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Final degree project

Implementation of a biomarker-based algorithm for the management of patients with mild traumatic brain injury in the emergency department

A quasi-experimental study

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A la Dra. Cristina Ramió per la seva paciència, predisposició, i per transmetre'm el mateix caliu que transmet a tots els seus pacients.

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1. ABSTRACT

Background: mild traumatic brain injury (mTBI) is a common presentation in emergency rooms (ER), often requiring cranial computed tomography (cCT) to rule out intracranial injuries. However, excessive reliance on cCT and confusion in their criteria to be performed can result in unnecessary radiation exposure, increased healthcare costs, and prolonged ER stays. Recent advances suggest that blood TBI biomarkers, such as GFAP and UCH-L1, may represent an accurate screening tool to identify patients at low risk of intracranial injuries, reducing cCT scan utilization. Nevertheless, these have yet to be implemented into clinical practice guidelines.

Objectives: to evaluate the implementation of a biomarker-based diagnostic algorithm for mTBI management in the ER of a tertiary hospital. We aim to assess its impact on the proportion of cCT performed and the length of ER stay, while ensuring patient safety.

Design: a quasi-experimental, pre-post implementation study will be conducted in a tertiary hospital. The pre-implementation period will include patients managed using standard protocols without biomarkers. The post-implementation period will introduce the new TBI biomarker-based algorithm.

Participants and methods: 225 patients will be included in each group using a consecutive sampling method and a recruitment period of 8 months. Patients aged ≥18 years presenting within 12 hours of a head trauma will be included. Data will be collected retrospectively from the existing database of the hospital for the first group and prospectively during visits to the ER for the second group.
Primary outcomes will be the proportion of cCT performed and ER time of stay. Secondary outcomes will include safety indicators such as reattendance rates and mortality related to mTBI. Results will be analyzed and compared by a statistician.

Keywords: mild traumatic brain injury, Emergency room, Cranial computed tomography, TBI biomarkers, GFAP, UCH-L1, Intracranial injuries, Diagnostic algorithm, Time of stay in ER.

2. ABREVIATIONS AND ACRONYMS

ATP: Adenosine triphosphate

BBB: Blood Brain Barrier

BIG: Brain Injury Guidelines

CCHR: Canadian CT Head Rule

CDC: Center for Disease Control

CEIC: Comitè d'Ètica I d'Investigació Clínica

cCT: Cranial Computed Tomography

CMIA: Chemiluminescent Microparticle Immunoassay

CT: Computed Tomography

DAI: Diffuse Axonal Injury

DM: Data Manager

EDTA: Ethylenediaminetetraacetic Acid

ER: Emergency Room

EV: Extracellular Vesicles

EUSEM: European Society for Emergency Medicine

GFAP: Glial Fibrillary Acidic Protein

GCS: Glasgow Coma Scale

HC: Co-Investigator Coordinator / Hospital Coordinator

HR: Hazard Ratios

IL: Interleukin

IQR: Interquartile Range

LOC: Loss of Consciousness

MAP: Microtubule-Associated Protein

MBP: Myelin Basic Protein

MI: Main Investigator

mSv: Millisievert

mTBI: Mild Traumatic Brain Injury

NEXUS II: National Emergency X-Radiography Utilization Study II

NFs: Neurofilament Proteins

NMDA: N-Methyl-D-Aspartate Receptor

NOC: New Orleans Criteria

NSE: Neuron-Specific Enolase

OR: Odds Ratios

PTA: Post-Traumatic Amnesia

RCCT: Randomized Control Clinical Trial

RLUs: Relative Light Units

SAP: Systems Applications and Products in Data Processing Registry

SC: Study Coordinator

SEMES: Sociedad Española de Medicina de Urgencias y Emergencias

SERAM: Sociedad Española de Radiología Médica

SPSS: Statistical Package for the Social Sciences

TBI: Traumatic Brain Injury

TNF: Tumor Necrosing Factor

UCH-L1: Ubiquitin C-Terminal Hydrolase-L1

WMA: World Medical Association

3. INTRODUCTION

3.1. TRAUMATIC BRAIN INJURY

3.1.1. Definition

The most widely accepted definition of traumatic brain injury (TBI) refers to any physical injury or functional impairment of the cranial contents caused by the application of sudden force to the skull (1).

Despite the existence of multiple definitions for TBI, in 2010, the Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health established what currently is the most accepted definition:

> "Any alteration in brain function, or other evidence of brain pathology, caused by an external force" (2).

The phrase "any alteration in brain function" includes a variety of manifestations:

- Decreased level of consciousness.
- Retrograde or anterograde amnesia.
- Neurological deficits of any kind.
- Altered mental state (e.g., confusion, disorientation, or bradypsychia).
- Focal neurological deficits.

The concept "or other evidence of brain pathology" refers to the variety of signs that can be found in clinically asymptomatic patients. Such evidence may include visual, neuroradiologic, or laboratory confirmation of damage to the brain. Modern imaging techniques are considered the gold standard, and biomarkers can also play an important role enabling a diagnosis in the following situations:

- Clinical consequences are subtle or delayed.
- Clinical diagnosis is confounded by a difficult context.
- There is a need to differentiate between signs as a product of TBI and signs related to other causes.

It is worth mentioning that although advanced diagnostic tests may play an important role in the diagnosis of TBI, clinical judgement is essential to determine if the trauma

is the primary cause of the observed impairment or whether the patient has any pre-existing neurological condition.

3.1.2. Etiology

"Caused by an external force" may include any of the following events, which represent the etiologies:

- The head being struck by an object.
- The head striking an object.
- The brain undergoing an acceleration/deceleration movement without direct external trauma to the head.
- A foreign body penetrating the brain.
- Forces generated from events such as a blast or explosion.

The primary causes of TBI are mainly falls and traffic or workplace accidents (3).

3.1.3. Classification

The main classification used for TBI is a clinical one based on the Glasgow Coma Scale (GCS). Patients are thus classified in 3 different severity groups: mild, moderate and severe TBI (4).

This classification presents with some limitations as it is a clinical based one. It does not give importance to imaging or fluid biomarkers to determine de presence of neuronal damage in patients with mild traumatic brain injury (mTBI). It is for this reason that further diagnostics tests along with a complete clinical history assessment are important for being able to stratify patients according to their true severity. Other factors that need to be considered when classifying patients for their severity are summarized in Table 1.

	Mild TBI	Moderate TBI	Severe TBI
Structural brain imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness (duration)	0-30 minutes	30 minutes to 24 hours	>24 hours
Altered mental state (duration)	≤24 hours	>24 hours	>24 hours
Post trauma amnesia (duration)	≤1 day	1-7 days	>7 days
Glasgow Coma Scale score*	13-15	9-12	<9

Table 1. Classification of TBI. A patient meeting the criteria in more than one category is classified into the higher severity level.

*Best score achieved in the first 24 hours after trauma (4).

3.1.3.1. Mild Traumatic Brain Injury

There is also not a clear definition on mTBI, as many research groups find disagreement when trying to reach a consensus about it.

The definition by the **Brain Injury Guidelines** (BIG) has recently proven to be the most reliable one (5).

The BIG classify any TBI as mild when any of the following criteria are met (6):

1. Glasgow Coma Scale (GCS) Score: a GCS score of 13 to 15.
2. Duration of Loss of Consciousness (LOC): the LOC should be less than 30 minutes.
3. Duration of Post-Traumatic Amnesia (PTA): the duration of PTA should be less than 24 hours. This includes any period of confusion, disorientation, or memory dysfunction immediately following the injury.

3.2. EPIDEMIOLOGY

3.2.1. Worldwide epidemiology

TBI remains a significant and growing public health challenge, standing as the leading cause of death and disability worldwide among all trauma-related injuries. The global incidence of all-cause, all-severity TBI is estimated at 939 cases per 100.000 people (7).

Each year an estimated 69 million individuals will suffer a TBI. The vast majority will be mild, as mTBI affects approximately 740 cases per 100.000 people, or a total of 55.9 million people each year. Mild TBI represents 81% of all TBI worldwide, whereas severe TBI accounts for 73 cases per 100.000 people, which can be estimated to represent 11% of all cases of TBI or 5’48 million people each year (7).

Road traffic accidents are still a significant cause of TBI, although their impact in the incidence on TBI and the burden of this condition differs across regions because of different regulations, infrastructures and cultures. While the incidence of TBI is highest in the North America / Canada and the Europe regions, the greatest overall burden of TBI is seen in the South East Asian region and the Western Pacific region (7).

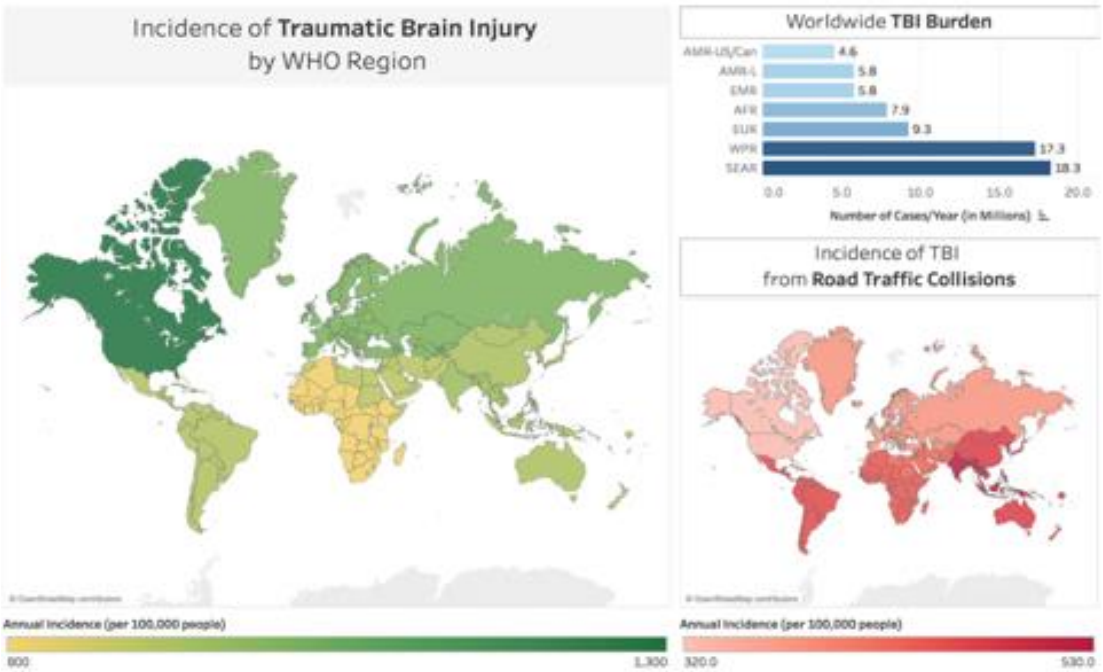

Figure 1. Map showing incidence of TBI (cases per 100,000 people) by WHO region (left). Bar graph (upper right) indicating the estimated volume of TBI annually across WHO regions. Map (lower right) showing incidence of TBI (cases per 100,000 people). From (7).

Age groups >75 years, 0-4 years and 15-24 are the ones with higher rates of emergency department visits and hospitalization and death related to TBI. (8)
Falls, being struck by an object and road transit injuries are the most common mechanisms of injury overall. When examining each of these principal mechanisms by age group, the pattern varies (8):

- Fall-related TBI: people aged >75 years have the highest rate, followed by the age groups 0-4 years and 65-74 years. (8)
- Being struck by an object: age groups with the highest rate include those aged 5-14 years, 0-4 years and 15-24 years. (8)
- Road transit injury-related TBI: the highest rates are represented by those aged 15-24 years, 25-34 years and 35-44 years. (8)

In children, the epidemiological patterns of TBI differ from those observed in adults:

- Children under 5 years: in this age group, falls account for most of the injuries treated in emergency departments and hospitals, though they result in relatively few fatalities. In contrast, motor vehicle incidents contribute to a smaller proportion of injuries but are responsible for nearly half of all fatalities in young children (9).
- Children aged 5–14 years: falls remain the leading cause of injuries requiring emergency care, followed by injuries related to sports or recreational activities, and then motor vehicle incidents. When considering hospitalizations, falls and motor vehicle injuries are the most common causes, with the latter becoming particularly prevalent in older children. Tragically, motor vehicle accidents are also the leading cause of fatal injuries, followed by incidents involving firearms (9).
- Adolescents aged 15 years and older: among teenagers, motor vehicle incidents emerge as the primary cause of brain injuries treated in both emergency departments and hospitals. Assaults and sports-related injuries also contribute significantly. However, fatalities in this age group are predominantly due to motor vehicle crashes and firearm-related injuries (9).
- Infants under 2 years: in infants less than a year old, falls are overwhelmingly the most common cause of brain injuries leading to hospitalization (72%), followed by cases of abusive head trauma (22%). For 1-year-olds, falls remain

the leading cause (36%), with motor vehicle crashes (9%) and abusive head trauma (5%) also contributing (9).

3.2.2. Epidemiological data in Spain

On a national level, the estimated incidence revolves around 20.000 cases of TBI per year requiring hospitalization, and the total annual incidence of TBI in Spain is estimated at 200 new cases per 100.000 population (10,11).

The main causes in Spain keep in line with the ones seen in studies focused on the global population: falls, road transit incidents, work related incidents, hits on/with the head, physical violence, sport related incidents (3).
Incidence tends to be greater in men than in women, and the maximum incidence can be found in the age group from 60 years onward. This group of the population represents approximately 60-70% of all cases of mTBI, and the cause often is a fall from the same height. The rest of cases of mTBI are represented by younger patients who suffer TBI during sports practice or road transit injuries (3).

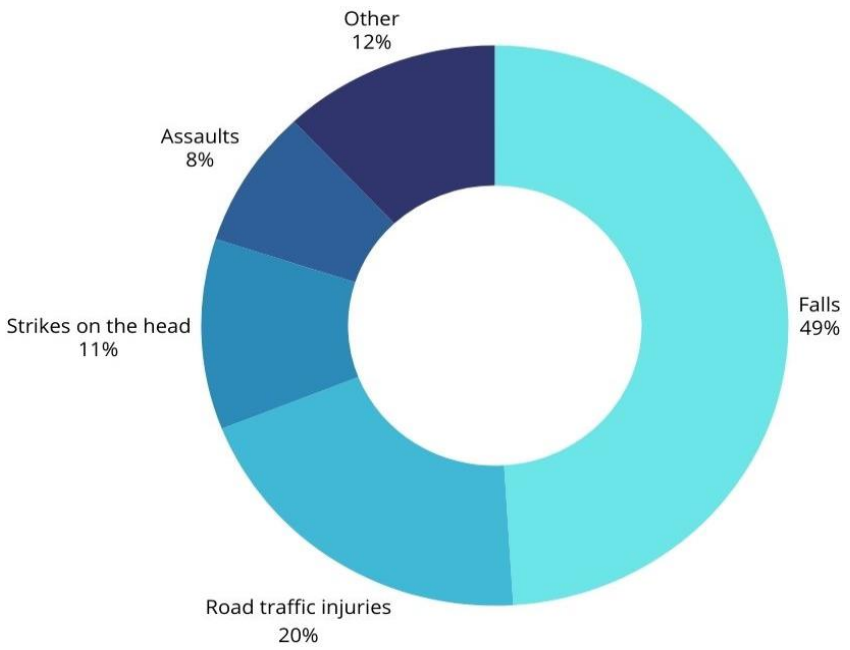

Figure 2. Main Causes of TBI in Spain. Adapted from (3).

3.3. TRAUMATIC BRAIN INJURY PATHOPHYSIOLOGY

Any force violently applied to the head might may lead to the brain, which is a soft tissue, hitting the intracranial surface of the skull, resulting in damage on different areas of the brain (12).
Injuries to the brain can be classified according to their temporality (12–17), all of them being a mix of the neuronal morphologic changes, functional alterations and after that, the pathophysiologic responses that cause the secondary injuries (12).

Although at first evaluation patients might not present with any symptoms related to mTBI, the first 24 hours are crucial, as it is within this period when most patients with risk factors for poor outcomes end up developing a neurological deterioration, which is an indicator of a previously silent primary injury (18).

3.3.1. Primary injuries

It is defined as the damage caused by direct, shear and rotational forces. It depends on the effects of the energy that the brain tissue has absorbed during the impact. We can further classify the mechanism of injury into (13):

1. **Diffuse mechanism injuries**: disruption of axons and blood vessels across the parenchyma due to rotational forces, which stretch and sometimes tear axons on the white matter tracts of the brain (e.g. diffuse axonal injury) (12).
2. **Focal injuries** (e.g. intracranial hematomas, skull fractures, lacerations, contusions and penetrating wounds). The patient's outcome is likely influenced significantly by the location and severity of the impact, as well as the depth and extent of brain penetration (12).

3.3.1.1. Diffuse injuries

Diffuse axonal injury (DAI) refers to a complex axonal injury of the white matter tracts that takes place after a traumatic brain injury involving shearing forces. The definition of this condition has evolved throughout the last decades, as research has shown that following the primary insult to the axons, a secondary cascade follows, which is also responsible for the axonal degeneration (19).

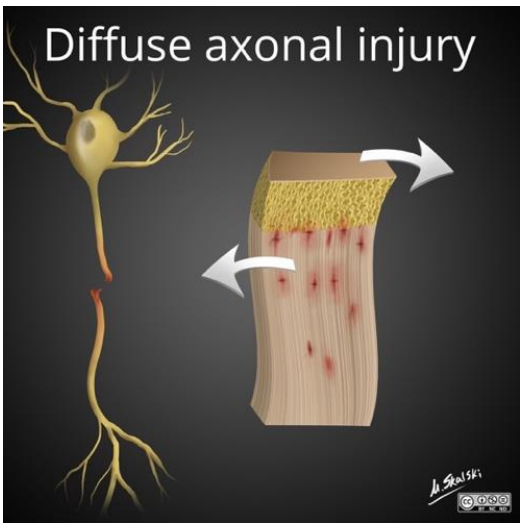

Figure 3. Illustration depicting the differential motion that causes axonal injury in head trauma. From (20).

Although DAI has been classified as a primary injury, both the primary and secondary pathological mechanisms of the injury will be explained in this section for coherence purposes:

- Primary axonal injury: axonal breakage leads to retraction and to the formation of axon retraction balls (19).
- Secondary axonal injury: after the shearing forces are applied to the brain, a pathological cascade of reactions occurs, mainly lead by the sudden influx of calcium inside the brain cells. Other processes follow, such as calpain-mediated hydrolysis, mitochondrial damage, imbalance in ion homeostasis, release of proapoptotic factors, activation of caspases, focal aggregation of amyloid precursor proteins, and finally, a glial reaction (19).

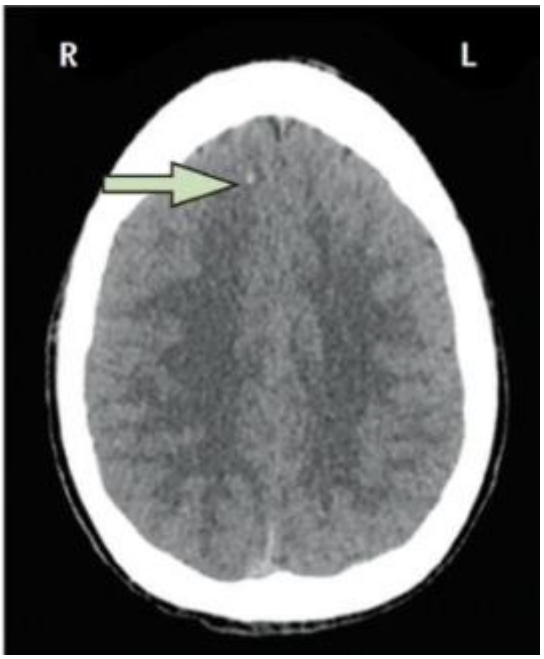

Figure 4. DAI (green arrow) on cCT. From (21).

The outcome of all these processes described is not only a disfunction of the brain cells, but also the degradation of the cytoskeleton network, which implies cellular death by apoptosis (19).

3.3.1.2. Focal injuries

Focal brain injuries often result from the brain striking the rigid surfaces of the anterior and middle cranial fossae, specially the frontal and temporal lobes. They can occur at impact sites, regardless of the presence of skull fractures, though fractures increase the risk of contusion and laceration. These injuries frequently coexist with diffuse brain injuries (22).

The most common types of focal injuries are brain contusions, subdural hematomas, and subarachnoid hemorrhages (23).

3.3.1.2.1. Brain contusion

Defined as a mixture of vascular and tissue harm that result in inflammation of a limited region of the brain, combined with blood coming from ruptured vessels (24).

Contusions happen because of the movement and forces applied to the brain in two directions within the boundaries of the skull. This type of injuries are also known as Coup-Countercoup mechanism (15). The result of this combination of shearing forces is a cortical lesion of the parenchyma that does not affect the glial-pial membrane. When this membrane is compromised, the lesion is named brain laceration (23).

Brain contusions range from microscopic hemorrhages to a confluent hemorrhagic necrotic lesion that expands through the cortex into the subcortical white matter (22). This expansion of a contusion is known as “contusion progression” and represents the secondary injury of a contusion.

As happens with DAI, following the primary insult, there is a secondary mechanism that further expands tissue damage. In this case, a vasogenic edema forms thanks to the release of inflammation factors that increase permeability in response to the ischemia experienced by the injured tissue (24).

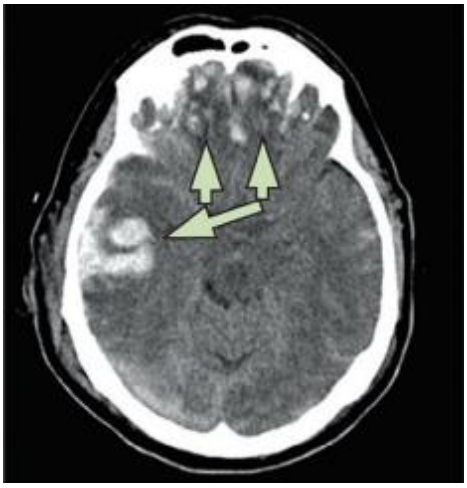

Figure 5. Brain contusions (green arrows) on cCT. From (21).

3.3.1.2.2. Intracranial hematoma

- *Epidural hematoma*: it involves bleeding between the dura mater and skull, typically caused by trauma that damages dural veins or arteries, often caused by skull fractures or, less commonly, bleeding through diploic veins in the bone marrow (15). A frequent cause of epidural hematoma is the rupture of the middle meningeal artery due to a fractured temporal bone. When the hematoma stems from arterial laceration, it can cause immediate neurological deterioration due to blood accumulation and a rapid increase in intracranial pressure, posing a significant danger in the acute phase of traumatic brain injury (15). Epidural hematomas characteristically do not cross the suture lines of the skull, as they are considered extradural (14).

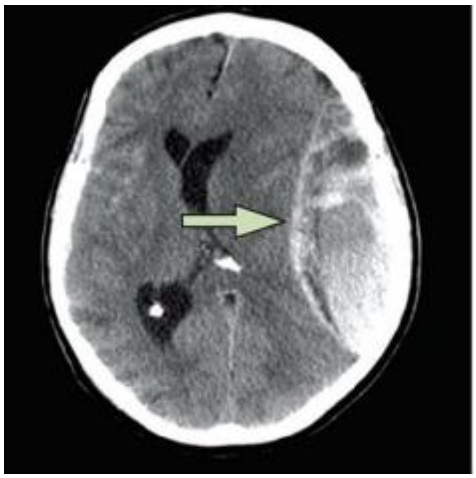

Figure 6. Epidural hematoma (green arrow) causing midline shift and increased intracranial pressure. From (21).

- *Subdural hematoma*: blood is confined to the area between the arachnoid membrane and the dura due to ruptured veins and is commonly observed in severe TBI cases, often involving damage to the pial arteries or the bridging cortical veins, allowing them to cross suture lines. While subdural hematomas develop more slowly than epidural hemorrhages, they can still lead to significant mass effect, causing mortality and functional impairment (14,15).

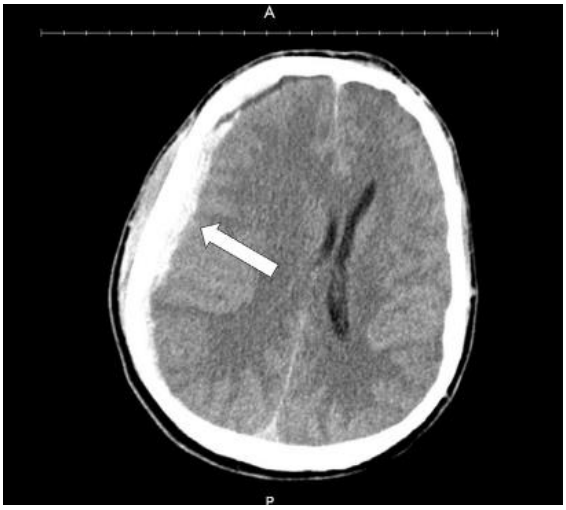

Figure 7. Subdural hematoma (white arrow) causing shifting of the midline. From (14).

- *Deep intracerebral hemorrhage*: lesions not in contact with the brain surface. The parenchyma is bleeding caused by the rupture of the intraparenchymal vessels at the moment of impact (15,22).

- *Intraventricular hemorrhage*: bleeding into the ventricles that might cause the dilation of the ventricular system and hydrocephalus.

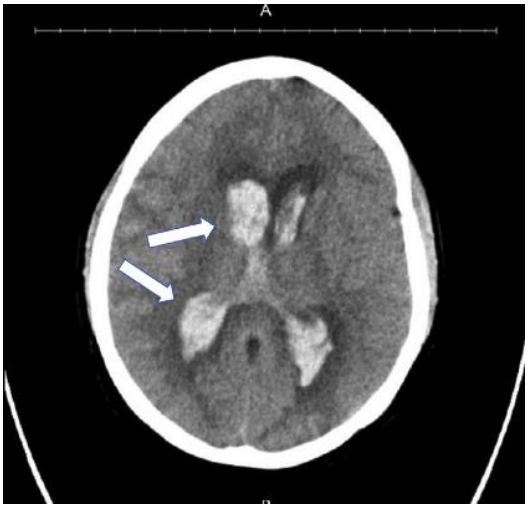

Figure 8. Intraventricular bleeding (white arrows) causing dilation of the ventricular system. From (14).

- *Subarachnoid hemorrhages*: bleeding into the subarachnoid space as a result from a disruption in the parenchyma or subarachnoid vasculature (25). If blood components hinder the arachnoid villi function, an obstruction in the drainage of cerebrospinal fluid might occur, with the subsequent onset of noncommunicating hydrocephalus (15).

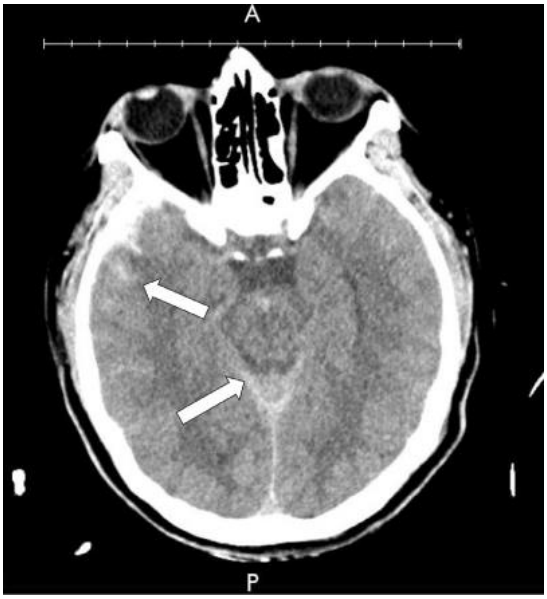

Figure 9. Subarachnoid hemorrhage. White arrows show the hyperdensities within the subdural space, indicating subarachnoid bleeding. From (14).

3.3.2. Secondary injuries

Injuries that depend on the pathological biochemical changes that follow the impact, which end up causing cellular damage and ultimately, death of neurons (13) . It is also defined as neuronal damage that results from ischemia, subsequent swelling, infection and intracranial hematoma (15) .

In the hours to days following the initial trauma, secondary injury develops, driven by a cascade of neuronal and glial dysfunction, metabolic disturbances, neuroinflammation, cerebral edema, and the release of various signaling and inflammatory molecules from neuronal, glial, and immune cells.

This complex process triggers a range of physiological responses, including blood-brain barrier (BBB) disruption, hypoperfusion, mitochondrial dysfunction, and oxidative stress, among other mechanisms. As a result, the impact of secondary injury can often surpass that of the primary insult in severity (16).

Molecular pathophysiological changes

The harmed brain tissue has a diminished metabolism because of low cerebral blood flow due to dysregulation of the cerebrovascular reactivity (12). These are thought to be the first steps of the pathophysiology, as they trigger an ischemia-like reaction, in which the brain starts anaerobic glycolysis, with the consequent gathering of lactic acid.

Anaerobic metabolism is not sustainable as the main source of energy for the cell for an extended period due to the toxicity of lactic acid. Consequently, ATP and glucose stores become depleted as they are being used for energy, and ultimately, ATP-dependent ion pumps come to a stop, causing the depolarization of the membrane.

In milder cases, the injury stretches cell membranes, causing sodium to flow into the cell, potassium to exit, and calcium levels within axons to rise. This surge in calcium activates the enzyme calpain, which breaks down cytoskeletal proteins, resulting in irreversible damage to axons.

Elevated calcium levels also activate NMDA receptors, further intensifying neuronal depolarization. The effort to restore ionic balance places significant strain on

membrane pumps, leading to even more glucose depletion, mitochondrial calcium accumulation, exacerbation of changes in oxidative metabolism, and an increase in lactate production.

These metabolic disturbances contribute to acidosis and swelling within the cells (16), known as edema. Edema is a result of increased membrane permeability, and is also one of the main factors contributing to neuronal death (15).

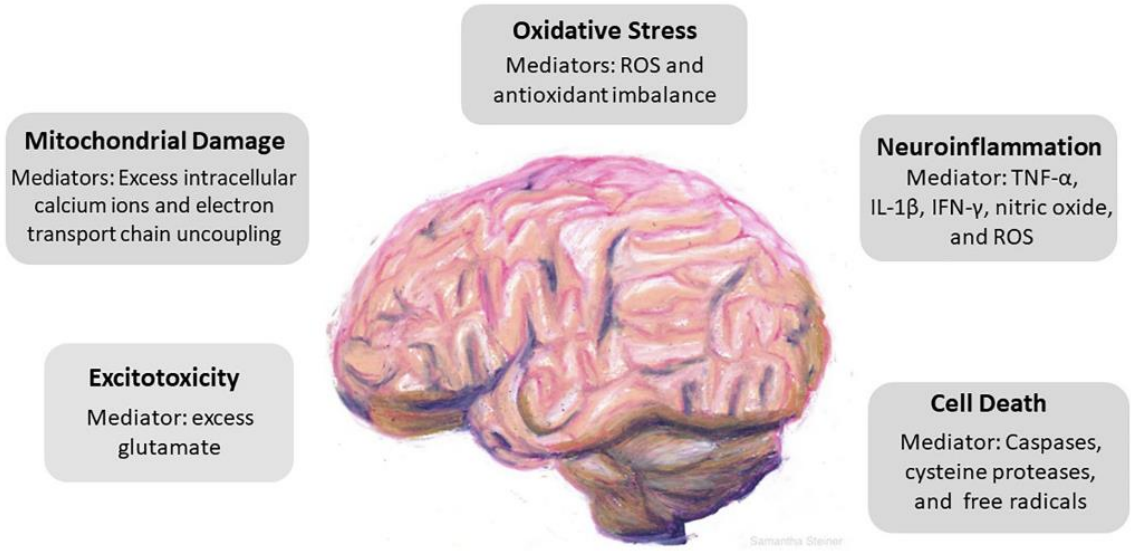

Figure 10. Cascade of cellular events driven by traumatic brain injury. From (17).

In addition to the metabolical changes and the increased membrane permeability, another process called excitotoxicity takes place (17). This process consists in excitatory neurotransmitters, such as glutamate and aspartate being released, which causes the activation of variety of inflammatory cytotoxic processes (activation of proteases, lipid peroxidases, and phospholipases), which sequentially increase the intracellular accumulation of oxygen radicals and free fatty acids (15), further damaging neurons.

Ongoing hemorrhage and brain edema leads to mass effect and anatomical herniation of intracranial structures, further perpetuating neurological injury through axonal stretch and/or vascular disruption (16).

All these mechanisms are both the cause and the result of membrane cellular disruption, vascular system destruction, and ultimately, apoptosis and necrosis (15).

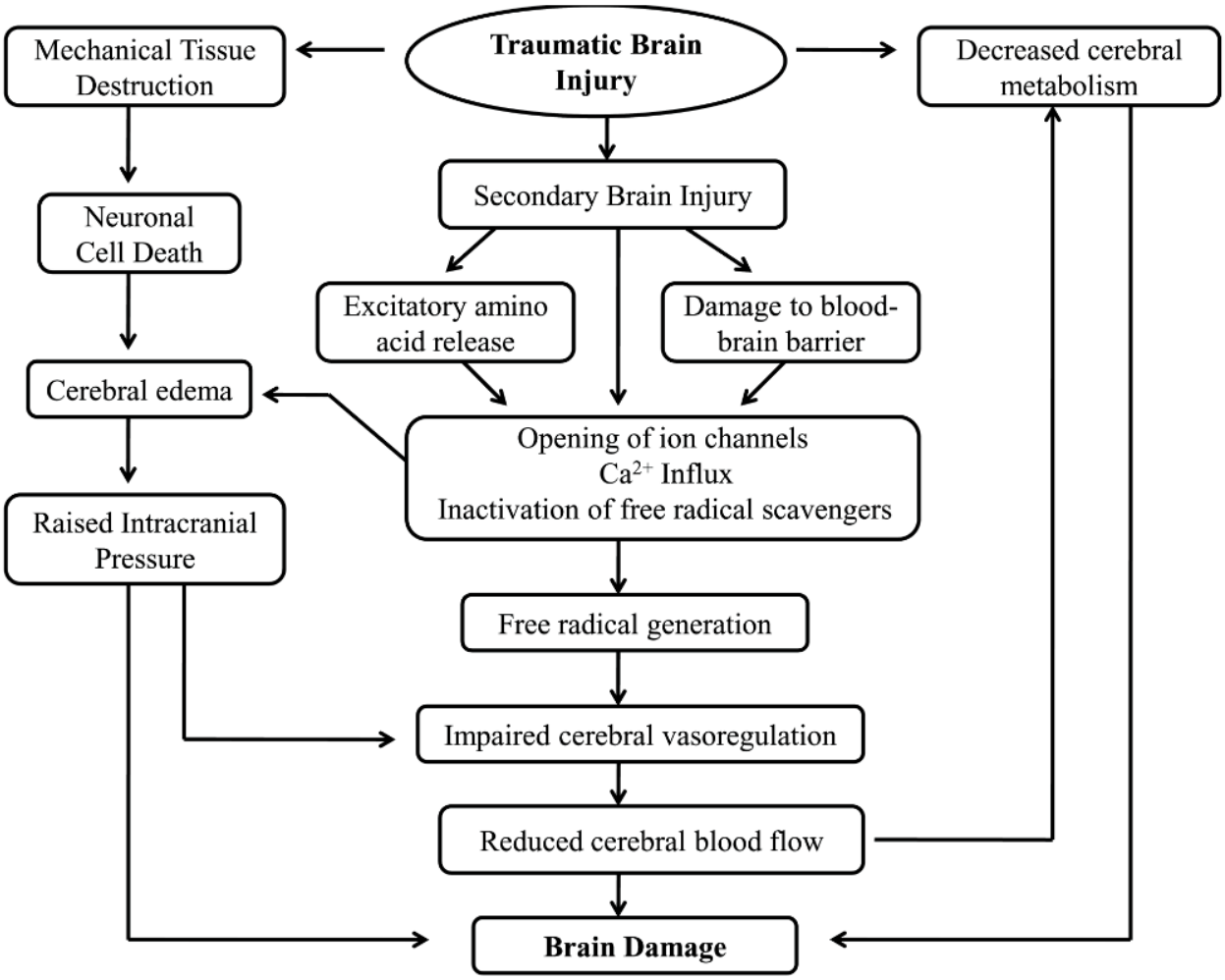

Figure 11. Alternative representation of the contributing events in the pathophysiology of TBI, also including the macroscopic consequences, such as raise in intracranial pressure. Note that it is a circular process where all changes are influenced by one another, ultimately resulting in neuronal death and brain damage. From (15).

3.4. BRAIN BIOMARKERS

TBI biomarkers can be defined as proteins resulting from axonal, neuronal or glial cell damage after an episode of traumatic brain injury (26).

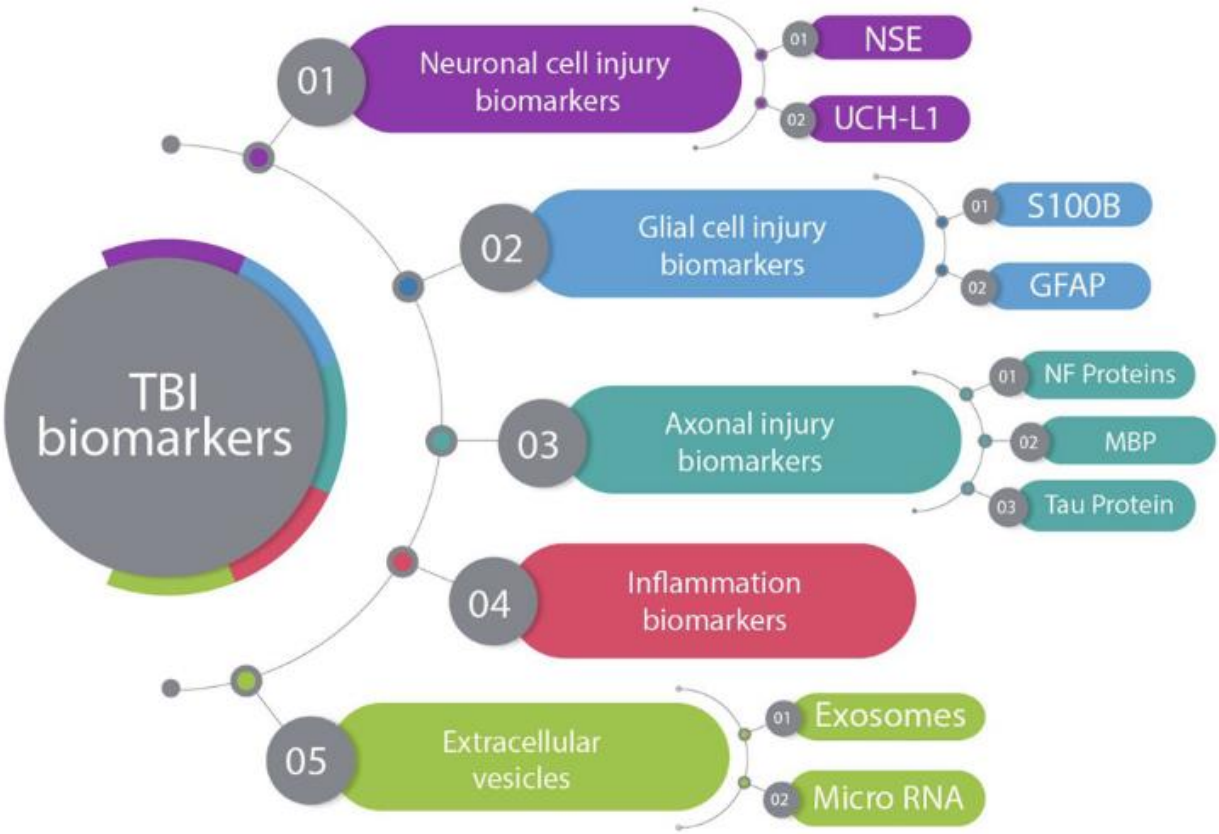

Figure 12. Schematic representation of the different types of TBI biomarkers that denote many processes such as neuronal injury, glial injury, axonal injury, and inflammation. From (26).

3.4.1. Neuronal cell body injury biomarkers

3.4.1.1. Neuron-Specific Enolase (NSE)

NSE is an enzyme that is present in the cytoplasm of neurons that takes part in the glycolysis pathway (27). Although higher levels of NSE have shown association with unfavorable outcomes in TBI patients, it presents with a big limitation when used as a diagnostic tool, since NSE concentrations are also high in erythrocytes. Therefore, NSE levels are altered when hemolysis is present, even without the presence of TBI (26,28).

3.4.1.2. Ubiquitin C-Terminal Hydrolase-L1 (UCH-L1)

UCH-L1 is a cytoplasmic enzyme of the neuronal soma that contributes to removing degraded and denaturalized neuronal proteins both in physiological and pathological conditions. It is thought to be a functional biomarker and one that serves as a barometer of neuronal cell body injury even in patients with mTBI, as it is a central nervous system specific protein. (28).

UCH-L1 can be detected at the time of injury in the plasma of patients, with a peak in concentration around 8h. After 48h, the plasma levels rapidly decrease (29).

3.4.2. Glial cell injury biomarkers

3.4.2.1. Glial Fibrillary Acidic Protein (GFAP)

GFAP is the main protein of cytoskeletal filaments in astrocytes. However, GFAP also exists in the peripheral nervous system and enteric glial cells. GFAP participates in neuronal support and maintenance and helps activate glial cells. Following TBI, astroglia cells are activated in order to induce gliosis or glial scar formation, so the expression of GFAP increases (26–28).

GFAP levels are measurable at the time of injury, reaching a peak in concentration around 20h after the injury. GFAP levels remain elevated for at least 72 hours (30).

3.4.2.2. S100B Protein

S100B is a calcium binding protein present in astroglia cells, as well as in some other tissues such as melanocytes, bone marrow cells, lymphocytes, chondrocytes and adipocytes (26).

It plays a role in the regulation of intracellular levels of calcium in the brain cells, and it protects the neurons against the inflammation cascade after a TBI (26).

The lifespan of the protein after being released to peripheral fluids is short, so blood testing should be assessed in the first 6 hours after TBI (30).

3.4.3. Axonal injury biomarkers

3.4.3.1. Neurofilament Proteins (NFs)

NFs are the primary component of the neuronal cytoskeleton, and they provide stability and integrity in their phosphorylated form. NFs consist of three different subunits: a light subunit (NF-L), a medium subunit (NF-M), and a heavy subunit (NF-H).

After TBI, the activation of the pathophysiological cascade (proteases, calpain and phosphatase calcineurin) causes the filaments to dephosphorylate, undergo proteolysis and dissociation. NFs are specific to neurons, so their detection in cerebrospinal fluid and blood indicates neural death and axonal disintegration. NFs release lasts for days after the trauma (26,28).

3.4.3.2. Tau Protein

Tau is a microtubule-associated protein (MAP) that can be found mainly in neurons. Its function is to stabilize axonal microtubules and control their movement, doing so through phosphorylation (26). When phosphorylation is excessive, Tau accumulates and forms the fibrillary tangles that can be seen as the cause of neurodegenerative diseases such as Alzheimer's Disease or Parkinson's Disease. These characteristics provide Tau with the ability of performing as a long-term predicting factor of injury severity and clinical outcome in patients that suffer TBI (26,28,30).

As explained with NFs, Tau can also be found in body fluids for days. Its serum concentration peaks at 2 days. (26,30).

3.4.3.3. Myelin Basic Protein (MBP)

MBP is an oligodendrocyte protein and a key structural component of the myelin sheath covering nerve fibers. Its function is to maintain the correct structure of myelin. MBP can be degraded by proteases such as calpain, and this can cause the degradation of axons and the myelin sheath, as happens in TBI (28).

MBP or its degradation products can be released in fluids but their release is delayed, and not specific for central nervous system injury, as injury in the peripheral nerves also increases MBP blood concentration (26).

3.4.4. Inflammation biomarkers

Both primary and secondary TBI injuries work as stimuli for inflammatory processes via activation of inflammatory proteins released mainly by leukocytes and microglia cells. Inflammatory biomarkers are potentially helpful in disease monitoring, injury diagnosis and prediction of long-term outcomes. However, they are not specific for TBI, as any disease that implies cellular injury could force their levels to be elevated.
The cytokines that have been studied as biomarkers for TBI are Interleukins (IL) IL-1, IL-6, IL-8, IL-10, and TNF-a (26).

3.4.5. Extracellular vesicles

Extracellular vesicles (EVs) are particles covered by a membrane that take part in intercellular communication. They can be secreted from all types of brain cells and can work as indicators for the state of glial cells and neurons. EVs may contribute to regeneration after stressful conditions, and they can work as biomarkers for the diagnosis, prognosis and treatment of different diseases, TBI being amongst them (26).

3.4.6. Choice of TBI biomarkers

The selection of biomarkers from this study was guided by a combination of factors. One of the main factors has been diagnostic accuracy of biomarkers as it is crucial to ensure safety of all participants of this study.

Nevertheless, it cannot be the only reason of choice of biomarker, as other specific limitations must be considered. One of the strongest limitations that biomarkers present is that even though more than 20 biomarkers are being researched, only 4 of them will be available for detection at the starting point of this study. These include **UCH-L1, GFAP, S100B, NSE**.
Moreover, amongst these 4, other drawbacks have been identified:

- On one hand **S100B** already has a significant body of research regarding its clinical applicability and has already been validated as part of the decision making process in the Scandinavian Guidelines for mTBI (31).
  Another point is that the rapid kinetics of S100B make their determinations unreliable after 6 hours. A shorter determination timeframe means that less

patients could benefit from biomarker determinations, as not all patients get to the ER within the first 6 hours (31,32). Furthermore, GFAP and UCH-L1 have shown to outperform S100B in terms of diagnostic accuracy for patients with mTBI (33).

- On the other hand, **NSE** has very little evidence as a screening tool for mTBI. Additionally, its serum kinetics are poorly characterized, and thus could not be assessed for clinical applicability (33,34). Finally, its blood levels are highly influenced by polytraumatic events, as NSE is also abundant in circulating red cells and levels might arise when hemolysis is present (26,28).

In contrast, strong evidence supports **GFAP and UCH-L1** as robust and accurate predictors for intracranial injuries for mTBI, especially when used in combination (35,36). Studies have suggested that both biomarkers complement each other, as UCH-L1 represents axonal injury, and GFAP is a marker for astroglial damage. Their combination is believed to provide not only a more precise diagnostic screening tool, but also a better representation of the pathophysiology of TBI (36).

In conclusion, the decision to prioritize UCH-L1 and GFAP reflects their availability, diagnostic reliability, and their practicality to be used for the purpose of our study.

3.5. DIAGNOSTICS / CLINICAL PATHWAYS OF MILD TRAUMATIC BRAIN INJURY

3.5.1. Prehospital management

Although this section is focused on the management of mTBI patients in an emergency room setting, we find it worth mentioning that prior to the arrival, patients might already have undergone a telematic triage system to guarantee a proper use of medical resources. This process is known as prehospital management (3).

The first clinical evaluation, which is carried out telephonically, has the aim of identifying the necessity of mobilization and assignation of resources according to clinical factors that paint a first picture of the injury severity. The factors are the following:

- Consciousness level alteration or other neurological signs.
- Motor alteration.
- Patient history of antiaggregant or anticoagulant drug intake.
- Patient history of coagulopathy, hemorrhagic disorders.
- Important bleeding.
- Traumatism characteristics and mechanism of injury.
- Suspicion of a medical cause related to TBI.
- Patient neurosurgical history or history of previous brain injury.

These factors will lead to the activation of different resources. Patients with no critical signs or risk factors, might be attended on the spot by a medicalized mobile unit, whereas patients that need further testing, will require a medicalized mobile unit followed by transport to a hospital.

In both scenario, a medicalized unit will carry out a first ABCDE evaluation and stabilization of the patient, which focuses on the following points (37):

Airway

Any patient with a TBI has a risk of altered level of consciousness that can lead to a compromised airway. First step should be to explore the airway to detect the presence of foreign bodies, signs of trauma, loose teeth or excess saliva. Listening is also helpful

as it helps determine whether there is ventilation or not, being a silent airway a sign of complete obstruction.

After a quick evaluation of the airway and exclusion of cervical spine injury, the “head tilt-chin lift” maneuver can be used to open the airway and maintain it open. Medical devices such as Guedel canula might be used to ensure the correct permeability of the airway, and in cases where all the previous measures fail to ensure a good ventilation, intubation might be the last resource (37).

Breathing

It is important to identify the work of breathing. Signs such as use of accessory muscles indicates greater effort and suggests either airway issues or hypoxia. A normal respiratory rate should be between 12-20 breaths per minute. Rhythm in breathing should also be checked, as TBI patients might have an increased intracranial pressure, which can alter breathing patterns (37).

It is crucial to address any oxygenation issues, as oxygenation represents an independent indicator of poor outcomes in TBI. To properly correct any oxygenation issues through oxygen therapy, arterial blood gas measurements and oxygen saturation of hemoglobin should be measured (37).

Circulation

Circulation must be assessed to ensure correct brain perfusion. As described earlier, intracranial hemorrhage represents a big portion of the injuries found in TBI, making it a challenge to maintain adequate circulation.

Signs such as pallor, cold extremities, longer capillary refill time and alterations in cardiac pulse or blood pressure might indicate a circulatory disfunction. In the context of TBI, that should orientate towards the presence of intracranial injury (37).

Any hemorrhage should be promptly treated to stop further blood loss.

Disability

Under disability the neurological status of the patient is assessed. The main aspect to focus on will be the level of consciousness. The most used and standardized scale for the evaluation of the consciousness level or neurological status is the GCS (38).

Glasgow Coma Scale (GCS)

- **Eye opening**: in a normal state of consciousness, eye opening should be spontaneous. If the levels of consciousness are altered, a check for reactivity to sound or pain should be done. Pain can be induced exerting pressure on the nail bed, the trapezius notch or the supraorbital notch (37).
- **Best verbal response**: an orientated patient should be able to vocalize their name, time of day and place. If one of these is incorrect, the patient is considered confused (37).
    - "Words" means that the patient is expressing through meaningless sentences or random words.
    - "Sounds" means that the patient is making noises such as groans or moans.
    - "No response" represents a lack of verbal response of any kind, including sounds.
- **Best motor response:** it evaluates the movement of the patient, both voluntary or reflex movement. Best motor response refers to the fact that some patients might have disability on one side of the body, with the contralateral side still available for evaluation (37).
    - "Obeys commands for movement" means the patients can listen to orders and carry them out. An example would be "lift your arms".
    - "Localizes pain" means the patient reacts to the pain exerted and reaches out to the exact point.
    - "Normal flexion/withdrawal to pain" is represented by the patient's withdrawal of the nail bed when pressured, flexing their arm.
    - "Abnormal flexion/withdrawal to pain" consists of a flexion of the arms towards their chest, flexion of their wrists, formation of a fist in the hand, and rotating the legs inward.
    - "Abnormal extension to pain" causes the patient to extend their arms, flex their wrists, and extend their legs and rotate their feet inwards.
    - No response" means the patient does not move at all when pain is provoked.

In Figure 13, a visual representation of the GCS is displayed.

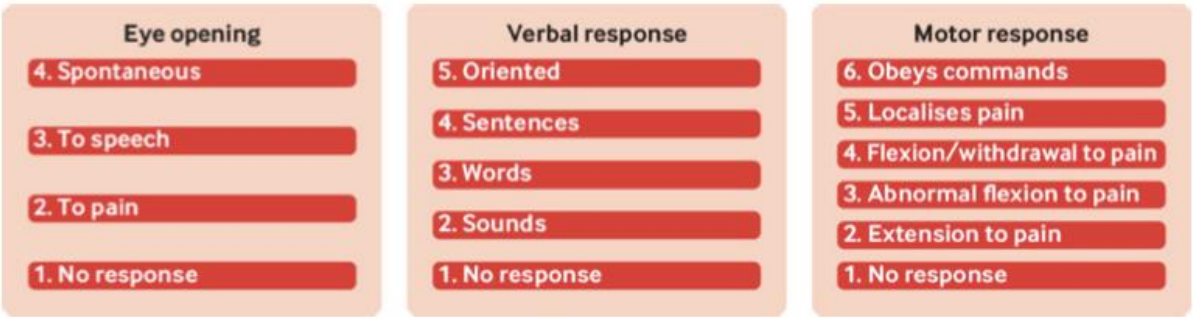

Figure 13. Glasgow coma scale. Score the best level of response seen for each component. The result of the score is calculated by adding the three components. From (39).

Pupillary response to light

Pupillary response has a lot of clinical relevance when examining the neurological status of the patient. Injuries in different structures of the brain of the central nervous system can cause abnormal responses.

Normal pupils are defined as isochoric and with proper constriction reactivity to light. Significant asymmetry in the context of TBI can be a sign of intracranial hemorrhage (37).

Exposure

During the "exposure" part of the exam, the patient is evaluated for any injuries or wounds that may raise concern. This includes thoroughly examining both the front and back of the patient, paying particular attention to areas like the head where hair can conceal injuries, and assessing the abdomen for distension indicative of internal bleeding. Any site impacted during the trauma must be carefully inspected.

Temperature must be monitored closely, as brain injuries may impair thermoregulation, resulting in hypothermia or hyperthermia. Abnormal core temperatures are linked to poorer outcomes in traumatic brain injuries (37).

3.5.2. Hospital management

Stabilization and severity and risk assessment

Patients who require a hospital setting and thus are transported to the hospital, or those patients that attend the emergency department on their own, go through a triage system (40), where a quick assessment through ABCDE is repeated to monitor fluctuations or to detect any signs of severity.

When patients are ruled with a lower priority level (IV or V) through the triage system (Annex 1), their care is not urgent, and there might be a delay between time of arrival and the time when they receive medical attention.

Although mTBI has a low rate of complications, in some particular cases such as complex or severe mechanisms of injury, patients might be considered as a higher priority regardless of their classification according to the BIG criteria (3).

After triage, they receive the first hospital assessment by a doctor, where a more meticulous neurological exam is done. This evaluation goes beyond the GCS and pupillary response, and aims at obtaining more information about the current neurological status of the patient, as well as information about factors that might increase the risk of intracranial injuries (3).

Factors that need to be evaluated include (3):

- Mechanism of injury and etiology
- Loss of consciousness following trauma (duration and/or progression in time)
- Loss of memory following trauma (duration and intensity)

Once the neurological status is known and the patient is stabilized, it is crucial to conduct a proper anamnesis and complete clinical examination, as some symptoms and sings are risk factors for intracranial injury and should be considered to identify which patients would need further testing (3):

- Neurological deficit
- Coagulopathy, bleeding disorders, anticoagulant or antiplatelet drugs
- >65 years
- Intoxicated patients
- Vomiting
- Headache

- Posttraumatic seizures
- Episode amnesia
- Evidence of injury on the head/neck region
- History of brain injury or neurosurgery.

Neuroimaging techniques

Cranial computed tomography (cCT) is considered the gold standard diagnostic tool for evaluating intracranial injuries in patients with mTBI. Even though the lack of use could mean a greater risk of not diagnosing patients who do have an intracranial injury, its routine use is resource-intensive and exposes patients to radiation. The prevalence of intracranial abnormalities in mTBI ranges from 7-10%, with only about 1% requiring neurosurgical intervention (41,42).

To guide and standardize CT use, decision-making criteria like the Canadian CT Head Rule (CCHR), New Orleans Criteria (NOC), CDC guidelines, and National Emergency X-Radiography Utilization Study II (NEXUS II) have been developed. All these protocols aim at the early detection of patients that could in fact present with intracranial injury after mTBI. At the same time, they help avoid abusive use of this resource.

A recent systematic review comparing the diagnostic accuracy of clinical decision protocols found that both the CCHR and the NOC have strong negative likelihood ratios (0.04 and 0.08, respectively) for identifying patients at low risk of requiring neurosurgical intervention (42,43).

The CCHR outlines seven clinical factors to support the decision to perform a cCT (44):

- GCS score below 15 two hours after injury.
- Suspected or confirmed depressed or open skull fracture.
- Any signs of a basal skull fracture.
- Two or more episodes of vomiting.
- Age 65 years or older.
- Retrograde amnesia lasting more than 30 minutes.
- High-risk mechanisms of injury, such as motor vehicle collisions, falls, or explosive injuries.

According to the NOC, which are applied only to patients with minor head trauma and a GCS score of 15, the following seven clinical factors support the decision to perform a cCT (41):

- Headache.
- Vomiting.
- Seizures.
- Intoxication from alcohol or drugs.
- Persistent anterograde amnesia.
- Age over 60.
- Visible injury above the clavicle.

Based on Nexus II criteria, cCT is recommended for patients with one of the following (41):

- Significant skull fractures accompanied by scalp hematoma.
- Neurological deficits.
- GCS scores of 14 or lower.
- Abnormal behavior.
- Coagulopathy.
- Persistent vomiting.
- Older than 64 years old.

Current CDC Guidelines recommend using the CCHR to provide decision support and improve head CT utilization in adults with mTBI. They also recommend using the NEXUS Head CT or the NOC, although they point out that the lower specificity of the latter two may lead to more unnecessary testing (45).

	Canadian CT Head Rule	New Orleans Criteria	NEXUS Head CT
High-risk features for predicting patients with CIBI	Any one of: • Failure to reach GCS score of 15 within 2 hours of injury • Suspected open skull fracture • Signs of basal skull fracture • Vomiting more than once • Age greater than 64 y	Any one of: • Headache • Vomiting • Age over 60 y • Drug or alcohol intoxication • Deficits in short-term memory • Physical evidence of trauma above the clavicles • Posttraumatic seizure	Any one of: • Evidence of skull fracture • Scalp hematoma • Neurologic deficit • Abnormal level of alertness • Abnormal behavior • Persistent vomiting • Coagulopathy • Age 65 y or greater
Exclusion Criteria	• Age <16 y • Blood thinners • Seizure after injury	• GCS score of <15 • Age ≤3 y	• GCS score of <15

CIBI, clinically important brain injury; *CT*, computed tomography; *GCS*, Glasgow Coma Scale.

Table 2. Clinical decision tools. From (45).

To represent the hospital management currently in use in emergency services, a decision making algorithm has been developed (Figure 14). This algorithm summarizes the steps mTBI patients currently go through upon their arrival to the ER. In other words, this algorithm is the one in use without accounting for TBI biomarkers.

Moderate to severe TBI are criteria by themselves that automatically indicate performing a cCT, so their management is not represented. The same happens to patients with risk factors.

TBI biomarker determinations

Blood-based biomarkers have shown promise in predicting the presence of intracranial injuries after mTBI (33,35,46–49). However, they have yet to be implemented into clinical diagnostic workflows. To reach this purpose, an algorithm that bases clinical decisions on the ability of TBI biomarkers to determine cCT eligibility has been developed (Figure 14) (3):

In this new algorithm, prehospital care is the same regardless of the availability or eligibility for biomarker determinations. Furthermore, upon arrival to the ER, patients undergo the same triage system, where they are assessed for the severity of mTBI, as well as for the presence of any risk factors that deserve further testing.

Patients at vital risk, or with TBI classified as moderate or severe are immediately excluded from the possibility of discharge without undergoing a cCT. These two groups of patients require having a cCT performed because their risk of intracranial lesions surpasses the potential benefits of avoiding a cCT (3,30).

The same happens with patients presenting with risk factors for intracranial injuries. Patients in whom risk factors are identified during their initial evaluation are not eligible for biomarker determinations, because no matter the results, cCT should still be warranted, as their risk for presenting an intracranial injury is greater than any potential benefits that could come from avoiding a cCT.

Risks associated with intracranial injuries are considered in the proposed algorithm (Figure 15), and include:

- Neurological deficit.
- Coagulopathy or bleeding disorders.
- Anticoagulant or antiplatelet drugs.
- 65 years or older.
- Alcohol or drug intoxication.
- 2 or more vomiting episodes.
- Headache.
- Posttraumatic seizure.
- Short-term memory loss or episode amnesia.
- Evidence of injury in the head/neck region.
- Dangerous mechanism of injury.
- Previous surgery or injury of the brain.

If patients are classified as mTBI according to the BIG criteria and present no symptoms or factors of risk, then two different scenarios arise (Figure 15) (3,30):

- If **less than 12 hours** have gone by, a rapid serum/plasma test for GFAP and UCH-L1 biomarkers is advised to help decide whether a cCT is necessary. Samples for this test are processed in the clinical laboratory, with results available in approximately 30-60 minutes.

  Negative biomarker tests for GFAP and UCH-L1 in the first 12 hours after mTBI have a high negative predictive value for the absence of intracranial injury. Patients can then be safely discharged after receiving proper reattending recommendations about symptoms of risk.

  In any case where there is any clinical doubt, a cCT is performed regardless of biomarker results.

- If **more than 12 hours** have gone by, biomarker determinations significantly decrease their sensitivity and negative predictive values, which means their determinations are not reliable enough to base clinical decisions. In this context, clinical judgment must prevail, and the option of performing a cCT must be

considered, as well as keeping patients at observation during at least 6 hours to control potential risks.

In cases when a cCT is finally performed:

- If cCT is negative and the clinical status of patients is optimal, patients can be discharged after a 6 hour observation period.
- If cCT presents any significant findings of acute brain damage, the neurosurgery service of the hospital should be informed so they can decide on whether to perform surgery or not. ICU should also be advised for the inherent vital risks that intracranial injuries represent.

When patients are discharged, regardless of the pathway through which the decision has been made, they should receive verbal and written recommendations about their possible evolution, as well as advice for when to consider revisiting the ER (3).

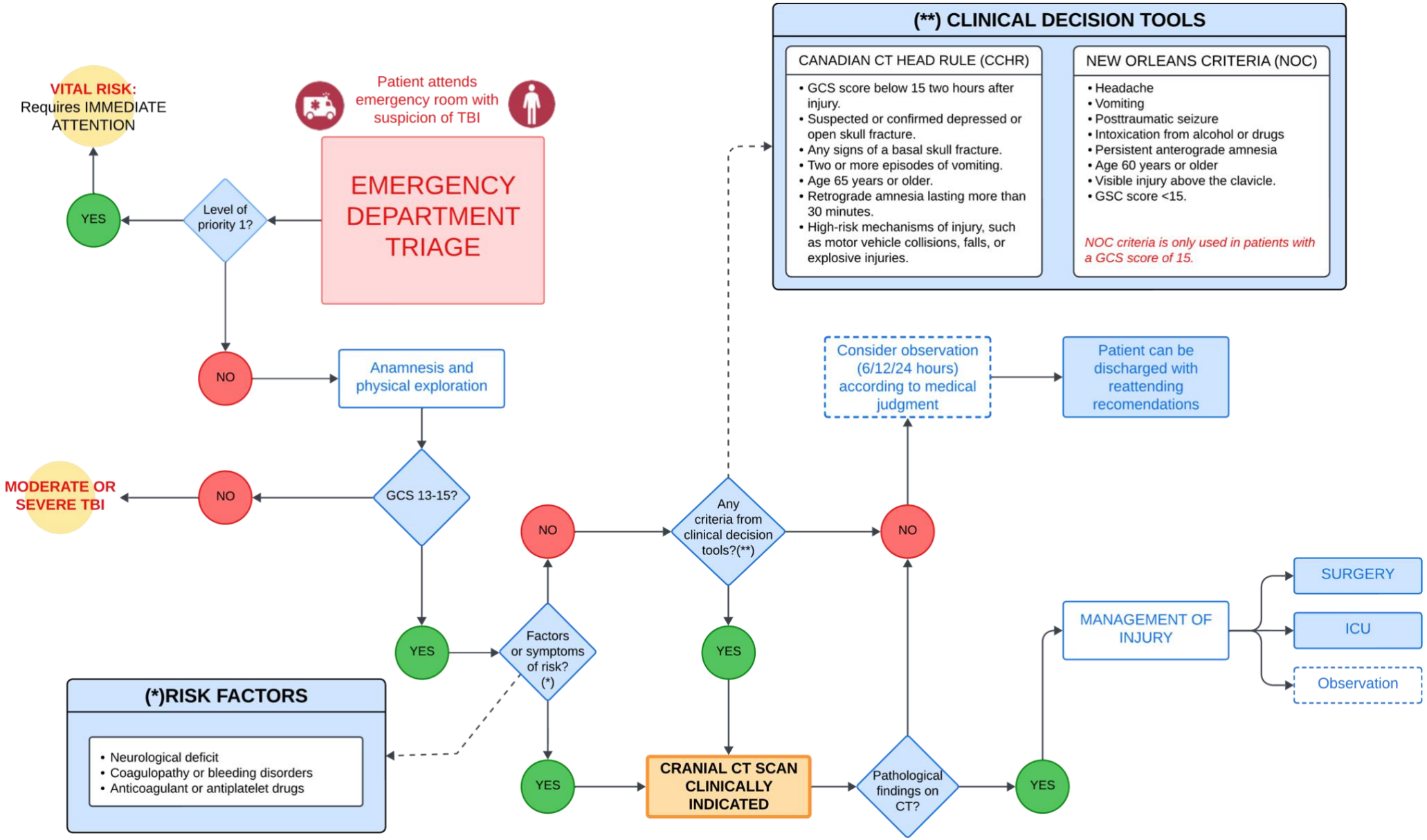

Figure 14. Algorithm for the management of mTBI patients using clinical decision tools, without the use of TBI biomarkers. By author.

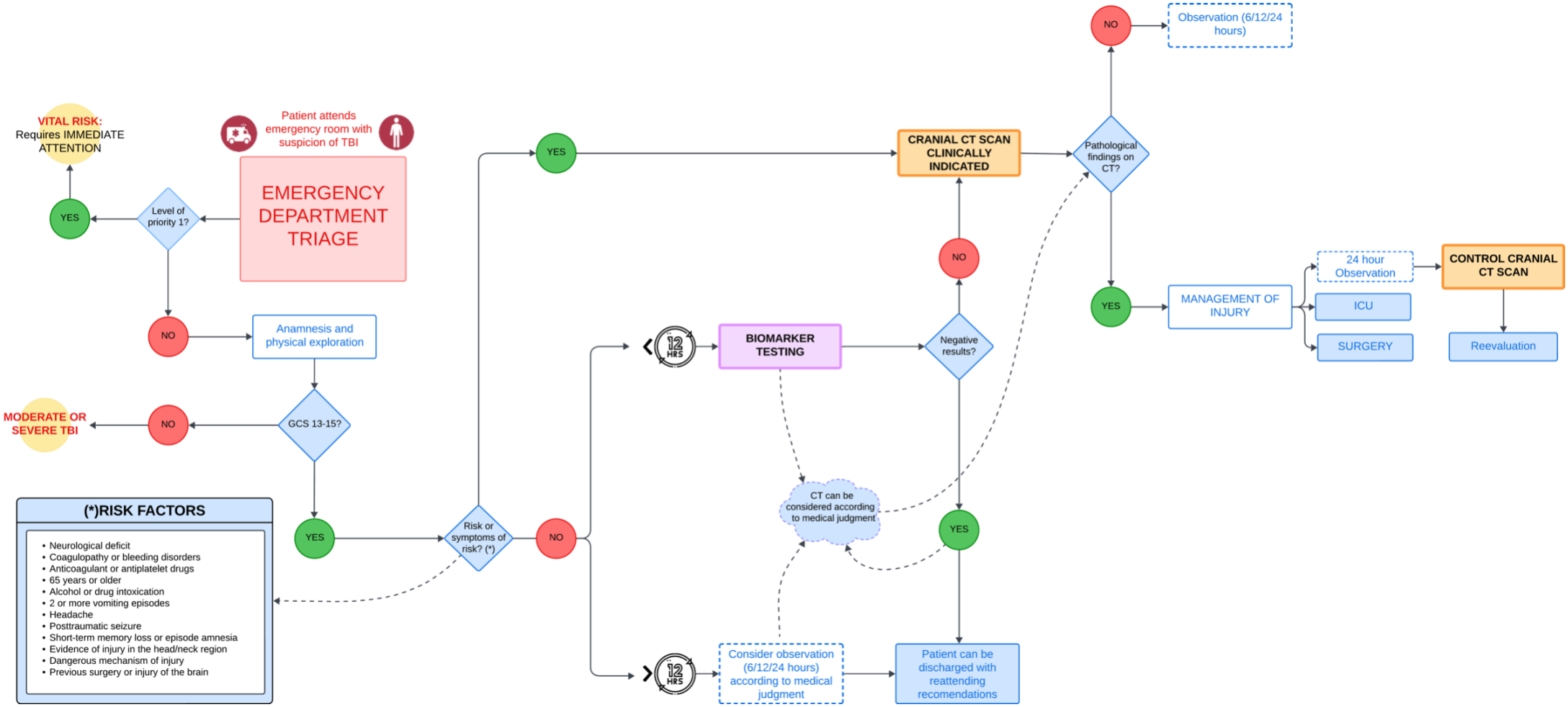

Figure 15. Algorithm for the management of mTBI patients using TBI biomarkers. Adapted from (30).

4. JUSTIFICATION

TBI is a very relevant entity worldwide, with an estimated incidence of 69 million people each year. Specially, mTBI keeps on representing most of the cases (7).
We believe that the high incidence of this entity underscores the need for effective and safe diagnostic tools to manage these patients in emergency settings.

Current diagnostics algorithms in emergency department settings still contemplate cCT as the gold standard tool to rule out intracranial injuries in patients suffering from mTBI. However, cCT present some limitations and considerable drawbacks.

On one hand, specific negative points about cCT and its technique can be made.
First, the exposure to radiation that patients undergo, with a mean of 1’62 mSv of minimum effective dose, equivalent to one year of natural radiation (50). Second, the high cost and low availability of the technique, with a cost of 88€ per scan in our National Health System (51). Finally, the limited rate of findings in mTBI cases, where evident brain injury might be found in only a small proportion of patients (7-10%) (3).

On the other hand, consensus on indications of cCT only exists in moderate to severe TBI, whereas for mTBI it is still a controversial subject (52).
Clinical rules such as the Canadian Head Rule for CT or the New Orleans Criteria have been developed to assess this problem. While these clinical rules provide guidance, they differ across guidelines leading to confusion and variability when used in clinical practice. This often results in the overuse of cCT, and it could be the reason why such guidelines have not been able to significantly reduce cCT rates in mTBI patients (45,52).
Moreover, radiologists at Sociedad Española de Radiología Médica (SERAM) claim this criterion to still lack sensitivity, and express the need for a more precision-medicine oriented approach, where cCT is truly only used in patients who are at risk of developing an intracranial injury after mTBI, thus avoiding unnecessary diagnostic tests (3).

In this context where questions are being raised about when to perform cCT and whether it is the right technique to safely discharge mTBI patients, other diagnostic

tools have emerged as alternatives that could solve these problems. That is the case of TBI Biomarkers (28,30–33,35,46–49,53–58).

Biomarkers such as Ubiquitin C-Terminal Hydrolase-L1 (UCH-L1) and Glial Fibrillary Acidic Protein (GFAP) have shown promise in identifying TBI, offering a non-invasive, rapid and with an excellent diagnostic performance when compared to the gold standard, cCT. Studies have reported that using the complementary kinetics of these two biomarkers, an intracranial lesion can be ruled out with a sensitivity of 95’8% and a negative predictive value of 99’3%, and they suggest that approximately 30% of cCT could be avoided in mTBI patients thanks to the use of mTBI biomarkers (35).

However, while existing research has validated the diagnostic accuracy of these biomarkers, there is still a critical gap on the real-world implementation of biomarkers in emergency department workflows (30).

To address this gap, this study evaluates the integration of TBI Biomarkers into a novel ER algorithm created for this study, which has been specifically designed to standardize decision-making for mTBI patients. By doing this, the study goes beyond proving the diagnostic accuracy of TBI biomarkers, which has been the main focus of research for the last decade and to this date. Contrarily, it focuses on broader clinical and operational impacts, which include patient safety, reductions in cCT performed, reductions on time of stay in the ER. All these variables can be summarized as overall ER efficiency.

By bridging the gap between the validation of TBI biomarker as accurate diagnostic tests, and their clinical implementation, this study aims to provide actionable evidence that can act as the fundament for an improved and more efficient management of mTBI patients in a real-world clinical setting.

5. HYPOTESIS

5.1 MAIN HYPOTHESIS

The implementation of a biomarker-based algorithm (including GFAP and UCH-L1) for diagnostic management of mTBI in a hospital emergency department improves the efficiency of patient care by **reducing the rates of imaging tests performed** and **optimizing diagnostic and discharge or derivation times.**

5.2 SECONDARY HYPOTHESIS

- The implementation of a TBI biomarker-based algorithm **does not compromise patients' safety,** as it does not increase neither reattending rates nor mortality.

6. OBJECTIVES

6.1 MAIN OBJECTIVE

To evaluate whether the implementation of a biomarker-based algorithm (including GFAP and UCH-L1) for diagnostic management of mTBI in a hospital emergency department improves the efficiency of patient care by reducing the number of imaging tests performed and optimizing diagnostic and discharge or derivation times.

6.2 SECONDARY OBJECTIVES

- To determine whether the implementation of a TBI-biomarker based algorithm is as safe as current clinical decision tools when deciding which patients are eligible for cCT, evaluated through reattending and mortality rates.

7. MATERIALS AND METHODS

7.1. STUDY DESIGN

This is a unicentric **observational analytical quasi-experimental study** that uses an **interrupted time series design** to evaluate the impact of the implementation of a biomarker-based algorithm (including GFAP and UCH-L1) in the diagnostic management of mTBI in the emergency department of Hospital Universitari Doctor Josep Trueta.

The study will compare data from two distinct periods that will divide patients in two groups:

- Patients who were given care at the hospital during the pre-implementation period (September 2024 - May 2025). This group will be referred as retrospective group.
- Patients who were given care at the hospital during the post-implementation period (May 2025 - January 2026). This group will be referred as prospective group.

These two groups will be created **without randomization**.

Nevertheless, this type of design will still allow for the assessment of changes in clinical outcomes, diagnostic efficiency, and resource utilization.

7.2. SETTING

The study will be conducted in the emergency department at **Hospital Universitari Doctor Josep Trueta,** the tertiary hospital of the **Girona province** where patients with suspected TBI are routinely evaluated. The study will be performed in a real-world clinical setting to assess the feasibility and utility of a new mTBI algorithm as a diagnostic management tool for mTBI patients.

7.3. STUDY POPULATION

The population of this study will be patients older than 18 years who attended the emergency department and were ruled as mTBI according to the BIG criteria (6) during the period between September 2024 and May 2025, and patients who will attend the

emergency department of the same hospital and are ruled as mTBI according to the same criteria during the period between May 2025 and January 2026.

As a reminder, the BIG criteria are as follows (all 3 must be met):

1. Glasgow Coma Scale (GCS) Score: a GCS score of 13 to 15.
2. Duration of Loss of Consciousness (LOC): the LOC should be less than 30 minutes.
3. Duration of Post-Traumatic Amnesia (PTA): the duration of PTA should be less than 24 hours. This includes any period of confusion, disorientation, or memory dysfunction immediately following the injury.

7.3.1. Inclusion criteria

General inclusion criteria (for both periods):

- Patients aged ≥18 years.
- Patients presenting to the emergency department with a clinical history of trauma to the head and within the first 12 hours after the injury.
- Classification of mTBI according to the BIG criteria (GCS, LOC, and PTA thresholds).

Specific inclusion criteria for the pre-implementation period (retrospective group):

- Patients assessed without the use of biomarkers.
- Medical records available in the hospital's database with all the following variables documented:
    - Demographic data: age and sex.
    - Clinical features upon arrival:
        - Severe headache.
        - Acute neurological disorder.
        - Nausea or vomiting.
        - Signs of intracranial hypertension.
        - Periocular or retroauricular hematomas suggestive of skull base fracture.
    - Injury timing: time elapsed since the head trauma occurred.
    - Mechanism of injury: high-energy trauma or other mechanisms.

- Medication history: use of antiplatelet or anticoagulant agents.
- Relevant comorbidities: presence of coagulopathies (congenital or acquired).
- Imaging data: whether the patient underwent a cCT within 12 hours of injury, and if so, the results (e.g., intracranial injuries).
- Length of stay in the emergency department.
- Clinical evolution: information about reattendance or mortality at 7 and 30 days.

Specific inclusion criteria for the post-implementation period (prospective group):

- Patients assessed with the inclusion of biomarkers (GFAP and UCH-L1) as part of the diagnostic workflow.
- Blood samples collected within 12 hours of the injury.
- cCT performed within 12 hours of injury (if required according to the biomarker results).
- Signed informed consent provided after being informed of the study's objectives and procedures.

7.3.2. Exclusion criteria

General exclusion criteria (for both periods):

- Patients younger than 18 years or older than 64 years.
- Comorbidities or risk factors increasing the likelihood of intracranial injuries:
  - History of prior treatment with antiplatelet and/or anticoagulant medications.
  - History of congenital or acquired hemophilic or coagulopathic disorders.
  - Patients presenting clinical signs of severity, such as intense headache, acute neurological disorder, 2 or more vomits or other signs of intracranial hypertension, periocular or retroauricular hematoma suggestive of a skull base fracture.
  - History of high-energy trauma mechanism.
- Moderate or severe TBI (e.g., GCS <13, LOC >30 minutes, or PTA >24 hours).
- Patients with drug or alcohol intoxication upon arrival.

- Pregnant or breastfeeding patients.
- cCT not performed within the required timeframe (12 hours post-injury).
- Patients who cannot undergo a cCT for other reasons.

Specific exclusion criteria for the pre-implementation period (retrospective group):

- Patients whose medical records lack any of the required information listed in the pre-implementation inclusion criteria**.**

Specific exclusion criteria for the post-implementation period (prospective group):

- Patients for whom an accurate clinical history cannot be obtained (due to language barriers or baseline cognitive impairment) or those in whom an estimated time of injury is unknown.
- Blood samples unavailable or collected after 12 hours post-injury.
- Unable to provide informed consent.

7.3.3. Withdrawal criteria

- Patients who withdraw their consent after initially agreeing to participate.
- Incorrect initial classification of TBI severity or subsequent clinical findings that reveal that patients no longer meet the criteria for mTBI.
- Discovery of significant comorbidities (e.g., severe coagulopathies, active malignancy, or chronic neurological disorders) that were not initially apparent but are identified after enrollment.
- Discovery of unanticipated conditions such as pregnancy or maternal breastfeeding after enrollment.
- Non-adherence to study protocol: patients who do not undergo a cCT within the designated time frame or biomarker testing delayed beyond acceptable limits.
- Development of any adverse events, such as clinical deterioration requiring immediate intervention (e.g., urgent surgery, worsening neurological symptoms, or ICU admission), preventing the completion of study protocols. Patients might suffer a torpid evolution of their symptoms at any point and be reclassified as moderate or severe TBI.

- Logistical or technical issues:
    - Missing or incomplete cCT data.
    - Blood samples improperly stored or insufficient for analysis.
    - Errors in sample labeling or laboratory processing.

7.4. SAMPLE

7.4.1. Sample collection

7.4.1.1. Retrospective group

Data collection will be conducted from the hospital's clinical database between September 2024 and May 2025 for the pre-implementation period.

Patients from this group will be selected using a retrospective consecutive sampling method. This approach involves identifying and including all cases that meet the predefined inclusion criteria and none of the exclusion criteria from the existing medical records of patients treated between September 2024 and May 2025 in the emergency department of Hospital Universitari Doctor Josep Trueta.

The retrospective nature ensures that the data that will be collected was generated prior to the implementation of the biomarker protocol and without researcher influence, while the consecutive sampling ensures a representative sample of the population treated during this timeframe, as all eligible cases are systematically included without omissions.

7.4.1.2. Prospective group

Data will be collected between May 2025 and January 2026. Biomarker data will only be available for the post-implementation period, as the protocol involving these biomarkers will be introduced around May 2025.

This group will be selected using a prospective consecutive sampling method, in which all patients admitted at the emergency department of Hospital Universitari Doctor Josep Trueta who meet the inclusion criteria and do not meet the exclusion criteria, will be offered to participate in the current study. Judgement for eligibility will be done by trained clinical research staff to ensure that inclusion and exclusion criteria are met.

After being informed, if they consent to participate, their diagnostic process will be carried through the new biomarker-based algorithm (Figure 15).

7.4.2. Sample size

The estimated incidence of traumatic brain injury in Spain revolves around 20.000 cases of TBI per year requiring hospitalization, and the total annual incidence of TBI in Spain is estimated at 200 new cases per 100.000 population (10,11).
Mild TBI represents approximately 80% of all cases of TBI (7).

According to emergency care doctors of Hospital Universitari Doctor Josep Trueta, approximately of 700 patients are treated for TBI in their department every year. From this data, we can estimate an annual incidence of mTBI in our hospital of 567 cases every year.

Accepting an alpha risk of 0.05 and a beta risk of 0.8 in a two sided test, 196 patients would be needed in each group to be able to identify a statistically significant difference, expected to be of 30% according to prior estimations. However, considering a potential drop-out rate of 15%, the final sample size needed is **225 patients** in each group.

Computations were carried out with Prof. Dr. Marc Saez' software based on the package "pwr" of the free statistical environment R (version 4.2.2) and Cohen J. (59), Chapter 7.

7.4.3. Estimated time of recruitment

Knowing that 225 patients are needed in each group, and assuming an estimated flow of 567 mTBI patients each year, the required sample size would be obtained in an **8 month period**. If the required number of samples is obtained prior to the scheduled date, or the sample size has not been obtained at the end of this projected time frame, the study's duration will be modified.

7.4.4. Acceptance rate assurance

To ensure the targeted sample size is reached, we plan to enhance the participation of patients by giving clear information about the study objectives and the voluntary nature of their participation. The information will be given by trained healthcare professionals in addition to the information sheet (Annex 2) and consent form (Annex 3).

The research team will address any concerns raised during the informed consent process, and follow-up support will be provided during their entire stay in the emergency department.

Emphasis will be given to the following points:

1. Patients will be able to understand that biomarkers determinations will be performed using a plasma sample, for which a phlebotomy is required. Given the case when a venous access is already indicated for other reasons, it will be used to avoid having to generate more discomfort on the patient by performing another venipuncture.
2. An explanation will be given to the patients emphasizing on the potential benefits of the study, as well as the potential risks. Focus will be put in explaining that imaging techniques would be performed following wider clinical criteria regardless of the existence of this project, which could increase the probability of getting a cCT performed.
3. Emphasis will be placed on the voluntary nature of participation, the confidentiality of their data, and their right to withdraw from the study at any time without affecting their medical care.

7.5. VARIABLES

7.5.1. Independent variable

7.5.1.1. Use of traumatic brain injury biomarkers

The independent variable of this study is the **diagnostic algorithm used for the management of patients with mTBI**. This is a dichotomous nominal qualitative variable since it only has two categories:

1. **Management of patients without the use of biomarkers (retrospective group)**: this reflects the standard diagnostic approach currently in use (Figure

14). It relies primarily on clinical evaluation and CT imaging, based on established guidelines such as the Canadian CT Head Rule or the New Orleans Criteria. cCT imaging is performed when deemed necessary according to these clinical guidelines.

All patients that meet our inclusion criteria and none of our exclusion criteria and were given care during our defined pre-implementation period (September 2024 and May 2025) will represent the first group of this variable.

2. **Management of patients using biomarkers as a diagnostic tool (prospective group):** this represents the proposed algorithm, where blood biomarkers (GFAP and UCH-L1) are integrated into the diagnostic process to guide clinical decision-making, determining whether a cCT is necessary or not (Figure 15).

   All patients that meet our inclusion criteria and none of our exclusion criteria that receive medical attention during our defined post-implementation period (May 2025 and January 2026) will represent this group.

The choice of this independent variable is central to the study's aim of evaluating whether the integration of biomarkers into the diagnostic workflow improves the efficiency of the medical care provided to patients with mTBI without compromising their safety.

The comparison of these two distinct diagnostic algorithms allows us to assess their impact on key outcome variables, such as the proportion of patients who had a cCT performed and patients' time of stay before discharge or transfer.

7.5.2. Main dependent variables

For the main dependent variables described in this section, data will be obtained from the Hospital Electronic Health Records (SAP), which grant access to the clinical history of patients included in this study.

- For the pre-implementation period data will be collected retrospectively.
- For the post-implementation period data will be collected prospectively.

7.5.2.1. Performing of cCT

This is a qualitative dichotomous variable. It is measured as the **performing or not of a cCT (Yes/No).** Since each patient will receive at most one cCT (*), this dichotomous representation is equivalent to assessing the proportion of patients who underwent cCT imaging in each group.

> **Since this study focuses on the influence that biomarker results have on the usage of cCT upon arrival and within 12 hours after injury, **only the first cCT performed on a patient will be considered**. Follow-up cCT fall under different criteria nonrelated to biomarker determinations and are outside the scope of this study.*

Cranial CT are considered and counted if they are performed between patients' admission in our emergency department and their discharge or transfer to another department.

This variable is analyzed to assess whether the implementation of a biomarker-based diagnostic algorithm reduces the proportion of patients who receive cCT when presenting at the emergency department with mTBI.

7.5.2.2. Time of stay in the emergency department

This is a quantitative continuous variable. It will be measured in units of time (minutes), with results presented as **median time of stay and interquartile range (IQR)**.
This variable represents the total amount of time that a patient with mTBI spends in the emergency department, from admission to either discharge or transfer to another department.

This study focuses on the global efficiency of an emergency department when dealing with mTBI. For this reason, rather than stratifying the different intervals of time that occur while patients stay in our department (time from arrival to diagnosis, time from diagnosis to treatment, time from treatment to discharge), we chose to assess the overall time of stay as a single variable. Thus, to measure this variable in each patient, a simple calculation of the difference between time of admission and time of discharge or transfer will be done.

Time of stay is analyzed to assess whether the implementation of a biomarker-based diagnostic algorithm reduces the overall time spent by patients in the emergency department.

7.5.3. Secondary dependent variables

For both secondary dependent variables described in this section, data will also be obtained from the Hospital Electronic Health Records (SAP), which grant access to the clinical history of patients included in this study.

- For the pre-implementation period data will be collected retrospectively.
- For the post-implementation period data will be collected prospectively.

7.5.3.1. Emergency room return during the first 72 hours

This variable represents whether patients return to the emergency department for a second evaluation in the first 72 hours after being discharged. This is a dichotomous qualitative variable. It is described as **reattendance to the emergency department or not (Yes/No).** Patients are categorized into two groups as follows:

- Returned to the emergency department after being discharged (Yes)
- Did not return to the emergency department after being discharged (No)

Return to the emergency department will only be considered when the reason of reattendance is directly related to mTBI or any of its potential acute complications. More specifically, only the following symptoms will be considered as related to TBI:

- Physical: headache, nausea, vomiting, balance problems, dizziness, visual problems, fatigue, sensitivity to noise or light, numbness or tingling, feeling dazed or stunned.
- Cognitive: feeling mentally “foggy”, feeling mentally slowed down, difficulty concentrating, difficulty remembering, forgetful of recent conversations, confused about recent events, answers questions slowly.
- Emotional: irritability, emotional lability, sadness, nervousness.
- Sleep: drowsiness, sleeping less or more than usual, trouble falling asleep.

The main purpose of this variable is to compare whether significant safety differences exist between both intervention groups, as quicker discharge times, although based

on reliable tests, could mean greater risks of overlooking latent injuries that could present themselves at a future time.

7.5.3.2. Mortality at 7 and 30 days

This secondary dependent variable measures the **mortality rate** among patients with mTBI within 7 and 30 days post-injury. This is a dichotomous qualitative variable, where patients are categorized based on survival status within 7 and 30 days post-injury. The two categories are as follows:

- Deceased: patients who died as a direct result of complications related to mTBI within 7 or 30 days following the injury.
- Alive: patients who survived the initial 7 or 30 days following the injury and did not die due to complications associated with mTBI.

The causes of death considered as directly related to mTBI are the same complications described in section 3.3. Traumatic brain injury pathophysiology. These include:

- Brain contusion
- Epidural hematoma
- Subdural hematoma
- Deep Intracerebral hemorrhage
- Intraventricular hemorrhage
- Subarachnoid hemorrhages

Data for this variable will be gathered from the Hospital Electronic Health Records (SAP and eCAP), which compilates data regarding mortality from patients included in our study. Death certificates will also be used to confirm cause of death and to ensure accurate classification of mortality due to mTBI complications.
Both in-hospital and post-discharge mortality will be considered in this variable as long as the date of death is included within the first 30 day period.

The main reason for the use of this variable is to evaluate whether the implementation of a new algorithm that includes TBI biomarkers introduces any risk to patients'

survival. In other words, it seeks to confirm that the implementation of the new biomarker-based algorithm does not negatively impact mortality rates.

7.5.4. Covariates

The covariates summarized in Table 3 have been selected as part of our study to control the effect they could have in our dependent variables. While they are not directly related to our independent variable, when not considered, they could generate confusion in the results.

Covariates	Description	Categories	Measuring instrument
Age	Quantitative continuous categorized as qualitative ordinal	- 18-40 years old - 41-65 years old	Clinical records
Sex	Qualitative dichotomous	- Male - Female	Clinical records
Mechanism of injury	Qualitative nominal	- Same height fall - Object striking the head - Head striking an object - Low energy road transit injury - Sports related trauma	Patient interview and clinical records
GCS score	Qualitative ordinal	- 13 - 14 - 15	Neurological examination using the Glasgow Coma Scale
Loss of consciousness	Qualitative dichotomous	- Yes - No	Patient interview and clinical records
Post traumatic amnesia	Qualitative dichotomous	- Yes - No	Patient interview and clinical records
Vomiting	Qualitative dichotomous	- Yes - No	Patient interview and clinical records
Time from injury to admission	Quantitative continuous		Patient interview and clinical records
cCT result	Qualitative dichotomous	- Presence of intracranial injuries (positive) - Absence of intracranial injuries (negative)	Report from radiologist evaluating cCT

Table 3. Covariates

Age might have influence on the amount of cCT performed, as doctors tend to be careful with the wide range of comorbidities older patients tend to have and are more aggressive in the decision-making process, not wanting to overlook possible injuries in older patients. This could lead to a higher use of CT depending on the age group, as well as longer observation periods.

Mortality could also be influenced by age, as older patients tend to present with complications after mTBI.

mTBI includes a GCS score from 13-15. Different scores could be perceived as more severity within the mTBI group, and thus influence clinical decision, perhaps leading to higher cCT usage or longer hospital stay. Mortality could also be influenced by GCS. The same phenomena could be observed in patients presenting with different types of mechanism of injury, LOC, PTA, vomiting and longer times between injury and admission, so they have also been considered.

cCT results are another relevant covariate considered due to their potential influence on one of the primary dependent variables: time of stay in the emergency department. Patients with positive cCT findings are likely to have longer stays in the emergency department, as they require further diagnostic evaluation or treatment, and longer waiting times while organizing their transfer to another department. Conversely, patients with negative CT results are typically discharged more quickly, as their required observation times are shorter. This could confound the results.

7.6. STUDY INTERVENTION

This study will have patients divided into two groups: patients who received medical care for mTBI using current diagnostic algorithms to decide whether a cCT was justified; and patients who will be given medical care using the new algorithm that includes the determination biomarkers as part of the decision-making process.

In the first group (retrospective group) no new intervention is required, as included patients will be those who were already treated at the emergency department of Hospital Universitari Doctor Josep Trueta de Girona for mTBI without the availability of biomarkers in their diagnostic process (Figure 14). Data regarding these patients will be extracted from the existing database of patients who suffered this pathology between September 2024 and May 2025.
At the time of their attention, this group of patients already gave their verbal consent to receive the considered appropriate medical care in the emergency department.

On the other hand, we will have another group of patients (prospective group) who attend the emergency department at Hospital Universitari Doctor Josep Trueta de Girona for mTBI after the beginning of this study, time when the new algorithm containing biomarkers as part of the diagnostic workflow will already be available (Figure 15).
Patients from this group will receive a clear explanation of their pathology, including the potential complications, as well as the diagnostic tools available and their inherent risks. Additionally, all details related to the study will be provided though the protocol's information sheet, which contains information regarding objectives, new algorithm, duration of analytical and imaging tests, follow-up, confidentiality, implications of the results, risks and benefits, etc. (Annex 2).

After a detailed description, patients will be proposed to participate in the study as the group of patients who will be managed using the new algorithm for mTBI (Figure 15). If patients voluntarily agree to participate in the study, they will receive the informed consent document (Annex 3), which they will have to sign and return to be included in the study.

The two algorithms do not differ up until the moment where the clinician must decide which diagnostics tests need to be performed on the patient, so both of our groups will undergo the same routine triage system and thorough clinician evaluation. This serves the primary purpose of compiling the following information:

- Level of priority.
- Neurological status (Glasgow Coma Scale and other features specified on section 3.5. Diagnostics / Clinical pathways of mild traumatic brain injury).
- Anamnesis and physical exam.

This initial evaluation serves the purpose of estimating the initial severity, while at the same time determining whether patients meet all the inclusion criteria, and none of the exclusion criteria.

When this study reaches its starting point, the main difference between the two groups will be that blood samples from integrants of the second group will be essential so the levels of their TBI biomarkers (UCH-L1 and GFAP) can be determined using laboratory assays. On the other hand, patients who form the retrospective group, might not have been drawn blood if it was not indicated for their risk factors or for other non-TBI related causes.

Blood samples will be drawn using a simple venous access, ideally the same one established, if necessary, at their arrival at the emergency department.

From this point, results from TBI biomarker testing in the prospective group will be the main reason to decide whether patients deserve to have a cCT performed on them or not. However, it is worth remembering that patients should not meet any of the withdrawal criteria at any point of the study, and that the sole finding of one risk factors (e.g. unknown coagulopathy) will have enough weight to indicate a cCT regardless of TBI biomarker results, as well as to end participation on this study.

7.6.1. Measuring instruments

All methodologies and procedures will adhere strictly to standardized guidelines and protocols.

Some instruments used in our study already play an important role into standard clinical practice, and it is not the intention of this study to interfere with any aspects of their execution.

7.6.1.1. TBI Biomarkers (GFAP and UCH-L1)

The determination of TBI biomarkers is done on a sample of blood from patients. The process of quantification has the following steps (60):

1. Blood Sample Collection

   Venous blood samples will be collected from all eligible participants during routine blood drawings performed as part of their standard emergency care protocol. If a blood drawing was not indicated for other reasons, a phlebotomy will be performed with the specific indication of quantifying plasma TBI biomarkers.

2. Specimen storage and transport

   This assay uses plasma as the specimen. All blood samples must be collected using standard EDTA tubes, and they should be processed (centrifuged) within 2 hours after they have been drawn, to separate the clot from the plasma before their analysis. For their processing, a centrifugation of a minimum of 21.000 g-minutes is also needed to eliminate platelets and other particles.

   Given the case where samples could not be processed in the first 2 hours after drawing, they could be stored at room temperature for a maximum of 8 hours. If needed, they can be stored at colder temperatures for longer, although at the same centrifugation process is needed prior to their storage to separate the clot from the plasma.

3. Laboratory Analysis

   UCH-L1 and GFAP will be determined using *i-Stat TBI Assay by Abbot* ®. This is a chemiluminescent microparticle immunoassay (CMIA) panel used in human plasma, which provides a semiquantitative result that can be interpreted through the *Alinity I System* ®.

   The analysis is done using specific cartridges that contain all necessary agents for the reaction and posterior result determination. These kits are called **GFAP Reagent Kit 04W17** and **UCH-L1 Reagent Kit 04W19**. The contents of each kit include:

- Microparticles covered in monoclonal antibodies specific for each biomarker.
- Specific anti-biomarker antibodies conjugate marked in acridinium.
- Assay specific diluent: tampon solution.

These contents are used as follows:

I. Binding Phase:

The sample is combined with anti-biomarker (GFAP or UCH-L1) antibody-coated paramagnetic microparticles and a diluent specific for each assay. The target biomarker in the sample binds to the specific antibody-coated microparticles.

II. Washing:

The mixture is washed to remove unbound substances.

III. Conjugate Addition:

An acridinium-labeled anti-biomarker antibody conjugate (specific for GFAP or UCH-L1) is added to form the reaction mixture and is incubated.

IV. Second Washing Cycle:

Another washing cycle is performed to remove excess conjugate.

V. Chemiluminescent Reaction:

Pre-activation and activation solutions are added to trigger the chemiluminescent reaction, and the resulting light is measured in relative light units (RLUs). The RLUs are directly proportional to the amount of biomarker present in the sample.

4. Results

Cut-off values are already optimized for the target population of this study for both biomarkers:

Although results are given separately for both biomarkers, the processing software included in the *Alinity i System* interprets their values and provides results as a dichotomic qualitative variable:

- Positive: when any of the biomarkers is over their cut-off value point.
- Negative: when both biomarkers are under their cut-off value point.

Biomarker	GFAP	UCH-L1
Cutoff value	35.0 ng/L	400.0 pg/mL

5. Cost

According to the manufacturer representative (Abbott Laboratories) i-STAT kits retail for approximately 16€ per test (61).

7.6.1.2. Computed tomography

Cranial CT images will be acquired with a **CT scanner** (Aquilion ONE, Canon Medical Systems ®). Already existing protocols from the Radiology department of our hospital will be used for the performing of cCT scans.

Specialized radiologists will be in charge of reporting results from cCT. The final report of results will be registered in the Hospital Electronical Health Records (SAP). Results will ultimately determine the specific management each patient requires.

7.6.2. Safety

Mild TBI is a condition with low mortality rates, with only an exceptional 0’1% mortality rate, a minimal 1% of patients with mTBI needing neurosurgery interventions, and only 7-10% patients presenting significant findings on cCT (42). This makes the overall setting of our study inherently safe, as most patients recover without severe complications.

The implementation of our new algorithm will be restricted to priorly selected patients according to the inclusion criteria, which ensures that every single patient will receive a tailored diagnostic approach, proportional to their individual clinical condition.

5.6.2.1. mTBI Biomarker determination safety

Determination of TBI biomarkers as part of the intervention will be performed through blood sampling, which will be drawn through reference phlebotomy guidelines (62), already widely used in clinical practice. These guidelines are designed to reduce risks such as hematomas, infections, or discomfort for patients. The nursing teams involved are already trained in these procedures, and no additional training will be required.

7.6.2.2. Cranial CT safety

Cranial CT scans are also routine for the management of our target population and will be performed using updated reference protocols, which ensure good balance

between the amount of radiation used and the quality of the image obtained. Radiology teams, including technicians and radiologists, are fully trained in these procedures, and no additional training will be necessary for the study.

In conclusion, participation in this study does not involve significant additional risks, as there are no supplemental procedures that could represent potential hazards for the patient. However, our algorithm aims to achieve faster discharge times, which mean shorter observation periods. Although very unlikely, this could increase risk of complications on our target population. To neutralize the potential risks, patients will be given clear information (Annex 5) for reattendance to emergency department, emphasizing on symptoms of risk that would deserve further evaluation.

The potential risks associated to patients in need of neurosurgical or other treatments are not within the scope of the study's accountability.

7.7. DATA COLLECTION

For data collection, a secure computer-based database will be developed by the data manager to systematically compile all information gathered before, during, and after the intervention. Data will initially be recorded in a standardized data collection sheet (Annex 6), designed to capture all relevant study variables, before being transferred to the database by the clinical coordinator.

To protect patient confidentiality, all identifying information will undergo a pseudonymization process, ensuring that patient identity remains coded and inaccessible to unauthorized personnel. Each patient will be assigned a unique identification number.

7.7.1. Study groups

To understand how data will be collected, a reminder of the two groups participating in the study is presented:

1. **Patients assessed for mTBI without the use of TBI biomarkers (retrospective group)**: Data from the first group will be extracted from the already existing database of patients who received medical attention for mTBI between September 2024 and May 2025 at the Hospital Universitari Doctor Josep Trueta de Girona.
   This time frame has been chosen to ensure an adequate sample size, accounting for the flow of patients attending our emergency department.

2. **Patients that will be assessed for mTBI using TBI biomarkers (prospective group):** Data for this group will be collected prospectively during the study, following the same standardized procedures used for the retrospective group. All information will be entered into the data collection sheet and subsequently transferred to the new database.

7.7.2. Data workflow

The main investigator and the data manager will oversee the review and extraction of data for the retrospective group, ensuring all relevant information is accurately transferred into the standardized data collection sheet and then into the database.

For the prospective group, co-investigators will be responsible for collecting data and completing the data collection sheet. To streamline the process and ensure comprehensive data collection, updates will be recorded at three specific time points:

- Before patient discharge
- 7 days after discharge
- 30 days after discharge

The process will have the following steps:

1) Initial action upon arrival of patients with mTBI

   When a patient presents at the emergency department is classified as mTBI, the emergency room doctor in charge will assess whether they meet all inclusion criteria and none of the exclusion criteria. If so, they will be extended an invitation to participate.

2) Communication with potential participants

   Patients will be informed about the purpose of the study and will be provided with the information sheet (Annex 2) and the consent form (Annex 3). Emphasis will be placed on the voluntary and confident nature of participation, along with the right to withdraw from the study at any time.

   Upon agreement to participate, participants will be required to hand back the signed consent using the provided prepaid envelope.

3) Data collection about clinical, TBI biomarkers and CT findings

   Information regarding clinical findings, TBI biomarkers and CT findings, including final diagnosis as well as data about covariates, will be collected in the computer based database by the hospital coordinator. This kind of data will be extracted from medical history, emergency room clinical reports, and radiologists cCT reports.

Once the data is complete, the clinical coordinator will review the data sheets and transfer the finalized information into the secure computer-based database. In case of

uncertainties, the clinical coordinator and the emergency medicine doctors will collaborate to clarify any discrepancies.

Once the data from every patient is collected, it will be sent to the statistician to analyze.

7.8. FLOWCHART

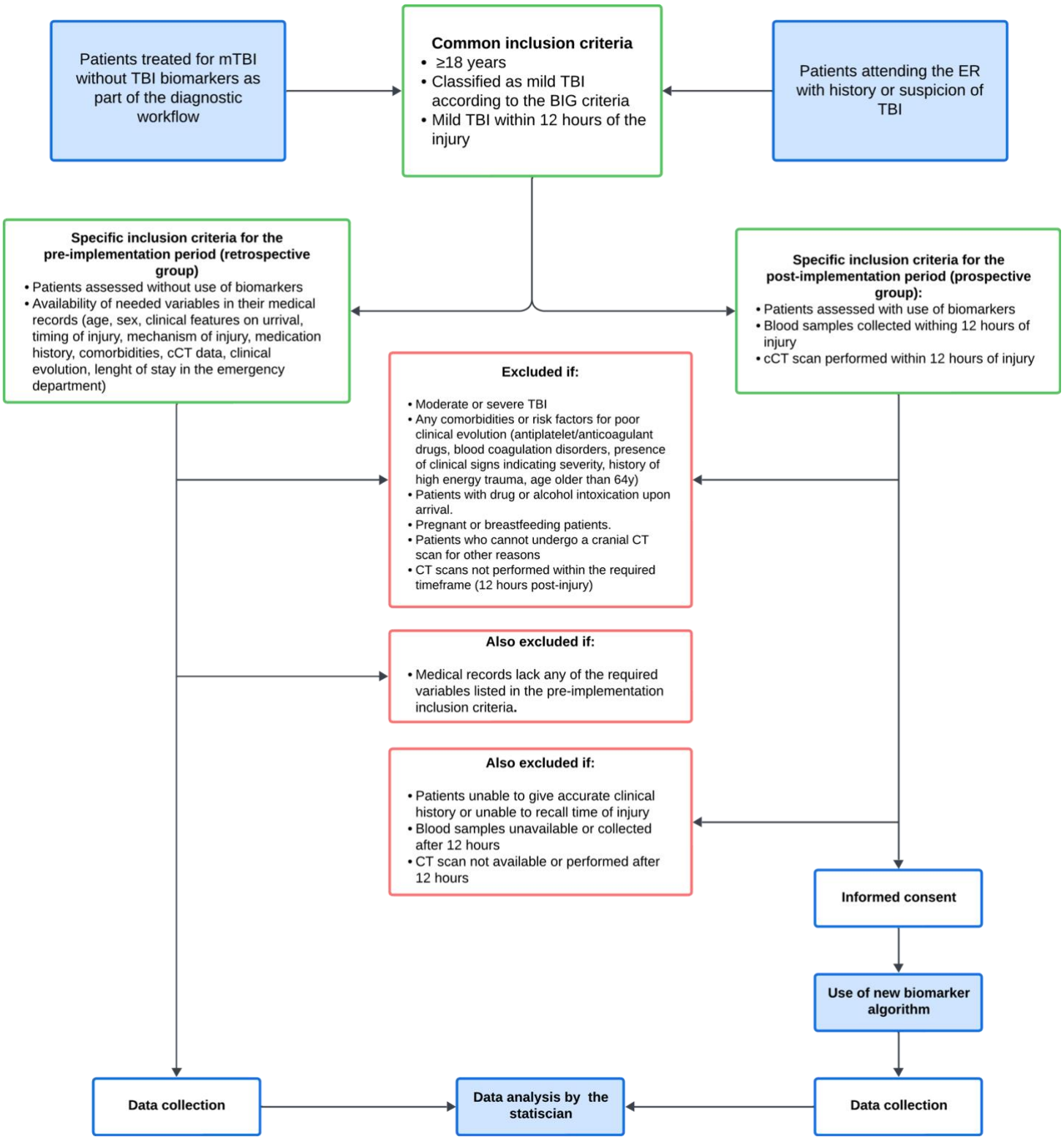

Figure 16. Flowchart describing the pathways of inclusion and exclusion for both groups of patients. By author.

8. STATISTICAL ANALYISIS

The statistical analysis will be conducted by a professional statistician using Statistical Package for Social Sciences (SPSS) version 29.01. Results will be considered statistically significant if the p-value is ≤0.05, and a 95% confidence interval will be applied in all tests.

8.1. STUDY DESIGN OVERVIEW

The study involves a comparative analysis of two diagnostic algorithms for mTBI management: one using biomarkers and one without the use of biomarkers. Data is collected from two distinct time periods: a pre-implementation period (September 2024 – May 2025) where no biomarkers were used, and a post-implementation period (May 2025 – January 2026) where biomarkers will be integrated into the diagnostic workflow. This quasi-experimental, pre-post study design allows for evaluation of the impact of biomarkers on key outcome measures.

8.2. DESCRIPTIVE ANALYSIS

8.2.1. Independent variable

Descriptive statistics for the distribution of patients in each group will be presented as counts and percentages.

Categories:

1. Management without biomarkers (pre-implementation period).
2. Management with biomarkers (post-implementation period).

8.2.2. Dependent variables

- Performing of cCT: presented as total number of cCT and proportions stratified by pre- and post-implementation periods.
- Time of stay in the Emergency Room: presented as median and interquartile range.
- Mortality at 7 and 30 Days: mortality rates will be expressed as counts and percentages for each category (alive/deceased).
- Return to ER in the first 72 hours after discharge: return rates will be expressed as counts and percentages for each category (returned/did not return).

In summary, qualitative variables will be summarized as proportions (independent variable, cCT performed, mortality at 7 and 30 days, and return to ER during first 72 hours). The only quantitative variable is time of stay in the ER. As it follows an asymmetrical distribution, it will be summarized using median and interquartile range (IQR).

8.2.3. Covariates

Covariates considered for this study are age, sex, mechanism of injury, GCS score, loss of consciousness, post-traumatic amnesia, vomiting, time from injury to admission, and cCT result.

Summary statistics for these covariates will include frequencies for qualitative variables and means/standard deviation or medians/IQR for quantitative variables.

8.3. INFERENCE

8.3.1. Primary outcomes

8.3.1.1. Analysis of cCT scans performed

The cCT performed will be analyzed as a qualitative dichotomous variable (cCT performed: yes/no). To evaluate the effect of the biomarker-based algorithm on the use of cCT, the analysis will proceed as follows:

1. Bivariate analysis: comparison of proportions of cCT performed between pre- and post-implementation groups will be conducted using the **chi-squared test**. If more than 20% of expected cell frequencies are below 5, **Fisher's exact test** will be applied instead.
2. Multivariate analysis: to account for potential confounding factors that could influence the decision to perform a cCT, a **logistic regression model** is constructed, which will evaluate the odds of requiring a cCT adjusting for the covariates outlined in section 7.5.4. Covariates. Results are presented as odds ratios (OR) with 95% confidence intervals and p-values for each covariate included in the model.

8.3.1.2. Analysis of the time of stay in the emergency room

The time of stay in the emergency department will be analyzed as a quantitative continuous variable, measured in minutes, as follows:

1. Bivariate analysis: **Kaplan-Meier survival analysis** will be used to compare survival curves of time of stay in the emergency room between pre- and post-implementation periods. Survival curves for each group will be generated and compared using the **log-rank test**, assessing the null hypothesis that the survival distributions are the same in both groups.
2. Multivariate analysis: a **Cox model** with proportional hazards regression will be used to identify factors associated with the risk of stay in the ER while controlling for potential confounders. For each covariate, changes in mortality risk will be expressed as Hazard Ratios (HR). Covariates are outlined in section 7.5.4 Covariates.

8.3.2. Secondary outcomes

8.3.2.2. Analysis of return to ER within the first 72 hour

The return of patients to the ER will be analyzed as a qualitative dichotomous variable (returned: yes/no).

1. Bivariate Analysis: A **chi-square test or Fisher's exact test** will be used to compare the proportion of patients who return to the emergency department within 72 hours between the pre- and post-implementation periods. The null hypothesis is that there is no significant difference in reattendance rates between the two groups.
2. Multivariate Analysis: A **logistic regression model** will be used to identify factors associated with the likelihood of reattendance within 72 hours, while controlling for potential confounders. Results will be presented as odds ratios (OR) with 95% confidence intervals and p-values for each covariate included in the model. Potential confounders are described in section 7.5.4 Covariates.

8.3.2.3. Analysis of mortality at 7 and 30 days

The mortality of patients because of mTBI will be analyzed as a qualitative dichotomous variable (alive: yes/no).

1. Bivariate Analysis: A **chi-square test or Fisher's exact test** will be used to compare the proportion of patients who died after discharge or transfer from the emergency room at 7 or 30 days after injury between the pre- and post-implementation periods. The null hypothesis is that there is no significant difference in mortality rates between the two groups.
2. Multivariate Analysis: A **logistic regression model** will be used to identify factors associated with the likelihood of death within the periods established, while controlling for potential confounders. Results are presented as odds ratios (OR) with 95% confidence intervals and p-values for each covariate included in the model. Potential confounders are described in section 7.5.4 Covariates.

9. WORKING PLAN AND CHRONOGRAM

9.1. RESEARCH TEAM MEMBERS

This study will be conducted in Hospital Universitari Doctor Josep Trueta, where a multidisciplinary research team will be established, consisting of the following key members:

- **Main investigator (MI):** they will be responsible of formulating the study, writing the protocol and submitting it for approval, as well as leading the study, being in contact with the hospital coordinator and making sure every process is carried out the way it should.
- **Study coordinator (SC):** they will be the coordinator of the research team, the one in charge of assigning tasks. An emergency medicine specialist will occupy this role. The SC is the person who will keep close contact with the MI in case any doubts might arise. Every 3 months, the SC will meet with the MI.
- **Co-investigator coordinator / Hospital coordinator (HC):** they will oversee the study by coordinating co-investigators, ensuring the collection of data into the record template is properly carried out by the emergency doctors responsible for each patient. This role will be filled by an emergency medicine specialist.
- **Co-investigators:** Emergency departments are always working, thus, to make sure that all shifts are covered, several co-investigators will be appointed in accordance with hospital staff shifts. In each shift, the following professionals will participate:
  - **Emergency room doctors:** they will be the ones responsible for giving medical attention to each patient with mTBI. The HC will supervise the management of every patient included in the study.
  - **Clinical analyst:** they will be responsible of supervising determination of TBI biomarkers once the blood sample has been obtained from patients. The person in charge of all **laboratory technicians** on each shift.
  - **Imaging technician:** they will perform the cCT scans.
  - **Radiologist:** they will report the findings on cCT scans performed.

- **Nurses:** it includes all nurses implicated in the attention of patients in the emergency room. Nurses from all the following sections will participate: emergency triage, rapid assessment circuit, critical and semicritical boxes, A, B and C boxes.

- **Data manager (DM):** they will be responsible for managing the data collection during the study, as well as overseeing data processing, quality control, and report for the final analysis of the study. They will essentially create the database.
- **Professional statistical analyst:** they will do the analysis of all the data obtained.
- **Scientific researcher**: they will collaborate to interpret the results, write the paper and present results.
- **Other staff:** other physicians involved in the management of patients, nursing assistants, etc.

9.2. STUDY STAGES

This project will be developed during an estimated period of two years (starting May 2025 and finishing in September 2026), but time can vary depending on the time required to obtain the sample size. If needed, an extension of time will be requested.
The steps of this quasi-experimental study will be done according to the following order, grouped in 6 stages each consisting of different activities.

9.2.1. Stage 0: Elaboration of the protocol and study design (4 months: November 2024 – February 2025)

1) **First session:** (November 2024, completed): meeting with the intention to think about this project and the gaps of information there were in this area of study. The development of this project was accorded by Dr. Cristina Ramió Lluch and Quim Porta Caubet.
2) **Bibliographic research and protocol elaboration** (November 2024 – January 2025, completed): extensive bibliographic research has been carried out in order to compilate all the latest evidence on TBI biomarker use for mTBI patients. The redaction of this protocol was also elaborated during this period.

3) **Participating hospital contact** (February 2025): the MI will present the protocol at *Hospital Universitari Doctor Josep Trueta* for them to participate in this study.
4) **Database creation** (February 2025): Hospital Universitari Doctor Josep Trueta already has a database that contains all the information from patients included in the retrospective group, and will be compiled following the Data Collection instructions to identify patients eligible. Instructions are outlined in section 7.7. Data collection.

   All this retrospective information will be added to a new database, created specifically for this study protocol to further organize information, leaving non relevant information out of our database.

   The database for the prospective group will be created by the data manager to compile the information provided in Data Collection Sheet, which will be obtained in the future as patients from this group are included in the study.

9.2.2. Stage 1: ethical approval (February 2025 – April 2025)

This protocol will be presented to the Comitè d'Ètica I d'Investigació Clínica (CEIC) of Hospital Universitari Doctor Josep Trueta for its revision and approval. Any objections raised by the CEIC will be considered and appropriately incorporated into the protocol.

9.2.3. Stage 2: Preparation and coordination (April 2025)

1) **Meeting** (April 2025): the MI will meet with the hospital research team to decide who will be assigned as SC.
2) **Informative sessions** (April 2025): all other members included in the study will be made aware of the purpose of the study, and the clinical value that TBI biomarkers could add to their day to day practice. The new algorithm for management of mTBI patients will be explained in detail, ensuring the understanding of its indications and safety. They will also receive a copy of this protocol.

   In these sessions they will also learn how to use the Data Collection Sheet and the database correctly, emphasizing on where every bit of information needs to be written down.

9.2.4. Stage 3: Sample recruitment, intervention and data collection (8 months: May 2025 – January 2026)

1) **Sample recruitment**: patients who meet all the inclusion criteria and none of the exclusion criteria will be invited to participate in the study, as detailed in previous sections. The recruitment of patients for this study will be done using a non-probabilistic consecutive method. Considering the required sample size of 225 patients a time of recruitment of 8 months is needed.
2) **Intervention**: as patients present to the emergency department and are eligible to participate in the study, our intervention will take place, as they will be assessed using the newly proposed algorithm, which includes the use of TBI biomarkers.
3) **Data collection**: data will be collected in the Data Collection Sheets during their time at the emergency room and at the time of discharge, as outlined in section 7.7. Data collection. Posteriorly, data will be transferred into the database.
4) **Data update**: data from their survival status will be updated 7 and 30 days after discharge or transfer to another medical department. Data from whether they came back to the ER will be registered if the return was during the first 72.

9.2.5. Stage 4: Data analysis and interpretation (2 months: February 2026 – March 2026)

1) **Statistical analysis** (February 2026): An independent statistician will analyze all the data collected through the statistical tests mentioned in section 8. Statistical Analysis. Posteriorly, they will also interpret the results.
2) **Results and conclusions** (March 2026): The statistician will present the results to the MI, who will transfer them to the whole research team so a discussion about the outcomes can be done. After this, the research team will draw conclusions.

9.2.6. Stage 5: Final article elaboration (April 2026)

The MI and the research team will collaborate to draft an article presenting the study's explanation, results and conclusions.

9.2.7. Stage 6: Publication and dissemination of the results (May 2026)

The article will be edited and supervised by an English speaking proofreader and submitted to open-access and international emergency medicine journals. Additionally, it will be showcased at national and international congresses to present the conclusions drawn from the investigation. All actions regarding dissemination of the article will be led by the MI and SC.

STAGE	TASK	PERRSONNEL	TIME																		
			2024		2025												2026				
			Nov	Dec	Jan	Feb	Mar.	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May
STAGE 0	First session	MI																			
	Bibliographic research and protocol	MI																			
	Participating hospital contact	MI																			
	Database creation	DM																			
STAGE 1	Ethical approval	CEIC																			
STAGE 2	Meeting																				
	Informative sessions																				
STAGE 3	Sample recruit.																				
	Intervention																				
	Data collection																				
	Data update																				
STAGE 4	Statistical analysis																				
	Conclusions																				
STAGE 5	Final article elaboration																				
STAGE 6	Publication and dissemination																				

Table 4. Chronogram

10. STUDY BUDGET

The estimated budget for this study is detailed below. It includes personnel costs, material costs, and dissemination expenses.

10.1. EXPENSES NOT CONSIDERED IN THE STUDY

- **Healthcare professionals and research team**: personnel participating in the research team will not receive additional compensation, as it is considered that their motivations for joining the study are not incentivized for any economic reasons, and that their participation does not require any significant additional efforts. Researchers are rewarded by the scientific prestige and the intellectual gains that come from the study. Furthermore, all their required tasks for the correct development of the study will be realized during their working hours, so there will be no additional costs.
- **Cranial CT images**: cranial CT images used in the study are part of routine clinical practice and do not involve supplementary costs. In fact, the purpose of this study is to reduce the economic burden that this technique generates.
- **Protocol design**: No compensation has been given for the bibliography search and the protocol design.

10.2. STUDY EXPENSES

10.2.1. Personnel expenses

- **Statistician**: A qualified statistician responsible for conducting the statistical analysis will be compensated at a rate of 40€ per hour for a total of 30 hours.
- **Data manager**: A data manager services will be contracted to manage the data collection process, supervising its quality. They will also transfer the final data report to the statistician for the final analysis. The compensation will be of 40€ per hour for a total of 15 hours.
- **Linguistic correction by a certified proofreader**: correction of a document to adequate English has a closed price of 300€/article.

10.2.2. Material expenses

- **TBI biomarker testing**: The used i-STAT cartridges retail for approximately 16€ per test. 225 tests will be done to cover the required sample size.
- **Printing materials**: printing materials include every document that will be printed for this protocol's existence (study protocol and information sheets).
  The protocol information sheet includes 4 pages, whereas the informed consent form, reattending recommendations, and data collection sheets are only one page. Thus, 7 pages will need to be printed for each patient. Considering our sample of 225 patients, the amount of pages needed is 1.575 pages.

10.2.3. Publishing fees

- **Article publication fees**: An estimated budget of 1.500€ is destined to publication fees.

10.2.4. Dissemination fees

- **National and international congresses inscriptions**: the Congress of the Spanish Society of Emergency Medicine (SEMES) and the Congress of the European Emergency Medicine (EUSEM) will be included in the budget. Budget will cover expenses of transport, daily allowance and accommodation.

EXPENSES	COST X UNIT	UNIT	SUBTOTAL	TOTAL
PERSONNEL EXPENSES				
Data manager	40€/h	15h	600€	2.100€
Statistician	40€/h	30h	1.200€	
Linguistic correction	300€/article	1	300€	
MATERIAL EXPENSES				
TBI biomarkers testing	16€	225€	3.600€	3.615,75€
Printing materials	0,01€	1.575	15,75€	
PUBLISHING FEES				
Article open access publication	1.500€/article	1	1.500€	1.500€
DISSEMINATION FEES				
National congress	1.250€	1	1.250€	3.750€
International congress	2.500€	1	2.500€	
				10.965,75€

11. ETHICAL AND LEGAL CONSIDERATIONS

Comitè d'Ètica i d'Investigació Clínica (CEIC)

This protocol will be submitted to the Clinical Research Ethics Committee of the Hospital Universitari Doctor Josep Trueta, known as the **Comitè d'Ètica i d'Investigació Clínica (CEIC)**. Obtaining approval from this committee is essential prior to initiating the study. Any concerns or recommendations raised by the CEIC will be thoroughly reviewed, addressed, and integrated into the protocol as necessary.

11.1. ETHICAL PRINCIPLES

This study will adhere to the ethical standards outlined in the **Declaration of Helsinki** (last revised in the 75th WMA General Assembly, Helsinki, Finland, October 2024) (63). Additionally, it will comply with the **Principles of Biomedical Ethics by Beauchamp and Childress**:

- **Autonomy**: it is defined by recognizing patients' capacities to make choices related to their health, based on their own values and preferences.

  Patient autonomy will be respected through a written informed consent process (Annex 3). Participants will receive an information sheet (Annex 2) about the study, written in accessible language, explaining its purpose, procedures, and potential risks and benefits. Patients will have the freedom to participate or withdraw at any point without facing any negative consequences.

- **Beneficence**: it is the moral obligation to act for the benefit of others or for their best interest.

  The use of TBI biomarkers in clinical decision-making aims to reduce unnecessary CT imaging, thus minimizing radiation exposure and its associated risks. By improving the precision of risk stratification, the study seeks to provide safer and more effective care for mTBI patients.

- **Non-Maleficence**: this principle emphasizes avoiding harm or exposing patients to unnecessary risks.

  To uphold this principle, exclusion criteria have been established to ensure that patients at risk of having intracranial injuries are not denied a cCT when clinically indicated. Additionally, withdrawal criteria have been defined to protect participants if new signs of risk emerge after their initial evaluation.

The biomarker tests used in this study require only minimally invasive blood sample collection, which poses no significant risks to participants. Furthermore, cCT currently are part of the routine clinical care for the subset of patients in whom they are deemed necessary, so they would not act as a new potential harm.

By adhering to these safeguards, this study ensures that participants are not exposed to unnecessary risks or harm.

- **Justice:** it is defined by ensuring that all patients, regardless of background, have an equal opportunity to participate avoiding discrimination.

  The study guarantees equitable treatment by making sure that all patients who meet the inclusion criteria and none of the exclusion criteria have the same possibility to enter the study. Everyone will be given the same information and there will be no discrimination based on gender, socioeconomic status, or ethnicity, ensuring an unbiased and fair distribution of resources.

11.2. ADHERENCE TO LEGAL FRAMEWORK

Researchers must respect the right to decide whether they accept or refuse participation in the study. This is in accordance with "*Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente" (64).*

The study will comply with all legal and ethical parameters required for conducting biomedical research involving human subjects, ensuring the protection and rights of participants in accordance with the "*Ley 14/2007, de 3 de julio, de Investigación Biomédica*" (65).

Privacy and confidentiality

All patient data will be anonymized and handled in strict compliance with the following regulations:

- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (66).
- Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales (67).

Data will be stored in a secure, password-protected database accessible only to authorized researchers. All collected data will be used solely for the purposes of this study.

Transparency and conflicts of interest

All researchers involved will declare the absence of any conflicts of interest. The study results, including unfavorable outcomes or adverse events, will be published with complete transparency to uphold the integrity of the research and contribute to the broader scientific community.

12. STRENGHTS AND LIMITATIONS

12.1. LIMITATIONS

One of the main limitations of the quasi-experimental design is the **lack of randomization** when creating the two groups in this study. Additionally, the comparison of two different time periods may introduce potential biases, such as temporal changes in clinical practice, patient demographics, or other external factors. These limitations could affect the internal validity of the study and restrict its ability to establish a definitive causal relationship between the intervention and the outcomes.

Furthermore, there is risk of a potential **selection bias**, as the groups are non-equivalent, and the sampling method is a consecutive non-probabilistic one. This introduced bias could mean that our sample may not fully represent the entirety of the population, leading to unrepresentative results. However, multivariate analysis should mitigate this problem, as it will adjust for potential confounding factors and enhance the study's internal validity.

Another limitation is that due to the nature of the intervention and the study design, both patients and clinicians are aware of the group they integrate, making a double-blind setting impossible. This lack of blinding could introduce **observational biases**. However, the main outcomes, which are the rates of cCT performed, or the time spent in the emergency department, are objective measures, and are thus difficult to be influenced by subjectivity in data collection.

The **unicentric nature** of the study may also be perceived as a limitation, as results from a single center may not be generalizable to other settings, where resources used in this study might not be available yet. However, this design was chosen to prioritize high internal validity over external validity, ensuring accurate results for our specific tertiary hospital setting.

The **strict inclusion and exclusion criteria** proposed might limit the applicability of mTBI biomarkers to the broader population. However, by relaxing the inclusion criteria, the safety of our intervention would be affected, as patients who have risk factors

nonrelated to their TBI episode (e.g. blood coagulation disorders) could experience potentially life-threatening complications when discharged without being properly diagnosed.

Finally, patient **withdrawals** could pose challenges. To account for this, the sample size was calculated with a 15% drop-out rate in mind, ensuring sufficient statistical power despite potential losses.
As we rely in retrospective data for a part of our study, we could incorporate errors of incomplete or inaccurate information, known as **information bias**. This can affect the validity of the obtained results, as missing or inconsistent data are exclusion criteria, and could limit the accuracy of the conclusions that come from the study.

As mentioned in previous sections, clinical judgement will always prevail regardless of TBI biomarker results. This could introduce **variability in the implementation** of the algorithm proposed, as not all doctors who will participate in this study have the same background and experience, which are clear influencing factors on their decision-making and judgment. To try and limit variability of clinical judgment, the informative sessions carried out will emphasize on the importance of adherence to the algorithm, as well as its safety and accuracy for diagnosing low-risk patients.

12.2. STRENGHTS

The main strength of this study is that it is designed in a **real-world setting**. This is crucial, as the evidence generated is directly applicable to current clinical practice guidelines used in the emergency room. This design also provides results that are directly reflective of the true impact on the efficiency of the department and its patients care.
In other words, thanks to the study design, results will not be hypothetical, but rather realistic, and will be able to directly improve decision-making processes in the management of mTBI.

Another strength of a quasi-experimental study is that although it does not generate the same weight of evidence as a randomized controlled clinical trial (RCCT), it is **simpler and cheaper to carry out**. In addition, it is the only viable study design when

a RCCT is not a viable option. In our subject, it would not have been viable because with our intervention we hope to avoid performing a considerable proportion of cCT with the same safety for both groups. Making a group of patients undergo cCT and its radiation dosage because of randomization would not have been ethical considering there is already sufficient evidence that proves the sensitivity of TBI biomarkers to predict intracranial injuries.

Furthermore, the retrospective nature of the recruitment of one group of our study allows us to **save considerable amounts of time** during the sampling process, as data can be collected from already existing Hospital Electronic Medical Records (SAP) without the need of waiting for the flow of patients into the ER.

To avoid the lack of comparability that pre-post studies usually present, specific inclusion and exclusion criteria have been developed for both groups to make the **groups very similar** between themselves. This serves the purpose of controlling potential confounding factors. Moreover, a multivariate analysis for differences between patients and this will allow us to know the true effects of our intervention.

13. HEALTH IMPACT

Mild TBI is by far the most common severity of TBI. Although the majority of mTBI patients recover without complications, a subset may have intracranial lesions that require prompt diagnosis and management. Current practice relies heavily on cranial cCT as the gold standard for detecting such lesions. However, its widespread use for all mTBI cases has significant drawbacks, including unnecessary exposure to ionizing radiation, overuse of healthcare resources, longer stays at the emergency department, and increased healthcare costs.

This study aims to evaluate the potential of a TBI biomarker based algorithm to optimize the management of mTBI. Biomarkers represent a non-invasive, rapid, and accessible method for stratifying patients based on their risk of intracranial injury. Their integration into clinical pathways could provide a safe and effective alternative to the current clinical criteria for CT imaging, particularly in low-risk patients.

Potential impact on the National Heathcare System stemming from the implementation of TBI biomarkers in clinical workflow could include:

- **Reduced radiation exposure**: Many mTBI patients with low risk of intracranial injury currently undergo cCT unnecessarily. A TBI biomarker based algorithm could serve as a reliable tool to rule out significant injuries, sparing patients from radiation exposure.
- **Efficient Resource Utilization**: By identifying patients at low risk for significant injuries, emergency departments could prioritize cCT imaging for moderate to high-risk cases, reducing wait times and alleviating overburdened imaging services.
- **Enhanced Patient Experience**: Avoiding unnecessary cCT can reduce patient anxiety, streamline the diagnostic process, and improve satisfaction with care, as well as reduce the patient's own waiting time before discharge.
- **Economic Savings**: With fewer unnecessary scans, healthcare systems could reduce costs associated with imaging, as TBI biomarkers represent a much cheaper expense than cCT.

If our hypothesis is confirmed, this study could redefine the management of mTBI patients, allowing to receive the same quality of medical attention without compromising their safety. Moreover, this would alleviate the burden on emergency departments by reducing over-reliance on cCT imaging, freeing up resources for other critical needs.

In the long term, these findings could support the integration of TBI biomarkers into official clinical practice guidelines. This approach aligns seamlessly with the principles of precision medicine, offering a more targeted and efficient patient management strategy while contributing to the sustainability of healthcare systems.

14. FEASIBILITY

This study is meticulously designed to ensure feasibility, with minimal impediments to its successful execution:

- The study will be conducted at the Hospital Universitari Dr. Josep Trueta, a tertiary care hospital with a multidisciplinary team that includes emergency physicians, radiologists, neurosurgeons, and clinical analysts, all of whom are used to managing patients with traumatic brain injuries. The hospital is already equipped with the necessary imaging infrastructure (CT scanners) and laboratory capacity for processing biomarkers (reagents and processing platforms), ensuring that no major additional equipment or system modifications are required.
- Based on prior patient flow and TBI prevalence in this center, we estimate that the required sample size of 225 patients for the prospective group can be achieved within a reasonable timeframe of 8 months. Data for the retrospective group will be obtained from the hospital's clinical database. This dual approach minimizes recruitment delays while maintaining the integrity of the study design.
- To ensure consistency in algorithm use, informative sessions will be held for all involved healthcare professionals. These sessions will review the study protocol and emphasize the new addition of our TBI biomarker based algorithm for TBI evaluation. Given that cCT interpretation and basic biochemical determinations (as simple as TBI biomarker determination) are routine practices in this hospital, no additional intensive training is required, further facilitating the study's feasibility.
- A secure, computer-based database will be used to collect and store study data, including biomarker results, cCT findings, and patient demographics. The main investigator and a dedicated data manager will oversee data collection to ensure completeness and accuracy.
- Professional statisticians will analyze the data using advanced statistical software. This ensures that all analyses are carried out rigorously and efficiently.
- The budget required for the study is minimized, ensuring efficient resource utilization without compromising the integrity of the research.

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16. ANNEXES

ANNEX 1. EMERGENCY ROOM PRIORITY LEVELS

Level	Category	Characteristics	Attention time
I	**Critical**	Critical situations with immediate life-threatening risk. Requires reanimation.	Immediate
II	**Emergency**	Very urgent situations with predictable life-threatening risk. High-risk cases, with physiological instability, and/or severe pain.	Immediate nursing attention / medical attention in 7 minutes
III	**Urgency**	Urgent situations with potential life-threatening risk. Patients are physiologically stable but require multiple diagnostic evaluations	30 minutes
IV	**Standard**	Less urgent situations, potentially complex but without life-threatening risk. Standard cases in hospital emergency services.	45 minutes
V	**Not urgent**	Non-urgent situations, safe to delay care. Clinical-administrative problems or low-complexity clinical issues requiring minimal diagnostic/therapeutic resources.	60 minutes

Table 5. Spanish triage system. Adapted from (40).

ANNEX 2. INFORMATION SHEET

FULL INFORMATIU PEL PARTICIPANT

Ens dirigim a vostè per convidar-lo a participar de manera voluntària a l'estudi "Implementació de Biomarcadors de Traumatisme Cranioencefàlic (TCE) a un algoritme de decisió clínica d'urgències per pacients amb traumatisme cranioencefàlic lleu". L'estudi ha estat aprovat pel Comitè d'Ètica d'Investigació Clínica de l'Hospital Universitari Doctor Josep Trueta d'acord amb la legislació vigent, els principis enunciats en la declaració de Hèlsinki i a les guies de bona pràctica clínica.

La intenció d'aquest document es proporcionar-li tota la informació necessària sobre l'estudi perquè pugui decidir de forma completament voluntària i per criteri propi si vol participar-hi o no. Així doncs, li preguem que llegeixi atentament tota la informació d'aquest document, i en cas que li sorgeixin dubtes, s'adreci al professional sanitari que li ha proporcionat aquest document, per tal de resoldre'ls abans de prendre una decisió.

Se'l convida com a potencial participant degut a que vostè ha acudit al servei d'urgències de l'Hospital Universitari Doctor Josep Trueta amb un antecedent de traumatisme cranioencefàlic que s'ha classificat com a lleu gràcies a l'entrevista clínica realitzada pel personal sanitari.

Descripció general del projecte

Objectius de l'estudi

L'objectiu principal de l'estudi és investigar si existeix una millora en l'eficiència del tractament de pacients amb TCE lleu gràcies a la implementació dels biomarcadors Proteïna Àcida Fibril·lar Glial (GFAP) i Hidrolasa Ubiqüitina Carboxi-Terminal L1 (UCH-L1) en la presa de decisions clíniques. Al mateix temps, l'estudi pretén descobrir si aquesta implementació és igual de segura que l'algoritme que s'ha utilitzat en els últims anys.

El TCE lleu és una patologia de baix risc de presentar complicacions. Tot i així, avui en dia encara es realitzen tomografies computades (TC) a gran part dels pacients,

fent que sigui una prova amb baixa proporció de troballes significatives. Als pacients on no hi ha troballes i només se'ls realitza la TC com a cribratge per tal de poder-los donar l'alta, se'ls exposa a unes dosis de radiació considerables. L'estudi planteja la hipòtesi que aquestes dosis de radiació són potencialment evitables.

Els biomarcadors de TCE, per altra banda, són molècules que han demostrat precisió coma a eines diagnòstiques, i capacitat de predir les complicacions associades al TCE lleu.
Aquests biomarcadors es poden detectar a la sang i serveixen per determinar si un pacient presenta un risc suficientment elevat de tenir alguna complicació després d'un TCE lleu, i per tant si mereix una exploració amb TC, o si per contra, pot ser donat d'alta de manera segura sense necessitat d'haver-se de sotmetre a una TC.

Per tal de comprovar la hipòtesi, l'estudi pretén analitzar si, gràcies a la implementació d'aquests biomarcadors en un nou algoritme, hi ha una reducció de la proporció de tomografies computades (TC) realitzades, reduint d'aquesta manera la radiació innecessària, els temps d'espera dels pacients, els costos sanitaris, i si al mateix temps, tot això no compromet la seguretat dels pacients.

Característiques dels participants
Per tal de participar en l'estudi, els pacients han de tenir més de 18 anys, i haver acudit a urgències amb un antecedent de TCE en les 12 hores prèvies a l'arribada. A més, han d'haver estat classificats com a pacients de severitat lleu i de baix risc.
Si durant l'estada a urgències s'identifica algun factor de risc no conegut o es produeix un deteriorament clínic, els pacients deixaran de ser elegibles per l'estudi, i passaran a ser tractats com a pacients d'alt risc.

Col·laboració sol·licitada
Un cop s'hagi classificat els pacients com a TCE lleu i s'hagi descartat que presentin algun factor de risc, se'ls realitzarà una mínima punxada per tal d'obtenir una mostra de sang. En cas que ja s'hagi hagut d'obtenir una mostra de sang per alguna altra indicació, s'utilitzarà el mateix accés venós, sense necessitat de realitzar una altra punxada. La mostra serà enviada al laboratori, lloc on es processarà i s'analitzaran

les concentracions de biomarcadors de TCE (GFAP i UCH-L1). A partir d'aquí, es plantejaran dos escenaris:

- Si les concentracions de biomarcadors a la sang del pacient son suficients com per considerar el resultat positiu, es realitzarà una TC per tal de descartar la presència de lesions intracranials resultants del TCE.
  Independentment del resultat de la TC, els pacients romandran en observació un mínim de 6 hores.
- Si les concentracions de biomarcadors a la sang del pacient no superen el límit establert, i per tant el resultat és negatiu, no es realitzarà una TC. En aquest cas, els pacients podran ser donats d'alta de manera segura sense la necessitat de realitzar la TC, ni de romandre un mínim de 6 hores en observació.
  Abans de rebre l'alta, els pacients rebran un full informatiu de reconsulta. En aquest document, hi constaran els símptomes pels quals els pacients haurien de tornar a visitar-se a urgències per ser revalorats.

Un cop s'assoleixi el nombre de pacients necessaris, l'estudi analitzarà les dades obtingudes i les compararà amb les dades recopilades durant un període en que no existien els biomarcadors de TCE.

Resumint, si vostè proporciona el seu consentiment, el que determinarà si el seu cas requereix de la realització d'una TC o no seran els biomarcadors de TCE. Posteriorment les seves dades seran recopilades i incloses en l'estudi.
Si vostè no proporciona consentiment per la seva participació, rebrà atenció mèdica segons l'algoritme utilitzat de manera habitual en la pràctica clínica, i les seves dades d'història clínica no seran utilitzades per analitzar resultats.

Compensació econòmica

No s'ofereix cap compensació econòmica per participar a l'estudi ni tampoc suposa cap cost addicional pel pacient. La participació és totalment voluntària.
Tot i no obtenir cap benefici econòmic, gracies a la seva ajuda i la d'altres participants, i si finalment es confirmen les hipòtesis, el benefici repercutirà en els futurs pacients atesos al servei d'urgències de l'Hospital Universitari Doctor Josep Trueta.

Riscs i beneficis de la participació en l'estudi

Riscs

La participació en aquest estudi no implica riscos addicionals significatius, doncs l'única prova diagnòstica innovadora del nou algoritme proposat són els biomarcadors, els quals es determinen mitjançant una mostra de sang. No es realitzarà cap altra procediment que no formi part dels algoritmes d'actuació en pràctica actualment.

No obstant, el nou algoritme plantejat té com a objectiu reduir els temps d'observació dels pacients i agilitzar el procés d'estada a urgències. Aquest fet, tot i que és molt poc probable, podria augmentar lleument el risc de complicacions en la nostra població diana. Per tal de neutralitzar aquest possible risc, els participants que siguin donats d'alta sense període d'observació, rebran un full amb informació clara i detallada sobre els símptomes d'alerta que podrien requerir una nova avaluació mèdica, així com instruccions de dirigir-se a urgències en cas que apareguin aquests símptomes. Veure el full "Informació important pels pacients a l'alta".

Beneficis

La participació en l'estudi podria suposar que certs pacients, en l'escenari en que els biomarcadors de TCE tinguin un resultat negatiu, podrien ser donats d'alta sense necessitat de sotmetre's a la radiació d'una TC, i per tant d'una manera molt més ràpida.

A part dels beneficis individuals, si es confirmen les hipòtesis, els resultats contribuiran a millorar l'eficiència del maneig clínic de TCE lleus en un futur, reduint l'ús innecessari de TC i reduint els costos sanitaris associats a cada pacient.

Tractament de dades i confidencialitat

Si vostè accepta participar en l'estudi, es recolliran les seves dades corresponents a la història clínica i els resultats de les proves complementàries realitzades durant l'estada al departament d'Urgències. Totes les dades recollides s'introduiran en un formulari i posteriorment s'emmagatzemaran a una base de dades de manera totalment anònima.

La informació obtinguda serà totalment confidencial. La recollida i l'anàlisi de dades serà de forma anònima d'acord amb la Llei Orgànica de Protecció de Dades de Caràcter Personal i Garantia de Drets Digitals (3/2018) i el Reglament 2016/679 del Parlament i Consell Europeu. Només els investigadors de l'estudi tindran accés a les seves dades personals. El seu nom quedarà codificat i no serà possible identificar el nom de les persones de les quals provenen les dades. La informació serà només utilitzada amb finalitats d'investigació.

Un cop finalitzat l'estudi, els resultats seran publicats per tal que altres centres i investigadors es puguin beneficiar de les troballes del nostre estudi. En cas de publicació, qualsevol dada de caràcter personal serà tractada de forma anònima per tal que no sigui possible identificar els participants.

Dubtes i agraïments

En cas de tenir algun dubte respecte l'estudi, durant la seva estada a urgències pot consultar-ho amb el personal sanitari. Si li sorgeix algun dubte després d'haver estat donat d'alta, pot realitzar les consultes amb l'investigador principal o amb la resta de l'equip de recerca mitjançant la següent adreça de correu electrònic: _____ o el següent número de telèfon: _____.

Estem a la seva disposició per ajudar-lo.

Ens agradaria remarcar que la decisió de participar o no en l'estudi no modificarà l'interès per tal d'aconseguir proveir-los de la millor atenció mèdica disponible. Sigui quina sigui la decisió, l'equip de recerca vol transmetre el seu agraïment pel seu temps i atenció.

ANNEX 3. INFORMED CONSENT

CONSENTIMENT INFORMAT

Títol de l'estudi: Implementació de Biomarcadors de Traumatisme Cranioencefàlic (TCE) a un algoritme de decisió clínica d'urgències per pacients amb traumatisme cranioencefàlic lleu.

Jo,

_____,

amb DNI _____, de nacionalitat _____, major d'edat, amb domicili _____,

Declaro que:

- He rebut, llegit i entès el "Full informatiu pel participant" relacionat amb l'estudi.
- He rebut la informació suficient per part dels membres de l'equip de recerca en relació a les característiques i objectius de l'estudi, possibles riscs i beneficis, i la importància de la meva contribució.
- He pogut adreçar els meus dubtes sobre l'estudi i aquests han estat solucionats satisfactòriament per part dels membres de l'equip de recerca.
- Entenc que la meva participació és de caràcter voluntari.
- Entenc que puc revocar el meu consentiment informat sobre la meva participació a l'estudi en qualsevol moment, sense haver de donar motius i sense que això repercuteixi en la qualitat del procés assistencial.
- Dono permís perquè les dades de la meva història clínica siguin usades per l'equip investigador per fins relacionats amb aquest estudi. Se m'ha informat de l'ús científic que es farà de les dades personals.
- Entenc que les meves dades seran tractades en el marc de la legalitat, sempre respectant la confidencialitat.
- Entenc que puc sol·licitar la retirada de les meves dades de l'estudi en qualsevol moment del mateix.
- Declaro que se m'ha entregat una còpia impresa del "Full informatiu pel participant" i una còpia signada d'aquest Consentiment informat.

- D’acord amb la informació rebuda fins el moment, ACCEPTO VOLUNTÀRIAMENT la meva participació a l’estudi especificat.

A _____, ____ de _____ de 20___.

SIGNATURA DE L’INVESTIGADOR SIGNATURA DEL PARTICIPANT

ANNEX 4. WITHDRAWAL OF CONSENT FORM

FORMULARI DE RETIRADA DEL CONSENTIMENT

Jo _____, amb DNI _____, revoco el meu consentiment prèviament signat per participar en l'estudi *"Implementació de Biomarcadors de Traumatisme Cranioencefàlic (TCE) a un algoritme de decisió clínica d'urgències per pacients amb traumatisme cranioencefàlic lleu".*

A _____, ____ de _____ de 20___.

SIGNATURA DEL PARTICIPANT

ANNEX 5: RECOMMENDATIONS AFTER DISCHARGE

INFORMACIÓ IMPORTANT PELS PACIENTS A L'ALTA

La seguretat dels participants del nostre estudi *"Implementació de Biomarcadors de Traumatisme Cranioencefàlic (TCE) a un algoritme de decisió clínica d'urgències per pacients amb traumatisme cranioencefàlic lleu"* és una prioritat.

És per aquest motiu, que li preguem que llegeixi atentament i tingui present la següent llista de símptomes que podrien ser indicatius de mala evolució després d'un traumatisme cranioencefàlic.

- Mal de cap intens o persistent.
- Nàusees o vòmits, especialment si són repetitius.
- Problemes d'equilibri o marejos.
- Problemes de visió (visió borrosa o doble).
- Fatiga extrema o debilitat sense causa aparent.
- Sensibilitat exagerada al soroll o a la llum.
- Sensació de formigueig o entumiment a extremitats.
- Sensació de confusió, com si estigués atordit.
- Sensació de tenir el "cap espès" o de no pensar amb claredat.
- Lentitud mental o dificultat per respondre amb normalitat.
- Dificultats per concentrar-se o recordar coses.
- Oblidar converses recents o esdeveniments propers.
- Confusió respecte a esdeveniments recents.
- Respostes lentes a preguntes o indicacions.
- Irritabilitat o canvis d'humor marcats.
- Sensació de tristesa sense motiu aparent.
- Nerviosisme o ansietat exacerbada.
- Somnolència excessiva durant el dia.
- Dormir menys o més hores de les habituals.
- Dificultat per conciliar el son o per mantenir-se adormit.

Caldrà tenir en compte aquests símptomes sempre i quan siguin de nova aparició després del traumatisme cranioencefàlic, o si no s'expliquen per qualsevol altra causa.

En cas que apareguin aquests símptomes, serà necessari que es consulti de nou al departament d'Urgències de l'Hospital Universitari Doctor Josep Trueta per tal de rebre una nova exploració.

Aquestes indicacions estan dissenyades per protegir la seva salut i assegurar un seguiment adequat després del traumatisme en cas que sigui necessari. Si té qualsevol dubte, no dubti en consultar amb l'investigador principal o amb la resta de l'equip de recerca mitjançant la següent adreça de correu electrònic: _____ o el següent número de telèfon: _____.

ANNEX 6: DATA COLLECTION SHEET

FORMULARI DE RECOLECCIÓ DE DADES

Codi del participant: _____

Professional responsable: _____

Data: __ / __ / ____ **Hora d'arribada: _____**

Dades del pacient:

Edat: ___ **Sexe:** □ Masculí □ Femení

Dades de l'episodi:

- Mecanisme lesiu: □ Caiguda
  □ Crani impacta contra un objecte
  □ Objecte impacta contra el crani
  □ Accident de trànsit de baixa energia
  □ Traumatisme relacionat amb l'esport

- Puntuació GCS: □ 13 □ 14 □15
- Pèrdua de consciència: □ Sí □ No
- Amnèsia post episodi: □ Sí □ No
- Vòmits: □ Sí □ No

- Temps transcorregut des del trauma fins a l'admissió: _____

- Resultat de biomarcadors de TCE: □ Positiu □ Negatiu

Variables d'estudi:

- Realització de Tomografia Computada cranial: □ Sí □ No
  Resultat de la Tomografia computada cranial: □ Positiu □ Negatiu
- Temps d'estada al departament d'urgències: _____
- Reconsulta al departament d'urgències a les primeres 72 hores: □ Sí □ No
- Èxitus: Als 7 dies: □ Sí □ No
  Als 30 dies: □ Sí □ No