UNIVERSITAS AIRLANGGA
FAKULTAS KEDOKTERAN
Kampus A Jl. Mayjen. Prof. Dr. Moestopo, 47 Surabaya 60132 Telp. (031) 5020251 Fax (031) 5022472
Laman : https://fk.unair.ac.id, e-mail : info@fk.unair.ac.id

SURAT TUGAS

Nomor : 7986 / UN3.FK/I/TD.06/2023

Wakil Dekan I Fakultas Kedokteran Universitas Airlangga dengan ini menugaskan :

1.	Prof. Dr. S. Ugroseno Yudho Bintoro, dr., Sp.PD., K-HOM.,FINASIM	Ketua
2.	Prof. Dr. Usman Hadi, dr.,Sp.PD.,K.PTI	Anggota
3.	Prof. Dr. Yoes Prijatna Dachlan, dr., M.Sc., Sp.Par(K)	Anggota
4.	Prof. Dr. Nasronudin, dr., Sp.PD., K-PTI., FINASIM	Anggota
5.	Prof. Dr. Jaap Middeldorp	Anggota
6.	Heny Arwati, Dra., M.Sc., Ph.D	Anggota
7.	Dr. Soebagijo Adi Soelistijo, dr.,Sp.PD, K-EMD.,FINASIM, FACP	Anggota
8.	Dr. H. Budi Utomo, dr., M.Kes	Anggota

Sebagai Ketua / Anggota Panitia Ujian Tahap Pertama (Tertutup) Program Doktor Fakultas Kedokteran Universitas Airlangga atas nama Insani Budiningsih, dr.,M.Imun peserta Program Doktor Program studi Ilmu Kedokteran angkatan tahun 2019/2020 yang diselenggarakan pada tanggal 31 Juli 2023.

Surat tugas ini diterbitkan sementara untuk menunggu keluarnya Surat Keputusan dari Dekan Fakultas Kedokteran Universitas Airlangga.

Surabaya, 13 Juli 2023

a.n. Dekan,
Wakil Dekan I,

Dr. dr. A.C. Romdhoni, Sp.T.H.T.B.K.L., Subsp.Onk. (K), FICS
NIP. 197609022008011009

UNIVERSITAS AIRLANGGA

FAKULTAS KEDOKTERAN

Kampus A Jl. Mayjen. Prof. Dr. Moestopo, 47 Surabaya 60132 Telp. (031) 5020251 Fax (031) 5022472
Laman : https://fk.unair.ac.id, e-mail : info@fk.unair.ac.id

Nomor : 7985/UN3.FK/I/PK.03/2023 13 Juli 2023
Lamp : 2 Berkas
Hal : Mohon Kesediaan untuk menjadi Panitia Penguji Disertasi

Yth.

1. Prof. Dr. S. Ugroseno Yudho Bintoro, dr., Sp.PD., K-HOM.,FINASIM (Ketua)
2. Prof. Dr. Usman Hadi, dr.,Sp.PD.,K.PTI
3. Prof. Dr. Yoes Prijatna Dachlan, dr., M.Sc., Sp.Par(K)
4. Prof. Dr. Nasronudin, dr., Sp.PD., K-PTI., FINASIM
5. Prof. Dr. Jaap Middeldorp
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7. Dr. Soebagijo Adi Soelistijo, dr.,Sp.PD, K-EMD.,FINASIM, FACP
8. Dr. H. Budi Utomo, dr., M.Kes

Dengan hormat,

Sehubungan dengan selesainya penulisan disertasi peserta Program Doktor angkatan tahun 2019/2020,

Nama : Insani Budiningsih, dr.,M.Imun ELPT :507
NIM : 011917017303
Judul :EPSTEIN-BARR VIRUS (EBV) DNA CIRCULATING IN PATIENTS WITH P. *falciparum*, *P. vivax*, AND MIXED INFECTIONS TRIGGER TNF-α, IFN-γ, IL-10, TGF-β CYTOKINE LEVELS IMPLICATIONS

Promotor : Prof. Dr. Usman Hadi, dr.,Sp.PD.,K.PTI
Ko Promotor : Prof. Dr. Yoes Prijatna Dachlan, dr., M.Sc., Sp.Par(K)

Ujian Disertasi rencananya diselenggarakan :

Hari, Tanggal : Senin, 31 Juli 2023
Pukul : 13.00 – 16.00 WIB
Tempat : Ruang Ujian 1 Pascasarjana FK UNAIR

Maka dengan ini mohon kesediaan Saudara untuk menjadi Ketua / Anggota panitia Penguji Disertasi tersebut, terlampir kami sampaikan pernyataan kesediaan untuk diisi dan dilampirkan pada kami dalam waktu yang tidak terlalu lama guna diproses lebih lanjut.

Demikian atas perhatian Saudara, kami ucapkan terima kasih.

a.n. Dekan
Wakil Dekan I

Dr. dr. A.C Romdhoni, Sp.T.H.T.B.K.L., Subsp.Onk. (K), FICS
NIP. 197609022003011009

Tindasan :
- Kepala Sub. Bagian Akademik
- Kepala Sub. Bagian Sarana dan Prasarana
- Kepala Sub. Bagian Keuangan

DISSERTATION

EPSTEIN-BARR VIRUS (EBV) DNA CIRCULATING IN PATIENTS WITH *Plasmodium falciparum*, *Plasmodium vivax*, AND MIXED INFECTIONS TRIGGER TNF-α, IFN-γ, IL-10, TGF-β CYTOKINE LEVELS IMPLICATIONS

INSANI BUDININGSIH

011917017303

STUDY PROGRAM DOCTORAL MEDICAL SCIENCE

FACULTY OF MEDICINE UNIVERSITY OF AIRLANGGA

SURABAYA

2023

VALIDATION PAGE

EPSTEIN-BARR VIRUS (EBV) DNA CIRCULATING
IN PATIENTS WITH *Plasmodium falciparum*, *Plasmodium vivax*, AND MIXED
INFECTIONS TRIGGER TNF-α, IFN-γ, IL-10, TGF-β
CYTOKINE LEVELS IMPLICATIONS

WHICH HAS BEEN APPROVED
IN JULY 31st, 2023

By
Promoter

Prof. Usman Hadi dr., Ph.D., Sp.PD-KPTI.FINASIM
Employee ID Number: 1954063020200361O1

Co-promoter

Prof. Dr. Yoes Prijatna Dachlan, dr., MSc., SpPar(K)
Employee ID Number: 19410285972031005

ABSTRACT

Quantitative cytokine level of TNF-α, IFN-γ, IL-10, TGF-β and circulating Epstein-Barr virus DNA load in individuals with acute malaria due to *Plasmodium falciparum* or *Plasmodium vivax* or double infection in a malaria endemic region in Indonesia

Insani Budiningsih

Plasmodium falciparum malaria and Epstein-Barr Virus (EBV) infection are risk factors in the development of Burkitt Lymphoma (BL). In Indonesia, 100% of the population is persistently infected with EBV early in life and at risk of developing EBV-linked cancers. Currently, 10.7 million people in Indonesia are living in malaria-endemic areas. This cross-sectional study was initiated to investigate how acute malaria dysregulates immune control over latent EBV infection. Using blood and plasma samples of 68 patients with acute malaria and 27 healthy controls, we measured the level of parasitemia for each *Plasmodium* type (*Plasmodium falciparum*, *Plasmodium vivax*, and Mixed (*Plasmodium falciparum* and *Plasmodium vivax*)) by microscopy and rapid test. The level of 4 regulatory cytokines was determined by quantitative ELISA and the level of circulating EBV DNA load by real-time PCR targeting the single copy EBNA 1 sequence. All *Plasmodium*-infected cases had high level parasitemia (>1000 parasites/ul blood) except for one case. EBV-DNA levels were significantly more elevated in *Plasmodium falciparum* and *Plasmodium vivax* infections ($P<0.05$) compared to controls. EBV-DNA levels were not related to age, gender, malaria symptoms, or *Plasmodium* type. TNF-α and IL-10 levels were increased in malaria cases versus controls, but IFN-γ and TGF- β levels were comparable between the groups. Only TNF-α levels in *Plasmodium falciparum* cases showed a clear correlation with elevated EBV DNA levels ($R^2 = 0.8915$). This is the first study addressing the relation between EBV (re)activation and cytokine responses during acute malaria, revealing a clear correlation between pro-inflammatory cytokine TNF-α and EBV-DNA levels, specifically in *Plasmodium falciparum* cases, suggesting this cytokine to be key in dysregulating EBV homeostasis during acute *Plasmodium falciparum* malaria.

Keywords: Epstein-Barr Virus (EBV), Malaria, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium falciparum* and *Plasmodium vivax* double infections, Cytokines, TNF-α, IFN-γ, IL-10, TGF-β, Immune system