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Review Article

Prevalence of Cardiovascular Complications in Malaria: A Systematic Review and Meta-Analysis

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Abstract. Recent studies have suggested that malaria may affect the cardiovascular system. The aim of this systematic review and meta-analysis was to determine the prevalence of cardiovascular complications in symptomatic malaria patients. We searched databases such as Pubmed, Embase, Cochrane, and Web of Science (January 1950–April 2020) for studies reporting on cardiovascular complications in adults and children with malaria. Cardiovascular complications were defined as abnormalities in electrocardiogram (ECG), cardiac biomarkers, and echocardiography on admission or during outpatient examination. Studies of patients with known heart disease or cardiovascular evaluation performed after the start of intravenous antimalarial medication were excluded. The study was registered in International Prospective Register of Systematic Reviews (PROSPERO) (No.: CRD42020167672). The literature search yielded 1,243 studies, and a total of 43 studies with symptomatic malaria patients were included. Clinical studies (n = 12 adults; n = 5 children) comprised 3,117 patients, of which a majority had *Plasmodium falciparum* (n = 15) and were diagnosed with severe malaria (n = 13). In random-effects models of adults, the pooled prevalence estimate for any cardiovascular complication was 7% (95% CI: 5–9). No meta-analysis was conducted in children, but the range of abnormal ECG was 0–8%, cardiac biomarkers 0–57%, and echocardiography 4–9%. We analyzed 33 cases (n = 10 postmortem), in which the most common cardiovascular pathologies were myocarditis and acute coronary syndrome. All histopathological studies found evidence of parasitized red blood cells in the myocardium. Cardiovascular complications are not uncommon in symptomatic adults and children with malaria. Additional studies investigating malaria and cardiovascular disease are encouraged.

INTRODUCTION

Despite progress in global control and elimination efforts, malaria remains a widespread parasitic disease. In 2018, approximately 228 million cases and 405,000 deaths worldwide were attributed to malaria.[1] In low- and middle-income countries, malaria remains a major burden on local health services, demanding frequent hospitalizations and adding to morbidity.[2] Although malaria mortality has decreased markedly since 2000, a concomitant increase in cardiovascular deaths has been reported in malaria-endemic areas.[3,4] Despite links between parasitic infections and cardiovascular disease have been demonstrated previously,[5] the relationship between malaria and cardiovascular illness is poorly investigated.

Among the human malaria species, infection with *Plasmodium falciparum* is considered the most lethal. Uncomplicated malaria may arise as a result of *P. falciparum* infection, which is often characterized by periodic fever, body ache, and diarrhea; yet, the disease may also develop into its complicated forms often designated as severe or complicated malaria.[6] A known complication to severe malaria is rapid fluid depletion, which may affect the cardiac output.[7] Cerebral malaria and severe malarial anemia are well-characterized forms of severe disease caused by *P. falciparum*. This results mostly from a combination of events involving structural modifications and expression of parasite adhesion molecules in the infected erythrocyte that promote their accumulation in specific organs such as the brain and placenta,[8,9] triggering local inflammation that participates in parasite clearance with a downside contribution to the pathological outcomes of severe malaria.[10] The cytoadhesive properties of *Plasmodium vivax* remain less well described.[11] Although no studies have demonstrated cytoadherence of infected erythrocytes to the myocardial endothelium, autopsy data suggest that infected erythrocytes may block myocardial capillaries[12] consequently, leading to mechanical blood flow obstruction and potential myocardial ischemia.[13,14] Other proposed mechanisms involve release of parasite toxins causing apoptosis of cardiac myocytes[15] and impairment of vascular endothelial function, resulting in upregulation of pro-inflammatory cytokines and myocardial dysfunction.[16–18] At present, the pathophysiology between malaria and cardiac illness is not entirely understood, and an appraisal of the most common cardiovascular complications in the acute setting of malaria may prove beneficial to improve both treatment and prognosis of patients. Therefore, the aim of this systematic review and meta-analysis was to provide an estimate of the prevalence of the most commonly reported cardiovascular complications in malaria.

METHODS

We included clinical studies, case reports, and series of cases addressing cardiovascular complications caused by malaria infection. Reporting was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses. This systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO; No.: CRD42020167672).

Selection criteria. We included full-text reports on patients in all ages who were positive for malaria infection with

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P. falciparum, *Plasmodium ovale*, *P. vivax*, *Plasmodium malariae*, or *Plasmodium knowlesi* verified by microscopy of Giemsa-stained peripheral blood films, quantitative buffy coat, rapid diagnostic tests, or polymerase chain reaction. Other types of *Plasmodium* were excluded. We included patients with both mild and severe infections as defined by the WHO.[19] Cardiovascular complications had to be reported on admission and involved abnormalities in electrocardiograms (ECG), cardiac biomarkers, and echocardiography. Postmortem studies were only required to report autopsy findings. We excluded articles in languages other than English, animal and in vitro studies, vertical transmission and studies of patients with concomitant parasite infections, congenital heart disease, heart transplant, or known heart disease at baseline. We also excluded reports on patients who underwent cardiovascular evaluation after treatment start of intravenous antimalarial medication, as this may induce iatrogenic cardiac complications.[20,21]

Search strategy. We searched in PubMed, Embase, Cochrane, and Web of Science from January 1950 to April 2020. We applied a broad search string to increase the sensitivity of the search, and some of the following search terms were used: "Malaria" OR "*P. falciparum*" OR "*P. vivax*" AND "Heart Disease" OR "Cardiovascular." The full search strings for each of the databases are displayed in Supplemental Table 1. We also examined the reference lists of all included articles to identify additional articles fulfilling our inclusion/exclusion criteria.

Data collection. The literature search and screening of titles and abstracts were performed by two independent reviewers (A. E. H. and P. B.). After this step, duplicates were removed, and full-text reports were assessed for eligibility by the same reviewers. Any disagreements were resolved by consensus. Data extraction was independently performed by A. E. H. and L. C. G. For all studies, we assessed country, sample size, clinical characteristics (age and gender), cardiovascular risk factors, diagnostic method, species, severity, parasite density, and data on cardiovascular complications at admission. According to guidelines in cardiovascular medicine, we extracted data on common alterations related to myocardial damage, involving ECG changes,[22,23] biomarkers,[24] and echocardiography.[25] For ECG, this involved deviations from sinus-rhythm and ST-segment changes. Abnormal levels of cardiac biomarkers (i.e., troponins, N-terminal pro-brain natriuretic peptide) and echocardiographic parameters (i.e., left ventricular ejection fraction [LVEF])[25] were assessed according to internationally recognized reference ranges.[26,27] When studies presented individual person data, we extracted the frequency of abnormal cardiac parameters. When studies compared cardiovascular complications in malaria cases versus controls, these data were also extracted. For clinical studies (longitudinal, cross-sectional, and case–control), we extracted data on cardiovascular mortality when available. In case reports and series of cases, we also obtained information on histopathology where available. Studies with pediatric populations were defined as ≤ 17 years old and adult populations ≥ 18 years old.

Bias assessment. We used the study quality assessment tool from the National Heart, Lung, and Blood Institute for observational cohort and cross-sectional studies.[28] Two investigators (A. E. H. and L. C. G.) applied this tool to clinical studies to assess risk of bias. The assessment yielded an overall good quality of included clinical studies (Supplemental Table 2).

Statistics. We applied a random-effects model for pooling proportions of cardiovascular complications in adults.[29] This was performed using the *metaprop* command in STATA (StataCorp, College Station, TX). Because of a limited number of studies, no meta-analysis was conducted in children. The variation across studies caused by heterogeneity was assessed by the I^2 value. However, for abnormal echocardiography in adults, I^2 was not assessed because of few included studies. A forest plot was constructed showing the prevalence of cardiovascular complications among all studies together with the pooled measure. Subgroup meta-analyses were conducted for each of the cardiovascular complications (ECG, biomarkers, and echocardiography). In addition, we conducted meta-regression models to determine if country, year, species, and severity affected our results. We assessed potential publication bias using Egger's test in each subgroup.[30] We considered reported P-values < 0.05 as significant. All statistical analyses were performed using STATA (version 14.2, College Station, TX).

RESULTS

The literature search and identification of records in bibliographies yielded 1,243 studies, of which 1,087 were excluded based on title and abstract. A total of 156 studies were assessed in full text, of which 43 fulfilled the inclusion criteria. The studies were divided in two major categories, the first involving 17 clinical studies[31–47] and the second 26 case reports and series of cases[48–73] (Figure 1).

Clinical studies. Clinical studies of adults (n = 12) and children (n = 5) were conducted from 1992 to 2020 and involved a total of 3,117 patients (n = 2,403 adults and n = 714 children), of which one study[57] accounted for 49% of all patients (n = 1,531) (Table 1).

Fifteen studies assessed infection with *P. falciparum*, of which a majority examined severe malaria cases (n = 13).[31,32,34–36,39,41–47] Studies were conducted in Southeast Asia (n = 6),[31,32,34,37,38,41] Germany (n = 5),[35,36,39,40,42] Africa (n = 5),[43–47] and South America (n = 1).[33] The most commonly reported cardiovascular parameters are displayed in Table 2.

Adults. All studies but one involved hospitalized patients[33] (all studies: age 18–70 years; 33% female; median parasite density 30,295/μL). In subgroup meta-analyses, the pooled prevalence estimate for abnormal ECG was 7% (95% CI: 3–10) (n = 7),[32,33,37,38,40–42] cardiac biomarkers 8% (95% CI: 5–12) (n = 6),[34,36,38–41] and echocardiography 17% (95% CI: 11–23) (n = 3)[32,34,42] (Figure 2). The overall pooled prevalence estimate for cardiac complications was 7% (95% CI: 5–9). Considerable heterogeneity was present (I^2 = 0.90). In meta-regression models, the presence of severe malaria cases in the included studies significantly affected the prevalence estimate of cardiac biomarkers (P = 0.03). Country, year, and species did not affect the results (P < 0.05 for all; Supplemental Table 3). Egger's test indicated publication bias among studies reporting on ECG (P = 0.016) and biomarkers (P = 0.024) but not in the echocardiography subgroup (P = 0.87). Two studies[34,42] examined patients at follow-up, of which only one found persistent echocardiographic alterations.[34] Details are displayed in Supplemental Table 4.

Children. All studies were conducted on *P. falciparum* in Africa (age 3 months–10 years; 52% female; median parasite

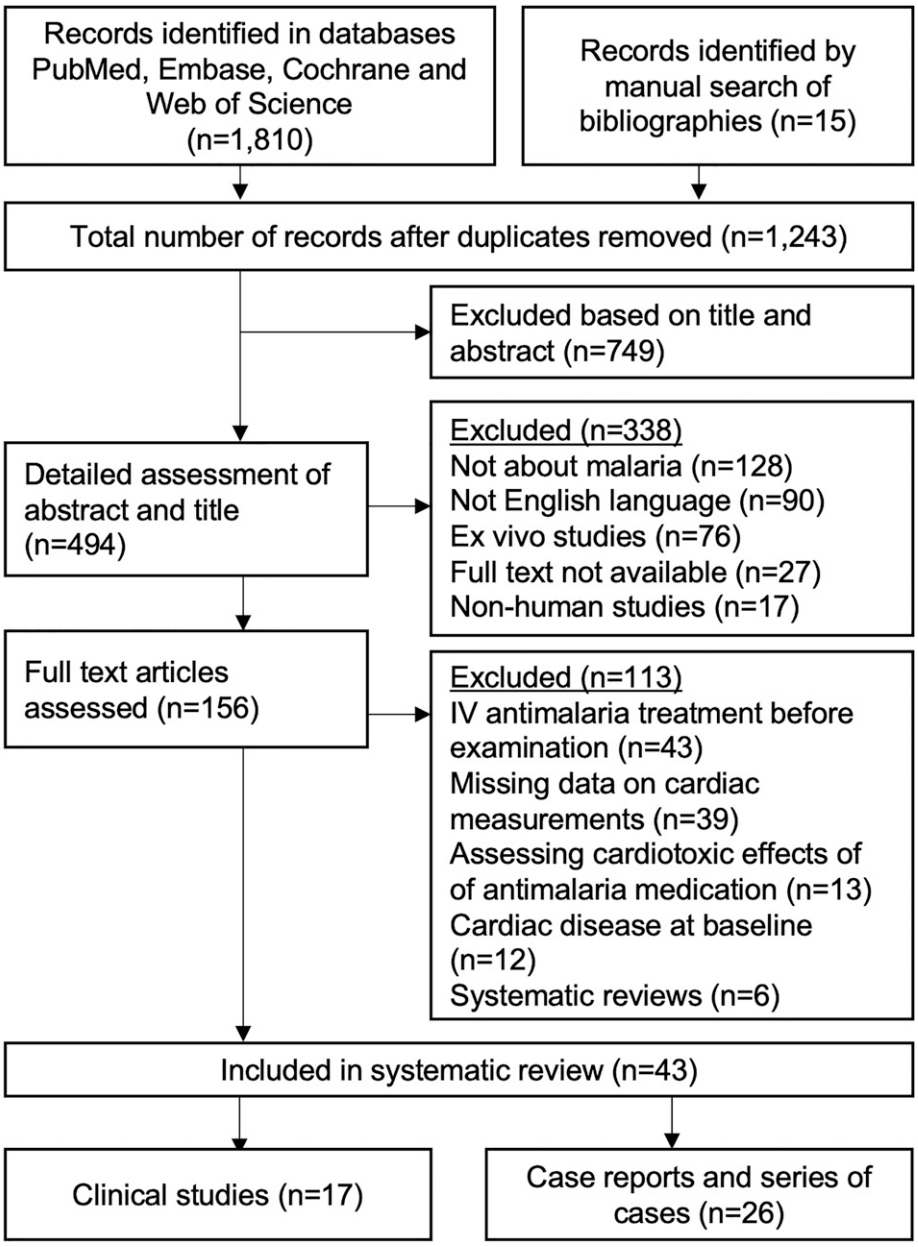

FIGURE 1. Flowchart. Flowchart of included studies in the systematic review and meta-analysis.

density 35,384/μL). Only one study reported ECG abnormalities with a frequency of 0%,[44] whereas four studies reported abnormal cardiac biomarkers ranging from 0% to 58%.[39,43,44,46] The frequency of abnormal echocardiography ranged from 4% to 9% (n = 4).[43–46] One study[43] found that biomarkers and echocardiography had normalized after 42 days of follow-up. Additional details are found in Supplemental Table 5.

Case reports and series of cases (Figure 3). We analyzed 33 case reports and series of cases (n = 29 adults; n = 4 children; Figure 2) from 1954 to 2019 (age range 1–6 years; 36% female). A majority of infections were caused by *P. falciparum* (n = 18) and *P. vivax* (n = 12) (Supplemental Table 6).

Adults. Abnormalities in ECG were present in 55% of cases,[48,50,53,56,58,60,65–67,69,70] whereas 14% had increased troponins (TnT/TnI).[60,66,67,70] Five reports found decreased LVEF.[53,56,58,68,71] However, in four reports,[56,58,68,71] this normalized at follow-up (range 5–120 days). Most patients were diagnosed with myocarditis (n = 9)[53,56–60,68,70,71] and acute coronary syndrome (n = 4).[48,49,66,69]

Children. All cases were hospitalized,[54,61,63] of which three[61,63] had acute heart failure, as determined by the LVEF range 22–35%, and one had myocarditis.[54] In two cases, the LVEF was normal at follow-up.[54,61]

Postmortem. Ten cases were analyzed (n = 9 *P. falciparum*, n = 1 *P. knowlesi*)[51,52,55,64,72] (Supplemental Table 6). All studies reported inflammation and infiltrates of parasitized red blood cells in the myocardium and cardiac blood vessels.

DISCUSSION

Cardiovascular complications in malaria have been reported since the beginning of the nineteenth century,[74] but

TABLE 1
Frequency of cardiovascular complications in clinical studies according to adult and pediatric populations

Author, year	Country	Sample size	SM, *n* (%)	Species	Diagnosis	Population	Frequency of abnormal cardiac parameters		
							Electrocardiogram, *n* (%)	Biomarkers, *n* (%)	Echocardiography, *n* (%)
Adult populations (*n* = 12)									
Bhardwaj[31]	India	74	7 (9)	Pf	PBF	Hospitalized	N/A	+	N/A
Ray[32]	India	27	27 (100)	Pf, Pv	PBF	Hospitalized	4 (15)	N/A	5 (19)
Alencar-Filho[33]	Brazil	26	0	Pv	PBF	Outpatient	N/A	+	+
Nayak[34]	India	100	100 (100)	Pf,Pv	PBF	Hospitalized	9 (9)	14 (14)	17 (17)
Stauga[35]	Germany	79	12 (15)	Pf	PBF	Hospitalized	N/A	+	N/A
Herr[36]	Germany	28	7 (25)	Pf	PBF	Hospitalized	N/A	7 (25)	N/A
Mehmood[37]	Pakistan	97	0	Pv	PBF	Hospitalized	1 (1)	N/A	N/A
Jain[38]	India	1,531	0	Pf, Pv	QBF	Hospitalized	22 (1)	22 (1)	N/A
Ehrhardt[39]	Germany	63	11 (17)	Pf	N/A	Hospitalized	N/A	28 (44)	N/A
Günther[40]	Germany	161	0	Pf	PBF	N/A	23 (14)	1 (1)	N/A
Mohapatra[41]	India	195	110 (100)	Pf	PBF	Hospitalized	12 (6)	13 (7)	N/A
Franzen[42]	Germany	22	0	Pf, Pv	PBF	Hospitalized	5 (23)	N/A	3 (14)
Pediatric populations (*n* = 5)									
Nguah[43]	Ghana	183	183 (100)	Pf	PBF	Hospitalized	N/A	106 (58)	+
Mocumbi[44]	Mozambique	45	18 (40)	Pf	PBF	Hospitalized	0	0	2 (4)
Murphy[45]	Uganda	33	17 (53)	Pf	PBF	Hospitalized	N/A	N/A	3 (9)
Janka[46]	Mali	53	53 (100)	Pf	PBF	Hospitalized	N/A	+	+
Ehrhardt[47]	Ghana	400	200 (50)	Pf	PBF	Hospitalized	N/A	226 (57)	N/A

N/A = not applicable; Pf = *Plasmodium falciparum*; Pv = *Plasmodium vivax*; PBF = peripheral blood film; QBF = quantitative buffy test; SM = severe malaria. + Indicates no individual patient data available, but data for malaria cases were significantly different compared with controls.

no systematic reviews have assessed this topic. This study had three principal findings. First, in clinical studies of symptomatic adults with malaria, the pooled prevalence estimate of cardiovascular complications was 7% (95% CI: 5–9). Second, in case reports and series of cases, the most common cardiac pathologies were myocarditis and acute coronary syndrome. Third, significant heterogeneity was present among studies reporting on cardiovascular complications in malaria patients.

Infection with *Plasmodium* may result in a variety of symptoms, ranging from uncomplicated disease to severe symptoms and even death. Many factors influence the likelihood of progression into severe symptoms, including malaria species, age, and host immunity.[75] During the course of severe malaria, the myocardium appears to be a heavily parasitized organ.[76,77] This is in line with the post-mortem cases we assessed, which all demonstrated parasitized erythrocytes in the myocardium.[51,52,55,64,72] After successful invasion of the erythrocyte, *P. falciparum* modifies the cytoadhesive properties of the erythrocyte.[9] This may allow the accumulation of infected erythrocytes in the myocardial capillaries, leading to mechanical obstruction, reduced tissue perfusion, and disease.[13,14] Although less common, studies have also demonstrated how *P. vivax*–infected erythrocytes also may adhere to the endothelium.[11,13,78] Likely, accumulation in the capillaries and microcirculation in the myocardium may result in regional dysfunction, leading to pathological alterations in ECG, biomarkers, and echocardiographic parameters. Those are the same parameters that we found affected in a majority of clinical studies of *P. falciparum* patients on admission.[31,32,34–36,39–47,57]

Although the definition of severe malaria includes *cardiovascular collapse*, this commonly refers to algid malaria,[79] a state of circulatory shock accompanied by bacteremia. As stated by the WHO, the presence of myocardial dysfunction and left ventricular impairment is considered very rare in severe malaria.[7] By contrast, we found that in studies with severe *P. falciparum*, cardiovascular complications were frequently reported on admission. The most recurring pathologies were ST-segment changes and elevated creatine

TABLE 2
Most commonly reported cardiovascular complications in clinical studies

	Adult population	Pediatric population
Electrocardiogram	Nonspecific ST changes (*n* = 4) Sinus tachycardia (*n* = 2) First degree AV-block (*n* = 2) Sinus bradycardia (*n* = 2)	Arrhythmia of any kind (*n* = 1)
Cardiac biomarkers	Creatine kinase MB (*n* = 6) NT-proBNP (*n* = 6) Troponin (TnT/TnI) (*n* = 5) Myoglobin (*n* = 4) Cystatin C (*n* = 3) H-type fatty acid binding protein (*n* = 2) MR-proANP (*n* = 1)	Troponin (TnT/TnI) (*n* = 2) NT-proBNP (*n* = 2) Creatine kinase MB (*n* = 1) Myoglobin (*n* = 1) Cystatin C (*n* = 1) H-type fatty acid binding protein (*n* = 1)
Echocardiography	LV ejection fraction (*n* = 4) LV end-diastolic dimension (*n* = 3) Diastolic dysfunction (*n* = 2) LV end-systolic dimension (*n* = 1)	LV ejection fraction (*n* = 1) LV end-diastolic dimension (*n* = 1)

AV = atrioventricular; LV = left ventricular; MB = myocardial band; MR-proANP = MR–pro-atrial natriuretic peptide; NT-proBNP = *N*-terminal–pro-brain natriuretic peptide; TnT/I = troponin T and I.

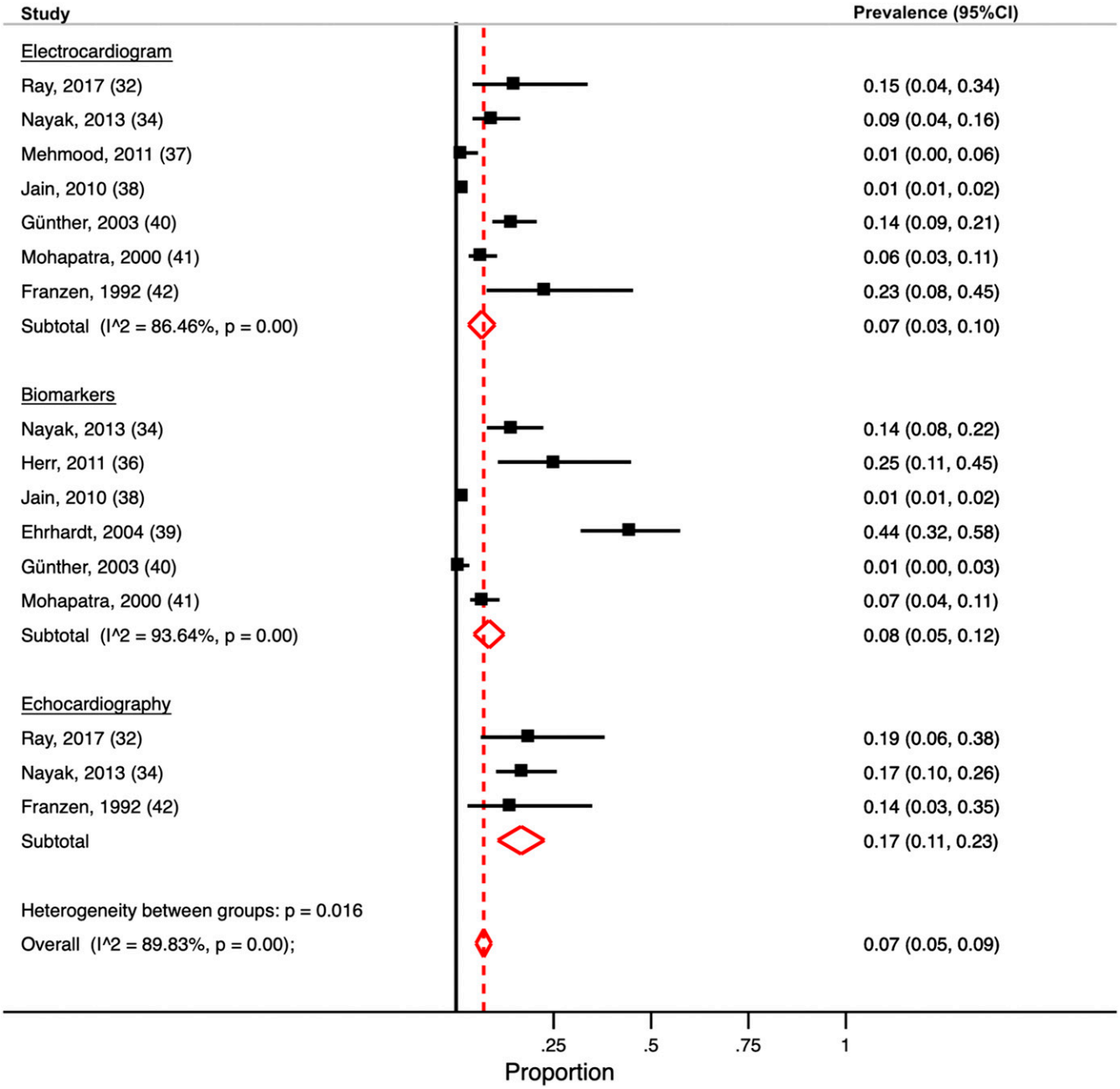

FIGURE 2. Meta-analysis of cardiovascular complications. Forest plot for random-effects meta-analysis displaying the proportions and pooled estimate for having cardiovascular complications. Subgroup meta-analysss are conducted for abnormal electrocardiogram, biomarkers, and echocardiography. Solid black lines indicate the prevalence estimate for each included study. Red dashed line indicates the pooled prevalence estimate for any cardiovascular complication. This figure appears in color at www.ajtmh.org.

kinase myocardial band (CK-MB) and, specifically, two studies demonstrated impaired left ventricular function at admission (Table 2).[32,34] Considering that malaria may rapidly progress to complications and death without appropriate treatment, an appraisal of cardiovascular parameters in the clinical setting could potentially serve as early indicators of disease severity. In addition, it is known that multiple affected organ systems during the course of severe malaria are associated with mortality.[80] As only three studies assessed cardiac parameters prospectively, and given that they presented inconsistent data from small populations,[34,42,43] it remains uncertain if cardiac complications may proceed beyond the acute setting, and also may contribute to development of long-term heart disease, such as heart failure.[81]

In the two studies that examined *P. vivax* patients,[33,37] cardiovascular complications were also reported. Unlike *P. falciparum*, *P. vivax* seldom develops hyperparasitemia, but may lead to a greater inflammatory response and endothelial activation per parasite than *P. falciparum*.[82] Recently, it was proposed that *P. vivax* inflammation may be responsible for pulmonary injury.[83] One-third of all analyzed case reports had

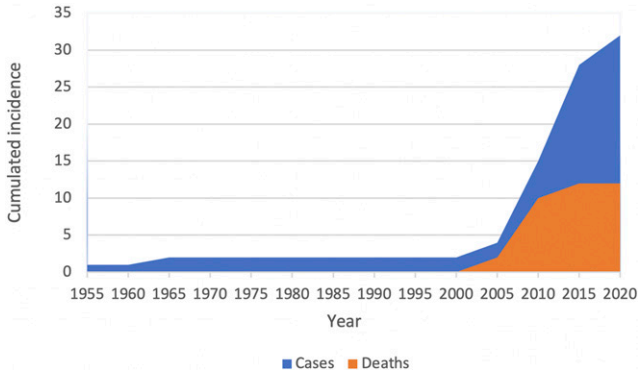

FIGURE 3. Cumulated incidence of malaria cases and cardiovascular death. Cumulated reporting of malaria cases (blue) and cardiovascular death (orange) according to time period. Data are from the included case reports and series of cases. This figure appears in color at www.ajtmh.org.

P. vivax, of which 75% were diagnosed with myocarditis and/or pericarditis. Several of the pro-inflammatory cytokines associated with *P. vivax*,[84,85] particularly tumour necrosis factor-alfa, are known to potentiate myocardial inflammation.[86] Albeit speculative, *P. vivax* may potentially be related to active inflammatory damage of the myocardium. However, this should be explored in future clinical studies.

Considerable heterogeneity was observed in the reporting of cardiac complications ($I^2 = 0.90$), and only a minority of studies reported on all three parameters (ECG, biomarkers, and echocardiography).[34,44] We found that studies included a wide range of biomarkers (Table 2), and that several studies lacked to provide cutoff values for categorizing biomarkers as elevated.[31,33–36,38,43] Only four of seven studies with echocardiography reported on the LVEF,[33,34,42,43] which is a key ultrasonographic parameter. Also, studies failed to provide the diagnostic method for malaria[39] and parasite density.[37,38,40,41,44,45] The heterogeneity and lack of standardized reporting of cardiovascular complications in malaria witness that no guidelines nor prior large-scale clinical studies have investigated this topic. In comparison, features of respiratory impairment in malaria have been addressed in clinical studies[83] and reports by the WHO,[7,87–89] yielding a systematic approach to describe pulmonary changes. A similar systematic approach to cardiovascular complications in malaria is encouraged.

Limitations. We only included studies reporting on cardiovascular complications, which could lead to an overestimation of the frequency of these parameters. Publication bias may have affected our results, as severe cases of malaria are more likely to be published. This is supported by Egger's tests, which indicated publication bias in studies reporting on ECG and cardiac biomarkers. Lack of systematic reporting, different objectives, and use of different control groups (healthy[31,33,35,36] versus uncomplicated malaria[32,39,41]) may have affected our results. Malaria is not a uniform disease; it may therefore be controversial to include several species in the same study. Severe malaria is more common in children < 5 years old,[90] indicating pathophysiological differences between adult and pediatric populations. Despite this, cardiovascular complications, and also left ventricular impairment,[43] were present at almost the same frequency in children as for adults. Five studies reported on imported malaria in Germany,[35,36,39,40,42] which constitutes a major limitation, as immunity profiles[91] may be different. Considering that the cytoadhesive properties of *P. falciparum* may differ according to geographical regions,[92] and the assessed studies came from Africa, Asia, and South America, this could potentially affect cardiovascular impairment. Assessment of cardiac biomarkers and echocardiography requires expensive laboratory facilities and equipment, which may be limited in malaria-endemic and resource-constrained settings. Underreporting, misdiagnosis, and incorrect data may have influenced our analyses. Secondary complications to severe malaria disease, including anemia, renal failure, and acute respiratory distress syndrome, could have been misdiagnosed or contributed to cardiovascular disease. Only a minority of clinical studies reported on cardiovascular mortality; hence, we could not assess this. Recent studies have hypothesized that malaria through various pathways may be linked to hypertension, which is also a major risk factor for cardiac disease.[93–95] Unfortunately, only a minority of studies reported on hypertension.[32–34,36,37,42,44]

CONCLUSION

To the authors' knowledge, this is the first systematic review to assess cardiovascular complications in malaria. The key findings are that abnormalities in ECG, cardiac biomarkers, and echocardiography were not uncommon in children and adults with malaria. However, great heterogeneity was present in the assessed studies, indicating a need for standardized protocols with adequate data registering, streamlining of methods and measurements to better characterize the relationship between malaria and the cardiovascular system.

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