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Rhabdomyolysis in Emergency Care: Recent Advances in Pathophysiology, Biochemical Diagnosis, and Management-An Updated Review.

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Abstract

Background: Rhabdomyolysis (RM) is a clinical syndrome characterized by skeletal muscle damage and the release of intracellular components, including creatine kinase (CK), myoglobin, and electrolytes, into the circulation. It can result from traumatic injuries, excessive physical exertion, medications, infections, and metabolic disorders. Delayed recognition and inadequate management may lead to acute kidney injury (AKI), electrolyte disturbances, compartment syndrome, and multiorgan dysfunction. Advances in diagnostic technologies and artificial intelligence (AI) have created new opportunities to improve early detection and risk assessment.

Aim: This review aims to summarize recent advances in the etiology, pathogenesis, complications, diagnosis, AI-assisted assessment, and treatment of RM, with emphasis on clinical evaluation and strategies to prevent serious complications.

Methods: A narrative review approach was used to discuss relevant evidence concerning the mechanisms of muscle injury, clinical manifestations, diagnostic biomarkers, imaging techniques, predictive models, and current therapeutic approaches.

Results: RM develops through mechanisms involving ATP depletion, intracellular calcium accumulation, oxidative stress, and disruption of muscle cell membranes. CK and myoglobin remain the principal biochemical markers, while imaging and emerging biomarkers may provide additional diagnostic information. AI-based models have demonstrated potential for predicting AKI and mortality, with some studies reporting better performance than conventional severity scores. Early identification of the underlying cause, intravenous fluid resuscitation, electrolyte monitoring, and appropriate management of renal complications remain central to treatment. However, evidence supporting routine use of bicarbonate, mannitol, and diuretics remains insufficient.

Conclusion: Early recognition and individualized management are essential to reduce RM-associated complications and improve patient outcomes.

Keywords: Rhabdomyolysis; Acute kidney injury; Creatine kinase; Myoglobin; Diagnosis; Artificial intelligence; Fluid resuscitation.

Introduction

Rhabdomyolysis (RM) is a potentially life-threatening clinical condition characterized by the disruption of skeletal muscle cell integrity, resulting in the rapid release of intracellular components into the systemic circulation. These components include creatine kinase (CK), myoglobin (Mb), potassium, phosphate, and other intracellular electrolytes and proteins. Their accumulation in the bloodstream can produce systemic metabolic disturbances and damage multiple organs, particularly the kidneys. Acute kidney injury (AKI) represents one of the most serious complications of RM and is associated with increased morbidity, prolonged hospitalization, and mortality, particularly in patients with severe muscle injury or delayed treatment [1–3]. Rhabdomyolysis can develop following a wide range of conditions and exposures. Common causes include traumatic injuries, crush syndrome, prolonged immobilization or muscle compression, strenuous physical exercise, heat-related illnesses, drug-induced muscle toxicity, alcohol and substance abuse, infections, metabolic disturbances, and inherited muscle disorders. Among adults, trauma and medication-related muscle injury are recognized as major contributing factors. Several commonly prescribed medications, including statins and certain antimicrobial and psychotropic agents, may also contribute to muscle damage, particularly when combined with other risk factors or used in susceptible individuals. Furthermore, genetic and

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metabolic myopathies can predispose individuals to recurrent episodes, sometimes following relatively minor physical exertion or physiological stress. The pathophysiology of RM involves a complex sequence of cellular and biochemical events. Damage to the muscle cell membrane disrupts normal ion regulation, leading to increased intracellular calcium concentrations. This calcium overload activates intracellular proteolytic enzymes and phospholipases, promotes mitochondrial dysfunction, and increases the production of reactive oxygen species. These processes contribute to further cellular injury and muscle fiber necrosis. The subsequent release of myoglobin and other intracellular substances into the circulation can impair renal function through several mechanisms, including renal vasoconstriction, oxidative tubular injury, and the formation of myoglobin-containing casts within renal tubules. Dehydration, metabolic acidosis, and reduced renal perfusion can further aggravate kidney injury.

Despite improvements in clinical research, diagnostic technologies, and emergency medical care, the early recognition and management of RM remain challenging. Its clinical presentation varies considerably, ranging from mild muscle discomfort and weakness to severe muscle swelling, dark-colored urine, electrolyte abnormalities, and systemic complications. The classical triad of muscle pain, weakness, and dark urine is not consistently present, which may delay clinical suspicion and diagnosis. Consequently, laboratory investigations play a central role in identifying the conditions. Serum CK is the principal biochemical marker used to establish the diagnosis, although myoglobin, renal function parameters, and electrolyte measurements provide additional information about disease severity and associated complications. Management primarily focuses on early recognition of muscle injury, correction of fluid and electrolyte disturbances, and prevention of acute kidney injury. Intravenous isotonic crystalloid administration is the cornerstone of treatment in appropriate patients, as it helps maintain renal perfusion and supports the elimination of circulating myoglobin. Careful monitoring of urine output, renal function, CK concentrations, and serum electrolytes is essential to guide treatment and identify complications. Urinary alkalinization using sodium bicarbonate may be considered in selected clinical circumstances; however, its routine use remains controversial because evidence supporting its superiority over conventional fluid therapy is limited. Similarly, mannitol and other diuretics are not routinely recommended for preventing kidney injury. Renal replacement therapy may become necessary when patients develop conventional indications, including refractory hyperkalemia, severe metabolic acidosis, fluid overload, or persistent renal failure.

Recent advances in understanding RM have emphasized the importance of individualized risk assessment, early biochemical monitoring, and the identification of patients at increased risk of severe complications. Clinical prediction tools, including the McMahon score, have been developed to estimate the risk of renal replacement therapy or mortality by incorporating laboratory parameters and clinical characteristics. In addition, emerging research is investigating the molecular mechanisms underlying muscle injury, oxidative stress, inflammation, and renal tubular damage, potentially providing new opportunities for targeted therapeutic interventions. Overall, rhabdomyolysis represents an important medical emergency that requires a multidisciplinary approach involving emergency physicians, intensivists, nephrologists, and clinical laboratory specialists. Although many patients recover completely with timely recognition and appropriate supportive treatment, delayed diagnosis or inadequate management may result in acute kidney injury, life-threatening electrolyte disturbances, cardiac arrhythmias, compartment syndrome, and death. Therefore, understanding its underlying mechanisms, recognizing its diverse clinical presentations, and applying evidence-based diagnostic and therapeutic strategies are essential for improving patient outcomes.

Etiology of Rhabdomyolysis

Rhabdomyolysis (RM) is a multifactorial condition associated with numerous physical, chemical, and biological factors that cause skeletal muscle injury and the subsequent release of intracellular components into the systemic circulation. Identifying the underlying etiology is essential for establishing an accurate diagnosis, selecting appropriate treatment, preventing recurrent episodes, and reducing the risk of complications, particularly acute kidney injury (AKI). However, determining the precise epidemiological distribution of RM remains challenging because prospective studies are limited and mild cases are frequently underdiagnosed or underreported. Based on the available clinical literature, the principal causes of RM can be classified into three major categories: physical, chemical, and biological factors.

Physical Causes

Physical factors represent an important category of RM, particularly among patients presenting to emergency departments following traumatic injuries or extreme physical exertion. These factors include direct muscle trauma, prolonged compression, crush injuries, excessive exercise, electrical injuries, burns, and disturbances in body temperature regulation. Among these causes, trauma and prolonged muscle compression are particularly significant because they can produce extensive muscle ischemia and cellular damage. Crush injuries frequently occur during earthquakes, building collapses, wars, industrial accidents, and major road traffic collisions. Prolonged compression restricts

local blood circulation, reduces oxygen delivery to skeletal muscle cells, and promotes cellular energy depletion. The resulting ischemia disrupts membrane integrity and intracellular calcium regulation, ultimately leading to muscle fiber necrosis. The risk of developing RM increases substantially when a large muscle mass remains compressed for several hours. The duration and severity of compression, the extent of tissue damage, and the patient's hydration and circulatory status influence the development of systemic complications [1]. Excessive physical activity is another recognized cause of RM. Exertional rhabdomyolysis may develop following prolonged endurance exercise, intensive resistance training, military training, competitive sports, or sudden participation in strenuous physical activities without adequate conditioning. High-intensity exercise increases metabolic demands within skeletal muscle and may exceed the muscle's capacity to maintain cellular homeostasis. Heat exposure, dehydration, and inadequate recovery further increase susceptibility to muscle injury. Military personnel, athletes, and individuals undertaking intensive fitness programs represent populations in which exertional RM may occur [4,5].

Chemical Causes

Chemical causes include prescription medications, illicit substances, alcohol, toxic compounds, and metabolic disturbances involving electrolytes. Drug-induced RM is an important clinical concern because several substances can interfere with normal skeletal muscle metabolism, mitochondrial function, ATP production, and cellular membrane stability. These disturbances increase intracellular calcium concentrations and promote muscle fiber damage [6–8]. Statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, are among the medications associated with muscle toxicity. Although most patients tolerate statin therapy, some develop muscle-related adverse effects ranging from mild myalgia to severe RM. The risk may increase with higher doses, drug interactions, renal or hepatic impairment, and individual susceptibility. Muscle symptoms may appear after treatment initiation or following changes in medication exposure. Therefore, unexplained muscle pain, weakness, or significant CK elevation in patients receiving statins requires clinical assessment and consideration of medication discontinuation or modification [9]. Other substances associated with RM include cocaine, amphetamines, heroin, excessive alcohol consumption, and certain antimicrobial, antipsychotic, and anesthetic agents. Additionally, electrolyte abnormalities, particularly hypokalemia, hypophosphatemia, and severe sodium disturbances, may impair skeletal muscle function and increase the risk of cellular injury.

Biological Causes

Biological factors constitute the third major category and include infectious diseases, venomous animal bites, inflammatory conditions, autoimmune disorders, and inherited metabolic or muscular diseases. Infectious rhabdomyolysis may develop following viral, bacterial, or other systemic infections. Viruses such as influenza and other pathogens can produce direct muscle injury or trigger inflammatory responses that contribute to muscle fiber destruction. In pediatric populations, infectious causes account for approximately one-third of reported RM cases, highlighting the importance of considering infection during the evaluation of children presenting with muscle pain, weakness, or elevated CK concentrations [10–12]. Snakebites and insect bites may also cause RM through venom-mediated muscle injury, systemic inflammation, and disturbances in cellular metabolism. Furthermore, autoimmune inflammatory myopathies can produce progressive muscle damage, while inherited metabolic disorders and genetic myopathies may predispose individuals to recurrent episodes, particularly following exercise, fasting, infection, or physiological stress.

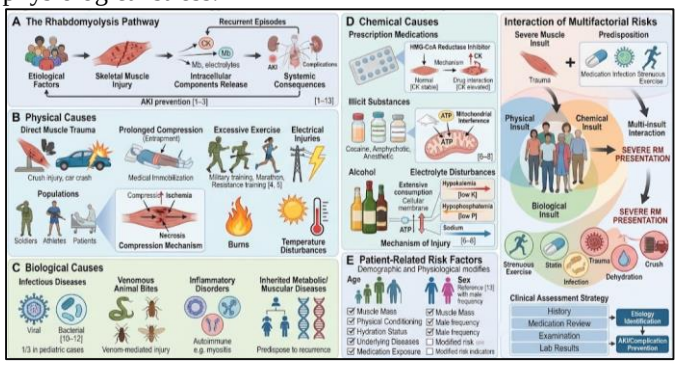


Figure-1: Etiology of Rhabdomyolysis.

Patient-Related Risk Factors

In addition to the primary etiological categories, individual characteristics influence susceptibility to RM and the severity of its clinical presentation. Age, sex, muscle mass, physical conditioning, hydration status, underlying diseases, and medication exposure may modify the risk. RM is reported more frequently among males, potentially reflecting differences in skeletal muscle mass, exercise exposure, and occupational or behavioral factors. However, it can affect individuals of either sex and across all age groups [13]. Overall, the etiology of RM is complex and frequently multifactorial. Some patients develop the condition following a single major insult, whereas others experience muscle injury through the interaction of several predisposing factors, such as strenuous exercise, dehydration, medication exposure, and infection. Consequently, identifying the underlying cause requires a comprehensive clinical history, medication review, physical examination, and appropriate laboratory investigations. Recognizing these etiological factors is fundamental to early intervention, prevention of complications, and the

development of individualized management strategies.

Pathogenesis of Rhabdomyolysis

The pathogenesis of rhabdomyolysis (RM) involves a complex series of biochemical and cellular events that ultimately result in skeletal muscle fiber injury, membrane disruption, and the release of intracellular components into the systemic circulation. Although the initiating factors vary according to the underlying cause, most pathogenic pathways converge on a common mechanism characterized by excessive intracellular calcium (Ca^{2+}) accumulation. Calcium overload plays a central role in the progression of muscle cell injury by activating destructive enzymatic pathways, impairing mitochondrial function, increasing oxidative stress, and promoting cellular necrosis. Three interconnected mechanisms are particularly important in the development of this process: depletion of intracellular adenosine triphosphate (ATP), disruption of muscle cell membrane integrity, and increased production of reactive oxygen species (ROS).

Intracellular ATP Depletion and Calcium Overload

Under physiological conditions, skeletal muscle cells maintain a stable intracellular ionic environment through energy-dependent membrane transport systems. The sodium-potassium adenosine triphosphatase (Na^+/K^+-ATPase) and calcium-transporting ATPases are essential for maintaining appropriate intracellular concentrations of sodium, potassium, and calcium. However, traumatic injury, prolonged ischemia, excessive muscular activity, and toxic exposures can impair cellular energy production and reduce ATP availability [14]. ATP depletion compromises the activity of the Na^+/K^+-ATPase, resulting in intracellular sodium accumulation and disruption of the normal transmembrane sodium gradient. This disturbance affects the sodium-calcium exchanger, which may operate in reverse mode under certain ionic conditions, promoting calcium entry into the muscle cell. Simultaneously, reduced ATP availability impairs calcium removal through plasma membrane calcium pumps and disrupts calcium sequestration by intracellular organelles, particularly the sarcoplasmic reticulum. Mitochondrial dysfunction further reduces the cell's ability to regulate calcium concentrations. Consequently, excessive calcium accumulates within the cytoplasm, initiating several destructive biochemical processes [12,15].

Muscle Cell Membrane Disruption

Damage to the sarcolemma, the plasma membrane surrounding skeletal muscle fibers, represents another important mechanism contributing to intracellular calcium overload. Physical trauma, ischemia, toxins, medications, and inflammatory processes can directly or indirectly compromise membrane structure and permeability. Once membrane integrity is disrupted, extracellular calcium enters the muscle cell along its electrochemical gradient, further increasing intracellular calcium concentrations [2,3]. Excessive intracellular calcium activates several calcium-dependent enzymes, particularly phospholipase A2 and proteases such as calpains. Phospholipase A2 promotes the degradation of membrane phospholipids, while calcium-dependent proteases contribute to the breakdown of structural and contractile proteins. These enzymatic activities damage the sarcolemma and intracellular membrane systems, including mitochondrial and sarcoplasmic reticulum membranes. The resulting structural deterioration further impairs cellular ion regulation and accelerates muscle fiber destruction [12,16]. Additionally, sustained calcium accumulation can stimulate persistent muscle contraction and increase metabolic energy requirements. Because ATP production is already compromised, the muscle cell becomes increasingly unable to maintain normal physiological functions. This creates a progressive cycle of energy depletion, calcium accumulation, enzymatic activation, and membrane damage.

Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is another major contributor to the pathogenesis of RM. Mitochondrial impairment and ATP depletion promote the generation of reactive oxygen species, including superoxide anions ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2). Under normal physiological conditions, antioxidant defense systems regulate ROS concentrations and prevent excessive oxidative damage. However, when ROS production exceeds the antioxidant capacity of the cell, oxidative stress develops [15–17]. Excessive ROS production causes lipid peroxidation, protein oxidation, and damage to nucleic acids. Lipid peroxidation weakens cellular and organelle membranes, increasing their permeability and facilitating further calcium accumulation. Protein oxidation alters the structure and function of enzymes, membrane transporters, and contractile proteins. Mitochondrial damage also compromises oxidative phosphorylation, further reducing ATP synthesis and increasing ROS generation. These interconnected processes establish a self-amplifying cycle of mitochondrial dysfunction and cellular injury.

Muscle Fiber Necrosis and Systemic Complications

The combined effects of calcium overload, enzymatic activation, oxidative stress, and mitochondrial dysfunction eventually lead to irreversible skeletal muscle cell injury and necrosis. As muscle fibers deteriorate, intracellular substances are released into the circulation in substantial quantities. These include creatine kinase (CK), myoglobin, potassium, phosphate, and other cellular

constituents. The systemic accumulation of these substances contributes to the major complications of RM. Myoglobin is particularly important because its renal effects include oxidative tubular injury, renal vasoconstriction, and intratubular cast formation, especially in patients with dehydration or reduced renal perfusion. Potassium and phosphate release can produce significant electrolyte disturbances, while severe hyperkalemia may cause potentially fatal cardiac arrhythmias. Overall, the pathogenesis of RM is characterized by the interaction of energy depletion, intracellular calcium dysregulation, membrane destruction, and oxidative stress. These mechanisms are closely interconnected and progressively amplify muscle cell injury. Understanding these biochemical pathways provides an important foundation for early diagnosis, risk assessment, and therapeutic interventions aimed at preventing extensive muscle damage and subsequent renal and systemic complications.

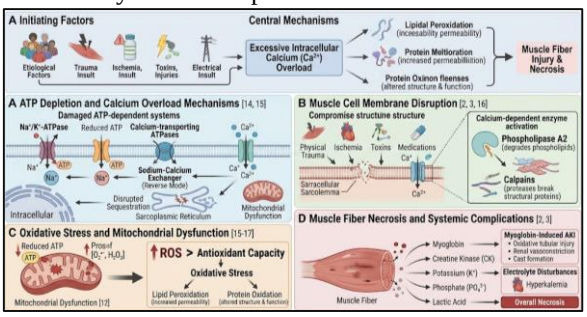


Figure-2: Pathophysiology of Rhabdomyolysis.

Complications of Rhabdomyolysis

Rhabdomyolysis (RM) is associated with a wide range of complications resulting from the extensive destruction of skeletal muscle fibers and the subsequent release of intracellular substances into the systemic circulation. The release of myoglobin (Mb), potassium, phosphate, creatine kinase (CK), organic acids, and other cellular components disrupts normal physiological homeostasis and may cause significant tissue and organ dysfunction. The severity of complications depends on the extent of muscle injury, the underlying cause, the patient's hydration status, the presence of pre-existing diseases, and the time between symptom onset and treatment initiation. Although some patients experience mild and reversible manifestations, severe RM may result in life-threatening conditions, including acute kidney injury (AKI), electrolyte disturbances, compartment syndrome, disseminated intravascular coagulation (DIC), and acute liver injury [18].

Acute kidney injury is the most frequent and clinically significant complication of RM. The association between muscle injury and renal failure was recognized during World War II, when Bywaters and colleagues described four casualties following the London bombing incident who presented with limb swelling, reddish-brown urine, and circulatory shock. These observations contributed to the development of the clinical concept of crush syndrome [19]. The reported incidence of RM-associated AKI ranges from approximately 13% to 50%, depending on the studied population, severity of muscle injury, and diagnostic criteria [20–22]. Its development involves several interconnected mechanisms, including intravascular volume depletion, renal vasoconstriction, oxidative stress, and direct tubular toxicity caused by circulating myoglobin. Following extensive muscle destruction, large quantities of myoglobin enter the bloodstream. Because myoglobin is a relatively small protein, it passes freely through the glomerular filtration barrier and enters the renal tubular system. Under conditions of dehydration and acidic urine, myoglobin interacts with tubular proteins and forms casts that obstruct renal tubules. This process reduces tubular flow and contributes to epithelial cell injury and necrosis [9,21]. Furthermore, the heme component of myoglobin releases free iron, which promotes the generation of reactive oxygen species and lipid peroxidation. These oxidative processes damage renal tubular cells and aggravate ischemic injury. Simultaneously, hypovolemia reduces renal blood flow, increasing susceptibility to tubular damage. The combination of these mechanisms contributes to the development of AKI. Importantly, even relatively mild AKI may be associated with increased mortality, emphasizing the importance of early recognition, adequate fluid management, and continuous monitoring of renal function [20,23].

Electrolyte abnormalities are common in RM and may produce serious cardiovascular, neurological, and metabolic complications. Skeletal muscle represents the major intracellular reservoir of potassium and contains substantial quantities of phosphate and calcium. Therefore, extensive muscle cell destruction results in the release of these ions into the extracellular compartment, disturbing their normal physiological concentrations. Hyperkalemia is among the most dangerous early complications of RM. The rapid release of intracellular potassium can increase serum potassium concentrations above the normal range, commonly defined as greater than 5.0 mEq/L [24]. Metabolic acidosis frequently accompanies severe muscle injury because of tissue ischemia, lactate accumulation, and impaired renal acid excretion. Acidosis may further aggravate hyperkalemia by promoting the redistribution of potassium from intracellular to extracellular compartments [25]. Severe hyperkalemia can alter cardiac electrical conduction and produce potentially fatal arrhythmias, including ventricular tachycardia, ventricular fibrillation, and cardiac arrest. Consequently, electrocardiographic assessment and serial potassium measurements are essential in patients with significant muscle injury. Hypocalcemia is another characteristic biochemical abnormality, particularly during the early phase of RM. It develops because calcium enters damaged

muscle cells and accumulates in injured tissues, while released phosphate promotes calcium-phosphate deposition. Hyperphosphatemia further contributes to reduced circulating calcium concentrations. During recovery, calcium may return from damaged muscle tissues into the circulation, occasionally resulting in secondary hypercalcemia. Thus, calcium abnormalities may change throughout the clinical course of RM and require careful monitoring. Hyperphosphatemia, hyperuricemia, and metabolic acidosis may also occur. These disturbances can contribute to renal injury, cardiovascular instability, and other systemic complications.

Acute compartment syndrome is an important local complication of severe RM, particularly following crush injuries, extensive trauma, and prolonged muscle compression. Skeletal muscles are organized into anatomical compartments surrounded by relatively noncompliant connective tissue structures, particularly fascia. Under normal conditions, these compartments maintain sufficient pressure to support muscle function and tissue perfusion. In RM, damaged muscle fibers develop cellular swelling, while inflammatory responses increase vascular permeability and promote fluid accumulation within the affected tissues. This produces progressive edema and increases the volume of the compartment contents [26]. Because the surrounding fascia has limited capacity to expand, increasing tissue volume results in elevated intracompartmental pressure. When this pressure becomes sufficiently high, it compromises venous drainage and reduces the pressure gradient required for adequate capillary perfusion. Consequently, local ischemia develops and further damages muscle fibers and surrounding nerves [27]. This process may establish a vicious cycle in which ischemia aggravates muscle injury, causing additional edema and further increasing compartment pressure. Clinically, patients may experience severe pain, pain during passive stretching, tense swelling, sensory disturbances, and eventually motor impairment. Untreated compartment syndrome can cause irreversible muscle necrosis, permanent neurological deficits, and limb dysfunction. Urgent clinical assessment and, when indicated, surgical fasciotomy are essential to prevent permanent tissue damage.

Disseminated intravascular coagulation is a serious systemic complication that may develop in patients with severe RM, particularly when associated with extensive trauma, shock, infection, or systemic inflammation. DIC is a pathological syndrome characterized by widespread activation of the coagulation cascade, resulting in the formation of microvascular thrombi and consumption of platelets and coagulation factors. This can produce simultaneous microvascular thrombosis and an increased risk of bleeding. The development of DIC involves several interacting mechanisms, including endothelial injury, platelet activation, excessive thrombin generation, impaired natural anticoagulant pathways, altered fibrinolysis, complement activation, and systemic inflammatory responses [28]. During RM, extensive skeletal muscle destruction releases intracellular substances and procoagulant components, including tissue factor and thromboplastin-related activity. These substances may contribute to coagulation pathway activation and promote thrombus formation within small blood vessels [26]. Widespread microvascular thrombosis can impair tissue perfusion and aggravate organ dysfunction. Meanwhile, consumption of platelets and coagulation factors may result in spontaneous bleeding or excessive bleeding following invasive procedures. DIC is associated with substantial mortality, particularly when it occurs alongside multiorgan dysfunction. Therefore, platelet counts, prothrombin time, activated partial thromboplastin time, fibrinogen concentrations, and D-dimer levels should be assessed when clinical findings suggest a coagulation disorder.

Acute liver injury represents another potential complication of RM. Approximately 25% of affected patients may demonstrate biochemical evidence of liver involvement, with greater susceptibility among individuals with pre-existing hepatic disorders [28]. The mechanisms underlying liver injury are complex and involve the effects of circulating myoglobin, heme-related oxidative stress, systemic inflammation, and impaired tissue perfusion. Extensive muscle cell destruction releases large amounts of myoglobin into the circulation. During myoglobin metabolism, its heme component can release free iron, which promotes oxidative reactions and the generation of reactive oxygen species. The liver plays a central role in heme metabolism and clearance. However, excessive heme exposure may exceed normal protective mechanisms and contribute to oxidative damage within hepatic tissues. Free heme can induce lipid peroxidation, disrupt cellular membranes, and interfere with mitochondrial function. These effects may promote hepatocyte injury through necrotic and apoptotic pathways [29]. Additionally, severe RM may be accompanied by dehydration, hypotension, and systemic inflammatory responses, which can compromise hepatic blood flow and oxygen delivery. These disturbances may further aggravate liver injury. Biochemical abnormalities frequently include increased serum aminotransferases, particularly aspartate aminotransferase (AST) and alanine aminotransferase (ALT). However, interpretation requires caution because skeletal muscle itself contains substantial amounts of AST and some ALT. Therefore, elevated aminotransferase concentrations do not necessarily indicate primary hepatic injury. Assessment of bilirubin, alkaline phosphatase, gamma-glutamyl transferase, and coagulation

parameters can help determine whether significant hepatic dysfunction is present. In severe cases, the complications of RM may occur simultaneously and contribute to multiorgan dysfunction. For example, extensive muscle destruction can produce hypovolemia, hyperkalemia, metabolic acidosis, AKI and cardiac instability.

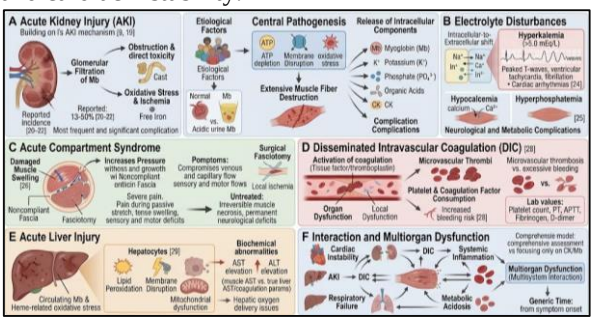


Figure-3: Complications of Rhabdomyolysis.

When accompanied by compartment syndrome, systemic inflammation, or DIC, the clinical condition may deteriorate rapidly. The interaction between these complications highlights the importance of comprehensive assessment rather than focusing exclusively on CK concentrations or myoglobin levels. Continuous monitoring of renal function, urine output, electrolytes, acid-base balance, cardiac rhythm, coagulation parameters, and clinical signs of compartment syndrome is essential in patients with severe RM. Overall, the complications of rhabdomyolysis range from reversible biochemical abnormalities to life-threatening organ failure. Acute kidney injury remains the principal concern, while hyperkalemia, compartment syndrome, DIC, and hepatic involvement contribute to disease severity and adverse outcomes. Early identification of these complications, appropriate intravenous fluid administration, correction of electrolyte abnormalities, timely surgical intervention when indicated, and organ-supportive treatment are fundamental components of effective clinical management. A multidisciplinary approach involving emergency physicians, intensivists, nephrologists, surgeons, and clinical laboratory specialists can improve the detection and management of complications and reduce the risk of mortality.

Diagnosis of Rhabdomyolysis

The diagnosis of rhabdomyolysis (RM) requires a comprehensive clinical assessment that combines medical history, physical examination, biochemical investigations, and imaging studies. Early recognition is essential because delayed diagnosis may increase the risk of acute kidney injury (AKI), electrolyte disturbances, cardiac arrhythmias, and other systemic complications. However, diagnosing RM can be challenging because its clinical manifestations vary considerably according to the underlying cause, severity of muscle injury, and individual patient characteristics. The classical triad of muscle pain, muscle weakness, and dark-colored urine occurs in only approximately 10% of patients, meaning that its absence does not exclude the condition [66]. Therefore, clinicians should maintain a high index of suspicion when evaluating patients with unexplained fatigue, fever, nausea, vomiting, muscle tenderness, or reduced urine output, particularly when relevant risk factors are present.

Obtaining a detailed medical history represents the first step in diagnosing RM. Clinicians should investigate potential triggering factors, including recent trauma, prolonged immobilization, crush injuries, strenuous exercise, exposure to extreme temperatures, dehydration, and electrical injuries. Medication history is equally important, particularly regarding statins, antipsychotics, antimicrobial agents, and other drugs associated with muscle toxicity. Alcohol consumption, illicit drug exposure, recent infections, dietary or metabolic disturbances, and previous episodes of muscle injury should also be considered. Family history may provide important information about inherited metabolic disorders and genetic myopathies, particularly in patients with recurrent episodes or muscle injury following relatively minor physical exertion. Physical examination should assess muscle tenderness, swelling, weakness, skin changes, and signs of compartment syndrome. Clinicians should also evaluate hydration status, blood pressure, heart rate, peripheral circulation, and urine output. Urine color and quantity provide additional diagnostic clues. Dark brown or tea-colored urine may indicate myoglobinuria, although its absence does not exclude RM. A urine dipstick positive for blood with few or no red blood cells on microscopic examination suggests the presence of myoglobin or free hemoglobin. These findings should be interpreted alongside serum biomarkers and renal function tests [8].

Muscle biopsy is not routinely required to establish the diagnosis of RM because the pathological findings are frequently nonspecific and may vary according to the underlying etiology. Some patients demonstrate limited histological abnormalities, whereas others exhibit extensive muscle fiber necrosis and inflammatory changes. Zhao et al. [30] retrospectively examined skeletal muscle biopsy findings in 26 patients with RM and reported considerable variation in pathological changes among different etiological groups. Exercise-induced muscle injury generally produced less severe structural abnormalities, whereas drug- and toxin-associated RM more frequently demonstrated necrotizing muscle pathology. Primary neuromuscular disorders represented a less common finding. Despite these limitations, muscle biopsy may provide valuable information when an underlying inherited, inflammatory, metabolic, or primary neuromuscular disorder is suspected. It can help distinguish different muscle diseases and guide

subsequent investigations and treatment. However, because biopsy is invasive and does not usually change the immediate management of acute RM, it should be reserved for selected cases, particularly those involving recurrent or unexplained muscle injury [8,30].

Imaging investigations support the diagnosis of RM by identifying the distribution and extent of muscle injury, evaluating associated traumatic lesions, and detecting complications such as compartment syndrome. Ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are the principal imaging modalities used in clinical practice [3,31]. Ultrasound is a non-invasive, accessible, and relatively inexpensive imaging technique that allows real-time assessment of skeletal muscle abnormalities. It can identify muscle swelling, changes in echogenicity, disruption of normal muscle architecture, and fluid accumulation within or around affected tissues. Common sonographic findings include increased muscle thickness, heterogeneous echogenicity, indistinct muscle fiber patterns, and localized hypoechoic or anechoic regions. Extensive muscle injury may produce diffuse architectural disorganization accompanied by surrounding edema and fluid collections [37]. Carrillo-Esper et al. [32], Nassar et al. [33], and Hans et al. [34] described abnormalities including disorganized muscle fibers, altered echogenicity, and fluid accumulation in patients with RM. These observations demonstrate the potential value of ultrasound in identifying muscle pathology and monitoring recovery. The main advantages of ultrasound include rapid examination, absence of ionizing radiation, portability, and relatively low cost. However, its diagnostic sensitivity depends on the operator's experience, and its examination field is relatively limited. Some pathological changes may also appear late, reducing its usefulness during the earliest stages of muscle injury. Therefore, ultrasound findings should be interpreted alongside clinical and laboratory results [38].

CT provides rapid assessment of extensive anatomical regions and is particularly useful in patients with traumatic injuries or suspected associated complications. Typical findings in RM include muscle enlargement, fascial thickening, areas of reduced muscle density, edema, and focal regions of necrosis or calcification. CT can demonstrate the distribution and extent of muscle damage and help identify associated injuries involving bones and surrounding soft tissues. Multislice CT and three-dimensional reconstruction further improve anatomical assessment and differentiation between muscles, tendons, ligaments, bones, and fluid collections. Lu et al. [35] reported heterogeneous areas of reduced muscle density with focal or linear enhancement in affected tissues. Mian et al. [36] also described muscle swelling and surrounding soft-tissue edema in a patient with cocaine-associated RM. Despite its diagnostic advantages, CT exposes patients to ionizing radiation and provides less soft-tissue contrast than MRI. Consequently, it is generally not the preferred imaging modality for uncomplicated RM but remains valuable when rapid evaluation is necessary or MRI is unavailable or contraindicated.

MRI provides high-resolution visualization of skeletal muscle and is particularly useful for identifying the distribution, severity, and extent of muscle injury. Unlike CT, MRI does not involve ionizing radiation and offers superior soft-tissue contrast. It can also help differentiate muscle edema from necrosis and other pathological changes. Typical MRI findings include muscle enlargement, diffuse or patchy signal abnormalities, increased signal intensity on T2-weighted and short-tau inversion recovery (STIR) images, and variable signal changes on T1-weighted sequences. Contrast-enhanced imaging may demonstrate heterogeneous or peripheral enhancement depending on the severity and stage of muscle injury. Lu et al. [35] described different MRI patterns in patients with RM, including diffuse muscle signal abnormalities and heterogeneous changes associated with more extensive muscle injury. These findings support the use of MRI for evaluating muscle involvement and distinguishing different patterns of tissue damage. MRI offers several advantages, including high sensitivity, multiplanar imaging, and detailed soft-tissue assessment. However, its limitations include high cost, limited availability, prolonged examination time, and the need to transfer patients to specialized imaging facilities. These limitations may restrict its use in critically ill patients who require immediate intervention. Nevertheless, MRI remains particularly valuable when the diagnosis is uncertain, when extensive muscle involvement requires assessment, or when the extent of tissue injury must be determined before surgical intervention.

Biochemical Biomarkers

Laboratory investigations represent the cornerstone of RM diagnosis and monitoring. Several biomarkers reflect skeletal muscle injury, although their diagnostic performance differs according to their biological characteristics, release kinetics, and clearance mechanisms. Creatine kinase (CK) remains the principal diagnostic marker, while myoglobin, lactate dehydrogenase (LDH), aminotransferases, and emerging molecular biomarkers provide complementary information [39–51]. CK is an intracellular enzyme involved in energy metabolism and the reversible conversion of creatine and adenosine triphosphate. It is widely distributed in skeletal muscle, cardiac muscle, and other tissues. Three major isoenzymes are recognized: CK-MM, CK-MB, and CK-BB. CK-MM is the predominant isoenzyme associated with skeletal muscle injury. A

serum CK concentration exceeding five times the upper reference limit is commonly used as the biochemical criterion for diagnosing RM. A concentration greater than approximately 1,000 U/L is also frequently used in clinical practice, although diagnostic thresholds vary according to the laboratory reference range and clinical context [22]. Following muscle injury, CK concentrations generally begin to increase within 2–12 hours, reach peak levels within 24–72 hours, and subsequently return toward baseline over approximately 3–6 days [31]. Markedly elevated CK concentrations, particularly above 5,000 U/L, are associated with increased risk of AKI in several clinical populations, especially following traumatic and crush injuries. However, CK concentrations do not directly reflect renal damage and should not be used independently to predict clinical outcomes. Their interpretation must consider the underlying etiology, hydration status, renal function, and other laboratory findings. Furthermore, substantial interindividual variability and relatively low specificity can complicate the interpretation of CK measurements.

Myoglobin is an oxygen-binding protein found primarily in skeletal and cardiac muscle. Following muscle fiber destruction, it enters the circulation rapidly and is filtered through the kidneys. Its early release makes it a useful marker for detecting recent muscle injury and assessing the risk of renal complications. Unlike CK, myoglobin has a short circulating half-life, generally approximately 2–4 hours under normal clearance conditions. Its serum concentration may peak within approximately three hours after muscle injury and return toward baseline within 6–8 hours [8,41,44]. Serum myoglobin concentrations of 1,000 ng/mL or higher have been associated with an increased risk of AKI in clinical studies [41]. Higher concentrations may also indicate an increased likelihood of requiring renal replacement therapy. For example, concentrations exceeding 15 mg/L have been associated with a greater probability of hemodialysis in some patient populations [54]. Although myoglobin has limited sensitivity when measured at a single time point, it may provide valuable prognostic information because it contributes directly to renal tubular injury. Its rapid clearance, however, means that delayed sampling may underestimate the extent of muscle damage. Therefore, myoglobin measurement is most useful when interpreted alongside CK concentrations, renal function parameters, and the timing of symptom onset.

LDH is an intracellular enzyme involved in the conversion of pyruvate to lactate during cellular energy metabolism. It is distributed across several tissues, including skeletal muscle, liver, heart, and kidneys. Increased serum LDH activity indicates cellular damage but is not specific to RM. Following strenuous exercise, LDH concentrations may increase within approximately 3–6 hours and return toward baseline within 24 hours. However, the magnitude and duration of elevation depend on the intensity of muscle injury and other contributing conditions [45]. LDH is inexpensive, widely available, and useful as a complementary biochemical marker. Nevertheless, its relatively low sensitivity and specificity prevent its use as an independent diagnostic test. It may provide additional information regarding tissue injury and inflammatory processes, particularly when interpreted with CK and other laboratory parameters [53,58].

ALT and AST are enzymes involved in amino acid metabolism and are commonly measured to assess liver function. However, both enzymes are also present in skeletal muscle, particularly AST. Consequently, extensive muscle injury may produce elevated aminotransferase concentrations without primary hepatic disease. Following RM, ALT and AST generally reach their highest concentrations within approximately 3–4 days and may require 6–10 days to return toward baseline. In severe cases, elevations may persist for several weeks [53]. Although these enzymes lack sufficient specificity for diagnosing RM independently, their concentrations may correlate with CK levels. Chandel et al. [59] reported that an AST concentration of at least 110 U/L demonstrated 97.1% sensitivity and 85.7% specificity for identifying CK concentrations of at least 5,000 U/L in their studied population. Thus, aminotransferases may provide supportive diagnostic information when CK testing is unavailable or when additional assessment of muscle and hepatic involvement is required.

MicroRNAs (miRNAs) are small non-coding RNA molecules, generally consisting of approximately 21–23 nucleotides, that regulate gene expression through interactions with target messenger RNA. Several muscle-specific miRNAs have been investigated as potential biomarkers of skeletal muscle injury. These include miR-1, miR-133a, miR-133b, and miR-206. Their circulating concentrations may increase following muscle damage and intensive exercise. Chalchat et al. [47] demonstrated increased concentrations of these miRNAs immediately after prolonged endurance exercise. Experimental investigations have also suggested that muscle-specific miRNAs may demonstrate greater sensitivity and specificity than CK under certain conditions. Bailey et al. [63] reported diagnostic performance reaching approximately 80% sensitivity and 95% specificity in a rat model. Despite their potential, miRNAs remain investigational biomarkers. Their clinical application is limited by analytical costs, differences in sample processing, short circulating half-lives, limited standardization, and the absence of established diagnostic thresholds. Further clinical validation is necessary before routine implementation.

Several additional biomarkers have been investigated to improve the detection and assessment

of RM. These include aldolase (ALD), fatty acid-binding proteins (FABPs), carbonic anhydrase III (CAIII), and myosin light chain 3 (Myl3). ALD is a glycolytic enzyme found mainly in skeletal muscle, liver, and brain tissues. Its serum concentration increases following muscle injury, although its response is relatively delayed. Combining ALD with CK may improve the assessment of muscle damage [31]. FABPs, particularly heart-type fatty acid-binding protein (H-FABP), are released rapidly following muscle injury. Their circulating concentrations may increase within a few hours, reach peak levels within approximately 2–6 hours, and return toward baseline within 24 hours. Experimental studies suggest that FABPs may improve diagnostic accuracy when combined with CK and AST [49,50]. CAIII is a cytoplasmic enzyme highly expressed in skeletal muscle and involved in cellular metabolic processes. Its concentration may increase rapidly following exercise-induced muscle injury, reaching approximately two to two-and-a-half times baseline levels within six hours [31,64]. Myl3 is a component of the myosin protein complex expressed in cardiac and skeletal muscle. Experimental investigations suggest that changes in its circulating concentration may reflect muscle injury severity. However, its diagnostic specificity and clinical usefulness in RM require further investigation [50,65]. Overall, these emerging biomarkers offer potential advantages in identifying early muscle injury and improving diagnostic assessment. Nevertheless, their limited availability, cost, and lack of standardized clinical thresholds currently restrict routine application.

Integrated Diagnostic Approach

The diagnosis of RM should rely on the integration of clinical findings, biochemical investigations, and imaging results rather than a single diagnostic parameter. A detailed history should identify possible causes, including trauma, prolonged compression, excessive exercise, extreme temperature exposure, medication use, alcohol consumption, infection, and inherited muscle disorders. Serum CK measurement remains the primary laboratory investigation, while myoglobin provides additional information about early muscle injury and the risk of renal complications. Electrolytes, serum creatinine, blood urea nitrogen, calcium, phosphate, and acid-base parameters should be assessed to identify associated metabolic abnormalities and AKI. Urinalysis can provide supportive evidence of myoglobinuria. Imaging should be selected according to clinical requirements. Ultrasound provides rapid bedside assessment, CT is useful in traumatic injuries and extensive anatomical evaluation, and MRI offers detailed visualization of muscle abnormalities. Ultimately, early recognition requires clinicians to maintain suspicion even when the classical clinical triad is absent. Combining medical history, physical examination, serial CK measurements, renal function assessment, and appropriate imaging provides a comprehensive approach to diagnosis, risk stratification, and timely treatment. This integrated strategy is essential for reducing diagnostic delays and preventing serious complications associated with rhabdomyolysis.

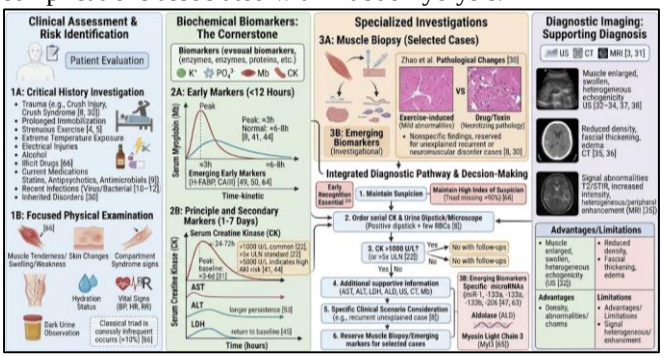


Figure-4: Diagnostic Approaches of Rhabdomyolysis.

Artificial Intelligence-Assisted Diagnosis

Rhabdomyolysis (RM) is a complex clinical syndrome characterized by skeletal muscle injury and the release of intracellular components, including creatine kinase (CK), myoglobin, and electrolytes, into the circulation. Its clinical presentation varies according to the underlying cause, severity of muscle damage, and presence of complications such as acute kidney injury (AKI), electrolyte disturbances, and multiorgan dysfunction. Accurate diagnosis and risk assessment therefore require the integration of medical history, physical examination, laboratory investigations, imaging findings, and relevant biomarkers. In large hospitals, experienced physicians generally perform this assessment through interdisciplinary collaboration involving emergency medicine, intensive care, nephrology, and laboratory medicine specialists. However, this approach requires considerable time and medical resources. Delays in identifying high-risk patients may also increase the risk of complications and prolong hospitalization. Recent advances in artificial intelligence (AI) have created opportunities to improve the diagnosis, risk stratification, and prognosis of patients with RM. Machine learning algorithms can analyze large volumes of clinical data, identify relationships between multiple variables, and generate predictions that may not be readily apparent through conventional statistical approaches. These models may support physicians in identifying patients at increased risk of AKI, renal replacement therapy (RRT), and in-hospital mortality. Several studies have reported that machine learning models can achieve better predictive performance than established severity assessment systems, including the Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II), and Simplified Acute Physiology Score II (SAPS II) [67–69].

Liu et al. [70] developed an interpretable machine learning model to predict mortality among patients with RM admitted to intensive care units (ICUs). The investigators evaluated five machine learning algorithms, including extreme gradient boosting (XGBoost), logistic regression, support vector machine, random forest, and naive Bayes. The study included 938 patients from the Medical Information Mart for Intensive Care III (MIMIC-III) and eICU Collaborative Research Database (eICU-CRD). All five models achieved area under the receiver operating characteristic curve (AUC) values greater than 0.80, indicating good discriminatory performance. XGBoost demonstrated the highest predictive accuracy, with an AUC of 0.871. This performance exceeded that of the conventional SOFA score and Acute Physiology Score III, which achieved AUC values of 0.747 and 0.721, respectively. The researchers also applied Shapley Additive Explanations (SHAP) to rank predictors according to their contribution to the model's predictions. This approach improved interpretability by showing how individual clinical variables influenced the estimated risk of mortality. Such transparency is important because physicians need to understand the factors underlying an AI-generated prediction before incorporating it into clinical decisions. AI-based prediction may also support the early identification of renal complications. Poorsarvi Tehrani et al. [71] used data from the Bam earthquake to develop a prediction model for early detection of AKI among patients with RM. The model achieved a maximum specificity of 99.24% and sensitivity of 94.44%. These findings suggest that predictive algorithms may help identify patients who require closer renal monitoring and early supportive management, particularly in mass-casualty incidents where healthcare resources are limited. However, the performance of such models requires evaluation in other patient populations and healthcare settings before routine clinical implementation. In addition to machine learning, logistic regression has been widely used to identify clinical and biochemical variables associated with disease progression and adverse outcomes. El-Abdellati et al. [72] applied univariate logistic regression to determine cutoff values for predicting AKI in patients with RM. The reported thresholds included CK concentrations above 773 U/L, serum myoglobin (sMb) above 368 μg/L, and urinary myoglobin (uMb) above 38 μg/L. These biomarkers may contribute to early risk assessment when interpreted alongside renal function, hydration status, electrolyte concentrations, and the patient's clinical condition. Candela et al. [73] reported that myoglobin concentrations exceeding 8,000 U/L were associated with the development of moderate-to-severe AKI (grades 2–3) and chronic kidney disease (CKD). Such findings highlight the potential value of combining biochemical markers with predictive models to improve the identification of patients at risk of renal complications.

Another important contribution to RM risk assessment is the prediction model developed by McMahon et al. [74]. Using logistic regression, the investigators developed a scoring system to estimate the risk of RRT and in-hospital mortality. The model demonstrated good discrimination, with a C statistic of 0.82 (95% confidence interval [CI], 0.80–0.85) in the derivation cohort and 0.83 (95% CI, 0.80–0.86) in the validation cohort. This model illustrates how routinely available clinical and laboratory variables can be combined to support early risk stratification. It may help clinicians identify patients who require intensive monitoring and anticipate the need for renal support. Nevertheless, the decision to initiate RRT should remain based on established clinical indications, including refractory hyperkalemia, severe metabolic acidosis, fluid overload, and uremic complications, rather than a prediction score or CK concentration alone. Beyond diagnosis and prognosis, machine learning may contribute to the assessment of drug-related muscle injury. RM can develop following exposure to several medications, including statins and other agents associated with muscle toxicity. Drug interactions may increase systemic drug exposure and alter the risk of muscle injury. Machine learning techniques can analyze pharmacological, clinical, and patient-related data to identify potentially harmful drug combinations and predict adverse reactions. These applications may support medication safety assessments, improve pharmacovigilance, and guide the development and clinical use of drugs associated with RM [75,76].

Despite these advances, AI-assisted diagnosis still faces several challenges. Predictive models depend on the quality, completeness, and representativeness of the datasets used for their development. Differences in patient characteristics, laboratory measurement methods, diagnostic criteria, and healthcare resources may affect model performance across institutions. Models developed using retrospective ICU databases may not provide equivalent accuracy in emergency departments or general hospital populations. Furthermore, some algorithms operate as black boxes, limiting clinicians' ability to understand their predictions. Explainable AI approaches, external validation, and prospective clinical studies are therefore essential before widespread implementation. Overall, AI-assisted diagnosis represents a promising development in RM management. By integrating clinical characteristics, laboratory biomarkers, medication exposure, and other patient data, AI models may improve early risk identification and support decisions regarding monitoring and treatment. However, these technologies should complement rather than replace clinical judgment. Their successful integration into emergency and critical care practice will depend on validation in diverse populations, transparent

decision-making, and demonstration of improved patient outcomes.

Treatment of Rhabdomyolysis

The management of rhabdomyolysis (RM) aims to prevent further skeletal muscle injury, maintain renal perfusion, reduce the risk of acute kidney injury (AKI), and manage potentially life-threatening complications. Despite advances in understanding the pathophysiology of RM, high-quality clinical evidence supporting specific treatment strategies remains limited. Few randomized controlled trials have evaluated early interventions, and most current recommendations rely on retrospective studies, observational data, case reports, and experimental investigations [8,17]. Consequently, treatment decisions should consider the underlying cause, severity of muscle injury, renal function, electrolyte disturbances, and overall clinical condition. The initial management priorities involve identifying and eliminating the causative factor and promptly detecting complications. Potential triggers, including traumatic compression, excessive physical activity, medications, toxins, infections, and metabolic disturbances, should be addressed whenever possible. Clinicians should assess vital signs, hydration status, urine output, renal function, CK concentrations, and serum electrolyte levels. Particular attention should be given to hyperkalemia because it can cause life-threatening cardiac arrhythmias. Patients with severe RM may require early hospital admission and multidisciplinary management. Intravenous fluid administration represents the cornerstone of treatment, particularly in patients with significant muscle injury or evidence of dehydration. Early fluid resuscitation aims to restore circulating volume, improve renal perfusion, maintain urine flow, and reduce the accumulation of myoglobin and other muscle-derived substances in the renal tubules. Isotonic saline is commonly used for initial resuscitation. However, the optimal fluid composition, volume, administration rate, and target urine output remain subjects of debate. Previous studies have reported fluid requirements ranging from 3 to 24 L during the first 24 hours, with target urine outputs ranging from 2 to 12 L [6,16,77]. These broad ranges should not be applied routinely to every patient. Fluid administration must be individualized according to body weight, hemodynamic status, renal function, urine output, and the risk of fluid overload. Excessive fluid administration in patients with impaired renal function or established oliguria may cause pulmonary edema and other complications.

The use of sodium bicarbonate and mannitol has also been investigated as an adjunct to fluid therapy. Urinary alkalinization with bicarbonate may reduce myoglobin precipitation and oxidative injury within renal tubules. Mannitol has been proposed to increase urine flow and reduce tissue edema. Some studies have suggested that combining these agents with saline resuscitation may reduce the risk of RM-associated AKI [78]. However, available evidence does not support their routine administration in all patients. Similarly, loop diuretics should not be used routinely to prevent AKI or force diuresis. Isotonic crystalloid administration, with careful monitoring, remains the preferred initial approach for most patients [16,79]. Patients who develop severe AKI or life-threatening complications require additional interventions. Renal replacement therapy (RRT) should be considered when standard indications arise, including refractory hyperkalemia, severe metabolic acidosis, fluid overload, and uremic complications. RRT does not prevent AKI and should not be initiated solely because CK or myoglobin concentrations are elevated. Electrolyte abnormalities, particularly hyperkalemia, require prompt correction and cardiac monitoring. Hypocalcemia generally requires treatment only when symptomatic or associated with serious complications, because calcium administration during the early phase of RM may increase calcium deposition in injured muscle tissue. Overall, successful RM treatment depends on early recognition, removal of the underlying cause, individualized fluid resuscitation, continuous monitoring, and timely management of complications. Further prospective studies and randomized controlled trials are needed to establish standardized treatment protocols and determine the optimal role of adjunctive therapies.

Conclusion:

Rhabdomyolysis is a potentially life-threatening condition that requires early recognition, accurate diagnosis, and appropriate clinical management. Its diverse causes and complex pathophysiological mechanisms contribute to variable clinical presentations and complications, particularly acute kidney injury, electrolyte disturbances, and multiorgan dysfunction. CK and myoglobin remain essential diagnostic biomarkers, supported by clinical assessment, renal function testing, and imaging when indicated. Emerging biomarkers and AI-based prediction models may improve early diagnosis and identify patients at increased risk of adverse outcomes. However, their clinical application requires further validation in prospective studies and different healthcare settings. Treatment primarily involves eliminating the underlying cause, restoring circulating volume through individualized intravenous fluid therapy, and monitoring renal function and electrolyte balance. Current evidence does not support the routine use of bicarbonate, mannitol, or diuretics in all patients. Renal replacement therapy should be reserved for established clinical indications. Future research should focus on developing standardized diagnostic criteria, evaluating treatment strategies through controlled clinical trials, and validating AI-assisted

tools to support clinical decision-making and improve patient outcomes.

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