

Syndrome Of Inappropriate Antidiuretic Hormone (Siadh) In Lung Cancer

Novita Andayani¹, Cut Asmaul Husna^{2,3*}

¹Department of Pulmonology, Faculty of Medicine, University of Syiah Kuala, 23374, Banda Aceh, Indonesia

²Resident of Pulmonology, Faculty of Medicine, University of Syiah Kuala, 23374, Banda Aceh, Indonesia

³Department of Microbiology, Faculty of Medicine, University of Malikussaleh, 24351, Lhokseumawe, Indonesia

*Corresponding Author : cutasmaulhusnadr@gmail.com

Abstrak

Kanker paru merupakan salah satu kanker paling mematikan pada laki-laki maupun perempuan. Kanker paru secara umum terbagi 2 yaitu small cell lung carcinoma dan non small cell lung carcinoma. Small cell lung carcinoma (SCLC) mewakili sekitar 15% dari semua kanker paru. Sindrom paraneoplastik terjadi pada 10% kasus kanker paru dan menjadi sekelompok kelainan yang berkaitan dengan sekresi polipeptida fungsional atau hormon dari sel tumor. Syndrome of inappropriate antidiuretic hormone merupakan salah satu sindrom paraneoplastik yang memiliki keterkaitan erat dengan SCLC dan dikaitkan dengan survival yang lebih buruk. Kunci dalam memahami SIADH adalah hiponatremia yang terjadi pada sindrom ini tidak disebabkan oleh kekurangan Na⁺, melainkan karena kelebihan cairan. Syndrome of inappropriate antidiuretic hormone yang terjadi merupakan kejadian sekunder yang disebabkan oleh pelepasan antidiuretic hormone akibat lisis tumor maupun karena tumor mengeluarkan ADH ektopik. Hiponatremia pada SCLC merupakan faktor prognostik negatif pada pasien rawat inap dan pasien dengan penyakit stadium lanjut

Kata Kunci : *kanker paru; small-cell lung carcinoma (sclc); syndrome of inappropriate antidiuretic hormone; hiponatremi; pasien*

Abstract

Lung cancer is one of the deadliest cancers in both men and women. Lung cancer is generally divided into 2, categories: small-cell lung carcinoma and non-small-cell lung carcinoma. Small cell lung carcinoma (SCLC) represents approximately 15% of all lung cancers. Paraneoplastic syndromes occur in 10% of lung cancer cases and constitute a group of disorders associated with the secretion of functional polypeptides or hormones from tumor cells. The syndrome of inappropriate antidiuretic hormone is a paraneoplastic syndrome that is closely related to SCLC and is associated with worse survival. The key to understanding SIADH is that the hyponatremia that occurs in this syndrome is not caused by Na⁺ deficiency but rather by excess fluid. The syndrome of inappropriate antidiuretic hormone that occurs is a secondary event caused by the release of antidiuretic hormone due to tumor lysis or because the tumor releases ectopic ADH. Hyponatremia in SCLC is a negative prognostic factor in hospitalized patients and patients with advanced disease

Keywords: *lung cancer; small-cell lung carcinoma (sclc); syndrome of inappropriate antidiuretic hormone; hyponatremia; patient*

Introduction

Lung cancer is one of the deadliest cancers in both men and women. The death rate exceeds that of the three most common types of cancer in the world combined (colon, breast, and pancreatic cancer). According to *Global Cancer Statistics 2020*, Lung cancer cases in men are 14.3% of the total cancer with mortality is 21.5% per year, while in women, it is the 2nd most common cancer after breast cancer with a percentage of 11.4% but is the main cause of death (18%) of total cancer deaths (1,2).

Lung cancer is generally divided into two types, namely small-cell *lung carcinoma* (SCLC) and non-small-cell *lung carcinoma* (NSCLC), accounting for 15% and 85% of all lung cancers, respectively. Neuroendocrine tumors account for approximately 20% of lung cancers and the majority (up to 15%) are of the SCLC type. *Small cell lung carcinoma* includes clinicopathologically distinct cancers characterized by neuroendocrine differentiation, early metastatic spread, and an early response to cytotoxic therapy (3,4).

Paraneoplastic syndromes are a group of clinical disorders associated with malignant disease. Paraneoplastic syndromes are most commonly reported in lung cancer, reaching 10% with the most common histology type *small cell lung cancer (SCLC)*. One of these syndromes is paraneoplastic endocrinology which generally develops due to the synthesis of hormones or precursors. Excessive peptide hormones become active products in tissues that cause endocrine syndrome. One of the endocrine paraneoplastic syndromes that can appear in lung cancer is the syndrome of *inappropriate antidiuretic hormone* (YES) (5). SCLC lung cancer has a neuroendocrine origin, and paraneoplastic syndromes are more common in this type of cancer. Paraneoplastic syndromes can be found in 7-15% of all patients with lung cancer. Systemic symptoms and syndromic paraneoplastic findings develop in 50% of patients with SCLC, which develops secondary to lung cancer and increases disease severity (6). *Non-small-cell lung carcinoma* (NSCLC) much less commonly produces polypeptide hormones capable of producing paraneoplastic syndromes. Cases of SIADH associated with NSCLC malignancies and benignancies, including squamous cell carcinoma (SCC), have been reported since the 1950s, but the mechanism of occurrence has not been clarified (17).

The condition SIADH is often associated with many causes, including incidental treatment, concomitant diseases, and side effects of antineoplastic treatment or the disease

itself. Although not often life-threatening, it is usually associated with prolonged hospitalization, delay in scheduled chemotherapy, worsening of a status performance score, and patient quality of life, and can also negatively impact treatment response and survival. Some data in SCLC suggest that hyponatremia is often associated with the *syndrome of inappropriate antidiuretic hormone* (7).

Small Cell Lung Carcinoma

Small-cell lung carcinoma is a malignant epithelial tumor consisting of small cells with little cytoplasm, indistinct cell borders, fine granular nuclear chromatin, and absent or inconspicuous nucleoli. The cells are round, oval, or spindle-shaped with a prominent nuclear mold. The number of mitoses is high. Almost all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and thyroid *transcription factor-1* (TTF-1) (8). *Small cell lung carcinoma* represents approximately 15% of all lung cancers and is characterized by a very high proliferation rate, a strong predilection for early metastasis, and a poor prognosis. SCLC genome profiling revealed extensive chromosomal rearrangements and a high mutational burden, including functional inactivation of the tumor suppressor genes TP53 and RB1 (9).

The main cause of lung cancer, including SCLC, is tobacco smoke (cigarettes). Risk increased with smoking intensity and duration, with men who currently smoked >30 cigarettes daily having an OR of 111.3 for developing SCLC. While more than 95% of SCLC cases occur in smokers or former smokers, other etiologic agents, including bischloromethyl ester, nickel, vinyl chloride, asbestos, cadmium, radon, arsenic, and radiation, have been implicated as contributors thought to be influential in the development of this disease. Lung cancer, both NSCLC and SCLC, will cause various manifestations and complications, including paraneoplastic syndrome (10).

The staging classification used for SCLC, limited *stage* and extensive *stage*, has been revised by the IASLC. According to VALG, the limited stage consists of a disease limited to one hemithorax, with the involvement of ipsilateral and supraclavicular regional lymph nodes, the primary tumor and regional nodes can be adequately treated and completely covered with radiation. Patients with metastases outside the hemithorax were found in 60% of cases, classified as extensive-stage disease. Without treatment, the median survival time is approximately 12 to 17 weeks for patients with LSCLC (*limited*

stage small cell lung cancer), and 5 to 6 weeks for patients with ESCLC (*extensive stage small cell lung cancer*) (11).

Syndrome of Inappropriate Antidiuretic Hormone Secretion (YES)

Syndrome of inappropriate antidiuretic hormone (SIADH) is a condition involving sustained secretion or performance of arginine *vasopressin* (AVP), which occurs in conditions of normal or increased plasma volume. Decreased water secretion and water retention cause hyponatremia (serum $\text{Na}^+ < 135 \text{ mmol/L}$) with concomitant hypo-osmolality (serum osmolality $< 280 \text{ mOsm/kg}$) whereas increased urine osmolality is characteristic of SIADH (12,13). *Syndrome of inappropriate antidiuretic hormone (SIADH)* is caused by free water retention secondary to dysregulation of antidiuretic hormone (ADH) release. Characterized by hyponatremia, low serum osmolality, high urine osmolality, and sustained urinary sodium excretion in the absence of other causes of hyponatremia (19). SIADH manifests as euvolemic hypoosmolar hyponatremia characterized by low serum osmolality and high urine osmolality in the absence of diuretic treatment, adrenal insufficiency, heart failure, cirrhosis, or hypothyroidism (14).

Lung cancer has the potential to synthesize and secrete peptides or hormones, leading to various endocrine syndromes. There are several criteria for diagnosing paraneoplastic endocrine syndrome. In particular, the presence of hormones in tumor tissue is not always necessary for clinical diagnosis. Several endocrine paraneoplastic syndromes have been reported, one of which is the *syndrome of inappropriate antidiuretic hormone*. Paraneoplastic endocrinological syndromes generally develop due to the increased production of hormones or hormone precursors by malignant cells (5).

Syndrome of inappropriate antidiuretic hormone is generally caused by an underlying disease, or hereditary, known as nephrogenic SIADH, originating from increased function of the vasopressin 2 (V2) receptor in the kidney. Many conditions can cause SIADH, including central nervous system (CNS) disorders that can increase the release of ADH from the pituitary gland, leading to SIADH; malignancies such as SCLC are the most common tumors that cause ectopic ADH production; drugs related to SIADH work by increasing the release or effect of ADH; surgery is associated with hypersecretion of ADH; lung diseases, especially pneumonia (viral, bacterial, and tuberculosis);

hormone deficiencies: hypopituitarism and hypothyroidism; infections (*Human Immunodeficiency Virus*) (15).

Antidiuretic hormone levels are generally increased in lung cancer patients with SIADH. In addition, patients may also have increased levels of atrial natriuretic peptide. Symptoms of SIADH rarely manifest when plasma sodium levels are higher than 125 mEq/L. Plasma sodium levels below 125 mEq/L can cause symptoms such as weakness, fatigue, nausea, headache, lethargy, and confusion, while levels below 120 mEq/L can cause seizures and coma. ⁶Based on the definition of Bartter and Schwartz, the diagnosis of SIADH can be made by finding serum Na < 134 mEq/l, plasma osmolality < 275 mOsm/kg, urine osmolality > 500 mOsm/kg, high urine sodium concentration (> 20 mEq/l), absence of clinical signs of volume reduction, normal adrenal function, and normal thyroid function. The presence of SIADH is a marker of poor prognosis (5).

Mechanism SIADH pada *Small Cell Lung Carcinoma*

The pathogenesis of paraneoplastic syndromes shows some evidence of mechanisms in the form of the production of special substances by tumor cells (in the form of hormones, growth factors, vasoactive peptides, cytokines, enzymes, or other signal molecules) that specifically lead to the development of paraneoplastic syndromes, an abnormal immune response of the host organ against neo-antigens produced by tumors or other tumor products (6). Endocrinological paraneoplastic syndromes generally develop due to excessive synthesis of hormones or hormone precursors with low bioactivity or the conversion of product precursors in tumor tissue to more effective ones. *Syndrome of inappropriate antidiuretic hormone* clinical diagnosis has been reported to occur in 7% -16% of SCLC cases. Approximately 70% of paraneoplastic SIADH cases are related to SCLC. The SCLC stage was not associated with the incidence of SIADH. SCLC patients with hyponatremia have shorter survival times than patients with normal serum sodium levels (5).

Serum ADH levels are elevated in the majority of SIADH cases associated with SCLC, and basic studies suggest that severe hyponatremia may predict a worse prognosis. Ectopic ADH secretion by malignant cells is the most common mechanism by which SIADH can develop. Research on SCLC states that both ADH and atrial natriuretic

peptide (ANP) are triggers of SIADH. The quantity of ADH is closely related to the development of hyponatremia (19).

SIADH cases are also associated with NSCLC and other malignancies, including squamous *cell carcinoma* (SCC), but the mechanism cannot be explained in detail. Research shows that patients with biopsy-proven NSCLC may develop hyponatremia secondary to SIADH. Case reports demonstrate SIADH following the initiation of radiation therapy. The explanation is said to be secondary to ADH release due to tumor lysis (19). Tumor lysis syndrome (TLS) is a potentially life-threatening complication of chemotherapy, and given the high mortality rate associated with this syndrome, rapid recognition of this syndrome is essential for its treatment. Risk factors for the development of TLS include large disease volume, rapid cancer growth, chemosensitivity of the malignancy, azotemia, high lactate dehydrogenase (LDH) levels, hyperuricemia, and/or hyperphosphatemia (28)

The key to understanding the pathophysiology, signs, symptoms, and treatment of SIADH is that the hyponatremia that occurs in this syndrome is not caused by a lack of Na⁺, but rather by excess fluid. *Syndrome of inappropriate antidiuretic hormone* consists of hyponatremia, inappropriately increased urine osmolality (>100 mOsm/kg), and decreased serum osmolality in euvolemic patients. *Syndrome of inappropriate antidiuretic hormone secretion* should be diagnosed if these findings occur in the setting of normal cardiac, renal, adrenal, hepatic, and thyroid function; in the absence of diuretic therapy; and in the absence of other factors known to stimulate ADH secretion, such as hypotension, severe pain, nausea, and stress (15,16)

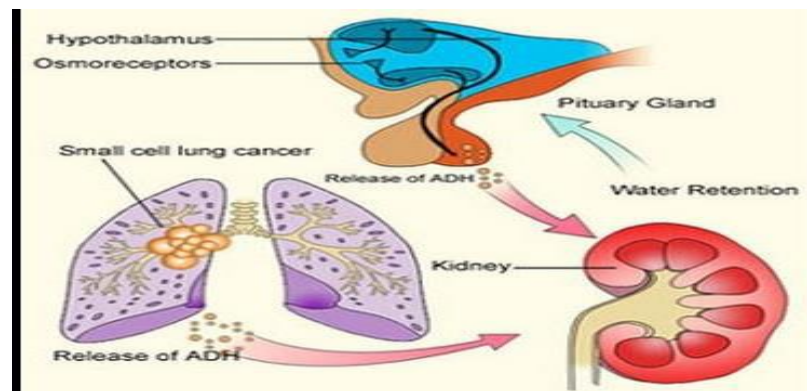


Figure 1. Pathophysiology of SIADH

Serum ADH levels are elevated in most cases of SIADH, and more severe hyponatremia may predict a worse prognosis. Ectopic ADH secretion by malignant cells is the most common mechanism for the development of SIADH. All germ *cells* The SCLC studied produced ANP and/or ADH mRNA and peptides, while none of the 10 *cell lines of the NSCLC* produced ADH mRNA or peptides, and only two produced ANP mRNA. Selective expression of prepro-AVP-NP II, a precursor of ADH, has also been demonstrated in SCLC, confirming the accepted mechanism of SIADH in this type of malignancy (17).

Various chemotherapy agents can cause SIADH. The mechanism of this effect may be triggering abnormal ADH release or the drug making existing ADH work in a more potent manner than normal. Cisplatin may induce unknown factors that act on the hypothalamic-pituitary axis to influence ADH release (18). It is stated that SIADH can occur as a secondary event caused by the release of ADH due to tumor lysis. This phenomenon was previously only seen in patients with SCLC (19).

Hyponatremia in Lung Cancer

Changes in sodium levels in the body are often caused by clinical conditions involving excess or deficiency of fluid volume. Hyponatremia is defined as a serum sodium concentration <135 mEq/L, while hypernatremia is >150 mEq./L. Hyponatremia occurs due to excess water retention in the ECF, loss of sodium from the ECF, or a combination of both. Hyponatremia is a condition that represents relative water excess in conjunction with an impaired ability of the kidneys to excrete electrolyte-free water. Hyponatremia can occur along with hypovolemia, euvolemia, or hypervolemia. A decrease in serum sodium causes a shift of water from the ECF to the ICF, causing cellular swelling or edema. Seizures and coma result from a decrease in plasma Na^+ to <110 mEq/L. The most feared complication in patients with hyponatremia is acute cerebral edema (20,21)

Hyponatremia is defined as a serum sodium (Na^+) concentration below 135 mmol/l,1 with varying degrees of severity (mild 130–134 mEq/l, moderate 125–129 mEq/l and severe <125 mEq/l. Classification of hyponatremia depends on the level of osmolarity serum: isotonic (275–295 mOsm/kg), hypertonic (>295 mOsm/kg), and hypotonic (<275 mOsm/kg).7 According to its onset, hyponatremia is classified as acute

hyponatremia (if it develops within 48 hours) and chronic hyponatremia (if it develops >48 hours), a time period that allows the brain to initiate adaptive mechanisms. Patients with acute hyponatremia show different changes that can vary from non-specific symptoms such as headache, nausea, vomiting, and muscle cramps to life-threatening conditions such as bradycardia, hypertension, impaired body temperature regulation, cerebral herniation, seizures and coma. Chronic hyponatremia usually presents as an asymptomatic condition or, at worst, results in weakness, nausea, vomiting and loss of appetite (7).

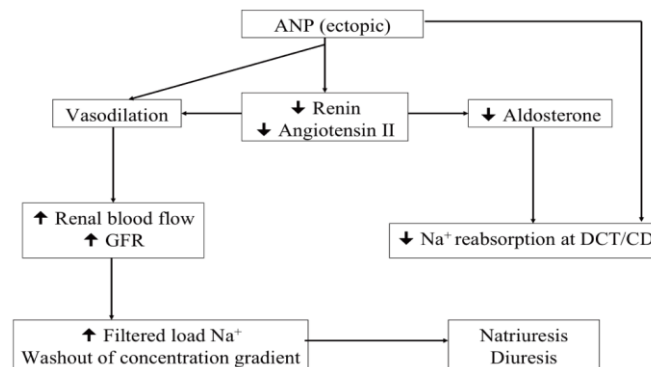


Figure 2. Renal hemodynamic function of ANP causes increased sodium excretion²³

Hyponatremia and hyperosmolality can cause acute edema of brain cells. Rigid calvaries prevent brain volume expansion beyond a certain point, after which brain cells must adapt to persistent hypo-osmolality. However, a rapid increase in brain water content of more than 5-10% can cause severe brain edema and herniation and be fatal.²⁵ The severity of the clinical presentation depends on the severity of hyponatremia as well as the rate of decline in serum sodium concentration (7).

Palliative antineoplastic drugs and cancer therapies are also known to cause hyponatremia, and many are directly linked to SIADH. Other underlying conditions, such as pain and nausea, or routine hospitalization can also cause hyponatremia, which contributes to the complexity of the disease. The incidence of hyponatremia among patients with lung cancer was higher than previously reported, which was 76% of lung cancer patients. A total of 46% of SCLC patients experienced episodes of moderate/severe hyponatremia compared with 27.4% of NSCLC (22).

Governance

Treatment of hyponatremia generally depends on the presenting symptoms, severity, onset, and the patient's extracellular volume status. Symptoms that arise require immediate attention to prevent disease complications. The development of chronic hyponatremia also makes the brain susceptible to osmotic demyelination if serum sodium is corrected too quickly. Correction of severe symptomatic hyponatremia in patients with SIADH or other euvolemic states or hypervolemia can be achieved by administering hypertonic saline (3%) by infusion or bolus (27). Restriction of water intake, correcting the underlying cause, administration of intravenous diuretics and concentrated saline solutions along with demeclocycline have been described as treatment options (18).

Patients with euvolemic hypo-osmolality due to SIADH do not respond to isotonic saline, and this will sometimes result in worsening hyponatremia. In chronic hyponatremia (48 hours) secondary to SIADH, fluid restriction is considered first-line treatment in patients without severe symptoms or no suspected hypovolemia. A fluid restriction of 500 to 1000 ml/day is recommended, according to the severity of hyponatremia. Pharmacological therapy generally consists of vaptan (a specific vasopressin 2 receptor antagonist) or demeclocycline. Other treatment options include loop diuretics or urea combinations. *Demeclocycline* is a tetracycline derivative antibiotic with marketing authorization in the UK for the treatment of chronic hyponatremia associated with SIADH secondary to malignant disease, in cases where fluid restriction is ineffective and in patients who do not have cirrhosis. Although how it works is not yet clear, it is thought that demeclocycline induces nephrogenic diabetes insipidus in approximately 60% of patients with hyponatremia secondary to SIADH, resulting in decreased urine concentration and rebalancing of body sodium concentration. The onset of action is unpredictable; it usually occurs after 2-5 days but can last longer (29).

Vasopressin receptor antagonists (VRA) is a class of drugs known to be efficacious and safe for the treatment of hyponatremia. In recent years, VRA, especially tolvaptan, has played an important role compared with conventional therapy (water restriction or 3% hypertonic saline solution) for the treatment of hyponatremia. Oral tolvaptan is indicated for euvolemic hyponatremia caused by a syndrome of inappropriate antidiuretic hormone secretion (SIADH) (26).

Prognostic

People with severe hyponatremia experience higher mortality, especially in the elderly. Asymptomatic patients have a lower risk for neurologic sequelae but can still develop osmotic demyelination if corrected quickly. Restriction of water intake, correcting the underlying cause, and administration of intravenous diuretics and concentrated saline solutions along with demeclocycline have been described as the treatment of choice (14). Hyponatremia is a prognostic and predictive factor in cancer patients and has a negative influence on performance status and hospitalization. Another study showed a significant difference between the length of hospital stay in cancer patients with hyponatremia and patients with eunatremia (24).

Another study showed a correlation between the degree of hyponatremia and the risk of in-hospital death by considering 130 mEq/l as the cutoff, patients with moderate to severe hyponatremia had a 4.28 times higher risk of death than patients with normal to mild hyponatremia. Hyponatremia affects performance status in different disease settings, including palliative care. Most of the available data concerns chest tumors, especially SCLC (7).

Conclusion

Syndrome of inappropriate antidiuretic hormone (SIADH) is a condition involving sustained secretion or performance of AVP that occurs in conditions of normal or increased plasma volume. Symptoms in SIADH patients reflect the brain's attempt to prevent a decrease in serum sodium concentration by moving excessive amounts of water from the extracellular to the intracellular space, following an osmotic gradient. *Syndrome of inappropriate antidiuretic hormone* is a paraneoplastic syndrome that is closely related to SCLC. People with severe hyponatremia experience higher mortality, especially in the elderly. Serum ADH levels are elevated in most cases of SIADH and more severe hyponatremia may predict a worse prognosis, reducing *performance score* and increasing the length of treatment.

Bibliography

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics. *CA Cancer J Clin*. 2014;64(1):9–29.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries *CA Cancer J Clin*. 2021;0(0):1–41.
3. Kalemkerian GP. Staging and imaging of small cell lung cancer. *Cancer Imaging* (2011) 11, International Cancer Imaging Society
4. Govindan R, Page N, Morgensztern D, et al. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29.
5. Kanaji N, Watanabe N, et al. Paraneoplastic syndromes associated with lung cancer. *WJCO 5th Anniv Special Issues* (1): Lung cancer. 2014
6. Tas D. Paraneoplastic Syndromes in Lung Cancer. *Lung Cancer - Strategi DiagnosisTreat*. 2018. <http://dx.doi.org/10.5772/intechopen.79127>
7. Fiordoliva I, Meletani T, Baleani MG, et al. Managing hyponatremia in lung cancer: latest evidence and clinical implications. *Ther Adv Med Oncol*. 2017;1–9.
8. Kalemkerian GP, Akerley W, Bogner P, et al. Small Cell Lung Cancer. *J Natl Compr Canc Netw*. 2013;11(1):78–98.
9. Rudin MC, Brambilla E, et al. Small-cell lung cancer. *Nature Reviews Disease Primers* vol. 7, no: 3. 2021
10. Fishman JA, Grippi MA, Kotloff RM, et al. *Fishman's Pulmonary Disease and Disorders Fifth Edition*. New York: Elsevier Saunder; 2015.
11. Patterson GA, Copper JD, et al. *Pearson's Thoracic & Esophageal Surgery*, 3rd edition. Vol. 2 Esophageal. 2008. Elsevier
12. Cuesta M, Thomson CJ. The syndrome of inappropriate antidiuresis (SIAD). *Best Pr Res Clin Endocrinol Metab*. 2016;30(2):175–87.
13. Kanaji N. Prognosis of Patients with Paraneoplastic Syndromes Associated 22 with Lung Cancer. *Austin J Pulm Respir Med*. 2014;1(2):3–5.
14. Kotoulas C, Panagiotou I, Tsipas P, et al. Inappropriate antidiuretic hormone secretion due to squamous cell lung cancer. *Asian Cardiovasc Thorac Ann*. 2014;0(0):1–3.
15. Yasir M, Mechanic OJ. Syndrome of Inappropriate Antidiuretic Hormone Secretion. *StatPearls Publ* [Internet]. 2020; Available from: <https://www.ncbi.nlm.nih.gov/books/NBK507777/22>.
16. Mentrasti G, Scortichini L, Torniai M, et al. Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH): Optimal Management. *Ther Clin Risk Manag*. 2020;16:663–72.
17. McDonald P, Lane C, Rojas GE, et al. SIADH in non-small cell lung carcinoma: a case report. *Ecancermedicalscience*. 2012;6:279
18. Kotoulas C, Panagiotou I, Tsipas P, et al. Inappropriate antidiuretic hormone secretion due to squamous cell lung cancer. *Asian Cardiovasc Thorac Ann*. 2014;0(0):1–3.
19. Iyer P, Ibrahim M, Siddiqui W, et al. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as an initial presenting sign of non-small cell lung cancer. report and literature review. *Respir Med Case Rep*. 2017;22:164–7.
20. Sherwood L. *Human Physiology: from cells to systems*. 6th ed. Jakarta: EGC; 2011.
21. Guyton AC; Hall JE. *Textbook of medical physiology*. Jakarta: EGC; 2016.

22. Castillo JJ, Glezerman IG, Boklage SH, et al. The occurrence of hyponatremia and its importance as a prognostic factor in a cross-section of cancer patients. *BMC Cancer*.2016;31:28–32.
23. Mansoor SE, Kagen DI, Kansagara D. Case Report: Hyponatremia of malignancy – An alternative mechanism? Syndrome of inappropriate atrial natriuretic peptide (SIANP). *F1000 Res*. 2014;3:194
24. Fiordoliva I, Meletani T, Baleani MG, et al. Managing hyponatremia in lung cancer:latest evidence and clinical implications. *Ther Adv Med Oncol*. 2017;1–9.
25. Elhassan EA, Schrier RW. Hyponatremia: diagnosis, complications, and management including V2 receptor antagonists. *Curr Opin Nephrol Hypertens*. 2011;20(2):161–8.
26. Vecchis RD, Cantatrione C, Mazzei D, Baldi C, Vasopressin Receptor Antagonists for the Correction of Hyponatremia in Chronic Heart Failure: An Underutilized Therapeutic Option in Current Clinical Practice. *J. Clin. Med*. 2016, 5, 86;doi:10.3390/jcm5100086 www.mdpi.com/journal/jcm
27. Castillo Jj, Vincent Ma, Justice E. Diagnosis and Management of Hyponatremia in Cancer Patients. *The Oncologist* 2012;17:756–765 www.TheOncologist.com
28. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127(1):3–11.
29. Miell J, Dhanjal P, Jamookeeah C. Evidence for the use of demeclocycline in the treatment of hyponatremia secondary to SIADH: a systematic review. *International Journal of Clinical Practice Published by John Wiley & Sons Ltd. Int J Clin Pract*, December 2015, 69, 12, 1396–1417