Vol. 9 No. B (2021): B - Clinical Sciences



Published: 2020-12-26

Pharmacology

Controlled Clinical Trial Effect of Noni Fruit Extract (Morinda citrifolia) Toward Overactive Bladder Women through Observation of High-Sensitivity C-reactive Protein in Urine Levels

Edy Ardiansyah, M. F. G. Siregar, R. A. Ganie, I. B. utra (Author)

706-710

PDF

Gastroenterohepatology

The Potential of Vitamin D3 to Repaired Mucosal Injury in Dextran Sulfate Sodium Induced Acute Colitis in Mice

Satrio Wibowo, Krisni Subandiyah, Kusworini Handono, Sri Poeranto (Author) 931-936

PDF

Anorectal Manometry on Children: A Moroccan Series and Literature Review

HANANE DELSA, Ilham Serraj, Mohamed Khalis, Nawal Kabbaj (Author) 337-343

PDF

Mesenteric Vessel Thrombosis Treatment Experience

Vladimir Beloborodov, Vladimir Vorobev, Svetlana Sokolova, Aleksandr Frolov, Denis Kornilov, Ludmila Sorokina, Igor Golub (Author)

PDF

Increase Serum Tumor Necrosis Factor Alpha decreased Serum Cholesterol Level, but not Albumin, in Hemodialysis Patients with Non-Fibrotic Hepatitis C Infection

Rudi Supriyadi, Nenny Agustanti, Marcella Adisuhanto (Author) 614-619

PDF

The Effect of Uncaria gambir Roxb. Extract on Superoxide Dismutase Activity in Proteinuric Wistar Rats Model

Rosmayanti Syafriani Siregar, Aznan Lelo, Delyuzar Harris, Oke Rina Ramayani, Muhammad Ichwan (Author) 1505-1509

PDF

The Relationship between Serum Sclerostin Levels and Bone Mineral Disorders and Vascular Calcification in Hemodialysis Patients

Emad Abdallah, Nevine Sherif, Osama Mosbah, Amna Metwally (Author); Ibrahim Abd ElAzim; Ola Mahmoud, Mohamed Farouk, Samah Mamdouh, Samya El-Shishtawy, Asmaa Mohamed (Author) 1664-1671

PDF

Interleukin-31 Serum And Pruritus Dimension After Acupuncture Treatment In Hemodialysis Patients: A Randomized Clinical Trial

Dedi Ardinata, Rozaimah Zain-Hamid, Irma. D. Roesyanto-Mahadi, Hasan Mihardja (Author) 196-201

PDF

The Effect of Bariatric Surgery versus Intensive Medical Care on Prevention of Microalbuminuria in Patients with Type 2 Diabetes: 3 Year Experience of a Prospective Study

Amin Soliman; Haythum Soliman, Mervat Naguib (Author) 202-207

202-207

PDF

The Correlation between Estimated Glomerular Filtration Rate and Parathyroid Hormone Levels in Predialysis-chronic Kidney Disease Adult Patients at Sanglah General Hospital, Bali, Indonesia

1098-1104

PDF

The Role of Endoscopic Retrograde Cholangiopancreatography in the Management of Biliary Complication Post-Laparoscopic Cholecystectomy

Mohamed Abdzaid Akool, Samer Makki Mohamed Al-Hakkak, Alaa Abood Al-Wadees (Author) 313-317

PDF

Bismuth Classification of Bile Duct Injury and Its Association with Increasing 30 Days Mortality after Revision Surgery

Budhi Ida Bagus, Metria Ida Bagus, Setyawati Ida Ayu (Author)

272-275

PDF

Vascular Endothelial Growth Factor Levels Difference among Hepatocellular Cancer Patients Based on Barcelona Clinic Liver Cancer Staging

Darmadi Darmadi, Riska Habriel Ruslie, Cennikon Pakpahan (Author)

797-80

PDF

The Difference of Hypoxic Inducible Factor-1 α , Vascular Endothelial Growth Factor, and Transforming Growth Factor- β 1 Based on Liver Fibrosis Severity in Patients with Chronic Henatitis B

Libya Husen, Gontar Alamsyah Siregar, Masrul Lubis (Author)

PDF

Nephrology

Spectrum of Complications of Patients with Chronic Kidney Disease on Maintenance Continuous Ambulatory Peritoneal Dialysis: An Experience of Tertiary Nephrology Center in Naiaf City-Iraq

Evan Noori, Rawaa Hadi, Yasir Sharba , Zahraa Fathi Sharba (Author) 1529-1534

Sianny Herawati, Yenny Kandarini, I Putu Yuda Prabawa (Author)

PDF

Health-Related Quality of Life Difference between Early Diagnosed and Finished Therapy of Nephrotic Syndrome in Children

Riska Habriel Ruslie, Darmadi Darmadi, Cennikon Pakpahan (Author) 801-805

PDF

Midkine as an Early Biomarker of Contrast-induced Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome: A Single-center Prospective Study

Mohamed Ahmed, Gamal Hamed Ibrahim, Mahmoud Adel, Amira Ismail, Abdallah Almaghraby, Mahmoud Abdelnabi (Author)

983-989

PDF

The Relationship between Nutritional Status and Latent Tuberculosis in Routine Hemodialysis

Ria Bandiara, Lilik Sukesi, Astried Indrasari, Iceu Dimas Kulsum, Mohammad Rudiansyah (Author) 945-951

PDF

Predominant Factors Affecting Sexual Dysfunction on Patients with Continuous Ambulatory Peritoneal Dialysis

Yuswinda Kusumawardhani, Krisna Yetti, I Made Kariasa (Author) 373-377

PDF

Serum Level of Uromodulin as an Early Predictor Marker of Kidney Disorders

Salwa Mostafa El-Shebini, Hend A. Essa, Maha I. A. Moaty, Nihad H. Ahmed, Ahmed M. S. Hussein, Magda S. Mohamed, Salwa T. Tapozada (Author)

Cardiology

The Risk Factors of Coronary Heart Disease and its Relationship with Endothelial Nitric Oxide Synthase

Eka Fithra Elfi, Eva Decroli, Ellyza Nasrul, Yanwirasti Yanwirasti, Eryati Darwin (Author) 451-456



Knowledge and Application of Cardiovascular Disease Prevention Guidelines among Family Physicians: A Cross-sectional Study

Oleksii Korzh, Yevgenii Nikolenko, Anna Titkova, Yelizaveta Lavrova, Kira Vovk (Author)



The Role of Neutrophil Lymphocyte Ratio as a Major Adverse Cardiac Events Predictor and Its Correlation with Coronary Severity in Acute Coronary Syndrome Patients with Chronic Kidney Disease: A Case Control and Cross-Sectional Study

Suzanna Immanuel, Eka Ginanjar, Fahrani Imanina Putri Nurtyas, Ninik Sukartini, Yusra Yusra, Merci Monica B. R. Pasaribu (Author)

1758-1763

PDF

Lipid Accumulation Product as an Index for Visceral Obesity and Cardiovascular Risk among a Sample of Obese Egyptian Women

Nayera E. Hassan, Sahar A. El-Masry, Gamila S. M. El-Saeed, Mohamed S. El Hussieny (Author) 1229-1236

PDF

Primary Percutaneous Coronary Intervention in the Left Main ST-Elevation Myocardial Infarction and Cardiogenic Shock on Octogenarian Patient with Single Remaining Vessel

Mochamad Yusuf Alsagaff, Kandita Arjani, Yudi Oktaviono, Sondang Sitorus (Author) 363-366

PDF

Left Atrial Appendage Function Assessment by Tissue Doppler Transesophageal Echocardiography in Acute Ischemic Stroke Patients

One-year Outcome of Different Unprotected Left Main Percutaneous Coronary Interventions Techniques in Acute Coronary Syndromes

Amr El-Hadidy, Mohamed Ali, Mahmoud Adel Gawish, Ayman Moharram, Khaled Taema (Author) 878-884

PDF

Implantable Cardiac Device Infections Prevalence: Diagnostic and Therapeutic Implications

Hend Yahia, Abdo Alazab, Randa Aly, Sameh Elmaraghi, Ashraf Andraos (Author) 909-916

PDF

The The Correlation between Serum Amyloid A, Mean Platelet Volume, and Creatine Kinase Myocardial B in Acute Coronary Syndrome

Syaiful Anwar, Purwanto Adhipireno, Ria Triwardhani, Edward Kurnia Setiawan Limijadi (Author) 286-289

PDF

NT pro- B-type Natriuretic Peptide in the Small Ventricular Septal Defect in Children

Rahmat Budi Kuswiyanto, Putria Apandi, Dany Hilmanto, Muhammad Hasan Bashari, Sri Endah Rahayuningsih (Author)

1677-1680

PDF

Association between Coronary Artery Disease and Left Ventricle Remodeling Parameters in Hypertensive Patients: A Cross-Sectional Study in a Limited Resource Setting

Badai Tiksnadi, Erwan Martanto, Abednego Panggabean, Ary Indriana Savitri, Alberta Claudia Undarsa (Author)

1364-1369

PDF

Comparison of 24 h ECG Holter Monitoring with Real-time Long-term ECG Monitoring System using ECGalert Software and Savvy Single-Lead Patch

Lidija Poposka, Marija Vavlukis, Hristo Pejkov, Marjan Gusev (Author) 12-17

PDF

Tamer Abdel Mawla, Osama Momtaz, Mohamed Abdel Gayed, Gomaa Abdelrazek (Author) 858-864

PDF

Survival and Prognostic Factors After Carotid Artery Stenting in Patients with Concomitant Coronary Disease

Georgi Goranov, Maria Tokmakova, Petar Nikolov (Author) 1470-1479

PDF

Cardiovascular Diseases Healthy Diet Related Knowledge among a Sample of the General Population in Egypt

Marwa M. Zein, Ahmed Taher Mahmoud, Ahmed Sallam El Hawary, Nelly Hegazy (Author) 1764-1771

PDF

The Outcomes of Transcatheter Closure in Patients with Patent Ductus Arteriosus at Haji Adam Malik General Hospital, Indonesia

Putri Amelia, Rizky Adriansyah, Bastian Lubis, Muhammad Akil (Author) 208-211

DDE

PDF

Introduction of Cardiac Magnetic Resonance Imaging in Kosovo: First Fifty Consecutive Patients Registry Report

Ted Trajcheski, Lulzim Brovina, Biljana Zafirova, Lada Trajceska (Author)

417-425

PDF

Admissions and In-hospital Outcomes of Acute Coronary Syndromes during Corona Virus Disease 19 Pandemic in Albania

Leonard Simoni, Ilir Alimehmeti, Astrit Ceka, Ermir Tafaj, Mirald Gina, Alban Dibra, Artan Goda (Author) 593-599

PDF

Comparative Preliminary Analysis of Umbilical Cord Blood-, Healthy Adult Peripheral Blood- and Myocardial Infarct Peripheral Blood-Derived Endothelial Progenitor Cells

Wireni Ayuningtyas, Rachmawati Noverina, Dedy Kurniawan, Astrid F. Khairani, Nur Atik, Firman F. Wirakusumah, Ahmad Faried (Author)

85-90

PDF

Neurological Sequelae Following Pediatric Cardiac Interventions

Hala Mounir Agha, Mai Mahmoud Hussien, Marian Y Girgis, Omneya Gamal Eldin Afify, Mervat Ahmed Haroun (Author)

137-143

PDF

Myocardial Perfusion Grade by Coronary Angiography can Predict Final Infarct Size and Left Ventricular Function in Patients with ST-elevation Myocardial Infarction Treated with a Pharmaco-invasive Strategy

Amal Hafez Ahmed, Amr El-Hadidy, Mohamed Helmy, Ashraf Hussein, Abdalla Elagha (Author) 184-190

PDF

Pulmonology

Cardiovascular Risk in Patients with COPD: Cardiovascular Comorbidities in Patients with COPD Increase CAT and mMRC Dyspnea Scores

Jagoda Stojkovic, Emilija Antova, Dragana Stojkovikj (Author)

PDF

The Diagnostic Value of Urinary Secretory Antigen Target of 6 kDa in Childhood Pulmonary

Agustin Iskandar, Ella Melissa Lawanto, Maimun Zulhaidah, Ery Olivianto, Kusworini Handono, Muhammad Anshory, Andrea Aprilia, Aryati Aryati (Author) 841-846

Comparing the Asthma Control and Anti-inflammatory Effects of Different Fixed Combinations of Inhaled Corticosteroids Plus Long-acting Beta 2 Agonist; A Randomized Clinical Trial

Ashraf Elsayed Sileem, Ahmed Ali, Hanan Elnahas, Ahmed M. Gouda (Author)

PDF

Diaphragmatic Function Assessed by Bed Side Ultrasonography in Patients with Sepsis or Septic Shock Admitted to Intensive Care Unit

Amal Zaki, Helmy Hassan El Ghawaby, Mostafa Mahmoud Mohammed Gad, Amira Mohamed Ismail, Amr Shafiq Nawar (Author)

1417-1423

PDF

Associated Factors of the Results of Pulmonary Tuberculosis Treatment During the COVID-19 Pandemic in Makassar City

Syahridha Syahridha, Nasrum Massi, Ahyar Ahmad, Irawaty Djaharuddin (Author) 1001-1005

PDF

Does Neurally Adjusted Ventilatory Assist Compared to Pressure Support Ventilation Decrease Patient Ventilator Asynchrony?

Hussam Abd Elfatah Mohamed, Mohamed Amin Fakher, Moamen Arafa, Khaled Abd Wahab Selem, Alia Abd El Fatah (Author)

96-100

PDF

Assessment of Lung Parenchyma Recovery after Antibiotic Administration using Lung Ultrasound in Critically III Patients with Pneumonia

Mai Adel Sahbal, Mohammed Omar Alghoneimy, Sally Salah Eldin, Amr Elsayed Elhadidy, Mahmoud Muhammad Kenawy (Author)

480-485

PDF

Neurology

PDF

Recent Advances in the Treatment of Gliomas: The Multimodal Care Therapy

Omar Ibrahim, Mohamed A. Hafez, Helmy Abdel Haleem, Hussein El Maghraby (Author) 503-508

PDF

Psychiatry

Levels of Interleukin 6 as a Predictor of Metabolic Syndrome in Schizophrenic Patients Receiving Combination Therapy of Typical and Atypical Antipsychotics

Syamsuddin Saidah, Lisal T. Sonny, Haryani Lilik, Bahar Burhanuddin, Rasyid Haerani, Thioritz Wempy (Author)

600-607

PDF

Factors Correlating with the Emotional and Behavioral Problems among Adolescents with Legal Problems

Sri Hartini, Yuniske Penyami, Yayi Prabandari (Author) 1061-1065

PDF

Psychometric Properties of Iranian Version of Emotional Processing Scale

Shirali Kharamin, Ali Asghar Shokraeezadeh, Yasaman Ghafaryan Shirazi, Mohammad Malekzadeh (Author) 217-224

PDF

The Association between Smartphone Addiction and Insomnia Incidence in Students of the Faculty of Medicine Udayana University Batch of 2020 during the Coronavirus Disease-19 Pandemic

Anak Agung Bagus Putra Indrakusuma, I. Made Angga Sayoga, Stevanus Christian Surya, Agung Wiwiek Indrayani, I Gusti Ayu Artini (Author)

1207-1214

PDF

Characteristics of Guillain-Barre Syndrome Patient Underwent Hyperbaric Oxygen Therapy at Lakesla 2016–2019

Ni Komang Sri Dewi Untari, Kurnia Kusumastuti, Guritno Suryokusumo, I Ketut Sudiana (Author)

PDF

Negative Correlation between Serum Brain-derived Neurotrophic Factor Levels and Obesity Predictor Markers and Inflammation Levels in Females with Obesity

Slamet Raharjo, Adi Pranoto, Purwo Sri Rejeki, Ahmad Syahru Mubarok Harisman, Yualita Putri Pamungkas, Olivia Andiana (Author)

1021-1026

PDF

Association of Vitamin D Level and Nerve Conduction Study Parameters with Cognitive Function in Diabetic Neuropathy Patients

Aida Fithrie, Fasihah Irfani Fitri, Muhammad Reza Putra (Author)

72-78

PDF

Integrated Clinical Pathways: Communication and Participation in a Multidisciplinary Team

Mateja Šimec, Sabina Krsnik, Karmen Erjavec (Author)

1549-15

PDF

Online Health Survey on Epileptic Children during Coronavirus Disease-2019 Pandemic

Ashraf Azmy, Eman Mones Abushady, Mones M. Abu Shady (Author) 392-397

PDF

Adolescents with Internet Gaming Disorder are more likely to have Lower Score of Cognitive Function: A Cross-sectional Study among Junior High School Students in Yogyakarta,

Indarwati Setyaningsih, Agus Budi Bowo Leksono, Paryono Muhrodji, Abdullah Syafiq Edyanto, Amelia Nur Vidyanti (Author)

1111-1116

Menopause Anxiety and Depression; How Food Can Help?

Suzanne Fouad, Salwa M. El Shebini, Maha Abdel-Moaty, Nihad Hassan Ahmed, Ahmed Mohamed Saied Hussein, Hend Abbas Essa, Salwa T. Tapozada (Author)

64-71

PDF

Correlation between Interleukin-6 Levels and Total PANSS Scores in Batak People with Schizophrenia

Suniaty Dapotria Lumbantoruan, Elmeida Effendy, Mustafa M. Amin (Author) 107-111

PDF

Endocrinology

Concordance between Triglyceride Glucose Index and Admission Insulin Resistance Index in Non-diabetic Subjects of Acute Coronary Syndrome

Andi Irham, Husaini Umar, Fabiola Maureen Shinta Adam, Idar Mappangara, Syakib Bakri, Risna Halim, Alfian Zainuddin (Author)

1044-1047

PDF

Influence of Ramadan Fasting on Hemoglobin A1C, Lipid Profile, and Body Mass Index among Type 2 Diabetic Patients in Najran City, Saudi Arabia

Hatem Mohamed, Anass M. Abbas, Mohammed Ayed Huneif, Seham M. Alqahtani, Awad Mohamed Ahmed, Asaad M. A. Babker, Ehab A. M. Elagab, Parvez I. Haris (Author) 318-325

PDF

Association of Plasminogen Activator Inhibitor-1 and Cardiovascular Events Development in

Yelena Laryushina, Viktoriya Parakhina, Lyudmila Turgunova, Dinara Sheryazdanova, Raushan Dosmagambetova, Anar Turmukhambetova, Olga Ponamareva, Maria Orbetzova (Author) 726-733

The Effect of Soy Milk on Mounting Latency, Mounting Frequency, and Reproductive Development in Male Wistar Rats (Rattus Norvegicus)

Nurdiana Nurdiana, Pradnyawati Chania, Rifzi Nurvitasari, Azmiatun Nisa, Styan Wahyu Diana, Evalina Izzatur Rochmah, Elly Mayangsari, Bambang Rahardjo, Wayan Indrawan, Husnul Khotimah, Karyono Mintaroem, Dicky Faizal Irnandi (Author)

670-678

PDF

Serum Vitamin D Levels and Risk Factors for Cardiovascular Complication in Diabetes

Rina Amelia, Juliandi Harahap, Hendri Wijaya, Sry Suryani Widjaja, Isti Ilmiati Fujiati, Rusdiana Rusdiana (Author)

1394-1397

PDF

The Role Vascular Endothelial Growth Factor, Control Glycemic, Lipid Profile, and Hypoxiainducible Factor 1-Alpha at Type 2 Diabetic Patients in North Sumatera, Indonesia

Rusdiana Rusdiana, Sry Suryani Widjaja, Rina Amelia, Siti Syarifah, Rusmalawati Rusmalawati (Author) 1215-1218

PDF

The Prevalence of Signs of Thyroid Pathology among Students of the Karaganda Medical University According to the Survey

Bekov Yernur Kasipovich, Omarbekova Nazgul Kakenovna, Akhmetova Mensulu Kanatovna, Pozdnyakova Yelena Vladimirovna, Moldabayeva Altyn Kabdollovna, Umirbaeva Assel Iltaevna, Alibieva Dinara Toleutayevna, Alyiev Ondassyn Minbaevich, Batyrbekova Lyazat Sarsenbaevna (Author) 1329-1332

PDF

Non-alcoholic Fatty Liver and Vitamin D Levels in Extremely Obese Individuals: A Case-Control Study

Mohamed Sayed, Ebthal Mahmoud Abozeid, Hoda M. Amin, Naglaa M. Elsayed, Yasser H. Nassar, Hend A. Elsheimy (Author)

541-546

PDF

The Clinical Course of Rheumatoid Arthritis in Kazakhstani Patients

Argul Issilbayeva, Assel Meiramova, Almagul R. Kushugulova, Zhanar B. Akhmetova, Damir Biktashev, Baglan B. Abdakhina, Aliya T. Aituganova, Yekaterina Zueva, Karina Karlygash, Professor Bayan Alkenovna (Author)

1352-1358

PDF

Metabolic Syndrome as a Factor Affecting on Intima-Media Thickness in Patients with

Lyudmila Gennadievna Turgunova, Anna Andreevna Shalygina, Lyazat Kataevna Ibrayeva, Ana Akylbecovna Turmuhambetova (Author) 411-416

PDF

Sexual Dysfunction and its Determinants in Male Patients with Rheumatoid Arthritis

Hassan O. Ghareeb, Ghada M. Khafagy, Hatem H. Eleishi, Hala A. Hussein, Marwa D. Hasan (Author) 350-355

PDF

Hematology

Effects of the FOXO3a rs 4946936 Gene Polymorphism on the FOXO3a Transcription Factor in Chronic Granulocytic Leukemia Patients

Shinta Oktya Wardhani, Hani Susianti, Pudji Rahayu, Yuyun Prabowowati Yueniwati (Author) 1156-1159

PDF

Blast Cells Count Influences Bleeding Incidence in Acute Leukemia: Preliminary Study in South Kalimantan, Indonesia

Edward Kurnia Setiawan Limijadi, Qintani Cantika Ismail, Dwi Retnoningrum, Wivina Riza Devi, Anugrah Riansari (Author)

900-902

PDF

Evaluation of Anemia in the Residents of Tambaklorok Exposed to Plumbum

Infants of Hypothyroid Mothers at Risk of Developing Hypothyroidism: A Cross-sectional Study in Qassim Region of Saudi Arabia

Mariam S. Alharbi (Author)

1398-1404

PDF

Comparison of 3 Medicine Groups Used to Control Glycemic and Glycated Hemoglobin Levels in Newly Diagnosed Type 2 Diabetes Patients

Ngoc Chau Nguyen, Hoai Thuong Pham, Diep Thao Pham, Thi Minh Hoang, Thi Phuong Lan Dam, Thi Hang Ho, Duy Quy Dang, Nhu Binh Do, Quang Thuan Huynh (Author)

PDF

Impact of Nutritional Intervention on Serum Level of Interferon Gamma and Insulin Resistance in Obese Women: Considerations during the COVID-19 Crisis

Hend A. Essa, Salwa M. El Shebini , Maha I. M. Moaty , Nihad H. Ahmed , Magda S. Mohamed , Salwa Tawfik Tapozada (Author)

176-18

PDF

Rheumatology

Frequency of Fibromyalgia in a Sample of Iraqi Patients in Mosul with Ischemic Heart Disease

Ali Younis, Mohammad Harith Alsaaty (Author)

1672-1676

PDF

Epidemiological Trends of Rheumatoid Arthritis and PADI4, PTPN22, and HLA-DRB9 Genes Distribution in the Kazakhstan Population

Argul Issilbayeva, Almagul Kushugulova, Assel Meiramova, Samat Kozhakhmetov, Zhanar Akhmetova, Madiyar Nurgaziyev, Laura Chulenbayeva, Dmitriy Babenko, Jeannette Kunz, Professor Bayan Alkenovna (Author)

747-757

PDF

Budi Santosa (Author)

831-835

PDF

the The Correlation between Pituitary Gonadotrophins, Gonadal Sex Steroid Hormone with Ferritin Level in Pubertal Females with Thalassemia Major at Wassit Province - Iraq 2020

Ahmed Ansaf , Safaa A. Faraj, Safaa Kazem (Author)

806-810

PDF

Ecto-5'nucleotidase (CD73) May Predict Occurrence and Grade of GVHD in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Rasha I. Ibrahim, Maha El- Zimaity, Nevine N. Moustafa, Mohamed Hamdi Attia, Walaa A. Elsalakawy, Rana Z. Abass (Author)

154-160

PDF

High STAT5A Expression is Associated with Major Molecular Response Achievement Failure of Chronic Phase Chronic Myeloid Leukemia Patients Receiving Hydroxyurea before Imatinib: A Cross-sectional Study

Ikhwan Rinaldi, Anastasia Putri, Melva Louisa, Sukamto Koesnoe (Author) 1160-1167

PDF

Efficacy and Safety of Convalescent Plasma Transfusion Administered as Adjunctive Treatment to Standard Treatment in Moderate, Severe, and/or Critically III Patients with COVID-19 in Dr. M. Djamil General Hospital

Irza Wahid, Eifel Faheri, Eka Putra Andani, Fauzar Fauzar, Dia Rofinda Zelly, Widyarman Widyarman, Irvan Medison, Emilzon Taslim, Tuti Handayani (Author)
1489-1493

PDF

Coagulopathy of Coronavirus Disease 2019: A Case Series

Jonathan Arifputra, Harlinda Haroen, Linda Wilhelma Ancella Rotty, Pearla Fidei Cindy Lasut, Cecilia Hendratta (Author)

301-307



Evaluation of the Thyroid Status and Types of Thyroid Dysfunction in Beta-Thalassemia Major Patients More Than 9 Years of Age in Wassit, Iraq 2020

Ahmed I. I. Ansaf , Safa Faraj, Hussien A. Abdul-Azziz (Author) 1405-1409



The Levels of FoxO3a Predict the Failure of Imatinib Mesylate Therapy among Chronic Myeloid Leukemia Patients

Shinta Oktya Wardhani, Hani Susanti, Puji Rahayu, Yuyun Yueniwati, Jonny Fajar (Author) 255-259



Hematologic Autoimmune Manifestation Secondary to Coronavirus Disease 19 Infection – A Single-Center Experience

Sanja Trajkova, Simona Stojanovska, Nevenka Ridova, Svetlana Krstevska-Balkanov, Aleksandra Pivkova-Veljanovska, Lidija Cevreska, Marija Popova-Labacevska, Irina Panovska-Stavridis (Author) 940-944



Oncology

Wnt Signaling and Cadherin Expressions in Different Staging of Colorectal Cancer as Biomarkers for Metastasis: Study of SW480, COLO 320DM, and HCT116 Cellines

Luminturahardjo Winarko, Pudji Rahajoe, Djoko Soeatmadji, Karyono Mintaroem (Author) 763-770



Analysis of Complications Development Predictors after Radical Prostatectomy

Vladimir Vorobev, Vladimir Beloborodov, Vladimir Luchkevich, Dmitriy Shmakov, Olga Baklanova, Stepan Sidorov, Bator Sharakshinov (Author)

1575-1579

PDF

Winarko Winarko, Pudji Rahayu, Djoko Soeatmadji, Karyono Mintaroem (Author) 651-658

PDF

Innovative Non-Irradiating and Non-Invasive Per Fraction Control System in Radiotherapy: Surface-Guided Radiation Therapy Experience of Casablanca Cancer Center

Asmaa Naim, Safae Mansouri, Kamal Saidi, Redouane ELBaydaoui, Mohamed Reda Mesradi (Author) 826-830



Citrus sinensis (L) Peels Extract Inhibits Metastasis of Breast Cancer Cells by Targeting the Downregulation Matrix Metalloproteinases-9

Meiny Suzery, Bambang Cahyono, Nur Dina Amalina (Author) 464-469



The Evaluation of Methylated Septin 9 in Blood Plasma and Tissue Biopsies for the Early Detection for Asymptomatic Colon Cancer

Ahmed Ageeb Kassid, Omar F. Abdul-Rasheed, Nawal Mehdi AlKhalidy (Author) 1462-1469



Determination of Significant Pretreatment Factors that Predict Survival in Indonesian Subjects with Breast Cancer

Citra Aryanti, Putu Anda Tusta Adiputra, Tjokorda GB Mahadewa, Sri Maliawan, I. N. W. Steven Christian, Ida Bagus Made Suryawisesa (Author)

1458-1461



Serum Vitamin Levels among Iraqi Cancer Patients Receiving Chemotherapy

Mohammed Salim Abdulrahman, Hedef D. El-Yassin, Nada. A. S. Al-Alwan (Author) 231-234



The Comparison of 25-Hydroxyvitamin D3 between Patients With and Without Cervical Cancer

Dodi Suardi, Feny Renita, Andi Kurniadi, Akhmad Yogi Pramatirta, Raden Tina Dewi Judistiani, Yudi Mulyana Hidayat, Budi Setiabudiawan (Author)

564-568

PDF

High Expression of Parathyroid Hormone-related Protein and Tumor Necrosis Factor- α in Cancer Cells as Risk Factors for Hypercalcemia in Bone Metastases Lytic Lesions

Made Wahyu Dharmapradita, I Ketut Suyasa, Made Bramantya Karna, I Wayan Juli Sumadi, Kadek Gede Bakta Giri, Cokorda Krishna Dalem Pemayun, Claudia Santosa (Author) 290-296

PDF

Can Estrogen Receptor, Progesterone Receptor, and Proliferative Index be Considered as Isolated Prognostic Factors of Overall Survival in Early luminal Breast Cancer?

Marija Karakolevska-Ilova, Milka Zdravkovska, Djengis Jasar, Gordana Petrushevska, Elena Simeonovska-Joveva (Author)

1313-1322

PDF

Age as an Independent Factor in the Permanent Chemotherapy-Induced Amenorrhea Incidence in Breast Cancer Patients at Dr. Moewardi Hospital, Surakarta, Indonesia

Mudib Mudib, Kristanto Yuli Yarso, Henky Agung Nugroho (Author)

PDF

Quality of Life and Sexual Functioning of Women after Breast Cancer Surgery

Stana Pačarić, Želimir Orkić, Andrea Milostić-Srb, Tajana Turk, Nikolina Farčić, Štefica Mikšić, Silvia Adamčević, Ivan Erić, Zvjezdana Gvozdanović, Nika Srb (Author)

PDF

Differences in the Expression of β -Catenin Nucleus/Cytoplasm Ratio e-Cadherin and n-Cadherin and Correlation of β -Catenin Cytoplasm and Cadherin in Model of Duke D Stage Colorectal Cancer Cell Line

Analysis Survival of Breast Cancer with Brain Metastases Treated with Different Fraction Whole Brain Radiotherapy Concomitant with Capecitabine

Rudiyo Yeoh, Iskandar Japardi, Aznan Lelo, R. Susworo, Jacub Pandelaki, Adang Bachtiar, Suzy Indharty, Hendriyo Yeoh, Juli Jamnasi, William Omar, Sudibio Sudibio (Author) 569-572

PDF

Moist Exposed Burn Ointment Effectiveness for Capecitabine Associated Grade II and III Hand Foot Syndrome on Stage III Colonic

Budhi Ida Bagus, Nunik Agustriani, Rieva Ermawan, Suwardi Suwardi, Amru Sungkar, Ikhdin R. Saadhi (Author)

971-974

PDF

Antiproliferative Activity of Selected Triterpene Acids from Rosemary on Metastatic Melanoma Cell Line WM-266-4

Suzana Isaković-Vidović, Barbara Dariš, Željko Knez, Kristina Vidović, Dejan Oprić, Polonca Ferk (Author) 515-521

PDF

De novo Stage IV Luminal Breast Cancer: Yes or No for Local Treatment? Serial Cases and Review

Marija Karakolevska-Ilova, Elena Simeonovska Joveva, Aleksandar Serafimov (Author) 1-5

DDE

PDF

Quality of Life of Bulgarian Breast Cancer Female Patients

Galina Yaneva, Tsonka Dimitrova, Dobri Ivanov, Gergana Ingilizova, Sergei Slavov (Author) 925-930

PDF

Clinical Characteristic of Thoracic Malignancy Patients with Coronavirus Disease 2019 Related to Mitigation Strategy in Dharmais National Cancer Center Hospital, Indonesia

Arif Hanafi, Noorwati Soetandyo, Achmad Mulawarman Jayusman, Leovinna Widjaja, Fifi Dwijayanti, Priscillia Imelda (Author)

692-697



Relationship between CD 163 Tumor-Associated Macrophages and Colorectal-Cancer Stem Cell Markers

Imelda Rey, Agung Putra, Dharma Lindarto, Fauzi Yusuf (Author) 1381-1386

1301-130

PDF

The Reactive Carbonyl Derivatives of Proteins, Methylglyoxal, and Malondialdehyde in Blood of Women with Breast Cancer

Sabina Zhumakayeva, Larissa Muravlyova, Valentina Sirota, Vilen Molotov-Luchansky, Ryszhan Bakirova, Nailya Kabildina, Xeniya Mkhitaryan, Ainura Zhumakayeva (Author)

509-514

PDF

Open Versus Percutaneous Approach of Renal Tumor Biopsy at Cipto Mangunkusumo Hospital: A Single-center Experience

Luki Ertandri, Agus Rizal A.H. Hamid, Meilania Saraswati, Chaidir A. Mochtar, Rainy Umbas (Author) 547-551

PDF

Analysis Predictors of the Outcome of Adjuvant of Hormone Therapy on Estrogen Receptorpositive Breast Cancer in Indonesia

Hardisman Dasman, Wirsma Arif Harahap, Daan Khambri (Author) 847-851

PDF

The Effect of Chemotherapy on Estradiol Levels in Patients with HER 2-Overexpression Breast Cancer in Dr Moewardi General Hospital, Surakarta, Indonesia

lmam Hafidh Zaini, Widyanti Soewoto, Ida Bagus Budhi (Author)

1570-1574

PDF

Synergistic Cytotoxic Effect of Honey Bee Venom and Cisplatin on Tongue Squamous Cell Carcinoma Cell Line

PDF

Neoadjuvant Chemotherapy Effect on Predictive Value of Sentinel Lymph Node Biopsy using Single Method Methylene Blue in Breast Cancer Patients at Low-resource Country

Muhammad David Perdana Putra, Kristanto Yuli Yarso, Brian Wasita (Author)

PDF

Dermatology

Coenzyme Q10 Supplementation as an Adjuvant Therapy Potentially Increase Serum Superoxide Dismutase Levels in Acne Vulgaris Patients

Carissa Adriana, Asih Budiastuti, Kabulrachman Kabulrachman, Retno Indar Widayati, Puguh Riyanto, Muslimin Muslimin (Author)

444-450

PDF

Retrospective Analysis of 170 Patients Followed up with Herpes Zoster and Postherpetic Neuralgia in Nothern Cyprus

Dua Cebeci, Seide Karasel (Author) 583-587

PDF

Risk Factors of Type 1 Leprosy Reaction in Leprosy Patients attending Leprosy Division of Dermatology and Venereology Outpatient Clinic of Dr Soetomo General Hospital in 2017–2019: A Retrospective Study

Brigita Rosdiana, Linda Astari, Astindari Astindari, Cita Rosita Sigit Prakoeswa, Iskandar Zulkarnain, Damayanti Damayanti, Budi Utomo , M. Yulianto Listiawan (Author) 1359-1363

PDF

Dermatological Manifestation in Coronavirus Disease 2019 Patients in Iraq

Anfal L. Al-Harbawi, Qasim S. Al Chalabi, Hala N. Alsalman, Mohammad S. Saeed (Author) 1085-1091

PDF

Sabreen Amar, Amr Helmy Mustafa El-Bolok, Sherif Farouk El-Gayar, Maii Ibrahim Sholkamy (Author) 1739-1744

PDF

Efficacy, Safety and Cost Effectiveness of Metronomic Low Dose Versus Intermittent High Dose Capecitabine in Metastatic Breast Cancer

Hala Elsebaie, Wael Samir Makar Yassa, Shaimaa Lasheen, Noha Ibrahimlbrahim (Author) 1048-1053

PDF

Outcome Analysis and Prognostic Factors in Patients of Glioblastoma Multiforme: An Indonesian Single Institution Experience

Sudibio Sudibio, Jellyca Anton, Handoko Handoko, Tiara Bunga Mayang Permata, Henry Kodrat, Endang Nuryadi, Henry Riyanto Sofyan, Rahmad Mulyadi, Renindra Ananda Aman, Soehartati Gondhowiardjo (Author)

1410-141

PDF

A Hybrid Convolutional Neural Network-Support Vector Machine for X-ray Computed Tomography Images on CancerA Hybrid Convolutional Neural Network-Support Vector Machine for X-ray Computed Tomography Images on Cancer

Jane Aurelia, Zuherman Rustam (Author)

1283-1289

PDF

Correlation between Grading Histopathology and Sentinel Lymph Node Metastasis in Early Breast Cancer in University of Sumatera Utara Hospital

Dedy Hermansyah, Gracia Pricilia, Arjumardi Azrah, Yolanda Rahayu, Desiree A. Paramita, Edwin S. Siregai (Author)

679-682

PDF

Evaluating the Natrium Iodide Symporter Expressions in Thyroid Tumors

Aisyah Elliyanti, Rony Rustam, Tofrizal Tofrizal, Yenita Yenita, Yayi D. Billianti Susanto (Author) 18-23

Effect of Purple Passion Fruit Extract Cream (Passiflora edulis Sims var. Edulis) 6% against Striae Distensae

Chyntia Giska Aryunisari, Imam Budi Putra, Nelva K. Jusuf (Author)

720-725

PDF

Vitamin D Deficiency among Females with Acne Vulgaris in Relation to Sun Exposure: A Cross-sectional Study

Ghada Abdelrahman Elfadil, Nosiba Ahmed Mohammed, Abdelgadir Elmugadam, Marwan Ismail, Abd Elgadir Alamin Altoum, Ahmed L. Osman (Author)

1301-1304

PDF

Vitamin D Receptor Gene Polymorphisms Fokl rs2228570, Apal rs797523, and Taql rs731236 in Multibacillary Leprosy Patients

Ramona Dumasari Lubis, Irma D. Roesyanto-Mahadi, Yahwardiah Siregar, Putri Chairani Eyanoer (Author) 112-115

PDF

The Comparison between Free Thyroxine and Thyroid-Stimulating Hormone Levels on Melasma Severity: A Cross-Sectional Study

Comparing FT4 and TSH on Melasma Severity

Yusnita Rahman, Roro Inge Ade Krisanti, Wismandari Wisnu, Irma Bernadette S. Sitohang (Author) 426-431

PDF

Correlation of Melanin Content with Collagen Density in Keloid Patients

Herman Y. L. Wihastyoko, David S. Perdanakusuma, Setyawati Soeharto, Edi Widjajanto, Kusworini Handono, Bambang Pardjianto (Author)

265-271

PDF

Evaluation of Modified Melasma Area and Severity Index in Hyperthyroid Patients Receiving Anti-thyroid Drugs

Irma Bernadette S. Sitohang, Benny Nelson, Melani Marissa, Wresti Indriatmi, Wismandari Wisnu (Author) 344-349

PDF

The Effectiveness of Autologous Serum and Single-dose Oral Doxycycline in the Treatment of Acne Vulgaris: A Pilot Clinical Trial

Muhammad Nasrum Massi, Muhlis Yunus, Anis Irawan Anwar, Khairuddin Djawad, Siswanto Wahab, Rahmawati Minhajat, Uleng Bahrun, Ilhamjaya Patellongi, Gemini Alam, Ni Nyoman Sri Budayanti (Author) 1602-1606

PDF

The Effectiveness of Lumbricus rubellus Extract Toward Interleukin-10 and Immunoglobulin E and Atopic Dermatitis Scoring Index (SCORAD)

Farida Tabri, Pipim Septiana Bayasari, Rosani Sri Camelia Nurdin, Anis Irawan Anwar, Anni Adriani, Farida Ilyas (Author)

1428-1434

PDF

Development of Propolis (Apis trigona)-loaded Nanoemulgel for Improved Skin Penetration of Caffeic Acid: The Effect of Variation of Oleic Acid Concentration

Afdil Viqar Viqhi, Marianti A. Manggau, Sartini Sartini, Elly Wahyudin, Latifah Rahman, Risfah Yulianti, Andi Dian Permana, Satria Aztasaury Awal (Author)

1264-1278

PDF

Evaluation of Pre-operative Dermoscopy in Early Diagnosis of Non-melanocytic Skin Cancer

Reihane Bislimi Berisha, Djordje Dzokic, Shkendije Dobruna (Author)

1660 1662

PDF

Identification of Sarcoptes scabiei by Clinical Examination and Follow-up Examination in Medan City, Indonesia

Afrida Aryani Nasution, Imam Budi Putra, Mutiara Indah Sari (Author) 1633-1636

PDF

Infective Diseases

PDF

Synthetic Food Coloring as an Alternative to Worm Egg Staining Ascaris lumbricoides

Steven Soenjono, Budi Setiawan, Rahmah Siti Wulandari, Suyana Suyana, Marta Atik Martiningsih (Author) 1541-1543

PDF

Epidemiology Survey of Measles in Kazakhstan

Aygerim Zhuzzhasarova, Dinagul Baesheva, Bayan Turdalina, Aliya Seidullaeva, Alena Altynbekova, Madiyar Nurgaziev, Bakhytzhan Abdullaev, Almagul Kushugulova (Author) 704-710

PDF

The Use of Eosinophil Count in Predicting the Need of Coronavirus Disease 2019 Patient for Treatment in Intensive Care Unit

Ngakan Ketut Wira Suastika, Ketut Suega (Author)

631-635

PDF

The Effect of Lemongrass Leaves and Stalks Extracts using Methanol as The Eco-friendly Larvicides on Fourth Instar Aedes aegypti Larvae

Tjut Mariam, Ade Oktiviyari, Ahmad Yamin Harahap (Author) 937-939

PDF

Health Belief Associated with Adherence to Health Protocol in Preventing Coronavirus Diseases on Patients' Family

Riza Fikriana, Frastiqa Fahrany, Syahril Ali Rusli (Author) 1011-1015

PDF

Readiness of Medical Teams Caring for COVID-19 in the Intensive Care Units: A National Web-Based Survey in Indonesia

Mochamat Helmi, Djayanti Sari, Andreasta Meliala, Laksono Trisnantoro (Author) 1785-1790

web-

Clinical Signs and Laboratory Parameters as Predictors of Mortality among Hospitalized Human Immunodeficiency Virus-Infected Adult Patients at Tertiary Hospital in Surabaya

Rentha Monica Simamora<mark>, Muhammad Vitanata Arfijanto,</mark> Musofa Rusli, Budi Utomo, Cennikon Pakpahan, Mr. Garry Prasetyo Adi (Author)

497-502

PDF

Profile of COVID-19 Patients in Dr. Moewardi Hospital Surakarta Indonesia

Cahyono Hadi, Cipta Pramana (Author)

1621-1624

PDF

The Behavior of Using Masks during the Coronavirus Disease 19 Pandemic in Malang Regency, Indonesia: Application of Theory of Planned Behavior and Social Support

Riza Fikriana, Al Afik, Mila Maula Marinda (Author)

1006-101

PDF

Identification of Leptospira Serovar in Leptospirosis Suspect Serum in Manggala Subdistrict, Makassar City

Syamsuar Manyullei, Hasnawati Amqam, Sri Indi Rahmadanti (Author)

PDF

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Ngakan Ketut Wira Suastika, Ketut Suega (Author)

of Coronavirus Disease 2019

1561-1564

PDF

The Role of Sex, Ethnicity, Age, and Nutritional Status in the Seropositivity of the Measles

H. R. Teni Nurlatifah, Wisnu Barlianto, I Wayan Arsana Wiyasa, H. M. S. Chandra Kusuma, Tita Luthfia Sari, Novilia Sjafri Bachtiar (Author)

1219-1223

PDF

Composite Bacterial Infection Index and Serum Amyloid A Protein in Pulmonary Tuberculosis Patients and their Household Contacts in Makassar

Irda Handayani, Muhammad Nasrum Massi, Yanti Leman, Rosdiana Natzir, Ilhamjaya Patellongi, Subair Subair, Najdah Hidayah, Ayu Andini Wulandari, Handayani Halik (Author) 557-562

PDF

Impacts of Pharmacy Intervention on Appropriateness of Antibiotics Use in Pneumonia

Azizah Nasution, Khairunnisa Khairunnisa, Syed Azhar Syed Sulaiman (Author) 786-792

PDF

Platelet Index in Patients with Confirmed Coronavirus Disease 2019 Cases

Haerani Harun, Christin Rony Nayoan, Ipfi White, Nur Syamsi, Andi Alfia Mutmainnah Tanra, Sarifuddin Sarifuddin (Author)

1705-1709

PDF

The Attitude and Behavior Related to Social Distancing as Prevention Transmission of Coronavirus Disease 19 among Adolescents Living in Coastal Area of Indonesia

Eko Mulyadi, Abd Wahid, Arif Rahman Hakim (Author) 659-662

PDF

Diagnostic and Prognostic Value of Plasma Gelsolin in Multiorgan Failure in Patients with Sepsis

Ahmed El-Maghraby, Hossam Mowafy, Emad Omer, Hazem El-Akabawy, Iris Nessim (Author) 29-35

PDF

Gynecology and Obstetrics

The Role of Early Initiation of Breastfeeding in the Duration of the Third Stage of Delivery and the Amount of Blood Loss in the Fourth Stage in Spontaneous Vaginal Delivery

Sarma Lumbanraja, Wardy Susanto Marpaung, Teuku Mohammad Ichsan, Ichwanul Adenin, Roy Yustin Simanjuntak (Author)

742-746

PDF

Adaptation of the Edinburgh Postnatal Depression Scale in the Indonesian Version: Selfreported Anxiety and Depression Symptoms in Pregnant WomenAdaptation of the Edinburgh Postnatal Depression Scale in the Indonesian Version: Self-reported Anxiety and **Depression Symptoms in Pregnant Women**

Dewi Nirmala Sari, Hervita Diatri, Kemal Siregar, Hadi Pratomo (Author)

1654-1659

PDF

Is It Necessary to Perform a Routine Antibiotic Prophylaxis before an Elective Surgery of Cesarean Section?

Sergei Belyaev, Larysa Nazarenko, Liliya Dubrova, Olena Fedota (Author)

836-840

PDF

The New Detection Method of Ovarian Follicle Development Using Digitized Wide Area

Noviyanti Noviyanti, Yuyun Yueniwati, Bambang Rahardjo, Karyono Mintaroem, Erick Khristian (Author)

PDF

Micronutrient Content and Total Lactic Acid Bacteria of Dadiah Pudding as Food **Supplementation for Pregnant Women**

Zuhrah Taufiqa, Dian Novita Chandra, Helmizar Helmizar, Nur Indrawaty Lipoeto, Badriul Hegar (Author) 1149-1155

PDF

Comparison of Maternal and Neonatal Outcomes in Teenage and Reproductive Age Pregnancy at Tertiary Hospital in West Java, Indonesia

Body Mass Index and Other Factors Related to Mastalgia: A Cross Sectional Study

Rehab Sabry, Tamer M. Kolib, Marwa Ahmed, Heba G. Elnahas (Author) 1586-1590

PDF

A Comparison between The Incidence of Paresthesia in Median and Paramedian Approaches of Intrathecal Anesthesia in Parturients Undergoing Cesarean Sections: A Randomized **Controlled Trial**

Reham Mahrous, Mahmoud Alalfy, Hatem Hassan, Omar Nagy, Omnia Mandour, Amera Yehia, Amr K Abdel Hakeem (Author)

793-796

PDF

Antenatal Obstetric Hospitalization: Risk Factors and Pregnancy Outcomes in the University of Calabar University Teaching Hospital, Calabar - A Retrospective Review

Ubong Bassey Akpan, Chidinma Enweremadu, Emmanuel Monjok, Thomas Agan (Author) 235-239

PDF

Determination of Urine Protein Levels and Analysis of Differences in Vascular Endothelial **Growth Factor Levels between Early Onset and Late Onset Preeclampsia**

Engga Lift Irwanto, Eryati Darwin, Donel S, Djong Hon Tjong Tjong (Author) 552-556

PDF

Sperm Quality and Deoxyribonucleic Acid Fragmentation after 5 and 10 min Centrifugation with Swim-Up Processing Technique: A Prospective Cohort Study

Binarwan Halim, Jesselyn Angellee, Hilma Putri Lubis, Bob Bachsinar (Author) 626-630

PDF

A Comparison between Intrathecal Nalbuphine and Fentanyl for Intraoperative Pain Management during Uterine Exteriorization in Cesarean Section: A Randomized Controlled Trial

Sherif Abdullah Mohamed, Ahmed Elsonbaty, Mohamed Elsonbaty (Author)

533-540

Windi Nurdiawan, Ahmad Raihan Hidayat Koto, Zulvayanti Zulvayanti, Nur Atik, Hadi Susiarno, Dini Hidayat, Dini Pusianawati, Fadhilah Zulfa (Author)

1080-1084

PDF

Impact of Anemia in Pregnant Women on the Neonatal Conditions

Raisa Aringazina, Gulnara Kurmanalina, Yerlan Bazargaliyev, Victoria Kononets, Bakhtiyar Kurmanalin, Anes Bekkuzhin (Author)

1185-1188

PDF

Malpresentation of the Fetus in Singleton Pregnancies after In Vitro Fertilization

Sergei Svetoslavov Slavov (Author)

PDF

Antioxidant Activity of Purslane (Portulaca oleracea L.) Leaf Extract on the Levels of Ovarian Oxidative Stress and Reproductive Hormone in Rattus norvegicus Exposed to Cigarette

Astika Gita Ningrum, Endyka Erye Frety, Ivon Diah, Zidni Hasbuna Shabran, Rida Eka Setiani, Erni Rosita Dewi (Author)

1535-1540

PDF

Cell-free DNA in Human Follicular Fluid as Biomarker for Intracytoplasmic Sperm Injection Procedure Outcome

Maanee Azzam, Adeela Hamood, Hind Abdulkadim (Author)

1745-1750

PDF

Evaluation of Uterine Cavity Abnormality using Saline Infusion Sonohysterography Before In Vitro Fertilization

Ichwanul Adenin, Hilma Putri Lubis, Binarwan Halim (Author) 917-920

PDF

PDF

Results of Using the Robson Classification in Kazakhstan

Assel Askarovna Altayeva, Saule Shaykenovna Issenova, Egle Machtejeviene, Gani Zhandiyarovich Bodykov, Balzira Nagashibaevna Bishekova (Author)

663-669

PDF

Oral Anaerobic Microflora and Pregnancy Complication

Irena Andonova, Vasil Iliev (Author)

1681-1685

PDF

The Sexual Function of Primiparous Women after Normal Delivery and Cesarean Section **According to the Female Sexual Function Index**

Eighty Mardiyan Kurniawati, Sandy Irwanto, Nalini Muhdi (Author)

PDF

Anxiety Levels and Behavioral Changes among Pregnant Women Amidst the Coronavirus Disease-19 Pandemic at Fauziah Mother and Child Hospital Tulungagung, East Java

Sutrisno Sutrisno, Ayu Rizky Widowati, Nina Rini Suprobo (Author) 1441-1445

PDF

Clinical Profiles, Demographic Features, and Maternal Outcomes among Coronavirus Disease Positive Pregnant Women: A Cross-sectional Study

Zaheera Saadia, Robina Farrukh, Sumaira Kanwal, Quratulain Shahzad (Author) 486-491

PDF

Comparative Analysis of Beet Juice and Red Guava Juice against Erythrocyte and Hematocrit Levels in Post-partum Women

Cut Nurhasanah, Andri Idiana, Putri Santi, Yushida Yushida (Author)

821-825



Analysis of Delivery in Singleton Pregnancies Achieved by In Vitro Fertilization

Sergei Slavov, Gergana Ingilizova, Galina Yaneva (Author)

885-889



The Assessment of Intrapartum Transperineal Ultrasonographic Parameters for their Effectiveness in Evaluation of Progress of Labor and Prediction of Mode of Delivery in Egyptian Women

Gamal Abdelsameea Ibrahim, Ahmed Soliman Nasr, Fatma Atta, Mohamed Reda, Hend Abdelghany, Nihal M. El-Demiry, Mohamed Shalaby (Author)

1037-1043



Omega-3 Fatty Acids plus Vitamin E Cosupplementation versus Vitamin E in Fibrocystic Breast Patient with Mastalgia: A Randomized Controlled Trial

Marwa Mostafa Ahmed, Eman Ahmed Rushdy, Dalia Ahmed Aboul Azm , Rehab Mohamed Sabry, Heba Galal El Nahas (Author)

116-121

PDF

Effectiveness of Pre-operative Rectal Misoprostol in Reducing Blood Loss during Cesarean Section for Placenta Previa and Manual Removal of Retained Placenta: A Parallel Placebo-Controlled Study

Ubong Akpan, Udeme Asibong, Kazeem Arogundade, Chinyere Akpanika, Mabel Ekot, Saturday Etuk (Author)

161-166

PDF

Pediatrics

Phenomenology Study of Stunting Nutrition for Babies in the Work Area of Pante Kuyun Health Center, Aceh Jaya District

Amiruddin Amiruddin, Bustami Bustami, Anasril Anasril, Tri Mulyono Herlambang, Muhammad Husaini, Sri Gustini (Author)

Tina Christina Lumban Tobing, Teddy Ontoseno, Sri Rahayuningsih, Ratna Akbari Ganie, Yahwardiah Siregar (Author)

1795-1798

PDF

The Relationship between Vitamin D Levels and Clinical Outcomes of Neonatal Sepsis in Haji Adam Malik Hospital Medan, Indonesia

Kamsiah Kamsiah, Beby Syofiani Hasibuan, Karina Sugih Arto (Author)

698-703

PDF

Association of Comorbid with Developmental Quotient in Down Syndrome Children

I Gusti Ayu Trisna Windiani, Ni Made Dewi Aryati, I Gusti Agung Ngurah Sugitha Adnyana, Ni Luh Sukma Pratiwi Murti, Soetjiningsih Soetjiningsih (Author)

1484-1488

PDF

Knowledge, Attitude, and Behavior of Parents toward School Reopening Amidst Coronavirus Disease 2019 Pandemic in Indonesia

Andry Juliansen, Gilbert Sterling Octavius, Alexa Ovilia Tan, Chelsea Serena Br. Pardede, Cindy Clarissa Thandy, Clauvinna Adhityana Lie Fisca, Jeremiah Hilkiah Wijaya (Author)

1190-1197

PDF

Local Snacks and Virtual Nutrition Counseling Services Increasing Growth of Stunting Children

Nadimin Nadimin, Kartini B. Theresia Dewi, Abdul Salam, Adriyani Adam (Author) 331-336

PDF

The Risk Factors of Bacterial Meningitis in Late-Onset Neonatal Sepsis

Ni Made Reditya Noviyani, I Made Kardana, Dewi Sutriani Mahalini, Ida Bagus Gede Suparyatha, Ketut Ariawati, Gusti Ayu Putu Nilawati, Made Sukmawati (Author)

1224-1228

PDF

462-467

PDF

The Differences in Transaminase Enzyme Levels among Children with Acute Diarrhea due to Rotavirus and Non-rotavirus

Samitha Wijaya, I Putu Gede Karyana, Eka Gunawijaya, Ida Bagus Subanada, I Gusti Agung Ngurah Sugitha Adnyana, Komang Ayu Witarini (Author)

1075-1079

PDF

Vitamin D Deficiency in Children with Chronic Renal Disease

S. B. Dyussenova , M. Y. Gordiyenko , G. B. Serikova, S. A. Turlybekova, A. A. Issayeva, N. A Yerimbetova, V. O. Goroshko (Author)

1751-1757

PDF

Necrotizing Enterocolitis in Preterm Infants Born to Mother with COVID-19

Dina Angelika, Risa Etika, Angelica Diana Vita, Setya Mithra, I Dewa Gede Ugrasena (Author) 1499-1504

PDF

The Differences of Left Lateral and Head Elevation Position toward Heart Rate of Newborns with Asphyxia in the Perinatology Room RSUD Dr. Soediran Mangun Sumarso Wonogiri

Noerma Shovie Rizqiea, Septy Nur Aini, Ratih Dwilestari Puji Utami, Ratnawati Ratnawati, Khairunisa Wardani (Author)

492-496

PDF

Determinant Factors of Stunting in Under-Five Children

Yusni Podungge, Endah Yulianingsih, Hasnawatty S. Porouw, Elsa Saraswati, Magdalena Martha Tompunuh, Juli Gladis Claudia, Rabia Zakaria, Rahma Labatjo (Author)

PDF

Relationship between Environmental Factors and Rheumatic Heart Disease

Prevalence of Sleep Disorders in Adolescents and its Relation with Screen Time during the COVID-19 Pandemic Era

I Gusti Ayu Trisna Windiani, Ni Made Reditya Noviyani, I. Gusti Agung Ngurah Sugitha Adnyana, Ni Luh Sukma Pratiwi Murti, Soetjiningsih Soetjiningsih (Author)

297-300

PDF

Pro- and Anti-vaccination among Mothers in Deciding Children's Immunization: A Qualitative Study

Aisyah Nur Izzati, Retno Indarwati, Makhfudli Makhfudli, Budi Utomo, Eka Mishbahatul M. Has, Yuni Sufyanti Arief, Hidayat Arifin (Author)

385-391

PDF

Lactose versus Lactose Free Regimen in Children with Acute Diarrhea

Sinan Abdulrazzaq, Faten Alaa Jaafar , Zahoor Abdulmohsin Mohammed (Author) 1279-1282

PDF

Serum Biomarkers of Environmental Enteric Dysfunction and Growth Perspective in Egyptian Children

Maged A. El Wakeel, Ghada M. El-Kassas, Shaimaa A. Hashem, Hasanin M. Hasanin, Walaa H. Ali, Alshaimaa A. Elkhatib, Hiba Sibaii, Nevein N. Fadl (Author)

1625-1632

PDF

Factors Related to School Readiness in Children: A Cross-Sectional Analytic Study of Elementary School Children in Manado

Lydia Wangke, Gregory Joey, Nurhayati Masloman, Hesti Lestari (Author) 1387-1393

PDF

Effect of Exercise-Induced Lipolysis on Serum Vitamin D Level in Obese Children: A Clinical Controlled Trial

Lamiaa K. Elsayyad, Alaa Shafie, Mazen Almehmadi, Amal F. Gharib, Ahmad El Askary, Tarek Alsayad, Alsufiany Muhsen, Hatem Allam (Author)

PDF

Massage Therapy Can Prevent the Risk of Autism Spectrum Disorders in Children

Andy Martahan Andreas, Ratna Djuwita, Helda Helda, Rini Sekartni, Sri Hartati R. Suradijono, Thjin Wiguna, Angela B. M. Tulaar, Yusuf Kristianto, Hendrik Hendrik (Author)

1556-1560

PDF

Preoperative Microbiological Screening in Pediatric Assessment of Skeletal Dysplasias Cases **Before Planned Orthopedic Surgery**

Milka Dikova, Svetla Todorova Nikolova, Alexandre Loukanov (Author) 281-285

PDF

Determinants of Stunting Prevention among Mothers with Children Aged 6–24 Months

Esti Yunitasari, Retnayu Pradanie, Hidayat Arifin, Dita Fajrianti, Bih-O Lee (Author) 378-384

PDF

Fecal Markers of Environmental Enteric Dysfunction and their Relation to Faltering Growth in a Sample of Egyptian Children

Maged A. El Wakeel, Ghada M. El-Kassas, Gihan Fouad Ahmed, Walaa H. Ali, Eman Mohamed Elsheikh, Salwa Refat El-Zayat, Nevein N. Fadl, Iman H. Kamel, Thanaa M. Rabah (Author)

PDF

Importance of the Pneumococcus in Community-acquired Pneumonia in Tender-age Infants on the Background of Vaccination

Aliya A. Zhanpeissova, B. T. Tukbekova, S. B. Akhmetova, B. Dyusseno Sandugash, K. Zh. Alimshaikhina, G. A. Sarmankulova (Author)

1525-1528

PDF

260-264

PDF

Assessment of a Nutrition Education Program designed to Enhance Mothers' Attitudes on Infants and Young Children feeding in Sudan

Ekhlas A. I. Mohammed, Zainab Taha, Agba A. A. Gadah-Eldam, Mariam M. El hidai (Author) 620-625

PDF

The Association Between Nutritional Status and Risk of Developmental Disorder in Children in Denpasar Bali Indonesia

I Gusti Ayu Trisna Windiani, Ni Kadek Wiwik Agustini, I. Gusti Agung Ngurah Sugitha Adnyana, Soetjiningsih Soetjiningsih, Ni Luh Sukma Pratiwi Murti (Author) 687-691

PDF

Study of Neuropeptide Substance P as A Marker of Pain in Newborn Infant

Safaa ELMeneza, Iman ElBagoury, Enas Tawfik, Amel Tolba (Author)

1615-1620

PDF

A Pattern of Glomerular Diseases in Egyptian Children: A Single-center Experience

Hoda Atef Abdelsattar Ibrahim, Ava Amin, Ahmed Zeid , Samar Sabry , Hesham Safouh (Author) 1305-1312

PDF

Effectivity of Esomeprazole Compared with Lansoprazole in the Treatment of Pediatric with Gastritis

Fini Kollins, Supriatmo Supriatmo, Rina Saragih, Ilhamd Ilhamd (Author) 1424-1427

PDF

Mean Platelet Ratio, Neutrophil to Lymphocyte Ratio, and the Risk of Febrile Seizures in Children Aged 6-59 Months

Albert Kurniawan, Maria Steffany Lainama, Wienta Diarsvitri (Author)

Association between Bisphenol A Urine Level with Low-Grade Albuminuria in Egyptian **Children and Adolescent**

Nermine Mahfouz, Ebtissam Salah, Ayman Armaneous, Mai M. Youssef, Mones Mahmoud Abu Shady, Sara Sallam, Mona Anwar, Safaa Morsy, Jihan Hussein (Author)

1092-1097

PDF

Cystatin and Glomerular Filtration Rate in Obese Versus Non-obese Adolescents

Azza Abd El-Shaheed, Nermine N. Mahfouz, Reham F. Fahmy, Mona A. Elabd, Hiba Sibaii, Salwa Refat El-Zayat, Mahitab I. El-Kassaby, Hagar H. Mourad (Author)

1453-1457

PDF

Effect of Lactobacillus plantarum DAD-13 and Fructo-oligosaccharides on Short-Chain Fatty **Acid Profile and Nutritional Status in Indonesian Stunting Children**

Delima Gunawan, Mohammad Juffrie, Siti Helmyati, Endang S. Rahayu (Author) 1790-1796

PDF

Impact of Papaya (Carica papaya L.) on Breast Milk Production Enhancement of Nursing Mothers at Teling Atas Public Health Center, Wanea Subdistrict, Manado City

Ellen Pesak, Fredrika N Losu, Robin Dompas, Freike Lumy, Gusti Ayu Tirtawati, Dian Pratiwi, Kusmiyati Kusmiyati, Fiani A Djojobo, Atik Purwandari, Bongakaraeng Bongakaraeng, Nonce Nova Legi, Rivolta Walalangi, Esther N Tamunu, Jon Welliam Tangka (Author)

240-243

PDF

Iron Status in Preschool Children with Normal Hemoglobin, Egypt

Osama El-Asheer, Mary S. Naeem , Fardos H. Abd El Aal , Madleen A. A. Abdou, Khalil Abdel Khalek Mohamed (Author)

1342-1346

PDF

Relationship between Serum 25(OH)D Levels and Blood Pressure in Children with Nephrotic Syndrome

Rosmayanti Syafriani Siregar, Oke Rina Ramayani (Author); Winson Chitra, Rafita Ramayati

276-280

PDF

The Relationship between Hair Zinc Levels and Drug-resistant Epilepsy in Children at Sanglah Hospital

I Gusti Ngurah Made Suwarba, Dewi Sutriani Mahalini, I Gusti Ngurah Agung Jayadhi Widyakusuma (Author)

996-1000

PDF

Comparing Levels of Urinary Phthalate Metabolites in Egyptian Children with Autism Spectrum Disorders and Healthy Control Children: Referring to Sources of Phthalate Exposure

Manal A. Shehata, Ebtissam M. Salah El-Din, Mai M. Youssef, Mones M. Abushady, Inas R. El-Alameey, Engy A. Ashaat, Amr S. Gouda, Walaa S. Nazim (Author)

1640-1646

PDF

A Determinant Analysis of Stunting Prevalence on Under 5-Year-Old Children to Establish **Stunting Management Policy**

Diah Mutiarasari, Miranti Miranti, Yuli Fitriana, David Pakaya, Puspita Sari, Bohari Bohari, Muhammad Sabir, Rosa Dwi Wahyuni, Ryzqa Ryzqa, Veni Hadju (Author)

PDF

Deferasirox Effect on Serum Ferritin in Iraq Patients with Hemoglobinopathies: A Single Center Experience

Khalaf Hussein Hasan, Aspazija Sofijanova, Luma Hassan, Nasir Al-Allawi (Author) 144-148

PDF

Zinc Status in Beta-Thalassemia Major

Khalaf Hussein Hasan, Hasan Abdulla Aswad, Aspazija Sofijanova (Author) 149-153

Surgery

Surgical Management of Parkinson's Disease: The Role of Lesioning Procedures in Developing Countries in the Modern Era

Sameh Abdelbari, Hanan Abdallah Amer, Bassem Mohamed Ayoub, Ramy Kamel (Author) 1241-1262



The Role of Chewing Gum on Post-operative Bowel Recovery after Gynecological Laparoscopic Surgery: A Short Report and Updated Review

Nicko Pisceski Kusika, Imelda E. B. Hutagaol, Muhammad Yusuf, Suyanto Suyanto, Shinta Puja Tilusari (Author)

1123-1127

PDF

Quantification of Alcohol Dehydrogenase Concentration for Traumatic Brain Injury in Alcohol-intoxicated Patients as a Predictor of Severity and Prognosis

Muhammad Z. Arifin, David Atmaja, Ahmad Faried (Author)

212-216

PDF

Clinical and Radiological Predictors of Ventriculoperitoneal Shunt Insertion in Myelomeningocele Patients

Ahmed M. F. El Ghoul, Ahmed Hamdy Ashry, Mohamed Hamdy El-Sissy , Ibrahim Mohamed Ibrahim Lotfy (Author)

522-532

PDF

Clinical Experience with PEGylated Hyaluronic Acid Fillers: A 3-year Retrospective Study

Raffaele Rauso, Giovanni Francesco Nicoletti, Pierfrancesco Bove, Giuseppe M. Rauso, Romolo Fragola Giorgio Lo Giudice, Nicola Zerbinati (Author)

1168-1173

PDF

Relationship between 25(OH)D and Colorectal Cancer Prevalence at Dr. Moewardi Hospital Surakarta-Indonesia: A Cross-Sectional Study

PDF

Correlation of Wells Score, Caprine Score, and Padua Score with Risk of Hypercoagulation Condition Based on D-dimer in Intra-articular, Periarticular, and Degenerative Fracture Patients of Inferior Extremity

Thomas Erwin Christian Junus Huwae, Ahmad Heifan, Muhammad Alwy Sugiarto (Author) 1580-1585

PDF

Prognostic Indices of Surgical Outcome in Cervical Spondylotic Myelopathy: A Clinical Prospective Study

Ahmed A. Marei, Mohamed Reda Rady, Hazem Mostafa Kamal, William C. Welch, Mohamed A. Hafez (Author)

438-443

PDF

Monitoring and Prevention the Risk of Diabetic Foot Ulcer Infection during Coronavirus Disease-19 Pandemic: A Narrative Review and Perspective Algorithm

Mariya Dmitriyeva, Saken K. Kozhakhmetov, Dulat K. Turebayev, Saltanat N. Urazova, Talgat M. Omarov, Nurbek S. Igissinov, Medet T. Toleubayev (Author)

577-582

PDF

The Role of Instrumentation in the Healing Process of Spinal Tuberculosis: An Experimental Study

Tjuk Risantoso, Mohammad Hidayat, Hidayat Suyuti, Aulani Niam (Author) 457-463

PDF

Incidence of latrogenic Lumbar Spinal Instability after Laminectomy, Discectomy or Facetectomy

Ahmed A. Hafez, Ahmed Hamdy Ashry, Ahmed Elsayed, Amr El Tayeb, Mohamed Badran Abdel Salam ElShenawy (Author)

588-592

PDF

Tegoeh Winandar, Agus Raharjo, Hari Wujoso, B. Rina A. Sidharta, Budhi Ida Bagus (Author) 1591-1595

PDF

Graptophyllum pictum Extract in the Treatment of Experimental Hemorrhoids: Effects on Vascular Leakage and Matrix Metalloproteinase-9 Levels

Bernadus Parish Budiono, Sigit Adi Presetyo, Ignatius Riwanto, Sulistyaningsih Sulistyaningsih, Eriawan Agung Nugroho (Author)

1785-1789

PDF

Brachial Plexus Injury Surgical Service in Time of Coronavirus Disease 2019 Pandemic Experience from a Single Tertiary Orthopaedic Hospital in Indonesia

Seti Aji Hadinoto, Tito Sumarwoto, Mohammad Erstda Trapsilantya (Author)

PDF

Risk Factors and Incidence of Deep Venous Thrombosis in Non-severe Coronavirus Disease-

Srdjan Babic, Aleksandar Babic, Milica Stojicic, Milena Gencic, Slobodan Tanaskovic, Dragana Radoicic, Predrag Gajin, Igor Atanasijevic, Nenad Ilijevski (Author) 1446-1452

PDF

Arthroscopic Shaver Design Parameters Controlled Laboratory Testing

Nader Hafez, Mostafa R. A. Atia, Amr A. Elfeky, Mohamed El-Anwar (Author) 326-330

PDF

A Prospective Randomized Study of the Safety and Efficacy of Transforaminal Lumbar Interbody Fusion Versus Posterior Lumbar Interbody Fusion in the Treatment of Lumbar Spondylolisthesis: A Cost utility from a Lower-middle-income Country Perspective and Review of Literature

Nasser El-Ghandour, Mohamed Sawan, Atul Goel, Ahmed Assem Abdelkhalek, Ahmad M. Abdelmotleb, Taher Ali, Mohamed S. Abdel Aziz, Mohamed A. R. Soliman (Author) 636-645

Loose Thick Seton Suture Stimulates Rapid Healing and Lower Recurrence Rate in the Treatment of High Type Fistula in Ano

Samer Makki Mohamed Al-Hakkak, Alaa Abood Najim Al-Wadees, Saad Ab-Razq Mijbas, Ashraf Sami MuhammadMuhammad (Author)

1180-1184

PDF

Comparison of the Unilateral and the Bilateral Pedicle Screw Fixation without Using an Interbody Cage: Randomized Clinical Trial

Alexey Lychagin, Vadim Cherepanov, Marina Lipina, Ivan Vyazankin (Author) 398-402

PDF

Dynamics of Quality of Life Indicators in Patients with Chronic Synovitis of the Knee Joint after Arthroscopic Laser Double-mode Synovectomy

Alexey Lychagin, Yang Yanbin, Sergey Ivannikov, Stefka Radenska-Lopovok, Roza Yavlieva, Vladimir Surin, Yuliya Goncharuk, Ivan Vyazankin, Marina Lipina (Author)

1054-1060

PDF

Application of the surgical Apgar score (SAS) to predict postoperative complication(s) in the patients with traumatic brain injury: Study of single center in Indonesia

Muhammad Z. Arifin, Andi N. Sendjaja, Ahmad Faried (Author)

225-229

PDF

Role of Neutrophil-to-Lymphocyte Ratio as a Predictor of Systemic Inflammatory Response Syndrome in Blunt Abdominal Trauma Following Emergency Laparotomy in Sanglah General Hospital, Denpasar

I Made Dwi Purnamantara, I Ketut Wiargitha, Tjok Gede Bagus Mahadewa (Author) 1105-1110

PDF

Postoperative Recovery Quality after General Anesthesia in Patients Undergoing Emergency Surgery

I Gusti Agung Gede Utara Hartawan, Made Violin Weda Yani, Tjokorda Gde Agung Senapathi, I Made Gede Widnyana, Christopher Ryalino, Cynthia Dewi Sinardja, Adinda Putra Pradhana (Author) 715-719

PDF

Correlation of Tumor Necrosis Factor-α Expression with Pain Level in Degenerative Lumbar Canal Stenosis Patients

Ery Kus Dwianingsih, Yudha Mathan Sakti, Rahadyan Magetsari, David Yosua Parulian Hutahaean, Galih Prasetya Sakadewa, Paramita Dyah Lasmana, Nicolaas C. Budhiparama, Ery Kus Dwianingsih (Author) 1135-1139

PDF

The Effect of Topical Corticosteroid Time of Application on Fibroblast and Type III Collagen Expression in Oryctolagus cuniculus with Deep Dermal Burn Wound (As an Indicator for the Best Time to Start Topical Corticosteroid Application in Preventing Hypertrophic Scar)

Loelita Lumintang, I Made Suka Adnyana, Agus Roy Hamid, Hendra Sanjaya, Nyoman Golden, Putu Astawa, Made Darmajaya, I Wayan Juli Sumadi (Author)

964-970

PDF

Perineal Rectosigmoidal Resection for Complete Rectal Prolapse

Hussein Alkatrani, Mamoon Mahmood Basrah (Author)

1727-1729

PDF

The Epidemiology of Knee Arthroscopy during Coronavirus Disease 2019 Pandemic

Asep Santoso, Iwan Budiwan Anwar, Tangkas SMHS Sibarani, Pamudji Utomo, Zarkasyi Arimukti, Ibnu Yudistiro, Muhammad Abdul Hamid (Author)

683-686

PDF

Short and Intermediate Outcome of Endovascular Aortic Aneurysmal Repair, A multicenteric Study

Mohamed Hosny Sayed, Mohammed Ali Hassan, Ahmed Samir Hosny , Hisham Rashid, Mohamed Hosni El Dessoki (Author)

1494-1498

Ashraf Zaghloul, Ahmed Abdelbary, Amr Fergany, Hatem Aboulkassem, Waleed Mohamed Fadlalla (Author)

367-372

PDF

Delayed Treatment of Acute Subdural Hematomas: Retrospective Outcome Analysis of 215 Patients

Kanat Akhmetov, Serik Akshulakov, Yerzhan Adilbekov , Altynshash Jaxybayeva, Mariya Dmitriyeva, Medet Toleubayev (Author)

779-785

PDF

Platelet Concentrate In Lumbar Interbody Cage Fusion: A New Era of Modality Of Fusion

Mohamed Mohi EL din, Ahmed Salah Hassan, Tarek Ahmed Tareef, Mohammad Baraka, Mohamed Gabr Ahmed H. Omar (Author)

356-362

PDF

Assessment of Serum Ionized Calcium in the Perioperative Period in Patients Undergoing Total Thyroidectomy

Muqdad Fuad, Ahmed Modher (Author) 1203-1206

203-120

PDF

Orthopedic Department of Education Center and Service Provide During Coronavirus Disease-2019 Pandemic: An Experience from Single-Center Hospital

Bagus Jati Nugroho, Bintang Soetjahjo, Udi Heru Nefihancoro, Rieva Ermawan, Rhyan Darma Saputra, Galih Santoso Putra, Fathih Kaldani, Muhammad David Perdana Putra, Zaltri Rhani Lebang, Dea Alberta Setiawati (Author)

250-254

PDF

Higher Rate of Patellofemoral Problems After Anterior Cruciate Ligament Reconstruction using Hamstring Autograft

Krisna Yuarno Phatama, Romy Darmawansa, I Gusti Ngurah Arga Aldrian Oktafandi, Felix Cendikiawan, Alva Pribadi, Lasa Dhakka Siahaan, Sholahuddin Rhatomy, Edi Mustamsir (Author)



Three-dimensional printing applications in the neurosurgery: A pilot study

Moneer Faraj, Bassam Arkawazi, Zaid Al-Attar (Author)

403-406

PDF

A Comparative Study of Pediatric Fracture Shaft Femur Fixating by Plate and Screws Using Lateral Approach Between Subvastus Lateralis and Transvastus Lateralis Outcome

Haider O. Hayat Ali Al-Faily, Saif Nabeel Abd Alwahab, Mohammed Sh. Al-Edanni, Sadeq A. Al-Mukhtar, Ghadeer H. Majeed (Author)

1791-1794

PDF

Evaluation of Extreme Hip Joint Movement after Total Hip Arthroplasty: A Retrospective Study

Iwan Budiwan Anwar, Emile van der Heide, J. Jamari, Eko Saputra, Asep Santoso, Denny Adriansyah, Zarkasyi Arimukti (Author)

1296-1300

PDF

Epidemiology and Characteristics of Burn Patients in Dr. Soedarso General Hospital during 2017 – 2020: Retrospective Study

Doni Setiawan, Winsen Haryono (Author)

711-714

PDF

Penetrating Scrotal Injuries: A War Time Experience in a Civilian Setup

Ammar Fadil Abid, Naimet Naoum (Author)

PDF

Robotic Radical Prostatectomy at the Egyptian National Cancer Institute: Overcoming the Challenges in the Initial Case Series

811-815

PDF

Short-term Follow-up of Early Reconstructive Surgery Management in Neglected Supracondylar Humeral Fractures

Tito Sumarwoto, Seti Aji Hadinoto, Herlambang Pranandaru, Hanif Andhika, Cholahuddin Phatomy, Pamudji Utomo (Author)

24-28

PDF

Experiences of Renal Stone Fragmentation with the Use of the Ultrasound-guided Minipercutaneous Nephrolithotipsy in 650 Patients

Duong Van Trung, Trinh Hoang Hoan, Nguyen Van Hoang (Author); Tran Hong Quan 36--41

PDF

Comparative Study between Neopterin and Alvarado Score in the Diagnosis of Acute Appendicitis and Its Severity

Zuhair B. Kamal, Raghad E. Naji, Hiba A. Ali (Author) 42-47

PDF

Autoplasty by Displaced Aponeurotic Flap: Results of a New Method of Inguinal Hernias Surgical Treatment

Saule Tulegenovna Sapiyeva, Nurkassi Tulepbergenovich Abatov, Makash Tynyshtykpaevich Aliyakparov, Yoshihiro Noso, Ruslan Muratovich Badyrov, Elena Sergeevna Badyrova (Author)
48-54

PDF

Management of Infected Charcot Neuroarthropathy due to Diabetes Mellitus with Half Pins External Fixator and Pinning: A Case Series

Maria Florencia Deslivia, Claudia Santosa, Putu Teguh Aryanugraha, Sherly Desnita Savio, Ketut Kris Adi Marta, I Wayan Subawa, Putu Astawa (Author) 60-63

Single Level Lumbar Disk Herniation: Conventional Discectomy versus Interbody Fusion with **Bilateral Pedicular Fixation**

Ahmed K. Abdelaziz, Ehab Abdel Haleem, Ahmed M. Ali, Omar El Falaky, Helmy Abdel Haleem (Author) 122-129

PDF

Ophtalmology

Sensitivity and Specificity of Sheard and Percival's Criteria for the Diagnosis of Young People with Near-heterophoria

Saif Hassan Alrasheed, Amel Mohamed Yousif, Maiid A. Moafa, Abd Elaziz Mohamed Elmadina Mohammad Alobaid (Author)

1128-1134

PDF

Ocular Trauma Trends in Indonesia: Poor Initial Uncorrected Visual Acuity Associated with Mechanism of Injury

Sauli Ari Widjaja, Yoshimune Hiratsuka, Koichi Ono, Ima Yustiarini, Nurwasis Nurwasis, Akira Murakami (Author)

903-908

PDF

Estimation of the Level of Glycosylated Hemoglobin as a Predictor Factor to Bevacizumab Injection in Diabetic Macular Edema in a Sample of Iraqi Patients

Hasanain Hasan Attar, Farooq Mohammed Abbas, Haider Layikh (Author)

1480-1483

PDF

The The Effect of Colors and Positional Noise on Reading Performance with Non-words-Part

Abdullah Alsalhi, Nadia Northway, Glyn Walsh, Abd Elaziz Mohamed Elmadina (Author) 244-249

PDF

PDF

Expression of Cytokeratin 6 and 16 in Middle Ear Cholesteatoma

Jacky Munilson, Yan Edward, Lorensia Fitra Dwita, Hirowati Ali (Author) 1323-1328

PDF

Expressions of Nuclear Factor-kappa B and Peroxisome Proliferator-activated Receptor-**Gamma Proportional with Clinical Staging of Nasopharyngeal Carcinoma**

Farhat Farhat, Elvita Rahmi, Jessy Chrestella, Osvaldo Williamson, Raudah Putri Syari (Author) 1347-1351

PDF

Radiology and Radiotherapy

Intraoral Radiographic Processing Skills among Dentists in Saudi Arabia

Hisham Abbas, Abdullah Isaam Arabi , Badia Baroudi, Shaima'a Makhdom , Mazen Ahmed Alwadani, Elaf Sami Al Akhdar, Ahmad Majed Alshareef (Author)

1027-1030

PDF

Electron Beam Measurements Employing Electron Montecarlo Algorithm on TrueBeam STx® and Clinac iX® Linear Accelerators

Kamal Saidi, Othmane Kaanouch, Hanae El Gouach, Mohamed Reda Mesradi, Mounir Mkimel, Redouane El Baydaoui (Author)

1730-1738

PDF

Descriptive Analysis of Chest Computed Tomography Scan in Coronavirus Disease 2019 Pneumonia: Correlation with Reverse Transcription-polymerase Chain Reaction and Clinical

Rusli Muljadi, Mira Yuniarti, Ricardo Tan, Teodorus Alfons Pratama, Ignatius Bima Prasetya, Allen Widysanto, Gilbert Sterling Octavius (Author)

865-871

PDF

Cyclic Adenosine Monophosphate, Inositol 1,4,5-trisphosphate, Calcium, and Phosphorylated Myosin Light Chain Regulation Through M2 and M3 Muscarinic Receptors of Scleral Fibroblast Cells in Rat Myopia Model

Nanda Wahyu Anandita, Nurdiana Nurdiana, Endang Sri Wahyuni, Hidayat Sujuti (Author) 890-899

PDF

Visual Function of Drivers and its Relation to the Occurrence of Road Traffic Accidents in Saudi Arabia

Sulaiman Aldakhil, Godwin Ovenseri-Ogbomo, Majid Moafa, Waleed Alghamdi, Muhammed Alluwimi, Suliman Alghnam (Author)

1016-1020

PDF

Evaluation of Visual Function Requirements for Public Jobs in Saudi Arabia

Majid A. Moafa, Waleed Alghamdi, Mohammed Alluwimi, Sulaiman Aldakhil, Ismail Abuallut, Mansour Alghamdi, Saif Alrasheed (Author)

608-613

PDF

Association between Artificial Reproductive Technology and Retinopathy of Prematurity

Kiril Slaveykov, Kalina Trifonova, Hristo Mumszhiev (Author)

6-11

PDF

The Effect of Color and Positional Noise on Reading Performance in Human Vision

Abdullah Alsalhi, Nadia Northway (Author); Glyn Walsh; Abd Elaziz Mohamed Elmadina (Author) 130-135

PDF

Ear, Nose and Throat

Nutritional Status of Patients with Nasopharyngeal Carcinoma

Yussy Afriani Dewi, Arief Fakhrizal, Shinta Fitri Boesoirie, Ayu Hardianti Saputri (Author) 1435-1439

The Value of Ultrasound Elastography in Diffuse Thyroid Disease among a Sample of Iraqi **Population**

Hiba Mohammed Abdulwahid, Lubna Ali Hussein, Areege Mustafa Kamal (Author) 1647-1653

PDF

Reevaluation of the Correlations between Ultrasound Features of Thyroid Nodules and **Grades of Bethesda Classification**

Ermal Tako, Blerina Cela, Mailinda Ikonomi (Author)

734-741

PDF

Radiation-induced Mucositis in Patients with Oropharyngeal Cancer Treated with Moderate Acceleration of Intensity-modulated Radiation Therapy and Simultaneous Integrated Boost **Concomitant with Weekly Cisplatin**

Lenche Kostadinova, Gjusen Selim (Author); Petar Chakalaroski, Snezana Smickoska, Marina Stoleska, Danilo Nonkuloski

PDF

Anesthesiology

The Efficacy of O-Mac®, Patent Video Laryngoscope, and Conventional Laryngoscope for Intubation in the Operating Room

Jorza Sepmiko, Tjok Gde Agung Senapathi, Made Wiryana, I. Putu Kurniyanta, I. Made Gede Widnyana, Ida Bagus Krisna Jaya Sutawan (Author)

PDF

Profile of Sepsis Patients Treated in Intensive Care Unit of Sanglah Hospital Denpasar

Merry Merry, I Gusti Agung Gede Utara Hartawan, I Wayan Aryabiantara, Dewa Ayu Mas Shintya Dewi (Author)

1701-1704

Intensive Care

Use of Lung Ultrasound for Assessment of Lung Recruitment Maneuvers in Patients with ARDS

Waheed A. Radwan, Mohamed M. Khaled, Ayman G. Salman, Mohmed A. Fakher, Shady Khatab (Author) 952-963



Lung Ultrasound versus Pulmonary Auscultation in Detecting Pulmonary Congestion in the Critically III

Abdou Ibrahim, Hesham Mohamed Elbeny, Randa Soliman, Soliman Belal (Author)



Comparison of Neutrophil Gelatinase-associated Lipocalin and Renal Resistive Index as Acute Kidney Injury Predictor in Critically III Patients at ICU H. Adam Malik Hospital Medan

Muhammad Aldi Rivai Ginting, Achsanuddin Hanafie, Bastian Lubis (Author)

1637-1639

PDF

What Is Preparedness and Capacity of Intensive Care Service in Indonesia to Response to COVID-19? A Mixed-method Study

Mochamat Helmi, Djayanti Sari, Andreasta Meliala, Laksono Trisnantoro (Author) 1686-1694



Effect of Glucose-Insulin-Potassium Infusion on Hemodynamics in Patients with Septic Shock

Hassan Effat, Ramy Khaled, Ahmed Battah, Mohamed Shehata, Waleed Farouk (Author)



Predictive Score Model of Clinical Outcomes Sepsis in Intensive Care Unit Tertier Referral **Hospital of Eastern Indonesia**

Metta Octora, Ni Made Mertaniasih, Bambang Pujo Semedi, Eko Budi Koendhori (Author)

626-631

PDF

A Preliminary Scoring Model to Predict In-hospital Mortality Risk for Geriatric Patients with

Nyoman Astika, Dwijo Anargha Sindhughosa, R.A. Tuty Kuswardhani, Ida Bagus Amertha Putra Manuaba (Author)

872-877

PDF

Salat Dhuha Improves Haemodynamic: A Randomized Controlled Study

Elman Boy, Aznan Lelo, Amira Permatasari Tarigan, Yetty Machrina, Yusni Yusni, Juliandi Harahap, Rosita Juwita Sembiring, Santi Syafril, Gusbakti Rusip, Cindy Azzahra Freeman (Author) 1695-1700

PDF

The Prevalence of Functional Disability and Associated Factors among Older People Attending Primary Health-care Centers in Riyadh City

Abdullah Alhalafi, Maysoon Al-Amoud, Reema Aldahman, Eman Abd-Ellatif, Doaa Omar (Author) 975-982



Plasma Levels of Interleukin-6 and the Cluster of Differentiation 4/Cluster of Differentiation 8 Ratio in Frailty among Community-dwelling Older People

Sri Sunarti, Nurria Indriyaningrum, Caesarius Wahono, Djoko Soeatmadji, Achmad Rudijanto, Retty Ratnawati, Setyawati Soeharto Karyono, Maryunani Maryunani (Author) 1333-1341

PDF

High Circulating Sclerostin Level as Osteoporosis Risk Factor in Male Geriatric Population at Sanglah Hospital Bali

Sandra Suryarini, RA. Tuty Kuswardhani, I. Gusti Lanang Ngurah Agung Artha Wiguna (Author) 1032-1036



PDF

Ultrasound-Guided Preload Indices during Different Weaning Protocols of Mechanically Ventilated Patients and its Impact on Weaning Induced Cardiac Dysfunction

Dina Zeid, Walid Ahmed, Randa Soliman, Abdou Alazab, Ahmed Samir Elsawy (Author) 1370-1380



Attenuation of the Airway and Cardiovascular Responses to Extubation in Chronic Smokers by Prior Treatment with Dexmedetomidine, Fentanyl, and their Combination

Naglaa A. Ahmed, Ashraf M. Yehia, Ahmed H. Mohamed, Asmaa Abdulwahhab (Author) 1290-1295



Rehabilitation

Therapeutic Education and Physiotherapy in Low Back Pain Management

Stilyana Romanova, Kristin Grigorova, Antoaneta Dimitrova (Author) 1778-1784

PDF

The Use of Bioacoustic Stimulation of the Respiratory System in Complex Medical Rehabilitation at a Health Resort Facility for Patients who have had COVID-associated Pneumonia

Mikhail Bragin, Evgeny Goloborodko, Gennady Erofeev, Sergey Razinkin, Alexey Vladimirovich Sukhinin , Anna Kish, Irina Mikhlik, Ksenia Vladimirovna Zolotareva (Author)

PDF

Geriatrics

The Effect of Walking Exercise and Consumption of Steeping Chamomile Flowers (Matricaria recutita) on Depression in the Elderly in Langsa City

T. Iskandar Faisal, Nuswatul Khaira, Nora Veri, Magfirah Magfirah, Dewita Dewita, Alchalidi Alchalidi, Yuni Sari (Author)

Association of Appendicular Skeletal Muscle Mass and Central Obesity Parameters with Lipid **Profiles in Older Women**

Lazuardhi Dwipa, Syarief Hidayat, Senov Eka Permadi, Evan Susandi, Alif Bagus Rakhimullah, Yuni Susanti Pratiwi (Author)

921-924

PDF

Study of the Incidence of Some Chronic Diseases Among patients with Long-term Physical Disabilities

Sevdalina Alekova Todorova (Author)

1140-1148

PDF

Potential of Omega-3 Supplementation on Muscle Mass, Muscle Strength, and Physical **Performance in Elderly Community**

Nur Riviati, Taufik Indrajaya, Erial Bahar, Dobi Saputra Burni (Author) 55-59

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Clinical Signs and Laboratory Parameters as Predictors of Mortality among Hospitalized Human Immunodeficiency Virus-Infected Adult Patients at Tertiary Hospital in Surabaya

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Abstract

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BACKGROUND: The morbidity and mortality rates due to human immunodeficiency virus (HIV) infection are still high despite various and advanced efforts in the management given for HIV/AIDS patients

AIM: This study proposed that clinical signs and laboratory parameters could be expected to predict the patient's mortality.

METHODS: This retrospective study was done by collecting 408 medical records of adult HIV/AIDS inpatients at a tertiary hospital in Surabaya from January 1, 2017, to December 31, 2019. Bivariate analysis using Chi-square test was carried out on nine variables, which were Glasgow Coma Scale (GCS) <15, hypotension, PaO,/FiO, <400 mmHg, elevated liver enzymes, hemoglobin levels <10 mg/dl, platelet count <150,000/mm³, eGFR <60 ml/min/1.73 m², albumin levels <3.5 mg/dl, and body mass index (BMI) <18.5 kg/m2. Variables which met the criteria would be included in the multivariate analysis using logistic regression.

RESULTS: Based on bivariate analysis, mortality was found to be significantly associated with GCS <15, hypotension, PaO₂/FiO₂, elevated liver enzymes, platelet count <100,000 mm³, eGFR <60 ml/1.73kg/m², albumin levels <3.5 mgdl, and BMI <18.5 kg/m². However, based on multivariate analysis, there were five variables which were found to be able to independently predict the patients' mortality, those were GCS <15 (OR 11.625), hypotension (OR 6.062), PaO_/FiO_< 400 mmHg (OR 7.794), eGFR <60 ml/min/1.73 m² (OR 2.646), and albumin levels <3.5 mg/dl (OR 4.091).

CONCLUSION: GCS <15, hypotension, PaO₂/FiO₂ <400 mmHg, eGFR <60 ml/1.73g/m², and albumin levels < 3.5 mg/dl were found as the independent risk factors which could predict the hospitalized HIV/AIDS patients'

Introduction

Human immunodeficiency virus (HIV) is a retrovirus that attacks human immune cells, especially CD4 T cells, resulting the decreasing of the number of CD4 T cells which then can cause the weakening of body's immune system [1]. HIV can directly damage body's tissues and organs through an inflammatory process that causes organ dysfunction and leads to mortality. Heretofore, HIV/ AIDS has been becoming a global health problem with a high mortality rate and increasing number of sufferers every year [2], [3].

There have been various studies conducted to deepen the understanding of the characteristics and predictor factors of HIV-infected adult people's mortality. Some mortality predictors reported were platelets, glomerular filtration rate, liver function, serum albumin, CD4 values, and body mass index (BMI) [4], [5], [6]. The previous retrospective and prospective studies showed a variety of data relating to the characteristics of the research subject, socioeconomic conditions, and the length of the study conducted [7], [8], [9], [10].

Studies discussing about predictors of mortality among HIV/AIDS patients in Indonesia are still limited, whereas knowing the characteristics and factors that influence mortality is very important to improve medical interventions for HIV/AIDS patients. Therefore, this study was aimed to determine the characteristics and factors that could predict the HIV/ AIDS patients' mortality using simple parameters through clinical signs and laboratory examinations that have been routinely carried out since the beginning of the patient hospitalization.

B - Clinical Sciences Infective Diseases

Methods

Study design and population

This research was conducted at a tertiary referral hospital in Surabava, the capital of the province of East Java which has the highest number of HIV/AIDS sufferers in Indonesia. This study was a retrospective study done by collecting the medical record data which was obtained using systematic sampling from January 1, 2017, to December 31, 2019. The inclusion criteria included medical record of men and women inpatients aged ≥18 years who have been diagnosed with HIV/AIDS. The HIV/AIDS diagnosis was obtained from the ICD coding listed on the medical resume. Some data which were excluded in this study were including medical records of HIV/AIDS patients who discharged at their own request, patients who had traumatic brain injury, patients who had organ dysfunction before being diagnosed with HIV/AIDS, patients who had hematological disorders before being diagnosed with HIV/AIDS, patients diagnosed with cancer that was not related to HIV/AIDS, the pregnant patients, the missing data, the incomplete data, as well as the corrupt data.

Data collection

The data were collected using a data recording form which contained the characteristics and variables of the research. Characteristics of the research's subjects were in the form of demographic and clinical data. The demographic data included the patient's age, gender, place of residence, marital status, education level, HIV risk factors, and length of the hospital stay. Moreover, the clinical data included HIV clinical stage according to the WHO, ART therapy status, Glasgow Coma Scale (GCS), PaO₂/FiO₂ ratio, blood pressure, SGOT level, SGPT level, creatinine level, glomerular filtration rate, hemoglobin level, platelet count, serum albumin level, and BMI.

The independent variables in this study were GCS <15, hypotension, PaO₂/FiO₂ <400 mmHg, elevated liver enzymes, hemoglobin levels <10 mg/dl, platelet counts <150.000/mm³, eGFR <60 ml/min/1.73 m², albumin levels <3.5 mg/dl, and BMI <18.5 kg/m². Hypotension was defined as systolic blood pressure <100 mmHg or diastolic blood pressure <60 mmHg. Elevated liver enzymes were defined as SGOT levels with values above 50 μ/L or SGPT levels with values above 70 μ/L [11]. This study used the CKD-EPI formula for the glomerular filtration rate. Many studies suggested that the CKD-EPI formula was more preferable than MDRD and CG for calculating the glomerular filtration rate in the HIV patient population. The CKD-EPI formula did not require any information regarding body weight, unlike CG which used to bias the results of glomerular filtration rate [10], [12], [13].

Results

In this study, most of the HIV/AIDS patients hospitalized were male with a total of 274 people (67.2%). Furthermore, the female patients were 134 people or 32.8% of total data gained. In terms of age, it was found that the age ranged from 19 years old for the youngest to 70 years old for the eldest. Moreover, data of the patients' marital status were recorded as followed: 204 patients (50%) were married, 158 patients (38.7%) were single, and 46 patients (11.3%) were widowers or widows. In addition, most of the patients, which were 87.5% of total data or 357 patients to be exact, had high school education background.

The average length of HIV/AIDS patient's the hospital stay in this study was 4 days, with 1 day for the shortest treatment duration and 54 days for the longest one. In terms of transmission risk factors, there were 81 patients (19.8%) heterosexual risk, which was the highest risk factor in this study according to the data which has been collected. Most of the patients, specifically 390 patients (95.6%) were domiciled in Surabaya, while only 18 patients (4.4%) were domiciled outside Surabaya. Based on further data from 408 patients who underwent the treatment, it was known that the mortality rate was 31.1% (127/408).

The clinical characteristics used in this study included ART therapy status, the WHO clinical stage, GCS, PaO₂/FiO₂ ratio, systolic and diastolic blood pressure, eGFR, SGOT, SGPT, hemoglobin, platelets, albumin, and BMI. These clinical characteristics are shown in Table 1.

From the medical record data collected, it was known that 207 patients (50.7%) were on ART therapy, 173 patients (42.4%) had never received ART treatment, and 28 patients (6.9%) stopped taking ART treatment. Most of the subjects in this study, as many as 299 patients (73.3%), were at Stage 4 based on the WHO clinical stage. A total of 322 patients (78.9%) had a GCS of 15. The data of PaO_2/FiO_2 ratio showed the ratio value of \geq 400 in 286 patients (70.1%) and <400 in 122 patients (29.9%). As many as 322 patients (78.9%) had systolic blood pressure of \geq 100 mmHg. Moreover, most of the patients had diastolic blood pressure of \geq 60 mmHg, while 46 patients (11.3%) had diastolic blood pressure below 60 mmHg.

Based on the obtained data, there were 312 patients (76.5%) who had eGFR \geq 60 ml/min/1.73 m². The AST data showed that 199 patients (48.8%) had AST \leq 50 μ /L, which was almost the same as those with AST >50 μ /L, specifically 209 patients (51.2%). The SGPT data reported that most patients had SGPT values \leq 70 μ /L, specifically 332 patients (81.4%). As for the hemoglobin data, there was no significant difference between the ones who had Hb \geq 10 mg/dl and the ones

Table 1: Clinical characteristics

Characteristics	n	%	Result
ART therapy status			
Naive	173	42.4	
Receiving ART	207	50.7	
Loss to follow-up	28	6.9	
WHO clinical stage			
Stage 1	0	0	
Stage 2	0	0	
Stage 3	109	26,7	
Stage 4	299	73,3	
GCS		,-	
GCS =15	322	78.9	
GCS <15	86	21.1	
PaO ₂ /FiO ₂	00	21.1	
PaO ₂ /FiO ₂ ≥400	286	70.1	
PaO ₂ /FiO ₂ <400	122	29.9	
Systolic blood pressure	122	23.5	
≥100 mmHq	322	78.9	
<100 mmHg	86	21.1	
Diastolic blood pressure	00	21.1	
	362	88.7	
≥60 mmHg	362 46	00.7 11.3	
<60 mmHg	40	11.3	
eGFR	040	70.5	
eGFR ≥60 ml/menit/1.73 m ²	312	76.5	
eGFR <60 ml/menit/1.73 m ²	96	23.5	
SGOT	100	40.0	
SGOT ≤50 μ/L	199	48.8	
SGOT >50 μ/L	209	51.2	
SGPT 470 #	000	0.1.4	
SGPT ≤70 µ/L	332	81.4	
SGPT >70 µ/L	76	18.6	
Hemoglobin			
Hb ≥10 mg/dl	206	50.5	
Hb <10 mg/dl	202	49.5	
Platelet count			
≥150,000/mm ³	323	79.2	
<150,000/mm ³	85	20.6	
Albumin levels			
≥3.5 mg/dl	154	37.7	
<3.5 mg/dl	254	62.3	
BMI			
BMI ≥18.5 kg/m ²	205	50.2	
BMI <18.5 kg//m ²	203	49.8	

GCS: Glasgow Coma Scale, BMI: Body mass index.

who had Hb <10 mg/dl. There were at least 206 patients (50.5%) who had Hb \geq 10 mg/dl and 202 patients (49.5%) who had Hb <10 mg/dl. In addition, most of the patients, specifically 323 patients (79.2%) had \geq 150,000 platelet count. Moreover, there were 254 patients (62.3%) who had an albumin value <3.5 mg/dl and 205 patients (50.2%) had a BMI \leq 18.5 kg/m².

The bivariate analysis in this study used Chi-square analysis in which if p < 0.05, the variable would be feasible to be included in the multivariate analysis. From the results of the bivariate analysis, there were eight variables that had a significant correlation with the HIV/AIDS patients' mortality, namely, GCS <15 (p = 0.000), the ratio of PaO $_2$ /FiO $_2$ (p = 0.000), hypotension (p = 0.000), eGFR < 60 ml/min/1.73 m² (p = 0.000), platelet count <150.000 mm³ (p = 0.012), albumin level <3.5 mg/dl (p = 0.000), and BMI ≤18.5 kg/m² (p = 0.000). These eight variables would be included in the multivariate analysis to see which variable was dominant in influencing the hospitalized HIV/AIDS patients' mortality.

Multivariate analysis in this study used logistic regression analysis. The multivariate analysis which showed significant independent variables on the HIV/ AIDS patients' mortality in this study was including GCS <15 (OR 11.625), PaO_2/FiO_2 <400 mmHg (OR 7.794), hypotension (OR 6.062), eGFR <60 ml/min/1.73 m² (OR 2.646), and albumin levels <3.5 mg/dl (OR 4.091). These bivariate analysis and multivariate analysis are shown in Table 2.

Table 2: Analysis univariate and multivariate

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
GCS <15	11.960 (6.851-20.878)	0.000	11.625 (5.410-24.981)	0.000
PaO ₂ /FiO ₂ <400 mmHg	11.705 (7.114–19.259)	0.000	7.794 (4.063-14.950)	0.000
Hypotension	12.738 (7.259-22.240)	0.000	6.062 (2.980-12.329)	0.000
eGFR <60 ml/min/1.73 m ²	3.317 (2.061-5.340)	0.000	2.646 (1.314-5.328)	0.008
Elevated transaminase	3.216 (2.051-5.043)	0.000	1.824 (0.946-3.516)	0.104
enzyme				
Hemoglobin <10 mg/dl	1.452 (0.952-2.213)	0.082		
Platelet count	1.873 (1.143-3.069)	0.012		
<150,000/mm ³				
Albumin levels <3.5 mg/dl	5.680 (3.274-9.852)	0.000	4.091 (1.846-9.070)	0.001
BMI <18.5 kg/m ²	2.940 (1.891-4.571)	0.000	1.738 (0.919–3.264)	0.078

GCS: Glasgow Coma Scale, BMI: Body mass index.

Discussion

Neurological disorders associated with HIV/ AIDS include central nervous system infections, vascular complications. peripheral neoplasms. neuropathy, and myopathy, Various studies which have been conducted in developing countries showed that most neurological disorders occurred due to the opportunistic infections [14]. The most frequently used parameter for measuring the impaired central nervous system function is the GCS, which is a neurological scale that aims to assess a person's consciousness. Parameters of organ function disorders, such as APACHE II and SOFA score, classify the central nervous system dysfunction if the GCS is <15 [15].

In this study, GCS <15 was a very significant variable on the hospitalized HIV/AIDS patients' mortality (OR 1.625; CI 95% 5.410–24.981; p = 0.000). The results of this study supported previous study's result in which the patients with GCS <15 had death risk of 7.84 times higher (95% CI 2.03–30.27) [16], [17]. The rate resulted from the previous study was lower than the research we conducted. This could be caused by the differences of the study subjects' characteristics.

Respiratory system disorders are complications which are often found in HIV/AIDS patients and cause morbidity as well as mortality. The mechanism of HIV in causing respiratory system disorders, which in this case is lung damage, is related to systemic and lungs inflammation. Other factors which also play a role in causing lung damage are direct HIV infection to the lungs, smoking, and the effect of ARVs on lung toxicity [18]. PaO_a/FiO_a ratio is an indicator of respiratory disorders, which in this study referred to the limit according to the SOFA score. In this study, PaO₂/FiO₂ ratio had a significant correlation with the mortality of HIV/AIDS patients with an OR 7.794 (95% CI 4.063-14.950). A study using the PaO₂/FiO₂ ratio was also conducted by Chiliza et al. in which the subjects were HIV patients with PCP infection. In this study, the PaO₂/FiO₂ ratio was considered as a significant predictor of mortality (HR 3.8; 95% CI 1.68.9; p = 0.0030) [19]. Likewise, the similar result was also found in a study conducted by Wu et al., in which PaO₂ <70 as one of the mortality predictors had an HR of 7.328 (95% CI 3.621-14.830) on HIV/AIDS patients' mortality [20].

B - Clinical Sciences Infective Diseases

Cardiovascular dysfunction in HIV/AIDS patients can be caused by direct viral mechanisms, opportunistic infections, and the use of ART [21]. The mechanism of the HIV virus in causing myocardial damage remains unclear. However, it is suspected that there are changes in the function of Th lymphocytes which then cause severe inflammation of the myocardium [22]. Opportunistic infections caused by Toxoplasma gondii, Mycobacterium tuberculosis, and Cryptococcus neoformans are common in AIDS myocarditis [23]. Treatment with ARVs, especially for the NRTI group, causes a lot of cardiomyopathy through mitochondrial damage which eventually causes myocardial dilatation and dysfunction. Moreover, hypotension is a condition that occurs due to impaired cardiovascular function. This condition indicates the decreasing of cardiac output which can lead to impaired tissue perfusion [24]. This study found that hypotension correlated significantly with the mortality of HIV/AIDS patients by which an OR of 6.062 (95% CI OR 2.980-12.329). These results supported previous research conducted by Bloomfield et al. which resulted IR value of 5.2 (CI 95% 4.8-5.7) [25].

HIV-infected patients have a higher risk of developing kidney disease, terminal renal failure, and death due to kidney disease. A study carried out on 306 HIV/ AIDS patients in China found that the prevalence of kidney problems experienced by hospitalized HIV/AIDS patients reached 5.56% [26]. Disruption of kidney function in HIV/ AIDS-infected patients can be caused by acute kidney failure, HIV-associated nephropathy, and the presence of comorbid chronic kidney disease [27]. Multivariate analysis done in this study showed that impaired renal function had a significant correlation to HIV/AIDS patients' mortality with an OR 2.646 (95% CI 1.314-5.328). This study supported the research conducted in Jakarta [6] as well as the research conducted by Wyatt et al. However, there was a slight difference between the result of this study and a study conducted by Wyatt et al. Categorized into acute renal failure and chronic kidney disease, Wyatt et al study stated that acute renal failure (OR=5.84; 95% CI 5.11-6.65) possessed higher mortality risk compared to chronic kidney disease (OR=1.97%; 95% CI 1.59-2.45) [28].

Reduced glomerular filtration rate is associated with the increasing of cardiovascular events causing mortality in general population. In populations with decreased glomerular filtration, there was an increase in apolipoprotein B and a decrease in apolipoprotein A1, which is a risk factor for coronary heart disease. It was also found that there was an increase in fibrinogen and homocysteine, as well as C-reactive protein which is associated with atherosclerosis. The atherosclerosis itself can increase the risk of cardiovascular disease in the decreased glomerular filtration population [29]. The decreasing of erythropoietin hormone can cause anemia which then results in increasing the endothelial activation and left ventricular hypertrophy. This condition can increase the cardiovascular risk which leads to morbidity and mortality [30]. Disorders of electrolytes or acid base and fluid retention in impaired kidney function can also increase the mortality risk [6].

Several studies have also tried to find a correlation between low albumin levels and mortality in HIV/AIDS patients. Some have found that hypoalbuminemia could be an independent predictor of HIV/AIDS patients' mortality. Low albumin levels (<3.5 g/ dl) are associated with the progression of HIV patients to AIDS [8], [28]. In subjects with CD4 <200 who had albumin levels <3.5 g/dl, the mortality rate was 8 times higher than those with albumin levels > 3.5 g/dl [8]. Research on the correlation between serum albumin and mortality in HIV/AIDS patients has also been conducted and showed that patients with albumin levels <3.5 g/dl at the beginning of ART therapy had mortality rate 4.53 times higher than the subjects who had albumin levels >3.5 g/dl (95% CI) [31]. In our study, albumin levels <3.5 mg/dl had a significant correlation with the HIV/AIDS patients' mortality (OR 4.091, 95% CI OR 1.846-9.070). Furthermore, receiver operating characteristic (ROC) curve analysis was also performed for the hypoalbuminemia variable. Based on the analysis of the ROC curve, it was found that the area under the curve was 0.751 with p = 0.027. The best cutoff point for albumin level to predict mortality outcome was in the value of 3.02 with sensitivity of 71.7% and specificity of 70.5% (Figure 1).

There were also some variable which showed insignificant result in multivariate analysis, those were platelet count, elevated liver enzymes, and BMI. Platelet count <150,000 mm³ in HIV/AIDS patients causes mortality, generally due to the occurrence

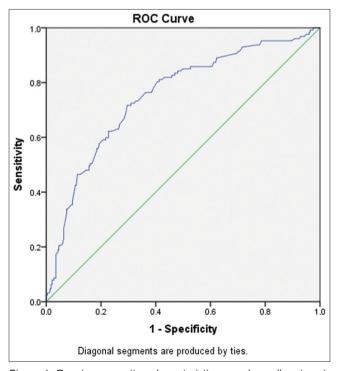


Figure 1: Receiver operating characteristic curve hypoalbuminemia to predict mortality. The best cutoff point value for albumin level for predicting the mortality outcome was 3.02 with sensitivity of 71.7% and specificity of 70.5%

of impaired central nervous system function which caused by intracranial bleeding characterized by the GCS. Elevated liver enzymes can be associated with mortality generally through the occurrence of acute liver failure causing encephalopathy which eventually leads to impaired central nervous system function which is also characterized by GCS. BMI <18.5 kg/m² can cause mortality due to susceptibility toward hypoalbuminemia-associated infection, in which hypoalbuminemia itself showed a significant correlation with HIV/AIDS hospitalized patients' mortality in multivariate analysis.

Conclusion

The mortality percentage of hospitalized HIV/AIDS patients in this study was recorded at the value of 31.1%. Multivariate analysis which showed GCS <15, hypotension, PaO_2/FiO_2 <400 mmHg, eGFR <60 ml/1.73 kg/m², and albumin levels <3.5 mg/dl was found as an independent risk factors for predicting the hospitalized HIV/AIDS patients' mortality. Early intervention on these significant variables is expected to be able to improve the mortality rate of hospitalized HIV/AIDS patients.

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