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A micro-epidemiological report on the unstable transmission of malaria in Aligarh, India

Sana Aqeel [a,*], Ansari Naheda [a], Adil Raza [b], Wajihullah Khan [a,*]

[a] Section of Parasitology, Department of Zoology, Aligarh Muslim University, Aligarh, U.P., India
[b] Department of Microbiology, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, U.P., India

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ABSTRACT

India contributes approximately 70% to the malaria burden of Southeast Asia. The transmission of disease in the country is generally hypoendemic, seasonal and unstable. Most researchers focus upon the hyperendemic malarious regions with stable malaria transmission. There is paucity of data regarding malaria transmission in hypoendemic regions, here we are presenting an epidemiological picture of clinical manifestations through a hospital-based survey in Aligarh, India, during 2016–18. Two thousand sixty-eight patients were diagnosed with malaria infection in Jawaharlal Nehru Medical College and Hospital (JNMCH), out of which 1104 were enrolled for clinical analysis. Ninety per cent of the cases were reported during July–November, and the rest in the dry season. A progressive increase in the prevalence rate was observed during the study period, i.e. 4.8, 7.57 and 8.7% in 2016, 2017 and 2018, respectively. Of the total cases, 75.77% had *vivax* malaria, while rest suffered from *falciparum* malaria. The risk of disease was significantly higher in the age group 0–15 years compared to all other age groups ($p < .0001$). The infection rate was higher in males (61%) compared to females (39%) $p < .0001$. Overall 8.6% of the patients had severe malaria who fulfilled the WHO criteria. The increasing rate of malaria infection during the study period and a considerable no. of severe vivax malaria cases warrant an efficient disease monitoring system, pointing towards the need to carry out micro-epidemiological studies in order to estimate the real burden of malaria in the country.

1. Introduction

Malaria has a substantial contribution towards public health problem worldwide and serves as a significant contributor to human morbidity and mortality. The epidemiology of malaria varies in different parts of the world as it is dependent on etiological factors, climate, topography, and vector ecology (Paaijmans et al., 2012). The factors controlling malaria transmission in India are diversified. The epidemiology of malaria is considered 'highly intricate' owing to the wide-ranging geography, ecological diversity, and climatic variations. These factors regulate the breeding of widely spread nine anopheline mosquito vectors that transmit the malaria parasites (Kumar et al., 2007). The transmission intensity is variable in different parts of the country as there is an overlap of vector and parasite species (Das, 2015). Being the second most populous country in the world (1.3 billion population),

* Corresponding author at: Section of Parasitology, Department of Zoology, Aligarh Muslim University, Aligarh, U.P., India.
E-mail address: wajihullahkhan@yahoo.co.in. (W. Khan).

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India's public health system has to face numerous challenges for the approximation and control of national malaria burden and proper implementation of surveillance programs (Directorate of National Vector Borne Disease Control Programme, 2012NVBDCP, 2012). The co-endemicity of *Plasmodium falciparum (Pf)* and *P. vivax (Pv)* infections in India pose another challenge for malaria eradication projects, as the two parasite species may differ in transmission kinetics and their spatial distributions (Singh et al., 2009). As for the global burden of *Plasmodium vivax* is concerned India ranks third (Wangdi et al., 2016). Hackett, 1937 rightly stated, "Everything about malaria is so moulded by local conditions that it becomes a thousand epidemiological puzzles".

According to WHO report 2017, fifteen countries in sub-Saharan Africa and India are acquitted for nearly 80% of the malaria burden worldwide. However, only five of them accounted for approximately one-half of the malaria burden, in which India's contribution is 4% (WHO, 2017). Among these countries, only India reported progress in reducing its malaria burden in 2017 compared to 2016 (WHO, 2018). Malaria epidemics have plagued many parts of India and Pakistan, whereas many regions of the country experience unstable transmission due to the local climes, especially in parts of Northern India (Sharma et al., 1985). The instability of malaria outbreaks magnifies the clinical complications associated with the disease. Unstable transmission may cause frequent epidemics; however, there are knowledge gaps regarding the epidemic periodicity of malaria in India (Singh, 2009). Although Uttar Pradesh (UP) does not come under the epidemiologic states of malaria in India, it adds significantly to the *vivax* malaria burden of the country (Jambulingam et al., 1991). A recent study reports that ten states are accountable for more or less 89% of *vivax* malaria, of which, Odisha, Jharkhand, Madhya Pradesh, Uttar Pradesh, and Gujarat, reports 64% cases (Anvikar et al., 2016). Most of the research studies focus on the hyperendemic regions with stable malaria transmission; no systematic study has examined the trends of malaria infection in UP. However, we conducted a micro epidemiological study (hospital-based survey) in a low-endemicity peri-urban setting, i.e. Aligarh, a city in the state of UP, India, where both *Pf* and *Pv* infections are reported (Asma et al., 2014; Khan et al., 2011). Human malaria infections encompass a wide range of clinical presentations which are at times life-threatening. The complications that occur during the disease are often influenced by host-parasite interaction, environmental factors, antimalarials, immunity, age, and gender of host (Mackintosh et al., 2004). In this study, we aim to depict the rate of malaria infection in patients of different age groups and their clinical presentations.

2. Materials and methods

2.1. Study area

Aligarh is located in the middle portion of the doab, the land between the Ganges and the Yamuna rivers, and lies 145 km S-E of the capital, New Delhi. The climate here is monsoon-influenced, humid and of sub-tropical type. This area witnesses a long dry season from November to May followed by a rainy season from June to October. The highest and lowest average temperatures in June and January remains approximately 34.2 °C and 14 °C respectively, maximum rainfall occurs in August (average of 246 mm) whereas the minimum is recorded in November (average of 3 mm) (World weather online, 2018). This weather condition corresponds to the unstable transmission of malaria where distinct differences are apparent in the transmission patterns during the dry and wet season. The study was conducted during 2016–2018 in Jawaharlal Nehru Medical College and Hospital (JNMCH) of Aligarh Muslim University by recruiting the subjects having an acute febrile illness. This is the main hospital in Aligarh, equipped with acute care and diagnostic facilities which attracts the nearby rural and sub-urban masses. A constant influx of the febrile and malaria-positive cases provides an opportunity to the researchers for in-depth clinical analysis. Approximately 10,000 cases of febrile illness are reported annually. The febrile individuals attending the outpatient, indoor patients, paediatrics, and various other departments of JNMCH were diagnosed by laboratory technicians for malaria positivity.

2.2. Sampling and diagnosis

Venous blood was drawn from the febrile patients and examined for the presence of *Plasmodium* spp. by microscopy, Quantitative Buffy Coat analysis and rapid diagnostic test (RDT), as per the need. Specific diagnosis of malaria was made by examining thick blood smears and with the help of rapid diagnostic kit CareStart™ Malaria Ag P.f/Pan (ACCESS BIO. INC., NJ, USA).

A record was maintained for all the febrile and malaria positive patients who reported to JNMCH between January 2016 and December 2018. Malaria positive patients' demographic information, disease history and symptoms were also recorded. They were categorised into the severe and mild type of malaria as per the WHO guidelines. All data were recorded systematically in EpiInfo™ 9.0 (CDC, Atlanta, Georgia, USA).

Trained physicians of the hospital carried out standard clinical evaluation of the reporting patients. The malaria positive subjects were treated according to the national drug policy for malaria treatment.

2.3. Clinical assessment

Clinical laboratory data was available for 1104/2068 patients. As per the WHO criteria, patients were classified into uncomplicated or complicated type. Patients with fever >38 °C headache, chills or malaise were regarded as uncomplicated/mild. Whereas, a clinical case was considered to be complicated/severe if one or more of the following clinical or laboratory parameters were found irrespective of *Plasmodium* species: Haemoglobin <7 g/dL in adults and < 5 g/dL in children was considered as severe anaemia, for renal dysfunction serum creatinine >1.5 mg/dL, severe thrombocytopenia ≤20,000 platelets/μL and hyperparasitaemia >50,000 parasites/ μL were the indicative values/numbers.

2.4. Ethical approval

The protocol for the study was approved by the Institutional Ethics Committee of Jawaharlal Nehru Medical College, Aligarh Muslim University. All procedures performed in the study were in accordance with the 1964 Helsinki declaration and its later amendments.

2.5. Meteorological reports

Information regarding monthly weather for Aligarh district for the period of three years (1st January 2016 to 31st December 2018), was retrieved from the India Meteorological Department, Ministry of Earth Sciences, Government of India (India Meteorological Department, 2018).

2.6. Statistical analysis

For statistical analysis, GraphPad™ Prism 7.04 software (San Diego, California, USA) was used. The data were expressed as counts, percentages for categorical variables and as mean ± standard deviation (SD). Patients were divided into five age groups (0–15, 16–30, 31–45, 46–60, and 60 above) to find out the associability of infection with age, gender and disease severity. The per cent parasitaemia, with mild and severe anaemia, was also calculated in order to work out the degree of severity of disease. The connection of disease with variables such as gender, area of residences was determined by the $\chi 2$ test with Yates correction ($p < .05$). The differences between the age-groups, species distribution and three-year prevalence were tested by the non-parametric tests and regression analysis. The numbers of mixed infections were scarce throughout the study; therefore, they were not included in the data.

3. Results

Trends and differences in the overall rate of malaria infection were analysed monthly as well as annually for three consecutive years.

3.1. Febrile and malaria positive cases

A total of 32,642 febrile patients were registered during 2016–2018 for the morbidity surveillance. Among those, 2068 subjects were diagnosed as malaria positive by the hospital (Fig. 1). Of which, 1567 (75.77%) had *vivax* malaria, and the rest *falciparum* malaria (24.22%) ($p = .012$ by Regression analysis). During the three years of the survey, the febrile, as well as the malaria-positive subjects attending the JNMCH increased. Four hundred twenty-three cases were recorded in 2016, 788 in 2017 (1.86 times) and 857 (2.02 times) in 2018 (Fig. 2). The prevalence during 2016 vs. 2017 ($p = .03$) and 2016 vs. 2018 ($p = .009$) vary significantly, whereas 2017 vs. 2018 ($p = .89$) is not significant as determined by Yates continuity corrected chi square test. While the conventional malaria season in Aligarh is from July to November, the *Pf* and *Pv* cases were recorded year-round, though much less in the dry season. The patient influx during the wet season was far more than in the dry season. The annual rains always preceded the climax of malaria season, i.e. in June, July and August, the number of patients remained high

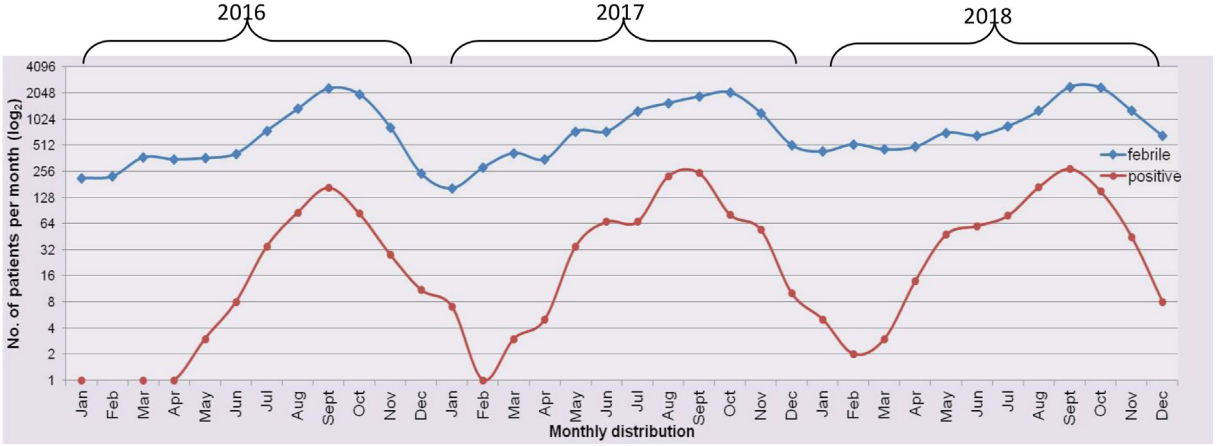

Fig. 1. The trend of febrile and malaria positive patients at JNMCH during the study period (2016–2018).

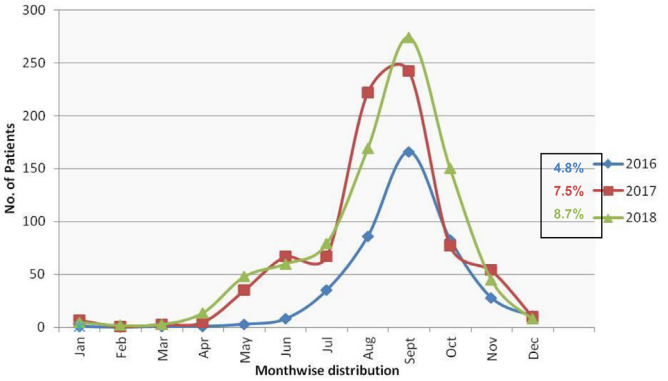

Fig. 2. Month-wise distribution of malaria infection during 2016–18 (rate of infection is indicated in the box).

from Aug to Oct throughout the study, and the peak transmission was observed in September which was always concomitant with the rains. Fig. 3 depicts the distribution of vivax and falciparum malaria among all the cases and rainfall distribution.

3.2. Age/gender-specific analysis and disease severity

Comparatively a higher number of males (61%) were recorded during the course of study compared to females who represented only 39% ($p = .03$, chi square test with Yates correction). Distribution of *Pf* and *Pv* infection in male and female patients is shown in Fig. 4. The gender bias was evident in every age group; it was greater in the age group 0–15 years, (62.05% male and 37.95% female, $p = .02$) (Fig. 5A &B). The highest infection and gender bias was observed in the age group 0 to 15 years ($p = .01$ regression analysis). Frequency of complicated malaria in the patients of different age groups is shown in Fig. 5C. Moreover, a more significant proportion of severe malaria (SM) was more pronounced among children of 0 to 5 years, with hyperparasitaemia. Among parasitaemic individuals (2068), 8.6% met with the WHO criteria of SM. Table 1 represents the general characters of patients and the proportion of SM cases in *Pf* and *Pv* infections. Age could be a risk factor for SM, but seasonal variation and year of attendance also influenced prevalence. Disease severity in malaria patients during the wet season was higher than that reported in the dry season. A comparatively lesser no. of SM patients was recorded during the year 2016 as prevalence was low during this year compared to 2017 and 2018. Patients over the age of 45 years and below 15 years, irrespective of *Pv*/*Pf* infection were hospitalised in a higher ratio than those between the ages of 15–30 and 31–45 years, point towards the vulnerability of older and youngest populations for severe malaria in the survey area which happens to be a low transmission setting.

Severe anaemia was a common clinical manifestation which was reported in 80% of the complicated cases. But the cerebral malaria was rare and was found only in five cases during this study. A few reported cases had convulsions, hypotension, thrombocytopenia, liver and kidney dysfunction or a combination of above clinical manifestations. There was a trend for a slightly higher percentage of complications in *Pf* cases, but the difference between clinical presentation in *Pf* and *Pv* was not statistically significant (Fig. 6A & B, Table 2). The patients who had hepatic dysfunction were also severely anaemic, and anaemic patients also had a tendency of convulsions but such patients were fewer in numbers. Significant bleeding was also observed in five patients.

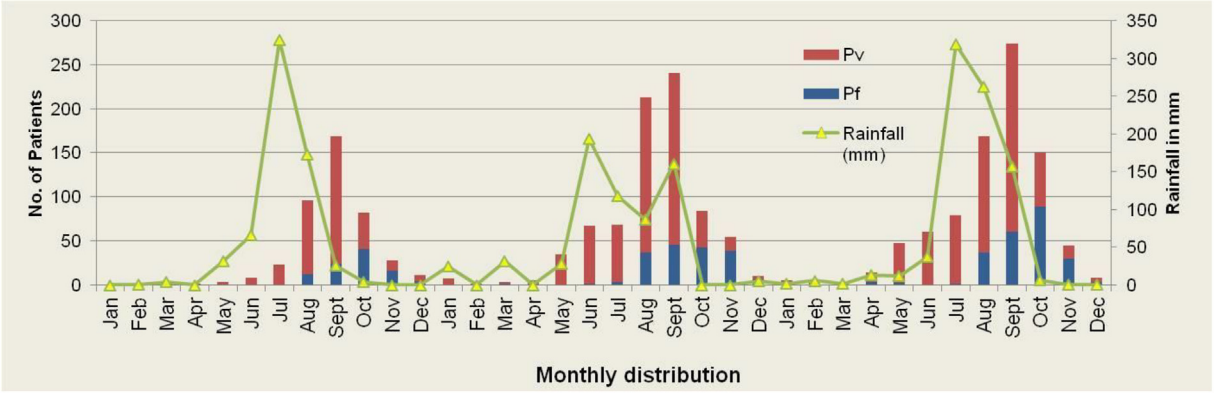

Fig. 3. Month-wise distribution of malaria positive cases (*Pf* and *Pv*) and average rainfall during the study period (2016-18).

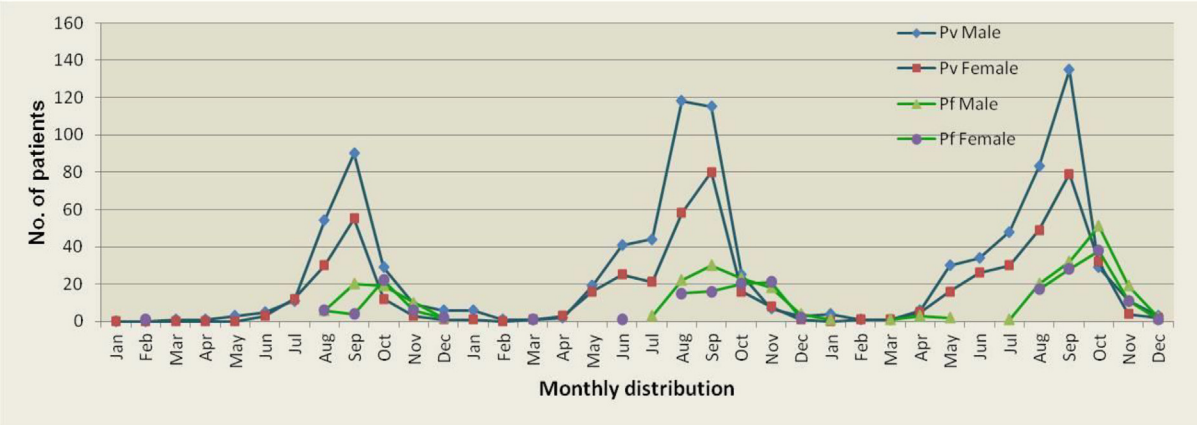

Fig. 4. Species-wise distribution of *Plasmodium* in male and female infected patients.

4. Discussion

The present study was conducted to have a comprehensive understanding of malaria infection, its periodicity and characteristics in an unstable transmission setting, based on the cases observed in a critical care facility. We observed a prevalence rate of 4.8, 7.57 and 8.7% in 2016, 2017 and 2018, respectively; which is in agreement with the findings of Khan et al., who reported malaria prevalence and species distribution for the years 1999–2009 in Aligarh (Khan et al., 2011). Nonetheless, the peak transmission was evident in the wet season but *Pv* and *Pf* patients turned up throughout the year at JNMCH, though not in significant numbers in the dry season. The year-round occurrence of *Pv* cases was higher than *Pf,* which may be attributed to the capability of *Pv* species to survive as dormant hypnozoites in the liver and re-emerge during the dry season, which never happens in *Pf* (White, 2011). Although the prevalence of *Pv* is throughout the year, maximum cases were recorded during the wet season of transmission. *Pv* appears earlier than *Pf* during the transmission season as its gametocytes appear in the blood in 16 days after inoculation whereas it takes 21 days in *Pf*; therefore the transmission peaks for *Pv* are observed a bit earlier (Boyd and Kitchen, 1937). Anopheline vectors play a pivotal role in malaria transmission. A survey carried out during 2000–2002 in Aligarh to screen the anopheline spp., reported *Anopheles culicifacies* (37.02%) as the predominant sp. which is responsible for rural malaria, while *Anopheles stephensii* (8.78%), another critical vector for urban malaria. Anopheline vectors were recorded in higher numbers from July to November, that coincides with the wet season of malaria transmission (Khan, 2001). High prevalence of *An. culicifacies* could be implicated for the dominance of rural malaria (84.5%) in this region.

Pv infections were recorded more frequently at JNMCH, particularly in the age group 0–15, but both *vivax* and *falciparum* malaria were associated with disease severity. Approximately 30% of all the *Pv* cases in India are reported in the younger subjects, i.e., children aged 1–14 years; however, this age group is only 12% of the total population (NVBDCP, 2012). Recently, many studies have emphasised upon the severity of *vivax* malaria in the Asian continent; some of them had indicated that *Pv* might be as pathogenic as *Pf* if parasite density is high (Anstey et al., 2009; Baird, 2007; Mueller et al., 2009; Yadav et al., 2012), which is also true for our study. The no. of complicated cases in India represents a complex disease burden of malaria with varying dominance of *Pv* and *Pf* across the country.

Male-dominance/ sex-bias was observed consistently throughout the study in all the age groups for both *Pv* and *Pf* infections, which is in consensus with previous reports where prevalence was influenced by the age and gender of the subjects especially in unstable regions of transmission (Chery et al., 2016; Gerardin et al., 2017; Idro et al., 2006; Keffale et al., 2019; Modiano et al., 1998). However most of such studies are indeterminate regarding the cause of male dominancy in malaria infection, some attribute it to the increased exposure of males to outdoors/ mosquito bites (Chery et al., 2016; Sur et al., 2006). A study conducted by Pathak et al., 2012 in hypoendemic region of India suggests age-dependent sex bias, a greater disease incidence in post-pubertal males and lowest disease incidence below the age of 10 years. On the contrary we observed greatest gender bias in children aged 0–15 years as compared to all the other age groups as shown in Fig. 5B, however there was no significant difference between these sex ratios. The reason for greater male bias among children of age group 0–15 remains unexplained; it could be attributed to the bias in access to the health facility in case of females due to existing social norms in some rural societies. However this parameter needs a thorough investigation in future studies.

As far association with age is concerned, our study represents 46.6% patients from the age group 0–15. Many studies from hypoendemic areas associate clinical immunity to the infection with age while others suggest all age groups are equally susceptible to the disease (Rolfes et al., 2012). However the results remain inconclusive until in-depth analysis of some immunological biomarkers are carried out for every age group, pertaining to the development of clinical immunity in the population. Hence, immunological investigations will be carried out in future research.

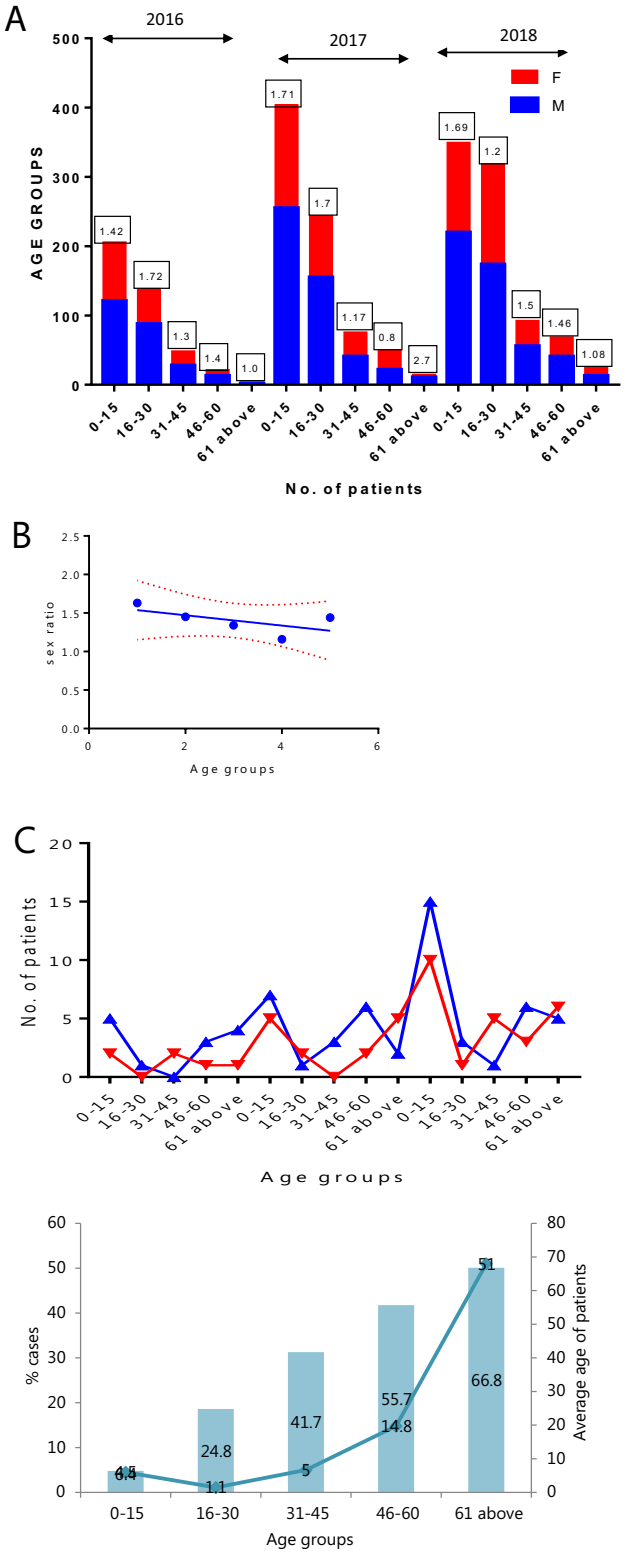

Fig. 5. A Age and gender-wise distribution of patients during the study period (text box above each bar denotes M:F). B Average sex ratio in the five age groups. C Distribution of complicated cases in various age groups and male/females. D Percentage of complicated cases and average age of the patients in each age group

Table 1
General characteristics of patients.

Variable / value	*P. falciparum*	*P. vivax*	Odds ratio (CI)	*P* value*
No. of patients	501/2068	1567/2068	3.12	$p < .0001$
	24%	76%	(2.78–3.5)	
Residence				
Rural	416	1269	1.01	ns (chi-square test)
Urban	85	298	(0.91–1.2)	
Gender				
Male	288	976	1.01	ns
Female	213	591	(0.86–1.2)	
Admitted (%)	369/501 (73.6%)	886/1567 (56.5%)	0.7677 (0.32–0.89)	$p = .001$
Disease severity				
Mild	273 (88%)	737 (92.8%)	2.406	$p < .0001$
Severe	57 (12%)	57 (7.2%)	(1.6–3.5)	
Anaemia (%)				
Mild	148 (48.2%)	339(42.6%)	1.4	ns
Severe	31 (10%)	46(6.3%)	(0.88–2.3)	

ns- non significant.
Analysed by chi-square test with Yate's continuity.

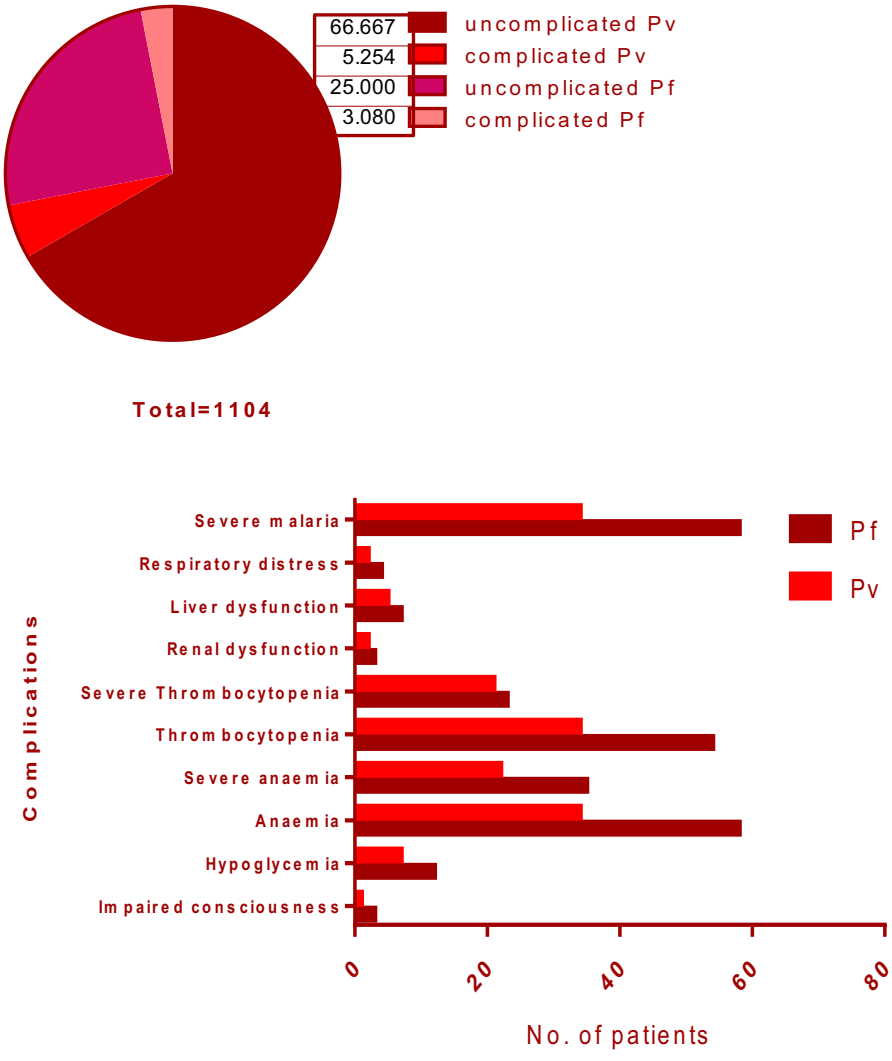

Fig. 6. A&B Clinical categorization of patients showing no. of uncomplicated and complicated cases with the pertaining complications in *Pf* and *Pv* cases.

Table 2
Mean values of clinical parameters in *Pf* and *Pv* patients.

Clinical parameters	*Pf* ($n = 310$)		*Pv* ($n = 794$)		P value (*t*-test)
	Mild ($n = 273$)	Severe ($n = 37$)	Mild ($n = 737$)	Severe ($n = 57$)	
Blood glucose level (gm/dL)	219	165	210	167	ns
Haemoglobin level (g/dL)	10.45	9.21	10.3	9.8	ns
Platelet count ($x10^3/\mu L$)	221	167	119	159	ns
Serum creatinine (mg/dL)	1.1	1.7	1.08	1.54	ns
Serum Bilirubin (mg/dL)	0.6	1.1	0.7	1.1	ns
% Parasitaemia	1.56 ± 1.8	1.72 ± 1.68	0.75 ± 0.95	1.13 ± 0.79	ns

In the admitted patients *Pf* infection was greater than that of *Pv* and the complicated cases had at least one severe malaria feature indicated by WHO. Patients with more than one severity criteria generally had *Pf* infection. Youngest and oldest patients showed maximum complications which is in accordance with other studies showing age-dependency of complications in severe malaria (Baird, 2019; Hay et al., 2010; Khan, 2001; Snow et al., 1997). The unstable areas of malaria transmission pose an aggravated risk of disease severity in children and adults above the age of 60, which may be responsible for different socio-economic outcomes not evident in stable transmission (Kiszewski and Teklehaimanot, 2004).

Lastly we observed that an increase in number of malaria cases was considerable and significant. Also there was a considerable burden of severe *vivax* malaria; this may be of interest for the ongoing malaria control efforts in the country. The results obtained in the present study differ from the reports available nationally and globally. The underestimation of disease burden may be due to underreporting and misdiagnosis at the government-based health care facilities or due to inaccessibility of the facility in remote areas. This calls for a proper intervention for the disease monitoring system to systematically track the progress of malaria eradication goals. There are numerous evidence of under-reporting of malaria cases nationally as well as globally. The problem of underestimation has been argued upon in several other studies, possibly a disparity of 9–50 times may exist in the reporting and actual burden of disease (Das et al., 2012; Hay et al., 2010; Kumar et al., 2007). Such statistical records could be misleading when taken into account for supporting the elimination and control efforts. The WHO and the various national agencies of malaria endemic countries are making persistent efforts to reach their eradication goals. However, it is the need of the hour to fully explore the local factors influencing the risk and spread of disease and further incorporate them during the discourse of malaria elimination strategies in order to make the concept of micro-epidemiology functional. This would help in making the control program more situation-specific and target the focal outbreaks at small spatial scales.

5. Conclusion

Our study portrays the clinico-epidemiological picture of malaria transmission and highlights the primary demographic variables (age, gender, and residential area), and disease severity in *Plasmodium*-infected individuals reporting at the JNMCH (a critical care facility) in a peri-urban setting. The study suggests a possible age-dependent susceptibility and gender bias that will be deeply analysed in future investigations. The limitation of the study was that we could not collect clinical data for all the 2068 patients. Only 1104 clinical reports could be retrieved for analysis of result during the present study. Moreover a sensitive technique like PCR could be used in addition to microscopy and RDT for more precise diagnosis in future studies. Independent micro-epidemiological studies and hospital-based surveys can play an important role in determining the actual burden of malaria and discerning the existing epidemiological records.

Authors' contributions

WK and SA conceived the study; SA, AN and WK designed the study protocol; AR carried out the clinical assessment and diagnosis; SA and AN carried out the sample collection, analysis and interpretation of these data. SA and WK drafted the manuscript; SA, AN and WK critically revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Declaration of Competing Interest

None.

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