norepinephrine results in an increase in corticotropin-releasing hormone levels and low norepinephrine levels produce low corticotropin-releasing hormone levels. An effective approach to correct sleep disorders can be to reduce cortisol levels and stabilize the dys-function of the HPA axis, this will reduce the long-term risk associated with increased cortisol levels. [19]

During sleep (sleep-S) and wakefulness (wake-W) are different and appear to be opposite changes in the organism. Some neurons that come from the cortex region, display very high activity during wakefulness and paradoxical sleep (paradoxical sleep-ps), while the front brain basal is very active during slow wave sleep (slow wave sleep-SWS), the brain stem is very active during waking, but the origin of the substantianigra remains active throughout the sleep-wake cycle. Local activities and different conjunctive / liaison activities that occur simultaneously during various stages of sleep-wake, Koella discusses sleep-wake patterns in terms of "local vigilance," this is a consequence of local neural network reactivity, which is responsible for the output of this system. Neurotransmitters are involved in various aspects (or local precautions) of complex behaviors. [20]

The activity of the dorsal raphe nucleus neurons and the raphe pallidus nucleus shows a gradual decrease with sleep speed and firing of these neurons at the lowest speed during paradoxical sleep. There is 5-HT release during waking and 5-HT reduction during slow wave sleep and paradoxical sleep. There is an elongated latency in paradoxical sleep and a very long hypnogenic effect. This consideration led to a new concept of the role of 5-HT in the sleep-wake setting. [20]

Jouvet stated that 5-HT works as a transmitter and neuropeptide, is released during waking and then works as a neurohormone which results in the release of hypnogenic factors responsible for slow wave sleep and paradoxical sleep. Slow wave sleep (SWS) and paradoxical sleep are caused by two factors that depend on 5-HT and slow wave sleep regulated by a mechanism that mediates receptors and gives effect that does not activate in the wake, is not directly responsible for induction of sleep. Bonvallet& Block and Bonvallet& Allen R.S. has suspected a negative feedback system between the core of the solitary tract and the reticular formation. [20]

Koella suspected that 5-HT had an anti-wake effect. Koella proposed that nucleus activation of the solitary tract

Figure 1. Stages of sleep during the night in young adults.
by 5-HT acting in the post-rheumatic area had an inhibitory effect on arousal activity in the reticular formation. In cats, 5-HT precursors increase drowsiness, in addition to having a direct effect on promoting sleep, it also works as an ‘antiwake’ agent. [21] It is an antagonist of catecholaminergic involvement in arousal. Paradoxical sleep is in accordance with Jouvet, and paradoxical sleep expression may depend on 5-HT. The antagonism of paradoxical sleep by 5-HT antagonists involves two mechanisms. First, it affects the sequence of events that lead to the synthesis and release of the factors responsible for paradoxical sleep. The second mechanism actively inhibits the system such as the raphe rostralis or locus coeruleus (derived from the catecholaminergic system). [20]

The specific role for 5-HT in triggering paradoxical sleep, to some extent challenged by 5-HTP, 5-HT uptake inhibitors, 5-HT agonists and antagonists, all reduce paradoxical sleep and function within normal limits or work above critical levels for induction and sleep maintenance. Recent studies use specific 5-HT agonists / antagonists who suspect that 5-HT2 receptors are involved in the maintenance of deep slow wave sleep (DSWS). The functional role of the 5-HT1 location in sleep-wake regulation must still be defined because there is no specific 5-HT1 antagonist. The exact location of work for most of the newly synthesized drugs is unknown. It will be interesting to know whether they are working on a hypnogenic structure suspected by Jouvet, Sleep is not localized at the center, but depends on an integrated work system. [20]

Most of the serotonergic innervation of the cerebral cortex, amygdala, forebrain (BFB-Basal Fore Brain), thalamus, preoptic and hypothalamic regions, raphe nucleus, locus coeruleus and pontin reticular formation form from the nucleus raphe dorsalis (dorsal raphe nucleus-DRN). 5-HT receptors can be classified into at least seven classes, designated 5-HT1-7. [21]

Body cells containing 5-HT are present in two main groups at or near the nucleus of the brain stem raphe. The rostral group, which is localized to the pons / mesencephalon, contains the raphe dorsalis (dorsal raphe nucleus-DRN) and median (median raphe nucleus-MRN) nuclei, while the caudal group, located in the medulla, is mainly composed of the raphe magnus nucleus, obscurus and pallidus ( each raphe Magnus-NRM nuclei, nuclei raphe obscurus-NRO and nuclei raphe pallidus-NRP). [22]

The overall rate of raphe 5-HT neuron discharge correlates with the arousal level throughout the sleep-wake cycle, it has been shown that serotonergic neuron activity modulates the motor system which can be separated from the arousal state. Increased activity of 5-HT neurons during REM sleep does not cause awakening, and shows complex motor behavior, but is unresponsive to bright light and mild tactile stimuli. [22]

Arousal may be accompanied by a dramatic decrease in the activity of 5-HT neurons. Injectable microbes from carbachol to the tegmentum during waking reduced the activity of dorsal raphe nucleus (DRN) serotonergic neurons to 97% below the baseline level of pre-drug administration.

Similar results were obtained using mephenesin, a central muscle relaxant, which also suppressed the activity of 5-HT neurons without affecting arousal. A significant reduction in the level of serotonergic neuron discharge can also be seen in physiological conditions. In an orientation reaction, when animals are very attentive, DRN activity and 5-HT neurons are stopped. [22]

1.2 The relationship between 5-HT and Insomnia
In patients with insomnia, those with severe sleep disorders, when compared with low sleep disorders, secrete higher amounts of cortisol, especially at night. It is still a matter of debate if activation of the HPA system observed in insomniacs is secondary to sleep deprivation or, conversely, a marker of increased central corticotropic releasing hormone activity. Increased corticotropin releasing hormone tone, perhaps after repeated exposure to stress, such as in post-traumatic stress disorder (PTSD), may be primarily responsible for sleep disorders. Increased activity of the hypothalamus pituitary axis before bed causes sleep fragmentation and sleep deprivation which has been shown to increase cortisol levels in the afternoon. [23]

It was hypothesized that the process of “S (sleep)” increases when you wake up and exponentially decreases during sleep. This factor is responsible for the intensity of slow wave sleep (which is indirectly estimated by the delta power spectrum of the sleeping EEG). If several 5-HT neuron systems are included in the sleep process (S), then they must be active during wakefulness and inactivity during sleep. Administration of parachlorophenylalanine (PCPA) during sleep deprivation actually suppresses slow wave sleep during rebound while paradoxical sleep (PS) still occurs (Sallanon et al 1983). So it can be postulated that some 5-HT neurons (N. dorsalis raphe) regularly firing in a clock mode such as waking up can participate in the sleep process by measuring the duration and intensity of the wake. The release of 5-HT when awake in a strategic location from the anterior hypothalamus may cause a post-synapse genome cascade that will lead to sleep. Second, is the post-synapse target of 5-HT. It has become clear that following the whole of insomnia only after the lesion is located either in the raphe system or in the preoptic area (McGinty and Sterman 1968) and the possibility that, in some ways, 5-HT and preoptic regions participate in sleep mechanisms. In fact, very small microinjection doses of L-5HTP (0.2-0.5 mg) in the preoptic region can restore long physiological sleep time in cats made completely insomnia by PCPA injections (Denoyer et al 1989). The delay between 5-HTP injections and sleep onset is around 40 minutes. This relatively long delay shows that 5-HT has triggered a cascade of events in the preoptic region and possibly the neighboring suprachiasmatic nucleus. Immunohistochemical use of 5-HT has served to localize the smallest hypnogenic area where microinjection of 5-HTP can restore sleep. In cats that are truly insomnia after cellular lesions from the lateral preoptic region, it is possible to recover sleep for several hours by injecting small doses of muscimol (GABA agonist) at the level of the posterior hypothalamus, a histaminergic rich region containing
neurons that play a decisive role in ‘wake up’. A possible hypothesis is that the GABAergic system originates from the lateral preoptic region and descends to the posterior hypothalamus possibly inhibiting the building neurons located in this area. [24]

Daily rhythms tend to change, and show their own rhythms. After spending life in such conditions for long periods of time, staging various biological rhythms, such as sleep-wake and temperature, has been shown to change. In such conditions, the reciprocal interaction of the phase in the circadian rhythm is disrupted. Most people wake up spontaneously in the morning when body temperature starts to rise from the lowest level, and falls asleep at night when the body’s temperature starts to drop from the highest level. Once reciprocal interactions are disrupted, the phase of the relationship between body temperature and sleep-wake circadian rhythms is interrupted. This condition, known as circadian desynchronization, can produce a variety of physical and mood disorders. [25]

It is likely that the results of circadian desynchronization in unsatisfactory physical, mental and/or emotional conditions may cause a decrease in physical activity. Decreasing physical activity is not enough to activate the serotonergic system, which is difficult to activate without morning light. Negative cycles are as follows (densely filled lines in Figure 2) so that they can postulate on them with delayed wake up times, delayed sleep times, and irregular lifestyles. [25]

1.3 Depression in Elderly
Depression is a psychiatric disorder that occurs most often in the elderly. Elderly is closely related to various changes due to aging processes such as anatomical/physiological changes, various diseases or pathological conditions as a result of aging, and psychosocial influences on organ function. [26] Depression is a psychiatric disorder that occurs most often in elderly patients. Depression in the elderly is a result of the interaction of biological, physical, psychological, and social factors. [27]

1.4 5-HT Deficiency is a Risk Factor of Depression
5-HT is a neurotransmitter that gives more influence on broad brain function. From the raphe core, 5-HT neurons project on almost all parts of the central nervous system, thus making serotonergic tissue one of the most widespread neurochemical systems in the brain. Hippocampus receives projections of 5-HT solid fibers mainly from neurons in the median raphe nucleus and is rich in various types of 5-HT receptors. The broad distribution of central 5-HT nerves for a variety of functions that can be controlled by 5-HT, including food intake, sleep, memory and learning, thermoregulation, sexual behavior, cardiovascular function, mobilization, endocrine regulation, and psychoaffective tone. [28]

![Figure 2. Schematic image of the development of asynchronizaton.](image)

The black lines constitute vicious circles, and enhancement of these circles is involved in entering into the chronic phase of asynchronizaton. Certain unknown factors (broad red line) might act as promoters for progression from the early phase into the chronic phase of asynchronizaton. [25]

![Figure 3. Several functions mediated by 5-HT receptors. Schematic description of type 5-HT receptors and their involvement in physiological conditions, and psychoaffective physiopathology.](image)

Limiting the speed of 5-HT synthesis, is an important factor in the pathophysiology of depression and the response of antidepressant drugs. Evidence of abnormalities in the retrieval system of 5-HT in major depression is like an abnormality in some of the various types of 5-HT receptors. 5-HT1A and 5-HT2 postmenaptic receptors become very important. Cooperative and competitive interactions may be important in the functioning of the 5-HT system and abnormalities in this connection is a possible factor in the pathophysiology of major depression. The function of these post-synapse receptors in depression has been examined with various pharmacological investigations and post-death studies. It is doubtful that every single neurotransmitter is entirely responsible for the pathogenesis or pathophysiology of depression because of the extensive interaction between neurotransmitters at the level of the body cells and terminal areas. Research contrary to what was done by Moreno
et al. (2006) found that 5-HT blood concentrations, platelet 5-HT, and tryptophan did not differ between depressed patients and controls. Post-administration of antidepressants (fluoxetine or citalopram) 5-HT blood concentrations and 5-HT platelets decrease. [29]

1.5 Body Mass Index
De Wit et al’s (2008) study found that BMI and depression are non-linear U-shaped, which was obtained from 43,458 samples. In the category of underweight and obese associated with an increased incidence of depression, while the normoweight and overweight categories were not associated with depression. [30] 5-HT levels were also inversely proportional to body mass index. [31]

1.6 Blood Pressure
The role played by 5-HT in hypertension is still unclear. With the discovery of 5-HT in the blood, it is reasonable that 5-HT would be considered a pathological factor in hypertension, promoting an increase in total peripheral resistance. Arteries isolated from human and experimental hypertensive models show classic hyperreactivity from 5-HT. The work of 5-HT in vivo is far more complex and the up-take of 5-HT appears to be impaired in human platelets such as hypertension that platelets appear “activated”. [32]

The hypothesis suggests that activity is reduced of the 5-HT pathway plays a causal role in the pathophysiology of depression. Part of the evidence for the original 5-HT hypothesis is the finding that tricyclic antidepressants inhibit 5-HT and noradrenaline reuptake and, possibly, 5-HT activity is increased in depressed patients. [33]

1.7 The relationship between 5-HT and Depression
Women experience depression almost twice as much as men. [34] Regulatory abnormalities of the adrenal hypothalamic-pituitary axis and the sympathoadrenomedullary system have been identified in depression and anxiety disorders, and this disorder is clearly precipitated by stress. [35]

Corticotropin releasing hormone triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary corticotropin, triggering the release of adrenal glucocorticoids. Stress response is suppressed by glucocorticoid feedback in the brain and pituitary. Abnormalities of the hypothalamus-pituitary-adrenal axis (HPA), which is manifested by hypercortisolemia and circadian rhythm disturbances of cortisol secretion, are a major phenomenon in depression. The pathophysiology of anxiety and depression disorders involving excessive response to stress is supported by evidence that the corticotropin releasing hormone system, vasopressin and noradrenergic experience hyperaevitation in patients. Steroid sex hormones play a role in increasing women’s vulnerability to anxiety and depression disorders. Glucocorticoids work through several mechanisms, in several locations, to inhibit their own release. At the pituitary level, glucocorticoids show a direct effect on gene transcription for adrenocorticotropic hormone precursors, proopiomelanocorticotropin (POMC) and subsequent storage of adrenocorticotropic hormone peptides in the anterior pituitary. Research has shown that glucocorticoids interact with corticotropin releasing hormone receptors in the anterior pituitary, and acutely inhibit the binding of CRH to their receptors and chronically reduce a number of corticotropin releasing hormone receptors. Direct effects such as glucocorticoids on corticotropin releasing hormone receptors can explain some of the inhibitory work of glucocorticoids in adrenocorticotropic hormone release in vivo. Glucocorticoids work at the site of the brain to modulate the activity of the HPA axis. Preliminary research by McEwen and colleagues (1968) showed a very high affinity uptake of corticosterone in hippocampal mice that were cut in their adrenal glands injected in vivo with radiolabelled steroids. This receptor is not labeled based on dexamethasone [3H], so it is suspected that there are several types of glucocorticoid receptors. Observation of the receptor heterogeneity has been expanded by deKloet and colleagues, who then demonstrated two types of glucocorticoid receptors: mineralocorticoid (MR) receptors which have high affinity especially for glucocorticoid corticosterone, and glucocorticoid receptor (GR), which preferentially binds dexamethasone. Glucocorticoid receptors are widely distributed throughout the brain, while mineralocorticoid receptors exist mainly in the hippocampus. In addition to work in the pituitary and hypothalamus, there is strong evidence from experimental animals, that the hippocampus is the primary feedback location for glucocorticoids in the brain. The serotonergic system plays an important role in both stress and anxiety responsiveness. A fundamental hypothesis of the etiology of anxiety and depression is that this disorder may be due to a relative lack of 5-HT. This is mainly based on animal studies and also about the effectiveness of antidepressants and anxiolytics of serotonin reuptake blockers. Activation of the 5HT3 synapse receptor appears to produce an anxiogenic effect while 5HT1A activation and possibly the 5HT2C receptor post-treatment seems to have a more anxiolytic effect. Both stress and glucocorticoids modulate 5-HT transmission. Acute stress levels of glucocorticoids increase 5-HT exchange and increase the response of hippocampal neurons to 5HT1A receptor stimulation. Glucocorticoid levels persist as they accompany chronic social stress, downregulation of the hippocampal 5HT1A receptor occurs when the 5HT2 receptor in the cerebral cortex is upregulated. Hypofunctional 5-HT may have further consequences for glucocorticoid secretion, because 5-HT seems to be an important regulator of glucocorticoid feedback. [36, 37]

2 METHODS
This research was conducted at PucangGading Nursing House in Semarang in July 2017 and also includes neuroscience, especially in the field of neurogeriatry. This research is an observational analytic study with cross sectional approach. The study began with identification of depression
with insomnia in the elderly. Then the two groups had been studied for the effect of decreased 5-HT serum levels and its characteristics on the risk of insomnia and depression. The target population of this study is the elderly population. While the accessible population of this study is elderly at the research location, PucangGading Nursing Home Semarang, which fulfill the inclusion and exclusion criteria. The method that has been used to select the subject of this research is by using consecutive sampling.

Inclusion Criteria.
1) Age > 60 years old
2) Agree to participate in research
3) Elderly with substance/alcohol dependent
4) Experiencing insomnia
5) Experiencing depression

Exclusion Criteria
1) Not being cooperative
2) Currently being hospitalized
3) Consume sleeping pills for the last 1 week
4) Experiencing dementia
5) Suffered from stroke
6) Suffered from cancer
7) Suffered from headache
8) Major depression with psychotic

3 DISCUSSION
We have collected the data using operational boundaries such as Insomnia Sleep Index Questionnaire to assess insomnia and also by using Geriatric Depression Scale 15 (Yesavage) for depression. 5-HT serum levels was measured with ELISA by sending our sample to the laboratory. The others variables were measured by asking for identity and objective examination in patients.

Table 2. Characteristic distribution

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt; 70</td>
<td>20</td>
<td>50.0</td>
</tr>
<tr>
<td></td>
<td>&gt; 70</td>
<td>14</td>
<td>48.3</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>4</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>36</td>
<td>90.0</td>
</tr>
<tr>
<td>BMI</td>
<td>Underweight</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>31</td>
<td>77.5</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>7</td>
<td>17.5</td>
</tr>
<tr>
<td>5-HT</td>
<td>Low</td>
<td>22</td>
<td>55.8</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>18</td>
<td>45.0</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>12</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>28</td>
<td>70.0</td>
</tr>
<tr>
<td>Depression</td>
<td>No depression</td>
<td>29</td>
<td>72.5</td>
</tr>
<tr>
<td></td>
<td>High possibility of depression</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>No insomnia</td>
<td>13</td>
<td>32.5</td>
</tr>
<tr>
<td></td>
<td>Mild Insomnia</td>
<td>17</td>
<td>42.5</td>
</tr>
<tr>
<td></td>
<td>Moderate Insomnia</td>
<td>9</td>
<td>22.5</td>
</tr>
<tr>
<td></td>
<td>Severe Insomnia</td>
<td>1</td>
<td>2.5</td>
</tr>
</tbody>
</table>

With a population of 40 elderly, 27 (67.5%) study participants experienced insomnia consisting of 17 (42.5%) participants of mild insomnia, 9 (22.5%) participants with moderate insomnia and 1 (2.5%) participants of severe insomnia. The lowest depression score was 0, the highest depression score was 14. The lowest ISI score was 1, the highest score was 24. The lowest MMSE score was 25, the highest MMSE score was 30. With 29 samples without depression, 9 samples with the possibility of depression, and 2 samples of depression. Table 2 Of the total population of 29 (72.5%) participants without depression, 9 (22.5%) participants were most likely to be depressed, and 2 (5.0%) participants experienced depression. The frequency of distribution shows the youngest age is 60 years, the oldest age is 95 years with an average age of 69.5 years. The lowest BMI is 18.36, the highest BMI is 29.00. The lowest serum 5-HT level was 13.50 ng / mL, the highest serum 5-HT level was 94.65 ng / mL.

Table 3. The Relationship of all variable with Insomnia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Insomnia Without</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>14</td>
<td>6</td>
<td>54.5</td>
<td>0.723#0.778 0.193 3.130</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>5</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>4</td>
<td>13.8</td>
<td>0.0 0.560$ - - -</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>25</td>
<td>86.2</td>
<td>100</td>
</tr>
<tr>
<td>BMI</td>
<td>Underweight</td>
<td>3</td>
<td>10.3</td>
<td>4 36.4 0.075$ 0.202 0.036 1.121</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>20</td>
<td>69.0</td>
<td>8 27.3 1.000$ 0.833 0.178</td>
</tr>
<tr>
<td>Depression</td>
<td>Depression</td>
<td>11</td>
<td>37.9</td>
<td>2 18.2 0.286$ 2.750 0.499 15.143</td>
</tr>
<tr>
<td></td>
<td>No depression</td>
<td>18</td>
<td>62.1</td>
<td>9 81.8</td>
</tr>
</tbody>
</table>

Notes :# Chi-Square test
$ Fisher’s Exact test
There was no significant association between increasing age with insomnia. Table 3 Sleep complaints are a common complaint in older people as age increases, which is often diagnosed as insomnia, [38] while other studies have found that insomnia is a comitant disease not merely a disease of aging, which is most commonly found in the elderly. [39]
There was no significant relationship between sex and insomnia Table 3 contrary to the hypothesis proposed by Maes and Meltzer (1995) and Matza (2003), that gender differences related to 5-HT metabolism, with a 5-HT susceptibility and more HPA axis systems a great deal of environmental stress in women can contribute to a higher incidence of depression in women. [40]
There was no significant relationship between depression and insomnia
The lowest depression score was 0, the highest depression score was 14. The lowest ISI score was 1, the highest score was 24. The lowest MMSE score was 25, the highest MMSE score was 30. With 29 samples without depression, 9 samples with the possibility of depression, and 2 samples of depression. Table 2 Of the total population of 29 (72.5%) participants without depression, 9 (22.5%) participants were most likely to be depressed, and 2 (5.0%) participants experienced depression. The frequency of distribution shows the youngest age is 60 years, the oldest age is 95 years with an average age of 69.5 years. The lowest BMI is 18.36, the highest BMI is 29.00. The lowest serum 5-HT level was 13.50 ng / mL, the highest serum 5-HT level was 94.65 ng / mL.
Table 1. Operational definitions of variables

<table>
<thead>
<tr>
<th>No</th>
<th>Variable</th>
<th>Operational Boundaries</th>
<th>Instrument</th>
<th>Cara Pengukuran</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Insomnia</td>
<td>Using the Insomnia Sleep Index questionnaire</td>
<td>Insomnia Sleep Index</td>
<td>Ordinal</td>
</tr>
<tr>
<td>2</td>
<td>5-HT serum level</td>
<td>Measured with ELISA</td>
<td>ELISA</td>
<td>Interval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Measured using the Geriatrics Depression Scale - Short Forme scale</td>
<td>Geriatric Depression Scale 15 (Yesavage)</td>
<td>Ordinal</td>
</tr>
</tbody>
</table>
| 3  | Depresi | 1-4: not depression  
5-9: most likely depression.  
≥ 10: depression | ID Card | Interval |
| 4  | Age of patient | Patient age obtained from patient identity cards. | Weight scale | Ordinal |
| 5  | BMI | Obtained from body weight and height of the patients | Weight scale | Ordinal |
|     |          | Obtained by measurement using cuff | Inova cuff | Ordinal |
| 7  | Sex | Obtained by identity card | Nominal | |

Table 4. The Relationship of all variable with Depression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Depresi</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>8</td>
<td>61.5</td>
<td>12</td>
<td>44.4</td>
</tr>
<tr>
<td>&lt; 70</td>
<td>5</td>
<td>38.5</td>
<td>15</td>
<td>55.6</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>11.1</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>88.9</td>
<td>12</td>
<td>92.3</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>1</td>
<td>7.7</td>
<td>6</td>
<td>22.2</td>
</tr>
<tr>
<td>Under/Normoweight</td>
<td>12</td>
<td>92.3</td>
<td>21</td>
<td>77.8</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>23.1</td>
<td>9</td>
<td>33.3</td>
</tr>
<tr>
<td>Normal</td>
<td>10</td>
<td>76.9</td>
<td>18</td>
<td>66.7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11</td>
<td>84.6</td>
<td>18</td>
<td>66.7</td>
</tr>
<tr>
<td>Without insomnia</td>
<td>2</td>
<td>15.4</td>
<td>9</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Table 5. The relationship between 5-HT serum level with age

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
<th>r</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.640</td>
<td>0.076</td>
<td>40</td>
</tr>
<tr>
<td>5-HT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The results are obtained:  
0-7 = not clinically significant insomnia  
8-14 = mild insomnia  
15-21 = insomnia clinically (moderate)  
22-28 = insomnia clinically (severe)

Research conducted by Buysse DJ, Tu XM, Cherry CR (1999), Jindal (2009), and Paudel, Taylor (2008) stated that most patients with depression reported insomnia, some (16-20%) showed hypersonnia. [43, 44] Sleep disorders were important predictors of outcome depression, those with severe sleep disorders tended to respond to psychosocial interventions [42], and had a greater likelihood of relapse [45, 46], and suicide [47]. Sleep disturbance remains an important prognostic in all phases of depression, insomnia is a risk factor for subsequent depression in young adults [48, 49] and is an aggravating factor of depression at the end of life. [50] Baglioni C, Riemann D. (2012) has an odds ratio = 2.1 (CI = 1.9-2.4), shows that people with insomnia have a 2-fold risk of becoming depressed, compared with people without difficulty sleeping. [51] There was no significant relationship between BMI and insomnia Table 3 which was contrary to research conducted by Godin et al who conducted research on the elderly (age ≥ 65 years) followed for 10 years (Dijon part of The Three Cities Study, 1999-2010), showing subjects with BMI high risk of developing depression compared with subjects with a normal BMI. There was no significant relationship between blood pressure and insomnia. [52]

From the results of the analysis, it was found that the cut-off point of serum 5-HT levels against insomnia was = 35,605 ng / mL. Figure 3 From the results of the analysis, it
was found that the cut-off point of serum 5-HT levels to depression was \(22.485 \text{ ng} / \text{mL}\). From the bivariate analysis, there was a significant association between 5-HT levels \(\geq 35.6 \text{ ng} / \text{mL}\) for protection at 21.6 times. Table 6 for the occurrence of insomnia, compared with 5-HT levels \(<35.6 \text{ ng} / \text{mL}\) (95% CI, 3.535 \(\pm\) 131.979, \(p = 0.000\)), and found a significant relationship between 5-HT levels \(\geq 22.485 \text{ ng} / \text{mL}\) to protect as much as 7.875 times. Table 7 for depression, compared with 5-HT levels \(<35.6 \text{ ng} / \text{mL}\) (95% CI, 1.781 up to 34.828, \(p = 0.006\)). The data above shows that 5-HT levels really affect protection against insomnia and depression.

1. Bivariate analysis between 5-HT serum level with insomnia
   1.1. 5-HT serum level as an indicator of insomnia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without insomnia</th>
<th>p OR</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>&lt; 35.6</td>
<td>24</td>
<td>82.8</td>
<td>2 18.2</td>
</tr>
<tr>
<td>35.6</td>
<td>5</td>
<td>17.2</td>
<td>9 81.8</td>
<td></td>
</tr>
</tbody>
</table>

Note: $Fisher’s Exact test

2. Bivariate analysis of 5-HT serum level with depression
   2.1. 5-HT serum level as an indicator of depression

Multivariate analysis between 5-HT serum level with insomnia

\[\text{Figure 3. ROC curve. Area below curve ROC } 0.846 (95\% \text{ CI } 0.708 \pm 0.958 \text{, } p < 0.001)\]
From multivariate logistic regression Table 9 analysis obtained after 4 steps, age variables and 5-HT which affected depression with p and OR values for ages p = 0.112, OR = 0.238 and serotonin p = 0.005, OR = 0.081. Logistic regression equation: Y = 1.327 - 1.434 (Age) - 2.519 (5-HT), and after going through 5 steps Table 8, variable 5-HT which affected insomnia with p = 0.001 and OR = 0.046. Logistic Regression Equation: Y = 2.485 - 3.073 (5-HT).

### 4 CONCLUSION

Depressive symptoms have association with sleep disturbances. In outpatients insomnia symptoms are very common, undertreated, and indicative of a more severe depression. Complaints of insomnia are common in the elderly general population, with more than 67.5% of men and women in our study reporting. As insomnia is frequently determined by a cut-off point on a scale, this could explain why the prevalence rates are often reported to be higher in women. Sleep disorders were important predictors of outcome depression. Depressive symptoms have an association with sleep disturbances; future studies should address temporality of depression and sleep disturbances.

### 5 DECLARATIONS

### 6 AUTHORS' CONTRIBUTIONS

Conceived the study and wrote the manuscript: Retnaningsih Conducted and analyzed the data: Damson, Herlambang Y
7 AVAILABILITY OF DATA AND MATERIALS
Data in this study were obtained by observational analytic study with cross sectional approach... All primary data used to construct the bivariate data, multivariate data, and summary tables are available by contacting the authors of this study.

8 FINANCIAL SUPPORT AND SPONSORSHIP
None.

9 CONFLICTS OF INTEREST
The authors declare no conflict of interest.

10 ETHICAL APPROVAL AND CONSENT TO PARTICIPATE
Not applicable.

11 CONSENT FOR PUBLICATION
Not applicable.

12 COPYRIGHT
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