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Review

Epidemiology and Sex-Related Differences in Extracranial Complications in ICU Patients with Traumatic Brain Injury

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Abstract: Traumatic Brain Injury (TBI) is one of the leading causes of death and disability worldwide. Patient treatment and management pose a challenge for healthcare systems. The prognosis of these patients may be influenced by factors such as sex. This study aims to describe the clinical parameters of patients hospitalized in the Intensive Care Unit (ICU) of a Spanish hospital due to Trauma Brain Injury and to establish differences based on sex. Methodology: An observational, cross-sectional, and analytical study was conducted from March 2015 to December 2019. All patients admitted to the ICU during this period who presented isolated significant Traumatic Brain Injury, defined as an abbreviated injury scale (AIS) ≥ 3, were included. Data on baseline characteristics, mechanism of injury, substance use, and acute management in the prehospital and hospital stages (including the need for hospitalization) were recorded. A descriptive and inferential analysis was conducted using the chi-square test. Results: A total of 950 patients were ultimately included. The majority of the patients were men (723) with a mean age of 45.16 (± 17.55). There were statistically significant differences in terms of the mechanism of injury ($p<0.001$), with occupational accidents, sports-related accidents, and assaults being more frequent in men, and self-harm attempts, falls, and traffic accidents being more common in women. Sex-based differences were found in alcohol and other drug consumption, with higher alcohol consumption in men and higher use of other drugs in women. There were no differences in the need for prehospital intubation, but differences were found in the extra hospital resources used in patient care based on biological sex. Conclusions: There are sex-based differences in individuals with TBI regarding the mechanism of injury, substance use, and the need for prehospital care resources or intubation, which should be taken into account when establishing intervention plans

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1. Introduction

Traumatic Brain Injury (TBI) is one of the main causes of morbidity and mortality in the world. TBI is associated with one-third of injury-related deaths in the United Stated (US) [1]. In Spain, the annual incidence of TBI is estimated at 200 new cases/100,000 inhabitants [2–4] According to its epidemiological distribution, TBI is one of the main causes of death due to trauma worldwide, the rate is 579 per 100,000 people/year, mainly due to falls and/or traffic accidents. depending on sex, age, and/or country (higher in developing countries) [5]

In recent years, it has become a public health problem due to the high prevalence, social factors, and the socio-familial repercussions after the event [1]. It is expected to surpass other pathologies as a cause of death and disability by 2030, which has repercussions for health systems, not only economically, which are estimated in countries like Canada at more than $8 billion by 2031, but also in the adequacy of therapeutic maintenance measures for patients, with the development of new diagnostic tools, neurosurgical centers, and intensive care treatments, which can help reduce mortality rates [6–10]

TBI is defined as an alteration of the brain's anatomy and function caused by violent exchanges of mechanical energy [11]., This alteration is one of the most important causes of morbidity and mortality in people under 45 years of age. Three types are distinguished: mild, moderate, and severe, from the clinical point of view, using the Glasgow Coma Scale. Falls are the main cause of trauma, followed by trauma and motor vehicle accidents [12], The future of these patients depends on the prognostic factors of this injury. In recent years, the sex variable has been included in research regarding prognosis and outcome [5,9,13]. Similarly, there have been various studies in recent years that include this factor and contribute to a better understanding of TBI [10], There are important social, cultural, and economic differences that can influence the prognosis of TBI [6–10], so different studies indicate the importance of knowing the epidemiological characteristics to understand the etiology and improve the design of appropriate intervention programs to reduce injuries [1,12]. Despite this, differences in lack of representation in clinical trials persist [14]. The objective of the present study is to describe, from a biological sex perspective, the clinical and evolutionary parameters of patients with traumatic brain injury.

2. Materials and Methods

The data are extracted from the register of trauma in in the intensive care unit called "RETRAUCI," (Reg which is an observational, prospective, and multicenter nationwide registry currently encompassing 52 ICUs in Spain. It is an initiative led by a group of Intensive Medicine professionals in Spain and sponsored by the Trauma and Neurocritical work group of the Spanish Society of Intensive Medicine and Coronary Units Endorsed by the Neurointensive Care and Trauma Working Group of the Spanish Society of Intensive Care Medicine, it operates on an electronic database. At present, it includes 50 registered ICUs with 124 investigators collecting data from trauma patients via a web-based system (www.retrauci.org). For this study, we exclusively utilize data from Hospital La Paz in Madrid, Spain.

All patients who met the following inclusion criteria were selected for the study: patients admitted to the participating ICUs from March 2015 to December 2019 who presented isolated significant Train Brain Injury, defined as an abbreviated injury scale point score (AIS) ≥ 3 were included. Patients with AIS head < 3 or patients with AIS ≥ 3 in any other anatomical area were not included in the study. Data on epidemiology, acute management in the prehospital and in-hospital stages, type and severity of injury, resource utilization, complications, and outcomes were recorded. Patients were followed up until hospital discharge.

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2.1. Procedure

Quantitative variables are described using the mean and standard deviation. The normality of the distribution was analyzed using the Shapiro–Wilks test. Categorical variables are expressed via their frequency distributions and percentages. For the inferential analysis, the Chi-square test or Fisher exact test for independent samples was performed with Statistical Package for Social Sciences SPSS 25, (SPSS Inc., Chicago, IL, USA) software was used.

3. Results

A total of 950 patients were admitted to this study based on the inclusion criteria. The majority of the patients were men (723, with a mean age of 45.16 and a standard deviation of ± 17.55). According to the mechanisms of injury (Table 1), we identified a statistically significant positive relationship between sex and the mechanism of trauma production. Most of the trauma occurred in men, with traffic accidents and falls being the main mechanisms for non-intentional trauma, and aggression and self-harm being the main mechanisms for intentional trauma.

Table 1. Mechanism of Production of Trauma.

Intentionality of Trauma	Sex		TOTAL
	Men	Women	
Non-intentional Traffic.	336	114	450
	46.60%	50.22%	47.47%
Non-intentional falls.	160	60	220
	22.19%	26.43%	23.21%
Non-intentional Laboral Accidents	50	1	51
	6.93%	0.44%	5.38%
Non-intentional Sport Activities	34	4	38
	4.72%	1.76%	4.01%
Non-Intentional other activities	24	2	26
	3.33%	0.88%	2.74%
Intentional Aggression	57	7	64
	7.91%	3.08%	6.75%
Intentional Autolysis.	47	37	84
	6.52%	16.30%	8.86%
Unknown	15	2	15
	2,07%	0.88%	1.58%
TOTAL	723	227	950
	100 %	100 %	100 %
	χ^2 de Pearson = 48.3903	**Pr = 0.000**	

Based on the type of mechanism (defined as the ultimate cause leading to admission to the intensive care unit, irrespective of intent), we identified a statistically significant relationship between sex and traffic accidents. It is noteworthy that the highest percentage of men were involved in vehicle or bicycle accidents, followed by falls, being struck, and injuries from stabbing weapons. The majority of all trauma cases involved contusions were in men, with 655 cases compared to 220 in women while penetrating trauma was reported in only 51 men versus 4 women. (Table 2)

Table 2. Type of mechanism and sex-related significant.

Type of mechanism and significant biological sex	Sex		TOTAL
	Men	Women	
Vehicle/Bicycle Accidents	320	68	388
	48.85%	30.91%	44.34%
Struck	65	53	118
	9.92%	24.09%	13.49%

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Fall/precipitation	219	95	314
	33.44%	43.18%	35.89%
White/fire weapon	51	4	55
	7.79%	1.82%	6.29%
Total	655	220	875
	100 %	100 %	100 %
	χ^2 de Pearson = 50.1629 Pr = 0.000		

Regarding the positive association (Pr = 0.000) between alcohol, drugs, and biological sex , we highlight that most of the trauma cases are not related to alcohol (76.84% among men, 90.71% among women). In cases related to alcohol, the majority of the incidences were in men (23.16%). (Table 3)

Table 3. Relation between alcohol and drugs and sex.

Alcohol	Sex		TOTAL
	Men	**Women**	
No	554	205	759
	76.84 %	90.71%	80.15%
Yes	167	21	188
	23.16%	9.29%	19.85%
TOTAL	721	226	947
	100 %	100 %	100 %
	χ^2 de Pearson = 20.8047 Pr = 0.000		
Drugs	Sex		TOTAL
	Men	Women	
No	82	12	94
	11.39 %	5.29 %	9.93%
Yes	638	215	853
	88.61 %	94.71%	90.07%
Total	720	227	947
	100 %	100 %	100%
	χ^2 de Pearson = 7.1888 Pr = 0.007		

Concerning drugs, it is noteworthy that the majority of traumas are related to drugs, with 88.61% in men and 94.71% in women. Regarding the type of pre-hospital care, intubation, and sex, out of a total of 865 patients, we found a greater significance in patients transferred in a mobile ICU, followed by conventional non-medicalized transport, and in third place, transfers to the ICU by helicopter, with the highest percentage being men in all cases. To intubation, out of a total of 614 patients, approximately 70% did not require this technique, while a total of 32 patients, both men and women, required intensive ventilation care, with the number of people requiring another alternative airway being negligible. About psychotropic drug consumption and biological sex, a high percentage of men and a lower proportion of women, out of a total of 949 patients, did not consume depressant drugs, with habitual consumption in 35 men and 11 women of the total. Chronic use of these medications is greater in men compared to women (Tables 4 and 5).

Table 4. Relation between Prehospital Care and Intubation.

Prehospital Care	Biological Sex		TOTAL
	Men	**Women**	
Intensive Care Ambulance	657	208	865
	95.08%	94.12%	94.85%
Basic Care Ambulance	110	10	20
	1.45 %	4.52 %	2.19%
Helicopter	16	0	16
	2.32%	0.00 %	1.75%

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Not necessarily Prehospital Care	8	3	11
	1.16%	1.36%	1.21%
Total	691	221	912
	100 %	100 %	100 %
χ^2 de Pearson = 12.4216	**Pr = 0.006**		
Prehospital intubation	Biological Sex		TOTAL
	Men	**Women**	
No	469	145	614
	66.5%	66.21%	66.45%
Yes	228	72	300
	32.34%	32.88%	32.47%
Alternative airway control devices	8	2	10
	1.13%	0.91%	1.08%
Total	705	219	924
	100 %	100 %	100 %
	χ^2 de Pearson =	0.0930	Pr = 0.955

Table 5. Relation between psychotropics and sex.

Psychotropics	**Biological Sex**		**Total**
	Men	**Women**	
No	646	195	841
	89.47 %	85.90%	88.62 %
Yes	35	11	46
	4.85%	4.85%	4.85 %
Chronic use	41	21	62
	5.68%	9.25%	6.53 %
Total	722	227	949
	100 %	100 %	100%
	χ^2 de Pearson =	3.6221	**Pr = 0.163**

4. Discussion

TBI is a major cause of death and hospital admissions worldwide, and European studies indicate differences in data among different countries, justifying the need for comparative epidemiological studies to quantify the impact across different countries [12]. Therefore, the objective of the study is to epidemiologically describe, from a biological sex perspective, the clinical evolution and parameters associated with TBI.

When analyzing admission data by sex, in our population, 76.05% of admissions are male, consistent with similar studies where the proportion of male admissions is always higher, even though the distribution of the general population is similar [15]. Various previous studies indicate differences in ICU admissions, with a higher likelihood of ICU admission for men [16–18]. We found studies indicating that TBI is often more severe and lethal in men, although, considering the severity of injuries, a higher percentage of women are affected [1,19,20]. However, Breeding [21] suggests a higher hospital mortality in males, as different studies already indicate that the subsequent sequelae may be influenced by the social construction of biological sex [21], justifying the need to investigate the causes of this biological sex disparity [21].

In our study, we found a positive significance in the mechanism of trauma production. It is noteworthy in the female biological sex the higher percentage of patients whose reason is intentional self-harm, similar to other studies where women were more likely to suffer injuries as passengers or from suicidal falls, while men were at a higher risk of suffering injuries from motorcycle accidents [16–18]. The evolution of the causes of accidents should be assessed, as indicated in epidemiological studies elsewhere, there has been an increase in injuries due to the use of electric scooters or similar devices that modify the traditional pattern and could also be classified as an independent mechanism from vehicles in the future [15].

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In the study population, the previous consumption of alcohol and drugs was analyzed, with higher proportions in males (23.16%) compared to females (9.29%). Long-term differences in sequelae have not been assessed in this study, but we found different articles [23–25] indicating a worse evolution and worse sequelae with previous alcohol consumption. On the other hand, another aspect that should be considered in follow-up studies is the possibility of an increase in these substances in the recovery process and a greater likelihood of long-term sequelae [26].

Regarding the consumption of psychotropic drugs and biological sex, the number of women who consumed this medication chronically was higher compared to men (9.25% vs 5.68%). The analytical results obtained for both sexes who did not consume psychotropic drugs were very similar, with a higher percentage in men (89.47% vs 85.90%), or had consumed them before their admission, with the percentage being the same for both sexes in this case (4.85%). Studies such as Jakob's indicate that it may be common to find the use of stimulants, although there is no association with mortality, it is related to increased hospital stays [27]. Upon reviewing the literature, more results were found for patients recovering from brain injury who require the consumption of psychotropic drugs due to post-traumatic stress after the injury, as described in several scientific articles by Albrecht JS [28,29].

Among the measured variables, concerning patients who required orotracheal intubation (OTI), in our study, there were no significant differences in terms of biological sex, with a higher number of patients not requiring it compared to those who did (32.34% in men and 32.88% in women). However, individualized clinical indication should be taken into account, and there is no standardized protocol on when and how to perform the process, as different studies sometimes recommend rapid sequence intubation in the face of the risk of airway obstruction and/or hypoxia at the accident site. Others advocate for the use of bag-mask ventilation at low pressures and early transfer to a referral center [30–34]. Intervention in the event of respiratory deterioration is crucial, and some studies already indicate a reduction in morbidity and mortality in patients who have undergone early prehospital intubation [35]. Subsequently, in the ICU, studies such as Villemeure-Poliquin indicate that tracheotomy in the ICU was associated with lower mortality compared to prolonged endotracheal intubation in patients with moderate to severe TBI [34].

In conclusion, it is worth noting that the influence of sex on the severity of patients in an Intensive Care Unit (ICU) has been a topic of growing interest in medical research. Over the years, it has been observed that sex can play a significant role in the clinical presentation, response to treatment, and outcomes of patients admitted to the ICU, both in prognosis and survival. Certain investigations have determined that sex can influence susceptibility to certain critical illnesses, as well as the physiological response and recovery of patients. Cohort studies have found significant differences in disease severity and mortality between men and women among a cohort of ICU-admitted patients. Women were found to have a higher probability of presenting certain critical conditions, such as severe sepsis, while men showed a higher incidence of severe traumatic injuries. These findings highlight the importance of considering sex as a relevant factor in the assessment and management of patients in the ICU [36–38]

5. Limitations of the Study

This study allows for a description and analysis of a significant number of patients with TBI, providing an objective overview of the characteristics of patients admitted for TBI in a first-level hospital. However, it has limitations such as being a study conducted in a single hospital center.

6. Implication for Nursing Practice

Nurses play a crucial role in both the prevention and management of head trauma and other accident-related injuries. By understanding the epidemiological data, nurses can identify high-risk groups and tailor their educational efforts to those populations. For instance, nurses can develop targeted educational programs aimed at young men, focusing on the dangers of alcohol and psychotropic drug use and their link to accidents and head trauma. Additionally, nurses can advocate for and participate in public health campaigns that promote safe behaviors and substance abuse prevention. In the clinical setting, nurses can utilize this epidemiological information to assess

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patients more effectively, prioritize care for high-risk individuals, and implement appropriate interventions that may reduce the severity and frequency of head trauma cases. Furthermore, by being aware of the epidemiological trends, nurses can contribute to more efficient resource allocation and management, ensuring that healthcare services are directed where they are most needed.

7. Conclusion

1. Extracerebral complications after suffering a traumatic brain injury (TBI) occur frequently, being more common in male patients who have consumed alcohol or drugs before admission to the unit.

2. The percentage of individuals requiring intubation does not differ significantly by sex.

3. From a practical point of view, the findings suggest that sex-specific strategies may not be necessary for early recognition of extracerebral complications in the ICU in patients with TBI.

4. Alcohol consumption and TBI are bidirectionally related; In fact, alcohol intoxication is one of the strongest predictors of TBI, and a substantial proportion of these occur in intoxicated individuals.

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Declaration of AI use: Hereby, the authors declare that not IA has been used in the process of making this article.

References

1. Mollayeva, T.; Mollayeva, S.; Colantonio, A. Traumatic brain injury: sex, gender and intersecting vulnerabilities. Nature reviews. Neurology 2018, 14, 711-722, 10.1038/s41582-018-0091-y. Available online: https://www.ncbi.nlm.nih.gov/pubmed/30397256.
2. Mak, C.H.K.; Wong, S.K.H.; Wong, G.K.; Ng, S.; Wang, K.K.W.; Lam, P.K.; Poon, W.S. Traumatic Brain Injury in the Elderly: Is it as Bad as we Think? Curr Tran Geriatr Gerontol Rep 2012, 1, 171-178, 10.1007/s13670-012-0017-2. Available online: https://link.springer.com/article/10.1007/s13670-012-0017-2.
3. Bárcena-Orbe, A.; Cañizal-García, J.M.; Mestre-Moreiro, C.; Calvo- Pérez, J.C.; Molina-Foncea, A.F.; Casado-Gómez, J.; Rodríguez-Arias, C.A.; Rivero-Martín, B. Revisión del traumatismo craneoencefálico. Neurocirugía (Asturias, Spain) 2006, 17, 495-518, 10.1016/S1130-1473(06)70314-1. Available online: https://dx.doi.org/10.1016/S1130-1473(06)70314-1.
4. Giner, J.; Mesa Galán, L.; Yus Teruel, S.; Guallar Espallargas, M.C.; Pérez López, C.; Isla Guerrero, A.; Roda Frade, J. Traumatic brain injury in the new millennium: A new population and new management. Neurología (Barcelona, English ed.) 2022, 37, 383-389, 10.1016/j.nrl.2019.03.012. Available online: https://www.ncbi.nlm.nih.gov/pubmed/31153686.
5. Nguyen, R.; Fiest, K.M.; McChesney, J.; Kwon, C.; Jette, N.; Frolkis, A.D.; Atta, C.; Mah, S.; Dhaliwal, H.; Reid, A.; Pringsheim, T.; Dykeman, J.; Gallagher, C. The International Incidence of Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Canadian journal of neurological sciences 2016, 43, 774-785, 10.1017/cjn.2016.290. Available online: https://dx.doi.org/10.1017/cjn.2016.290.
6. Puvanachandra, P.; Hyder, A.A. Traumatic brain injury in Latin America and the Caribbean: a call for research. Salud pública de México 2008, 50, s3-s5, 10.1590/S0036-36342008000700002. Available online: http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S0036-36342008000700002&lng=en&tlng=en.
7. Valderrama-Molina, C.O.; Giraldo, N.; Constain, A.; Puerta, A.; Restrepo, C.; León, A.; Jaimes, F. Validation of trauma scales: ISS, NISS, RTS and TRISS for predicting mortality in a Colombian population. Eur J Orthop Surg Traumatol 2017, 27, 213-220, 10.1007/s00590-016-1892-6. Available online: https://link.springer.com/article/10.1007/s00590-016-1892-6.

8. Voss, J.D.; Connolly, J.; Schwab, K.A.; Scher, A.I. Update on the Epidemiology of Concussion/Mild Traumatic Brain Injury. Curr Pain Headache Rep 2015, 19, 32, 10.1007/s11916-015-0506-z. Available online: https://link.springer.com/article/10.1007/s11916-015-0506-z.
9. Faul, M.; Coronado, V. In Epidemiology of traumatic brain injury; Handbook of Clinical Neurology; Elsevier Health Sciences: Netherlands, 2015; Vol. 127, pp 3-13.
10. Mollayeva, T.; Colantonio, A. Gender, Sex and Traumatic Brain Injury: Transformative Science to Optimize Patient Outcomes. Healthcare quarterly (Toronto, Ont.) 2017, 20, 6-9, 10.12927/hcq.2017.25144. Available online: http://www.longwoods.com/content/25144.
11. Menon, David K., MD, PhD; Schwab, K., PhD; Wright, D.W., MD; Maas, Andrew I., MD, PhD Position Statement: Definition of Traumatic Brain Injury. Archives of physical medicine and rehabilitation 2010, 91, 1637-1640, 10.1016/j.apmr.2010.05.017. Available online: https://www.clinicalkey.es/playcontent/1-s2.0-S0003999310006507.
12. Majdan, M.; Plancikova, D.; Brazinova, A.; Rusnak, M.; Nieboer, D.; Feigin, V.; Maas, A. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. The Lancet. Public health 2016, 1, e76-e83, 10.1016/S2468-2667(16)30017-2. Available online: https://dx.doi.org/10.1016/S2468-2667(16)30017-2.
13. Moscote-Salazar, L.R.; M Rubiano, A.; Alvis-Miranda, H.R.; Calderon-Miranda, W.; Alcala-Cerra, G.; Blancas Rivera, M.A.; Agrawal, A. Severe Cranioencephalic Trauma: Prehospital Care, Surgical Management and Multimodal Monitoring. Bulletin of emergency & trauma 2016, 4, 8-23. Available online: https://www.ncbi.nlm.nih.gov/pubmed/27162922.
14. Bah, M.G.; Naik, A.; Barrie, U.; Dharnipragada, R.; Eden, S.V.; Arnold, P.M. Racial and gender disparities in traumatic brain injury clinical trial enrollment. Neurosurgical focus 2023, 55, E11, 10.3171/2023.8.FOCUS23421. Available online: https://search.proquest.com/docview/2885537569.
15. Zou, J.; Fang, H.; Zheng, J.; Ma, Y.; Wu, C.; Su, G.; Liu, X.; Liu, J.; Gao, J.; Zhang, J.; Zhu, D.; Shi, X.; Huang, X. The epidemiology of traumatic brain injuries in the fastest-paced city in China: a retrospective study. Frontiers in neurology 2023, 14, 1255117, 10.3389/fneur.2023.1255117. Available online: https://search.proquest.com/docview/2895706880.
16. Larsson, E.; Lindström, A.; Eriksson, M.; Oldner, A. Impact of gender on post- traumatic intensive care and outcomes. Scandinavian journal of trauma, resuscitation and emergency medicine 2019, 27, 115, 10.1186/s13049-019-0693-4. Available online: https://www.ncbi.nlm.nih.gov/pubmed/31870391.
17. Mikolić, A.; van Klaveren, D.; Groeniger, J.O.; Wiegers, E.J.A.; Lingsma, H.F.; Zeldovich, M.; von Steinbüchel, N.; Maas, A.I.R.; Roeters van Lennep, J.E.; Polinder, S. Differences between Men and Women in Treatment and Outcome after Traumatic Brain Injury. Journal of neurotrauma 2021, 38, 235-251, 10.1089/neu.2020.7228. Available online: https://www.ncbi.nlm.nih.gov/pubmed/32838645.
18. Joestl, J.; Lang, N.W.; Kleiner, A.; Platzer, P.; Aldrian, S. The Importance of Sex Differences on Outcome after Major Trauma: Clinical Outcome in Women Versus Men. Journal of clinical medicine 2019, 8, 1263, 10.3390/jcm8081263. Available online: https://www.ncbi.nlm.nih.gov/pubmed/31434292.
19. Colantonio, A.; Mroczek, D.; Patel, J.; Lewko, J.; Fergenbaum, J.; Brison, R. Examining Occupational Traumatic Brain Injury in Ontario. Can J Public Health 2010, 101, S58-S62, 10.1007/BF03403848. Available online: https://www.jstor.org/stable/41995343.
20. Chang, V.C.; Guerriero, E.N.; Colantonio, A. Epidemiology of work-related traumatic brain injury: A systematic review. American journal of industrial medicine 2015, 58, 353-377, 10.1002/ajim.22418. Available online: https://api.istex.fr/ark:/67375/WNG-0R44HXG5-H/fulltext.pdf.
21. Breeding, T.; Martinez, B.; Katz, J.; Nasef, H.; Santos, R.G.; Zito, T.; Elkbuli, A. The Association Between gender and Clinical Outcomes in Patients With Moderate to Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis. The Journal of surgical research 2024, 295, 791-799, 10.1016/j.jss.2023.11.035. Available online: https://dx.doi.org/10.1016/j.jss.2023.11.035.
22. Haag, Halina L., MSW, RSW; Caringal, M., MHSc; Sokoloff, S., MLIS; Kontos, P., PhD; Yoshida, K., PhD; Colantonio, Angela, PhD, OT Being a Woman With Acquired Brain Injury: Challenges and Implications for Practice. Archives of physical medicine and rehabilitation 2016, 97, S64-S70, 10.1016/j.apmr.2014.12.018. Available online: https://www.clinicalkey.es/playcontent/1-s2.0-S0003999315000994.
23. Weil, Z.M.; Corrigan, J.D.; Karelina, K. Alcohol Use Disorder and Traumatic Brain Injury. Alcohol research 2018, 39, 171-180. Available online: https://www.ncbi.nlm.nih.gov/pubmed/31198656.
24. Tsitsopoulos, P.P.; Marklund, N.; Rostami, E.; Enblad, P.; Hillered, L. Association of the bleeding time test with aspects of traumatic brain injury in patients with alcohol use disorder. Acta Neurochir 2020, 162, 1597-1606, 10.1007/s00701-020-04373-y. Available online: https://link.springer.com/article/10.1007/s00701-020-04373-y.
25. Beaulieu-Bonneau, S.; St-Onge, F.; Blackburn, M.; Banville, A.; Paradis-Giroux, A.; Ouellet, M. Alcohol and Drug Use Before and During the First Year After Traumatic Brain Injury. The journal of head trauma rehabilitation 2018, 33, E51-E60, 10.1097/HTR.0000000000000341. Available online: https://www.ncbi.nlm.nih.gov/pubmed/28926484.

26. Wickens, C.M.; Mann, R.E.; Stoduto, G.; Toccalino, D.; Colantonio, A.; Chan, V. Work-related and non-work-related mild traumatic brain injury: Associations with mental health and substance use challenges in a Canadian population-level survey. Work (Reading, Mass.) 2024. Available online: https://www.ncbi.nlm.nih.gov/pubmed/38393873.
27. Jakob, D.A.; Lewis, M.; Benjamin, E.R.; Haltmeier, T.; Schnüriger, B.; Exadaktylos, A.K.; Demetriades, D. Pre-injury stimulant use in isolated severe traumatic brain injury: effect on outcomes. Eur J Trauma Emerg Surg 2023, 49, 1683-1691, 10.1007/s00068-022-02095-7. Available online: https://link.springer.com/article/10.1007/s00068-022-02095-7.
28. Albrecht, J.S., Ph.D; Mullins, D.C., Ph.D; Smith, Gordon S., M.B., Ch.B., M.P.H; Rao, V., M.D Psychotropic Medication Use among Medicare Beneficiaries Following Traumatic Brain Injury. The American journal of geriatric psychiatry 2017, 25, 415-424, 10.1016/j.jagp.2016.11.018. Available online: https://www.clinicalkey.es/playcontent/1-s2.0-S1064748116303220.
29. Albrecht, J.S.; Rao, V.; Perfetto, E.M.; Daniel Mullins, C. Safety of Antidepressant Classes Used Following Traumatic Brain Injury Among Medicare Beneficiaries: A Retrospective Cohort Study. Drugs Aging 2018, 35, 763-772, 10.1007/s40266-018-0570-2. Available online: https://link.springer.com/article/10.1007/s40266-018-0570-2.
30. Perlman, R.; Tsai, K.; Lo, J. Trauma Anesthesiology Perioperative Management Update. Advances in anesthesia 2023, 41, 143-162, 10.1016/j.aan.2023.06.003. Available online: https://dx.doi.org/10.1016/j.aan.2023.06.003.
31. Bossers, S.M.; Schwarte, L.A.; Loer, S.A.; Twisk, J.W.R.; Boer, C.; Schober, P. Experience in Prehospital Endotracheal Intubation Significantly Influences Mortality of Patients with Severe Traumatic Brain Injury: A Systematic Review and Meta-Analysis. PloS one 2015, 10, e0141034, 10.1371/journal.pone.0141034. Available online: https://www.ncbi.nlm.nih.gov/pubmed/26496440.
32. Gravesteijn, B.Y.; Nieboer, D.; Maas, A.; Andelic, N.; Audibert, G.; Azouvi, P.; Barzó, P.; Beauvais, R.; Beer, R.; Bellander, B.; Berardino, M.; Bragge, P.; Brazinova, A.; Buki, A.; Bullinger, M.; Calappi, E.; Cameron, P.; Carbonara, M.; Chieregato, A.; Clusmann, H.; Coburn, M.; Correia, M.; Dahyot-Fizelier, C.; De Keyser, V.; Boogert, H.d.; Depreitere, B.; Donoghue, E.; Dreier, J.; Ezer, E.; Feigin, V.L.; Foks, K.; Frisvold, S.; Gagliardo, P.; Galanaud, D.; Gao, G.; Glocker, B.; Golubovic, J.; Gratz, J.; Gravesteijn, B.; Gruen, R.L.; Gupta, D.; Haagsma, J.A.; Horton, L.; Hutchinson, P.J.; Jones, K.; Kolias, A.G.; Kompanje, E.; Koraropoulos, E.; Kovács, N.; Kowark, A.; Laureys, S.; Lingsma, H.; Castaño-León, A.M.; Majdan, M.; Manara, A.; Martino, C.; Menon, D.; Misset, B.; Murray, L.; Negru, A.; Nelson, D.; Nyirádi, J.; Olubukola, O.; Perlbarg, V.; Pirinen, M.; Ples, H.; Posti, J.P.; Ragauskas, A.; Rhodes, J.; Richardson, S.; Rocka, S.; Roe, C.; Rosenfeld, J.V.; Rosenlund, C.; Rossi, S.; Rueckert, D.; Sandor, J.; Schäfer, N.; Schmidt, S.; Schoechl, H.; Schou, R.F.; Sorinola, A.; Stamatakis, E.; Stewart, W.; Taylor, M.S.; Tenovuo, O.; Vámos, Z.; van der Naalt, J.; van Dijck, J.T.J.M.; van Essen, T.A.; Vargiolu, A.; Vega, E.; Velt, K.; Voormolen, D.; Wiegers, E.; Wilson, L.; Winzeck, S.; Yang, Z.; Younsi, A.; Zelinkova, V. Tracheal intubation in traumatic brain injury: a multicentre prospective observational study. British journal of anaesthesia: BJA 2020, 125, 505-517, 10.1016/j.bja.2020.05.067. Available online: https://dx.doi.org/10.1016/j.bja.2020.05.067.
33. Gravesteijn, B.Y.; Menon, D.; Steyerberg, E.W.; Maas, A.I.R.; Lingsma, H.F.; Åkerlund, C.; Adams, H.; Andelic, N.; Andreassen, L.; Anke, A.; Audibert, G.; Azouvi, P.; Bartels, R.; Beer, R.; Bellander, B.; Beretta, L.; Blaabjerg, M.; Borgen, L.; Brorsson, C.; Caccioppola, A.; Carbonara, M.; Chevallard, G.; Citerio, G.; Coburn, M.; Cooper, J.; Cnossen, M.; Czosnyka, M.; Degos, V.; Donoghue, E.; Dulière, G.; Ercole Ari, A.; Ezer, E.; Foks, K.; Frisvold, S.; Furmanov, A.; Galanaud, D.; Giga, L.; Golubovic, J.; Grossi, F.; Hutchinson, P.; Jankowski, S.; Karan, M.; Kondziella, D.; Kovács, N.; Lingsma, H.; Manara, A.; Martino, C.; Mattern, J.; McFadyen, C.; McMahon, C.; Menovsky, T.; Muraleedharan, V.; Murray, L.; Nair, N.; Negru, A.; Noirhomme, Q.; Nyirádi, J.; Ortolano, F.; Payen, J.; Persona, P.; Peul, W.; Ples, H.; Pomposo, I.; Radoi, A.; Raj, R.; Rhodes, J.; Richter, S.; Rocka, S.; Roe, C.; Roise, O.; Rosenlund, C.; Rossaint, R.; Rossi, S.; Sahuquillo, J.; Sakowitz, O.; Schou Rico, F.; Sorinola, A.; Stamatakis, E.; Kowalk, A.; Stocchetti, N.; Takala, R.; Tamás, V.; Tenovuo, O.; Thomas, M.; Tibboel, D.; Tolias, C.; Tudora, C.; Vallance, S.; Van der Steen, G.; Vanhaudenhuyse, A.; Wijk, R.; Vargiolu, A.; Vik, A.; Vilcinis, R.; Volovici, V.; Williams, G.; Wolf, S.; Zeiler, F.; Ziverte, A.; Zoerle, T. Variation in the practice of tracheal intubation in Europe after traumatic brain injury: a prospective cohort study. Anaesthesia 2020, 75, 45-53, 10.1111/anae.14838. Available online: https://onlinelibrary.wiley.com/doi/abs/10.1111/anae.14838.
34. Villemure-Poliquin, N.; Costerousse, O.; Lessard Bonaventure, P.; Audet, N.; Lauzier, F.; Moore, L.; Zarychanski, R.; Turgeon, A.F. Tracheostomy versus prolonged intubation in moderate to severe traumatic brain injury: a multicentre retrospective cohort study. Can J Anesth/J Can Anesth 2023, 70, 1516-1526, 10.1007/s12630-023-02539-7. Available online: https://link.springer.com/article/10.1007/s12630-023-02539-7.
35. Shafique, M.A.; Haseeb, A.; Asghar, B.; Kumar, A.; Chaudhry, E.R.; Mustafa, M.S. Assessing the impact of pre-hospital airway management on severe traumatic Brain injury: A systematic review and Meta-analysis. The American journal of emergency medicine 2024, 78, 188-195, 10.1016/j.ajem.2024.01.030. Available online: https://dx.doi.org/10.1016/j.ajem.2024.01.030.

 doi:10.20944/preprints202407.0684.v1

36. Zettersten E, Jäderling G, Bell M, Larsson E. Sex and gender aspects on intensive care. A cohort study. J Crit Care. 2020 Feb;55:22-27. doi: 10.1016/j.jcrc.2019.09.023. Epub 2019 Oct 25. PMID: 31683118.
37. Luethi N, Bailey M, Higgins A, Howe B, Peake S, Delaney A, Bellomo R; ARISE investigators. gender differences in mortality and quality of life after septic shock: A post-hoc analysis of the ARISE study. J Crit Care. 2020 Feb;55:177-183. doi: 10.1016/j.jcrc.2019.11.002. Epub 2019 Nov 8. PMID: 31739087.
38. Lat TI, McGraw MK, White HD. Gender Differences in Critical Illness and Critical Care Research. Clin Chest Med. 2021 Sep;42(3):543-555. doi: 10.1016/j.ccm.2021.04.012. PMID: 34353458; PMCID: PMC8328243.