Traumatic brain injury and its association with cardiac dysfunction

by Mahsa Mirbirjandian, MD

Division of Neurosurgery

Department of Experimental Surgery, McGill University

Montreal, QC, Canada

October 2020

A thesis submitted to the Faculty of Graduate Studies and Research at McGill University in partial fulfillment of the requirements of the degree of Master of Science in Experimental Surgery

To my parents,
whose heavenly embrace is the reason for all my achievements today.

Dedicated to my lovely parents and my brother, Ehsan, for their endless support along this way.
Their selflessness will always be remembered.

Table of Contents

Abstract

Background

Traumatic brain injury (TBI) is a serious public health concern that accounts for one-third of all unintended trauma-related deaths worldwide. Even in the absence of direct damage to extracranial organs, 89% of patients with severe TBI can experience substantial organ dysfunction. Organ dysfunction can occur at any phase of the treatment period, from acute setting to rehabilitation. The cardiovascular manifestations related to nontraumatic head disorders (e.g., ischemic stroke or aneurysmal subarachnoid hemorrhage) are commonly known. Some studies have also reported on cardiovascular manifestations in TBI patients. However, the relationship between cardiac dysfunction incidence and the severity of intracranial injury has been less studied. In particular, the relationship between intracranial hypertension and cardiac dysfunction has received little attention. In the present study, we address the abovementioned literature gap by undertaking the following research objectives: 1) determining the incidence of cardiac dysfunction in patients with TBI; 2) characterizing the types of ischemic, myocardial, and electrical cardiac dysfunctions; 3) determining the risk factors for developing cardiac complications; and 4) measuring the possible impact of cardiac dysfunction on patient outcomes.

Methods

In this retrospective observational research, we studied adult patients with acute TBI that required cardiac monitoring and who were admitted to the emergency room between April 1, 2016 and March 31, 2018. We used the Provincial Trauma Registry, the TBI database, and the OACIS electronic medical record system to collect the data of patients with traumatic injuries, including age, gender, mechanism of trauma, initial Glasgow Coma Scale (GCS), injury severity score, associated injuries, medical history, brain computed tomography (CT) scan findings, troponin and creatine kinase levels, laboratory test results, as well as the incidence of intracranial hypertension and its duration and severity. We employed electrocardiograms and echocardiograms to detect cardiac electrical and myocardial abnormalities. Based on the impaired levels of cardiac enzymes and electrical and myocardial abnormalities, we identified cardiac dysfunction in the patients. We further considered previous records of cardiac disease in the patients' understudy. We used

multiple logistic regression analysis to investigate the relationship among the variables indicated in the research objectives outlined above.

Results

A total of 921 met the criteria for participation in the study. Among them, 28.7% had previous cardiovascular dysfunctions. Cardiac dysfunction was observed in 63.8% after admission. We found that 9.6% of the patients had ischemic cardiac dysfunction, 57.4% had electrical dysfunction, and 0.4% had myocardial dysfunction. The results show a lower prevalence of cardiac dysfunction in older patients and those with cardiac risk factors (P-value = 0.0007 and 0.0004, respectively). Findings indicate a relationship between the patients' initial GCS and the occurrence of cardiac dysfunction (P-value = 0.0607). Meanwhile, we found no significant relationship between cerebral hemorrhage and incidence of cardiac disorders. In addition, no meaningful relationship was found between intracranial hypertension and occurrence of cardiac dysfunction. The findings further demonstrate that patients with orthopedic problems (including fractures) are more likely to develop cardiac dysfunction. In terms of patient outcomes, we found an inverse relationship between high serum creatinine kinase and troponin levels and the patients' Glasgow Outcome Scale (GOS) (P-value = 0.017 and 0.000, respectively). The results also show that the impact of cardiac arrhythmia and ST segment changes on the GOS level is significant (P-value = 0.002 and 0.006, respectively).

Conclusion

In this study, we found that a large portion of patients with TBI developed cardiac dysfunction (63.8%). Our findings indicate that a relationship exists between initial GCS level and cardiac dysfunction. However, there was no statistically significant relationship between cerebral hemorrhage and increased intracranial pressure with the occurrence of cardiac disorder. This could be ascribed to the limited number of patients with high intracranial pressure in our sample. In addition, the presence of underlying cardiac risk factors was inversely related to the occurrence of cardiac dysfunction. The small sample size for certain variables, such as injury severity score, is a limitation of this study.

Résumé

Contexte

Les lésions cérébrales traumatiques (LTC) sont un problème de santé publique important qui est à l'origine d'un tiers de tous les décès accidentels liés à des traumatismes dans le monde. Même en l'absence de dommages directs aux organes extracrâniens, 89 % des patients atteints de lésions cérébrales traumatiques graves peuvent présenter un dysfonctionnement important de leurs organes. Le dysfonctionnement des organes peut survenir à n'importe quel moment de la période de traitement, de la phase aiguë à la période de réadaptation. Les manifestations cardiovasculaires liées aux troubles non traumatiques de la tête (par exemple, accident ischémique cérébral ou hémorragie sous-arachnoïdienne anévrysmale) sont communément connues. Peu d'études ont également fait état de manifestations cardiovasculaires chez les patients atteints de tuberculose. Cependant, la relation entre l'incidence des dysfonctionnements cardiaques et la gravité de la lésion intracrânienne a été moins étudiée. En particulier, l'étude de la relation entre l'hypertension intracrânienne et le dysfonctionnement cardiaque a reçu peu d'attention. Dans cette étude, nous comblons cette lacune en nous penchant sur les objectifs de recherche suivants : 1) Déterminer l'incidence des dysfonctionnements cardiaques chez les patients ayant subi un traumatisme crânien 2) Caractériser le type de dysfonctionnement cardiaque ischémique, myocardique et électrique 3) Déterminer les facteurs de risque de développement de complications cardiaques 4) Mesurer l'impact possible d'un dysfonctionnement cardiaque sur le résultat du patient.

Méthodes

Dans cette recherche rétrospective et observationnelle, nous étudions les patients adultes atteints de LTC Nous avons utilisé le registre provincial des traumatismes, la base de données des lésions traumatiques et le système de dossier médical électronique OACIS pour recueillir des données sur les patients souffrant de lésions traumatiques. Ces données comprennent l'âge, le sexe, le mécanisme du traumatisme, le Score initial de Coma de Glasgow (SCG), le score de gravité des blessures, les blessures associées, les antécédents médicaux, les résultats des scanners cérébraux, les niveaux de troponine et de créatine kinase, les résultats des tests de laboratoire, l'incidence de l'hypertension intracrânienne ainsi que sa durée et sa gravité. Nous avons utilisé des électrocardiogrammes (ECG) et des échocardiogrammes pour détecter les anomalies électriques

cardiaques et myocardiques. En se basant sur les niveaux d'enzymes cardiaques altérés et les anomalies électriques et myocardiques, nous avons identifié un dysfonctionnement cardiaque chez les patients. Nous avons en outre examiné les antécédents de maladies cardiaques chez les patients en doublon. Nous avons utilisé une analyse de régression logistique multiple pour étudier la relation entre les variables indiquées dans les objectifs de recherche décrits ci-dessus.

Résultats

921 patients répondaient aux critères de participation à l'étude. 28,7 % d'entre eux présentaient un dysfonctionnement cardiovasculaire antérieur. Un dysfonctionnement cardiaque a été observé chez 63,8 % d'entre eux après leur admission. Nous avons constaté que 9,6 % des patients présentaient un dysfonctionnement cardiaque ischémique, 57.4 % un dysfonctionnement électrique et 0,4 % un dysfonctionnement myocardique. Les résultats montrent une prévalence plus faible du dysfonctionnement cardiaque chez les patients âgés et chez ceux qui présentent des facteurs de risque cardiaque (valeur P = 0,0007 et 0,0004, respectivement). Les résultats indiquent une relation entre le SCG initiaux du patient et l'apparition d'un dysfonctionnement cardiaque (valeur P = 0,0607). Nous n'avons pas trouvé de relation significative entre les hémorragies cérébrales et l'incidence des troubles cardiaques. En outre, nous n'avons pas trouvé de relation significative entre l'hypertension intracrânienne et l'apparition de dysfonctionnements cardiaques. Les résultats indiquent en outre que les patients présentant des problèmes orthopédiques (y compris des fractures) sont plus susceptibles de développer un dysfonctionnement cardiaque. En ce qui concerne les résultats des patients, nous avons constaté une relation inverse entre des taux sériques élevés de créatinine kinase et de troponine et le Score de Résultat de Glasgow (SRG) des patients (valeur P = 0,017 et 0,000, respectivement). Les résultats montrent également que l'impact de l'arythmie cardiaque et des changements du segment ST sur les niveaux de SRG est significatif (valeur P = 0,002 et 0,006, respectivement).

Conclusion

Dans cette étude, nous avons constaté qu'une grande partie des patients atteints de tuberculose développaient un dysfonctionnement cardiaque (63,8 %). Nos résultats suggèrent une relation entre les niveaux de SCG initiaux et le dysfonctionnement cardiaque. Cependant, il n'y avait pas de relation statistiquement significative entre l'hémorragie cérébrale et l'augmentation de la

pression intracrânienne et l'apparition de troubles cardiaques. Cela pourrait être dû au petit nombre de patients présentant une pression intracrânienne élevée dans notre échantillon. En outre, la présence de facteurs de risque cardiaque sous-jacents était inversement liée à l'apparition de dysfonctionnements cardiaques. La petite taille de l'échantillon pour certaines variables, telles que le score de gravité des blessures, est l'une des limites de cette étude.

Acknowledgments

I would like to express my special gratitude and appreciation to my supervisor, Dr. Judith Marcoux, and my co-supervisor, Dr. Jeremy Grushka, for providing their invaluable guidance, support, and encouragement. This project could not be accomplished without their indispensable feedback.

I would also like to extend my gratitude to Dr. Jacqueline Joza for providing precious learning opportunities and information along this way. Her valuable comments were very influential in the conclusions of the study.

I am grateful to Dr. Jose Correa for helping me to conduct statistical analysis.

It is a great pleasure to acknowledge Professor. Alireza Ahmadsimab and Dr. Ghahhar Zavosh, whose assistance was crucial in the completion of this project. I owe everything I know about data analysis to these two people.

My heartfelt thanks go to the staff of the Montreal General Hospital, neurology, and neurosurgery department, notably Ms. Gail Brathwaite, for her positive energy and kindness; my friends and colleagues, Taraneh Rafiezadeh, Sayeh Khanjani, Katayoun Sayar, and Pouyan Ahangar, for their help and support.

And last but not least, nobody has been more important to me in pursuing this project than my family members, my mother by her endless love and support, my father by his constant encouragement, and my beloved brother, who has encouraged me to overcome difficult times.

Contributions of Authors

Mahsa Mirbirjandian (candidate): Performed the data collection, literature review and the analytic calculations. The candidate wrote the manuscript with support from Dr. Marcoux.

Dr. Judith Marcoux (primary investigator): Main supervisor responsible for the candidate throughout the data collection and thesis preparation and contributed to the interpretation of the results. Dr. Marcoux provided scientific insight and guidance, workspace, and patients' electronic medical record access, and supervision through the study.

Dr. Jeremy Grushka (co-supervisor): Provided surgical knowledge and helped through the study.

Dr. Jacqueline Joza (advisor): Provided scientific cardiac input through the study.

Dr. Jose Correa (statistician): Provided statistical knowledge and assisted the candidate in analyzing the data.

Author contributions and statements of originality

The work described in this manuscript is carried out by the author and is original. This study described the factors that can contribute to cardiac dysfunction after a traumatic brain injury.

Chapter 1 – Thesis Introduction

Definition:

Traumatic brain injury (TBI), which is a major public health issue and a significant cause of morbidity and mortality worldwide, especially in North America (1-3), can be characterized as the disruption of brain function or other evidence of brain pathology induced by an external physical force (4). TBI accounts for one-third of all unintentional injury-related deaths (5) and can result in lifelong cognitive, emotional, sensorimotor, and so many other impairments, even among patients with mild TBI (6). The effect of these conditions can be substantial, including considerable functional impairment leading to adverse psychological and long-term socio-economic implications.

Despite its widespread and long-term impact, TBI is often referred to as the "silent epidemic" because the subsequent disabilities are often invisible. As a result, the general public remains largely unaware of it. Since 1995, the Center for Disease Control and Prevention (CDC) has defined TBI as a head injury arising from blunt or penetrating trauma or acceleration–deceleration forces resulting in one or more of the following: decreased level of consciousness, amnesia, objective neurological or neuropsychological abnormalities, skull fractures, diagnosed intracranial lesions, or head injury recognized as the cause of death on the death certificate (7).

Classification:

Trauma scoring systems inform physicians about the injury severity and help them determine the direction of trauma management. Scoring systems can also be used for critical decision-making when a trauma patient has just arrived at the emergency room (ER) and a quick decision has to be made as to whether or not the patient needs emergency surgery (8, 9).

Although many diseases have entered a comprehensive and meaningful molecular classification phase, TBI is most often classified predominately by its clinical severity or physical mechanism. There are several classifications of TBI. The majority of clinical treatment trials for TBI have classified patients based on the neurological injury severity criteria (10). The most common approaches used by researchers include the 1) Revised Trauma Score, which is a simplified scale consisting of the Glasgow Coma Scale (GCS), respiratory rate, respiratory expansion, systolic

blood pressure, and capillary refill, yielding an overall score of between 1 to 16 to assess the injury severity (11) and the 2) Abbreviated Injury Scale (AIS), which classifies injuries by body region according to the relative severity (12). The AIS and the Injury Severity Score (ISS) are the scales that measure extracranial injury and physiological instability that can impact the outcome (13, 14). ISS is designed to determine the severity of multiple body region injuries and correlates with mortality, morbidity, and hospitalization time following trauma. It is used to describe the term "major trauma". The ISS scores range from 1 to 75, and major trauma (or polytrauma) is defined as an ISS that is greater than 15.

The 15-point GCS that measures the level of consciousness after TBI is the most commonly used standardized scoring scale for assessing TBI severity in adults. Patients with a GCS score of 3 to 8 are categorized as having severe TBI. This category has the highest mortality and morbidity rates. GCS level of 9 to 12 are classified as moderate TBI, and 13 to 15 as mild TBI (Table 1).

Table 1: Criteria used to classify TBI severity (15)

	TBI severity		
Criteria	**Mild**	**Moderate**	**Severe**
Structural imaging	Normal	Normal or Abnormal	Normal or Abnormal
Loss of consciousness	<30 minutes	30 minutes to 24 hours	>24 hours
Post-traumatic amnesia	0-1 day	>1 and <7 days	≥7 days
Glasgow Coma Scale score[a]	13-15	9-12	3-8
Abbreviated Injury Scale score: Head	1-2	3	4-6

[a] Best available score in 24 hours

Neuroimaging is important for determining the anatomical nature of intracranial damage and for managing patients with acute brain injury. It is important to understand the critical pathophysiological conditions that are responsible for poor outcome. The Marshall classification of TBI is a computed tomography (CT)-derived measurement that uses CT-visible pathologies (e.g., edema, focal lesions, intracranial hemorrhage) to predict outcomes in patients with TBI. This system was first published in 1992 and remains one of the most commonly used CT finding-based grading systems for acute TBI (16, 17). Patients with grade I scores have the lowest mortality rate (10%), while those with grade IV have mortality rates greater than 50%.

Epidemiology:

Incidence, morbidity and mortality, economic burden, and general consequences:

As a substantial cause of death and disability, TBI contributes to approximately 30.5% of all injury-related deaths in developed countries like Canada and the United States and affects over 1.7 million people annually (18, 19). Among them, nearly 275,000 are admitted and 52,000 die, with a significant portion of them being elderly (20).

TBI has a substantial economic and social impact. The lifetime cost of medical care for severe TBI ranges from $600,000 to $1.8 million per case, with a tenfold increase in the value of lost productivity, such as becoming bedridden (21, 22). Additionally, TBI survivors face long-term neuropsychiatric sequelae, and high medical costs are required for their rehabilitation (21, 23-28). Healthcare expenditure in 2008 amounted to CAD 141.4 billion, accounting for 10.7 percent of the Canadian gross domestic product (GDP). This number is expected to continue to increase in the future, according to the Canadian Institute for Health Information (29). In light of these challenges, decision-makers have turned their attention to the cost of illness. Acquired brain injury is one of the most important areas that should be addressed to improve healthcare accountability and long-term sustainability of healthcare expenditures. Statistics demonstrate that the number of hospital visits due to brain injury has increased significantly over time (5). One explanation for this exponential rise may be increased awareness about sports-related concussions among public and healthcare professionals. Another reason may be the higher number of injuries caused by falls in the elderly population.

The prevalence of TBI-related emergency visits, hospitalizations, and deaths differs between gender and even age. The data for 2013 revealed that the highest rates were observed among persons aged ≥ 75 years, 0–4 years, and 15–24 years. Moreover, males were more susceptible to brain trauma than females. The main injury mechanisms for all age groups included falls (accounting for more than 47% of all TBI), motor vehicle crashes, being hit by/against an object, and assaults (5). Young children (aged 0–4 years) were most likely to suffer TBI from injuries sustained from being struck by/against an object, while adolescents and young adults (aged 15–24 years) experienced the highest rate of motor vehicle injuries. Falling was the most prevalent cause of head injury among seniors aged 75 years or older, resulting in the highest fatal injury incidence

(18). Furthermore, a disproportionate number of bicycling and sports-related TBI was noted among 5- to 24-year-old persons. Compared with other age groups, this age group was four times more likely to sustain a bicycling-related TBI and eight times more likely to sustain a sports-related TBI.

Many patients with TBI, particularly those with moderate and severe TBI, experience significant long-term neurobehavioral sequelae that can negatively affect their reintegration into social, family, and professional life. Different secondary pathological conditions, including seizures, neurodegenerative diseases, neuroendocrine dysregulation, sleep disorders, and impaired neuropsychological functions, such as reduced attention, concentration, or memory problems, can result from TBI (30-35). One study estimated that up to 43% of hospitalized TBI survivors experience a long-term disability (36). Long-lasting somatic symptoms after mild TBI, such as chronic headaches, chronic pain syndromes, dizziness, and visual disturbances, are also referred to as "post-concussion syndrome". The cognitive symptoms that are commonly observed include attention deficits, slowed information processing, reduced verbal and working memory, and impaired executive functions. Psychiatric symptoms, such as depressed mood, agitation, irritability, anxiety, poor motivation, social withdrawal, and interpersonal difficulties, are also reported frequently (37, 38). TBI's adverse neuropsychological sequelae can influence an individual's function in both social and occupational environments for 6 to 12 months after injury or even longer. Up to 20% of survivors do not return to work within one year after TBI (22, 39). In an interview conducted by Ponsford, Olver, and Curran with a group of 175 individuals who suffered a TBI two years before the study and underwent rehabilitation, 33% of them still required assistance with community and transportation skills, and more than 50% of those who had been working previously were no longer employed (40). In addition, persisting cognitive, behavioral, and emotional problems were reported by approximately 67% of the patients.

Pathophysiology:

Head injuries include a wide range of severity, from patients who do not require medical evaluation or assistance to those who die immediately after the trauma. Mechanical forces applied to the skull and transmitted to the brain during trauma can result in focal or diffuse cerebral injury.

Brain damage may be caused by several mechanisms, including primary and secondary injuries. The primary effects result from mechanical forces that disrupt the brain's structural integrity and the blood–brain barrier, such as contusion or diffuse axonal injury (DAI). DAI is one of the most frequently experienced pathological features of TBI that may take place in the absence of impact forces but depends on inertial forces that are usually caused by motor vehicle collisions and, in some situations, by falls and assaults (41-45). These inertial forces are commonly induced by rapid head rotational motions or sudden accelerations–decelerations that deform the white matter and contribute to DAI. This subsequent tissue damage is characterized by axonal stretching, disruption, and eventual separation of nerve fibers (41, 46).

Secondary injury occurs due to alterations in the biomolecular and physiological brain structures following these impacts. The brain-derived micro-particles (produced by injured tissues) play a critical role in developing TBI-associated coagulopathy (47).

Cerebral injury may also occur due to traumatic hematomas (e.g., subdural, epidural, subarachnoid, and intraparenchymal hematomas). Various additional factors may complicate the injury, including focal or diffuse cerebral edema, obstructive hydrocephalus, increased intracranial pressure (ICP), hypoxic-ischemic injury, trauma-induced hypotension as a result of volume depletion or blood loss, subsequent coronary hypoperfusion, infection, excessive catecholamine release as a result of sympathetic overactivity, inflammatory response, neurotoxicity, protease activation, excitotoxin and free radical release, lipid peroxidation, and phospholipase activation. These related problems can increase post-traumatic mortality and morbidity (48).

Traumatic neurological injuries and increased ICP can lead to direct stimulation of specific trigger zones in the brain, including A1, A5, the solitary tract nucleus, and the hypothalamus (49). Stimulation of these brain regions results in increased catecholamine release, autonomic instability, and systemic inflammatory response (49, 50).

In a prospective study on 216 patients with severe TBI, Karamanos et al. showed that episodes of persistently elevated ICP following TBI are correlated with substantially higher mortality (51). Additionally, ischemia or compression of the brain stem can increase the vagal tone. Clinical symptoms, including neurogenic hypertension, myocardial ischemia, or cardiac dysrhythmias,

may occur as a result of the hyperdynamic cardiovascular response to lesions in these brain areas (52).

An autonomic dysfunction that presents as a paroxysmal sympathetic hyperactivity (PSH) is a consequence of TBI. This syndrome can manifest as a simultaneous, paroxysmal transient increase in sympathetic and motor activity recognized in a group of survivors of severe acquired brain injury (53). PSH is characterized by episodes of autonomic hyperresponsivity to non-detrimental stimuli, which include various combinations of hypertension, hyperthermia, tachycardia, tachypnea, sweating, increased muscle tone, and other symptoms of sympathetic hyperactivity (56, 57). Although PSH can result from any cause of acquired brain injury, the majority of published cases ascribe it to TBI (79.4 % of PSH cases) (54). The reported incidence of PSH in both adults and children with severe TBI varies from 8% to 33% (55).

Even in the absence of direct extracranial organ damage, 89% of patients with severe TBI may show substantial organ dysfunction, which is independently associated with worse outcomes and can impact a large number of systems. Organ dysfunction may occur in the acute setting or even during rehabilitation (58). Complications can involve the cardiovascular, respiratory, immunological, hematological, and endocrinology systems and can influence early management and long-term outcomes.

Prognosis:

Diagnostic and therapeutic decisions are usually dependent on the patient's prognosis. Besides, in such a critical situation, prognostic information is essential in counseling patients and their relatives. Depending on the severity and mechanism of the injury, the mortality and morbidity rates differ. The most important primary features of poor prognostic outcomes of brain injury patients are described in a recently completed evidence-based document (79). The GCS score measured after resuscitation ranges from 3 to 9, which is equivalent to severe brain damage, indicating a linear relationship with poor outcome (death, vegetative state, or severe neurological disability). The risk of adverse outcome rises dramatically with age, particularly in people over 60 years old. Hypotension at admission is also associated with a doubling in the risk of mortality (80). The Marshall CT classification and evidence of traumatic subarachnoid hemorrhage are the two most potent CT characteristics with strong TBI prognosis associations. The presence of an epidural

hematoma is the next most powerful predictor (81). Another important indicator of poor prognosis identified in a brain CT scan is the occlusion of the cisterns around the midbrain, indicating brain swelling and herniation. The shifting of the brain's midline due to contusion or hemorrhage is another poor prognostic indicator (82).

Outcomes:

Some patients who survive serious head injury due to intensive therapy in the acute stage make a satisfactory recovery. Others suffer from complications ranging from an inconvenient feeling to those that make the patient completely dependent. Many of these young survivors face many years of disability, which typically affects both physical and mental functions. Although the separate components of disability after brain injury have frequently been described, particularly those that can be assessed through psychometric testing, what matters to the patient is the net impact of all these separate disabilities on his/her functioning as a person, which includes the extent of dependency on others. Physicians mostly use prognostic estimates towards therapeutic decision making and resource allocation. Precise outcome predictions are also important for providing accurate information to families and caregivers.

For efficient outcome prediction, multiple clinical factors, such as the pupillary exam, GCS, and intracranial pathology, need to be considered together in a prognostic model. Studies have shown that these factors are strongly associated with a functional outcome in TBI patients. The Glasgow Outcome Scale (GOS) is a widely recognized standard primary endpoint for assessing a patient's outcome (83). The GOS has five ordered categories: death, vegetative state, severe disability, moderate disability, and good recovery. The GOS reliably evaluates patients' overall social outcomes based on a structured interview, which concentrates on social and personal functioning without the need for comprehensive neurological and psychological evaluations.

Chapter 2 – Cardiac consequences. A review

Mechanism:

Cardiac dysfunction has been documented in TBI patients, and this TBI-related cardiac dysfunction is associated with in-hospital mortality. Mashaly and Ako et al. suggested two pathophysiological mechanisms for this brain–heart interaction in their studies that focus on a sudden catecholamine excess condition and inflammatory cascade (59, 60). Some pieces of evidence can determine the presence of this brain–heart interaction, such as left ventricular dysfunction characterized by reduced left ventricular ejection fraction (LVEF) and new regional wall motion abnormalities found in a considerable number of brain-dead patients in the studies conducted by Gilbert and Seiler et al. (61, 62). Although we did not examine brain dead patients in our research, reviewing these studies could help us understand that the echocardiographic changes observed in TBI patients can be considered as a stress-induced cardiac dysfunction secondary to an acute brain injury.

Autonomic changes:

Based on Fernandez-Ortega and Krishnamoorthy et al.'s observations in their studies, patients with TBI demonstrate symptoms reflecting autonomic impairment and elevated catecholamine levels, including increased heart rates, respiratory rates, and blood pressures (63, 64).

Most patients experience a hypotensive episode during TBI surgery (65), and it has been shown that post-TBI hypotension (systolic blood pressure <90 mmHg) is directly related to both mortality and poor condition (66, 67). The presence of large or multiple lesions on CT scans constitutes a risk factor for intraoperative hypotension (65). It has been documented in some experimental models that abnormal ICP induced by intracranial lesions can cause cardiac impairment (68-70).

Electrocardiographic changes:

In terms of electrical cardiac dysfunction, up to 73% of TBI patients demonstrate electrocardiogram (ECG) changes (71). These changes can include anything from sinus tachycardia to ischemic changes and repolarization abnormalities, such as ST segment changes, QTc prolongation, pathological T waves, and U waves (71, 72). Póvoa et al. mentioned that

repolarization abnormalities, such as ST-T change and QTc and QT segment prolongation, had the highest incidence of 37.5% among post-TBI ECG changes (73). In a study of 30 patients with severe TBI conducted by Hackenberry et al., a prolonged QTc interval was found in 90% of the patients, while 53% had various nonspecific ST segment and T wave changes (74). Singla et al. (2002) demonstrated that although these ECG changes are often transient, they are associated with poorer outcomes and substantial mortality (75). These changes can occur in the absence of known atherosclerotic coronary artery disease.

The management of cardiovascular consequences in the TBI population may be of particular important as it can play a role in preventing secondary brain injury due to hypotensive episodes. Early ECG can be an affordable test to screen for cardiac dysfunction before ordering more expensive and invasive tests.

Cardiac biomarker levels:

Serum cardiac troponins are well-known biomarkers that are exclusively released from impaired myocardial cells regardless of the underlying triggers. Elevated troponins have been documented in acute traumatic and nontraumatic head injuries. Hays and Diringer found an association between positive troponin I and higher mortality rate in patients with intracerebral hemorrhage (76). In addition, in patients with surgically treated intracerebral hemorrhage, the elevation of troponin level upon admission was a significant risk marker for in-hospital mortality even after adjustment for age, gender, and volume of hemorrhage (77).

Echocardiographic changes:

According to Prathep et al. (2014), the occurrence of elevated cardiac biomarkers, including troponin I and creatine phosphokinase-MB isoenzyme, within two weeks after TBI was associated with abnormal echocardiography (78). They also described a range of different echocardiographic findings in TBI patients, including regional wall motion abnormalities (17.5%) and global systolic impairment (12%). The number of abnormal echocardiographic findings was higher in patients with more severe TBI, based on the GCS. An abnormal echocardiogram finding was another significant independent predictor of in-hospital mortality in TBI patients after adjusting for age, gender, and AIS (78).

Despite the frequency of TBI in the general population and the high incidence of secondary end-organ dysfunction after TBI, its possible effect on cardiac function has received little attention outside of case reports and limited case series.

Objective and hypothesis

Cardiac events are among the most important complications of acute brain injury. In blunt TBI, the heart could be affected either directly as a part of polytrauma or indirectly due to trauma-induced hypotension with subsequent coronary hypo-perfusion. On the one hand, the management of cardiac dysfunction in patients with TBI may be of particular importance because it may play a role in preventing secondary brain injury caused by hypotensive episodes. On the other hand, treatment of cardiac dysfunction following TBI can be very difficult because anti-platelets or anticoagulants, which are common treatments for cardiac problems, cannot be prescribed to these patients at the beginning of the treatment period because of the relative risk of developing an intracranial hemorrhage after TBI.

Despite the significant impact of TBI on general health and the high incidence of secondary end-organ dysfunction after TBI, its potential impact on cardiac function and possible risk factors for developing cardiac complications have received little attention, and a deficiency still remains that needs to be addressed. Likewise, it is essential to rule out the effects of the factors that may influence outcomes.

This research aims to investigate abnormal ECG and echocardiographic findings after TBI and their correlation with cardiac dysfunction. We further examine the cardiac complications of cerebral trauma, identify patients who may develop cardiac dysfunction, and establish how to minimize the incidence of these complications by exerting more control over certain factors that can be effective in causing complications.

We hypothesize that TBI is associated with cardiac dysfunction, including ischemic events, electrical changes, and myocardial dysfunction. Furthermore, we hypothesize that the occurrence of cardiac dysfunction is proportional to the severity of the intracranial injury, particularly intracranial hypertension.

Chapter 3 – Methodology

Participants:

This research is a retrospective observational cohort study conducted at Montreal General Hospital (MGH), which is a level one trauma centre in Montréal, Québec. Each year, MGH receives around 10,000 trauma victims, including more than 1,500 who sustained significant injuries requiring intensive care, surgery, and rehabilitation. The study was performed on all adult patients with acute TBI who presented to the ER and required cardiac monitoring in the ER or intensive care unit (ICU) for over two years from April 1, 2016 to March 31, 2018.

Patients with cardiac trauma (cardiac contusion or penetrating cardiac trauma) and patients aged less than 16 years were excluded from the study. We also excluded patients who presented long after the accident due to long-term complications of brain injury. The charts were identified using the Provincial Trauma Registry, the TBI data bank, and the OACIS electronic medical record system, which provided the full records of admission and hospitalization of all patients with traumatic injuries who were admitted to the hospital.

Clinical Measures:

Following the Institutional Review Board's approval, baseline demographics, medical history, and clinical and radiographic findings were collected for all identified patients with acute TBI who received care between 2016 and 2018 by using the TBI data bank (clinical database already collected for all admitted patients with TBI), the Trauma Registry (ministry-mandated clinical database for all trauma patients), and the patients' electronic charts (OACIS). Almost all patients received a GCS score upon admission to classify the TBI severity. Patients with a GCS of ≥13 were considered mild, 9–12 moderate, and ≤ 8 severe. The following data were collected for each subject:

1) **Age**
2) **Gender**

3) **Mechanism of trauma:** Refers to the method by which damage to organs occurs. Health care providers use the trauma mechanism to determine how likely a serious injury has occurred. In this category, we included falls, assaults, work accidents, etc.

4) **Initial GCS:** GCS is used by emergency medical services, nurses, and physicians to assess a person's consciousness level after a head injury and applies to all acute trauma patients.

5) **Incidence of loss of consciousness:** Loss of consciousness after a brain trauma should be taken seriously, and the person should be carefully monitored. Patients with more severe injuries experience a loss of consciousness at the time of trauma, lasting from a few minutes or hours to weeks or even months.

6) **Injury severity score (ISS):** The Injury Severity Score (ISS) is an established medical score to assess trauma severity. It correlates with mortality, morbidity, and hospitalization time after trauma.

7) **Associated injuries and complications:** Traumatic injuries can range from minor isolated wounds to complex injuries involving multiple organ systems. In this column, we included fractures, internal organ injuries, etc. For complications, we considered infections like Pneumonia, embolisms, thromboses, post-operation hemorrhages, etc.

8) **Past medical history:** Includes all diseases mentioned in patients' medical records.

9) **Classified home medications:** Includes anti-arrhythmic medications, oral anticoagulant, anti-platelet, anti-hypertension, anti-epileptics, etc.

10) **Brain CT findings:** Includes type, location, and size of intracranial hemorrhages or contusions, Marshall grade, etc.

11) **Cardiac enzymes:** Includes Troponin and Creatinine Kinase (CK) levels (and the time of the peak levels)

12) **Laboratory test results and electrolytes values:** Includes Hemoglobin, Sodium, Potassium, Calcium, Magnesium, etc. By examining the normal range of each test, we then investigated the presence of anemia, hypo, and hyperkalemia, etc.

13) **Drug or medication intoxication and Alcohol rate:** The existence of narcotics such as Amphetamines, Benzodiazepines, Cocaine, etc. in patients' blood and blood levels of Ethanol at the time of admission was recorded in this column.

14) **Incidence of hypotensive events:** Hypotension is the medical term for low blood pressure (less than 90/60 mmHg).

15) **Hemorrhagic shock:** Reduced tissue perfusion due to significant blood loss, resulting in an insufficient supply of oxygen and nutrients required for cell activity.

16) **Need for vasopressors:** Vasopressors are a powerful class of medications that increase mean arterial pressure (MAP) by inducing vasoconstriction.

17) **Estimated blood loss** (volume: ml): It means the amount of blood lost in milliliters during surgery.

18) **Presence of septicemia:** Septicemia means the potentially life-threatening invasion of the bloodstream by pathogenic agents and especially bacteria along with their toxins from a localized infection (as of the lungs or skin) that is accompanied by acute systemic illness and is diagnosed through a blood culture.

19) **Incidence of intracranial hypertension, duration, and severity** (values of highest levels): Intracranial hypertension is a serious neurological condition that occurs when there is a sustained rise in intracranial pressure (ICP) of more than 15 to 20 mm Hg. It happens when the three intracranial components—blood, brain, and cerebrospinal fluid (CSF)—are no longer able to compensate for volume fluctuations occurring within the cranium.

20) **Length of stay in ICU** (days)

21) **Length of stay in hospital** (days)

22) **GOS:** The Glasgow Outcome Score applies to patients with a brain injury that allows an objective evaluation of their recovery in six categories and provides a long-term rehabilitation prediction to return to work and everyday life.

Baseline and periodic electrocardiograms and rhythm strips from the ER and ICU were also retrieved to detect electrical abnormalities and analyzed by a cardiologist according to the following criteria:

1) Rate

2) Rhythm and presence of cardiac arrhythmias

3) PR interval (PR prolongation >200 ms)

4) QRS duration (QRS prolongation >120 ms)

5) QT interval/corrected QT interval (using the Bazett formula, considered prolonged >460 ms in females and >440 ms in males)

6) ST-segment changes (elevation or depression)

7) Heart blocks

8) Presence of cardiac ischemic events

9) Monitored brady and tachyarrhythmias (sinus bradycardia <60/min, sinus tachycardia >100/min)

10) Repolarization abnormalities

Information on the installation of a pacemaker during or before hospitalization was also recorded

Patients' echocardiograms were also evaluated based on the following findings:

1) **Left Ventricular Ejection Fraction (LVEF):** This is a measurement of how much blood the left ventricle pumps out with each contraction and expressed as a percentage. A normal cardiac ejection fraction may be between 50 and 70 percent.

2) **Left atrial size** (volume: ml): The left atrium plays a major role in cardiac physiology by collecting blood during systole and modulating left ventricular filling during diastole (84). Normal left atrial diameter is < 4.1 cm in men and < 3.9 cm in women.

3) **Regional wall motion abnormalities:** Defined as regional abnormalities in contractile function. Ischemic heart disease is the most common cause of wall motion abnormalities.

4) **Right ventricular dysfunction:** Can occur in a number of clinical scenarios, including pressure overload, cardiomyopathies, ischemic, congenital, or valvular heart disease, arrhythmias, and sepsis.

5) **Presence of pericardial effusion:** The presence of an abnormal amount of fluid in the pericardial space. It can be caused by a variety of local, systemic and traumatic disorders, or it may be idiopathic.

6) **Presence of valvular diseases, type, and severity of valvular involvement:** Valvular cardiac disease is characterized by injury or defect in one of the four cardiac valves including the mitral, aortic, tricuspid, or pulmonary. Any cardiac valve can become

stenotic or insufficient (also termed regurgitant or incompetent), causing hemodynamic changes long before symptoms.

We categorized cardiovascular disease into three different subgroups, namely, ischemic, electrical, and myocardial cardiac dysfunction. Cardiac dysfunction was described as the presence of elevated levels of troponin I (more than 0.04 nanograms per millilitre, consistent with the institution's reference value) and creatine kinase (more than 195 units per litre in males and more than 160 units per litre in females) in laboratory studies, presence of repolarization and other electrical and ischemic abnormalities diagnosed by electrocardiography, presence of several variables including left ventricular systolic dysfunction (LVEF less than 50%), regional wall motion abnormalities diagnosed by echocardiography, and cardiac pacemaker insertion.

The presence of ischemic heart disease is determined by high troponin levels, elevation or depression in the ST segment in the ECG, and regional wall motion abnormality on echocardiography.

Cardiac electrical changes were examined based on conditions such as tachycardia or bradycardia, heart blocks, PR prolongation (more than 200 milliseconds), and QRS widening (more than 100 milliseconds) in the patient's ECG.

Factors such as high levels of creatinine kinase and troponin, pericardial effusion, hypotension, regional wall motion abnormalities, and LVEF less than 50% diagnosed by echocardiography determine the presence of myocardial dysfunction.

We also assessed the presence of underlying cardiac disease in patients before admission due to brain injury by reviewing their records and medications prescribed in the past, the presence of a pre-installed cardiac pacemaker, and previous electrocardiographic or echocardiographic abnormalities.

Finally, we investigated the relationship between cardiac dysfunction and TBI severity, CT findings, and intracranial hypertension occurrence and severity. We also determined the risk factors for developing cardiac complications and measured the possible impact of cardiac dysfunction on the patient's outcome.

Imaging Data:

The admission cranial CT scans were analyzed and reported by a radiologist who was blinded to the ECG findings. The type of SAH was recorded as diffuse or focal. The SDH site was classified according to the regions to which it overlaid as unilateral, bilateral, interhemispheric, parafalcine, tentorial, and posterior cranial fossa. We also examined and noted the presence of cerebral contusion, intraventricular and epidural hemorrhage, and its volume which was measured as the largest width on axial cuts. Moreover, we recorded the presence of high ICP, the period that the pressure was high, and its highest levels. The Marshall grade was measured by using the CT scan's visible pathologies (e.g., edema, focal lesions, intracranial hemorrhage).

Ethical Considerations:

1) Oversight

This study was performed in accord with the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2014),* as well as respecting the requirements set out in the applicable standard operating procedures of the Research Institute of the McGill University Health Centre and the McGill University Health Centre Research Ethics Board. The McGill University Health Centre Research Ethics Board reviewed this study and was responsible for monitoring it at all participating institutions in the Québec health and social services network.

2) Confidentiality

As outlined in this protocol, only data relevant to this study were collected by the research team. All the information collected during the research project remained confidential to the extent required and provided by law.

Patient data were de-identified and coded. The code was kept by the principal investigator in a password protected digital file behind the MUHC firewall.

3) Informed consent

Due to the observational nature of the study and in place of individual informed consent of participants, authorization to access patient charts was obtained from the Director of Professional Services (DPS).

Statistical Analysis:

The data were summarized as mean, standard deviation (SD), or percentage. The prevalence and type of cardiac dysfunction in the admitted patients with TBI were determined and described based on the patients' genders. The correlation matrix was plotted to show the correlation coefficients between variables. Multiple logistic regression analysis was used to investigate risk factors on the probability of cardiac dysfunction. The binary outcome of interest was whether the patient developed a cardiac dysfunction (defined as cardiac dysfunction). The risk factors of interest were age, sex, GCS on admission, length of stay in the hospital, hemorrhagic shock, laboratory test results (including anemia, hyper creatinine, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, hypoglycemia, hyperglycemia), brain CT scan characteristics (including Marshall grade, SDH, SAH, contusion, high ICP), medical history (including autoimmune/inflammatory/rheumatology diseases, cardiac risk factors, neurological disease), mechanism of trauma (including assault, fall), and associated injuries (including chest and pulmonary injury, internal organ injury, skull fracture, non-skull fractures such as rib fractures, spinal fractures, etc.).

Multicollinearity was assessed by checking the variance inflation factor on a multiple regression model with the same dependent and independent variables (85). The 2 log-likelihood ratio test was used to test the overall significance of the model (Table 2). The fit of the model was assessed by the Hosmer–Lemeshow goodness-of-fit Chi-square test (Table 3). We plotted several diagnostic statistics against the predicted values using estimated values and Pearson and Deviance residuals to assess outliers and detect influential observations (Figure 1) (86). All statistical tests of the hypothesis were two-sided and performed at the 0.05 level of significance. All analyses were performed using the SAS software (version 13.0, SAS Institute Inc.).

Table 2: Model Convergence Status

The convergence criterion (GCONV=1E-8) was satisfied.

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	1156.762	1058.843
SC	1161.542	1226.140
-2 Log L	1154.762	988.843

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	165.9193	34	<.0001
Score	152.2130	34	<.0001
Wald	130.6215	34	<.0001

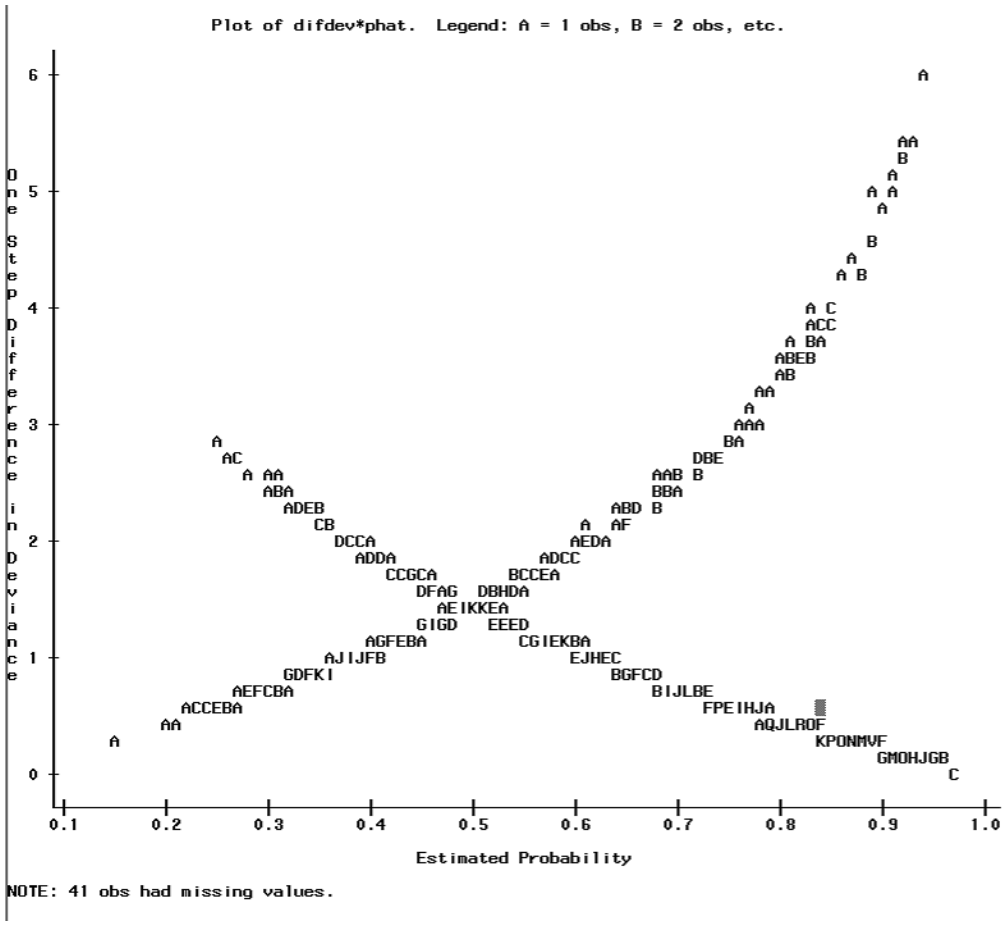
Table 3: The LOGISTIC Procedure (Partition for the Hosmer and Lemeshow Test)

		Cardiac dysfunction dependent variable = 1		Cardiac dysfunction dependent variable = 0	
Group	Total	Observed	Expected	Observed	Expected
1	88	26	26.42	62	61.58
2	88	26	34.02	62	53.98
3	88	44	40.66	44	47.34
4	88	50	47.01	38	40.99
5	88	60	53.32	28	34.68
6	88	59	60.69	29	27.31
7	88	72	67.23	16	20.77
8	88	67	72.36	21	15.64
9	88	77	76.30	11	11.70
10	88	78	81.00	10	7.00

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-Square	DF	Pr > ChiSq
11.3949	8	0.1803

Figure 1: The fit of the model

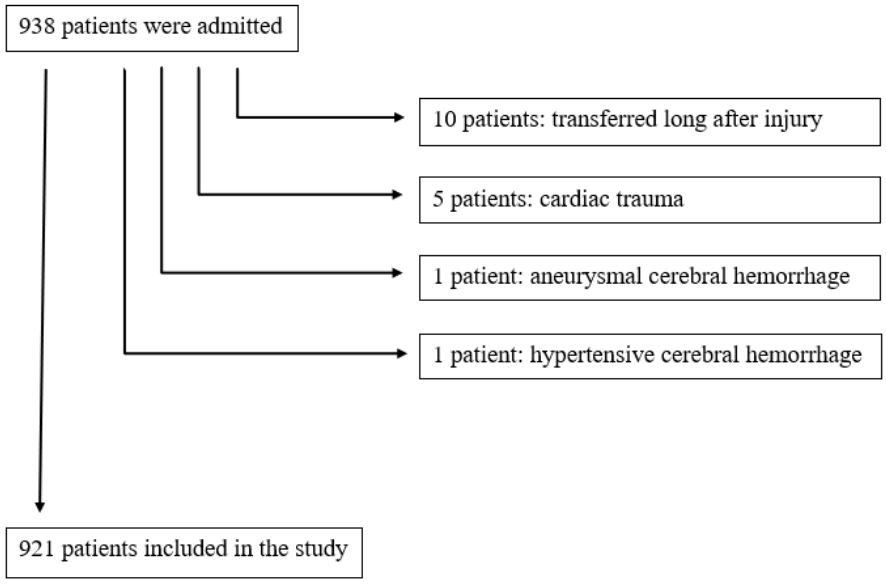


Chapter 4 – Results

Study Population:

938 patients were admitted to the Montreal General Hospital between April 1st, 2016, and March 31st, 2018, fulfilling this study's inclusion criteria. 17 patients were excluded, as they had cardiac trauma or transferred to this hospital long after the primary injury or were not traumatic cases (had a cerebral aneurysmal hemorrhage or cerebral bleeding due to high blood pressure) (Figure 2). Finally, after eliminating the mentioned cases, 921 patients fulfilled the required criteria to participate in the study and were included in the final analysis. All demographics and clinical characteristics of patients included in our study are shown in Table 4.

Figure 2: Patient enrollment flow diagram



The mean (±SD) age was 68.5 (±19.5) years. 68.8 % of patients were male and 31.1 % were female. After examining the previous ECGs and pre-admission echocardiograms, and considering the patients' cardiovascular history, the presence of previous cardiovascular dysfunction was confirmed in 28% of patients.

Falls (55.5 %) and driving accidents (29 %) were the most common causes of traumatic brain injuries in our patients. Results revealed that 46.9% of the patients (432 out of 921) had isolated TBI, while the rest had various associated orthopedic and intraabdominal injuries, with the mean (±SD) Injury Severity Score of 22.4 (±10.6). 88 (9.5 %) patients died during hospitalization.

Table 4: Descriptive statistics summarize all variables of interest in this study (N: 921)

Variable	**Value**
Age (years), mean (±SD)	68.5 (±19.5)
Sex F/M, n (%)	287 / 634 (31.1% / 68.8%)
GCS, mean (±SD)	13 (±4)
GOS, mean (±SD)	4.4 (±1.3)
ISS, mean (±SD)	22.4 (±10.6)
Length of stay in hospital (days), mean (±SD)	18.3 (±23.3)
Length of stay in ICU (days), mean (±SD)	8.2 (±9.4)
Past medical history, n (%)	
Autoimmune / Inflammatory / Rheumatology (Crohn disease, Rheumatoid Arthritis, Lupus, etc.)	119 (12.9%)
Cardiac risk factors (Diabetes Mellitus, hypertension, etc.)	470 (51%)
Cardiovascular (history of myocardial infarction, cardiomyopathy, etc.)	219 (23.7%)
Neurological disease (Epilepsy, Alzheimer, etc.)	172 (18.6%)
Mechanism of trauma, n (%)	
Assault	59 (6.4%)
Driving accidents	268 (29%)
Fall	512 (55.5%)
Work accidents	16 (1.7%)
Associated injuries, n (%)	
Chest and pulmonary injury	105 (11.4%)
Internal organ injury	45 (4.8%)
Skull fracture	151 (16.3 %)
Non-skull fractures (rib fractures, spinal fractures, etc.)	383 (41.5 %)
ECG characteristics, n (%)	
ST-segment elevation	10 (1.08 %)
ST-segment depression	13 (1.4 %)
Tachycardia	

Sinus tachycardia	74 (8.03 %)
Rapid response AF	53 (5.7 %)
Atrial flutter	7 (0.7 %)
Supraventricular tachycardia	10 (1.08 %)
Bradycardia	
Sinus bradycardia	71 (7.7 %)
Slow response AF	4 (0.4 %)
PR interval prolongation (more than 200 milliseconds)	45 (4.8 %)
QRS widening (more than 100 milliseconds)	163 (17.6 %)
QTc prolongation (more than 440 milliseconds)	320 (34.7 %)
AV blocks	
1st degree AV block	38 (4.1 %)
2nd degree AV block	3 (0.3 %)
3rd degree AV block	2 (0.2 %)
Nonspecific AV block	14 (1.5 %)
Repolarization abnormality	216 (23.4 %)
Cardiac pacemaker, n (%)	
Already had	23 (1.06 %)
Inserted during the admission	15 (0.6 %)
Echocardiographic characteristics	
LVEF percentage, mean (±SD)	56.8 (±14.4)
Regional wall motion abnormality, n (%)	43 (4.6 %)
Pericardial effusion, n (%)	6 (0.6 %)
Right ventricular dysfunction, n (%)	
Mild	14 (1.5 %)
Moderate	5 (0.5 %)
Severe	0 (0 %)
Laboratory test results	
Anemia	774 (84 %)
Hyponatremia	319 (34.6 %)
Hypernatremia	286 (31 %)
Hypokalemia	389 (42.2 %)
Hyperkalemia	271 (29.4 %)
Hypocalcemia	233 (25.2 %)
Hypomagnesemia	414 (44.9 %)
Hypophosphatemia	389 (42.2 %)
Hypoglycemia	51 (5.5 %)

Hyperglycemia	278 (30.1 %)
High Creatinine	216 (23.4 %)
High Troponin	157 (17 %)
High Creatine Kinase	224 (24.3 %)
Brain CT scan characteristics	
Marshall grade, mean (±SD)	2.7 (±1.5)
SAH	403 (43.7 %)
Focal	197 (21.3 %)
Diffuse	206 (22.3 %)
Contusion	314 (34 %)
IVH	121 (13.1%)
SDH	514 (55.8 %)
Unilateral	323 (35 %)
Bilateral	172 (18.6 %)
EDH	42 (4.5 %)
High ICP	58 (6.2 %)
Highest ICP levels, mean (±SD)	31.2 (±6.3)
Duration of high ICP (days), mean (±SD)	6.2 (±5.2)

Cardiac Characteristics:

448 patients had at least one ECG during the hospitalization period, and 145 patients with at least one Echocardiogram. For certain patients, several ECGs and echocardiograms were performed, all of which were evaluated. Repolarisation abnormalities, QRS widening, and rhythm abnormalities were the majority of abnormal findings in ECGs. These include ST-segment changes, Atrial Fibrillations (AF), and tachyarrhythmias. Other abnormal ECG findings included bundle branch blocks, atrioventricular blocks (AV blocks), and PR interval prolongation. The elevation and depression of the ST segment were observed in 1.08 and 1.4% of ECGs, respectively. AV blocks (1^{st}, 2^{nd}, 3^{rd} and nonspecific) were visible in 57 (6.1 %) of ECGs. A cardiac pacemaker was implanted for 23 (1.06 %) patients prior to hospitalization and for 15 (0.6 %) patients during hospitalization.

The mean (±SD) LVEF percentage in patients' echocardiograms was 56.8 (±14.4). Regional wall motion abnormalities and pericardial effusion were observed in 4.6 and 0.6 % of echocardiograms,

respectively. 8 % of echocardiograms showed mild right ventricular dysfunction, and 5.5 % demonstrated severe dysfunction.

Cardiac biomarkers, including Troponin and Creatine Kinase, were checked for 598 (64.9 %) and 350 (38 %) patients, respectively. A total of 157 patients (17 %) had elevated Troponin levels, and 224 (24.3 %) had elevated Creatine Kinase levels.

Finally, by examining several different factors, we investigated the presence of cardiac dysfunction in patients and found that cardiac dysfunction has happened in 588 (63.8%) of patients after TBI. Cardiac dysfunction has been classified into three categories of ischemic, electrical, and myocardial dysfunction, based on laboratory tests, ECG, and echocardiography findings of patients. Examinations revealed that 89 (9.6%) of patients have ischemic cardiac dysfunction, 529 (57.4%) have electrical dysfunction, and 4 (0.4%) have myocardial dysfunction. Table 5 indicates categorized cardiac dysfunction depending on the type of dysfunction and sex of patients (Table 5).

Table 5: The incidence of ischemic, myocardial, and electrical cardiac dysfunctions in male and female patients with a traumatic brain injury

Variable	**Female(N:287)**	**Male(N:634)**	**Total (N:921)**
Previous cardiac dysfunction (Y/N)	92 / 195 (32% / 68%)	173 / 461 (27.2% / 72.8 %)	265 / 656 (28.7% / 71.3%)
after admission cardiac dysfunction	177 / 110 (61.6% / 38.4%)	411 / 223 (64.8% / 35.2%)	588 / 333 (63.8% / 36%)
after admission ischemic dysfunction	28 / 259 (9.7% / 90.3%)	61 / 573 (9.6% / 90.4%)	89 / 832 (9.6% / 90.4%)
after admission electrical dysfunction	153 / 134 (53.3% / 46.7%)	376 / 258 (59.3% / 40.7%)	529 / 392 (57.4% / 42.6%)
after admission myocardial dysfunction	0 / 287 (0% / 100%)	4 / 630 (0.6% / 99.4%)	4 / 917 (0.4% / 99.6%)

Brain CT scan characteristics:

914 patients had a brain CT scan recording on admission. Brain abnormalities, including hemorrhage, contusion, hygroma, pneumocephalus, etc. were observed in 75.4% of brain CT scans. Marshall grade was calculated for all patients who had a brain CT scan. The mean (±SD) Marshall grade was 2.7 (±1.5). Among the various types of intracranial pathologies noted on CT scan, the most common type in patients was subdural (55.8 %) and then subarachnoid hemorrhages (43.7 %). Unilateral subdural hemorrhage was more common among patients than bilateral hemorrhage. The number of patients with diffuse subarachnoid hemorrhage was also higher than the focal type. Other cerebral hemorrhages patients experienced included cerebral contusion (34 %), intraventricular hemorrhage (13.1 %), and epidural hemorrhage (4.5 %), respectively. 58 patients experienced high Intracranial Pressure (ICP) levels during the hospitalization period (6.2 %), and 7 patients died of elevated ICP.

Brain CT scans of 15 (1.6 %) patients demonstrated diffuse axonal injury. 14 (1.5 %) brain CT scans showed pneumocephalus, 13 (1.4 %) Subdural Hygroma, 2 (0.2 %) pontine hemorrhages, and 1 (0.1 %) acute brain infarct.

Laboratory test results:

Anemia (84 %), hypomagnesemia (44.9 %), hypokalemia (42.2 %), and hypophosphatemia (42.2 %) were the most common laboratory results disorders and electrolyte abnormalities in patients, respectively.

Association with baseline, clinical, and radiographic characteristics:

We created a correlation matrix in the first step to determine the relationship between the variables. The correlation findings are summarized in Table 6. You can understand from this matrix that there are clinically rational correlations between multiple variables. For instance, there is a significant relationship between age and fall as a mechanism of the accident, the prevalence of cardiac risk factors as underlying diseases, the severity of brain damage (Marshall grade), and the incidence of a cerebral hemorrhage, including subdural, subarachnoid and intraventricular hemorrhages.

Table 6: The correlation matrix between different variables

Variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)	(21)	(22)	(23)	(24)	(25)	(26)	(27)	(28)	(29)	(30)
(1) Age	1																													
(2) Sex	0.160***	1																												
(3) GCS initial	0.322***	0.0799***	1																											
(4) Length of stay in hospital	-0.145***	-0.0683***	-0.267***	1																										
(5) Hemorrhagic shock	-0.115***	0.00589	-0.142***	0.0809***	1																									
(6) Anemia	0.0953***	0.0363	-0.0977***	0.136***	0.0505**	1																								
(7) Hyper Creatinine	0.279***	0.289***	0.0402*	0.00721	0.110***	0.143***	1																							
(8) Hypernatremia	0.130***	0.0517**	0.0342	0.206***	-0.102***	0.177***	0.0312	1																						
(9) Hyponatremia	-0.0262	-0.0174	-0.272***	0.311***	0.0548**	0.167***	0.0666***	0.0618**	1																					
(10) Hypokalemia	-0.0582**	0.0789***	-0.0930***	0.218***	0.000667	0.217***	-0.000867	0.0902***	0.386***	1																				
(11) Hyperkalemia	0.104***	0.0444*	0.00224	0.108***	0.107***	0.112***	0.328***	0.190***	0.105***	-0.0511**	1																			
(12) Hypocalcaemia	0.0962***	0.202***	-0.00699	-0.0735***	-0.0157	0.165***	0.145***	0.176***	0.184***	0.199***	0.196***	1																		
(13) Hypomagnesemia	-0.0375*	0.137***	-0.1000***	0.180***	0.147***	0.209***	0.0766***	0.155***	0.351***	0.386***	0.163***	0.285***	1																	
(14) Hypophosphatemia	-0.0687***	-0.000213	-0.254***	0.275***	0.0115	0.218***	-0.0785***	0.273***	0.420***	0.395***	0.0533**	0.311***	0.466***	1																
(15) Hypoglycemia	0.0559**	-0.0661***	-0.0129	-0.0220	0.0611**	0.0889***	0.183***	0.166***	0.0622**	-0.0155	0.191***	0.0823***	0.0149	0.00486	1															
(16) Hyperglycemia	0.147***	-0.0311	-0.00844	0.0814***	-0.0347	0.0367	0.222***	0.0544**	0.0787***	0.0533**	0.204***	0.0885***	0.133***	0.116***	0.0148	1														
(17) Marshall grade	0.124***	-0.114***	-0.125***	0.155***	-0.0608**	0.0230	-0.0754***	0.0279	0.0757***	-0.0380*	-0.0467*	-0.0304	0.0821***	0.123***	-0.113***	0.155***	1													
(18) SDH	0.164***	-0.119***	-0.0390*	0.139***	-0.101***	-0.0156	-0.0399*	0.0286	0.0596**	0.0494**	-0.00774	0.0135	0.0512**	0.120***	-0.0336	0.135***	0.552***	1												
(19) SAH	0.102***	0.102***	-0.194***	0.130***	0.0682***	0.0884***	0.185***	0.0836***	0.137***	0.00299	0.0833***	0.0677***	0.0848***	0.0681***	0.0882***	0.0840***	0.0166	0.0500**	1											
(20) Contusion	-0.154***	-0.0102	-0.224***	0.254***	-0.0296	-0.00104	-0.00950	0.0950***	0.108***	0.0970***	-0.0428*	-0.0408*	0.0145	0.126***	-0.0797***	0.113***	0.0292	0.207***	0.385***	1										
(21) High ICP	-0.151***	-0.0922***	-0.479***	0.162***	0.0246	0.0442*	-0.0871***	0.0788***	0.103***	0.0000388	-0.0570**	-0.102***	0.0665***	0.0751***	0.0129	-0.0495**	0.234***	0.0958***	0.110***	0.172***	1									
(22) Autoimmune/Inflammatory/Rheumatology	0.183***	0.119***	0.0965***	0.000160	0.0620**	0.0660***	0.247***	0.0144	-0.0309	-0.00937	0.0217	0.0697***	-0.0563**	0.0656***	0.148***	0.0924***	0.0852***	0.00282	0.0348	0.00408	-0.0847***	1								
(23) Cardiac risk factors	0.618***	0.118***	0.303***	-0.167***	-0.0869***	0.105***	0.256***	0.0507**	0.0669***	-0.0398*	0.148***	0.0945***	0.0349	-0.0563**	-0.0412*	0.220***	0.130***	0.144***	0.0327	-0.149***	-0.175***	0.194***	1							
(24) Neurological disease	0.0449*	-0.0841***	-0.0384*	0.0170	-0.0680***	0.0643***	-0.0663***	0.0473*	0.0877***	0.148***	-0.0561**	-0.0183	0.0413*	0.127***	0.0646***	0.0448*	0.135***	0.173***	0.0714***	-0.0177	0.0271	0.00867	0.0700***	1						
(25) Assault	-0.311***	-0.0661***	-0.0937***	-0.0360	0.0792***	0.0750***	-0.0820***	-0.0493**	0.0311	0.0260	0.0822***	-0.0418*	-0.0147	-0.0195	-0.0144	-0.106***	0.0786***	0.0910***	-0.0100	0.0280	0.0276	-0.0594**	-0.228***	0.0347	1					
(26) Fall	0.508***	0.135***	0.168***	-0.0637***	-0.0805***	0.0812***	0.186***	0.179***	-0.0303	0.0676***	0.0690***	0.0364	0.0245	-0.0141	0.0361	0.0931***	0.152***	0.197***	0.144***	-0.00579	-0.114***	0.140***	0.407***	0.140***	-0.300***	1				
(27) Chest and pulmonary injury	-0.162***	0.0497**	-0.0359	0.0479*	0.151***	0.0506**	-0.0388*	0.0804***	0.134***	0.0223	0.0292	0.0102	0.0923***	0.0718***	-0.0435*	0.0778***	-0.214***	-0.168***	-0.110***	-0.0411*	-0.0320	-0.0272	0.0634***	-0.130***	0.0387*	-0.145***	1			
(28) Internal organ injury	-0.200***	-0.0270	-0.0378*	0.105***	0.252***	0.0363	-0.00766	-0.0123	0.0301	-0.0111	0.0154	-0.0492**	0.0305	-0.0152	0.0372	-0.0430*	0.0846***	-0.129***	-0.00315	-0.0483*	0.0114	0.0728***	-0.154***	-0.0789***	-0.0291	-0.103***	0.122***	1		
(29) Skull fracture	-0.153***	0.00532	-0.126***	0.0569**	0.182***	0.0292	-0.0148	-0.0616**	0.0941***	0.0631***	0.0690***	0.0958***	0.109***	0.119***	-0.0529***	-0.00406	-0.0303	-0.00616	0.107***	0.154***	0.0833***	0.0730***	-0.0261	-0.0701***	0.0896***	-0.0435*	0.103***	-0.0370	1	
(30) Non-skull fractures	-0.196***	0.0817***	0.0830***	0.101***	0.173***	0.0536**	-0.0479*	-0.138***	0.00368	0.0472*	-0.0252	-0.107***	0.0325	-0.0407*	0.0835***	-0.104***	-0.361***	-0.321***	-0.129***	-0.0416*	-0.0628***	-0.0356	-0.131***	-0.126***	-0.0190	-0.258***	0.336***	0.143***	0.201***	1

* p<0.05 ** p<0.01 *** p<0.001

As a second step and to determine independent risk factors associated with the development of cardiac dysfunction and their relative impact, we used multiple logistic regression analysis (Table 7). We found that older patients and those with cardiac risk factors had a lower prevalence of cardiac dysfunction (P-value = 0.0007 and 0.0004, respectively). The duration of stay in the hospital was not related to the incidence of cardiac dysfunction (P-value = 0.1263). We eliminated the injury severity score and loss of consciousness from the list of variables due to a large amount of missing data in these two variables.

The patient's initial GCS had a slight significant relationship with the occurrence of cardiac dysfunction (P-value = 0.0607). The results of laboratory tests and electrolyte levels did not show statistical significance. There was no significant relationship between cerebral hemorrhages and the incidence of cardiac disorders. However, there is a low significant relationship between cerebral contusion and cardiac dysfunction (P-value = 0.0653). No meaningful relationship was found between intracranial hypertension and the occurrence of cardiac dysfunction (P-value = 0.4844). There is also a low significant relationship between cardiac dysfunction and falling (P-value = 0.0662). We omitted 'driving accidents' from the list of trauma mechanisms due to its strong correlation with falling, which in turn creates a multicollinearity problem in the regression model. The findings indicate that patients with skull fractures and non-skull fractures (such as rib fractures, spinal fractures, etc.) are more likely to develop cardiac dysfunction (P-value = 0.0176 and 0.0108, respectively).

Table 7: Multiple logistic regression results

Independent Variable: Cardiac dysfunction Number of observations = 880	The LOGISTIC Procedure Analysis of Maximum Likelihood Estimates				
	DF	Standard Estimate	Wald Error	Chi-Square	Pr > ChiSq
Intercept	1	2.5395	0.5526	21.1221	<.0001
Age	1	-0.0183	0.00540	11.4701	0.0007***
Sex	1	0.0241	0.0884	0.0744	0.7850
Injury severity criteria:					
GCS initial	1	-0.0498	0.0266	3.5171	0.0607*
Length of stay in hospital	1	-0.00742	0.00486	2.3375	0.1263
Hemorrhagic shock	1	-0.0335	0.3870	0.0075	0.9310
Laboratory test results:					
Anemia	1	-0.1309	0.2391	0.2995	0.5842
Hyper Creatinine	1	-0.0310	0.1027	0.0908	0.7631

Hypernatremia	1	-0.1952	0.2098	0.8660	0.3521
Hyponatremia	1	-0.00062	0.1809	0.0000	0.9972
Hypokalemia	1	0.1848	0.1800	1.0537	0.3047
Hyperkalemia	1	-0.1575	0.1841	0.7321	0.3922
Hypocalcemia	1	-0.1781	0.1965	0.8211	0.3649
Hypomagnesemia	1	-0.1890	0.1977	0.9139	0.3391
Hypophosphatemia	1	0.2648	0.2175	1.4826	0.2234
Hypoglycemia	1	0.3651	0.3772	0.9369	0.3331
Hyperglycemia	1	-0.0124	0.1823	0.0047	0.9456
Brain CT scan characteristics:					
Marshall grade	1	0.0204	0.0684	0.0890	0.7654
SDH	1	0.0765	0.1055	0.5257	0.4684
SAH	1	0.0728	0.0969	0.5651	0.4522
Contusion	1	0.1887	-0.1024	3.3979	0.0653*
High ICP	1	0.1342	0.1919	0.4889	0.4844
Past medical history:					
Autoimmune / Inflammatory / Rheumatology	1	0.2997	0.2274	1.7370	0.1875
Cardiac risk factors	1	-0.6894	0.1963	12.3276	0.0004***
Neurological disease	1	0.1931	0.1963	0.9673	0.3253
Mechanism of trauma:					
Assault	1	-0.3275	0.3746	0.7641	0.3821
Fall	1	-0.3576	0.1946	3.3753	0.0662*
Associated injuries:					
Chest and pulmonary injury	1	-0.00931	0.2821	0.0011	0.9737
Internal organ injury	1	0.9389	0.5268	3.1766	0.0747+
Skull fracture	1	0.5889	0.2480	5.6382	0.0176**
Non-skull fractures	1	0.4786	0.1878	6.4962	0.0108**
p values in brackets, ****:p<0.001, ***:p<0.01, **:p<0.05, *:p<0.1					

As the final step, we checked for the Variance Inflation Factor (VIF) test in the regression model to assess multicollinearity between dependent and independent variables. The regression model estimates that the coefficients become unstable as the degree of multicollinearity increases, and the standard errors for the coefficients become highly inflated. As a rule of thumb, a variable whose VIF values are greater than 10 may need further investigation. The VIF test in our model shows there is no multicollinearity problem in the regression (mean VIF = 1.60). It means that the variables have little effect on each other and does not create any major multicollinearity problem (Table 8).

Table 8: The degree of multicollinearity

Variable	VIF	Variable	VIF
Fall	3.69	High Creatinine	1.36
Age	2.27	Hypokalemia	1.35
Hypophosphatemia	1.96	Hyperglycemia	1.30
Marshall grade	1.89	Hyponatremia	1.29
GCS initial	1.86	Hypocalcaemia	1.27
SDH (yes/no)	1.86	Hemorrhagic shock	1.26
Assault	1.79	Anemia	1.25
Cardiac risk factors	1.75	Internal organs injury	1.25
Hypomagnesemia	1.66	Hyperkalemia	1.23
Hypernatremia	1.58	Skull fracture	1.23
Contusion (yes/no)	1.53	Chest and pulmonary injury	1.22
SAH (yes/no)	1.48	Sex	1.17
Length of stay in hospital (days)	1.46	Autoimmune/inflammatory/rheumatology disease	1.13
Non-skull fractures	1.45	Hypoglycemia	1.10
High ICP (yes/no)	1.38	Neurologic disease	1.09
Mean VIF	1.60		

We finally examined the effect of various cardiac factors on patients' Glasgow Outcome Score (GOS) (Table 9). The findings indicate an inverse relationship between high serum Creatinine Kinase and Troponin levels and patients' outcomes (P-value = 0.017 and 0.000, respectively). The model also demonstrates that the impact of cardiac arrhythmia and ST-segment changes on GOS levels is significant (P-value = 0.002 and 0.006, respectively). However, no significant relationship was observed between repolarization abnormality and ischemic events on the GOS level (P-value = 0.157 and 0.467, respectively).

Table 9: The effect of cardiac factors on patients' Glasgow Outcome Score (GOS)

Source	SS	df	MS	Number of obs = 916
Model	238.43415	6	39.739025	F(6, 909) = 23.18
Residual	1558.51236	909	1.71453505	Prob > F = 0.0000
Total	1796.94651	915	1.96387596	R-squared = 0.1327
				Adj R-squared = 0.1270
				Root MSE = 1.3094

Independent variable: GOS Number of observations= 916	The LOGISTIC Procedure Analysis of Maximum Likelihood Estimates			
	Coef.	Std. Err.	t	Pr > t
Intercept	5.058692	.087704	57.68	0.000
High Creatine Kinase	-.2484503	.1036291	-2.40	0.017*
High Troponin	-1.073516	.1190458	-9.02	0.000***
Cardiac arrhythmia	-.341085	.1077711	-3.16	0.002**
ST-segment change	-.2703482	.0972119	-2.78	0.006**
Repolarization abnormality	-.1896763	.1338092	-1.42	0.157
Cardiac ischemic event	.119431	.164088	0.73	0.467
p values in brackets, ***: p<0.001, **:p<0.01, *:p<0.05, +:p<0.1				

Variance Inflation Factor (VIF) matrix		
Variable	**VIF**	**1/VIF.**
Repolarization abnormality	1.69	0.591624
Cardiac ischemic event	1.50	0.668425
Cardiac arrhythmia	1.45	0.690455
ST-segment change	1.25	0.801825
High Troponin	1.08	0.925310
High Creatine Kinase	1.05	0.952142
Mean VIF	1.34	

Chapter 5 – Discussion, conclusion, and future directions

In the study that comprised 921 patients with TBI, a large number of the patients developed cardiac dysfunction (588, 63.8%). The incidence of cardiac dysfunction following TBI ranges significantly (varying from 0% to 50%) among current studies (78, 87-91). This disparity can be attributed to variations in the study design, sample size, age of the patient population, TBI severity, and heterogeneity in the definition of cardiac dysfunction. In their study of 59 patients with isolated TBI, Krishnamoorthy et al. found that ECG changes (particularly repolarization abnormalities and prolonged QTc) are common after TBI (64), which is consistent with our findings.

The possible explanations for the high incidence of cardiac events after brain trauma in our study include the following:

1. Some of the patients could have had an undiagnosed cardiac event recently that was not recorded nor captured by history-taking. The precedent undiagnosed cardiac issues could also have led to brain trauma. For instance, a transient ischemic attack in conjunction with a cardiac disease could cause people to fall from heights or become involved in a car accident.
2. For elderly patients or those with pre-existing cardiac conditions, TBI can cause stress, leading to aggravation of their cardiac complications.
3. Cardiac complications could be caused by brain damage alone. For instance, Gilbert and Seiler et al. (61, 62) found left ventricular dysfunction and new regional wall motion abnormalities in a considerable number of brain-dead patients. In another study, Póvoa et al. (73) showed electrical cardiac dysfunction, including repolarization abnormalities, in 37.5% of TBI patients.

This high percentage of cardiac disease in patients with brain trauma can have a detrimental effect on their evaluation and treatment process. For instance, some common treatments for cardiac complications, such as anticoagulants or anti-platelets, cannot be prescribed early in the treatment period to patients with brain trauma. These therapeutic restrictions of cardiac dysfunction in the setting of an acute TBI can make the treatment process more complicated and increase morbidity and mortality.

The prevalence of electrical cardiac dysfunction in patients was higher than ischemic and myocardial disorders. This is due to the fact that echocardiogram was not available for a big portion of patients in our study. The low percentage of myocardial dysfunction could be described to the small number of available echocardiograms for our patients.

There was no statistically significant relationship between the incidence of cardiac dysfunction and cerebral hemorrhage (such as subarachnoid, subdural, and epidural hemorrhage, or even intracranial hypertension). However, a weak relationship was observed between cerebral contusion and cardiac disorder. Due to multicollinearity, it was not possible to include SDH (unilateral/bilateral) and SAH (focal/diffuse) simultaneously in the multiple logistic regression. However, after accounting for multicollinearity, we still did not find any significant relationship between the severity of cerebral hemorrhage and cardiac dysfunction (P-value = 0.925 for SDH unilateral/bilateral and 0.427 for SAH focal/diffuse). This finding is in line with previous studies that did not find any relationship between ECG abnormalities and SDH characteristics, including side, size, or mass effect onto deeper structures (92). The authors' interpretation of this finding is that considering the extra-parenchymal location of SDH, the deep grey matter structures or the insula are not affected directly, except for a large SDH that can cause a mass effect and elevated ICP.

In addition, the findings suggest that there was no significant relationship between higher Marshall degrees (which predict worse outcomes in patients with intracranial injuries) and cardiac complications. Our results show a significant relationship between the occurrence of cardiac dysfunction and lower GCS levels in patients. It means that patients who had lower levels of consciousness on arrival at the hospital and responded less to stimuli were more likely to experience cardiac problems. This finding is consistent with a prospective study of 32 patients with moderate to severe TBI, which found that a low GCS score on admission was one of the risk factors for developing systolic dysfunction (89).

Except for the relationship between GCS levels and cardiac dysfunction, our findings reject the hypothesis regarding a link between the occurrence of cardiac dysfunction and the severity of the intracranial injury. In particular, our findings show that there is no significant relationship between the occurrence of cardiac dysfunction and intracranial hypertension. This could be explained by

the fact that the number of patients with elevated ICP in our research was not that high (58 patients, 6.2%). Therefore, the results are not conclusive due to insufficient data.

Our findings demonstrate that the incidence of cardiac disease is higher in younger patients admitted to the hospital with TBI. This finding is consistent with the results of previous studies, indicating that younger age is a risk factor for developing systolic dysfunction after moderate to severe TBI (93). This result can be explained by the fact that younger people are more likely to suffer from severe injuries and serious traumas (e.g., car accidents, assault, suicide attempts, work accidents, etc.). Another reason could be associated with the greater myocardial catecholamine responsiveness in young people (89).

In assessing the severity of the injury, we were not able to consider the injury severity score and loss of consciousness in our analysis due to a large portion of missing data in our sample for these two variables. We only had initial GCS and Marshall grade to assess the severity of the injury. The incidence of cardiac dysfunction was significantly related to the initial GCS. However, GCS is not an appropriate predictor for the development of cardiac dysfunction in TBI patients due to its low correlation with the actual extent of TBI (94). If sufficient ISS and loss of consciousness data are included, perhaps a strong and meaningful relationship could be found between the injury severity score and cardiac dysfunction.

Our findings suggest the existence of a weak relationship between cardiac dysfunction and falling, which is one of the most common trauma mechanisms.

The findings also provide support for a negative relationship between the history of underlying cardiac risk factors (including diabetes mellitus, hypertension, hyperlipidemia, smoking, and obesity) and cardiac complications among patients. We expect people with cardiac risk factors to be more likely to develop cardiac dysfunction in the future; however, we only examined patients during their hospitalization. The majority of the patients in our study were older adults with a cardiac risk factor and who may not be taking proper care to address their underlying disease. However, when they were in the hospital, all of their vital signs and test results (such as blood sugar, blood pressure, etc.) were closely monitored. This can explain the negative relationship between the existence of underlying cardiac risk factors and cardiac dysfunction incidence, and

demonstrates that more routine care may be needed for patients with cardiac risk factors, for example, considering special clinics to routinely monitor the medical condition of diabetic patients or patients with high blood pressure.

We found a strong relationship between orthopedic problems, including skull fractures and non-skull fractures, and cardiac dysfunction. Our findings further suggest that patients with internal organ injuries are more likely to develop cardiac dysfunction. This can be related to extreme bleeding following orthopedic complications or internal organ injury, which reduces the ventricular preload.

An inverse relationship was noted between high serum creatinine kinase, high troponin levels, cardiac arrhythmia, ST segment changes, and patients' GOS. This means that patients with cardiac changes that resemble ischemia (ST-segment changes) and elevated cardiac enzymes are expected to require a prolonged rehabilitation period before being able to return to work and everyday life. This finding is in line with other studies which demonstrated that electrocardiographic changes following neurologic hemorrhage can influence a patient's outcome. For example, a study of 588 patients with aneurysmal cerebral hemorrhage reported that ischemic-like changes after aneurysmal SAH were correlated with a higher mortality rate (95). In two other studies conducted by Collier and Xin et al., the extent of ECG changes was found to be correlated with brain damage severity. In addition, greater ST and QT changes were associated with a worse neurological outcome (71, 96).

Conclusion and future directions:

The present study provides insights for practitioners treating patients with cardiac problems resulting from TBI. Our analysis would help practitioners identify TBI patients who are prone to developing cardiac dysfunction caused by brain injuries. It provides insights for minimizing the incidence of cardiac complications by considering important factors, such as the patients' age, GCS, orthopedic, and internal organ injuries. Ultimately, by performing electrocardiography and echocardiography for high-risk patients, they can be screened for cardiac dysfunction, thereby helping identify these conditions at an early stage and facilitating the proper treatment of high-risk patients.

This study has a number of limitations. First, exact information on the subtype and severity of the pre-existing cardiovascular diseases could not be obtained in a retrospective study. ECG and echocardiographic data prior to the participants' presentation to the hospital with TBI were only available in certain cases. Therefore, we could not precisely determine how many of the ECG and echocardiographic abnormalities were chronic. The exclusion of patients with a cardiovascular disease based on history may have led to selection bias. We also did not have enough data for a few variables, such as the injury severity score. This limitation could be eliminated by conducting a prospective study. To overcome the limitation of missing data, future research in this avenue can focus on studying cardiac complications in patients with intracranial hypertension in a prospective rather than retrospective way. Another important next step would also be to compare the incidence of cardiac dysfunction between patients with and without TBI.

References

1. Rutland-Brown W, Langlois JA, Thomas KE, Xi YLJTJohtr. Incidence of traumatic brain injury in the United States, 2003. 2006;21(6):544-8.
2. Greenwald BD, Burnett DM, Miller MAJAoPM, Rehabilitation. Congenital and acquired brain injury. 1. Brain injury: epidemiology and pathophysiology. 2003;84(3 Suppl 1):S3-S7.
3. Organization WH. Neurological disorders: public health challenges: World Health Organization; 2006.
4. Silver JM, McAllister TW, Arciniegas DB. Textbook of traumatic brain injury: American Psychiatric Pub; 2018.
5. Faul M, Xu L, Wald M, Coronado V. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths, 2002–2006. March, 2010. 2017.
6. Chesnut R, Carney N, Maynard HJERTA. Rehabilitation for traumatic brain injury. Rockville, Md: Agency for Health Care Policy and Research. 1999;2:1-176.
7. Prevention I. Control: Traumatic Brain Injury. Centers for Disease Control and Prevention Web site. 2011.
8. Zhu G, Wang F, Liu WJJoimr. Classification and prediction of outcome in traumatic brain injury based on computed tomographic imaging. 2009;37(4):983-95.
9. Kondo Y, Abe T, Kohshi K, Tokuda Y, Cook EF, Kukita IJCc. Revised trauma scoring system to predict in-hospital mortality in the emergency department: Glasgow Coma Scale, Age, and Systolic Blood Pressure score. 2011;15(4):R191.
10. Yurkewicz LJJoN. Clinical trials in head injury. 2002;19(5):503.
11. Gilpin D, Nelson PJI. Revised trauma score: a triage tool in the accident and emergency department. 1991;22(1):35-7.
12. Wong TH, Krishnaswamy G, Nadkarni NV, Nguyen HV, Lim GH, Bautista DCT, et al. Combining the new injury severity score with an anatomical polytrauma injury variable predicts mortality better than the new injury severity score and the injury severity score: a retrospective cohort study. 2016;24(1):25.
13. Baker SP, o'Neill B, Haddon Jr W, Long WBJJoT, Surgery AC. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. 1974;14(3):187-96.
14. Civil ID, Schwab CWJJoT, Surgery AC. The Abbreviated Injury Scale, 1985 revision: a condensed chart for clinical use. 1988;28(1):87-90.
15. Brasure M, Lamberty GJ, Sayer NA, Nelson NW, MacDonald R, Ouellette J, et al. Multidisciplinary postacute rehabilitation for moderate to severe traumatic brain injury in adults. 2012.
16. Smits M, Dippel DW, de Haan GG, Dekker HM, Vos PE, Kool DR, et al. Minor head injury: guidelines for the use of CT—a multicenter validation study. 2007;245(3):831-8.
17. Stiell IG, Wells GA, Vandemheen K, Clement C, Lesiuk H, Laupacis A, et al. The Canadian CT Head Rule for patients with minor head injury. 2001;357(9266):1391-6.
18. Taylor CA, Bell JM, Breiding MJ, Xu LJMSS. Traumatic brain injury–related emergency department visits, hospitalizations, and deaths—United States, 2007 and 2013. 2017;66(9):1.
19. Chen H, Iraji A, Jiang X, Lv J, Kou Z, Liu T, editors. Longitudinal analysis of brain recovery after mild traumatic brain injury based on groupwise consistent brain network clusters. International Conference on Medical Image Computing and Computer-Assisted Intervention; 2015: Springer.
20. Haring RS, Narang K, Canner JK, Asemota AO, George BP, Selvarajah S, et al. Traumatic brain injury in the elderly: morbidity and mortality trends and risk factors. 2015;195(1):1-9.

21. Brain TJJA. Rehabilitation of persons with traumatic brain injury. 1999;282:974-83.
22. Finkelstein E, Corso PS, Miller TR. The incidence and economic burden of injuries in the United States: Oxford University Press, USA; 2006.
23. Faul M, Coronado V. Epidemiology of traumatic brain injury. Handbook of clinical neurology. 127: Elsevier; 2015. p. 3-13.
24. Hoofien D, Gilboa A, Vakil E, Donovick PJJBi. Traumatic brain injury (TBI) 10? 20 years later: a comprehensive outcome study of psychiatric symptomatology, cognitive abilities and psychosocial functioning. 2001;15(3):189-209.
25. McGarry LJ, Thompson D, Millham FH, Cowell L, Snyder PJ, Lenderking WR, et al. Outcomes and costs of acute treatment of traumatic brain injury. 2002;53(6):1152-9.
26. Miller T, Zaloshnja E, Hendrie D. The cost of traumatic brain injuries and return on helmet investment in the United States. Neurotrauma and critical care of the brain: Thieme Verlag; 2009. p. 445-60.
27. Rockhill CM, Jaffe K, Zhou C, Fan M-Y, Katon W, Fann JRJJon. Health care costs associated with traumatic brain injury and psychiatric illness in adults. 2012;29(6):1038-46.
28. Vangel Jr SJ, Rapport LJ, Hanks RA, Black KLJAjopm, rehabilitation. Long-term medical care utilization and costs among traumatic brain injury survivors. 2005;84(3):153-60.
29. Information CIfH. National health expenditure trends, 1975 to 2011. CIHI Ottawa, ON; 2011.
30. Alvin Jr M, Allen RW, James LGJN. Psychosocial functioning at 1 month after head injury. 1984;14(4):393-9.
31. Annegers JF, Hauser WA, Coan SP, Rocca WAJNEJoM. A population-based study of seizures after traumatic brain injuries. 1998;338(1):20-4.
32. DeKosky ST, Blennow K, Ikonomovic MD, Gandy SJNRN. Acute and chronic traumatic encephalopathies: pathogenesis and biomarkers. 2013;9(4):192.
33. Lye TC, Shores EAJNr. Traumatic brain injury as a risk factor for Alzheimer's disease: a review. 2000;10(2):115-29.
34. Masel BE, Scheibel RS, Kimbark T, Kuna STJAopm, rehabilitation. Excessive daytime sleepiness in adults with brain injuries. 2001;82(11):1526-32.
35. Vespa PMJCoicc. Hormonal dysfunction in neurocritical patients. 2013;19(2):107-12.
36. Selassie AW, Zaloshnja E, Langlois JA, Miller T, Jones P, Steiner CJTJohtr. Incidence of long-term disability following traumatic brain injury hospitalization, United States, 2003. 2008;23(2):123-31.
37. Ashman TA, Spielman LA, Hibbard MR, Silver JM, Chandna T, Gordon WAJAopm, et al. Psychiatric challenges in the first 6 years after traumatic brain injury: cross-sequential analyses of Axis I disorders. 2004;85:36-42.
38. Binder LMJJoC, Neuropsychology E. Persisting symptoms after mild head injury: A review of the postconcussive syndrome. 1986;8(4):323-46.
39. Kersel DA, Marsh NV, Havill JH, Sleigh JWJBi. Neuropsychological functioning during the year following severe traumatic brain injury. 2001;15(4):283-96.
40. KRAUS JF, Black MA, Hessol N, Ley P, Rokaw W, Sullivan C, et al. The incidence of acute brain injury and serious impairment in a defined population. 1984;119(2):186-201.
41. Adams JH, Doyle D, Ford I, Gennarelli T, Graham D, McLellan DJH. Diffuse axonal injury in head injury: definition, diagnosis and grading. 1989;15(1):49-59.
42. Adams JH, Graham D, Doyle D, Lawrence A, McLellan DJTL. Diffuse axonal injury in head injuries caused by a fall. 1984;324(8417-8418):1420-2.
43. Blumbergs PC, Jones NR, North JBJJoN, Neurosurgery, Psychiatry. Diffuse axonal injury in head trauma. 1989;52(7):838-41.
44. Gennarelli TA, Thibault LE, Adams JH, Graham DI, Thompson CJ, Marcincin RPJAoNOJotANA, et al. Diffuse axonal injury and traumatic coma in the primate. 1982;12(6):564-74.

45. Grady MS, McLaughlin MR, Christman CW, Valadka AB, Fligner CL, Povlishock JTJJoN, et al. The use of antibodies targeted against the neurofilament subunits for the detection of diffuse axonal injury in humans. 1993;52(2):143-52.
46. JTaSJ P. Head Trauma: Basic, preclinical, and clinical directions. John Wiley abd Sons I (ed) Traumatic axonal injury. New York; 2002.
47. Tian Y, Salsbery B, Wang M, Yuan H, Yang J, Zhao Z, et al. Brain-derived microparticles induce systemic coagulation. 2015.
48. Marion DW. Evidenced-based guidelines for traumatic brain injuries. Guiding Neurosurgery by Evidence. 19: Karger Publishers; 2006. p. 171-96.
49. Šedý J, Kuneš J, Zicha JJJon. Pathogenetic mechanisms of neurogenic pulmonary edema. 2015;32(15):1135-45.
50. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ESJPr. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. 2000;52(4):595-638.
51. Karamanos E, Teixeira PG, Sivrikoz E, Varga S, Chouliaras K, Okoye O, et al. Intracranial pressure versus cerebral perfusion pressure as a marker of outcomes in severe head injury: a prospective evaluation. 2014;208(3):363-71.
52. Kaufman HH, Timberlake G, Voelker J, Pait TGJMCoNA. Medical complications of head injury. 1993;77(1):43-60.
53. Baguley IJ, Perkes IE, Fernandez-Ortega J-F, Rabinstein AA, Dolce G, Hendricks HT, et al. Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. 2014;31(17):1515-20.
54. Perkes IE, Menon DK, Nott MT, Baguley IJJBI. Paroxysmal sympathetic hyperactivity after acquired brain injury: a review of diagnostic criteria. 2011;25(10):925-32.
55. Hinson HE, Sheth KNJCoicc. Manifestations of the hyperadrenergic state after acute brain injury. 2012;18(2):139-45.
56. Rabinstein AA, Benarroch EEJCTOiN. Treatment of paroxysmal sympathetic hyperactivity. 2008;10(2):151-7.
57. Rabinstein AAJNr. Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. 2007;29(7):680-2.
58. Zygun DA, Kortbeek JB, Fick GH, Laupland KB, Doig CJJCcm. Non-neurologic organ dysfunction in severe traumatic brain injury. 2005;33(3):654-60.
59. Ako J, Sudhir K, Farouque HO, Honda Y, Fitzgerald PJJTAjom. Transient left ventricular dysfunction under severe stress: brain-heart relationship revisited. 2006;119(1):10-7.
60. Mashaly HA, Provencio JJJCCjom. Inflammation as a link between brain injury and heart damage: the model of subarachnoid hemorrhage. 2008;75(2):S26.
61. Gilbert EM, Krueger SK, Murray JL, Renlund DG, O'Connell JB, Gay WA, et al. Echocardiographic evaluation of potential cardiac transplant donors. 1988;95(6):1003-7.
62. Seiler C, Laske A, Gallino A, Turina M, Jenni RJTJoh, Transplantation lttopotISfH. Echocardiographic evaluation of left ventricular wall motion before and after heart transplantation. 1992;11(5):867-74.
63. Fernandez-Ortega JF, Prieto-Palomino MA, Garcia-Caballero M, Galeas-Lopez JL, Quesada-Garcia G, Baguley IJJJon. Paroxysmal sympathetic hyperactivity after traumatic brain injury: clinical and prognostic implications. 2012;29(7):1364-70.
64. Krishnamoorthy V, Rowhani-Rahbar A, Chaikittisilpa N, Gibbons EF, Rivara FP, Temkin NR, et al. Association of early hemodynamic profile and the development of systolic dysfunction following traumatic brain injury. 2017;26(3):379-87.
65. Sharma D, Brown MJ, Curry P, Noda S, Chesnut RM, Vavilala MSJJona. Prevalence and risk factors for intraoperative hypotension during craniotomy for traumatic brain injury. 2012;24(3):178.

66. Pietropaoli JA, Rogers FB, Shackford SR, Wald SL, Schmoker JD, Zhuang JJTJot. The deleterious effects of intraoperative hypotension on outcome in patients with severe head injuries. 1992;33(3):403-7.
67. Zafar SN, Millham FH, Chang Y, Fikry K, Alam HB, King DR, et al. Presenting blood pressure in traumatic brain injury: a bimodal distribution of death. 2011;71(5):1179-84.
68. Schrader H, Hall C, Zwetnow NJAns. Effects of prolonged supratentorial mass expansion on regional blood flow and cardiovascular parameters during the Cushing response. 1985;72(3):283-94.
69. Shanlin RJ, Sole MJ, Rahimifar M, Tator CH, Factor SMJJotACoC. Increased intracranial pressure elicils hypertension, increased sympathetic activity, electrocardiographic abnormalities and myocardial damage in rats. 1988;12(3):727-36.
70. Shivalkar B, Van Loon J, Wieland W, Tjandra-Maga TB, Borgers M, Plets C, et al. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. 1993;87(1):230-9.
71. Xin F, DU F-h, Tian J-pJCmj. The electrocardiographic changes in acute brain injury patients. 2012;125(19):3430-3.
72. Krishnamoorthy V, Prathep S, Sharma D, Gibbons E, Vavilala MSJIjoccmp-r, official publication of Indian Society of Critical Care Medicine. Association between electrocardiographic findings and cardiac dysfunction in adult isolated traumatic brain injury. 2014;18(9):570.
73. Póvoa R, Cavichio L, Almeida ALd, Viotti D, Ferreira C, Galvão L, et al. Electrocardiographic abnormalities in neurological diseases. 2003;80(4):355-8.
74. Hackenberry L, Miner ME, Rea GL, Woo J, Graham SHJCcm. Biochemical evidence of myocardial injury after severe head trauma. 1982;10(10):641-4.
75. Singla S, Garg P, Mehta RJJotIMA. Electrocardiographic changes in craniocerebral trauma--could they serve as prognostic indicators? 2002;100(3):188-90.
76. Hays A, Diringer MNJN. Elevated troponin levels are associated with higher mortality following intracerebral hemorrhage. 2006;66(9):1330-4.
77. Garrett MC, Komotar RJ, Starke RM, Doshi D, Otten ML, Connolly ESJNc. Elevated troponin levels are predictive of mortality in surgical intracerebral hemorrhage patients. 2010;12(2):199-203.
78. Prathep S, Sharma D, Hallman M, Joffe A, Krishnamoorthy V, Mackensen GB, et al. Preliminary report on cardiac dysfunction after isolated traumatic brain injury. 2014;42(1).
79. Foundation BT, Surgeons AAoN. Management and prognosis of severe traumatic brain injury: Amer Assn of Neurological Surg; 2000.
80. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. 1993;34(2):216-22.
81. Murray GD, Butcher I, McHugh GS, Lu J, Mushkudiani NA, Maas AI, et al. Multivariable prognostic analysis in traumatic brain injury: results from the IMPACT study. Journal of neurotrauma. 2007;24(2):329-37.
82. Marshall LF, Gautille T, Klauber MR, Eisenberg HM, Jane JA, Luerssen TG, et al. The outcome of severe closed head injury. 1991;75(Supplement):S28-S36.
83. Waxman K, Sundine MJ, Young RF. Is early prediction of outcome in severe head injury possible? Archives of surgery. 1991;126(10):1237-42.
84. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. 2006;47(12):2357-63.
85. Allison PD. Logistic regression using SAS: Theory and application: SAS institute; 2012.
86. Hosmer DW. Lemeshow S. Applied logistic regression. New York. 2000.
87. Cuisinier A, Maufrais C, Payen J-F, Nottin S, Walther G, Bouzat PJSjot, resuscitation, et al. Myocardial function at the early phase of traumatic brain injury: a prospective controlled study. 2016;24(1):129.

88. Hasanin A, Kamal A, Amin S, Zakaria D, El Sayed R, Mahmoud K, et al. Incidence and outcome of cardiac injury in patients with severe head trauma. 2016;24(1):1-6.
89. Krishnamoorthy V, Rowhani-Rahbar A, Gibbons EF, Rivara FP, Temkin NR, Pontius C, et al. Early systolic dysfunction following traumatic brain injury: a cohort study. 2017;45(6):1028.
90. Krishnamoorthy V, Sharma D, Prathep S, Vavilala MSJCria. Myocardial dysfunction in acute traumatic brain injury relieved by surgical decompression. 2013;2013.
91. Serri K, El Rayes M, Giraldeau G, Williamson D, Bernard FJSjot, resuscitation, medicine e. Traumatic brain injury is not associated with significant myocardial dysfunction: an observational pilot study. 2016;24(1):31.
92. Busl KM, Raju M, Ouyang B, Garg RK, Temes REJNc. Cardiac abnormalities in patients with acute subdural hemorrhage. 2013;19(2):176-82.
93. Venkata C, Kasal JJCm, research. Cardiac dysfunction in adult patients with traumatic brain injury: a prospective cohort study. 2018;16(3-4):57-65.
94. Grote S, Böcker W, Mutschler W, Bouillon B, Lefering RJJon. Diagnostic value of the Glasgow Coma Scale for traumatic brain injury in 18,002 patients with severe multiple injuries. 2011;28(4):527-34.
95. Coghlan LA, Hindman BJ, Bayman EO, Banki NM, Gelb AW, Todd MM, Zaroff JG, IHAST Investigators. Independent associations between electrocardiographic abnormalities and outcomes in patients with aneurysmal subarachnoid hemorrhage: findings from the intraoperative hypothermia aneurysm surgery trial. Stroke. 2009 Feb 1;40(2):412-8.
96. Collier BR, Miller SL, Kramer GS, Balon JA, Gonzalez III LS. Traumatic subarachnoid hemorrhage and QTc prolongation. Journal of Neurosurgical Anesthesiology. 2004 Jul 1;16(3):196-200.