MANAGEMENT OF PATIENTS WITH MILD TRAUMATIC BRAIN INJURY AND RECOMMENDATIONS

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1. PROJECT RATIONALE, OBJECTIVES AND METHODOLOGY

RATIONALE

Mild traumatic brain injury (TBI) is currently a health priority because it has a high incidence, results in a large number of consultations in emergency departments and generates high consumption of resources, as there are no specific symptoms that enable identification of patients at risk of acute intracranial injury (AII)[1].

Procedures and guidelines for the management of patients with mild TBI are widespread in clinical practice, but the approval of the first rapid serum/plasma test of specific brain biomarkers represents an opportunity to propose an updated and consensual algorithm to standardize the management of these patients in Spain.

OBJECTIVE OF THE PROJECT

The **objective of the project** was to analyze the management of patients with possible mild TBI in emergency situations and to issue recommendations for improving the approach to this disease.

To this end, a **multidisciplinary Advisory Committee** (AC) was established, consisting of 14 health care professionals with experience in the approach to mild TBI, covering both outpatient and inpatient management.

METHODOLOGY

The project was structured in **three phases** (Fig. 1) carried out between December 2022 and May 2023:

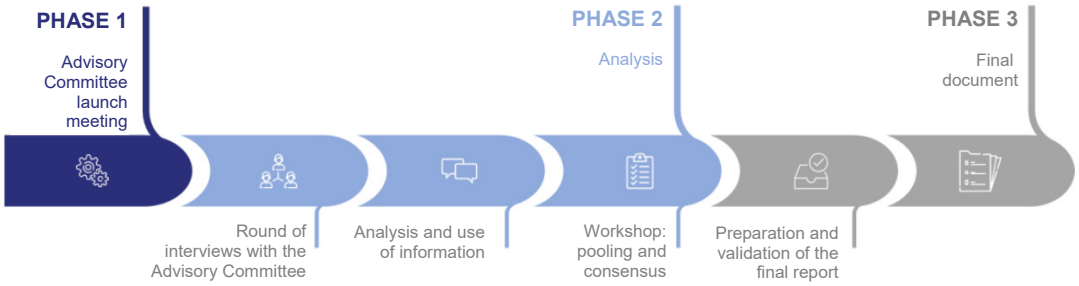

Figure 1. Project methodology

PHASE 1 LAUNCH

During the initial phase of the project, a **launch meeting** was held during which, in addition to reviewing the objectives and methodology, agreeing on the scope of the project and identifying key factors for success, the following aspects were discussed:

- The current situation and the main challenges in the management of patients with possible mild TBI in emergency situations in Spain.
- The current situation regarding blood biomarkers in mild TBI and their implementation in clinical practice.

Screening of information, documentation and literature relevant to the project was also carried out during this first phase.

PHASE 2 LAUNCH

LITERATURE REVIEW AND INTERVIEWS

Alongside the screening of information from the previous phase, a **literature search** of clinical practice guidelines, consensus, protocols, care processes and other reference documents on the management of mild TBI was conducted.

Analysis of the information enabled the definition of a first version of the care pathway for patients with mild TBI, from which a **semi-structured script was designed** for conducting **individual interviews with all AC members**.

Some of the key aspects covered during the interviews were: analysis of the current situation and identification of critical points; availability of tools during the evaluation of mild TBI; study of acute brain damage and overuse of neuroimaging tests; the current outlook on the use of blood biomarkers in mild TBI and the expected impact on clinical practice with the arrival of the first rapid serum/plasma test for specific biomarkers; and identification of areas for improvement or key elements of good practice in the management of patients with mild TBI at every stage of the care pathway.

WORKSHOPS

After the interviews, there were two **workshops with the AC**, in which the main conclusions of the literature review and the interviews were presented with the **aim of validating and agreeing on**:

- The definition of mild TBI.
- The care process.
- Recommendations.
- The content and structure of the final report.

PHASE 3 FINAL DOCUMENT

This last phase consisted of **preparing the final report** and its review and validation by the AC.

Lastly, there was a **final report validation and project closure meeting**.

2. ADVISORY COMMITTEE

EMERGENCY MEDICINE

- **Dr. Moya, Francisco** *(Coordinator).* Coordinator of International Medical Services, Hospital Vithas Xanit Internacional (Vithas Xanit International Hospital), Málaga, Spain; Undersecretary of International Relations, SEMES; Associate Professor, Faculty of Health Sciences, University of Málaga.
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- **Dr. Vicente, Agustina.** Head of Emergency Radiology, Hospital Universitario Ramón y Cajal, Madrid, Spain; member of the Advisory Committee of SERAU; former Treasurer and former Vice-President of SERAU.

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3. INTRODUCTION

TBI is the leading cause of death and disability globally among all traumatic injuries and represents a major public health problem, as well as involving significant costs to health systems and society[2-4].

3.1 DEFINITION AND CLASSIFICATION OF TBI

There is no universally accepted definition of TBI, but there are various published descriptions, which may cause further difficulty in the standardized management of this disease[1,5].

For the purposes of this consensus and using for reference the definition from the NICE guidelines[6], TBI is defined as ***"any trauma caused by an external mechanical force in the cranioencephalic region leading to suspected acute brain injury."***

For their part, the clinical criteria that point to suspected acute brain injury allow TBI severity to be classified as **mild, moderate or severe** according to the duration of loss of consciousness, alteration of consciousness or post-traumatic amnesia (Fig. 2) [3,4].

	Mild TBI	Moderate TBI	Severe TBI
Structural image of the brain	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-traumatic amnesia (duration)	<1 day	1-7 days	>7 days
Glasgow Coma Scale score	13-15	9-12	<9

Figure 2. TBI classification

However, this lack of uniformity in definition often means that, for practical purposes, severity classification is based on clinical assessment **of the level of consciousness** using the **Glasgow Coma Scale** (GCS). This scale is divided into three parameters: best eye response, best verbal response and best motor response. The levels of response in the components of the GCS are scored from 1, for no response, up to normal values of 4, for eye opening, 5, for verbal response and 6, for motor response (Fig. 3)[7].

Eye opening	Verbal response	Motor response
4. Spontaneous 3. To verbal commands 2. To painful stimulus 1. No response	5. Orientated 4. Confused conversation 3. Inappropriate words 2. Incomprehensible sounds 1. No response	6. Obeys commands 5. Localizes pain 4. Withdrawal from pain 3. Flexion to pain 2. Extension to pain 1. No response

Figure 3. Glasgow Coma Scale scoring

The findings in each component of the scale can be added together for a total GCS score ranging from 3 to 15, with 3 being the worst and 15 being the highest. This gives a less detailed description, but does provide an overview of the patient's severity level (Fig. 4) [4,7].

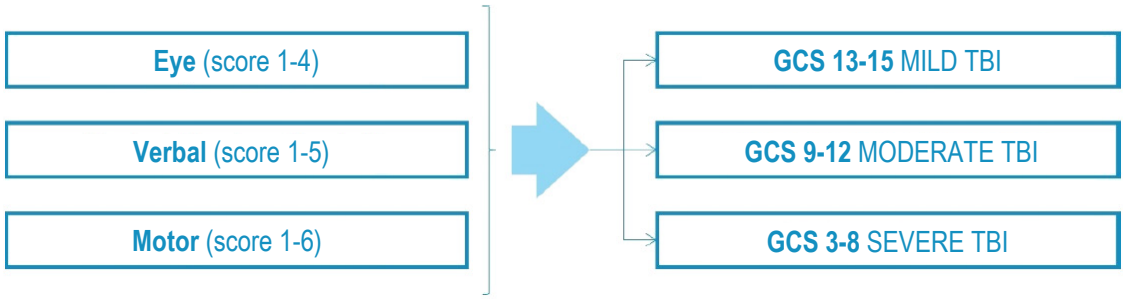

Figure 4. Initial severity of TBI according to GCS [4]

While some guidelines consider patients with GCS 13-15 to have **mild TBI**, others limit this to GCS 14 and 15, and some even include only GCS 15 patients in this classification. To this end, the **World Health Organization** (WHO) Working Group carried out a comprehensive literature review to **establish several unified criteria** for its definition. After analyzing and identifying more than 20 different definitions used in the literature, there was a **proposal to define mild TBI as**[5]:

An acute brain injury resulting from mechanical energy to the head caused by an external mechanical force. The criteria for clinical identification include:

- One or more of the following:
  - confusion or disorientation
  - loss of consciousness lasting 30 minutes or less

- post-traumatic amnesia lasting less than 24 hours
- and/or other transient neurological abnormalities, such as focal signs, seizures and intracranial injury that does not require surgery;

- GCS score of 13-15 points 30 minutes after the injury or later when receiving medical attention.

These manifestations of mild TBI should not be caused by drugs, alcohol, medications, other injuries or treatment for other injuries (e.g., systemic, facial or intubation injuries), other problems (e.g., psychological trauma, language barrier or coexisting medical conditions), or caused by penetrating head trauma.

Therefore, for the purposes of this document, mild TBI is defined as ***"any trauma in the cranioencephalic region leading to suspected acute brain injury using WHO clinical criteria for identification***." However, it is necessary to clarify that these criteria include diagnostic confirmation after computed tomography (CT) with regard to the "intracranial injury not requiring surgery" criterion and that, in this context, it would be excluded because it would provide evidence instead of suspicion.

3.2 MAIN CAUSES

The main causes of TBI are **falls** and **traffic or work-related accidents**, and to a lesser extent blows to the head by/against any object, physical violence and contact sports, among others[8].

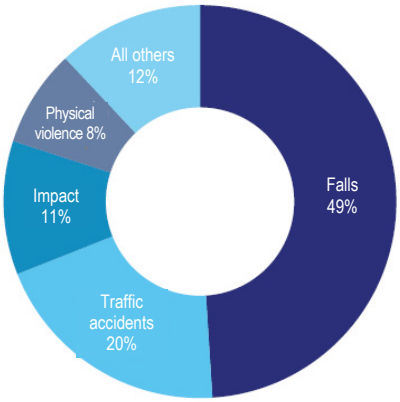

Figure 5. Main causes of TBI

Historically, road traffic accidents have been the primary cause of TBI and, furthermore, have been associated with serious injuries. However, changes in the demographics of the Spanish population, combined with preventive measures, have led to a change in the clinical profile of patients with TBI, with **falls from various heights becoming increasingly frequent** (Fig. 5)[9.10].

3.3 EPIDEMIOLOGY

In the absence of consensus on the definition of TBI, the results of epidemiologic studies are highly variable, which impedes accurate understanding of the incidence of TBI. However, it is considered a **"silent epidemic"**, due to the large number of people affected. Some studies suggest that 50-60 million new cases of TBI occur annually worldwide, of which **more than 90% are mild**[4,9].

Specifically, it is estimated that there will be at least 2.5 million new cases of TBI each year and the age-adjusted incidence of patients with TBI admitted to hospitals is **200-300 per 100,000 inhabitants per year**, with broad variations between countries, which probably reflect differences in the methodology of studies rather than a real variation in incidences between European countries[3,4,9].

In any case, the true incidence of TBI is likely to be higher than reported, given that the incidence of **mild TBI**, which accounts for **80-90% of all cases**, is underestimated in most studies[3].

Generally, the rate of TBI tends to be **higher in men than in women**, with the **maximum incidence being among adults aged 60 to 65 and above**[1.10]. Treatment of TBI in patients over 65 years of age has increased in recent years. Advances in medicine and better out-of-hospital care, coupled with increased population life expectancy, may explain this change in epidemiology[1]. In clinical practice, it is estimated that approximately 60-70% of cases of mild TBI occur in patients aged 60-65 years with previous comorbidities, with the main cause being a fall from standing height (60-82%)[1]. The other 30% corresponds mainly to younger patients who suffer TBI during physical activity.

4. MANAGEMENT OF PATIENTS WITH MILD TBI

This section primarily deals with the **general aspects** of the management of mild TBI in Spain. After this general overview, there is the **description** of the care process for patients with mild TBI, including **out-of-hospital** and **in-hospital management** in the emergency department. The process described is illustrated in the appendices to this document.

4.1 GENERAL ASPECTS OF MANAGING MILD TBI

Concern over the **identification of patients** with mild TBI at **high risk of AII**, plus the lack of objective tools available during the assessment to determine the neurocognitive status of patients, has led to an **exponential increase** in requests for **cranial CT** from emergency departments[1,11]. This lack of objectivity is more evident in certain patients, where there may be some confusion as to whether the symptoms are caused by TBI or are due to drug abuse or alcohol consumption, or even to the presence of underlying diseases (e.g., Alzheimer's) or other neurodegenerative diseases that do not allow the incident, the associated symptoms or the injury mechanism to be understood with certainty.

Some of the main **effects of mild TBI are immediate** and occur within a few hours of the injury, although signs and symptoms may peak in severity at any time from **hours to months** after the cause of the injury. Cognitive impairments are common, particularly visual and motor reaction times, information processing, memory and attention. However, in a minority of cases TBI may also produce intracranial injuries that are visible on a CT scan[12]. Only 7-10% of patients with mild TBI have intracranial abnormalities detected by CT, of which it is estimated that **fewer than 1% require neurosurgical intervention.** Mortality, meanwhile, is a very rare outcome (0.1%)[1,12,13]. Specifically, the lesions considered to have a low risk of progression and requiring neurosurgical intervention are: mild convexity subarachnoid hemorrhage, intraparenchymal hematoma or hemorrhagic contusion in a single location, and subdural or epidural hematoma, all measuring less than or equal to 4 mm[1].

Therefore, the small percentage of patients presenting with these characteristics and the very low mortality associated with mild TBI, together with the increase in associated costs, saturation of the departments involved and the risks of radiation exposure (especially important in people under 20 years of age), **have challenged the widespread use of emergency head CT in mild TBI[1,14,15].**

There is consensus on performing head CT in patients with moderate or severe TBI, but controversy remains over which mild TBI patients should undergo this diagnostic test[16]. These facts and the goal of reducing unnecessary testing have driven the search for tools that can effectively and safely identify patients at low risk of AII. Various protocols and clinical guidelines have been developed for groups of specific risk factors or criteria, aimed at the early identification of patients who may have AII, and therefore require neuroimaging tests or hospital observation[1,16-22]. However, the lack of clinical specificity and the need for more evidence in certain population groups with risk factors enable a degree of justification for the differences between guidelines and their limited impact on reducing the number of CTs performed. The sensitivity of these criteria for identifying patients at low risk of intracranial lesion following a mild TBI may be lower than originally described[17,18,23-25]. Therefore, there are currently **no universally accepted standards** and the use of these protocols within Spain is center dependent – i.e., there is no homogeneity between the autonomous communities, health areas and centers within the same region regarding the use of a common consensus, pathway, protocol, guide or action manual for the management of patients with mild TBI.

In short, one of the main challenges in managing these patients is the need to optimize resources through **more detailed risk stratification** in order to define the best approach for each patient.

In this vein, there have been significant advances in recent decades in the study of **blood biomarkers** to improve the diagnosis and clinical characterization of patients with possible brain damage. In turn, this has presented an important opportunity to gain understanding of the pathophysiology of the condition and to better support clinical decision-making.

Direct impact or acceleration-deceleration forces applied to the head can cause both immediate and delayed impairment of the blood-brain barrier/gliovascular unit. The disruption of the tight junction complexes and the integrity of basement membranes result in increased permeability. Injury causes oxidative stress and triggers primary vascular damage, causing proteins to leak into the blood, as well as increased production of proinflammatory mediators and upregulation of expression of cell adhesion molecules on the surface of brain endothelium, which promotes the influx of inflammatory cells into the traumatized brain parenchyma and extravasation of red blood cells[26,27].

More than 20 brain proteins have been identified in blood, some of which have been shown to predict head CT results in mild TBI (Fig. 6)[28-30]. **Origin** and **release kinetics** are two key factors in the study of these molecules and their usefulness as biomarkers.

Origin	**Neuronal**		**Glial**		**Axonal injury**	
Biomarker	**NSE**	**UCH-L1**	**GFAP**	**S100β**	**NfL**	**Tau**
Point of release	Acute: minutes to hours	Acute: minutes to hours	Acute and subacute: hours to days	Acute: minutes to hours	Subacute and chronic: hours to months	Subacute to chronic: hours to months
Significant extracranial contribution	Erythrocytes	Some expression in gonads, adrenals	Highly specific to the brain	Adipose, muscle, skin	Axonal	Liver, kidney, testicles, peripheral nerves
Characteristic	Blood levels depend on hemolysis	Hyperacute – acute	Highly specific to the brain	Elevated in extracranial lesions	May remain elevated for months	Long-term outcome biomarker (dementia)

Figure 6. Potential blood biomarkers in TBI.

Acronyms: GFAP – glial fibrillary acid protein; NFL – neurofilament light chain; NSE – neuron-specific enolase; UCH-L1 – ubiquitin C-terminal hydrolase L1.

Specifically, the **S100β protein** has been one of the most widely studied blood biomarkers, and has even been included in some clinical guidelines and triage areas for the initial care of patients with mild TBI in Europe[19,25,31]. Although several studies have demonstrated its high sensitivity and negative predictive value for acute head CT[30], the use of S100β has not become widespread in clinical practice. Some of the causes of this that have been identified are: elevated protein in the absence of TBI, depending on the injury mechanism, due to the existence of extracranial sources (adipose tissue, musculoskeletal tissue and melanocytes); the time course of the biomarker in peripheral body fluids (its presence must be determined within 3 hours of the trauma); and the robustness of existing data[29,32-39].

Other biomarkers studied are **glial fibrillary acidic protein (GFAP)** and **ubiquitin C-terminal hydrolase L1 (UCH-L1)** and specifically the combination of both for assessment in the acute period following TBI.

UCH-L1 is one of the most abundant proteins in the brain. It represents 1-5% of total neuronal protein and is located exclusively in the neurons[40-41]. It is involved in the elimination of degraded and denatured proteins following oxidative phenomena[40].

GFAP is a protein derived from astrocyte tissue, the expression and release of which is specific to the brain. This quality makes it unique as a biomarker of brain injury in various situations, such as traumatic damage, ischemic events and certain neurodegenerative disorders[42]. It is a monomeric protein with a molecular weight of 52 kDa, released into the blood through the blood-brain barrier when its integrity is affected by traumatic injury. There is an early plasma peak on the first day, with a gradual decrease during the first week from the third day of progression[29,34,43].

GFAP and UCH-L1 levels are measurable in peripheral blood from the first hour after the injury and peak at approximately 18 and 8 hours, respectively[14]. Both values decrease over time; however, GFAP values remain elevated beyond 72 hours[14]. The difference in origin and kinetics has highlighted the importance of measuring both proteins when assessing patients in the acute phase after TBI. The results of the study conducted by Bazarian et al. indicated a sensitivity of 95.8%, a negative predictive value of 99.3% and a specificity of 40.4%, enabling the recent CE marking (European conformity) and FDA approval of the first rapid serum/plasma test for specific biomarkers for mild TBI – GFAP and UCH-L1. These findings indicate that the test can **reliably predict the absence of All displayed on a CT scan**. This represents a **paradigm shift in how the condition is evaluated**, with the availability of a test that – when performed on adults over 18 years of age within 12 hours after the trauma – could reduce unnecessary head CT scans by up to 38%[17].

The authors agree that, with the currently available evidence, its use in clinical practice may mean: shortened hospital waiting times for patients, thereby improving hospital department efficiency and patient experience; reduced exposure to radiation from head CT; improved assessment of patients who are inebriated or have an underlying disease or other neurodegenerative disorders; and mitigated overload of the services and health care workers involved, among other things. In addition, according to the future lines of research,

it has great potential as a prognostic tool and a multitude of advantages in out-of-hospital settings if developed as a point-of-care test.

4.2 OUT-OF-HOSPITAL MANAGEMENT

The flowchart for out-of-hospital management of patients with mild TBI is attached (Annex 1).

4.2.1 TELEPHONE TRIAGE

The requester **accesses** the **Coordination Center (CC)** by means of a **speed-dial number.** This is a multidisciplinary device intended for the **management of health care resources,** and is tasked with providing a response **according to the event or the severity of the situation.** This response ranges from giving recommendations to allocating mobile care resources.

An **initial telephone triage** is carried out from the CC to classify the demand for care according to severity and appropriate response time. To this end, the operator asks for, as a minimum, the exact **location** and best accesses, the **reason** for the request (trying to identify signs of priority or compromised vital signs) and a **contact telephone number**[44].

Following this initial analysis and having ruled out signs of priority due to life-threatening signs or polytraumatized patients, the approach to which is beyond the scope of this document, the questioning is continued in order to assess the **possible risk of TBI** and the need to **mobilize and allocate resources**. The main factors included in telephone triage to determine TBI risk are:

- Changes in level of consciousness.
- Motor alterations.
- Personal history, especially taking antithrombotic drugs.
- Characteristics of the accident and injury mechanism.

In specific cases where the trauma was due to a **fall**, it is particularly important to attempt to **determine the cause**, i.e. whether it was a chance event or whether there may be an underlying medical cause or process (e.g., cardiac, history of epilepsy) that resulted in TBI.

If it is established that the cause of TBI was **accidental** and the patient **does not present signs** of possible neurological damage, it is recommended that the patient be **kept under observation at home** and provided with information and recommendations on possible progression. In cases where the patient cannot remain under observation at home, hospital transfer may be recommended, always at the patient's discretion.

4.2.2 ACTIVATING RESOURCES

In the event that the patient requires **in-person assessment,**, a decision is made, based on severity criteria, whether to mobilize a non-medicalized mobile unit to directly **transfer** the patient to a **hospital**; or a medicalized mobile unit to **provide medical assistance at the location of the incident**.

In general, and specifically in TBI, **a medicalized unit** is requested for patients who meet criteria such as:

- Loss of consciousness and other neurological signs or symptoms.
- Dangerous injury mechanism, considered to be the ejection of occupants from or the overturning of a motor vehicle, running over a pedestrian or cyclist, or falling from heights greater than one's own standing height or five steps[45,46].
- Suspected medical cause associated with TBI.
- Major bleed.
- Coagulopathy, bleeding disorder, anticoagulants or antiaggregants.
- Previous brain injury/neurosurgery.

Otherwise, when in-person assessment is considered necessary, but there are no severity criteria, a non-medicalized mobile unit is activated to transfer the patient directly to the appropriate hospital. In this case, if upon arrival at the incident location the patient's status does not match the information obtained thus far, vital signs are taken to inform the CC of

the change in the patient's clinical conditions. Testing of vital signs includes measuring blood pressure, respiratory rate, heart rate, oxygen saturation and a blood glucose check.

Generally, the patient's condition may be considered to have deteriorated or be of a severity greater than identified during telephone triage when:

- The patient has variations in their neurological status (agitation, disorientation, confusion, unconsciousness)
- Or other signs of severity (extreme paleness, sweating or tachypnea).

Once informed, the CC will decide whether to proceed with the direct transfer to the hospital or to mobilize a medicalized unit to provide medical assistance at the location of the incident.

If the patient requires **medical assistance** at the location of the incident, the medicalized unit performs an **initial ABCDE assessment** and **stabilizes** the patient. The unit then assesses brain damage with the aim of ruling out other more severe forms of TBI using the **neurological assessment**[46,47] (Table 1) and **history** – this should include assessment of **symptoms** and **risk factors** (Table 2) and identify possible **alarm signs**[16] (Table 3).

Neurological Assessment
• Assessment of level of consciousness according to the GCS. • Assessment of existence of post-traumatic amnesia (considering intensity and duration). • Assessment of loss of consciousness (duration and progression). • Existence of focal neurological deficits or asymmetries in the neurological examination.

Table 1 – Elements of neurological assessment in TBI

In situ assessment should rule out moderate or severe TBI, cases of which would be beyond the scope of this document.

Symptoms and Risk Factors
• Neurological deficit. • Bleeding disorder, hemorrhagic disorder, anticoagulants or antiplatelet agents, excluding acetylsalicylic acid monotherapy if not accompanied by other signs or symptoms[18]. • ≥65 years • Intoxication (alcohol or drugs). • Vomiting (≤2) • Headache. • Post-traumatic seizures. • Short-term memory loss or amnesia of episode. • Evidence of head or neck injury. • Previous brain injury/neurosurgery.

Table 2 – Symptoms and risk factors aimed at early identification of patients who may present with acute intracranial lesion

Alarm Signs
• GCS <15 at 2 hours post TBI • Suspected cranial collapse or open fracture • Signs of skull base fracture: hemotympanum, raccoon eyes, otolichorrhea, Battle's sign (retroatrial mastoid ecchymosis). • Vomiting (>2)

Table 3 – Alarm signs to assess in patients with mild TBI

After assessment, patients with risk factors and/or neurological signs or symptoms, as well as patients who cannot remain under observation at home, will be transferred to the hospital.

A patient can be transferred by the medicalized unit itself or, if their situation and conditions allow, a request can be made to the CC for a non-medicalized unit to transfer the patient to the hospital, thus making them operational faster.

4.3 IN-HOSPITAL MANAGEMENT

The flowchart for in-hospital management of patients with mild TBI is attached (Annex 2).

4.3.1 ADMISSION AND ASSESSMENT

The patient is transferred by **ambulance** to the emergency department assigned by the CC, although a large proportion of patients with suspected mild TBI are ambulant and make their way to the emergency department **on their own**, either alone or accompanied.

When the patient arrives at the hospital emergency department, there are well-established and **structured triage** models for managing the **influx of patients** based on their **severity**. The SET (*Sistema Español de Triaje* – Spanish Triage System) and the MTS (Manchester Triage System) are two of the most widely distributed systems in Spain, although there are others that are implemented at a local level that are more adapted to each reality[48]. These triage models are structured into prioritization levels, which are associated with a color and waiting time for receiving medical attention (Figs. 7 and 8):

Level	Color	Category	Waiting time (min.)
I	Blue	Resuscitation	Immediate
II	Red	Emergency	7 (*)
III	Orange	Urgent	30
IV	Green	Less urgent	45
V	Black	Not urgent	60

Figure 7. Relationship between scales and severity levels in the SET. *(*) Immediate nursing.*

Level	Color	Category	Waiting time (min.)
1	Red	Immediate attention	0
2	Orange	Very urgent	10
3	Yellow	Urgent	60
4	Green	Normal	120
5	Blue	Not urgent	240

Figure 8. MTS classification levels.

Cases of patients with vital urgency or obvious risk to life (priority 1) are put promptly in the "Critical" or "Resuscitation" box. The approach to these patients is beyond the scope of this document.

In general, cases of mild TCE are treated with **urgency level IV** (normal or less urgent) without the need for immediate attention and with longer waiting times. In some cases, patients may be prioritized to levels II or III – for example, mild TBI with severe injury mechanism.

Once categorized, a **primary assessment** and **patient stabilization** are performed. The **neurological assessment** (Table 1) is then performed and the patient history and clinical examination are updated, taking into account the out-of-hospital assessment previously performed and recorded, including assessment of **symptoms and risk factors** (Table 2). This limits neuroimaging tests in patients for whom the risk is very low or nonexistent[1,46]. This is especially important in the assessment of patients with mild TBI, because around 90% of requested head CT scans are normal[1,12,13]. In addition, on certain occasions and according to medical criteria, a general blood test is requested that includes, if appropriate, biomarkers and coagulation time.

4.3.2 STUDY OF ACUTE BRAIN DAMAGE

After assessment, patients with **GCS 15 without symptoms or risk factors** (Table 2) may be discharged for home observation with verbal and written information on recommendations concerning possible progression. However, depending on medical criteria and the individual clinical situation, **it is possible to request determination of the GFAP and UCH-L1 combination and assess an observation period (6-12-24 hours)** if fewer than 12 hours have elapsed since the trauma, in order to rule out the need for a head CT scan.

For patients with **GCS 13-14** or **GCS 15 but with symptoms or risk factors** (Table 2), the test to perform would depend on the time elapsed since the trauma. If the **time is greater than 12 hours**, a head CT scan is recommended.

Otherwise, if the **time is less than 12 hours**, rapid serum/plasma testing of the specific GFAP and UCH-L1 biomarkers is recommended to assist decision-making as regards the need for a head CT scan. The process for using the test involves conventional processing of samples that arrive at the clinical analysis laboratory, with **results available after 30-60 minutes**.

4.3.3 RECOMMENDED ACTION

All actions should be assessed based on the **individual needs of each patient**. The recommended **observation period** varies from 6 to 24 hours, depending on the findings, associated risk factors and patient progression. In any case, the patient is **discharged** with verbal and written information on **recommendations** concerning potential progression, provided that they are **clinically well** and there are no post-traumatic risk factors other than age alone.

A **negative result** of the **GFAP and UCH-L1** biomarker analysis in the **first 12 hours** after trauma **is associated with absence of intracranial injury** due to the high negative predictive value of this analysis. These patients are discharged for observation at home, with verbal and written information on recommendations concerning potential progression, provided that the patient has recovered and is asymptomatic.

However, **a CT scan can be requested** regardless of the biomarker results, based on medical criteria and considering the clinical situation of each patient.

When a head CT scan is requested and performed, the **radiology specialist reports** to the emergency physician and issues a decision **report** based on the findings of the imaging test.

Patients with a **CT scan without pathological findings** who have no risk factors and who have not experienced clinical deterioration or persistence of symptoms **are discharged** for observation at home, with verbal and written information on recommendations concerning possible progression, after an observation period of at least six hours.

Otherwise, in the event of **pathological findings** or if the **patient's symptoms are not consistent** with the radiological results, a **consultation with the Neurosurgery department** is arranged. After assessment by Neurosurgery, the patient is sent to the Intensive Care Unit, and undergoes emergency surgery or is kept under observation for 24 hours for clinical reassessment and a new follow-up CT scan. Depending on the results, the patient is either discharged by the Neurosurgery department with recommendations and referred for outpatient follow-up, or admitted to the department.

4.3.4 SPECIAL PRECAUTIONS IN PATIENTS ON ANTICOAGULANT TREATMENT

The **coagulation status** of patients with mild TBI who are on antithrombotic treatment should be ascertained by requesting a standard **INR** coagulation test in the case of patients taking vitamin K antagonists (**VKAs**), while **kidney function and time of last drug intake** should also be ascertained in the case of patients on direct oral anticoagulants (**DOACs**).

If there is uncertainty about DOAC intake, a DOAC level test or specific clotting tests may be requested if available[49].

If **CT shows pathological findings** (bleeding), it is recommended that anticoagulant drugs are immediately **stopped** and **reversed**:

- VKAs (if INR>2) with prothrombin complex concentrate (PCC) and vitamin K. Fresh frozen plasma (FFP) may be used if no PCC is available.
- If the patient is taking the thrombin inhibitor dabigatran, its specific reversal agent (idarucizumab) should be used. If this is unavailable, PCC is used.
- If the patient is being treated with Xabans, otherwise known as direct factor Xa inhibitors (apixaban, edoxaban or rivaroxaban), PCC is used since the specific reversal agent (andexanet alfa) is not yet available here.

In cases with **normal CT results**, once the observation time has elapsed, the anticoagulation regimen can continue, with assessment of the need to adjust the dose according to INR in the case of VKAs or depending on kidney function for DOACs.

Communication and **coordination** with **hematology** specialists may be necessary for this patient profile.

5. RECOMMENDATIONS

Below are the general recommendations for the management of patients with mild TBI; however, in any event, the medical criterion will prevail, taking into account the patient's clinical situation.

HOSPITAL TRANSFER CRITERIA

- **Transfer to a hospital center** patients with mild TCE who meet at least one of the following criteria:
    - Neurological deficit.
    - Coagulopathy, bleeding disorder, taking anticoagulants or antiplatelet agents, excluding acetylsalicylic acid monotherapy if not accompanied by other signs or symptoms.
    - ≥65 years
    - Poisoning.
    - Neurological signs and symptoms.
    - Loss of consciousness or amnesia.
    - Dangerous injury mechanism.
    - Evidence of head or neck injury.
    - Previous brain injury/neurosurgery.
    - Inability to remain under observation at home.

RECOMMENDED ACTION FOR USE OF BIOMARKERS

- Request determination of the combination of **GFAP and UCH-L1** within **12 hours** after trauma in patients with **GCS 15 with symptoms and/or risk factors, GCS 14** or **GCS 13**.

- Patients with **GCS 15 without symptoms or risk factors** or with a **negative result** of the GFAP and UCH-L1 biomarker analysis **may be discharged** for observation at home, as long as the patient has recovered and has no symptoms.

- **Where more than 12 hours have elapsed** since the trauma or there is a **positive result** of the GFAP and UCH-L1 biomarker analysis, urgent head CT is indicated.

RECOMMENDED ACTION AFTER CT RESULTS

- If there are **no pathological findings on the CT**, patients may be **discharged** for observation at home, provided they are **clinically well** and there are no post-traumatic risk factors other than age alone.

- Consult the **Neurosurgery department** if the **CT reveals pathological findings** or if the patient's clinical condition is **inconsistent** with the **radiological findings**.

- Request a **follow-up CT**:

    1. If an initial CT revealed pathological findings, regardless of the patient's good clinical condition and after a 24-hour observation period.

    2. If symptoms persist or the patient experiences neurological deterioration during the observation period.

6. EXECUTIVE SUMMARY

For the purposes of this consensus and due to the lack of a universally accepted definition, mild TBI is defined as *"any trauma to the cranioencephalic region leading to suspected acute brain injury using the WHO clinical criteria for identification."*

Computed tomography (CT) of the head is currently the standard diagnostic tool for assessing intracranial injuries in patients with any degree of acute traumatic brain injury and identifying patients who require immediate surgery. There is widespread consensus on the use of head CT in patients with moderate (GCS 9-12) or severe (GCS 3-8) TBI, but there is disagreement on which patients with mild TBI (GCS 13-15) should undergo this test, due to the low prevalence of intracranial abnormalities detected by CT and the negligible mortality associated with mild brain damage.

Together with the need for a greater number of objective tools to determine the neurocognitive status of these patients, this lack of consensus has led to an exponential increase in head CT requests from emergency departments.

Recent decades have seen significant advances in the study of blood biomarkers that help improve the diagnosis and clinical characterization of patients with potential brain damage, thereby reducing unnecessary testing.

This is proven by the recent CE marking and FDA approval of the first rapid serum/plasma test for the specific biomarkers GFAP and UCH-L1 in mild TBI. The results suggest that this test may be incorporated into the standard of care as a decision aid in the assessment of adult patients with GCS 13-15 within 12 hours after the injury to determine the need for CT. This situation offers the possibility of proposing an updated algorithm to attempt to standardize the management of mild TBI in emergency situations in Spain.

When an individual requests assistance through a speed-dial number, the CC will be responsible for providing a response based on the event or the severity of the situation as determined by means of telephone triage. This response ranges from making recommendations (if the TBI was accidental and the patient shows no signs of possible neurological damage) to allocating mobile care resources (where it is determined that the patient requires in-person assessment). This assessment may be carried out by means of medical assistance provided at the location of the incident and/or by transferring the patient to the appropriate hospital.

Upon arrival in the emergency department, whether by ambulance or their own means, patients with suspected mild TBI are treated in a less urgent category after life-threatening situations, polytrauma or more severe forms of TBI are ruled out (for which specific protocols are available). The aim of the assessment is to identify the presence of signs, symptoms and/or risk factors for intracranial injury. Neuroimaging tests are limited to patients at higher risk, given that around 90% of requested head CT scans are normal in the context of mild TBI.

Rapid serum/plasma testing of the specific biomarkers GFAP and UCH-L1 in the first 12 hours after trauma is a complementary tool during assessment that aids decision-making to rule out the need for head CT in patients with GCS 15 with symptoms and/or risk factors, GCS 14 or GCS 13.

A negative test result is associated with the absence of intracranial injury due to its high negative predictive value. Therefore, after a negative result for GFAP and UCH-L1 determination, patients may be discharged for observation at home, provided that they have recovered and have no symptoms.

If more than 12 hours have elapsed since the trauma or if the biomarker result is positive, a head CT is performed. In the event of pathological findings or if that the patient's symptoms are not consistent with the radiological results, a consultation is held with the Neurosurgery department to continue assessing the patient. Otherwise, patients with a CT scan that shows no pathological findings who have no risk factors and who have not experienced clinical deterioration or persistence of symptoms may be discharged for observation at home.

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ACRONYMS

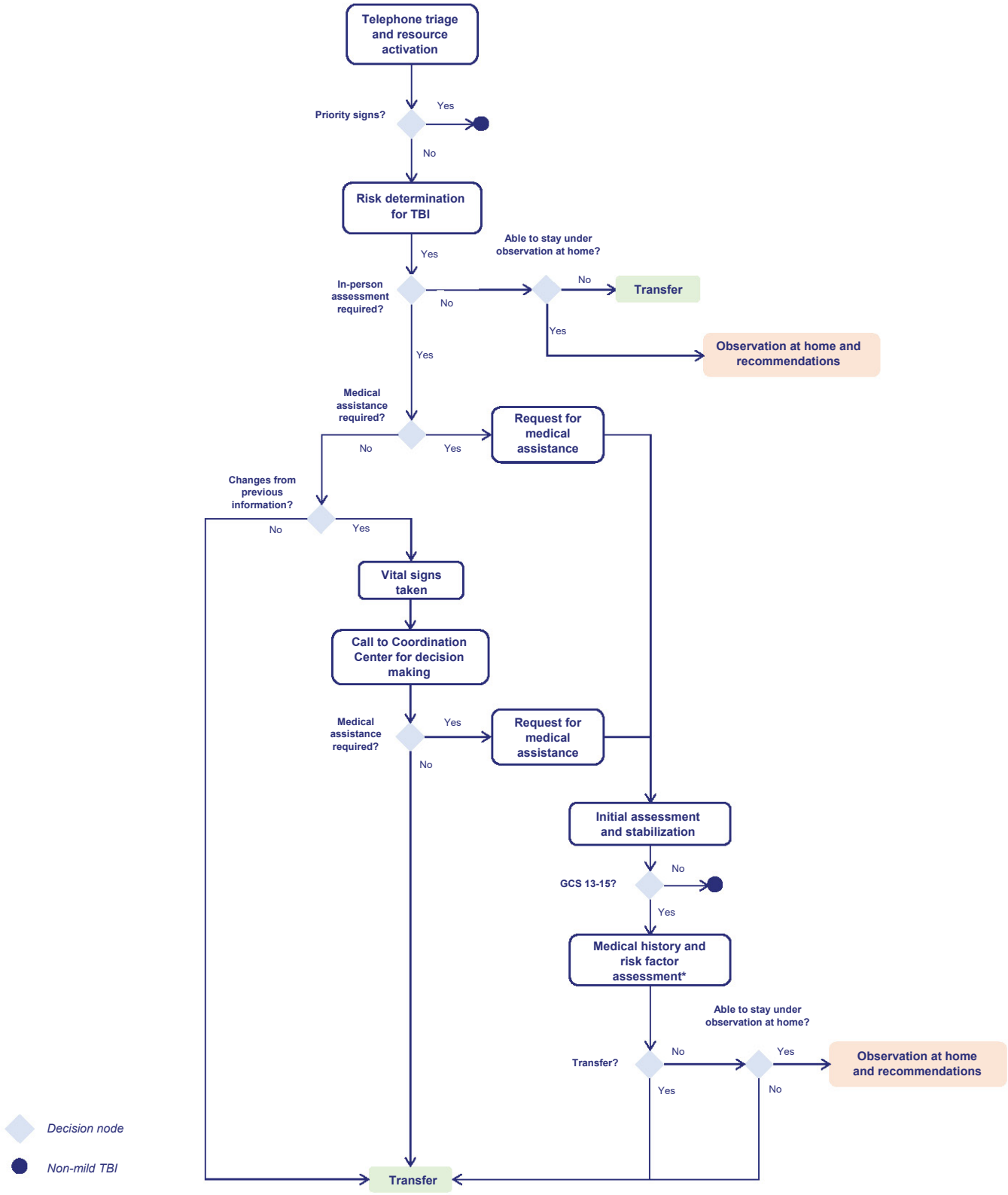
DOACs	Direct oral anticoagulants
VKAs	Vitamin K antagonists
AC	Advisory Committee
CC	Coordination Center
PCC	Prothrombin complex concentrate
GCS	Glasgow Coma Scale
FDA	Food and Drug Administration
GFAP	Glial fibrillary acid protein
AII	Acute intracranial injury
MTS	Manchester Triage System
NfL	Neurofilament light chain
NSE	Neuron-specific enolase
WHO	World Health Organization
FFP	Fresh frozen plasma
SET	*Sistema Español de Triaje* (Spanish Triage System)
CT	Computed tomography
TBI	Traumatic brain injury
UCH-L1	Ubiquitin carboxyl-terminal hydrolase L1

APPENDIX 1. OUT-OF-HOSPITAL MANAGEMENT

OUT-OF-HOSPITAL EMERGENCIES

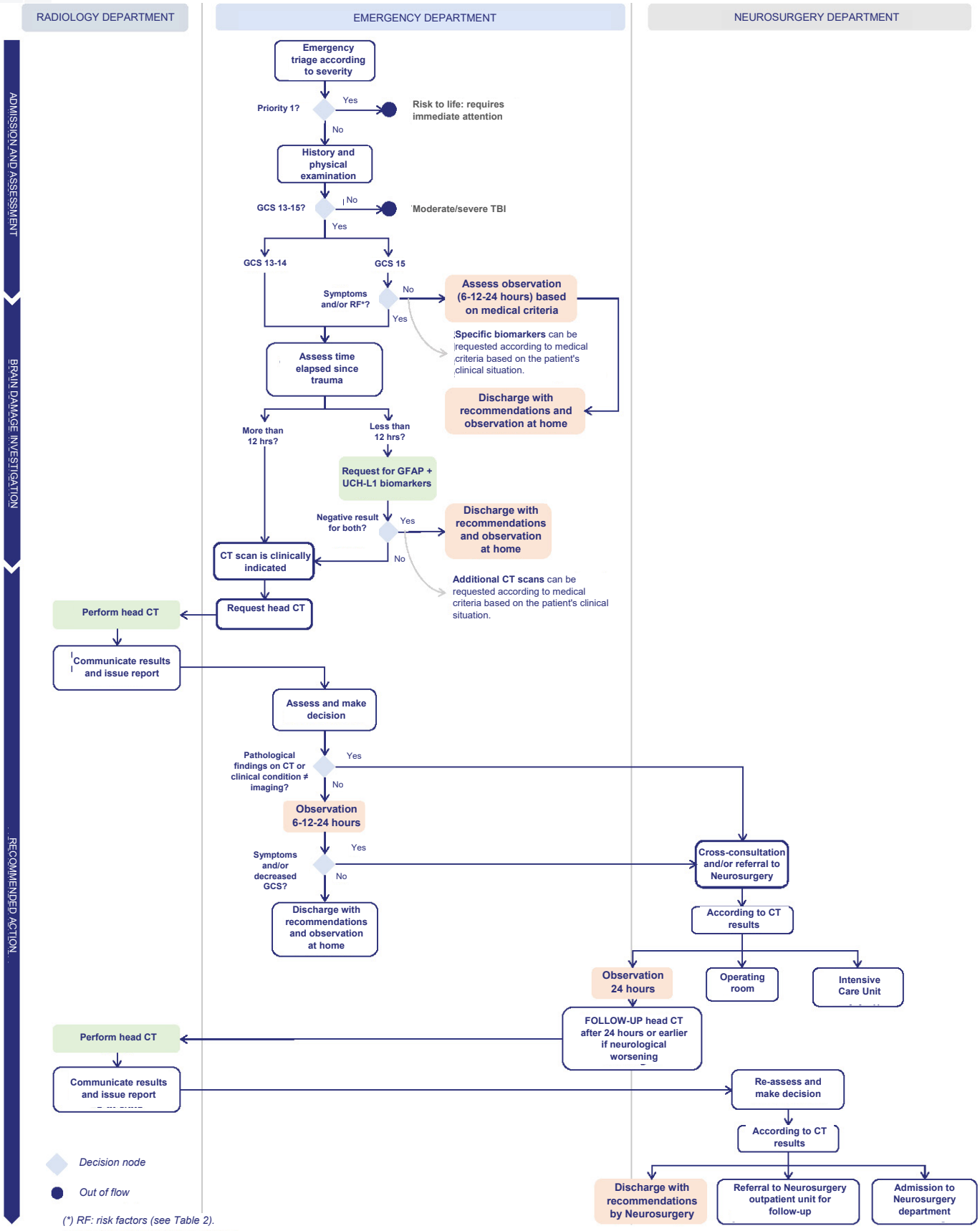
TELEPHONE TRIAGE

RESOURCE ACTIVATION



(*) (see Table 2).

APPENDIX 2. IN-HOSPITAL MANAGEMENT



SEMES

Sociedad Española de Medicina de Urgencias y Emergencias (Spanish Society of Emergency Medicine)

MANAGEMENT OF PATIENTS WITH MILD TRAUMATIC BRAIN INJURY AND RECOMMENDATIONS