Review

The Emergence, Epidemiology, and Etiology of Haff Disease

PEI Pei, LI Xiao Yan, LU Shuang Shuang, LIU Zhe, WANG Rui[#], LU Xuan Cheng[#], and LU Kai[#]

Haff disease is a type of human rhabdomyolysis characterized by the sudden onset of unexplained muscular rigidity and an elevated serum creatine kinase level within 24 h after consuming cooked aquatic products. Here, we reviewed a previous study on Haff disease and summarized the clinical manifestations, epidemiological characteristics, and etiological data to confirm the incidence and global epidemiology of the disease and identify the most common seafood vectors. Future directions for Haff disease study will include further prospective etiological studies and the development of prevention and control strategies.

Key words: Rhabdomyolysis; Seafood; Haff disease; Crayfish; Epidemiology

Haff disease is a type of human rhabdomyolysis characterized by the sudden onset of unexplained muscular rigidity and an elevated serum creatine kinase (CK) level within 24 h after consuming cooked freshwater or seawater products[1]. Haff disease was first identified in the summer and autumn of 1924 near the Königsberger Haff shores along the Baltic coast[2-4]. The clinical manifestations of this disease mainly involve the sudden onset of rhabdomyolysis with severe muscle pain. In most patients, this is accompanied with myoglobinuria, significant increases in the serum levels of CK and myoglobin (Mb), and potential increases in the levels of other muscle enzymes [e.g., lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase (ALT)]. Epidemiological studies revealed that patients with Haff disease had consumed cooked fish, including burbot (*Lota lota*) and pike (*Esox* spp.), or other aquatic products within 24 h prior to the onset of illness.

Similar outbreaks of Haff disease have occurred in many countries since its initial identification. The identified patients had consumed various types of cooked fish or other aquatic products, including burbot (*L. lota*), buffalo fish (*Ictiobus cyprinellus*), crayfish (*Procambarus clarkii*), freshwater pomfret (*Colossoma brachypomus*), *Cambaroides* spp., Atlantic salmon (*Salmo salar*), and boxfish (*Ostraciontidae* spp.). Increases in human standards of living have led to the increasing availability of fish for consumption and, consequently, increasing reports of Haff disease. However, the specific cause of Haff disease remains unclear. Chemical analyses of suspicious fish samples, blood samples, and urine samples from cases for possible toxins, drugs, and hazardous elements produced negative results or toxin levels below the toxicity thresholds. Currently, the following criteria are used to define cases of Haff disease: (1) a history of consuming cooked aquatic products within 24 h prior to the onset of illness, (2) a markedly elevated (i.e., fivefold or greater increase over the normal levels) serum creatine phosphokinase level, and (3) a CK muscle/brain (CK-MB) fraction of < 5%[5].

Several studies regarding the clinical manifestations, epidemiological characteristics, and pathogenic factors of Haff disease have been conducted since it was first reported in 1924. These studies have laid a solid foundation to confirm the pathogenic and influencing factors of Haff disease, to determine the means of preventing and controlling the occurrence of this disease, and to support further studies. This paper reviews the previous studies of Haff disease that have been conducted worldwide while suggesting future research directions according to trends in the development of related disciplines.

The Epidemiology of Haff Disease In the 9-year period after the first report of Haff disease in 1924, more than 1,000 cases with similar symptoms were reported along the Haff shores during the summer and autumn seasons[1]. In the United States, most patients with Haff disease had consumed buffalo fish (*I. cyprinellus*) before the onset of illness[6-8]. In 2008, an outbreak of 27 cases of Haff disease was reported in the Amazon region of Brazil, where the affected patients had consumed silver carp (*Mylossoma* spp.), black-finned colossoma (*Colossoma macropomum*),

doi: 10.3967/bes2019.096
Chinese Center for Disease Control and Prevention, Beijing 102206, China

or freshwater pompano (*Piaractus brachypomus*)[9]. From June 2016 to April 2017, 67 cases of Haff disease associated with the consumption of Olho-de-boi (*Seriola* spp.) or badejo (*Mycteroperca* spp.) were reported in Salvador, Brazil[10]. In Japan, 13 sporadic cases of Haff disease were reported between 1990 and 2008, and all patients had a history of consuming boxfish (Ostraciontidae)[11-12]. These data demonstrate the particular epidemiological characteristics of Haff disease, including a dietary history of cooked fish or other aquatic products within 24 h of the onset of illness and a location near a coastline, lake, or river.

In China, the number of cases of Haff disease has increased gradually since the initial report of 6 confirmed cases associated with the consumption of crayfish in Beijing during August 2000[13]. In 2009, a reported outbreak of 54 cases in Guangdong was attributed to the consumption of freshwater pomfret (*C. brachypomus*)[14]. However, most Chinese cases involved a dietary history of crayfish. Regarding the timing and location of Haff disease onset in China, cases have been reported during July and August of each year, which correlates strongly with the crayfish consumption season[15-18]. This pattern is also consistent with the observed concentration of cases in areas with crayfish production and high-volume consumption, such as Jiangsu, Anhui, and Hubei provinces[15]. Ma Shaolei et al. performed a spatial autocorrelation analysis to determine the incidence and spatial structure of crayfish-related rhabdomyolysis syndrome in Nanjing during 2016. Notably, a global spatial autocorrelation of the high prevalent regions revealed that cases were concentrated mainly in urban areas adjacent to the Yangtze River[17]. The literature reviewed for this report included 1,118 patients with age ranging from 4 to 97 years, of which 484 (43.29%) were male. This finding was consistent with another study on the communal consumption of crayfish, which found no statistical difference in the incidence of Haff disease between female and male subjects[19].

Clinical Features As previously noted, Haff disease is characterized mainly by the sudden idiopathic onset of rhabdomyolysis, which refers to a variety of pathological changes caused by hereditary or acquired factors such as crush wounds, drug toxicants, striated muscle cell damage, cell membrane channels, and/or an abnormal energy supply. These conditions damage the cell membrane integrity and expose the contents of cells, which include enzymes such as Mb and CK, and toxic ionic and small molecule substances. Accordingly, rhabdomyolysis is often accompanied with life-threatening metabolic disorders and acute renal failure (ARF)[20-23]. The observed association of Haff disease with a history of consuming freshwater or seawater foods within the previous 24 h excludes other potential etiologies of rhabdomyolysis syndrome such as excessive exercise, trauma, alcoholism, hereditary disease, drug use, infection, or metabolic abnormalities[24,25].

Tables 1 and 2 summarize the existing reports of Haff disease in the literature, including the serum levels of CK and creatine kinase isoenzyme, which are important for the diagnosis of Haff disease. Although most reported patients were discharged after hospitalization for symptomatic treatment, the tables describe the incidence of complications or other symptoms and related deaths. Additional information about the affected subjects is also presented in both tables.

Haff disease is associated with varying degrees of muscle pain, which is concentrated mainly in the neck and shoulders or lower back[7,40], and this pain is usually the initial presenting sign[57]. Severe cases also experience muscle tingling that is exacerbated by activity[19,28]. In some cases, reddish-brown- or brown-colored urine is observed, and symptoms may be combined with limb or general weakness, chest discomfort, headache and dizziness, and/or gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain, and diarrhea)[16,26,28,30-32,34,36,39-42,44,46,48,54,58]. Table 3 presents the distribution of clinical manifestations in 641 cases reported in China that met the above-stated criteria for Haff disease.

Regarding laboratory tests, elevated serum levels of various kinases, including CK, CK isoenzyme, lactate dehydrogenase, and aspartate aminotransferase are observed in Haff disease[7,15,16,19,26,28,30,31,37-41,44-46,48,58-60]. Of these, the increase in CK is the most evident, with peak values as high as 39,164 U/L[47]. Additionally, a routine urinalysis may reveal blood or protein in the urine[7,19,30,32,34,38-40,44], with ARF in some cases[19]. In some cases, routine blood testing revealed an increased white blood cell count, elevated neutrophil percentage, and hemoglobin and platelet levels within the normal ranges[7,39,40]. Moreover, slightly elevated liver function markers (ALT) and normal renal function were observed in some cases[39,40]. Cardiologic evaluations may reveal a cardiac troponin T level of < 0.1 ng/mL and normal electrocardiography findings[34,44]. Regarding muscle function, electromyography may reveal myogenic

Table 1. Outbreaks of haff disease after the consumption of cooked aquatic products

Period	Country	Consumed aquatic products	Sex	Age (years)	Symptoms and investigation findings	Reference
1924	Königsberger Haff shores	Burbot, eel, pike	/	/	Sudden, severe muscular rigidity and coffee-colored urine. Few patients died; seabirds and cats reportedly died after consuming fish in the wild.	[1,3,4]
1942.2–1943.4	Sweden, Lake Ymsen	Eel, burbot, burbot liver, bream	M7F4	/	Intense pain in the legs and back, and blackish-brown-colored urine within 20 h after meals. Two deaths: one involved uremia, and the other exhibited signs of sepsis, renal affectation, and moderate hematuria. Both cases had fairly poor health due to previous illnesses and privations earlier in the year. In 1941, the fish in the lake died, as did mergansers and divers that landed on the lake during migration. Cats and foxes in the shore area died after consuming the fish.	[2]
1984.6/1985/1986.4	United States	Buffalo fish	6	/	Tests of the remains of a fish meal suggested a neutral lipid as the causative agent.	[1]
1997.3	United States	Buffalo fish	F2	70, 73	Neck pain and subsequent upper limb stiffness, rigidity, paralysis, and extreme sensitivity even to light touch 8 h after meals; creatine kinase (CK), 25,000 IU/L; CK muscle/brain (CK-MB) fraction at peak values, 2.7% and 0.5%.	[6]
1997.3	United States	Buffalo fish	M1	33	Left-sided chest pain that radiated to the left arm 8 h after meals; CK, 4,140 IU/L; CK-MB, 1.4%.	[6]
1997.6	United States	Buffalo fish, carp	M1F1	66, 58	Generalized body aches and muscle stiffness 6 h after the meal; CK, 17,700 IU/L; CK-MB, 4.8% and 4.5%.	[6]
1997.8	United States	Buffalo fish	M1	87	Stiffness and generalized muscle tenderness 21 h after the meal; CK, 2,226 IU/L; CK-MB, 2.1%.	[8]
2001	United States	Crawfish	9	/	Myalgia (n = 2, 22.2%), chest pain (n = 9, 100%), nausea or vomiting (n = 9, 100%), and brown-colored urine (n = 2, 22.2%); CK, 6,000–8,670 IU/L; CK-MB, < 5% (100%).	[8]
2001.9	United States	Salmon	M1F1	61	Weakness and muscle ache; CK, 285–411 U/L.	[9]
1990–2008	Japan	Boxfish	13	/	Severe muscle pain and black-colored urine.	[26]
2007.8	Japan	Cowfish	M1	40	Myalgia, nausea, chest pressure, and dyspnea; peak CK, 182910 IU/L. Cardiopulmonary arrest and acute renal failure developed after 59 h, and hemodiafiltration was performed. On hospital day 16, the patient died of cardiac arrest caused by hyperkalemia, which was probably induced by myocytolysis.	[11]
2008.6–9	Brazil	Silver dollar, black-finned colossoma	M15F12	13-80	Myalgia (n = 27, 100%), chest pain (n = 19, 70.4%), neck pain (n = 17, 62.9%), muscular stiffness (n = 13, 48.1%), pain upon light touch (n = 12, 44.4%), weakness (n = 11, 40.7%), nausea (n = 11, 40.7%), muscle contracture (n = 10, 37%), dark-colored urine (n = 9, 33.3%), vomiting (n = 9, 33.3%), malaise (n = 8, 29.6%), and diarrhea (n = 4, 14.8%); CK, 2,795 U/L (range, 1,444–36,896 U/L). In 2 patients, myoglobin levels exceeded 700 U/L.	[9]
2011	Brazil	*Mylossoma duriventre*	M1	48	Sudden, progressive, diffuse, and lancing abdominal pain accompanied by two episodes of vomiting, progressive polymyalgia (predominantly in the lower limbs), asthenia, and progressively disabling muscular weakness within 2 h; creatine phosphokinase (CPK), 4,456U/L.	[12]
2014	United States	Buffalo fish	F1	34	Back pain radiating to the chest, into the neck, and into both buttocks; peak CK, 30,549 IU/L.	[7]
2013	United States	Buffalo fish	M1	48	Sudden-onset diffuse myalgia, especially in the legs, chest, and back associated with mild diaphoresis and dark brown-colored urine. Urinalysis was positive with 4+ hemoglobin; CPK, 16,192IU/L; serum myoglobin, > 4,000 ng/mL. His mother had previously consumed buffalo fish.	[27]
2014.12	United States	Grass carp	F2	54	Body pain and weakness within 4 h, associated with 3 episodes of non-bilious and non-bloody vomiting the previous night; CK, 19,124 UL.	[28]
2016.6–2017.4	Brazil	Olho-de-boi, badejo	67	43 (17–75)	Cases reported from December 1, 2016, to January 31, 2017. M9F6. Patients manifested neck/trapezium pain (n = 14, 93.3%), arm pain (n = 14, 93.3%), thigh or leg pain (n = 13, 86.7%), back pain (n = 10, 66.7%), dark-colored urine (n = 8, 53.3%), thoracic pain (n = 2, 13.3%), abdominal pain (n = 2, 13.3%), throat pain (n = 1, 6.7%), muscle weakness (n = 6, 40%), and rash (n = 4, 26.7%); CK, 743–105755 U/L; CK-MB, 1.9 %–6.3%. Thirteen patients were hospitalized; 2 cases of *acute kidney injury* and 0 death.	[10]

Table 2. Outbreaks of haff disease after the consumption of cooked aquatic products in China

Period	City	Consumed aquatic products	Sex	Age (years)	Symptoms and investigation findings	References
2000.8	Beijing	Crayfish	M1	42	Severe myalgia with weakness 7 h after eating 500 g of crayfish; CK, 10,150 U/L. Mild symptoms in another young male patient.	[29]
2000.8	Beijing	Crayfish	M1	40	Moderate myalgia with weakness after 7 h; CK, 2,000 U/L.	[29]
2000.8	Beijing	Crayfish	F1	38	Moderate myalgia with weakness 12 h after eating 500 g of crayfish; CK, 376 U/L. Symptoms improved but relapsed 4 days later at an 8-h time point after consuming leftover crayfish. Her child (M/8) had mild myalgia and nausea.	[29]
2000.8	Beijing	Crayfish	F1	36	Severe myalgia with weakness 7 h after eating 500 g of crayfish. Symptoms improved 6 h later. A pediatric patient developed mild weakness.	[29]
2000.8	Beijing	Crayfish	F1	40	Moderate myalgia with weakness 15 h after eating 400 g of crayfish; CK, 6,000 U/L.	[29]
2000.8	Beijing	Crayfish	F1	36	Myalgia and weakness 7 h after eating 20 pieces of crayfish. Symptoms improved 12 h later.	[29]
2009.1	Lianzhou, Guangdong	Pomfret	M36F18	43 (4–74)	Symptom onset 7 h (range, 10 min–41.5 h) after eating 50–70 g of pomfret, including weakness (*n* = 45, 83%), myalgia (*n* = 41, 76%), nausea (*n* = 34, 63%), abdominal pain (*n* = 34, 63%), dry mouth (*n* = 25, 46%), vomiting (*n* = 25, 46%), and dizziness (*n* = 18, 33%), diarrhea (*n* = 18, 33%), and headache (*n* = 12, 22%); severity/serum CPK, 11,696U/L.	[14]
2010.8	Nanjing, Jiangsu	Crayfish	M9F14	36 (20–79)	Symptom onset, including myalgia (*n* = 23, 100%), brown-colored urine (*n* = 9, 39.1%), numbness of the limbs (*n* = 4, 17.4%), nausea (*n* = 4, 17.4%), weakness (*n* = 3, 13%), vomiting (*n* = 3, 13%), chest tightness (*n* = 3, 13%), abdominal pain (*n* = 3, 13%), chest pain (*n* = 2, 8.7%), and diarrhea (*n* = 2, 8.7%), 4.8 h (range, 3–12 h) after eating; CK, 4,655 U/L.	[30]
2010.7–8	Nanjing, Jiangsu	Crayfish	M4F7	28 (9–38)	Symptom onset, including myalgia (*n* = 11, 100%), weakness (*n* = 9, 81.8%), brown-colored urine (*n* = 7, 63.6%), nausea (*n* = 5, 45.5%), vomiting (*n* = 2, 18.2%), and hoarse voice (9.1%) 3–9 h after eating 10 pieces of crayfish; CK, 2,013–18,520 (7,952.2) U/L.	[31]
2010.7–9	Nanjing, Jiangsu	Crayfish	M1	38	Myalgia with brown-colored urine 6 h after eating; CK, 3,600 U/L. His wife and daughter developed similar symptoms.	[32]
2010.7–9	Nanjing, Jiangsu	Crayfish	F1	21	Myalgia with brown-colored urine 1 h after eating; CK, 2,176 U/L. One of the 7 people who ate with the referent patient developed similar symptoms.	[32]
2010	Shijiazhuang, Hebei	Crayfish	M1	26	Myalgia with weakness; CK, 27,174 U/L. Pathological analysis of the left biceps brachii muscle revealed rhabdomyolysis.	[33]
2012.8	Nanjing, Jiangsu	Crayfish	M1	44	Myalgia, chest tightness, and shortness of breath 5 h after eating 10 pieces of crayfish; CK, 1,600 U/L; CK-MB, 926 U/L.	[34]
2012.8	Nanjing, Jiangsu	Crayfish	M1	31	Myalgia, chest tightness, and shortness of breath 7 h after eating 10 pieces of crayfish; CK, 1,056 U/L; CK-MB, 135 U/L. A second person who ate 4–5 pieces of crayfish did not develop symptoms.	[34]
2012.8	Yangzhou, Jiangsu	Crayfish	M1F2	30–37	Myalgia and vomiting 7–8 h after eating 20–40 pieces of crayfish; CK, 350–5,472 U/L. Three additional people did not develop symptoms.	[15-16]
2012.8	Yangzhou, Jiangsu	Crayfish	M1	38	Myalgia 7 h after eating 30 pieces of crayfish; CK, 3,470 U/L. Four other people did not develop symptoms.	[15-16]
2013.8	Huai'an, Jiangsu	Crayfish	M1	18	Myalgia 6 h after eating 30 pieces of crayfish; CK, 622 U/L; CK-MB, 73.1 U/L.	[15]
2013.6	Shanghai	Crayfish	M1	66	Myalgia, weakness, muscle rigidity, oliguria, brown-colored urine, and shortness of breath 12 h after eating; CK, 1,600 U/L; CK-MB, 926 U/L. The patient was diagnosed with Haff disease complicated by multiple organ failure. His condition deteriorated despite supportive and symptomatic treatments, and he ultimately died.	[35]

Continued

Period	City	Consumed aquatic products	Sex	Age (years)	Symptoms and investigation findings	References
2014.7	Wuhu, Anhui	Crayfish	M1	41	Myalgia, weakness, and brown-colored urine 12 h after eating 1 kg of crayfish; CK, 3,599 U/L; CK-MB, 179 U/L.	[36]
2014.8	Wuhu, Anhui	Crayfish	M1	43	Myalgia 11 h after eating 0.5 kg of crayfish; CK, 1,187 U/L; CK-MB, 52 U/L.	[36]
2014.8	Nanjing, Jiangsu	Crayfish	M1F1	32–33	Myalgia 8–13 h after consuming 10–20 pieces of crayfish; CK, 500–3,685 U/L; CK-MB, 64–114 U/L.	[15]
2015.10–2016.9	Shanghai	Crayfish	M35F18	52 (16–97)	Myalgia, diarrhea, or vomiting (n = 1 each); CK, 3,561 U/L; CK-MB, 187 U/L.	[37]
2015.5	Yancheng, Jiangsu	Crayfish	M1	62	Abdominal pain, vomiting, aversion to cold, and purpura 4–5 h after eating 10 pieces of crayfish; CK, 901.4 U/L; CK-MB, 29.1 U/L. *The patient developed symptoms of multiple organ failure and was discharged after rescue in the intensive care unit.*	[38]
2016.7–8	Nanjing, Jiangsu	Crayfish	M72F125	38 (17–67)	Symptom onset within 2.5–12 h, including myalgia (n = 197, 100 %), brown-colored urine (n = 90, 45.7 %), weakness (n = 47, 23.8%), nausea (n = 30, 15.2%), chest tightness (n = 25, 12.7%), vomiting (n = 20, 10.2%), chest pain (n = 19, 9.6%), numbness of the limbs (n = 18, 9.1%), abdominal pain (n = 16, 8.1%), and diarrhea (n = 15, 7.6%); CK, 4,657±2,178 U/L; CK-MB, 3,135±1,547 U/L.	[39]
2016.7–8	Wuhu, Anhui	Crayfish	M37F7	12–70	Myalgia (n = 107, 100%), brown-colored urine (n = 65, 60.75%), numbness of the limbs (n = 48, 44.86%), chest tightness (n = 42, 39.25%), nausea and vomiting (n = 8, 7.48%), diarrhea (n = 4, 3.74%), and abdominal pain (n = 3, 2.8%); CPK, 5,024 U/L.	[40]
2016.7–9	Guangdong	Crayfish	M18F30	11–59	Symptom onset, including myalgia (n = 45, 93.8%), weakness (n = 23, 47.9%), shortness of breath (n = 19, 39.6%), and chest tightness (n = 19, 39.6%), 7 h (range, 1–19 h) after eating 20 (range, 2–60) pieces of crayfish; CK, 67–36,164 U/L; CK-MB exceeding the normal limits in 26 cases, CK exceeding the normal limits in 20 cases.	[41]
2016.7–10	Wuhu, Anhui	Crayfish	M31F71	38	Symptom onset, including myalgia (n = 102), weakness (n = 86, 84.3%), chest tightness (n = 42, 41.2%), abdominal pain and diarrhea (n = 19, 18.63%), nausea and vomiting (n = 16, 15.7%), and brown-colored urine (n = 2), 5.42 h after eating 11.67±6.19 pieces of crayfish; CK, 4,479.52 U/L; CK-MB, 172.56 U/L.	[42]
2016.7–8	Nanjing, Jiangsu	Crayfish	M28F38	36 (18–76)	Symptom onset, including myalgia (n = 66, 100%) and brown-colored urine (n = 19, 28.8%), within 5.5 h (range, 1–24 h); CK, 3271 IU/L (range, 223–163,200 IU/L); CK-MB, 78.1 ng/mL (range. 3.7–1,676 ng/mL).	[43]
2016.6–8	Ma'anshan, Anhui	Crayfish	M28F62	42 (11–84)	Symptom onset, including myalgia (n = 90, 100%), weakness (n = 62, 68.89%), brown-colored urine (n = 11, 12.22%), chest pain (n = 6, 6.67%), nausea (n = 5, 5.56%), abdominal pain (n = 2, 2.22%), and shortness of breath (n = 1, 1.11%), within 1–15 h; CK, 6249.36 U/L; CK-MB, 383.99 ng/L.	[44]
2016.7	Wuhu, Anhui	Crayfish	M7F33	/	Myalgia 40, brown-colored urine 1.	[45]
2016.8	Wuhan, Hubei	Crayfish	M1	38	Myalgia, weakness, nausea, and vomiting 11 h after eating 500 g of crayfish; CK, 6,440 U/L.	[46]
2016.8	Wuhan, Hubei	Crayfish	F1	37	Myalgia, weakness, nausea, and vomiting 6 h after eating 500 g of crayfish; CK, 1,057 U/L.	[46]
unknown	Baoding, Hebei	Crayfish	F1	43	Weakness after 20 h; CK, 39,164 U/L; CK-MB, 646 U/L.	[47]
unknown	Baoding, Hebei	Crayfish	M1	27	Abdominal pain, nausea, and vomiting within 15 h; CK, 24,356 U/L; CK-MB, 421 U/L.	[47]
unknown	Baoding, Hebei	Crayfish	F1	36	Myalgia and weakness within 6 h; CK, 20,110 U/L; CK-MB, 1,016 U/L.	[47]
2016.7–8	Nanjing, Jiangsu	Crayfish	M35F49	39 (15–89)	Onset of symptoms, including myalgia (n = 84, 100%), brown-colored urine (n = 52, 61.2%), shortness of breath (n = 42, 50%), nausea (n = 21, 25%), vomiting (n = 16, 19%), weakness (n = 13, 15.5%), and numbness of the limbs (n = 12, 14.3%), within 7.86 h; CK, 6,105.49 U/L.	[48]

Continued

Period	City	Consumed aquatic products	Sex	Age (years)	Symptoms and investigation findings	References
2016.7–10	Nanjing, Jiangsu	Crayfish	M50F28	34	Myalgia, weakness, chest tightness, and brown-colored urine within 6–24 h; CK, 8,976±2,354 U/L.	[49]
2016.8	Shenzhen, Guangdong	Crayfish	M1F 3	22–41	Myalgia (n = 4) and nausea (n = 1) within 4–6 h; CK, 1452–15534 IU/L; CK-MB, 1.3–4.8%.	[50, 51]
2016.8	Hong Kong	Crayfish	F1	55	Myalgia within 4 h.	[52]
2016.9	Hong Kong	Crayfish	F1	30	Myalgia within 5 h. Two other people did not develop symptoms.	[52]
2016.8	Hefei, Anhui	Crayfish	F1	25	Myalgia and nausea 5.5 h after eating 30 pieces of crayfish; CK-MB, 37.7 ng/mL.	[53]
2016.6–7	Nanjing, Jiangsu	Crayfish	M14F34	38 ± 11	Myalgia, weakness, nausea and vomiting, abdominal pain, diarrhea, and chest tightness within 2–24 h.	[54]
2016.7–8	Nanjing, Jiangsu	Crayfish	M9F32	38	Myalgia, weakness, and elevated CK within 24 h.	[55]
Unknown	Nanjing, Jiangsu	Crayfish	M1	31	Chest, back, and shoulder pain, whole-body numbness, and nausea and vomiting 6 h after the meal; CK, 371 (range, 20–1,74U/L); CK-MB, 33 (range, ±18 U/L). Intravenous fluid hydration and bicarbonate infusion 5 h later. Diffuse myalgia accompanied with chest tightness, *rapid and shallow respiration, and a few bilateral pulmonary crackles. Computed tomography led to a diagnosis of Haff disease complicated by acute lung injury. It remains unknown whether the lung was the direct target of the toxin.*	[56]

damage[31], while a pathological analysis of the painful muscle may reveal rhabdomyolysis[33].

Despite the above findings, the prognosis of Haff disease is good. With supportive treatment, including rest, intravenous fluid hydration, and bicarbonate infusion, the symptoms resolve, and the levels of muscle enzymes return to normal. However, a few serious cases may develop renal and other organ failures. In 2015, one case of rhabdomyolysis syndrome in Yancheng, Jiangsu, was attributed to the consumption of crayfish. The patient subsequently developed septic shock, multiple organ dysfunction syndrome, and acute renal failure. Although he became critically ill, he was discharged after treatment in the intensive care unit (ICU)[38]. Furthermore, a 31-year-old man in Nanjing was diagnosed with Haff disease after consuming cooked crayfish. After a 5-hour period of hospitalization, the patient developed an acute lung injury. He was treated with intravenous fluid hydration and bicarbonate infusion and was discharged after 9 days. It remains unknown whether the lung was the direct target of the toxin in that case[56].

Haff disease is rarely associated with mortality. In 2013, one male patient in Shanghai developed muscle pain, fatigue, muscle rigidity, oliguria, brown-colored urine, and shortness of breath 12 h after

Table 3. Clinical manifestations of confirmed cases in China

Clinical manifestation	Number	Percent(%)
Myalgia	632	98.60
Brown-colored urine	257	40.09
Weakness	184	28.71
Nausea	105	16.38
Vomiting	87	13.57
Chest tightness	72	11.23
Shortness of breath	44	6.86
Diarrhea	39	6.08
Chest pain	32	4.99
Numbness	31	4.84
Dry mouth	26	4.06
Abdominal pain	24	3.74
Headache	12	1.87
Voice hoarseness	1	0.16
Aversion to cold	1	0.16
Purpura	1	0.16

consuming crayfish. A laboratory examination revealed a CK level of 358.6 U/L. Following a misdiagnosis of lumbar disc herniation, he was admitted to the hospital with multiple organ failure but died after receiving treatment in the ICU[35]. Generally, an early and accurate diagnosis and provision of active therapy to prevent complications are key factors required to improve patient outcomes.

Causes of Haff Disease Three categories of factors are known to cause rhabdomyolysis[20,61,62]: physical factors, nonphysical factors, and genetic factors. Physical factors include squeezing and trauma, exercise and excess muscle activity, status epilepticus, electric shock, high fever, and heatstroke. Nonphysical factors include drugs, such as statins, poisons, bacterial (e.g., *Legionella*) and viral infections (influenza A, B), and electrolyte imbalances (e.g., hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia). Genetic factors include autoimmune diseases (e.g., polymyositis and dermatomyositis), endocrinological and genetic metabolic diseases (e.g., diabetes), and factors that can cause rhabdomyolysis.

Studies of the risk factors of Haff disease have been conducted consistently since the discovery of the disease. Descriptive epidemiological studies have suggested an etiology associated closely with the consumption of cooked seawater or freshwater foods. Furthermore, analytical epidemiological studies (e.g., case-control and cohort studies) and chemical analyses of collected biological samples have been conducted to determine the risk factors for Haff disease in cooked aquatic products, and a toxicity test has been developed to establish an animal model of Haff disease. One unmatched case-control study conducted in Nanjing in August 2010 involved the administration of a telephone/face-to-face questionnaire survey on food consumption in 20 patients with rhabdomyolysis syndrome and in 25 patients who had shared food with the patients. Subsequently, the subjects' dietary histories, disease statuses, background diseases, alcohol consumption during the suspected crayfish meals, physical training habits, and allergic histories were investigated, and an association was found between the consumption of > 10 pieces of crayfish and an increased risk of disease[63]. In 2009, Huang Qiong et al. conducted a retrospective cohort study on an outbreak of Haff disease caused by freshwater pomfret in Guangdong Province. Of the 3,857 Jiubei residents, 159 people had consumed pomfrets, and 50 members of this subgroup became ill. A dose-response relationship between fish consumption and elevated serum levels of muscle enzymes (CK, CK-MB, aspartate aminotransferase) were observed. Residents who did not eat fish were unaffected[14]. Although these studies demonstrate a close association between the consumption of cooked aquatic products and the occurrence of Haff disease, the specific etiological factors require further investigation.

Previous studies have screened food samples and biological samples from patients for drugs and toxicants known to cause rhabdomyolysis syndrome. In one study by Buchholz et al., recovered leftovers and uncooked buffalo fish from the same lot were tested for active sodium channel biotoxins [e.g., ciguatoxin (the toxin of ciguatera) or saxitoxin (the toxin associated with paralytic shellfish poisoning)], cyanobacterial toxins (e.g., the blue-green algal toxins microcystin or nodularin), organophosphates, and arsenic. However, the tests produced negative results or values below the toxicity thresholds[1]. Huang Qiong et al. tested fish, water, and soil samples for microcystins, toxins (including scorpion toxin, chelating base, histamine, ractopamine, F^-, CL^-, NO^{3-}, NO^{2-}, and SO_4^{2-}), and 26 heavy metals (Be, Na, Mg, Al, K, Ca, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Mo, Ag, Cd, Sn, Sb, Ba, Tl, Pb, Th, and U) using chemical analysis techniques and methods such as liquid chromatography-mass spectrometry (MS), ion chromatography, gas chromatography-MS, inductively coupled plasma-MS, and atomic force spectroscopy. Similarly, the results were either negative or below the toxicity thresholds[14]. In a cytotoxicity and hemolysis analysis of palytoxins, Chen Xiaofeng et al. revealed that methanol/water gills, intestines, and glands extracts from crayfish were not inhibited effectively by ouabain, indicating that the rhabdomyolysis-inducing toxin was not an allergen or palytoxin[64]. According to Chen Yan et al., a chemical analysis of crayfish samples purchased from a market and of blood and urine samples from 2 cases did not reveal any possible toxins, drugs, and hazardous elements among at least 200 screened compounds with known relevance to rhabdomyolysis (e.g., macrolides, sulfonamides, polyether antibiotics, β-agonists, organophosphorus pesticides, aniline, phenylamine, m-nitroaniline and p-nitroaniline, arsenic, cadmium, and other heavy metals)[63]. He Ying[65] found that although cyanobacteria, equisetum, and heavy metals induced increases in the serum CK level in the Institute of Cancer Research (ICR) mice, the related changes in

enzyme activities were insufficient to induce Haff disease and did not cause symptoms of rhabdomyolysis in the ICR mice. No substances currently known to cause rhabdomyolysis were detected in samples of aquatic products consumed by patients with Haff disease or in the urine and blood samples of these patients.

Accordingly, researchers conducted animal experiments and established a mouse model of rhabdomyolysis to determine the substances in cooked aquatic products that cause Haff disease. Buchholz et al. separated the extracts of buffalo fish samples into water-soluble, nonpolar lipid and polar lipid fractions, which were administered intraperitoneally and orally to laboratory mice. Mice-fed hexane-soluble products exhibited behavioral changes consistent with muscle impairment and red-brown-colored urine in the bladders[1]. Huang Qiong et al. found that samples of freshwater pomfret from the same reservoir could induce muscle damage in mice[14]. Moreover, some batches of crayfish induced rhabdomyolysis syndrome in some mice in a dose-dependent manner[41].

Some Chinese scholars have speculated that rhabdomyolysis syndrome may be related to an allergic reaction. Accordingly, LIN Jiang Wei conducted a series of studies of crayfish poisoning but ultimately did not detect an association between sea anemone toxin and allergic reactions. Moreover, Huang Qiong et al.[41] observed that crayfish liver and pancreas could induce a decrease in the serum total immunoglobulin G antibody level, suggesting a weak or nonexistent association between rhabdomyolysis and allergy.

Professor Adgren suggested that the manifestations of Haff disease were consistent with a disease known as Chastek paralysis, which was first observed on silver fox farms in the United States. Subsequently, Ender and Helgebostad demonstrated that Chastek paralysis could be induced by a diet deficient in vitamin B1. Interestingly, Green and Evans reported that certain types of fish, particularly carp, contain a substance that inactivates vitamin B1. Moreover, foxes with Chastek disease recovered rapidly when treated with high doses of vitamin B1[2]. However, the potential association between Haff disease and vitamin B1 deficiency has not been studied further.

In summary, the etiology of Haff disease remains unknown. Further study is required to determine whether cooked aquatic products contain an unknown heat-stable, tissue-specific, and non-neurotoxic pathological factors or whether the consumption of cooked aquatic foods activates particular signaling pathways that induce rhabdomyolysis.

The literature demonstrates an evident global increase in the number of reports of Haff disease since its first report in 1924. A review of this literature demonstrated that the existing research was based mostly on case reports from hospitals. Accordingly, the current body of knowledge faces several shortcomings. First, since the main clinical manifestation of Haff disease is muscle pain, many potential cases with mild symptoms may not have been detected. Second, researchers have used different approaches to verify their hypotheses regarding the etiology of Haff disease, and accordingly, the study was not conducted systematically. Different researchers may not have considered the relevant case conditions and contributing factors because of limitations specific to their scenarios. Researchers may also have insufficient data on the health risks associated with disease-causing food cultures and ecological environment factors. For example, in a study of Haff disease in Beijing in 2000, the researcher lacked trace data about the *Cambaroides* spp. consumed by the subjects and did not collect food or biological samples for further studies of the causative factors. Third, few studies have explored rhabdomyolysis in experimental animals, such as mice, and such research remains in the initial exploration stage. To date, all experimental materials have been sampled from patients' leftovers and from reservoirs where the aquatic foods were caught. Any previously drawn conclusions will require further validation because the epidemiological hypothesis and directions of animal experiments remain unclear. Therefore, future studies of the health hazards, epidemiological characteristics, and influencing factors related to Haff disease and new animal models are required. This research can be approached through the following aspects:

(1) The epidemiological characteristics and influencing factors, including the collection and classification of previous cases of Haff disease. Researchers could construct a Haff disease case monitoring system and perform retrospective investigations in high-incidence provinces. Epidemiological investigations should use standard questionnaires to collect case information, and biological, food, and environmental samples should be collected. Descriptive epidemiological studies to clarify the health hazards and epidemiological characteristics of the disease should be developed

systematically, and case-control and cohort studies should be conducted to determine the influencing factors.

(2) Research on the health risk factors associated with the culture, transportation, sales, and ecological environments of disease-causing aquatic foods (e.g., crayfish, burbot, buffalo fish). In China, Haff disease is mainly caused by the consumption of crayfish, and ecological studies should investigate the reservoirs and wild fishing areas of these organisms. Risk factors associated with breeding, transportation, and sales practices should be explored for possible health risk factors.

(3) Establishment of an animal model of rhabdomyolysis syndrome and animal test study. An animal model of rhabdomyolysis syndrome should be established using experimental animals of different species and germ lines. Pilot experiments based on epidemiological studies should be conducted in these animal models to verify the hypotheses of epidemiological investigations and to screen positive samples.

In conclusion, Haff disease, an idiopathic form of rhabdomyolysis syndrome associated with the consumption of freshwater marine products, has important impacts on human health, socioeconomic development, and stability. Haff disease can easily induce a social panic, given the acute incidence and potential severity and its association with the consumption of cooked aquatic foods. An understanding of the influencing and pathological factors associated with Haff disease would contribute significantly to preventing the occurrence of disease and would positively influence healthy dietary choices and the formulation of relevant industrial standards.

Author Contributions Conceived and designed the manuscript, LU Xuan Cheng, WANG Rui, and PEI Pei; searched and read the papers, PEI Pei, LU Shuang Shuang, LI Xiao Yan, and LIU Zhe; wrote the manuscript, PEI Pei; critically revised the manuscript, LU Xuan Cheng and WANG Rui; and provided the final approval of the manuscript to be published, LU Kai, LU Xuan Cheng, and WANG Rui.

Competing Interests None of the authors have competing interests to declare.

[#]Correspondence should be addressed to WANG Rui, PhD, Tel: 86-13520153670, E-mail: wangrui@chinacdc.cn; LU Xuan Cheng, PhD, Tel: 86-137180700001, E-mail: luxc@chinacdc.cn; LU Kai, PhD, Tel: 86-15210365022, E-mail: lukai@chinacdc.cn

Biographical note of the first author: PEI Pei, female, born in 1995, bachelor's degree, majoring in public health.

Received: February 22, 2019;
Accepted: August 22, 2019

REFERENCES

1. Buchholz U, Mouzin E, Dickey R, et al. Haff disease: from the Baltic Sea to the U.S. shore. Emerg Infect Dis, 2000; 6, 192−5.
2. Berlin R. Haff disease in Sweden. Acta Med Scand, 1948; 129, 560−72.
3. Dörbeck F. Zur Ätiologie der Haffkrankheit. Klin Wochenschr, 1926; 5, 799.
4. Rosenow G, Tietz L. Die Haffkrankheit. Klin Wochenschri, 1924; 3, 1991−3.
5. Diaz JH. Global incidence of rhabdomyolysis after cooked seafood consumption (Haff disease). Clin Toxicol (Phila), 2015; 53, 421−6.
6. Centers for Disease C, Prevention. Haff disease associated with eating buffalo fish--United States, 1997. MMWR, 1998; 47, 1091−3.
7. Paul V, Shamah S, Garankina O, et al. Rhabdomyolysis after fish consumption: Haff's disease. QJM, 2014; 107, 67−8.
8. Langley RL, Bobbitt WH, 3 rd. Haff disease after eating salmon. South Med J, 2007; 100, 1147−50.
9. dos Santos MC, de Albuquerque BC, Pinto RC, et al. Outbreak of Haff disease in the Brazilian Amazon. Rev Panam Salud Publica , 2009; 26, 469−70.
10. Bandeira AC, Campos GS, Ribeiro GS, et al. Clinical and laboratory evidence of Haff disease - case series from an outbreak in Salvador, Brazil, December 2016 to April 2017. Euro Surveill, 2017; 22, 15.
11. Taniyama S, Sagara T, Nishio S, et al. [Survey of food poisoning incidents in Japan due to ingestion of marine boxfish and their toxicity]. Shokuhin Eiseigaku Zasshi , 2009; 50, 270−7.
12. Tolesani Junior O, Roderjan CN, do Carmo Neto E, et al. Haff disease associated with the ingestion of the freshwater fish Mylossoma duriventre (pacu-manteiga). Rev Bras Ter Intensiva, 2013; 25, 348−51.
13. Yuan Yun. Clinical analysis of 6 cases of Haff disease. Chin J Med, 2001; 81, 1530. (In Chinese)
14. Huang X, Li Y, Huang Q, et al. A past Haff disease outbreak associated with eating freshwater pomfret in South China. BMC Public Health, 2013; 13, 447.
15. Zong Wenqi, Chen Shizhen, Yuan Baojun, et al. Epidemiological investigation and analysis of crayfish-related rhabdomyolysis syndrome in Jiangsu Province from 2012 to 2014. Journal of Food Safety and Quality Testing, 2015; 10, 4258−61. (In Chinese)
16. Zhu Lei. Investigation of two crayfish related rhabdomyolysis syndrome events. Prev Med Forum, 2015; 9, 700−1. (In Chinese)
17. Ma Shaolei, Xu Changsheng, Liu Songqiao, et al. Epidemiological characteristics of crayfish-related rhabdomyolysis syndrome in Nanjing in 2016: a multi-center retrospective survey. Chin Critical Care Med, 2017; 9, 805−9. (In Chinese)
18. Chan TY. The Emergence and Epidemiology of Haff Disease in China. Toxins, 2016; 8, 12.
19. Xie Guoxiang. Epidemiological investigation of rhabdomyolysis syndrome caused by crayfish. Modern Prev Med, 2012; 20, 5239−40.
20. Zutt R, van der Kooi AJ, Linthorst GE, et al. Rhabdomyolysis: review of the literature. Neuromuscul Disord, 2014; 24, 651−9.
21. Li Huanming, Li Xin, Li Shuguang. Research progress on the relationship between crayfish consumption and rhabdomyolysis. Shanghai Preventive Medicine, 2016; 11, 818−21. (In Chinese)

22. Hu Panpan, Ren Xiaohu, He Ling, et al. Research progress on Chinese crayfish related Haf disease. Chin J Food Hygiene, 2018; 1, 113−9. (In Chinese)
23. Chen Binzhuan, Wang Yuchun. Research progress in rhabdomyolysis syndrome. J Molecular Imaging, 2017; 04, 474−7. (In Chinese)
24. Ma Ning, Li Fengqin, Li Ning, et al. Overview of foodborne rhabdomyolysis syndrome. Chin J Food Hygiene, 2010; 6, 564−7. (In Chinese)
25. Sun Guiju. Haf disease and food safety. J Southeast University (Medical Science Edition), 2010; 6, 699−701. (In Chinese)
26. Shinzato T, Furusu A, Nishino T, et al. Cowfish (Umisuzume, Lactoria diaphana) poisoning with rhabdomyolysis. Intern Med , 2008; 47, 853−6.
27. Herman LL, Bies C. Haff disease: rhabdomyolysis after eating buffalo fish. West J Emerg Med, 2014; 15, 664−6.
28. Louis JV, Sein S, Lyon C, et al. Two Cases of Rhabdomyolysis (Haff Disease) After Eating Carp Fish. J Investig Med High Impact Case Rep, 2016; 4, 2324709616663230.
29. Yuan Yun, Chen Qingyu. Report of six cases of Haff disease caused by eating sputum. Chin J Neurol, 2001; 6, 343. (In Chinese)
30. Chen Xufeng, Huang Peipei, Kang Jian, et al. Clinical analysis of 23 cases of swollen rhabdomyolysis. Chin Emergency Med, 2010; 10, 1062−5.
31. Han Ling, Zhang Jun. Analysis of 11 cases of rhabdomyolysis syndrome caused by crayfish. J Int Med, 2011; 5, 6. (In Chinese)
32. Tong Wei, Yin Guilan. Nursing care of two cases of rhabdomyolysis caused by crayfish. Nursing Practice and Research, 2011; 19, 157−8. (In Chinese)
33. Xie P, Hu J, Huang JM, et al. Crayfish-related Haff disease rhabdomyolysis; diagnosis supported by bone scintigraphy. Hell J Nucl Med, 2013; 16, 60−1.
34. Yuan Baojun, Wu Gaolin, Guo Baofu. Analysis of 2 cases of new rhabdomyolysis syndrome in Nanjing. Jiangsu Preventive Medicine, 2013; 4, 43−4. (In Chinese)
35. Feng G, Luo Q, Zhuang P, et al. Haff disease complicated by multiple organ failure after crayfish consumption: a case study. Rev Bras Ter Intensiva, 2014; 26, 407−9.
36. Gan Lin, Li Qian, Gong Nengkai. Two cases of rhabdomyolysis caused by eating crayfish. J Liaoning Med College, 2015; 3, 111−2, 7. (In Chinese)
37. Li Xin, Li Huanming, Li Shuguang, et al. Epidemiological characteristics of rhabdomyolysis syndrome in Putuo District, Shanghai. Shanghai Prev Med, 2017; 06, 498−9. (In Chinese)
38. Zong Wenqi, Chen Shizhen, Lu Jinfeng. A case report of severe cases of rhabdomyolysis syndrome caused by lobster. Jiangsu Prev Med, 2016; 2, 227−8. (In Chinese)
39. Chen Xufeng, Huang Peipei, Zhang Jinsong, et al. Clinical analysis of 197 cases of rhabdomyolysis caused by crayfish. Chin J Emergency Med, 2016; 12, 1269−72. (In Chinese)
40. Chu Nengwu, Chen Cheng. Analysis of 107 cases of rhabdomyolysis syndrome caused by crayfish. J Int Med, 2017; 5, 429−30. (In Chinese)
41. Huang Qiong, Zhao Min, Wang Fengyan, et al. Population epidemiological investigation of crayfish-related rhabdomyolysis syndrome and triggering experiments in mice. Chin J Food Hygiene, 2017; 3, 269−76. (In Chinese)
42. Liu Caixin, Liu Peng, Wang Xueqian, et al. Epidemiology and laboratory characteristics of 102 cases of crayfish caused by rhabdomyolysis. J Yichun University, 2017; 9, 62−4. (In Chinese)
43. Liu Wei, Cao Hongyu, Li Ang, et al. Single-center clinical analysis of Haf disease. Advances in Modern Biomed, 2017; 27, 5247−50. (In Chinese)
44. Tang Xiaofei, Shen Xinru, Qian Guangrong, et al. Clinical analysis of 90 cases of crayfish-related rhabdomyolysis syndrome. Anhui Med J, 2017; 5, 595−7. (In Chinese)
45. Wang Juan, Jiang Jinghan, Zhu Mengqian, et al. The etiology of rhabdomyolysis syndrome in 40 cases of crayfish consumption. J Shenyang Med College, 2017; 4, 345−7. (In Chinese)
46. Wang Yunfeng. Two cases of rhabdomyolysis caused by eating crayfish in Wuhan. Neurological Injury and Functional Reconstruction, 2017; 5, 469−70. (In Chinese)
47. Zong Jie, Yan Juan, Meng Qingyi. Three cases of misdiagnosis of Haff disease and literature review. Clinical Misdiagnosis and Mistreatment, 2014; 5, 39−42. (In Chinese)
48. Xiao Feng, Qin Haidong, Liu Xiaodong, et al. Clinical analysis and treatment of 84 cases of 'lobster disease'. J South University, 2017; 5, 757−9. (In Chinese)
49. Wen Yanfang, Fei Libo, Di Jia, et al. Clinical analysis of 78 cases of rhabdomyolysis caused by crayfish. Southeast National Defense Med, 2017; 1, 76−7. (In Chinese)
50. Yang WX, Fan KL, Leung LP. A cluster of patients with rhabdomyolysis after eating crayfish. CJEM, 2018; 20, S48−S50.
51. Daily S. Four Hospitalized after Eating Too Much Crawfish 2016. http://www.szdaily.com/content/2016-08/09/content_13700987.htm. [2018-10-25]
52. Health Do. Suspected Cases of Rhabdomyolysis after Consumption of Crayfish 2016. http://www.info.gov.hk/gia/general/201609/08/P2016090800898p.htm. [2018-10-25]
53. Wang Sihai, Han Ninglin, Li Xueyu, et al. Tongli Erjun method combined with western medicine for the treatment of crayfish-induced rhabdomyolysis syndrome. New Chinese Medicine, 2018; 1, 180−1. (In Chinese)
54. Lv Jian. First-aid and nursing of patients with rhabdomyolysis caused by eating crayfish. Practical J Clinical Nursing, 2016; 10, 24−5. (In Chinese)
55. Han Zhenqiang. Clinical diagnosis and treatment of rhabdomyolysis syndrome caused by crayfish. Jilin Traditional Chinese Medicine, 2017; 5, 463−5. (In Chinese)
56. Qian J, Sha D. Haff disease complicated by acute lung injury after crayfish consumption: a case report. Clin Toxicol (Phila), 2018; 56(6), 449−51.
57. He F, Ni J, Huang JA, et al. Clinical features of Haff disease and myositis after the consumption of boiled brackish water crayfish: a retrospective study of 96 cases at a single centre. Int Emerg Med, 2018.
58. Zhang B, Yang G, Yu X, et al. Haff disease after eating crayfish in east China. Intern Med (Tokyo, Japan), 2012; 51, 487−9.
59. Guo B, Xie G, Li X, et al. Outbreak of Haff disease caused by consumption of crayfish (Procambarus clarkii) in nanjing, China. Clin Toxicol (Phila), 2019; 57, 331−7.
60. Liu C, Wang H, Zhu C, et al. Diagnostic and Differential Diagnostic Significance of Laboratory Markers in Crayfish-Associated Rhabdomyolysis. Ann Clin Lab Sci, 2018; 48, 146−51.
61. Vale A. Rhabdomyolysis. Medicine, 2016; 44, 93−4.
62. Cervellin G, Comelli I, Benatti M, et al. Non-traumatic rhabdomyolysis: Background, laboratory features, and acute clinical management. Clin Biochem, 2017; 50, 656−62.
63. Chen Y, Yuan B, Xie G, et al. Outbreak of Haff Disease caused by consumption of crayfish (Procambarus clarkii), Nanjing, Jiangsu Province, China. Food Control, 2016; 59, 690−4.
64. Chen XF, Lin JW, Pan TM, et al. Investigation of the hazardous substance causing crayfish-induced rhabdomyolysis via a mouse model, a hemolysis assay, and a cytotoxicity assay. Fisheries Sci, 2015; 81, 551−8.
65. He Ying. Analysis of factors related to Hough's disease caused by Procambarus clarkii [Master]: Yangzhou University; 2013. (In Chinese)