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Susceptibility to Plasmodium Vivax Infection Among Genetic Variant of Duffy-Positive Individuals: A Systematic Review and Meta-analysis

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Abstract

Introduction: Malaria is a major public health problem and affecting over million individuals globally. Susceptibility or resistance to malaria infection depends on host-parasite interaction associated with intrinsic factors of Red Blood Cell. It is linked with Glucose-6-phosphate dehydrogenase (G6PD) enzyme and Duffy blood group system. However, the susceptibility and resistance rate of malaria in Duffy blood group system is controversial.

Objective: The main objective of this evidence based review was determining the pooled proportion of P. vivax among Duffy phenotype positive individuals.

Methods: Articles were extensively searched in bibliographic databases and grey literatures using entry terms or phrases. For studies meeting the eligibility criteria, the first author's name, year of publication, study design and area, total sample size, number of cases and proportion were extracted using Microsoft-excel and followed exported to stata 11 for further statistical analysis. Random effect model was done to estimate the pooled proportion. Higgin's (I2) statistics was used to check heterogeneity. Egger's statistical test and funnel plot were used to measure publication bias.

Results: A total of, 10 articles with 2,555 study participants were retrieved to determine the pooled proportion of plasmodium vivax among Duffy variant phenotype. The overall pooled proportion of plasmodium vivax among Duffy positive individuals was 25.6%; 95%, CI : 20.30-30.10, I2: 98.4%, p < 0.001. The pooled proportion in Duffy variant phenotype were 32.30%; 95% CI: 20.11%-44.46%, I2: 97.8%, p < 0.001, 26.50%; 95% CI: 15.42%-37.58%, I2: 98.1%, p < 0.001 and 18.33%; 95%CI: 11.16%-25.50%, I2: 97.6%, p < 0.001 in FY (a+b+), FY (a+ b) and FY (ab+), respectively. **Conclusion:** According to the finding, the proportion of plasmodium pivax was high among Duffy positive individuals. The FY (a+b+) phenotypype accounts highest proportion of P.vivax, suggesting that FY (a+b+) individaulas may be prone to P. vivax infection. Hence, the genetic polymorhism of Duffy blood group system can be multifactorial genetic factor for susceptibility to Plasmodium vivax infection. The finding has an important implication for malria epdemilogy and targetad intervention of Plsamodium vivax in endemic areas where specific FY genotype predominance.

Keywords: Duffy positive, Malaria, Plasmodium vivax, Meta-analysis

Introduction

Malaria is a parasitic disease caused by Plasmodium species that is transmitted to humans through the bite of an infected Anopheles female mosquito. It continues to be a major public health problem and affecting over 215 million individuals with 438000 deaths in 2015. The disease is caused by Plasmodium species namely P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi. Plasmodium falciparum and vivax are the

most pathogenic species which transmitted to humans through Anopheles mosquito bites [1]–[3]. The burden of P. falciparum and P. vivax clinically associated with patent parasitemia [4], [5]. Indeed, P. vivax is the most common malaria species. More than one-third of the world's populations are at risk of P. vivax malaria infection due its dormant hepatic phase and survival in colder climates than other malaria species [6]. In addition, susceptibility or resistance to malaria infection depends on host-parasite interaction. Red blood cell (RBC) variations that can confer malaria protection are glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency and Duffy-negative. Deficiency of G6PD enzyme lead for oxidative damage of RBC membrane. About 8% of malaria proportion in malaria endemic area is due to G6PDH deficiency [7], [8]. In addition, susceptibility to P. vivax has been associated with the Dufy blood group antigens (FYa and FYb). The Duffy polymorphisms alter the binding to the parasite's (DBP), invasion and malaria density in the RBC surface [9]. Plasmodium vivax requires the cognate FY glycoprotein receptor, Duffy blood antigen receptor for chemokine (DARC) protein to infect RBC during their asexual lie cycle [10], [11]. The phenotypic distribution of malaria as follows; 31.1% in FY (a + b-) 42.7% in FY (a + b +), 24.9% in FY (a-b +) and 0.4% in FY (a-b-) [12]. Conversely, recent studies reported that Duffy-negative individuals are at higher risk of P. vivax infection [13], [14]. In contrary to this, the proportion of P.vivax rare in Africa in associated with lack of Duffy antigen expression [15]. Evidences showed that the P.vivax infection among western central African blacks is attributed to Duffy negativity [16]. Furthermore, study conducted in Ethiopia revealed controversial proportion of P.vivax among Duffy positive and negative individuals [17]. The susceptibility rate of malaria infection in Duffy blood group system is paradoxical and less clear. Therefore, this evidence-based review was aimed to determine the pooled proportion of P.vivax among Duffy variant phenotype in order to elucidate susceptibility rate and invasion of P. vivax infection of Duffy positive erythrocyte. Hence, the finding from this study would offer evidence-based information to target on malaria control and prevention.

Methods

Design and protocol registration

This systematic review and Meta-analysis was designed to estimate global pooled proportion of P. vivax among Duffy positive individuals in order to determine the susceptibility rate for Duffy variant phenotype. The result was reported based on Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) [18]. Pocket studies conducted on P. vivax among Duffy positive individuals were used to conduct this study. The review protocol was submitted for registration in international Prospective Register of Systematic Review (PROSPERO).

Eligibility criteria

Community and institutional based studies conducted on malaria among Duffy positive variant phenotype and reporting P.vavix were included in this review. However, case reports, articles without full texts or abstracts and articles that did not report the outcome of interest were excluded.

Data source and searching strategy

Articles were retrieved from electronic databases (PubMed, MEDLINE, HINARI, Embase, Scopus, Cinahl, African online archives and other source like Google scholar. In addition to account for the studies omission during electronic database searches, a direct Google search was carried using listed reference in included articles. Comprehensive and extensive searching strategy has been employed using condition, context, population and outcome of interest (CoCoPop) formulating questions and searching terms were ("Malaria), ("Plasmodium species"), ("Plasmodium vivax"), ("Duffy blood group"), ("Duffy associated receptors for chemokine"), ("Duffy phenotype") and ("Duffy genotype"). The searching terms were combined using the Boolean operators "OR" and "AND" to fit the advanced searching of articles. Additionally, the above and other related entry terms were used to search individually in various databases.

Study selection and quality assessment for risk of bias

Three independent authors (GM, SS, and DM) identified the articles from data bases and other sources. Searched records were combined to Endnote-X7 to remove duplicates records. Using eligibility criteria, two reviewers (DA and SS) assessed the title, abstract and full-text of records for data abstraction. Disagreements between two independent reviewers (SS and DM) were settled by GM in order to reach a consensus. The quality of the articles was carefully assessed by three authors (GM, DM and SS). The full texts of the articles

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were used to determine either the study met the selection criteria or the eligibility of the article was in doubt. The Joanna Brigg Institute (JBI) quality assessment manual was used to assess the methodological validity of each study design [19]. Using the critical appraisal checklists, cross-sectional studies were reviewed for the following criteria: (1) inclusion criteria (2) study subject and setting description; (3) valid and reliable exposure measurement; (4) objective and standard eligibility criteria used; (5) confounder management (6) confounder management strategies; (7) valid and reliable outcome measurement; and (8) valid statistical analysis. Similarly for case-control studies: (1) comparable case and control group; (2) appropriateness of case and control; (3) appropriate case definition and control selection; (4) standard measurement of exposure; (5) similarity in exposure measurement for case and control; (6) handling of confounder; (7) strategies to identify bias; (8) standard and valid of outcome measurement; (9) appropriate duration for exposure and (10) valid and reliable of statistical methodology. Based on JBI checklist criteria, articles scored average of $\geq 50\%$ were included in meta-analysis (Table in S1).

Data extraction

After the assessment of the methodological quality and allover characteristics of articles, data items were subjected to data extraction sheet using Microsoft Excel sheet. For each articles, meeting the eligibility protocol, first author's name, total sample size, publication year, study design, study area, Duffy phenotype, number of case and proportion were extracted for each article.

Outcome of interest

The outcome of interest was the pooled proportion of P.vivax among Duffy variant phenotypic patients.

Data analysis

Both random and fixed effect models were used to estimate the pooled proportion P. vivax using Stata version 11. The degree of heterogeneity was checked using Higgins's I^2 statistics to estimate total variability in effect size estimation [20]. The substantial heterogeneity $I^2 > 50\%$ was observed. The I^2 at 95% CI ranging from 0-100% were 98.1%,97.8%,97.6% in estimating pooled proportion of P. vivax in variant Duffy phenotype of FY (a+b-), FY (a+b+) and FY (a-b+), respectively. A p-value of < 0.005 was used to declare significant heterogeneity. Therefore, random effect model was used to adjust the observed variability. Publication bias was checked using a funnel plot and Egger's statistical test using cutoff A p-value of < 0.05. Egger's statistical test showed presence of significant publication bias. Therefore, trim fill analysis was performed. Finally, sensitivity analysis was carried to determine the individual study impact on the pooled effect size.

Results

Description and search results of included articles

A total of 367 articles were retrieved from PubMed, Cochrane Library, Google Scholar, SCOPUS, Web of Science, Psyc INFO and African online archives. Three hundred and forty nine articles remained after removing 18 duplicate articles. From the remaining, 247 articles were excluded after reviewing the tittle and abstract. Finally, 102 full-length articles were thoroughly reviewed by predetermined eligibility criteria. From those full-length articles, 69 articles were omitted due to insufficient information and 17 were excluded because their full-text reported mixed malaria species (P. vivax and P. falciparum undifferentiated). Furthermore, 6 were omitted because their full texts were not accessible. A total of, 10 articles with 2,555 study participants were included in qualitative and quantitative and meta-analysis, respectively (Fig.1). From those included, 1 was conducted in Thailand [21], 1 in Iran [22], 1 (Beljium) [23], six were in Brazil [24]–[29] and 1 in India [30]. Eight were cross-sectional studies [21], [22], [24]–[29] and two were case control (Table 1). The highest frequency distribution of P. vivax was found among FY (a+b+) phenotype (Fig. 2).

Quality and heterogeneity

Quality of each included studies were assessed by using JBI critical appraising tool to minimize risk of bias. The assessment of each item was graded as poor quality ($< 50\%$) good (50-75%) and high quality ($> 75\%$) (Table S1). Included studies exhibited the substantial heterogeneity. In estimating pooled proportion of P. vivax, the I2 was 98.4%: P < 0.001. In variant Duffy phenotype of FY (a+b-), FY (a+b+) and FY (a-b+), I^2 were 98.1%, 97.8%, 97.6%, respectively at 95% CI: P < 0.001 (Fig. 6 and 7).

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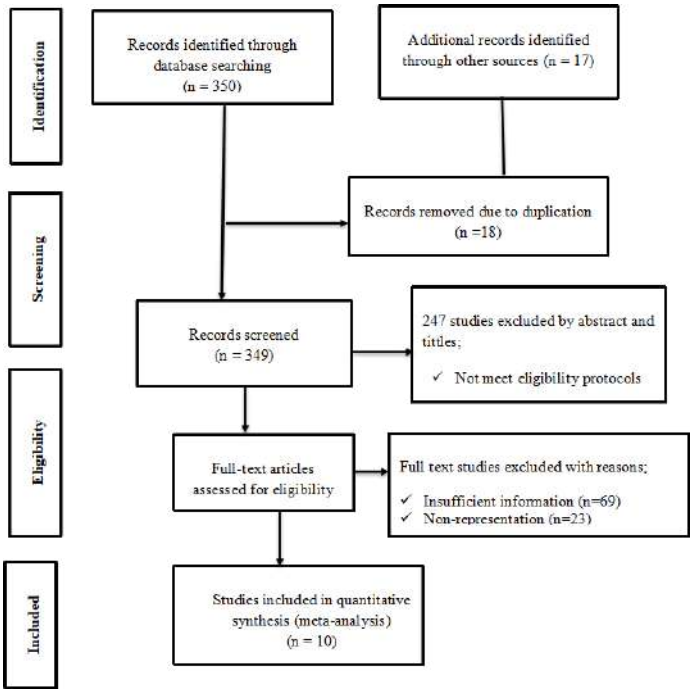


Fig. 1. PRISMA flow diagram of study selection process

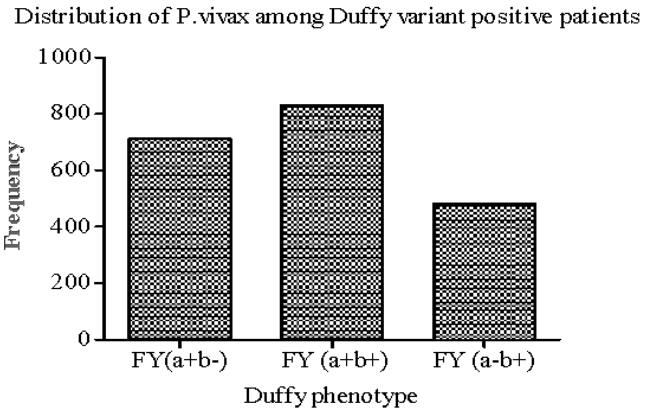


Fig. 2. PRISMA flow diagram of study selection process

Sensitivity analysis

Each study had no effect on the pooled estimate of proportion indicating the precise aggregate result. While pooling the proportion by omitting one study at a time, the results were consistent and accurate (Table 3).

Publication Bias

The funnel plot was used to assess the impact of small-studies effect or publication bias on estimated pooled proportion. Visual inspection of a funnel plot demonstrated that asymmetric distribution of P. vivax among Duffy positive patients (Figs. 3, 4 and 5). Furthermore, Egger's regression test was used. The Egger's test showed marginally significant publication bias at p value $=< 0.001$ (Table 2). **Std Eff**: Standard Effect; **Coef**: Coefficient:**T**: T- test Statistics; **Std. Err**: Standard Error; **P**: P-value of significance by assuming null zero value; **Conf. Interval**: Confidence Interval.

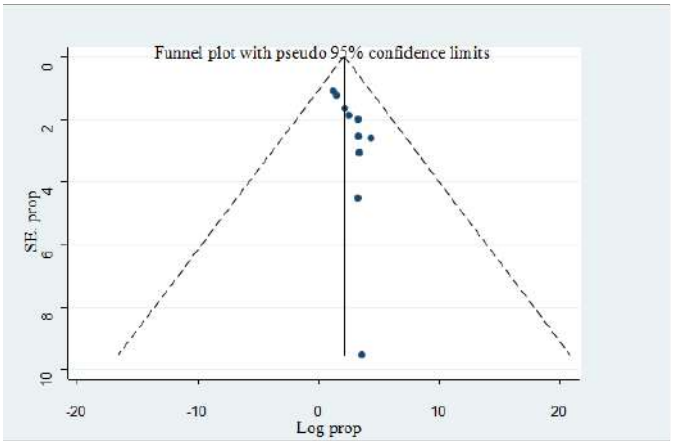


Fig. 3. Funnel plot showing publication bias of included articles for pooling proportion of P. vivax among (Fy a+b-) Duffy phenotype. Dot on the black line represents each individual article. Y-axis shows the standard error of proportion. The x-axis shows log proportion of the included articles.

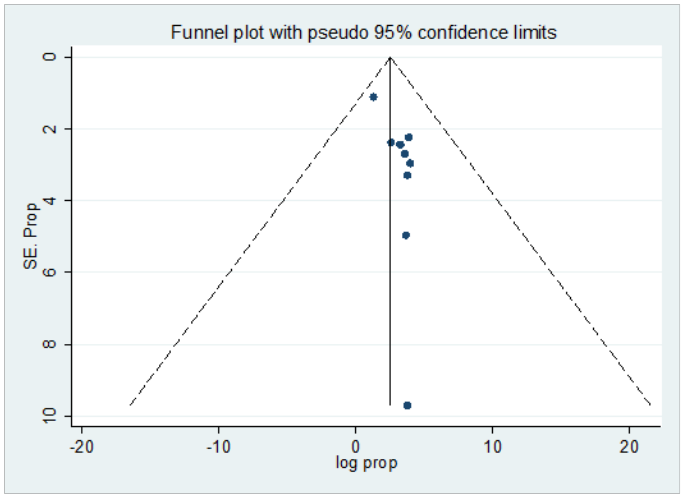


Fig. 4. Funnel plot showing publication bias of included articles for pooling proportion of P. vivax among (Fy a+b+) Duffy phenotype. Dot on the black line represents each individual article. Y-axis shows the standard error of proportion. The x-axis shows log proportion of the included articles.

Pooled estimated proportion of P. vivax

The overall pooled proportion of P. vivax among Duffy positive individuals was 25.6%; 95%, CI: 20.30-30.10, I^2: 98.4%, at p-value < 0.001. Furthermore, the pooled proportion in

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TABLE 1
SUMMARY CHARACTERISTICS OF RESEARCH ARTICLES INCLUDED IN QUANTITATIVE ANALYSIS OF SYSTEMATIC REVIEW AND META-ANALYSIS (N=10)

S/N	Author (Ref)	Year	Study area	Study design	Duffy phenotype	Sample size	Cases	Proportion (%)
1	Hongfongfa P. et al (21)	2022	Thailand	Cross-sectional	FY(a+b-)	200	167	83.5
					FY(a+b+)	200	26	13
					FY(a-b+)	200	7	3.5
2	Miri M. et al (22)	2014	Iran	Cross-sectional	FY(a+b-)	320	42	13.32
					FY(a+b+)	320	83	26
					FY(a-b+)	320	33	10.31
3	Van R. et al (23)	1985	Belgium	Case-control	FY(a+b-)	26	10	38.46
					FY(a+b+)	26	11	42.31
					FY(a-b+)	26	4	15.39
4	Ferreira N. et al (24)	2021	Brazil	Cross-sectional	FY(a+b-)	225	70	31.1
					FY(a+b+)	225	96	42.7
					FY(a-b+)	225	56	24.89
5	Albuquerque S. et al (25)	2010	Brazil	Cross-sectional	FY(a+b-)	497	140	28.12
					FY(a+b+)	497	236	47.48
6	Carvalho T. et al (26)	2012	Brazil	Cross-sectional	FY(a+b-)	96	26	27.08
					FY(a+b+)	96	37	38.54
					FY(a-b+)	96	31	32.3
7	Abou-A. et al (27)	2019	Brazil	Cross-sectional	FY(a+b-)	287	63	4.72
					FY(a+b+)	287	148	51.57
					FY(a-b+)	287	72	25.08
8	Cavasini C. et al (28)	2007	Brazil	Cross-sectional	FY(a+b-)	312	90	28.85
					FY(a+b+)	312	109	34.94
					FY(a-b+)	312	109	34.94
9	Storti-M. et al (29)	2009	Brazil	Cross-sectional	FY(a+b-)	312	30	9.61
					FY(a+b+)	312	76	24.36
					FY(a-b+)	312	46	14.74
10	Gai P. et al (30)	2019	India	Case-control	FY(a+b-)	280	10	3.6
					FY(a+b+)	280	10	3.6
					FY(a-b+)	280	1	1.3

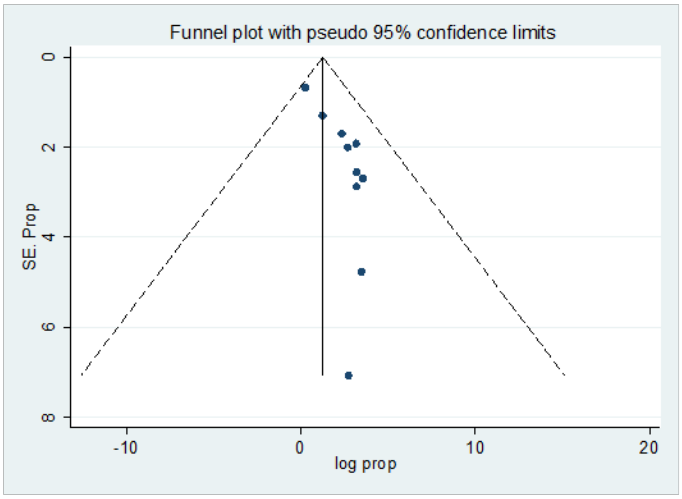


Fig. 5. Funnel plot showing publication bias of included articles for pooling proportion of P. vivax among (Fy a-b+) Duffy phenotype. Dot on the black line represents each individual article. Y-axis shows the standard error of proportion. The x-axis shows log proportion of the included articles.

Duffy variant phenotype were as follows; 32.30%; 95% CI: 20.11%-44.46%, I^2: 97.8%, p $<$ 0.001, 26.50%; 95% CI: 15.42%-37.58%, I^2: 98.1%, p ¡ 0.001 and 18.33%; 95%CI: 11.16%-25.50%, I^2: 97.6%, p $<$ 0.001 in FY (a+b+), FY (a+ b) and FY (ab+), respectively (Fig. 6 and 7).

Trim and fill analysis

Trim and fill analysis for each variant Duffy phenotype was conducted, then five studies were added and the total number of the studies becomes 15 in each variant Duffy phenotype. The pooled proportion of P. vivax in FY (a-b+), FY (a+ b-) and FY (a+ b+) positive individuals were 5.4%, 8.3% and 15.3% respectively at p-value $<$ 0.001 (Table 4). To address potential publication bias, a trim-and-fill analysis was applied. After adjustment, the pooled prevalence across all genotypes was decreased: FY(a-b+) dropped to 3.7%, FY(a+b-) to 6.8%, and FY(a+b+) to 12.7%. This reduction indicates

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TABLE 2
REGRESSION RESULTS BY DUFFY PHENOTYPE

Phenotype	Parameter	Coef.	Std. Err	t	P> $\|t\|$	95% CI
FY (a+b-)						
	Slope	-19.57	6.08	-3.22	0.01	[-33.60, -5.53]
	Bias	15.61	2.61	5.96	0.000	[9.57, 21.65]
FY (a+b+)						
	Slope	-17.16	4.01	-4.28	0.003	[-26.60, -7.91]
	Bias	15.01	1.50	10.06	0.000	[11.57, 18.45]
FY (a-b+)						
	Slope	-0.73	0.68	-1.10	0.30	[-2.30, 0.83]
	Bias	7.10	0.86	8.24	0.000	[5.10, 9.07]

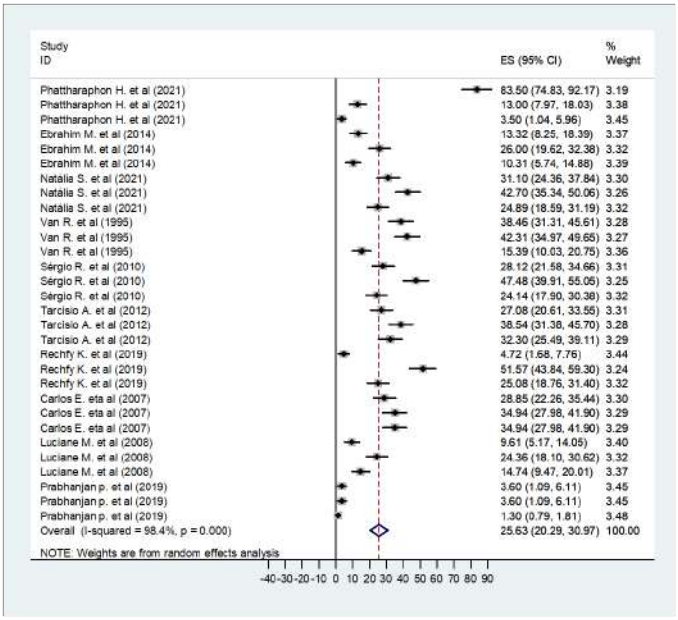


Fig. 6. forest pilot showing overall pooled proportion of P.vivax among Duffy positive individuals.

that smaller studies or those reported lower prevalence may be underrepresented which might inflate unadjusted estimates. Indeed, fixed-effect estimates remained statistically significant, but, random-effect model the estimates found insignificant, highlighting uncertainty due to heterogeneity.

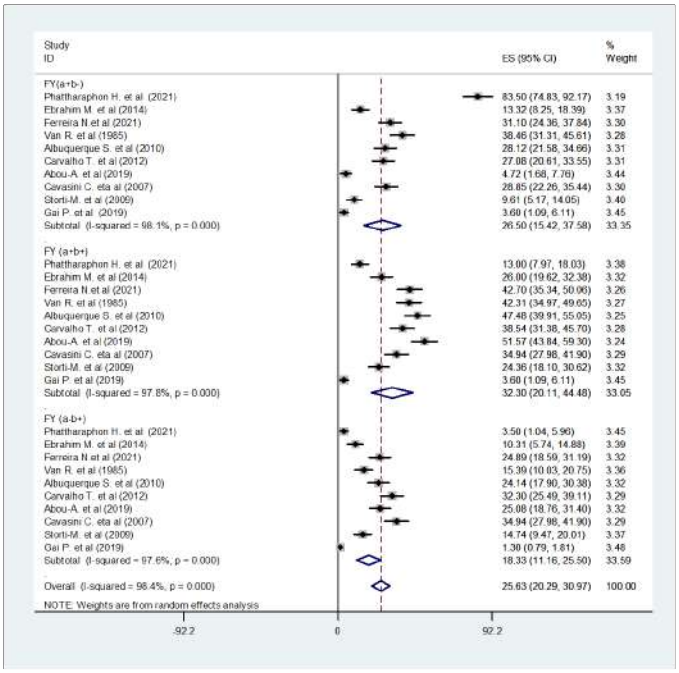


Fig. 7. Forest plot showing pooled proportion of P.vivax in Duffy variant phenotype. The size of the x-axis shows the estimate of pooled proportion. In the pooled point calculation, the black dot in the middle of the gray box reflects the estimate pooled proportion of each study and the line shows the 95% CI of the estimates. The gray boxes represent Duffy variant phenotypic weight that contributes to the estimated pooled proportion. I-squared illustrates the heterogeneity between the included articles.

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TABLE 3
SENSITIVITY ANALYSIS OF PROPORTION OF P.VIVAX AMONG DUFFY VARIANT INDIVIDUALS

Study omitted	Estimate	Lower (95%)	Upper (95%)
FY (a+b-)			
Phattharaphon H. et al	20.22	12.10	28.33
Ebrahim M. et al	28.02	15.64	40.40
Natalia S. et al	25.90	14.27	37.72
Van R. et al	25.17	13.77	36.58
Sérgio R. et al	26.33	14.48	38.18
Tarcisio A. et al	26.45	14.56	38.33
Rechfy K. et al	29.04	16.09	41.99
Carlos E. et al	26.25	14.43	38.07
Luciane M. et al	28.45	15.89	41.00
Prabhanjan P. et al	16.48	29.15	41.83
Combined	26.49	15.42	37.58
FY (a+b+)			
Phattharaphon H. et al	34.45	20.59	48.39
Ebrahim M. et al	33.01	19.51	46.51
Natalia S. et al	31.15	18.43	43.86
Van R. et al	31.19	18.45	43.93
Sérgio R. et al	30.62	18.18	43.05
Tarcisio A. et al	31.61	18.66	44.56
Rechfy K. et al	30.17	18.00	42.32
Carlos E. et al	32.01	18.89	45.13
Luciane M. et al	33.20	19.64	46.76
Prabhanjan P. et al	26.63	35.48	44.34
Combined	32.30	20.11	44.48
FY (a+b-) Continued			
Phattharaphon H. et al	20.17	10.54	29.81
Ebrahim M. et al	19.27	11.36	27.17
Natalia M. et al	17.60	10.31	24.87
Van R. et al	18.67	11.01	26.34
Sérgio R. et al	17.68	10.37	24.98
Tarcisio A. et al	16.78	9.81	23.74
Rechfy K. et al	17.57	10.30	24.83
Carlos E. et al	16.50	9.65	23.34
Luciane M. et al	18.74	11.06	26.42
Prabhanjan P. et al	12.60	20.36	28.12
Combined	18.33	11.16	25.50

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TABLE 4
TRIM-AND-FILL ANALYSIS OF POOLED PROPORTION OF P. VIVAX AMONG DUFFY PHENOTYPE POSITIVE INDIVIDUALS

FY (a-b+)						
Method	Pooled estimate	Lower CI	Upper CI	Z-value	P-value	No. of studies
Fixed	7.80	6.82	8.75	15.79	0.000	10
Random	18.43	10.86	26.00	4.77	0.000	
Q (df=9) = 399.10, $p < 0.001$; Between-studies variance = 139.56; Q (df=14) = 876.80, $p < 0.001$; Between-studies variance = 233.73						
Trim-and-Fill Iterations						
Iteration	Estimate	Tn	No. to trim	Diff		
1	7.78	50	5	55		
2	3.67	52	5	4		
3	3.67	52	5	0		
Filled Meta-analysis						
Method	Pooled estimate	Lower CI	Upper CI	Z-value	P-value	No. of studies
Fixed	3.67	2.78	4.56	8.07	0.000	15
Random	5.35	-2.52	13.23	1.33	0.18	
FY (a+b-)						
Fixed	14.86	13.701	16.05	24.84	0.000	10
Random	26.55	13.62	39.48	4.03	0.000	
Q (df=9) = 976.45, $p < 0.001$; Between-studies variance = 421.85; Q (df=14) = 22275.51, $p < 0.001$; Between-studies variance = 750.44						
Trim-and-Fill Iterations						
Iteration	Estimate	Tn	No. to trim	Diff		
1	14.86	45	4	55		
2	8.96	49	5	8		
3	6.75	51	5	4		
4	6.75	51	5	0		
Filled Meta-analysis						
Fixed	6.75	5.70	7.805	12.53	0.000	15
Random	8.34	-5.402	22.40	1.18	0.24	
FY (a+b+)						
Fixed	20.78	19.37	22.20	28.76	0.000	10
Random	32.18	19.62	44.74	5.02	0.000	
Q (df=9) = 596.00, $p < 0.001$; Between-studies variance = 395.15; Q (df=14) = 1256.93, $p < 0.001$; Between-studies variance = 621.80						
Trim-and-Fill Iterations						
Iteration	Estimate	Tn	No. to trim	Diff		
1	20.78	47	4	55		
2	13.35	52	5	10		
3	12.67	53	5	2		
4	12.67	53	5	0		
Filled Meta-analysis						
Fixed	12.68	11.40	13.94	19.51	0.000	15
Random	15.23	2.47	28.10	2.33	0.24	

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Discussion

Erythrocyte variants, such as the sickle-cell trait and Duffy blood antigen polymorphism influence malaria susceptibility and resistance. The association of Duffy antigen receptor coding DARC, a glycosylated erythrocyte membrane protein which correspond to the phenotype FYA/FYA (FY (a+, b), FYA/FYB (FY (a+, b+)) and FYB/FYB (FY (a, b+) with malaria susceptibility is globally unclear [31]–[33]. The manifestation of malaria is not only caused by the infecting parasite but also by pro-inflammatory host responses, which is attributed to pathophysiological condition. Moreover, the DARC as receptor diverse chemokine's can influence the clinical manifestation of malaria [34]. It is fact that individuals who are Duffy-negative are typically resistant to P. vivax infection. However, recent evidence based study found that the Duffy-negativity is no longer barrier to P.vivax [35]. Furthermore, FYA/FYA was associated with increased susceptibility to P.vivax [25]. The hypothesis of different studies suggesting that Duffy blood antigen and P.vivax infection is paradoxical. In this regard, this study determined the pooled proportion of P. vivax among Duffy positive individuals in order to elucidate the susceptibly rate. Currently obtained result showed that the overall pooled proportion of P. vivax among Duffy positive individuals was 25.6/%; 95%, CI: 20.30-30.10. In addition, the pooled proportion of P.vivax in Duffy variants were; 32.30%; 95% CI: 20.11%-44.46%) among FY (a+b+) followed by FY (a+ b) and FY (ab+) (26.50%; 95% CI: 15.42%-37.58%) and 18.33%; 95% CI: 11.16%-25.50%, respectively. The finding was consistent with the finding of Systematic Review and Mata-analysis conducted among Duffy-negative individuals (25%; 95%, CI: 3%-53.10 [35]. Similarly the finding was consistent with study conducted in Brazil for Duffy phenotypes of FY (a+b+) and FY (a+b-) accounting 34.94% and 28. 85%, respectively [28]. On the other hand, the overall pooled proportion was higher than studies conducted in Brazil in the case Duffy negative (6.9%) and Duffy positive (14.2%) [26]. This indicating that the risk of P. vivax infection among Duffy-negative was not significantly different from that of Duffy-positive individuals. The proportion of P.vivax among (a+ b) from this study was higher than the report of study conducted in Sudan (14.2%) [36]. The finding was also higher than the study conducted in India (3.6%, 3.6% and 1.31%) among FYA/A, FYA/B and FYB/B Duffy genotype, respectively [30]. However, the findings for FY (a b+) from this study was lower than study in Sudan (67.9%) [36] and Brazil (34.94%) [28]. This is due to the fact that Ethnic variation of distribution of Duffy antigen of study population despite of malaria infection. Meanwhile, FYA allele is common in Europeans and Orientals but uncommon in African Negroes. Furthermore, the FYB is more common in white populations than in Asian and Negroid population. Moreover, the frequency of FYA and FYB are common in Brazilian amazon population [37], [38]. In addition, a remarkable difference among DARC variants concerning the susceptibility to clinical manifestation of malaria could be another reason. The distribution of Duffy blood system and P. vivax in Africa is heavily influenced by human genetics and malaria epidemiology. Recent genome-based studies across African populations have explored proportion of P.vivax ranging 1-100% among Duffy negative population (FY (a-b-) [15]. It is controversial as compared with the finding of this study. This could be disparity in population, malaria endemic range. Malaria extends beyond East Africa and spread in to high areas Duffy negative (FY (a-b-). Low parasitemia in Duffy-negative infections might indicate that P. vivax has a limited ability to invade Duffy-negative individuals [15]. Moreover, other Duffy independent pathways that enable erythrocyte invasion such as Erytrocyte binding protien (EBP)/DBP2 region II could be another reason. This liggnad has been found to bind in Duffypositive and Duffy-negative human erythrocytes at low frequency [39], [40]. Besides, study in india showed higher odds of P.vivax in associated with DARC (AOR: 1.60; 95%

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CI: 1.14-2.22) [30]. In addition, the finding of this study was suggestive of Duffy positive individuals as suscepptibale to P.vivax infection.

Strenght and limitation of the study

Through a varies of searching engines, articles were thoroughly retrieved. The the study protocol was designed in accordance with the PRISMA guidelines. However, have there are some potential limitations. First, majority of the inluded articles were conducted in Brazil which might lead to geographic bias. Second, source of substaial hetrogeniety was not identified.

Conlusion and recommendatiion

The finding of this systematic review and meta-analysis demonstrated FY (a+b+) presented the highest proportion of P.vivax, indicating that FY (a+b+) individuals may more susceptible to P. vivax infection. It is scientificlly plausable that Duffy blood group system increase susceptibility to P. vivax in individuals even differing in the levels of exposure to malaria and Duffy gene polymorphmism. In this regard, considering Duffy positive individuals in P. vivax endemic areas for malaria surveillance is alongside recommendations. Therfore, futher commulastive evidence on the effect of Duffy blood group system on susceptiblity to P.vivax is required to clarify the mechanism of Duffy blood group system in P.vivax invasion of RBC memberane.

List of Acronyms

DARC: Duffy Antigen Receptor for Chemokines;
G6PD: Glucose-6-Phosphate Dehydrogenase;
JBI: Joanna Briggs Institute;
PRISMA-PPRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols;
PROSPERO: International Prospective Register of Systematic Reviews;
RBC: Red Blood Cell.

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

Data availability

All relevant data are within the manuscript and its supporting information files.

Competing interest

The authors have declared that they have no competing interest

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Author's contribution

GM: Conceived idea and designed the study, conducted literature reviews, extracted and analyzed data, interpreted findings and wrote the manuscript. Study selection, data, extraction, quality evaluation and article review were done by GM, SS, EA, DM, and AG. Supervision, analysis and interpretations as well as a thorough evaluation of the manuscript's scientific content were done by DM and SS. All authors approved the manuscript.

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