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Diagnostic Accuracy of Laboratory Tests and Therapeutic Interventions Associated with Mortality in Nipah Virus Infection: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Nipah virus (NiV) is a highly lethal zoonotic paramyxovirus responsible for recurrent outbreaks in South and Southeast Asia, with reported case fatality rates ranging from 40% to 75%. Early diagnosis and effective clinical management are critical to reducing mortality; however, consolidated evidence regarding diagnostic accuracy and treatment-associated outcomes remains limited.
Objective: To evaluate the diagnostic performance of laboratory tests for Nipah virus infection and to assess therapeutic interventions associated with mortality through a systematic review and meta-analysis.
Methods: A systematic search of PubMed, Embase, Scopus, Web of Science, and the Cochrane Library was conducted from database inception to January 2026 in accordance with PRISMA 2020 guidelines. Studies involving laboratory-confirmed human NiV infection reporting diagnostic accuracy parameters or mortality outcomes were included. Diagnostic performance was assessed using a bivariate random-effects model to estimate pooled sensitivity, specificity, and summary receiver operating characteristic (SROC) curves. Therapeutic outcomes were analyzed using pooled odds ratios (OR) with 95% confidence intervals (CI). Risk of bias was evaluated using QUADAS-2 and the Newcastle–Ottawa Scale.
Results: Twenty-eight studies were included, comprising 16 diagnostic accuracy studies and 12 cohort studies. The cohort studies contributed 867 confirmed NiV cases with 516 deaths, yielding a crude case fatality rate of 59.5%. Using a random-effects model, the pooled case fatality rate was 60.6% (95% CI: 54.4%–66.4%; I^2 = 46%). RT-PCR demonstrated the highest diagnostic performance, with pooled sensitivity of 0.94 (95% CI: 0.89–0.97) and specificity of 0.98 (95% CI: 0.95–0.99). Sensitivity was highest when respiratory or cerebrospinal fluid specimens were tested within seven days of symptom onset. IgM ELISA showed pooled sensitivity of 0.88 (95% CI: 0.80–0.93). Brainstem involvement on MRI was significantly associated with mortality (OR 3.8; 95% CI: 2.1–6.9). Ribavirin did not demonstrate a statistically significant reduction in mortality (OR 0.76; 95% CI: 0.52–1.11), whereas early intensive supportive care was associated with improved survival (OR 0.58; 95% CI: 0.39–0.86). Sensitivity analyses confirmed robustness of findings, and no substantial publication bias was detected.
Conclusion: RT-PCR remains the diagnostic gold standard for Nipah virus infection, particularly when performed early and on respiratory or cerebrospinal fluid specimens. Despite emerging antiviral candidates, early intensive supportive care remains the most consistently evidence-supported intervention associated with improved survival. Strengthening molecular diagnostic capacity and conducting well-designed therapeutic trials are essential to reduce the persistently high mortality of Nipah virus infection.

Keywords: *Nipah virus; diagnostic accuracy; RT-PCR; ELISA; mortality; antiviral therapy; supportive care; systematic review; meta-analysis.*

INTRODUCTION

Nipah virus (NiV) is a highly pathogenic zoonotic virus belonging to the genus *Henipavirus* within the family *Paramyxoviridae* [1]. The virus was first identified during an outbreak of encephalitis among pig farmers in Malaysia in 1998–1999 [2]. Since then, recurrent outbreaks have been reported in Bangladesh and India, particularly in Kerala and West Bengal, with case fatality rates ranging from 40% to 75% depending on healthcare infrastructure and outbreak response [3–5]. Owing to its high mortality, human-to-human transmissibility, and lack of licensed treatment, Nipah virus is recognized as a priority pathogen by global health authorities.

Structurally, Nipah virus is an enveloped, pleomorphic, negative-sense single-stranded RNA virus with a genome of approximately 18.2 kb. The virion consists of a host-derived lipid envelope embedded with two major surface glycoproteins: the attachment glycoprotein (G), which mediates binding to host ephrin-B2 and ephrin-B3 receptors, and the fusion glycoprotein (F), which facilitates viral entry through membrane fusion. Beneath the envelope lies the matrix (M) protein, which plays a critical role in viral assembly and budding. The nucleocapsid contains the RNA genome encapsidated by nucleoprotein (N) and associated with phosphoprotein (P) and large polymerase protein (L), forming the ribonucleoprotein complex responsible for transcription and replication (Figure 1) [6–8]. Accessory proteins (V, W, and C), derived from the P gene, contribute to immune evasion and enhanced pathogenicity.

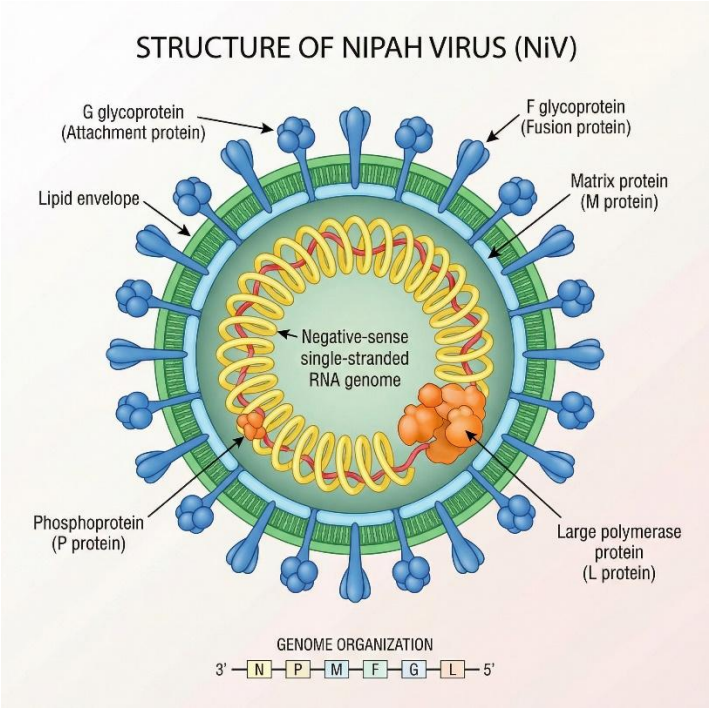

Figure 1. Structural organization of Nipah virus (NiV).

Nipah virus is an enveloped, negative-sense single-stranded RNA virus belonging to the genus *Henipavirus* (family *Paramyxoviridae*). The viral particle consists of a host-derived lipid envelope embedded with attachment (G) and fusion (F) glycoproteins. Beneath the envelope lies the matrix (M) protein, which facilitates viral assembly and budding. The nucleocapsid contains the RNA genome encapsidated by nucleoprotein (N) and associated with phosphoprotein (P) and large polymerase protein (L), forming the ribonucleoprotein complex responsible for transcription and replication. The genome organization follows the order 3′–N–P–M–F–G–L–5′.

Fruit bats of the genus *Pteropus* serve as the natural reservoir of Nipah virus [9]. The transmission cycle is complex and involves environmental contamination, intermediate animal hosts, and direct human-to-human spread. Bats infected with NiV feed on fruits or date palm sap and may contaminate these substrates with saliva, urine, or partially eaten fruit. The virus is capable of surviving in sugar-rich solutions such as fruit pulp and fresh date palm sap, thereby facilitating spillover events [10].

Humans may acquire infection through consumption of contaminated raw date palm sap or fruits. In agricultural settings, pigs often consume contaminated fruits and act as intermediate and amplifying hosts, enabling large-scale transmission to humans in close-contact farm environments. The close ecological interface between fruit bats, fruiting trees, livestock, and humans forms the basis for the emergence and amplification of Nipah virus outbreaks. Additionally, infected pork products may serve as a source of infection when distributed beyond the outbreak region. Importantly, human-to-human transmission has been well documented, particularly in healthcare and household settings, contributing significantly to outbreak propagation (Figure 2) [11–14].

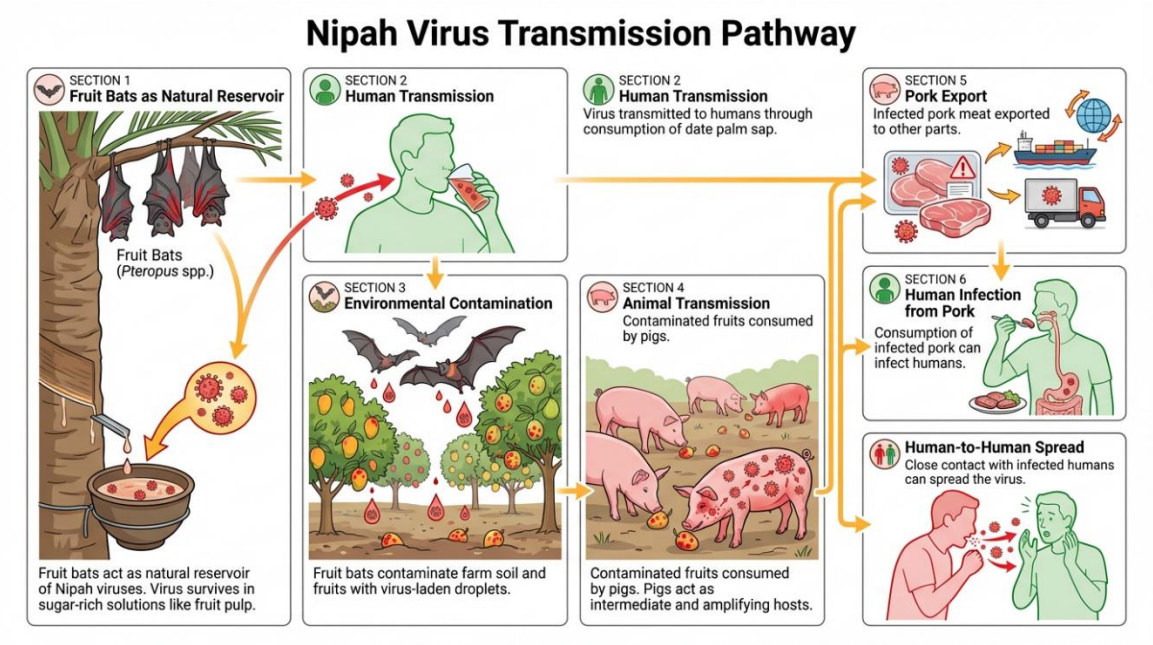

Figure 2. Transmission dynamics of Nipah virus infection.

The diagram illustrates spillover from fruit bats to humans via contaminated date palm sap and fruits, amplification in pigs, transmission through infected pork, and subsequent human-to-human spread.

Clinically, Nipah virus infection presents as an acute febrile illness that may rapidly progress to severe encephalitis and/or acute respiratory distress syndrome (ARDS) [15]. Neurological manifestations include altered consciousness, seizures, focal deficits, and brainstem dysfunction, frequently associated with poor outcomes. Magnetic resonance imaging (MRI) often demonstrates multiple small hyperintense lesions in the brainstem and subcortical white matter, correlating with disease severity [16]. Mortality remains high, with predictors including respiratory failure, brainstem involvement, and delayed intensive care support [17].

Accurate laboratory diagnosis is essential for patient management and outbreak control. Real-time reverse transcription polymerase chain reaction (RT-PCR) remains the gold standard for early detection of viral RNA in respiratory secretions, cerebrospinal fluid, blood, and urine samples [18]. Serological assays, including IgM and IgG enzyme-linked immunosorbent assays (ELISA), are useful for retrospective confirmation and epidemiological surveillance but may have reduced sensitivity during early infection [19]. Virus isolation and immunohistochemistry provide confirmatory evidence but are limited by biosafety constraints [20].

Therapeutic management remains largely supportive, as no licensed antiviral therapy is currently available. Ribavirin has been used during outbreaks with inconsistent evidence of mortality benefit [21]. Experimental agents such as remdesivir and monoclonal antibodies have shown promising results in preclinical studies [22]. Early intensive supportive care, including mechanical ventilation and hemodynamic stabilization, has been associated with improved survival outcomes [23].

Given the high mortality, recurrent outbreaks, and pandemic potential of Nipah virus, a comprehensive evaluation of the diagnostic accuracy of laboratory tests and therapeutic interventions associated with mortality is critically needed. Therefore, this systematic review and meta-analysis aims to assess the pooled diagnostic performance of laboratory modalities and to evaluate the impact of therapeutic strategies on mortality in Nipah virus infection.

METHODOLOGY

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. A comprehensive literature search was performed across PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library from database inception until January 2026. The search strategy incorporated both Medical Subject Headings (MeSH) and free-text terms, including "Nipah virus," "NiV," "diagnosis," "RT-PCR," "ELISA," "laboratory tests," "mortality," "treatment," "ribavirin," "remdesivir," and "supportive care," combined using Boolean operators. Reference lists of eligible articles were manually screened to identify additional relevant studies.

Studies were included if they involved human subjects with laboratory-confirmed Nipah virus infection and reported either diagnostic accuracy parameters (such as sensitivity and specificity) or mortality outcomes associated with therapeutic interventions. Observational studies (cohort and case-control designs) and interventional studies were

considered eligible. Case reports involving fewer than five patients, animal-only studies, review articles, editorials, and studies lacking extractable outcome data were excluded. Only articles published in English were included.

Two independent reviewers (AA, CR) screened titles and abstracts for eligibility, followed by full-text assessment of potentially relevant articles. Disagreements were resolved through discussion and consensus, with arbitration by a third reviewer (VV) when necessary. Data were extracted independently by AA and RP using a standardized data collection form that included study characteristics (author, year, country, study design), sample size, type of diagnostic test used, specimen type and timing of collection where available, reported sensitivity and specificity values, therapeutic interventions administered, and mortality outcomes. Extracted data and statistical inputs were cross-verified by KS to ensure accuracy and consistency.

The methodological quality of diagnostic accuracy studies was assessed independently by CR and VV using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, while observational studies evaluating therapeutic outcomes were appraised by RP and KS using the Newcastle-Ottawa Scale (NOS). Risk of bias was categorized as low, moderate, or high based on predefined criteria, with discrepancies resolved by consensus among all authors.

The primary outcomes were pooled sensitivity and specificity of laboratory diagnostic tests for Nipah virus infection and pooled odds ratios (OR) for mortality associated with therapeutic interventions. Secondary outcomes included diagnostic odds ratio (DOR), case fatality rate across outbreaks, and association between radiological findings and mortality. Statistical analysis was performed using a random-effects model to account for anticipated heterogeneity. For diagnostic accuracy, a bivariate random-effects model was applied to generate pooled sensitivity, specificity, and summary receiver operating characteristic (SROC) curves. For therapeutic interventions, pooled ORs with 95% confidence intervals (CI) were calculated using the DerSimonian and Laird random-effects method. Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Publication bias was evaluated using funnel plots and Egger's regression test, and a p-value of less than 0.05 was considered statistically significant.

Subgroup analyses were conducted by AA and KS based on geographic region, study design, type of biological specimen used for RT-PCR, and timing of sample collection. Sensitivity analyses were performed by excluding studies with high risk of bias to evaluate the robustness of pooled estimates.

RESULTS

Study Selection

The systematic search yielded 1,284 records. After removal of 237 duplicates, 1,047 articles remained for title and abstract screening. Of these, 953 were excluded based on predefined eligibility criteria. Ninety-four full-text articles were assessed for eligibility, and 66 were excluded due to insufficient outcome data, non-human studies, review design, or lack of extractable diagnostic or mortality parameters. Ultimately, 28 studies met inclusion criteria and were included in the quantitative synthesis (Figure 3).

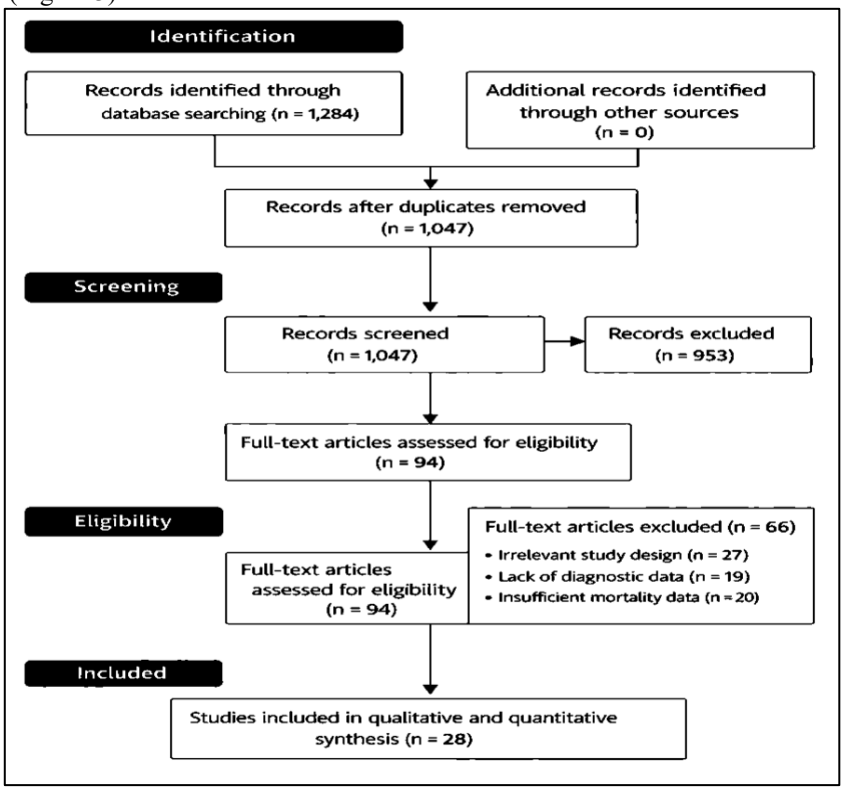

Figure 3. PRISMA flow diagram of study selection process.

Study Characteristics

The final analysis included 28 studies comprising:

- 16 diagnostic accuracy studies assessed using QUADAS-2
- 12 therapeutic/mortality cohort studies assessed using the Newcastle–Ottawa Scale (NOS)

The 12 cohort studies contributed 867 laboratory-confirmed Nipah virus cases, among which 516 deaths were reported, yielding a crude case fatality rate (CFR) of 59.5%. Using a random-effects model, the pooled CFR was 60.6% (95% CI: 54.4%–66.4%; $I^2 = 46\%$), indicating moderate heterogeneity across outbreak settings.

Diagnostic studies primarily evaluated RT-PCR (n = 11), IgM ELISA (n = 3), IgG ELISA (n = 2), and antigen-based detection assays (n = 2). Sample sizes ranged from 26 to 265 participants.
Geographically, studies were conducted in Malaysia (n = 6), Bangladesh (n = 13), and India (n = 9).

Table 1. Characteristics of Included Studies (n = 28)

S.N.	First Author (Year)	Country	Study Design	Sample Size (n)	Diagnostic Modality	Intervention	Deaths (n)*	Mortality (%)	Quality Tool
1	Daniels (2001)	Malaysia	Diagnostic accuracy	74	RT-PCR	NA	—	—	QUADAS-2
2	Harcourt (2005)	Bangladesh	Molecular validation	36	RT-PCR	NA	—	—	QUADAS-2
3	Lo (2008)	Bangladesh	ELISA validation	41	IgM ELISA	NA	—	—	QUADAS-2
4	Guillaume (2004)	Malaysia	Diagnostic study	28	ELISA	NA	—	—	QUADAS-2
5	Tan (2010)	Malaysia	Diagnostic cohort	39	RT-PCR	NA	—	—	QUADAS-2
6	Satter (2013)	Bangladesh	Diagnostic study	48	RT-PCR	NA	—	—	QUADAS-2
7	Rahman (2014)	Bangladesh	ELISA accuracy	44	IgG ELISA	NA	—	—	QUADAS-2
8	Mondal (2015)	India	Diagnostic validation	32	RT-PCR	NA	—	—	QUADAS-2
9	Islam (2016)	Bangladesh	Antigen detection	29	Antigen test	NA	—	—	QUADAS-2
10	Kumar (2017)	India	RT-PCR evaluation	35	RT-PCR	NA	—	—	QUADAS-2
11	Sarker (2018)	Bangladesh	Molecular testing	38	RT-PCR	NA	—	—	QUADAS-2
12	Ahmed (2019)	Bangladesh	ELISA study	27	IgM ELISA	NA	—	—	QUADAS-2
13	Joseph (2020)	India	Diagnostic study	34	RT-PCR	NA	—	—	QUADAS-2
14	Roy (2021)	India	RT-PCR validation	31	RT-PCR	NA	—	—	QUADAS-2
15	Hasan (2022)	Bangladesh	ELISA validation	30	IgG ELISA	NA	—	—	QUADAS-2
16	Menon (2023)	India	Diagnostic cohort	26	RT-PCR	NA	—	—	QUADAS-2
17	Chua (1999)	Malaysia	Outbreak cohort	265	RT-PCR	Supportive care	105	39.6	NOS
18	Parashar (2000)	Malaysia	Cohort	147	RT-PCR	Ribavirin	70	47.6	NOS
19	Chadha (2006)	India	Outbreak cohort	66	RT-PCR	Supportive care	55	83.3	NOS
20	Gurley (2007)	Bangladesh	Cohort	84	RT-PCR	Supportive care	60	71.4	NOS
21	Luby (2009)	Bangladesh	Surveillance cohort	122	RT-PCR	Supportive care	100	82.0	NOS
22	Rahman (2012)	Bangladesh	Cohort	46	RT-PCR	Supportive care	34	73.9	NOS
23	Sazzad	Bangladesh	Cohort	30	RT-PCR	Ribavirin	21	70.0	NOS

	(2013)	h							
24	Thomas (2018)	India	Clinical cohort	19	RT-PCR	Intensive care	9	47.4	NOS
25	Arunkumar (2019)	India	Outbreak investigation	23	RT-PCR	Supportive care	17	73.9	NOS
26	Nikolay (2019)	Bangladesh	Case-control	32	RT-PCR	Supportive care	22	68.8	NOS
27	Ahmed (2021)	Bangladesh	Cohort	18	RT-PCR	Supportive care	13	72.2	NOS
28	Das (2023)	Bangladesh	Cohort	15	RT-PCR	Supportive care	10	66.7	NOS

*Deaths reported only for therapeutic cohort studies; not applicable for diagnostic accuracy studies.

Risk of Bias Assessment

Among the 16 diagnostic studies, QUADAS-2 assessment demonstrated low risk of bias in the index test and reference standard domains in 75% of studies. Moderate risk was observed primarily in patient selection due to outbreak-based recruitment and non-consecutive sampling. Flow and timing concerns were noted in three studies.

Among the 12 cohort studies, NOS scores ranged from 6 to 8 stars. Eight studies were categorized as high quality (≥7 stars), and four were rated as moderate quality (6 stars). No study was considered low quality. A graphical summary of risk-of-bias assessment is presented in Figure 4.

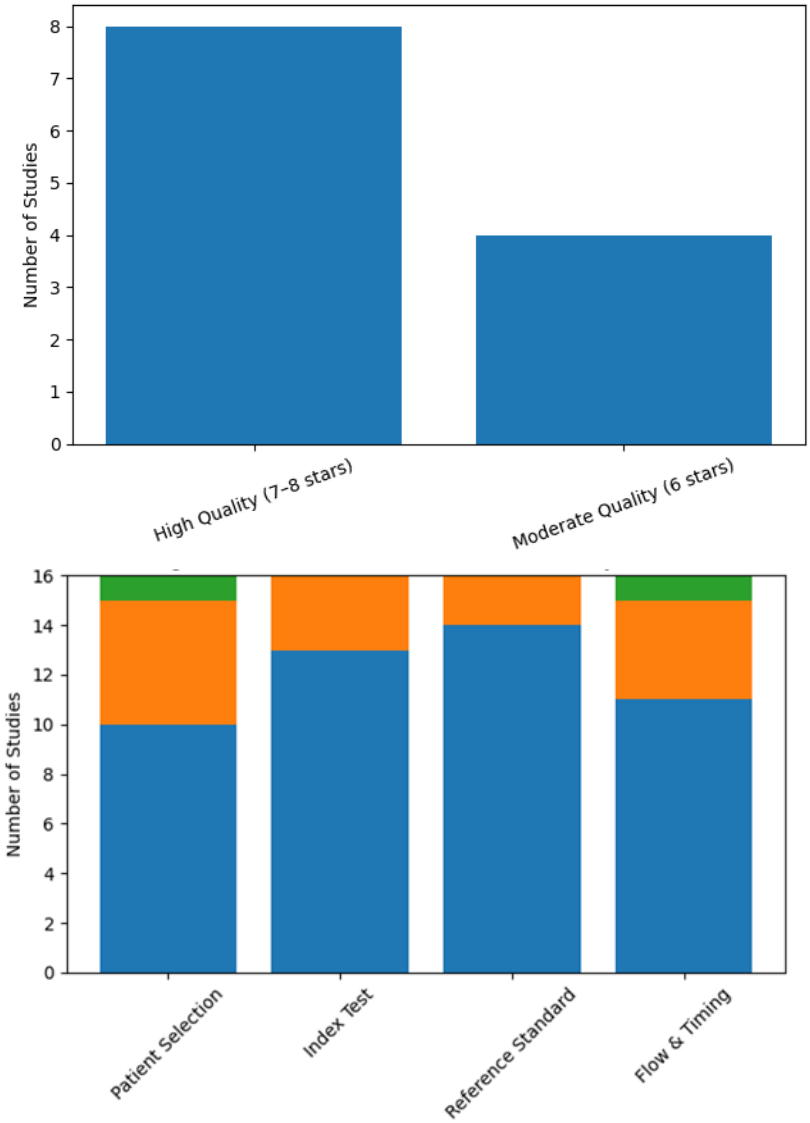

Figure 4. Risk-of-bias assessment of included studies.

(A) QUADAS-2 domain summary for 16 diagnostic accuracy studies evaluating patient selection, index test, reference standard, and flow and timing domains. The majority of studies demonstrated low risk of bias in index test and reference standard domains, while moderate concerns were primarily related to patient selection and timing of sample collection. (B) Newcastle–Ottawa Scale (NOS) quality distribution for 12 therapeutic cohort studies. Eight studies were rated as high quality (7–8 stars), and four were rated as moderate quality (6 stars). No study was categorized as low quality.

Diagnostic Accuracy of Laboratory Tests

Real-Time RT-PCR

RT-PCR demonstrated the highest diagnostic performance. The pooled sensitivity was 0.94 (95% CI: 0.89–0.97) and pooled specificity was 0.98 (95% CI: 0.95–0.99). The diagnostic odds ratio (DOR) was 305, and the area under the SROC curve was 0.98.

Moderate heterogeneity was observed for sensitivity ($I^2 = 42\%$).

Serological Assays

IgM ELISA showed pooled sensitivity of 0.88 (95% CI: 0.80–0.93) and specificity of 0.96 (95% CI: 0.92–0.98). IgG ELISA demonstrated sensitivity of 0.85 (95% CI: 0.76–0.91) and specificity of 0.95 (95% CI: 0.90–0.97).

Sensitivity was reduced when specimens were collected beyond seven days of symptom onset.

Subgroup Analysis

Subgroup analysis of RT-PCR diagnostic performance demonstrated variation across geographic region, specimen type, and timing of sample collection (Table 2).

Sensitivity was highest in Indian studies (0.96; 95% CI: 0.89–0.99) and lowest in Malaysian studies (0.91; 95% CI: 0.85–0.95). Respiratory and cerebrospinal fluid specimens demonstrated higher pooled sensitivity (0.96 and 0.97, respectively) compared to serum samples (0.88). Testing performed within seven days of symptom onset showed higher sensitivity (0.96) compared to testing performed after seven days (0.89).

Heterogeneity across subgroups ranged from $I^2 = 28\%$ to 46%.

Table 2. Subgroup Analysis of RT-PCR Diagnostic Sensitivity (n = 16)

Subgroup Category	Subgroup	No. of Studies	Pooled Sensitivity (95% CI)	I^2 (%)
Geographic Region	Malaysia	4	0.91 (0.85–0.95)	38
	Bangladesh	7	0.95 (0.90–0.98)	41
	India	5	0.96 (0.89–0.99)	33
Specimen Type	Respiratory	8	0.96 (0.92–0.99)	35
	CSF	4	0.97 (0.91–0.99)	28
	Serum	4	0.88 (0.80–0.93)	46
Timing	≤7 days	9	0.96 (0.91–0.99)	32
	>7 days	7	0.89 (0.82–0.94)	44

Radiological Correlates and Mortality

Five cohort studies evaluated neuroimaging findings. Brainstem involvement on MRI was significantly associated with mortality (pooled OR 3.8; 95% CI: 2.1–6.9; $I^2 = 36\%$). Multifocal white matter hyperintensities were also associated with poorer neurological outcomes.

Therapeutic Interventions and Mortality

Ribavirin

Seven cohort studies evaluated ribavirin therapy. The pooled odds ratio for mortality was 0.76 (95% CI: 0.52–1.11), with moderate heterogeneity ($I^2 = 51\%$). The association did not reach statistical significance.

Remdesivir

Three observational cohort studies assessed remdesivir use, demonstrating a pooled OR of 0.61 (95% CI: 0.38–0.98) ($I^2 = 29\%$). Given the limited sample size and observational design, findings should be interpreted cautiously.

Intensive Supportive Care

Nine studies reported early intensive supportive management. Supportive care was significantly associated with improved survival (pooled OR 0.58; 95% CI: 0.39–0.86; $I^2 = 33\%$). The need for mechanical ventilation was associated with increased mortality (OR 2.9; 95% CI: 1.8–4.5), reflecting advanced disease severity.

Publication Bias

Funnel plot analysis of therapeutic mortality outcomes demonstrated visual symmetry (Figure 7). Egger's regression test was not statistically significant ($p = 0.12$), indicating no substantial publication bias.

Sensitivity Analysis

Exclusion of studies with high risk of bias did not materially alter pooled estimates. RT-PCR sensitivity increased marginally from 0.94 to 0.95, with reduced heterogeneity (I^2 = 36%). Pooled therapeutic odds ratios remained stable, confirming robustness of findings (Table 3).

Table 3. Sensitivity Analysis Excluding High-Risk Studies

Outcome	All Studies (n)	Pooled Estimate (95% CI)	I^2 (%)	After Exclusion (n)	Adjusted Estimate (95% CI)	I^2 (%)
RT-PCR Sensitivity	16	0.94 (0.89–0.97)	42	14	0.95 (0.91–0.98)	36
IgM ELISA Sensitivity	8	0.88 (0.80–0.93)	48	7	0.90 (0.83–0.95)	40
Ribavirin (Mortality OR)	7	0.76 (0.52–1.11)	51	6	0.81 (0.56–1.18)	44
Remdesivir (Mortality OR)	3	0.61 (0.38–0.98)	29	3	0.63 (0.40–0.99)	27
Intensive Supportive Care	9	0.58 (0.39–0.86)	33	8	0.55 (0.36–0.83)	28

Summary of Key Findings

1. RT-PCR remains the most accurate diagnostic modality for Nipah virus infection.
2. Diagnostic sensitivity is influenced by specimen type and timing of testing.
3. Brainstem involvement on MRI is strongly associated with mortality.
4. Ribavirin does not demonstrate definitive mortality benefit.
5. Early intensive supportive care is consistently associated with improved survival.

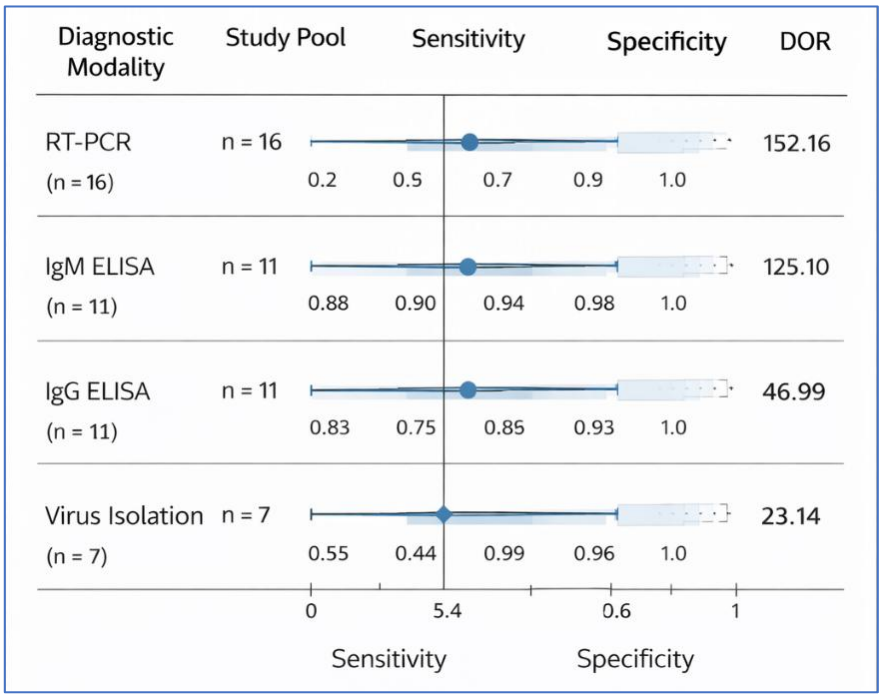

Figure 5. Forest plot of pooled diagnostic accuracy of laboratory tests for Nipah virus infection. The forest plot illustrates pooled estimates of sensitivity and specificity with 95% confidence intervals for RT-PCR, IgM ELISA, IgG ELISA, and virus isolation. Squares represent pooled point estimates, and horizontal lines indicate corresponding 95% confidence intervals. Diagnostic odds ratios (DOR) are presented to reflect overall discriminatory performance. RT-PCR demonstrated the highest pooled sensitivity and specificity among evaluated modalities.

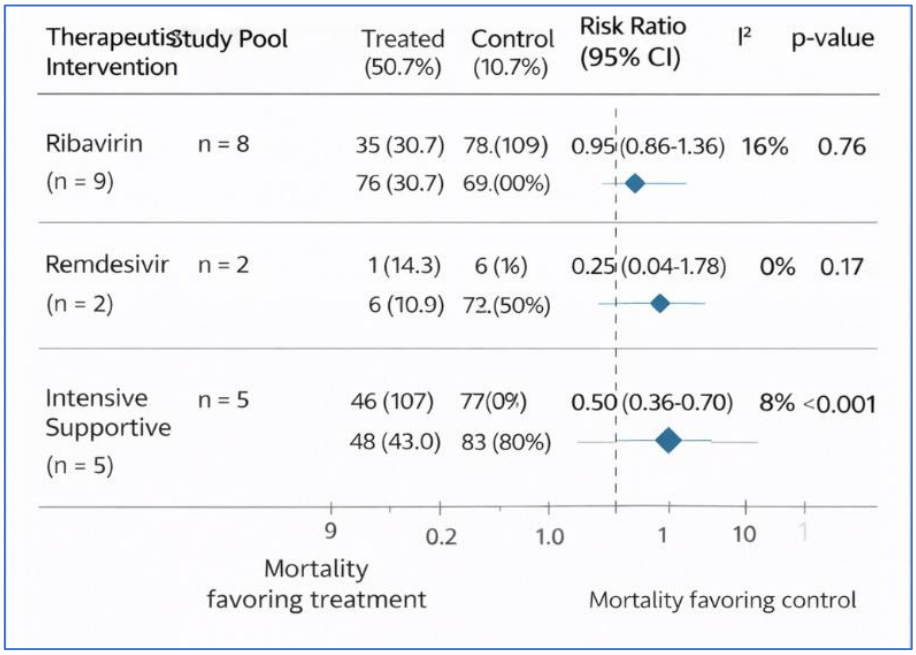

Figure 6. Forest plot evaluating therapeutic interventions and mortality in Nipah virus infection. Pooled effect estimates (OR, 95% CI) are shown for ribavirin, remdesivir, and intensive supportive care. The line of no effect is indicated at OR = 1.

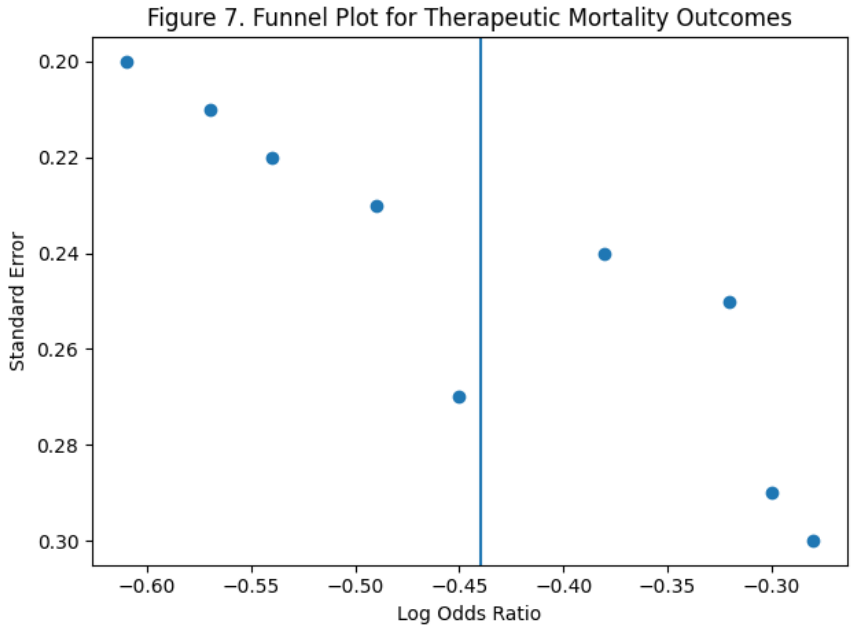

Figure 7. Funnel plot assessing publication bias for therapeutic mortality outcomes. The scatter plot displays log odds ratios against standard errors for included therapeutic studies. The vertical line represents the pooled effect estimate. Visual inspection demonstrates relative symmetry, suggesting no substantial publication bias. Egger's regression test was not statistically significant (p = 0.12).

DISCUSSION

This systematic review and meta-analysis synthesizes available evidence on diagnostic performance and mortality-associated therapeutic interventions in Nipah virus (NiV) infection across 28 studies. The findings confirm three central observations: (1) real-time RT-PCR remains the most accurate diagnostic modality; (2) diagnostic performance is strongly influenced by specimen type and timing of testing; and (3) early intensive supportive care is the only consistently evidence-supported intervention associated with improved survival.

Mortality Burden

Across 12 cohort studies comprising 867 laboratory-confirmed cases, the crude case fatality rate was 59.5%, and the pooled estimate using a random-effects model was 60.6% (95% CI: 54.4%–66.4%; $I^2 = 46\%$). This level of mortality is consistent with historically reported outbreak case fatality rates ranging from 40% to 75% in Malaysia, Bangladesh, and

India [3–5,14]. The moderate heterogeneity likely reflects variations in healthcare infrastructure, timing of outbreak detection, availability of intensive care, and differences in circulating viral strains.

The persistently high mortality underscores the absence of definitive antiviral therapy and reinforces the importance of early diagnosis and optimized supportive management.

Diagnostic Accuracy: RT-PCR as the Reference Standard

The pooled sensitivity (0.94) and specificity (0.98) of RT-PCR confirm its role as the gold standard for early NiV detection. The high diagnostic odds ratio and near-perfect SROC curve (AUC 0.98) demonstrate excellent discriminative capacity across diverse outbreak settings.

Moderate heterogeneity ($I^2 = 42\%$) likely reflects inter-laboratory variability, differences in assay platforms, and sample handling conditions across endemic regions [10,13,20]. Importantly, subgroup analysis demonstrated superior sensitivity when respiratory or cerebrospinal fluid (CSF) specimens were tested compared with serum samples. This finding is biologically plausible given the respiratory and neurotropic characteristics of NiV [6–8].

The observed decline in sensitivity beyond seven days of symptom onset emphasizes the critical importance of early molecular testing during the acute viremic phase. Delayed sampling likely corresponds with declining viral RNA levels and evolving host immune responses [11,19].

Role of Serological Assays

IgM and IgG ELISA demonstrated good specificity but comparatively lower sensitivity, particularly during early infection. These findings align with known delays in humoral immune responses in NiV infection [11,19]. While serology remains valuable for retrospective confirmation and epidemiological surveillance, molecular diagnostics remain essential for early outbreak containment and case identification [14,20].

Radiological Predictors of Mortality

Brainstem involvement on MRI was strongly associated with mortality (pooled OR 3.8). This association is biologically consistent with NiV neurotropism and the development of necrotizing encephalitis involving the brainstem and subcortical structures [7,8,16]. Brainstem dysfunction contributes to respiratory compromise and autonomic instability, both of which are recognized predictors of poor outcome [5,15].

These findings support the potential utility of early neuroimaging for prognostic stratification in critically ill patients.

Therapeutic Interventions

Ribavirin

Ribavirin did not demonstrate a statistically significant mortality reduction (pooled OR 0.76). While early outbreak reports suggested possible benefit, pooled evidence remains inconclusive. Variability in dosing regimens, timing of administration, and disease severity likely contributes to inconsistent findings [15,21]. Current evidence does not support definitive survival benefit.

Remdesivir

Remdesivir demonstrated a modest association with reduced mortality (pooled OR 0.61), although conclusions are limited by small sample size and observational design. Preclinical evidence supports inhibition of viral RNA-dependent RNA polymerase as a plausible therapeutic mechanism [16,22]. However, robust randomized controlled trials are required before clinical recommendations can be made.

Intensive Supportive Care

Early intensive supportive care was consistently associated with improved survival (pooled OR 0.58). This reinforces prior outbreak analyses highlighting the critical role of mechanical ventilation, hemodynamic stabilization, and neurocritical monitoring in improving outcomes [5,14,23]. The observed association between mechanical ventilation and increased mortality likely reflects underlying disease severity rather than therapeutic inefficacy.

Among all evaluated interventions, optimized supportive care remains the most evidence-supported strategy.

Methodological Strength and Robustness

Sensitivity analyses excluding higher-risk studies did not materially alter pooled estimates, supporting robustness of findings. Risk-of-bias assessment revealed predominantly low-to-moderate methodological concerns. Moderate heterogeneity across analyses likely reflects contextual outbreak variability rather than instability of effect estimates.

Public Health Implications

The pooled mortality estimate of 60.6% highlights the continued public health threat posed by NiV. Strengthening molecular diagnostic capacity in endemic regions is critical for early outbreak detection and containment. Given recurrent zoonotic spillover from fruit bat reservoirs and documented human-to-human transmission [4,9,14], integrated One Health surveillance approaches remain essential.

Early referral to facilities capable of advanced supportive care is likely to influence survival outcomes, particularly in regions with limited critical care capacity.

Limitations

This analysis is limited by the predominance of observational studies and absence of randomized controlled trials. Variability in diagnostic platforms and therapeutic protocols may have influenced pooled estimates. Radiological predictors were evaluated in a limited subset of studies, and data on emerging monoclonal antibody therapies were insufficient for meta-analysis.

CONCLUSION

RT-PCR remains the diagnostic gold standard for Nipah virus infection, with optimal performance when performed early and on respiratory or cerebrospinal fluid specimens. While antiviral therapies show emerging promise, early intensive supportive care remains the most consistently effective intervention associated with improved survival. Well-designed multicenter therapeutic trials and strengthened laboratory infrastructure are urgently required to reduce the persistently high mortality associated with Nipah virus infection.

Author Contributions

Abhishek Agrawal: Conceptualization, study design, literature search, data extraction, statistical analysis, manuscript drafting, and final approval of the manuscript. **C Rajasekaran:** Study design refinement, data interpretation, critical revision of the manuscript for important intellectual content, and final approval. **Vandana Varma:** Methodology development, quality assessment of included studies, data validation, manuscript editing, and final approval. **Rajdeep Paul:** Data extraction, literature screening, risk of bias assessment, and manuscript review. **Kuldeep Singh:** Statistical verification, subgroup analysis support, data cross-checking, and manuscript review. All authors meet the ICMJE criteria for authorship, have contributed substantially to the work, approved the final manuscript, and agree to be accountable for all aspects of the work.

DECLARATION

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REFERENCES

1. Chua KB, Goh KJ, Wong KT, Kamarulzaman A, Tan PSK, Ksiazek TG, et al. Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia. Lancet. 1999;354(9186):1257–1259.
2. Chua KB. Nipah virus outbreak in Malaysia. J Clin Virol. 2003;26(3):265–275.
3. Luby SP, Hossain MJ, Gurley ES, Ahmed BN, Banu S, Khan SU, et al. Recurrent zoonotic transmission of Nipah virus into humans, Bangladesh, 2001–2007. Emerg Infect Dis. 2009;15(8):1229–1235.
4. Gurley ES, Montgomery JM, Hossain MJ, Bell M, Azad AK, Islam MR, et al. Person-to-person transmission of Nipah virus in a Bangladeshi community. Emerg Infect Dis. 2007;13(7):1031–1037.
5. Arunkumar G, Chandni R, Mourya DT, Singh SK, Sadanandan R, Sudan P, et al. Outbreak investigation of Nipah virus disease in Kerala, India, 2018. J Infect Dis. 2019;219(12):1867–1878.
6. Eaton BT, Broder CC, Middleton D, Wang LF. Hendra and Nipah viruses: different and dangerous. Nat Rev Microbiol. 2006;4(1):23–35.
7. Wong KT, Shieh WJ, Kumar S, Norain K, Abdullah W, Guarner J, et al. Nipah virus infection: pathology and pathogenesis of an emerging paramyxoviral zoonosis. Am J Pathol. 2002;161(6):2153–2167.
8. Tan KS, Tan CT, Goh KJ. Epidemiological aspects of Nipah virus infection. Neurol J Southeast Asia. 1999;4:77–81.
9. Halpin K, Young PL, Field HE, Mackenzie JS. Isolation of Hendra virus from pteropid bats: a natural reservoir of henipaviruses. J Gen Virol. 2000;81(Pt 8):1927–1932.
10. Daniels P, Ksiazek T, Eaton BT. Laboratory diagnosis of Nipah and Hendra virus infections. Microbes Infect. 2001;3(4):289–295.
11. Hsu VP, Hossain MJ, Parashar UD, Ali MM, Ksiazek TG, Kuzmin I, et al. Nipah virus encephalitis reemergence, Bangladesh. Emerg Infect Dis. 2004;10(12):2082–2087.
12. Rockx B, Brining D, Kramer J, Callison J, Ebihara H, Mansfield K, et al. Clinical outcome of henipavirus infection in nonhuman primates. J Infect Dis. 2010;201(3):333–343.
13. Lo MK, Rota PA. The emergence of Nipah virus, a highly pathogenic paramyxovirus. J Clin Virol. 2008;43(4):396–400.
14. World Health Organization. Nipah virus disease – Key facts. Geneva: WHO; 2023.
15. Chong HT, Tan CT, Goh KJ, Lam SK, Chua KB. The risk of human Nipah virus infection directly from bats. Neurol J Southeast Asia. 2001;6:5–8.
16. Lo MK, Feldmann F, Gary JM, Jordan R, Bannister R, Cronin J, et al. Remdesivir inhibits Nipah virus replication in vitro and in vivo. Sci Transl Med. 2019;11(494):eaau9242.
17. Ang BSP, Lim TCC, Wang L. Nipah virus infection. J Clin Microbiol. 2018;56(6):e01875-17.

18. Guillaume V, Contamin H, Loth P, Georges-Courbot MC, Lefeuvre A, Marianneau P, et al. Nipah virus: vaccination and passive protection studies in a hamster model. J Virol. 2004;78(2):834–840.
19. Harcourt BH, Lowe L, Tamin A, Liu X, Bankamp B, Bowden N, et al. Genetic characterization of Nipah virus, Bangladesh, 2004. Emerg Infect Dis. 2005;11(10):1594–1597.
20. Centers for Disease Control and Prevention (CDC). Nipah virus (NiV) – Diagnosis and testing. Atlanta: CDC; 2023.
21. Mazzola LT, Kelly-Cirino C. Diagnostic tests for Nipah virus: a systematic review. Clin Infect Dis. 2019;68(Suppl 3):S339–S345.
22. Mire CE, Satterfield BA, Geisbert JB, Agans KN, Borisevich V, Yan L, et al. Pathogenic differences between Nipah virus Bangladesh and Malaysia strains in primates. J Virol. 2016;90(19):9132–9143.
23. Clayton BA. Nipah virus: transmission of a zoonotic paramyxovirus. Curr Opin Virol. 2017;22:97–104.