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ORIGINAL ARTICLE

THE ROLE OF IL-1B, IL-10 AND IFNA IN ADULTS INFECTED WITH *PLASMODIUM VIVAX* MALARIA IN DIYALA PROVINCE, IRAQ

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ABSTRACT

Background: *Plasmodium vivax* malaria is a serious disease that affects all age groups and causes high mortality. This study aimed to investigate the immune response in adults infected with *Plasmodium vivax* malaria in Iraq.

Materials & Methods: This case control study was conducted in Khanaqin Hospital/ Diyala province during the period from December 2023 to May 2024. In this Study, (5) ml of whole blood was collected from (50) adult patients previously diagnosed with *Plasmodium vivax* malaria and from (50) healthy individuals as a control group.

Results: There was total 100 patients. Patient mean age (34.82 ± 1.55) was significantly lower than controls (39.98 ± 1.87; P=0.03). Levels of *P. vivax* IgG (14.31 ± 0.94 vs. 0.07 ± 0.01), IFN-α (96.41 ± 3.69 vs. 19.14 ± 1.009), IL-1β (13.98 ± 1.91 vs. 1.73 ± 0.33), and IL-10 (25.20 ± 1.19 vs. 4.94 ± 0.25) were all significantly higher in patients (all P ≤ 0.0001). IgG levels strongly correlated with IFN-α (r=0.785), IL-1β (r=0.400), and IL-10 (r=0.737) (all P=0.0001), but weakly and negatively with age (r=-0.219, P=0.028). ROC analysis showed perfect differentiation (AUC=1.0, 100% sensitivity/specificity) at IgG cutoff >1.0. A mutation in IL-1β (SNP rs1143629) was identified, with the wild-type CC altered to CT/TT.

Conclusion: We detected direct correlations between *P. vivax* IgG antibody level and INF-α, IL-1β & IL-10 levels. These correlations were statistically highly significant (P=0.0001,0.0001, 0.0001). Also, a mutation occurred to IL-1ß gene in SNPs rs1143629 of the wild CC which was change to TT and CT respectively.

KEY WORDS: Epidemics; IL-1B; IL-10; IFNα; Malaria; Mosquitoes; *Plasmodium vivax*.

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INTRODUCTION

Malaria is increasing in Iraq and despite the success of the 1957 WHO–assisted malaria controls programme. Iraq faced severe epidemics of *Plasmodium vivax* malarias following war of 1991. No precise figure is available but the report by WHO in 2000 regarded Iraq as to have "a very serious malaria problem with incomplete to nonexistent reporting of malaria cases, particularly in northern areas where most cases occur".[1] The experts in the Iraqi army anticipate that "troops will be highly exposed to biting insects such as mosquitoes and sandflies during nighttime patrols because they are using night vision devices". No coalition consensus is available on antimalarial drug choice. Many US troops use daily doxycyclines.[2] The major question is do either of such regimens actually protect the coalition troops from malarial infection? History is illuminating.[3] Because P vivax is the major malaria species in Iraq.[4]

Macrophages, epithelial cell, fibroblast and endothelial cell synthesize IL-1β mainly in responses for the damage-related molecular pattern or the pathogen-related molecular pattern which signals via the pattern recognition receptor (PRRs).[5] Different cells and tissues express IL-1β, but it is specially plentiful in lymphatic organs and macrophages, like thymus, bone marrow, lymph nodes and spleen. Furthermore, the non-lymphoid organs secrete IL-1β like liver,

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lungs and digestive system.[6] The synthesis of IL-1β occurs in the form of 269 amino acids precursors proteins which are proteolytic ally cleaved through caspase-1 or other serines protease activation in time of inflammations into active form, that contains 153 amino acids in its C-terminus.[7]

The following effects of IL-1β are important including: (1) endothelial cell induction (2) neutrophil diapedesis activation (3) stimulations of cytokine productions in (T & B) lymphocytes. The pro inflammatory cytokines (IL-1β) have essential roles in disease-associated inflammations, discomforts and fevers.[8] IL-1β is involved in cellular processes e.g. differentiations, proliferations and deaths. There are limited investigations on IL-1β in regard to malaria with inconsistency in the results; thus, conclusions on IL-1β in different malaria types are not well-explained. Nevertheless, meta-analyses for assessing variations in the levels of IL-1β between different malaria types, such as differences between patients having severe malarial diseases, patients having uncomplicated malaria and healthy control individuals have been conducted. The results of the present study will tell future studies on the role of IL-1β in the severity of malarial infection.[9]

Inflammations are suppressed by IL-10 secreted from CD4+ T cell via T cells function's inhibition and upstream activities of the antigens presenting cell (APC).[10] Initially, IL-10 was recognized in Th-2 lymphocytes, but was since then defined in the IFNγ secreting Tbet+ Th1, Fox-P3+ CD4+ regulatory T (Treg) as well as IL-17 secreting CD4+ T (Th17) cell, in addition to several populations of innate and innate-like immune cells. The production of IL-10 by Th1 lymphocytes began as essential mechanisms to inhibit inflammations in face of intractables infections.[11]

During malarial infection, IFN-α response and signaling pathways develop. There will be a recognition to the parasite's pathogen-associated molecular pattern (PAMP) like RNA and DNA Toll-like receptor (TLR) on endosome membrane, such as TLR7, TLR9 and probably TLR8, with activation of the MYD88-TRAF6-IRF7 signaling cascades to induce IFN- α production.[12] The parasite's RNA is sensed in the cytosol by MDA5 (may be RIG-I too) resulting in MAVS-TBK1-IRF3 signal activation with production of IFN-α.[13] The DNA of malaria in cytosols is sensed through cGAS, leading to STING-TBK1-IRF3 signaling pathway activation for IFN-Is production.[14] This study aimed to investigate the immune response in adults infected with *Plasmodium vivax* malaria in Iraq.

MATERIALS AND METHODS

In this Case-control study study, (5) ml whole blood was collected from (50)) adult patients previously diagnosed with *Plasmodium vivax* malaria with symptoms include fever, chills, headache, muscle aches, and vomiting. Some patients may also experience nausea, and from (50) healthy individuals were selected with no symptoms as a control group. The study was conducted in Khanaqin Hospital/ Diyala province about 8 months during the period from December 1st 2023 to 1st May 2024, sampling method was Non-probability purposive sampling, the malaria IgG antibody ELISA kit was used to estimate malarial antibodies Malaria IgG antibody-Malaria IgG antigen is the basis for the kit's ELISA analytical biochemical method.

Uses a quantitative sandwich enzyme immunoassay technology and a colorimetric detection system to identify Malaria IgG antigen targets in samples. A microplate has been pre-coated with an antibody specific to IL-1beta. The immobilized antibody binds any IL-1beta that is present after standards and samples are pipetted into the wells. Additional immunologic metrics are mentioned above. This kit utilizes the Double Antibody Sandwich ELISA technique. The pre-coated antibody is an anti-Human TNF-alpha monoclonal antibody, while the detection antibody is a biotinylated polyclonal antibody. Samples and biotinylated antibodies are added into ELISA plate wells and washed out with PBS or TBS after their respective additions to the wells.

IL-10. The biotin conjugated anti IL-10 antibody was used as the detection antibody.[15] The standards and pilot samples were added to the wells subsequently. After incubation, unbound conjugates were removed by wash buffer. Then, biotinylated detection antibody was added to bind with IL-10 conjugated on coated antibody.

The color depth and the testing factors in samples are positively correlated. For detection IFN-α gene and gene sequence by signer sequencer Primer used for Sequence 5`-3` Annealing Temp. (°C) Product size (bp):

IL1B-FTGTAAAACGACGGCCAGTCCTGGACTCT-CATTCATTCTAC

IL1B-R CAGGAAACAGCTATGACCTCGAAGAG-GTTTGGTATCTG

The SPSS version 20 program was applied involving (Mean±SD) as well as the t test for analyzing the data. $P < 0.05$ value is regarded as significant.

PCR Component calculation

No. of Reaction	20	rxn	Annealing temperature of primers	55,60
Reaction Volume /run	25	µl	Length of PCR product (bp)	664

Statistical analyses

RESULTS

Demographic data reveald that the mean±SD of age in the patients group was (34.82±1.55), compared to its mean±SD in the control group (39.98±1.87) with a significant differences (P=0.03). The distribution of infection between age groups revealed a highest infection rates was in age groups (17-31) and (32-46) years 21 (42.0%), while in the age group (47-66) years was 8 (16%) with significant variation (P=0.05). There was no significant differences between rural and urban residents among malaria infected patients 25 (50%) for each (P=0.09). Also according to the sex, the females patients constituted 31 (62.0%) more than males 19 (38.0%) with no significant variation (P= 0.18) as shows in Table 1.

The mean level of *P. vivax* IgG of malaria infection was (14.31±0.94) in comparison to controls (0.07±0.01) with a highly significance difference (P≤0.0001), and the mean level of INF-α was (96.41±3.69) in the patients in comparison with the controls (19.14±1.009) with a highly significant difference (P≤0.0001). Also the mean level of IL-1β was (13.98±1.91) in the patients in comparison with the controls (1.73±0.33) with a highly significance variations (P≤0.0001). Moreover, mean level of IL-10 was (25.20±1.19) in the malaria patients in comparison with control group (4.94±0.25) and highly significant variation (P≤0.0001) as observed in Table 2.

Table (2): Mean levels of *P. vivax* IgG, INF-α, IL-1β and IL-10 in studied groups

Test	Study	Means	SE	T-test	P values
P. vivax IgG	Case	14.31	0.94	15.10	≤0.0001 H.S
	Control	0.07	0.01		
INF-α	Case	96.41	3.69	20.18	≤0.0001 H.S
	Control	19.14	1.009		
IL-1β	Case	13.98	1.91	6.31	≤0.0001 H.S
	Control	1.73	0.33		
IL-10	Case	25.20	1.19	16.57	≤0.0001 H.S
	Control	4.94	0.25		

H.S: highly significant

The findings in our study demonstrated direct correlations between *P. vivax* IgG antibody levels and INF-α, IL-1β & IL-10 levels with (r=.785**,.400**,.737**) respectively. The correlations are highly significance (P=0.0001,0.0001 and 0.0001) respectively, while our findings also showed negative correlations between IgG level and ages at (r=-.0219) with P-value=.028 as seen in Tables 3.

Levels of IL-10 and IL-6 had positive correlation with parasitemia and with total levels of IgG; however, they had negative correlation with the gestational ages at delivery from vivax-infected women. In the

Table 1: Demographical picture of the study groups.

Tests		Cases	Controls	P-values	
Ages (M±SE)		34.82 ±1.55	39.98 ±1.87	0.03	S
Ages range (Years)	(17-31)	21 (42.0%)		0.05	S
	(32-46)	21 (42.0%)			
	(47-66)	8 (16.0%)			
Rural		25 (50.0%)		0.9	N.S
Urban		25 (50.0%)			
Total		50 (100.0%)			
Sexes	Male	19 (38.0%)		0.18	N.S
	Female	31 (62.0%)			
Total		50 (100.0%)			

Table 3: Correlation analysis of P. vivax IgG antibody levels with INF-α, IL--β & IL-10 levels.

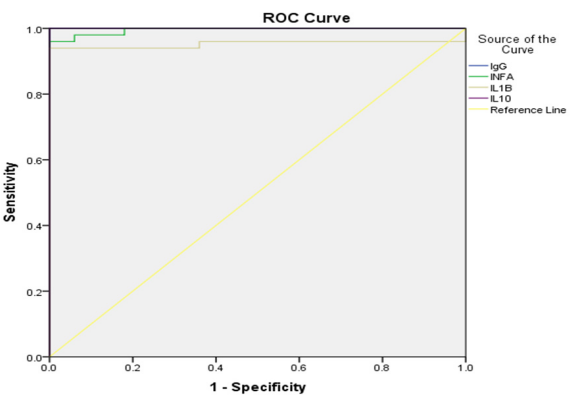
		IgG	Age	INF-α	IL-1β	IL-10
P. vivax IgG	Pearson Correlation	1	-.219*	.785**	.400**	.737**
	P values		.028	.000	.000	.000
	N	100	100	100	100	100
*. Correlations are significance in 0.05 levels (2 tailed)						
**. Correlations are significance in 0.01 levels (2 tailed)						

Table 4: ROC analysis between cases and control with the studied parameters.

Test	Area	cutoff	SE	P-value	95% C.I		Sensitivity	Specificity
					Lower Bound	Upper Bound		
IgG	1.000	1.08	.000	.000	1.000	1.000	100	100
INF-α	.995	31.7	.004	.000	.987	1.000	96	100
IL1-β	.953	8.92	.028	.000	.897	1.000	94	100
IL10	1.000	9.94	.000	.000	1.000	1.000	100	100

analysis of multivariate linear regressions, IgGs 1, 2 & 4 had negative and positive correlations with IL-10 and IL-6, respectively, in infection with *P. Vivax*. The relationship between infection and the increase in cytokine levels was positive, which confirms that these interleukins are directly affected by the severity of the disease.

Analysis of receivers operating characteristics curves (ROC) is performed for assessing diagnostics IgG values in malaria patient. The findings for ROC analyses of *P. vivax* IgG antibody, as shown in **Table 4 & Figure 1**, excellent predictions for AUC values results was seen in IgG with (P = .0001) at 1.0. The specificity and sensitivity were 100% at optimal cut off values > 1.0 which differentiates patient from controls.



The results provide concise guides for interpretation ofcurves and areas of receiver operating characteristic (ROC) under the values of (AUC) curve in studies of diagnosis accuracy. The analysis of ROC is potent tools for assessing the index tests' diagnosis performance, that are tests applied to identify condition or diseases. AUC value summerizes the ROC curve metric that represent the test's ability for distinguishing between disease & healthy persons. The AUC value is ranging from 0.5 and 1.0, with a 0.5 values indicates that tests are not better than chances at differentiation between disease and healthy persons. The 1.0 value is indicative of perfect discriminations.

Figure (2): Amplification of specefic region of IL-1ß among *Plasmodium vivax* malaria infection patients

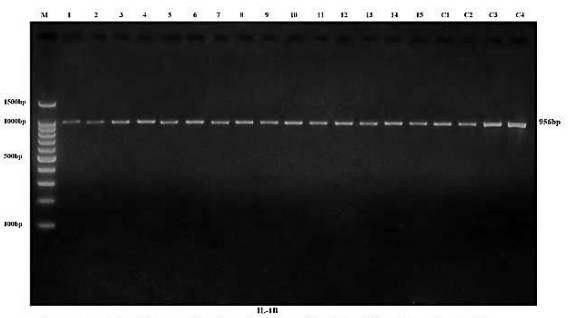


Figure 2: Results of the amplification of IL-1B specific region of blood samples species were fractionated on 2% agarose gel electrophoresis stained with Eth.Br. M: 100bp ladder marker. Lanes 1-C4resemble 956 bp PCR products.

It was revealed in table (5) and figure (3) that mutation happened in IL-1ß genes at rs1143629 SNPs, and wild CC is altered to TT & CT respectively in comparison to controls.

Table 5: Variation of wild SNPs of IL-1ß

IL1B GENE ID: 3557			
SNPs: rs1143629			
Wild: CC			
Variation: C>T			
Samples ID	**Genotype**	**Samples ID**	**Genotype**
1	TT	11	CT
2	CT	12	CT
3	CT	13	TT
4	CC	14	CT
5	CT	15	CC
6	CT	C1	CC
7	CT	C2	CT
8	CT	C3	TT
9	TT	C4	TT
10	TT	C5	CT

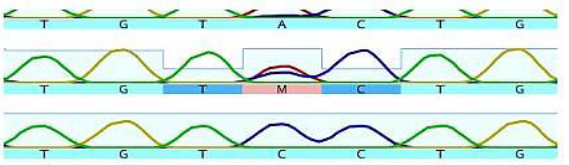


Figure 3: Analysis of SNP rs16944 of IL1B gene using Sanger sequencing. Single "T" peak indicative of a T homozygous allele. Single "C" peak indicative of a C homozygous allele. Presence of the "A" and "C" peak indicative of T/C heterozygous allele.

The current results showed that there are genetic mutations in the wild SNPs rs1143629 of IL-1ß gene where the nucleotide sequence TT was changed to CT or CC, respectively, which indicates the effect of *Plasmodium vivax* malaria infection on IL-1ß. Harati-Sadegh, *et al,* (2021) showed total of (13) investigations are involved. They detected significance associations between IL-1β−31T>C polymorphisms & lower gestational disease risks under codominants CT vs. CC [OR= 0.74, CI (0.59-0.92)] & dominants CT+TT vs. CC [OR= 0.74, CI (0.60-0.91)] contrasting a genetic model.

DISCUSSION

This study investigated the immune response in adults infected with *Plasmodium vivax* malaria in Iraq. In this current Case-Control Study, (5) ml of whole blood was collected from (50) adult patients previously diagnosed with *Plasmodium vivax* malaria and from (50) healthy individuals as a control group. Levels of *P. vivax* IgG, IFN-α, IL-1β, and IL-10 were all significantly higher in patients (all P ≤ 0.0001). IgG levels strongly correlated with IFN-α (r=0.785), IL-1β (r=0.400), and IL-10 (r=0.737) (all P=0.0001), but weakly and negatively with age (r=-0.219, P=0.028).

Souza, et al, demonstrated that the previous exposures to malaria was noticed via anti-total IgG antibodies to the PvMSP119 antigens, which raised inflammatory responses to infections during pregnancy periods of infected women. Levels of IL-10 and IL-6 had positive correlation with parasitemia and with total levels of IgG; however, they had negative correlation with the gestational ages at delivery from vivax-infected women. In the analysis of multivariate linear regressions, IgGs 1, 2 & 4 had negative and positive correlations with IL-10 and IL-6, respectively, in infection with *P. Vivax*.[16] The AUC value is ranging from 0.5 and 1.0, with a 0.5 values indicates that tests are not better than chances at differentiation between disease and healthy persons. The 1.0 value is indicative of perfect discriminations.[17]

According to the demographical picture, the prevalence between the ages; the results found the mean age (34.82±1.55) compared to the healthy control had moral differences compared to the control group. The findings were in agreement with Kayiba *et al.* which reported presence of frequent spread of malaria infections among young people and people up to 50 years.[18] While the prevalence of *plasmodium vivax* infections betwen the rural and urban area was equal and these findings disagreed with Tesfaye and Teshome, who found that rural areas are more affected than urban areas.[19] But the models in this research were collected from a hospital in Khanaqin district and this area is considered semi-rural because it is a small area with overlapping communities and there was no difference between the urban and rural areas. The infection rate was higher among females than males, which is consistent with Okiring *et al.*, who reported that malaria incidence diagnosed per 1000 person yearly was 735 in female and 449 in male .[20]

The results of high IgG antibodies in the malaria agreed with Bourke, *et al,* who showed that a highly significant increase in the levels of *Plasmodium vivax* IgG in the sera and blood plasma of infected patients and its presence in the haptozoan stage after its invasion of the bloodstream in infected persons in Africa.[21] Also there was increased levels of INF-α among infected patients with Malaria vivax compared to the control group. The immune regulatory protein (IFN-α) is antiproliferative, antiangiogenic and proapoptotic protein. It is known that IFN-α promotes the T helper (Th) 2 to Th1 shift in the host's immune system, resulting in enhancing the cell-mediated cytotoxicity against tumor cell, and this results was in a harmony with (He *et al,* 2020) who revealed that there is a response of IFN-α and the signaling pathway in malarial infection. The parasite pathogen-associated molecular pattern (PAMP) like RNA and DNA are identified by the Toll-like receptor (TLR) on the endosome membranes, e.g. TLR7, TLR9 and probably TLR8, with the activation of MYD88-TRAF6-IRF7 signaling cascades to induce IFN- α production.[22] Nevertheless, mean level of IL-1ß elevated in P. viavax infection, Mahittikorn, et al, reported that IL-1β is involved in cellular processes e.g. differentiations, proliferations and deaths. There are limited investigations on IL-1β in regard to malaria with inconsistency in the results; thus, conclusions on IL-1β in different malaria types are not well-explained. Nevertheless, meta-analyses for assessing variations in the levels of IL-1β between different malaria types, such as differences between patients having severe malarial diseases, patients having uncomplicated malaria and healthy control individuals have been conducted.[23] In addition, there was a highly levels of IL-10 with *Plasmodium vivax* infection. Previously, it was known that the cytokine (IL-10) has a powerful anti-inflammatory characteristics and plays key roles in reducing host immune responses to pathogenic organisms, thus they prevent host's damage and maintain normal tissue homeostasis. Cytokines are in charge of all symptoms and pathologic changes, and the infection outcomes rely upon the reciprocal regulations of pro and anti-inflammatory cytokines. IFN-gamma and IL-10 can mediate such process and the production of these cytokines may be influenced by the single nucleotide polymorphism (SNP) on

these cytokines' genes. In our study, the association between IL-10/IFN-γ level, parasitaemia,and their gene polymorphism were investigated and the involvement of pro-inflammatory and regulatory balances during natural immune responses among people infected with *Plasmodium vivax* was noticed Medina *et al.*[24]

Stratified analyses regarding type of a disease revealed that 511C>T variants, under the recessive CC vs. CT+TT models, promoted the preterm birth risk by 1.29 folds, with a relationship between 2 polymorphisms of IL-1β, 511C>T & +3954C>T, with overall risk gestational disease risks. On contrary, 31T>C variants lowered the incidence of these disorders.[25] In addition, (Ahmed, *et al,* 2024) stated that (IL-1β) genetic variations and severe coronavirus diseases 2019 (COVID-19) were critical for the development of new predictor and therapeutic target.[26] Furthermore, Vlasenko et al, demonstrated the significance SNP-proportion assessment in pro-inflammatory cytokines and their antagonists of IL-1 superfamilies in the healthy people in addition to the individual SNPs ratio in certain patient groups as monitoring parameters for epidemiological surveillances of the infectious diseases.[26] Nasralla, et al, found that the SNPs rs1143627 genome undergoes multiple mutations due to parasitic infections combined with viruses.[27]

CONCLUSION

This study demonstrates that adults infected with *Plasmodium vivax* malaria in Diyala Province, Iraq, exhibit significantly elevated levels of IgG antibodies and pro-inflammatory (IL-1β, IFN-α) and anti-inflammatory (IL-10) cytokines compared to healthy controls. Strong positive correlations were found between *P. vivax* IgG levels and IFN-α, IL-1β, and IL-10, indicating a coordinated immune response during infection. Additionally, a genetic mutation in the IL-1β gene (SNP rs1143629) was identified, where the wild-type CC was altered to CT or TT in infected individuals, suggesting a potential genetic influence on immune regulation in malaria. These findings highlight the roles of both humoral and cellular immune mechanisms in *P. vivax* infection and propose cytokine levels and genetic variants as potential biomarkers for disease severity or targets for therapeutic intervention.

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CONFLICT OF INTEREST
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.