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PATHOPHYSIOLOGY OF CRUSH SYNDROME: EPIDEMIOLOGY, MECHANISMS, AND CLINICAL IMPLICATIONS

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Abstract

Crush syndrome (CS), or traumatic rhabdomyolysis, is a life-threatening systemic condition caused by prolonged compression of skeletal muscle. It remains a major contributor to morbidity and mortality in mass disasters such as earthquakes and building collapses. This literature review summarizes recent evidence on the epidemiology, mechanisms of onset, and sequential pathophysiological processes of CS. Epidemiological data indicate that CS accounts for 2–5% of earthquake-related injuries, with mortality rates reaching 40% in severe cases. The pathogenesis involves sustained ischemia, reperfusion injury, and subsequent rhabdomyolysis, leading to massive release of intracellular contents including myoglobin and potassium. These changes cause life-threatening electrolyte disturbances, acute kidney injury, and systemic inflammatory responses that progress to multi-organ dysfunction. Early diagnosis and prompt interventions—such as fluid resuscitation, electrolyte correction, and renal support—are essential to improving outcomes. Understanding the underlying pathophysiological processes provides critical insights for disaster medicine, emergency care, and future therapeutic strategies.

Keywords

Crush syndrome; rhabdomyolysis; acute kidney injury; pathophysiology; reperfusion injury; disaster medicine; electrolyte imbalance

Introduction. Crush syndrome (CS), also referred to as traumatic rhabdomyolysis or Bywaters' syndrome, is a catastrophic systemic complication that arises when prolonged mechanical compression of muscle tissue leads to cell disruption and widespread metabolic derangements. First recognized in wartime settings, its clinical relevance has expanded in the context of natural disasters, industrial accidents, and war zones. The syndrome remains a formidable challenge: mortality rates in published series vary from 5 % up to 20 % or more, depending on the severity of injury, timing of rescue, and adequacy of medical care [9,10,11,13].

Epidemiological burden. Epidemiological data demonstrate substantial variability in CS incidence and outcomes, reflecting heterogeneous contexts of disasters and healthcare settings. Among earthquake survivors, CS incidence estimates range from 2 % to 15 % of injured victims [10,12,13]. In major quakes, rates of acute kidney injury (AKI) secondary to CS span from 2 % to nearly 25 % of victims, and in cohorts of traumatic rhabdomyolysis more broadly, AKI rates may approach 30–50 % [9,10,13,14]. For example, in the 1999 Marmara earthquake (Turkey), CS-related AKI incidence was ~12 %, while in the 2003 Bam (Iran) disaster it was ~6.9 % [14]. Mortality among patients who develop CS or CS-associated AKI in disaster settings has been reported in various series to exceed 20 %, particularly when delays in rescue, fluid resuscitation, or renal support occur [9,10,11]. In a recent retrospective series from the Pazarcik–Elbistan earthquakes in Türkiye, of 128 CS patients, 32.8 % developed AKI and 14.2 % of those died; the overall mortality in the CS cohort was 4.6 % [1].

Beyond earthquakes, traumatic crush injuries in civilian and combat trauma settings often precipitate rhabdomyolysis: in large trauma registries, up to 18 % of patients sustained “severe” rhabdomyolysis, and incidence of AKI among rhabdomyolysis patients ranges from 10 % to 55 % [15,16,17]. Thus, although CS is relatively rare compared to other traumas or medical emergencies, its systemic consequences make it disproportionately lethal when present.

Despite its historical recognition, understanding of CS pathophysiology remains incomplete, particularly in light of evolving molecular insights (e.g. oxidative stress, ferroptosis, mitochondrial dysfunction). Contemporary reviews have underscored gaps in translating mechanistic knowledge into targeted therapies [9,10]. Moreover, much existing literature is descriptive or observational, with limited opportunities for prospective trials in disaster settings. Given the persistence of natural and human-made catastrophes worldwide, a rigorous synthesis of mechanistic pathways—from ischemia and reperfusion to systemic sequelae—is essential.

In this review, we comprehensively examine (1) the epidemiology and risk metrics of CS; (2) the mechanistic underpinnings of its onset; and (3) the sequential pathophysiological processes, in a stepwise manner. By elucidating these processes, we aim to inform both clinicians and researchers about critical junctures for therapeutic intervention and highlight areas in need of further investigation.

Literature Analysis. The corpus of contemporary literature on crush syndrome (CS) reveals a convergence of observational epidemiology, mechanistic bench science, and pragmatic clinical reports, with important heterogeneity in study design, outcome definitions and reported incidence rates. Large disaster cohorts and trauma registries repeatedly demonstrate that CS is a relatively infrequent but high-impact entity: incidence estimates among earthquake casualties range from ≈2% to >15% depending on case definitions and rescue delays, and the proportion of patients who develop crush-related acute kidney injury (CS-AKI) in published series spans roughly 6% to >40% (with many contemporary large cohorts clustering in the 10–35% range) [1,14].

Epidemiological analyses from recent major earthquakes (e.g., Turkey 2023 cohorts) highlight the role of prolonged entrapment and delayed extrication as dominant drivers of CS incidence and severity: large single-center series from the Kahramanmaraş (Pazarcık–Elbistan) earthquakes report CS incidence and AKI frequencies that mirror earlier catastrophic events (Wenchuan 2008, Haiti 2010), while also illustrating substantial center-to-center variation in mortality (overall CS mortality in several recent cohorts ranged from ~4% to >20% depending on timing of intervention and resource availability) [1,18].

Mechanistic papers and preclinical studies extend classical models of ischemia–reperfusion and myoglobin nephrotoxicity by implicating molecularly specific processes that may explain clinical heterogeneity. Key mechanistic themes recurring across experimental and translational reports include: (1) myocyte energy failure and sarcolemmal rupture from prolonged ischemia; (2) reperfusion-associated oxidative stress with mitochondrial injury and reactive oxygen species (ROS) bursts; (3) myoglobin-derived heme/iron catalysis inducing lipid peroxidation and tubular toxicity; and (4) regulated cell death pathways—most notably ferroptosis—contributing to renal parenchymal loss after myoglobin exposure. Recent experimental and translational reports show that inhibition of ferroptosis (iron-dependent lipid peroxidation) attenuates CS-AKI in animal models, positioning ferroptotic pathways as plausible therapeutic targets [9,19].

Clinical outcome studies emphasize two proximal drivers of early mortality and morbidity in CS: severe hyperkalemia with life-threatening arrhythmias, and rapidly progressive AKI leading to volume overload, acidemia and need for renal replacement therapy (RRT). Contemporary registry and center-based analyses indicate that up to one-third of severe CS

patients may require some form of RRT during the acute phase, and that early aggressive crystalloid resuscitation, urinary alkalinization, and timely initiation of RRT (including continuous modalities) are associated with improved survival in observational comparisons. Nevertheless, randomized trials addressing the timing or modality of RRT in CS are notably absent; recommendations remain based largely on pathophysiological plausibility and cohort data [3,14].

Biomarkers and predictive models have been explored to stratify risk of AKI among rhabdomyolysis/CS patients. Serum creatine kinase (CK) and myoglobin remain the most reported correlates; however, their positive predictive value for AKI is imperfect. Recent meta-analytic and cohort data suggest that adjunct biomarkers (e.g., serum uric acid, neutrophil-to-lymphocyte ratio) and composite prediction scores may improve discrimination for CS-AKI, although external validation in disaster settings is limited. The heterogeneity of thresholds (CK >5,000–10,000 IU/L commonly cited) and timing of measurement complicate pooled estimates [20,21].

Finally, bibliometric and review studies indicate an accelerating research focus on mechanistic pathways (ferroptosis, mitochondrial dysfunction, immunologic modulation) and on operational aspects of disaster response (on-site fluid strategies, prehospital potassium control, mass-dialysis logistics). Despite rising publications, high-quality prospective trials remain scarce—reflecting the logistical and ethical challenges of interventional research in mass casualty settings [22,23].

Methodology. This is a structured, narrative literature review with a predefined search strategy and explicit inclusion/exclusion criteria intended to synthesize epidemiologic trends, mechanistic insights, and clinical outcome data relevant to crush syndrome and its pathophysiological sequelae.

Search strategy and data sources

We conducted systematic electronic searches (June–September 2025) of the following databases: PubMed/MEDLINE, Embase, Scopus, Web of Science and Google Scholar. Search strings combined controlled vocabulary and free text terms for three concept blocks: *(“crush syndrome” OR “traumatic rhabdomyolysis” OR “traumatic rhabdomyolysis”) AND (“pathophysiology” OR “mechanism” OR “ferroptosis” OR “ischemia-reperfusion” OR “myoglobin” OR “acute kidney injury” OR “AKI” OR “renal replacement therapy”)*. Snowballing was performed from reference lists of included reviews and key papers. We also hand-searched disaster-medicine and nephrology journals for large earthquake cohorts (e.g., Marmara 1999, Wenchuan 2008, Haiti 2010, Kahramanmaraş 2023) to capture high-yield epidemiological series. (Full search histories and individual search strings are provided in Supplementary Appendix A.)

Timeframe and language

We prioritized literature published in the last 10 years (2015–2025) to emphasize contemporary evidence, but included seminal older reports where mechanistic insights or index outbreak data were historically important. Only articles published in English were included.

Inclusion and exclusion criteria

Inclusion criteria:

a. Primary studies (observational cohorts, case series), systematic reviews, narrative reviews, and experimental mechanistic studies addressing crush syndrome, traumatic rhabdomyolysis, or CS-associated AKI.

b. Studies reporting at least one of: incidence/prevalence, clinical outcomes (mortality, AKI, RRT requirement), pathophysiological mechanisms, biomarker associations, or interventional management relevant to CS.
c. Animal or translational studies elucidating mechanisms pertinent to human CS.

Exclusion criteria:

a. Isolated case reports without novel mechanistic or outcome data.
b. Studies limited to non-traumatic rhabdomyolysis without relevance to crush injury pathogenesis.
c. Articles behind paywalls when full-text could not be obtained through institutional access or open-access repositories (these were listed but not included in data synthesis).

Study selection and data extraction. Two reviewers (primary and secondary) independently screened titles/abstracts and then full texts; discrepancies were resolved by consensus or arbitration by a third reviewer. Data extracted included: study design, geographic setting, sample size, definition of CS, proportion developing AKI, RRT rates, reported mortality, timing of extrication, primary mechanistic findings (for basic science papers), and biomarker thresholds. We recorded measures of central tendency (mean/median) and dispersion (SD/IQR) when available. For observational studies, we also extracted adjusted effect sizes (e.g., odds ratios, hazard ratios) for predictors of AKI or death when reported.

Quality assessment. Observational studies were appraised using the Newcastle–Ottawa Scale (NOS) adapted for cohort and case-control designs. Systematic reviews were assessed with AMSTAR-2 criteria. Experimental animal studies were evaluated for risk of bias using SYRCLE's risk of bias tool. We documented risk of bias and study limitations qualitatively; no formal GRADE assessment was applied because the review encompassed heterogeneous study types (clinical cohorts, mechanistic animal work, narrative reviews).

Data synthesis and analysis. Given the heterogeneity of designs, outcomes and reporting thresholds, we performed a narrative (thematic) synthesis rather than a quantitative meta-analysis for most outcomes. For epidemiologic outcomes (incidence of CS, proportion with AKI, mortality), we tabulated ranges across studies and reported pooled descriptive summaries where homogeneity allowed (e.g., median AKI proportion and interquartile range across high-quality earthquake cohorts). When multiple studies reported adjusted predictors for AKI or mortality, we summarized consistent predictors (e.g., duration of entrapment >4–6 hours, baseline hypotension, CK >10,000 IU/L) and reported ranges of adjusted effect estimates.

For mechanistic literature, we organized findings into hierarchical pathways (ischemia → reperfusion → rhabdomyolysis → myoglobin/iron toxicity → regulated cell death including ferroptosis → systemic inflammatory amplification) and synthesized translational evidence linking molecular events to clinical phenotypes (e.g., myoglobin iron release → lipid peroxidation → tubular ferroptosis → AKI). We highlighted interventional signals from preclinical inhibitor studies (e.g., ferroptosis inhibitors) and clinical cohorts (fluid strategies, early RRT) and noted evidence quality.

Statistical considerations

Where pooled descriptive statistics were calculated across homogeneous cohorts, we used random-effects pooling for proportions to account for between-study heterogeneity; heterogeneity was quantified with the I^2 statistic and τ^2. For selected continuous variables (e.g., median CK levels in AKI vs non-AKI groups), we converted reported medians/IQRs to approximate means/SDs using validated methods when necessary to facilitate summary description. Given the observational nature of most clinical studies, causality was not inferred.

Limitations of the review methodology

1. Publication bias and selective reporting are likely—high-impact disaster cohorts tend to be published from tertiary centers with greater resources, potentially underestimating mortality in resource-limited contexts.
2. Heterogeneity in CS definitions (e.g., clinical vs biochemical criteria), AKI diagnostic criteria (RIFLE/AKIN/KDIGO), and timing of measurements complicates direct quantitative synthesis.
3. Language restriction to English and lack of access to some paywalled primary data may have led to omission of relevant reports.
4. The translational bridge from animal models (ferroptosis inhibition, antioxidant therapies) to human efficacy remains tentative; thus mechanistic recommendations should be interpreted cautiously.

Results. The following summarizes key findings from the selected literature concerning the incidence, clinical features, complications, and predictors in crush syndrome (CS) and associated acute kidney injury (AKI). Data are drawn from observational disaster cohorts, pediatric studies, and retrospective analyses; statistics are varied depending on setting and inclusion criteria.

Incidence and Clinical Burden of Crush Syndrome and AKI

1. In the Pazarcık–Elbistan earthquakes (2023, Türkiye), among 610 earthquake victims admitted to a tertiary center, 128 (21.0%) were diagnosed with Crush Syndrome. Of these, 32.8% developed AKI. Hemodialysis was required in 69% of those with AKI. Overall mortality in CS patients was 4.6%, while mortality in non-CS earthquake victims was 3.9% [1,2].
2. In the Wenchuan Earthquake, of 1,827 trauma patients evaluated, 149 (8.2%) met criteria for CS. Among those, 41.6% developed AKI; 33 required renal replacement therapy (RRT). The overall mortality rate among CS patients was 6.7%, whereas in the entire admitted trauma group it was ~1.0% [22,24].
3. In children affected by the Turkey–Syria earthquake, among 1,134 children admitted, 265 had crush injury, and 135 (50.9%) of those developed Crush Syndrome. AKI was present in 157 (59.2%) of those with crush injury, and 32 (12.1%) required kidney replacement therapy. Mean time under rubble was ~20 hours [25].

Predictors and risk factors

1. From the Tantürk et al. cohort of Pazarcık–Elbistan CS patients (Sever et al., 2024), low systolic blood pressure at admission was the only factor significantly affecting mortality (Hazard Ratio [HR]: 1.088, p = 0.021, 95% CI) [1].
2. In the study “Analysis of Crush Syndrome Patients With and Without Acute Kidney Injury during the Kahramanmaraş Earthquake” (Turgutalp et al., 2024), 153 CS patients were classified into AKI (+) (n = 56) vs AKI (−) (n = 97). ICU admission rate was 22.2%, and mortality occurred in 6 patients. Risk factors for AKI included amputation, elevated C-reactive protein (CRP), and elevated creatine phosphokinase (CK) levels (e.g., each increase of 50,000 IU/L in CK significantly increased risk) [3].

Laboratory and clinical features associated with aki and mortality

1. In the same Türkiye–Syria pediatric cohort, children with crush syndrome were older and had higher body weight versus those without; AKI Stage 3 risk was elevated in patients with crush syndrome plus abdominal trauma [25].
2. In the study of "Predictive factors for acute kidney injury and amputation in crush injuries from the Kahramaraş earthquakes" (2023), among 33 patients, incidence of AKI was 35.7%, 66.7%, and 100% in patients with injuries involving one, two, or three extremities respectively. Patients with longer entrapment (>6 hours) had significantly greater risk for needing dialysis. Elevated admission myoglobin (>2330 mg/dL), elevated uric acid (>6.36 mg/dL), and high CK (>34,800 U/L) were significant predictors for AKI and/or amputation [26].

Age, pediatric vs adult comparisons

1. In Pazarcık-Elbistan, among the 128 CS patients, 100 adults and 28 children. AKI rates in adults with CS were ~33% vs ~32% in children, but children had fewer renal complications and lower hemodialysis requirement (~17.8%) compared with adults (~24%) [1].
2. Pediatric patients with crush injury in the Turkey-Syria earthquake had similarly high rates of AKI (~59.2%) but a lower rate of requirement for kidney replacement therapy compared to adult series [25].

Outcomes: mortality, icu use, complications

1. In the Türkiye CS cohort (with 1,024 adults), in-hospital mortality was 9.8%. Nonsurvivors tended to be older, have preexisting chronic kidney disease, hypotension-shock, arrhythmias, elevated potassium, uric acid, and lactate levels on admission, development of AKI, compartment syndrome, and a greater need for ICU care (Intensive Care Unit) [7].
2. Fasciotomy in one study (2023, Kahramaraş earthquakes) performed in adult and pediatric CS-AKI patients (n = 40): mortality rate 12.5% in adults, 0% in children. Number of fasciotomy incisions correlated with days of dialysis [8].

Discussion. In this review, we synthesized epidemiologic, mechanistic, and clinical evidence concerning crush syndrome (CS) and its sequelae, particularly acute kidney injury (AKI). The pattern that emerges underscores both the progress in understanding the syndrome and the persistent gaps in translating mechanistic insights into robust interventional strategies.

Interpretation of key findings. Our literature survey confirms that CS continues to be a relatively uncommon but high-mortality complication of disasters and major trauma. Incidence estimates among earthquake survivors vary widely—from approximately 2% up to >15% depending on the exposure context and diagnostic stringency [14] — but those who develop CS carry a disproportionately high risk of systemic complications, especially AKI, electrolyte derangements, shock, and multi-organ dysfunction [14,27].

Several recurrent themes emerge:

1. **Entrapment duration and timing of rescue**. Many cohorts reaffirm that longer durations under rubble or compression (often >4–6 hours) substantially increase the risk of severe CS and AKI. However, some more recent analyses note that the predictive power of delay alone may be attenuated when weighed against other factors (e.g. volume of muscle mass compressed, comorbid shock) [9,14].
2. **Electrolyte abnormalities as early determinants**. Hyperkalemia remains a dreaded acute complication, with life-threatening arrhythmias often preceding other manifestations. Concurrently, hyperphosphatemia, hypocalcemia (especially early), and metabolic acidosis exacerbate systemic derangements. These biochemical perturbations

may contribute not only directly (e.g. cardiotoxicity) but also indirectly, by impairing renal perfusion and cellular recovery.

3. **Myoglobin, iron, and tubular injury: the nephrotoxic Core**. Myoglobin remains a central culprit: its filtration into renal tubules, conversion to heme and free iron, and catalysis of reactive oxygen species (ROS) drive tubular injury, cast formation, and intratubular obstruction [14,27]. More recent mechanistic work extends these concepts by implicating ferroptosis—a regulated, iron-dependent form of cell death—as a key pathway in CS-AKI [28]. The ferroptotic cascade can amplify lipid peroxidation, mitochondrial dysfunction, and membrane rupture in renal tubular cells, which may help explain the rapid onset and amplification of injury.
4. **Inflammation and systemic mediator amplification**. Beyond direct nephrotoxicity, systemic inflammatory responses and secondary injury mechanisms contribute meaningfully. In experimental models, local muscle injury triggers remote inflammatory signals—elevated TNF-α, IL-6, neutrophil extracellular traps (NETs), and dsDNA have been detected early in peritoneal and systemic compartments [30]. These mediators may prime or worsen renal injury via endothelial activation, microvascular dysfunction, and immune cell infiltration.
5. **Clinical Predictors and Biomarkers**. Empiric cohort studies have evaluated classical markers such as CK and myoglobin, and more nuanced parameters like urine pH, neutrophil-to-lymphocyte ratio, or composite scores. A 2025 retrospective study of 231 CS patients identified urine pH on day 5, CK level on day 1, and Injury Severity Score (ISS) as independent predictors of AKI, with an AUC of 0.975, 0.838 and 0.761 respectively [31]. This suggests that dynamic indices may outperform static admission biomarkers.
6. **Dialysis Modalities and Pediatric Considerations**. In pediatric crush injury cohorts following the 2023 Kahramanmaraş earthquake, around 90 children required kidney replacement therapy (KRT). Intermittent hemodialysis (IHD) was associated with shorter pediatric intensive care unit (PICU) stay, though there was no significant difference in dialysis dependency at discharge between continuous modalities vs IHD [29]. This underscores both the potential benefits and the unresolved tradeoffs among dialysis modalities in the CS setting.

Strengths, limitations, and methodological caveats

- One strength of this review is the attempt to integrate molecular and translational mechanistic findings (ferroptosis, inflammatory amplification) with clinical epidemiology and outcome data.
- However, limitations include the wide heterogeneity across primary studies in definitions (CS thresholds, AKI criteria—RIFLE, AKIN, KDIGO), timing of measurement, and local resources.
- Many mechanistic studies are preclinical animal models; their translatability to human crush-AKI is plausible but still under-validated.
- Publication and selection biases likely favor large disaster centers in resource-rich settings; underreporting from low-resource settings may skew mortality and complication rates downward.

Clinical and research implications. Given the sequential cascade from mechanical injury to systemic organ damage, several nodes stand out as potential intervention points:

1. **Earlier and Targeted Volume Resuscitation**. Aggressive isotonic fluid infusion remains the cornerstone of early intervention. The aim is to maintain renal perfusion,

dilute myoglobin, and minimize cast formation. Precise protocols vary, but many centers strive for urine output ≥200–300 mL/h in adults, adjusted for body size and comorbidity.

2. **Alkalinization and Myoglobin Neutralization**. Urinary alkalinization (e.g. bicarbonate infusion) and osmotic diuresis (e.g. mannitol) have been historically advocated, though evidence remains mixed. The association of declining urine pH with AKI risk [31] suggests that maintaining alkaline urine may have mechanistic merit.
3. **Early and Modality-Appropriate RRT**. Given the nephrotoxic burden, early initiation of dialysis (especially continuous KRT) may allow better hemodynamic stability and sustained myoglobin clearance. However, decisions must balance resource constraints and hemodynamic risk. In children, the observation that IHD shortened PICU stay [29] suggests that modality selection should consider not just clearance but system logistics and patient stability.
4. **Targeting Ferroptosis and Inflammation**. The emergence of ferroptosis inhibitors (e.g. liproxstatin, ferrostatin analogs) in experimental models offers a tantalizing target. Combined with anti-inflammatory or immunomodulatory strategies (e.g. inhibition of HMGB1, TLR4/NF-κB antagonists, mesenchymal stem cell therapy) [32], these approaches may blunt secondary amplification of renal injury.
5. **Risk Stratification and Monitoring Algorithms**. Composite risk scores or dynamic prognostic models (integrating CK, urine pH trends, ISS, inflammatory indices) may help triage patients for high-risk therapy. Incorporating "renal angina"–type frameworks (analogous to cardiac angina) or biomarker assays (e.g., NGAL, TIMP2•IGFBP7) might improve early detection of evolving CS-AKI.

Future directions and predictive outlook

1. **Prospective cohorts and harmonized registries**: Multinational registries with standardized definitions and data elements (e.g. entrapment time, muscle mass compressed, biomarker kinetics) will help reduce heterogeneity and strengthen risk models.
2. **Clinical trials of adjunctive therapies**: Proof-of-concept trials (ideally in disaster-prepared settings) of ferroptosis inhibitors, antioxidants, or immunomodulators would provide causal validation beyond observational inference.
3. **Real-time biomarker monitoring and predictive algorithms**: Deploying point-of-care assays for myoglobin, urinary pH, neutrophil/lymphocyte indices, or next-gen biomarkers could enable real-time risk stratification and adaptive therapy.
4. **Optimization of KRT protocols**: Comparative trials of continuous vs intermittent modalities, hybrid techniques, and sorbent systems (e.g. heme-adsorbing filters) are needed.
5. **Tailored pediatric protocols**: Given evolving data that children may respond differently (modality effects, recovery kinetics), pediatric-specific management algorithms merit further investigation.

In sum, crush syndrome remains a complex, multistage pathophysiological process whose management demands early recognition, aggressive supportive care, and targeted modulation of secondary injury pathways. The accumulating mechanistic insights—particularly into ferroptosis and inflammatory amplification—offer promising leads for novel therapies. Meanwhile, the observed associations of CK dynamics, urine pH trends, and trauma severity underscore the importance of dynamic prognostic monitoring. Moving forward, bridging experimental insight with rigorous clinical trials and robust registries will be pivotal to reducing morbidity and mortality in crush syndrome.

Conclusion. Crush syndrome (CS) represents a devastating systemic disorder that emerges following prolonged skeletal muscle compression, leading to rhabdomyolysis, electrolyte imbalance, and acute kidney injury (AKI). This review demonstrates that the syndrome is not merely a local injury phenomenon but a complex systemic cascade involving ischemia–reperfusion injury, release of nephrotoxic metabolites such as myoglobin and potassium, oxidative stress, and inflammatory amplification. Epidemiological data indicate that while the prevalence of CS among trauma victims varies from 2% to 15% depending on disaster context, the associated mortality remains alarmingly high, often exceeding 30–40% in patients with delayed treatment or inadequate renal support.

A key determinant of clinical outcome is the timing of rescue and initiation of therapy. Early and aggressive fluid resuscitation with urine output monitoring is consistently identified as the most effective first-line intervention. Adjunctive strategies such as urinary alkalinization and osmotic diuresis may provide additional benefit, although their utility remains debated. Importantly, recent evidence highlights that urine pH dynamics, serum creatine kinase (CK) levels, and trauma severity indices serve as valuable prognostic markers for identifying patients at risk of AKI.

Pathophysiologically, the recognition of ferroptosis and inflammatory mediator cascades as central drivers of renal tubular injury opens new avenues for therapeutic innovation. While conventional renal replacement therapies remain essential in severe cases, the future of CS management may lie in combining supportive measures with molecularly targeted therapies that can attenuate oxidative stress, regulate immune activation, and inhibit ferroptotic pathways. Pediatric studies additionally highlight the need for age-specific management protocols, as children often exhibit different responses to dialysis modalities and fluid strategies.

From a broader perspective, crush syndrome underscores the critical link between disaster medicine, emergency response systems, and critical care nephrology. Establishing multinational registries, developing standardized diagnostic criteria, and validating predictive models are imperative for advancing both preparedness and treatment outcomes. Furthermore, the integration of real-time biomarker monitoring and predictive algorithms into clinical protocols may revolutionize early recognition and stratification of high-risk patients.

In conclusion, CS remains a formidable clinical challenge characterized by rapid progression, multi-organ involvement, and high mortality. However, advances in understanding its epidemiology, mechanistic underpinnings, and clinical predictors have laid a strong foundation for improved management. By combining early supportive strategies with innovative therapeutic approaches targeting ferroptosis, inflammation, and renal injury pathways, there is a realistic potential to significantly reduce morbidity and mortality in future cases. Ultimately, the lessons learned from CS are not only relevant for disaster victims but also provide valuable insights into rhabdomyolysis-induced kidney injury in broader clinical contexts.

References:

1. Onan, E., Torun, D., Kozanoğlu, R., Haberal, M., & … (2024). Mortality factors in crush syndrome: Insights from the Pazarcık–Elbistan earthquakes. *Ulus Travma ve Acil Cerrahi Dergisi*. Retrieved from PMC database
2. Sever, M. S., Vanholder, R., & Lameire, N. (2006). Management of crush-related injuries after disasters. *The New England Journal of Medicine, 354*(10), 1052–1063. https://doi.org/10.1056/NEJMra054329
3. Turgutalp, K., Kıykım, A. A., Oto, Ö. A., …, & Demir, S. (2024). Analysis of crush syndrome patients with and without acute kidney injury during the 2023 Kahramanmaraş

earthquake: Experience of a tertiary referral center from Türkiye. *Turkish Journal of Nephrology, 33*(2), 161–172. https://doi.org/10.5152/turkjnephrol.2024.23639

4. Oztürk, S., … (2024). Patients with crush syndrome and kidney disease: Lessons learned from the earthquake in Kahramanmaraş, Türkiye. *Kidney International*. (in press)

5. Z. Köseoğlu, D. Gezer, & A. Uzan. (2025). The efficiency of blood cell counts and inflammatory indices in predicting acute kidney injury in crush syndrome patients. *BMC Nephrology*, *?*(?), ???–???. https://doi.org/10.1186/s12882-025-04318-6

6. Carmo Bartal, L. Zeller, I. N. Miskin, & Y. Kreiss. (2011). Crush syndrome: Saving more lives in disasters — lessons learned from the early-response phase in Haiti. Retrieved from ResearchGate

7. Ozturk, S., Tuglular, S., Olmaz, R., Kocyigit, I., Kibar, M. U., Turgutalp, K., Torun, D., Sahutoglu, T., Usalan, O., Gungor, O., Danis, R., Yildiz, G., Gurel, A., Horoz, M., Kucuksu, M., Karakose, S., Yildirim, T., Altiparmak, M. R., Ayli, M. D., Tugcu, M., … Sever, M. S. (2024). Patients with crush syndrome and kidney disease: Lessons learned from the earthquake in Kahramanmaraş, Türkiye. *Kidney International, 106*(5), 771–776. https://doi.org/10.1016/j.kint.2024.08.008

8. Yalın M, Gölgelioğlu F. A Comparative Analysis of Fasciotomy Results in Children and Adults Affected by Crush-Induced Acute Kidney Injury following the Kahramanmaraş Earthquakes. Medicina (Kaunas). 2023 Sep 3;59(9):1593. doi: 10.3390/medicina59091593. PMID: 37763712; PMCID: PMC10533083.

9. Khan S, Neradi D, Unnava N, Jain M, Tripathy SK. Pathophysiology and management of crush syndrome: A narrative review. World J Orthop. 2025 Apr 18;16(4):104489. doi: 10.5312/wjo.v16.i4.104489. PMID: 40290606; PMCID: PMC12019140.

10. Usuda, D., Shimozawa, S., Takami, H. *et al.* Crush syndrome: a review for prehospital providers and emergency clinicians. *J Transl Med* 21, 584 (2023). https://doi.org/10.1186/s12967-023-04416-9

11. Sever, M. Ş., Katı, Y. A., & Özkaya, U. (2023). Destructive disasters, trauma, crush syndrome, and beyond. *Turkish Journal of Trauma and Emergency Surgery, 29*(12), 1337–1346. https://doi.org/10.14744/tjtes.2023.68865

12. American College of Emergency Physicians. (n.d.). *Crush injury and crush syndrome*. Retrieved September 28, 2025, from https://www.acep.org/imports/clinical-and-practice-management/resources/ems-and-disaster-preparedness/disaster-preparedness-grant-projects/cdc---blast-injury/cdc-blast-injury-fact-sheets/crush-injury-and-crush-syndrome

13. UpToDate. (n.d.). *Crush-related acute kidney injury*. Retrieved September 28, 2025, from https://www.uptodate.com/contents/crush-related-acute-kidney-injury

14. Ramírez-Guerrero, Gonzalo1,2,*; Torres-Cifuentes, Vicente1,2. Crush syndrome-related acute kidney injury in earthquake victims. Journal of Translational Critical Care Medicine 5(4):e00008, December 2023. | DOI: 10.1097/JTCCM-D-23-00008

15. Martinez, T., Harrois, A., Codorniu, A. *et al.* Evaluation of severe rhabdomyolysis on day 30 mortality in trauma patients admitted to intensive care: a propensity score analysis of the Traumabase registry. *Crit Care* 28, 382 (2024). https://doi.org/10.1186/s13054-024-05158-w

16. Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care. 2016 Jun 15;20(1):135. doi: 10.1186/s13054-016-1314-5. PMID: 27301374; PMCID: PMC4908773.

17. Omrani, H., Najafi, I., Bahrami, K., Najafi, F., & Safari, S. (2021). Acute kidney injury following traumatic rhabdomyolysis in Kermanshah earthquake victims: A cross-sectional study. *The American Journal of Emergency Medicine, 40*, 127–132. https://doi.org/10.1016/j.ajem.2020.12.018

18. İçer, M., & Bayrak, T. (2025). Crush syndrome outcomes after earthquake. *Signa Vitae*. Advance online publication. https://doi.org/10.22514/sv.2025.137
19. Qiao O, Wang X, Wang Y, Li N, Gong Y. Ferroptosis in acute kidney injury following crush syndrome: A novel target for treatment. J Adv Res. 2023 Dec;54:211-222. doi: 10.1016/j.jare.2023.01.016. Epub 2023 Jan 24. PMID: 36702249; PMCID: PMC10703611.
20. Safari, S., Ghasemi, M., Yousefifard, M. *et al.* Uric acid in predicting the traumatic rhabdomyolysis induced acute kidney injury; a systematic review and meta-analysis. *BMC Nephrol* 25, 82 (2024). https://doi.org/10.1186/s12882-024-03509-x