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Outbreak of Haff disease caused by crayfish in China: a systematic review

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Abstract

Background Haff disease is a condition that has emerged in China in recent years, primarily associated with the consumption of crayfish. Despite its increasing incidence, the exact cause of Haff disease remains unknown, prompting further investigation into its potential triggers and risk factors. The purpose of this system review is to investigate and summarize the current understanding of Haff disease and provide insights into the etiology and pathogenesis of Haff disease by collecting and analyzing data from a large number of patients.

Method Systematic searches were conducted in PubMed, CNKI, and Wanfang Databases to investigate and summarize Haff disease by crayfish consumption in China over recent years. The search included observational studies published up to May 1, 2024.

Result This review collected data from 1437 patients and conducted a comprehensive analysis of symptoms. In-depth examinations of patient symptoms revealed that nearly all patients exhibited abnormally elevated serum creatine kinase levels and muscular pain, while some also experienced changes in urine color, abdominal discomfort, and chest pain. Risk factors associated with Haff disease from crayfish consumption included high crayfish consumption, alcohol use, the consumption of specific crayfish organs such as the head, liver, and pancreas, and the consumption of wild crayfish.

Conclusion Haff disease is indeed related to the consumption of crayfish, which may be due to the presence of an unknown heat stable toxin in crayfish. During the research process, many risk factors were identified, and it is recommended that people who consume crayfish pay attention to these risk factors and take appropriate preventive measures to minimize the risk of illness.

Keywords Haff disease, Crayfish, Symptoms, Heat stable toxin

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Introduction

In China, there is an annual occurrence of rhabdomyolysis (RM) attributed to crayfish consumption, characterized by symptoms such as elevated creatine kinase levels, muscle pain, and muscle weakness. A study showed that the overall mortality rate of rhabdomyolysis syndrome is 21% [1]. However, it is worth noting that there are very few cases of Haff disease caused by consuming crayfish and most cases can be cured after treatment, only one patient died due to misdiagnosis and multiple organ failure [2].The specific etiological factors underlying crayfish-induced RM remain undetermined. Epidemiological analyses of patients to identify causative factors, which can lead to a more comprehensive understanding of RM. Because the incidence rate of RM caused by crayfish is low, and the symptoms can heal when they are mild, so that fewer cases can be collected, but according to the collected cases, there are strong regional factors, seasonal factors and gender factors.

Rhabdomyolysis

Rhabdomyolysis is a clinical response to skeletal muscle injury, resulting in the release of intracellular substances and their accumulation in the extracellular space. This overload disrupts elimination mechanisms, leading to muscle damage, myoglobinuria, electrolyte imbalances, and the potential development for acute kidney injury (AKI) [3]. RM can stem from various causes, including traumatic, non-traumatic exertional, non-exertional, and genetic factors (Table 1) [4].

The mechanistic basis of RM involves the disruption of the cell membrane and adenosine 5'-triphosphate (ATP) failure, which results in the influx of calcium ions into the cell due to membrane disruption and sodium-potassium pump dysfunction. This, in turn, triggers continuous muscle contraction, energy depletion, and subsequent breakdown of myocytes [5]. The pathophysiology predominantly revolves around the destruction of muscle membranes and the release of intracellular components into the systemic circulation. Clinical manifestations may vary, but the diagnosis is confirmed when serum creatine kinase levels increase to levels exceeding five times the upper limit of normal (>2000 IU/L) [4].

Table 1 Causes of rhabdomyolysis

Traumatic exertional	Non-traumatic exertional	Non-exertional	Genetic
Crush injuries	Strenuous activities	Alcohol	McArdle's disease
Compression	Seizures	Drugs	Tarui's disease
Electrical injury	Sickle cell trait	Toxin	
Vascular or orthopedic surgey	Exposure to extreme heat	Infections	
	Malignant hyperthermia	Electrolyte imbalance	
	Neuroleptic malignant syndrome		

Haff disease

Haff disease is a variant of rhabdomyolysis (RM) characterized by the sudden onset of unexplained muscle stiffness, elevated creatine kinase levels, and severe muscle pain within 24 h of consuming aquatic products [6]. The initial identification of Haff disease traces back to 1924 in the Baltic Sea region, where subsequent outbreaks occurred seasonally during the summer and autumn along the shores of Haff (shallow lagoon) and sporadically in the Baltic States over the following nine years [7, 8].

Various types of aquatic products have been implicated in causing Haff disease, including burbot (Lota lota), pike (Esox spp.), and freshwater eel (Anguilla anguilla) in the Baltic States [7, 8], largemouth buffalo fish and Atlantic salmon in the United States [9, 10], raw boxfish in Japan [11] and Amazonian freshwater fish in Brazil [12]. Additionally, cases of Haff disease have been associated with the consumption of freshwater pomfret and crayfish in both China and the United States (Fig. 1) [13].

Crayfish

The scientific name of crayfish is Procambarus clarkii, which is classified under the order Decapoda, suborder Reptilia, family Cambaridae. It was introduced to China by Japan in the 1930s. According to the 2022 China Crayfish Industry Development Report, in 2021, China's crayfish aquaculture system covered an area of 17,333 square kilometers, resulting in a production of 2.6336 million tons. Crayfish farming primarily occurs in the Yangtze River Basin, while wild crayfish populations are distributed across the country. Various crayfish farming methods include pond farming, mixed farming with crabs or fish, polder farming, paddy farming, and woodland farming (Fig. 2).

Despite crayfish's popularity among consumers, an increasing number of Haff disease cases have been diagnosed after consuming crayfish since 2000, leading to heightened consumer apprehension. According to a recent questionnaire survey, we collected a total of 138 valid data points, and the age distribution of the patients are mainly in the 20–40 years old. A total of 84.78% of people ate crayfish, 5.07% of whom have experienced discomfort, and 10.1% of whom were close to someone who had experienced discomfort. Crayfish exhibit a remarkable ability to thrive in diverse environmental conditions, occupying a prominent position in the nutrient network. They can even grow and reproduce normally in heavily polluted rivers [14, 15]. Crayfish cultivated in

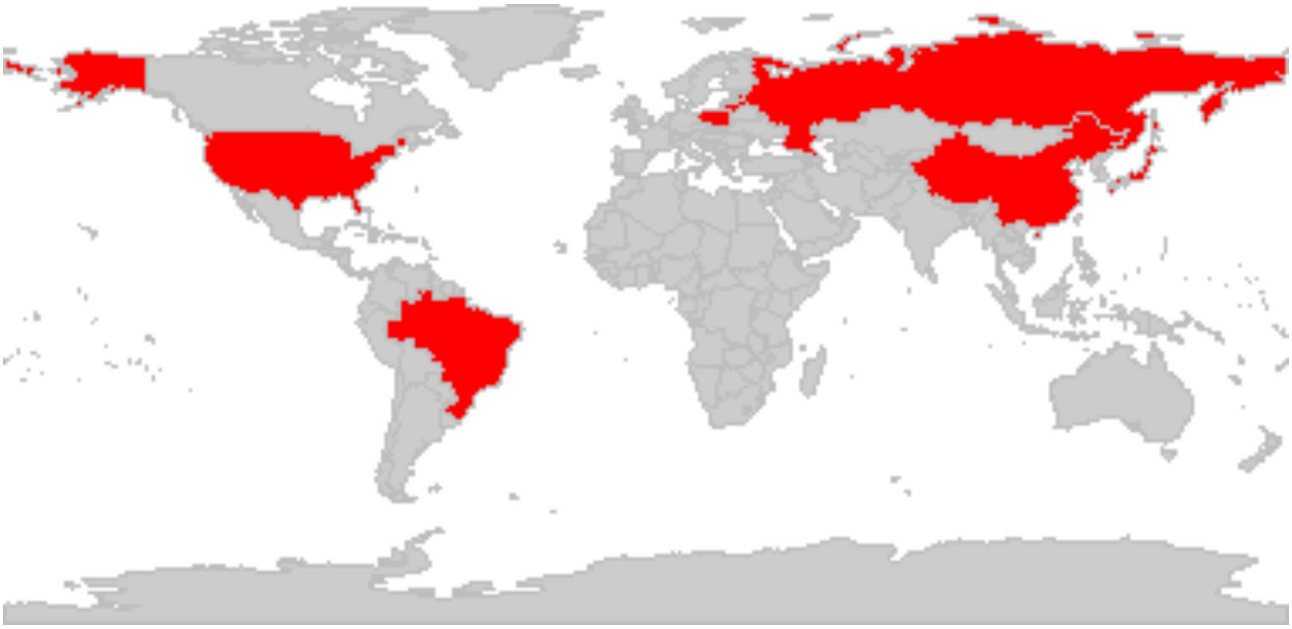

Fig. 1 The global distribution of Haff disease

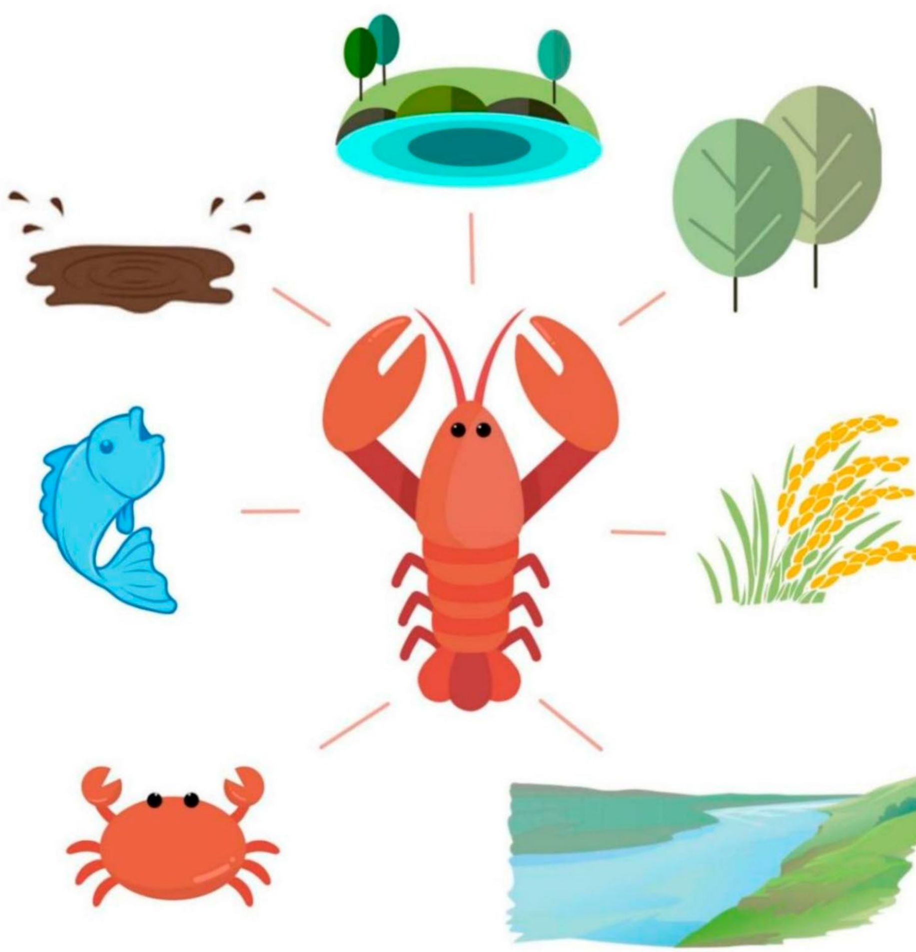

Fig. 2 The different origins of crayfish

contaminated environments tend to accumulate harmful contaminants that can adversely affect human health upon consumption, potentially leading to severe health consequences, including life-threatening situations [16].

Method

Literature search strategy

We systematically gathered and organized patent data through an extensive search across PubMed (covering the period from 2000 to 2024), Wanfang Data (2000 to 2024), and CNKI (2000 to 2024). Our literature search work began in April 2023 and ended in April 2024. The search query utilized keywords such as "crayfish," "crawfish," and "Procambarus clarkii," in conjunction with "Haff disease" or "RM".

Eligibility criteria

The inclusion criteria for this review are as follows: (1) cases of rhabdomyolysis in China; (2) Crayfish intake; (3) cohort studies design of the study. If the study is duplicated or lacks sufficient data support, it will be excluded (see Table 2). Four authors conducted independent literature screening and reached a consensus through discussion.

Data extraction

Following the full-text review, the selected papers were included for data extraction. Three researchers independently extracted data from each eligible study. Extract the following parameters: time, location, number of cases, gender, age, symptoms, and intake of crayfish. And record the data features (median, mean, etc.).

Table 2 Search strategy adopted in the present systematic review

Search strategy	Details
Search string	"crayfish," OR "crawfish," OR "Procambarus clarkii," AND "Haff disease" OR "rhabdomyolysis".
Databases	Pubmed, Wanfang data and CNKI
Inclusion criteria	- P (patients/population): patients with rhabdomyolysis - I (intervention/exposure): crayfish intake - C (comparisons/comparators): time, location, number of cases, gender, age, symptoms, and intake of crayfish - O (outcome): the reason of Haff disease caused by crayfish - S (study design): Cohort study
Exclusion criteria	Experimental studies investigating in vitro or animal models. Study design: editorial, commentaries, expert opinions, letters to the editor, review articles, original non-cohort studies, and articles with insufficient details.
Time filter	2000 to 2024
Language filter	None

Quality assessment

In order to evaluate whether the article was included in the study, three researchers independently evaluated all initially included articles and jointly decided on the articles to be included in the study through discussion. This process ensures the quality of the articles included. Considering the limited number of cases and we use published research results for our research. Analysis was also conducted based on gender, age, and symptoms. Due to these reasons, bias was not evaluated.

Results

As shown in Fig. 3, this comprehensive search yielded 26 results from PubMed, 29 from Wanfang Data, and 146 from CNKI. To ensure data integrity and relevance, we meticulously refined the dataset. We initially excluded 22 duplicate results, followed by the elimination of 70 results that did not pertain to case studies. In addition, according to the inclusion and exclusion criteria, 108 articles were excluded. Subsequently, we selected 23 articles that met our inclusion criteria. From these articles, we synthesized a dataset comprising 1437 cases of Haff disease associated with crayfish consumption in China spanning the years 2000 to 2020(Table 3).

In China, the onset of Haff disease due to crayfish consumption was initially observed in Beijing in 2000. Subsequently, there was a recurrence of cases in Nanjing in 2010, followed by incidences reported in various regions, including Jiangsu, Hebei, Shanghai, Anhui, Hubei, Guangdong, and Hong Kong over the subsequent decade. As depicted in Fig. 4, the majority of cases were concentrated in the middle and lower reaches of the Yangtze River Basin. Notably, the crayfish implicated in the Guangdong incident were traced back to the Yangtze River basin.

Causes of Haff disease were reported almost every year from 2010 to 2020, with outbreaks concentrated in the summer and a significant higher number of female patients than male patients. As shown in Fig. 5, the age distribution of patients ranged from 4 to 70 years old. As shown in Table 4, almost all patients had abnormal muscle pain (96.4%), and some patients showed changes in urine color (10.9%), abdominal pain (15.4%) and chest pain (26.6%).

It shows clearly that the number of cases increased significantly in 2016, and there are studies that point out that the outbreak was related to the flooding that occurred in the Yangtze River basin in 2016 (Fig. 6). For example, during 2016 and 2017 in Tongling, Anhui Province, it was found that the number of cases decreased greatly in 2017. An outbreak of Haff disease also occurred in Wuhan, Hubei in 2014. These cases indicates that the outbreak may be related to flooding [24, 25].

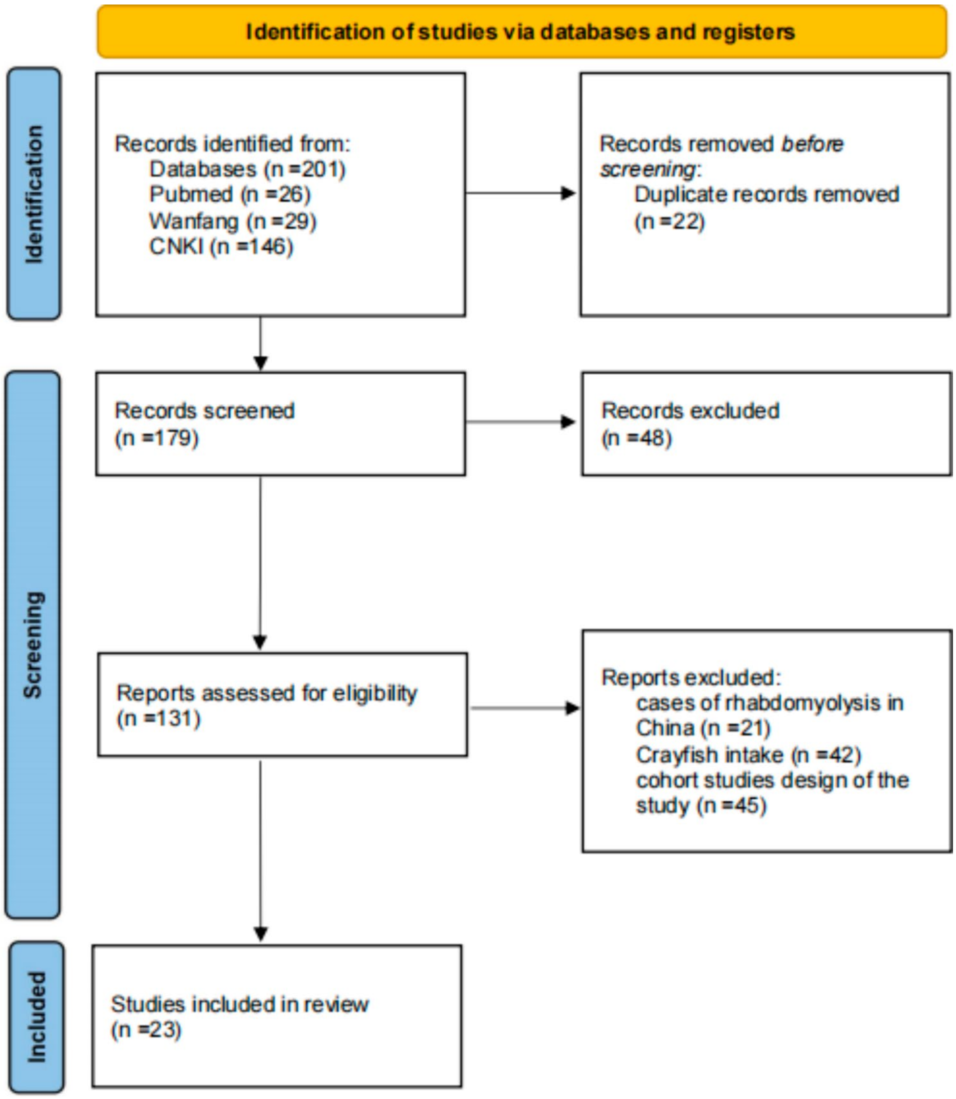

Fig. 3 Identification of studies via databases and registers

Li identified an aggregated outbreak of Haff disease in the Yangtze River in 2016, notably in Nanjing, Jiangsu Province, Wuhu, Anhui Province, and Maanshan, Anhui Province [28]. They determined that consuming crayfish roe and alcohol were risk factors for the disease, with a higher consumption of crayfish roe significantly increasing the risk.

In 2016, an outbreak of Haff disease occurred in Guangdong Province. Huang conducted investigations and mouse experiments and revealed that the disease-causing crayfish originated from the Yangtze River [31]. Only 18.9% of patients consumed crayfish meat alone, while others consumed various crayfish parts. Animal experiments corroborated epidemiological findings, indicating variability in infectivity among individuals.

Zha studied Haff disease cases in Maanshan city, Anhui Province, in 2016. They found that a small percentage of crayfish came from farms (5%), while the majority were either wild-caught (79%) or suspected to be wild-caught (16%) [24]. Additionally, consuming more than ten crayfish significantly increased the risk of Haff disease.

Li investigated Haff disease cases in Hubei Province from 2013 to 2017 [23]. They discovered that the number of confirmed cases exceeded the number of reported cases in the Hubei Foodborne Disease Surveillance System, suggesting potential underreporting or limitations in the surveillance system.

Pei analyzed Haff disease outbreaks in Wuhan, Hubei Province, Maanshan, Anhui Province, in 2019, and in Guangzhou, Guangdong Province, in 2020 [30]. The majority the crayfish processed at home (82.22%), and most of the crayfish had an unknown origin (71.11%), with 92.31% of crayfish with clear origins originating from wild catches. Their case-control study highlighted

Table 3 Outbreaks of Haff disease after eating crayfish

Period	Province	City	Number of cases	Sex	Age	Symptoms	Intake of crayfish
2000.8 [17]	Beijing		6	4F2M	38.6[a](36~42)[b]	Myalgia(100%), brown-colored urine(NA%), abdominal pain(NA%), chest pain(NA%), CK, 3705.2[a](376~10150)[b] U/L	500[a] g
2010.8 [18]	Jiangsu	Nanjing	23	14F9M	35.8[a](20~79)[b]	myalgia(100%), brown-colored urine(39.1%), abdominal pain(13%), chest pain(8.7%), CK,4655[a] U/L	NA
2010.7 [19]	Jiangsu	Nanjing	3	2F1M	NA	myalgia(100%), brown-colored urine(0%), abdominal pain(0%), chest pain(0%), CK,(8681~36360)[b] U/L	NA
2010.8-9 [19]	Jiangsu	Nanjing	11	7F4M	28[a](9~38)[b]	myalgia(100%), brown-colored urine(63.6%), abdominal pain(NA%), chest pain(NA%), CK,7952.2[a](2013~18520)[b] U/L	10[a] pieces
2010.7-9 [19]	Jiangsu	Nanjing	2	1F1M	29.5[a](21,38)[b]	myalgia(100%), brown-colored urine(100%), abdominal pain(NA%), chest pain(NA%), CK,14,675[a](2176,27174)[b] U/L	30[a](20~63)[b] pieces
2010 [20]	Hebei	Shijiazhuang	1	1 M	26	myalgia(100%), brown-colored urine(NA%), abdominal pain(NA%), chest pain(NA%), CK, NA	NA
2012.8 [21]	Jiangsu	Yangzhou	4	2F2M	35.5[a](30~39)[b]	myalgia(100%), brown-colored urine(0%), abdominal pain(0%), chest pain(14%), CK,3561[a](350~14870)[b] U/L	30[a](20~40)[b] pieces
2012.8 [21]		Nanjing	2	1F1M	37.5[a](31~44)[b]		10[a] pieces
2013.8 [21]		Huaian	1	1 M	18		30 pieces
2013.6 [2]	Shanghai		1	1 M	66	myalgia(100%), brown-colored urine(100%), abdominal pain(0%), chest pain(0%), CK,1600U/L	
2014.7-8 [22]	Anhui	Wuhu	2	2 M	42.5[a](41,42)[b]	myalgia(100%), brown-colored urine(50%), abdominal pain(NA%), chest pain(NA%), CK,2393[a](1187, 3599)[b] U/L	0.75[a] kg(0.5 kg, 1 kg)[b]
2014.8 [21]	Jiangsu	Nanjing	2	1F1M	32.5[a](32~33)[b]	myalgia(100%), brown-colored urine(0%), abdominal pain(NA%), chest pain(NA%), CK,2092.5[a](500, 3685)[b] U/L	8-13[b] pieces
2015.10-2016.9	Shanghai		53	18F35M	52[a](16~97)[b]	myalgia(100%), brown-colored urine(NA%), abdominal pain(NA%), chest pain(NA%), CK,3561[a] U/L	NA
2015.5	Jiangsu	Yancheng	1	1 M	62	myalgia(100%), brown-colored urine(NA%), abdominal pain(100%), chest pain(NA%), CK,901.4 U/L	10 pieces
2016.6-9 [23]	Jiangsu	Nanjing	327	NA	37.9 ± 12.4	myalgia(98.06%), brown-colored urine(2.61%), abdominal pain(11.65%), chest pain(36.89%), CK,2146[a] U/L	30[a](20~44)[b] pieces
2016.7-9 [23]	Anhui	Wuhu	270	187F83M	37.69[a](26~51)[b]	myalgia(100%), brown-colored urine(2.2%), abdominal pain(15.9%), chest pain(4.1%), CK,2144[a] U/L	NA
2016.7-9	Guangdong	Guangzhou	10	30F18M	11~59[b]	myalgia(93.8%), brown-colored urine(8.3%), abdominal pain(16.7%), chest pain(39.6%), CK,(67~36164)[b] U/L	20[a](2~60)[b] pieces
		Shenzhen	21				
		Zhongshan	8				
		Foshan	4				
		Zhuhai	2				
		Qingyuan	2				
		Dongguan	1				
2016.7-9 [24]	Anhui	Maanshan	226	140F86M	NA	myalgia(100%), brown-colored urine(10.3%), abdominal pain(29.9%), chest pain(41.6%), CK, NA	NA
2016.8-9	Hong Kong		2	2 F	42.5[a](30,55)[b]	myalgia(100%)	NA
2016.8	Anhui	Hefei	1	1 F	25	myalgia	30 pieces

Table 3 (continued)

Period	Province	City	Number of cases	Sex	Age	Symptoms	Intake of crayfish
2016.7-8 [25]	Anhui	Tongling	69	37F32M	37.4 ± 12.2	myalgia(98.8%), brown-colored urine(NA%), abdominal pain(6.2%), chest pain(9.9%), CK, ≥ 1000 U/L(85.2%)	$(2\sim60)^b$ pieces
2017.7-8 [25]			12	11F1M			
2017.7-8 [26]	Jiangsu	Nanjing	103	64F39M	36.9 ± 11.8	myalgia(100%), brown-colored urine(47.5%), abdominal pain(13.8%), chest pain(19.4%), CK, NA U/L	NA pieces
2017.7-8 [27]	Guangdong	Guangzhou	4	2F2M		myalgia(100%), brown-colored urine(100%), abdominal pain(0%), chest pain(0%), CK,6157 ± 5464 U/L	600.0 ± 294.4 g
2013 [28]	Hubei		1	76F53M	$4\sim70^b$	myalgia(92%), brown-colored urine(NA%), abdominal pain(28%), chest pain(40%), CK,$(71\sim1440350)^b$ U/L	NA
2014 [28]			22				
2015 [28]			3				
2016 [28]			102				
2017 [28]			1				
2018–2019 [29]	Hubei	Wuhan	64	45F19M		myalgia(73.4%), brown-colored urine(NA%), abdominal pain(NA%), chest pain(14.1%), CK, 2618.95 ± 3201.71 U/L	>10 pieces
2019 [30]	Hubei	Wuhan	36	29F16M	32.80 ± 9.64	myalgia(100%), brown-colored urine(11.1%), abdominal pain(NA%), chest pain(51.11%), CK, 2315.50^a U/L	16.86^a pieces
2019 [30]	Anhui	Maanshan	9				
2020.6-9 [30]	Guangdong	Guangzhou	25	17F8M	$32.76^a(21\sim52)^b$	myalgia(100%), brown-colored urine(20%), abdominal pain(28%), chest pain(36%), CK, $2061^a(128\sim17851)^b$ U/L	$14.28^a(5\sim25)^b$ pieces

Note: [a]average, [b]range, CK reference range 42–186 U/L, N.A.=not available

that consuming crayfish roe significantly increased the risk of RM, and each additional crayfish consumed escalated the risk.

The consumption of crayfish may lead to Haff disease, which has a range of clinical manifestations mainly due to rhabdomyolysis

Therefore, we attempted to identify the possible causes of Haff disease starting from the etiology of rhabdomyolysis. There are many causes of RM, the main ones being illicit drugs, alcohol abuse, medical drugs, trauma, viral myositis, and strenuous exercise, in addition to the presence of an underlying disease. The outbreak of Haff disease caused by crayfish has led to research on its causes, which has previously been conducted in the following areas.

RM may be associated with heavy metals, pesticides and antibiotics but the association was not significant

Because of the industrialization of human society, heavy metal pollution is prevalent in nature, and the pathogenicity of crayfish may be related to heavy metal pollution [32]. Crayfish have a strong ability to survive, grow and reproduce in environments with excessive levels of heavy metals, enriching heavy metals in their bodies through sediments and biological chains, and posing a risk to human health [16, 33]. The main heavy metals that are enriched in crayfish are cadmium (Cd), arsenic (As), lead (Pb) and so on. Among them, Cd can have adverse effects on teeth, bones, kidneys, etc [34]. As is carcinogenic [35]. Pb is a chronic poison that affects the mental health of children and causes mental retardation [36]. Excessive intake of heavy metals may lead to symptoms such as acute kidney damage in humans, so it is necessary to state whether heavy metals are the cause of the outbreak of Haff disease [37]. The average heavy metal concentrations in farmed crayfish were lower than those in wild crayfish [38]. An assessment of the association between trace element enrichment in crayfish and health risks in China revealed that crayfish consumption was associated with cancer risk in some provinces, and the risk was greater in children than in adults [39]. The hepatopancreas of crayfish is the tissue with the highest concentration of heavy metals, followed by the gills, exoskeleton, and muscle. The Pb and Cd contents of wild crayfish are slightly higher than the limits for human consumption recommended by the World Health Organization (1989), the U.S. Environmental Protection Agency (2000) and China's national safety standards [40]. Hubei Entry-Exit Inspection and Quarantine Bureau through the filing of crawfish farming waters in Hubei Province, reported that the detection of heavy metals such as hydrargyrum (Hg), Pb, As, Cd and other heavy metals in crawfish did not exceed the maximum allowable residues in China and other countries and organizations. The average residue level is low and the risk to human health is relatively

Fig. 4 The provinces of China where Haff disease caused by crayfish has been reported from 2000 to 2020

small. The results for other provinces are basically the same [41, 42]. Consumption of farmed crayfish has a very low effect on RM syndrome.

The development of agriculture and animal husbandry has introduced pesticide contamination into the natural environment, which can ultimately find its way into the human food chain through bioconcentration [43]. Crayfish have demonstrated the ability to thrive and reproduce in environments with pesticide residues, leading to numerous studies exploring the health risks associated with crayfish grown in pesticide-contaminated settings [16]. Many pesticides, including herbicides, insecticides, and fungicides, can potentially induce RM in humans [44]. Generally, when pesticides enter the natural environment, they have the potential to degrade, and when used responsibly, they are less likely to result in excessive pesticide residues in animals [45]. However, it's crucial to note that severe pesticide contamination, such as the presence of chlordecone, can lead to persistent pesticide residues throughout various parts of crayfish. In these instances, these residues may not clear naturally in the short term, potentially contributing to the development of conditions such as prostate cancer [16, 46]. Consequently, while the impact of pesticides on crayfish consumption-related RM is generally low, the consumption of crayfish subjected to severe pesticide contamination can significantly affect human health.

With the advent of aquaculture, antibiotics have become a widespread tool for disease prevention and treatment [47]. Antibiotics primarily enter aquatic animals through their feed, with only a small portion being absorbed, while the majority remains in the environment [48, 49]. The excessive use of antibiotics, particularly unapproved antibiotics, poses risks to human health, aquatic animal production, and environmental safety [50]. Researchers conducted examinations of antibiotic levels in crayfish from Xuyi, Jiangsu Province, revealing a detection rate of 62% in 2017 and 63% in 2018. The highest furacilin content was found in crayfish shells and heads, while crayfish meat contained the lowest furacilin content. Notably, the detected antibiotic levels complied with relevant international regulations [51]. Studies have indicated a significantly higher incidence of RM when antibiotics like DAP are combined with statins, compared to when statins alone are used [52]. Furthermore, research has demonstrated that Maduramicin can induce RM in mice, suggesting a potential risk of Maduramicin entering the natural environment [53]. Antibiotics are

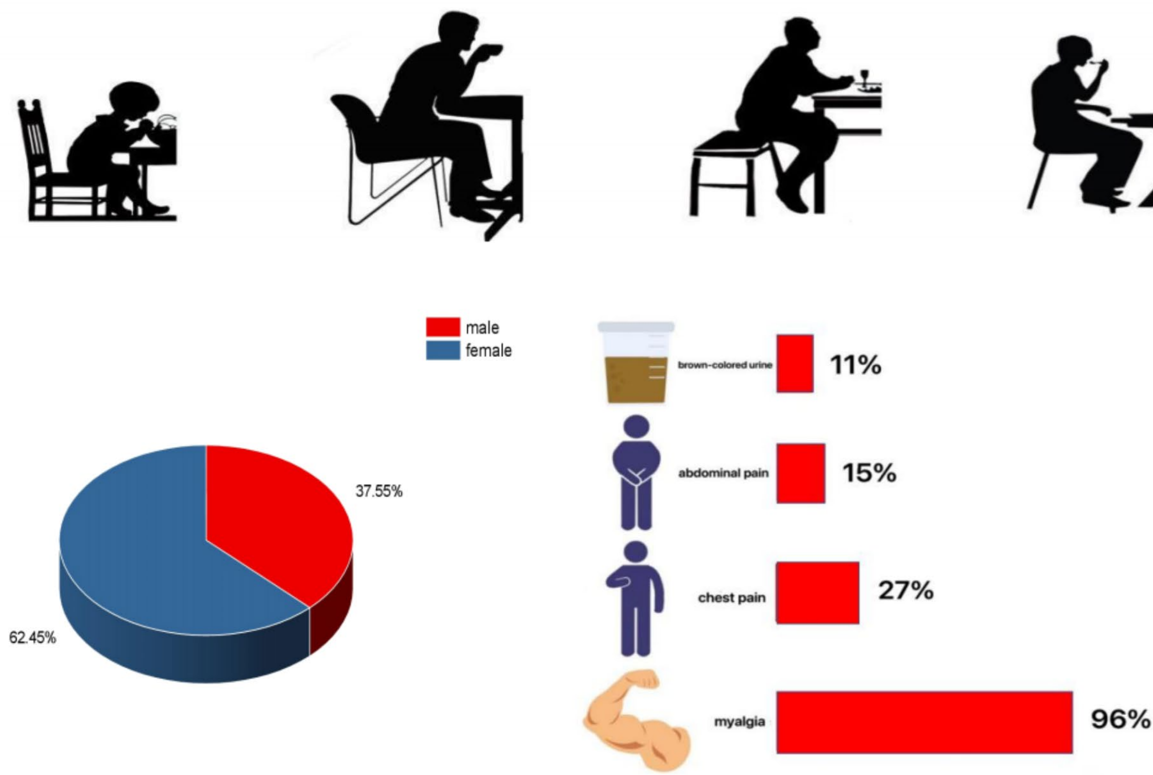

Fig. 5 Patient's age gender and symptom chart

Table 4 Symptoms and incidence rate of Haff disease

Symptoms	incidence rate
Myalgia	96.4%
Chest pain	26.6%
Abdominal pain	15.4%
Brown-colored urine	10.9%

commonly detected in the global farming industry, indicating that antibiotics are a plausible factor contributing to Haff disease [49, 54–56].

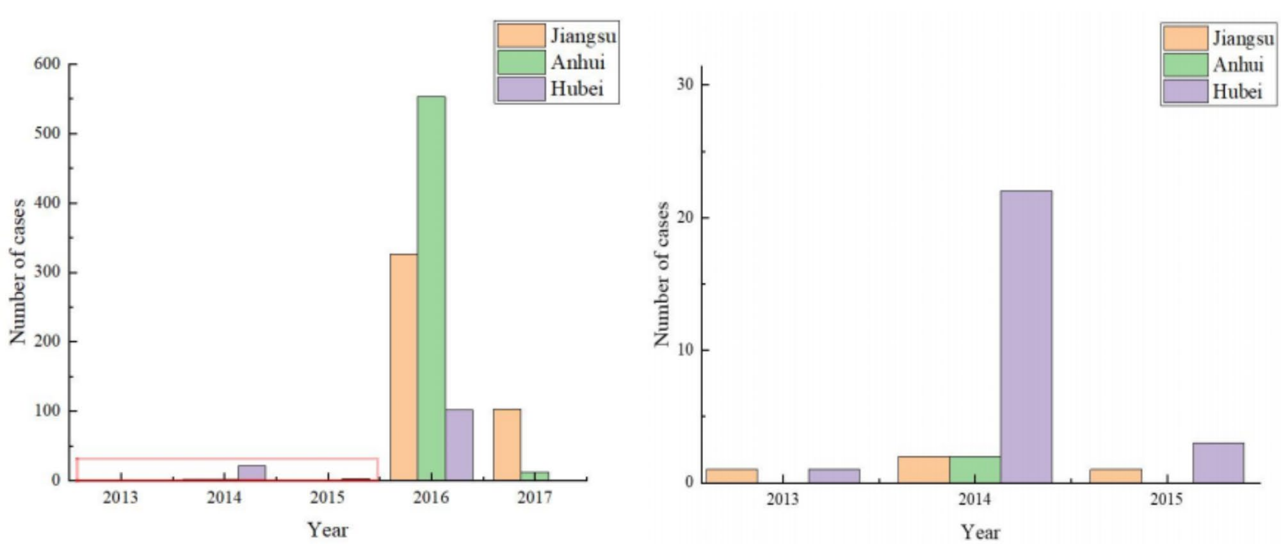

Fig. 6 Number of Haff disease in three main province from 2013 to 2017

No relationship between RM and the use of crayfish wash powder

To make the color of crayfish more vibrant and easier to sell, there are many unscrupulous merchants use crayfish washing powder to clean the crayfish. Currently, the main components of crayfish washing powder is oxalic acid, citric acid, sulfites, etc., and consumers are prone to heart failure and fatal arrhythmias and life-threatening after long-term intake of oxalic acid [57].The oxalic acid content in crayfish can be determined by ion chromatography, and the researchers have concluded that the oxalic acid component can be detected in crayfish after cleaning them with crayfish washing powder [58]. As research progressed, researchers found that crayfish wash powder is readily soluble in water and that citric acid and sulfite are permitted food additives whose toxic effects do not cause RM but may lead to liver damage, apoptosis and obesity [59–61].

Some viruses appear in aquatic products, and some toxins in the crayfish may cause Haff disease

Since all of the cases reported so far have been due to the consumption of cooked crayfish, the scientific community generally agrees that there is a heat-stable toxin that causes RM [13]. At the time of the outbreak of Haff disease cases in the United States, the U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) analyzed known aquatic toxins including: ciguatoxin, saxitoxin, brevetoxin, tetrodotoxin. palytoxin, domoic acid, okadaic acid, and two blue-green algal or cyanobacterial toxins, microcystin and nodularin, but unfortunately all the samples tested were negative [8]. Among these toxins, ciguatoxin, saxitoxin, and tetrodotoxin belong to sodium channel blockers, which do not cause rhabdomyolysis [62]. The earliest literature suggested that a palytoxin or palytoxin-like agent in aquatic products causes RM, and the mechanism of action of palytoxin is almost identical to that of RM [63, 64]. In Japan, palytoxin was detected in the crab and sardines that caused the Haff disease, while no palytoxin toxin was detected when the same batch of crayfish consumed at the time of the Haff disease was tested in China [64–66]. Palytoxin mainly causes neurotoxicity, but RM from crayfish consumption is more likely to cause muscle toxicity, and palytoxin is more toxic, so it is thought that the real cause is not palytoxin [64–66]. It has also been suggested that crawfish contain cyanotoxin, which causes RM after consumption, but this toxin was not detected in the same batch of crawfish consumed at the time of illness [67–69]. Cyanobacteria are often found in the crayfish growing environment, increasing the possibility of toxin accumulation. Some studies have pointed out that crayfish can still survive in the presence of toxic cyanobacteria, and the body produces microalgal cyst toxins. Most toxins are present in the hepatopancreas and intestine, the muscle content is very low. But humans will ingest the entire abdomen, so there is a possibility of microalgal toxin poisoning [70]. Currently, the scientific community believes that there is an unknown thermostable toxin that causes symptoms associated with RM in consumers. More research is needed to identify this thermostable toxin as a means to identify the cause of and prevent the occurrence of Haff disease.

Discussion

This review comprehensively analyzes Haff disease cases resulting from crayfish consumption between 2000 and 2020 in China, summarizing the collected data. Although the prevalence of rhabdomyolysis (RM) is typically higher in men, it is noteworthy that the number of Haff disease cases associated with crayfish consumption is significantly greater in women [23]. The main reasons for the high proportion of female patients are twofold. Firstly, female patients may have substances related to certain toxins in their bodies; Secondly, women prefer to eat crayfish [30, 58]. In the previously mentioned questionnaire, 66.67% of people consumed alcohol while consuming crayfish, 40% sucked on the head portion of the crayfish, 55% consumed crayfish yolk, and 75% consumed the crayfish without removing the threads. The risk of RM is notably increased when consuming crayfish roe and hepatopancreas, as well as when consuming alcohol alongside crayfish [23, 30, 58]. Furthermore, consuming crayfish sourced from the wild significantly elevates the likelihood of developing Haff disease, this may be related to heavy metals, unknown toxins in the wild [24, 30]. The surge in Haff disease cases observed in 2016 may be attributed to the floods that year [25]. The rainstorm and flood in the Yangtze River basin made the farmed crayfish escape to the wild. At the same time, the flood made some viruses widely spread in the flood areas. After that, the residents would go to the wild to catch crayfish for sale or consumption, which may be the reason for the sharp increase of cases of Haff disease caused by eating crayfish after the flood [23, 28]. Research has indicated that individuals with a high Body Mass Index (BMI) are more susceptible to RM, and the use of certain medications like aspirin, codeine, and simvastatin may exacerbate RM, more research is needed to understand these interactions and their implications for individuals at risk of rhabdomyolysis [8].

It is necessary to acknowledge the limitations of this work. Because this study aimed to investigate a rare disease in a specific population, we had access to a limited sample size, which may have affected the generalizability of this work. Due to insufficient public awareness of symptoms and healthcare needs, cases of Haff disease may be underreported, leading to a lack of prevalence and accurate data for the disease. Due to the lack of a comprehensive food traceability system, it is difficult for us to trace the origin of crayfish that caused Haff disease. If the system is established, it will make epidemic management more effective. Although this study emphasizes various risk factors, the impact on vulnerable groups has not been evaluated, and further exploration of these impacts is needed. Several challenges persist in the study of crayfish-induced Haff disease:1. It is difficult to trace the same batch of crayfish that caused Haff disease. 2. Low awareness among residents can lead to delayed or unreported mild symptoms and missed CDC notifications. 3. Potential underreporting within the foodborne disease surveillance system. 4. Limited resources and technical capabilities for identifying disease-causing toxins.These challenges can be addressed through various strategies:1. Establish a comprehensive food traceability system to track the source of crayfish. 2. Raise public awareness regarding the importance of seeking prompt medical attention and reporting symptoms, as early treatment often leads to faster recovery. 3. Strengthen the development of a foodborne disease detection system and ensure timely reporting of eligible cases. 4. Maintain continuous monitoring of Haff disease resulting from crayfish consumption and conduct timely analysis of water quality in the Yangtze River basin to predict and prevent future outbreaks.

Conclusion

Current evidence suggests that Haff disease is related to the consumption of aquatic products. However, the cause of Haff disease caused by crayfish is currently unknown. More cases and samples are needed for further research to obtain more reliable results.Through the analysis of this review, we have excluded many possible factors and concluded that a certain heat stable toxin is highly likely related to the disease.

Suggestions

Analysis of the above literature can provide consumers with the following recommendations: (1) Seek medical attention promptly if you feel unwell after consuming crayfish or other aquatic products to ensure timely treatment and minimize harm. (2) Eating the breeding crayfish. (3) It is necessary to provide safety education to the public after floods, as the consumption of crayfish has led to a significant increase in cases of Haff disease. This will enable the public to consume crayfish more safely. (4) Limit the quantity of crayfish consumed in a single serving. (5) Thoroughly clean crayfish by removing their guts and threads before cooking. (6) Avoid consuming crayfish roe, liver, and pancreas. (7) Refrain from consuming crayfish after strenuous exercise or when taking medications that may lead to rhabdomyolysis. (8) Moderate alcohol consumption and avoid excessive wine or alcoholic beverages when consuming crayfish. (9) Patients or relevant departments of the hospital should report to the relevant monitoring system, which can enable the CDC to obtain accurate incidence rate and disease symptoms. (10)We need to improve research techniques and methods for foodborne diseases to present them more clearly to people.

Supplementary Information

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Supplementary Material 1

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F.X.: conceived and designed the experiments, analyzed and interpreted the data. C.G.: analyzed and interpreted the data. Y.W.: analyzed and interpreted the data. Y.Z.: conceived and designed the experiments. The first draft of the manuscript was written by F.X. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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