

UNIVERSITÀ DEGLI STUDI DI TORINO
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Tesi di Specializzazione

NaVIGATING THE PRESSURE,
Unveiling Plasma Sodium Fluctuations in
Traumatic Brain Injury

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The lunatic is in my head
The lunatic is in my head
You raise the blade, you make the change
You rearrange me 'till I'm sane
You lock the door and throw away the key
And there's someone in my head, but it's not me

Roger Waters for Pink Floyd, *Brain Damage*

Abstract

We investigate the relationship between plasma sodium fluctuations and intracranial pressure (ICP) in traumatic brain injured (TBI) patients, employing machine learning algorithms to analyze data from a national database. Plasma sodium levels are critical in maintaining osmotic balance and cerebral homeostasis, and deviations can significantly impact ICP, a key factor in patient outcomes post-TBI.

The study examines relative changes in plasma sodium (ΔNa) and ICP (ΔICP) to assess the influence of sodium variability on ICP dynamics. Additionally, the time patients spent with sodium and ICP values above or below established thresholds — termed Na Dose and ICP Dose — was quantified to determine the impact of prolonged dysregulation on patient outcomes. The study considers sodium fluctuations above threshold (hypernatremia), below threshold (hyponatremia) as well as within normal limits.

The dataset utilised is a subpart of a database sourced from a network of Italian intensive care units (ICUs), comprising 63 hospitals and 77 ICUs. This contains high-intensity and high-frequency data, enabling precise monitoring of both sodium and ICP in TBI patients. Machine learning algorithms were applied to uncover patterns and relationships that may not be immediately apparent through traditional statistical approaches.

Patients were categorized into three Therapy Intensity Levels (TIL) to evaluate the impact of clinical interventions on ICP control and to estimate cerebral compliance using TIL as a surrogate marker.

The results demonstrate a strong correlation between ΔNa and ΔICP , with significant sodium fluctuations leading to greater ICP instability. Moreover, prolonged periods of Na Dose and ICP Dose were associated with poorer clinical outcomes, emphasizing the need for precise management of sodium levels and ICP in TBI care.

Italian abstract

Questo studio indaga la relazione tra le fluttuazioni del sodio plasmatico e la pressione intracranica (ICP) nei pazienti con trauma cranico (TBI), utilizzando algoritmi di machine learning per analizzare dati ad alta frequenza provenienti da una banca dati nazionale. I livelli di sodio plasmatico sono fondamentali per mantenere l'equilibrio osmotico e l'omeostasi cerebrale, e le deviazioni possono influire significativamente sull'ICP, un fattore chiave per i risultati clinici post-TBI.

Vengono esaminate le variazioni relative del sodio plasmatico (ΔNa) e dell'ICP (ΔICP) per valutare l'influenza della variabilità del sodio sulla ICP. Inoltre, è stato quantificato il tempo trascorso dai pazienti con valori di sodio e ICP al di sopra o al di sotto delle soglie stabilite — definiti come Na Dose e ICP Dose — per determinarne l'impatto sull'outcome. Sono state considerate le fluttuazioni del sodio sopra la soglia (ipernatremia), sotto la soglia (iponatremia) e all'interno dei limiti normali.

Il dataset utilizzato è una sotto-parte di una banca dati ad alta risoluzione, raccolta da una rete di unità di terapia intensiva (ICU) italiane, che comprende 63 ospedali e 77 ICU in tutto il paese. Questa banca dati contiene dati fisiologici ad alta intensità e frequenza, consentendo un monitoraggio preciso del sodio e dell'ICP nei pazienti critici con TBI. Gli algoritmi di machine learning sono stati applicati a questo dataset per rilevare pattern e relazioni che potrebbero non essere immediatamente evidenti con approcci statistici tradizionali.

I pazienti sono stati categorizzati in tre Livelli di Intensità Terapeutica (TIL) per valutare l'impatto degli interventi clinici sul controllo dell'ICP e stimare la compliance cerebrale utilizzando i TIL come marker surrogato.

I risultati dimostrano una forte correlazione tra ΔNa e ΔICP , con fluttuazioni del sodio che portano a una maggiore variabilità dell'ICP. Inoltre, periodi prolungati di Na Dose e ICP Dose elevati sono stati associati a esiti clinici peggiori, sottolineando la necessità di una gestione precisa dei livelli di sodio nei pazienti con TBI.

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Chapter 1

Plasma sodium, the salt of life

1.1 Plasma sodium, safeguarding osmoregulation

Human cells require a tightly regulated extracellular fluid salinity for survival. This regulation is primarily controlled by the osmoregulatory system, which manages water intake and excretion to maintain plasma sodium concentration within a narrow range of 135 to 142 mmol/L, or a more permissive range of 135 to 145 mmol/L. Disruptions to this system can have significant consequences. In the context of traumatic brain injury (TBI) or other neurological insults, dysregulation of sodium homeostasis — through mechanisms like diabetes insipidus or cerebral salt wasting — can lead to extreme fluctuations in plasma sodium concentration. These shifts not only affect fluid balance but can also exacerbate cerebral edema or dehydration, complicating the management of intracranial pressure (ICP) and overall patient outcomes. Therefore, tight regulation of sodium levels becomes especially critical in the neurocritical care setting.

Plasma sodium concentration directly impacts cell volume, with hypernatremia indicating hypertonicity (cell shrinkage) and hyponatremia usually¹ signifying hypotonicity (cell swelling). Failure to maintain this balance leads to hypotonic or hypertonic stress, exposing cells to potentially dangerous swelling or shrinkage, respectively. The main actors of relationship are sodium, potassium and water within the body. While sodium is primarily found in extracellular fluid and potassium intracellularly, their combined concentration in total body water dictates the tonicity of plasma and its effects on cell volume.

¹This could also be related to hyponatremic state or pseudohyponatremia

1.2 Tonicity, osmolarity and osmolality: a clarification

Tonicity, osmolarity, and osmolality are related but distinct concepts often used in physiology, especially when discussing fluid balance and the movement of water between different compartments in the body.

Osmolarity refers to the total concentration of solute particles per liter of solution, it is measured in Osmoles per liter (Osm/L).

In simpler terms it measures the concentration of solutes in a given volume of solvent and does not consider the permeability of a biological membrane nor the type of solute.

Osmolality is the total concentration of solute particles per kilogram of solvent, usually water (Osm/kg).

Could be seen as a more accurate measure than osmolarity because it's not affected by temperature or pressure changes both of which can alter volume. It measures how many solutes are dissolved in a specific weight of solvent, making it particularly useful in biological systems where small variations in fluid volumes matter. In clinical practice for example, blood plasma osmolality is often measured to assess hydration status and is usually around 285-295 mOsm/kg.

Tonicity explains the ability of an extracellular solution to generate a water movement in or out of a cell by osmosis, depending on the solute concentration. As it's a qualitative measure that describes the effect of a solution on cell volume, it has no direct units.

Tonicity is related to osmolarity but focuses on non-penetrating solutes that can't cross the cell membrane - also known as effective osmoles - thus affecting water movement and cell volume. When a cell is in an isotonic environment there's no net movement of water. When a cell is exposed to a lower concentration of non-penetrating solutes compared to the inside (hypotonic fluid), water will move into the cell, causing it to swell. On the contrary, when a cell is exposed to a hypertonic solution, water will move out, causing it to shrink.

Sodium (and glucose in cases of insulin deficit), as obligate extracellular solutes acts as effective osmoles and contribute both to osmolality and tonicity, urea in contrast contributes to osmolality without affecting tonicity as is membrane-permeable.

While water crosses cell membranes freely through aquaporins, solute concentrations (osmolalities) should be equal inside and outside of cells. Na/K-ATPase pump is key in maintaining sodium largely extracellular and potassium mainly intracellular and osmotic gradients are quickly abolished by water movement. This way, the concentration of sodium in the extracellular fluids (ECF) should equal the concentration of sodium plus potassium in total body water (TBW), as described by the Edelman equation [32]. So, plasma sodium concentration is influenced both by sodium and potassium balance as well as water balance. Consequently, a noticeable decrease in the total potassium body content will induce a decrease in plasma sodium concentration.

1.3 Sodium swings, how the cells adapt over time

Brain capillaries consist of tight endothelial junctions intertwined by astrocytic foot processes, the so-called blood-brain barrier (BBB), that sodium can't cross and will instead act as an active osmolyte. Consequently, abnormal plasma sodium levels will cause water movement into or out of the brain.

Unsurprisingly, since plasma sodium affects brain volume, its regulation is influenced by hypothalamic osmoreceptors in the brain.

Regulation of serum sodium level is strictly related to water metabolism through antidiuretic hormone (ADH or vasopressin) via the hypothalamic osmostat. Hence plasma sodium concentration responds to changes in water ingested, infused or excreted which can contain large amounts of concentrated salt or could be electrolyte-free water. There are opposing mechanisms regulating sodium retention (sympathetic nervous system and the renin-angiotensin-aldosterone system) and sodium excretion (natriuretic peptides).

In addition, nonosmotic ADH mechanisms are involved. Factors such as hemodynamic instability, pain, drugs (antibiotics, osmolar therapy, opiates) will alter the osmotic threshold for ADH release. Lastly, we, as clinicians, often restrict fluids intake and the patient in intensive care unit has a suppressed oral intake, making the entire picture even more complex.

When changes in plasma sodium occur the cell adapts to the new state, or at least tries to.

After decreases in plasma osmolality, water moves into the brain along osmotic gradients. In response, the brain rapidly loses both extracellular and intracellular solutes (Na^+ , Cl^- and K^+). Na^+ and Cl^- losses begin very rapidly, generally within 30 min, whereas brain K^+ losses peak at about 3h. [37]

Cells contain also organic osmolytes—small intracellular molecules such as glutamate, taurine, and myo-inositol. In a hypotonic state, the cell releases these molecules, while in a hypertonic state, transporters are upregulated to increase their reuptake, with the goal of maintaining minimal changes in cell volume.

Like many adaptive mechanisms, these processes require time to engage and disengage. If sodium levels change too rapidly, vascular injury can occur due to sudden brain shrinkage, or the brain may swell abruptly, leading to increased intracranial pressure. In some cases, the adaptive mechanisms can make the situation even worse—for example, the release of glutamate may lower the seizure threshold. In general terms the brain is much better at losing organic solutes than to reaccumulate them, in contrast to rapid electrolyte movements (mainly Na^+ and Cl^-).

Astrocytes act as osmotic buffers protecting neurons from osmotic stress by moving taurine and others small molecules. Those changes are within 24 to 48 hours as the upregulation or down-regulation takes time - if a sodium turbulence occurs before the new steady state, astrocytes could be osmolyte-depleted and therefore unable to respond properly.

This explains why rapid changes in sodium levels must be corrected quickly, before slower adaptive mechanisms based on organic osmoles take effect, and why gradual changes should be managed slowly for the same reason (see fig:1.1). Notably, if the brain is already partially injured, these mechanisms become inefficient and could potentially cause further damage to the salvageable brain tissue [1].

1.4 Salt disruptions, dysnatremias in the brain injured patient

Disturbances of plasma sodium concentrations are generally defined as dysnatremias, those are quite common in the brain injured patient and are associated with poor neurological outcomes and mortality. Brain injury can both induce and result in dys-

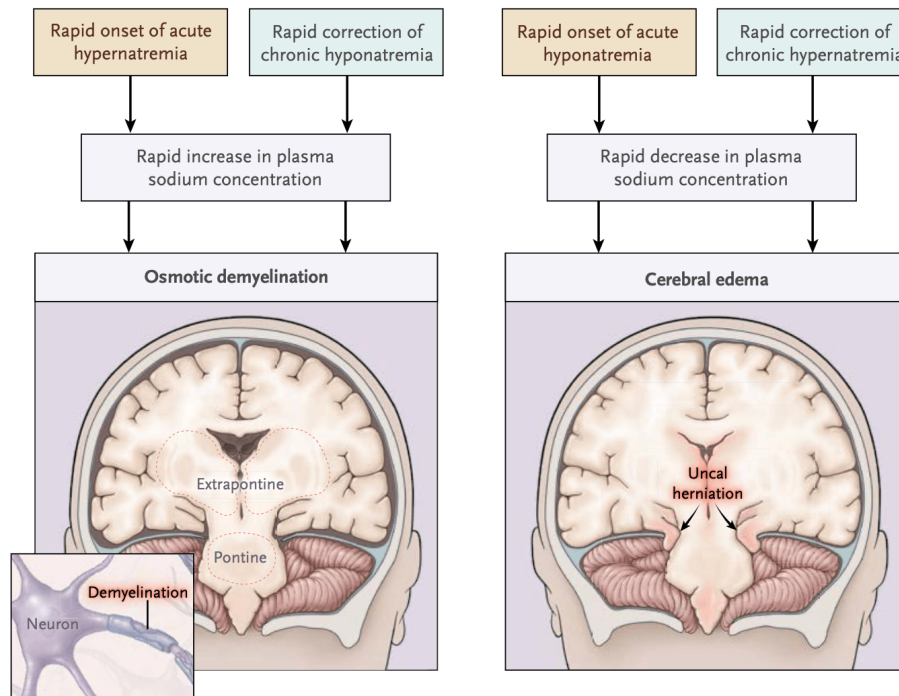


Figure 1.1: Both a rapid onset and a rapid correction of hyponatremia and hypernatremia can cause brain damage. A rapid increase in the level of plasma sodium, either from acute hypernatremia or from rapid correction of chronic hyponatremia, can cause osmotic demyelination. Cerebral edema is a complication of acute hyponatremia and of rapid correction of chronic hypernatremia. Modified from Sterns[32].

natriemias.

Hyponatremia is defined as a serum sodium lower than 135 mmol/L. The highest incidence of hyponatremia is found in subarachnoid hemorrhage (up to 60% of patients), followed by traumatic brain injury (up to 50% of patients). The most serious complication is definitely fatal cerebral edema and herniation.

Through aquaporins water moves from the ECF to the intracellular compartment resulting in astrocytic swelling. Water is routed selectively inside glial cells to initially spare the neurons. When placed in a hyposmotic fluid, astrocytes activate a mechanism known as *regulatory volume decrease*. The most immediate response consists in the shifting of liquid from the interstitial space to the cerebrospinal fluid. In order to counterbalance the increase in water volume, brain cells rapidly adapt by extruding osmotically active electrolytes, this is a temporary measure as it wanes within a few hours (3 to 12 hours[30][1]). If hyponatremia is sustained, a second slower adaptive

response begin, based on the efflux of organic solutes. At 48h from hyponatremia onset, the efflux of inorganic solutes still results in a potentially critical 40% increase of brain water volume[1]. The timespan required for the brain to expel more than 90% of organic osmoles is the physiological basis for discriminating between acute (<48h) and chronic (>48h) hyponatremia[26].

Although many conditions can lead to hyponatremia, in the brain injured those are commonly related to the syndrome of inappropriate release of antidiuretic hormone (SIADH) and cerebral salt wasting syndrome (CSW).

In SIADH, serum antidiuretic hormone levels are erroneously high, resulting in inappropriately elevated urine osmolality secondary to urinary loss of sodium, despite hyponatremia.

Cerebral salt wasting is primarily a natriuresis problem, thus euvolemia and hypervolemic state are often present in SIADH, whereas hypovolemia is common in untreated CSW.

At the opposite end of the spectrum, **hypernatremia** is defined as serum sodium higher than 145 mmol/L. Glial cells and neurons begin to lose water as a result of the osmotic gradient, while the brain tries to maintain a stable intracellular volume. To protect against shrinkage, brain moves water from the cerebrospinal fluid into the interstitium, followed by early uptake of ions and late accumulation of organic osmoles. In the brain injured patient is common to err on the hypernatremic state, usually as result of osmotherapy for the management of cerebral edema, though can also be unintended as result of diabetes insipidus or other iatrogenic drugs.

Mannitol induces hypernatremia by increasing free water loss, while hyperonic saline directly increases plasma sodium.

Central diabetes insipidus (CDI) occurs in case of vasopressin deficit or as a component of the pituitary stalk injury. Hypernatremia may also manifest as a complication of anterior communicating aneurysm rupture or injury to anterior hypothalamus[24].

1.5 The water wars, understanding SIADH, Cerebral Salt Wasting and Diabetes Insipidus

In the intricate balance of fluid and electrolyte regulation, three conditions already briefly described stand out for the complex interplay in patients with brain injuries: Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), Cerebral Salt Wasting (CSW), and Diabetes Insipidus (DI), deserving further exploration. Together,

these conditions represent a “water war” within the body, where misregulation of fluids and electrolytes can quickly escalate to worrisome situations.

The **Syndrome of Inappropriate Antidiuretic Hormone Secretion** (SIADH) - recently renamed as SIAD (syndrome of inappropriate antidiuresis) - is characterized by excessive release of antidiuretic hormone (ADH), leading to water retention and dilutional hyponatremia. This disorder is frequently encountered in neurocritical care patients, particularly following traumatic brain injury (TBI), subarachnoid hemorrhage, and neurosurgical procedures. In SIADH, the kidneys retain free water, resulting in euvolemic hyponatremia with high urine osmolality and sodium concentration.

The diagnostic criteria include several key markers. Hyponatremia is a hallmark feature, with serum osmolality below 270-275 mOsm, indicating hypotonic plasma. Despite this, urine osmolality is typically elevated, often exceeding 300 mOsm, though values between 100-300 mOsm may place the diagnosis into question. Another important diagnostic feature is high urinary sodium concentration, which suggests that sodium is being excreted despite low plasma sodium levels. Clinically, patients with SIADH appear euvolemic, showing no signs of fluid overload or dehydration. Additionally, the hyponatremia should not be attributable to renal failure, as renal function typically remains intact unless the glomerular filtration rate (GFR) falls below 20-25 ml/min. Common treatments for SIADH involve addressing any reversible causes and promoting adequate protein and salt intake. Fluid restriction to <500-1000 ml/day can be effective in about half of patients, although often difficult.²

For more resistant cases, oral urea is a preferred treatment, and SGLT2 inhibitors have also shown efficacy in clinical trials. Additionally, ADH inhibitors (vaptans) are also used, salt tablets may be an alternative when other treatments are contraindicated.

Often confused with SIADH due to overlapping clinical features, **Cerebral Salt Wasting** (CSW) is distinguished by hypovolemia caused by excessive renal sodium loss. CSW typically occurs in response to brain injury and is associated with high urinary sodium excretion and polyuria. The pathophysiology involves disruption of sympathetic pathways or increased secretion of natriuretic peptides (BNP, ANP), leading to renal salt wasting. The existence of CSW remains controversial, as it can be difficult to distinguish from SIADH due to their similar laboratory profiles. Despite conflicting reports on the prevalence of CSW, evidence suggests it may be linked to aldosterone

²Fluid restriction is less likely to succeed if urine osmolality is greater than 500 mOsm or urine sodium exceeds 130 mM.[38]

deficiency in certain patients. Treatment generally includes hypertonic therapy for hyponatremia and isotonic fluids with fludrocortisone to correct hypovolemia, aiming to restore fluid balance. Notably, both CSW and SIADH can be managed with hypertonic saline, although their underlying mechanisms differ[33].

In contrast to SIADH and CSW, **diabetes insipidus** (DI) results from the inability to produce or respond to ADH, leading to excessive water loss and hypernatremia. DI is common in patients with severe brain injury, particularly those involving the hypothalamus or pituitary gland. This condition is marked by polyuria, low urine osmolality, and elevated serum sodium. DI is managed by replacing vasopressin activity with desmopressin (a synthetic ADH analogue) but this carries the risk of free water retention, which can lead to rebound hyponatremia if not monitored. A common and effective method to treat hypernatremia is the DDAVP clamp, where a high dose of desmopressin (e.g., 2 mcg IV every 8 hours) is used. However, once hypernatremia is controlled, the dose should be reduced to allow some free water excretion, thus avoiding hyponatremia[22].

While SIADH, CSW, and DI all affect sodium and water balance, the primary difference lies in their impact on volume status. SIADH presents with euvolemia, CSW with hypovolemia, and DI with hypovolemia and hypernatremia. Early and accurate diagnosis is crucial in tailoring treatments to the specific disorder, as each requires a vastly different approach—fluid restriction for SIADH, fluid and salt repletion for CSW, and hormone replacement for DI. Failure to distinguish between these conditions can result in improper treatment, exacerbating brain injury and worsening outcomes.

Chapter 2

Under pressure, ICP in Traumatic Brain Injury

Intracranial pressure (ICP) is a critical parameter in the management of traumatic brain injury (TBI), serving as a window into the brain's dynamic response to injury. After a traumatic event, the brain's natural mechanisms to regulate pressure — via fluid shifts, blood flow adjustments and tissue compliance as according to Monro-Kellie doctrine — are often compromised.

Elevated ICP is one of the most determinant complications in TBI, as it not only reflects underlying pathology but also drives secondary brain injury by reducing cerebral perfusion, increasing ischemia, and damaging neuronal tissue. Even small shifts in intracranial dynamics can dictate life-or-death outcomes, making ICP not only a marker of injury but also a factor in the recovery process.

In brain-injured adults, an intracranial pressure (ICP) greater than 20-22 mmHg is generally recognised as the threshold for intracranial hypertension[13]. However, while this is important, the interpretation of ICP is far more complex than the value itself[3].

2.1 Brain volumes, intracranial components

It was all the way back to the 1783 when Monro stated that the blood content within the skull should have been constant, so the amount of inflow should have equalized the outflow. Kellie perfected this assumption: any volume within the skull cannot be displaced without being replaced by another component, when a displacement is not possible a consequent increase in intracranial volume would result in increased ICP.

While often described as static component as it is nearly incompressible, the brain parenchyma (the functional tissue of the brain) can actually change its volume over time, shrinking in response to injury or swelling, primarily in the component of glial cells. This tissue modification occurs gradually, impacting the brain's compliance (its ability to tolerate changes in volume without relevant changes in brain pressure).

The blood volume instead, both in the arterial and venous compartment, significantly influence ICP.

The arterial side can rapidly adjust cerebral blood flow (CBF) by constricting or dilating blood vessels within seconds. The so-called *cerebral autoregulation* keeps the CBF constant despite fluctuations in systemic blood pressure. This ensures that the brain receives a consistent supply of oxygen and nutrients, even when blood pressure changes. Cerebral autoregulation operates effectively within a specific range of mean arterial pressure (MAP), typically between 60 and 150 mmHg in healthy individuals. New insights would otherwise suggest though a more narrow range as smaller pial arteries dilates more than bigger arteries, consequently important intersubject variability for active autoregulation does exist[17].

The venous compartment plays a crucial role in ICP determination. Nearly 70% of blood makes up a significant portion of the total blood in the brain is venous within the skull, CVP is then closely linked to ICP. Bridging veins form a connection between the brain's deep venous and superficial venous systems. Closely associated with cerebrospinal fluid, these veins consist primarily of intima tissue, making them highly collapsible and distensible. As a result, they function like a Starling resistor, preventing retrograde transmission of abrupt increase of central venous pressure (CVP) to ICP. However, as ICP increases, the bridging veins begin to collapse, raising outflow resistance. Once a critical closing pressure is reached, venous outflow is halted entirely[39].

Cerebrospinal fluid (CSF), though relatively small in volume compared to other components (about 150ml), is vital for maintaining pressure equilibrium within the skull, distributing and equalising changes in ICP. The concept of *CSF compensatory reserve*, which refers to the CSF's ability to accommodate volume fluctuations without altering intracranial pressure (ICP), depends on the lumbar sac's capacity for expansion and the continuous fluid exchange within the recently explored glymphatic system[3].

Each cerebral volume exhibits its own dynamic and contributes to compensate for

any rise in ICP, through various chemical and physical mechanisms and at different rates. The ICP reflects the overall system's elasticity and compliance.

2.2 Cerebral compliance, the silent buffer

The relationship between pressure and volume defines the compliance of a system, so one does exist also for the brain and express the relationship between any increase in volume related to an increase in ICP.

At first, volume increases cause only a slight rise in pressure so long as the compensation systems and cerebral autoregulation work, but once the system's buffering capacity is exceeded, ICP rises steeply. These changes are not necessarily associated with specific ICP number thresholds, as we can find patients with signs of intracranial hypertension within a "normal range" of ICP as patients that still demonstrate a good compliance in spite of ICP above thresholds [SISTEMARE REFERENZA FIGURA](#) (see fig.2.2).

Following traumatic brain injury, both intracranial and systemic factors contribute to the rise in intracranial pressure. In the initial hours after injury, expanding hematomas pose the greatest risk. However, in the days that follow, other mechanisms such as fluid accumulation, impaired autoregulation, ischemia, and the expansion of contusions further increase intracranial pressure. When a mass lesion forms, it creates a pressure gradient that distorts brain tissue, leading to midline shifts and brain displacement either medially or caudally, resulting in herniation, a medical emergency that requires immediate intervention to prevent irreversible and often fatal damage to the brainstem.

The vascular consequences of elevated intracranial pressure arise from reduced cerebral perfusion pressure (CPP, as the difference between mean arterial pressure and intracranial pressure). CPP drives cerebral blood flow but the adequate one vary between patients. As CPP declines, cerebral blood flow may become insufficient for proper tissue perfusion, leading to ischemia. This, in turn, triggers cytotoxic edema, exacerbating intracranial pressure even further[34].

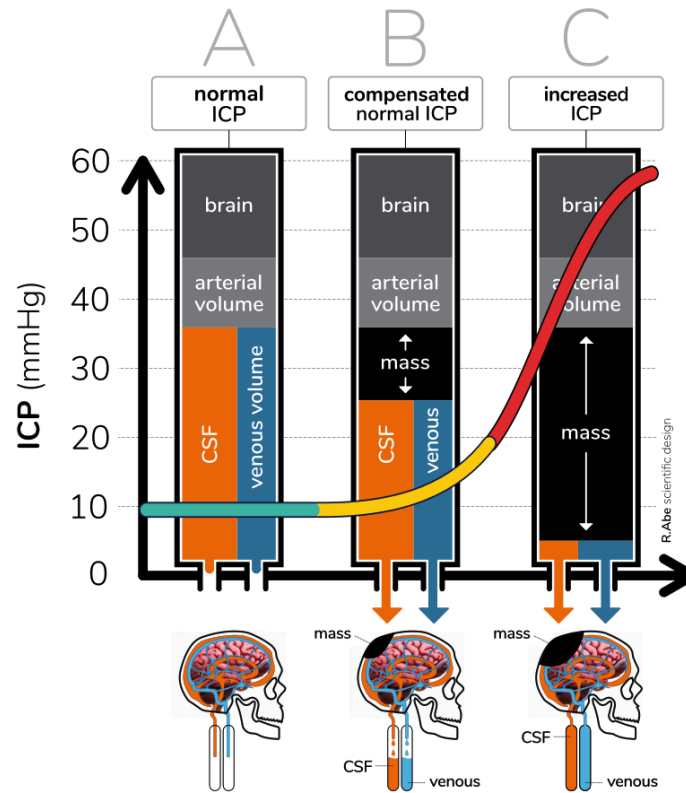


Figure 2.1: Different phases of the cerebral compliance. In the first phase (A), compensatory system is effective and ICP does not change. In a second phase (B), the compensatory system starts to fail following more increase in volume. CSF and veins outflow are starting to be overloaded, beginning brain deformation and CBF impairment. In a third phase (C), the compensatory system is exhausted, brain deformation and loss of compliance are evident. Modified from Godoy et al.[8]

2.3 ICP waveform, more than a number

The intracranial pressure (ICP) waveform is a graphical representation of pressure changes within the skull over time. It reflects the pulsatile nature of ICP, influenced by arterial blood flow, venous outflow, and cerebrospinal fluid (CSF) dynamics. The classical representation of the waveform is the one we see at the bedside that shows ICP over time (time domain representation)¹.

The ICP waveform in the time domain can provide different insights depending on the duration being analyzed, ranging from moments or seconds to a timeframe as long as one hour.

¹The frequency domain representation also exists, but it requires additional software and hardware for the spectral analysis [3]

The waveform is typically divided into three main components or peaks:

1. **P1 (Percussion wave)**: This represents the arterial pressure transmitted through cerebral arteries, synchronous with the systolic peak of the arterial waveform.
2. **P2 (Tidal wave)**: the second peak is directly proportional to the brain's compliance as it represents the increase in cerebral blood volume. In a normal ICP waveform, P2 is lower than P1, indicating good cerebral compliance. When P2 is higher than P1, it suggests reduced compliance, meaning the brain's ability to compensate for volume changes (like increased blood volume or swelling) is diminished.
3. **P3 (Dicrotic wave)**: Corresponds to the closure of the aortic valve and reflects venous outflow. It is typically the smallest of the three peaks.

In healthy individuals or patients with good cerebral compliance, the waveform shows a descending pattern where $P1 > P2 > P3$. As brain compliance decreases, P2 rises and surpasses P1. In the final more severe stage, the waveform resembles a triangular shape, where the individual peaks are no longer distinguishable. The $P1/P2$ ratio reflects this relationship, with a normal ratio being greater than 1. In pathological conditions, values of 1 or less are typically observed.

Zooming out on the timeline new waveforms pattern can arise. Those are called *Lundberg waves* and are classified as:

- **A waves or “plateau waves”**: These are characterized by a rise in ICP until a plateau phase followed by a decrease, often reaching values of 50-100 mmHg, lasting for several minutes (5-20 minutes). They are consequence of a drop in arterial blood pressure (ABP) that causes cerebral vasodilation, reducing cerebral perfusion pressure (CPP), leading to more vasodilation and higher ICP. As plateau waves represent a temporary brain hypoperfusion, those are often associated with ischemia and prompt intervention to prevent irreversible brain damage is needed. *Sistemare queste due frasi!!* To note, plateau waves can also terminate spontaneously after a few minutes. Are associated with critically reduced cerebral compliance, typically found in young patients with low midline-shift.
- **B waves**: B waves are oscillations in ICP within 10 to 20 mmHg. They last 30s to a couple of minutes and are often associated with increase in CBF so are related to brain metabolism. Their meaning is contradictory: for some are

early indicators of impaired compliance, for others the greater the amplitude of B waves the better is the outcome[3].

- **C waves:** C waves are the least significant clinically, often linked to autonomic nervous system activity.
- **Respiratory waves:** Respiratory waves are synchronous with breathing, they've been associated with increased resistance to CSF circulation so can correlate with intracranial compliance in patients with hydrocephalus.

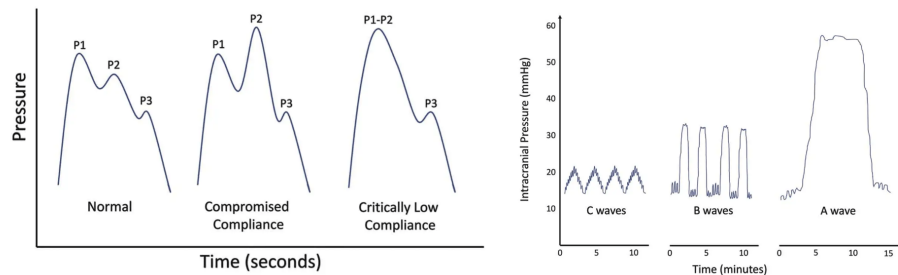


Figure 2.2: Left: Intracranial pressure (ICP) waveforms. Normal waveform shows $P1 > P2 > P3$, with compromised intracranial compliance $P2 > P1$.

Right: Lundberg intracranial pressure waves. A waves reflect critically exhausted intracranial compliance. B waves likely occur because of impaired cerebral perfusion and may suggest impaired intracranial compliance. C waves may be seen in normal physiology and are likely related to sympathetic activity. Modified from Liotta et al.[21]

2.4 The pressure within, ICP monitoring

All international guidelines provide the ICP threshold of 22mmHg as the cutoff to start treatment. But to know this value we have to monitor ICP in the first place.

Intracranial pressure monitoring is recommended for all patients with survivable severe traumatic brain injury who show abnormalities on the admission computed tomography (CT) scan. Additionally, monitoring is advised for certain patients with a normal CT scan, such as those over 40 years of age with hypotension or abnormal pain responses (e.g., abnormal flexion or extension). An external ventricular drain (EVD)

is placed in a brain ventricle and connected to a transducer for monitoring intracranial pressure (ICP). While alternative invasive methods, such as intraparenchymal probes, microstrain gauges, and fiberoptic catheters, are gaining popularity due to ease of use, they do not allow for cerebrospinal fluid (CSF) drainage, which is a key method for reducing ICP. Catheters can also be placed in the subdural space after hematoma evacuation, but these offer less reliable ICP measurements and no CSF drainage. Thus, the EVD remains the standard of care for ICP monitoring.

The concept of ICP monitoring has although been questioned by some trials, it's needless to say though that any improvement in outcomes must come from the treatments guided by intracranial pressure monitoring, rather than from the monitoring itself[34]. Additionally, non-invasive methods for monitoring ICP now offer several options and could serve as a viable alternative, although their measurements may not be as precise as those obtained through an external ventricular drain (EVD) or catheter.

To add further complexity, is the specific ICP number truly essential? As mentioned earlier, the waveform itself can provide far more valuable insights, and newer, individualized approaches are emerging, moving away from the 'one size fits all' model. Additionally, the accuracy of the number itself is subject to various errors, such as transducer placement, regional differences in ICP within the skull, and the zero drift phenomenon².

In general, intracranial pressure (ICP) remains equal or shows a similar trend between hemispheres, even in cases of acute brain injury. However, an ICP gradient can rapidly develop just before brain herniation. Although the mean ICP and amplitude may vary, they usually follow the same trend. The differences in ICP readings are often more pronounced in the initial hours after admission, especially before resuscitation. Major determinants of these variations include the presence of focal pathologies and lesion volume. Studies in primates have shown that an infarct size affecting $\geq 20\%$ of the hemisphere is associated with significant ICP gradients, suggesting the importance of placing the sensor in the injured area[4].

In addition to ICP variations, the concept of *ICP dose* could mark a significant shift in understanding. This approach emphasises the cumulative effect of elevated pressure over time, making it a critical factor in evaluating the long-term impact on brain tis-

²Zero drift refers to the gradual shift in baseline readings of ICP microtransducers over time. This can result in inaccurate ICP values due to factors like sensor aging, temperature changes, or mechanical issues.[20]

sue. Rather than focusing solely on momentary pressure spikes, the ICP dose accounts for prolonged periods of increased ICP, which is particularly harmful in regions with notable pressure gradients. The ICP dose is represented visually as the area under the curve where intracranial pressure exceeds a set threshold, measured in mmHg/h. This metric captures both the intensity and duration of intracranial hypertension, serving as an indicator of secondary brain injury. Studies have shown that the ICP dose correlates with mortality and functional outcomes, and its sensitivity improves when high-resolution data is used[29].

While the ICP dose quantifies the burden of elevated pressure over time, monitoring cerebral perfusion pressure (CPP) offers a more comprehensive understanding of brain health. CPP reflects the balance between ICP and mean arterial pressure (MAP), directly measuring the brain's ability to maintain adequate blood flow and autoregulation. Monitoring CPP may be superior to ICP alone, as it accounts for both pressure and perfusion, providing insight into the risk of ischemic injury, which is critical for preventing secondary brain damage.

In this context, *CPP burden*[41] can be viewed as the counterpart to ICP dose. The intensity and duration of CPP burdens are closely linked to outcomes, with the brain's tolerance to these insults varying based on the state of autoregulation. Notably, tolerance to both low and high CPP is greater when the insult duration is short, and patients with intact autoregulation are better equipped to handle fluctuations in CPP[9]. The ability to visualize both ICP and CPP thresholds, along with the duration and extent of these insults, paves the way for identifying personalized ICP and CPP targets.

2.5 Pressure relief, strategies for ICP control

ICP control is a cornerstone of neurocritical care, as elevated ICP can lead to reduced CPP, ischemia and brain herniation, making timely intervention critical. Over the years, ICP control strategies have evolved from basic monitoring to a more comprehensive, individualized approach aimed at minimizing secondary brain injury and improving patient outcomes.

Therapeutic approaches for managing ICP are diverse, ranging from non-invasive techniques such as head elevation and sedation to more aggressive interventions like hyperosmolar therapy, CSF fluid drainage and surgical decompression. Each of these methods targets different mechanisms ranging from controlling cerebral edema, en-

hancing venous outflow or directly removing excess cerebrospinal fluid. More advanced targeted therapies like barbiturate coma, hypothermia, and controlled hyperventilation expand the treatment toolkit, allowing a tailored intervention based on the patient's specific condition and ICP trends.

In the past decade, ICP management has shifted towards standardized protocols using a staircase approach[34] that progressively escalates treatment intensity. This strategy begins with medical interventions like sedation and analgesia to manage pain and agitation, followed by hyperosmolar agents (mannitol, hypertonic saline) to reduce brain volume through plasma expansion and water extraction across the blood-brain barrier. While effective, both agents have side effects such as dehydration with mannitol and sodium imbalances with saline. Other interventions like hyperventilation reduce ICP but risk cerebral ischemia, while barbiturates lower ICP by depressing cerebral metabolism, though serious side effects limit their use to refractory cases.

On the surgical side, options include CSF drainage, hematoma evacuation, and decompressive craniectomy. Drainage, though simple, carries risks like herniation with lumbar catheters, and continuous drainage limits ICP monitoring accuracy. Decompressive craniectomy, while offering additional volume to compensate for brain swelling, has been controversial due to mixed outcomes in trials, highlighting the need for careful patient selection and further research on its efficacy.

The stepwise approach allows for less aggressive, safer treatments to be used initially, reserving more invasive interventions for cases of refractory intracranial hypertension. However, significant variability exists between centers and countries in how these strategies are applied. Moreover, there is no consistent evidence showing clear benefits from more aggressive treatments such as barbiturates, hypothermia, decompressive craniectomy, and hyperventilation, especially regarding their impact on long-term outcomes, in particular aggressive strategies applied in sicker patients seems to ameliorate mortality but not the neurological outcome[27].

The staircase approach has been further simplified into the Therapy Intensity Level scale (TIL or Tier)[42]. The TIL approach allows clinicians to categorise treatment strategies based on the intensity of interventions required for each individual patient as treatments within a TIL are considered empirically equivalent[12]. This should allow for more flexible interventions based on the patient's condition than possible more rigid escalation protocol. (see fig. 2.3)

However, significant variability between centers and countries persists due to the

CHAPTER 2. UNDER PRESSURE, ICP IN TRAUMATIC BRAIN INJURY

lack of definitive guidelines, differences in available resources, and the absence of clear evidence demonstrating a beneficial impact on outcomes[27].

Modern ICP control strategies should go beyond simple pressure reduction. Emerging techniques like cerebral autoregulation monitoring, ICP waveform analysis, and personalised pressure thresholds are shifting the focus towards a more dynamic, patient-specific approach. These advancements aim not just to manage elevated ICP, but also to optimise cerebral blood flow, oxygenation and metabolism, providing a more holistic and comprehensive view of brain health.

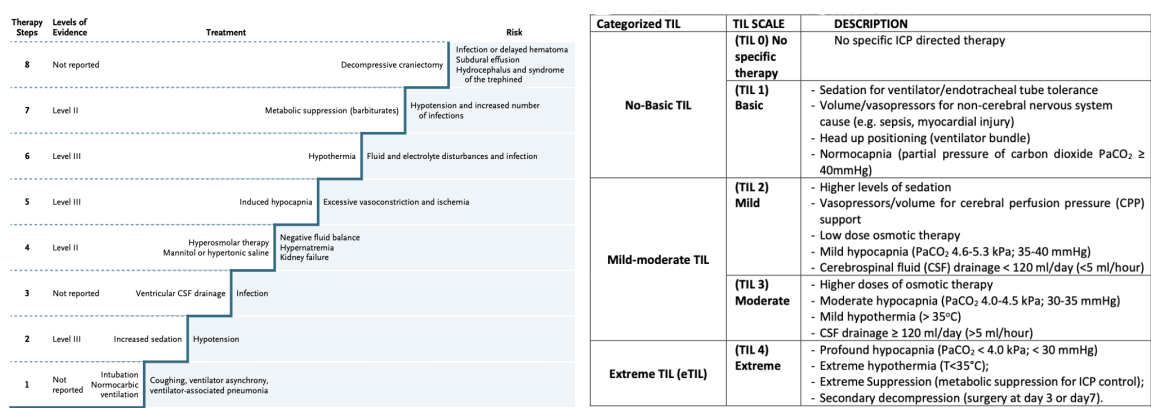


Figure 2.3: Staircase approach to intracranial hypertension and Therapy Intensity Level scale. Modified from Stocchetti et al.[34] and Robba et al.[27].

Chapter 3

Na⁺vigating the pressure, sodium fluctuations

The team behind this study started as a research team for a three-day datathon event in Lecco, Italy in November 2023 - the GiViTHON - endorsed by the Clinical Data Science of Istituto di Ricerche Farmacologiche Mario Negri IRCCS and Politecnico di Milano. Ten multidisciplinary teams composed of clinicians, nurses, statisticians, and biodata analysts have been challenged to respond to clinical questions and use the subset database for population selection and key variables extractions.

3.1 Introduction

Traumatic brain injury (TBI) is a critical public health issue that frequently leads to long-term disabilities or death. After a TBI, the brain's ability to regulate itself can be significantly compromised, resulting in a cascade of physiological disruptions. One of the most important of these is impaired autoregulation, which leads to instability in intracranial pressure (ICP) and compromised cerebral perfusion pressure (CPP). Consequently, cerebral blood flow can be reduced, increasing the risk of *secondary brain injury* through ischemia, hypoxia, and further swelling.

The primary aim of treatment is to prevent secondary brain injury. This concept relies on distinguishing between injured brain tissue and salvageable brain tissue. While one portion of the brain may be irreversibly damaged, other areas remain viable but at risk due to inadequate blood flow or rising ICP. Failure to manage these can worsen the damage in these vulnerable regions, ultimately exacerbating the overall brain injury.

Dysnatremias have already been recognized as a marker of severity of disease and

related to mortality in the critically ill patient. There is however accumulating evidence that even mild abnormalities of serum sodium could be linked to disease severity and mortality, including changes within the normal range[28].

Serum sodium levels are tightly regulated in the human body, but patients with TBI are at higher risk of developing dysnatremias due to various factors such as hyperosmolar therapy, diabetes insipidus and SIADH. Both hypernatremia[23][36] and hyponatremia [40] have been linked to higher mortality rates and worse outcomes in traumatic brain injury (TBI) patients as well as in aneurysmal subarachnoid hemorrhage (aSAH)[19][2], highlighting the importance of sodium regulation as a key therapeutic goal for individuals with elevated intracranial pressure. While managing serum sodium levels is important, fluctuations in sodium concentration, rather than just the absolute levels, may also contribute to injury.

We therefore investigate the relationship between fluctuations in plasma sodium (ΔNa) and intracranial pressure (ΔICP) to evaluate how sodium variability influences ICP dynamics. Fluctuations are represented as time patients spent with sodium and ICP levels above or below predefined thresholds — referred to as Na Dose and ICP Dose — as well as fluctuations within physiologic range.

3.2 Materials and methods

3.2.1 Study population

The cohort of critically ill patients with TBI was enrolled from a subpart of the Margherita3 electronic health record database - developed by the Italian Group for the Evaluation of Interventions in Intensive Care Medicine[7] - which contains the comprehensive clinical data of 5730 **CONTROLLARE NUMERO PAZIENTI** patients of about 70 italian intensive care units (ICUs) registered between **AGGIUNGERE LE DATE**.

The patients were searched based on the International Classification of Diseases (ICD-10) code. The inclusion criteria identified 411 **CONTROLLARE NUMERO PAZIENTI** patients who were diagnosed with TBI.

For most of the study variables, the software immediately ran an automatic check for internal consistency, generating queries then sent to physicians for resolution before incorporation of the new data into the database.

The inclusion criteria were as follows: (1) age ≥ 18 years, (2) TBI as cause of admission, (3) at least one intracranial pressure (ICP) reading, (4) at least one plasma sodium value. The exclusion criteria were as follows: (1) expected ICU admission patients, (2) ICU admission after elective surgery, (3) ICU stay of less than 72h (20 patients). Patients who died within 72 hours of ICU admission were excluded to focus the analysis on those with potentially salvageable brain injuries.

3.2.2 Data Collection

Baseline parameters within the first day after ICU admission were collected including demographics (e.g., sex, age, weight, admission type), comorbidities (e.g., myocardial infarction, congestive heart failure, chronic pulmonary disease, and renal disease), assessment scale scores (Glasgow Coma Scale, GCS and Acute Physiologic Assessment and Chronic Health Evaluation, APACHE II Scoring System), intracranial pressure and pupil reactivity.

We gathered all serum sodium measurements from ICU admission up to 14 days, or until death, whichever occurred first. Additionally, we recorded data on various therapies, including extraventricular drainage, use of osmotherapy, barbiturate coma, hypothermia, among others. Lastly, we collected outcome data such as 14-day ICU mortality and overall ICU mortality.

The features extracted can be seen in Tables 3.1 and 3.2.

The features extracted can be seen in Tables 3.1 and 3.2.

Feature	Category	Count_n (%)
SEX	M	321 (78.10%)
TYPE	Chirurgico d'urgenza	229 (55.72%)
TYPE	Medico	182 (44.28%)
OUTCOME	alive at 14 days	357 (86.86%)
PUPIL	anisocoria	217 (52.80%)
Hypernatremia	True	259 (63.02%)
Hyponatremia	True	154 (37.47%)

Table 3.1: Categorical Feature Statistics

Feature	Mean (unit)	Range (unit)[mean-std, mean+std]
Altezza	173.24 (cm)	[160.63 - 185.86] (cm)
Peso	81.53 (kg)	[66.77 - 96.28] (kg)
BMI	25.46 (kg/m ²)	[21.31 - 29.61] (kg/m ²)
Best GCS during first 24h hours	6.29	[3 - 9.84]
Best GCS Motor response during first 24h hours	3.05	[1.13 - 4.97]
AGE	54.83 (years)	[36.75 - 72.90] (years)
APACHE II Score	27.46	[22.64 - 32.29]
First Sodium Value	139.59 (mmol/L)	[135.11 - 144.07] (mmol/L)
Time to Hypernatremia	48.97 (h)	[5.95 - 91.99] (h)
Time to Hyponatremia	55.32 (h)	[0 - 111.96] (h)
Na min first 14 days	135.11 (mmol/L)	[126.35 - 143.87] (mmol/L)
Na max first 14 days	148.33 (mmol/L)	[141.57 - 155.87] (mmol/L)
Na SD first 14 days	3.53 (mmol/L)	[1.08 - 5.97] (mmol/L)

Table 3.2: Continuous Feature Statistics. APACHE: Acute Physiology and Chronic Health Evaluation, BMI: Body Mass Index, GCS: Glasgow Coma Scale, Na max: maximum serum sodium over 14 days, Na min: minimum serum sodium over 14 days, Na SD: standard deviation of plasma sodium over 14 days

3.2.3 Generation of Variables and Definitions

3.2.4 Generation of Variables and Definitions

Serum Sodium Concentration on Admission and Na Dose Serum sodium concentration on admission was defined as the first available sodium measurement after admission to the Intensive Care Unit (ICU). Hyponatremia and hypernatremia were defined as conditions where at least three consecutive serum sodium values were below 135 mmol/L or above 145 mmol/L, respectively. The *Na Dose* was defined as the area under the curve (AUC) where plasma sodium remains below (for hyponatremia) or above (for hypernatremia) the respective thresholds over time. This metric quantifies the extent and duration of sodium abnormalities, providing a cumulative measure of sodium imbalance.

Glasgow Coma Scale (GCS) The Glasgow Coma Scale (GCS) on admission was defined as the first available GCS score after admission to the ICU, with a specific focus on the motor component (GCSm). Additionally, we evaluated the best and worst GCS scores within the first 24 hours to assess the patient’s neurological status over time.

Intracranial Pressure (ICP) Dose The *ICP Dose* is defined as the area under the curve (AUC) where intracranial pressure (ICP) exceeds 22 mmHg, a threshold linked to worse outcomes in traumatic brain injury. It quantifies the combined magnitude and duration of elevated ICP, offering a measure of intracranial hypertension severity.

Analysis of Plasma Sodium and ICP Fluctuations We explored the predictive value of the ratio between changes in intracranial pressure (DeltaICP) and plasma

sodium (ΔNa) - expressed as $\Delta\text{ICP}/\Delta\text{Na}$ - considering the dynamic nature of their relative changes over time.

To achieve this, we first generated continuous curves for both Na and ICP using linear interpolation. For Na, linear interpolation was applied between the first and last available sodium concentration values, generating interpolated values at one-minute intervals across the entire timeframe. The same interpolation process was applied to the ICP data, resulting in a continuous curve of ICP values at one-minute intervals. This step ensures a consistent temporal resolution for both variables, enabling a detailed analysis of their fluctuations.

Using a literature-based timeframe[37][30] to estimate the delay between changes in plasma sodium and corresponding changes in ICP, we applied a grid search method based on Granger causality¹ to identify the best-fitting time difference. This optimal value (τ) was then used to shift the ICP curve relative to the sodium curve. ΔNa and ΔICP were defined, corrispectively, as the time differences between consecutive values for both Na and ICP, based on the time-lag between the Na curve and the ICP curve (represented by the previously defined τ).

The concept of τ is crucial in this context as it represents the time delay between a change in Na (cause) and its resulting effect on ICP (effect). For instance, if we consider time points T_0 and T_1 for Na, and the same time points for ICP, it would be incorrect to directly correlate these changes without accounting for the time it takes for a change in Na to affect ICP.

By selecting the τ that maximized the predictive accuracy of the ML models, we ensured that the time-series alignment was optimized for subsequent analysis. This iterative optimization provided a tailored approach for each patient, enhancing the reliability of the calculated $\Delta\text{ICP}/\Delta\text{Na}$ values and their use in predicting patient outcomes.

Bisogna inserire il concetto di delta time

3.2.5 Statistical analysis and machine learning models development

FIL LASCEREI SCRIVERE A TE

¹Granger causality is a statistical method that tests whether past values of one variable can predict future values of another. If one variable improves the prediction of another, it is said to “Granger-cause” the other.

3.3 Results

3.3.1 Patient Demographics and Clinical Features

INSERIRE TABELLA DESCRITTIVE, PERCHE LE METTIAMO SOPRA?

3.3.2 Relationship between serum sodium fluctuations and intracranial pressure

VALUTARE INSIEME SE E COME HA SENSO INSERIRE QUESTO PARAGRAFO, IN RIFERIMENTO A QUEL 60% CIRCA

3.3.3 Relationship Between Na Dose and ICP Dose on outcome

SAREBBE IL MODELLO 2

3.3.4 Relationship between sodium fluctuations and ICP fluctuations (DeltaDelta) on outcome

SAREBBE IL MODELLO 3

3.3.5 Subgroup analysis: TIL

SAREBBE IL DISCORSO SUI TIL CON LE VARIE TABELLE

3.4 Discussion

We found that serum sodium fluctuations and relative ICP fluctuations, are a significant predictor of mortality, in line with findings from Harrois et. al.[11]

In our study, even after adjusting for baseline severity, fluctuations in serum sodium and ICP, even within normal ranges, were still linked to 14-day mortality.

The DeltaICP/DeltaNa ratio suggests that larger fluctuations in serum sodium are associated with the need for higher therapy intensity levels, raising the possibility that acute sodium variations may partially explain the relationship between DeltaICP/DeltaNa and patient outcomes.

Severe dysnatremia has long been associated with higher mortality rates. Sodium disorders are often caused by excessive administration or restriction of free water,

but they are also linked to various comorbidities. Additionally, treatments such as surgery[25][28], trauma or other acute illnesses[31] can trigger or exacerbate these imbalances.

However, emerging evidence[5] indicates that even mild deviations from normal sodium levels or simple fluctuations in sodium values may also carry significant clinical implications, especially in the brain injured patient. While this is well documented in subarachnoid hemorrhage [15][19][2][35][6][10], the effect on TBI has only recently been explored[11].

Our findings are significant for several reasons. First, understanding the risk factors associated with mortality helps clinicians make informed decisions about how often to monitor sodium levels, the type of fluids administered (hypotonic vs. isotonic), and how much sodium levels are allowed to fluctuate. Second, identifying sodium fluctuations as an independent risk factor for hospital mortality highlights the need to further explore their physiological causes and impacts, which could help clinicians identify at-risk patients earlier and potentially reduce mortality rates.

In our DeltaICP/DeltaNa analysis, we found that larger fluctuations in DeltaICP/DeltaNa were associated with higher mortality, this could be driven by DeltaNa alone. Rapid changes in sodium levels over a short time may pose a greater risk to patients due to the fast cerebral fluid shifts that occur. In response to hypertonic conditions in the extracellular space, brain cells attempt to restore osmotic balance by absorbing organic osmoles, a process that requires time. Sudden shifts in extracellular sodium can lead to intracellular fluid and electrolyte imbalances, resulting in cellular edema, particularly in an already injured brain with compromised or slower adaptive mechanisms. Additionally, it remains challenging to determine how our interventions might affect the unsalvageable brain—could our therapies inadvertently harm the very salvageable brain tissue we aim to protect in the first place?

It's plausible that patients who died or had poor neurological outcomes at 14 days were exposed to a broader range of sodium concentrations due to the need for therapies like hypertonic saline. Although the delta/delta ratio is a relative measurement, the overall variation appears low. This counterintuitive result could be attributed to minimal fluctuation occurring at consistently high levels of Na (as part of the therapeutic strategy) and ICP (due to exhausted cerebral compliance).

3.4.1 Limitations and current prospectives

This is a retrospective study, and as such, it carries the inherent limitations associated with this type of research.

We did not assess neurological outcomes nor the Glasgow Outcome Coma Scale was available in our database. This limitation should be addressed in future studies investigating sodium fluctuations in TBI patients.

We didn't assessed the impact of intravenous fluid administration on sodium variability, as it was challenging to extract detailed information regarding the specific types of hypertonic saline[14] used for osmolar therapy. For similar reasons, we didn't assessed the impact of diabete insipidus through desmopressin administration, as considering it alone as a surrogate marker wouldn't have been enough to diagnose DI or to discriminate with other brain-related plasma sodium disorders (SIADH or CSW).

Although we adjusted for TIL, serum sodium fluctuations may still be a reflection of overall illness severity. Nevertheless, dysnatremias remain a known risk factor and should be incorporated into future predictive models for mortality in TBI patients, including fluctuations within normal limits, rather than dismissed as a mere consequence of disease severity.

Additional limitations in the subanalysis of patients within TIL therapy categories, beyond the already mentioned hypertonic saline, include missing data on decompressive craniectomy[16] and other interventions that are difficult to associate with specific treatment goals. For instance, it's unclear whether vasopressors were used to manage elevated ICP or for other hemodynamic purposes, further complicating the analysis.

Lastly, patients who died within the first three days were excluded, which may limit the generalizability of our results.

3.5 Conclusion

While doses of potassium, glucose, and water are routinely adjusted, sodium is typically administered at standard concentrations as long as serum levels remain within an acceptable or desired range. This is common practice in many ICU patients and is well tolerated in most cases. However, for some individuals, the sodium content may not align with their intravascular volume or neuroendocrine status, leading to impaired sodium homeostasis. Until it is definitively proven that dysnatremia is merely a non-causal marker of an underlying harmful systemic process, it is prudent to assume that even slight sodium fluctuations and the resulting osmotic shifts could be detrimental. Therefore, the focus should perhaps shift to sodium fluctuations, or even osmolality. Minimizing sodium fluctuations to maintain a stable sodium trajectory and osmolality might be of more importance than sodium levels themselves.

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Bibliography

- [1] M. Baba, D. Alsbrook, S. Williamson, S. Soman, and A. R. Ramadan. Approach to the Management of Sodium Disorders in the Neuro Critical Care Unit. *Current Treatment Options in Neurology*, 24(8):327–346, Aug. 2022.
- [2] J. Bales, S. Cho, T. K. Tran, G. A. Korab, N. Khandelwal, C. F. Spiekerman, and A. M. Joffe. The Effect of Hyponatremia and Sodium Variability on Outcomes in Adults with Aneurysmal Subarachnoid Hemorrhage. *World Neurosurgery*, 96:340–349, Dec. 2016.
- [3] G. Cucciolini, V. Motroni, and M. Czosnyka. Intracranial pressure for clinicians: It is not just a number. *Journal of Anesthesia, Analgesia and Critical Care*, 3(1):31, Sept. 2023.
- [4] A. L. D’Ambrosio, D. J. Hoh, W. J. Mack, C. J. Winfree, M. N. Nair, A. Ducruet, R. R. Sciacca, J. Huang, D. J. Pinsky, and E. S. Connolly. Interhemispheric intracranial pressure gradients in nonhuman primate stroke. *Surgical Neurology*, 58(5):295–301; discussion 301, Nov. 2002.
- [5] M. Darmon, E. Diconne, B. Souweine, S. Ruckly, C. Adrie, E. Azoulay, C. Clec’h, M. Garrouste-Orgeas, C. Schwebel, D. Goldgran-Toledano, H. Khallel, A.-S. Dumenil, S. Jamali, C. Cheval, B. Allaouchiche, F. Zeni, and J.-F. Timsit. Prognostic consequences of borderline dysnatremia: Pay attention to minimal serum sodium change. *Critical Care (London, England)*, 17(1):R12, Jan. 2013.
- [6] M. E. Eagles, M. K. Tso, and R. L. Macdonald. Significance of fluctuations in serum sodium levels following aneurysmal subarachnoid hemorrhage: An exploratory analysis. *Journal of Neurosurgery*, 131(2):420–425, Aug. 2019.
- [7] S. Finazzi, G. Mandelli, E. Garbero, M. Mondini, G. Trussardi, M. Giardino, M. Tavola, and G. Bertolini. Data collection and research with MargheritaTre. *Physiological Measurement*, 39(8):084004, Aug. 2018.

- [8] D. A. Godoy, S. Brasil, C. Iaccarino, W. Paiva, and A. M. Rubiano. The intracranial compartmental syndrome: A proposed model for acute brain injury monitoring and management. *Critical Care*, 27(1):137, Apr. 2023.
- [9] F. Güiza, G. Meyfroidt, I. Piper, G. Citerio, I. Chambers, P. Enblad, P. Nillson, B. Feyen, P. Jorens, A. Maas, M. U. Schuhmann, R. Donald, L. Moss, G. Van den Berghe, and B. Depreitere. Cerebral Perfusion Pressure Insults and Associations with Outcome in Adult Traumatic Brain Injury. *Journal of Neurotrauma*, 34(16):2425–2431, Aug. 2017.
- [10] T. Harada, Y. Uozumi, H. Fukuoka, S. Miyake, D. Yamamoto, Y. Okamura, T. Ishii, S. Tatsumi, T. Mizobe, H. Aihara, K. Tanaka, E. Kohmura, and T. Sasayama. The impact of hormonal dynamics and serum sodium fluctuations on symptomatic vasospasm after subarachnoid hemorrhage. *Journal of Clinical Neuroscience*, 103:131–140, Sept. 2022.
- [11] A. Harrois, J. R. Anstey, M. Van Der Jagt, F. S. Taccone, A. A. Udy, G. Citerio, J. Duranteau, C. Ichai, R. Badenes, J. R. Prowle, A. Ercole, M. Oddo, A. Schneider, S. Wolf, R. Helbok, D. W. Nelson, D. J. Cooper, R. Bellomo, The TBI Collaborative, K. Long, A. Rodrigues, A. Lozano, E. Saxby, A. Vargiolu, H. Quintard, M. Guillemes, A. Sisson, G. Allen, N. Baro, and M. Kofler. Variability in Serum Sodium Concentration and Prognostic Significance in Severe Traumatic Brain Injury: A Multicenter Observational Study. *Neurocritical Care*, 34(3):899–907, June 2021.
- [12] G. W. J. Hawryluk, S. Aguilera, A. Buki, E. Bulger, G. Citerio, D. J. Cooper, R. D. Arrastia, M. Diringer, A. Figaji, G. Gao, R. Geocadin, J. Ghajar, O. Harris, A. Hoffer, P. Hutchinson, M. Joseph, R. Kitagawa, G. Manley, S. Mayer, D. K. Menon, G. Meyfroidt, D. B. Michael, M. Oddo, D. Okonkwo, M. Patel, C. Robertson, J. V. Rosenfeld, A. M. Rubiano, J. Sahuquillo, F. Servadei, L. Sutter, D. Stein, N. Stocchetti, F. S. Taccone, S. Timmons, E. Tsai, J. S. Ullman, P. Vespa, W. Videtta, D. W. Wright, C. Zammit, and R. M. Chesnut. A management algorithm for patients with intracranial pressure monitoring: The Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intensive Care Medicine*, 45(12):1783–1794, Dec. 2019.
- [13] G. W. J. Hawryluk, G. Citerio, P. Hutchinson, A. Kolias, G. Meyfroidt, C. Robba, N. Stocchetti, and R. Chesnut. Intracranial pressure: Current perspectives on physiology and monitoring. *Intensive Care Medicine*, 48(10):1471–1481, Oct. 2022.

BIBLIOGRAPHY

- [14] D. N. Holden, J. J. Mucksavage, J. A. Cokley, K. S. Kim, N. L. Tucker, M. S. Esordi, and A. M. Cook. Hypertonic saline use in neurocritical care for treating cerebral edema: A review of optimal formulation, dosing, safety, administration and storage. *American Journal of Health-System Pharmacy*, 80(6):331–342, Mar. 2023.
- [15] D. Jin, S. Jin, B. Liu, Y. Ding, F. Zhou, and Y. Jin. Association between serum sodium and in-hospital mortality among critically ill patients with spontaneous subarachnoid hemorrhage. *Frontiers in Neurology*, 13:1025808, Oct. 2022.
- [16] J. H. Kim, Y.-H. Choo, H. Jeong, M. Kim, E. J. Ha, J. Oh, and S. Lee. Recent Updates on Controversies in Decompressive Craniectomy and Cranioplasty: Physiological Effect, Indication, Complication, and Management. *Korean Journal of Neurotrauma*, 19(2):128, 2023.
- [17] S. P. Klein, V. De Sloovere, G. Meyfroidt, and B. Depreitere. Differential Hemodynamic Response of Pial Arterioles Contributes to a Quadriphasic Cerebral Autoregulation Physiology. *Journal of the American Heart Association*, 11(1):e022943, Jan. 2022.
- [18] E. J. Kouloulas, A. G. Papadeas, X. Michail, D. E. Sakas, and E. J. Boviatsis. Prognostic value of time-related Glasgow coma scale components in severe traumatic brain injury: A prospective evaluation with respect to 1-year survival and functional outcome. *International Journal of Rehabilitation Research. Internationale Zeitschrift Fur Rehabilitationsforschung. Revue Internationale De Recherches De Readaptation*, 36(3):260–267, Sept. 2013.
- [19] H. Labib, M. A. Tjerkstra, B. A. Coert, R. Post, W. P. Vandertop, D. Verbaan, and M. C. Müller. Sodium and Its Impact on Outcome After Aneurysmal Subarachnoid Hemorrhage in Patients With and Without Delayed Cerebral Ischemia. *Critical Care Medicine*, 52(5):752–763, May 2024.
- [20] C. Li, D. Hang-Gen, Y. Li-Chun, H. Min, Z. Guo-Jun, T. Yong, W. Cheng, H. Bi-Lie, and L. Hong-Yu. Zero drift of intraventricular and subdural intracranial pressure monitoring systems. *Chinese Journal of Traumatology*, 16, Nov. 2015.
- [21] E. M. Liotta. Management of Cerebral Edema, Brain Compression, and Intracranial Pressure. *Continuum (Minneapolis, Minn.)*, 27(5):1172–1200, Oct. 2021.

BIBLIOGRAPHY

- [22] T. E. MacMillan, T. Tang, and R. B. Cavalcanti. Desmopressin to Prevent Rapid Sodium Correction in Severe Hyponatremia: A Systematic Review. *The American Journal of Medicine*, 128(12):1362.e15–24, Dec. 2015.
- [23] U. Maggiore, E. Picetti, E. Antonucci, E. Parenti, G. Regolisti, M. Mergoni, A. Vezzani, A. Cabassi, and E. Fiaccadori. The relation between the incidence of hypernatremia and mortality in patients with severe traumatic brain injury. *Critical Care*, 13(4):R110, 2009.
- [24] E. Mahanna, H. McGrade, A. Afshinnik, I. Iwuchukwu, A. K. Sherma, and V. Sabharwal. Management of Sodium Abnormalities in the Neurosurgical Intensive Care Unit. *Current Anesthesiology Reports*, 5(4):387–392, Dec. 2015.
- [25] D. C. Marshall, J. D. Saliccioli, R. J. Goodson, M. A. Pimentel, K. Y. Sun, L. A. Celi, and J. Shalhoub. The association between sodium fluctuations and mortality in surgical patients requiring intensive care. *Journal of Critical Care*, 40:63–68, Aug. 2017.
- [26] C. Rafat, M. Flamant, S. Gaudry, E. Vidal-Petiot, J.-D. Ricard, and D. Dreyfuss. Hyponatremia in the intensive care unit: How to avoid a Zugzwang situation? *Annals of Intensive Care*, 5(1):39, Dec. 2015.
- [27] C. Robba, F. Graziano, A. Guglielmi, P. Rebora, S. Galimberti, F. S. Taccone, G. Citerio, the SYNAPSE-ICU Investigators, W. Videtta, G. Domeniconi, M. E. Giménez, M. Fumale, E. D. Amundarain, M. Casanova, M. Reade, E. Hallt, D. Pearson, I. Seppelt, R. Helbok, V. Davidovich, G. Meyfroidt, I. A. Crippa, L. Mebis, P. Biston, S. Van De Velde, G. Denis, P. Kurtz, S. Y. Wayhs, M. Sekhon, D. Griesdale, A. Rigamonti, J. M. Montes, R. Pérez-Araos, J. H. Mejia-Mantilla, A. Gempeler, R. Mendoza, N. Kovac, H. B. Gutiérrez, V. Spatenkova, M. Fencel, R. Gal, O. Hrdy, K. Vrbica, J. Skola, E. Provaznikova, J. Kletecka, P. Lavicka, V. Spatenkova, P. Bresil, M. Levin, P. Bresil, J. Thomsen, T. E. Larsen, H. W. Hoffmeyer, M. O. Holm, J. B. Andersen, B. Majholm, M. Smitt, H. S. Eddelien, M. Jibaja, F. Maldonado, M. F. García, K. Asehnoune, B. Pons, G. Audibert, M. Lucca, G. Besch, P. Banco, K. Asehnoune, R. Cinotti, H. Q. Uintard, B. Soyer, A. Caillard, C. Gakuba, R. Sonnevile, S. Wolf, K. Fuest, L. Albrecht, S. Grotheer, S. M. Krieg, S. J. Schaller, C. Vrettou, E. Kontoudaki, A. Efthymiou, E. Palli, D. Makris, C. Diakaki, C. Iasonidou, A. Dimoula, G. Koukoulitsios, G. Kyriazopoulos, N. Pantelas, S. Tsikriki, E. E. Stamou, C. Vrettou, A. Giannopoulos, E. Mouloudi, P. S. Hoi, Y. C. Cheuk, H. K. Darshana, K. Tánzos, G. Nardai,

- Z. Szentkereszty, H. Sapra, D. Gupta, K. Sharma, S. Anand, A. Luthra, S. Bloria, R. Chauhan, N. Panda, A. Ozair, B. Kilapong, A. Alsudani, G. Citerio, A. Soragni, A. Motta, A. Marudi, E. Bertellini, A. Caricato, C. Gelormini, E. Ioannoni, E. Stival, S. Silva, F. Pozzi, I. Brunetti, A. Cortegiani, E. Picetti, F. Villa, I. Calamai, M. C. Casadio, M. C. Quartarone, M. Grandis, F. Magni, S. D. Bianco, C. Bonetti, V. Buldini, A. Giugni, S. M. Zerbi, M. Carbonara, A. Cotoia, A. Izzì, O. Sabelnikovs, M. Elhadi, H. Ahmed, S. A. Ñ. Silva, G. A. G. López, G. S. Shrestha, S. Maskey, T. Bajracharya, K. Nilam, P. Kifle, L. Rajbanshi, Y. B. Roka, O. Idowu, K. M. Mukhtar, J. L. P. Portilla, K. Kojder, I. Aragao, R. Freitas, M. Simoes, D. Batista, C. Pacheco, F. Assunção, L. Lencastre, P. Cavaleiro, M. Abdelaty, A. Gritsan, S. K. Sergey, D. Nikolay, Y. Arabi, P. Gradisek, P. Forjan, M. Škoti, S. F. Ribaric, P. Gradisek, N. Milivojevic, S. Kozar, R. Badenes, A. B. Ortiz, M. C. Lopez, L. Galarza, L. Corral, A. Lores, R. Soley, L. Pariente, P. L. Ojeda, M. D. A. Verdu, L. J. Y. Dominguez, M. I. G. Perez, M. Anglada, P. Duque, A. Serrano, B. Monleon, V. Blazquez, M. Oddo, S. A. Maillard, P. Morelli, J.-P. Miroz, E. Favre, W. Sellami, M. Lamperti, J. Dibù, R. Sivities, A. Kolias, C. Thompson, C. Hawthorne, J. Roberts, L. Prisco, R. Lightfoot, J. I. Suarez, L. Rivera-Lara, S. Muehlschlegel, J. Padilla, S. Sivakumar, and D. Olson. Treatments for intracranial hypertension in acute brain-injured patients: Grading, timing, and association with outcome. Data from the SYNAPSE-ICU study. *Intensive Care Medicine*, 49(1):50–61, Jan. 2023.
- [28] Y. Sakr, S. Rother, A. M. P. Ferreira, C. Ewald, P. Dünisch, N. Riedemann, and K. Reinhart. Fluctuations in Serum Sodium Level Are Associated With an Increased Risk of Death in Surgical ICU Patients*. *Critical Care Medicine*, 41(1):133–142, Jan. 2013.
- [29] A.-L. Schönenberg-Tu, D. Cysarz, B. Petzold, C. B. Blümel, C. Raak, O. Fricke, F. Edelhäuser, and W. Scharbrodt. Pressure Time Dose as a Representation of Intracranial Pressure Burden and Its Dependency on Intracranial Pressure Waveform Morphology at Different Time Intervals. *Sensors*, 23(19):8051, Jan. 2023.
- [30] N. W. Seay, R. W. Lehigh, and A. Greenberg. Diagnosis and Management of Disorders of Body Tonicity—Hyponatremia and Hypernatremia: Core Curriculum 2020. *American Journal of Kidney Diseases*, 75(2):272–286, Feb. 2020.
- [31] S. Sen, N. Tran, B. Chan, T. L. Palmieri, D. G. Greenhalgh, and K. Cho. Sodium variability is associated with increased mortality in severe burn injury. *Burns &*

BIBLIOGRAPHY

- Trauma*, 5, Dec. 2017.
- [32] R. H. Sterns. Disorders of Plasma Sodium — Causes, Consequences, and Correction. *New England Journal of Medicine*, 372(1):55–65, Jan. 2015.
- [33] R. H. Sterns and S. M. Silver. Cerebral salt wasting versus SIADH: What difference? *Journal of the American Society of Nephrology: JASN*, 19(2):194–196, Feb. 2008.
- [34] N. Stocchetti and A. I. Maas. Traumatic Intracranial Hypertension. *New England Journal of Medicine*, 370(22):2121–2130, May 2014.
- [35] A. A. Topjian, A. Stuart, A. A. Pabalan, A. Clair, T. J. Kilbaugh, N. S. Abend, P. B. Storm, R. A. Berg, J. W. Huh, and S. H. Friess. Greater Fluctuations in Serum Sodium Levels Are Associated With Increased Mortality in Children With Externalized Ventriculostomy Drains in a PICU*:. *Pediatric Critical Care Medicine*, 15(9):846–855, Nov. 2014.
- [36] A. Vedantam, C. S. Robertson, and S. P. Gopinath. Morbidity and mortality associated with hypernatremia in patients with severe traumatic brain injury. *Neurosurgical Focus*, 43(5):E2, Nov. 2017.
- [37] J. Verbalis. Brain volume regulation in response to changes in osmolality. *Neuroscience*, 168(4):862–870, July 2010.
- [38] A. M. Warren, M. Grossmann, M. Christ-Crain, and N. Russell. Syndrome of Inappropriate Antidiuresis: From Pathophysiology to Management. *Endocrine Reviews*, 44(5):819–861, Sept. 2023.
- [39] M. H. Wilson. Monroe-Kellie 2.0: The dynamic vascular and venous pathophysiological components of intracranial pressure. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, 36(8):1338–1350, Aug. 2016.
- [40] T. Yumoto, K. Sato, T. Ugawa, S. Ichiba, and Y. Ujike. Prevalence, Risk Factors, and Short-term Consequences of Traumatic Brain Injury-associated Hyponatremia. *Acta Med. Okayama*, 69(4), 2015.
- [41] T. Zoerle, T. Birg, M. Carbonara, P. Smielewski, M. M. Placek, E. R. Zanier, C. A. I. Åkerlund, F. Ortolano, N. Stocchetti, CENTER-TBI High Resolution

- ICU Sub-Study Participants and Investigators, A. Anke, R. Beer, B.-M. Bellander, E. Beqiri, A. Buki, M. Cabeleira, A. Chierogato, G. Citerio, H. Clusmann, E. Czeiter, M. Czosnyka, B. Depreitere, A. Ercole, S. Frisvold, R. Helbok, S. Jankowski, D. Kondziella, L.-O. Koskinen, A. Kowark, D. K. Menon, G. Meyfroidt, K. Moeller, D. Nelson, A. Piippo-Karjalainen, A. Radoi, A. Ragauskas, R. Raj, J. Rhodes, S. Rocka, R. Rossaint, J. Sahuquillo, O. Sakowitz, P. Smielewski, N. Sundström, R. Takala, T. Tamosuitis, O. Tenovuo, A. Unterberg, P. Vajkoczy, A. Vargiolu, R. Vilcinis, S. Wolf, A. Younsi, and F. A. Zeiler. Accuracy of Manual Intracranial Pressure Recording Compared to a Computerized High-Resolution System: A CENTER-TBI Analysis. *Neurocritical Care*, 38(3):781–790, June 2023.
- [42] P. Zuercher, J. L. Groen, M. J. Aries, E. W. Steyerberg, A. I. Maas, A. Ercole, and D. K. Menon. Reliability and Validity of the Therapy Intensity Level Scale: Analysis of Clinimetric Properties of a Novel Approach to Assess Management of Intracranial Pressure in Traumatic Brain Injury. *Journal of Neurotrauma*, 33(19):1768–1774, Oct. 2016.