Original Article

Determination of Blood Biomarkers in Mild Traumatic Brain Injury (mTBI), GFAP and UCH-L1, in Patients Admitted to the Emergency Department with Suspected Mild TBI

Determinação de Biomarcadores Sanguíneos no Traumatismo Cranioencefálico (TCE) Ligeiro, GFAP e UCH-L1, em Doentes Admitidos no Serviço de Urgência com Suspeita de TCE Ligeiro

Catarina Lima da Silva[2*], Anunciação Ruivo[3], Rui Malheiro[4,5,6], Lara Santos[3], Teresa Campos[3], Fernando Moura[1,7], Carla Freitas[1,2]

1. Serviço de Urgência da Unidade Local de Saúde do Tâmega e Sousa, Penafiel, Portugal
2. Serviço de Cirurgia Geral da Unidade Local de Saúde do Tâmega e Sousa, Penafiel, Portugal
3. Serviço de Imunohemoterapia da Unidade Local de Saúde do Tâmega e Sousa, Penafiel, Portugal
4. Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Portugal
5. EPI Unit, Instituto de Saúde Pública da Universidade do Porto, Portugal
6. Unidade de Saúde Pública, Unidade Local de Saúde São João, Porto, Portugal
7. Serviço de Anestesiologia da Unidade Local de Saúde do Tâmega e Sousa, Penafiel, Portugal

Corresponding Author/Autor Correspondente:
Carla Freitas [carlafreitas@ulsts.min-saude.pt]
Serviço de Urgência da ULSTS, Avenida do Hospital Padre Américo 210, 4564-007 Guilhufe, Penafiel, Portugal

https://doi.org/10.34635/rpc.1104

Received/Recebido: 22/04/2025 **Accepted/Aceite:** 08/05/2025 **Published online/Publicado online:** 21/06/2025 **Published/Publicado:** 30/06/2025

ABSTRACT

Introduction: Traumatic brain injury (TBI) is one of the most common conditions in the emergency department (ED), representing a public health issue with substantial economic impact. The risk of severe acute intracranial injury increases the need for cranial computed tomography (CT). Serum biomarkers of acute brain injury, such as glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase-L1 (UCH-L1), have emerged as potential alternatives.
Methods: This was a screening study conducted in the ED in 2024. Adult patients admitted with mild TBI within 12 hours of injury, and meeting the criteria for cranial CT were included. For each participant, UCH-L1 and GFAP levels were assessed. The cranial CT scan was considered positive in the presence of brain injury. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were estimated for the presence of both biomarkers combined and separately for UCH-L1 and GFAP.
Results: A total of 315 patients were enrolled, and 13 were excluded for not meeting the inclusion criteria. Acute traumatic intracranial lesions were diagnosed in 14 patients (4.6%). The use of UCH-L1 alone yielded a sensitivity of 50% and a NPV of 96%. GFAP demonstrated a sensitivity of 100% and a NPV of 100%. When considering the positivity of both biomarkers, sensitivity and NPV remained at 100%, with a potential reduction in cranial CT scans of 23.2%.
Conclusion: The findings of this study suggest that these serum biomarkers may be used to reliably rule out brain injury in patients with mild TBI, providing a strong level of confidence.

Keywords: Biomarkers; Brain Injuries, Traumatic/diagnosis; Brain Injuries, Traumatic/diagnostic imaging; Craniocerebral Trauma/diagnosis; Craniocerebral Trauma/diagnostic imaging

RESUMO

Introdução: O traumatismo cranioencefálico (TCE) é uma das condições mais comuns no serviço de urgência (SU), representando um problema de saúde pública com impacto económico substancial. O risco de lesão intracraniana aguda grave aumenta a necessidade de tomografia computorizada (TC) craniana. Os biomarcadores séricos de lesão cerebral aguda, como a proteína ácida fibrilar glial (GFAP) e a hidrolase-L1 do terminal carboxilo da ubiquitina (UCH-L1), emergiram como potenciais alternativas.
Métodos: Este foi um estudo de rastreio conduzido no SU em 2024. Foram incluídos doentes adultos admitidos com TCE ligeiro nas 12 horas seguintes à lesão e que cumpriam os critérios para TC craniana. Para cada participante, foram avaliados os níveis de UCH-L1 e GFAP. A TC craniana foi considerada positiva na presença de lesão cerebral. Foram estimadas a sensibilidade, especificidade, valor preditivo positivo (VPP) e valor preditivo negativo (VPN) para a presença de ambos os biomarcadores em conjunto e separadamente para UCH-L1 e GFAP.
Resultados: Foram incluídos 315 doentes no total, 13 foram excluídos por não cumprirem os critérios de inclusão. Lesões intracranianas traumáticas agudas foram diagnosticadas em 14 doentes (4,6%). A utilização isolada de UCH-L1 resultou numa sensibilidade de 50% e num VPN de 96%. A GFAP demonstrou uma sensibilidade de 100% e um VPN de 100%. Ao considerar a positividade de ambos os biomarcadores, a sensibilidade e o VPN mantiveram-se em 100%, com uma potencial redução de 23,2% nas TC cranianas.

Palavras-chave: Biomarcadores; Lesões Encefálicas Traumáticas/diagnóstico; Lesões Encefálicas Traumáticas/diagnóstico por imagem; Traumatismos Craniocerebrais/diagnóstico; Traumatismos Craniocerebrais/diagnóstico por imagem

INTRODUCTION

Traumatic brain injury (TBI) represents one of the most prevalent conditions in the Emergency Department (ED), with an estimated incidence of up to 849 cases per 100 000 inhabitants in Europe and over 5 million hospital admissions annually in the United States of America. It constitutes a major public health concern with substantial economic implications, remaining the leading cause of mortality and morbidity among young adults.[1,2]

TBI results from an external mechanical force applied to the head and encompasses a broad spectrum of functional impairments, both short and long-term, potentially affecting cognition, sensory processing, language, and emotional regulation.[3] In 1993, TBI was classified according to severity as mild, moderate, or severe. Mild TBI is defined by a Glasgow Coma Scale (GCS) score between 13 and 15, loss of consciousness lasting less than 30 minutes, and retrograde amnesia not exceeding 24 hours.[4]

The main concern in cases of mild TBI (mTBI) is the potential of clinically significant acute intracranial injury, which may occur in up to 7% of patients and is associated with a mortality rate of approximately 0.9%.[5] Such injuries are often not readily detectable through physical examination, particularly in elderly patients with pre-existing neurological conditions or in those under the influence of alcohol or illicit substances. As a result, there has been a growing reliance on cranial computed tomography (CT), contributing to ED overcrowding, increased radiation exposure, and rising healthcare expenditures, frequently without a corresponding clinical benefit.[6,7]

Serum biomarkers of acute brain injury – glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) – have emerged as promising tools in addressing these challenges. In the context of acute TBI, disruption of the blood-brain barrier and gliovascular unit leads to oxidative stress and vascular injury, resulting in the release and subsequent detection of these brain-specific proteins in the peripheral blood.[8] Both GFAP and UCH-L1 become quantifiable within the first hour post-injury in the presence of brain damage, with peak serum concentrations observed at approximately 20 and 8 hours, respectively.[9]

A multicenter study conducted by Bazarian *et al* in 2018 reported a sensitivity of 95.3%, specificity of 40.4%, and a negative predictive value (NPV) of 99.3% for these biomarkers in detecting acute intracranial lesions in patients with mTBI, supporting their clinical utility in safely ruling out significant injury.[10] GFAP and UCH-L1 have since been incorporated into clinical decision-making algorithms for TBI in several European countries, marking a paradigm shift in the initial assessment of these patients in the emergency setting.[6,11]

METHODS

The aim of this study was to assess the utility of serum biomarkers in cases of mTBI, with a particular focus on their sensitivity and NPV for the identification of intracranial lesions in patients presenting to the ED of the Unidade Local de Saúde do Tâmega e Sousa (ULSTS). The study also aims to validate the applicability of these biomarkers within the Portuguese population.

This was a screening study conducted between May 27, 2024, and August 13, 2024, in line with the principles of the 2024 Declaration of Helsinki. Approval was granted by the institutional ethics committee under the reference code SEFI. CI.013.00.

Patients were enrolled if they presented to the ED with mTBI sustained within the past 12 hours, if they were aged 18 years or older and if they met the criteria for cranial computed tomography (CT) imaging. According to the current national clinical guideline issued by the Portuguese Direção-Geral da Saúde in 1999, such criteria include: age over 65 years, anticoagulant therapy, substance intoxication, new-onset neurological symptoms, history of epilepsy or prior neurosurgical intervention.[12]

All participants (or their legal representatives) provided written informed consent. Clinical and diagnostic data were retrieved from the institutional electronic medical records (SClínico® and Clinidata® systems).

Descriptive analysis was performed using absolute and relative frequencies for categorical variables, and medians with interquartile ranges for continuous variables.

The two biomarkers were analysed for each participant, serum levels of UCH-L1 and GFAP, measured using a chemiluminescent microparticle immunoassay (CMIA) for in vitro diagnostics on the Alinity i® system. Results were interpreted according to the cutoff values specified in the assay manufacturer's instructions for use: ≥400 pg/mL for UCH-L1 and ≥35 pg/mL for GFAP were considered positive. Cranial CT reports were reviewed to determine the presence of acute traumatic brain lesions.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were estimated, along with their corresponding 95% confidence intervals (95% CI). A significance level of 0.05 was adopted. These metrics were calculated for the presence of both positive biomarkers, as well as separately for UCH-L1 and GFAP.

Statistical analysis was conducted using R® software, version 4.4.0, and Microsoft Excel® 2016.

RESULTS

A total of 315 patients were included in this study, of whom 13 were excluded for not meeting the inclusion criteria, specifically the criteria for performing a cranial CT.

According to the descriptive analysis of our sample (Table 1), the majority of the patients (57.6%) were over 70 years old, and 161 (53.4%) were female. Most patients (83.4%) presented to the ED following a same-height fall, and 94.3% had a GCS score of 15. A total of 52 patients (17.2%) were receiving anticoagulant therapy, either with direct oral anticoagulants or vitamin K antagonists.

Table 1 – Descriptive analyses of the sample

Variable	n(%)
Age	
≤ 40 years	20 (6.62)
40-64 years	62 (20.5)
65-70 years	46 (15.2)
>70 years	174 (57.6)
Gender	
Masculine	141 (46.6)
Feminine	171(54.4)
Cause of the trauma	
Same-height fall	252 (83.4)
Othe	50 (16.6)
GCS Score	
15	285 (94.3)
14	16 (5.29)
13	1 (0.33)
Acute traumatic intracranial lesions	14 (4.63)
Anticoagulant therapy	52 (17.2)
Antiplatelet therapy	65 (21.5)

Acute traumatic intracranial lesions, including hemorrhage, contusion, or fracture, were diagnosed in 14 patients (4.6%).

The levels of UCH-L1 alone yielded a sensitivity of 50% (95% CI: 23%–77%) and a NPV of 96% (95% CI: 92%–98%). In our sample, the GFAP achieved a sensitivity of 100% (95% CI: 77%–100%), identifying all cases with intracranial lesions, with an NPV of 100% (95% CI: 96%–100%). The initial use of this biomarker for diagnosing lesions could potentially reduce the number of cranial CTs performed by 29.1%. When considering the positivity of both biomarkers, the sensitivity and NPV were also 100% (95% CI: 77%–100% and 96%–100%, respectively). In this case, the reduction in cranial CTs utilization would be 23.2%. These statistical results are presented in Fig. 1.

DISCUSSION

GFAP and UCH-L1 biomarkers have proven to be effective tools for ruling out intracranial lesions in patients with mTBI, offering high sensitivity and NPV. Their use in the emergency setting may significantly reduce the need for cranial CT.

TBI represents a major burden on healthcare systems from medical, economic, and social perspectives, with millions of ED admissions worldwide. Most TBI patients are elderly, frail and on some form of anticoagulant or antiplatelet therapy, often resulting in prolonged stays in the ED. Prolonged exposure to this potentially hostile environment may lead to several acute medical exacerbations, including infection and delirium, particularly when patients remain in the ED for more than 24 hours.[13]

Radiation exposure from cranial CTs is another concern. Although the low radiation dose used in trauma imaging has significantly reduced cancer risk, making routine use of this imaging modality in emergency settings acceptable,[14] recent

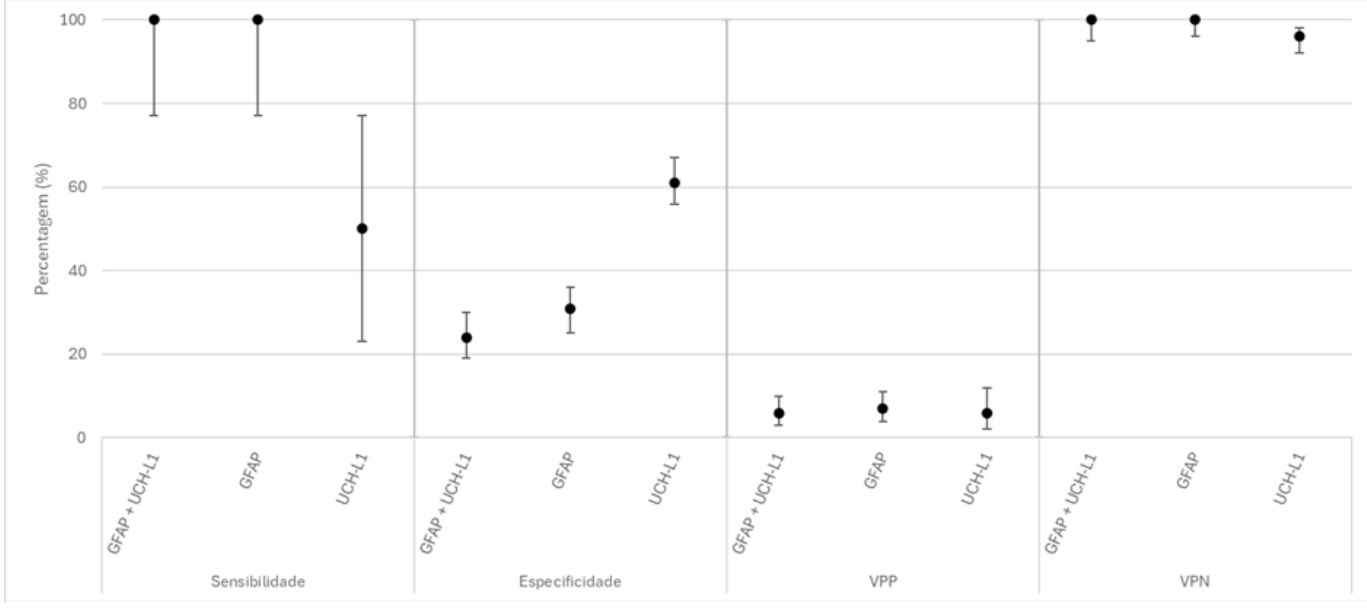

Figure 1. Analysis of sensitivity, specificity, positive predictive value (VPP) and negative predictive value (VPN)

data suggests that the overall mortality risk from malignancy increases by approximately 0.01% per body CT scan. However, it is important to note that this risk is cumulative over a lifetime and therefore not negligible.[15]

Portuguese national guidelines for the management of TBI mandate cranial CT in high-risk patients, as well as a CT re-evaluation approximately 24 hours after the trauma in patients receiving anticoagulant therapy. This leads to a substantial increase in imaging requests and contributes to ED overcrowding. One Portuguese study conducted in a central hospital estimated the annual cost of this approach at up to €163 000.[16] In our sample, no patient benefited from the 24-hour post-trauma repeated cranial CT, as no lesion progression was identified compared to the initial scan. Only one patient underwent neurosurgical intervention, and no deaths were recorded during the first 3 months of follow-up.

The logistical and human resource costs associated with the prolonged ED stay of these patients should not be underestimated, including overcrowding and healthcare worker fatigue.

The results of this study demonstrate that serum biomarkers may be used to rule out brain injury in mTBI patients with a strong level of confidence, achieving very high sensitivity and NPV, thereby lowering the risk of missing actual cases to a minimal threshold".

Given their high sensitivity, these serum biomarkers used in combination, may serve as a valuable first-line screening tool for intracranial lesions in post-mTBI patients in the ED setting. Cranial CT could be reserved for patients with positive biomarker results. When measured together, these biomarkers could reduce the number of cranial CTs performed by 23%, offering significant financial, time, and resource management benefits.

Our findings also suggest that the isolated use of GFAP may be equally effective, potentially reducing the number of cranial CTs by 29%. However, this result must be confirmed by more robust studies, as the isolated use of this biomarker is not yet approved.

The results obtained in this study are consistent with findings reported in the existing literature, suggesting that the Portuguese healthcare context may also benefit from the clinical implementation of these biomarkers.

These biomarkers are already integrated into mTBI management protocols in several European countries. Validation for the Portuguese population is necessary to support their incorporation into national protocols, and the results obtained are in line with international evidence. We believe that this study, conducted in an ED that serves a large population (500 000 inhabitants) with a high trauma burden, may perform as an initial step toward revising the national approach to a highly prevalent condition such as TBI in Portugal.

Regarding the limitations of this study, despite being conducted in a high-volume trauma center, the number of patients included for statistical analysis within the predefined period was limited, with only a small percentage (4.6%) presenting with CT confirmed intracranial lesions.

This was also a single-center study, which should be followed by a multicenter project involving contributions from other national hospitals.

CONCLUSION

Serum biomarkers of acute brain injury (GFAP and UCH-L1) may be used to reliably rule out the diagnosis of acute brain lesions in patients with mild traumatic brain injury, thereby reducing the number of cranial CTs performed, lowering associated healthcare costs and decreasing patient length of stay in the ED.

LEARNING POINTS

- Traumatic brain injury represents one of the most prevalent conditions in the Emergency Department, being a major public health concern with substantial economic implications.
- There has been a growing reliance on cranial computed tomography to rule out acute traumatic intracranial lesions in patients that suffered mild traumatic brain injury.
- Serum biomarkers – GFAP and UCH-L1 – have emerged as an alternative to the cranial CT.
- This study validated the use of these biomarkers in the Portuguese population, allowing them to be used to reliably rule out the diagnosis of acute brain lesions in patients with mild traumatic brain injury.

ACKNOWLEDGEMENTS / AGRADECIMENTOS

The authors would like to thank all healthcare professionals involved in trauma care at the Emergency Department of ULSTS for their support and collaboration, which made this study possible. The authors also express their gratitude to all the patients who agreed to participate in the study.

AWARDS AND PREVIOUS PRESENTATIONS / PRÉMIOS E APRESENTAÇÕES ANTERIORES

The oral presentation "Determination of Blood Biomarkers in Mild Traumatic Brain Injury (mTBI), GFAP and UCH-L1, in Patients Admitted to the Emergency Department with Suspected Mild TBI" was awarded first prize at the First National Congress of the Portuguese Society of Emergency and Urgent Care Medicine, in 2024.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares

CONTRIBUTORSHIP STATEMENT

CLS and CF: Study design, data collection and drafting of the article.
AR: Study design, data collection, laboratory work and critical review of the article.
RM: Statistics analysis and critical review of the article.
LS and TC: Data collection and laboratory work.
FM: Critical review of the article.
All authors approved the final version to be published.

DECLARAÇÃO DE CONTRIBUIÇÃO

CLS e CF: Desenho do estudo, recolha de dados e redação do artigo.
AR: Desenho do estudo, recolha de dados, trabalho laboratorial e revisão crítica do artigo.
RM: Análise estatística e revisão crítica do artigo.
LS e TC: Recolha de dados e trabalho laboratorial.
FM: Revisão crítica do artigo.
Todos os autores aprovaram a versão final a ser publicada.

REFERENCES

1. Brazinova A, Rehorcikova V, Taylor MS, Buckova V, Majdan M, Psota M, et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. J Neurotrauma. 2021;38:1411-40. doi: 10.1089/neu.2015.4126.
2. Taylor CA, Bell JM, Breiding MJ, Xu L. Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2007 and 2013. MMWR Surveill Summ. 2017;66:1-16. doi: 10.15585/mmwr.ss6609a1.
3. Menon DK, Schwab K, Wright DW, Maas AI; 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. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil. 2010;91:1637-40. doi: 10.1016/j.apmr.2010.05.017.
4. Lefevre-Dognin C, Cogné M, Perdrieau V, Granger A, Heslot C, Azouvi P. Definition and epidemiology of mild traumatic brain injury. Neurochirurgie. 2021;67:218-21. doi: 10.1016/j.neuchi.2020.02.002.
5. Easter JS, Haukoos JS, Meehan WP, Novack V, Edlow JA. Will Neuroimaging Reveal a Severe Intracranial Injury in This Adult With Minor Head Trauma?: The Rational Clinical Examination Systematic Review. JAMA. 2015;314:2672-81. doi: 10.1001/jama.2015.16316. Erratum in: JAMA. 2017;317:2021. doi: 10.1001/jama.2017.5136.
6. Temboury Ruiz F, Moya Torrecilla F, Arráez Sánchez MA, Arribas Gómez I, Vicente Bártulos A, Gallego España FJ, et al. Traumatismo craneoencefálico leve y biomarcadores de lesión cerebral aguda. Rev Esp Urg Emerg. 2024;3:31-6.
7. Su YS, Schuster JM, Smith DH, Stein SC. Cost-Effectiveness of Biomarker Screening for Traumatic Brain Injury. J Neurotrauma. 2019;36:2083-91. doi: 10.1089/neu.2018.6020.
8. Chodobski A, Zink BJ, Szmydynger-Chodobska J. Blood-brain barrier pathophysiology in traumatic brain injury. Transl Stroke Res. 2011;2:492-516. doi: 10.1007/s12975-011-0125-x.
9. Ghaith HS, Nawar AA, Gabra MD, Abdelrahman ME, Nafady MH, Bahbah EI, et al. A Literature Review of Traumatic Brain Injury Biomarkers. Mol Neurobiol. 2022;59:4141-58. doi: 10.1007/s12035-022-02822-6.
10. Bazarian JJ, Biberthaler P, Welch RD, Lewis LM, Barzo P, Bogner-Flatz V, et al. Serum GFAP and UCH-L1 for prediction of absence of intracranial injuries on head CT (ALERT-TBI): a multicentre observational study. Lancet Neurol. 2018;17:782-9. doi: 10.1016/S1474-4422(18)30231-X.
11. Backus BE, Moustafa F, Skogen K, Sapin V, Rane N, Moya-Torrecilla F, et al. Consensus paper on the assessment of adult patients with traumatic brain injury with Glasgow Coma Scale 13-15 at the emergency department: A multidisciplinary overview. Eur J Emerg Med. 2024;31:240-9. doi: 10.1097/MEJ.0000000000001140.
12. Direção Geral de Saúde. Protocolo nacional para a abordagem dos traumatismos crâneo-encefálicos. Lisboa: DGS; 1999. [27 Fevereiro 2025]; Available from: https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/circular-normativa-n-05gabdg-de-05051999-pdf.aspx.
13. Gardner RC, Dams-O'Connor K, Morrissey MR, Manley GT. Geriatric Traumatic Brain Injury: Epidemiology, Outcomes, Knowledge Gaps, and Future Directions. J Neurotrauma. 2018;35:889-906. doi: 10.1089/neu.2017.5371.
14. Schultz CH, Fairley R, Murphy LS, Doss M. The Risk of Cancer from CT Scans and Other Sources of Low-Dose Radiation: A Critical Appraisal of Methodologic Quality. Prehosp Disaster Med. 2020;35:3-16. doi: 10.1017/S1049023X1900520X.
15. Bos D, Guberina N, Zensen S, Opitz M, Forsting M, Wetter A. Radiation Exposure in Computed Tomography. Dtsch Arztebl Int. 2023;120:135-41. doi: 10.3238/arztebl.m2022.0395.
16. Ribeiro da Costa T, Batata R, Oliveira S, Fernandes A, Sousa S, Vaz Silva F, et al. Economic Impact of Surveillance of Head Trauma Patients with Coagulopathy and Normal Initial Computed Tomography Scan (ECO-NCT). Acta Med Port. 2025;38:16-22. doi: 10.20344/amp.21661.