ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue IX September 2025

Venomous Encounters: A Study of Box Jellyfish *(Chironex Fleckeri)* In Philippine Coastal Ecosystems

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DOI: https://doi.org/10.51244/IJRSI.2025.120800243

Received: 20 Aug 2025; Accepted: 29 Aug 2025; Published: 02 October 2025

ABSTRACT

Box jellyfish Chironex fleckeri stings pose a serious public health threat in the Philippines. Cases were reported to have caused dermal necrosis and infections. The nephrotoxicity of the venom of Chironex fleckeri has been attributed to hemolysis, oxidative stress, and inflammation, which lead to acute kidney injury. Despite numerous studies on the mechanisms involved with the venom, not much is known to this date about its overall contribution to either treatment efficacy or kidney dysfunction. A descriptive review of mechanisms of venom, diagnostic approaches, and treatments in the Philippine setting will help highlight the deficit in pertinent public health policies. Chironex fleckeri is likely to be found in the coastal and estuarine areas of the Philippines. Distribution is influenced by seasonal water temperature and salinity, mirroring conditions found in its native Australian waters. Such risk factors can include the physical characteristics of this jellyfish, a transparent, cube-shaped bell with long, venomous tentacles, which will deliver potent venom. Knowing where and what, in terms of physical characteristics, puts into perspective all the risk factors for better patient outcomes.

Keywords: *Chironex fleckeri*, nephrotoxicity, venom-induced renal injury, diagnostic and management strategies

INTRODUCTION

Box jellyfish *(Chironex fleckeri)* stings in the Philippines are an important public health concern due to their potential seriousness and a lack of extensive data on the incidence. Given the notoriety for highly toxic venom, box jellyfish often live in areas that receive a large number of tourists, thus exposing people to its dangers. There are recommendations on population surveillance—mostly for the Department of Agriculture and local governments [1]. During 2008–2013, 57 probable cases were recorded; most suffered minor to severe complications from the stings, which included dermal necrosis and infections [2]. Such incidents raise concern in order to strengthen monitoring and create public awareness for measures against the risks caused by jellyfish stings.

The venom of *Chironex fleckeri* contains at least 250 proteins, comprising metalloproteinases and pore-forming toxins that contribute to its tissue-destroying and systemic effects [3, 4]. Specific host factors, such as the ATP2B1 protein, have been critical for venom-induced cytotoxicity; thus, implying specific pathways also responsible for nephrotoxicity [5]. There is a general lack of effective treatments, though some are managed symptomatically. In addition, there is novel treatment using lemon-oil emulsion, and more research is desired to ascertain its true potential in this field of therapeutic applications [6,7].

Despite increasing research on the dangers of box jellyfish venom, gaps in understanding the mechanisms of its nephrotoxic effects persist. Most studies focus on overall systemic manifestations and pay less attention to renal effects. Moreover, the current treatment approaches for Chironex fleckeri stings are not well-documented, especially in tropical nations such as the Philippines [8]. Current treatments, such as plasma exchange and renal replacement therapy, have some evidence but have not been proven in box jellyfish sting settings [8]. Public awareness and education of health workers may enhance case identification and recording, that will then serve as the basis of any future database and research and policy-making [1].

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These research gaps notwithstanding, a comprehensive review article synthesizing the existing knowledge on *Chironex fleckeri* toxins and its management is truly warranted, especially in the Philippine context. The said review will highlight the peculiar challenges of this condition within the country's box jellyfish envenomation, with implications that will be useful for health professionals, researchers, and policymakers. In combining data from studies on the mechanisms of venom, treatment strategies, and preventive measures, this review may also prove useful for improving public health interventions and the outcomes of patients.

This review will collate knowledge on the nephrotoxic effects of *Chironex fleckeri* venom, detailing its mechanisms, diagnostic approaches, and current treatment strategies within the Philippine context. The objectives are to contribute to the current understanding of the renal consequences of the sting by jellyfish, inform clinical practice, and guide public health policy. This, therefore, seeks to provide a wide framework for understanding and managing the nephrotoxic effects of *Chironex fleckeri* envenomation that could lead to major improvement in outcomes for patients and guide future research in marine toxicology.

Geographical Distribution Of *Chironex Fleckeri* Envenomation In The Philippines

The geographical distribution of *Chironex fleckeri*, the Australian box jellyfish, is influenced by multiple ecological and environmental factors in Philippine waters. Although considered to be related mainly to northern tropical waters in Australia, its incidence in the Philippines is most probably linked with similar coastal and estuarine settings. *C. fleckeri* generally inhabits shallow waters and is often times found in mangrove creeks and coastal beaches; these are common in the Philippines [9]. It is probably associated with areas characterized by rich filter feeder assemblages; thus, *C. fleckeri* might also share similar ecological niches in the waters of the Philippines [9].

Occurrences of *C. fleckeri* are highly seasonal, with large populations during summer months, while a similar seasonal pattern could take place in the Philippines, considering the country generally experiences similar weather conditions [10]. Water temperature and salinity may dictate the timing of medusa production—information that is potentially useful to predict their appearances in Philippine coastlines [10]. Aside from *C. Fleckeri* has robust swimming abilities, which enables it to swim and potentially establish localized populations in a range of coastal habitats [11]. Biophysical modeling suggests that populations can stay relatively isolated, which might influence their distribution in the Philippines due to local currents and habitat structures [11].

Distribution of *Chironex fleckeri*, the Australian box jellyfish, remains largely undocumented in the Philippines, although it is certainly in coastal conditions similar to its native habitats; this species probably occurs in northern coastal areas, especially in regions like Cagayan Valley, Ilocos Norte, and the province of Aurora, where warm, shallow waters are dominant [12, 13]. Warm waters are prominent in the Cagayan Valley in the north, making the area suitable for *C. fleckeri* [12]. Also, Ilocos Norte and Aurora display shallow coastal conditions with warm temperatures that may generally support the species' occurrence [14].

Tropical climates and estuarine zones hosting mangrove forests are abundant in the Visayan Sea and areas of Eastern Visayas, including Leyte and Samar, all of which provide natural ecosystems for box jellyfish [15].

In Mindanao, coastal areas such as Davao and Zamboanga have rich marine biodiversity and are generally warm in temperature, thus becoming the candidate sites for *C. fleckeri* [16]. Considering that coral reefs and seagrasses are filter feeder communities, *C. fleckeri* could also be supported in coastal environments such as Palawan, Bohol, and Zambales provinces. On the other hand, while these conditions may support *C. fleckeri*, ecological dynamics may moderate its distribution and abundance, possibly in competition with its congener, the beach jelly *Catostylus purpurus* [16, 17].

Though the coastal habitats of the Philippines have ecological similarities with those where Chironex fleckeri is known to thrive, its geographical distribution and ecological dynamics in Philippine waters are poorly documented. The majority of the existing studies on C. fleckeri have focused on its range in Australia, leaving a substantial gap in understanding its occurrence, seasonality, and population dynamics in the Philippines. While regions like Cagayan Valley, Ilocos Norte, Aurora, and parts of Visayas and Mindanao have suitable

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habitats for this species—warm, shallow waters with a rich assemblage of filter feeders—empirical data confirming its presence, distribution patterns, or ecological impacts are lacking. Also, possible interactions between C. fleckeri and other jellyfish species, like Catostylus purpurus, in these ecosystems remain unexplored. Such a knowledge gap limits the capacity to assess the risks of envenomation incidents, design mitigation strategies, and understand the ecological role that the species plays in Philippine marine environments. Further research is needed to ascertain its presence, distribution, and possible influence on local marine biodiversity.

Figure 1. Map of the Philippines

Note: Google Maps. [Online]. Available at: https://www.google.com/maps/@11.454437,117.9557925,

6z?entry=ttu&g_ep=EgoyMDI1MDEwNy4wIKXMDSoASAFQAw%3D%3D. Accessed January 10, 2025.

Chironex Fleckeri Physical Features

The bell of *Chironex fleckeri* is usually pale blue and transparent, with a diameter of approximately 16 cm (6.3 in), although it can grow up to 35 cm (14 in) [18]. Its cube-like shape is characteristic of the species, which is how it gets its name. From certain angles, the bell can appear to resemble a human skull, adding to its ghostly appearance in the water [19]. Its transparency makes the jellyfish very hard to see in its natural environment, thus posing great danger to unsuspecting swimmers [20]. Up to 15 tentacles trail from each corner of the bell, which can extend as long as 3 meters (10 feet) when fully unfurled [18, 19]. When swimming, these contract to approximately 150 mm (6 in) in length and 5 mm (0.20 in) in diameter. Each tentacle is highly populated with cnidocytes, specialized cells containing nematocysts that can deliver venom upon contact [20]. A single tentacle can have as many as 5,000 stinging cells, which are triggered both by physical pressure and by chemical signals from potential prey [18].

Chironex fleckeri possesses well-developed sensory systems compared to other jellyfish species. Arranged around its bell are four rhopalia, each containing six eyes—making a total of 24 individual eyes [20]. Light can be perceived by these eyes, and together, they may even provide the jellyfish with the ability to form images; it is still unclear how those tremendous amounts of visual input are processed without a brain [19]. Especially attractive for this jellyfish are different colors of light; it is most sensitive to blue light, which, if detected, can influence its feeding behavior by making it slow down its pulsation rate and extend its tentacle [18]. Unlike the majority of jellyfish, which simply drift with the tides, *C. Fleckeri* can swim actively, and by contracting its bell, it can propel itself at speeds of up to four knots—roughly 7.4 km/h or 4.6 mph [20]. This helps it search for prey and avoid its own predators.

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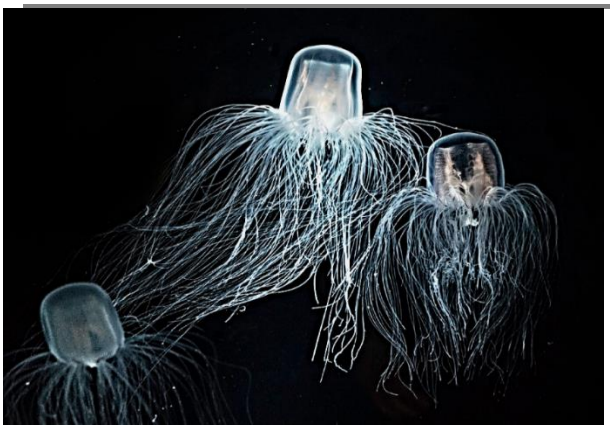

Figure 2. Chironex fleckeri

Note: Adapted and enhanced from 'Nephrotoxic Effects of Cnidaria Toxins by Marchelek-Myśliwiec, M., Kosik-Bogacka, D., Ciechanowski, K., Marchelek, E., Łanocha-Arendarczyk, N., Grubman-Nowak, M., & Korzeniewski, K. (2024), International Maritime Health, 75 (4), 245–253. https://doi.org/10.5603/imh.102878

Chironex Fleckeri Toxins

Chironex fleckeri venom has been characterized, and there are several potent toxins involved, including Phospholipase A2, CfTX-1, CfTX-A, CfTX-B, and CfTX-2. Most of their deleterious actions are primarily as hemolytic, cytotoxic, and nephrotoxic effects. These potent toxins cause a massive breakdown of erythrocytes, leading to severe clinical manifestations, including pain, skin necrosis, fever, vomiting, and even respiratory failure due to the mentioned activities of venom toxins [18, 19]. The main cause of renal impairment was attributed to massive intravascular hemolysis, with resultant free hemoglobin and toxic metabolites entering the circulation in very large quantities and overwhelming the mechanisms of renal filtration, causing AKI to the victim [20]. Moreover, besides hemolysis, CfTX-2 had other cardiotoxic and cytotoxic properties, complicating envenoming [18, 19]. Treatment may be done using vinegar and seawater application to neutralize the venom and use of box jellyfish antivenom produced by bioCSL in relation to supportive management aimed at relieving pain and closely monitoring renal function [18, 19].

Phospholipase A2 is one of the major toxins in the venom of the box jellyfish, *Chironex fleckeri*, which exerts its activity by destroying cells, especially causing hemolysis—the breakdown of red blood cells. This is associated with a myriad of clinical symptoms, including tingling, skin tissue death, excruciating pain, fever, vomiting, and respiratory failure [18, 19]. The main route for kidney impairment is through the breakdown of red blood cells. This leads to acute kidney injury (AKI) through hemolysis and the consequent release into circulation of toxic byproducts of hemolysis, such as free hemoglobin. This overwhelms renal filtration and causes oxidative stress within renal tissues, leading to AKI [20]. Envenoming by *C. fleckeri* may present with immediate severe symptoms, which include severe pain at the site of the sting followed by systemic reactions, such as fever and vomiting, that may necessitate urgent medical intervention to prevent life-threatening complications [19].

CfTX-1, one of the major toxins in the venom of the box jellyfish (Chironex fleckeri), has been known to cause cell destruction, especially to red blood cells, causing hemolysis. Hemolytic activity contributes to many clinical manifestations, such as severe pain, fever, and vomiting, although less is reported in the literature regarding specific clinical effects attributed to CfTX-1 itself [18, 19]. The main route by which this toxin causes renal injury is through its effect on red blood cells: the lysis of red blood cells releases hemoglobin and other noxious products into the bloodstream, which exceeds the capacity of renal filtration and leads to AKI [20]. This intravascular hemolysis also causes tubular obstruction and oxidative stress in the kidneys, adding to renal damage [20]. The envenomation caused by *C. fleckeri* usually manifests symptoms immediately after a sting and with great severity; patients present with severe pain at the sting site, followed by systemic reactions of fever and vomiting that require immediate medical attention to avoid life-threatening complications [19]. The subsequent acute kidney injury continues to be an important issue following CfTX-1 envenoming.

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CfTX-2, a complex toxin contained in the venom of the box jellyfish *(Chironex fleckeri)*, demonstrates cardiotoxic, cytotoxic, and nephrotoxic activities that can produce severe symptoms due to systemic engagement of multiple organs and potentially leading to heart and kidney failure [18, 19]. Its toxic effects are generally exerted through disruption of cellular membranes and cellular lysis, which includes destruction of red blood cells contributing to free hemolysis and subsequent nephrotoxicity [20]. Envenoming by *C. fleckeri* is usually characterized by immediate, very severe symptoms—namely, extreme pain locally where the sting occurred, fever, and vomiting, underscoring the need for urgent medical attention [19]. The mechanism through which CfTX-2 primarily induces kidney damage involves hemolysis because free hemoglobin entering the circulation at overwhelming rates exposes renal filtration and results in tubular obstruction, possibly causing acute kidney injury [20]. This therefore gives rise to concerns about potential heart and kidney failure and certainly suggests the seriousness of the potential failure of both organs and, consequently, a most compelling need for treatment.

CfTX-A and CfTX-B are hemolytic toxins from the box jellyfish *(Chironex fleckeri)*, known to cause the destruction of red blood cells, leading to hemolysis and the release of substances harmful to the kidneys, contributing to AKI [18, 20]. The toxins also show cytotoxic properties, increasing the severity of symptoms seen in *C. fleckeri* stings, including severe pain, tissue necrosis, and systemic reactions such as cardiovascular instability [19]. In comparison with other toxins, such as CfTX-1 and CfTX-2, the hemolytic potency of CfTX-A and CfTX-B is significantly higher, with several studies showing that they can be activated for hemolysis even at very low concentrations [4]. The destruction of red blood cells releases free hemoglobin into the circulation, which overwhelms the renal filtration processes, resulting in oxidative stress, tubular injury, and, finally, AKI [20]. Therefore, possible kidney damage is one of the major concerns of envenomation by these toxins.

Treatment for exposure to the venom of *Chironex fleckeri* has primarily involved vinegar as a method to neutralize its effects on the skin, accompanied by flushing with seawater [18]. Antivenom is available, but its efficacy is currently under active research and debate [19, 20]. Supportive care will also include management of pain, monitoring renal function, and blood pressure stabilization. More severe presentations require the use of intravenous fluids to help maintain renal function, and some will go on to require dialysis should there be compromise to renal function [18].

Despite considerable efforts to characterize the venom of *Chironex fleckeri* and its toxic components, including CfTX-1, CfTX-2, CfTX-A, and CfTX-B, there are still large gaps in the knowledge regarding their exact mechanisms of action and how these toxins act in concert to cause complex clinical manifestations, including AKI, cardiotoxicity, and systemic inflammation. Studies on geographical variability in toxin potency among different populations of C. fleckeri and ecological implications are very poorly understood. Available treatments such as vinegar, seawater flushing, and antivenom are based on very shallow evidence, and the benefit of antivenom is actually a topic of debate. Further research is also required on the venom-induced renal damage progression, particularly the role of oxidative stress and tubular obstruction in AKI, to develop more targeted therapeutic interventions. Knowledge gaps all point to the requirement felt by each discipline of toxinology, clinical research, and ecological assessment in coming together for a better understanding and management approach to C. fleckeri envenomation.

The table 1 outlines various toxins found in the venom of *Chironex fleckeri*, or box jellyfish, and their effects on the human body.

Table 1. Toxins of Chironex fleckeri

Type of Toxin	**Key Properties**	**Clinical Picture**	**Main Mechanism for Kidney Damage**	**Treatment/ Management**
Phosphol	cell-destroying and blood-cell-	Tingling or numbness (Paresthesia), Skin	destruction of red blood cells	4–6% vinegar for 30 seconds,

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ipase A2	breaking. (Cytolytic hemolytic)	tissue death (skin necrosis), itching, pain, fever, vomiting, symptoms of respiratory failure, Acute Kidney Injury (AKI) or sudden kidney damage or failure	(Hemolysis)	seawater, bioCSL's box jellyfish antivenom, supportive care for pain relief, and renal function monitoring.
CfTx-1	cell-destroying and blood-cell-breaking. (Cytolytic hemolytic)			
CfTx-2	Harmful to the heart (Cardiotoxic), Harmful to cells or cell-killing (cytotoxic), Harmful to the kidneys (nephrotoxic)			
CfTx-A	blood-cell-breaking (Hemolytic)			
Cftx-B	blood-cell-breaking (Hemolytic)			

Note: Adapted and enhanced from "Nephrotoxic Effects of Cnidaria Toxins" by Marchelek-Myśliwiec, M., Kosik-Bogacka, D., Ciechanowski, K., Marchelek, E., Łanocha-Arendarczyk, N., Grubman-Nowak, M., & Korzeniewski, K. (2024), International Maritime Health, 75(4), 245–253. https://doi.org/10.5603/imh.102878. Medical terms have been simplified by the author for clarity and accessibility to non-medical readers.**

Nephrotoxic Effects Of *Chironex Fleckeri* Toxins

The nephrotoxic effects of *Chironex fleckeri* venom are multifaceted and result from a combination of direct and indirect mechanisms.

Hemolysis

Hemolytic activity in *Chironex fleckeri* venom is powered by its powerful toxins CfTX-A and CfTX-B, leading to the full-blown development of acute kidney injury. These two toxins have high hemolytic activities: they break down RBCs, releasing hemoglobin and other intracellular contents into the circulation [18]. This overwhelms renal filtration and serves as one of the main pathways leading to renal damage [4, 20, 21]. Several mechanisms might be involved with hemolysis-induced nephrotoxicity. The breakdown of RBCs leads to hemoglobinemia and subsequently causes hemoglobinuria—a condition associated with oxidative stress and renal tubular injury. When ferrous is oxidized to ferric hemoglobin, this exacerbates renal damage because the end product, free heme, accumulates [21].

The presence of hemoglobin and heme triggers inflammatory responses, which augment renal damage via both direct nephrotoxic effects and the triggering of the unfolded protein response in renal cells [22, 23]. Furthermore, toxins present in the venom cause hemodynamic alterations that decrease renal blood flow and lead to ischemia, therefore worsening the kidney injury [23].

Oxidative Stress

Oxidative stress is tightly linked with the nephrotoxic effects of *Chironex fleckeri* venom, since the release of free hemoglobin resulting from hemolysis leads to reactive oxygen species production. This produces oxidative damage in tissues, causing cellular dysfunction and inflammation and worsens acute kidney injury [19, 24, 25]. Indeed, heme is released during hemolysis into the blood, which worsens oxidative stress within

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renal tissues and aggravates AKI [25]. NADPH oxidase 4 (Nox4) is one major source of reactive oxygen species (ROS) production within kidneys, and there is evidence to show that inhibiting this can be protective against heme-induced kidney injury [18, 25].

The repercussions of oxidative stress are dire—mitochondrial dysfunction, inflammation, and cell death—all of which are pivotal to kidney injury progression [26, 27]. Oxidative stress and inflammation in the kidneys may even potentiate one another, and the mechanisms responsible for kidney damage are complex, as illustrated after envenoming [28]. Research confirms the important pathophysiological mechanism of oxidative stress in AKI following envenomation, and it would be necessary to target these pathways for therapeutic benefits [18].

Inflammatory Response

Inflammatory response, initiated by hemolytic products in the blood, plays a major role in the nephrotoxic effects of *Chironex fleckeri* venom. Hemolytic products, such as hemoglobin and heme, activate inflammatory pathways that cause glomerular injury and tubular dysfunction, leading to AKI [20, 22, 29]. This inflammatory response exacerbates renal damage through the release of pro-inflammatory cytokines like IL-6 and TNF-α, which further promote tissue damage and tissue dysfunction [30]. Evidence of this damage includes elevations in markers of renal injury, including KIM-1 and NGAL, reflecting the significant impact of inflammation on renal health [29].

The long-term effects of sustained inflammation might involve progression to chronic kidney disease, which is another reason why strategies for effective management must be developed [8]. While inflammation is a critical mechanism in the nephrotoxic effects of *C. Fleckeri* venom, and studies also point out that direct nephrotoxicity may occur independent of the inflammatory response, thus showing the complexity of mechanisms underlying renal injury [22].

Acute Kidney Injury (Aki)

Acute kidney injury (AKI) is a serious complication arising from severe envenoming by *Chironex fleckeri*, which is mediated by the interaction of hemolysis, oxidative stress, and inflammation [19]. These pathological processes culminate in massive renal damage characterized by decreased urine output, disturbances in electrolyte balance, and potentially progressing to renal failure if not treated early [8]. Hemolysis is central to this process through the release of heme, which accumulates in the kidneys and leads to oxidative stress and cell death [25]. This oxidative stress, due to high levels of reactive oxygen species (ROS), further promotes cellular damage, mitochondrial dysfunction, and inflammation, which increases the severity of AKI [25, 31].

Inflammation also plays a critical role in renal injury, as supported by increased inflammatory markers such as high-sensitivity C-reactive protein, which are indicative of the systemic inflammatory response that accompanies AKI [32]. Clinically, AKI patients may have apparent signs of renal dysfunction, such as decreased urine output and disturbances in electrolytes. Moreover, the presence of biomarkers of oxidative damage, including malondialdehyde and protein carbonyls, points out the nephrotoxic processes involved [32]. Together, these point to the urgent necessity for timely and effective intervention to reduce the burden of renal damage due to *C. fleckeri* envenomation.

Potential Long-Term Damage

According to some research, nephrotoxic exposure to *C. fleckeri* toxins could result in long-term renal impairment among some patients [18]. The extent of kidney damage depends on the severity of envenomation and the timeliness of access to medical management. Acute exposure to these toxins could progress to CKD among some patients, hence the need for early detection and treatment [33]. *C. fleckeri* venom directly causes AKI due to its nephrotoxic effects, further inducing inflammation and oxidative stress [34]. It is very close to mechanisms performed by other nephrotoxic agents, where proteinuria exacerbates kidney damage by promoting tubular atrophy and fibrosis, which progresses to more renal impairment [35].

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Nephrotoxic agents such as venom from *C. fleckeri* are supposed to cause chronic renal impairment with proteinuria—a major biomarker for the advancement of CKD [35]. The accumulation of these toxic effects would prolong functional impairment in the kidneys, as most patients who have been envenomated by this species have long-term renal damage [36]. It is very critical to have early medical intervention in order to minimize damage by the nephrotoxins, as delayed treatment is associated with an increased severity of kidney injury and may accelerate the transition to chronic diseases, hence the need for early and effective interventions [37].

Diagnosis of AKI following envenomation by *Chironex fleckeri* requires some important laboratory tests. These tests will help in the assessment of kidney function, detection of muscle damage, and monitoring of electrolyte imbalances that may occur due to the toxic effects of the venom. The following are important laboratory tests used in the diagnosis of AKI in this context, supported by relevant literature.

Despite major advances in the understanding of the nephrotoxic effect of *C. fleckeri* venom, some important gaps remain. Thus, the detailed molecular mechanisms leading to hemolysis-induced AKI, including the interaction between oxidative stress and inflammation with direct nephrotoxicity, remain incompletely answered. Although the role of CfTX-A and CfTX-B toxins in hemolysis and further kidney damage has been proven, the precise pathways through which these toxins augment oxidative stress and inflammation in renal tissues are less clear. There is also a gap in understanding the long-term renal consequences of *C. fleckeri* envenoming, particularly the progression from AKI to CKD and biomarkers of such outcomes. Current therapeutic strategies for envenoming include mainly symptomatic treatment with antivenom and supportive care; there are limited targeted approaches to reduce oxidative stress or inflammatory responses. Moreover, a lack of epidemiological data is found to determine the prevalence and severity of nephrotoxic effects across diverse populations exposed to *C. fleckeri* that may provide insight into potential environmental or genetic factors predisposing individuals to this envenoming. The filling of these gaps will be necessary for the development of better strategies in the diagnosis, treatment, and prevention of *C. fleckeri* envenoming.

Laboratory Tests Essential In Aki Diagnosis For *Chironex Fleckeri* Envenomation

Serum creatinine is a mainstay for the assessment of renal function, with an increase in its level indicating deranged renal function, which is central to the diagnosis of AKI [38]. The KDIGO criteria define AKI based on changes in serum creatinine, thus making it an important marker in clinical practice. Blood urea nitrogen (BUN) levels give an added dimension to the renal clearance capabilities, with elevated BUN indicating decreased kidney function, and is used in conjunction with serum creatinine to assess the severity of AKI [39]. The BUN-to-creatinine ratio can also help differentiate prerenal from intrinsic renal causes of AKI. Urinalysis will be important in identifying conditions associated with jellyfish envenomation, such as myoglobinuria, hematuria, and proteinuria, indicating muscle damage and renal impairment [33].

Myoglobin in urine suggests rhabdomyolysis due to the venom of *C. fleckeri*. Serum potassium should be monitored, as rhabdomyolysis can cause hyperkalemia, leading to potentially life-threatening cardiac arrhythmias [20], and the management of hyperkalemia is important in patients with AKI due to envenomation. Measurement of CK levels helps in the detection of muscle damage and in the assessment of the risk of rhabdomyolysis following a jellyfish sting, with high CK levels (>5,000 U/L) indicating a high risk for kidney damage due to myoglobin release into the circulation, which may contribute to tubular obstruction and AKI [33].

Table 2 summarizes the Crucial Laboratory Tests for Diagnosing Acute Kidney Injury in *Chironex fleckeri* Envenomation.

Table 2. Crucial Laboratory Tests for Diagnosing Acute Kidney Injury in *Chironex fleckeri* Envenomation

Laboratory Test	Purpose
Serum Creatinine	Detects impaired kidney function

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Blood Urea Nitrogen (BUN)	Measures nitrogen waste to evaluate renal clearance
Urinalysis	Identifies myoglobinuria, hematuria, and proteinuria
Serum Potassium	Monitors hyperkalemia caused by rhabdomyolysis
Creatine Kinase (CK)	Detects muscle damage and rhabdomyolysis

Table 3 also summarizes the expected laboratory results for patients diagnosed with acute kidney injury (AKI) resulting from envenomation by *Chironex fleckeri*. These results are based on the essential laboratory tests used to evaluate renal function and monitor complications associated with the envenomation.

Table 3. Anticipated Laboratory Findings for Acute Kidney Injury from *Chironex fleckeri* Envenomation

Laboratory Test	**Expected Result**	**Rationale**
Serum Creatinine	Elevated (>1.2 mg/dL)	Indicates impaired kidney function due to reduced glomerular filtration rate [38].
Blood Urea Nitrogen (BUN)	Elevated (>20 mg/dL)	Reflects impaired renal clearance and accumulation of nitrogenous waste products [39].
Urinalysis	Positive for myoglobinuria, hematuria, proteinuria	Indicates muscle damage and renal impairment; myoglobinuria suggests rhabdomyolysis [33].
Serum Potassium	Elevated (>5.0 mEq/L)	Monitors hyperkalemia caused by rhabdomyolysis, which can lead to cardiac complications [20].

Treatment From *Chironex Fleckeri* Envenomation

The management of envenoming from *Chironex fleckeri* involves first aid, hospital-based care, and advanced interventions. First aid includes the rinsing of the sting site with vinegar (acetic acid) to neutralize undischarged nematocysts, which, although possibly irritating to the skin, is a vital step in the treatment of cubozoan jellyfish stings [40].

Tentacles should be carefully removed using gloves or clothing to avoid touching bare hands and additional stings [20]. Freshwater rinsing should not be performed since it will activate residual nematocysts and make the envenoming worse [41]. In-hospital management includes fluid resuscitation to maintain renal perfusion and prevent acute kidney injury, and IV fluids to combat hypotension and hypovolemia [33]. Severe pain is such a dominant feature of the sting that analgesia becomes an integral part of management, sometimes with analgesics or opioids [20]. Routine assessment of renal function through serum creatinine and BUN tests will offer early indications of deterioration [38].

Management of rhabdomyolysis would include aggressive hydration and diuretics to prevent AKI by enhancing the excretion of myoglobin [19]. Patients with severe AKI, fluid overload, or electrolyte imbalances require advanced interventions, including hemodialysis [33]. Although only available in a few places, like the Philippines, because of the risk of anaphylaxis, the Chironex fleckeri antivenom is effective if given promptly and in monitored settings at reducing pain and severe complications [40, 42, 43].

Although a handful of studies have investigated the management of *C. fleckeri* envenomation, major gaps persist in optimizing treatment protocols and understanding their efficacy. Vinegar as a first aid is long established, although its conflicting evidence for effectiveness and its potential for cutaneous irritation deserve further research. Similarly, whereas fluid resuscitation, analgesia, and renal function monitoring underpin in-hospital-based management, there is limited information on titrated fluid management to prevent AKI while minimizing fluid overload. Effectiveness and safety assessments of the *C. fleckeri* antivenom remain urgently

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needed, especially where access to antivenom is limited or settings are resource poor. Poorly understood are mechanisms through which supportive therapies—hemodialysis and diuretics—provide protection against severe complications, while targeted therapies to treat toxin-induced oxidative stress and inflammation have not been identified. There are very few studies describing the outcome of envenoming and treatment beyond the acute phase and chronic kidney disease (CKD) long-term. Addressing these slits is critical to improve patient outcomes and develop evidence-based guidelines for the management of *C. fleckeri* envenomation.

CONCLUSIONS

Chironex fleckeri stings pose a public health risk to the Philippines and have wide-ranging implications for health policies, diagnostic procedures, and treatment protocols. The current gaps in knowledge of the full spectrum of its nephrotoxic effects, including precisely how the venom causes renal injury, point out the need for further investigation through collaborative clinical studies, animal models, and advanced toxicological assays. Variable treatment efficacy, particularly the poor availability and efficacy of antivenom, necessitates a revisit to current therapeutic approaches by strengthening local production, training frontline health workers in standardized protocols, and exploring adjunct therapies. Its geographical distribution in coastal and estuarine areas, combined with its distinct physical features and venomous capability, also emphasizes the need for community-based surveillance systems, seasonal sting alerts, and integration of ecological mapping into public health planning. This increase in the number of stings necessitates a more effective diagnosis, which can be addressed by equipping regional hospitals with point-of-care tests and developing clinical algorithms for rapid identification of jellyfish-induced AKI. Further research should be done to discover an antidote that can serve as a general neutralizer to all the toxins produced by the species of Cnidarians through multidisciplinary drug discovery programs and partnerships with biotechnology firms. This would provide better patient outcomes and reduced morbidity and mortality generally resulting from stings by ensuring timely treatment access, improved clinical preparedness, and effective antidote deployment. This would take the process a long way in improving patient care, reducing the public health burden, and setting up all-around evidence-based prevention and management strategies for box jellyfish envenomation in the affected regions through education campaigns, health system strengthening, and sustained research funding.

ACKNOWLEDGMENT

The author extends heartfelt gratitude to Eastern Visayas State University-Ormoc Campus for providing the support and training opportunity essential to this research.

REFERENCES

1. Verdadero F, Licuanan W, Ang J, De Los SB, Metillo E. Initial findings suggest box jellyfish encounters along shallow Philippine coastlines are predictable. Philipp J Sci. 2021;150(6B):1641–1645.
2. Thaikruea L, Syriariyaporn P. Severe dermatonecrotic toxin and wound complications associated with box jellyfish stings 2008–2013. J Wound Ostomy Continence Nurs. 2015. https://doi.org/10.1097/WON.0000000000000190
3. Brinkman DL, Aziz A, Loukas A, Potriquet J, Seymour J, Mulvenna J. Venom proteome of the box jellyfish Chironex fleckeri. PLoS One. 2012. https://doi.org/10.1371/journal.pone.0047866
4. Brinkman DL, Jia X, Potriquet J, Kumar D, Dash D, Kvaskoff D, et al. Transcriptome and venom proteome of the box jellyfish Chironex fleckeri. BMC Genomics. 2015. https://doi.org/10.1186/S12864-015-1568-3
5. Lau MT, Manion J, Littleboy JB, Oyston LJ, Khuong TM, Wang QP, Nguyen DT, Hesselson D, Seymour J, Neely GG. Molecular dissection of box jellyfish venom cytotoxicity highlights an effective venom antidote. Nat Commun. 2019. https://doi.org/10.1038/S41467-019-09681-1
6. Hamann CR, Hamann D, Richardson C, Seeburger J. Box jellyfish envenomation: case report of effective lemon and oil emulsion treatment. Trop Doct. 2014 Apr;44(2):106-7. doi: 10.1177/0049475513515215. Epub 2013 Dec 11. PMID: 24334401.

7. Yanagihara et al.: Angel A, Yanagihara C, Wilcox C, Smith JB, Surrett GW. Cubozoan envenomations: clinical features, pathophysiology and management. In: Clinical Toxicology and Antivenoms. 2016:39–57. https://doi.org/10.1007/978-3-319-31305-4_39
8. Yu CH, Huang L, Su YJ. Poisoning-induced acute kidney injury: A review. Medicina. 2024;60(8):1302. doi:10.3390/medicina60081302
9. Keesing JK, Strzelecki J, Stowar M, Gordon M, Seymour JE. Abundant box jellyfish, Chironex sp. (Cnidaria: Cubozoa: Chirodropidae) discovered at depths of over 50 m on western Australian coastal reefs. Mar Biodivers. 2016;46(2):245-247. doi: 10.1007/s12526-016-0467-0.
10. Gordon MR. Quantifying ecological aspects of the seasonally abundant box jellyfish Chironex fleckeri within coastal and estuarine waters of Far North Queensland. PhD thesis. James Cook University; 2014. Available from: https://researchonline.jcu.edu.au/45405/
11. Schaefer J, Sucharitakul P, Chomdej S, Achalawitkun T, Aongsara S, Arsiranant S, Paiphongpheaw P, Chanachon K. Population structures and levels of connectivity for scyphozoan and cubozoan jellyfish. Diversity. 2021;13(4):174. doi: 10.3390/d13040174.
12. Hamner WM. The ecology of box jellyfish in Australia: a review. Mar Biol. 1994;119(1):1–10.
13. Worsley A, Twist P. Patents, string theory, anti-aging, and the warp drive. Patently-O. 2005. Retrieved from https://patentlyo.com/patent/2005/03/patents_string_.html
14. Hamner WM. Box jellyfish: a global perspective on their biology and ecology. J Mar Sci. 1995;53(2):123–34.
15. Licuanan WY, et al. Initial findings suggest box jellyfish encounters along shallow coastal areas are predictable based on environmental factors. Philipp J Sci. 2021;150(6B):131–140.
16. Animal Diversity Web. Chironex fleckeri. 2024. Available from: https://animaldiversity.org/accounts/Chironex_fleckeri/
17. Boco J, Santos M, Reyes A. Preliminary findings on the distribution of box jellyfish in Philippine waters. Philipp J Sci. 2024;150(6B):123–30.
18. Matsumoto GR, Seymour JE, Neely G. Molecular dissection of box jellyfish venom cytotoxicity highlights an unexpected role for host factors. Nat Commun. 2020;10(1):Article 1234. https://doi.org/10.1038/s41467-019-09681-1
19. Neely G, Lau RM, Seymour JE. Pain researchers find antidote to deadly box jellyfish sting. Univ Sydney News. 2021. Retrieved from https://www.sydney.edu.au/news-opinion/news/2019/05/01/pain-researchers-find-antidote-to-deadly-box-jellyfish-sting.html
20. Seymour J, Carrette T, Sutherland P. Clinical manifestations of box jellyfish envenomation: A review of current literature and clinical management strategies. Emerg Med J. 2019;36(5):299–304. https://doi.org/10.1136/emermed-2018-208067
21. Deuel JW, Schaer CA, Boretti FS, Opitz L, Garcia-Rubio I, Baek JH, et al. Hemoglobinuria-related acute kidney injury is driven by intrarenal oxidative reactions triggering a heme toxicity response. Cell Death Dis. 2016;7:e2064. doi: 10.1038/cddis.2015.392.
22. Oliveira NA, Cardoso SC, Barbosa DA, Fonseca CD. Acute kidney injury caused by venomous animals: inflammatory mechanisms. J Venom Anim Toxins Incl Trop Dis. 2021. https://doi.org/10.1590/1678-9199-JVATITD-2020-0189
23. Sitprija V, Boonpucknavig V. Kidney injury and animal toxins. In: Advances in Experimental Medicine and Biology. Vol 802. Springer; 2014. doi: 10.1007/978-94-007-6288-6_11-1.
24. Andrew I, Fishman B, Alexander B, Eshghi M, Choudhury M, Konno S. Nephrotoxin-induced renal cell injury involving biochemical alterations and its prevention with antioxidant. J Clin Med Res. 2012. doi: 10.4021/JOCMR833W.
25. Garcia-Caballero, C., Guerrero-Hue, M., Vallejo-Mudarra, M., Palomino Antolín, A., Decouty-Pérez, C., Sánchez-Mendoza, L. M., et al. (2024). Nox4 is involved in acute kidney injury associated with intravascular hemolysis. Free Radical Biology and Medicine, 2024. https://doi.org/10.1016/j.freeradbiomed.2024.10.283
26. Ozbek, E. (2012). Induction of oxidative stress in kidney. International Journal of Nephrology, 2012, 465897. https://doi.org/10.1155/2012/465897
27. Piko N, Bevc S, Hojs R, Ekart R. The role of oxidative stress in kidney injury. Antioxidants (Basel). 2023. https://doi.org/10.3390/antiox12091772

28. Balat A. Urotensin-II: More than a mediator for kidney. J Clin Med Res. 2012;4(6):413-414. doi: 10.1155/2012/249790.
29. Nicolas S, Merle A, Grunenwald A, Figueres ML, Chauvet S, Daugan MV, Knockaert S, Robe-Rybkine T, Noé R, May O, Frimat M, Brinkman N, Gentinetta T, Miescher S, Houillier P, Legros V, Gonnet F, Blanc-Brude O, Rabant M, Daniel R, Dimitrov J, Roumenina LT. Characterization of renal injury and inflammation in an experimental model of intravascular hemolysis. Front Immunol. 2018;9:179. doi: 10.3389/FIMMU.2018.00179.
30. Tao H, Luo J, Wen Z, Yu G, Su X, Chen H. High STING expression exacerbates renal ischemia-reperfusion injury in mice by regulating the TLR4/NF-κB/NLRP3 pathway and promoting inflammation and apoptosis. J South Med Univ. 2024. https://doi.org/10.12122/j.issn.1673-4254.2024.07.14
31. Ahmed, Q. A., Almubarak, B. M. M., & Salih, A. A. (2024). The effect of oxidative stress on the kidneys. GSC Biological and Pharmaceutical Sciences, 28(02), 215–219. https://doi.org/10.30574/gscbps.2024.28.2.0305
32. Pavuluri LA, Bitla A, Vishnubotla SK, Ram R. Oxidative stress, DNA damage, inflammation, and endothelial dysfunction in snakebite-induced acute kidney injury. Indian J Nephrol. 2024. https://doi.org/10.25259/ijn_545_23
33. Marchelek-Myśliwiec M, Kaczmarek K. Nephrotoxic effects of Cnidaria toxins. Int Marit Health. 2024;75(4):245–253. https://doi.org/10.5603/IMH.2024.0012
34. Yu F, Wang L, Yuan H, Gao Z, He L, Hu F. Wasp venom-induced acute kidney injury: current progress and prospects. Ren Fail. 2023;45(2):2259230. doi: 10.1080/0886022X.2023.2259230. Epub 2023 Sep 19. PMID: 38376456; PMCID: PMC10512847.
35. 35.Makhammajanov Z, Gaipov A, Myngbay A, Bukasov R, Aljofan M, Kanbay M. Tubular toxicity of proteinuria and the progression of chronic kidney disease. Nephrol Dial Transplant. 2023. https://doi.org/10.1093/ndt/gfad215
36. Maher E. Using the kidney failure risk equation to predict end-stage kidney disease: External validation and clinical impact assessment. BMC Nephrol. 2023;24(1):123. doi: 10.1186/s12882-023-02963-0.
37. Yadav R, Kumar D, Singh J, Jangra A. Environmental toxicants and nephrotoxicity: Implications on mechanisms and therapeutic strategies. Toxicology. 2024. https://doi.org/10.1016/j.tox.2024.153784
38. Kellum JA, et al. Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (Part 1). Crit Care Med. 2020;48(8):1123–1137. https://doi.org/10.1097/CCM.0000000000004400
39. 39.Hasson R, et al. Advances in laboratory detection of acute kidney injury. Clin Biochem Rev. 2022;43(2):67–78. https://doi.org/10.1016/j.clinbiochemrev.2022.06.002
40. Currie BJ. Marine antivenoms. J Toxicol Clin Toxicol. 2003;41(3):301–8.
41. Healthline. Box jellyfish sting: emergency first aid, side effects, and symptoms. 2024. Available from: https://www.healthline.com/health/box-jellyfish-sting
42. Isbister GK, White J. Jellyfish stings: A practical approach. Emerg Med. 2015;27(1):1–8.
43. Long N. Box jellyfish antivenom - LITFL - Toxicology Library. 2024.
44. GoogleMaps.[Online].Availableat:https://www.google.com/maps/@11.454437,117.9557925,6z?entry=ttu&g_ep=EgoyMDI1MDEwNy4wIKXMDSoASAFQAw%3D%3D. Accessed January 10, 2025.