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Review Article

Advances in rhabdomyolysis: A review of pathogenesis, diagnosis, and treatment

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ABSTRACT

Rhabdomyolysis (RM) is a multifactorial clinical syndrome characterized by the disintegration and necrosis of muscle tissue, leading to the release of cellular contents into the circulation. One of the most severe complications of RM is acute kidney injury, with a mortality rate of 20%–50%. Early and timely diagnosis is the key to improving the prognosis of patients with RM. The etiology of RM is complex and associated with various trauma drugs, medications, and hereditary diseases, and the clinical symptoms are nonspecific. Therefore, its diagnosis highly relies on the doctor's experience and the level of medical equipment. However, RM often occurs in situations with limited medical resources, such as natural disasters, battlefields, and large-scale traffic accidents. In these scenarios, the varying levels of expertise among rescue personnel can lead to delays in diagnosis and treatment, thereby increasing the risk of mortality. This article provides a comprehensive review of the etiology, pathogenesis, complications, diagnostic, and treatment methods of RM. It also aims to offer new perspectives on the diagnosis and prognosis of RM by integrating machine learning and artificial intelligence. It is believed that this article can help pre-hospital rescuers and in-hospital doctors have a comprehensive understanding of RM to improve the patients' outcomes and overcome the challenges.

1. Introduction

Rhabdomyolysis (RM) is a disease in which the integrity of cell membranes is altered due to trauma, drugs, and genetics, and the cellular contents (such as creatine kinase (CK), myoglobin (Mb), and electrolytes) are released into the bloodstream in large quantities rapidly, resulting in tissue and organ damage. In severe cases, it can lead to kidney failure, significantly increasing the patient's risk of death.[1–3] RM can be caused by various reasons, including trauma, prolonged compression, excessive exercise, exposure to drugs and toxins, and hereditary myopathies, with the most common triggers for RM in adults being trauma and medications. With advancements in technology and medical research, our comprehension of RM has markedly improved in recent years. Nevertheless, controversies remain, especially regarding early diagnosis and prognostic assessment. Currently, the primary methods for treating RM in clinical practice include fluid replacement, alkalinization of urine, and promoting urination. Renal dialysis may also be used as an adjunct treatment for patients with renal failure. In most cases, timely identification and appropriate treatment can prevent complications and adverse outcomes. However, due to the nonspecific clinical manifestations of RM and the significant individual differences, it is easy to overlook and misdiagnose, thus missing the best time for treatment.

2. Etiology of RM

Due to the absence of prospective studies on RM and the underreporting of many mild cases, obtaining precise epidemiological data presents a challenge. After comprehensively reviewing the existing literature, we classified the causes of RM into 3 primary categories: physical, chemical, and biological (Table 1). Physical causes encompass factors such as tissue compression, trauma, endurance exercise, and thermoregulation imbalances, among others. Among these, compression and trauma stand as the most prevalent triggers of physical RM, which are commonly found in catastrophic events such as earthquakes, wars, and major traffic accidents. Compression can result in prolonged muscle ischemia

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Table 1
Etiology of rhabdomyolysis.

Physical	Chemical	Biological
Crush injury	Medications	Toxin
Crush syndrome	Anticholinergic agents	Insect stings
Burns	Phenothiazines	Snake venom
Endurance exercise	Aspirin	Infection
Army training	Electrolyte disorders	Viral
Unaccustomed exercise	Hypo-/hyper-natremia	Bacterial
Ultramarathon race	Hypokalemia	Protopathy
Triathlon	Hypocalcemia	Genetic disorders
Ultra-endurance events	Illicit drugs	Autoimmune disorders
Electrocution	Cocaine	Endocrinologic conditions
Hypothermia	Heroin	
Heat stroke	Alcohol	
	Alcohol withdrawal syndrome	

and impede oxygen transport to cells. When the weight of the crushing object exceeds 30% of an individual's body weight and the compression persists for more than 5–6 h, the likelihood of developing RM significantly rises.[1] Furthermore, strenuous activities frequently contribute to RM. Activities like militant training and intense fitness routines can lead to exertional RM.[4,5] Chemical factors involve substances such as illicit drugs, medications, and electrolyte disorders. Among these, the most common is drug-induced RM, which disrupts normal muscle cell function by interfering with adenosine triphosphate (ATP) production or increasing muscle membrane permeability.[6–8] One of the most common causes is the consumption of HMG-CoA reductase inhibitors or statin drugs. RM can manifest within 2–3 weeks of initiating such medication. It is crucial to discontinue the medication immediately if patients report muscle pain or the CK levels rise above the usual.[9] Biological factors encompass infections, snake and insect bites, and various primary diseases, including genetic and autoimmune disorders. Among all reported pediatric RM cases, infectious RM accounts for approximately one-third of the total.[10–12] Various diseases and injuries and patient characteristics like gender and age influence RM. For instance, it is more prevalent in males with substantial muscle mass.[13]

3. Pathogenesis of RM

The various causes of RM may differ, but the core mechanism is intracellular Ca^{2+} overload, which mainly attributed to the following points: (1) Depletion of intracellular ATP leads to dysfunction of ion pumps.[14] Dysfunction of the Na^+/K^+ ATPase leads to an increase in intracellular Na^+ concentration, which in turn enhances the activity of the $2Na^+/Ca^{2+}$ exchanger, accelerating the transport of Ca^{2+} into the cell. At the same time, the functions of Ca^{2+} pumps and Ca^{2+} transport proteins on organelles such as the sarcoplasmic reticulum and mitochondria are also impaired, preventing the deposition of excess Ca^{2+} in the cytoplasm, leading to an increase in intracellular Ca^{2+} concentration.[12,15] (2) Some underlying causes can damage the integrity of the muscle cell membrane. After the integrity of the cell membrane is altered, extracellular Ca^{2+} continuously enters the cell driven by the chemical gradient, further exacerbating intracellular Ca^{2+} overload. Ca^{2+} overload can activate phospholipase A2 and various calcium-dependent proteases, dissolving cellular phospholipid membranes (such as those of mitochondria, sarcoplasmic reticulum, and other organelle membranes) and exacerbating the damage to various membrane structures within the cell.[2,3,12,16] (3) Cellular oxidative stress is increasing. The reduction of ATP leads to an increase in reactive oxygen species (ROS, O_2, and H_2O_2), which can oxidize the fundamental structural components of various organelles within the cell (such as proteins, lipids, and nucleic acids). Their destruction further exacerbates damage to cellular structure and function.[15–17] In summary, the process of RM is a vicious cycle leading to the death of muscle cells. After the necrosis of muscle cells, toxic substances are released into the circulation, inducing damage to adjacent capillaries and local edema, which further leads to multiple organ dysfunction (Fig. 1).

4. Complications of RM

Following RM, cellular contents are released into the bloodstream, giving rise to disturbances in the internal environment. This can lead to a range of tissue and organ dysfunctions, including acute kidney injury (AKI), liver injury, compartment syndrome, disseminated intravascular coagulation (DIC), and more (Fig. 2).[18]

4.1. AKI

RM can lead to various complications, with AKI being the most common and severe. The earliest report on the connection between RM and AKI can be traced back to World War II. Bywaters and his colleagues[19] described the clinical symptoms of 4 casualties from the London bombing incident, which included limb swelling, reddish-brown urine, and shock, and they introduced the concept of crush syndrome. It is reported that the incidence of RM-AKI is approximately 13%–50%. The occurrence of AKI is a combined result of hypovolemia, aciduria, and accumulation of Mb in the renal tubules.[20–22] Following RM, excessive Mb is released into the bloodstream. Lacking a specific binding protein, Mb is freely filtered by the glomerulus. Under acidic urine conditions, Mb precipitates, forming casts that cause tubular obstruction and necrosis, accompanied by intense renal vasoconstriction.[9,21] In addition, Mb induces the release of free iron via heme and catalyzes the production of free radicals, which further exacerbates ischemic tubular injury.[20] While it is widely accepted that kidney damage is due to Mb deposition in the kidney, the specific mechanism of its occurrence remains a topic of debate. Notably, even mild forms of AKI can result in significant mortality risks.[23] Therefore, vigilance and early identification of this condition are crucial.

4.2. Electrolyte disturbance

The various ions in the human body are fundamental to maintaining normal physiological functions. Once electrolyte imbalances occur, they can not only disrupt multiple organ functions but also can be life-threatening. Most potassium ions in the human body are stored in skeletal muscle cells. When RM occurs, the release of skeletal muscle cell contents results in serum potassium

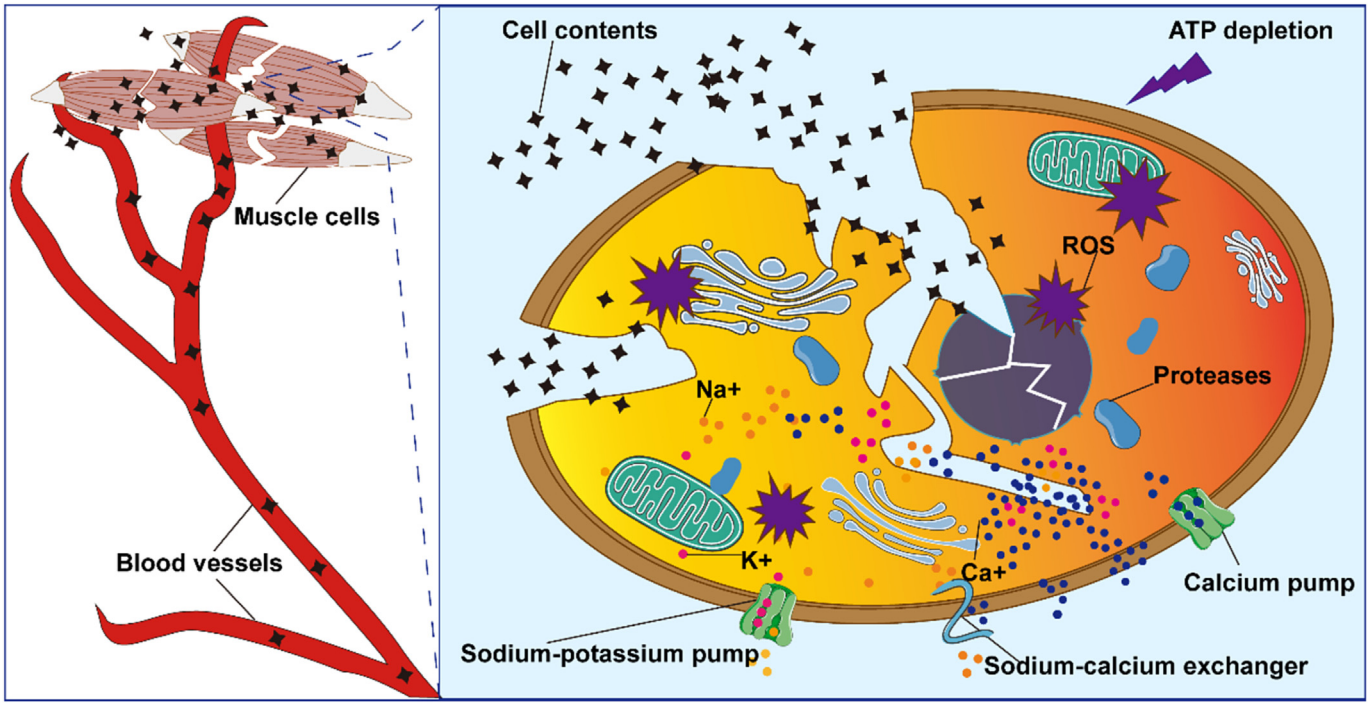

Fig. 1. Pathogenesis of RM. When muscle cells are damaged, muscle contraction intensifies, ATP consumption increases, and cell membrane integrity changes. ATP depletion inhibits Na^+/K^+ ATPase function, preventing the regular transport of Ca^{2+} out of the cell. Simultaneously, extracellular Ca^{2+} continuously enters the cell through the damaged membrane, resulting in calcium overload. This, in turn, calcium-dependent proteases and phospholipases are activated, causing damage to mitochondria, the sarcoplasmic reticulum, and cell membrane integrity, ultimately leading to cell apoptosis.
RM: rhabdomyolysis; ATP: adenosine triphosphate; ROS: reactive oxygen species.

levels rapidly exceeding the normal range, causing hyperkalemia (>5.0 mEq/L).[24] Simultaneously, various organic acids (such as lactic acid, uric acid, etc.) released into the circulation due to skeletal muscle cell damage can lead to metabolic acidosis, further exacerbating hyperkalemia.[25] Early stages of RM can also present with hypocalcemia, intensifying hyperkalemia's cardiac toxicity. The inorganic phosphates released by damaged skeletal muscle cells can cause hyperphosphatemia and the formation of calcium phosphate deposits on damaged muscle cells and other tissues, further exacerbating hypocalcemia. As RM progresses, calcium from the damaged cell cytoplasm will also be released into the plasma, potentially leading to hypercalcemia in later stages.

4.3. Compartmental syndrome

Compartment syndrome is a common complication of RM. Most skeletal muscles are encased within compartments formed by bones, fasciae, and other structures. When RM occurs, fluid accumulates intracellularly, causing local edema and an increase in the volume of the contents within these fascial compartments.[26] Due to the lack of elasticity in the muscle fascia and other connective tissues, the pressure inside these compartments rises. This elevated pressure impedes blood supply and venous blood return to the local muscle tissues, leading to venous hypertension and progressive tissue ischemia.[27]

4.4. DIC

DIC is not an independent disease but rather a common final pathway of coagulopathy in the progression of many diseases, which is a clinical pathological syndrome with a mortality rate as high as 31%–80%. The pathogenesis of DIC is multifaceted and involves endothelial dysfunction and vascular injury, effective initiation of coagulation pathways and platelet aggregation, impairment of anticoagulation systems, shutdown of fibrinolysis, activation of the complement system, and upregulation of the inflammatory response.[28] During RM, damaged muscle cells release various prothrombotic substances (mainly thromboplastin) that activate the coagulation cascade, leading to the onset of DIC.[26]

4.5. Acute liver injury

Among patients with RM, about 25% also exhibit liver damage, especially those with underlying liver diseases.[28] When RM occurs, a significant amount of Mb is released into the bloodstream due to the disruption of cellular structures, which in turn produces a large amount of heme. Heme is a complex molecule, and its pro-oxidant properties can amplify oxidative stress in cells, leading to cellular damage. Critically, the liver, the primary organ for heme metabolism and clearance, is particularly susceptible to heme's effects. Heme may reduce hepatic blood flow, subsequently affecting the oxygen and nutrient supply to the liver. Additionally, heme can directly induce hepatocyte injury, leading to cell necrosis and apoptosis.[29] Therefore, it is essential to closely monitor liver function and implement appropriate therapeutic measures to prevent further organ damage.

5. Diagnostic of RM

5.1. Medical history

RM has diverse causes and often presents with non-specific clinical features. Only about 10% of RM patients will experience the typical symptoms of muscle pain, muscle weakness, and hematuria. To avoid misdiagnosis or missed diagnosis of RM, when patients present with suspected RM symptoms like general fatigue,

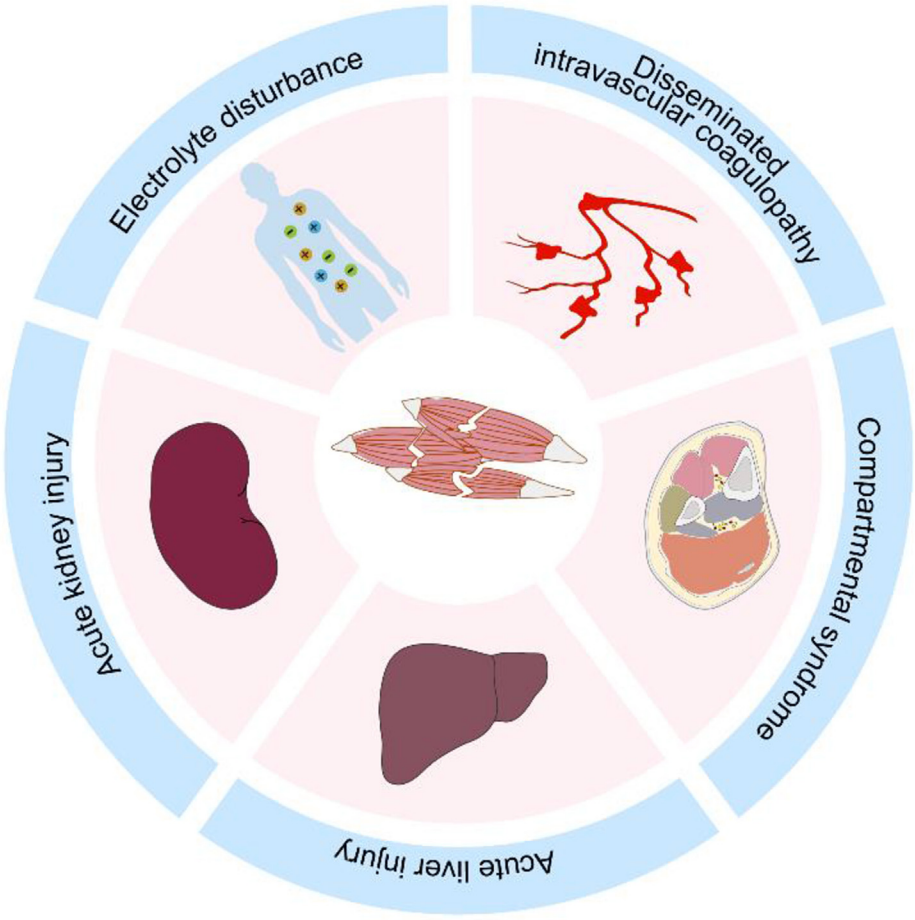

Fig. 2. Common complications of rhabdomyolysis.

fever, nausea, vomiting, and muscle pain, clinicians should consider an initial diagnosis based on relevant risk factors in the patient's history, such as trauma, excessive exercise, medication, infection, food intake, and excessive alcohol consumption.

5.2. Muscle biopsy

Muscle damage in RM patients tends to be non-specific, and most patients have no significant pathologic changes on muscle biopsies. Zhao et al.[30] conducted a retrospective analysis of the skeletal muscle biopsy pathology results of 26 RM patients. They found that skeletal muscle damage varied widely among RM patients with different etiologies. Exercise-induced skeletal muscle damage is usually not severe, while drug- and toxicity-induced ones tend to present as necrotizing muscle disease, and primary neuromuscular disease is less common.[30] Muscle biopsy has specific diagnostic value for primary skeletal muscle diseases since it is an invasive procedure. It should be selectively performed based on the patient's medical history before the onset of the disease and is generally not recommended as the first choice.[8]

5.3. Imaging

Imaging is valuable in assessing the extent of muscle damage, injuries to other organs, and complications.[3] With the continuous advancement of technology, imaging examinations such as ultrasound (US), CT, and MRI have become common diagnostic tools.[31] The results from these imaging studies can significantly enhance the diagnosis of RM and guide clinical decision-making (Table 2).[32–36]

5.3.1. US examination

US examination can identify potential muscle injuries and monitor the healing process.[31] The history of the diagnosis of RM using the US began in the early 1980s. The published case reports and varied causes of RM may give different macroscopic changes and possibly different US appearances. The most frequent pathological findings described in the publications were as follows: (1) General thickening of the striated muscles; (2) Muscle fiber texture is indistinct and heterogeneous with enhanced echogenicity; (3) A localized spindle-shaped uniform hypoechoic or anechoic appearance can be observed for smaller lesions. The muscle texture becomes indistinct when the extensive lesions present diffuse heterogeneous echogenicity. Adjacent to these areas, a net-like hypoechoic exudate and edema is evident; (4) Irregular anechoic areas of fluid can be seen in the muscle interstices and between the muscle and skeleton.[37] The US is a non-invasive and quick procedure that allows for real-time dynamic observation. It displays muscle pathologies of RM, and the sonogram is easy to recognize (differentiation from muscle tears, hematomas/abscesses, and other diseases is essential). US-guided needle biopsy may be considered when diagnostic differentiation remains inconclusive.

Table 2
Diagnostic imaging techniques for RM.

Imaging techniques	Study (year)	Species	Sample size	Causes	Findings	Advantages	Disadvantages
US	Carrillo-Esper et al.[32] (2016)	Human	1	Long-term fixation of legs	Disordered direction of muscle fibers, indistinct glass images, thickening of muscle fascia, and presence of anechoic zones.	(1) Cheap, easily accessible, and fast; (2) Clear image; (3) Non-invasive examination	(1) Low sensitivity; (2) Late appearance; (3) Smaller inspection area
	Nassar et al.[33] (2016)	Human	1	Weight lifting, polysubstance abuse	The sonogram showed areas of both increased and decreased echogenicity of the biceps muscle, as well as disorganized muscle fibers with surrounding areas of fluid. The muscle boundary was preserved, and the biceps tendon was intact.		
	Hans et al.[34] (2020)	Human	1	NI	Longitudinal images demonstrated hypoechoic areas of muscle, disorganization of the fascicular architecture, irregularity of the muscle fibers, and some hyperechogenicity in the muscle.		
CT	Lu et al.[35] (2007)	Human	2	NI	The affected muscles revealed heterogeneously hypodense with dot-like or linear streaky enhanced foci within an area of rim enhancement.	(1) Clear image; (2) Short scanning time; (3) High-density resolution; (4) Cover a large anatomic region; (5) Define the extent of muscular damage	(1) Nuclear radiation; (2) Poor soft tissue contrast
	Mian et al.[36] (2011)	Human	1	Cocaine	CT demonstrated swelling of the right masseter muscle and parotid gland with associated soft-tissue edema and fat stranding in the subcutaneous tissue.		
MRI	Lu et al.[35] (2007)	Human	9	NI	For type 1 R M, the affected muscles revealed homogeneously isointense to hyperintense on T1-weighted images, homogeneously hyperintense on T2-weighted and STIR images, and homogeneously enhanced on contrast-enhanced MR images without evidence of myonecrosis. For type 2 R M, the affected muscles revealed homogeneously or heterogeneously isointense to hyperintense on T1-weighted images, heterogeneously hyperintense on T2-weighted and STIR images.	(1) High sensitivity; (2) Radiation-free; (3) Non-invasive examination; (4) Evaluate the distribution and extension of muscle lesions; (5) Multi-directional, multi-sequence imaging; (6) High soft-tissue resolution	(1) High cost; (2) Long time for the analysis; (3) Patients need to be transferred to specialized centers; (4) Unsuitability with claustrophobic patients and large usage in patients with severe diseases
	Mian et al.[36] (2011)	Human	1	Cocaine	Homogeneous isointensity to slight hypointensity on T1-weighted images, heterogeneous hyperintensity on T2-weighted images, and STIR. Post-contrast images demonstrated heterogeneous dot-like or linear enhancement in the right masseter muscle.		

RM: rhabdomyolysis; US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; NI: no information; STIR: short-tau inversion recovery.

Limitations of the US include its confined examination scope, dependence on the operator's skill level, and lower sensitivity.[38]

5.3.2. CT

CT imaging of RM patients reveals thickened fascia, swollen damaged muscles, patchy areas of low-density necrosis and edema, and surrounding speckled high-density calcifications.[38] CT can effectively cover large anatomical areas, clearly describing the extent and range of muscle involvement. It is particularly suitable for patients contraindicated or intolerant to MRI.[3] Furthermore, CT scans are fast and produce clear images. In particular, multi-slice spiral CT and three-dimensional reconstruction techniques can precisely differentiate bones, tendons, ligaments, muscles, gas, and liquids. CT is valuable for diagnosing RM. However, due to its radiation exposure, CT is not the first choice for RM diagnosis.

5.3.3. MRI

MRI represents a non-invasive diagnostic technique with several advantages, including the absence of radiation exposure and the capability for multi-directional and multi-sequence imaging. With its superior soft tissue resolution, MRI has become the imaging technology of choice for the evaluation and diagnosis of muscle injuries.[31] This technique allows precise delineation of the extent and distribution of muscular involvement, while facilitating the differentiation between reversible and irreversible changes in damaged muscle. In cases of RM, MRI typically demonstrates diffuse muscle swelling with unclear boundaries. There is a decreased signal on T1-weighted images and an increased signal on T2-weighted images and short-tau inversion recovery sequences. Patchy or filamentous uneven signals can be observed within these areas. Notably, MRI demonstrates significantly superior sensitivity

in the detection of muscle pathology compared to both CT and US. The extended acquisition time required for MRI may pose significant challenges in critically ill patients, particularly with regard to maintaining adequate patient compliance during the procedure. Furthermore, MRI is associated with substantial costs and requires significant infrastructure, which may limit its accessibility for rapid diagnosis, potentially leading to a delayed diagnosis. Nevertheless, MRI continues to be one of the most reliable radiological methods for the clinical diagnosis of RM. Particularly in fasciotomy, MRI serves as the imaging method of choice for precise assessment of both the spatial distribution and severity of muscle lesions.

5.4. Biomarkers

Early identification and management of RM can effectively prevent potential complications and reduce mortality. Given the multifactorial etiology and complex mechanisms underlying RM, biomarkers can assist clinicians in making more timely and precise assessments of disease onset, progression, and severity (Table 3).[39-51]

5.4.1

CK is a widespread enzyme in organs and tissues that catalyzes the reversible reactions of creatine and adenosine triphosphate and is closely related to mitochondrial oxidative phosphorylation.[31] CK has 3 major isoenzymes: CK-MM, CK-MB, and CK-BB. CK-MM reflects skeletal muscle diseases, CK-MB diagnoses acute myocardial infarction, and CK-BB is significant for brain injury and gastrointestinal malignancies. CK levels greater than 5 times the upper limit of normal are clinical diagnostic criteria for RM.[22] However, studies have shown that CK >1000 U/L is not the best predictor for organ function and clinical prognosis. In cases of RM caused by other etiologies such as infection, trauma, crush injuries, etc., CK >5000 U/L demonstrates superior predictive of AKI.[41] After the onset of RM, serum CK levels began to rise in 2–12 h, peaked in 24–72 h, and returned to baseline levels in 3–6 days.[31] The pathogenesis of CK and RM-AKI is not directly related, but CK levels >5000 U/L are strongly associated with renal failure and renal replacement therapy (RRT) after crush injury.[22] RRT effectively prevents AKI when CK levels remain >2000 U/L in patients diagnosed with RM.[22] The etiology of RM influences the predictive performance of CK, and there is a high correlation between serum CK levels and AKI levels in trauma cases, especially more significant in crush injury cases.[52] Notably, the optimal threshold for CK to diagnose RM injury has been controversial, and CK levels are highly individualized, with a high sensitivity but poor specificity for diagnosing RM.[31]

5.4.2. Mb

Mb is a protein in skeletal muscle and cardiac muscle cells responsible for transporting oxygen from the muscle membrane to the mitochondria.[53] Mb does not rely on lymphatic transport and can be rapidly released into the bloodstream, which has excellent advantages in the early prediction of RM.[54,55] After RM occurs, the concentration of Mb in the blood peaked at 3 h and returned to normal after 6–8 h.[8] The predictive power of Mb is grossly underestimated due to its rapid kinetics. CK has a half-life of 1.5 days in blood, but Mb has a half-life of just 2–4 h in blood.[41,44] In fact, Mb only has a shorter half-life (1–6 h) in healthy individuals, and its clearance effect is significantly delayed in severe RM patients. Mb not only predicts muscle injury but also serves as a direct mediator of RM-AKI, potentially offering a significantly superior approach to risk stratification for renal injury compared to CK.[42,55] Serum Mb (sMb) ≥1000 ng/mL is a risk factor for AKI by multivariate analysis.[41] Using sMb ≥1000 ng/mL as a diagnostic criterion for RM can better stratify patients' risk of AKI development and mortality. One study found that Mb concentration can also predict hemodialysis.[54] When the Mb level in the blood is higher than 15 mg/L, the likelihood of patients requiring hemodialysis will double. Additionally, it has been found that Mb-AKI occurred when blood Mb levels were higher than 3865 μg/L (receiver operating characteristic=0.88). In summary, despite the low sensitivity in diagnosing RM, Mb is a better predictor of RM-AKI than CK.

5.4.3. Lactate dehydrogenase (LDH)

LDH is a housekeeping protein that catalyzes the interconversion of pyruvate and lactate, and nicotinamide adenine dinucleotide (reduced) and nicotinamide adenine dinucleotide. The composition of isoenzymes (LDH-1 to LDH-5) varies in different tissues, and the specificity of elevated isoenzymes can be utilized to differentiate RM from other diseases.[56,57] LDH is involved in skeletal muscle metabolism usually at a low level in the blood, and its serum activity is a marker of cellular damage. The concentration of LDH peaked 3–6 h after the high-intensity exercise and returns to the baseline level within 24 h, with an increase typically between 1.2 and 1.3 times the upper reference limit (URL).[45] Research indicates that LDH plays an important role in the development of inflammation and AKI, serving as a suitable and cost-effective prognostic indicator for risk stratification in patients with RM-AKI, but its specificity and sensitivity for diagnosing muscle injury are relatively poor.[53,58]

5.4.4. Alanine aminotransferase/aspartate aminotransferase (ALT/AST)

ALT and AST are 2 widely distributed aminotransferases in the body, mainly present in the liver, muscles, heart, and other organs. Unlike CK and Mb, ALT and AST have slower response kinetics. After RM injury, ALT and AST peak at 3–4 days and return to baseline levels at 6–10 days.[53] In severe cases, abnormalities may persist for 2–3 weeks. Because of lacking specificity and sensitivity, RM cannot be diagnosed effectively when tested individually, but serum ALT and AST levels are closely related to CK. Chandel et al.[59] proposed an AST threshold concentration and formula for predicting CK levels, resulting in a 97.1% sensitivity and 85.7% specificity for detecting AST values ≥110 U/L for CK values ≥5000 U/L. Therefore, CK levels can be predicted by ALT and AST in the absence of CK data, while the diagnostic accuracy of RM can be significantly improved by using these 2 factors in combination with CK.

5.4.5. MicroRNAs (miRNAs)

MiRNAs are endogenous non-coding RNA molecules with a size of approximately 21–23 bases that regulate gene expression by inhibiting the translation of target messenger RNA. Their dysregulation is important to cell and organ damage.[60,61] Research has found that miRNAs can regulate muscle generation and adaptive response to exercise. It can distinguish specific stress signals induced by changes in duration, mode, and type of exercise, allowing each tissue to express a specific spectrum of miRNAs.[60,62] MmiR-206, miR-1, miR-133a, and miR-133 b are muscle-specific miRNAs. Chalchat et al.[47] found that these 4 miRNAs were upregulated immediately after the end of a 24 h-high-intensity run. Bailey et al.[63] tested their predictive performance using a rat model and showed that all 4 miRNAs outperformed CK (up to 80% sensitivity and 95% specificity). With the advantages of good stability, easy accessibility, and convenient amplification, miRNAs are expected to be candidates for the best muscle injury biomarkers.

5.4.6. Other biomarkers

Some relatively innovative, “non-traditional” biomarkers have also been recently proposed for RM diagnostics. However, research on its clinical effectiveness is still in embryo, so it has not been widely used in clinical. Aldolase (ALD) is a glycolytic enzyme mainly

Table 3
Biomarkers for diagnosing and monitoring RM.

Biomarkers	Study (year)	Species	Sample size	Causes	URL	Time to increase > URL	Time to highest values	Advantages	Disadvantages
CK	Bäcker et al.[39] (2023)	Human	772	Marathons and weightlifting	CK by greater than or equal to 5 times the baseline	2–12 h	24–72 h	(1) Reflects the amount of injured muscle; (2) High sensitivity; (3) High diagnostic performance; (4) High prognostic performance; (5) Low cost; (6) High availability; (7) High throughput; (8) High standardization	(1) Very prone to oxidation; (2) High inter-individual variability; (3) Low specificity and selectivity; (4) Difficult to provide universal URL cut-offs; (5) CK activity strongly depends on extracellular glutathione concentration; (6) Low CK values are associated with an increased mortality
	Laitselart et al.[40] (2022)	Human	51	War	CK peak >1000 U/L	NI	NI		
	Simpson et al.[22] (2016)	Human	232	Trauma, medical, and perioperative complications	CK > 1000 U/L	<1 day	24–72 h		
Mb	Wu et al.[41] (2022)	Human	161	Strenuous exercise	sMb ≥1000 ng/mL	NI	NI	(1) High predictive value for the development of acute kidney injury; (2) Higher prognostic accuracy for myocardial injury; (3) High prognostic performance; (4) High availability; (5) High throughput; (6) Moderate cost	(1) Low sensitivity; (2) Extremely short plasma half-life; (3) High cost; (4) Lack of standardization; (5) Difficult to provide universal URL cut-offs; (6) High inter-individual variability
	Tarazona et al.[42] (2021)	Human	857	Trauma	Myoglobin> 1938 μg/L	NI	NI		
	Moulla et al.[43] (2018)	Human	281	Bariatric surgery	Myoglobin value over 3000 ng/mL	NI	1 day		
	Kasaoka et al.[44] (2010)	Human	30	Trauma, burns, and ischemia, among others	NI	NI	2 days		
	Lippi et al.[45] (2008)	Human	15	A 21-km, half-marathon	Mb > 72 ng/mL	0–3 h	3 h		
LDH	Lippi et al.[45] (2008)	Human	15	A 21-km, half-marathon	LDH> 480 U/L	0–3 h	3 h	(1) Low cost; (2) High availability High throughput; (3) High standardization	(1) Late appearance; (2) Low specificity and sensitivity
ALT	Martinez et al.[46] (2023)	Human	272	Hemorrhagic trauma	NI	NI	3 days	(1) Low cost; (2) High availability High throughput; (3) High standardization; (4) High sensitivity	Lower specificity and sensitivity than CK
	Lippi et al.[45] (2008)	Human	15	A 21-km, half-marathon	NI	NI	24 h		
AST	Martinez et al.[46] (2023)	Human	272	Hemorrhagic trauma	NI	NI	3 days	(1) Low cost; (2) High availability; (3) High throughput; (4) High standardization	(1) Low prognostic performance; (2) Late appearance; (3) Lower specificity and sensitivity than CK
	Lippi et al.[45] (2008)	Human	15	A 21-km, half-marathon	AST>50 U/L	NI	3 h		
miRNAs	Chalchat et al.[47] (2021)	Human	11	Ultra-endurance sports	NI	NI	0 h	(1) High sensitivity and specificity; (2) Faster kinetics than CK; (3) Positively correlated with troponin T level; (4) More relevant than CK or Mb to represent the magnitude of muscle damage	(1) Short half-life; (2) Not clinically validated; (3) High cost; (4) Deficient availability; (5) Low throughput; (6) High influence of preanalytical variables; (7) High-interlaboratory variation; (8) No decision cutoffs; (9) Challenging analytical technique; (10) No (external) quality control
ALD	Nozaki et al.[48] (2009)	Human	12	Neuromuscular	NI	NI	NI	High throughput	(1) High cost; (2) Low availability; (3) Low standardization
FABP	Goldstein et al.[49] (2017)	Rats	34	Marcaine	NI	NI	2 h	(1) Improves diagnostic certainty when combined with AST and CK; (2) High sensitivity; (3) High specificity; (4) Levels in blood correspond to the severity of muscle injury	(1) High cost; (2) Low availability; (3) Low standardization
		Rats	51		NI	NI	1 h		

(*continued on next page*)

Table 3 (*continued*)

Biomarkers	Study (year)	Species	Sample size	Causes	URL	Time to increase > URL	Time to highest values	Advantages	Disadvantages
	Tonomura et al.[50] (2012)			Various myotoxic and non-myotoxic compounds					
CAIII	Nishita et al.[51] (1995)	Horses	216	NI	NI	NI	NI	High specificity	(1) High cost; (2) Low availability (3) Low throughput; (4) Low standardization
Myl3	Tonomura et al.[50] (2012)	Rats	51	Various myotoxic and non-myotoxic compounds	NI	NI	NI	(1) Improves diagnostic certainty when combined with AST and CK; (2) High sensitivity; (3) Levels in blood correspond to the severity of muscle injury	Low specificity

RM: rhabdomyolysis; URL: upper reference limit; CK: creatine kinase; Mb: myoglobin; LDH: lactate dehydrogenase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; miRNAs: microRNAs; ALD: aldolase; FABP: fatty acid-binding proteins; CAIII: carbonic anhydrase III; Myl3: myosin light chain 3; sMb: Serum Mb; NI: no information.

present in the skeletal muscle, liver, and brain. The dynamics of serum ALD are slow, and the ALD level significantly increases 48 h after muscle injury.[31] It is worth noting that ALD combined with CK can evaluate the extent of muscle damage. Fatty acid-binding proteins (FABPs) are a family of proteins with 9 different forms, one of which H-FABP is predominantly found in the heart and skeletal muscles.[57] After high-intensity exercise, FABP concentration rises rapidly, peaking within 2–6 h, and returns to the baseline level within 24 h.[31] Carbonic anhydrase III (CAIII) is a cytoplasmic enzyme highly expressed in skeletal muscle and involved in various physiological processes such as oxidative stress, mitochondrial ATP synthesis, and autoimmunity.[64] Compared with CK, AST, and ALD, CAIII has a faster kinetics. After high-intensity exercise, CAIII levels rapidly increase to 2–2.5 times the baseline level, peaking within 6 h, and almost returning to baseline within 24 h.[31] Myosin light chain 3 (Myl3) is an important light chain in the myosin molecule, primarily expressed in cardiac and skeletal muscle.[65] While Myl3 is primarily used to study cardiac cell injury, its concentration changes can also reflect muscle cell damage. Tonomura and colleagues[50] found that Myl3 concentrations can accurately detect heart and skeletal muscle injuries.

Early identification of RM is crucial for timely and effective treatment. The clinical symptoms of RM vary significantly among individuals, with the classic triad of myalgia, weakness, and tea-colored urine occurring in only about 10% of patients.[66] Without sufficient experience or adequate knowledge of etiology, it is easy to miss diagnose, make misdiagnose, or miss the optimal treatment window. Therefore, in the diagnostic process of RM, it is essential to conduct a detailed inquiry into the patient's medical history, including factors such as prolonged pressure, trauma, high-intensity endurance exercise, exposure to extreme temperatures, medication or alcohol use, symptoms of infection, family history, and changes in urine color and quantity, among other high-risk information.[8] Additionally, a comprehensive assessment should be conducted by integrating imaging studies, biochemical analyses, and physical examination findings.

6. Artificial intelligence (AI)-assisted diagnosis

RM is a clinical syndrome with complex mechanisms and a wide range of etiologies. Currently, in large hospitals, RM can be diagnosed by experienced physicians by combining the patient's medical history, imaging, laboratory test results, and some biomarkers. However, this process necessitates close interdisciplinary collaboration, which inevitably increases the demand on already limited medical resources and presents dual risks to patients, encompassing both health and economic consequences. With the continuous development of AI, constructing computer models to assist or even replace human experts in disease diagnosis and prognosis management has become a new research direction. It showed a superior predictive performance for disease progression and mortality to existing disease severity classification systems, such as SOFA, APACHE II, or SAPS II, etc.[67–69] Liu et al.[70] developed an interpretable machine model for predicting mortality in patients with RM in the intensive unit (ICU), using 5 machine learning methods (eXtreme gradient boosting, logistic regression, support vector machine, random forest, naive bayes). The study included 938 data from the MIMIC-III and eICU-CRD databases, and the results showed that the area under the curve (AUC) values of the 5 machine learning models in predicting the mortality of ICU-RM patients were all higher than 0.8. The AUC values of eXtreme Gradient Boosting were as high as 0.871, which was significantly higher than the traditional clinical scores SOFA and acute physiology score III (AUC values of 0.747 and 0.721, respectively). In the model, each predictor is ranked based on the contribution of the SHAPvalue,

which will help physicians better understand the model decision-making process. Poorsarvi Tehrani et al.[71] used the Bam earthquake data to establish a prediction model for the early detection of AKI rate in patients with RM, and the best specificity and sensitivity of the model were 99.24% and 94.44%, respectively. In addition, logistic regression is widely used to predict the risk factors associated with disease development and mortality. El-Abdellati et al.[72] used univariate logistic regression to obtain the best cutoff values for the prediction of AKI (CK >773 U/L; sMb >368 μg/L, uMb >38 μg/L). Candela et al.[73] found that more than 8000 U/L Mb can indicate the occurrence of AKI2-3 grade and CKD. McMahon et al.[74] established a risk prediction for RRT and in-hospital mortality through logistic regression, with a C statistic of 0.82 (95% confidence intervals 0.80–0.85) for the prediction model in the derivation cohort and 0.83 (0.80–0.86) in the validation cohort. It is worth mentioning that machine learning can also be used to indicate the effect of drug interactions on RM, and to guide the development and use of related drugs.[75,76]

7. Treatment of RM

Currently, there is no high-quality data, such as randomized controlled trials, providing clear treatment evidence for early intervention in RM. Most recommendations are based on retrospective studies, case reports, and animal experiments.[8,17] The most important steps after suspected or confirmed RM are: (1) identify and eliminate pathogenic factors to prevent ongoing damage to the body, and (2) rapidly identify potential life-threatening complications. For severe patients, intravenous access should be established quickly to initiate fluid therapy. However, there is no consensus on the standards for the composition, volume, starting time, infusion rate, and target urine output of supplemental fluids. Researches have shown that within the first 24 h of onset, a fluid replacement volume of 3–24 L and a target urine output of 2–12 L can effectively improve RM.[6,16,77] The addition of bicarbonate and mannitol after initial saline resuscitation can also prevent RM-AKI.[78] However, there is still insufficient evidence to support the routine use of interventions such as bicarbonate, mannitol, and loop diuretics. In most RM patients, the use of isotonic saline for fluid resuscitation is sufficient to prevent the occurrence of AKI.[16,79] For patients with severe AKI and other life-threatening complications (such as hyperkalemia, hypocalcemia, hyperazotemia, fluid overload, etc.), renal replacement therapy should be considered.[77]

8. Conclusions and prospect

At present, there are still many problems in the diagnosis and prognosis management of RM, such as a single data model, and strong subjectivity. Most of the existing studies are retrospective studies, serious lack of patient data, poor specificity and accuracy of diagnostic markers, and an inability to stratify the risk of the disease. Our work aims to improve the diagnosis and prognosis management of RM. Currently, we developed an electrical impedance tomography device having the capable of non-invasively detecting muscle injuries. It designs and fabricates a flexible planar sensor array with a rectangular electrode arrangement, and obtain a strong validation in small animal models.[80] We are also working on the development of a multimodal-based intelligent assisted diagnostic system. This intelligent assistance system will integrate images, narrative texts (e.g., chief complaints, which include current and past medical history), and structured fields (e.g., demographic and laboratory test results) to provide a comprehensive and objective diagnosis and prognosis intervention for RM. We are confident that this system will be available shortly and it will greatly improve the accuracy of early diagnosis of RM, reduce the burden on patients, and help promote the optimal use of medical resources in any harsh environment. However, to fully realize the potential of AI application in RM, it still requires collaboration between medical and AI research to continuously develop and validate models with improved performance, aiming to enhance patient outcomes and advance diagnostic medicine.

CRediT authorship contribution statement

Bo-Fan Yang: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Duo Li:** Writing – review & editing, Writing – original draft, Funding acquisition, Data curation. **Chun-Li Liu:** Supervision. **Yu Luo:** Supervision. **Jie Shi:** Writing – review & editing, Supervision. **Xiao-Qin Guo:** Writing – review & editing, Supervision. **Hao-Jun Fan:** Supervision, Funding acquisition, Conceptualization. **Qi Lyu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Ethical statement

Not applicable.

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Declaration of competing interests

None of the authors have any conflicts of interest to declare.

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