Comparative Analysis Of Mortality Patterns Associated With Plasmodium Falciparum And Plasmodium Vivax In A Hyperendemic Region Of Bihar, India

Dr. Sudha Prabha[1]*

[1*]Research Scholar Department of Zoology, B.N. Mandal University, Madhepura, Bihar, India

***Corresponding Author:** Dr. Sudha Prabha
[*]Research Scholar Department of Zoology, B.N. Mandal University, Madhepura, Bihar, India

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Abstract
Plasmodium falciparum and Plasmodium vivax co-exist with Malaria in regions of India that are hyperendemic, imposing a high mortality burden and having a dissimilar impact on the severe disease outcomes. The proposed study has made a comparative evaluation of the patterns of species-specific mortality in the selected hyperendemic districts of Bihar using retrospective observational cohort design on the basis of regularly collected clinical and surveillance data. One thousand two hundred and eighty-four laboratory confirmed cases of malaria were studied comprising 742 cases of P. falciparum and 542 cases of P. vivax. Mortality was observed to be more in P. falciparum (8.2% than in P. vivax (3.3%), where death cases were at both ends of the age and mainly among patients who presented with diabetes complications. Multivariate logistic regression revealed that P. falciparum infection on its own was a significant predictor of death following the factors of age, sex, and severity of disease but IVs at presentation were shown to be the most significant factor of death. Even if the death rate related to P. vivax was less in absolute terms, the fact that fatal consequences did occur highlighted the fact that vivax malaria is not always benign when it comes to hyperendemic areas with limited resources. The observation shows the significance of species based risk stratification, early diagnosis, and prompt referral of severe malaria in order to minimize death caused by malaria in endemic countries like Bihar, India.

Keywords: Malaria mortality; Plasmodium falciparum; Plasmodium vivax; hyperendemic region; disease severity; Bihar, India

1. INTRODUCTION

Malaria is a significant health issue in most regions of the world with a significant portion of the world disease burden lying in India especially in socioeconomically disadvantaged and climatically conducive places. Bihar is a region of sustained malaria outbreak because of a synergistic interaction of ecological favourableness to the amplification of the vectors, populace concentration, and restricted healthcare, and tardy care-seeking conduct in rural and peri-urban areas. Despite the fact that the most popular species that cause malaria in India Plasmodium falciparum and Plasmodium vivax contribute unequally to the mortality rate and severe disease at the regional level, their role is not well defined. Learning species-specific mortality patterns in hyperendemic environments is essential to inform specific clinical management practices and maximization of malaria control interventions to reduce the number of preventable deaths.

1.1. Background of the Study

Malaria-related morbidity and mortality remain a major issue in multiple endemic states in India, although the country has been making sustained efforts to control malaria, the ecological conditions are favorable to the breeding of vectors, seasonal peaks, and health system limitations in rural regions contribute to the high-risk environment in Bihar. Traditionally, Plasmodium falciparum has been known as the main cause of severe and fatal malaria with Plasmodium vivax commonly being regarded as relatively harmless, but recent clinical data has been showing striking complications and fatal outcomes of vivax malaria, making traditional risk stratification methods challenging. The risk of severe disease and mortality is further increased by late diagnosis, inaccessibility to timely and rightful antimalarial treatment and a high burden of comorbid conditions in hyperendemic areas. It is against this background that region-specific proofs on species-based mortality trends, both demographic and clinical determinants are inadequate, which highlights the necessity to carry out comparative studies in order to shape specific clinical care and general health policies that may minimize deaths due to malaria in endemic areas, including Bihar.

1.2. Rationale for Species-Specific Mortality Analysis

Malaria mortality requires species-specific analysis due to the fact that Plasmodium falciparum and Plasmodium vivax have significant differences in biological activity, course of illness, and treatment response, and thus result in dissimilar

risks of severe morbidity and mortality. Though the mechanism of cytoadherence and microvascular obstruction in falciparum malaria has been proven to cause life-threatening complications, there is a growing body of evidence indicating that vivax malaria may also lead to severe manifestations and fatal outcomes especially in the areas where there is delayed diagnosis, poor access to healthcare and high prevalence of comorbid conditions. Aggregated mortality among those species are likely to obscure clinically significant differences in risk profile and is counter-productive in developing specific clinical management interventions in areas like Bihar where both species are hyperendemic, and there are often limited health care facilities available. Specific mortality analysis of a species thus offers a more accurate epidemiological insight to the fatal risk and allows more effective triage and treatment prioritization, as well as informing context sensitive malaria control policies to minimize fatalities that can be prevented.

1.3. Objectives of the Study

- To contrast the mortality patterns of species-specific Plasmodium falciparum and Plasmodium vivax infections in a high-endemic area of Bihar, India.
- To study age- and clinical severity-wise distribution of malaria-related death cases in P. falciparum and P. vivax cases.
- To determine the independent predictors of mortality in patients with malaria, especially in terms of parasite species, severity at presentation and demographic characteristics.

2. LITERATURE REVIEW

Manning et al. (2011) studied clinical characteristics and prognosis of severe malaria due to Plasmodium falciparum, Plasmodium vivax and mixed infections among hospitalized children in Papua New Guinea. According to the study, malaria caused by falciparum had a close relationship with the increased rate of severe complications and worse clinical outcomes than malaria caused by vivax; nevertheless, the percentage of the children and people having severe disease due to vivax infection was also considerable. The authors noted that mortality was majorly associated with the falciparum infections, however, severe vivax cases were responsible to receive fatal outcome, thus it is difficult to insist on the traditional point of view regarding vivax malaria as an insignificant one. They highlighted the importance of clinical risk assessment of species in endemic children.

Tjitra et al. (2008) carried out a prospective study in Papua, Indonesia, to examine the clinical outcome of multidrug-resistant infections of Plasmodium vivax. It was found that vivax malaria commonly had serious clinical presentation such as severe anemia and respiratory distress, and caused a significant share of fatal cases. The authors have indicated that failure to treat the parasites and the delay in clearing of the parasite facilitated the development of severe infection and death in patients with vivax infection. The results were very robust in suggesting that P. vivax was no longer a consistently mild infection especially in an environment where drug resistance was emerging.

Genton et al. (2008) tested the relationship between Plasmodium vivax, mixed infections, and severe malaria among children in Papua New Guinea. The researcher established that vivax and mixed-species infections had a significant association with severe clinical manifestations, such as severe anemia and respiratory complications. Even though a bigger proportion of the severe and fatal cases was caused by falciparum malaria, vivax infections independently added their contribution to the burden of severe disease. The authors deduced that the strategies of control that concentrated solely on falciparum malaria could not anticipate the clinical effects of vivax malaria in endemic children.

Barcus et al. (2007) evaluated the population risk factors that are severe and fatal in vivax and falciparum malaria in hospitalized malaria patients in northeastern Papua in Indonesia. The research indicated that age, late presentation, and severity of the disease at the initial stage of admission were major factors that determined the mortality in both species. The Falciparum malaria was more linked with increased mortality rate although vivax malaria also led to serious disease and mortality especially to the susceptible populations. The authors emphasized the relevance of early diagnosis and timely clinical care to minimize species-specific mortality in the hospital environment with limited resources.

Mendis et al. (2001) reported the global burden of Plasmodium vivax malaria and also emphasized the long underestimation of this malaria in malaria control programs. The review also indicated that vivax malaria was associated with high morbidity and had a significant role in causing severe disease outcomes usually not captured in surveillance systems mainly based on falciparum malaria. The authors claimed that the clinical and population health consequence of vivax malaria was inadequately addressed and thus there was a knowledge gap in prevention, diagnosis and treatment interventions. Their work in turn highlighted the urgency of new focus on vivax malaria as part of malaria control and eradication agendas.

3. METHODOLOGY

This paper examined mortality trends in a hyper endemic area of Bihar, India in relation to Plasmodium falciparum and Plasmodium vivax with the help of routinely collected clinical and surveillance data. The methodological approach was developed to allow comparing the outcome of mortality and taking into consideration demographic and clinical factors.

3.1. Research Design

A retrospective observational cohort design was used. The outcomes of mortality associated with laboratory-confirmed cases of P. falciparum and P. vivax malaria were compared in the study within a specific study timeframe. This design was chosen based on capturing real world clinical outcomes in standard healthcare facilities and also enables one to

compare mortality pattern across species of parasite. This was done using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) principles of observational research.

3.2. Data Collection

Information was gathered using various healthcare facilities and district level surveillance data in the selected Bihar hyperendemic districts. The same case definitions and diagnostic criteria were used to provide consistency in the data sources.

- **Clinical Records Review:** Inpatient case files, hospital admission registers and discharge summaries were reviewed to obtain information on the diagnosis of malaria, severity of clinical outcomes, treatment administered, complications and in-hospital morbidity outcomes.
- **Surveillance and Laboratory Data:** Malaria surveillance records of districts and laboratory registers were reviewed to identify laboratory confirmed cases according to peripheral blood smear microscopy and /or rapid diagnostic tests. Cross verification of mortality data with the hospital death registers was done to reduce under reporting.

3.3. Sample

The sample population was 1, 284 confirmed cases of malaria through laboratory tests reported in the selected hyperendemic districts of Bihar between the study period. Among them, 742 were the cases caused by Plasmodium falciparum and 542 cases by Plasmodium vivax. Inclusion criteria were that the infecting species was identified with a high level of certainty based on the observation of peripheral blood on a microscope slide and/or by rapid diagnostic methods and the outcome (survived or died) was recorded. The patients were both adults and pediatric to represent the epidemiological situation of malaria in the area. The final analysis was only done on mixed infections, cases where the exact species could not be identified, and missing outcome data.

3.4. Data Analysis Techniques

Species-specific mortality patterns and factors related to them were analyzed by using descriptive and inferential statistical methods.

- **Descriptive statistics** were employed to describe demographic factors, malaria clinical profiles, and general mortality rates of malaria species.
- **Case fatality rate estimation** was done on P. falciparum and P. vivax alone so that mortality burden could be compared directly.
- **Chi-square tests** were used to test the variation in mortality rates in the two parasite groups.
- **Logistic regression analysis** was carried out to determine the relationship between malaria species and mortality, after control on age, sex, and disease severity indicators.
- **Stratified analysis** was applied to test the trends of mortality with respect to age and severity categories.

4. RESULT AND DISCUSSION

This section gives the comparative mortality trends recorded between the patients infected with Plasmodium falciparum and Plasmodium vivax as part of the study population. Findings are presented in absolute values and percentages to show the reality of the burden of mortality in demographic and clinical subgroups.

4.1. Result

Distribution of Malaria Cases by Species and Outcome

In the analysis, 1,284 laboratory-confirmed cases of malaria were used. Among them, 742 (57.8%) were infected by the P. falciparum and 542 (42.2%) by the P. vivax. The ratio of overall mortality was more in P. falciparum cases than in P. vivax cases.

Table 1 shows the general distribution of malaria cases and mortality rates with respect to the infecting species. The following table offers the comparative description of the Plasmodium falciparum and Plasmodium vivax infections burden among the study population and demonstrates the species-specific differences in survival and mortality.

Table 1: Distribution of malaria cases and mortality by species

Species	Total Cases (n)	Survived (n)	Died (n)	Case Fatality Rate (%)
P. falciparum	742	681	61	8.2%
P. vivax	542	524	18	3.3%
Total	**1,284**	**1,205**	**79**	**6.2**

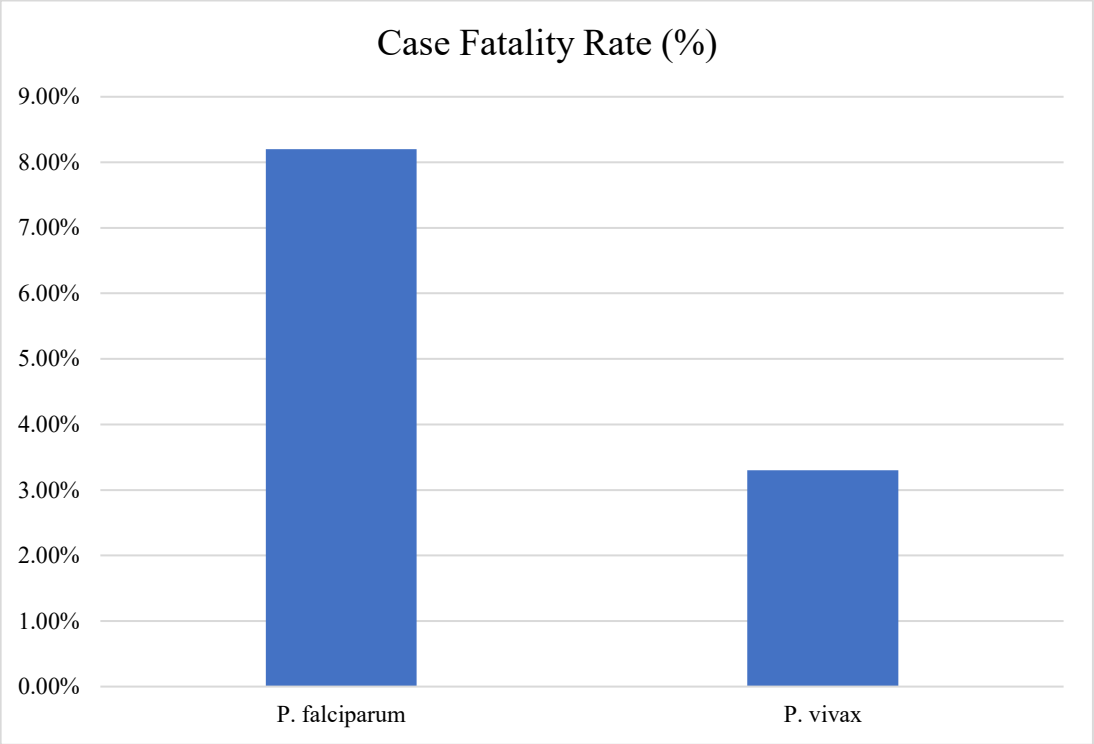

Figure 1: Visual representation of Case Fatality Rate (%)

Table 1 displays that Plasmodium falciparum was a bigger proportion of total malaria cases as well as a disproportionate cause of total mortality in the study population. The fatality rate of P. falciparum infections was over twice that of P. vivax and the risk of death caused by malaria due to falciparum in this hyperendemic area was significantly higher. Despite the fact that p. vivax made up a significant proportion of the overall cases, its mortality associated rate was relatively lower, which Favors its rather less aggressive clinical pattern. Nevertheless, the fact that P. vivax cases result in a fatal outcome more often serves to highlight that vivax malaria cannot be regarded as a completely benign disease, especially in resource-limited environments were delayed diagnosis and comorbidity, or lack of access to timely treatment can lead to even worse disease outcomes. These results supported the necessity of species-specific risk stratification and gave clinical management of falciparum malaria precedence, as well as the importance of ongoing attention to severe cases of vivax infection.

Age-wise Distribution of Mortality

Deaths were more common among children aged below 5 years and adults older than 50 years. P. falciparum contributed more percentage to all age groups in terms of death.

In order to investigate the age-related susceptibility to malaria-related mortality, the deaths were stratified between pertinent age groups in both plasmodium falciparum and plasmodium vivax infections. This stratification allowed evaluating whether the burden of mortality was concentrated in certain age groups in the study population.

Table 2. Age-wise distribution of deaths by malaria species

Age Group (years)	P. falciparum Deaths (n)	P. vivax Deaths (n)	Total Deaths (n)
< 5	14	5	19
5–14	11	3	14
15–49	23	7	30
≥ 50	13	3	16
Total	**61**	**18**	**79**

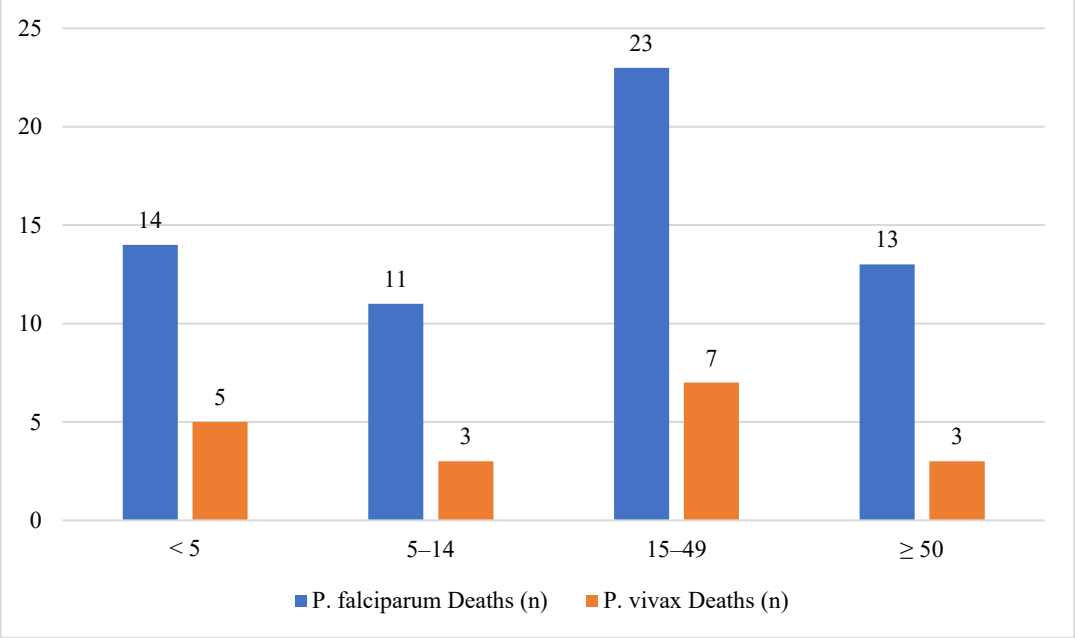

Figure 2: Visual Representation of Age-wise distribution of deaths by malaria species

The age-specific pattern of mortality indicated that there was no even distribution of deaths throughout the life span but rather more deaths were concentrated on the ends of the age bracket. The number of children under the age of five years as a proportion of deaths was quite high, as children are more biologically vulnerable because of the lack of well-developed immunity and high susceptibility to severe malaria. On the same note, increased mortality in the age group of 50 years and older can be explained by age-related changes in the physiological reserve and the underlying comorbid conditions, which can intensify the disease and make it more difficult to clinically manage. P. falciparum was consistently responsible for more deaths than P. vivax across all ages, and it is clear why it is more virulent and likely to lead to serious complications. The continued deaths attributed to falciparum among the economically productive population (15-49 years) also demonstrated the socioeconomic implication of malaria on a wider population; premature death among this group of people can have a heavy burden on the household and the community.

Mortality by Clinical Severity at Presentation

Patients who had severe malaria manifestations had significantly increased mortality especially in infections with P. falciparum.In an attempt to investigate the clinical scenario of mortality, the deaths were also analyzed based on the severity of the disease at presentation. The patients were classified as either having uncomplicated malaria or severe/complicated malaria depending upon the clinical characteristics described at the point of admission. This stratification allowed to evaluate the difference in the mortality burden depending on clinical severity between Plasmodium falciparum and Plasmodium vivax infections.

Table 3: Mortality according to disease severity

Disease Severity	P. falciparum (Deaths / Cases)	P. vivax (Deaths / Cases)	Total Deaths (n)
Uncomplicated	9 / 512	6 / 463	15
Severe/Complicated	52 / 230	12 / 79	64
Total	**61 / 742**	**18 / 542**	**79**

As Table 3 indicates, most of the deaths associated with malaria were among patients reporting to have an advanced or complicated disease as the burden of which is significantly higher in P. falciparum infections. Although a significant share of total cases was contributed by uncomplicated malaria, it was a relatively small cause of death, which showed that at the early stage of the illness, the disease was relatively easy to manage in the environment of a routine clinic. Conversely, serious cases like brain involvement, deep-seated anemia, dyspnea, and dysfunction of multiple organs were closely related to mortality, especially in the falciparum malaria. The relatively increased mortality rate of severe P. falciparum cases can be explained by the fact that such parasites are well known to have pathogenic mechanisms such as microvascular sequestration and increased parasite biomass which predispose the patient to the rapid development of clinical deterioration. Despite the mortality rate was lower in absolute terms in severe P. vivax cases, the fact that mortal outcomes in this cohort were observed proves the conventional view of vivax malaria as always benign and the necessity of critical clinical follow-ups. These results demonstrate the urgent role of early diagnosis, timely referral, and intensive treatment of severe cases of malaria to minimize deaths that can be prevented in hyperendemic areas.

Factors Associated with Mortality

Infection with P. falciparum was significantly related to increased odds of death after controlling age and sex and disease severity as against P. vivax. In both species, severe disease at presentation was the most predictive of fatal outcome.

Table 4: Binary Logistic Regression Analysis of Factors Associated with Mortality

Dependent Variable: Mortality (0 = Survived, 1 = Died)

Predictor Variable	B	S.E.	Wald	Sig. (p)	Exp(B) (Adjusted OR)	95% CI for Exp(B)
Age (≥50 years)	0.88	0.29	9.23	0.002	2.41	1.36 – 4.29
Sex (Male)	0.21	0.24	0.76	0.382	1.23	0.77 – 1.98
Disease Severity (Severe)	2.31	0.31	55.3	<0.001	10.08	5.45 – 18.65
Species (P. falciparum)	0.93	0.28	11.02	0.001	2.54	1.47 – 4.38
Constant	-4.12	0.52	62.7	<0.001	—	—

Multivariate logistic regression analysis showed that P. falciparum infection, but not P. vivax infection, was significantly related to a high probability of death after controlling age, sex, and the severity of the disease (adjusted odds ratio [AOR] = 2.54, p = 0.001). The strongest predictor of fatal outcome was severe malaria at presentation (AOR = 10.08, p < 0.001) which implies that there is a significantly higher risk of death with complicated disease. Age, old age (50 years and above) was also significantly correlated with the risk of mortality, but sex was not significantly correlated with mortality.

4.2. Discussion

The present study has offered a comparative evaluation of patterns of mortality in relation to Plasmodium falciparum and Plasmodium vivax in a hyperendemic area of Bihar, India and indicated definite species-specific variations in lethal consequences. The role of falciparum malaria as the major cause of malaria mortality in endemic site was reconfirmed by the substantially higher case fatality rate among P. falciparum infections. The observation is in line with the known pathogenic profile of P. falciparum that is characterized by increased parasite biomass, cytoadherence, and microvascular sequestration resulting in extreme organ dysfunction. In comparison, despite it being a major share of the overall malaria cases, the mortality rate associated with P. vivax was relatively lower, which confirms its historically considered lower virulence. Nevertheless, the fact of fatalities in vivax-carrying patients in the current study contradicts the long-standing hypothesis of vivax malaria as always clinically harmless and a necessity of increased clinical attention even in patients initially diagnosed with non-falciparum malaria.

Age-stratified analysis showed that the extreme age groups were disproportionately clumped in terms of mortality with little children and geriatrics having more fatality. Such examples are probably symptoms of underlying biological susceptibility, such as immature immune response during early childhood and age-related loss of physiological resistance in older people, which is compounded by an increased number of comorbid conditions. The endurance of the falciparum-related mortality at all age groups, including the economically viable population, brings into focus the wider social and economic consequences of malaria in hyper endemic countries like Bihar. Early deaths among adults in the working age are not only a problem to individual families but also lead to the perpetuation of poverty and a lack of productivity at the community level.

It turned out that clinical severity at presentation was the strongest predictor of mortality and that severe or complicated malaria contributed to the overwhelming proportion of mortality. This observation builds up the paramount significance of early diagnosis and timely instigation of relevant antimalarial therapy before it escalates into life threatening complications. The excessive mortality rate of severe P. falciparum cases indicates the dynamic nature of the falciparum malaria that may rapidly transform to cerebral malaria, severe anemia, respiratory distress and multi-organ failure unless treated effectively. Although fewer people were killed as a result of severe P. vivax cases, their occurrence also confirms the emerging evidence that vivax malaria can lead to severe and fatal outcomes in the context of certain epidemiological and clinical settings, especially in populations that had late access to healthcare, or had co-morbid nutritional and infectious conditions.

The independent existence of P. falciparum infection in raising the risk of death after age, sex, and severity of the disease was confirmed by multivariate analysis and further supported the idea that the species-specific biological consequences led to fatal outcome in addition to the clinical presentation alone. The high prevalence of severe disease and mortality highlights systemic failure in early disease diagnosis, referral route, and lack of access to critical care in hyperendemic and resource-limited regions. These results imply that enhancing the peripheral diagnostic capacity, prompt referral of severe cases as well as by enhancing the availability of the intensive supportive care at secondary and tertiary levels constitute key elements of malaria mortality reduction measures.

Regarding the public health issue, the research outlines the necessity of differentiated clinical risk stratification on the basis of parasite species and severity of the disease. Although continuous malaria control operations have been focused on falciparum malaria, the witnessed death toll in vivax cases implies that the operation must take an integrated strategy that does not underrate the clinical importance of non-falciparum malaria. Specific measures aimed at early detection of the disease in vulnerable populations, communal education to minimize the delay in care-seeking and enhancing facility-based control of severe malaria may help in making significant improvements of the preventable mortality rates due to malaria in hyperendemic countries like Bihar.

The results of the study must be viewed in the frames of its limitations, such as the retrospective nature of the study and use of routinely collected clinical records that might be incompletely documented and may misclassify patients by disease severity. Also, deaths that did not take place in the formal healthcare institutions might not have been sufficiently measured, and as a result, community level deaths might be underestimated. Even in the face of such shortcomings, the researchers can gain relevant information on mortality patterns and the necessity of species-specific malaria control and clinical management approaches due to the large sample size and comparative framework specific to the species.

5. CONCLUSION

This study was able to show that malaria-related death did differ clearly between species in a highly endemic area in Bihar, where Plasmodium falciparum was leading to a disproportionate share of fatal consequences in comparison to Plasmodium vivax. Death was drawn at both ends of age and was highly influenced by clinical severity at presentation with the severe form of malaria becoming the most powerful predictor of death in both species. The falciparum infection on its own, even after demographic factors and severity of the disease were taken into account, was a risk factor of mortality, which highlights the chronic clinical negligence of this type of infection in endemic areas. Even though P. vivax-related mortality among people was not as high in absolute terms, the frequency of lethal outcomes confirms the risk of vivax malaria as a disease with a homogeneous benign image and the need to pay close attention to clinical care. Together with these results, they highlight the significance of early diagnosis, early referral, and species-informed risk stratification to prevent preventable deaths associated with malaria in resource-constrained, hyperendemic countries like Bihar, India.

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