THE KIDNEY AT RISK: UNDERSTANDING CRUSH SYNDROME-RELATED ACUTE KIDNEY INJURY

Özgür Akın OTO1, Mehmet Şükrü SEVER1

1Istanbul University, Istanbul Faculty of Medicine, Department of Nephrology, Istanbul, Turkiye

ORCID IDs of the authors: Ö.A.O 0000-0003-0928-8103; M.Ş.S. 0000-0002-6074-2239

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ABSTRACT

Crush syndrome (systemic manifestations of traumatic rhabdomyolysis) is the second leading cause of death after earthquakes or other destructive disasters. Crush-related acute kidney injury (AKI) is the most important Component of crush syndrome, and medical professionals living in disaster-prone regions should know about its pathophysiology, clinical and laboratory features, complications, and treatment. Pathogenesis of AKI on the basis of crush injuries is multifaceted. The most important mechanism is compartment syndrome-related hypovolemia, and consequent renal hypoperfusion, which may result in ischemic acute tubular necrosis. Also, rhabdomyolysis-related myoglobinuria may result in the formation of kidney-damaging myoglobin casts and direct tubular toxicity. Formation of uric acid plugs, oxidant injury, increased serum levels of cytokines, and still many other factors may take a role in the pathogenesis as well. Crush syndrome can cause serious electrolyte imbalances, sepsis, and bleeding, which can further exacerbate AKI. Early recognition and appropriate management, which includes aggressive hydration and management of electrolyte imbalances can help to prevent or minimize kidney damage. This review provides an overview of the pathophysiology, complications, and treatment of AKI in the context of Crush syndrome.

Keywords: Crush syndrome, acute Kidney injury, rhabdomyolysis

ÖZET


Anahtar Kelimeler: Ezilme sendromu, akut böbrek hasan, rhabdomyoliz

Corresponding author/İletişim kurulacak yazar: Özgür Akın OTO – maviozgurluk@gmail.com
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INTRODUCTION

Crush syndrome is the second most frequent cause of death after earthquakes and can lead to several complications, including acute kidney injury (AKI), sepsis, acute respiratory distress syndrome, bleeding, hypovolemic shock, cardiac failure, arrhythmias, electrolyte disturbances, and psychological trauma (1).

Crush-related AKI is a life-threatening complication of crush injuries that can occur after destructive natural disasters or man-made catastrophes. It is essential for medical professionals, especially those living in disaster-prone regions, to have knowledge about the pathophysiology, complications, and treatment of this condition.

Crush injuries can cause damage to the kidneys due to the compression of muscle tissues, leading to baromypathy-related compartment syndrome, and rhabdomyolysis, a condition that results in the release of myoglobin into the bloodstream (2). These events can lead to hypovolemia, hypoperfusion of the kidneys, formation of kidney-damaging myoglobin casts, and finally AKI. In addition, traumatic rhabdomyolysis can cause electrolyte imbalances, sepsis, and bleeding, which can further exacerbate kidney injury (3-5).

Medical professionals should be aware of the signs and symptoms of crush-related AKI, including decreased urine output, elevated serum creatinine and blood urea nitrogen levels, and electrolyte imbalances. Early recognition and appropriate management, including aggressive hydration and management of electrolyte imbalances, can help prevent or minimize kidney damage.

This review focuses on the pathophysiology, complications, and treatment of AKI, which is a major component of Crush syndrome.

Definitions

“Crush injury” indicates a direct injury by collapsing material and debris causing manifest muscle swelling and/or neurological disturbances in the affected parts of the body. The injury to the soft tissues, muscles, and nerves can be a result of primary direct trauma and ischemia secondary to compression. A severe crush injury can lead to muscle necrosis (rhabdomyolysis) and subsequent complications.

Rhabdomyolysis refers to the destruction of striated muscle cells, resulting in the release of intracellular components into the bloodstream. This condition can arise from traumatic or non-traumatic causes and may result in a range of clinical and laboratory abnormalities. Nontraumatic rhabdomyolysis may develop on the basis of ischemic, genetic/metabolic, toxic, and oncologic factors (6). While various cutoff limits for serum creatine phosphokinase (CK) levels have been suggested for diagnosing rhabdomyolysis, generally, levels exceeding five times the upper limit of normal for a given local laboratory are considered indicative of the condition. The cutoff values have been proposed to range from 500 to 3000 U/L (7-9).

Crush syndrome is a pathological condition resulting from systemic manifestations of traumatic rhabdomyolysis. This condition is primarily caused by the compression of muscle tissue for a sustained period of time, leading to hypovolemia, muscle necrosis, and the release of various intracellular contents, such as myoglobin, potassium, uric acid, phosphorus, thromboplastin, nucleic acids, creatine, and creatine phosphokinase. Hypovolemia and increased serum levels of these substances can have toxic effects on various organs and systems, leading to a range of systemic manifestations. The clinical manifestations of Crush syndrome include AKI, sepsis, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), hypovolemic shock, cardiac failure, arrhythmias, and electrolyte disturbances (10).

Factors affecting AKI incidence in disaster victims

Crush syndrome occurs in 2-5% of victims of catastrophic earthquakes and 30-50% of traumatic rhabdomyolysis patients (11, 12). Pediatric patients have a lower risk of experiencing crush-related injury and mortality (12).

Acute kidney injury incidence in disaster victims is affected by various factors such as the severity of the disaster, population density of the affected area, quality of buildings, timing, and effectiveness of rescue efforts. The efficacy of rescue efforts is a crucial factor, as delayed or inefficient rescue efforts result in more deaths and fewer cases of AKI. Hence, disasters with similar intensity may result in marked differences in AKI numbers. For example, the incidence of AKI was almost four times higher in the Bam earthquake in Iran than in the Gujarat earthquake in India, despite both having approximately 20,000 deaths (13). The difference was explained by the daytime occurrence of the Gujarat disaster, thus instant deaths due to head trauma (14). The collapse of the Twin Towers in New York resulted in only one case of AKI despite more than 3000 deaths (15).

In some disasters, the need for dialysis was high. For instance, the Kobe earthquake had a dialysis requirement of 54%, and the Marmara earthquake had a dialysis requirement of 75% (16, 17). Dialysis was required in 6.5% of 1975 patients admitted to the hospital in the Bam earthquake, and the majority of victims were rescued in less than four hours, which might explain the lower rate of dialysis requirement compared with other reports (18). In the Kobe earthquake, the need for hemodialysis was directly correlated with increased serum creatine kinase levels (17). Therefore, the severity of traumatic rhabdomyolysis is a crucial factor in the development of AKI in disaster victims.
Earthquakes and acute kidney injury: Pathophysiological links
Pathophysiology of Crush syndrome can be considered under the headings of 1) Pathogenesis of traumatic rhabdomyolysis, and 2) pathogenesis of rhabdomyolysis-induced AKI as well as other systemic symptoms and signs of rhabdomyolysis (Crush syndrome) (2). Compression of the muscles (baromyopathy) is the initial event in traumatic rhabdomyolysis, which causes an increased permeability of sarcolemma (2). Consequently, substances abundant within the muscle cells (i.e. potassium, myoglobin, phosphate), move to the extracellular environment, while, sodium, chloride, water, and calcium diffuse into the cell, according to their electrochemical gradients, which results in cellular swelling (leading to “compartment syndrome”) (19). Increased intracellular calcium activates proteolytic enzymes that cause lysis of the muscle fibers (rhabdomyolysis). Muscular ischemia on the basis of increased intramuscular pressure as well as ischemia-reperfusion injury, which develops during the rescue of the victims, contribute to the pathogenesis of muscle cell necrosis (20).

The details of these pathophysiological processes are as follows. After surpassing a critical threshold of free calcium concentration, persistent muscle contraction occurs, leading to the depletion of ATP reserves. This, in turn, triggers mitochondrial impairment, causing oxidative stress, and activating proteases, phospholipases, and other enzymes that cause damage to myofibrils and membrane phospholipids. The outcome is the breakdown of myocytes and the discharge of harmful intracellular components into the extracellular microenvironment. Local accumulation of these products causes microvasculature damage, producing capillary leak, subsequently causing the compartmental syndrome, which increases pressure on the capillaries triggering occlusion of the microcirculation and rapidly depleting myoglobin oxygen content. Similarly, creatine, phosphate, and glycogen stores are exhausted as well, and severe ATP depletion ensues (21). However, in ischemic tissue injury, most of the damage occurs after flow into the damaged tissue is restored. In this case, leukocytes migrate into these particular tissues after reperfusion has started, and the production of free radicals starts after the availability of oxygen (reperfusion injury) (22). In cases of limb injury or compression, intramuscular pressure can exceed 240 mm Hg, resulting in ischemia and potentially causing rhabdomyolysis. It is possible for compartment syndrome to occur independently and result in full-blown rhabdomyolysis, despite the presence of normal arterial pedal pulses and warm skin in patients with anterior tibial compartment syndrome (19).

The primary pathophysiological mechanisms involved in the development of AKI are hypovolemia-induced renal hypoperfusion, renal vasoconstriction, intraluminal cast formation, and direct cytotoxicity induced by myoglobin (23). Inflammation plays a crucial role in this process, as it triggers the storage of large amounts of body water in the muscle tissue, leading to limb swelling and compression of blood vessels and nerves, known as compartment syndrome. This inflammation also leads to severe hypovolemia, a major cause of AKI.

Decreased circulating calcium levels can lead to immediate negative cardiac inotropism and arrhythmias, further worsening kidney hypoperfusion contributing to AKI (7). Later, calcium may also induce tissue calcification (24).

One of the critical compounds released from muscle cells is potassium. Hyperkalemia, in combination with hypocalcemia, provokes arrhythmias and negative inotropism, making it pathophysiologically more devastating. High anion gap acidosis, further exacerbates hyperkalemia. Phosphorus release causes hyperphosphatemia, worsening of hypocalcemia, and leads to calcium-phosphorus deposits in the kidneys (6).

During rhabdomyolysis, large amounts of myoglobin are released from the muscle tissue and filtered by the glomeruli. This leads to tubular cast formation and obstruction, particularly in cases of hypovolemia, increasing the risk of AKI (25). The liver metabolizes myoglobin to bilirubin, which is also a nephrotoxic agent. Finally, nucleotide release causes hyperuricemia, which is another cause of cast formation and kidney damage (26).

In disaster situations, victims are at high risk of AKI due to various precipitating factors beyond rhabdomyolysis. These factors include bleeding, dehydration, sepsis, urinary tract obstruction, surgical interventions, and intoxication. In addition, the chaotic nature of emergency situations in disasters can lead to incompatible blood transfusions, which may cause further kidney damage (13).

Acute kidney injury in crush-related injuries: Causes and manifestations
AKI may range from mild to severe and can even require dialysis. The severity of AKI depends upon various factors such as the extent of muscle injury, degree of volume...
depletion, presence or absence of underlying comorbid conditions, and the development of complications such as sepsis (5, 8). Similar to other types of AKI, crush-associated AKI can originate mainly from three distinct etiologies: prerenal, intrarenal, and postrenal.

Prerenal AKI can occur due to severe hypovolemia, which is common among victims of crush-related injuries. The loss of access to water while being trapped for hours or days leads to ongoing losses resulting in negative fluid balance. Vascular injury can cause bleeding leading to hypovolemic shock. Upon rescue, decompression at the sites of muscle injury can result in reperfusion-related third spacing of fluid leading to compartment syndrome, hypovolemia, and prerenal AKI (21).

Intrarenal AKI is typically caused by rhabdomyolysis. The characteristic manifestation of rhabdomyolysis-related acute tubular necrosis (ATN) is dark red, brown, or black urine. However, urine may not be discolored in some patients with rhabdomyolysis-related ATN if their urine is diluted from aggressive fluid resuscitation. Microscopic evaluation of the urinary sediment often reveals pigment-granular casts. AKI resulting from heme pigment-induced ATN is usually characterized by an initial oliguric period, followed by polyuria, which usually starts within one to three weeks after the primary event. Some cases may present with a non-oliguric course. Although not a general rule, the first stage of AKI following a crush injury is typically characterized by oliguria, which can last 7 to 21 days (27). Oliguric AKI is generally associated with a poor prognosis (5, 28). During the early oliguric phase of AKI following crush, patients are subject to more severe uremia and fluid-electrolyte disturbances.

Other causes of intrarenal AKI include ischemic or toxic injury from prolonged shock, sepsis, use of nephrotoxic agents, cardiac failure, arrhythmias, or transfusion reactions. Postrenal AKI may develop due to traumatic injury or obstruction of the urinary outflow tract, mostly in patients suffering from pelvic trauma.

Diagnostic markers and other metabolic abnormalities
Rhabdomyolysis is a condition characterized by the release of creatine kinase (CK) from damaged muscles into the circulation. This can result in a significant increase in serum CK levels, with levels peaking within 24 hours of injury and declining thereafter (29). While the degree of CK elevation does not always predict the development of AKI, there is a weak correlation between peak CK level and serum creatinine (23). Mildly elevated CK-MB levels may be seen in the absence of myocardial involvement. In addition to CK, peak plasma myoglobin levels may also correlate with AKI, but this test is less commonly used in clinical practice. CK levels can rise dramatically after muscle injury, but the degree of elevation does not always correlate with the development of AKI. Patients with peak CK levels >16,000 units/L are more likely to develop AKI, but AKI is uncommon when peak CK levels are under 5000 to 10,000 units/L (30). Myoglobin levels may correlate more closely with AKI than CK, but myoglobin levels may have resolved by the time the patient presents with AKI (31).

Abnormalities of serum calcium are common. Hypocalcemia can occur in up to two-thirds of patients, and it is due to the increase in serum phosphate and the subsequent deposition of calcium phosphate into injured muscle, as well as decreased bone responsiveness to parathyroid hormone (PTH). Hypercalcemia can occur during the recovery phase of rhabdomyolysis in up to 20 to 30% of patients (32, 33). This is due, in part, to the mobilization of calcium that has been deposited in the injured muscle.

Phosphate may also be elevated in patients with rhabdomyolysis, leading to hyperphosphatemia and a mild to moderate high anion gap acidosis (7).

Intra-myocyte enzymes, including AST, ALT, LDH, and aldolase, may also increase in patients with rhabdomyolysis. These may be the first biochemical abnormalities to be detected, and they are often initially misinterpreted as indicating liver disease.

Patients with rhabdomyolysis may exhibit hyperuricemia due to the discharge of nucleosides from impaired myocyte nuclei, leading to the synthesis of purines in the liver and their eventual conversion to uric acid. In severe cases of rhabdomyolysis, thromboplastin release from cells may cause the onset of disseminated intravascular coagulation (7).

Prevention
The importance of early and adequate fluid resuscitation to prevent AKI in patients with rhabdomyolysis due to crush injury is well established (34). Studies on fluid resuscitation have mostly come from retrospective reports of rhabdomyolysis in subjects with crush injuries. Inadequate volume repletion can result in AKI, and therapy instituted much later can increase the incidence of AKI in over 50% of patients (35).

Crush syndrome-related AKI can be prevented by enhancing kidney perfusion and increasing urine flow to wash out obstructing casts. The goal of preventive therapy is to correct volume depletion as soon as possible. Fluid administration should be started before extrication in entrapped subjects who are prone to develop Crush syndrome. The volume of fluids should be adjusted at a rate of 1 L per hour. Patients with rhabdomyolysis may require massive amounts of fluid (up to 20 liters) to trigger and maintain a vigorous diuresis. Children similarly require early and aggressive fluid resuscitation (36). Fluid administration should be closely monitored, with the timing and rate of fluid administration, volume of fluids, and
It is important to note that the optimal type and rate of fluid repletion may vary depending on the individual patient's medical condition and response to treatment.

Generally, the recommended fluid administration rate for the first 24 hours is 500 mL/hour, provided there is no evidence of fluid overload, and the patient can be closely monitored. The rate of fluid administration is reduced after the first 24 hours but is still maintained at a rate higher than the urine output if there is no evidence of fluid overload. The amount of fluid administered to a patient is influenced by various factors such as age, weight, medical history, and the specific clinical scenario. The appropriate fluid balance is crucial in the early stages of treatment. In the early phase of Crush syndrome, excessive fluid can seep into the damaged muscles, making fluid administration critical. For an adult weighing 75 kg and with an appropriate urine response, up to 12 L of fluid can be administered per day. After the infusion of this solution, one can expect a urinary output of 8 liters. Therefore, it is reasonable to give 4 to 4.5 L more fluid than the total losses of the previous 24-hour period (19). In chaotic disaster situations where monitoring patients is difficult, fluid administration should be less aggressive to avoid volume overload (37). In these circumstances, it is recommended to give a more modest volume of fluids, up to a maximum of 6 L per day when close monitoring is not possible. In older adults or anuric patients, who are prone to cardiac failure, it is particularly important to be cautious when repleting fluids.

However, in the absence of direct comparative studies, the Renal Disaster Relief Task Force (RDRTF) of the International Society of Nephrology (ISN) recommends the use of isotonic saline as the preferred fluid for volume replacement during extrication in the context of a massive disaster (38). This recommendation is based on the availability and well-described efficacy of isotonic saline for this purpose.

If isotonic saline plus 5% Dextrose is available, it may be used as an alternative since it provides the added benefit of supplying calories and attenuating hyperkalemia. However, the use of bicarbonate added to hypotonic saline as a replacement fluid is not recommended due to the lack of evidence supporting its efficacy in this setting and the potential for adverse effects (38).

In cases of metabolic acidosis, bicarbonate therapy is used to alkalinize the plasma. It should be used with caution due to its potential risks, such as promoting calcium phosphate deposition and inducing or worsening the manifestations of hypocalcemia by both a direct membrane effect and a reduction in ionized calcium levels. The target urine pH is >6.5, and bicarbonate administration is discontinued if the arterial pH exceeds 7.5, the serum bicarbonate exceeds 30 mEq/L, or the patient develops symptomatic hypocalcemia (39).

The use of mannitol in preventing AKI is a topic of controversy, as its effectiveness is uncertain and may even be harmful in patients with rhabdomyolysis (40). It is important to note that mannitol should not be administered to patients with oligoanuria. Before administering mannitol, it is important to perform a test dose to determine if there is an increase in urine output (41). If a desired diuresis of around 200-300 mL/hour is not achieved, mannitol administration should be stopped to avoid the risk of hyperosmolality and volume overload.

Isotonic solutions used for fluid repletion often contain potassium, which can cause hyperkalemia in patients with Crush syndrome. Therefore, the use of such preparations is contraindicated in these patients. Plasma potassium levels should be monitored frequently until stabilized (41).

In case serum potassium concentration cannot be measured due to field conditions, electrocardiography (ECG) can provide useful information. In disaster situations, point-of-care devices like iSTAT can be used to measure electrolyte and creatinine levels directly and detect hyperkalemia early, identifying patients who require urgent dialysis (42). A retrospective analysis of a large series after acute trauma has shown that nephrotoxic drugs play an important role in the development of AKI in at least one-third of patients (43). Another analysis conducted on the treatment of the Marmara earthquake showed that a considerable quantity of nephrotoxic antibiotics and NSAIDs were administered. Hence, it is imperative to meticulously review all the drugs administered to patients during each visit and discontinue the use of any nephrotoxic drugs.

For patients who have not had a bladder catheter inserted before hospitalization, one should be placed after excluding urethral bleeding or laceration that is characterized by blood at the urethral meatus. However, the use of catheters carries a risk of infection, especially during disasters (41). Therefore, catheters should only be used
when necessary, such as in cases of unconsciousness, pelvic trauma, possible urethral obstruction, immobilization, or surgery. The catheter should be removed, unless there is an obligatory indication.

The management of Crush syndrome requires careful attention to maintaining renal perfusion and avoiding fluid overload. One crucial aspect of this management is the urine output goal, which is set at approximately 200 to 300 mL/hour for patients who can be closely monitored, such as in a hospital or triage setting. However, it is essential to monitor patients closely to prevent fluid overload, which can lead to pulmonary congestion. Limb swelling alone may not represent volume overload, and other signs should be taken into account. Although frequently used to determine volume status, absolute CVP values can be misleading and often do not predict the response to volume infusion. Absolute values are increased not only in hypervolemia, but also in other disease states, such as cardiac failure. For that reason, relative changes may be more useful than absolute values in reflecting intravascular volume status (44).

**Treatment**

Conservative treatment for AKI includes measures such as adequate hydration, discontinuation of nephrotoxic medications, and treatment of underlying medical conditions. In addition to conservative treatment, dialysis may be initiated and used as intensively as necessary to manage the patient’s condition.

Consequently, the therapeutic approach during the oliguric period differs significantly from that during the subsequent polyuric phase. The duration of oliguria can vary widely, depending on the length and severity of the initial ischemia, the recurrence of ischemia, and the association of nephrotoxic insults. Some patients may recover within days, while others may require dialysis for a week (41).

Given that most of the life-threatening complications occur during the oliguric period, it is essential to closely monitor patients during the first 2 weeks of treatment. Once patients survive this period, most will eventually recover kidney function and be discharged.

AKI can be treated with various renal replacement therapy options, including intermittent hemodialysis, continuous renal replacement therapy, and peritoneal dialysis. Each modality presents unique medical and logistical challenges (45), (Table 1).

**Table 1:** Unique advantages and disadvantages of different renal replacement therapy modalities

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<th>RRT Type</th>
<th>Advantage</th>
<th>Disadvantage</th>
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| IHD      | - High clearance rate of low molecular weight solutes  
          - Possibility of anticoagulant-free dialysis  
          - Possibility to dialyze more than one patient on a single machine on the same day | - Technical equipment and experienced personnel are required  
- Set priming may aggravate the picture in hypotensive or hypotension-prone patients  
- Higher risk of dialysis imbalance syndrome |
| CRRR     | - It provides better fluid control  
          - Reduced risk of dialysis imbalance syndrome  
          - Possibility of higher calorific intake  
          - CAVH provides the advantage of treatment without the use of electricity and pumps  
          - Equipment requirement is very low | - Requirement for continuous heparinisation in patients with hemorrhage or hemorrhagic diathesis  
- Low removal capacity for small molecular weight solutes  
- Capacity to treat only one disease per machine  
- The need to transport heavy and bulky fluid bags to the disaster site |
| PD       | - Possibility of dialysis without the need for vascular access  
          - Simpler technique and fewer hemodynamic problems  
          - No requirement for water or electricity infrastructure | - Low clearance for low molecular weight substances  
- Dialysis may be difficult under sterile conditions  
- May be contraindicated if the patient cannot lie supine or has abdominal wall infection, intestinal obstruction, large abdominal hernia, marked obesity and/or aortic aneurysm  
- The need to transport heavy and large fluid bags to the disaster area |

RRT: Renal Replacement Therapy, IHD: Intermittent haemodialysis, CRRT: Continuous renal replacement therapies, PD: Peritoneal dialysis, CAVH: Continuous arterio-venous haemofiltration
Intermittent hemodialysis is an effective option that can treat multiple patients with a single dialysis machine in a day. Short sessions of two to three hours can prevent life-threatening hyperkalemia. But this approach requires technical support, experienced personnel, electricity, and water supplies, which may be difficult to access during a disaster.

Continuous renal replacement therapy is another option that can gradually remove solutes and fluid. However, it can only treat one patient per machine and requires experienced personnel, electricity, and large quantities of substitution fluid. Moreover, continuous anticoagulation can cause bleeding in patients who are severely injured.

Peritoneal dialysis is a technically simple option that can be initiated quickly, and it requires no electricity or tap water supplies. However, it may be challenging to use in patients with abdominal or thoracic trauma, and it requires substantial quantities of sterilized dialysate. In non-hygienic field conditions, it can result in complications. Moreover, both continuous renal replacement therapy and peritoneal dialysis are less efficient than intermittent hemodialysis in removing potassium.

In light of all this information, although CRRT or PD can be used depending on availability and patient needs, IHD should be preferred as the first choice in renal replacement therapy. Conventional dialysis indications are also valid in this patient group. However, it may be more liberal to start dialysis in patients with crush-related AKI due to the frequency of fatal complications such as severe hyperkalemia (41).

Logistic issues
Disasters occur intermittently; therefore malpractice is frequent during disasters (46). Also, there is a disparity between healthcare demand and supply, which results in not only logistic but also ethical dilemmas (47). Both of these drawbacks can be minimized by predisaster preparedness, which targets improving problems towards disaster-related medical information and interventions and also reducing post-disaster chaos (48). These preparations may take place at international, national, and regional levels, and aim to answer the questions of who, when, what, and how before, during, and after disasters (49). Discussing all these issues is out of the scope of this review, and the reader is referred to other sources for a detailed description of these problems and their solutions (49, 50).

CONCLUSIONS
Crush syndrome is the second most frequent cause of deaths following the direct impact of trauma in destructive disasters. Although its clinical course is highly complicated, which necessitates intact city and medical infrastructure, and also experienced personnel, surviving patients may enjoy full recovery and rehabilitation as well. Therefore, careful follow-up and proper treatment of these patients are vital in order to save as many lives as possible after mass disasters.

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