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Respiratory Complications of *Plasmodium vivax* Malaria: Systematic Review and Meta-Analysis

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Abstract. Malaria, a major global public health problem, is mainly caused by *Plasmodium falciparum* and *Plasmodium vivax*, and is responsible for nearly half a million deaths annually. Although *P. vivax* malaria was not believed to cause severe disease, recent robust studies have proved otherwise. However, the clinical spectrum and pathogenesis of severe vivax malaria and, especially, its respiratory complications remain poorly understood. A systematic search for articles reporting respiratory complications associated with vivax malaria was performed in Lilacs, Cochrane, Scielo, Web of Science, and Medline databases irrespective of publication date. Prevalence of acute respiratory distress syndrome (ARDS) and associated mortality among vivax patients were calculated from cross-sectional and longitudinal studies, whereas factors associated with mortality were calculated from data pooled from case reports and series of cases. A total of 101 studies were included (49 cross-sectional or longitudinal and 52 case reports or series of cases). Prevalence of ARDS was 2.8% and 2.2% in children and adults, respectively, with nearly 50% mortality. Moreover, female sex ($P = 0.013$), having any comorbidity ($P = 0.036$), lower body temperature ($P = 0.032$), lower hemoglobin ($P = 0.043$), and oxygen saturation ($P = 0.053$) values were significantly associated with mortality. *Plasmodium vivax* malaria respiratory complications included ARDS and were associated with high mortality. Demographics and clinical characteristics upon presentation to hospital were associated with mortality among patients with respiratory complications in vivax malaria. This study reaffirms the evidence of severe and fatal complications of *P. vivax* malaria and its associated respiratory complications.

INTRODUCTION

Malaria is a major global public health problem with 3.4 billion people at risk over 91 endemic countries and territories in 2016.[1] Despite improvements since 2000, malaria still imposes a great burden causing 212 million cases and 429,000 deaths in 2015.[1] Of five *Plasmodium* species causing human malaria, *Plasmodium vivax* is the most widespread[2] with great impact in endemic regions,[3] and responsible for 41% of malaria-related cases, 0.7% of world malaria deaths, and 9% of malaria deaths outside Africa.[1] The World Health Organization (WHO) estimated 8.5 million cases and 3,100 deaths from vivax malaria in 2015.[1]

Although falciparum malaria is definitely considered more lethal, it is now evident that *P. vivax* infection also causes severe disease and death.[4,5] The clinical spectrum of vivax malaria ranges from asymptomatic infection to severe disease.[6,7]

Recognizing and managing malaria respiratory complications is challenging for health-care practitioners in endemic areas. The spectrum ranges from cough and acute breathlessness, to pulmonary edema, acute respiratory distress syndrome (ARDS), and death even after malaria treatment initiation.[8–13] In a recent review of severe falciparum malaria cases, respiratory distress (RD) was reported in 25% of adults and 40% in children, whereas ARDS was found in up to 25% of adults; associated mortality was nearly 50% with intensive care and 80% without ventilator support.[14] Recently, respiratory complications have also been reported in non-falciparum malarias including *P. vivax*.[15–22]

The underlying pathogenic mechanisms of respiratory complications associated with vivax malaria are not entirely understood.[23] Robust evidence for lung impairment in *P. vivax* malaria has only emerged recently. Therefore, the primary objective of this review was to describe the prevalence and mortality of respiratory complications in vivax malaria. Secondary objectives were to describe geographical variation, clinical characteristics, risk factors for mortality, and associated pathogenesis.

METHODS

A systematic review addressing respiratory complications caused by *P. vivax* malaria was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24,25] We systematically identified studies reporting respiratory complications (Table 1). The last search was performed in November 2016. Additional studies were obtained through search of references. No date or language restrictions were applied. All study designs with primary data were included.

We reviewed titles and abstracts to confirm they included data on malaria infection, human population, *P. vivax* mono-infection, and respiratory complications. Included studies were assessed for eligibility through full-text review and excluded when reporting inconclusive *Plasmodium* species, non-respiratory complications, or if these were secondary to other organ impairment. All reviews were conducted by two independent reviewers (Fernando Val and Kim Machado) and disagreements were resolved by consensus.

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TABLE 1
Search strategy

Database	Search strategy
Lilacs Cochrane Scielo	(vivax AND pulmonary) OR (vivax AND respiratory) OR (vivax AND ARDS)
Web of Science	(*Plasmodium vivax* malaria AND pulmonary) OR (*Plasmodium vivax* malaria AND respiratory) OR (*Plasmodium vivax* malaria AND respiratory distress) OR (*Plasmodium vivax* malaria AND pulmonary oedema) OR (*Plasmodium vivax* malaria AND ards) OR (*Plasmodium vivax* malaria AND human ards)
Medline/PubMed	*Plasmodium vivax* malaria (MeSH Term) AND pulmonary; *Plasmodium vivax* malaria (MeSH Terms) AND respiratory; *Plasmodium vivax* malaria (MeSH Term) AND respiratory distress; *Plasmodium vivax* malaria (MeSH Term) AND pulmonary oedema; malaria AND ards; (*Plasmodium vivax* malaria [MeSH Terms]) AND human ards (MeSH Terms)

Measures and definitions. In cross-sectional and longitudinal studies, the following data were retrieved: sample size, number of severe and pulmonary malaria (PM, defined as any evidence of respiratory complication detected by any clinical and/or laboratorial alteration), and mortality. In this study, pediatric population referred to individuals under 17 years of age, and adult population to those 18 years or older. The type of respiratory complication was used exactly as reported in the original study. Case reports and series of cases were used to describe demographic, clinical, laboratory, and disease characteristics and any histopathological findings. Nine additional cases with vivax PM from Manaus, Brazil,[26] were included. The following definitions were used: presence of comorbidities and other alterations were any reported at medical examination; altered clinical status at baseline was any clinical alteration at admission; presence of signs and symptoms in previous days to hospital presentation; any disease symptom previous to admission; time of RD onset was defined by time between admission and RD; timing of RD onset and start of antimalarial treatment; whether RD started before or after antimalarial treatment initiation; noninvasive oxygen supplementation was any oxygen support excluding those via intubation.

Statistical analyses. To compare PM proportion among pediatric and adult populations, type of respiratory complication, and age group data were pooled, categorized (1—prevalence of PM among all cases, 2—prevalence of PM among severe cases, and 3—mortality due to PM), and compared. Data from case reports were described as mean and one standard deviation or median and interquartile range and tested according to normality. Independent *t* tests, Wilcoxon Mann–Whitney (frequency of children versus adults; survivors versus non-survivors) or χ^2 test were applied. Significance was set as $P < 0.05$. Analyses were performed using STATA version 12.1 (Stata Corp., Colege Station, TX).

RESULTS

The original search returned 608 studies. After duplicate removal and review of titles and abstracts, 84 studies were included. After inclusion of 17 additional papers, a total of 101 studies were analyzed and separated in two major groups, the first containing 49 studies (cross-sectional or longitudinal studies) and the second 52 case reports and series of cases (Figure 1).

Study characteristics. Longitudinal and cross-sectional studies: Data were extracted from 49 studies reporting respiratory complications in *P. vivax* malaria[26–74] (Supplemental Table 1). There was heterogeneity in the terminology used to describe respiratory complications. A total of 29 studies (59.1%) reported ARDS, 10 (20.4%) RD, two (4%) respiratory failure, one (2%) lung injury, one (2%) pulmonary edema, one (2%) acute respiratory distress, and the remaining five (10.2%) a combination between ARDS, RD, acute lung injury, and pulmonary edema. A total of 42 studies (85.7%) adopted WHO definitions for PM, whereas the remaining used general or country-specific definitions or did not report the adopted definition (Table 2).

Case reports and series of cases: A total of 67 cases were analyzed (58 cases from included case reports and series of cases,[11–13,58,59,75–118] and additional nine cases from Manaus, Brazil[26]). The earliest identified report was from 1993 (Figure 2). Cases were predominantly from India (Table 3) and diagnosed mainly by peripheral blood films (Table 4).

Respiratory complications frequency and mortality. Overall, 450,115 patients were pooled from longitudinal and cross-sectional studies; 5,448 with severe disease, 453 developing PM, and 74 deaths. The overall prevalence of respiratory complications was 0.1% among patients and 8.3% among severe cases, with a mortality of 16.3% (Supplemental Table 1).

According to WHO-defined regions,[1] the highest frequency of PM (8.7%) occurred in southeast Asia. More details are found in Supplemental Table 2.

Frequency of ARDS was 2.4% in 23 studies, mostly in hospitalized patients (N = 3,574 patients) (Table 5). A total of 1,156 developed severe malaria, 85 presenting ARDS (7.3%). Mortality among patients with ARDS was 49.5%. In children, ARDS frequency was 2.8% (48.3% mortality). In adults, 2.2% presented ARDS (50% mortality). There was no statistical difference in ARDS prevalence (P = 0.315) and mortality (P = 0.787) between children and adults.

On the other hand, among patients who died due to vivax-associated respiratory complications, pulmonary malaria was present in 52.9%, in a series of 17 autopsies cases, the best reference for that purpose, despite the limited sample. Out of these, two had confirmed ARDS on histopathology.[13] In Papua, 26 out of 65 patients with *P. vivax* infection who died had any respiratory complication, that is, 40%, similar to the autopsy series.[119]

Clinical and epidemiological case characteristics. Among individual case reports, there was a slight predominance of male sex (57.6%). Most cases (73.1%) aged between 19 and 49 years. Comorbidities and other relevant medical conditions were described in 33.3%, (i.e., hypertension, diabetes, hypercholesterolaemia, β-thalassaemia, parasites coinfections, previous histoplasmosis, previous myocardial infarction, malignant vasovagal syndrome, occasional tobacco use, and chronic obstructive pulmonary disease). Two patients were pregnant. Most patients presented with respiratory complications on hospital admission (55.2%), predominantly increased respiratory rate (75%) and heart rate

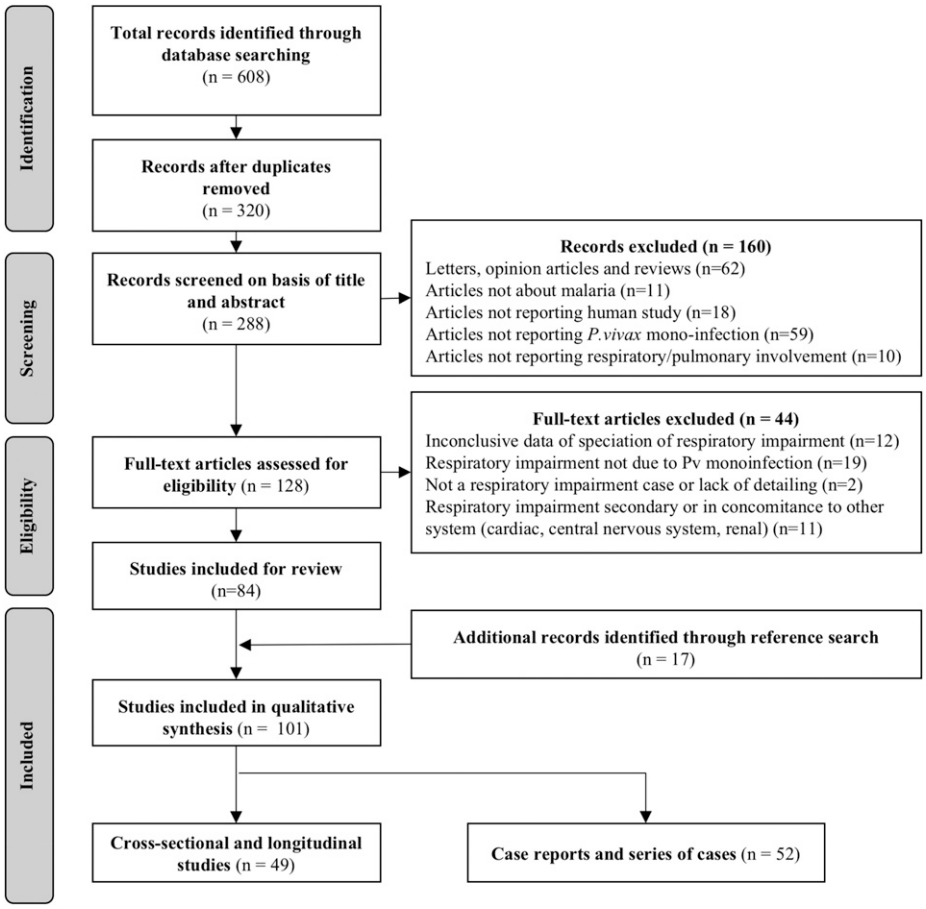

FIGURE 1. Flow chart of inclusion of studies reporting respiratory complications *Plasmodium vivax* malaria.

(62.2%), and/or reduced pulse oximetry (46.6%). Anemia (81.8%), thrombocytopenia (91.6%), and elevated liver enzymes (55.1%) were also observed. Median parasite density was 14,780 per μL (Table 6).

Vivax malaria diagnosis was performed in the first day in almost all cases. RD started before hospitalization in 27.1% and occurred after the start of antimalarial treatment in 62.7%. Parasite clearance occurred after RD onset in 87.2%. Median of hospitalization was 13 days (Table 6).

Almost all patients were reported to have received supplementary oxygen (98.2%): 33.9% were managed by non-invasive strategies, with positive pressure ventilation strategies in some cases. In the remaining 66.1%, invasive strategies were necessary with some reporting use of low-tidal volumes, moderate levels of positive end expiratory pressure, and other protective ventilation strategies. Other approaches adopted were prone positioning and extracorporeal membrane oxygenation (Table 6).

Survivors and non-survivors. Female sex was associated with higher mortality (P = 0.013). One female was pregnant. Comorbidities (P = 0.036) and respiratory complications at admission (P = 0.031) were more frequent among deceased patients. Body temperature (P = 0.032), hemoglobin level (P = 0.043), and oxygen saturation (P = 0.053) were lower at hospital presentation among non-survivors. Non-survivors were kept on oxygen support for less time (P = 0.026), with a great predominance of cases being reported to use invasive oxygen delivery strategies (P = 0.076). Moreover, these patients had shorter hospitalizations (P = 0.007) (Table 6).

Histopathological and functional studies. Few studies provided histopathological findings. A study published in 1993 revealed bronchiolitis obliterans organizing pneumonia.[103] Further studies reported the presence of monocytes, lymphocytes, and neutrophils in pulmonary microvasculature along with phagocytosed pigment and diffuse alveolar damage[110,115] accompanied by hyaline membrane formation.[13] Severe alveolar edema and congestion with infiltrates containing mononuclear cells and suggestive images of adhesion of *Plasmodium*-infected red cells to lung microvasculature were reported in an autopsy series.[120] Functional studies reported gas flow impairments with reduction of vascular component at presentation and improvement by day 7, and also with alveolar-capillary membrane component decreased at presentation with progressive deterioration after 14 days from treatment in severe vivax malaria.[121] Of note, a case without any clinical or laboratory evidence of vivax induced respiratory complications was reported in 1989 and showed a reversible diffuse lung uptake of technetium-99m sulfur colloid during acute and recovery periods, which could indicate, according to the authors, a malaria-induced increase in lung macrophages.[122]

DISCUSSION

Pulmonary edema and ARDS are features of severe falciparum malaria adopted since 1990,[123] and have been used

TABLE 2
Respiratory impairment and severe malaria definitions according to the literature

Author, year (reference)	Name	Definition
Bernard, 1994[146]	AECC definition	Timing: Acute onset; Radiograph: Bilateral infiltrates (frontal chest radiograph); PAWP: ≤ 18 mmHg or no clinical evidence of left atrial hypertension; Oxygenation: *ALI criteria:* PaO2/FiO2 ≤ 300/*ARDS criteria:* PaO2/FiO2 ≤ 200 (regardless of PEEP level)
The ARDS Definition Task Force, 2012[127]	Berlin definition	Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms; Chest imaging: Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules*; Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload†; Oxygenation: Mild (200 mmHg < PaO2/FiO2 ≤ 300 mmHg); Moderate (100 mmHg < PaO2/FiO2 ≤ 200 mmHg); Severe (PaO2/FiO2 ≤ 100 mmHg). Obs.: PEEP or CPA*P* ≥ 5 cm H_2O (Mild) or PEE*P* ≥ 5 cm H_2O (moderate and severe)
Riviello, 2016[128]	Kibali modification	Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms; Imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules by chest radiograph or ultrasound; PEEP requirement: No PEEP requirement, consistent with AECC definition; Origin of edema: respiratory failure not fully explained by cardiac failure or fluid overload†; Oxygenation: SpO2/FiO2 ≤ 315
WHO definitions and clinical features of respiratory impairment in malaria		
WHO, 1990[123]	Severe and complicated malaria	Pulmonary edema: Sudden development after one or two days of treatment in adults. Evidence may include fluid overload, raised central venous or pulmonary artery wedge pressures and grossly positive fluid balance. It may also develop suddenly after delivery in pregnant women in positive fluid balance. Risk factors include hyperparasitemia, renal failure, pregnancy. Metabolic acidosis and hypoglycemia may be associated
WHO, 2000[124]	Severe falciparum malaria	RD (associated acidosis): Raised RR, deep breathing and increased depth of respiration accompanied by a degree of intercostal indrawing (lower chest wall); pulmonary edema: later in course of disease with acute development. Presence of increased RR and chest x-ray evidencing pulmonary edema. PAWP may be normal.
WHO, 2012[147]	Severe malaria	RD (acidosis)—Clinical features: Deep breathing, with indrawing of the bony structures of the lower chest wall, in the absence of localizing chest signs, suggests metabolic acidosis. Indrawing of the intercostal spaces alone is a less useful sign; pulmonary edema – Clinical features: increase in the respiratory rate, preceded by chest signs (radiograph resembling ARDS), reduced PaO2. Hypoxia may cause convulsions and consciousness

(continued)

TABLE 2
Continued

Author, year (reference)	Name	Definition
		deterioration, and the patient may die within a few hours. In pregnant, it may develop suddenly and unexpectedly several days after admission or may occur immediately after childbirth
WHO, 2014[126]	Severe malaria	Bedside clinical classification of severe malaria (children and adults). RD (acidotic breathing): Mild—sustained nasal flaring and/or mild intercostal indrawing; Severe—either marked indrawing of the bony structure of the lower chest wall or deep (acidotic) breathing. Adults—Pulmonary edema: Radiologically confirmed, or oxygen saturation < 92% on room air with a respiratory rate > 30/minutes, often with chest indrawing and crepitation on auscultation; Acidosis: Severe acidosis manifests clinically as RD—rapid, deep, and labored breathing

AECC = American-European Consensus Conference; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; FiO_2 = fraction of inspired oxygen; PaO_2 = partial pressure of oxygen in arterial blood; PAWP = pulmonary artery wedge pressure; PEEP = positive end expiratory pressure; RD = respiratory distress; RR = respiratory rate; SpO_2 = peripheral capillary oxygen saturation; WHO = World Health Organization.

* Chest radiograph or computed tomography scan.

† Need objective assessment, as echocardiography, to exclude hydrostatic edema if no risk factor present.

also to define severe vivax malaria afterward. In this study, we proposed to estimate prevalence and mortality of respiratory complications in vivax malaria along with risk factors associated to death. The analysis of longitudinal and cross sectional studies showed that respiratory complications and ARDS occur in lower frequencies in vivax malaria, both in children and adults, but with a mortality resembling falciparum disease. Female gender, presence of comorbidities, and respiratory complications at hospital admission along with lower hemoglobin and body temperature measurements were associated with death.

Most of the studies were published before 2012 and used previous WHO definitions for respiratory complications.[124,125] Bedside clinical classification of RD has two degrees according to WHO with similar clinical features among children and adults.[126] Lung edema is a criterium for severe falciparum disease and is defined through clinical and radiological criteria.[126] ARDS, with a definition update in 2012,[127] was also commonly reported in studies analyzed in this review. Despite advances in ARDS diagnosis and treatment, most malaria-endemic areas are resource-poor settings. Therefore, misdiagnosis, underreporting, and incorrect management may occur. A more inclusive ARDS diagnostic tool, which withdraws positive end-expiratory pressure requirements and keeps only imaging and a single oxygen saturation cutoff value, has been developed, and despite lacking validation, it seems a promising epidemiological tool for ARDS.[128]

The presence of comorbidities and altered clinical and laboratory parameters at hospital admission may serve as early indicators of disease severity and risk of death. Underlying diseases, such as hypertension and diabetes, may indicate a greater hemodynamic compromise with an exacerbated inflammatory profile.[129] These might contribute to vivax mortality through disturbances in cytokine production, endothelial activation, altered thrombostasis, and further

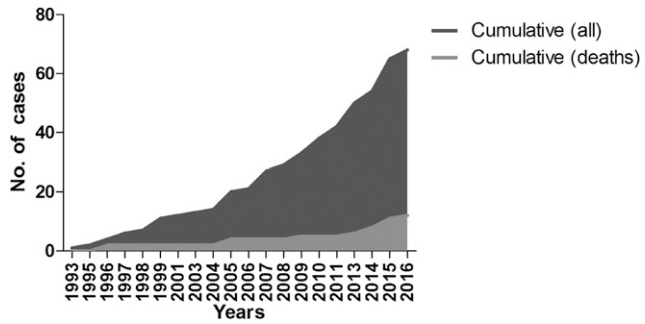

FIGURE 2. Cumulative number of cases and deaths from case reports.

TABLE 3
Number of pulmonary malaria cases and associated deaths, from case reports and series of cases of vivax malaria, by country of publication

Country of publication	No. of cases (% of total)	No. of deaths (% of deaths)
India	21 (31.4)	4 (33.3)
United States	10 (15)	0 (0)
Brazil	10 (15)	3 (25)
England	5 (7.6)	0 (0)
Colombia	4 (5.9)	3 (25)
Greece	2 (2.9)	0 (0)
Pakistan	2 (2.9)	0 (0)
Spain	2 (2.9)	0 (0)
Thailand	2 (2.9)	1 (8.3)
Germany	1 (1.5)	0 (0)
Italy	1 (1.5)	0 (0)
Malaysia	1 (1.5)	0 (0)
Mexico	1 (1.5)	0 (0)
Peru	1 (1.5)	1 (8.3)
Singapore	1 (1.5)	0 (0)
South Korea	1 (1.5)	0 (0)
Turkey	1 (1.5)	0 (0)
Venezuela	1 (1.5)	0 (0)
Total	67 (100)	12 (100)

TABLE 4
Methods used in case reports and series of cases for malaria diagnosis and types of parasitemia presentation

Method(s)	No. (% of total)
PBF + PCR	23 (34.8)
PBF + RDT	20 (30.3)
PBF	16 (24.2)
PBF + RDT + PCR	5 (7.6)
QBC + PCR	1 (1.5)
PBF + QBC + RDT	1 (1.5)
Total	66 (97.05)

PBF = peripheral blood film; PCR = polymerase chain reaction; RDT = rapid diagnostic test; QBC = quantitative buffy coat.

organ specific damage,[130] which may further explain findings from histopathological and functional studies.

Although vivax malaria rarely develops hyperparasitemia,[13] a hallmark of severe falciparum malaria,[126] greater inflammatory and endothelial activation per parasite occurs in vivax malaria when compared with falciparum disease.[131–133] Inflammatory exacerbation may cause pulmonary injury,[130] whereas elevated cytokines and other inflammatory-inducing molecules may be responsible for alveolar-capillary barrier loss and increased permeability.[134]

Several reports from different *Plasmodium* species show that respiratory impairment begins several hours after antimalarials start, even in the presence of declining or negative parasitemia. In a falciparum malaria study, 79 patients developed respiratory failure, in the first 48 hours in 42% and afterward in 46%.[135] Lung function studies revealed small airway obstructions and decreased diffusion capacity in both uncomplicated falciparum and vivax malaria.[121,136,137] The capillary volume compartment in vivax patients was reduced at admission, returning to normal after treatment, whereas the membranous compartment was normal at presentation but progressively deteriorated. According to the authors, the uncoupling of both compartments at different time points is consistent with *Plasmodium*-infected red cells sequestration and a progressive alveolar-capillary injury due to a posttreatment inflammatory response to parasite killing.[121] In vivax malaria, cytoadhesion of infected red cells to the endothelial cell layer is supported by recent studies.[138,139] In an autopsy series, seven out of 13 patients in which vivax was the probable or contributing cause of death presented pulmonary complications.[120] A lung tissue section from one of these patients presented images suggestive of sequestration of *P. vivax*-infected red cells within pulmonary vasculature. Interestingly, this sample was taken from a patient with negative peripheral parasitemia but with positive polymerase chain reaction for vivax in the lung.[120]

The high number of patients needing mechanical ventilation and other advanced life-support strategies, which are not always available in resource-poor settings, may have impacted mortality. Early malaria diagnosis accompanied by effective antimalarial therapy, rapid identification of oxygen saturation deterioration with prompt support, and identification of complications could avoid progression to death.[140]

The time of oxygen support and length of hospitalization were lower among those who died, evidencing a more severe clinical deterioration than in survivors. Similarly, in a clinical characterization of vivax malaria patients suffering from ARDS and acute lung injury, older age, use of invasive mechanical ventilation, hypoxemia, presence of other organ involvement

TABLE 5
Frequency and case fatality rate of ARDS among patients with Pv malaria according to age groups in hospital-based studies

First author, year (reference)	Location	Study population	No. of Pv patients				Frequency (%)		
			Total	Severe	ARDS	Deaths	ARDS /total	ARDS /severe	ARDS mortality
Studies with pediatric population (children under 18 years)									
Kochar, 2010[27]	India	Malaria hospitalizations	103	65	1	–	0.9	1.5	–
Singh, 2011[33]	India	Patient hospital presentations	108	23	0	0	0	0	0
Lança, 2012[28]	Brazil	Pv pediatric hospitalizations	24	24	3	0	12.5	12.5	0
Sharma, 2012[29]	India	Patients admitted to hospital	105	46	9	7	8.5	19.5	77.8
Yadav, 2012[30]	India	Severe vivax malaria	131	131	3	2	2.2	2.2	66.7
Gehlawat, 2013[32]	India	Severe vivax in children	18	18	1	1	5.5	5.5	100
Bhattacharjee, 2013[34]	India	Pv pediatric hospitalizations	168	168	2	0	1.1	1.1	0
Singh, 2013[35]	India	Patients admitted to hospital	61	38	5	3	8.2	13.1	60
Sharma, 2013[36]	India	Pv pediatric hospitalizations	261	54	3	–	1.1	5.5	0
Goyal, 2014[37]	India	Pv hospital admissions	47	–	2	1	4.2	–	50
Total			1026	567	29	14	2.8	5.1	48.2
Studies with adult population									
Kotwal, 2005[57]	Afghanistan	American soldiers	38	1	1	0	2.6	100	0
Sharma, 2009[60]	India	Records of malaria cases	221	–	3	3	1.3	–	100
Kochar, 2009[61]	India	Patients admitted to hospital	456	40	4	2	0.8	100	50
George, 2010[71]	India	Severe Pv admissions	30	30	1	1	3.3	3.3	100
Nayak, 2011[62]	India	Severe malaria cases	80	80	4	4	5	5	100
Srivastava, 2011[63]	India	Patient hospital presentations	50	41	3	0	6	7.3	0
Limaye, 2012[64]	India	Patients admitted to hospital	336	50	10	6	2.9	20	60
Mehmood, 2012[65]	Pakistan	Pv cases in Emergency Dept.	97	–	1	0	1	–	0
Singh, 2013[56]	India	Patients admitted to hospital	140	63	3	2	2.1	4.7	66.7
Rizvi, 2013[67]	India	Patients admitted to hospital	172	62	6	2	3.5	9.7	33.3
Muley, 2014[70]	India	Hospital admissions	100	–	6	1	6	–	16.6
Siqueira, 2015[26]	Brazil	Patients admitted to hospital	316	40	7	1	22.2	17.5	14.2
Siqueira, 2015[26]	India	Patients admitted to hospital	462	157	5	5	1.1	3.1	100
Jain, 2016[72]	India	Patients in Emergency Dept.	48	25	2	1	4.1	8	50
Total			2548	589	56	28	2.2	9.5	50

ARDS = acute respiratory distress syndrome; Dept. = department; Pv = *Plasmodium vivax*. Blank spaces mean no data was available in original paper.

TABLE 6
Characterization of selected characteristics according to outcome

Parameters	All No. (% of total)	Survival No. (% of total)	Non-survival No. (% of total)	*P* value*	Completeness n (%) (Survival and non-survival)
Demographics					
Total with individual information	67 (100)	54 (81.8)	12 (18.2)	–	66 (98.5)
Age (years)				0.371	65 (97)
Mean (1 SD)	39 (15)	40 (±14)	36 (±18)		
IQR (Range)	29–50 (15–75)	30–50 (15–74)	20–30 (19–75)		
Gender					
Male	38 (57.6)	34 (64.2)	3 (25)	**0.013**	65 (97)
Female	28 (42.4)	19 (35.8)	9 (75)		
Imported malaria case	27 (40.3)	22 (40.7)	4 (33.3)	0.635	65 (97)
Clinical and laboratory parameters at hospital admission					
Presence of comorbidities and other alterations	18 (33.3)	11 (25.6)	6 (60)	**0.036**	53 (79)
Altered clinical status at baseline	55 (91.7)	45 (90)	10 (100)	0.296	60 (89.5)
Malaria signs and symptoms in last days	58 (96.7)	48 (96)	10 (100)	0.520	60 (89.5)
Presence of respiratory complication	32 (55.2)	24 (50)	8 (88.9)	**0.031**	57 (85)
Respiratory rate (irpm)†	30 (± 10)	30 (±10)	29 (±10)	0.429	46 (68.5)
Heart rate (bpm)†	107 (± 20)	107 (±21)	107 (±15)	0.532	45 (67.2)
O_2 Saturation (%)‡	94 (82–98)	95 (86–99)	78 (75–88)	0.053	30 (44.8)
Body temperature (°C)†	38.36 (±1.4)	38.5 (±1.2)	37.5 (±1.7)	**0.032**	45 (67.2)
Hemoglobin (g/dL)†	10.3 (± 2.9)	10.63 (±2.8)	8.67 (±3.15)	**0.043**	44 (65.7)
Leukocytes ($\times 10^3/mm^3$)‡	6.6 (3.9–10)	6 (3.9–10)	8.7 (4–9.9)	0.921	47 (70.1)
Platelet count ($\times 10^3/mm^3$)‡	60 (35.5–95)	59 (36–91)	81 (34–120)	0.447	48 (71.6)
AST (IU/L)‡	56 (38–98)	60 (47–98)	36 (31–83)	0.118	29 (43.3)
ALT (IU/L)‡	62 (36–77)	67 (42–77)	34 (28–66)	0.092	29 (43.3)
Parasitemia ($\times 10^3/\mu L$)‡	14.8 (1.8–34)	13.1 (13–34)	15.4 (8–28.7)	0.811	22 (32.8)
Disease progression					
Duration of malaria symptoms (days)‡	6 (4–7)	5 (4–7)	7 (7–7)	0.289	53 (79.1)
P. vivax diagnosis on day 1	50 (84.7)	41 (83.7)	9 (90)	0.612	59 (88)
Time of onset of RD					
Before AM initiation	22 (37.3)	19 (38)	3 (33.3)	0.790	59 (88)
After AM initiation	37 (62.7)	31 (62)	6 (66.7)		
After RD, change of AM	12 (27.9)	10 (27.7)	2 (28.6)	0.966	43 (62.4)
Time of parasite clearance					
Before RD onset	5 (12.8)	3 (8.8)	2 (40)	0.052	39 (58.2)
After RD onset	34 (87.2)	31 (91.2)	3 (60)		
Supplementary oxygen use	56 (98.2)	47 (100)	9 (90)	**0.029**	57 (85)
Oxygen support use (days)‡	6 (3–10)	6 (4–10)	3 (1–5)	**0.026**	37 (55.2)
Type of oxygen support					
Noninvasive	18 (33.9)	17 (39.5)	1 (10)	0.076	53 (79.1)
Invasive (intubated)	35 (66.1)	26 (60.5)	9 (90)		
Time hospitalized (days)‡	13 (7–21)	14 (9–21)	4 (2–10)	**0.007**	43 (62.4)

ALT = alanine aminotransferase; AM = antimalarials; AST = aspartate aminotransferase; bpm = beats per minute; brpm = breaths per minute; IQR = interquartile range; RD = respiratory distress; SD = standard deviation. The bold highlights signify *P* values.

* Survival vs. non-survival groups.

† Mean (one standard deviation).

‡ IQR.

and comorbidities were considered risk factors for mortality.[141] The higher presence of comorbidities found among non-survivors, along with higher presentation to hospital with respiratory impairment, probably explain the outcome in this group.

The pathogenesis of respiratory complications is historically better characterized in *P. falciparum* infection with studies revealing important lung vascular alterations: congested capillaries, thickened alveolar septum, diffuse edema, and hyaline membrane formation[142]; endothelial cell swelling with narrowed capillary lumen, macrophages within interstitium and hemozoin[143]; and presence of inflammatory and *Plasmodium*-infected red cells within capillaries.[144] Essentially, and despite the progression and outcome of lung deterioration, the major difference between *P. falciparum* and *P. vivax* ARDS pathogenesis is the presence of more sequestration of parasitized red blood cells in the former[145] and scanty evidence in the second.[13,120]

Only studies containing respiratory complications were included, which may increase the prevalence estimates of respiratory complications. Furthermore, severe cases are more likely to be published, leading to a clear bias of publication. Also, calculating disease prevalence or clinical outcome among several studies published with different objectives and lack of standardization on data reporting were expected limitations. The publications' time range, different localities, and different case definitions may have affected, therefore, disease management and data reporting priorities, which may further have influenced the results of the present study. This lack of systematic reporting hampers broad data analysis and completeness.

CONCLUSIONS

To our knowledge, this is the first systematic review and meta-analysis attempting to estimate the frequency of

respiratory complications in different vivax malaria populations, its disease characteristics, factors associated with death, and histopathology. As in falciparum malaria, vivax disease also presents an important rate of respiratory impairment among severe cases, with elevated mortality among children and adults. Female sex, presence of comorbidities, respiratory status at hospital admission, and lower hemoglobin values were found to statistically differ between survivors and non-survivors. Multicenter studies are needed using standardized protocols with adequate data registering, confirmation of mono-infections through molecular methodologies, exclusion of comorbidities, and other concurrent infections to better characterize vivax clinical spectrum and, specifically, respiratory impairment.

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