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Original Research Article

Acute respiratory distress syndrome in *Plasmodium vivax* malaria. A case-control study of comparison between ARDS and non-ARDS patients in *P. Vivax* malaria

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ABSTRACT

Background: *Plasmodium vivax* was conventionally considered to be a benign parasite for centuries but in the recent years have proved to be a virulent parasite causing severe malaria. Acute respiratory distress syndrome (ARDS) is one of such severe complications with a significant morbidity and mortality. The objective of this study was to find the prevalence of ARDS and identify the associated factors that could potentially lead to ARDS in patients with vivax malaria.
Methods: A retrospective case-control study was conducted at a tertiary hospital in New Delhi. 329 patients with an established diagnosis of *Plasmodium vivax* mono-infection were identified using hospital medical records, the associated factors were evaluated and compared to calculate the odds of developing ARDS. All patients were categorized into ARDS cases and non-ARDS controls.
Results: The incidence of ARDS was 7% with a female sex predominance (60.86%). Mean urea (71.5 mg/dl), creatinine (2.7 mg/dl), and AST (97.8 units/l) elevation in addition to decreased hemoglobin (7.7 gm/dl) and platelets count (38,217 cells/µl) proved to be significantly associated with ARDS in our study.
Conclusions: *Plasmodium vivax* is a virulent parasite and can cause severe malaria even in the setting of isolated infection. Cytokine mediated diffuse inflammatory response is a postulated pathophysiology causing ARDS.

Keywords: Acute respiratory distress syndrome, Complicated malaria, India, Malaria

INTRODUCTION

Malaria is a serious acute febrile illness prevalent in tropical regions caused by the Plasmodium parasites through the bite of an infected female Anopheles mosquito. There are five different parasite species causing infection in humans: *Plasmodium falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi*.[1] In 2020, an estimated 241 million malaria cases were reported, and 4.5 million cases (2%) were caused by *Plasmodium vivax*.[2] South-East Asia accounted for about 2% (5 million) of malaria cases globally.[2] India is the leading country in the total malaria cases and deaths in the South-East Asia region, contributing to 83% and 82% respectively.[2] *Plasmodium vivax* contributed a little more than one-third of all the malaria cases here.[2]

Plasmodium falciparum poses the greatest threat due to the following complications: cerebral malaria, renal failure, acute respiratory distress syndrome, severe anemia, coagulopathy, and hypoglycemia.[1] Nevertheless, similar life-threatening complications are also observed in vivax malaria, questioning the grouping of vivax as a benign parasite.[3-5] Acute respiratory distress syndrome

(ARDS) is one of the critical complications that occur in malaria requiring management in an intensive care unit.[1] ARDS as per the 2012 Berlin definition is defined as the acute onset respiratory failure with bilateral pulmonary infiltrates in a chest radiograph and severe hypoxemia in the absence of cardiogenic pulmonary edema.[6] In 2016 Kigali modification of the Berlin definition was introduced for resource-limited settings, in this modification bilateral opacities should be documented with either chest radiograph or ultrasonography, and the oxygenation criteria could be met with a pulse oximetric oxygen saturation (SpO_2)/FiO_2 ≤315 without the requirement for PEEP. Cytokines, leukotrienes, and macrophage inhibitory factors along with platelet sequestration leads to increased alveolar permeability and disrupted alveolar fluid clearance in malaria-precipitating ARDS.[6,7]

Several publications in recent years reveal that *Plasmodium vivax* causes ARDS with a significant mortality rate.[8,9] There are reported cases of ARDS in vivax malaria in India reflecting this pattern, but the data available are limited in number, warranting an extensive study to be conducted to corroborate the vivax-ARDS association with statistical significance.[3-5,10] The objective of this study was to observe the prevalence of ARDS in vivax malaria. Additionally, we compared the symptoms and other associated factors between the patients who did and did not develop ARDS.

METHODS

This was a retrospective case-control study conducted in Hakeem Abdul Hameed Centenary hospital, a tertiary care center in New Delhi. The monsoon season in New Delhi is June and July, malaria cases are usually at their peak during the post-monsoon season in a year.[8] The data was collected from the hospital's medical records department from May 2017 to December 2019. Ethical clearance was taken from the hospital ethics committee before the commencement of the study.

The study included 370 hospitalized patients who tested positive for Plasmodium vivax infection (Figure 1). The diagnosis was documented either by a Giemsa-stained peripheral blood smear examination or a *Plasmodium vivax*-specific lactate dehydrogenase rapid-antigen test verified by our hospital quality assurance program.[11] Any patient with evidence of a mixed infection, such as *Plasmodium falciparum* or dengue co-infection, was excluded from the study. Detailed data regarding the history, physical examination, hematological tests performed using Sysmex Hematology analyzer, biochemical investigations performed using Siemens xpand biochemistry autoanalyzer, ultrasonography of abdomen using Samsung HS70 5D, and arterial blood gas analysis was done using GEM premier 3500 system were collected and documented in a spreadsheet.

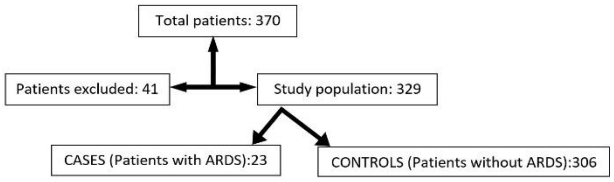

Figure 1: Selection of the study population and exclusion of mixed infection patients, and then the patients fulfilling the inclusion criteria were divided on the basis of ARDS into groups of cases and controls.

ARDS is identified as per Kigali's 2016 modification of ARDS by dividing the peripheral arterial oxygen saturation (SpO_2) by the fraction of oxygen in the inspired air (FiO_2). In ARDS patients (cases) the result was 315 or less and it was above 315 in non-ARDS patients (controls).[12,13] To exclude cardiogenic pulmonary edema echocardiogram was performed. Contrast-enhanced computed tomography was done for all ARDS patients to diagnose other possible etiologies like tuberculosis, viral, and other possible etiologies, and any such suspected patient was excluded from the study. After excluding other etiologies, patients who had developed ARDS within 7 days of the onset of fever were diagnosed with ARDS due to *P. vivax* malaria. The finalized patients were categorized into two groups: those who had malaria-associated ARDS as cases and those who did not have ARDS as controls.

Both the groups were compared based on the demography, clinical and laboratory parameters. Certain other complications apart from ARDS were also taken into consideration. All the data were tabulated in an excel sheet and compared using appropriate statistical formulas.

Statistical analysis

All the analysis was performed in SPSS 26. Categorical data were represented in percentage form and continuous data was represented in Mean±SD format. In categorical data, we use the Z test of proportion to compare two groups and for normally distributed data we use the independent t-test while for non-normal distributed data we use the Mann-Whitney test. To know the association of risk factors in ARDS versus non-ARDS patients we used univariate and multivariate analysis at a 95% confidence interval. P values less than 0.05 was considered significant for all the analysis

RESULTS

The incidence of ARDS was 7% and a striking female sex (60.86%) predominance in the ARDS group (case) was noted (Table 1). Most of the patients in the ARDS group had developed symptoms such as cough and tachypnea, specifically a respiratory rate of more than 20

per minute. These symptoms started within 48-72 hours of fever onset. Mean urea (71.5 mg/dl), creatinine (2.7 mg/dl), and AST (97.8 units/l) was noted to be significantly elevated in the ARDS cases than in the controls. Whereas mean Hb (7.7 gm/dl) and platelet counts (38,271 cells/µl) was noted to be significantly decreased in the ARDS cases than in the controls. Exhibited in detail in Table 2, 3 and 4.

Table 1: Comparison of demography details between ARDS (case) and non-ARDS (control) group.

Variable	Total patients (n=329)	Case (n=23)	Control (n=306)	P values
Age (mean age±SD)	31.04±13.23	34.13±13.05	30.81±13.24	0.247
Male	208 (63.22%)	9 (39.13%)	199 (65.03%)	0.0131
Female	121 (36.77%)	14 (60.86%)	107 (34.96%)	0.01314
Hypertension	2 (0.607%)	1 (4.347%)	1 (0.326%)	0.01684
Type2 diabetes mellitus	8 (2.431%)	1 (4.347%)	7 (2.287%)	0.53526
Hypothyroidism	6 (1.823%)	1 (4.347%)	5 (1.633%)	0.3072

Data are expressed as number and %. p-value was calculated using Z-score of two proportion between sever and mild groups. P value < 0.05 is considered as statistically significant difference.(SD: standard deviation at 95% confidence interval)

Table 2: Comparison of clinical features between ARDS (case) and non-ARDS (control) group

Variable	Total patients (n=329)	Case (n=23)	Control (n=306)	P values
	N (%)	N (%)	N (%)	
Fever	328 (99.69)	23 (100)	305 (99.67)	0.7816
Chills	308 (93.61)	23 (100)	285 (93.13)	0.1936
Vomiting	143 (43.46)	11 (47.82)	132 (43.13)	0.659
Body ache	195 (59.27)	7 (30.43)	188 (61.43)	0.0035
Headache	207 (62.91)	12 (52.17)	195 (63.72)	0.267
Abdominal pain	87 (26.44)	12 (52.17)	75 (24.50)	0.00374
Bleeding	36 (10.94)	5 (21.73)	31 (10.13)	0.0854
Cough	67 (20.36)	14 (60.86)	53 (17.32)	<0.00001
Breathlessness	40 (12.15)	22 (95.65)	18 (5.882)	<0.0001

Data are expressed as number and %. p-value was calculated using Z-score of two proportion between sever and mild groups. P-value < 0.05 is considered as statistically significant difference.

Table 3: Comparison of lab parameters between ARDS (case) and non-ARDS (control) group

Mean values	Total patients (n=329)	Case (n=23)	Control (n=306)	P values
Hemoglobin (g/dl)±SD	10.22±2.7	7.7±2.01	10.41±2.6	<0.001
Platelet count (cells/µl)±SD	55,400±38,360	38,217±44,427	56,766±36,348	<0.001
Urea (mg/dl)±SD±SD	37.5±28.4	71.5±61.0	33.93±18.02	0.001
Creatinine (mg/dl)±SD	1.15±1.1	2.76±3.4	1.03±0.62	0.058
Sodium (mEq/l)±SD	134.22±4.58	133.7±5.71	134.26±4.50	0.186
Potassium (mEq/l)±SD	3.91±2.50	4.06±0.75	3.90±2.59	0.033
Total Bilirubin (mg/dl)±SD	2.43±2.3	4.35±4.7	2.25±1.98	0.033
Conjugated Bilirubin (mg/dl)±SD	1.10±1.7	2.47±3.7	0.99±1.43	0.001
Unconjugated Bilirubin (mg/dl)±SD	1.56±4.6	1.87±1.2	1.53±4.9	0.003
AST (U/l)±SD	56.7±53.9	97.8±85.4	51.89±49.8	0.013
ALT (U/l)±SD	54.33±53.8	63.30±47.9	53.66±56.34	0.181
ALP (IU/l)±SD	134.94±60.29	136.17±55.78	130.55±60.69	0.382
TLC (cells/mm^3)±SD	4,800±2,400	6,225±3549	4,603±2,051	0.007
MCV (fl)±SD	88.25±9.43	86.52±9.91	88.38±9.41	0.291

Data are expressed as number and %. p-value was calculated using Z-score of two proportion between sever and mild groups. P-value < 0.05 is considered as statistically significant difference. (SD: standard deviation at 95% confidence interval, AST: aspartate aminotransferase, ALT: alanine transaminase, ALP: Alkaline phosphatase, TLC: total leucocyte count, MCV: Mean corpuscular volume)

Table 4: Comparison of complications between ARDS (case) and non-ARDS (control) group

Variable	Total patients (n=329)	Case (n=23)	Control (n=306)	P values
	N (%)	N (%)	N (%)	
Hemoglobin <7 g/dl	37 (11.246)	9 (39.13)	28 (9.15)	<0.0001
TLC <4000cells/mm^3	133 (40.42)	5 (21.73)	128 (41.83)	0.058
TLC 4000-10000cells/ mm^3	187 (56.83)	16 (69.56)	171 (55.88)	0.2005
TLC >10000cells/ mm^3	9 (2.735)	2 (8.695)	7 (2.287)	0.0687
PLC <50000cells/µL	161 (48.93)	19 (82.60)	142 (46.40)	0.0008
UREA >40mg/dL	92 (27.96)	17 (73.91)	75 (24.50)	<0.0001
Creatinine >3 mg/dl	7 (2.12)	5 (21.73)	2 (0.65)	<0.0001
Pottasium <3.5 mEq/l	88 (26.74)	4 (17.39)	84 (27.45)	0.2937
Bilirubin >3 mg/dl	70 (21.27)	10 (43.47)	60 (19.60)	0.00694
AST >135U/l	21 (6.382)	7 (30.43)	14 (4.575)	<0.0001
ALT >135U/l	14 (4.255)	1 (4.347)	13 (4.248)	0.98404
Bleeding	36 (10)	5 (21)	31 (10)	0.085
Cerebral malaria	11 (3.3)	3 (13)	8 (2.6)	0.007
Lactic acidosis	10 (3)	5 (21.7)	5 (1.6)	<0.001
Mortality	4 (1.2)	3 (13)	1 (0.32)	<0.0001

Data are expressed as number and %. p-value was calculated using Z-score of two proportion between sever and mild groups. P value < 0.05 is considered as statistically significant difference. (TLC: total leucocyte count, PLC: platelet count, AST: aspartate aminotransferase, ALT: alanine transaminase)

Table 5: calculation of odd's risk and p-value of different variables in ARDS Group vs. non-ARDS group by univariate linear, logistic regression analysis and then further assessment of significant variables in univariate analysis by applying multivariate logistic regression analysis and calculation of the p-value.

Variable	Odd's ratio	Std. error	Z	P	95% confidence interval
Univariate analysis					
Age	2.819	2.274	1.28	0.199	0.579-13.705
Sex	2.893	1.283	2.39	0.017	1.212-6.903
Urea	8.726	4.303	4.39	0.000	3.319-22.939
S. Creatinine	42.222	36.780	4.30	0.000	7.656-232.829
T. Bilirubin	3.153	1.402	2.58	0.010	1.319-7.538
AST	9.125	4.830	4.18	0.000	3.233-25.752
ALT	1.024	1.087	0.02	0.982	0.128-8.196
Hemoglobin	6.382	3.006	3.94	0.000	2.535-16.066
TLC >4,000	2.623	1.360	1.86	0.063	0.949-7.250
TLC >10,000	4.068	3.385	1.68	0.092	0.795-20.816
PLATELET	5.485	3.082	3.03	0.002	1.823-16.503
Multivariate analysis					
Sex	2.730	1.621	2.69	0.041	1.852-8.743
Urea	4.733	2.575	2.86	0.004	1.629-13.751
S. Creatinine	5.706	5.565	2.79	0.044	1.843-38.592
T. Bilirubin	1.715	0.915	1.01	0.312	0.602-4.883
AST	4.45	3.222	2.07	0.038	1.085-18.367
Hemoglobin	2.28	1.392	1.35	0.177	0.688-7.549
Platelet	2.73	1.720	1.59	0.111	0.794-9.390

Data are expressed as odd's ratio of each variable and % of standard error. p-value was calculated by calculating the Odds ratio (OR). p-value < 0.05 is considered as statistically significant difference. (Z: standard normal deviate, TLC: total leucocyte count, AST: aspartate aminotransferase, ALT: alanine transaminase)

Furthermore, in Table 5, the association between any single and/or multiple factors concerning the development of ARDS was derived by the application of univariate logistic regression and later multivariate logistic regression analysis on variables calculated to be statistically significant in univariate analysis. After multivariate calculation, it is established that the most significant relationship between the development of ARDS is associated with the female sex, rise in urea,

creatinine, and AST values. Total bilirubin, drop in hemoglobin and platelet count appears statistically significant but after multivariate analysis, their role in ARDS was not found to be significant.

DISCUSSION

As *Plasmodium vivax* was traditionally considered a benign parasite, a concrete mechanism behind the development of ARDS is not available as it is in the falciparum infection. In falciparum, the infected erythrocytes cytoadhere to chondroitin sulfate A; a receptor commonly expressed in pulmonary, cerebral, and placental microvasculature.[14-17] Similar cytoadherence and erythrocyte sequestration do occur in vivax malaria; however, it happens in a lesser magnitude than in falciparum infection.[7] Leukocyte aggregation (predominantly neutrophils) during febrile paroxysms is a phenomenon specific to vivax malaria and is mediated by the parasite-derived lipids in concert with host cytokines.[18,19] Such leukocyte accumulation frequently occurs in lungs, intestines, and brain micro-vasculatures.[7,20] The resulting cytokine activation might lead to increased alveolar permeability leading to ARDS in vivax malaria.[21,22]

The incidence of ARDS in our study was 7%, earlier publications quoted the incidence to be between 2.1 to 3.2% and a meta-analysis assembling several publications from 1900 to 2014 evidenced the incidence of ARDS in vivax malaria to be 2.8% with a mortality of 50%.[3-5,8,9] A possible explanation for this is that our study was conducted in a tertiary hospital comprising only hospitalized patients which could overestimate the actual incidence of ARDS. About two-thirds (60.86%) of the cases were females; an earlier study conducted in Rajasthan showed that nearly 62% of the hospitalized patients with severe vivax malaria in India were females. Nevertheless, a gender association with ARDS occurrences was not established.[4] Most of the common clinical features such as fever/chills were found in both groups; however, abdominal pain, cough, and breathlessness were highly prevalent in the ARDS cases than in the controls.

Among the hematologic parameters, severe anemia (Hb <7 gm/dl) in the ARDS cases was 39.13% while it was only 9.15% in the controls (Table 4). Recent studies showed evidence for increased erythrocytes fragility with *Plasmodium vivax*: around 50% of infected and 15% of non-infected RBCs were destroyed after passage through a 2 µ channel resembling the endothelial cells of the splenic sinusoids.[23,24] In addition to this, there is a possibility for encroachment of the vivax-infected erythrocytes within the pulmonary capillaries, and the killing of such parasites within the erythrocytes by host immune responses or antimalarial drugs might trigger an inflammatory response targeted in the lungs causing acute lung injury.[21,22,25] These could be the reasons for more patients with severe anemia in the ARDS cases than in the controls.

Thrombocytopenia is another most common hematologic complication in vivax malaria, and it has been well documented in several studies.[3,4,8,26] The percentage of patients with severe thrombocytopenia (platelet counts <50,000 cells/µl) is twofold higher in the ARDS cases (82.60%) than in the controls (46.40%), Table 4. It is proposed that immune complexes generated by the malarial antigen could lead to platelet sequestration in the spleen and phagocytosed by splenic macrophages.[27] Elevated TNF-∝ results in increased platelet trapping and consumption in inflamed blood vessels, which could be another reason for the severe thrombocytopenia occurring in ARDS cases.[28] Considering the total leukocyte count, leukopenia was prevalent in the controls. That is, the average percentage of patients with leukopenia was 41.83% in the controls while it was only 21.73% in the ARDS cases (Table 4). A pattern of leukopenia being protective against the development of ARDS was noted; however, the reverse of this pattern, leukocytosis being associated with ARDS was not observed.

Cytokine activation is widely accepted to be the main contributor to acute lung injury.[21,29,30] One could postulate that the observed hepatic and renal failure in ARDS cases, that is, elevated mean total bilirubin (4.3 mg/dl), urea (71.5 mg/dl), and creatinine (2.7 mg/dl) could be secondary to the ongoing cytokine-mediated inflammation resulting in a multi-organ-system failure (Table 3). After the application of multivariate analysis, as available in Table 5, it is plausible that the development of ARDS and renal injury are closely correlated and may share a common pathology. The predisposition of the female sex to ARDS is still unclear and needs further research. An isolated rise in AST levels is also significant to ARDS and as AST is released from various organs other than the liver like red blood cells, muscles, kidney, brain, etc. so hepatic pathology appears to be separate from renal pathology, where renal involvement predispose to ARDS, hepatic pathology has a statistically non-significant role in ARDS. Supporting our findings, a previous publication in Delhi documented pulmonary edema (13.8%), hyperbilirubinemia (25.9%), and severe anemia (56.9%) as significant findings in patients with one or multiple complications caused by *Plasmodium vivax*.[8] Some publications support the fact that ARDS in malaria infections are commonly observed in patients who develop sepsis or other modes of multi-organ failure from a diffuse inflammatory response.[30] Mortality in ARDS malaria was also noted to be statistically significant when compared to the non-ARDS group, which is historically said to be a benign disease.

The publications regarding *Plasmodium vivax* causing ARDS in our country are limited to either case reports or case series. This study, however, focuses on the associated factors in patients with *Plasmodium vivax* infection who might develop ARDS, this could aid in

formulating an early diagnosis and treatment plan. A case-control study about vivax-ARDS with this significant size has not been published by India so far.

However, a few limitations of our study are that this was a retrospective study falling under a moderate level of evidence in the hierarchy of evidence. As ARDS is a relatively rare severe complication of vivax malaria, a furthermore larger study population would efficiently demonstrate the impact of the associative factors in ARDS.

CONCLUSION

The specific derangements in the hematologic and biochemical parameters as discussed above could provide substantial evidence to anticipate respiratory distress in patients with severe vivax malaria. The destruction of erythrocytes and platelets in multiple micro vasculatures including the pulmonary capillaries triggers a cytokine-mediated diffuse inflammatory response leading to ARDS and multi-organ failure.[28] The role of cytokines in severe malaria-related studies is relatively rare in India; however, it would serve as a vast area for exploration in the future.

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