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Raden Suhartono, Chaidir Arif Mochtar, Idrus Alwi, Aida Lydia, Aria Kekalih, Vivian Soetikno, Teguh Dwi Nugroho

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## ORIGINAL ARTICLE

**Correlation of magnetic angiography with relative cerebral blood flow on arterial spin labeling using magnetic resonance imaging in acute ischemic stroke patients (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3547>)**

Utami Ambarsari, Arif Faisal, Hari Basuki Notobroto, Erna Furaidah, Yunita Lestari Indrianto, Naura Anindya Candini

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[Abstract](#)[pdf \(https://www.balimedicaljournal.org/index.php/bmj/article/view/3547/2248\)](https://www.balimedicaljournal.org/index.php/bmj/article/view/3547/2248)

## ORIGINAL ARTICLE

**Comparison of outcomes between a ruptured and unruptured intracranial aneurysm: results from an Indonesian cohort study (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3725>)**

Julius July, Patrick Putra Lukito, Vanessa Angelica, Jeremiah Hilkih Wijaya, Audrey Hamdoyo, Nyoman Aditya Sindunata, Rusli Muljadi

Online First: Dec 8, 2022 |

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ORIGINAL ARTICLE

**The role of serum ferritin level and disease severity in COVID-19 with type 2 diabetes mellitus patients**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3818>)

Fauzia Noor Liani, Sony Wibisono Mudjanarko, Hermina Novida

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ORIGINAL ARTICLE

**The effect of freeze-dried human amnion on New Zealand rabbit tendon healing**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3926>)

Melissa Anita Ayu Iustitiati, Sitti Rizaliyana, Agus Santoso Budi

Online First: Dec 19, 2022 |

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ORIGINAL ARTICLE

**Effectivity of uv-light exposure on bacterial and fungal growth in Channa striata collagen-chitosan composite dressing for wound healing**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3497>)

Ary Andini, Endah Prayekti, Nur Indah Kamaliyah, Nur Halimah

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**Stress, motivation, satisfaction, and learning achievement: A case study**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3553>)

Widya Addiarto, Yulia Rachmawati Hasanah

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## ORIGINAL ARTICLE

**Formation of woven bone in orthodontic tooth movement tension areas after giving Mangostin by expression of Runx-2 and IL-10** (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3971>)

Ida Ayu Arnawati, I Ketut Sudiana

Online First: Dec 20, 2022 |


 Abstract pdf (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3971/2419>)

## ORIGINAL ARTICLE

**Risk Factors of Titanium Mesh Exposure: Experience from a Tertiary Referral Center**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/2428>)

Christian Beta Kurniawan, Akhmad Imron, Muhammad Rainda Farhan

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## ORIGINAL ARTICLE

**Physical fitness assessment for lower limb disability: rationale and design to develop a new formula**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3520>)

Endang Ernandini, Trevino Aristarkus Pakasi, Dewi Irawati Soeria Santoso, Damayanti Tinduh, Listya Tresnanti Mirtha, Sally Aman Nasution, Anita, Nury Nusdwinuringtyas

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ORIGINAL ARTICLE

**Transcatheter aortic valve implantation: A review article**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3571>)

Starry Homenta Rampengan, Jansen Chitrahadinata

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**The description of pregnancy status and type of delivery attachment technique in postpartum mothers at the Roemani muhammadiyah hospital Semarang: assessed by latch score analysis**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3752>)

Machmudah, Esti Yunitasari, Mira Triharini, Sri Rejeki

Online First: Nov 26, 2022 |

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ORIGINAL ARTICLE

**Granulocyte colony-stimulating factor therapy as a bridging treatment for pediatric decompensated liver cirrhosis prior to liver transplantation: an open-label randomized clinical trial**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3527>)

Tri Hening Rahayatri, Alida Harahap, Aryono Hendarto, Hanifah Oswari, Rianto Setiabudy, Akmal Taher

Online First: Sep 23, 2022 |

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## ORIGINAL ARTICLE

**Brazilian propolis wax as an anti-type-IV-hypersensitivity agent in metal bracket orthodontic treatment**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3583>)

Grahita Aditya, Oedijani Santoso, Lisyani Budipradigdo Suromo

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## ORIGINAL ARTICLE

**Fibrin glue as a novel therapy for contracted socket in comparison to mitomycin-c and triamcinolone acetonide at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3687>)

Firda Ayu Muthie, Evelyn Komaratih, Sutjipto, Dyah Fauziah, Budi Utomo

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## ORIGINAL ARTICLE

**Indonesian community knowledge, attitude and behavior towards COVID-19 vaccination**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3757>)

Ingenida Hadning, Fanny Rohimatul Azizah Putri, Sherinda Syafa Ardhana

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## ORIGINAL ARTICLE

**Role of neutrophil gelatinase-associated lipocalin (NGAL) as a acute prerenal kidney injury marker: Exploring factors associated with its postoperative levels in hypotension-controlled otorhinolaryngology surgery (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3868>)**

Andy Nauman Saputra, Prananda Surya Airlangga, Bobby Abdul Rahman, Edward Kusuma, Prihatma Kriswidyatomo, Christrijogo Sumartomo

Online First: Dec 1, 2022 |

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ORIGINAL ARTICLE

**Clinical and laboratory comparison between End-Stage Kidney Disease patients with and without COVID-19: a cross-sectional study in a top referred hospital of West Nusa Tenggara (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3440>)**

I Gede Yasa Asmara, I Gusti Ngurah Ommy Agustriadi, I Made Sujaya, Salim Said Thalib, Rina Lestari, Suryani Padua Fatrullah, Komang Sri Rahayu Widiyasari, Indana Eva Ajmala, Metta Octora

Online First: Sep 5, 2022 |

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ORIGINAL ARTICLE

**Anti-inflammatory effects and potential mechanisms of *Mitragyna speciosa* methanol extract on  $\lambda$ -karagenan-induced inflammation model (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3535>)**

Hotimah Masdan Salim, Choirotussanijjah, Evi Sylvia Awwalia, Ilham Putera Alam

Online First: Sep 13, 2022 |

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**Calming effect of Javanese Handwriting Calligraphy, preliminary study based on neuroaesthetics (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3598>)**

Arman Yurisaldi Saleh, Miky Miky Endro Santoso, Wawan Murwantara, Retno Yulianti, Imam Prabowo

Online First: Dec 19, 2022 |

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## ORIGINAL ARTICLE

**High maternal homocysteine (Hcy) levels as a risk factor of preterm labor: a case-control study  
(https://www.balimedicaljournal.org/index.php/bmj/article/view/3701)**

Anak Agung Gede Putra Wiradnyana, Anak Agung Ngurah Jaya Kusuma, Tjokorda Gde Agung Suwardewa, Anom Suardika, Made Bagus Dwi Aryana, Nyoman Gede Budiana, Putu Doster Mahayasa, IP Popy Kusuardiyanto

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## ORIGINAL ARTICLE

**Haemoglobin Level of Pregnant Women was Associated with History of Anemia During Adolescent Period:  
Findings from the Indonesia Family Life Survey  
(https://www.balimedicaljournal.org/index.php/bmj/article/view/3783)**

Siti Riptifah Tri Handari, Anies, Martha Irene Kartasurya, Sri Achadi Nugraheni

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## ORIGINAL ARTICLE

**Diagnostic value of qualitative, semiquantitative, and quantitative parameter of dynamic contrast-enhanced MRI in musculoskeletal tumor  
(https://www.balimedicaljournal.org/index.php/bmj/article/view/3880)**

Elysanti Dwi Martadiani, I Wayan Juli Sumadi, I Wayan Gede Artawan Eka Putra, Faradilla Novita Anggreni, Budi Martono, Yori Primanda, Felicia Nike, Triningsih

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ORIGINAL ARTICLE

**Antioxidant activity of *Tinospora crispa* extracted with different ethanol solvents**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3467>)

Renny Novi Puspitasari , Sri Agus Sudjarwo, Agung Pranoto , Achmad Basori

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ORIGINAL ARTICLE

**Blockchain integration for hospital information system management**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3540>)

Naufal Adi Satrio, Sritrusta Sukaridhoto, M. Udin Harun Al Rasyid, Rizqi Putri Nourma Budiarti, Ilham Achmad Al-Hafidz, Evianita Dewi Fajrianti

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ORIGINAL ARTICLE

**Restarting living donor kidney transplant during COVID-19: a single center experience**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3615>)

Mochammad Fairuz Zahran, Tanaya Ghinorawa

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ORIGINAL ARTICLE

**The effect of fibrin glue on suppressing Transforming Growth Factor- $\beta$  (TGF- $\beta$ ) expression compared to Mitomycin-C (MMC) and Triamcinolone Acetonide (TCA) as antifibrotic agents in contracted socket prevention** (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3709>)

Nike Aswati, Luki Indriaswati, Sutjipto, Dyah Fauziah, Budi Utomo

Online First: Nov 9, 2022 |

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**Transcortical selective amygdalohippocampectomy for intractable mesial temporal lobe epilepsy: a review of outcomes in a single center (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3475>)**

Aris Catur Bintoro, Muhamad Thohar Arifin, Harsono, Amin Husni, Surya Pratama Brilliantika, Yuriz Bakhtiar, Novita Ikbar Khairunnisa, Rofat Askoro, Jacob Bunyamin, Soeharyo Hadisapurto, Zainal Muttaqin

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**The effect of syzygium polyanthum (wight) extract in histological changes of kidney in diabetic mice model (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3545>)**

David Sajid Muhammad, Hotimah Masdan Salim, Cici Dita Virlliana, Adyan Donastin, Agus Aan Adriansyah

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**The relationship between self efficacy and medication adherence in elderly with hypertension (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3723>)**

Nina Dwi Lestari, Vivi Nur Anisa

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## ORIGINAL ARTICLE

**Relationship between Vitamin D Levels and Platelet Function in the Elderly Patients with Coronary Heart Disease (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3911>)**

Charles Limantoro, Catharina Suharti, Trilaksana Nugroho, Friska Wilda Wijaya

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## ORIGINAL ARTICLE

**Acceptance of interprofessional education (IPE) for educators at health-based faculty universitas nahdlatul ulama Surabaya (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3495>)**

Wiwik Afridah, Trimartiana, Prihartini Widiyanti, Mochammad Bagus Qomaruddin

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## ORIGINAL ARTICLE

**The effect of Curcuma longa on fasting blood glucose, MMP-9 and IFN- $\gamma$  in diabetes mellitus: an experimental study (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3648>)**

Shafira Zahra Ovaditya, Surya Pratama Brilliantika, Chodidjah Chodidjah, Titi Sumarawati

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## ORIGINAL ARTICLE

**Platelet-rich fibrin (PRF) graft and amniotic membrane graft on transforming growth factor- $\beta$  (TGF- $\beta$ ) and type 1 collagen post conjunctival excision**



(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3733>)

Abdi Roy Nababan, Daniar Indah Suryowati, Evelyn Komaratih, Yulia Primitasari, Djoko Legowo, Paulus Budiono Notopuro, Hari Basuki Notobroto

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ORIGINAL ARTICLE

**Association between patient with muscle-invasive bladder cancer with the incidence of urinary tract infection in Karawang Regional Hospital: a single center study**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3823>)

Muhamad Iqbal Tafwid, Achmad Rizky Herda Pratama

Online First: Nov 9, 2022 |

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ORIGINAL ARTICLE

**The effect of ethanol extract of green meniran leaves (*Phyllanthus niruri* Linn) in a mixture of calcium hydroxide and 2% chlorhexidine digluconate on matrix metalloproteinase-9, transforming growth factor-1 levels, osteoclast, and osteoblast cells in Wist**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3965>)

Ni Kadek Eka Widiadnyani, I Nyoman Mantik Astawa, I Wayan Putu Sutirta Yasa, I Dewa Made Sukrama, I Made Bakta, Ida Bagus Putra Manuaba, I Wayan Suardana, I Made Sudarmaja

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ORIGINAL ARTICLE

**The importance of husband support for breastfeeding during pandemic COVID-19**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3556>)

Mega Silvian Natalia, Wahida Yuliana, Bawon nulhakim

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ORIGINAL ARTICLE

**Ultrasound assessment of femoral cartilage thickness among healthy Indonesian adults**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3667>)

Rita Vivera Pane, Aisyah, Hajar Ariani, Erwien Isparnadi, AUFAR ZIMAMUZ ZAMAN AL HAJIRI, ALBERT SETIAWAN

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ORIGINAL ARTICLE

**Relationship between CYP2C19 polymorphisms and weight gain in epilepsy patients treated with divalproex sodium: does gender matter?**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3748>)

Wardah Rahmatul Islamiyah, Nasronudin, Abdulloh Machin, Iin Ernawati, Paulus Sugianto

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ORIGINAL ARTICLE

**Correlation of S100B level and postoperative cognitive dysfunction (POCD) events among patients with ear, nose and throat (ENT) surgeries with controlled hypotension**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3847>)

Boby Abdul Rahman, Prananda Surya Airlangga, Andy Nauman Saputra, Prihatma Kriswidyatomo, Agustina Salinding, Hamzah, Maulidya, Muhtarum Yusuf

Online First: Dec 1, 2022 |


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ORIGINAL ARTICLE

**Comparative study of SOFA, WSESSSS, and CPIRO scoring systems as mortality predictors in a patient with complicated intra-abdominal infection**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3523>)

Gigih Laksamana Nugraha, Denny Septarendra, Tomy Lesmana

Online First: Oct 12, 2022 |

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ORIGINAL ARTICLE

**The effectiveness of topical hyaluronic acid on decreasing Interleukin-6 and acceleration of wound healing (Push Score) in Wagner II-III diabetic foot ulcer in Dr. Soetomo Hospital Surabaya**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3581>)

Christian Ibezaro Harazaki Gulo, Puruhito, Hermina Novida

Online First: Sep 5, 2022 |

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ORIGINAL ARTICLE

**The relationship of psychosocial problems to the severity of psoriasis vulgaris**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3855>)

Flora Marlita Lubis, Riana Miranda Sinaga

Online First: Dec 31, 2022 |

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ORIGINAL ARTICLE

**The effectiveness of the self-care management model in midwife care through android application as an effort to increase the ability of pregnant mothers in early detection of pregnancy at risk during the COVID-19 pandemic**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3430>)

Ika Mardiyanti , Annif Munjidah, Nanik Handayani, Siska Nurul Abidah, Hinda Novianti, Uliyatul Laili, Lailatul Khusnul Rizki

Online First: Sep 9, 2022 |

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## ORIGINAL ARTICLE

**Symptoms identification of ICD-11 based on clinical NLP mobile apps for diagnosing the disease (ICD-11) (https://www.balimedicaljournal.org/index.php/bmj/article/view/3533)**

Rizqi Putri Nourma Budiarti, Sritrusta Sukaridhoto, Ilham Achmad Al-Hafidz, Naufal Adi Satrio

Online First: Sep 13, 2022 |

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[Abstract](#)[pdf \(https://www.balimedicaljournal.org/index.php/bmj/article/view/3533/2219\)](https://www.balimedicaljournal.org/index.php/bmj/article/view/3533/2219)

## ORIGINAL ARTICLE

**Serum ferritin level in pediatric patients with acute lymphoblastic leukemia (ALL) in the early stage of diagnosis and remission phase (https://www.balimedicaljournal.org/index.php/bmj/article/view/3595)**

Novia, Nelly Rosdiana, Supriatmo

Online First: Nov 21, 2022 |

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## ORIGINAL ARTICLE

**Correlation of chest radiography of confirmed COVID-19 patients with comorbid hypertension and diabetes mellitus (https://www.balimedicaljournal.org/index.php/bmj/article/view/3691)**

Ana Majdawati, Annisa

Online First: Nov 15, 2022 |

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## ORIGINAL ARTICLE

**Body image and the level of stress in cervical cancer patients**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3769>)

Sri Rejeki, Eka Agustyaningrum, Macmudah, Nikmatul Khayati, Tri Hartiti, Dwi Nur Rahmantika Puji Safitri, Yanuan Ben Olina

Online First: Nov 26, 2022 |

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## ORIGINAL ARTICLE

**Regenerative alveolar bone in dental sockets of diabetic wistar rats post tooth extraction**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3874>)

Nanik Zubaidah, Muhammad Luthfi, Wisnu Setyari, Retno Palupi, Nur Imamatul Ummah, Ardyta Lintang Maheswari, Arif Rahman Nurdianto, Fathillah Abdul Razak

Online First: Nov 25, 2022 |

[Abstract](#)[pdf \(https://www.balimedicaljournal.org/index.php/bmj/article/view/3874/2331\)](https://www.balimedicaljournal.org/index.php/bmj/article/view/3874/2331)

## ORIGINAL ARTICLE

**Effect of aromatherapy blend essential oils (lemongrass and lemon) on sleep quality in pregnant women's third trimester** (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3453>)

Fritria Dwi Anggraini , Siska Nurul Abidah, Esty Puji Rahayu, Fauziyatun Nisa

Online First: Sep 9, 2022 |

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## ORIGINAL ARTICLE

**Stress due to online learning during the COVID-19 pandemic affects the menstrual cycle in college students** (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3538>)

Raden Khairiyatul Afiyah, Nurul Kamariyah, Lono Wijayanti, Siti Nur Hasina, Nisa Wahyu Dika Mila Sari, Ratna Yunita Sari, Rusdianingseh, Firman Suryadi Rahman

Online First: Sep 13, 2022 |

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ORIGINAL ARTICLE

**Association between serum TNF- $\alpha$  level with the incidence of metastases in women with breast cancer in Dr. Soetomo General Hospital, Indonesia**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3611>)

Rachman Efendi, Husnul Ghaib, Iskandar Ali

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 Abstract

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ORIGINAL ARTICLE

**Tracing management and epidemiological characteristics of close contact COVID-19 in primary health care**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3705>)

Dwi Yulianingsih Putri Hanardi, Erna Rochmawati

Online First: Nov 14, 2022 |

 Abstract

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ORIGINAL ARTICLE

**Diagnostic test of Immature Granulocyte Ratio (IG Ratio) to detect Early-Onset Neonatal Sepsis (EONS)**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3795>)

Sherly Karolina Simanjuntak, Sianny Herawati, Made Sukmawati, I Wayan Putu Sutirta Yasa, Ni Kadek Mulyantari, Anak Agung Wiradewi Lestari, I Nyoman Wande, I Made Ady Wirawan

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## ORIGINAL ARTICLE

**Renal function features in pediatric acute lymphoblastic leukemia during high-dose methotrexate chemotherapy (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3890>)**

Adkhiatul Muslihatin, Mia Ratwita Andarsini, Andi Cahyadi, Risky Vitria Prasetyo, I Dewa Gede Ugrasena, Maria Christina Shanty Larasanti

Online First: Nov 18, 2022 |

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## ORIGINAL ARTICLE

**The effect of Quran recitation on t-cell lymphocyte activity in mice model of breast cancer (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3473>)**

Akbar Reza Muhammad, Yunyastiti D. Palupi, Mega Astri, Hafid Algristian

Online First: Sep 9, 2022 |

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## ORIGINAL ARTICLE

**Effect of secretome of adipose stem cell (ASC) in photoaging skin (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3543>)**

Winawati Eka Putri, Anang Endaryanto, Damayanti Tinduh, Fedik Rantam, Hari Basuki Notobroto, Cita Rosita Sigit Prakoeswa

Online First: Sep 15, 2022 |

 Abstract

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## ORIGINAL ARTICLE

**A study of efficacy, safety, and acceptance of two combined oral contraceptive pills containing 150 mcg Levonorgestrel and 30 mcg Ethinyl Estradiol at Dr. Kariadi Hospital, Semarang, Indonesia**

(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3629>)

Syarief Thaufik Hidayat, Hary Tjahjanto, Robert Eria, Yenny Kartika Gozali

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ORIGINAL ARTICLE

**Transformation of the learning system in nursing education after the COVID-19 pandemic**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3720>)

Sulastri, Wachidah Yuniartika, Diah Ayu Agus Triana, Giyoto

Online First: Nov 16, 2022 |

 Abstract

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ORIGINAL ARTICLE

**Evaluation of dermoscopic photoaging score among multiethnic in Medan, Indonesia**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3810>)

Nelva Karmila Jusuf, Imam Budi Putra, Medina Muslim

Online First: Dec 13, 2022 |

 Abstract

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ORIGINAL ARTICLE

**Factors to accelerate the reducing stunting cases in Jombang regency, with optimal convergence actions and cross sectoral effort** (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3548>)

Rizki Amalia, Dini Setiarsih , Fildzah Karunia Putri , Paramita Viantry

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## ORIGINAL ARTICLE

**Utilization of local culture "Bapalas Bidan" as a postpartum counseling media on contraception tools**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3641>)

Noordiati, Wahidah Sukriani

Online First: Nov 17, 2022 |

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## ORIGINAL ARTICLE

**Liver function characteristics of COVID-19 patients with obesity at Dr. Soetomo Hospital: case series**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3727>)

Erwin Maulana Farmanda Putra, Umami Maimunah

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## ORIGINAL ARTICLE

**Clinicopathological characteristics and possible risk factors for extrauterine metastases in endometrial carcinoma**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3820>)

Teuku Mirza Iskandar, Very Great Eka Putra, Ediwibowo Ambari, Endy Cahyono, Lubena

Online First: Oct 13, 2022 |

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## ORIGINAL ARTICLE

### **A comparative study of full-thickness wound healing in rats using Nile tilapia skin and fresh human amnion (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3927>)**

Nyssa Claresta Adhya Sastri, Iswinarno Doso Saputro, Lobredia Zarasade

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ORIGINAL ARTICLE

### **Relationship between self-regulation with self- acceptance of hypertension patients during the covid- 19 pandemic period in Indonesia (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3499>)**

Umdatus Soleha, Ah Yusuf, Oedojo Soedirham, Ratna Yunita Sari, R. Khairiyatul Afiyah, Chilyatiz Zahroh, Immatul Faizah

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ORIGINAL ARTICLE

### **The impact of COVID-19 on personal hygiene behavior of female students in islamic boarding school (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3554>)**

Agustina Widayati, Umi Narsih, Homsiatu Rohmatin

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ORIGINAL ARTICLE

### **Fatigue and excessive daytime sleepiness among nurses (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3746>)**

Septian Mixrova Sebayang, Made Suandika, Ita Apriliyani, Suci Khasanah, Asmat Burhan, Noor Yunida Triana, Dwi Astuti

Online First: Nov 15, 2022 |

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## ORIGINAL ARTICLE

**The pattern of osteocyte in dental socket bone regenerative induced by hydroxyapatite bovine tooth graft (https://www.balimedicaljournal.org/index.php/bmj/article/view/3844)**

Nanik Zubaidah, Sri Kunarti, Nadira Nurin Febrianti, Arif Rahman Nurdianto, Wanda Oktaria, Muhammad Luthfi

Online First: Nov 9, 2022 |

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## ORIGINAL ARTICLE

**Post-Chemotherapy Monocytopenia as a Predictor of Chemotherapy – Induced Neutropenia in Breast Cancer Patients (https://www.balimedicaljournal.org/index.php/bmj/article/view/2844)**

Azril Okta Ardiansyah, IB. Tjakra Wibawa Manuaba, I Ketut Widiania

Online First: Sep 28, 2022 |

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## ORIGINAL ARTICLE

**The performance of various laboratory parameters to differentiate follicular thyroid carcinoma and follicular thyroid adenoma (https://www.balimedicaljournal.org/index.php/bmj/article/view/3521)**

Satriya Kelana, Dwi Hari Susilo, Sahudi

Online First: Oct 31, 2022 |

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## ORIGINAL ARTICLE

**Brachial artery and cephalic vein diameter as maturation predictors of brachiocephalic arteriovenous fistula in end-stage renal diseases with type 2 diabetes mellitus**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3573>)

Dedy Pratama, Ahmad Daenuri, Aria Kekalih, Patrianef Darwis, Muhammad Farel Ferian, Bany Faris Amin

Online First: Oct 4, 2022 |

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## ORIGINAL ARTICLE

**Strengthening community roles to reduce stunting in COVID-19 pandemic in indonesia rural areas: capacity building program for cadres and local government**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3753>)

Supriyatningsih Wenang, Ima Rismawati, Lidia Febrianti, Bambang Edi Susyanto, Gina Puspita, Alfaina Wahyuni, Arlina Dewi, Dianita Sugiyono, Sutantri, Diyah Nahdiyati, Anang Widhi Nirwansyah

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## ORIGINAL ARTICLE

**Association between cartilage biomarker level and functional outcome in knee osteoarthritis patients receiving dextrose prolotherapy: a cross-sectional study**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3395>)

Yose Waluyo, Agussalim Bukhari, Endy Adnan, Sari Rajwani Artika, Ahmad Yasin, Insani Nanda Wahyuni, Budu

Online First: Sep 12, 2022 |

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## ORIGINAL ARTICLE

**Medico-socio-economic perspective of congenital hydrocephalus patients treatment in dr. Soetomo Academic General hospital, Surabaya, Indonesia**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3586>)

Heru Kustono, Muhammad Arifin Parenrengi, Arief Wibowo, Agus Turchan, Kurnia Kusumastuti, Asra Alfauzi

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ORIGINAL ARTICLE

**Analysis of the effectiveness of sphenopalatine ganglion block on fentanyl needs in endoscopic endonasal surgery as measured by qNOX score**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3869>)

Agil Rumboko Sumitro, Agustina Salinding, Dedi Susila, Budi Sutikno

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 Abstract

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ORIGINAL ARTICLE

**Age and Gender as The Risk Factors for Mortality Rate in COVID-19 Patients**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3446>)

Maria Regina Rachmawati, Yudi Amiarno, Yeni Restuti, Wida Guslianti, Luzi Adriyanti, Nurul Fajriah

Online First: Dec 30, 2022 |

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ORIGINAL ARTICLE

**Comprehensive sanitation situation analysis based on complete components in community-based total sanitation**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3536>)

Abdul Hakim Zakkiy Fasya, Mursyidul Ibad, Dwi Handayani

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## ORIGINAL ARTICLE

**Grape (*Vitis vinifera* L.) skin extract reduced levels of SGPT and SGOT and improved the liver tissue structure of Wistar rats (*Rattus norvegicus*) fed a high-cholesterol diet**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3602>)

Siti Maryam, Ni Kadek Alit Arsani, Sartika Tangguda

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## ORIGINAL ARTICLE

**Factors related to family resilience during the COVID-19 pandemic**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3703>)

Martina Pakpahan, Lia Kartika, Mega Sampepadang

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## ORIGINAL ARTICLE

**Intensifying self-awareness of undergraduate students toward hypertension risk factors through health education**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3784>)

Ambar Relawati, Dewi Maulidawati

Online First: Nov 26, 2022 |

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## ORIGINAL ARTICLE

**Antioxidant potential effect combination of the bitter, red ginger, and turmeric extract with the DPPH method**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3882>)

Handayani, Ardyarini Dyah Savitri, Renny Novi Puspitasari, Aufar Zimamuz Zaman Al Hajiri, Rifky Dwi Aditya Iryawan, Arina Syukur, Miftah Ramadhan Purwoko, Syahrul Gusnaldi Prawidya

Online First: Dec 30, 2022 |

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ORIGINAL ARTICLE

**Clinical characteristics and mortality associated with COVID-19 in islamic hospital of Jemursari, Surabaya, Indonesia: A hospital-based retrospective cohort study**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3541>)

Evi Awwaliyah, Hotimah, Michio Shimabukuro

Online First: Sep 15, 2022 |

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ORIGINAL ARTICLE

**Implementation of the blood donation preservation strategy at Indonesian red cross (IRC) blood donor unit (BDU) Banda Aceh during the COVID-19 pandemic**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3622>)

Teuku Ilhami Surya Akbar, Maulana Ikhsan, Ratna Sari Dewi

Online First: Nov 28, 2022 |

 Abstract

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ORIGINAL ARTICLE

**Expression of Na<sup>+</sup>/K<sup>+</sup>ATPase and changes of corneal endothelium cell density after phacoemulsification with hypothermic perfusion**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3718>)

Ratih Justitia Kartika, Reni Prastyani, Dyah Fauziah, Soenarnatalina Melaniani, Wimbo Sasono

Online First: Nov 11, 2022 |

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## ORIGINAL ARTICLE

**The Effect of Beta vulgaris L. on the Malondialdehyde Levels in Male Wistar Rats Exposed to Cigarette Smoke (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3806>)**

Alya Berliana Suharso, Puspita Kusuma Dewi, Edward Kurnia Setiawan Limijadi, Amallia Nuggetsiana Setyawati

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## ORIGINAL ARTICLE

**Comparation of intestinal fatty acid binding protein (I-FABP) level between pre- and post-surgery and its associated determinants in patients with microscopic otorhinolaryngology surgeries (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3893>)**

Yuda Atmajaya, Mohammad Satriyo Wibowo, Prananda Surya Airlangga, Maulydia, Prihatma Kriswidyatomo, Muhtarum Yusuf, Budi Utomo

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## ORIGINAL ARTICLE

**Relationship between the amount of blood transfusion and the amount of iron chelation with blood and salivary ureum levels in children with beta thalassemia major (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3488>)**

Putu Gyzca Pradypta, Indah Titien, Putri Kusuma WM

Online First: Dec 30, 2022 |

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## ORIGINAL ARTICLE



## Distribution of blood-added tablets in adolescent girls in the COVID-19 pandemic (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3546>)

Pratiwi Hariyani Putri , Dini Setiarsih, Rizki Amalia

Online First: Sep 28, 2022 |

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ORIGINAL ARTICLE

## Stromal Tumor Infiltrating Lymphocytes (TIL) as a potential prognostic biomarker for recurrence in Locally Advanced Breast Cancer (LABC) patients (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3724>)

Dannu Novriandhika, Dwi Hari Susilo, Dyah Fauziah, Priangga Adi Wiratama, Desak Gede Agung Suprabawati

Online First: Nov 21, 2022 |

 Abstract

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ORIGINAL ARTICLE

## Application of DNA Barcoding for authentication of Balinese traditional medicinal plant Purnajiwa (*Kopsia arborea* Blume. and *Euchresta horsfieldii*) (Lesch.) Benn (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3815>)

Putu Eka Pasmidi Ariati, Maria Malida Vernandes Sasadara, I Gede Putu Wirawan, Made Sritamin, I Ketut Suada, I Nyoman Wijaya, Rindang Dwiyani, I Putu Sudiarta, Ida Ayu Putri Darmawati

Online First: Nov 21, 2022 |

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ORIGINAL ARTICLE

## Robusta BP-42 coffee bean extract is a new anti-tyrosinase candidate to reduce melanogenesis activity (<https://www.balimedicaljournal.org/index.php/bmj/article/view/3922>)

Ulfa Elfiah, David Sontani Perdanakusuma, Iswinarno Doso Saputro, Misnawi

Online First: Dec 30, 2022 |

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## ORIGINAL ARTICLE

**Exercise decrease the expression of MCP-1 in perivascular adipose tissue (PVAT) in obese mice (https://www.balimedicaljournal.org/index.php/bmj/article/view/3496)**

Hotimah Masdan Salim, Aisyah Aisyah, Michio Shimabukuro

Online First: Sep 11, 2022 |

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## ORIGINAL ARTICLE

**Frequency of Interleukin-6 rs 1800796 (-572G/C) and 2069837 (intron 2A/G), TNF- $\alpha$  rs1800750 (-376G/A), and 1800629 (-308G/A) polymorphism in COVID-19 patients with clinical degrees in Central Java (https://www.balimedicaljournal.org/index.php/bmj/article/view/3552)**

Reviono, Hendrastutik, Yulia Sari, Betty Suryawati, Darmawan ismail, Ketut Putu Yasa

Online First: Oct 3, 2022 |

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## ORIGINAL ARTICLE

**Protective effect of lavender essential oils on depression and multi-organ stress (https://www.balimedicaljournal.org/index.php/bmj/article/view/3655)**

Hafid Algristian, Tri Wahyuni Bintarti, Rani Nur Mukaromatim Baroroh, Qorieatul Leila, Reina Ulfa, Amelia Krismawati, Mifa Nurdiana, Giftania Wardhani Sudjarwo, Adhi Wibowo Nurhidayat, Irawan Satriotomo, Retno Handajani

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## ORIGINAL ARTICLE

**Expression of Superoxide Dismutase-1 (SOD-1) and changes of corneal endothelial morphology after phacoemulsification with hypothermic perfusion**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3734>)

Afia Nuzila Fadhlina, Luki Indriaswati, Nurwasis, Dyah Fauziah, Mahmudah

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## ORIGINAL ARTICLE

**Association between the levels of muscle-specific creatinine kinase (CK-MM) and the incidence of persistent myalgia in COVID-19 survivors**  
(<https://www.balimedicaljournal.org/index.php/bmj/article/view/3827>)

Aria Adhiatma, Christrijogo Sumartono Waloejo, Bambang Pujo Semedi, Hamzah , Prihatma Kriswidyatomo, Pudji Lestari

Online First: Nov 13, 2022 |

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## ORIGINAL ARTICLE

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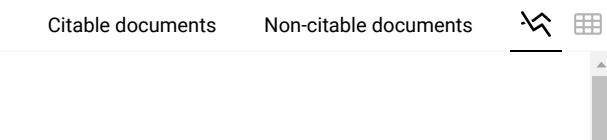
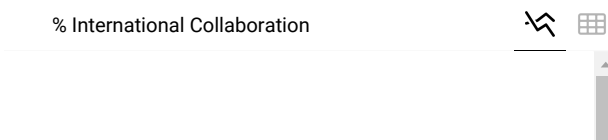
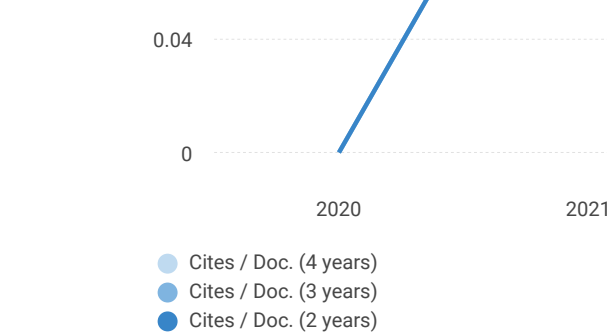
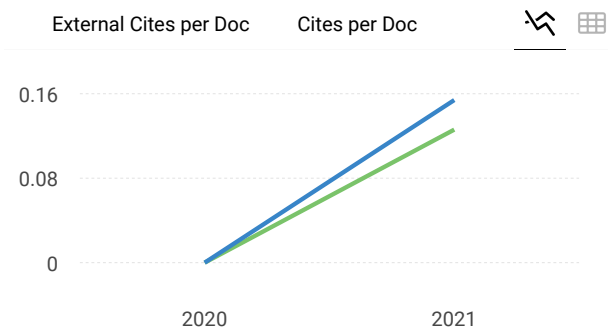
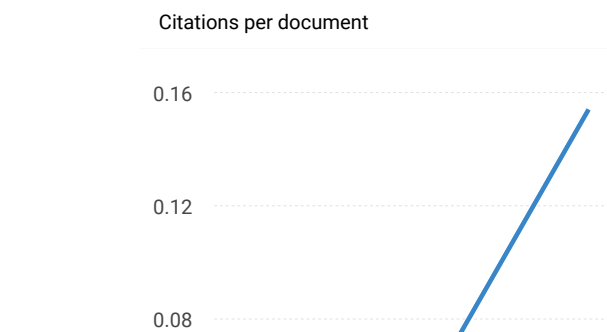
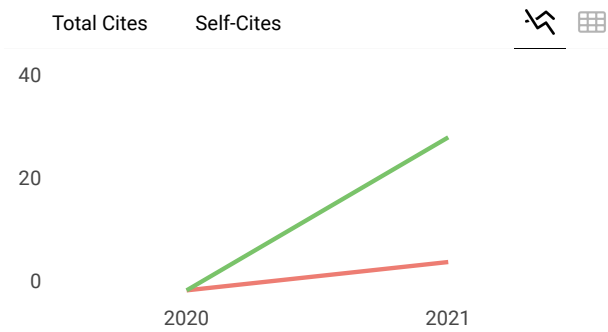
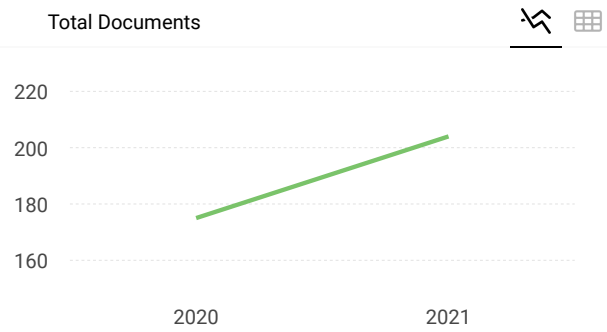
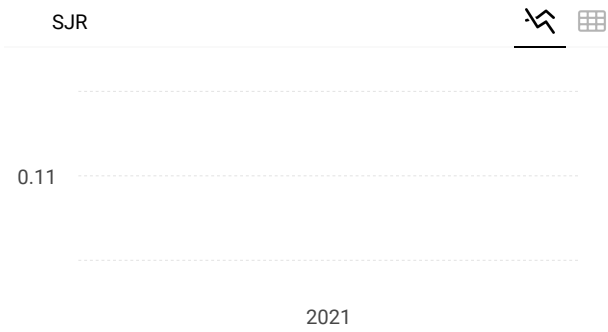
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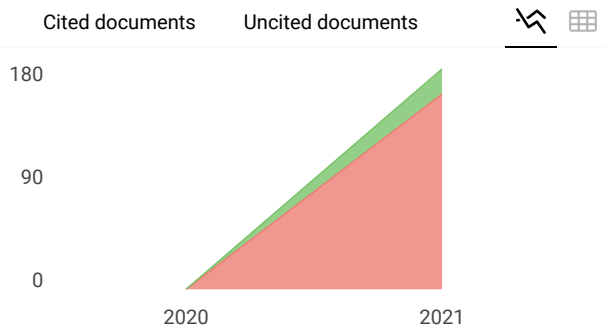
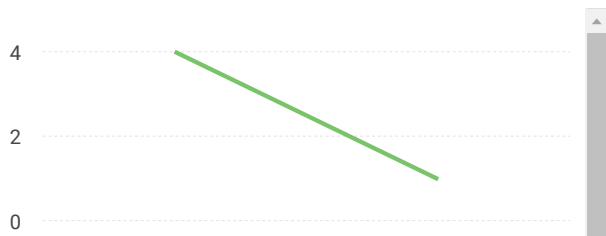
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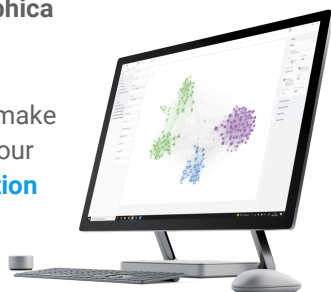
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## Lung damage reduction due to reperfusion injury of acute lower limb ischemia with and without pentoxifylline and vitamin c combination therapy: histopathological evaluation

Maikel Triyudi Tappang<sup>1\*</sup>, Yan Efrata Sembiring<sup>2</sup>, Willy Sandhika<sup>3</sup>



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### ABSTRACT

Several studies report an incidence of acute limb ischemia of approximately 1.5 cases per 10,000 persons per year. The mortality rate from acute limb ischemia ranges from 15-to 20% and the morbidity rate from 25% by amputation and 5-to 25% to fasciotomy. Revascularization is the main goal in the management of acute limb ischemia. Reperfusion of ischemic limbs can save limbs from amputation, but Ischemia-reperfusion injury can also cause systemic damage in the form of damage to body organs (lung, liver, kidney, heart, and brain tissue) which increases morbidity and mortality rates. Lung tissue is an easily affected target organ, and damage from Ischemia-reperfusion injury can cause acute lung injury and acute respiratory distress syndrome. These conditions damage the endothelium and epithelium of the lung parenchyma resulting in edema and impaired gas diffusion with a very high mortality rate of around 25-40%. The combination therapy of Pentoxifylline and Vitamin C in reducing the effect of Ischemia-reperfusion injury on lung tissues and have shown a protective effect of lung tissue damage due to ischemia-reperfusion injury in lower limbs.

**Keywords:** Acute limb Ischemia, reperfusion injury, lung, vitamin C, pentoxifylline.

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### INTRODUCTION

Acute limb ischemia (ALI) is characterized by a rapid reduction in leg perfusion that threatens leg viability and frequently necessitates urgent revascularization.<sup>1</sup> Restoring blood flow or reperfusion to ischemic tissue is essential to prevent permanent cell injury.<sup>2</sup> Revascularization is the main goal in the management of acute limb ischemia. Reperfusion of ischemic limbs can save limbs from amputation, but Ischemia-reperfusion injury can also cause systemic damage in the form of damage to body organs (lung, liver, kidney, heart, and brain tissue) which increases morbidity and mortality rates. Lung tissue is an easily affected target organ, and damage from Ischemia-reperfusion injury can cause acute lung injury (ALO) and acute respiratory distress syndrome (ARDS).<sup>3</sup> These conditions damage the endothelium and epithelium of the lung parenchyma resulting in edema and impaired gas

diffusion with a very high mortality rate of around 25-40%.

Pentoxifylline in particular inhibits neutrophil adhesion to the endothelium and prevents leukocyte degranulation.<sup>4</sup> Inhibition of neutrophil adhesion in lung tissue will reduce endothelial and epithelial cell damage in the lung parenchyma which can lead to pulmonary oedema and impaired gas diffusion in the lung parenchyma. Research by the University of Tehran showed a reduction in the inflammatory index after administration of pentoxifylline dissolved in 0.9% normal saline. Administration of pentoxifylline reduces ischemia-reperfusion injury due to skeletal muscle ischemia, as well as post-transplant lung and liver injury.<sup>5-7</sup>

Vitamin C is an endogenous antioxidant, which counteracts ROS, thereby reducing free radicals. Several experimental studies have shown that antioxidant vitamins, including ascorbic acid, produce cytoprotective effects by protecting

microvascular endothelium against neutrophil adhesion. Several experimental studies show that antioxidant vitamins including ascorbic acid can produce cytoprotective due to the reduction of free radicals. Lehr et al have shown that vitamin C protects the microvascular endothelium from neutrophil adhesion therefore can prevent microvascular circulation injury. Herbaczynska-Cedro et al have shown that vitamin C reduces the production of free radical oxygen in human circulating neutrophils. According to him, the effect of giving vitamin C against augmentation of lipid peroxidation induced by ischemia reperfusion injury (IRI) at a dose of different (range 30-100 mg/kgBb).<sup>6</sup> In an animal study by Baltalarli et al with Albino rats, there was a decline in plasma leukocyte sequestration (a parameter for pulmonary injury) after pretreatment with iloprost and vitamin C. Kearns et al also noted a reduction in the microvascular pulmonary injury due

to ischemia-reperfusion and respiratory burst activity of circulating neutrophils after administration of vitamin C.<sup>6,21</sup>

From previous studies, no one has raised the effect of combination therapy Pentoxifylline and Vitamin C in reducing the effect of Ischemia-reperfusion injury on lung tissues. Several studies have shown a protective effect of giving pentoxifylline in combination with other therapies and vitamin C in combination with other therapies and vitamin C is expected to increase the protection of lung tissue due to ischemia-reperfusion injury in lower limbs.

### Acute Limb Ischemia

Acute limb ischemia (ALI) is a condition that occurs due to a sudden decrease in arterial perfusion on the limbs, which could threaten the limb tissue and other organs' viability, and the onset time is less than two weeks. Several studies reported ALI incidence of approximately 1.5 cases per 10,000 persons per year. Populations at risk include smokers, people aged >50 years with diabetes mellitus, and kidney failure patients. Incidence in men compared to women is 2:1. The mortality rate from ALI ranges from 15-20% and the morbidity rate is 10-15% for bleeding, 25% for amputation, and 5-25% for fasciotomy. Comorbidities in ALI depend on the underlying etiology, namely due to embolism or due to thrombosis.<sup>1-3</sup>

Overall, the cause of ALI could be divided into emboli (38%) such as air, fat embolism, embolism due to arrhythmias and heart valve disease, thrombosis (41%) such as atherosclerosis, aortic dissection, hypercoagulable state, stent-graft (15%), external compression, iatrogenic (2%), and traumatic thrombosis (2%). In 90% of embolism cases, it's cardiogenic and most often obstructs the common femoral artery bifurcation and popliteal artery trifurcation. This occurs due to the detached thrombus in the atrium or ventricles in patients with atrial fibrillation or acute myocardial infarction. Acute leg ischemia due to thrombosis might be due to stent or graft occlusion in patients with chronic peripheral arterial disease undergoing angioplasty or peripheral artery bypass surgery.<sup>4,5</sup>

In ALI, metabolic changes occur from

aerobic to anaerobic due to ischemia, resulting in the formation of reactive oxygen species (ROS), a reactive chemical molecule that is responsible for cell damage. In ischemia-reperfusion injury (IRI) of the lower extremity, the endothelium integrity is damaged, resulting in capillary leakage which leads to interstitial edema and eventually the limb necrosis. This is followed by the release of inflammatory mediators such as Interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF), monocyte chemoattractant protein-1, and systemic complement activation, causing multi-organ dysfunction.<sup>6,7</sup>

The purpose of ALI treatment is to prevent the formation of thrombi and the aggravation of ischemia. Endovascular revascularization using catheter-directed thrombolysis, percutaneous aspiration thrombectomy, percutaneous mechanical thrombectomy, surgical therapy with thromboembolectomy, and anticoagulant medication are all used to treat acute limb ischemia. Patients who come with category I (viable ischemia) receive intervention in the form of thrombolysis within 6-24 hours. Prompt revascularization within six hours should be performed in ALI category II patients. The treatment option for ALI category IIa is less aggressive, which is through endovascular thrombolysis, while in more severe and threatening ischemia (category IIb) the treatment option is more invasive, which is thromboembolectomy surgery. In irreversible ischemia (category III) there is no indication for revascularization because the limb is no longer viable, therefore amputation is the treatment of choice.<sup>3,8,9</sup>

### Ischemic Reperfusion Injury

Ischemic reperfusion damage happens when blood supply to the tissue is interrupted for a few minutes to many hours (ischemia) and then restored (reperfusion). Complications might occur after revascularization due to life-threatening local and systemic reperfusion injuries. Local complications that occur are in the form of compartment syndrome and rhabdomyolysis. Data from 1992 to 2000 in the United States showed that approximately 5.3% of cases of ALI that were successfully revascularized required

fasciotomy due to compartment syndrome. Reperfusion in the limbs causes an increase in capillary permeability resulting in local edema and hypertension in the compartment. This obstructs the venules, capillaries, and arterioles, and if the intercompartmental pressure exceeds 30 mm Hg, muscle and nerve necrosis might occur. Muscle necrosis that occurs leads to rhabdomyolysis, which is characterized by myoglobinuria. Myoglobin excreted through the kidneys triggers lipid peroxidation and renal vasoconstriction, resulting in tubular necrosis.<sup>9</sup>

Ischemic reperfusion injury in ALI could affect distant organs, causing systemic damage. It also contributes as a factor that increases morbidity and mortality due to multiple organ dysfunction syndromes (MODS). Distant organs that could be affected are lung tissue, heart, kidneys, gastrointestinal tract, and central nervous system. Myocardial dysfunction that occurs is reversible, although in some cases inotropic or mechanical support is required. Arrhythmias after reperfusion are caused by rapid changes in ion concentrations in previously ischemic tissues. In the central nervous system, there is damage to the blood-brain barrier, resulting in leukocyte migration that produces ROS and damages brain tissue. These events manifest as sensory, motor, or cognitive impairment, or even death. Translocation of intestinal bacteria into the systemic circulation occurs due to increased intestinal permeability caused by the activation of cytokines.<sup>10</sup>

The final effect of reperfusion injury is MODS. The mortality rate in the intensive care unit correlates with the number of injured organs, where the mortality is 30-40% if it affects 1 organ, 50-60% if 2 organs are affected, and 80-100% if more than 3 organs fail.<sup>5,11</sup>

### Lung Tissue Damage Due to Ischemia-Reperfusion Injury

Lung tissue is the most commonly affected organ, where lung tissue injury could rapidly progress to respiratory failure. Lung tissue is an organ that is susceptible to damage due to neutrophil activation by ROS and metabolites produced by IRI, which in turn causes a fatal effect in the form of acute respiratory distress

syndrome (ARDS). The mechanism underlying the occurrence of lung tissue damage due to IRI is very complex and related to the role of polymorphonuclear (PMN) cells. In lung tissue, leukocyte infiltration, damage to the lung capillary barrier, pulmonary epithelial cell edema, and apoptosis occur.<sup>11</sup>

During the ischemia period, metabolites of inflammatory mediators are formed, such as Leukotriene B4 (LTB4), Thromboxane 2 (TXA2), and complement C5, which then activate neutrophils. When reperfusion occurs, these neutrophils accumulate in the pulmonary circulation, causing edema and damage to lung tissue. Several proinflammatory cytokines produced during IRI, particularly TNF- $\alpha$  and IL-1, also mediate lung tissue damage. TXA2 causes pulmonary vasoconstriction resulting in increased neutrophil and endothelial interactions. During the ischemia-reperfusion period, IL-8 produced by alveolar macrophages and lung tissue endothelial cells also plays a role in neutrophil activation in lung tissue.<sup>5,11</sup>

Damages to lung tissue are in the form of edema, alveoli congestion, bleeding, infiltration or aggregation of neutrophils in the alveoli or blood vessel walls, and thickening of the alveoli walls or locations with hyaline membranes. Lung tissue damage due to ischemia-reperfusion injury into 4 grades as follows:

- Grade 1 (normal): normal lung tissue parenchyma
- Grade 2 (mild): focal edema of a small amount of alveolar septum, mild congestion, less than 50 neutrophils in the alveolar septum per large visual field.
- Grade 3 (moderate): moderate edema of the alveolar septum or mild edema of multiple septums, moderate congestion, neutrophils in the alveolar septum 50 – 100 per large visual field.
- Grade 4 (severe): severe edema of the alveolar septum or mild edema of multiple septums, moderate congestion, neutrophils in the alveolar septum more than 100 per large visual field (5).

### Treatment of Ischemia-Reperfusion Injury (IRI)

The formation of ROS is one of the events that play an important role in IRI occurrence, therefore the objective of the given therapy is to reduce oxidative stress. Many therapeutic strategies to prevent or limit organ damage due to IRI have been conducted and have given good clinical results in humans, although several strategies are still under research that has not yet reached a clinical trial stage in humans. The treatment strategy could be in the form of surgical intervention such as ischemic preconditioning or pharmacological therapy for example with Aspirin-Triggered Lipoxin (ATL) analogs, anti-complements, and anti-cytokines, endothelin receptor antagonists, Leukotriene-B4 antagonists, or antioxidants such as vitamin E, vitamin C, allopurinol. However, reperfusion of ischemic tissue is still the therapy choice for preventing IRI in clinical practice.<sup>6,9</sup>

The ischemic preconditioning method is carried out by giving ischemia exposure for a short period, where this method could protect the tissue from the harmful effects of prolonged ischemia-reperfusion. Although the positive effects of this method have been demonstrated in many experimental animals, clinical data in humans are limited. Currently, the protective effects shown by this method are the restoration of cardiac contractility after coronary artery bypass surgery and reduction of liver injury in patients undergoing liver resection.<sup>7</sup>

The hypothermic strategy is intended to increase tissue tolerance to ischemia. Tissue hypothermia has been experimentally shown to decrease the inflammatory response and oxidative stress due to CIR.<sup>11</sup>

Pharmacological therapy that could be given is anti-complement, anti-leukocyte, and antioxidant. An experiment in rats that were given a C3 convertase inhibitor showed a reduction in myocardial infarction size by 44%. In addition, the administration of single-chain C5-specific antibodies in patients undergoing coronary artery bypass surgery has shown a significant reduction in complement and

leukocyte activation, myocardial injury, and cognitive dysfunction.<sup>6,12</sup>

Antileukocyte therapy is one of the therapies to reduce damage due to leukocyte activation during IRI. Its mechanism of action is to block the release of inflammatory mediators or endothelium and leukocyte attachment. The release of inflammatory mediators could be inhibited using IL-1 receptor antagonists, anti-TNF- antibodies, or platelet activation factor-LTB4 antagonists. One study showed that aspirin might induce lipoxin biosynthesis, a lipoxygenase product derived from arachidonic acid, thereby preventing neutrophil chemotaxis and transmigration. Administration of an aspirin-triggered lipoxin analog could prevent changes in vascular permeability and other organ damage mediated by neutrophils in rats subjected to limb IRI. Although this anti-leukocyte strategy has received limited clinical attention, it is effective in experimental animals with IRI.<sup>9,13,14</sup>

Administration of allopurinol, which aims to protect tissue from IRI, has been studied both in experimental animals and in humans. Administration of allopurinol reduces serum TNF-  $\alpha$  concentrations in IRI thereby reducing inflammation caused by IRI.<sup>13,15</sup>

A large number of animal studies have shown the success of therapies that act as antioxidants such as superoxide dismutase (SOD) enzymes, catalase enzymes, GPx enzymes, vitamin E, vitamin C, and  $\beta$ -carotene to reduce IRI damage by scavenging free radicals formed. The role of oxidative stress in IRI which is supported by clinical and experimental data makes antioxidant therapy very important as a defense mechanism to protect tissues.<sup>6,7,16,17</sup>

Pentoxifylline is a methylxanthine derivative with several hemorheological properties. Administration of pentoxifylline reduces ischemia-reperfusion injury due to skeletal muscle ischemia, as well as post-transplant lung and liver injury. It has various mechanisms of action, both at the molecular or cellular level, through inhibiting leukocyte interaction with endothelium.



Pentoxifylline could enhance neutrophils' chemotaxis response and also inhibit phagocytosis and superoxide production by neutrophils and monocytes. Pentoxifylline in particular inhibits neutrophil adhesion to the endothelium and prevents leukocyte degranulation. Inhibition of neutrophil adhesion in lung tissue will reduce damage to endothelial and epithelial cells in the lung parenchyma which might lead to pulmonary edema and impaired gas diffusion. Pentoxifylline has a beneficial effect in patients with ischemic reperfusion injury to the lung. This potential local effect is important for acute lung injury manifestation by inflammatory mediator's activation that circulates through the blood, lymph, and free radicals. Research by the University of Tehran showed that the administration of 40 mg/kg of pentoxifylline dissolved in 0.9% normal saline to 2 ml affected reducing the inflammatory index in ischemic reperfusion injury. Pentoxifylline should be administered after the ischemia period to reduce inflammatory mediators and free radical release.<sup>9,18,19</sup>

Vitamin C serves as an antioxidant by lowering the impact of ROS-free radicals. Several studies have indicated that antioxidant vitamins, particularly ascorbic acid, have a cytoprotective impact by reducing free radicals. Lehr et al. demonstrated that vitamin C protects the microvascular endothelium against neutrophil adhesion, implying that vitamin C might preserve the microvascular circulation. Furthermore, Herbaczynska-Cedro et al.<sup>6</sup> discovered that vitamin C inhibits the generation of oxygen free radicals in human circulating neutrophils. According to them, the effect of vitamin C on lipid peroxidation augmentation induced by IRI depended on the dosage (range 30-100 mg/kg bb).<sup>7,15,20</sup>

## CONCLUSION

Acute limb ischemia causes decreased blood flow to the lower limbs. Decreased blood flow results in hypoxia or anoxia of the tissues and stasis of the microcirculation. Reperfusion is done so that blood flow can immediately return to the tissues, which is very important to prevent permanent cell

injury. Reperfusion restores blood flow in the lower limbs, but is also accompanied by the release of inflammatory mediators (IL-1,6; TNF- $\alpha$ , Complomen C5, LTB<sub>4</sub>, TXA<sub>2</sub>) to the systemic which will trigger vascular dysfunction and ROS release. Vascular dysfunction and the release of ROS due to reperfusion injury will cause reperfusion injury to distant organs, namely lungs, kidneys, liver, heart.

The release of inflammatory mediators and neutrophil PMN activation which will activate ROS will accumulate in the pulmonary circulation, causing edema and lung damage. Lung tissue is an organ that is susceptible to damage due to neutrophil activation by ROS and metabolites produced by ischemic reperfusion injury, which in turn causes a fatal effect in the form of acute respiratory distress syndrome (ARDS). The mechanism underlying the occurrence of lung tissue damage due to CIR is very complex and this is related to the role of polymorphonuclear cells (PMN). In the lung tissue, leukocyte infiltration occurs, damage to the lung capillary barrier, pulmonary epithelial cell edema and apoptosis. Damage that occurs in lung tissue in the form of edema and/or infiltration or aggregation of neutrophils in the alveoli of the lung tissue. Based on the literature, it is explained that the administration of combination therapy with vitamin C and pentoxifylline is expected to reduce lung tissue damage due to acute lower limb ischemia reperfusion injury. Vitamin C serves as an antioxidant by lowering the impact of ROS-free radicals and Pentoxifylline in particular inhibits neutrophil adhesion to the endothelium and prevents leukocyte degranulation. Inhibition of neutrophil adhesion in lung tissue will reduce damage to endothelial and epithelial cells in the lung parenchyma.

## CONFLICT OF INTEREST

The author declares there is no conflict of interest regarding publication of current review.

## ETHICAL CONSIDERATION

Ethical clearance is not mandatory for review article.

## AUTHOR CONTRIBUTION

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