

# Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH): Optimal Management

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**Abstract:** Hyponatremia, defined as serum sodium concentration  $<135$  mEq/l, is the most common electrolyte balance disorder in clinical practice. Many causes are listed, but syndrome of inappropriate antidiuretic hormone secretion (SIADH) is certainly the most relevant, mainly in oncological and hospitalized patients. In this review, the pathophysiological and clinical aspects are described in detail. Patients' extensive medical history and structured physical and biochemical tests are considered the milestones marking the way of the SIADH management as to provide early detection and proper correction. We focused our attention on the poor prognostic role and negative effect on patient's quality of life of SIADH-induced hyponatremia in both malignant and non-malignant settings, stressing how optimal management of this electrolyte imbalance can result in improved outcomes and lower health costs.

**Keywords:** SIADH, hyponatremia, prognosis, neoplasms, lung cancer

## Introduction

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a condition characterized by hypotonic and euvoletic hyponatremia along with urinary hyperosmolality, resulting from antidiuretic hormone (ADH) release in the absence of adequate stimuli.

This term was first used in 1957, when Schwartz et al described hyponatremia caused by kidneys' inability to save sodium in two patients affected by lung tumor.<sup>1</sup>

The interest and knowledge on this clinical condition have increased considerably in recent years, so much so as to justify a change in its name, from SIADH to SIAD (syndrome of inappropriate antidiuresis), according to the fact that not all affected patients have increasing circulating ADH level, resulting from increased release by the pituitary gland or ectopic production. Abnormal ADH activity in renal receptors or constitutive activation of the V2 vasopressin receptor (V2R) has been identified as causes of inappropriate antidiuresis with normal or not measurable hormone levels.<sup>2</sup>

Hydrosaline balance is maintained under physiological conditions through a fine regulatory mechanism that combines hypothalamus, neurohypophysis, kidneys and hormones; among these, ADH is the most important. This hormone, also known as arginine vasopressin (AVP), is synthesized in hypothalamic supraoptic and paraventricular nuclei and then stored in hypophysis through axonal transport. From here it can be released as a consequence of osmotic and non-osmotic stimuli.<sup>3</sup>

Among the former, the most important is the effective osmotic pressure of plasma: when it reaches the threshold of 284 mOsm/kg or higher, the ADH level starts to rise. In the latter group, hypovolemia as well as nausea, vomiting, stress, drugs, hypoglycemia,

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post-surgery pain and others nociceptive stimuli are described. To date, three AVP receptors are known: V1a, V1b (V3) and V2. V1 receptors are responsible for the vascular effects of ADH, in particular their binding can lead to hypertensive effects causing smooth muscle cell contraction; V3 receptors are placed in pituitary gland and when activated, adrenocorticotropic hormone levels began to rise. Finally, V2Rs are found in endothelial cells and on the principal cells of renal collecting ducts membrane. It is due to V2Rs effects that ADH derived its name.<sup>4</sup> The final effects of this binding are the increased synthesis and exhibition of aquaporin-2 (AQP-2) water channels on the membrane of the collecting duct; consequently, the water passes passively into the hypertonic renal interstitium, eventually leading to urine concentration, water reabsorption and reducing plasma osmolality.

Therefore, the pathophysiological basis of SIADH (or SIAD) consists in an increase in the concentration of body water due to an augmented water intake, that overcomes renal diluting urine capability, and to ADH dysregulation too. However, in some cases, the down-regulated V2R binding capacity together with a reduction of kidney AQP-2 expression, realize the so-called phenomenon “escape from antidiuresis” as an attempt to normalize and eventually increase natremia, urine volume and renal water loss.<sup>5,6</sup>

Many causes of SIADH are listed (Table 1).

SIADH is the most important cause of hyponatremia in oncological and hospitalized patients.<sup>7,8</sup>

It is commonly found in patients with lung cancer, in particular small-cell lung cancer (SCLC): the prevalence in this group is estimated to be 7–16% and it seems that 70% of all SIADH due to malignancy is attributable to SCLC.<sup>9</sup> The incidence in other pulmonary cancers is lower (0.4–2%).<sup>10</sup>

In cancer patients, SIADH represents a paraneoplastic syndrome: for this reason, the clinical features related to hyponatremia are not necessarily related to tumor burden or metastatic sites. The cause must be sought in an ectopic AVP secretion by cancer cells: tumor regression due to a successful treatment can normalize plasma AVP concentrations.

In head and neck tumors, the SIADH incidence is 3%<sup>11</sup>; other SIADH associated malignancies are sarcomas, skin, gynecological, breast, urological, gastroenterological and haematological cancers.<sup>12</sup>

Several chemotherapeutic drugs are associated with SIADH too: patients treated with vinca alkaloids can experience hyponatremia because of the inappropriate osmoreceptor control of vasopressin secretion induced by vincristine and, less importantly, by vinblastine.<sup>13</sup>

peripheral neuropathy often described in these patients might be an indirect sign of their neurological toxicity.

Furthermore, cyclophosphamide can lead to SIADH through a double mechanism: acting on the nervous central system AVP release and by enhancing its action on renal collecting ducts membrane receptors. These effects are intensified by the high water intake of patients treated with cyclophosphamide; this is usually suggested to minimize the risk of hemorrhagic cystitis, but can lead to life-threatening water intoxication.

Among platinum compounds, cisplatin is associated with hyponatremia more than carboplatin. This drug acts through a dual mechanism too: stimulating vasopressin secretion and consequently leading to SIADH, and interfering with sodium reabsorption damaging renal tubules (salt-wasting nephropathy).<sup>14</sup>

Even targeted therapies, especially anti-angiogenic drugs, are described to determine hyponatremia: in particular patients with solid tumors treated with anti-VEGFR agents are those where the incidence of low sodium concentration is highest.<sup>15</sup> The exact mechanism underlying the increased incidence of hyponatraemia in those patients is still unknown: Khaja et al reported that augmented vasopressin release, due to low papillary solute concentration with high urinary osmolality, might be a possible explanation.<sup>16</sup>

Immune checkpoint inhibitors have revolutionized the world of cancer therapy. The most relevant side effects with these drugs are immune-related diseases, and hyponatremia seems to be linked to hypophysitis.<sup>17</sup>

Even palliative medications (non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, opioid analgesics), anticonvulsants, antipsychotics, antidiabetic and illicit drugs (eg MDMA) can be related to SIADH either increasing AVP release or by potentiation its action in the collecting duct.

Classically, inappropriate AVP secretion might also accompany the pulmonary disorders (such as bacterial or viral pneumonia, pulmonary abscess, tuberculosis, aspergillosis, asthma and cystic fibrosis) and disorders of the nervous system (such as infections, subdural hematoma or subarachnoid hemorrhage). Similarly pain, nausea, general anesthesia and stress are unconventional stimuli for the hypophysis secretion of vasopressin.

Other causes are idiopathic and transient (exercise-associated hyponatremia).

Hereditary conditions deserve a special mention: they can be found in infants and adults with hyponatremia and lack of

**Table I** Causes of SIADH

Tumors Associated with SIADH	Infectious Diseases	Disorders of the Nervous System	Drugs	Other Causes
Respiratory tract: lung, oropharynx Gastrointestinal tract: stomach, duodenum, pancreas Genitourinary tract: endometrium, ureter, bladder, prostate Other cancers: sarcomas, lymphomas, thymoma, neuroblastoma	Pulmonary: pulmonary abscess, bacterial or viral pneumonia, Tuberculosis, Aspergillosis Nervous System: brain abscess, encephalitis, meningitis, AIDS, Malaria, Rocky mountain spotted fever	Vascular diseases: subdural hematoma, subarachnoid haemorrhage, stroke, cavernous sinus thrombosis Others: brain tumors, hydrocephalus, head trauma, Multiple sclerosis, Guillain–Barré syndrome, Delirium tremens, Acute intermittent porphyria	Antidepressant SSRIs, Tricyclic, MAOI, Venlafaxine Anticonvulsant Antipsychotics Anticancer Drugs Vinca alkaloids, Platinum compounds, Ifosfamide, Melphalan, Cyclophosphamide, Methotrexate, Pentostatin, Targeted therapies, Immune checkpoint inhibitors Antidiabetic Drugs Chlorpropamide, Tolbutamide Others Opiates, MDMA, Interferon, Levamisole, NSAIDs, Clofibrate, Nicotine, Amiodarone, PPI, MABs Vasopressin Analogues Desmopressin, Oxytocin, Terlipressin, Vasopressin	Hereditary Gain of function mutation of the V2R Idiopathic Transient Asthma Cystic fibrosis Respiratory failure associated with positive-pressure breathing General anaesthesia Nausea Pain Stress

**Notes:** Data from Spasovski et al.<sup>18</sup>

**Abbreviations:** AIDS, acquired immune deficiency syndrome; SSRIs, selective serotonin reuptake inhibitors; MAOI, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxymethamphetamine; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; MABs, monoclonal antibodies.

urinary dilution, differently from SIADH. In these patients, AVP plasma levels are undetectable or very low, as they are due to gain-of-function mutations of the V2R gene. Then, the constitutively activated receptor induces water reabsorption in the collecting duct via the activation of AQP-2 receptors.<sup>2</sup>

## Clinical Manifestations

Clinical presentation of SIADH is related to both severity of hyponatremia and rapidity of onset, defining acute and

chronic form of hyponatremia. Symptoms reflect the brain's attempt to prevent the serum sodium concentration reduction by migrating the excessive quantity of water from the extracellular to the intracellular space, following the osmotic gradient and causing cerebral edema. When increase in brain water exceeds the skull capacity to contain brain expansion, it causes tentorial herniation and consequently death from respiratory arrest and/or vascular cerebral injure.

This usually happens when hyponatremia develops quickly, and the brain has too little time to readjust to this hypotonic environment. If the patient survives, the central nervous system carries out its adaptation process, which consists of the displacement of solutes, mainly potassium and small molecules, from brain cells to the extracellular space, trying to restore the brain volume. This process is realized in 12–48 hours, so this is why the threshold of 48 hours is used to distinguish the acute (<48 hours) from the chronic (>48 hours) hyponatremia.<sup>19</sup>

Neurological symptoms can be found in patients with chronic hyponatremia: with sodium value between 135 mEq/l and 125 mEq/l (mild hyponatremia) patients can be asymptomatic or can complain nausea, vomiting, dizziness. Furthermore, attention and gait instability are particularly high in the elderly.<sup>20</sup> Finally, they can have more often osteoporosis and bone fracture compared with normonatremic patients.<sup>21–23</sup>

Therefore, when sodium concentration is lower, patients can accuse loss of appetite, headache, irritability, attention deficit, confusion and disorientation.<sup>24</sup>

Finally, hyponatremia is even correlated with increased death risk.<sup>25,26</sup>

## Diagnostic Workup and Differential Diagnosis

Hyponatremia is mostly occasionally found during routine laboratory tests; however, it may be suspected in patients complaining of evocative neurological symptoms. It is therefore necessary to rapidly achieve differential diagnosis to ensure the right treatment for each patient.

Determining plasma osmolality is the first step in hyponatremia diagnostic workup. Unfortunately, rapid measurement of osmolality is not always available. It can be calculated using this formula:  $2 \times \text{Na (mmol/l)} + \text{glucose (mg/dl)}/18 + \text{urea (mg/dl)}/2.8$ .<sup>27</sup>

In the presence of normal or high osmolality (>280 mOsm/kg), excessive concentration of osmotically active solutes in plasma must be identified.<sup>7</sup> They might be exogenous or endogenous solutes that cannot pass through the cell membrane, remaining restricted to the extracellular fluid compartment and leading to osmotic water movement from intracellular to extracellular environment.

First of all, hyperglycemia must be checked and high concentration of mannitol should be ruled out: glucose and mannitol are the most important effective osmoles. Urea and alcohol on the other hand can easily cross cellular surface

contributing to measured osmolality but not to tonicity. For this reason, they are called “ineffective osmoles”: they can raise serum osmolality but do not induce hyponatremia. Pseudohyponatremia, a method-dependent serum sodium reduction, must be also excluded: it can occur when lipid or proteins concentrations are high, such as in severe hypertriglyceridemia and multiple myeloma. This can effectively hamper accurate measurement of sodium.<sup>28</sup>

In patients with hypotonic hyponatremia, the extracellular volume (ECV) should be evaluated through clinical history, physical examination and laboratory tests. Frequent symptoms and signs are vomiting or diarrhea, orthostatic hypotension, tachycardia, poor skin turgor and dry mucus membranes. These signs can identify hypovolemia. Elevation of creatinine, blood urea nitrogen, hematocrit and uric acid level are typical findings in these patients, but they are unspecific too. They can be influenced by dietary intake, for example. The measurement of renal sodium loss is more helpful: if the spot urine  $[\text{Na}^+]$  is >30 mEq/L, it is suggestive for a nephropathies or for diuretic use<sup>29</sup>; instead, a spot urine  $[\text{Na}^+] < 10$  mEq/L advises an extrarenal sodium loss.<sup>30</sup>

Conversely, ascites, subcutaneous and pulmonary oedema are all signs of increased ECV, that generally can be found in hypervolemic hyponatremia. Heart failure, cirrhosis and chronic kidney disease, along with acute kidney injury and nephrotic syndrome, are all severe conditions accompanied by either excessive AVP secretion or altered intrarenal factors, not allowing adequate free water excretion.<sup>29</sup>

In the absence of clinical history, patients that have not symptoms or signs suggestive for volume depletion or expansion should be considered euvolaemic. Euvolaemic hyponatremia takes place in the context of relative or absolute body water plethora and it can be attributed to several diseases.

Clinicians need to know urine osmolality on a spot urine sample: if it is <100 mOsm/kg H<sub>2</sub>O, that means maximum urine dilution, primarily caused by excessive water (or beer) intake, combined with low solute intake, as in potomania.<sup>31</sup>

If urine osmolality is  $\geq 100$  mOsm/kg H<sub>2</sub>O, other conditions must be considered: hypothyroidism, glucocorticoid deficiency and, the most common, SIADH.

SIADH diagnosis is still a diagnosis of exclusion and the criteria are the same initially described by Bartter and Schwartz in 1957. They are all listed in Table 2.<sup>32</sup>

Cerebral salt wasting (CSW), a condition causing hyponatremia in patients with central nervous system diseases, deserves a special mention. It is mostly described after aneurysmal subarachnoid hemorrhage but can be seen after a cerebral trauma, infective conditions, cancer (glioma,

metastatic carcinoma) and even after surgery for pituitary tumor or acoustic neuroma. Pathophysiology is not clear: some authors point the finger at the brain natriuretic peptide, released after brain damage and inhibiting renal sodium reabsorption. Others underline how an injured hypothalamus cannot improve sodium reabsorption and renin release.<sup>33</sup>

Distinguishing CSW from SIADH is important and challenging because of the opposite treatment options. Both the disorders have similar laboratory findings (reduced serum osmolality, urine osmolality >100 mOsm/kg, urine sodium concentration >30 mmol/l) but ECV is different: the patient with SIADH is euvolemic to hypervolemic, due to free water, conversely the one with CSW appears hypovolemic.

This fact translates into the different management: CSW patients should be treated mainly by solute repletion and frequently fludrocortisone, while SIADH patients must be treated with fluid restriction.<sup>34</sup>

## SIADH Treatment and Management

A few decades ago, attention was focused on the underlying disease or drug responsible. This was considered the best available option to treat SIADH. If the removal of the primary cause was not achievable, additional treatment

options included: fluid restriction, sodium administration via oral preparations or, in more severe cases, hypertonic (3%) saline continuous infusion or bolus.

Other treatment approaches for SIADH contemplated tetracycline demeclocycline and lithium. The former was administered since 1970 with limited results and poor accessibility, the latter were hampered by potentially significant adverse events and questionable efficacy.<sup>35–37</sup>

Urea represents a second-line potential treatment strategy, together with a combination of low-dose diuretic sodium chloride oral preparations.<sup>32</sup> However, this drug is hampered by low compliance, due to gastrointestinal side effects like nausea and debatable efficacy, despite accessible cost.

In order to ensure optimal management of SIADH, factors such as etiology, onset timing, severity, symptoms and extra-cellular volume status should lead the way of correction measures.

In asymptomatic patients with mild hyponatremia, fluid restriction (around 500–800 cc per day) should be taken into consideration as the first option for a gradual normalization of sodium levels. However, this approach fails due to poor patient's compliance and requires time to be effective in addition to renal function monitoring; moreover, it should be managed carefully in cancer patients with higher risk of hypovolemic situations and in need of chemotherapeutic infusions.<sup>38–40</sup>

On this topic, Furst et al suggested a formula based on urine/plasma electrolyte ratio to lead fluid restriction and facilitate the identification of those patients who will better respond to it.<sup>40</sup> Time of onset is another aspect that should guide the management of SIADH. In respect to this, physicians should consider acute, chronic and recurrent hyponatremia as separate settings in need of being managed differently.

In many cases of chronic hyponatremia, particularly in asymptomatic patients, identification and removal of the primary cause of this electrolytic imbalance can be even more effective than elevating the serum sodium concentration through treatment.

Infusion of hypertonic saline (3%) is highly recommended in acute situations with neurological symptoms. The guidelines advise a bolus of 100–150 mL in 10 minutes, which might be repeated 2 to 3 times until serum sodium increase by 5 mmol avoiding overcorrection.<sup>18</sup> No more than 10mmol in the first 24 hours or 8 mmol if there are risk factors must be reached in order to prevent severe damage to central nervous system, such as central pontine myelinolysis and ultimately coma and death. The recommendation is to carry on the correction until

**Table 2** SIADH Diagnostic Criteria

<b>Essential Criteria</b>
Effective serum osmolality <275 mOsm/kg
Urine osmolality >100 mOsm/kg with decreased effective osmolality
Evidence of clinical euvoemia
Increased urine sodium concentration >30 mmol/l with normal salt and water intake
Normal adrenal, thyroid, pituitary or renal function
No recent use of diuretic drugs
<b>Auxiliary Criteria</b>
Serum uric acid <0.24 mmol/l (<4 mg/dl)
Serum urea <3.6 mmol/l (<21.6 mg/dl)
Failure to correct hyponatraemia after 0.9% saline administration
Fractional sodium excretion >0.5%
Fractional urea excretion >55%
Fractional uric acid excretion >12%
Correction of hyponatraemia through fluid restriction

symptoms' disappearance, with careful monitoring of patient's conditions and serum sodium concentration to avoid hyponatremia overcorrection.

If the patient is symptomatic but hyponatremia occurred chronically, correction should be performed more gradually (1.5 to 2 mmol/L/h).<sup>41–43</sup>

Time for a new therapeutic approach to SIADH-induced hyponatremia has come with the introduction of AVP-antagonistic agents specific for V2R named vaptans. Tolvaptan is administered orally and has been approved in the US and Europe for the treatment of euvoaemic hyponatraemia caused by SIADH.

In the SALT-1 and SALT-2 studies, patients with SIADH were randomized to receive oral tolvaptan 15 mg daily or placebo. The correction rate of serum sodium levels in both the studies was significantly increased with the vaptan compared to placebo, drug toxicity was manageable and included thirst, dry mouth, liver toxicity and polyuria.<sup>44</sup> Moreover, Tolvaptan may interact with cytochrome metabolism of several molecules, not to mention its considerable cost.<sup>45</sup> Nevertheless, a double-blind randomized placebo-control clinical trial conducted by Salahudeen et al on cancer patients with SIADH proved the superiority of tolvaptan also in the malignant setting.<sup>44</sup>

Despite these findings, over the years first-line treatment with tolvaptan in SIADH has not been encouraged by European guidelines. As a matter of fact, tolvaptan, although effective, does not affect overall mortality, can result in overcorrection and has only been compared against placebo.<sup>46</sup>

Notably, in the study of Salahudeen et al, no overcorrection of serum sodium was reported in the tolvaptan group.<sup>44</sup>

Petereit et al demonstrated that treatment with tolvaptan may enable hyponatremic SCLC patients to receive chemotherapy and lead to an improvement in performance status.<sup>46</sup>

Moreover, a recent observational multicenter Italian study supported the role of tolvaptan in the armamentarium against cancer-related SIADH with a twofold positive effect: improving overall survival (OS) and reducing hospitalization length. On the counterpart, the investigators also observed a considerably increased duration of hospital stay in those patients not treated with tolvaptan.<sup>47</sup>

The lacking of comparative studies between tolvaptan and other available treatments for SIADH could be effectively addressed by the still unpublished results of the ASSERT study recently presented at ESMO Congress

2019. In this prospective, observational, multicenter and non-interventional study, moderate-to-severe hyponatremic cancer patients with SIADH treated with tolvaptan showed significantly higher overall and median survival (mOS), compared to those who received treatments other than tolvaptan according to hospital standards and guidelines.<sup>48</sup>

## SIADH and Prognosis: Impact and Implications

Along the years, several studies have thrown light on the negative prognostic impact of all-grade hyponatremia as an independent predictor of morbidity and mortality in hospitalized patients, regardless of the etiology.<sup>49–51</sup>

SIADH looms over this scenario as a major cause of hyponatremia in both malignant and non-malignant setting.<sup>8</sup>

A large piece of evidence has related the decrease of serum sodium levels to lower quality of life and poorer survival in some critical medical conditions, such as congestive heart failure, hepatic cirrhosis and renal disease, especially in elderly patients in treatment with concomitant medications.<sup>50</sup>

Since the prevalence of this metabolic disorder in institutionalized geriatric patients is high, it should be reported that even mild asymptomatic hyponatremia has been described to significantly increase the risk of bone fractures compared with normonatremic elder individuals, this is mainly due to its neurological effects (eg cognitive dysfunction; unsteady gait) and the odds of falling.<sup>21,52,53</sup>

Verbalis et al, using an animal model of the human SIADH, have demonstrated that persistent hyponatremia is responsible for the reduction of bone mass, mainly through an osteoclastic bone resorption. Remarkably, in this study, SIADH-induced hyponatremia occurred twice more than previously described in other multiple rat osteoporosis models.<sup>54</sup>

As stated by Ayus et al, in such frail patients, these observations raise serious implications on health outcomes and costs, therefore suggesting to monitor and promptly intervene on this impairment when assessed in geriatric patients, especially with medical records of orthopedic injuries.<sup>55</sup>

However, to our knowledge, prospective studies demonstrating that the correction of subnormal sodium levels affects clinical outcomes in this setting are still missing.

As mentioned above, this electrolytic imbalance is a consistent finding in cancer patients when SIADH is the underlying condition. Of note, it has been shown in a significant number of cases, to even precede tumor diagnosis.<sup>7,56</sup>

Irrespective of the origin, either due to chemotherapy agents or tumor presence, SIADH-related hyponatremia is associated with poorer survival in all types of cancer, with particular reference to SCLC.<sup>5,57</sup>

In SCLC, according to a large retrospective analysis on the prognostic value of SIADH-related hyponatremia carried out by Hansen et al, this electrolytic disorder has been shown to be present at diagnosis in almost half of the patients (44%) and correlate negatively with disease burden (lower serum sodium in advanced stage than limited disease). The same study proved hyponatremia to be significantly associated with poorer OS than normonatremic patients (7.7 vs 11.2 months,  $p=0.0001$ ). On the other hand, data showed no difference in both mOS and OS rates of hyponatremic patients from normonatremic controls, when successful therapeutic intervention was implemented.<sup>58</sup>

In a meta-analysis Corona et al explored the weight on the outcome of correction-refractory hyponatremia across different tumor types as well as other clinical conditions pointing out as an appropriate and timely treatment can lead to patient's benefit on survival, particularly when sodium  $>130$  mEq/l.<sup>59</sup>

Performance status (PS) is a well-established score that correlates with survival and response to treatment in cancer patients.<sup>60,61</sup>

In this regard, Tai et al showed SCLC patients with SIADH to have lower PS compared to those without SIADH at diagnosis.<sup>62</sup>

Sengupta et al also observed that initial hyponatremia may influence ECOG PS score at admission and might be associated with higher clinical stage of cancer, acting as a crucial element with a detrimental impact on prognosis since the beginning of the disease.<sup>63</sup>

In a systematic review of studies collected in an extended period of time, Castillo et al observed as the unfavorable prognostic role of this electrolytic disorder in SCLC was found to be an independent risk factor in 6 of 13 investigations included in their analysis.<sup>30</sup>

A more recent study confirmed hyponatremia as an indicator of shorter survival even after adjustment for age, gender, lactate dehydrogenase (LDH) level and PS in patients with limited and extensive SCLC.<sup>64</sup>

Recent study findings by Castillo et al would suggest a higher frequency of this metabolic impairment than previously reported in non-small cell lung cancer (NSCLC), traditionally considered less interested by SIADH.<sup>65</sup>

Despite little research has been engaged on the NSCLC subcategory, a few study evidences reinforce the negative impact of hyponatremia on tumor and inflammation status in resected NSCLC as well as on outcome in advanced disease treated with erlotinib.<sup>66</sup>

Finally, as previously demonstrated for SCLC, we ascertained how sodium normalization served as an independent prognostic factor on first-line therapy NSCLC for both OS and progression-free survival (PFS), stressing the relevance of an optimal and rapid hyponatremia correction for tumor response to treatment.<sup>67</sup>

Nevertheless, lung cancer is just the most common malignancy where SIADH influences the outcome. In fact, other tumors' survival has been associated negatively with hyponatremia: gastrointestinal and colorectal cancer,<sup>68,69</sup> pleural mesothelioma<sup>70</sup> and renal cell carcinoma (RCC).<sup>71</sup>

In the latter tumor entity, preoperative low serum sodium levels correlated independently and significantly with reduced OS and disease-free survival in RCC candidates for surgery.<sup>72</sup>

A growing interest in the scientific community is rising on hyponatremia predictive role of response to treatment. In this prospective, to better select those who could benefit from chemotherapy avoiding aimless toxicity in a well-known poor prognosis disease, Tiseo et al examined a substantial amount of cases with relapsed or recurrent SCLC in second-line treatment with topotecan, proving hyponatremia to be a useful tool for stratification in the decision-making process.<sup>73</sup>

In confirmation of previous findings that linked hyponatremia to lack of response to cytokines in metastatic RCC,<sup>71</sup> another study in advanced stage RCC evaluated the impact of impaired sodium to shorter time to treatment failure and disease control rate, therefore proposing as well as suggested in lung cancer, a predictive value for hyponatremia in this setting.<sup>74</sup>

If on one side the negative prognostic role of both hyponatremia and bone metastasis (BMs) it is well consolidated in NSCLC setting, on the other side, a relation between these two risk factors had not been investigated until Rinaldi et al proved, in a recent retrospective analysis, that stage IV NSCLC hyponatremic patients developed BMs significantly earlier (3.73 vs 5.76 months,  $p=0.0187$ ), their mOS was shorter than eunatremic patients without BMs, as expected, but also poorer than eunatremic controls with BMs. This observation points out the mutual weigh of the two variables.<sup>75</sup>

Even in palliative care, when chemotherapeutic intervention is no longer an option, intervening timely and appropriately on hyponatremia may be advantageous in order to preserve steady clinical conditions and avoid hospitalization in end-of-life situations.<sup>76</sup>

Despite only a few studies have been dedicated to the relationship between hyponatremia, length of hospitalization and related cost of stay, lately increased attention has been focused on the economic and medical impact of this condition on Healthcare System.<sup>77,78</sup>

In this regard, the results from an observational, multi-center, Italian study have recently been published. The study, designed with the aim of evaluating the SIADH clinical and financial repercussions on cancer patients, showed a considerably longer time of stay in those patients who did not achieve sodium normalization during hospitalization, furthermore severe and correction refractory-hyponatremia in institutionalized patients negatively and significantly correlated with OS rate.<sup>79</sup>

## Conclusion

As a solid body of literature has confirmed over the years, the prognostic role and negative effect on the patient's quality of life of SIADH-induced hyponatremia may be overcome by early and appropriate therapeutic intervention, indirectly resulting in improved outcomes and collaterally lower health costs.

In order to ensure a proper and prompt correction of subnormal sodium level with a positive impact on the patient's condition and survival, the SIADH treatment should be tailored on clinical characteristics, biochemical parameters and different settings of onset.

Recent study findings have reinforced the pharmacological approach based on tolvaptan for the optimal management of hyponatremia secondary to SIADH and its prognostic value in cancer setting.

## Disclosure

Prof. Dr Rossana Berardi reports personal fees from Otsuka, outside the submitted work. The authors report no other possible conflicts of interest in this work.

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