Бекбосынова Махаббат Сансызбаевна, д.м.н., КФ “University Medical Center”, Заместитель Председатель правления, Астана, Казахстан, E-mail: astanamaha@gmail.com *ORCID*0000-0003-2834-617X

Бәтпен Арман Нурланович, PhD, Национальный научный центр травматологии и ортопедии имени Академика Н.Д. Батпенова Зам. директора по стратегии и науке. г. Астана Казахстан E-mail *ORCID* [0000-0002-6661-8132](https://orcid.org/0000-0002-6661-8132)

Мукаров Мурат Аманжолович, к.м.н., КФ “University Medical Center”, Директор КАД кардиологии, врач кардиолог высшей категории, г. Астана Казахстан E-mail: mmukarov@gmail.com *ORCID* [0000-0003-2854-1952](https://orcid.org/0000-0003-2854-1952)

Канабекова Перизат Сержановна, врач-резидент Назарбаев Университет, Астана, Казахстан. E-mail perizat.kanabekova@nu.edu.kz. *ORCID* 0000-0001-5753-4271

Шақтыбек Жанерке Мұхтарқызы, КФ “University Medical Center”, Главный менеджер Департамента науки г. Астана Казахстан E-mail: zhanerke.shaktybek@nu.edu.kz *ORCID* 0009-0002-3726-060X

Сугралимова Мадина Максатовна, КФ “University Medical Center”, врач кардиолог, Астана Казахстан E-mail: sugralimova999@gmail.com *ORCID* 0000-0001-7388-5717

Мамасалиев Бакберген Мырзабекович, врач-травматолог, Многопрофильная городская больница №2, Астана, Казахстан E-mail:baxa\_medik\_88@mail.ru *ORCID* 0009-0002-6257-6323

Лукбанов Мейирбек Кайратович, врач-травматолог, Многопрофильная городская больница №1, Астана Казахстан E-mail:meirbek.lukbanov@gmail.com *ORCID* 0009-0008-7887-4994

Кожахметова Анар Ильясовна, Врач терапевт общеклинического отделения, Национальный научный центр травматологии и ортопедии имени академика Батпенова Н.Д., Астана , E-mail *anaramalika8324@gmail.ORCID 0000-0001-5580-002X*

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**Corresponding author:** Kozhakhmetova Anar Ilyasovna, 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

META-ANALISIS

**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 S5., 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

**Annotation**

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.

**Keywords**: *trauma; myocardial dysfunction; immunology.*

**КӨПЖАРАҚАТ КЕЗІНДЕГІ МИОКАРД ДИСФУНКЦИЯСЫ**

**Бекбосынова Махаббат С.**1**, Бәтпен Арман Н.**2**, Мукаров Мурат А.**1**, Шақтыбек Жанерке М.**1**, Сугралимова Мадина М.**1**, Мамасалиев Бакберген М.**3**, Лұқбанов Мейірбек К.**4**, Канабекова Перизат С**5**., Кожахметова Анар И.**2

*1 -«University Medical Center» корпоративтік қоры, Астана, Қазақстан*

*2 - Академик Н.Д.Батпенова атындағы травматология және ортопедия ұлттық ғылыми орталығы, Астана, Қазақстан*

*3 - №2 көпсалалы қалалық аурухана, Астана, Қазақстан*

*4 - №1 көпсалалы қалалық аурухана, Астана, Қазақстан*

*5- Назарбаев Университет, Астана, Казахстан*

**Тұжырым**

Көпжарақат-бұл әртүрлі органдар мен жүйелерді қамтитын жарақаттар кешенін сипаттау үшін қолданылатын термин. Жүрек жарақаты тікелей соққының салдарынан немесе қайталама асқыну ретінде жарақаттан туындауы мүмкін. Сондай-ақ ол нашар клиникалық нәтижелермен және ауруханаға жатқызудың ұзағырақ курстарымен байланысты. Жүректің зақымдануы құрылымдарға байланысты әртүрлі клиникалық көріністерге, соның ішінде, гипотензия, аритмия, күңкілдеу және тіпті асимптоматикалық көріністер ие болады. Клиникалық хаттамалар жарақаттың ауырлығына және катехоламиндерге қажеттілікке байланысты тропонин деңгейін өлшеуді ұсынады. Осы мақала аясында жүргізілген мета-анализде тропониннің жоғарылауының жүрек жеткіліксіздігінің дамуымен байланысы көрсетілген. Әрі қарай, хаттамалар ЭКГ сияқты диагностикалық скрининг құралдарына сүйенеді. Дегенмен, жүрек жарақатының болжамды белгісі ретінде пайдаланылуы мүмкін бірқатар биохимиялық молекулалар бар. Әдебиеттерге шолу көпжарақат патофизиологиясын, соның ішінде қабыну реакциясын және комплемент жүйесінің белсендірілуін талқылауға бағытталған және жүрек жарақатының әртүрлі биохимиялық маркерлерін зерттейді.

**Түйінді сөздер:** *жарақат; миокард дисфункциясы; иммунология.*

**ДИСФУНКЦИЯ МИОКАРДА ПРИ ПОЛИТРАВМЕ**

Бекбосынова Махаббат Сансызбаевна1, Бәтпен Арман Н.2, Мукаров Мурат Аманжолович1, Шактыбек Жанерке М.1, Сугралимова Мадина Максатовна1, Мамасалиев Бакберген Мырзабекович3, Лұқбанов Мейірбек Кайратұлы1, Канабекова Перизат Сержановна 5, Кожахметова Анар Илиясовна2.

*1 - Корпоративный фонд «University Medical Center», Астана, Казахстан*

*2 - Национальный научный центр травматологии и ортопедии имени академика Н.Д. Батпеновой, Астана, Казахстан*

*3 - Многопрофильная городская больница №2, Астана, Казахстан*

*4 - Многопрофильная городская больница №1, Астана, Казахстан*

*5- Назарбаев Университет, Астана, Казахстан*

**Аннотация**

Политравма — это термин, используемый для описания комплекса травм, затрагивающих различные органы и системы. Кардиальная травма может возникать в результате прямого удара или как вторичное осложнение. Она также ассоциируется с худшими клиническими исходами и более длительным периодом госпитализации. Кардиальная травма может иметь различные клинические проявления в зависимости от вовлечённых структур, включая гипотензию, аритмию, шумы и даже бессимптомное течение. Клинические протоколы предполагают измерение уровня тропонина, который коррелирует с тяжестью травмы и необходимостью в катехоламинах. Метанализ, проведённый в рамках данной работы, продемонстрировал связь между повышенным уровнем тропонина и развитием сердечной недостаточности. Далее, протоколы опираются на диагностические инструменты, такие как ЭКГ. Однако существует ряд биохимических молекул, которые могут использоваться в качестве прогностических маркеров кардиальной травмы. Обзор литературы сосредоточен на обсуждении патофизиологии политравмы, включая воспалительный ответ и активацию системы комплемента, и исследует различные биохимические маркеры кардиальной травмы.

**Ключевые слова:** *травма; дисфункция миокарда; иммунология.*

**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 [4,5]. 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 [6]. 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 [7].

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 were 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, clinical consequences 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 I² 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  | 2020 | 48,455 | 23,321 | Prospective population-based cohort study | Heart failure |
| Berge et al | 2021 | 314 | 163 | Prospective cohort | Heart failure |
| Zhang et al | 2022 | 6487 | 4361 | Retrospective cohort | Coronary stenosis |
| Firth et al | 2019 | 561 | 332 | Prospective | Cardiovascular events |
| Innocenti et al | 2021 | 325 | N/A | Prospective  | Mortality |
| Packer et al | 2021 | 3636 | 2767 | EMPEROR-Reduced trial | Heart failure |
| Suthahar et al | 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 2020 | 2.3  | 1.42  | 1.31 | 1.53 | <0.001 |
| Berge et al 2021 | 13 | 1.30 | 1.07 | 1.58 | <0.009 |
| Zhang et al 2022 | 9 | 1.14 | 1.11  | 1.17 | <0.05 |
| Firth et al 2019 | 0.068 | 2.15 | 1.29 | 3.58 | <0.003 |
| Innocenti et al 2021  | NA | 3.24 | 1.72 | 6.11 | <0.001 |
| Packer et al 2021 | 14 | 1.71  | 1.22 | 2.41 | <0.001 |
| Suthahar et al 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 [8]. 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 [9]. 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 [10]. 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 [11]. 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 [12]. 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 [13, 14]. 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 [13]. 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 previously 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 [15]. 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 [8]. 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 [16]. Recently published reports have documented elevated troponin levels in various experimental trauma models and species, including mice following multiple trauma [17], asphyxia and hemorrhage in newborn piglets [18], and multiple trauma with hemorrhagic shock in pigs [18].

Before it was established that damaged cardiomyocyte membranes contribute to the release of troponin, cell necrosis was considered the only mechanism for its release [19]. Besides necrosis and apoptosis, there is growing evidence of various possible mechanisms for reversible systemic elevation of troponin [19]. This reversible cardiomyocyte (CM) damage has been associated with the release of microparticles, membrane vesicles, and increased cell membrane permeability [20,21]. Fragmented cardiac troponin is expected to result from irreversible cardiomyocyte damage, while systemic elevation of undamaged troponin is associated with reversible damage [22]. Structurally bound troponin undergoes degradation by calpains, which are activated by increased intracellular calcium or changes in pH levels [19]. 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) [23]. Additionally, there is evidence that troponin I directly affects the heart; it has been shown to cause inflammatory heart disease in mice [24].

Another myocardial damage biomarker is HFABP, which is detected in the bloodstream earlier after myocardial infarction compared to troponin [25]. Systemic elevation of HFABP was recently observed at early stages following experimental multiple trauma in pigs [8]. 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 [50].

*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 [26], the release of high mobility group box 1 (HMGB-1) protein has been observed in humans within 30 minutes of injury [27], and it has been associated with injury severity, complement system activation, and mortality [27]. Additionally, in experimental models of multiple trauma, including chest trauma with hemorrhagic shock in pigs, elevated levels of HMGB-1 have been documented [28]. It is known that HMGB-1 can induce cardiomyocyte dysfunction, including cases of cardiac hypertrophy and heart failure [29], as well as ischemia and myocardial reperfusion injury [30]. 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 [31,32], as well as septic cardiomyopathy in mice [23]. DAMPs can contribute to increased intracellular calcium concentrations in cavernosal malformations, which are associated with bradycardia and bigeminy [23]. 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 [33,8,34]. Following systemic administration of extracellular histones in mice, there was an increase in inflammatory cytokines such as TNF, IL-1β, IL-6, and IL-10 [35]. Additionally, HMGB-1 has been linked to the production of inflammatory cytokines [36], including TNF, IL-1β, and IL-6 [37]. 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 [23]. Histones also decrease mitochondrial membrane potential and ATP production in a dose-dependent manner, leading to reduced cardiomyocyte contractility due to energy deficiency [23,38]. 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 [39].

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 [40]. Systemic elevation of midkine levels has been observed following bone fractures, burns, and traumatic spinal cord injury [41,42]. After release following a fracture, midkine remains elevated in patients for up to 42 days [41]. 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 [40]. Besides its effect on contractility through intracellular calcium changes, midkine also impaired mitochondrial function in cardiomyocytes and induced apoptosis [40].

*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 [38]. 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 [43].

In trauma patients, complement system activation has been noted with increased levels of ComC[44]. 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 [44]. In contrast to the threefold increase in C5a receptor (C5aR) expression in the myocardium after ischemia observed in experimental blunt chest trauma in mice [34], experimental asphyxia and hemorrhage in piglets [18], and experimental multiple trauma in pigs, C5a receptor factor (C5aR1) expression in the left ventricle was reduced [8]. This decrease in C5aR1 levels may be due to receptor internalization following binding with C5a, which significantly increases after trauma in animal models [45].

Systemic consumption of both classical and alternative complement system factors was demonstrated using the CH-50 test in pigs 6 hours after multiple trauma [46]. Additionally, neutrophils migrate to cardiac tissue following trauma, as shown in experimental blunt chest trauma in mice [34]. Neutrophil serine protease cleaves C5aR1, leading to its reduction after trauma [47]. In case with C5aR2, its loss mouse model with spinal cord trauma caused worse outcomes [48]. 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 [38,49].

**Discussion**

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 [51]. A common issue with many markers is sensitivity, as these molecules 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 [52]. 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 [50]. 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 [50]. 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.

**Conclusions**

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.

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**Authors' Contributions**

 Conceptualization, M.B. and A.B.; methodology, A.K.; software, Z.S and P.K.; validation, M.B., M.M. and A.B.; formal analysis, M.S.; investigation, P.K.; resources, B.M.; data curation, M.L.; writing—original draft preparation, A.K.; writing—review and editing – M.M.; visualization, P.K.; supervision, M.B.; project administration, Z.S.; funding acquisition, M.B.

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**Reference**

1. Iyengar, K. P., Venkatesan, A., Jain, V. K., Shashidhara, M. K., Elbana, H., &Botchu, R. (2023). Risks in the management of Polytrauma Patients: Clinical insights. *Orthopedic Research and Reviews*, *Volume 15*, 27–38. <https://doi.org/10.2147/orr.s340532>
2. World Health Organization. (n.d.). *Road traffic injuries*. World Health Organization. <https://www.who.int/news-room/fact-sheets/road-traffic-injuries>
3. Lord, J. M., Midwinter, M. J., Chen, Y.-F., Belli, A., Brohi, K., Kovacs, E. J., Koenderman, L., Kubes, P., &Lilford, R. J. (2014). The systemic immune response to trauma: An overview of pathophysiology and treatment. *The Lancet*, *384*(9952), 1455–1465. [https://doi.org/10.1016/s0140-6736(14)60687-5](https://doi.org/10.1016/s0140-6736%2814%2960687-5)
4. Lord, J. M., Midwinter, M. J., Chen, Y.-F., Belli, A., Brohi, K., Kovacs, E. J., Koenderman, L., Kubes, P., &Lilford, R. J. (2014). The systemic immune response to trauma: An overview of pathophysiology and treatment. *The Lancet*, *384*(9952), 1455–1465. [https://doi.org/10.1016/s0140-6736(14)60687-5](https://doi.org/10.1016/s0140-6736%2814%2960687-5)
5. Silk, E., Zhao, H., Weng, H., & Ma, D. (2017). The role of extracellular histone in organ injury. *Cell death&disease*, *8*(5), e2812. <https://doi.org/10.1038/cddis.2017.52>
6. Weber, B., Lackner, I., Gebhard, F., Miclau, T., &Kalbitz, M. (2021). Trauma, a Matter of the Heart-Molecular Mechanism of Post-Traumatic Cardiac Dysfunction. *International journalofmolecularsciences*, *22*(2), 737. <https://doi.org/10.3390/ijms22020737>
7. Lord, J. M., Midwinter, M. J., Chen, Y.-F., Belli, A., Brohi, K., Kovacs, E. J., Koenderman, L., Kubes, P., &Lilford, R. J. (2014). The systemic immune response to trauma: An overview of pathophysiology and treatment. *The Lancet*, *384*(9952), 1455–1465. [https://doi.org/10.1016/s0140-6736(14)60687-5](https://doi.org/10.1016/s0140-6736%2814%2960687-5)
8. Kalbitz, M., Schwarz, S., Weber, B., Bosch, B., Pressmar, J., Hoenes, F. M., Braun, C. K., Horst, K., Simon, T. P., Pfeifer, R., Störmann, P., Hummler, H., Gebhard, F., Pape, H. C., Huber-Lang, M., Hildebrand, F., & TREAT Research Group (2017). Cardiac Depression in Pigs after Multiple Trauma - Characterization of Posttraumatic Structural and Functional Alterations. *Scientific reports*, *7*(1), 17861. <https://doi.org/10.1038/s41598-017-18088-1>
9. Motz, B. M., Baimas-George, M., Barnes, T. E., Ragunanthan, B. V., Symanski, J. D., Christmas, A. B., Sing, R. F., & Ross, S. W. (2020). Mitigating clinical waste in the trauma intensive care unit: Limited clinical utility of cardiac troponin testing for trauma patients with atrial fibrillation. *American journalofsurgery*, *219*(6), 1050–1056. <https://doi.org/10.1016/j.amjsurg.2019.07.033>
10. Patel, N., Pena, C., Nesheiwat, Z., Zafrullah, F., & Eltahawy, E. (2022). Ventricular fibrillation arrest after blunt chest trauma in a 33-year-old man, commotio cordis?. *BMC cardiovascular disorders*, *22*(1), 252. <https://doi.org/10.1186/s12872-022-02689-4>
11. Mubayed, L., Romme, A., & Nguyen, H. H. (2020). QT Prolongation After Minor Head Trauma in a Pediatric Patient. *Pediatriccardiology*, *41*(2), 414–417. <https://doi.org/10.1007/s00246-019-02213-0>
12. Saric, P., Ravaee, B. D., Patel, T. R., & Hoit, B. D. (2018). Acute severe mitral regurgitation after blunt chest trauma. *Echocardiography (Mount Kisco, N.Y.)*, *35*(2), 272–274. <https://doi.org/10.1111/echo.13775>
13. Driessen, R., Doodeman, I., Bogaard, K., & Reichert, S. (2014). Contusio cordis, not an innocent diagnosis. *BMJ casereports*, *2014*, bcr2014204139. <https://doi.org/10.1136/bcr-2014-204139>
14. Jung, H., Cho, J. Y., Kim, G.-J., Lee, Y. ok, Lim, K. H., Hong, S. W., Jin, Y., & Son, S.-A. (2019b). Traumatic severe tricuspid regurgitation diagnosis after the progression of right ventricle function deterioration. *Trauma Case Reports*, *23*, 100239. <https://doi.org/10.1016/j.tcr.2019.100239>
15. Vasile, V. C., Chai, H. S., Abdeldayem, D., Afessa, B., & Jaffe, A. S. (2013). Elevated cardiac troponin T levels in critically ill patients with sepsis. *The American journal of medicine*, *126*(12), 1114–1121. <https://doi.org/10.1016/j.amjmed.2013.06.029>
16. Dou, L. W., Du, Z., Zhu, J. H., & Wang, T. B. (2022). Changes and significance of serum troponin in trauma patients: A retrospective study in a level I trauma center. *World journal of emergency medicine*, *13*(1), 27–31. <https://doi.org/10.5847/wjem.j.1920-8642.2022.016>
17. Braun, C. K., Kalbitz, M., Halbgebauer, R., Eisele, P., Messerer, D. A. C., Weckbach, S., Schultze, A., Braumüller, S., Gebhard, F., & Huber-Lang, M. S. (2017). Early structural changes of the heart after experimental polytrauma and hemorrhagic shock. *PloSone*, *12*(10), e0187327. <https://doi.org/10.1371/journal.pone.0187327>
18. Weber, B., Mendler, M. R., Lackner, I., Pressmar, J., Haffner-Luntzer, M., Höfler, S., Braun, C. K., Hummler, H., Schwarz, S., &Kalbitz, M. (2019). Tissue damage in the heart after cardiac arrest induced by asphyxia and hemorrhage in newborn pigs. *Pediatricresearch*, *86*(6), 709–718. <https://doi.org/10.1038/s41390-019-0505-6>
19. Mair, J., Lindahl, B., Hammarsten, O., Müller, C., Giannitsis, E., Huber, K., Möckel, M., Plebani, M., Thygesen, K., & Jaffe, A. S. (2018). How is cardiac troponin released from injured myocardium?. *European heart journal. Acutecardiovascularcare*, *7*(6), 553–560. <https://doi.org/10.1177/2048872617748553>
20. Demonbreun, A. R., & McNally, E. M. (2016). Plasma Membrane Repair in Health and Disease. *Current topicsinmembranes*, *77*, 67–96. <https://doi.org/10.1016/bs.ctm.2015.10.006>
21. Cooper, S. T., & McNeil, P. L. (2015). Membrane Repair: Mechanisms and Pathophysiology. *Physiologicalreviews*, *95*(4), 1205–1240. <https://doi.org/10.1152/physrev.00037.2014>.
22. Streng, A. S., Jacobs, L. H., Schwenk, R. W., Cardinaels, E. P., Meex, S. J., Glatz, J. F., Wodzig, W. K., & van Dieijen-Visser, M. P. (2014). Cardiac troponin in ischemic cardiomyocytes: intracellular decrease before onset of cell death. *Experimentalandmolecularpathology*, *96*(3), 339–345. <https://doi.org/10.1016/j.yexmp.2014.02.012>.
23. Kalbitz, M., Grailer, J. J., Fattahi, F., Jajou, L., Herron, T. J., Campbell, K. F., Zetoune, F. S., Bosmann, M., Sarma, J. V., Huber-Lang, M., Gebhard, F., Loaiza, R., Valdivia, H. H., Jalife, J., Russell, M. W., & Ward, P. A. (2015). Role of extracellular histones in the cardiomyopathy of sepsis. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*, *29*(5), 2185–2193. <https://doi.org/10.1096/fj.14-268730>
24. Bangert, A., Andrassy, M., Müller, A. M., Bockstahler, M., Fischer, A., Volz, C. H., Leib, C., Göser, S., Korkmaz-Icöz, S., Zittrich, S., Jungmann, A., Lasitschka, F., Pfitzer, G., Müller, O. J., Katus, H. A., &Kaya, Z. (2016). Critical role of RAGE and HMGB1 in inflammatory heart disease. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(2), E155–E164. <https://doi.org/10.1073/pnas.1522288113>.
25. Gami, B. N., Patel, D. S., Haridas, N., Chauhan, K. P., Shah, H., & Trivedi, A. (2015). Utility of Heart-type Fatty Acid Binding Protein as a New Biochemical Marker for the Early Diagnosis of Acute Coronary Syndrome. *Journal of clinical and diagnostic research : JCDR*, *9*(1), BC22–BC24. <https://doi.org/10.7860/JCDR/2015/11006.5451>
26. Relja, B., & Land, W. G. (2020). Damage-associated molecular patterns in trauma. *European journal of trauma and emergency surgery : official publication of the European Trauma Society*, *46*(4), 751–775. <https://doi.org/10.1007/s00068-019-01235-w>
27. Sloos, P. H., Maas, M. A., Meijers, J. C. M., Nieuwland, R., Roelofs, J. J. T. H., Juffermans, N. P., & Kleinveld, D. J. B. (2023). Anti-high-mobility group box-1 treatment strategies improve trauma-induced coagulopathy in a mouse model of trauma and shock. *British Journal of Anaesthesia*, *130*(6), 687–697. <https://doi.org/10.1016/j.bja.2023.01.026>
28. Horst, K., Hildebrand, F., Pfeifer, R., Hübenthal, S., Almahmoud, K., Sassen, M., Steinfeldt, T., Wulf, H., Ruchholtz, S., Pape, H. C., & Eschbach, D. (2016). Impact of haemorrhagic shock intensity on the dynamic of alarmins release in porcine poly-trauma animal model. *European journal of trauma and emergency surgery : official publication of the European Trauma Society*, *42*(1), 67–75. <https://doi.org/10.1007/s00068-015-0504-1>
29. Zhang, L., Liu, M., Jiang, H., Yu, Y., Yu, P., Tong, R., Wu, J., Zhang, S., Yao, K., Zou, Y., & Ge, J. (2016). Extracellular high-mobility group box 1 mediates pressure overload-induced cardiac hypertrophy and heart failure. *Journal of cellular and molecular medicine*, *20*(3), 459–470. <https://doi.org/10.1111/jcmm.12743>
30. Tian, Y., Charles, E. J., Yan, Z., Wu, D., French, B. A., Kron, I. L., & Yang, Z. (2019). 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. *The Journal of thoracic and cardiovascular surgery*, *157*(6), 2256–2269.e3. <https://doi.org/10.1016/j.jtcvs.2018.09.043>
31. Ward, P. A., &Grailer, J. J. (2014). Acute lung injury and the role of histones. *Translationalrespiratorymedicine*, *2*, 1. <https://doi.org/10.1186/2213-0802-2-1>
32. Karki, P., Birukov, K. G., & Birukova, A. A. (2020). Extracellular histones in lung dysfunction: A new biomarker and therapeutic target? *Pulmonary Circulation*, *10*(4), 1–8. <https://doi.org/10.1177/2045894020965357>
33. Braun, C. K., Kalbitz, M., Halbgebauer, R., Eisele, P., Messerer, D. A. C., Weckbach, S., Schultze, A., Braumüller, S., Gebhard, F., & Huber-Lang, M. S. (2017). Early structural changes of the heart after experimental polytrauma and hemorrhagic shock. *PloSone*, *12*(10), e0187327. <https://doi.org/10.1371/journal.pone.0187327>
34. Kalbitz, M., Amann, E. M., Bosch, B., Palmer, A., Schultze, A., Pressmar, J., Weber, B., Wepler, M., Gebhard, F., Schrezenmeier, H., Brenner, R., & Huber-Lang, M. (2017). Experimental blunt chest trauma-induced myocardial inflammation and alteration of gap-junction protein connexin 43. *PloSone*, *12*(11), e0187270. <https://doi.org/10.1371/journal.pone.0187270>
35. Kawai, C., Kotani, H., Miyao, M., Ishida, T., Jemail, L., Abiru, H., & Tamaki, K. (2016). Circulating Extracellular Histones Are Clinically Relevant Mediators of Multiple Organ Injury. *The American journal of pathology*, *186*(4), 829–843. <https://doi.org/10.1016/j.ajpath.2015.11.025>
36. Chen, R., Kang, R., & Tang, D. (2022). The mechanism of HMGB1 secretion and release. *Experimental &amp; Molecular Medicine*, *54*(2), 91–102. <https://doi.org/10.1038/s12276-022-00736-w>
37. Meng, X. Y., Wu, L., Zhou, Y. H., Liu, T., Han, Q. F., Zhang, D. Y., Wang, L. H., & Yao, H. C. (2016). High mobility group box 1 might be a novel therapeutic target in ischemia heart disease. *International journalofcardiology*, *206*, 42–43. <https://doi.org/10.1016/j.ijcard.2016.01.014>
38. Kalbitz, M., Fattahi, F., Herron, T. J., Grailer, J. J., Jajou, L., Lu, H., Huber-Lang, M., Zetoune, F. S., Sarma, J. V., Day, S. M., Russell, M. W., Jalife, J., & Ward, P. A. (2016). Complement Destabilizes Cardiomyocyte Function In Vivo after Polymicrobial Sepsis and In Vitro. *Journal ofimmunology (Baltimore, Md. : 1950)*, *197*(6), 2353–2361. <https://doi.org/10.4049/jimmunol.1600091>
39. Zhang, X., Lu, C., Gao, M., Cao, X., Ha, T., Kalbfleisch, J. H., Williams, D. L., Li, C., & Kao, R. L. (2014). Toll-like receptor 4 plays a central role in cardiac dysfunction during trauma hemorrhage shock. *Shock (Augusta, Ga.)*, *42*(1), 31–37. <https://doi.org/10.1097/SHK.0000000000000155>
40. Lackner, I., Weber, B., Baur, M., Haffner-Luntzer, M., Eiseler, T., Fois, G., Gebhard, F., Relja, B., Marzi, I., Pfeifer, R., Halvachizadeh, S., Lipiski, M., Cesarovic, N., Pape, H. C., Kalbitz, M., & TREAT Research Group (2019). Midkine Is Elevated After Multiple Trauma and Acts Directly on Human Cardiomyocytes by Altering Their Functionality and Metabolism. *Frontiersinimmunology*, *10*, 1920. <https://doi.org/10.3389/fimmu.2019.01920>
41. Fischer, V., Kalbitz, M., Müller-Graf, F., Gebhard, F., Ignatius, A., Liedert, A., & Haffner-Luntzer, M. (2018). Influence of Menopause on Inflammatory Cytokines during Murine and Human Bone Fracture Healing. *International journalofmolecularsciences*, *19*(7), 2070. <https://doi.org/10.3390/ijms19072070>
42. Lackner, I., Weber, B., Baur, M., Haffner-Luntzer, M., Eiseler, T., Fois, G., Gebhard, F., Relja, B., Marzi, I., Pfeifer, R., Halvachizadeh, S., Lipiski, M., Cesarovic, N., Pape, H. C., Kalbitz, M., & TREAT Research Group (2019). Midkine Is Elevated After Multiple Trauma and Acts Directly on Human Cardiomyocytes by Altering Their Functionality and Metabolism. *Frontiers in immunology*, *10*, 1920. <https://doi.org/10.3389/fimmu.2019.01920>
43. Brennan, F. H., Gordon, R., Lao, H. W., Biggins, P. J., Taylor, S. M., Franklin, R. J., Woodruff, T. M., & Ruitenberg, M. J. (2015). The Complement Receptor C5aR Controls Acute Inflammation and Astrogliosis following Spinal Cord Injury. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *35*(16), 6517–6531. <https://doi.org/10.1523/JNEUROSCI.5218-14.2015>
44. Yang, Z., Nicholson, S. E., Cancio, T. S., Cancio, L. C., & Li, Y. (2023). Complement as a vital nexus of the pathobiological connectome for acute respiratory distress syndrome: An emerging therapeutic target. *Frontiers in Immunology*, *14*. <https://doi.org/10.3389/fimmu.2023.1100461>
45. Hoth, J. J., Wells, J. D., Jones, S. E., Yoza, B. K., & McCall, C. E. (2014). Complement mediates a primed inflammatory response after traumatic lung injury. *The journal of trauma and acute care surgery*, *76*(3), 601–609. <https://doi.org/10.1097/TA.0000000000000129>
46. Lackner, I., Weber, B., Baur, M., Fois, G., Gebhard, F., Pfeifer, R., Cinelli, P., Halvachizadeh, S., Lipiski, M., Cesarovic, N., Schrezenmeier, H., Huber-Lang, M., Pape, H. C., &Kalbitz, M. (2020). Complement Activation and Organ Damage After Trauma-Differential Immune Response Based on Surgical Treatment Strategy. *Frontiersinimmunology*, *11*, 64. <https://doi.org/10.3389/fimmu.2020.00064>
47. van den Berg, C. W., Tambourgi, D. V., Clark, H. W., Hoong, S. J., Spiller, O. B., & McGreal, E. P. (2014). Mechanism of neutrophil dysfunction: neutrophil serine proteases cleave and inactivate the C5a receptor. *Journal ofimmunology (Baltimore, Md. : 1950)*, *192*(4), 1787–1795. <https://doi.org/10.4049/jimmunol.1301920>
48. Biggins, P. J. C., Brennan, F. H., Taylor, S. M., Woodruff, T. M., & Ruitenberg, M. J. (2017). The alternative receptor for complement component 5A, C5aR2, conveys neuroprotection in traumatic spinal cord injury. *Journal of Neurotrauma*, *34*(12), 2075–2085. <https://doi.org/10.1089/neu.2016.4701>
49. Fattahi, F., & Ward, P. A. (2017). Complement and sepsis-induced heart dysfunction. *Molecularimmunology*, *84*, 57–64. <https://doi.org/10.1016/j.molimm.2016.11.012>
50. Ritter, A., Lötterle, L., Han, J., Kalbitz, M., Henrich, D., Marzi, I., Leppik, L., & Weber, B. (2024). Evaluation of new cardiac damage biomarkers in Polytrauma: GDF-15, HFABP and UPAR for predicting patient outcomes. *Journal ofClinicalMedicine*, *13*(4), 961. <https://doi.org/10.3390/jcm13040961>
51. Alkireidmi, M. A., Al-Abbasi, F. A., Mehanna, M. G., & Moselhy, S. S. (2018). Biochemical markers as diagnostic/prognostic indicators for ischemic disease. *African health sciences*, *18*(2), 287–294. <https://doi.org/10.4314/ahs.v18i2.13>
52. Yan, W., Bläsius, F., Wahl, T., Hildebrand, F., Balmayor, E. R., Greven, J., & Horst, K. (2024). Lactate dehydrogenase can be used for differential diagnosis to identify patients with severe polytrauma with or without chest injury—a retrospective study. *PLOS ONE*, *19*(8). <https://doi.org/10.1371/journal.pone.0308228>
53. Suthahar, N., Lau, E. S., Blaha, M. J., Paniagua, S. M., Larson, M. G., Psaty, B. M., ... &deBoer, R. A. (2020). Sex-specific associations of cardiovascular risk factors and biomarkers with incident heart failure. *Journal ofthe American College ofCardiology*, *76*(12), 1455-1465.
54. Yan, I., Börschel, C. S., Neumann, J. T., Sprünker, N. A., Makarova, N., Kontto, J., ... &Westermann, D. (2020). High-sensitivity cardiac troponin I levels and prediction of heart failure: results from the BiomarCaRE consortium. *Heart Failure*, *8*(5), 401-411.
55. Berge, K., Lyngbakken, M. N., Myhre, P. L., Brynildsen, J., Røysland, R., Strand, H., Christensen, G., Høiseth, A. D., Omland, T., &Røsjø, H. (2021). High-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide in acute heart failure: Data from the ACE 2 study. *Clinicalbiochemistry*, *88*, 30–36. <https://doi.org/10.1016/j.clinbiochem.2020.11.009>
56. Zhang, Q., Wang, Y. F., Hu, X., Tan, Y. J., Gao, C., Chen, J., Han, F., Chen, J., & Yang, Y. (2022). Association of serum cardiac troponin I and severity of coronary stenosis in patients with varied renal functions: a retrospective cohort study. *BMJ open*, *12*(3), e054722. <https://doi.org/10.1136/bmjopen-2021-054722>
57. Firth, C., Kaur, T., Chakkera, H., Zhang, N., Shamoun, F., Steidley, E., Heilman, R., &Keddis, M. (2019). Cardiac Troponin T and Right Ventricular Systolic Pressure Predict Cardiovascular and Mortality Risk in Kidney Transplant Candidates. *American journalofnephrology*, *50*(6), 434–443. <https://doi.org/10.1159/000503807>
58. Innocenti, F., Palmieri, V., Stefanone, V. T., D’Argenzio, F., Cigana, M., Montuori, M., Capretti, E., De Paris, A., Calcagno, S., Tassinari, I., & Pini, R. (2021). Comparison of troponin I levels versus myocardial dysfunction on prognosis in sepsis. *InternalandEmergencyMedicine*, *17*(1), 223–231. <https://doi.org/10.1007/s11739-021-02701-3>
59. Packer, M., Januzzi, J. L., Ferreira, J. P., Anker, S. D., Butler, J., Filippatos, G., ... & EMPEROR‐ReducedTrialCommitteesandInvestigators. (2021). 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. *European journalofheartfailure*, *23*(9), 1529-1538.