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H- INDEX

74

PUBLICATION TYPE

Journals

ISSN

11766336, 1178203X

COVERAGE

2006-2025

INFORMATION

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How to publish in this journal

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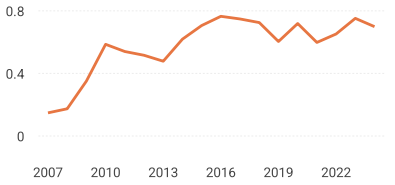

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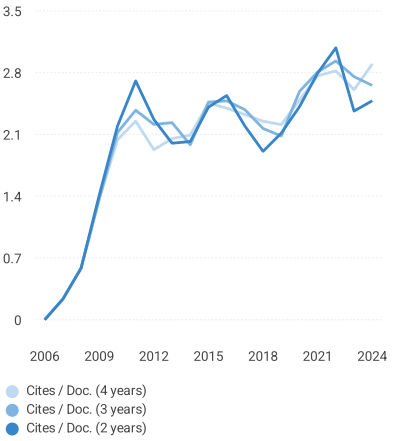

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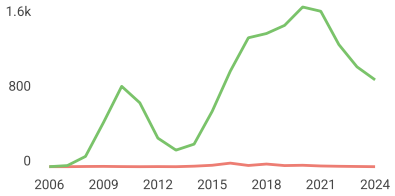

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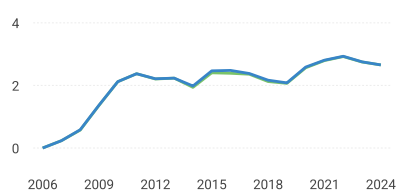

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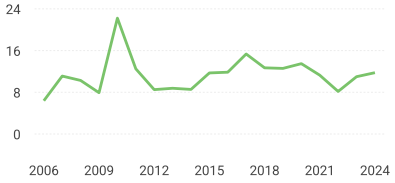

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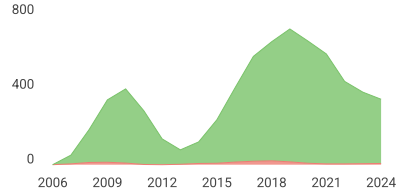

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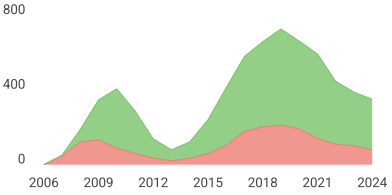

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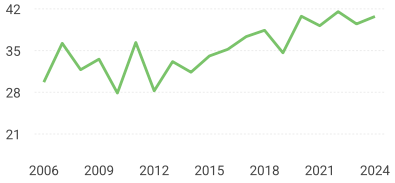

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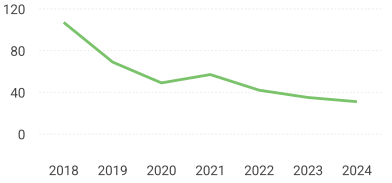

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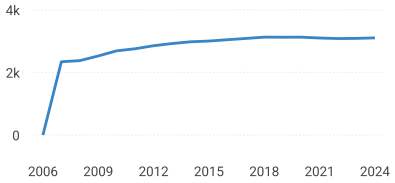

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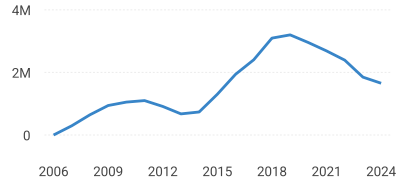

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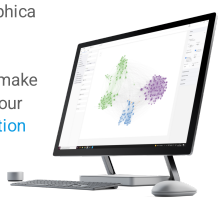

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ISSN: 1178-203X

Professor Garry Walsh

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Emeritus Reader in Inflammation & Immunity, Institute of Medical Sciences, University of Aberdeen, Aberdeen, United Kingdom

Professor Walsh

Dr. Walsh is reader in *Inflammation and Immunity* and principal investigator of the Asthmatic and Allergic Inflammation Group, School of Medicine and Dentistry, University of Aberdeen, UK. His group is part of the Immunology Research Programme, within the Division of Applied Medicine that was rated fourth equal in the UK in the 2008 research assessment exercise.

Dr. Walsh is honorary professor of inflammation and immunity, School of Medicine, Trinity College, Dublin, Ireland. His major research interests involve elucidation of the molecular mechanisms controlling the initiation and resolution of the inflammatory processes underlying asthma, COPD and allergic disease. Dr. Walsh has published over 60 peer-reviewed articles in international journals together with more than 60 invited editorials, reviews and book chapters. To date these publications have been cited over 3,300 times, giving an h-index of 33 (source ISI Web of Knowledge). Dr. Walsh has been an invited speaker and/or chairman at over fifty international meetings. In addition to his role as the editor-in-chief of *Therapeutics and Clinical Risk Management* he is the founding editor of the *Journal of Cell Death,* and *Clinical Medicine - Therapeutics*. He is also an editorial board member of the *Journal of Allergy* (section head), *International Journal of Biomedical Science, Biologics: targets and therapy, The Open Immunology Journal, The Open Inflammation Journal, The Open Allergy Journal* and the *Journal of Organ Dysfunction*.

Dr. Walsh is a regular reviewer for over 40 clinical and scientific journals and serves as a grant reviewer for UK and international funding bodies. Since 2003 he has been a European Commission evaluation expert for FP6 and FP7 and is currently vice-chair of the Evaluation Panel for Marie Curie Mobility Actions. Dr Walsh is a member of the MRC College of Experts affiliated to the Infection and Immunity Board and a member of Lung Cellular and Molecular Immunology (LCMI) Special Emphasis Panel, National Institutes of Health USA.

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ASSOCIATE EDITOR IN CHIEF

Department of Otolaryngology, National University of Singapore, National University Health System, Singapore

Dr. Deyun Wang is a Research Professor (tenure) and Director of Research, Department of Otolaryngology at the National University of Singapore and a member of the Research Task Force and Deputy Chair of the NUS Medicine Safety Committee. He is the International President of the Portmann Institute (France, October 2018-October 2021).

He has published over 350 peer-reviewed papers in prestigious medical journals (e.g., Science, Cell, Nature Biology, Allergy, Journal of Allergy and Clinical Immunology) and over 30 book chapters. He is an Associate Editor of *Allergy*, *Military Medical Research*, *International Archives of Allergy and Immunology*, and member of the editorial boards of more than twenty allergy, ENT and medical journals. He is a member of expert committees for European White Paper in Allergy, WHO Initiative – Allergic Rhinitis and its Impact on Asthma (ARIA 2001 and ARIA 2008), European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS, 2007, 2012, 2020), International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (2016, 2021), and International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis (2018).

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Poswar FDO, Henriques Nehm J, Kubaski F, Poletto E, Giugliani R

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Updated Perspectives on the Management of Drug-Induced Parkinsonism (DIP): Insights from the Clinic

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Therapeutic Options for the Management of Pompe Disease: Current Challenges and Clinical Evidence in Therapeutics and Clinical Risk Management

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Clinical Perspectives on Cardiac Rehabilitation After Heart Failure in Elderly Patients with Frailty: A Narrative Review

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Impulse Oscillometry, Small Airways Disease, and Extra-Fine Formulations in Asthma and Chronic Obstructive Pulmonary Disease: Windows for New Opportunities

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ORIGINAL RESEARCH

Intracranial Solitary Fibrous Tumor/Hemangiopericytoma Treated with Microsurgical Resection: Retrospective Cohort Analysis of a Single-Center Experience

Swaminathan S, Ruzevick J, Venur V, Halasz LM, Rockhill J, Gonzalez-Cuyar L, Cranmer LD, Ferreira Jnr M

Therapeutics and Clinical Risk Management 2022, 18:901-912

Published Date: 5 September 2022

REVIEW

A Health Technology Assessment Based on Chinese Guidelines: Glucagon-Like Peptide-1 Receptor Agonist in the Treatment of Type 2 Diabetes Complicated with Cardiovascular Disease

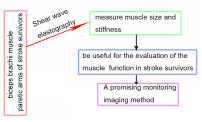
Xie Z, Li J, Yang S, Deng W, Chen J

Therapeutics and Clinical Risk Management 2022, 18:889-900

Published Date: 30 August 2022

ORIGINAL RESEARCH

Quantitative Evaluation of Biceps Brachii Muscle by Shear Wave Elastography in Stroke Patients



Wei HQ, Gan M, Li GY, Ma SH, Liu JH

Therapeutics and Clinical Risk Management 2022, 18:879-887

Published Date: 3 October 2022

ORIGINAL RESEARCH

Long-Term Consequences of Increased Activity of Urine Enzymes After Cardiac Surgery – A Prospective Observational Study

Biernawska J, Kotfis K, Szymańska-Pasternak J, Bogacka A, Bober J

Therapeutics and Clinical Risk Management 2022, 18:867-877

Published Date: 26 August 2022

ORIGINAL RESEARCH

The Association Between Circulating Sex Hormones and Central Serous Chorioretinopathy: A Case-Control Study

Zhao C, Huang Y, Chen L, Ye S, Liu XQ

Therapeutics and Clinical Risk Management 2022, 18:855-865

Published Date: 25 August 2022

ORIGINAL RESEARCH

Biologic Disease-Modifying and Other Anti-Rheumatic Drugs Use in Patients with Moderate-to-Severe Juvenile Idiopathic Arthritis Based on a Japanese Nationwide Claims Database

Hata T, Hirata A, Ota R, Hosohata K, Nishihara M, Neo M, Katsumata T

Therapeutics and Clinical Risk Management 2022, 18:843-853

Published Date: 24 August 2022

ORIGINAL RESEARCH

Impacts of Surgeons' Experience on Patients with Epiretinal Membrane: A Retrospective Study from 2015 to 2020 in Wenzhou Eye Hospital

Lin W, Ren W, Chen H, Wei Y

Therapeutics and Clinical Risk Management 2022, 18:835-841

Published Date: 20 August 2022

CORRIGENDUM

Discrepancy Between Forceps Biopsy and Resection in Colorectal Polyps: A 1686 Paired Screening-Therapeutic Colonoscopic Finding [Corrigendum]

Jiang Y, Wang J, Chen Y, Sun H, Dong Z, Xu S

Therapeutics and Clinical Risk Management 2022, 18:833-834

Published Date: 18 August 2022

EXPERT OPINION

Optimal Use of Perampanel in Elderly Asian Patients with Epilepsy: Expert Opinion

Huang CW, Boonyapisit K, Gunadharma S, Casanova-Gutierrez J, Jin L, Nayak D, Akamatsu N

Therapeutics and Clinical Risk Management 2022, 18:825-832

Published Date: 16 August 2022

ORIGINAL RESEARCH

Comparison of Diagnostic Value Between STE+LDDSE and CMR-FT for Evaluating Coronary Microvascular Obstruction in Post-PCI Patients for STEMI

Liu T, Wang C, Yin J, Wang L, Xuan H, Yan Y, Chen J, Bao J, Li D, Xu T

Therapeutics and Clinical Risk Management 2022, 18:813-823

Published Date: 15 August 2022

REVIEW

Risks of Digestive System Side-Effects of Selective Serotonin Reuptake Inhibitors in Patients with Depression: A Network Meta-Analysis

Wang Z, Li H, Kang Y, Liu Y, Shan L, Wang F

Therapeutics and Clinical Risk Management 2022, 18:799-812

Published Date: 13 August 2022

ORIGINAL RESEARCH

Assessing Metabolic Risk Factors for LVSI in Endometrial Cancer: A Cross-Sectional Study

Lin Q, Lu Y, Lu R, Chen Y, Wang L, Lu J, Ye X

Therapeutics and Clinical Risk Management 2022, 18:789-798

Published Date: 9 August 2022

RETRACTION

Vitamin D Reduces Falls and Hip Fractures in Vascular Parkinsonism but Not in Parkinson's Disease [Retraction]

Sato Y, Iwamoto J, Honda Y, Amano N

Therapeutics and Clinical Risk Management 2022, 18:787-788

Published Date: 10 August 2022

RETRACTION

Experience with Alendronate Treatment for Four Years among Japanese Men with Osteoporosis or Osteopenia and Clinical Risk Factors for Fractures [Retraction]

Iwamoto J, Sato Y, Uzawa M, Takeda T, Matsumoto H

Therapeutics and Clinical Risk Management 2022, 18:785-786

Published Date: 10 August 2022

ORIGINAL RESEARCH

Intertrochanteric Fracture Surgery Patients with Diabetes Mellitus are Prone to Suffer Perioperative Neurological and Endocrine/Metabolic Complications: A Propensity-Score Matched Analysis

Tang Y, Kang L, Guo M, Fan L

Therapeutics and Clinical Risk Management 2022, 18:775-783

Published Date: 6 August 2022

ERRATUM

Practical Management for Use of Eculizumab in the Treatment of Severe, Refractory, Non-Thymomatous, AChR + Generalized Myasthenia Gravis: A Systematic Review [Erratum]

Waheed W, Newman E, Aboukhatwa M, Moin M, Tandan R

Therapeutics and Clinical Risk Management 2022, 18:773-774

Published Date: 3 August 2022

ORIGINAL RESEARCH

Indocyanine Green Retention Test as a Predictor of Postoperative Complications in Patients with Hepatitis B Virus-Related Hepatocellular Carcinoma

Mai RY, Bai T, Luo XL, Wu GB

Therapeutics and Clinical Risk Management 2022, 18:761-772

Published Date: 2 August 2022

REVIEW

Role of Finerenone in the Treatment of Diabetic Kidney Disease: Patient Selection and Clinical Perspectives

Shaikh A, Ray J, Campbell KN

Therapeutics and Clinical Risk Management 2022, 18:753-760

Published Date: 29 July 2022

ORIGINAL RESEARCH

Evaluation of Risk Factors for Distant and Lymph Node Metastasis of Pancreatic Neuroendocrine Tumors

Molasy B, Zemła P, Mrowiec S, Grudzińska E, Kuśnierz K

Therapeutics and Clinical Risk Management 2022, 18:745-752

Published Date: 29 July 2022

ORIGINAL RESEARCH

Modified Perineal Reconstruction Combined with Anal Sphincter Repair for Obstetric Anal Sphincter Injuries

Wang X, Liu YN, Sun D, Chen S, Huang BL, Tai JD

Therapeutics and Clinical Risk Management 2022, 18:739-744

Published Date: 28 July 2022

REVIEW

Is There a Doctors' Effect on Patients' Physical Health, Beyond the Intervention and All Known Factors? A Systematic Review

Schnelle C, Clark J, Mascord R, Jones MA

Therapeutics and Clinical Risk Management 2022, 18:721-737

Published Date: 21 July 2022

REVIEW

Practical Management for Use of Eculizumab in the Treatment of Severe, Refractory, Non-Thymomatous, AChR + Generalized Myasthenia Gravis: A Systematic Review

Waheed W, Newman E, Aboukhatwa M, Moin M, Tandan R

Therapeutics and Clinical Risk Management 2022, 18:699-719

Published Date: 12 July 2022

REVIEW

A Profile of Avelumab Plus Axitinib in the Treatment of Renal Cell Carcinoma

Tiako Meyo M, Chen J, Goldwasser F, Hirsch L, Huillard O

Therapeutics and Clinical Risk Management 2022, 18:683-698

Published Date: 8 July 2022

ORIGINAL RESEARCH

Characteristics and Consequences of Medication Errors in Pediatric Patients Reported to Ramathibodi Poison Center: A 10-Year Retrospective Study

Tansuwannarat P, Vichiensanth P, Sivarak O, Tongpoo A, Promrungsri P, Sriapha C, Wananukul W, Trakulsrichai S

Therapeutics and Clinical Risk Management 2022, 18:669-681

Published Date: 30 June 2022

REVIEW

Zanubrutinib in Treating Waldenström Macroglobulinemia, the Last Shall Be the First

Deshpande A, Munoz J

Therapeutics and Clinical Risk Management 2022, 18:657-668

Published Date: 23 June 2022

ORIGINAL RESEARCH

Management Practice and Drug Related Problems and Its Contributing Factors Among Cervical Cancer Patients at Oncologic Center in Ethiopia: A Hospital-Based Retrospective Study

Kefale B, Engidaw MT, Tesfa D, Molla M, Yismaw MB

Therapeutics and Clinical Risk Management 2022, 18:643-655

Published Date: 10 June 2022

ORIGINAL RESEARCH

Cumulative Doses Predict the Risk of Furosemide-Induced Electrolyte Abnormalities in Critically Ill Neonates

Sridharan K, Al Madhoob A, Al Jufairi M

Therapeutics and Clinical Risk Management 2022, 18:633-641

Published Date: 9 June 2022

REVIEW

An Evaluation of Cabozantinib for the Treatment of Renal Cell Carcinoma: Focus on Patient Selection and Perspectives

Iaxx R, Lefort F, Domblides C, Ravaud A, Bernhard JC, Gross-Goupil M

Therapeutics and Clinical Risk Management 2022, 18:619-632

Published Date: 2 June 2022

ORIGINAL RESEARCH

Outcomes of 2111 COVID-19 Hospitalized Patients Treated with Hydroxychloroquine/Azithromycin and Other Regimens in Marseille, France, 2020: A Monocentric Retrospective Analysis

Lagier JC, Million M, Cortaredona S, Delorme L, Colson P, Fournier PE, Brouqui P, Raoult D, Parola P

Therapeutics and Clinical Risk Management 2022, 18:603-617

Published Date: 31 May 2022

ORIGINAL RESEARCH

Extensive Radiological Manifestation in Patients with Diabetes and Pulmonary Tuberculosis: A Cross-Sectional Study

Zhan S, Juan X, Ren T, Wang Y, Fu L, Deng G, Zhang P

Therapeutics and Clinical Risk Management 2022, 18:595-602

Published Date: 23 May 2022

RESPONSE TO LETTER

The Role of D-Dimers in the Initial Evaluation of COVID-19 [Response To Letter]

Baroiu L, Lese AC, Stefanopol IA, Iancu A, Dumitru C, Ciubara AB, Bujoreanu FC, Baroiu N, Ciubara A, Nechifor A, Anghel L, Tatu AL

Therapeutics and Clinical Risk Management 2022, 18:593-594

Published Date: 20 May 2022

ORIGINAL RESEARCH

Development and Validation of a Predictive Nomogram with Age and Laboratory Findings for Severe COVID-19 in Hunan Province, China

Jiang J, Zhong W, Huang W, Gao Y, He Y, Li X, Liu Z, Zhou H, Fu Y, Liu R, Zhang W

Therapeutics and Clinical Risk Management 2022, 18:579-591

Published Date: 17 May 2022

ORIGINAL RESEARCH

The Changes of Thyroid Function and Related Factors in Critical Patients without Thyroid Illness in ICU: A Retrospective Cross-Sectional Study

Zhang JN, Zhao XL

Therapeutics and Clinical Risk Management 2022, 18:571-578

Published Date: 16 May 2022

ORIGINAL RESEARCH

Discrepancy Between Forceps Biopsy and Resection in Colorectal Polyps: A 1686 Paired Screening-Therapeutic Colonoscopic Finding

Jiang Y, Wang J, Chen Y, Sun H, Dong Z, Xu S

Therapeutics and Clinical Risk Management 2022, 18:561-569

Published Date: 16 May 2022

ORIGINAL RESEARCH

Surgical Treatment of Clavicular Fractures, Refractures, Delayed and Non-Unions Using a Resorbable, Gentamicin-Eluting Calcium Sulphate/Hydroxyapatite Biocomposite

Peters J, Singh G, Hakobyan H

Therapeutics and Clinical Risk Management 2022, 18:551-560

Published Date: 9 May 2022

ORIGINAL RESEARCH

Which Frailty Evaluation Method Can Better Improve the Predictive Ability of the SASA for Postoperative Complications of Patients Undergoing Elective Abdominal Surgery?

Yin Y, Jiang L, Xue L

Therapeutics and Clinical Risk Management 2022, 18:541-550

Published Date: 5 May 2022

REVIEW

Systematic Review and Meta-Analysis on Colorectal Anastomotic Techniques

Steger J, Jell A, Ficht S, Ostler D, Eblenkamp M, Mela P, Wilhelm D

Therapeutics and Clinical Risk Management 2022, 18:523-539

Published Date: 4 May 2022

REVIEW

Clinical, Imaging, Histological and Surgical Aspects Regarding Giant Paraovarian Cysts: A Systematic Review

Stefanopol IA, Baroiu L, Neagu AI, Danila DM, Nechifor A, Miulescu M, Balan G, Vasile CI, Niculet E, Tatu AL

Therapeutics and Clinical Risk Management 2022, 18:513-522

Published Date: 29 April 2022

LETTER

Letter to the Editor: The Role of D-Dimers in the Initial Evaluation of COVID-19 [Letter]

Patel S

Therapeutics and Clinical Risk Management 2022, 18:511-512

Published Date: 28 April 2022

ORIGINAL RESEARCH

Treatment and Outcome of Castleman Disease: A Retrospective Report of 31 Patients

Tang D, Guo Y, Tang Y, Wang H

Therapeutics and Clinical Risk Management 2022, 18:499-509

Published Date: 26 April 2022

ORIGINAL RESEARCH

The Course and Anatomical Characteristics of Sciatic and Femoral Nerves in Unilateral Crowe Type-IV Hip Dysplasia

Song P, Kong X, Yang M, Ma M, Chai W

Therapeutics and Clinical Risk Management 2022, 18:491-497

Published Date: 26 April 2022

REVIEW

Is There a Surgeons' Effect on Patients' Physical Health, Beyond the Intervention, That Requires Further Investigation? A Systematic Review

Schnelle C, Clark J, Mascord R, Jones MA

Therapeutics and Clinical Risk Management 2022, 18:467-490

Published Date: 26 April 2022

ORIGINAL RESEARCH

A Nomogram for Predicting In-Hospital Major Adverse Cardio- and Cerebro-Vascular Events in Patients Undergoing Major Noncardiac Surgery: A Large-Scale Nested Case-Control Study

Wu X, Zhang J, Hu M, Gu L, Li K, Yang X

Therapeutics and Clinical Risk Management 2022, 18:457-465

Published Date: 22 April 2022

REVIEW

Role of Atogepant in the Treatment of Episodic Migraines: Clinical Perspectives and Considerations

Cohen F, Yuan H

Therapeutics and Clinical Risk Management 2022, 18:447-456

Published Date: 22 April 2022

ORIGINAL RESEARCH

Tuberculosis Surveillance in Romania Among Vulnerable Risk Groups Between 2015 and 2017

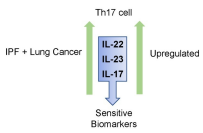
Munteanu I, Cioran N, van Hest R, Abubakar I, Story A, Chiotan D, de Vries G, Mahler B

Therapeutics and Clinical Risk Management 2022, 18:439-446

Published Date: 20 April 2022

ORIGINAL RESEARCH

Diagnostic Value of Serum Levels of IL-22, IL-23, and IL-17 for Idiopathic Pulmonary Fibrosis Associated with Lung Cancer



Zhang Q, Tong L, Wang B, Wang T, Ma H

Therapeutics and Clinical Risk Management 2022, 18:429-437

Published Date: 19 April 2022

ORIGINAL RESEARCH

High Measures of Pre-Chemoradiotherapy Platelet-to-Albumin Ratio Indicates Poor Prognosis in Locally Advanced Pancreatic Cancer Patients

Kucuk A, Topkan E, Selek U, Haksoyler V, Mertsoylu H, Besen AA, Pehlivan B

Therapeutics and Clinical Risk Management 2022, 18:421-428

Published Date: 14 April 2022

ORIGINAL RESEARCH

An Analysis of the Risk Factors for Adding-on Phenomena After Posterior Hemivertebral Resection and Pedicle Screw Fixation for the Treatment of Congenital Scoliosis Caused by Hemivertebral Malformation

Bao BX, Yan H, Tang JG, Qiu DJ, Wu YX, Cheng XK

Therapeutics and Clinical Risk Management 2022, 18:409-419

Published Date: 13 April 2022

REVIEW

Once-Daily Abrocitinib for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults and Adolescents Aged 12 Years and Over: A Short Review of Current Clinical Perspectives

Niculet E, Bobeica C, Stefanopol IA, Pelin AM, Nechifor A, Onisor C, Tatu AL

Therapeutics and Clinical Risk Management 2022, 18:399-407

Published Date: 13 April 2022

ORIGINAL RESEARCH

Optimal Medical Therapy for Secondary Prevention of Acute Coronary Syndrome: A Retrospective Study from a Tertiary Hospital in Sudan

Ahmed KO, Ahmed AM, Wali MB, Ali AH, Azhari MM, Babiker A, Yousef BA, Muddather HF

Therapeutics and Clinical Risk Management 2022, 18:391-398

Published Date: 8 April 2022

ORIGINAL RESEARCH

The Use of Muscle Relaxants and Reversal Agents in a Setting Without Cost Restrictions: Experience from a Tertiary Academic Hospital in the Netherlands

Martini CH, Honing GHM, Bash LD, Olofsen E, Niesters M, van Velzen M, Dahan A, Boon M

Therapeutics and Clinical Risk Management 2022, 18:379-390

Published Date: 8 April 2022

REVIEW

Migraine Prevention with Erenumab: Focus on Patient Selection, Perspectives and Outcomes

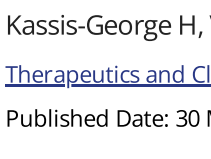
De Matteis E, Sacco S, Ornello R

Therapeutics and Clinical Risk Management 2022, 18:359-378

Published Date: 5 April 2022

ORIGINAL RESEARCH

Single Nucleotide Polymorphism in the 3' Untranslated Region of PRKAA2 on Cardiometabolic Parameters in Type 2 Diabetes Mellitus Patients Who Received Metformin



Virginia DM, Patramurti C, Fenty, Setiawan CH, Julianus J, Hendra P, Susanto NAP

Therapeutics and Clinical Risk Management 2022, 18:349-357

Published Date: 5 April 2022

ORIGINAL RESEARCH

Recombinant Activated Factor VII in Aortic Surgery for Patients Under Hypothermic Circulatory Arrest

Ise H, Ushioda R, Kanda H, Kimura F, Saijo Y, Akhyari P, Lichtenberg A, Kamiya H

Therapeutics and Clinical Risk Management 2022, 18:337-348

Published Date: 5 April 2022

ORIGINAL RESEARCH

The Role of D-Dimers in the Initial Evaluation of COVID-19

Baroiu L, Lese AC, Stefanopol IA, Iancu A, Dumitru C, Ciubara AB, Bujoreanu FC, Baroiu N, Ciubara A, Nechifor A, Anghel L, Tatu AL

Therapeutics and Clinical Risk Management 2022, 18:323-335

Published Date: 31 March 2022

REVIEW

Vericiguat in Heart Failure with a Reduced Ejection Fraction: Patient Selection and Special Considerations

Kassis-George H, Verlinden NJ, Fu S, Kanwar M

Therapeutics and Clinical Risk Management 2022, 18:315-322

Published Date: 30 March 2022

REVIEW

Ultrasound-Guided Posterior Quadratus Lumborum Block for Acute Postoperative Analgesia in Adult Patients: A Meta-Analysis of Randomized Controlled Trials

Lin C, Wang X, Qin C, Liu J

Therapeutics and Clinical Risk Management 2022, 18:299-313

Published Date: 29 March 2022

ORIGINAL RESEARCH

Clinical Efficacy of a Combination of Thymopentin and Antituberculosis Drugs in Treating Drug-Resistant Pulmonary Tuberculosis: Meta Analysis

Han YR, Wang TH, Gong WP, Liang JQ, An HR

Therapeutics and Clinical Risk Management 2022, 18:287-298

Published Date: 25 March 2022

REVIEW

Avatrombopag for the Treatment of Adult Patients with Chronic Immune Thrombocytopenia (cITP): Focus on Patient Selection and Perspectives

Tsykunova G, Ghanima W

Therapeutics and Clinical Risk Management 2022, 18:273-286

Published Date: 24 March 2022

ORIGINAL RESEARCH

Early Detection of Iron Overload Cardiomyopathy in Transfusion Dependent Thalassemia Patients in Sulaimaniyah City, Iraq

Ahmed RA, Salih AF, Omer SH, Rahman HS, Rasool LK

Therapeutics and Clinical Risk Management 2022, 18:259-271

Published Date: 22 March 2022

CLINICAL TRIAL REPORT

Strategy to Reduce Hypercapnia in Robot-Assisted Radical Prostatectomy Using Transcutaneous Carbon Dioxide Monitoring: A Prospective Observational Study

Lee HJ, Chae JS, An SM, Oh HW, Kim YJ, Woo JH

Therapeutics and Clinical Risk Management 2022, 18:249-258

Published Date: 17 March 2022

REVIEW

Diagnosis and Management of Genetic Causes of Middle Aortic Syndrome in Children: A Comprehensive Literature Review

Lazea C, Al-Khzouz C, Sufana C, Miclea D, Asavoaie C, Filimon I, Fufezan O

Therapeutics and Clinical Risk Management 2022, 18:233-248

Published Date: 16 March 2022

REVIEW

Evaluating the Safety of Maribavir for the Treatment of Cytomegalovirus

Gandhi RG, Kotton CN

Therapeutics and Clinical Risk Management 2022, 18:223-232

Published Date: 12 March 2022

ORIGINAL RESEARCH

Left Atrial Strain Helps Identifying the Cardioembolic Risk in Transient Ischemic Attacks Patients with Silent Paroxysmal Atrial Fibrillation

Arnăutu SF, Morariu VI, Arnăutu DA, Tomescu MC, Dan TF, Jianu CD

Therapeutics and Clinical Risk Management 2022, 18:213-222

Published Date: 10 March 2022

ORIGINAL RESEARCH

Effects of Combination Treatment in Hypertensive Patients with Depression: A Systematic Review and Meta-Analysis of 27 Randomized Controlled Trials

Wang L, Liu Q, Sun D, Xie J, Lao D, Zhang L

Therapeutics and Clinical Risk Management 2022, 18:197-211

Published Date: 5 March 2022

REVIEW

Research Progress of Olfactory Nerve Regeneration Mechanism and Olfactory Training

Hu B, Zhang J, Gong M, Deng Y, Cao Y, Xiang Y, Ye D

Therapeutics and Clinical Risk Management 2022, 18:185-195

Published Date: 5 March 2022

EXPRESSION OF CONCERN

Vitamin D Reduces Falls and Hip Fractures in Vascular Parkinsonism but Not in Parkinson's Disease [Expression of Concern]

Sato Y, Iwamoto J, Honda Y, Amano N

Therapeutics and Clinical Risk Management 2022, 18:183-184

Published Date: 4 March 2022

REVIEW

An Evaluation of the Efficacy and Safety of Vibegron in the Treatment of Overactive Bladder

Frankel J, Staskin D, Varano S, Kennelly MJ, Jankowich RA, Haag-Molkenteller C

Therapeutics and Clinical Risk Management 2022, 18:171-182

Published Date: 3 March 2022

ORIGINAL RESEARCH

Development and Validation of a Clinical and Laboratory-Based Nomogram for Predicting Coronary Microvascular Obstruction in NSTEMI Patients After Primary PCI

Liu T, Wang C, Wang L, Shi X, Li X, Chen J, Xuan H, Li D, Xu T

Therapeutics and Clinical Risk Management 2022, 18:155-169

Published Date: 27 February 2022

ORIGINAL RESEARCH

Comparison of Outcome and Quality of Life Between Thulium Laser (VelaTM XL) Enucleation of Prostate and Bipolar Transurethral Enucleation of the Prostate (B-TUEP)

Chen YT, Hou CP, Juang HH, Lin YH, Yang PS, Chang PL, Chen CL, Weng SC, Tsui KH

Therapeutics and Clinical Risk Management 2022, 18:145-154

Published Date: 24 February 2022

ORIGINAL RESEARCH

Percutaneous Internal Ring Suturing (PIRS) – The Benefits of Laparoscopic Inguinal Hernia Repair

Wolak PK, Strzelecka A, Piotrowska - Gall A, Wolak PP, Piotrowska I, Dąbrowska K, Wróbel J, Nowak-Starz G

Therapeutics and Clinical Risk Management 2022, 18:135-144

Published Date: 22 February 2022

ORIGINAL RESEARCH

Poor Sensorium at the Time of Intubation Predicts Polymicrobial Ventilator Associated Pneumonia

Natarajan R, Ramanathan V, Sistla S

Therapeutics and Clinical Risk Management 2022, 18:125-133

Published Date: 17 February 2022

ORIGINAL RESEARCH

A Real-World Study of Recombinant Human Growth Hormone in the Treatment of Idiopathic Short Stature and Growth Hormone Deficiency

Gou P, Cheng X, Leng J, Su N

Therapeutics and Clinical Risk Management 2022, 18:113-124

Published Date: 16 March 2022

ORIGINAL RESEARCH

Multivariable Analysis of Risk Factors Affecting Dislocation After Bipolar Hemiarthroplasty in Patients with Femoral Neck Fracture

Yang Y, Fu G, Li Q, Zhang R, Liao W, Ma Y, Zheng Q

Therapeutics and Clinical Risk Management 2022, 18:101-111

Published Date: 9 February 2022

REVIEW

Efficacy and Safety Profile of Remimazolam for Sedation in Adults Undergoing Short Surgical Procedures

Morimoto Y

Therapeutics and Clinical Risk Management 2022, 18:95-100

Published Date: 2 February 2022

REVIEW

Effectiveness of Biofeedback Therapy in Patients with Bowel Dysfunction Following Rectal Cancer Surgery: A Systemic Review with Meta-Analysis

Li H, Guo C, Gao J, Yao H

Therapeutics and Clinical Risk Management 2022, 18:71-93

Published Date: 2 February 2022

ORIGINAL RESEARCH

Risk Factors for Asymptomatic and Symptomatic Intracranial Atherosclerosis Determined by Magnetic Resonance Vessel Wall Imaging in Chinese Population: A Case–Control Study

Han Y, Zhang R, Yang D, Li D, Han H, Qiao H, Chen S, Wang Y, Yu M, Hong Y, Wang Z, Zhao X, Liu G

Therapeutics and Clinical Risk Management 2022, 18:61-70

Published Date: 12 January 2022

REVIEW

Pediatric Adrenal Insufficiency: Challenges and Solutions

Nisticò D, Bossini B, Benvenuto S, Pellegrin MC, Tornese G

Therapeutics and Clinical Risk Management 2022, 18:47-60

Published Date: 11 January 2022

ORIGINAL RESEARCH

Prognostic Implications of the Admission Cardiac Troponin I Levels and Door-to-Balloon Time on Clinical Outcomes in Patients with ST-Segment Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention

Zhao L, Xin M, Piao X, Zhang S, Li Y, Cheng XW

Therapeutics and Clinical Risk Management 2022, 18:31-45

Published Date: 7 January 2022

PERSPECTIVES

Nutritional and Physical Prehabilitation in Elective Orthopedic Surgery: Rationale and Proposal for Implementation

Briguglio M, Wainwright TW

Therapeutics and Clinical Risk Management 2022, 18:21-30

Published Date: 6 January 2022

ORIGINAL RESEARCH

Efficacy and Safety of Radiofrequency Ablation for the Treatment of Autonomously Functioning Thyroid Nodules: A Long-Term Prospective Study

Vu DL, Pham MT, Nguyen VB, Le TM

Therapeutics and Clinical Risk Management 2022, 18:11-19

Published Date: 6 January 2022

ORIGINAL RESEARCH

Delays to Hospital Presentation in Women and Men with ST-Segment Elevation Myocardial Infarction: A Multi-Center Analysis of Patients Hospitalized in New York City

Weininger D, Cordova JP, Wilson E, Eslava DJ, Alviar CL, Korniyenko A, Bavishi CP, Hong MK, Chorzempa A, Fox J, Tamis-Holland JE

Therapeutics and Clinical Risk Management 2022, 18:1-9

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Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Single Nucleotide Polymorphism in the 3' Untranslated Region of *PRKAA2* on Cardiometabolic Parameters in Type 2 Diabetes Mellitus Patients Who Received Metformin

Dita Maria Virginia[1], Christine Patramurti[2], Fenty[1,3], Christianus Heru Setiawan[1], Jeffry Julianus[2], Phebe Hendra[1], Nicholas Adi Perdana Susanto[3]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Sanata Dharma University, Yogyakarta, Indonesia; [2]Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Sanata Dharma University, Yogyakarta, Indonesia; [3]Bethesda Lempuyangwangi Hospital, Yogyakarta, Indonesia

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Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: https://youtu.be/AU5nCCK6s_g

Purpose: This study aimed to explore the association of *rs857148* A>C as 3′UTR variants with blood pressure, HbA1c profile, and lipid profiles as cardiometabolic parameters among patients with T2DM receiving metformin.

Patients and Methods: This cross-sectional analytic research was conducted with 114 consecutively selected patients with T2DM. Polymerase chain reaction-restriction fragment length polymorphism was conducted to determine *rs857148*. A total of 108 patients fulfilled inclusion and exclusion criteria.

Results: Genotype distribution agreed with the Hardy Weinberg Equation for Equilibrium ($p>0.05$) but wildtype allele was found as the minor allele. Subjects with CC genotype and C allele had enhanced HbA1c levels (OR=7.12; 95% CI=1.05–48.26; $p=0.04$; OR=1.66; 95% CI=1.06–2.60; $p=0.03$, respectively). It was confirmed by dominant model whereas subjects with AA tended to have reduced HbA1c compared to AC+CC genotype (OR=0.15; 95% CI=0.02–0.97; $p=0.047$). AC genotype had significant correlation to total cholesterol (OR=1.05; 95% CI=1.01–1.10; $p=0.03$) compared to AA genotype.

Conclusion: We conclude that polymorphism of *rs87148*, specifically CC genotype and C allele, has a significant association with HbA1c and total cholesterol after considering oral hypoglycemia agent dose, age, gender, and combination therapy, compared to AA genotype. Future studies that involve a larger sample population and more rigorous selection criteria are required.

Keywords: *PRKAA2*, rs857148, 3′UTR, cardiometabolic, type 2 diabetes mellitus

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is regarded as a serious public health problem, especially in developing countries.[1] Metformin is recommended as a cornerstone for initial therapy of T2DM. However, additional therapy may be added in combination when the target HbA1c has not been achieved.[2,3] Remarkably, the T2DM prevalence in Indonesia has been rising in the last two decades,[4] especially among the urban population.[5] Studies related to metformin efficacy either monotherapy or combination in Indonesian population found that our patients tend to have poor glycemic control.[6–8]

Several publications have declared glycemic response variations of metformin therapy, either monotherapy or combination therapy.[9–11] Furthermore, a group of patients could not tolerate the metformin's side effects.[12] A study among patients with T2DM who were covered national health insurance in Indonesia confirmed that the patients reported

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metformin side effects in the gastrointestinal tract.[13] On the other hand, it is well known that the main pharmacological mechanism of metformin is reducing gluconeogenesis in the liver besides sensitizing insulin and improving GLP-1.[14,15] Notably, adenosine monophosphate protein kinase (AMPK) contributed as the main target of the metformin mechanism.[16,17]

Individual genetic imprints are one of the causes of metformin effectiveness variability. The previous study confirmed that genetic variations affect metformin efficacy regarding pharmacokinetics and pharmacodynamics of metformin.[18–21] Recently, AMPK is the focused enzyme related to metformin pharmacodynamic. Xiao et al in 2021 reported that one of the subunits of AMPK, which is *PRKAG2*, is associated with metformin response among Chinese patients with T2DM.[21] AMPK has 3 subunits whereas AMPKα2, encoded by *PRKAA2*, plays a pivotal role during Thr-172 phosphorylation.[22,23]

Metformin has been reported to have a beneficial effect on blood pressure and lipid profiles. Hypertension risk could be reduced among metformin users who are newly diagnosed with T2DM.[24] Metformin has proven blood pressure reduction in patients with T2DM compared with insulin therapy.[25] Monotherapy metformin could significantly reduce triglyceride and low-density lipoprotein cholesterol (LDL-c) levels, and enhance (high-density lipoprotein cholesterol) HDL-c.[26] The various international guidelines recommend detecting and monitoring cardiometabolic parameters in addition to HbA1c level in patients with T2DM.[2,3] Therefore, it is important to assess cardiometabolic parameters to reduce cardiovascular disease risk in patients with T2DM.[27,28] Virginia et al in 2021 demonstrated that the *PRKAA2* genetic variation (rs9803799) had a significant association to cardiovascular risk among patients with T2DM receiving monotherapy metformin.[29]

However, few studies have observed the association of cardiometabolic parameters and AMPK subunit genetic variations. Single nucleotide polymorphism (SNP) rs857148 is a 3' untranslated region (UTR) of *PRKAA2* and located in chromosome 1:5,670,948.[30] Although this SNP is not located in the exon area, the 3' UTR has been confirmed to affect DNA stability and the micro RNA/mRNA interaction, mRNA stability, localization, translation, and degradation.[31–33] Therefore, this present study aimed to observe the influence of 3' UTR *PRKAA2* variants, especially rs857148 A>C, on blood pressure, HbA1c profile, and lipid profiles as cardiometabolic parameters among patients with T2DM consuming metformin.

Materials and Methods

This observational analytic research using a cross-sectional study design was conducted at the Bethesda Lempuyangwangi Hospital, Yogyakarta, Indonesia. The study included patients with T2DM who were 35–75 years old using national health coverage and have been consuming metformin either monotherapy or combination therapy for a minimum of 3 months consecutively. We excluded patients with other types of diabetes mellitus, including type 1, monogenic, and gestational, had eGFR<30 mL/min, and refused to sign informed consent. The minimum sample size was 98 participants according to our study design and using type 1 error rate 0.05, power 0.8, predicted risk ratio 2.0, and proportion 0.3. A total of 114 patients with T2DM were consecutively recruited in this study, and only 6 participants were excluded because they did not receive metformin.

Patient's data related to age, gender, blood pressure, and medication information were collected from medical records. Biochemical and genotyping data were obtained from blood samples were which collected during appointments. This study was approved by the Medical and Health Research Ethics Committee of Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (KE/FK/0520/EC/2021) and data were complied with the principles established by Declaration of Helsinki and promoted by the Committee on Publication Ethics (COPE). All enrolled participants signed an informed written consent before participating.

Biochemical Analysis

Blood samples were collected in the morning after 8–10 h fasting by venipuncture. Clinical biochemical analyses were performed at the Laboratory of Bethesda Lempuyangwangi Hospital. Laboratory tests included HbA1c and lipid profiles (total cholesterol, HDL-c, LDL-c, and triglycerides), which were measured in fresh samples. HbA1c was assayed using tetradecyl trimethyl ammonium bromide. Total cholesterol levels were determined by cholesterol oxidase method/CHOD

PAP. HDL-c and LDL-c were analyzed using direct methods. Glycerol-3-phosphate oxidase was applied to measure triglyceride levels.

DNA Extraction and Genotyping Analysis

Genomic DNA was extracted from peripheral blood in the K3EDTA tube by FavorPrep™ Genomic DNA Extraction Mini Kit following manufacturing procedures. The quality of DNA was evaluated using electrophoresis. Extracted DNA samples were stored at −70°C until genotyping analysis. Single nucleotide polymorphism (SNP) rs857148 was selected according to the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/). Genotyping was performed using polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP). One set of primers of forward 5'- GACTAAGTTTCTCCTGTGTTAGTGG-3' and reverse 5'-TTCCCAAAAGAGGTATGGACCC-3' was applied for the amplification 369 bp. Each individual sample contained 5 µL of DNA which was mixed with 12.5 µL of the GoTaq Green Master Mix® in a PCR tube. Following an initial denaturation step at 95 °C for 5 min. We conducted thirty five cycles of amplification including, denaturation (95°C for 20s), annealing (56.1°C for 30s) and extension (72°C for 30s), with a final extension step at 72°C for 5 min. The PCR products were electrophoresed on a 3% agarose gel to check PCR product size. *BSuRI* restriction enzyme (ThermoScientific) was applied to detect rs857148 in the *PRKAA2*. The reaction mixtures were incubated at 37°C for 2 h, were inactivated at 37°C for 20 min, then were electrophoresed on 1.5% agarose gel.

We did PCR condition optimization, including annealing temperature and primer concentration. Incubation duration during the restriction process was also optimized. Validation of genotyping procedure was done through replication of several samples randomly using the same method which was PCR-RFLP.

Statistical Analysis

Data are expressed as frequency (percentage) for categorical variables or as mean±standard deviation (SD) for continuous variables. We performed Anova or Kruskal Wallis as appropriate to compare clinical characteristics between *rs857148* genotypes. Multinomial logistic regression analysis was used to determine the association of *rs857148* with hypertension, HbA1c level, and lipid profile, where hypertension categorized as blood pressure >130/>80 mmHg. Multiple inherited models including dominant, recessive, and allelic models were applied to estimate the influence of *rs857148* on cardiometabolic parameters. A two tailed p-value < 0.05 was considered significant statistically. Two regression models were constructed to adjust potential confounders. Model 1 was adjusted for metformin dose, combination either sulfonylurea or insulin. Additionally, model 2 was adjusted for age, gender, metformin dose, glimepiride dose, and combination either sulfonylurea or insulin. We conducted all statistical procedures using SPSS software version 25.0 (IBM Corp., Armonk, NY)).

Results

Table 1 presents participants' characteristics with an average age 60.58±8.16 years old and predominately female subjects. Interestingly, the mean of HbA1c was considered poor glycemic control, but the mean of lipid profiles was adequate. Metformin as combination therapy was predominantly prescribed in our study sample.

We obtained different patterns of our PCR products after applying the BSuRI enzyme: wildtype homozygote (AA) indicated by one band of 369 bp, heterozygote (AC) indicated by three bands of 125, 244, and 369 bp, and mutant homozygote (CC) indicated by two bands of 125 bp and 244 bp (Figure 1). The genotype frequencies in our study sample were consistent with the Hardy-Weinberg equilibrium (HWE) equation (p=0.40). Table 2 shows clinical characteristics according to *rs857148* genotype. We found that only systolic blood pressure had a significant difference between the rs85714 genotype (p=0.03).

Table 3 displays the results of multiple regression analysis to detect any relationship between genotype model and cardiometabolic parameters. Overall, we discovered a significant relationship between SNP *rs857148* and HbA1c level in model 2. Subjects with CC genotype were detected to have significantly increased HbA1c levels (OR=7.12; 95% CI=1.05–48.26; p=0.04). It was asserted through recessive and allelic models where subjects with AA tended to have reduced HbA1c lower than those with AC+CC genotype, and subjects with C allele tended to have increased HbA1c levels (OR=0.15; 95% CI=0.02–0.97; p=0.047, OR=1.66; 95% CI=1.06–2.60; p=0.03, respectively). For the other

Table 1 Participants' Characteristics

Characteristics	Mean±SD/n (%)
Age (years)	60.58±8.16
Gender (female)	67 (62)
Blood pressure (mmHg)	137.67±20.21/77.02±10.87
HbA1c (%)	8.46±1.70
Total cholesterol (mg/dL)	196.12±39.14
HDL-c (mg/dL)	49.92±21.52
LDL-c (mg/dL)	137.57±72.39
Triglycerides (mg/dL)	158.04±102.17
Antidiabetic profiles:	
Monotherapy metformin	29 (26.9)
Metformin in combination with other OAD	79 (73.1)
Metformin dose (mg/day)	1440±364.77

Note: Numerical data were expressed as mean±standard deviation (SD), and categorical data were expressed as n (%).
Abbreviations: HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; OAD, oral antidiabetic agent(s).

cardiometabolic parameters, only total cholesterol was correlated with rs857148 calculated using model 2 (OR=1.05; 95% CI=1.01–1.10; p=0.03).

Discussion

A number of studies have explored the association between a list of genetic variants and cardiometabolic parameters.[34–36] To our knowledge, our study is the first study that observed the 3' UTR variant, especially *rs857148* related to cardiometabolic parameters, within the Yogyakarta population. This was the initial study related to personalized, patient-centered medicine, and we could only recruit a small number of participants. Cardiometabolic parameters in detail in this study include hypertension, HbA1c, and lipid profiles.

The association between hypertension and *rs857148* in our study is not well concluded yet. This is because we found significant statistical difference only in systolic blood pressure among the *rs857148* genotype, but not in diastolic blood pressure. Some studies have revealed the molecular explanation of AMPK and hypertension. AMPK activates sarcoplasmic/endoplasmic Ca2+-ATPase (SERCA), thus reducing ion Ca2+ devaluated, and the result is directly vascular smooth muscle relaxation.[37] Enhancing phosphorylated AMPK could suppress the expression of the angiotensin II type 1 receptor. Therefore, AMPK activation affects blood pressure.[38]

Our study has observed that subjects with CC genotype and C allele tended to have increased HbA1c levels after adjusted for metformin and glimepiride dose, age, gender, and considering combination therapy. Remarkably, there are limited association studies related to *rs857148*. We found a study that investigated the effect of *rs857148* variants on non-lung small cancer prognosis,[39] but no study that discussed the effect of HbA1c, previously. However, three SNPs of *PRKAA2* have been demonstrated in the previous study and it revealed no association to HbA1c.[40] These discrepancies could be due to the difference in the participants' selection. We recruited T2DM patients with less rigorous criteria than the previous study who engaged only newly diagnosed T2DM patients. Therefore, further studies are required focusing on *rs857148* with a larger sample population and applying more rigorous criteria to confirm the association that we found in our study.

A study among patients with T2DM performed by Sokolova et al in 2019 reported that phosphorylated AMPK was decreasing when the blood HbA1c level was increasing.[41] Luo et al in 2020 conducted a Mendelian randomization study

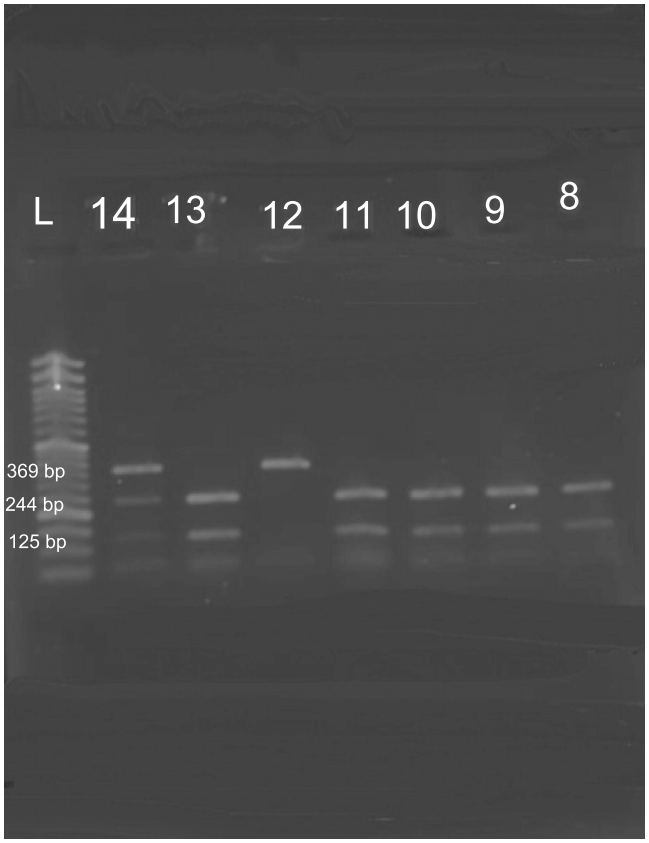

Figure 1 The PCR-RFLP results to determine *PRKAA2* rs857148 variants. L= ladder (marker 50 bp), 8, 9, 10, 11, 13 are mutant homozygote genotype, 12 is wildtype homozygote genotype, and 14 is heterozygote genotype.

and found that HbA1c reduction was instrumented by AMPK variants.[42] AMPK activation through phosphorylation induced by ATP/AMP changes and induced by metformin. Notably, AMPK controls energy metabolism in the whole body. Biologic functions of AMPK related to HbA1c include glycolysis promotion, glucose transport enhancing, and gluconeogenesis inhibition.[43,44] Therefore, it requires further investigations to confirm our findings, whether as the impact of T2DM or the effect of metformin.

Table 2 Patients' Clinical Characteristics Based on the Genotype of *rs857148*

Clinical Characteristics	AA (n=15)	AC (n=45)	CC (n=48)	*p*-value
	HWE = 0.40			
Age (years)	61.33±10.46	60.18±7.17	60.73±8.40	0.88
Systolic blood pressure (mmHg)	141.07±12.38	142.67±23.00	131.92±18.09	0.03[a]
Diastolic blood pressure (mmHg)	76.00±8.95	79.18±11.40	75.31±10.76	0.22
HbA1c (%)	8.17±1.84	8.54±1.77	8.47±1.61	0.76
Total cholesterol (mg/dL)	191.20±41.70	200.33±35.81	193.71±41.70	0.63
HDL-c (mg/dL)	51.60±15.70	48.31±13.36	50.90±28.46	0.81
LDL-c (mg/dL)	116.80±34.74	135.67±41.87	145.85±95.59	0.39
Triglycerides (mg/dL)	144.73±71.45	175.16±120.25	146.15±90.69	0.34

Notes: [a]$p<0.05$; Kruskal–Wallis test.
Abbreviations: HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol.

Table 3 Multiple Regression Analysis of *rs857148* and Cardiometabolic Parameters

Genotypes	Hypertension (Yes)		HbA1c (%)		Total Cholesterol (mg/dL)		HDL-c (mg/dL)		LDL-c (mg/dL)		Triglycerides (mg/dL)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Model 1												
AA	1.00 (reference)											
AC	0.31(0.06–1.66)	0.17	1.24(0.80–1.91)	0.33	1.01(0.99–1.02)	0.50	0.99(0.96–1.02)	0.62	1.01(0.99–1.02)	0.27	1.00(0.99–1.01)	0.42
CC	0.27(0.05–1.38)	0.12	1.51(0.06–2.39)	0.08	1.00(0.99–1.02)	0.74	1.00 (0.97–1.03)	0.99	1.01(0.99–1.03)	0.13	1.00(0.99–1.01)	0.98
Dominant	0.89(0.38–2.09)	0.78	1.29(0.96–1.73)	0.10	1.00(0.99–1.01)	0.80	1.01(0.99–1.02)	0.62	1.00(0.99–1.01)	0.22	1.00(0.99–1.02)	0.26
RecessiveAA	3.59(0.73–17.72)	0.12	0.74(0.49–1.13)	0.16	1.00(0.99–1.01)	0.58	1.00 (0.98–1.03)	0.81	0.99(0.98–1.00)	0.18	0.99(0.99 −1.01)	0.66
Allele A	1.00 (reference)											
Allele C	0.60(0.31–1.15)	0.12	1.22(0.99–1.50)	0.06	1.00(0.99–1.01)	0.90	1.00(1.00–1.01)	0.81	1.00(1.00–1.01)	0.12	0.99(0.99–1.02)	0.53
Model 2												
AA	1.00 (reference)											
AC	0.34 (0.03–4.39)	0.41	6.33 (0.92–43.71)	0.06	1.05 (1.01–1.10)	0.03*	1.07(0.97–1.20)	0.19	1.01(0.99–1.04)	0.34	1.01(0.99–1.02)	0.41
CC	0.47 (0.04–5.32)	0.54	7.12 (1.05–48.26)	0.04*	1.02 (0.99–1.06)	0.22	1.08 (0.97–1.21)	0.15	1.01 (0.99–1.04)	0.32	0.99 (0.98–1.01)	0.24
DominantCC	1.06 (0.27–4.23)	0.93	1.55 (0.78–3.07)	0.21	0.99 (0.97–1.01)	0.35	1.02 (0.98–1.05)	0.41	1.00 (0.99–1.01)	0.63	0.99 (0.98–1.00)	0.20
RecessiveAA	2.53 (0.24–27.12)	0.44	0.15 (0.02–0.97)	0.047*	0.97 (0.94–1.01)	0.10	0.93 (0.83–1.03)	0.16	0.99 (0.96–1.01)	0.30	1.00 (0.99–1.01)	0.88
Allele A	1.00 (reference)											
Allele C	0.85 (0.30–2.42)	0.76	1.66 (1.06–2.60)	0.03*	1.00 (0.99–1.02)	0.80	1.02 (0.99–1.06)	0.26	1.00 (0.99–1.01)	0.44	0.99 (0.99–1.00)	0.15

Note: *$p<0.05$.

Abbreviations: CI, confidence interval; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; OR, odds ratio.

Concerning the lipid profiles, no significant associations were found between *rs857148* and total cholesterol, HDL-c, LDL-c, and triglyceride in model 1. Nonetheless, model 2 showed that the AC genotype had a significant correlation to total cholesterol level compared to the AA genotype. Nevertheless, only a little effect of AC was detected to total cholesterol level where the odds ratio was only 1.05. This agrees with the study conducted by Jones et al in 2006, 5 SNPs of *PRKAA2* (rs1124900, rs2796516, rs2746342, rs2796498 and rs1418442) were significantly correlated to total cholesterol in a Caucasian population.[45]

The synthesis and disposal of cholesterol are coregulated through phosphorylation of key enzymes activated by AMPK. Those activated via sterol-regulatory element-binding protein (SREBP) and acetyl-CoA carboxylase (ACC) as the AMPK downstream.[46–48] An in vivo study revealed that AMPK influence the signalling of the mevalonate pathway 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase (HMGCR), thus regulating the cholesterol biosynthesis.[49]

As mentioned above, *rs857148* have not been observed related to cardiometabolic parameters, especially among T2DM patients, yet. We found one study that reported the frequency of the genotypes among health participants (as control of pancreatic cancer). The percentages of AA vs AC vs CC were 15.5%, 25.6%, and 11.3% respectively, among non-Hispanic whites as a control group.[50]

The clinical importance explained to us that the homozygote mutant of rs857148 could increase HbA1c than wildtype, even heterozygotes tend to increase total cholesterol. Since it is a pilot study among Indonesian subjects, it requires a larger sample to clarify our findings. However, these findings could indicate that rs857148 is worth considering as one of SNP contributing to cardiometabolic parameters, especially among patients with T2DM.

Notably, several limitations have been detected in our study. First, we could not explore whether the effect of SNP is influenced by pathologic conditions or metformin therapy because we did not collect HbA1c baseline and the information related to metformin as monotherapy or as combination therapy. Second, we did not measure physical activities, diet habits, and coexisting diseases that contribute to cardiometabolic physiologic. We have tried to minimalize these effects through multinomial logistical regression analyses. However, it would be better to apply more rigorous criteria during data collection.

Conclusions

In summary, CC genotype and C allele of rs857148 had a significant correlation to HbA1c level. Our study gives evidence that AC genotype could significantly increase total cholesterol compared to AA genotype. Since our results as a preliminary study showed significant findings, it requires further investigation with a larger sample and more rigorous criteria to determine the effect of metformin on *PRKAA2* variants accurately.

Abbreviations

T2DM, type 2 diabetes mellitus; AMPK, adenosine monophosphate protein; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; SNP, single nucleotide polymorphism; UTR, untranslated region; SERCA, sarcoplasmic/endoplasmic Ca2+-ATPase; SREBP, sterol-regulatory element-binding protein; ACC, acetyl-CoA carboxylase; HMGCR, mevalonate pathway 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase.

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Disclosure

The authors report no conflicts of interest in this work.

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