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A systematic review of case reports on mortality, modes of infection, diagnostic tests, and treatments for Nipah virus infection

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Abstract

Background: First identified in Malaysia in 1998, the Nipah virus is a paramyxovirus related to the Hendra virus. The clinical manifestation can vary from a silent infection to a life-threatening encephalitis. The World Health Organization (WHO) has documented 25 outbreaks in South Asia, resulting in 429 cases and 307 deaths to date. Currently, there are no approved treatments for the deadly Nipah virus infection, which is a serious threat to public health worldwide. Consequently, a review was conducted to examine the geographic distribution of the Nipah virus, mortality, transmission pathways, and available methods for diagnosis and treatment.

Methods: PubMed, Scopus, Web of Science, and Google Scholar servers were used to conduct a systematic search in compliance with the PRISMA guidelines. The results were tabulated and analyzed.

Results: A total of 12 studies (7 case series and 5 case reports) were included in the final analysis, and 92 cases were analyzed. The most frequent symptoms were fever (80%), myalgia (47%), headache (47%), shortness of breath/acute respiratory distress syndrome (n = 44.1%), altered sensorium (44.1%), and vomiting (42.6%). The most commonly used diagnostic test was RT-PCR (45.5%). The most common route of transmission reported is direct human contact with the infected patients. Treatment modalities include interventional procedures, antiviral drugs, and symptomatic treatment. The most common complications were seizures (39.2%) and altered sensorium (35.7%). The mortality rate was 73.9%.

Conclusion: It is crucial to emphasize the importance of early Nipah virus infection diagnosis and treatment to prevent life-threatening consequences.

Abbreviations: BSL = biosafety level, CSF = cerebrospinal fluid, ELISA = enzyme-linked immunosorbent assay, NiV = Nipah virus, RT-PCR = reverse transcription polymerase chain reaction, WHO = World Health Organization.

Keyword: Nipah virus

1. Introduction

The Nipah virus (NiV) garnered global attention during the Malaysian outbreak in 1998 and outbreaks have been reported almost every year since then. The recent outbreak has been reported from the Kozhikode district of Kerala in September of 2023. The World Health Organization (WHO) has reported 25 NiV outbreaks with 429 cases and 307 deaths so far in South Asia.[1] The Nipah virus and the Hendra virus, which closely aligns with the Nipah virus, belong to the *Henipavirus* genus within the family Paramyxoviridae. The fruit bats, particularly those in the genus *Pteropus*, serve as the primary reservoir. The virus can be transmitted to humans directly through human-to-human contact or indirectly through intermediary hosts like pigs. The diverse strains of Nipah, such as the

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Malaysian (NiV-M) and Bangladeshi (NiV-B), showcase variations in transmission dynamics, clinical features, and mortality rates. Acute encephalitis and respiratory illnesses are the most common severe forms of the NiV infection with the typical symptoms being fever, altered sensorium, headache, vomiting, myalgia, cough, and shortness of breath/acute respiratory distress syndrome. Mortality rate and occurrence of complications are more in cases infected with NiV-M.[2] Notably, the virus also exhibited its capacity to cause respiratory infections and encephalitis in pigs, although with a significantly lower mortality rate when compared with humans. The case fatality rates in humans are estimated at 40% to 75% by WHO. Owing to its high virulence, the Centre for Disease Control classified NiV as a biosafety level 4 (BSL-4) agent.

The Nipah virus was first discovered in 1999 during a pandemic among Malaysian pig farmers. Since then, no reports of new outbreaks in Malaysia.[3] After that, there have been many previous outbreaks, especially in Southeast Asian countries like Bangladesh, India, the Philippines, and Singapore.[4] Recurrent outbreaks have been reported in Bangladesh, and since 2001, outbreaks have happened almost every year. Periodically, the illness has also been detected in eastern India.[3]

In India, the first outbreak happened in Siliguri, West Bengal, in 2001.[5] There were 66 cases of encephalitis identified, and the case-fatality ratio was approximately 74%.[6] A second outbreak was recorded in Nadia, West Bengal, in 2007.[5] In the year 2018, another outbreak was noted in Kerala's Kozhikode and Malappuram districts, and there have been 17 deaths and 18 confirmed cases reported.[7] In one of the most recent outbreaks in India in September 2023, the State Government of Kerala reported 6 laboratory-confirmed cases of Nipah virus infection and 2 deaths. Also, 1288 contacts for the confirmed cases have been tracked down.[8] Because of the Nipah virus's high death rate and potential for widespread transmission, research on the virus is an absolute necessity. The dynamics of the virus's transmission, its reservoir hosts, and the environmental variables affecting outbreaks are currently poorly understood. There are also shortcomings in the development of potent medications and immunizations. It is imperative to comprehend these aspects to prevent and manage subsequent epidemics. Expert scientists have proposed that the NiV might follow COVID-19 as the next pandemic agent.[9] To handle the suspected cases more effectively, it is imperative to improve the knowledge of the virus and how it affects individuals through treatment protocols, infection control practices, and medication availability.[10]

This study aims to investigate the routes of virus transmission, analyze patterns of recovery in affected individuals, and comprehensively illustrate the various diagnostic and treatment modalities for the Nipah virus. The purpose of this research is to improve clinical outcomes and inform public health strategies by expanding our understanding of the mechanisms underlying the spread and effects of the Nipah virus on individuals.

2. Methods

The systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review was registered on PROSPERO (ID: CRD42023483089). Ethical approval was not necessary, as the study is a systematic review.

2.1. Data sources and search strategy

A comprehensive search was conducted in PubMed, Scopus, and Web of Science databases without publication period restriction. The keywords used for the search were "Nipah virus infection," "Nipah virus," "Nipah," and "Nipah case report." A manual search was performed in Google Scholar and reference lists.

2.2. Eligibility criteria

The studies were included or excluded as per the defined inclusion and exclusion criteria. Case reports or case series of patients affected by the Nipah virus, with demographic information and outcomes, were included in the study. The cases included had at least one of these components: diagnostic test, route of transmission, clinical presentation, or treatment. We considered the following exclusion criteria:

(1) Non-original studies, including conference abstracts, review articles, protocols, and editorials.
(2) Articles in a language other than English.
(3) Cases without demographic data and outcome.
(4) Unavailability of full texts.

2.3. Study selection

Revman software was used to organize the search results and remove duplicates. Eight authors independently screened 461 non-duplicated records, and the conflicts were resolved after a discussion with DA, SSM, and YI.

2.4. Data extraction

Required data were extracted by eight authors of the research team as follows: first author name, place of study, age, gender, diagnostic method, route of transmission, clinical features, complications, treatment, duration of treatment, and outcome. The results of the included articles are discussed in Table 1. The first author investigated the extracted data and settled any disagreements among the other authors.

2.5. Quality assessment

Joanna Briggs Institute Critical Appraisal tool (JBI) for case reports and case series was implemented to critically appraise the included studies. The Risk of bias was assessed by 8 authors independently. The Risk of bias of studies was reported based on the following cutoff: low risk of bias if 70% of answers scored yes, a moderate risk if 50% to 69% of questions scored yes, and a high risk of bias if yes scores were below 50%. Two studies reported a low risk of bias, 5 studies reported a moderate risk of bias and 1 study reported a high risk of bias.

2.6. Statistical analysis

All data were extracted onto a predesigned Excel sheet and represented in percentages, mean, and standard deviation for appropriate variables.

2.7. Ethical approval and informed consent

Ethical approval or informed consent was not needed, as the current study is a review of published articles.

3. Results

A total of 12 studies (7 case series and 5 case reports) were included in the final analysis. Data from the included studies are presented in Table 1. The selection process of articles is shown in the PRISMA diagram (Fig. 1).

3.1. Patient characteristics

The current study includes 92 cases from various regions, of which 30 (32.6%) were female and 62 (67.3%) were male. The mean age of the cases included is 39.2 years. Out of the above-mentioned cases, 67 (72.8%) cases were from Kerala, 17 (18.47%) cases were from Malaysia, 5 (5.4%) cases were from West Bengal, 2 (2.17%) cases were from Singapore and 1 (1.08%) case was from Bangladesh.

Table 1

Table representing patient characteristics, diagnostic methods, route of transmission, treatment, and outcome.

First author	Year of study	Place of study	Age, sex	Diagnostic method	Route of transmission	Clinical features	Complications	Treatment and duration (d)	Outcome
Wong et al[11]	2001	Malaysia	12F	Indirect IgG ELISA	Direct contact with pigs	Fever, right frontal headache, sudden jerking movements of left leg, numbness and weakness of the left leg	GTCS	IV phenytoin, penicillin, chloramphenicol [10]	Recovered
Chow et al[12]	2000	Singapore	51F	Capture IgM and IgG ELISA	Direct contact with pigs and bat droppings	Generalized malaise, altered sensorium, right lateral gaze palsy, bilateral nystagmus, right pronator drift, marked ataxia, mild bilateral motor weakness	Cerebellar dysfunction – a prolonged period of ataxia	IV acyclovir	Recovered with neurological sequelae (ataxia)
Chua et al[13]	1999	Malaysia	51M	(Posthumously diagnosed) indirect immunofluorescence assay, IgM capture ELISA	Direct contact with pigs	Fever, acute confusion, pain associated with myoclonus in the left arm, positive doll's eye reflex	Coma, flaccid tetra paresis, bradycardia, hypotension	IV acyclovir, IV midazolam, propofol infusion	Died
			34M	(Posthumously diagnosed) IgM capture ELISA	Direct contact with pigs	Fever, drowsiness, lethargy, hypertension, tachycardia	Segmental myoclonus, coma, hypotension not responding to fluids	N/A	Died
			52M	IgM capture ELISA (posthumously diagnosed)	Direct contact with pigs	Headache, nausea, fever, chills, left-sided horizontal nystagmus, hypertension, tachycardia	N/A	N/A	Died
Yadav et al[14]	2019	Kerala, India	27M (1), 59M (2), 53M (3), 18F (4), 48F (5), 52M (6), 27M (7), 31F (8), 26M (9), 19F (10)	RT-PCR, nested RT-PCR, IgM and IgG ELISA	*Pteropus spp.* bats	Fever, headache, vomiting, myalgia, cough, and rapidly progressing breathlessness	Altered sensorium and seizures	N/A	Died (1, 2, 3, 5, 6, 8, 9), recovered (7, 10)
Arunkumar et al[15]	2018	Kerala, India	27M (1), 45M (2), 100M (3), 48F (4), 17M (5), 28M (6), 59M (7), 53F (8), 31F (9), 48F (10), 45M (11), 47M (12), 19F (13), 48M (14), 27M (15), 32F (16), 52M (17), 23F (18), 27M (19), 55M (20), 75F (21), 28M (22), 25M (23)	Not done (1–5), real-time RT-PCR (6–23), IgM ELISA (6, 10, 11, 13–20, 22, 23), IgG ELISA (13, 15, 19, 20)	Fruit bats (1), direct human contact (2–23)	Fever (1–23), altered sensorium (1, 3, 5, 6, 7, 8, 10, 11–15, 17, 18, 20–22), headache (1, 7, 9–12, 15, 17–19, 22) myalgia (1, 3, 4, 9–12, 14–16, 18, 19, 22), cough (1, 4, 9, 10, 13, 15, 16, 19, 21, 23), shortness of breath/acute respiratory distress syndrome (1, 2, 4, 6–10, 12–23), vomiting (1, 3, 7–11, 16, 18, 20, 22), seizures (5, 15, 21)	N/A	N/A	Recovered (13, 19), died (1–12, 14–18, 20–23)

(*Continued*)

Table 1

(*Continued*)

First author	Year of study	Place of study	Age, sex	Diagnostic method	Route of transmission	Clinical features	Complications	Treatment and duration (d)	Outcome
Lim et al[16]	2003	Malaysia	47M (1), 42M (2), 37M (3), 55M (4), 41M (5), 51F (6), 24M (7), 65M (9), 24M (10), 55M (11), 48M (12)24 M (13)	IgM positive in CSF, Nipah culture negative (1–13)	Direct contact with pigs (1–13)	Seizures (1), cerebellar signs (2–4, 6, 8, 9), mono paresis (2, 4), diplopia (3, 8), tetra paresis (3), sensory loss (3), are flexia (3, 4), nystagmus (4), transient myoclonus (4, 8), stupor (5), VI palsy (6, 8), blurred vision (7), Horner syndrome (8), dysphonia (8), transient blindness (10), hallucinations (11), headache (12)	Coma (1–4)	N/A	Died (1), lost to follow-up (10), recovered (2–9, 11–13)
Arankalle et al[17]	2011	West Bengal	35M (1), 25M (2), 30F (3), 39M (4), 28M (5)	NiV RNA positive in lung and brain tissue (3), IgM positive in serum (4, 5), NiV RNA positive in CSF (4, 5)	Indirect contact with bats (1), direct human contact (2–5)	Fever, headache, nausea, vomiting, respiratory distress, pain in calf muscles, slurred speech, twitching of facial muscles, altered sensorium, (focal) convulsions, unconsciousness	N/A	N/A	Died (1–5)
Thulaseedaran et al[18]	2018	Kerala, India	26M (1), 49M (2), 48F (3), 23F (4), 48M (5), 27M (6), 19F (7), 32F (8), 75F (9), 25M (10)	RT-PCR (4–8, 10), Serology (9)	Human-to-human transmission, food contaminated by fruit bats	Fever (1–10), headache (1, 4, 7, 10), vomiting (1, 4, 7, 8), altered mental status (1, 2, 4, 5–10), seizures (1, 7, 9), meningitis (1, 7), diarrhea (1, 8, 10), myalgia (2–10), cough (2–4, 7, 8), hemoptysis (8), bilateral ptosis (10)	Viral encephalitis (1), respiratory distress (1–5, 7–10), myocarditis (3, 5, 8), refractory hypotension (4)	Intubated and ventilated (1, 2, 8), acyclovir (2), antibiotics (2, 3, 5, 6, 10), supportive measures (2–9), oseltamivir (3), inotropes (3, 8), invasive mechanical ventilation (4), ribavirin (6, 7, 9), noninvasive ventilation (5, 7, 9, 10) [8 hours – 21 d]	Died (1–5, 8–10), survived (6, 7)
Pallivalappil et al[19]	2020	Kerala, India	26M (1), 45M (2), 100M (3), 17M (4), 48F (5), 28M (6), 51F (7), 50M (8), 36F (9), 23F (10), 48M (11), 32F (12), 48F (13), 52M (14), 45M (15), 58M (16), 75F (17), 27M (18), 54M (19), 28M (20), 26M (21), 19F (22), 27M (23)		Exposure to fruit bats (1), direct human contact (2)	Fever, altered sensorium, tachycardia, hypertension, segmental myoclonus, segmental sweating, shortness of breath		Noninvasive ventilation, intermittent positive pressure ventilation, IV antibiotics, antiepileptics, mannitol, dexamethasone, antihypertensives, vasopressors, crystalloids, ribavirin, IV acyclovir (2–14 d)	
Yadav et al[20]	2021	Kerala, India	12M	RT-PCR, IgM antibodies in serum	Consumption of contaminated fruits	Fever, headache, disorientation, lack of consciousness	N/A	N/A	Died
Tambyah et al[21]	1999	Singapore	24M	Capture IgG and IgM ELISA	Direct contact with pigs	Fever, confusion, neck stiffness, drowsiness	N/A	Ceftriaxone, acyclovir, isoniazid[14]	Recovered
Stone[22]	2004	Bangladesh	2F	IgG antibodies in serum	Direct human contact	Fever, lethargy, inability to move legs	N/A	N/A	Died

ELISA = enzyme-linked immunosorbent assay, GTCS = generalized tonic-clonic seizure, IV = intravenous, NiV = Nipah virus, RT-PCR = reverse transcription polymerase chain reaction.

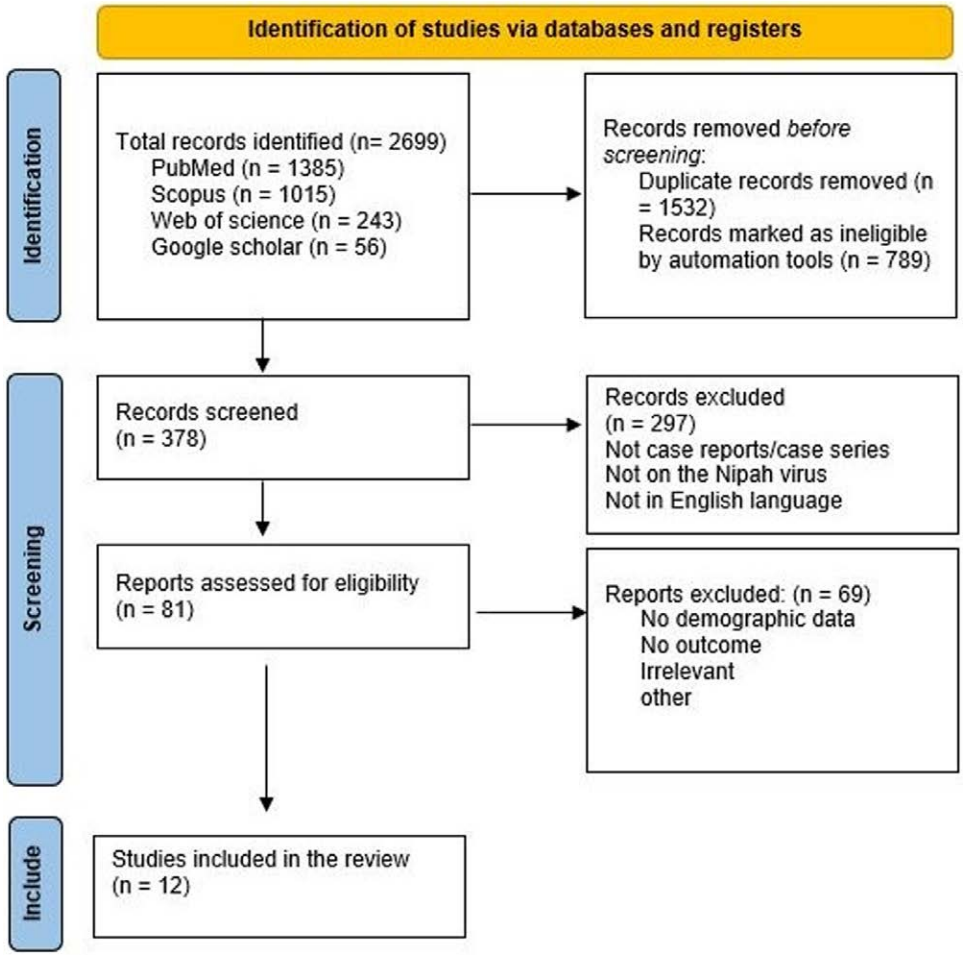

Figure 1. Search results from different databases.

3.2. Investigations

Out of 92 cases, diagnostic tests were reported in 77 cases. Reverse transcription polymerase chain reaction (RT-PCR) was the most commonly performed diagnostic test (n = 63, 81.8%). Enzyme-linked immunosorbent assay (ELISA) was the second most common mode of investigation. Various ELISA techniques used were IgM ELISA (n = 27, 35%), IgG ELISA (n = 17, 22.07%), and detection of IgM antibodies in CSF (n = 13, 16.8%). Diagnostic tests like NiV RNA in the brain, lung tissue, and CSF (n = 3, 3.8%), polymerase chain reaction (n = 3, 3.8%), serological tests (n = 7, 9.09%), and indirect immunofluorescent assay were also performed.

3.3 Route of transmission

The most common route of transmission reported is direct human contact with the infected patients. Out of 82 patients whose route of transmission is known, 59.76% (n = 49) were infected by direct human contact with the infected (either with respiratory secretions or body fluids of the infected), 37.8% (n = 31) were infected through zoonotic transmission, which includes direct contact either with pigs or bats (especially *Pteropus spp.* bats), and 2.44% (n = 2) were infected indirectly by consuming food contaminated with bats.

3.4. Clinical features

Out of the 68 cases whose clinical presentations were recorded, the most common clinical features of Nipah virus infections were found to be fever (n = 55, 80%), myalgia (n = 32, 47%), headache (n = 32, 47%), shortness of breath/acute respiratory distress syndrome (n = 30, 44.1%), altered sensorium (n = 30, 44.1%), vomiting (n = 29, 42.6%), cough (n = 27, 39.7%), seizures/convulsions (n = 8, 11.7%), cerebellar signs (n = 6, 8.82%), myoclonus (n = 5, 7.3%).

In addition to that, the occasional features were confusion(n = 3, 4.4%), diarrhea (n = 3, 4.4%), tachycardia (n = 3, 4.4%), hypertension (n = 3, 4.4%), nystagmus (n = 3, 4.4%), 6th cranial nerve palsy (n = 3, 4.4%), nausea (n = 2, 2.9%), lethargy (n = 2, 2.9%) chills (n = 2, 2.9%), weakness of the limbs (n = 2, 2.9%), diplopia (n = 2, 2.9%), meningitis (n = 2, 2.9%), monoparesis (n = 2, 2.9%), areflexia (n = 2, 2.9%), drowsiness (n = 2, 2.9%), unconsciousness (n = 2, 2.9%).

Other rare features included sensory loss, numbness, neck stiffness, right pronator drift, pain in calf muscles, hypotonia of the limbs, paraplegia, tetraparesis, doll's eye reflex, sudden jerking movements of the leg, ataxia, twitching of facial muscles, slurred speech, dysphonia, segmental sweating, bilateral ptosis, transient blindness, horner's syndrome, blurred vision, hemoptysis, hallucinations, stupor, coma, and death.

3.5. Complications

The total number of cases that had reported various complications is 28 (30.4%), out of the 92 cases. The most common complication was seizures (n = 11, 39.2%), followed by altered sensorium (n = 10, 35.7%). Other common complications were respiratory distress (n = 9, 32.1%) and coma (n = 7, 25%). Hypotension (n = 4, 14.2%) and myocarditis (n = 4, 14.2%) were occasional complications experienced by the patients.

Figure 2. Map depicting the geographical distribution of NiV in various outbreaks. NiV = Nipah virus.

Rarely reported cases were cerebellar dysfunction manifesting as prolonged ataxia, segmental myoclonus, flaccid tetraparesis, encephalitis, and bradycardia.

3.6. Treatment

Of the 92 patients studied, 39 patients (42.3%) received treatment. The average duration of treatment which was calculated for 19 patients was around 8.6 days with 1 patient receiving the treatment for as little as 1.8 hours to 1 patient receiving treatment for as long as 42 days. In a total of 39 patients who had received treatment, a wide array of pharmacotherapy and interventional therapy had been given to all those patients ranging from children aged 12 years to adults up to 75 years.

Among the 39 patients who had received treatment, a total of 14 patients had been placed under interventional procedures (N = 14, 35.8%) which included noninvasive, and invasive mechanical ventilation. 6 patients had been kept under noninvasive ventilation (N = 6, 15.3%) and 8 patients had undergone invasive ventilation (N = 8, 20.5%).

Among the pharmacotherapy modalities, 5 patients were placed on ribavirin (N = 5, 12.8%), 7 patients were treated with acyclovir (N = 7, 18%), 7 patients were continued on antihypertensive medications (N = 7, 18%), 8 patients were managed by supportive measures (N = 8, 20.5%), 4 patients had been given broad-spectrum antibiotics (N = 6, 15.3%), and 2 patients were administered inotropes (N = 2, 5.1%). The other pharmacotherapy given as a part of the treatment were oseltamivir, I.V. phenytoin, penicillin, chloramphenicol, midazolam, propofol, mannitol, dexamethasone, and crystalloids.

3.7. Outcome

Out of 92 patients, 68 were reported dead and 22 (23.9%) recovered. Some of the recovered patients presented with various disabilities such as finger weakness, 6 cranial nerve palsy, Horner syndrome, mono paresis, major depressive disorder, and neurological complications such as ataxia and nystagmus. The mortality rate of the above-mentioned cases is approximately 73.9%.

4. Discussion

The Nipah virus was discovered in 1998 as a result of an outbreak among Malaysian pig farmers in the Sungai Nipah village. An additional incident occurred in Singapore in March 1999, involving 11 personnel in the abattoir who were connected to pigs imported from a Malaysian farm that carried the NiV virus.[23]

After the initial identification, 3 nations described single or sporadic repeating epidemics: Bangladesh (the first outbreak was in 2001, and then there were subsequent outbreaks till 2023, except for the years 2002, 2006, and 2016), India (2001, 2007, 2018, 2019, 2021, 2023) and the Philippines in 2014.[8,23,24] Figure 2 depicts countries affected by different outbreaks.

Pteroptus species of fruit bats are the natural reservoirs of the Nipah virus.[25] The virus spreads to pigs through the consumption of fruits/date palm sap contaminated with saliva and urine and droppings of fruit bats.[26,27] Pig-to-pig transmission occurs through direct contact with urine, saliva, nasal and pharyngeal secretions. Repeated usage of the same needles without sterilization after each use for medical interventions and artificial insemination of boar semen also led to transmission of the virus among pigs.[27]

Transmission to humans from pigs occurs through activities that require proximity to pigs such as processing of baby pigs (clipping tails, tagging ears), administering injections or medication to pigs, assisting in the birth of piglets, assisting in pig breeding (collection of semen from boars and artificial insemination of sows), and handling of dead pigs.[27] In the current study, 37.8% of the patients were infected due to zoonotic transmission, predominantly due to handling pigs where as human-to-human transmission accounts for 59.76% of the infections. Direct consumption of date palm sap contaminated with saliva, and urine by humans leads to the acquiring of the infection.[26] Human-to-human transmission occurs mainly through respiratory droplets, proximity or contact with infected people, and exposure to body fluids, especially nasal secretions.[28]

NiV initiates infection through the oro-nasal route, with the site of initial replication believed to be in the lymphoid tissues and the epithelial cells of the bronchiole. NiV enters into blood vessels and is carried by circulating leukocytes through attachment with heparan sulfate without infecting the cells.[29] This is

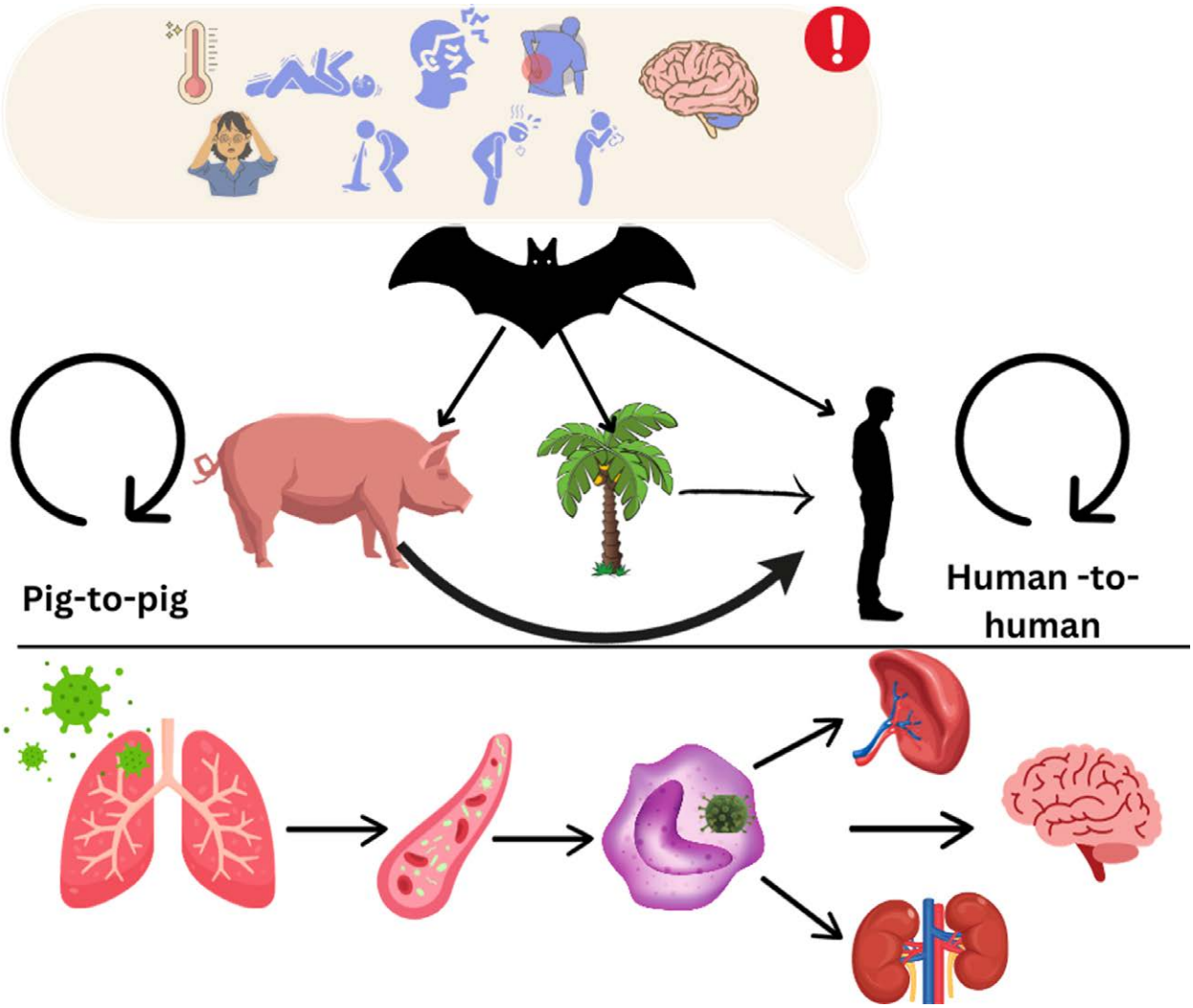

Figure 3. Pathophysiology, clinical features, and modes of transmission of the Nipah virus infection.

followed by secondary replication in the susceptible endothelium of the human body. The glycoproteins G and F of NiV facilitate viral entry by allowing fusion of viral and cellular membranes through conformational changes. The glycoprotein G of NiV targets endothelial cells, particularly those expressing Ephrin-B2 or Ephrin-B3. Ephrin-B2 is extensively distributed in the brain (especially in the prefrontal cortex, and the neuroepithelial cells), lungs, placenta, prostate, and in blood vessels across various tissues while Ephrin-B3 is predominantly expressed in the occipital lobe, the prefrontal cortex, and the amygdala of brain as well as in the heart and the prostate. The central nervous system (CNS) is primarily invaded hematogenously, although evidence suggests direct invasion via olfactory nerves is possible.[30] The clinical features of NiV infection are attributable to its involvement in the failure of multiple organs like lungs, kidneys, spleen, and brain due to vasculitis, thrombosis, and necrosis as a result of syncytia formation which is characterized by the expression of viral glycoproteins on the infected cell surfaces. Syncytia formation leads to multinucleated giant cell formation, contributing highly to the cytopathic effects observed during infection.[31] The high lethality of NiV infection is attributable to its evasion of the innate immune response, particularly through the inhibition of interferon activity.[32] Several complications are known to occur with varying frequencies which persuade for prompt diagnosis and treatment, to decrease morbidity in the surviving patients. They can be seizures, respiratory distress, coma, myocarditis, refractory hypotension, long-term neurological sequelae, late-onset encephalitis, relapse encephalitis, and some rare complications like cerebellar dysfunction. Figure 3 summarizes the pathophysiology, clinical presentation, and modes of transmission of the disease.

An early diagnosis of NiV infection is crucial to limit the outbreak and to provide appropriate care for the patient. NiV infection can be confirmed in several ways using both direct and indirect detection methods such as ELISA, RT-PCR, immunohistochemistry, and virus isolation. Reverse transcription polymerase chain reaction (RT-PCR) was the most common mode of investigation performed to confirm NiV infection, in the current study. Specimens for serological testing should be collected late in the course of infection, 10 to 14 days after onset. The National Cooperative Development Corporation India, recommends throat swabs, urine, and blood, before or after CSF for diagnosis. Samples must be collected safely and transported in triple container packing at 2 to 8°C. Storage at – 20°C is recommended beyond 48 hours of collection.[32]

ELISA-based serological tests can be used to detect IgM and IgG antibodies against the Nipah virus in the serum and cerebrospinal fluid (CSF) as reported in the current study. In most cases, IgM and IgG antibodies appear in the serum during the first week after onset of infection. IgG antibodies seem to persist up to 8 months in symptomatic patients, while IgM antibodies seem to persist from 3 to 7 months. RT-PCR is currently

considered the first-choice method for the diagnosis of acute NiV infection which was supported by the findings of our study.[33] Nasal swabs, cerebrospinal fluid, urine, and blood are commonly used for RT-PCR tests. Virus isolation from respiratory secretions, urine, cerebrospinal fluid, and other tissue specimens must be done in a BSL-4 laboratory. The line of choice for NiV is Vero cell lines. Cytopathic effects can be observed in 3 days.[32] Immunohistochemistry is used to detect NiV antigens in tissues such as lungs, kidneys, spleen, brain, and lymph nodes (not widely used).[34] Isolation of patients and the strict enforcement of infection control measures are essential. The main emphasis in managing NiV infection revolves around providing supportive care, rest, hydration, and addressing symptoms as they arise.[32] Acyclovir is advised for suspected encephalitis.[35]

Ribavirin, m102.4 monoclonal antibody, and Favipiravir have been considered for treating and preventing NiV infection. **Ribavirin** might delay but not prevent death after Nipah infection. The recommended treatment dosage is not defined, but it can follow the WHO guidelines for Lassa fever: a loading dose of 30 mg/kg for children and 2000 mg/kg for adults, followed by 10 days of therapy.[36] It was administered to 5 patients in our systematic review. An IV dose of m102.4, given 10 hours after NiV infection in ferrets, fully protected them. Positive studies in African Green Monkeys supported using m102.4 in humans, both compassionately and in a phase I clinical trial.[37] In a model of Nipah virus infection using Syrian hamsters, the successful administration of **favipiravir** was observed in hamsters subjected to lethal challenges.[36]

In the 1998/1999 Malaysia outbreak, an open-label ribavirin trial involved 140 treated patients, while a control group (n = 54) comprised those treated earlier or declining ribavirin. Ribavirin administration correlated with a 36% lower mortality and fewer neurological issues in survivors.[36,37] In the 2018 Kerala, India outbreak with 23 cases and only 2 survivors, oral ribavirin was administered to 6 patients, resulting in a 20% lower mortality compared to a group of 6 patients not receiving ribavirin, where 100% mortality was observed.[37]

Out of all the patients who had received treatment, only 7 patients had successfully recovered, and among those 6 patients were under the age of 30, highlighting the fact that the younger population had successful recovery with lesser neurological side effects. Upon careful analysis, 4 patients among the 7 patients who recovered were treated with ribavirin, showcasing the significance of ribavirin and its positive outcome in the young age group.

5. Recommendations

5.1. For locals and travelers

In the face of the potential threat posed by Nipah virus outbreaks, it becomes imperative for both residents and travelers to adopt vigilant measures and follow established recommendations to safeguard public health and prevent the further spread of this infectious disease as direct human contact with the infected (either with respiratory secretions or body fluids of the infected) is the most common route of transmission, as reported in the current systematic review. Individuals are encouraged to wash their hands using soap frequently, avoid close contact with infected bats or other animals such as pigs and cattle, steer clear of locations known to harbor bats, and refrain from contact with the blood or bodily fluids of individuals confirmed to have Nipah virus, since zoonotic transmission is a significant mode of spread. Additionally, the consumption of raw date juice should be avoided or done after boiling the raw date palm sap for 10 minutes.[38] The common clinical manifestations following infection with the Nipah virus involve fever, headache, vomiting, muscle aches, altered level of consciousness, disorientation, and respiratory difficulty.[5,38] These should alert the individual to seek medical attention immediately, particularly in the setting of an outbreak. Those confirmed to be infected are to be strictly isolated.[39]

5.2. For healthcare professionals

Healthcare workers should be on the lookout for any odd clusters of respiratory illnesses or encephalitis because these could be early signs of infection with the Nipah virus (NiV). To prevent nosocomial transmission, strict infection prevention and control measures need to be put in place. This covers the following: donning personal protective equipment (PPE), isolating suspected patients, and thoroughly cleaning hospital surfaces and equipment.

We recommend that, as a first step, handwashing stations for medical staff and patient attendants be set up and routinely stocked with soap and water in each hospital ward. Second, during NiV season, all hospitals in NiV infection-prone areas should admit patients with meningoencephalitis syndrome into an isolation room or ward and regularly provide gloves and masks for healthcare personnel when they are caring for meningoencephalitis patients. Due to the unavailability of laboratory diagnosis for NIV infection during the initial evaluation of patients with meningoencephalitis syndrome.[40] When a suspected case of NiV is identified, healthcare personnel should report the incident to the authorities and get tested for NiV.

6. Limitations

Our systematic review is significantly hindered by the scarcity of literature on the Nipah virus, impacting the precision of our findings. Numerous case reports and series were omitted due to insufficient demographic data and incomplete information. Most case reports lacked details on treatment, posing a heightened risk of biased information. In case series, the data was incomplete for a few cases or it was pooled for all the cases together, hindering data representation in the table. Despite these challenges, our research offers a current, exploratory summary of available data, acknowledging the unavailability of more extensive, well-designed studies at present.

7. Conclusion

The current study is the first of its kind to involve the demographics of the affected, clinical features, diagnostic methods, various routes of transmission, complications, treatment along with the duration and outcome of the patient.

On a note that can be helpful for physicians is that among all the patients who recovered successfully, were under 30 years and ribavirin was the major drug used in the treatment. An important shortcoming is that the majority of the treatment given was not definitive in completely treating, rather it was more helpful in prolonging the lives of the patients.

Since there's no reliable treatment or vaccine for the Nipah virus, it's crucial to emphasize recognizing the most common symptoms like fever, headache, muscle aches, altered consciousness, difficulty breathing, vomiting, and cough, especially in epidemic areas. People in areas previously affected by Nipah should be familiar with these signs and advised to promptly report to the nearest health center if they experience them. The most common route of spread of Nipah virus infection is human-to-human transmission which can be circumvented by following appropriate sanitation measures. We must conduct thorough surveillance and awareness campaigns to stress the need for locals to avoid interacting with pigs and bats, as zoonotic transmission is the second most common route of transmission.

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