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Global and regional mortality statistics of nipah virus from 1994 to 2023: a comprehensive systematic review and meta-analysis

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ABSTRACT

The mortality rate of Nipah virus (NiV) can vary in different regions, and its pattern across timelines has yet to be assessed. The primary objective is to perform a comparative analysis of mortality rates across different timelines and countries. Articles reporting NiV mortality from inception to November 2023 were analyzed in PubMed, Ovid Embase, Scopus, and Web of Science databases. A meta-analysis utilizing random-effects models determined the mortality rate secondary to NiV complications. The initial search strategy yielded 1213 records, of which 36 articles met the inclusion criteria, comprising 2736 NiV patients. The Global mortality rate of the Nipah virus in the 2014–2023 decade was 80.1% (CI: 68.7–88.1%), indicating a significant 24% increase compared to the preceding decade (2004–2013) with a mortality rate of 54.1% (CI: 35.5–71.6%). Among the countries analyzed for overall mortality from 1994–2023, India experienced the highest mortality rate at 82.7% (CI: 74.6–88.6%), followed by Bangladesh at 62.1% (CI: 45.6–76.2%), Philippines at 52.9% (CI: 30–74.5%), Malaysia at 28.9% (CI: 21.4–37.9%), and Singapore at 21% (CI: 8–45%). Subgroup analysis revealed that India consistently had the highest mortality rate for the past two decades (91.7% and 89.3%). The primary complication leading to mortality was encephalitis, accounting for 95% of cases. This systematic review and meta-analysis revealed a noteworthy surge in NiV mortality rates, particularly in the current decade (2014–2023). The escalation, with India reporting a concerning level of mortality of 89.3–91.7% in the past decades, signifies a pressing public health challenge.

KEYWORDS

Mortality rate; global death rate; nipah virus; case fatality rate; henipavirus

Introduction

The Nipah virus (NiV), classified within the Henipavirus genus of the Paramyxoviridae family, is of zoonotic origin, with fruit bats (Pteropus genus) serving as the primary animal host reservoir. Fruit bats carrying the virus can infect humans and other animals, such as pigs, through close contact or bodily fluids. NiV may also spread from person to person following a spillover event [1]. Previously recorded mortality rates range from 40% to 75%, highlighting the growing threat [2,3]. It is known to cause severe neurological and respiratory disease, which is highly lethal [4]. It results in an encephalitic syndrome that is characterized by several symptoms, including headaches, high fever (pyrexia), and neurological abnormalities like vomiting, dizziness, reduced or absent reflexes, and doll's-eye reflexes. Respiratory signs are the second most common type of Nipah virus infection after neurological symptoms. These include symptoms like cold, coughing, dyspnea, or difficulty breathing. Conversely, symptoms like constipation, diarrhea, gastritis, and stomach discomfort have also been reported, albeit less frequently [5].

Over the years, there have been several outbreaks of the Nipah virus (NiV), which has left a mark. It was initially identified in 1998, following the first documented outbreak in the Malaysian town of Sungai Nipah, where the virus spread from pigs to humans [6]. This outbreak subsequently extended to other pig-farming areas, resulting in a significant toll of 283 human cases of viral encephalitis and 109 fatalities between 29 September 1998, and December 1999. Initially, the illness in pigs was misattributed to Classical Swine Fever, while human deaths were thought to be caused by the Japanese encephalitis virus [7]. The virus also extended to Singapore, where abattoir workers were affected due to contact with live pigs

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imported from Malaysia, causing 11 cases and 1 death, after which pig imports were prohibited from Malaysia. In Bangladesh, 209 human cases were reported from April 2001 to 31 March 2012, resulting in a high mortality rate of 77%. India saw its first NiV outbreak in Siliguri, West Bengal, in 2001, and Kerala experienced multiple outbreaks, with the most recent occurring in 2023 [8].

Despite its rarity, the possibility of a global pandemic caused by NiV is concerning, driven by factors such as susceptible human populations, various viral strains capable of person-to-person transmission, and the mutability of RNA virus replication [9]. Alarmingly, despite over two billion people residing in NiV-endemic regions, no approved vaccine exists for protection against the disease. Currently, all research and development endeavors concerning NiV vaccines remain in the pre-clinical phase, having been tested in preclinical challenge models involving hamsters, ferrets, and/or AGMs [10]. Regrettably, specific antiviral treatments or vaccines for NiV are non-existent, and patients can only receive supportive care [5].

The significant gaps in our knowledge about the mortality rates of the Nipah virus highlight the necessity of an in-depth evaluation. Thus, the primary objective of this systematic review is to fill these knowledge gaps and offer a comprehensive understanding of the epidemiological landscape of NiV.

Methods

We followed and documented the systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Detailed PRISMA checklist is given in Supplemental Table 1.

Search strategy and selection criteria

We extensively searched various electronic databases, covering their entire existence until December 2023, without limiting the language. Three primary authors performed a literature review to decide the following databases: PubMed, Embase, Scopus, and Web of Science. Supplemental Table 2 provides the details of our search strategy. Three authors independently assessed the titles and abstracts of the identified studies, excluding those that did not align with the predefined inclusion and exclusion criteria related to the research question. This is followed by comprehensive full text screening of the remaining articles to identify relevant information, and any discrepancies in article selection were resolved through consensus.

Our inclusion criteria encompassed studies that satisfied the following conditions: they provided information on the mortality rate among Nipah virus patients and were observational, including retrospective and prospective cohorts, case-control studies, case series, and case reports, with a minimum of five cases. Studies were excluded from the meta-analysis if they did not report the mortality rate of the Nipah virus, fell into the category of review articles, involved animal studies, or featured less than five cases.

Data extraction and analysis

Two researchers systematically recorded data regarding both study-specific and patient-related details on a standardized form. Any discrepancies that arose during this process were addressed through consensus. The study-specific characteristics encompassed details such as the primary author, study duration/publication year, follow-up duration, geographic location of the studied population, and study design, while patient-related information included the total number of individuals affected by Nipah virus and the corresponding number of fatalities attributed to Nipah virus infection. Different studies reporting NiV mortality related to the same institution/database were excluded prior to data extraction process to avoid overlapping.

Quality assessment

Two investigators independently evaluated the methodological quality of observational studies using the Newcastle – Ottawa scale [11]. This scale involves scoring studies in three areas: selection (four questions), comparability (two questions) of study groups, and ascertainment of the outcome of interest (three questions). Each question is scored with a maximum of 1 point, except for the comparability of study groups, which allows for separate points based on age and/or sex control (maximum 2 points). We used the Joanna Briggs Institute (JBI) Critical Appraisal checklist to evaluate case series quality. Studies were categorized: below 50% as low quality (high bias risk), 50–70% as moderate quality (moderate bias risk), and above 70% as high quality (low bias risk) [12].

Statistical analysis

We utilized the random effects model to calculate the pooled mortality rate along with a 95% confidence interval (CI). The assessment of heterogeneity among study-specific estimates was conducted using the inconsistency index (I^2 statistic). This index gauges the proportion of total variances across studies attributable to heterogeneity rather than chance; a value exceeding 50% indicates substantial heterogeneity. In addition, we performed a sensitivity analysis by systematically removing one study at a time to assess the impact on the overall results. To evaluate publication bias, we conducted a visual inspection of funnel plots and implemented statistical tests, including Egger's

regression test and Begg & Mazumdar's rank correlation test. Univariate and multivariate meta-regression analysis was also performed. These analyses were executed using Comprehensive Meta-analysis Software (CMA) version 4.

Results

Eligible studies

We identified 1213 studies from 1994 to 2023. Out of these, 617 articles were removed as duplicates, and 594 titles and abstracts were screened. Subsequently, 70 articles were comprehensively evaluated for eligibility, identifying 36 potentially eligible full-text articles, with 34 exclusions, as depicted in Figure 1. Hence, 36 eligible articles were included for qualitative and quantitative evaluation.

Characteristics of the included studies

In total, 36 studies encompassing 2736 confirmed Nipah virus (NiV) cases were included from 1994 to 2023. Geographically, the breakdown of NiV cases manifests as follows: 1860 cases (68%) in Bangladesh, 687 cases (25.1%) in Malaysia, 152 cases (5.5%) in India, 20 cases (0.7%) in Singapore, and 17 cases (0.6%) in the Philippines. Notably, 70% of the patients were male. The median (interquartile) age of the patients was 35.7 (IQR: 24.7–39.4) years. The predominant study designs included cohort studies (63.8%) [13–33], followed by case-control studies (22.2%) [34–40], case series (8.3%) [41–43], and cross-sectional studies (5.5%) [44,45] as outlined in Supplemental Table 3. Geographically, Bangladesh emerged as the most frequently cited location, accounting for 42.8% of the reported studies. All the Niv cases were confirmed utilizing IgM and IgG

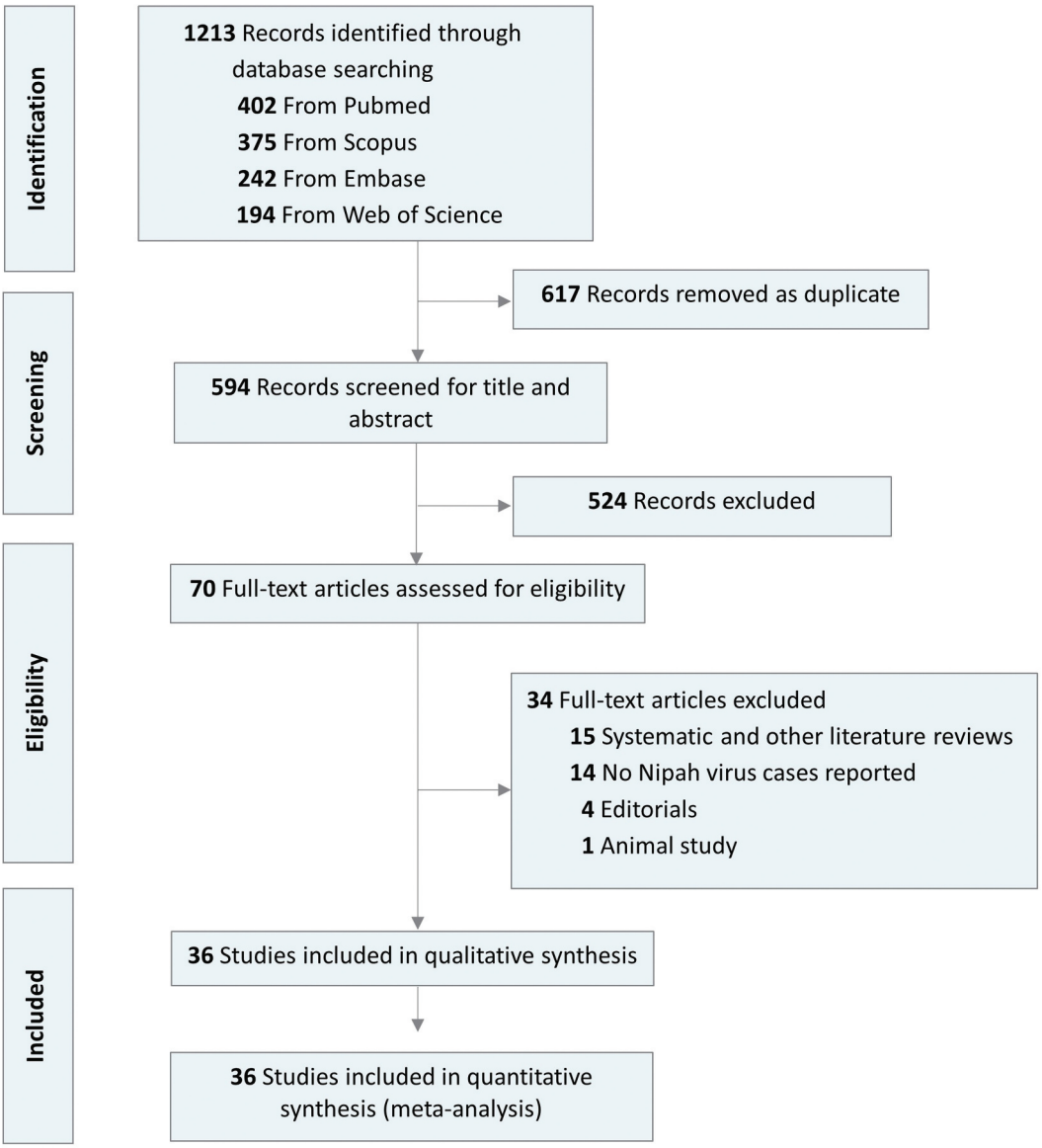

Figure 1. PRISMA flowchart illustrating study selection.

antibody detection by Enzyme-Linked Immunosorbent Assay (ELISA) or Real-Time Polymerase Chain Reaction (RT-PCR). Most of the samples are usually serum and CSF. For dead patients, brain tissue sampling with electron microscopy or immunohistochemistry (IHC) of the tissue was performed [19].

The decade-wise mortality rate of the Nipah virus

The trends in annual and decade-wise NiV mortality are plotted in Figure 2.

1994–2003

In the initial period spanning 1994 to 2003, the Nipah virus exhibited a mortality rate of 43.8% (CI: 32.9–55.3). The data revealed a moderate level of variability among the 12 studies, with Tau^2 (0.48) and I^2 (86.3%) (Figure 3). The significant heterogeneity, reflected in a Chi-squared value of 80.5 with 11 degrees of freedom (df) ($p < 0.0001$), positions this era as a baseline with a relatively lower mortality rate compared to subsequent decades.

2004–2013

Entering the subsequent decade (2004–2013), the mortality rate surged to 54.1% (CI: 35.5–71.6) across 15 articles. This period presented a substantial increase in variability, with Tau^2 (1.92) and I^2 (96.2%), indicating significant heterogeneity among the studies. The Chi-squared value of 374.8 with 14 degrees of freedom ($p < 0.0001$) highlights the need for nuanced interpretation and consideration of diverse findings. This decade marks a notable rise in mortality rates compared to the baseline.

2014–2023

The most recent decade (2014–2023) witnessed a striking escalation in the mortality rate, reaching 80.1% (CI: 68.7–88.1) based on eight articles. Heterogeneity decreased compared to the prior decade, with Tau^2 (0.42) and I^2 (54.6%). The Chi-squared value 17.6 with 8 degrees of freedom ($p = 0.02$) suggests more consistent findings. This decade stands out for a substantial increase in mortality rates compared to the baseline and the intermediate decade.

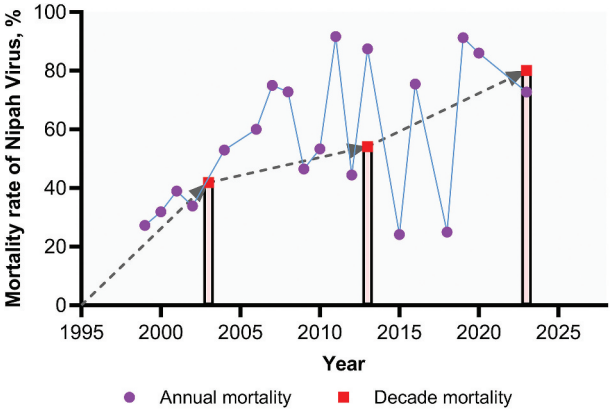

Figure 2. Annual and decade mortality rate trend for Nipah virus (1994–2023).

Global country-specific mortality rate

The analysis of country-specific mortality rates reveals distinct findings (Figure 4). In Bangladesh, the mortality rate is approximately 62.1% (95% CI: 45.6–76.2%), sourced from 19 studies, indicating significant differences and considerable heterogeneity ($I^2 = 96.1\%$, $p < 0.0001$). Malaysia, based on insights from seven studies, reports a comparatively lower rate of around 28.9% (95% CI: 21.4–37.9%), showcasing notable heterogeneity ($I^2 = 78\%$, $p < 0.0001$). India, encompassing seven studies, demonstrated the highest mortality rate of about 82.7% (95% CI: 74.6–88.6%) with minimal heterogeneity ($I^2 = 7\%$, $p = 0.37$). Singapore reveals a mortality rate of approximately 21% (95% CI: 8–45%) with minimal heterogeneity (I^2 <0.0001, $p = 0.38$) across two studies. However, the Philippines provides limited data, reporting a mortality rate of 52.9% from a single study (95% CI: 30–74.5%).

Overall, 95% of mortality is attributed to encephalitis, followed by acute respiratory distress (3.5%), sepsis (1%), and other causes (0.5%).

Subgroup analysis

Analyzing Nipah virus mortality rates across decades and regions reveals intriguing patterns (Table 1). In 1994–2003, Malaysia exhibited a comparatively lower mortality rate of 35% (95% CI: 29.9–40.4) than Bangladesh's higher rate of 71.8% (95% CI: 62.9–79.2).

Moving to the 2004–2013 decade, Bangladesh maintained a consistently high mortality rate of 57.1% (95% CI: 37.4–74.7). In contrast, Malaysia reported a notably lower rate of 7.7% (95% CI: 3.5–16.1), making it the decade with the lowest mortality in the selected countries. India displayed the highest in this decade with 91.7% (95% CI: 37.8–99.5%).

In the most recent decade (2014–2023), India consistently reported the highest mortality rate of 89.3% (95% CI: 80.4–94.5%), followed by Bangladesh with 74.9% (95% CI: 53.3–88.6%). Malaysia reported no cases during this period, while there was a new surge of NiV death in the Philippines population with 52.9%.

Risk of bias

Of the 23 cohort studies assessed, 13 were considered low risk of bias, and 10 had some concerns (Supplemental Table 4). For case-control studies, 7 were regarded as low risk of bias and one study has some concern (Supplemental Table 5). All cross-sectional and case series are considered low risk of bias.

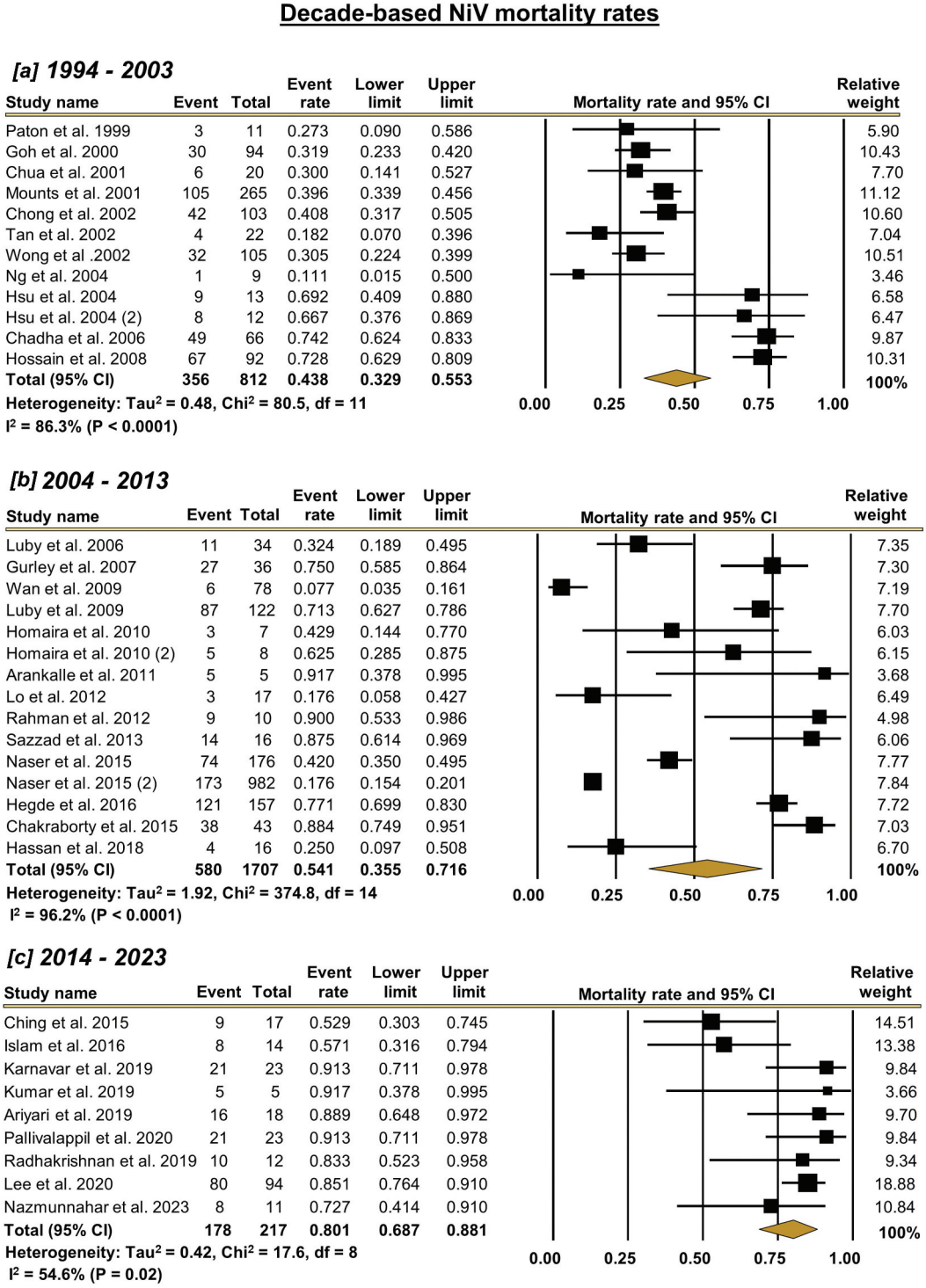

Figure 3. Forest plot illustrating the global decade-wise NiV mortality rate in [a] 1994–2003, [b] 2004–2013, and [c] 2014–2023.

Sensitivity analysis

In a sensitivity analysis examining mortality rates across the decades 1994–2003, 2004–2013, and 2014–2023, the removal of individual studies showed a minimal impact (Supplemental Figure S1). Surprisingly stable, the mortality rates fluctuated only within a narrow 4–5% range when studies were excluded. Similarly, the mortality rate for country-wise comparison showed minimal changes in one study removal (Supplemental Figure S2). Despite these minor variations, the overall mortality trends for each decade remained consistent. This highlights the robustness of the findings, suggesting that the reported mortality rates are reliable and not significantly influenced by specific studies.

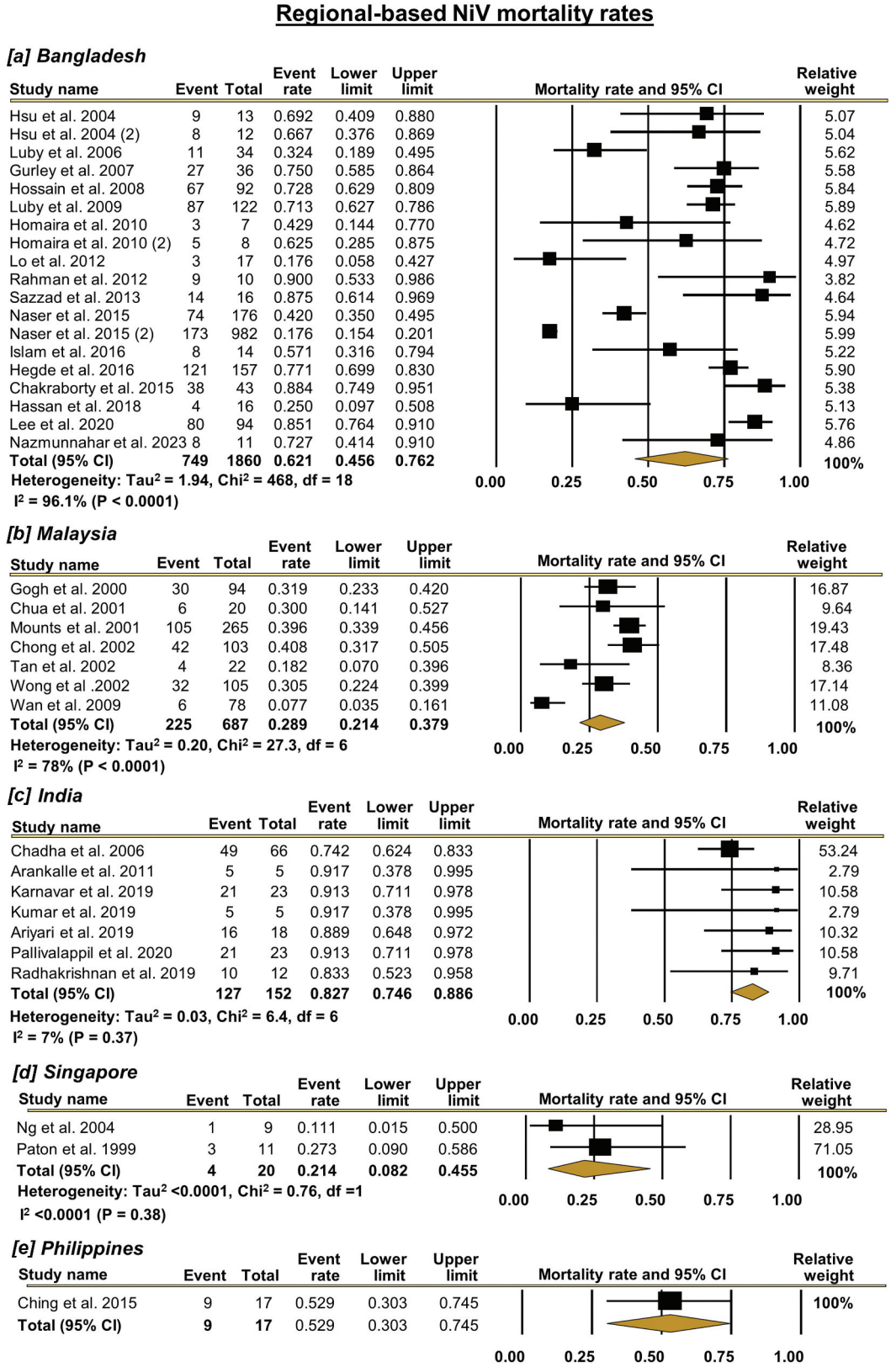

Figure 4. Forest plot illustrating the regional-specific NiV mortality rates in [a] Bangladesh, [b] Malaysia, [c] India, [d]Singapore, and [e] Philippines.

Meta-regression

To evaluate the heterogeneity of the NiV mortality outcomes, we performed univariate and multivariate meta-regression analyses to evaluate the associated variables. There was no statistically significant difference between the NiV mortality rates with age ($p = 0.24$), male ($p = 0.60$) and female sex ($p = 0.83$) variables (Figure 5).

Table 1. Subgroup analysis of stratified country-wise mortality in each decade.

Geographical locations	Number of studies	Number of observations, n	Number of events, n	Mortality per 100 Nipah virus patients	(95% CI)
1994–2003					
Malaysia	6	609	219	35	(29.9–40.4)
Bangladesh	3	117	84	71.8	(62.9–79.2)
Singapore	2	20	4	21.4	(8.2–45.5)
India	1	66	49	74.2	(62.4–83.3)
Subgroup analysis for 1994–2003 decade, pooled mortality = 43.8% (95% CI: 32.9–55.3%), I^2 = 86.3%, p-value <0.0001					
2004–2013					
Bangladesh	6	1624	569	57.1	(37.4–74.7)
Malaysia	1	78	6	7.7	(3.5–16.1)
India	1	5	5	91.7	(37.8–99.5)
Subgroup analysis for 2004–2013 decade, pooled mortality = 54.1% (95% CI: 35.5–71.6%), I^2 = 96.2%, p-value <0.0001					
2014–2023					
India	5	81	73	89.3	(80.4–94.5)
Bangladesh	3	119	96	74.9	(53.3–88.6)
Philippines	1	17	9	52.9	(30.3–74.5)
Subgroup analysis for 2014–2023 decade, pooled mortality = 80.1% (95% CI: 68.7–88.1%), I^2 = 54.6%, p-value = 0.02					

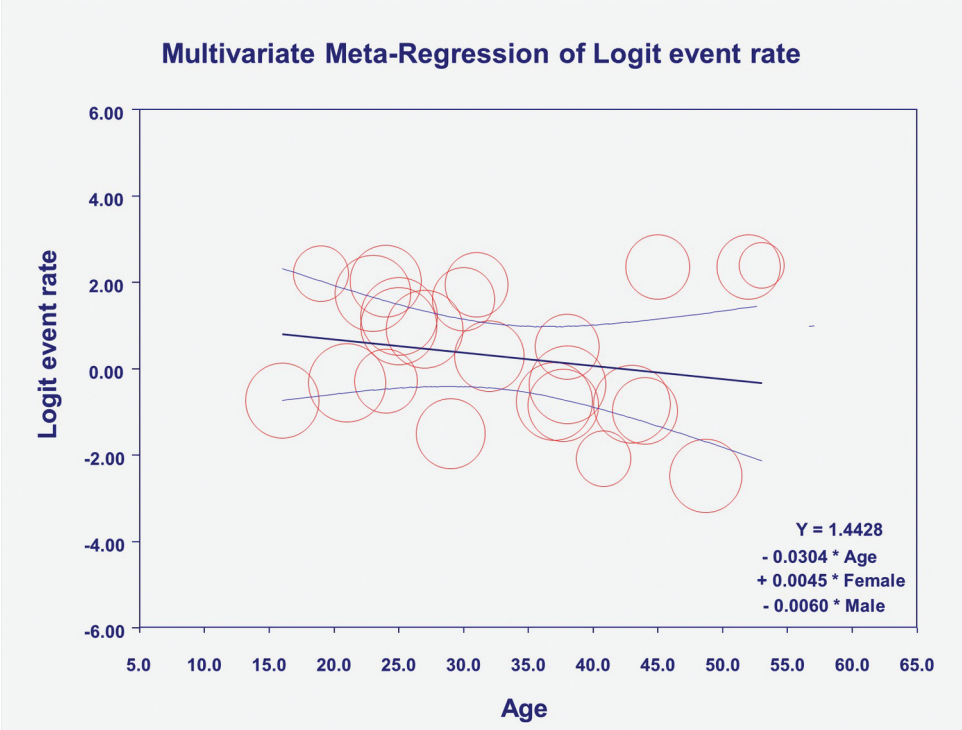

Figure 5. Multivariate Meta-regression analysis scatterplot for age and sex.

Publication bias

For 2004–2013, Egger regression suggested potential publication bias ($p = 0.04$), with a positive slope (0.24), aligning with funnel plot asymmetry (Supplemental Figure S3A). From 1994 to 2003, Egger regression ($p = 0.99$) and Begg & Mazumdar's test ($p = 0.404$) showed no publication bias as indicated by a symmetrical funnel plot (Supplemental Figure S4). There was no publication bias for 2014–2023 evident by Egger regression ($p = 0.91$) and Begg & Mazumdar's test ($p = 0.377$). (Supplemental Figure S3B). Similarly, there was the absence of publication bias across studies assessing NiV mortality rates based on geographical locations (Supplemental Figure S5). Detailed Egger's regression for the NiV mortality outcomes is given in Supplemental Table S6.

Discussion

In this systematic review and meta-analysis, we reviewed a total of 36 primary studies ranging from 1994 to 2023 that consisted of data regarding Nipah Virus (NiV) morbidity and mortality. The analysis revealed a concerningly high mortality rate for NiV with significant regional variations. India reported the highest mortality rate of 82.7%, followed by the Philippines at 52.9%, Bangladesh at 62.1%, Malaysia at 28.9%, and finally Singapore with the lowest mortality rate of 21%. We were also able to plot a trend of the decade-wise mortality rates for NiV, which pointed toward an almost two-times increase since its first discovery in 1999, indicating the significant impact of this infectious disease.

Chong et al. [17], for instance, suggested that in Malaysia and Singapore, the main mode of transmission was pig-to-human, unlike in Bangladesh and India, where it was mainly due to human-to-human and bat-to-human transmission. This hypothesis is also supported by the fact that pig consumption is significantly lower in Bangladesh and India. They also suggested that using barrier nursing techniques among Malaysian Health Care Workers (HCWs) may have significantly lowered early transmission among other HCWs and patients. Singapore and Malaysia took many other effective measures to limit the propagation of such outbreaks into epidemics and pandemics. For instance, they banned pig transport and introduced measures such as public education and national surveillance as well as pig culling [5]. Bangladesh and India, on the other hand, were seemingly more susceptible to this deadly virus due to a larger population of Pteropus fruit bats and many people living near them in rural areas [2,46]. They failed to enforce any of the aforementioned precautionary measures and these areas were often met with different and more infectious strains of NiV. Such factors, associated with the poor medical facilities and the expanding population may explain the reemergence of NiV in these countries [47].

India and Bangladesh had the highest mortality rate of 70–75% across the first decade of Nipah virus onset [20–22]. During the following 2004–2013 decade, the mortality rate of Bangladesh dropped by 15%, while India persistently reported a mortality rate of up to even 90% [36,42]. In contrast, Malaysia reported a lower mortality rate of 35% during the first decade, followed by a further drastic decline to 8% in the 2004–2013 decade [36,37]. This can be reflective of the high standard of measures enforced by the Malaysian Health Authority to combat future outbreaks. Similarly, Singapore emerged as one the earliest countries to contain Nipah virus recurrent outbreaks within the first decade and also reported the lowest mortality rate of 21.4% during that decade [13,48].

In the recent decade (2014–2023), NiV mortality has surged to an alarming 25–30% increase. A vast majority of it is contributed by India peaking up to 90% mortality [28,30,49]. This would be the 3rd consecutive decade of the highest mortality rate seen in the Indian population. Bangladesh follows closely with 75% mortality [40,45]. Although we were unable to determine the heterogeneity of the outcomes using the meta-regression analysis, we hypothesize that the highest mortality rates seen in countries like India and Bangladesh can be attributed to the lack of proper infrastructure and protocols to prevent or contain the NiV spread at its initial stages, compared to countries like Malaysia and Singapore.

Similar to the well-established SARS-CoV-2 which was responsible for causing COVID-19 in 2019, NiV has great potential to cause a pandemic and poses a global level threat. This is in favor of its unavailability of vaccine and treatment, varying viral course, emerging new strains, error-prone RNA replication, and nature to easily spread from a huge variety of living and non-living sources. Early in the recent pandemic, there was no hope for any vaccine to develop as soon as it did, and this was due to the immense economic crises and the huge tolls of deaths caused by COVID-19 that eventually sped up the process. NiV carries a similar risk of costing many countries a lot for its emergency responses simply because we are unprepared [50]. We found a decline in NiV mortality prior to the COVID-19 pandemic as evident from Figure 2. This can be partly due to the increased restrictions placed during the pandemic to contain COVID-19.

The only method to prevent and control this virus is by adopting effective surveillance and preventive measures. A few NiV-prone countries, like Malaysia and Bangladesh, were quick to implement a few surveillance strategies during and after the outbreaks. This consisted of event-based and sentinel surveillance. Ideally, every country should be ready with a surveillance team that includes personnel from different backgrounds such as epidemiologists, physicians, veterinarians, and law enforcement officers to be effective [4]. The most effective and efficient method would be mass public awareness. Such measures can easily minimize the leading causes of NiV outbreaks which may include infected livestock, lack of standard and droplet precautions among family members of infected individuals, and consumption of contaminated date palm sap and fruits.

In the end, like all studies, our research also has its strengths and limitations. Additionally, the inclusion of a sensitivity analysis further adds robustness to the findings, demonstrating that the reported mortality rates are consistent and not heavily influenced by specific studies. There are, however, a few limitations that should also be considered. Overall, this study significantly advances our understanding of NiV's global impact, but further research is needed to analyze the variations in mortality rates across different countries and the factors associated with it.

Conclusion

This is the largest systematic review to analyze historical trends in Nipah virus mortality rates, encompassing the virus's emergence to the current decade. Our findings highlight a substantial increase in mortality rates, particularly notable in the last decade, and a consistent upward trend across successive decades. Significantly, India demonstrates the highest mortality rates compared to other geographical locations.

Author contributions

SSV, PG and TYK were responsible for the conceptualization. SSV, PG, and TYK are responsible for the study design. SSV was

responsible for the literature searches. AS, FM, KK, SK, AP, LR, and SGK were responsible for the study selection. KK and SK were responsible for the data extraction. AS, FM, and SSV were responsible for the risk of bias assessments. SSV and RD were responsible for the meta-analysis. PG and SSV were responsible for the supervision. SSV, PG, TYK, and RD were responsible for the interpretation. SSV, AS, FM, and TYK were responsible for drafting the paper. All the authors were responsible for reviewing and revising the paper.

Disclosure statement

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