Review Article

Journal of Advanced Veterinary Research
(2026) Volume 16, Issue 3, 456-464

Koi Herpesvirus Disease: Current knowledge and future perspectives in aquaculture health

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ARTICLE INFO

Recieved: 01 January 2026

Accepted: 23 January 2026

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Keywords:

Koi herpesvirus, Cyprinid herpesvirus 3, Disease, Aquaculture biosecurity, Virus.

ABSTRACT

Koi Herpesvirus Disease (KHVD) is a highly contagious viral disease of common carp (*Cyprinus carpio*) and koi, caused by Cyprinid herpesvirus 3 (CyHV-3). This disease can cause high mortality, especially in young fish, significantly impacting the global fisheries economy. KHVD is typically characterized by epithelial lesions on the gills, skin ulceration, kidney damage, and basophilic intranuclear inclusions in epithelial cells, a hallmark of active infection. Clinical symptoms include lethargy, loss of appetite, impaired swimming behavior, gill hyperemia, excessive mucus production, and skin discoloration. Diagnosis of KHVD requires a combination of methods. Clinical and histopathological examinations can provide early indications, while serological and molecular detection methods such as PCR or qPCR are used to confirm acute and latent infections, including in asymptomatic carriers. Key risk factors include fish age, optimal water temperature for the virus (18–28°C), population density, environmental quality, and culture practices. Fish that survive infection can become latent carriers and potentially transmit the virus again, exacerbating the disease outbreak. Controlling KHVD requires an integrated strategy, including biosecurity, quarantine of new fish, management of density and water quality, and vaccination using live attenuated, inactivated, or subunit/DNA vaccines. This strategy aims to suppress virus spread, increase fish survival, and minimize economic losses. A thorough understanding of the pathology, epidemiology, and transmission mechanisms of KHVD are essential for effective and sustainable disease management in carp and koi aquaculture.

Introduction

Koi Herpesvirus Disease (KHVD) is a highly contagious viral disease of koi and common carp (*Cyprinus carpio*), with high mortality rates, often exceeding 80%, resulting in significant economic losses for the global aquaculture industry (Klafack *et al*., 2022). The disease is of concern due to its rapid and widespread spread, affecting fish populations in both commercial aquaculture and natural waters (Mahmud *et al*., 2025). The first cases of KHVD were reported in Israel and the United States in 1998, and since then the disease has spread to various regions, including Asia and the Middle East, posing significant challenges to fish health management and food safety (EFSA *et al*., 2017). In addition to its economic impact, KHVD also has ecological consequences, potentially reducing wild fish populations and disrupting the balance of aquatic ecosystems (Rathore *et al*., 2012).

The causative agent of KHVD is Cyprinid herpesvirus 3 (CyHV-3), a member of the Alloherpesviridae family, which exhibits a specific tropism for gill tissue, kidneys, and skin epithelium (Rakus *et al*., 2013). The virus is capable of entering a latent phase in carrier fish, allowing apparently healthy fish to transmit the infection to other populations (Tolo *et al*., 2021a). This biological characteristic complicates disease control, as spread depends not only on fish showing clinical symptoms but also on latent carriers that can trigger secondary outbreaks (Gotesman *et al*., 2013). Furthermore, latent infection can be reactivated by stressors such as fluctuations in water temperature, high fish density, or poor environmental quality, which in turn increases the risk of mass mortality in aquaculture ponds (Panicz *et al*., 2022).

The spread of KHVD is significantly influenced by environmental factors and human activities (Matsui *et al*., 2008). The international ornamental fish trade, the transportation of live fish between countries, and intensive aquaculture practices accelerate the spread of the virus across regions (Su and Su, 2018). Furthermore, climate change, which causes fluctuations in water temperature, can expand conditions favorable for virus replication, increasing the risk of outbreaks in both natural waters and aquaculture ponds (Omori and Adams, 2011). Unfavorable environmental conditions, such as poor water quality, high fish densities, and inadequate nutrition, also increase fish susceptibility to infection (Senthamarai *et al*., 2023). These factors emphasize the importance of evidence-based disease management, including strict biosecurity practices, routine fish population monitoring, and early detection of infection (Rathore *et al*., 2012).

The impact of KHVD on the aquaculture industry is not only direct, such as high mortality and stock loss, but also includes indirect effects, including additional costs for quarantine, vaccination, water quality management, and restrictions on the trade of live fish (EFSA *et al*., 2017). Ecologically, this virus has the potential to affect wild fish populations and alter the structure of aquatic communities, which in turn can affect ecosystem function in the long term (Tolo *et al*., 2023). This review aimed to present an up-to-date synthesis of KHVD, including virus characteristics, infection mechanisms and pathogenesis, clinical manifestations, diagnostic methods, control strategies, and future research directions. With a comprehensive understanding, this review is expected to become a scientific reference source for researchers, aquaculture practitioners, and policymakers to prevent, manage, and minimize the impact of KHVD effectively and sustainably, both from an economic and ecological perspective.

Etiology

Koi herpesvirus (KHV), scientifically known as CyHV-3, is the primary cause of KHVD, a highly contagious viral infection in common carp (*Cyprinus carpio*) and ornamental koi (Rathore *et al*., 2012). Taxonomically, this virus belongs to the family Alloherpesviridae, genus Cyprinivirus, with the species CyHV-3 (Kim *et al*., 2020). The family Alloherpesviridae belongs to the order Herpesvirales, which includes all herpesviruses with

ISSN: 2090-6277/2090-6269/

large double-stranded DNA (dsDNA) genomes and the ability to establish latent infections in poikilothermic vertebrate hosts, such as fish and amphibians (Hanson *et al*., 2011).

Morphologically, CyHV-3 is an enveloped virus with an icosahedral shape and a diameter of approximately 170–200 nanometers (Michel *et al*., 2010a). The virion consists of three main components: the capsid, the tegument, and the lipid envelope (Boutier *et al*., 2015). The capsid protects the viral DNA genome, while the tegument contains proteins that regulate viral gene expression and initial interactions with host cells (Michel *et al*., 2010b). The lipid envelope, derived from the host cell membrane during virus assembly, carries surface glycoproteins crucial for viral binding and entry into target cells (Brogden *et al*., 2015). This layered structure not only provides mechanical resistance but also allows CyHV-3 to adapt to a variety of aquatic environmental conditions (Graham *et al*., 2021).

The CyHV-3 genome is composed of linear double-stranded DNA of approximately 295 kilobase pairs (kbp) in length, making it one of the largest herpesvirus genomes infecting fish (Gao *et al*., 2018). Sequence analysis revealed over 150 open reading frames (ORFs) encoding proteins essential for replication, assembly, and regulation of latent infection (Neave *et al*., 2017). Most genes show conservative homology with other fish herpesviruses, such as Cyprinid herpesvirus 1 (CyHV-1) and Cyprinid herpesvirus 2 (CyHV-2), but several genes are unique to CyHV-3 (Davison *et al*., 2013). These specific genes are thought to play a role in virulence, adaptation to environmental temperature fluctuations, and evasion of the host immune response, explaining the virus's ability to persist in a wide range of aquatic ecosystem conditions and establish a latent infection that can be reactivated upon increasing temperatures (Rakus *et al*., 2013).

Phylogenetic analysis based on conservative genes, such as Deoxyribo Nucleic Acid (DNA) polymerase and terminase, indicates that CyHV-3 forms a distinct clade within the genus Cyprinivirus, distinct from other species in the family Alloherpesviridae (de Lucca Maganha *et al*., 2022). Molecular studies of various virus isolates have revealed significant genetic variation among strains from Asian, European, and American populations (Gotesman *et al*., 2013). Asian strains are generally considered more virulent, while European strains have relatively stable genetic characteristics (Kafi *et al*., 2025). Several studies have also identified hybrid strains resulting from recombination between Asian and European lineages, indicating adaptive evolution of the virus to the host and aquatic environment (Bavarsad *et al*., 2024; Gao *et al*., 2018; Sunarto *et al*., 2011). This genetic variability impacts differences in mortality rates, transmission capacity, and vaccine effectiveness in fish populations across geographic regions.

Host range

Koi herpesvirus has a limited host range, affecting only fish of the Cyprinidae family, primarily common carp (*Cyprinus carpio*) and its ornamental variety, the koi (Hu *et al*., 2021). Experimental studies and field observations indicate that this species is the only naturally susceptible host to productive infection by CyHV-3, with mortality rates reaching 80–100% under favorable environmental conditions, such as water temperatures between 18–28°C (Gaede *et al*., 2017).

Several studies have evaluated the ability of CyHV-3 to infect non-cyprinid fish species, including freshwater fish such as tilapia (*Oreochromis niloticus*), silver carp (Carassius auratus), and freshwater predatory fish, both in vivo and in vitro (Rakus *et al*., 2013; Suprapto *et al*., 2015; Tolo *et al*., 2021a). The results showed that the virus does not replicate effectively and does not cause the typical clinical symptoms of KHVD in species other than *Cyprinus carpio* (Tolo *et al*., 2021b). However, some fish in the Cyprinidae family can act as latent carriers without showing clinical signs, allowing passive spread of the virus through contact with susceptible carp or koi populations (Kempter *et al*., 2012).

This limited host range is related to the specificity of the cellular receptor and the viral entry mechanism, which allows CyHV-3 to efficiently recognize the gill, kidney, and skin epithelial cells of common carp, but is unable to establish productive infection in non-cyprinid host cells (Hedrick *et al*., 2005). This also explains why CyHV-3 has not shown evidence of cross-species transmission in the natural environment, allowing disease control efforts to focus on common carp and koi populations, including close monitoring of the seed and ornamental fish supply chains (Kim *et al*., 2020). The overall ecology and transmission pathways of Koi herpesvirus (Cyprinid herpesvirus 3) in common carp and koi are summarized in Figure 1.

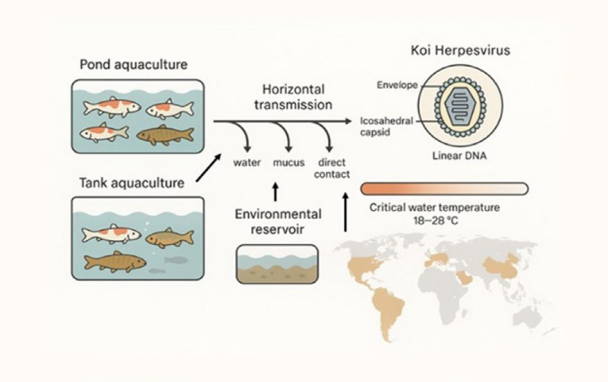

Figure 1. Schematic overview of the ecology and transmission cycle of koi herpesvirus (Cyprinid herpesvirus 3) in common carp and koi.

Epidemiology

KHVD is a highly contagious viral disease of common carp (*Cyprinus carpio*) and its ornamental variety, the koi (Zrnčić *et al*., 2020). Since its first report in the late 1990s, the disease has spread widely and is now considered one of the most economically damaging fish diseases worldwide (Iida and Sano, 2005). The causative agent, CyHV-3, has been detected in various regions, including Asia, Europe, the Middle East, and the Americas, demonstrating a high potential for global spread through the ornamental fish trade and the movement of food fish fry (Gotesman *et al*., 2013).

Table 1 presents a summary of the geographic distribution and epidemiological factors of KHVD in various countries, along with the year of the first reported disease incidence. The table highlights the chronological emergence of KHVD, beginning with the first recognized outbreak in Israel and the United States in 1998, followed by rapid international dissemination through ornamental fish trade and movement of infected carp and koi (Amin *et al*., 2018; Gilad *et al*., 2002). Each country listed demonstrates distinct epidemiological patterns influenced by fish population types, environmental conditions, and management practices (EFSA *et al*., 2017).

Overall, KHVD outbreaks were frequently associated with high-density aquaculture systems, uncontrolled fish transportation, and environmental stressors such as fluctuating water temperatures within the virus's optimal replication range (18–28°C) (Bergmann *et al*., 2020). Several countries, including Taiwan, South Korea, and Indonesia, reported the presence of latent carriers, which play a crucial role in maintaining the virus within farmed populations and facilitating repeated outbreaks (Kim and Kwon, 2013; Sunarto *et al*., 2011; Tu *et al*., 2004).

Recent reports from Europe (e.g., the United Kingdom, Germany, the Netherlands, and the Czech Republic) underscore the ongoing challenges in surveillance and control, with some regions employing intensive monitoring and genomic tracking to understand viral diversity and transmission pathways (Bercovier *et al*., 2005; Kane *et al*., 2025; Schlotfeldt, 2004; Úlehlová *et al*., 2023). Meanwhile, emerging data from Iran and Iraq indicate that KHVD continues to expand geographically, with newly identified genotypes and first-time detections recorded in the past few

years (Al-Jaf *et al*., 2024).

Environmental factors significantly influence the dynamics of KHVD epidemics. CyHV-3 exhibits an optimal temperature range for infection between 18–28°C, where viral replication is rapid and mortality is highest (Tolo *et al*., 2021). At temperatures below 13°C, viral activity slows, allowing latent infection that can be reactivated when temperatures rise again (Lin *et al*., 2017). Factors such as environmental stress, high population densities, water temperature fluctuations, and poor water quality have been shown to increase fish susceptibility to infection (Su and Su, 2018).

In addition, horizontal transmission through direct contact between fish, contaminated water, and unsterilized aquaculture equipment is a major route of virus spread (EFSA *et al*., 2017). Studies have shown that CyHV-3 can persist in water for several days, depending on temperature and organic matter content, increasing the potential for transmission in open aquatic environments (Honjo *et al*., 2012). Although evidence for vertical transmission from parent to offspring remains weak, the presence of latent carriers adds complexity to disease control in intensive aquaculture systems (Tadmor-Levi *et al*., 2017).

Globally, CyHV-3 is recognized by the World Organization for Animal Health (WOAH/OIE) as an important notifiable viral disease of freshwater fish (WOAH, 2022). This status reflects the threat of KHVD to international trade and the sustainability of the aquaculture industry (Rakus *et al*., 2013). Surveillance and genomic mapping of the virus in various countries have shown regional genetic variation, indicating the virus's ability to adapt to local environmental conditions and different farming practices (WOAH, 2019).

Pathogenesis

The pathogenesis of KHVD involves a complex interaction between the virus, host cells, and environmental factors, which determine the level of mortality and the extent of tissue damage (Cano *et al*., 2024). Infection begins when CyHV-3 virions attach to the surface of epithelial cells in the gills, skin, or digestive tract of susceptible fish (Gotesman *et al*., 2013). Glycoproteins on the viral surface play a role in specific binding to cell receptors, allowing the virus to enter the cell through endocytosis or membrane fusion, thus reaching the host cytoplasm (Banerjee and Mukhopadhyay, 2016).

After entering the host cell, the virus undergoes initial replication in the nucleus, followed by the expression of early, intermediate, and late genes encoding structural proteins, replication regulators, and virulence factors (Neave *et al*., 2017). Rapid replication in the gill and kidney epithelial tissues leads to epithelial cell necrosis, vascular damage, and impaired osmoregulatory and respiratory function (Siwicki *et al*., 2012). Because the gills are the primary target, infected fish often exhibit symptoms such as gill hyperemia, epithelial erosion, and impaired gas exchange, which contribute to high mortality, especially at an optimal temperature of 18–28°C (Putra *et al*., 2022).

In addition to direct damage from viral replication, KHVD pathogenesis is also influenced by the host immune response (Fujioka *et al*., 2015). CyHV-3 infection triggers activation of the innate immune system through the recognition of pathogen-associated molecular patterns (PAMPs) by Toll-like receptors (TLRs) and the induction of type I interferon production (Lu *et al*., 2024a). This activation promotes the expression

Table 1. Geographic distribution and epidemiology of KHVD.

Country	Reporting year	Fish population status	Main distribution routes	Environmental factors	Additional notes	Reference
Israel	1998 (first detection)	Wild & farmed koi/ common carp	Ornamental trade, fish movement	Temperature 18–28°C supports viral replication	First global KHVD case; baseline for global spread	(Amin *et al*., 2018)
United States of America	1998 (initial cases) subsequent reports since 1998	Wild & ornamental koi	International trade, transportation	Transport stress, high density, temperature effects	Early large-scale mortalities; continued surveillance in North America	(Gilad *et al*., 2002)
Japan	1999 (rapid early spread in Asia)	Commercial & ornamental koi	International trade	Water temperature fluctuations, environmental stress	Rapid dissemination across East Asia after 1999	(Aoki *et al*., 2007)
Taiwan	2000	Ornamental koi & goldfish	Ornamental trade	Water temperature influences viral replication	Reports of latent carriers in infected populations	(Tu *et al*., 2004)
South Korea	2000	Food-fish aquaculture & koi	Live fish trade	High fish density, poor water quality	Latent carriers increase outbreak risk	(Kim and Kwon, 2013)
Indonesia	2002 (initial report)	Farmed koi/goldfish & released populations	Fry movement, domestic trade	Poor water quality, high stocking density	Horizontal transmission dominant in intensive systems	(Sunarto *et al*., 2011)
Germany	2004 (initial detection) ONgoing genomic monitoring	Farmed and ornamental fish collections	Fish transportation & trade	Optimal replication temperature; regional genetic variation	Genomic monitoring indicates regional diversity; active reference labs	(Schlotfeldt, 2004)
Poland	2004 - continuous surveillance	Farmed goldfish & koi	Trade and transportation	Temperature fluctuations, density changes	Surveillance conducted by national authorities and WOAH	(Bergmann *et al*., 2006)
Netherlands	2005-intensive monitoring	Intensive aquaculture & trade	Trade and transportation	Water quality and population density	EU surveillance and prevention programs implemented	(Bercovier *et al*., 2005)
Czech Republic	Cluster cases (2018–2020)	Local pond outbreaks	Local fish movement, direct contact	Local environmental factors (temperature, density)	Cluster analysis shows repeated localized spread (2018–2020)	(Úlehlová *et al*., 2023)
United Kingdom (England & Wales)	Outbreak reports 2024–2025 (latest updates)	Multiple confirmed outbreak sites	Fish movement, domestic/ornamental trade	Temperature 16–28°C during clinical expression	FHI (UK) updated infected-site listings in 2024–2025; control actions applied	(Kane *et al*., 2025)
Iran	Evidence since ~2021; national surveillance studies 2024–2025	Widespread aquaculture sites affected	Fry movement, local trade	Farm density, temperature variation; Asian genetic lineages detected	National surveillance (hundreds of farms) identified Asian genotypes 1/2	(Kafi *et al*., 2025)
Iraq (Garmian)	First report in 2024	Local carp/koi populations	Fish release & local trade	Local environmental and management factors	First recorded detection in the Garmian region (2024)	(Al-Jaf *et al*., 2024)

of antiviral genes and the recruitment of immune cells such as macrophages and dendritic cells (Michel *et al*., 2010a). However, the virus also produces proteins capable of suppressing MHC expression, interferon signaling, and the apoptosis pathway, thus aiding immune evasion and allowing latent infection to occur (Zhang *et al*., 2022).

Latent infection is a hallmark of CyHV-3 pathogenesis. The virus can remain dormant in tissues such as the kidneys or lymphoid organs when water temperatures are low (<13°C) (Zheng *et al*., 2017). When environmental conditions return to optimal levels or the fish experience stress, the virus can reactivate, triggering active replication and spread to other fish populations (Waltzek *et al*., 2005). This mechanism explains the epidemiological pattern of KHVD, where apparently healthy carrier fish become sources of infection for new colonies (Yuasa *et al*., 2013).

Typical histopathological lesions of KHVD include gill epithelial necrosis, renal tubular degeneration, and intranuclear inclusions in epithelial cells (Pikulkaew *et al*., 2009). In fish killed by acute infection, nearly all hematopoietic and epithelial organs show severe damage, which accelerates death (Negenborn *et al*., 2015). Clinical severity and mortality are determined by the interaction between environmental factors (temperature, water quality, population density) and the virulence of the virus and the host immune response (Panicz *et al*., 2022).

Immune response

CyHV-3 infection in common carp (*Cyprinus carpio*) and koi stimulates a complex host immune system activation, involving both innate and adaptive immune mechanisms (Rakus *et al*., 2012). This immune response plays a critical role in determining the outcome of the infection, including virus elimination, control of replication, and the establishment of latent infection (Rakus *et al*., 2009).

Innate immune response

The innate immune response serves as the first line of defense against CyHV-3 infection (Jia *et al*., 2021). The virus is recognized by pattern recognition receptors (PRRs) on host cells, specifically Toll-like receptors (TLRs), which detect viral pathogen-associated molecular patterns (PAMPs) (Carty and Bowie, 2010). TLR activation triggers the Nuclear Factor-kappa B (NF-κB) pathway and interferon regulators, which then stimulate the production of type I interferon (IFN-I) and pro-inflammatory cytokines (Severa and Fitzgerald, 2007). IFN-I promotes the expression of antiviral genes (interferon-stimulated genes, ISGs) that suppress viral replication and limit its spread to other cells (Lang *et al*., 2022).

In addition, phagocytic cells such as macrophages and neutrophils play a role in engulfing free viruses and infected host cells, as well as producing reactive oxygen species and antimicrobial peptides to inhibit viral replication (Rakus *et al*., 2013). Activation of natural killer (NK)-like cells in fish is also thought to function to destroy infected cells before the virus can replicate massively (Tolo *et al*., 2021a).

Adaptive immune response

The adaptive immune system in fish becomes active several days after initial infection (Adamek *et al*., 2014). This response involves B and T lymphocytes, which are responsible for the production of specific antibodies, as well as effector cells (Baloch *et al*., 2022). B lymphocytes produce immunoglobulin M (IgM) specific to CyHV-3, which plays a role in neutralizing viral particles, facilitating phagocytosis, and preventing infection of new host cells (Gao *et al*., 2023). In addition, Cluster of Differentiation 4–positive ($CD4^+$) and Cluster of Differentiation 8–positive ($CD8^+$) T cell responses are also involved in viral antigen recognition and the elimination of infected cells (Rakus *et al*., 2012).

This immune system adaptation also allows for the formation of immunological memory, so that fish that recover from the initial infection have partial resistance to reinfection (Rakus *et al*., 2013). However, the virus is able to evade the adaptive immune response through immunosuppressive mechanisms, including suppression of Major Histocompatibility Complex (MHC) class I and II expression, cytokine modulation, and regulation of host cell apoptosis (Sausen *et al*., 2021). This evasion strategy plays a role in CyHV-3's ability to establish a latent infection, particularly in the kidneys and lymphoid organs, which can be reactivated when environmental conditions are favorable (Ouyang *et al*., 2013).

Pathology

KHVD pathology results from a complex interaction between viral replication, host immune response, and environmental conditions, which together determine the severity of lesions, organ damage, and high mortality in fish (Cano *et al*., 2024).

The gills are the primary organ infected, serving as both the entry route and the initial site of viral replication (Ababneh *et al*., 2020). Histopathological examination reveals extensive epithelial necrosis, loss of gill lamellar structure, and epithelial cell hyperplasia as a compensatory response to the damage (Bavarsad *et al*., 2024). Infiltration of mononuclear and polymorphonuclear inflammatory cells also occurs, exacerbating the tissue damage (Tu *et al*., 2004). The presence of basophilic intranuclear inclusions in epithelial cells indicates active viral replication (Badhusha *et al*., 2022). This gill damage impairs gas exchange and osmoregulation, contributing to clinical symptoms such as hypoxia and high mortality (Adamek *et al*., 2021).

The kidneys are also a vital organ affected by infection (Gray *et al*., 2002). Histopathological examination reveals degeneration and necrosis of the renal tubules, accumulation of cellular debris, and infiltration of lymphocytes and macrophages into the interstitium (Okoh *et al*., 2021). Damage to hematopoietic cells reduces the host's immune capacity, increasing susceptibility to secondary infections (Hedrick *et al*., 2006).

Lymphoid organs and the liver also show characteristic pathological changes (Rakus *et al*., 2013). The liver exhibits sinusoidal hyperemia and mild to moderate hepatocyte degeneration, while lymphocyte counts are decreased in lymphoid organs such as the spleen and thymus, reflecting the immunosuppressive effects of the virus (Gotesman *et al*., 2013). Mononuclear cell infiltration in lymphoid organs indicates a compromised immune response due to viral evasion mechanisms (Wang *et al*., 2024).

In addition, the skin and fins also develop pathological lesions, including epidermal ulceration, dermal necrosis, and inflammatory cell infiltration. Excessive mucus production is a protective response to epithelial damage, but this ulceration can facilitate secondary bacterial infections, potentially increasing mortality (Raj *et al*., 2011). The sequence of Koi herpesvirus entry, replication, tissue damage, latency, and temperature-driven reactivation in carp is summarized in Figure 2.

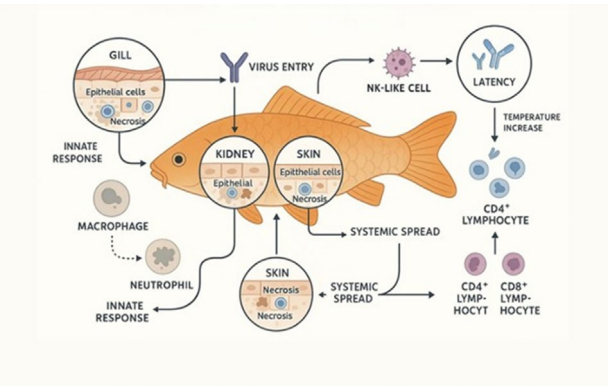

Figure 2. Schematic pathogenesis of koi herpesvirus in carp and associated host immune responses.

Clinical signs

CyHV-3 infection in common carp (*Cyprinus carpio*) and koi exhibits characteristic clinical symptoms that often precede mass mortality in susceptible populations (Panicz *et al*., 2022). These symptoms appear acutely, usually within 5–10 days of exposure, with severity influenced by the age of the fish, its physiological condition, and environmental factors such as water temperature and population density (Tolo *et al*., 2021a).

Early symptoms of infection include lethargy, decreased appetite, and reduced swimming activity, reflecting systemic stress from the viral infection and metabolic disturbances (Bavarsad *et al*., 2024). At the gill level, the virus causes hyperemia and epithelial erosion, disrupting gas exchange and causing tissue hypoxia, often causing fish to float at the surface or swim abnormally (Negenborn *et al*., 2015).

In addition to respiratory distress, infected fish also exhibit external lesions such as ulcerations on the skin and fins, as well as tissue thickening with excessive mucus production (He *et al*., 2023). These lesions reflect direct damage from the virus and increase the risk of secondary infection by opportunistic bacteria (Adamek *et al*., 2013). Some fish also experience changes in skin color, from pale to reddish patches, associated with local hyperemia and inflammation (Adamek *et al*., 2022).

Systemically, CyHV-3 infection can cause disorientation, difficulty swimming, and decreased responsiveness to external stimuli, due to impaired function of vital organs such as the kidneys and liver, as well as hypoxia caused by gill damage (Gotesman *et al*., 2013). High mortality can occur within 7–14 days at an optimal temperature of 18–28°C, while surviving fish often become latent carriers that can reactivate the infection when environmental conditions are favorable (Uchii *et al*., 2014).

The clinical symptoms of KHVD are characteristic but can mimic other diseases such as Spring Viremia of Carp Virus (SVCV) or secondary bacterial infections (Baloch *et al*., 2022). Therefore, a definitive diagnosis requires laboratory confirmation through histopathology, serology, or molecular detection of the virus (Kim *et al*., 2020). Nevertheless, recognizing clinical signs remains a crucial initial step in disease monitoring, particularly in intensive aquaculture and the international ornamental fish trade (El-Matbouli *et al*., 2007).

Diagnosis

The diagnosis of KHVD requires a multidisciplinary approach because the clinical symptoms can resemble other viral or bacterial infections in common carp (*Cyprinus carpio*) and koi (Al-Jaf *et al*., 2024). Accurate diagnosis combines clinical observation, histopathological examination, serological analysis, and molecular methods, allowing for specific, sensitive, and quantitative identification of the infection (Cabon *et al*., 2017).

Clinical diagnosis

Clinical symptoms of KHVD appear acutely, generally 5–10 days after exposure to the virus (Michel *et al*., 2010a). Infected fish exhibit lethargy, decreased appetite, impaired swimming, and changes in skin and fin color (Bergmann *et al*., 2020). External lesions, including skin ulceration, gill hyperemia, and excessive mucus production, are characteristic signs of infection (Kim *et al*., 2020). While clinical observation can provide an early indication, diagnosis based on symptoms alone is not specific enough because they can mimic other diseases such as SVCV or secondary bacterial infections (Gotesman *et al*., 2013).

Histopathological diagnosis

Histopathological examination is an important method for confirming KHVD (Gray *et al*., 2002). Analysis of gill tissue, kidney, skin, and lymphoid organs reveals epithelial necrosis, epithelial cell hyperplasia, inflammatory cell infiltration, and basophilic intranuclear inclusions, all indicators of active viral replication (Citarasu, 2024). These findings not only confirm infection but also provide information on viral tropism, the extent of tissue damage, and disease severity, which are valuable in assessing strain virulence and the effectiveness of experimental vaccines or therapies (Ronsmans *et al*., 2014).

Serological diagnosis

Serological methods, such as enzyme-linked immunosorbent assay (ELISA), are used to detect specific antibodies to CyHV-3 (Bergmann *et al*., 2017). This approach is effective in identifying fish that have been previously infected or are latent carriers, as well as in evaluating the immune status of aquaculture populations (Adkison *et al*., 2005). However, the sensitivity of serology to acute infection is limited because antibodies take time to develop and may not be detectable early in the infection (Bergmann *et al*., 2017).

Molecular diagnosis

Molecular approaches have become the gold standard in KHVD diagnosis because they offer high sensitivity and specificity (Bergmann *et al*., 2010). Various techniques have been developed to detect CyHV-3, including conventional Polymerase Chain Reaction (PCR), which allows identification of viral DNA from gill, kidney, or skin tissue in cases of acute or latent infection (Clouthier *et al*., 2017). In addition, quantitative PCR (qPCR) is used to determine the number of viral copies in tissues, making it useful in assessing the burden of infection and the potential for viral spread (Loose *et al*., 2020). Rapid methods such as Loop-mediated Isothermal Amplification (LAMP) are also available and can be applied directly in the field for efficient virus detection (Bavarsad *et al*., 2025). Gene targets frequently used in PCR or qPCR include ORF25, thymidine kinase (TK), and glycoprotein B (gB) of CyHV-3 (Monaghan *et al*., 2016). The advantage of these molecular methods lies in their ability to detect the virus even in fish without clinical symptoms, thus supporting biosecurity efforts and preventing the spread of disease in fish farming (Tolo *et al*., 2021a).

Differential diagnosis

In clinical and laboratory practice, the diagnosis of KHVD requires a differential approach, as the clinical symptoms and tissue lesions can mimic other infections (EFSA *et al*., 2017). KHVD must be distinguished from secondary bacterial infections and other viral diseases, particularly SVCV, which also affects goldfish (*Cyprinus carpio*) and koi (Machat *et al*., 2022).

Secondary bacterial infections frequently occur in fish infected with KHVD, exploiting epithelial damage to the skin, fins, or gills (Kane *et al*., 2025). Clinically, these infections may be present as ulcerations, mucopurulent exudates, or localized tissue erosions similar to KHVD lesions (Rakus *et al*., 2013). The main differences lie in the etiology and histopathological findings: bacterial infections are characterized by the presence of bacterial colonies in the tissues and a predominant polymorphonuclear inflammatory cell infiltration, whereas KHVD exhibits basophilic intranuclear inclusions in epithelial cells and extensive necrosis without primary bacterial colonization (El-Din, 2011).

SVCV produces clinical symptoms similar to KHVD, including lethargy, anorexia, hemorrhage, and high mortality (Kim *et al*., 2020). Pathological differences can be observed in the target organs and distribution of lesions. KHVD typically causes necrosis of the gills, kidneys, and epidermis, accompanied by characteristic intranuclear inclusions in epithelial cells (Gomez *et al*., 2011). In contrast, SVCV more frequently causes systemic hemorrhagic lesions, hematopoietic cell degeneration, and more prominent vascular changes (Ashraf *et al*., 2016). Molecular methods such as PCR or qPCR, specific for each virus, are essential tools for definitively differentiating the two diseases (Donohoe *et al*., 2015).

Differential diagnosis is crucial to ensure appropriate interventions, whether in clinical management, quarantine measures, or control strategies in intensive culture systems (Panicz *et al*., 2022). The combination of clinical observation, histopathological examination, and molecular detection allows for specific identification of KHVD, distinguishing it from secondary bacterial infections or other viral diseases, while preventing misdiagnosis that could increase the risk of disease spread (Sunarto *et al*., 2011).

Transmission

KHVD is a highly contagious viral disease of common carp (*Cyprinus carpio*) and koi (Colorio *et al*., 2020). The virus can spread through various transmission routes, both direct and indirect, which plays a crucial role in the disease's epidemiology and control strategies (Taylor *et al*., 2011).

The primary route of KHVD transmission is direct contact between fish (Taylor *et al*., 2010). The virus can be transmitted through water contaminated with secretions and excretions from infected fish, including mucus, urine, and gamete products (Gotesman *et al*., 2013). Physical contact between fish in ponds or culture tanks allows rapid spread, especially under high population densities (Bavarsad *et al*., 2024).

In addition to direct contact, horizontal transmission through water also plays a significant role in the spread of KHVD (Matras *et al*., 2019). The virus can persist in water for a period of time, allowing unexposed fish to become infected even without direct contact (Rakus *et al*., 2013). Environmental factors such as temperature, pH, and water quality influence the virus's stability and transmission efficiency (Honjo *et al*., 2010). Optimal water temperatures between 18–28°C support viral replication and accelerate transmission between fish (Joehnk *et al*., 2020).

Vertical transmission through the reproductive tract has also been reported, although the mechanism requires further investigation (Gao *et al*., 2023). The virus can attach to eggs or sperm, potentially making hatching fish latent carriers that can reactivate the infection when environmental conditions are favorable (Ito *et al*., 2024).

In addition, mechanical vectors such as farming equipment, fish tissue, or humans unhygienically moving fish or water can contribute to the spread of KHVD (Matras *et al*., 2019). This indirect transmission pathway emphasizes the importance of implementing biosecurity, sterilizing equipment, and quarantining new fish to prevent the virus from entering healthy ponds or farming systems (Tolo *et al*., 2021a).

Risk factors

KHVD is influenced by various risk factors that determine the level of infection, disease severity, and spread in common carp (*Cyprinus carpio*) and koi populations (Samsing *et al*., 2021). Understanding these factors is essential for designing effective control and prevention strategies in intensive aquaculture (Piačková *et al*., 2013).

One important risk factor is the age of the fish and their immune status (Ilouze *et al*., 2010). Young fish, such as fry and juveniles, are more susceptible to infection because their immune systems are not yet fully mature (Ronsmans *et al*., 2014). Conversely, adult fish that have been previously exposed or vaccinated may develop relative resistance or act as latent carriers, potentially reactivating the infection when stressed (Tolo *et al*., 2023).

Water temperature is a major environmental factor influencing KHVD risk (Lin *et al*., 2017). CyHV-3 has optimal activity between 18 and 28°C, making fish cultured within this temperature range more susceptible to infection (Michel *et al*., 2010a). Temperatures outside this range may reduce viral replication but do not completely eliminate the risk of transmission, and sudden temperature fluctuations can trigger reactivation of latent virus (Ilouze *et al*., 2010).

Population density and water quality are major risk factors (Su and Su, 2018). High density facilitates direct contact between fish, accelerating the spread of viruses (Gao *et al*., 2023). Furthermore, poor water conditions—such as low oxygen levels, extreme pH, or ammonia contamination—can weaken fish's immune systems and increase their susceptibility to disease (Mahmud *et al*., 2025).

Farm management and biosecurity practices significantly influence the risk of KHVD (Panicz *et al*., 2022). Practices such as using unsterilized equipment, introducing new fish without quarantine, or unhygienic fish transportation can increase the risk of virus introduction into the farming system (Tadmor-Levi *et al*., 2017). Furthermore, secondary infections by bacteria or parasites can exacerbate tissue damage and increase mortality in KHVD-infected fish (Okon *et al*., 2023).

Economic impact

KHVD has a significant economic impact on the global goldfish (*Cyprinus carpio*) and koi aquaculture industries (Wang *et al*., 2015). The disease is characterized by high mortality, particularly in juvenile fish, directly reducing stocks of both commercial and high-value ornamental fish (Sahoo *et al*., 2016). In uncontrolled outbreaks, mortality can reach 80–100%, causing direct losses in fish populations, negatively impacting farmer incomes and the market value of fish (Combe *et al*., 2023).

In addition to causing direct losses, KHVD also has indirect impacts. Farmers need to allocate additional resources for biosecurity implementation, such as quarantining new fish, sterilizing equipment, managing water quality, and conducting regular health monitoring to prevent the spread of the disease (Bavarsad *et al*., 2024). Fish that survive the infection have the potential to become latent carriers, which can trigger disease reactivation and spread to other ponds, prolonging production disruptions and increasing operational costs (Boutier *et al*., 2015).

The economic impact of KHVD is also reflected in the international ornamental fish trade, as an outbreak has the potential to trigger export bans, require additional quarantines, and lower global market prices (Rathore *et al*., 2012). The decline in demand and sales value due to concerns about the risk of this disease further burdens the finances of breeders and exporters (Tolo *et al*., 2021a).

In addition, KHVD can reduce production efficiency by inhibiting growth and reducing fish quality, triggering the need for medical intervention or experimental therapies, and increasing operational costs (Waqar *et al*., 2025). This combination of direct and indirect losses makes KHVD a significant economic threat to the aquaculture sector (Citarasu, 2024).

Ecological impact

KHVD not only causes losses to the goldfish (*Cyprinus carpio*) and koi aquaculture industries but also has significant ecological impacts on aquatic ecosystems (Panicz *et al*., 2022). This disease affects fish population composition, interspecies interactions, and the ecological balance in both natural and artificial habitats (Amin *et al*., 2018).

One significant ecological impact of KHVD is the decline in wild carp or koi populations released into the wild (Tolo *et al*., 2023). Mass mortality due to viral infection can reduce population density, impacting the local food chain, particularly predators that rely on carp as a primary resource (Garver *et al*., 2010). This decline can also trigger changes in interspecific competition and increase the dominance of invasive species, thus disrupting the ecosystem balance (McColl *et al*., 2016).

Furthermore, fish that survive infection can act as latent carriers, transmitting the virus to other wild fish populations (El-Matbouli and Soliman, 2011). This situation has the potential to trigger secondary outbreaks in non-target species that have not yet developed resistance to CyHV-3, thereby increasing the risk of biodiversity decline in these waters (Fabian *et al*., 2016).

KHVD can also disrupt the ecological role of fish in the ecosystem (Rathore *et al*., 2012). As herbivorous or omnivorous species, carp play a

role in controlling aquatic vegetation and nutrient cycling (Rakus *et al*., 2013). High mortality or population declines due to KHVD can impact ecological processes such as sedimentation, water quality, and plankton distribution, ultimately impacting other aquatic organisms (Matsui *et al*., 2008).

Environmental factors, including water temperature, habitat conditions, and the density of domestic fish released into natural waters, play a role in increasing the risk of KHVD spread (Shimizu *et al*., 2006). Therefore, implementing biosecurity management, controlling ornamental fish populations, and monitoring aquatic ecosystems are important strategies to reduce the ecological impact of this disease (Kent *et al*., 2009).

Vaccination

Vaccination is one of the most effective prevention methods against KHVD (Rojas-Peña *et al*., 2026). Given that this disease causes high mortality in goldfish (*Cyprinus carpio*) and koi, control through vaccination is crucial, especially in intensive culture systems (Su and Su, 2018). The primary goal of vaccination is to strengthen the fish's immune response, reduce mortality, and limit the spread of the virus between ponds or culture facilities (Liu *et al*., 2020).

Various vaccines have been developed for KHVD, each with its own advantages and limitations (Dhar *et al*., 2014). Live attenuated vaccines can stimulate a strong humoral and cellular immune response and provide long-term protection, but they carry the risk of reactivation or revertance to a virulent form (Saito *et al*., 2024). Inactivated vaccines are safer because the virus cannot replicate, but the immune response they elicit tends to be lower and often requires boosters or additional adjuvants (Tammas *et al*., 2024). Modern approaches, such as subunit and DNA vaccines, target specific viral antigens—for example, glycoprotein B or thymidine kinase—thus increasing safety and stimulating a specific immune response, although their effectiveness in the field remains to be evaluated (Lu *et al*., 2024b).

The route of vaccine administration also determines the effectiveness of immunization (Feraoun *et al*., 2022). Intraperitoneal injection produces a more consistent immune response and greater protection, but its application in large populations is difficult due to the increased labor required and the potential for stress on the fish (Wang *et al*., 2024). Conversely, administration via feed or immersion is more practical on an industrial scale, although the resulting immune response tends to be lower and requires repeat doses (Liu *et al*., 2020). Vaccination success is also influenced by factors such as age, physiological condition, immune status, and water temperature, all of which play a role in the fish's ability to generate an optimal immune response to the virus (Du *et al*., 2022).

Vaccination should be combined with biosecurity management strategies, new fish quarantine, density control, and water quality management for optimal effectiveness (Assefa and Abunna, 2018). Post-vaccination monitoring through antibody detection or molecular analysis is essential to evaluate the level of immune protection and detect potential latent carriers (Perelberg *et al*., 2008). With this integrated approach, vaccination can significantly reduce mortality, limit the spread of KHVD, and support the sustainability of carp and koi production in intensive culture systems (Klafack *et al*., 2022).

Control

Managing KHVD requires an integrated approach that includes biosecurity, environmental management, vaccination, and quarantine of new fish (Panicz *et al*., 2022). This strategy is crucial because KHVD spreads rapidly through direct contact, contaminated water, and latent carrier fish, making the risk of transmission high, especially in intensively farmed carp (*Cyprinus carpio*) and koi (Samsing *et al*., 2021).

The initial step in controlling KHVD is the implementation of strict biosecurity, including equipment sterilization, water flow regulation, and restricting access to humans or animals that could potentially carry the virus (Oidtmann *et al*., 2018). Consistent biosecurity implementation can prevent the virus from entering healthy ponds or aquaculture facilities (Ahmadivand *et al*., 2025). Furthermore, quarantining new fish before introducing them to the main population is crucial to detect latent carriers through clinical examination or molecular methods (Zheng *et al*., 2017).

Environmental management plays a crucial role in reducing the risk of outbreaks (Gotesman *et al*., 2013). Maintaining stable water temperatures outside the optimal range for viral replication (18–28°C) can reduce viral activity, while managing fish density, water quality, oxygen levels, and adequate nutrition increases the fish's immune resistance to infection (Joehnk *et al*., 2020). Preventing stress in fish is crucial, as stress can trigger reactivation of latent viruses and increase mortality (St-Hilaire *et al*., 2005). The integrated pathway for KHV diagnosis, short-term control, and long-term prevention in koi aquaculture is illustrated in Figure 3.

Figure 3. Conceptual flowchart of diagnostic, control, and preventive measures for koi herpesvirus in aquaculture.

Conclusion

KHVD, caused by CyHV-3, is a highly contagious viral disease of common carp (*Cyprinus carpio*) and koi, with high mortality and significant economic impact. Accurate diagnosis requires a combination of clinical observation, histopathological analysis, serology, and molecular detection. Effective control must incorporate biosecurity, quarantine, environmental management, and vaccination. This integrated approach can suppress virus transmission, enhance fish survival, and support the economic and ecological sustainability of common carp and koi production.

Acknowledgement

The authors thank Universitas Airlangga for the funding support with grant number 397/UN3.14/PT/2020.

Conflict of interest

The authors declare that there is no conflict of interest.

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