MYOCARDIAL DYSFUNCTION IN POLYTRAUMA

Bekbossynova Makhabbat S.[1], Batpen Arman N.[2], Mukarov Murat A.[1], Shaktybek Zhanerke M.[1], Sugralimova Madina M.[1], Mamasaliev Bakbergen M.[3], Lukbanov Meirbek K.[4], Kanabekova Perizat S.[5], Kozhakhmetova Anar I.[2]

[1]"University Medical Center" Corporate Fund, Astana, Kazakhstan
[2] National Scientific Center for Traumatology and Orthopedics named after Academician N.D. Batpenova, Astana, Kazakhstan
[3] Multidisciplinary City Hospital No. 2, Astana, Kazakhstan
[4] Multidisciplinary City Hospital No. 1, Astana, Kazakhstan
[5] Nazarbayev University, Astana, Kazakhstan

DOI:10.35805/BSK2024III008
Bekbossynova M. S.
https://orcid.org/0000-0003-2834-617X
Batpen A.N.,
https://orcid.org/0000-0002-6661-8132
Mukarov M.A.
https://orcid.org/0000-0003-2854-1952
Kanabekova P.S.,
https://orcid.org/0000-0001-5753-4271
Shaktybek Z.M.
https://orcid.org/0009-0002-3726-060X
Sugralimova M.M.
https://orcid.org/0000-0001-7388-5717
Mamasaliyev B.M.
https://orcid.org/0009-0002-6257-6323
Lukbanov M.K.
https://orcid.org0009-0008-7887-4994
Kozhakhmetova A.I.
https://orcid.org/0000-0001-5580-002X

recieved: 03.09.2024
accepted: 13.09.2024

Author for correspondence:
Kozhakhmetova A.I.,
General Clinical Department Physician, National Scientific Center of Traumatology and Orthopedics named after Academician N.D. Batpenov, Astana, Kazakhstan
ORCID 0000-0001-5580-002X Postal code: 010000
Address: Abylai Khan 15
Phone: +7 707 390 20 18
E-mail: anaramalika8324@gmail
ORCID: 0000-0001-5580-002X

Conflict of interest:
The authors declare no potential conflict of interest requiring disclosure in this article.

Keywords:
trauma; myocardial dysfunction; immunology.

Abstract

Trauma remains one of the leading causes of mortality worldwide, particularly among the young population. A significant number of people die within the first 48 hours due to acute cardiovascular pathology. Cardiac injury is a significant predictor of adverse outcomes following multiple trauma, associated with poor prognosis and prolonged hospitalization. Systemic elevation of cardiac troponin levels is linked to survival, the severity of trauma, and catecholamine consumption in patients after multiple trauma. Clinical signs of the so-called "commotio cordis" include arrhythmias, such as ventricular fibrillation and sudden cardiac arrest, as well as wall motion abnormalities. In trauma patients with inadequate hypotension and a lack of adequate response to fluid therapy, the possibility of cardiac injury should be considered. Therefore, a combination of electrocardiography, echocardiography, and the systemic determination of cardiomyocyte injury markers, such as troponin, appears to be an appropriate diagnostic method for identifying cardiac dysfunction after trauma. However, the mechanisms of post-traumatic cardiac dysfunction continue to be actively studied. The aim of this review is to discuss cardiac injury following trauma, focusing on the mechanisms of post-traumatic cardiac dysfunction related to inflammation and complement activation. The review illustrates the causal relationship between cardiac dysfunction and blunt chest trauma, multiple trauma, and hemorrhagic shock.

Introduction

Polytrauma, a condition in which a patient sustains multiple injuries affecting several organs or systems, is a leading cause of mortality among young people.[1] According to the World Health Organization (WHO) as of December 13, 2023, road traffic accidents are the primary cause of polytrauma, resulting in approximately 1.19 million deaths annually and causing disability in 20 to 50 million people.[2] In the early period following combined tissue damage and shock, hemostasis is disrupted, leading to the development of traumatic coagulopathy and massive bleeding. Many survivors of massive bleeding experience organ dysfunction, including cardiac dysfunction. Even in the absence of direct cardiac injury in polytrauma, recent studies indicate the development of asymptomatic myocardial dysfunction within specific time frames—1 to 3 days, 1 to 6 months after the injury—often associated with the development of systemic inflammation or the so-called "double hit" theory.[3] The "double hit" theory considers early and late complications of polytrauma through the lens of primary soft tissue and organ damage; secondarily, it considers the Systemic Inflammatory Response Syndrome (SIRS), respiratory distress,

coagulopathy, acidosis, ischemia/reperfusion syndrome, and hemodynamic instability.[3,4] The severity of post-traumatic cardiac dysfunction is determined not only by the degree of mechanical myocardial contusion but also by damage caused by the release of damage-associated molecular patterns (DAMPs), cytokines, complementopathy, and the activation of the acquired immune response.[5] This reaction begins within 30 minutes after severe trauma and represents an inflammatory response to blood loss and tissue damage. SIRS arises due to the release of endogenous factors known as DAMPs ("alarmins") following tissue injury. These molecules are released from activated immune cells or necrotic cells and trigger a potent inflammatory response. DAMPs activate immune cells and complement, leading to the rapid production of inflammatory mediators such as interleukins, resulting in a systemic inflammatory response.[3]

This issue remains unresolved, and patients after polytrauma are often not monitored on an outpatient basis by specialists, nor do they receive preventive treatment, leading to late presentation with cardiovascular pathology (CVD), which can result in the development of heart failure (HF). Therefore, the aim of this literature review is to study myocardial dysfunctions in polytrauma, associated with both direct cardiac injury and secondary injury due to systemic inflammation. Specifically, this review focuses on the study of all DAMPs associated with the development of heart failure.

Materials and Methods

Literature Search. To prepare this review article, literature search on the topic of myocardial dysfunction in polytrauma was conducted. The search included publications from PubMed and Google Scholar, Elibrary databases. The search was carried out using combinations of keywords such as "myocardial dysfunction", "heart dysfunction", "polytrauma", "immunology".

Inclusion criteria: articles published from 2014 to 2024, defined as original research articles, review articles, meta-analyses, clinical guidelines recommendations written in English language.

Exclusion criteria: non-original articles; case reports; articles without access to full texts; and duplicate articles.

As a result of the search, full text of 80 publications was reviewed. Selection of articles was made according to the inclusion and exclusion criteria. 17 articles which have met all the criteria were analyzed.

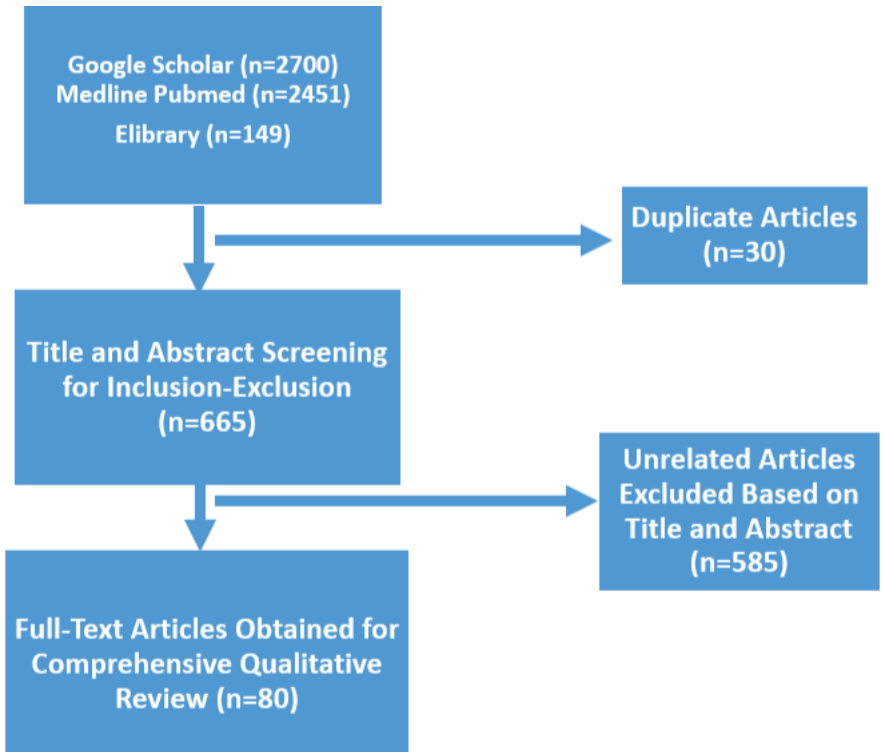

Figure 1.
Article selection algorithm for review.

Data Collection and Analysis. All selected articles were analyzed and information about mechanisms of myocardial dysfunction, mechanism of the immune response, clinicalconsequences of myocardial dysfunction in polytrauma were added to the results and discussion part.

In addition, meta-analysis was conducted following PRISMA guidelines to evaluate the association between elevated Troponin 1 levels and myocardial dysfunction. Literature search was performed using PubMed, covering publications from 2019 to 2023. Included studies were prospective and retrospective cohort, community-based cohort and reduced trail designs involving patients aged 18 and older, with sufficient data to calculate effect sizes. Studies that were case reports, reviews, non-human, or lacked necessary data were excluded. Two independent reviewers extracted data on study characteristics, population details, and Troponin 1 measurements. Statistical analyses involved calculating pooled effect sizes using a random-effects model, assessing heterogeneity with the I^2 statistic and performed by using R-studio software. The search in Pubmed returned 713 results, from which 144 full-text articles were screened covering the last 5 years. After applying the inclusion and exclusion criteria, seven studies describing the effect of Troponin 1 on heart failure were included in this meta-analysis.

Results

Table 1.
Characteristics of studies included in meta-analysis.

Author	Publication year	Sample size	Gender (M)	Study design	Event
Yan et al. [6]	2020	48.455	23.321	Prospective population-based cohort study	Heart failure
Berge et al. [7]	2021	314	163	Prospective cohort	Heart failure
Zhang et al. [8]	2022	6487	4361	Retrospective cohort	Coronary stenosis
Firth et al.[9]	2019	561	332	Prospective	Cardiovascular events
Innocenti et al.[10]	2021	325	N/A	Prospective	Mortality
Packer et al.[11]	2021	3636	2767	EMPEROR-Reduced trial	Heart failure
Suthahar et al.[12]	2020	22.756	12.087	community-based cohorts	Heart failure

Table 2.
Total troponin and hazard ratio results

	Heart failure				
	Troponin mean (ng/l)	Hazard ratio	95% CI low	95% CI high	p-value
Yan et al.,[6]*2020*	2.3	1.42	1.31	1.53	<0.001
Bergeet al.,[7]*2021*	13	1.30	1.07	1.58	<0.009
Zhang et al.,[8] *2022*	9	1.14	1.11	1.17	<0.05
Firth et al.,[9]*2019*	0.068	2.15	1.29	3.58	<0.003
Innocenti et al.,[10] *2021*	NA	3.24	1.72	6.11	<0.001
Packer et al.,[11] *2021*	14	1.71	1.22	2.41	<0.001
Suthahar et al.,[12] *2020*	NA	1.30	1.22	1.43	<0.05

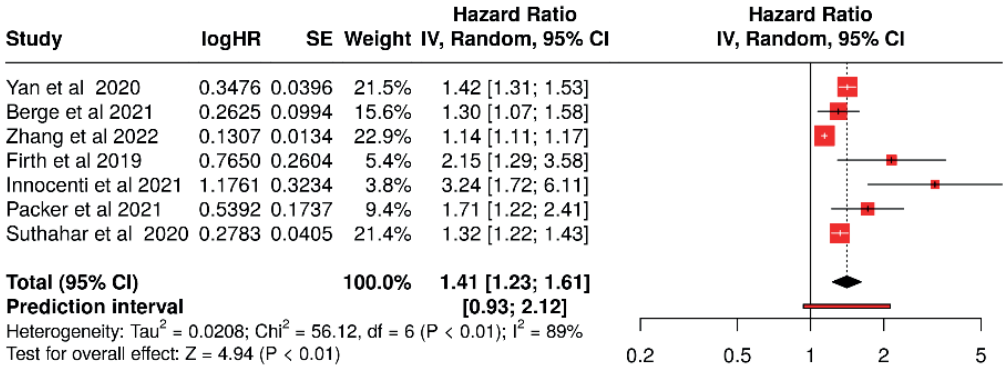

Figure 2.
Forest plot showing association between Troponin 1 and heart failure.

All hazard ratios calculated in studies were found to be greater than 1.0, which reflect the significance of the correlation. According to Figure 2 this meta-analysis suggests that elevated Troponin 1 increases the risk of heart failure by 41% on average (HR = 1.41), with a high degree of variability (heterogeneity) among the study results. The overall effect is statistically significant.

In this meta-analysis, the correlation between the increased level of troponin and the risk of heart failure highlights the potential of Troponin 1 as a biomarker for early detection and risk stratification in patients. The statistical significance of the overall effect, despite the heterogeneity among studies, suggests a robust association across diverse populations and study designs.

Discussion

Traumatic cardiac injury can present with a wide range of clinical manifestations, from asymptomatic conditions to near-fatal states. Studies of traumatic cardiac injury in pigs have shown reversible reductions in ejection fraction and fractional shortening.[13] In addition to these changes in systolic function, trauma may also affect diastolic function. To assess both systolic and diastolic functions after trauma, further research using echocardiographic measurements is required.

In addition to impairments in systolic and diastolic function, arrhythmias have been documented following trauma. Analysis of data from all trauma patients at a Level I trauma center accredited by the American College of Surgeons revealed that, over a period of two years, 258 patients were diagnosed with newly onset atrial fibrillation (AF) following trauma.[14] Literature on commotio cordis cites numerous cases of sudden cardiac death caused by a ball striking the chest. Blunt chest trauma can lead to ventricular fibrillation, which in turn can cause sudden cardiac death.[15] Besides direct impact on the heart, there are reports of arrhythmias developing in patients following trauma not associated with chest impact. For example, one case involved a child who experienced QTc interval prolongation after a mild concussion.[16] In addition to systolic and diastolic dysfunction and arrhythmias, valve insufficiency has also been noted following trauma. For instance, chordae tendineae rupture caused by trauma led to acute and severe mitral regurgitation, as described in cases following motor vehicle accidents.[17] Several published reports on traumatic valve injury have demonstrated a wide range of symptoms: some patients could remain asymptomatic for many years, while others became hemodynamically unstable immediately after the injury.[18,19] Valve injuries occurred as a result of direct high-energy chest trauma, such as motor vehicle accidents and falls from heights. The most likely mechanism is a sudden deceleration or compression of the blood column in the heart during a vulnerable phase of valve operation.[18] In conclusion, it should be noted that the topic of traumatic valve injuries may be underappreciated in contemporary studies of cardiac contusions due to the wide range of symptoms and the complexity of diagnosing them.

Biochemical Markers of Cardiac Injury. During tissue damage, various molecules are released into circulation that can indicate damage to that specific tissue, serving as markers. In myocardial injury, various proteins and DNA molecules are released, which were previous-

ly markers for other acute conditions, such as myocardial infarction. For example, troponins (T, C, I) are small proteins that play a key role in calcium-regulated cardiac muscle contraction. In critically ill patients, elevated levels of cardiac troponin T are associated with increased in-hospital mortality; however, there is no correlation with long-term survival differences.[20] Additionally, in ICU patients following multiple trauma, elevated troponin T levels correlated with ISS and AIS scores, as well as with survival and catecholamine needs.[13] After trauma, systemic elevation of troponin was associated with myocardial contusion in 15–45% of cases. Systemic elevation of troponin in trauma patients has been described as a sensitive biomarker for detecting cardiac complications, especially when combined with electrocardiogram.[20] Recently published reports have documented elevated troponin levels in various experimental trauma models and species, including mice following multiple trauma,[21] asphyxia and hemorrhage in newborn piglets,[22] and multiple trauma with hemorrhagic shock in pigs.[22]

Before it was established that damaged cardiomyocyte membranes contribute to the release of troponin, cell necrosis was considered the only mechanism for its release.[23] Besides necrosis and apoptosis, there is growing evidence of various possible mechanisms for reversible systemic elevation of troponin.[23] This reversible cardiomyocyte (CM) damage has been associated with the release of microparticles, membrane vesicles, and increased cell membrane permeability.[24,25] Fragmented cardiac troponin is expected to result from irreversible cardiomyocyte damage, while systemic elevation of undamaged troponin is associated with reversible damage.[26] Structurally bound troponin undergoes degradation by calpains, which are activated by increased intracellular calcium or changes in pH levels.[23] Various damage-associated molecular patterns (DAMPs), such as extracellular histones, are known to induce increased intracellular calcium in cardiomyocytes, occurring due to increased membrane permeability or the formation of reactive oxygen species (ROS).[13] Additionally, there is evidence that troponin I directly affects the heart; it has been shown to cause inflammatory heart disease in mice.[27]

Another myocardial damage biomarker is HFABP, which is detected in the bloodstream earlier after myocardial infarction compared to troponin.[28] Systemic elevation of HFABP was recently observed at early stages following experimental multiple trauma in pigs.[13] Clinical studies among polytrauma patients revealed increased levels of HFABP, as well as other proteins such as growth/differentiation factor 15 (GDF-15) and the surface receptor of the urokinase-type plasminogen activator (uPAR). Specifically, the concentrations of all three proteins in plasma were significantly higher in the subgroup of polytrauma patients with high troponin levels compared to healthy individuals. However, while the expression of HFABP decreased over time, the expression of uPAR and GDF-15 was higher at 24 hours compared to the time of admission.[29]

Inflammation-Linked Heart Damage Indicators. In response to early systemic inflammatory reactions, accompanied by the release of damage-associated molecular patterns (DAMPs) into the bloodstream,[30] the release of high mobility group box 1 (HMGB-1) protein has been observed in humans within 30 minutes of injury,[31] and it has been associated with injury severity, complement system activation, and mortality.[31] Additionally, in experimental models of multiple trauma, including chest trauma with hemorrhagic shock in pigs, elevated levels of HMGB-1 have been documented.[32] It is known that HMGB-1 can induce cardiomyocyte dysfunction, including cases of cardiac hypertrophy and heart failure,[33] as well as ischemia and myocardial reperfusion injury.[34] HMGB-1 also functions as a secondary DAMP molecule, interacting with extracellular histones through toll-like receptors (TLRs), particularly TLR-2, TLR-4, and TLR-9. Extracellular histones have been linked to traumatic lung injury and acute respiratory distress syndrome in humans,[35,36] as well as septic cardiomyopathy in mice.[13] DAMPs can contribute to increased intracellular calcium concentrations in cavernosal malformations, which are

associated with bradycardia and bigeminy.[13] Systemic release of circulating histones has been observed in rats with experimental blunt chest trauma, as well as in pigs and mice with multiple trauma.[13,21,37] Following systemic administration of extracellular histones in mice, there was an increase in inflammatory cytokines such as TNF, IL-1ß, IL-6, and IL-10.[38] Additionally, HMGB-1 has been linked to the production of inflammatory cytokines,[39] including TNF, IL-1ß, and IL-6.[40] Circulating histones accumulate in the heart and are associated with cardiomyocyte dysfunction, as well as dose-dependent production of reactive oxygen species (ROS) and increased intracellular calcium.[13] Histones also decrease mitochondrial membrane potential and ATP production in a dose-dependent manner, leading to reduced cardiomyocyte contractility due to energy deficiency.[13,41] TLR-4 has been found to play a key role in the development of cardiac dysfunction after trauma; its absence contributed to improved cardiac function in mice with traumatic hemorrhagic shock.[42]

Another molecule released by the heart in response to tissue damage is midkine. Midkine is an inflammatory cytokine and a heparin-binding growth and differentiation factor.[43] Systemic elevation of midkine levels has been observed following bone fractures, burns, and traumatic spinal cord injury.[43,44] After release following a fracture, midkine remains elevated in patients for up to 42 days.[44] Another mechanism through which midkine exerts damaging effects on human cardiomyocytes has been described. In this context, midkine caused significant changes in calcium handling by cells, manifested as increased amplitude of calcium delta peaks, reduced frequency of calcium peaks, and enhanced mRNA production of calcium-handling proteins such as sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA) and Na+/Ca2+ exchanger.[43]. Besides its effect on contractility through intracellular calcium changes, midkine also impaired mitochondrial function in cardiomyocytes and induced apoptosis.[43]

Changes in Complement System Activation. During experimental sepsis and following burn trauma, it has been found that the complement activation product, complement factor (C5a), causes significant dysfunction in cavernous malformations both in vitro and in vivo by interacting with C5a receptors.[41] Another study of spinal cord injury due to contusion in the mouse model, C5a caused most damage in the acute phase, while it had some protective utility later with contribution to hypertrophy and glial scar formation.[45]

In trauma patients, complement system activation has been noted with increased levels of ComC.[46] ComC activation leads to activation of other complement elements, which also is associated with the development of acute respiratory distress syndrome and multiple organ failure.[46] In contrast to the threefold increase in C5a receptor (C5aR) expression in the myocardium after ischemia observed in experimental blunt chest trauma in mice,[37] experimental asphyxia and hemorrhage in piglets,[22] and experimental multiple trauma in pigs, C5a receptor factor (C5aR1) expression in the left ventricle was reduced.[13] This decrease in C5aR1 levels may be due to receptor internalization following binding with C5a, which significantly increases after trauma in animal models.[47]

Systemic consumption of both classical and alternative complement system factors was demonstrated using the CH-50 test in pigs 6 hours after multiple trauma.[48] Additionally, neutrophils migrate to cardiac tissue following trauma, as shown in experimental blunt chest trauma in mice.[37] Neutrophil serine protease cleaves C5aR1, leading to its reduction after trauma.[49] In case with C5aR2, its loss mouse model with spinal cord trauma caused worse outcomes.[50] Furthermore, in the inflammatory state of CLP sepsis, the interaction of C5a with C5aR1 leads to an excess of cytosolic ROS and Ca2+i in cardiomyocytes.[41,51]

A biochemical marker is considered high-quality if it is detectable at early stages, measurable in peripheral materials such as blood or urine, sensitive, correlates with the severity of the patient's condition, and is analytically stable and measurable over time after the event.[52] A common issue with many markers is sensitivity, as these mole-

cules can be released by other organs. For example, lactate dehydrogenase (LDH) has been described as a promising indicator for screening chest trauma in patients with polytrauma. However, LDH is an enzyme found in many tissues, including the heart, lungs, liver, kidneys, skeletal muscles, and blood cells.[53] Therefore, elevated LDH levels in polytrauma patients require the exclusion of other sources of this enzyme.

Thus, many markers associated with cardiac injury need further investigation. For instance, GDF-15 has proven to be effective for predicting outcomes in polytrauma patients. This protein showed moderate correlation with ICU stay and hospital stay, and strong correlation with ventilation time and catecholamine requirements.[29] However, GDF-15 is expressed not only in the heart but also in various human tissues, including the placenta, kidneys, lungs, pancreas, skeletal muscles, liver, and brain. In this study, the authors relied on elevated GDF-15 levels in patients with high troponin levels.[29] Hence, clinical recommendations and protocols should consider the conditions under which specific markers were studied and their levels.

Additionally, the influence of other factors must be excluded. For instance, the correlation of complement factors C3a and C5a with the development of acute respiratory distress syndrome and multiple organ failure does not imply that these complications are solely caused by elevated levels of these factors. It is a multifactorial phenomenon influenced by the severity of the condition, the combination of injuries in polytrauma, the patient's pre-existing health status, and other factors. Therefore, when identifying certain molecules as cardiodepressive, meaning they impair cardiomyocyte function, it is essential to exclude the influence of other factors on cellular status.

Currently, the determination of molecular patterns associated with cardiac damage and other markers is not conducted at a clinical level. Existing protocols rely on troponin levels, ECG, and echocardiography when necessary, and incorporating additional markers is a lengthy process dependent on extensive research in this area.

Limitations. The limitations of this article include the use of a mixed method combining systematic review and meta-analysis. This could potentially cause the issue in analyzing the findings from diverse study designs. Additionally, the meta-analysis was performed only on the association between Troponin 1 and heart failure, while other relevant biomarkers were not analyzed. As a result, there can be potentially missing important markers of the condition. The relatively small number of sources included may also limit the generalizability of our findings to the broader population. Further research is needed to explore heart failure in more diverse populations and to examine additional biomarkers.

Conclusion

Studies show that polytrauma significantly impacts the development of myocardial dysfunction, which can arise both directly from heart damage and secondarily due to systemic inflammatory response. Various biomarkers, such as troponins and HFABP, help assess the extent of cardiac injury but remain insufficiently studied. Inflammatory processes and complement system activation play a crucial role in the development of myocardial dysfunction and require further investigation to improve the diagnosis and treatment of polytrauma patients. These results highlight the need for developing preventive and therapeutic measures aimed at minimizing cardiac complications in this patient group.

Acknowledgement: We would like to express our sincere gratitude to the "University Medical Center" Corporate Fund, the National Scientific Center for Traumatology and Orthopedics named after Academician N.D. Batpenov, Multidisciplinary City Hospital No. 2, Astana, and Multidisciplinary City Hospital No. 1, Astana, as well as the entire research team.

Authors' Contributions: M.B. and A.B: conceptualization; A.K.: methodology; M.L., Z.S. and P.K.: data collection, software; M.B., M.M. and A.B.: validation; M.S.: formal analysis; P.K.: investigation; B.M.: resources; M.B., A.K., M.M. and A.B.: writing original / draft preparation; A.K., M.M, P.K., M.B: writing review and editing; P.K., M.B.: visualization, supervision; M.B, Z.S.: project administra-

tion, funding acquisition.

Funding: This study was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan (grant No. IRN AP19678310).

References

1. Iyengar KP, Venkatesan AS, Jain VK, Shashidhara MK, Elbana H, Botchu R. Risks in the Management of Polytrauma Patients: Clinical Insights. Orthop Res Rev. 2023;15:27-38. doi:10.2147/ORR.S340532
2. Ahmed SK, Mohammed MG, Abdulqadir SO, et al. Road traffic accidental injuries and deaths: A neglected global health issue. Health Sci Rep. May 2023;6(5):e1240. doi:10.1002/hsr2.1240
3. Lord JM, Midwinter MJ, Chen YF, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. Oct 18 2014;384(9952):1455-65. doi:10.1016/S0140-6736(14)60687-5
4. Weber B, Lackner I, Gebhard F, Miclau T, Kalbitz M. Trauma, a Matter of the Heart-Molecular Mechanism of Post-Traumatic Cardiac Dysfunction. Int J Mol Sci. Jan 13 2021;22(2) doi:10.3390/ijms22020737
5. Silk E, Zhao H, Weng H, Ma D. The role of extracellular histone in organ injury. Cell Death Dis. May 25 2017;8(5):e2812. doi:10.1038/cddis.2017.52
6. Yan I, Borschel CS, Neumann JT, et al. High-Sensitivity Cardiac Troponin I Levels and Prediction of Heart Failure: Results From the BiomarCaRE Consortium. JACC Heart Fail. May 2020;8(5):401-411. doi:10.1016/j.jchf.2019.12.008
7. Berge K, Lyngbakken MN, Myhre PL, et al. High-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide in acute heart failure: Data from the ACE 2 study. Clin Biochem. Feb 2021;88:30-36. doi:10.1016/j.clinbiochem.2020.11.009
8. Zhang Q, Wang YF, Hu X, et al. Association of serum cardiac troponin I and severity of coronary stenosis in patients with varied renal functions: a retrospective cohort study. BMJ Open. Mar 28 2022;12(3):e054722. doi:10.1136/bmjopen-2021-054722
9. Firth C, Kaur T, Chakkera H, et al. Cardiac Troponin T and Right Ventricular Systolic Pressure Predict Cardiovascular and Mortality Risk in Kidney Transplant Candidates. Am J Nephrol. 2019;50(6):434-443. doi:10.1159/000503807
10. Innocenti F, Palmieri V, Stefanone VT, et al. Comparison of Troponin I levels versus myocardial dysfunction on prognosis in sepsis. Intern Emerg Med. Jan 2022;17(1):223-231. doi:10.1007/s11739-021-02701-3
11. Packer M, Januzzi JL, Ferreira JP, et al. Concentration-dependent clinical and prognostic importance of high-sensitivity cardiac troponin T in heart failure and a reduced ejection fraction and the influence of empagliflozin: the EMPEROR-Reduced trial. Eur J Heart Fail. Sep 2021;23(9):1529-1538. doi:10.1002/ejhf.2256
12. Suthahar N, Lau ES, Blaha MJ, et al. Sex-Specific Associations of Cardiovascular Risk Factors and Biomarkers With Incident Heart Failure. J Am Coll Cardiol. Sep 22 2020;76(12):1455-1465. doi:10.1016/j.jacc.2020.07.044
13. Kalbitz M, Schwarz S, Weber B, et al. Cardiac Depression in Pigs after Multiple Trauma - Characterization of Posttraumatic Structural and Functional Alterations. Sci Rep. Dec 19 2017;7(1):17861. doi:10.1038/s41598-017-18088-1
14. Motz BM, Baimas-George M, Barnes TE, et al. Mitigating clinical waste in the trauma intensive care unit: Limited clinical utility of cardiac troponin testing for trauma patients with atrial fibrillation. Am J Surg. Jun 2020;219(6):1050-1056. doi:10.1016/j.amjsurg.2019.07.033
15. Patel N, Pena C, Nesheiwat Z, Zafrullah F, Eltahawy E. Ventricular fibrillation arrest after blunt chest trauma in a 33-year-old man, commotio cordis? BMC Cardiovasc Disord. Jun 3 2022;22(1):252. doi:10.1186/s12872-022-02689-4

16. Mubayed L, Romme A, Nguyen HH. QT Prolongation After Minor Head Trauma in a Pediatric Patient. Pediatr Cardiol. Feb 2020;41(2):414-417. doi:10.1007/s00246-019-02213-0
17. Saric P, Ravaee BD, Patel TR, Hoit BD. Acute severe mitral regurgitation after blunt chest trauma. Echocardiography. Feb 2018;35(2):272-274. doi:10.1111/echo.13775
18. Driessen R, Doodeman I, Bogaard K, Reichert S. Contusio cordis, not an innocent diagnosis. BMJ Case Rep. May 8 2014;2014doi:10.1136/bcr-2014-204139
19. Jung H, Cho JY, Kim GJ, et al. Traumatic severe tricuspid regurgitation diagnosis after the progression of right ventricle function deterioration. Trauma Case Rep. Oct 2019;23:100239. doi:10.1016/j.tcr.2019.100239
20. Dou LW, Du Z, Zhu JH, Wang TB. Changes and significance of serum troponin in trauma patients: A retrospective study in a level I trauma center. World J Emerg Med. 2022;13(1):27-31. doi:10.5847/wjem.j.1920-8642.2022.016
21. Braun CK, Kalbitz M, Halbgebauer R, et al. Early structural changes of the heart after experimental polytrauma and hemorrhagic shock. PLoS One. 2017;12(10):e0187327. doi:10.1371/journal.pone.0187327
22. Weber B, Mendler MR, Lackner I, et al. Tissue damage in the heart after cardiac arrest induced by asphyxia and hemorrhage in newborn pigs. Pediatr Res. Dec 2019;86(6):709-718. doi:10.1038/s41390-019-0505-6
23. Mair J, Lindahl B, Hammarsten O, et al. How is cardiac troponin released from injured myocardium? Eur Heart J Acute Cardiovasc Care. Sep 2018;7(6):553-560. doi:10.1177/2048872617748553
24. Demonbreun AR, McNally EM. Plasma Membrane Repair in Health and Disease. Curr Top Membr. 2016;77:67-96. doi:10.1016/bs.ctm.2015.10.006
25. Cooper ST, McNeil PL. Membrane Repair: Mechanisms and Pathophysiology. Physiol Rev. Oct 2015;95(4):1205-40. doi:10.1152/physrev.00037.2014
26. Streng AS, Jacobs LH, Schwenk RW, et al. Cardiac troponin in ischemic cardiomyocytes: intracellular decrease before onset of cell death. Exp Mol Pathol. Jun 2014;96(3):339-45. doi:10.1016/j.yexmp.2014.02.012
27. Bangert A, Andrassy M, Muller AM, et al. Critical role of RAGE and HMGB1 in inflammatory heart disease. Proc Natl Acad Sci U S A. Jan 12 2016;113(2):E155-64. doi:10.1073/pnas.1522288113
28. Gami BN, Patel DS, Haridas N, Chauhan KP, Shah H, Trivedi A. Utility of Heart-type Fatty Acid Binding Protein as a New Biochemical Marker for the Early Diagnosis of Acute Coronary Syndrome. J Clin Diagn Res. Jan 2015;9(1):BC22-4. doi:10.7860/JCDR/2015/11006.5451
29. Ritter A, Lotterle L, Han J, et al. Evaluation of New Cardiac Damage Biomarkers in Polytrauma: GDF-15, HFABP and uPAR for Predicting Patient Outcomes. J Clin Med. Feb 8 2024;13(4)doi:10.3390/jcm13040961
30. Relja B, Land WG. Damage-associated molecular patterns in trauma. Eur J Trauma Emerg Surg. Aug 2020;46(4):751-775. doi:10.1007/s00068-019-01235-w
31. Sloos PH, Maas MAW, Meijers JCM, et al. Anti-high-mobility group box-1 treatment strategies improve trauma-induced coagulopathy in a mouse model of trauma and shock. Br J Anaesth. Jun 2023;130(6):687-697. doi:10.1016/j.bja.2023.01.026
32. Horst K, Hildebrand F, Pfeifer R, et al. Impact of haemorrhagic shock intensity on the dynamic of alarmins release in porcine poly-trauma animal model. Eur J Trauma Emerg Surg. Feb 2016;42(1):67-75. doi:10.1007/s00068-015-0504-1
33. Zhang L, Liu M, Jiang H, et al. Extracellular high-mobility group box 1 mediates pressure overload-induced cardiac hypertrophy and heart failure. J Cell Mol Med. Mar 2016;20(3):459-70. doi:10.1111/jcmm.12743
34. Tian Y, Charles EJ, Yan Z, et al. The myocardial infarct-exacerbating effect of cell-free DNA is mediated by the high-mobility group box 1-receptor for advanced glycation end products-Toll-like receptor 9

pathway. J Thorac Cardiovasc Surg. Jun 2019;157(6):2256-2269 e3. doi:10.1016/j.jtcvs.2018.09.043
35. Ward PA, Grailer JJ. Acute lung injury and the role of histones. Transl Respir Med. 2014;2:1. doi:10.1186/2213-0802-2-1
36. Karki P, Birukov KG, Birukova AA. Extracellular histones in lung dysfunction: a new biomarker and therapeutic target? Pulm Circ. Oct-Dec 2020;10(4):2045894020965357. doi:10.1177/2045894020965357
37. Kalbitz M, Amann EM, Bosch B, et al. Experimental blunt chest trauma-induced myocardial inflammation and alteration of gap-junction protein connexin 43. PLoS One. 2017;12(11):e0187270. doi:10.1371/journal.pone.0187270
38. Kawai C, Kotani H, Miyao M, et al. Circulating Extracellular Histones Are Clinically Relevant Mediators of Multiple Organ Injury. Am J Pathol. Apr 2016;186(4):829-43. doi:10.1016/j.ajpath.2015.11.025
39. Chen R, Kang R, Tang D. The mechanism of HMGB1 secretion and release. Exp Mol Med. Feb 2022;54(2):91-102. doi:10.1038/s12276-022-00736-w
40. Meng XY, Wu L, Zhou YH, et al. High mobility group box 1 might be a novel therapeutic target in ischemia heart disease. Int J Cardiol. Mar 1 2016;206:42-3. doi:10.1016/j.ijcard.2016.01.014
41. Kalbitz M, Fattahi F, Herron TJ, et al. Complement Destabilizes Cardiomyocyte Function In Vivo after Polymicrobial Sepsis and In Vitro. J Immunol. Sep 15 2016;197(6):2353-61. doi:10.4049/jimmunol.1600091
42. Zhang X, Lu C, Gao M, et al. Toll-like receptor 4 plays a central role in cardiac dysfunction during trauma hemorrhage shock. Shock. Jul 2014;42(1):31-7. doi:10.1097/SHK.0000000000000155
43. Lackner I, Weber B, Baur M, et al. Midkine Is Elevated After Multiple Trauma and Acts Directly on Human Cardiomyocytes by Altering Their Functionality and Metabolism. Front Immunol. 2019;10:1920. doi:10.3389/fimmu.2019.01920
44. Fischer V, Kalbitz M, Muller-Graf F, et al. Influence of Menopause on Inflammatory Cytokines during Murine and Human Bone Fracture Healing. Int J Mol Sci. Jul 16 2018;19(7) doi:10.3390/ijms19072070
45. Brennan FH, Gordon R, Lao HW, et al. The Complement Receptor C5aR Controls Acute Inflammation and Astrogliosis following Spinal Cord Injury. J Neurosci. Apr 22 2015;35(16):6517-31. doi:10.1523/JNEUROSCI.5218-14.2015
46. Yang Z, Nicholson SE, Cancio TS, Cancio LC, Li Y. Complement as a vital nexus of the pathobiological connectome for acute respiratory distress syndrome: An emerging therapeutic target. Front Immunol. 2023;14:1100461. doi:10.3389/fimmu.2023.1100461
47. Hoth JJ, Wells JD, Jones SE, Yoza BK, McCall CE. Complement mediates a primed inflammatory response after traumatic lung injury. J Trauma Acute Care Surg. Mar 2014;76(3):601-8; discussion 608-9. doi:10.1097/TA.0000000000000129
48. Lackner I, Weber B, Baur M, et al. Complement Activation and Organ Damage After Trauma-Differential Immune Response Based on Surgical Treatment Strategy. Front Immunol. 2020;11:64. doi:10.3389/fimmu.2020.00064
49. van den Berg CW, Tambourgi DV, Clark HW, Hoong SJ, Spiller OB, McGreal EP. Mechanism of neutrophil dysfunction: neutrophil serine proteases cleave and inactivate the C5a receptor. J Immunol. Feb 15 2014;192(4):1787-95. doi:10.4049/jimmunol.1301920
50. Biggins PJC, Brennan FH, Taylor SM, Woodruff TM, Ruitenberg MJ. The Alternative Receptor for Complement Component 5a, C5aR2, Conveys Neuroprotection in Traumatic Spinal Cord Injury. J Neurotrauma. Jun 15 2017;34(12):2075-2085. doi:10.1089/neu.2016.4701
51. Fattahi F, Ward PA. Complement and sepsis-induced heart dysfunction. Mol Immunol. Apr 2017;84:57-64. doi:10.1016/j.molimm.2016.11.012
52. Alkireidmi MA, Al-Abbasi FA, Mehanna MG, Moselhy SS. Biochemical markers as diagnostic/prognostic indicators for ischemic disease. Afr

Health Sci. Jun 2018;18(2):287-294. doi:10.4314/ahs.v18i2.13
53. Yan W, Blasius F, Wahl T, et al. Lactate dehydrogenase can be used for differential diagnosis to identify patients with severe polytrauma with or without chest injury-A retrospective study. PLoS One. 2024;19(8):e0308228. doi:10.1371/journal.pone.0308228