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Cell-Type-Specific Immune Reprogramming and Transcript-Protein Discordance in Peripheral Blood of Colorectal Cancer

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ABSTRACT

Colorectal cancer (CRC) is associated with systemic immune dysregulation, yet the extent to which individual immune lineages undergo coordinated transcriptional and proteomic reprogramming in peripheral blood remains unclear. Most studies rely on bulk profiling or tumor tissue analysis, limiting resolution of immune subset heterogeneity and transcript–protein relationships. To address this gap, we performed targeted single-cell multi-omic profiling of PBMCs from six CRC patients and six healthy controls using the BD Rhapsody™ platform to profile 399 immune-related genes and 30 surface proteins via AbSeq. Unsupervised clustering and multimodal annotation identified 14 immune populations spanning T cells, B cells, natural killer cells, and myeloid lineages. CRC samples demonstrated marked immune redistribution, most prominently a substantial expansion of monocyte subsets (50.7% vs. 18.5% in controls), accompanied by a reduction in memory T cell populations and enrichment of innate immune subsets. Differential expression analysis across seven major lineages revealed pronounced transcriptional reprogramming in classical monocytes, whereas lymphoid subsets displayed more moderate but consistent alterations. Notably, protein-level changes did not uniformly mirror transcript abundance. mRNA-protein concordance analysis using Kendall's tau demonstrated marker- and lineage-specific variability. Canonical markers such as CD4, CD8, CD62L, and CD14 showed strong positive correlations, particularly in CRC. In contrast, several lineage markers exhibited weak or context-dependent associations, and plasma cells demonstrated an inverse protein–transcript correlation for CD19, indicating regulatory mechanisms beyond transcriptional control. Collectively, these findings reveal lineage-specific immune remodeling in CRC and highlight widespread heterogeneity in transcript-protein coupling across immune subsets. Integrated single-cell multi-omic profiling provides critical insight into immune state definitions that cannot be inferred from transcriptomics alone.

Keywords: CRC; immune cell heterogeneity; PBMCs; single-cell multi-omics; transcript-protein correlation

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Evaluation of Metformin Induced Gastrointestinal Adverse Drug Reaction with Organic Cation Transporter OCT1 Genetic Variation in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Background: Metformin is the first line agent in treating Type 2 Diabetes Mellitus (T2DM). It is widely prescribed due to its safety profile, which does not cause hypoglycemic episodes, cheap in cost and is also weight-neutral. However, it could cause gastrointestinal discomfort, which accounts for about 20-30% of the population. Studies suggested that the gastrointestinal discomfort might be contributed by the genetic variation of gene SLC22A1, which encodes for OCT1 transporter. The prevalence of gastrointestinal adverse drug reaction (ADR) of metformin among Malaysian population and its associated genetic variation has scarcely been investigated. This study aims to evaluate the prevalence of metformin induced gastrointestinal ADR among T2DM patients and its association with OCT1 transporter SLC22A1 genetic variations of R61C and M420del. **Methods:** This study employed point prevalence and retrospective case control design involving patients identified from the Electronic Medical Record (EMR) system of a teaching hospital from May 2021 to June 2022. Patients were classified as either tolerant or intolerant to metformin. A total of 235 patients who have met the inclusion criteria were included in the study. For genetic screening, 55 patients underwent peripheral blood sample collection. The samples were subsequently sent to iPROMISE, UiTM Puncak Alam for DNA extraction and Nanopore sequencing. **Results:** It was found out that 27 (11.5%) from 235 patients, were metformin intolerance. However, there was no significant association between R61C and M420del genetic variations with metformin induced gastrointestinal intolerance. Interestingly, the study identified two variants (rs1867351 and rs628031) that may warrant further investigation in future studies to better understand their phenotypic impact. **Conclusion:** The results indicate that within Malaysian population, R61C and M420del do not serve as reliable biomarkers for metformin induced gastrointestinal ADRs. Further investigation of broader pharmacogenetic markers may help identify clinically relevant risk alleles associated with metformin intolerance.

Keyword: Metformin-induce gastrointestinal adverse drug reaction; OCT1 genetic variation; type 2 diabetes

Distinct Oral Microbiome Compositions in Type 2 Diabetes by Glycaemic Control and Periodontitis Status

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ABSTRACT

Type II Diabetes Mellitus (T2DM) is a major risk factor for periodontal disease, with growing evidence supporting a bidirectional relationship between the two conditions. However, key microbial contributors to periodontal risk in diabetic patients, particularly in Malaysia, remain poorly defined. This study aimed to compare oral microbiome profiles of individuals across glycaemic categories: healthy (H), prediabetes (P), well-controlled T2DM (WC) and poor-controlled T2DM (PC) - among individuals with periodontitis (PD+) and without periodontitis (PD-). A total of 130 participants were recruited and stratified into four groups based on HbA1c levels: healthy (<5.7%), prediabetes (5.7–<6.3%), well-controlled T2DM (6.3–<7.0%), and poorly-controlled T2DM (≥7.0%). Saliva and blood samples were collected, and comprehensive periodontal assessments were performed and validated by a registered periodontist. Microbial DNA was extracted using the QIAamp Microbiome Kit with host DNA depletion, followed by shotgun metagenomic sequencing and taxonomic profiling using CosmosID. Across all groups, the dominant phyla were Bacillota (54.53%), Actinomycetes (29.70%), Bacteroidota (9.67%), Patescibacteria (2.37%) and Pseudomonadota (2.32%). Higher proportions of Actinomycetes (33.42%) phyla were seen in T2DM groups PD-, whereas Bacillota (55.37%) was seen higher in T2DM groups PD+. *Rothia aeria (*Actinomycetes) was detected in HPD+ (9.57%) and T2DM PCPD+ (1.16%). Alpha and beta diversity analyses demonstrated significant microbial shifts across glycaemic stages and periodontal status, consistent with progressive dysbiosis associated with poorer glycaemic control ($p<0.05$). Linear Discriminant Analysis Effect Size (LEfSe) identified *Peptostreptococcus stomatis* as significantly enriched in T2DM WCPD+ (LDA=3.780, p=0.002), while *Alloprevotella sp000318095* was strongly enriched in T2DM PCPD+ (LDA=2.760, p=0.004). Collectively, these preliminary findings suggest glycaemia–associated oral microbial patterns and potential bacterial biomarkers linking metabolic dysregulation to periodontal inflammation, warranting further association analyses and validation in larger cohorts.

Keywords: Oral microbiome; periodontitis; type II diabetes mellitus

Acknowledgement: This project is funded by the Ministry of Higher Education under the Sukuk Prihatin Phase 2 grant scheme (PRIHATIN-2023-001).

Dual Targeting of HIF-2α and KLF6 Suppresses Angiogenic Signaling in Clear Cell Renal Cell Carcinoma

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ABSTRACT

Background: Clear cell renal cell carcinoma (ccRCC) is primarily driven by loss of Von Hippel-Lindau (VHL), leading to hypoxia-inducible factor 2-alpha (HIF-2α) accumulation and angiogenesis via vascular endothelial growth factor-A (VEGFA) upregulation. Recent evidence suggests that Krüppel-like factor 6 (KLF6) is co-opted in this process by regulating the pro-angiogenic factor platelet-derived growth factor beta (PDGFβ). Although KLF6 expression is partially HIF-2α-dependent, the functional interplay between HIF-2α and KLF6 in angiogenic signalling remains unclear. Here, we investigate their co-regulatory roles and the effects on endothelial cell function. **Methods:** Genetically engineered ccRCC in vitro models were generated as follows: (i) HIF-2α single repression (HA_VHL), (ii) KLF6 single repression (iKLF6), and (iii) combined HIF-2α/KLF6 repression (DT). VEGFA and PDGFβ mRNA expression, as well as secreted protein levels, were quantified by qPCR and ELISA, respectively. Angiogenic potential was assessed by treating endothelial cells with conditioned media from engineered ccRCC cells, followed by evaluation of cell proliferation and Matrigel-based tube formation assays. **Results**: Dual repression of HIF-2α and KLF6 resulted in additional downregulation of VEGFA and PDGFβ at both transcriptional and secreted protein levels compared with control and single-repressed cells. Endothelial cells treated with conditioned media from DT cells exhibited slower proliferation and tube-forming capacity, likely due to decreased levels of secreted VEGFA and PDGFβ. **Conclusion:** Overall, these findings demonstrate functional cooperation between HIF2α and KLF6 in regulating VEGFA and PDGFβ expression in ccRCC. The DT model, characterised by reduced secretion of both angiogenic factors, provided functional evidence that diminished VEGFA/PDGFβ availability reduced endothelial cell proliferation and tube formation. These results support a coordinated upstream regulatory mechanism driving angiogenesis in ccRCC and suggest that simultaneous targeting of HIF2α and KLF6 may be therapeutically relevant.

Keywords: Angiogenesis; clear cell renal cell carcinoma; HIF-2α; PDGFβ; VEGFA

Gut Microbial Signatures in Malaysian Children with Autism Spectrum Disorder

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ABSTRACT

Background: Gut microbiome alterations have been increasingly implicated in Autism Spectrum Disorder (ASD), however evidence from the multi-ethnic Malaysian population remains limited. This study characterised gut microbial profiles in Malaysian children with ASD and examined their association with symptom severity. **Methods**: We recruited 150 children with ASD and 169 neurotypical children (1-17 years). ASD diagnosis and severity were confirmed using Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria and the Childhood Autism Rating Scale, Second Edition (CARS2), respectively. Neurotypical children were screened using validated age-appropriate developmental assessments. DNA was extracted from faecal samples and subjected to shallow shotgun metagenomic sequencing. Sequencing reads underwent quality control and taxonomic profiling analysis. **Results**: Children with ASD showed distinct microbial community composition compared with neurotypical controls (Bray-Curtis, $p = 0.001$) and modestly reduced species richness ($p = 0.032$). At the genus level, five genera (CAG-269, Acutalibacter, Lawsonibacter, Slackia_A and Paratractidigestivibacter) were positively associated with ASD after adjustment for age and sex (all $q < 0.05$). At the species level, five taxa were enriched, and four taxa were reduced in ASD (all $q < 0.05$). After adjustment for age and sex, four taxa remained enriched in ASD (*Bifidobacterium longum, Bacteroides uniformis, Paratractidigestivibacter faecalis, and Lawsonibacter sp900066825*) while three taxa were reduced (*Clostridium_Q fessum, Veillonella parvula_A, and Odoribacter splanchnicus*) (all $q < 0.05$). No significant correlations were observed between CARS2 severity scores and alpha diversity indices. Although microbiome composition differed between minimal and severe ASD (Bray-Curtis, $p = 0.009$), no individual taxa were significantly associated with symptom severity ($p > 0.05$). **Conclusion**: Malaysian children with ASD demonstrate

modest reductions in microbial richness and altered gut microbial composition. Diagnostic status accounted for greater variation in microbial composition than symptom severity, suggesting that gut microbiome differences are more strongly associated with ASD presence than with clinical severity.
Keywords: Autism Spectrum Disorder; gut microbiome; Malaysia; shallow shotgun metagenomics; symptom severity

Acknowledgement: This project is funded by the Ministry of Higher Education under the Sukuk Prihatin Phase 2 grant scheme (PRIHATIN-2023-001).

Exploring Mutation Patterns and Neuroimaging Profiles in Early-Onset Alzheimer's Disease: A Scoping Review of Asian Cohorts

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ABSTRACT

Background: Early-onset Alzheimer's disease (EOAD) is primarily caused by pathogenic variants in *PSEN1*, *PSEN2* and *APP*. While genotype-neuroimaging correlations are well described in Western populations, mutation patterns in Asian cohorts remain less defined. This study investigates EOAD mutation profiles across Asia and evaluates their corresponding neuroimaging outcomes. **Methods:** A scoping review was conducted synthesising data from 36 studies of Asian cohorts published between 2016 and 2023, encompassing 177 genetically confirmed EOAD cases. Extracted variables included gene mutations, country of cohort, age of onset (AOO), and reported structural and functional neuroimaging findings. Mutation prevalence and imaging phenotypes were analysed descriptively across genes and geographic cohorts. **Results:** The majority of cases originated from China (n = 113) and Korea (n = 33), with additional cohorts from Turkey (n = 9), Malaysia (n = 5), Iran (n = 2), Taiwan (n=2), and India (n=1). The overall mean AOO was 48.7 years. *PSEN1* carriers demonstrated the earliest onset (mean AOO 45.1 ± 8.3 years), compared with *PSEN2* (52.4 ± 9.9 years) and *APP* (54.5 ± 5.5 years). The genetic landscape was dominated by *PSEN1* mutations (n = 107, 60.5%), followed by *PSEN2* (n = 43, 24.3%) and *APP* (n = 27, 15.3%). The most recurrent amino-acid alterations were p.Met139Leu and p.His169Asn. Several recurrent nucleotide variants were identified across multiple cohorts, including c.415A>T, c.2149G>A, and c.868+16G>T. Structural MRI frequently revealed medial temporal lobe and hippocampal atrophy, particularly among *PSEN1* carriers. *APP* and *PSEN2* mutations showed similar temporoparietal atrophy, but *APP* uniquely presented with ventricular dilation and periventricular white matter hyperintensities. FDG-PET/SPECT findings across studies commonly demonstrated temporoparietal and posterior cingulate hypometabolism. Conversely, *PSEN2* displayed variable functional patterns, including frontal and anterior temporal hypoperfusion, aligning with atypical clinical declines. **Conclusion:** This review maps distinct clinical and neuroimaging signatures of dominant EOAD genotypes in Asia. Defining these mutation-specific trajectories is crucial for precision diagnostics and stratifying patients for targeted therapeutic trials.

Serum Biomarkers as Predictors of Early Mild Cognitive Impairment: Findings from The Malaysian Cohort

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ABSTRACT

Background: Mild cognitive impairment (MCI) represents an early stage of cognitive decline preceding dementia and provides a critical window for early intervention. However, commonly used biomarkers such as cerebrospinal fluid amyloid and tau proteins are invasive and unsuitable for large-scale population screening. Routine serum biochemical parameters and metabolic syndrome (MetS), which reflect metabolic and vascular health, may serve as accessible indicators of early cognitive impairment. **Methods**: This study analysed 3,164 participants from The Malaysian Cohort who completed the Montreal Cognitive Assessment (MoCA) between 2022 and 2024. Early MCI was defined as MoCA 22. Associations between routine serum biochemical parameters, MetS, and early MCI were evaluated using two complementary analytical approaches: (i) single time-point logistic regression and (ii) serial measurement analysis using generalised estimating equations (GEE). All models were adjusted for demographic and lifestyle covariates. **Results:** Over a mean follow-up of 11.6 years, 27.3% of participants developed early MCI. In the adjusted single time-point analysis, older age, lower education level, and higher serum creatinine were independently associated with increased risk of early MCI. In contrast, serial measurement analysis identified higher serum potassium levels and elevated atherogenic index of plasma (AIP) as significant predictors of early MCI. MetS was consistently associated with increased risk of early MCI across analyses, with persistent MetS demonstrating a significant longitudinal association (OR 1.27, 95% CI 1.03-1.58). A dose-response trend was observed, where higher numbers of MetS components were linked to greater risk of early MCI. Notably, 41.4% of MCI cases occurred in the 50-59 age group, suggesting an earlier onset of cognitive impairment in this population. **Conclusion:** Routine serum biochemical parameters and metabolic syndrome are associated with early MCI among Malaysian adults. Long-term metabolic disturbances, particularly persistent MetS, elevated AIP, and higher potassium levels, may contribute to early cognitive decline. These findings highlight the potential value of routine metabolic markers for identifying individuals at risk of early cognitive impairment in population-based screening.

ETV6 Loss-of-Function Mutations as Precision Biomarkers of Relapse in Childhood Acute Myeloid Leukemia

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ABSTRACT

Background: Leukemia is the most common cancer in children, yet important gaps remain in understanding the genomic alterations underlying childhood acute myeloid leukemia (AML) compared with adult AML. Relapsed AML continues to be a leading cause of cancer-related mortality among pediatric patients. From a precision medicine perspective, defining relapse-associated genomic changes is critical for improving risk stratification and targeted therapeutic strategies. This study aimed to elucidate the molecular mechanisms driving relapse in childhood AML by characterising the mutational landscape across disease stages. **Methods**: Whole genome sequencing was performed on matched samples collected at diagnosis, remission, and relapse from three patients with de novo childhood AML. Sanger sequencing was used to validate candidate variants in an extended cohort of 47 patients, followed by functional analyses to evaluate biological relevance. **Results**: A total of 312 somatic mutations were identified, including 154 variants at diagnosis and 158 variants at relapse, comprising synonymous single nucleotide variants (SNVs), missense SNVs, deletions, insertion frameshifts, stop-gains, and splice-site alterations. Following prioritisation, 46 variants were retained at diagnosis (13-17 mutations per patient) and 49 variants at relapse (12-20 mutations per patient). Notably, 35 variants emerged exclusively at relapse, reflecting dynamic genomic evolution. Six potential driver mutations (*KIT, CDC73, HNF1A, RBM10, ZMYM4,* and *ETV6*) were implicated in relapse prediction, with recurrent alterations observed in *ETV6*. Functional analysis demonstrated that *ETV6* mutants (p.P25fs and p.N75fs) resulted in loss of tumour suppressor activity in vitro, supporting their potential role as candidate precision biomarkers. **Conclusion**: This study characterises genomic changes associated with relapse in childhood AML and highlights candidate driver mutations that may contribute to risk stratification and therapeutic decision-making. These findings provide additional genomic insights into pediatric AML pathogenesis and suggest potential applications in precision oncology approaches for relapse monitoring and patient management.

Exploratory Evaluation of Circulating LRG1 as a Candidate Biomarker of Chemotherapy Response in Colorectal Cancer Reveals Age-Associated Treatment Resistance

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ABSTRACT

Circulating biomarkers are increasingly used in precision oncology for minimally invasive monitoring of disease progression and treatment response. Leucine-rich alpha-2-glycoprotein-1 (LRG1) is a secreted protein implicated in tumour angiogenesis, inflammation and tumour progression in colorectal cancer (CRC). However, its clinical relevance as a circulating biomarker associated with chemotherapy response remains unclear. Serum LRG1 concentrations were measured by ELISA in 27 CRC patients undergoing systemic chemotherapy (FOLFOX and XELOX). Non-parametric statistical analyses were performed to examine associations between LRG1 levels and clinical variables, including treatment response, sex, ethnicity, chemotherapy regimen, carcinoembryonic antigen (CEA) trends, age at diagnosis, and number of chemotherapy cycles. Serum LRG1 levels showed moderate inter-individual variability (mean 0.055 ± 0.031; range 0.02-0.14). Comparable distributions of LRG1 concentrations were observed across multiple clinical subgroups, including treatment response, sex, ethnicity, chemotherapy regimen and CEA status, with no statistically significant differences detected. Correlation analysis showed weak and non-significant relationships between LRG1 levels and both age at diagnosis ($\rho = 0.164$) and chemotherapy cycles ($\rho = 0.286$). In contrast, logistic regression analysis identified age at diagnosis as a significant predictor of chemotherapy resistance (OR = 1.25 per year; $p = 0.042$), explaining approximately 44.7% of the variance in treatment response. In this exploratory cohort, circulating LRG1 levels were not strongly associated with chemotherapy response. However, increasing age at diagnosis emerged as a significant determinant of treatment resistance. These findings highlight the importance of integrating molecular biomarkers with clinical variables in predictive models for treatment stratification.

Keywords: Chemotherapy; colorectal; LRG1; resistance; serum

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Molecular Precision in Diabetes Management: Comparative Efficacy of α-Tocopherol and Tocotrienol-Rich Fraction on the T2DM Gene Interaction Network

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ABSTRACT

Background: Precision health prioritises customised therapies informed by molecular profiles. In Type II Diabetes Mellitus (T2DM), it is essential to identify supplements that alleviate metabolic inefficiency and neurodegeneration at the genetic level. The study sought to assess the effectiveness of α-tocopherol (ATF) and tocotrienol-rich fraction (TRF) in glycaemic regulation, neuronal preservation and mRNA gene expression. **Methods:** The method employed was the successful induction of Type 2 Diabetes Mellitus (T2DM) by a high-fat diet and modified multiple-dose streptozotocin (30 mg/kg) combined with 5% glucose hydration, resulting in a 100% success rate. Experimental groups (Normal, T2DM, ATF-supplemented, and TRF-supplemented) were observed over an eight-week period for glucose clearance rates and hippocampus cellular damage. Molecular profiling was performed using mRNA gene expression analysis utilising nCounter Advanced Analysis. **Results:** Both ATF and TRF markedly enhanced glucose clearance efficiency ($p < 0.05$). TRF exhibited enhanced precision in neuroprotection, safeguarding 100% of samples from significant hippocampus cell injury, in contrast to 66.7% in the ATF group. Molecular profiling demonstrated that TRF specifically altered a gene interaction network, resulting in the overexpression of Psen2, Socs2, and Irs2, alongside the downregulation of Apoe. **Conclusion:** TRF offers a more potent and specific molecular response compared to ATF, establishing it as a superior precision nutritional intervention for the prevention of T2DM-related neuronal damage.

Gut Microbiome Alterations in Systemic Lupus Erythematosus: Associations with Renal and Non-Renal Manifestations

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex autoimmune disease, and the gut microbiome is increasingly implicated in its pathogenesis. However, microbiome differences across renal and non-renal SLE manifestations remain incompletely defined. We performed gut microbiome profiling in SLE patients (renal and non-renal) and healthy controls. In this case-control study, genomic DNA was extracted from fecal samples and subjected to shotgun metagenomic sequencing (Illumina NextSeq 2000). Microbial composition was analysed using CosmosID. We included 181 patients with SLE (69 non-renal and 112 renal) and 110 healthy controls. Alpha diversity was significantly reduced in SLE compared with controls (Shannon, $p < 0.001$; Simpson, $p = 0.006$; Chao1, $p < 0.001$). Both SLE subgroups exhibited significantly decreased alpha diversity relative to controls (Chao1: $p = 0.001$ and $p < 0.001$, respectively), with no significant difference between renal and non-renal SLE ($p = 0.236$). Beta diversity (PCoA) revealed significant compositional differences between SLE and controls, and between SLE subgroups (PERMANOVA, all $p \leq 0.003$). Stratification by disease activity based on SLEDAI-2K (active > 0; inactive = 0) revealed no significant differences in alpha or beta diversity ($p > 0.05$). Multivariate analysis identified a positive association of *Ruminococcus_B gnavus* in SLE patients with renal involvement (β = 3.51, 95% CI: 2.54-4.47, FDR-adjusted q < 0.001), while *Bifidobacterium pseudocatenulatum* was positively associated with neuropsychiatric SLE (β = 5.39, 95% CI: 3.13-7.65, FDR-adjusted q = 0.0036). Overall, SLE was characterised by reduced microbial diversity and distinct compositional shifts, with specific taxa associated with particular clinical manifestations. These findings support further mechanistic and longitudinal studies to clarify microbiome-host interactions in SLE and their potential clinical relevance.

Keywords: Autoimmune disease; gut biomarker; gut dysbiosis; systemic lupus erythematosus

Acknowledgement: This project is funded by the Ministry of Higher Education under the Sukuk Prihatin Phase 2 grant scheme (PRIHATIN-2023-001).

Determinants of Antiretroviral Therapy Adherence among People Living with HIV in Asia: A Systematic Review

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ABSTRACT

Background: Adherence to antiretroviral therapy (ART) remains central to achieving viral suppression, preventing drug resistance, and improving survival among people living with Human Immunodeficiency Virus (HIV) in Asia. Although the test-and-treat strategy has expanded ART access across Asia, sustained adherence continues to pose a significant challenge. This systematic review synthesises recent evidence on the prevalence of ART adherence and its associated barriers and facilitators among adults living with HIV in Asian settings during the post-test-and-treat era. **Methods:** A systematic search of peer-reviewed literature published from 2015 onwards was conducted following PRISMA 2020 guidelines. Studies involving adults aged 18 years and above receiving ART in Asian countries were included. Data were extracted and synthesised narratively, and methodological quality was assessed using Joanna Briggs Institute critical appraisal tools appropriate to study design. **Results:** The electronic database search of PubMed and Scopus yielded a total of 697 records and subsequently a total of 24 studies met the inclusion criteria and were included in the final narrative synthesis. Across the included studies, reported adherence levels varied substantially between countries and populations. Common barriers to adherence included HIV-related stigma, forgetfulness, mental health difficulties, substance use, financial hardship, and disruptions to health services, particularly during the COVID-19 pandemic. Facilitators for adherence consistently identified were strong social and family support, higher treatment self-efficacy, trustful patient-provider relationships, simplified treatment regimens, and flexible service delivery models. These factors operated across individual, interpersonal, and health system levels, underscoring the multifaceted nature of adherence behaviour. **Conclusion:** Despite policy advances toward universal treatment, gaps in sustained adherence persist. Addressing ART adherence in Asia requires integrated and patient-centred strategies that extend beyond medication provision to include psychosocial support, stigma reduction and resilient health systems capable of maintaining continuity of care.

Transaminitis in Dengue Patients Admitted to a Teaching Hospital in Kuala Lumpur

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ABSTRACT

Transaminitis has been reported as potential predictive of severe dengue. Transaminitis refers to elevated serum aspartate (AST) and alanine transaminase (ALT), indicating liver dysfunction. This study aimed to determine the prevalence of transaminitis in dengue patients admitted to Hospital Canselor Tuanku Muhriz UKM (HCTM). Serum samples from NS1-positive dengue patients collected between May 2021 and April 2024 were included in this study. Clinical history and liver function test results were retrieved from medical records. Dengue virus serotyping was performed using multiplex PCR. A total of 436 serum samples from NS1-positive dengue patients were analysed. Of those, 139 (13.9%) were classified as dengue without warning signs (DwoWS), 274 (62.8%) as dengue with warning signs (DwWS) and 23 (5.3%) as severe dengue. The overall prevalence of transaminitis in dengue patients was 71.1% (n = 310). Severe dengue patients showed the highest prevalence of transaminitis (91.3%, n = 21), followed by DwWS (75.5%, n = 207) and DwoWS (59.0, n = 82). Transaminitis was more common in male (55.3%), secondary dengue infection patients (65.0%) and adult aged 30-39 years (23.5%). It was most frequently observed in dengue patients infected with DENV-2. The prevalence of transaminitis in this study was higher than those study in Nepal and India but lower than study in Uttar Pradesh.

Keywords: Dengue; Malaysia; prevalence; transaminitis

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High Sensitivity Measurable Residual Disease Next Generation Flow Cytometry Assay for Plasma Cell Myeloma: A Validation Exercise

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ABSTRACT

Introduction: Measurable residual disease (MRD) is a critical prognostic marker in plasma cell myeloma (PCM), strongly associated with relapse risk and long-term survival. The EuroFlow consortium has established standardised next-generation flow cytometry (NGF) protocols for MRD detection, enabling highly sensitive and reproducible assays across laboratories. This study aimed to perform an in-house validation of the EuroFlow MM MRD kit for PCM, ensuring assay reliability and sensitivity. **Objectives:** To validate a high-sensitivity NGF-based PCM MRD assay using the EuroFlow MM MRD kit by determining the limit of blank (LOB) and lower limit of quantification (LLOQ) in local laboratory conditions. **Methodology:** Uninvolved bone marrow (BM) samples from six adults were used to establish LOB by acquiring >10 million nucleated cells per sample and quantifying background events in MRD regions. For LLOQ, myeloma cells were spiked into pooled uninvolved BM samples. Standardised EuroFlow antibody panels and sample preparation protocols were applied, with optimised acquisition to achieve high event counts. Data were analysed with Infinicyt 2.0, including dual tube merge, Automatic Population Separator (APS), database guided comparison to normal plasma cell references, and supervised classification of aberrant plasma cell phenotypes. Quality control included event count verification, fluorescence scaling, and multidimensional residuals review. **Results:** The assay achieved a LOB of 3-7 background events and an LLOQ of 33-38 events in >10 million nucleated cells, corresponding to $<5 \times 10^{-6}$ (0.0005%) sensitivity level with excellent reproducibility (CV 9.82%). Infinicyt 2.0 enabled robust identification of aberrant plasma cells and consistent MRD gating, improving reproducibility across replicates. **Conclusion:** In house validation of the EuroFlow MM MRD kit in PCM confirmed its high sensitivity and reproducibility, meeting international standards and the threshold for clinical MRD monitoring, facilitating integration into routine clinical workflows. Establishing LOB and LLOQ in local laboratory conditions is essential to ensure assay reliability.

Peripheral T Cell Signaling Suppression in Colorectal Cancer Revealed by Targeted Single-Cell Multi-Omic Profiling

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ABSTRACT

Adaptive immune competence is essential for tumor surveillance, yet the functional signaling state of circulating T cells in colorectal cancer (CRC) remains poorly defined. While tumor-infiltrating lymphocytes have been extensively studied, the systemic adaptive immune compartment in peripheral blood has not been interrogated at combined transcript–protein resolution. We therefore focused specifically on defining T cell-intrinsic molecular programs associated with CRC. Peripheral blood mononuclear cells (PBMCs) from six CRC patients and six healthy controls were profiled using the BD Rhapsody™ targeted single-cell sequencing of 399 immune-related genes combined with 30 AbSeq surface proteins. Multimodal clustering resolved major T cell subsets, including naïve $CD4^+$, central memory $CD4^+$, effector $CD8^+$ and effector memory $CD8^+$ populations. Differential gene and protein expression analyses were performed, followed by functional enrichment using Gene Ontology (GO) and KEGG pathway analyses. CRC was characterised by consistent attenuation of adaptive signaling programs across T cell subsets. Downregulated genes converged on T cell receptor signaling, co-stimulatory pathways, cytokine-mediated communication and Th17 differentiation networks. Effector $CD8^+$ cells displayed altered expression of activation-associated molecules, suggesting functional modulation rather than simple expansion. Central memory $CD4^+$ and effector memory $CD8^+$ subsets showed the most pronounced pathway suppression signatures. These findings indicate that CRC is associated with systemic dampening of T cell signaling capacity at both transcript and protein resolution. The data support a model in which peripheral T cells in CRC exhibit functional attenuation of immune receptor–mediated pathways, potentially contributing to compromised adaptive responses. Targeted single-cell multi-omic profiling provides a high-resolution framework for identifying signaling-level immune alterations in cancer.

Keywords: CD4; CD8; colorectal cancer; single-cell sequencing; T cells

Acknowledgement: This project is funded by The Ministry of Higher Education, under the Fundamental Research Grant Scheme (FRGS/1/2021/SKK0/UKM/02/7).

Graph Cluster Approach in Identifying Novel Proteins and Significant Pathways Involved in Acute Myeloid Leukemia

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ABSTRACT

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy affecting both children and adults and is characterised by diverse molecular alterations and variable clinical outcomes. This heterogeneity complicates the identification of subtype-specific gene markers that could improve disease characterisation and support personalised therapeutic strategies. Graph-based approaches can capture both gene expression patterns and topological relationships within biological networks, making them useful for identifying disease-related genes. However, systematic graph-based gene selection approaches for AML remain limited. In this study, known AML-related genes were integrated with protein-protein interaction (PPI) data to construct an AML interaction network. The network was clustered using the DPClusOST algorithm across densities ranging from 0.1 to 1.0. Cluster significance was evaluated using a significance score (SScore) derived from Fisher's exact test. Clusters containing AML gene panels were further assessed using receiver operating characteristic analysis to determine the density with the highest area under the curve (AUC). Genes from the optimal clusters were subsequently analysed using differential gene expression and pathway enrichment analyses. At a cluster density of 1.0, 32 clusters were identified, in which 16 potential novel genes showed differential expression across AML subtypes, particularly RPL14, RPL4, RPL6, PDS5A, and WAPL in AML, RPS9 in CD34, and INSR in PML-RAR . Pathway enrichment analysis revealed that these genes were involved in several AML-related pathways and biological processes, including the PI3K/AKT signaling pathway, refractory macrocytosis, abnormalities of bone marrow stromal cells, and multiple lineage myelodysplasia. These findings demonstrate that graph-based clustering of protein interaction networks can effectively identify potential AML-associated genes and pathways. This integrative approach provides additional insight into AML pathobiology and may contribute to improved subtype characterisation and the development of more personalised therapeutic strategies.

Clinical Significance of *CYP1A1* in Lung Cancer Prognosis and Therapeutic Targeting

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ABSTRACT

Cytochrome P450 1A1 (CYP1A1) is implicated in carcinogen metabolism and lung tumorigenesis, yet its expression patterns, epigenetic regulation, prognostic significance, and therapeutic potential in lung cancer remain poorly defined. In this study, we conducted a comprehensive, multi-platform bioinformatics investigation to address these gaps. Tumor versus normal CYP1A1 expression was assessed using GEPIA2, UALCAN and GENT2 transcriptomic databases. Prognostic relevance was examined through survival analyses via KM-Plotter and OSLuca. DNA methylation profiling was performed to evaluate epigenetic regulation, and protein-protein interaction network analysis was conducted to identify functional partners of CYP1A1. Molecular docking, alongside in silico pharmacokinetic and toxicity profiling, was subsequently performed to screen and prioritise candidate inhibitors. We found that CYP1A1 expression was consistently downregulated in lung cancer relative to normal tissue across all datasets. GEPIA2 revealed approximately 21-fold and 10-fold reductions in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), respectively; UALCAN and GENT2 corroborated these findings with 7-fold and 2.7-fold decreases. Besides, survival analyses uncovered stage-dependent prognostic associations: elevated CYP1A1 expression correlated with worse overall survival across all stages (KM-Plotter HR = 1.14) and in stage II disease (OSLuca HR = 4.784), but with improved survival in stage I patients (OSLuca HR = 0.189). LUAD tumors exhibited significantly higher CYP1A1 promoter methylation than normal tissues ($p<0.001$), although overall levels remained within the hypomethylated range. Interaction network analysis implicated ANKRD32, FBXW7 and SGMS1 as functionally relevant partners. Virtual screening identified seven candidate inhibitors, with CID 3151 exhibiting favorable predicted pharmacokinetics and a reduced toxicity profile. In conclusion, this integrative analysis reveals context-dependent dysregulation and complex prognostic roles for CYP1A1 in lung cancer, while identifying promising inhibitor candidates warranting further experimental validation.

Context-dependent Rewiring of Autocrine TGFβ-associated Gene Regulation Under Serum Deprivation Condition in TNBC transduced cells

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ABSTRACT

Growth factors are critical drivers in cell growth and modulating signaling pathways. TGFβ is a classic growth factor playing a key role in orchestrating phenotypic features including in TNBC. Basic cell culture techniques require induction with serum growth factor for cells to grow. Owning to these causalities, studying TGFβ signaling in TNBC cell lines may influence the growth and downstream gene activation. Therefore, this study aims to observe the differential of downstream RhoA/ROCK1 changes and proliferative outcomes in our established TNBC cell lines. Lentiviral transduced TNBC cells were depleted with short hairpin RNA shTGFβ1, shTGFβ2 and shNT as control cell. Colony forming assays were carried out in two condition setup; serum-deprived (SD) media and serum complete (SC) media. RqPCR was carried out to assess expressions of downstream mRNA targets. Transduction efficiencies of TGFβ1 and TGFβ2 indicated significant depletion in both SD and SC ($p < 0.0001$). RhoA ($p < 0.0001$) and ROCK1 ($p = 0.003$) showed reductions in shTGFβ1 SC in SC condition, and RhoA reduction in shTGFβ1 SD condition ($p = 0.0007$). Reduction of RhoA ($p = 0.0045$) and ROCK1 ($p < 0.0001$) were observed in shTGFβ2 SC. Inversely, ROCK1 ($p < 0.0001$) showed increased expression, while RhoA remained unchanged. Colony forming assays indicated reduced proliferative effects in shTGFβ1 SD ($p = 0.037$) with a concordant expression of decreased proliferative marker Ki-67 ($p = 0.0029$), while proliferative significant increase was seen in shTGFβ1 SC ($p = 0.009$). This suggesting SD condition is optimal in carrying out TGFβ1 functional mechanism assessments. On the contrary, proliferative effects and Ki-67 expressions were seen increased in both SD and SC conditions in shTGFβ2 setup. These observations suggesting; (i) TGFβ1 may play a key role in controlling the downstream both canonical and non-canonical TGFβ pathways, (ii) rewirement of TGFβ signaling pathway by SD condition may trigger cell context stress adaptabilty. Further assessments are warranted for in-depth mechanisms understanding of TGFβ isoforms in our cell model.

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Patient-in-a-Dish in Malaysia: Establishment of the Blood-Derived iPSCs Platform for Precision Medicine Applications

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ABSTRACT

Induced pluripotent stem cells (iPSCs) are transformative in regenerative medicine, disease modelling and personalised therapy. Here, we report the successful reprogramming of erythroid progenitor cells derived from peripheral blood mononuclear cells (PBMCs) into iPSCs in Malaysia. PBMCs were isolated from healthy donors and disease patients following negative screening for infectious diseases, including HIV, Hepatitis B and Hepatitis C. The cells were expanded and differentiated into erythroid progenitors under defined culture conditions. Subsequently, reprogramming was performed using the episomal reprogramming system in combination with the Neon™ NXT electroporation platform, facilitating non-integrative and efficient iPSC generation. Emerging iPSC colonies demonstrated typical embryonic stem cell-like morphology. Current efforts are directed towards full characterisations, including immunocytochemistry for pluripotency markers (e.g., OCT4, SOX2, NANOG), karyotyping, and tri-lineage differentiation assays. This initiative establishes a local proof-of-concept platform and technical pipeline for iPSC derivation from blood-derived cells. This foundational work paves the way for the development of an ethnically relevant Malaysian iPSC biobank, which could support precision medicine, drug screening, and disease modelling in the regional context. In subsequent phases, disease-specific iPSC lines and genome editing strategies will be explored. Our study marks a pioneering step in Malaysia's stem cell landscape by establishing a reproducible, feeder-free, integration-free iPSC derivation protocol from PBMCs. This effort contributes to the expansion of iPSC-based applications in Southeast Asia and underscores the importance of building local capacity in regenerative research.

Advancing Precision Health in Resource-Limited Settings: Development of the ACE Score for Predicting Glycaemic Response to Empagliflozin

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ABSTRACT

Background: While empagliflozin confers cardiorenal protection independent of glycaemic control, HbA1c reduction remains a primary driver for prescribing in resource-limited settings. As glycaemic benefits vary, this study developed and validated the Assessment Criteria for Enhancing Empagliflozin Use (ACE) Score to identify patients likely to achieve an HbA1c reduction of at least 1%. **Methods:** This multicentre retrospective cross-sectional study included 425 adult patients with type 2 diabetes (T2DM) from 14 government clinics in Johor initiated on empagliflozin between August 2022 and January 2025. Glycaemic response was defined as an HbA1c reduction of 1%. Binary logistic regression identified independent predictors to construct a point-based ACE Score using baseline HbA1c, diabetes duration, and systolic blood pressure (SBP). Validation compared this tool against a seven-predictor continuous model using paired Receiver Operating Characteristic (ROC) analysis. **Results:** Predictors included baseline HbA1c ≥10% (+2 points), T2DM duration ≥5 years (+1 point), and SBP ≤1 40 mmHg (+1 point). Each 1-point score increase significantly improved response odds (OR 1.82; 95% CI 1.54-2.16; $p < 0.001$). The simplified ACE Score achieved an area under the curve (AUC) of 0.686 with 72.9% sensitivity. It demonstrated a stepwise response likelihood where high scorers (Score 4) attained a 72.0% likelihood of success compared to 25.0% for low scorers (Score -1 to 1). The continuous reference validation model reached an AUC of 0.754. **Conclusion:** The ACE Score is a validated, practical tool derived from real-world Malaysian data. It allows clinicians to rapidly stratify glycaemic response likelihood, supporting individualised prescribing and enhancing the efficiency of precision health interventions in busy primary care settings.

Precision Typing Coverage for Equitable Transfusion Planning

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ABSTRACT

Background: Precision public health uses population data to target services, improve equity, and optimise resources. In phenotype-matched transfusion, readiness depends not only on antigen frequencies but also on typing coverage and the efficiency of identifying uncommon phenotypes in routine donor pools. We aimed to quantify extended red cell typing coverage and translate coverage and screening-efficiency considerations into an equity-oriented framework for transfusion planning. **Methods:** We performed a retrospective analysis of anonymised donor records from a tertiary transfusion centre in Southern Malaysia (September 2023-September 2025). A total of 16,173 unique donors had complete ABO and full Rh typing. Extended phenotyping was conducted in clinically selected donor subsets. We quantified extended typing coverage (proportion of the donor pool typed by antigen system) and summarised screening-efficiency concepts to inform service planning. Based on these results, we proposed a tiered implementation framework for targeted typing and donor recruitment in a multiethnic setting. **Results:** Extended phenotyping coverage beyond ABO and full Rh was uneven: Kidd 30.3% (4,897/16,173), MN 8.8% (1,419/16,173), Ss 4.5% (732/16,173), and Duffy 2.0% (325/16,173). This distribution indicates a capacity gap for precision matching, with the most scalable opportunity in Kidd typing and limited reach for other systems. Screening-efficiency considerations suggest some uncommon phenotypes may require screening thousands of donors, supporting a shift from broad, untargeted expansion toward precision targeting. We translated these findings into a service strategy: (i) expand and optimise the highest-coverage systems for the greatest population benefit, (ii) use targeted donor recruitment to improve access to uncommon phenotypes, and (iii) prioritise low-coverage typing for high-risk clinical indications. **Conclusion:** In a real-world multiethnic donor pool, typing coverage is a key determinant of precision transfusion readiness. Coverage metrics combined with screening-efficiency thinking can guide equitable, resource-conscious expansion of phenotype-matched transfusion support in Malaysia.

Keywords: Blood service planning; precision public health; real-world data; transfusion readiness; typing coverage

Identifying Risk Factors for Laboratory-Confirmed Leptospirosis in Rural Malaysia: A Study from Jelebu District

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ABSTRACT

Background: Leptospirosis remains an important zoonotic disease and public health concern in Jelebu District, Negeri Sembilan, Malaysia. The rapid expansion of camping activities in local forest reserves underscores the need for strengthened surveillance and targeted intervention strategies. This study aimed to identify the demographic and exposure-related factors associated with laboratory-confirmed leptospirosis in Jelebu District. **Method:** A cross-sectional analysis was conducted using surveillance data of all reported leptospirosis cases in Jelebu District from year 2022 to 2025. Descriptive statistics were used to summarise case characteristics, while simple logistic regression (bivariate analysis) was performed to determine factors significantly associated with positive Microscopic Agglutination Test (MAT). **Results:** Of 167 reported leptospirosis cases analysed, 38.3% (n = 64) were laboratory-confirmed. The majority of the reported cases were male (77.2%), aged 19-59 years (62.9%), and of Malay ethnicity (65.3%), while Orang Asli accounted for 18.6%. Bivariate analysis revealed that cases reported during rainy epidemic season were significantly more likely to be confirmed (OR 2.45, 95% CI 1.29-4.65, p = 0.006). Male gender (OR 2.88, 95% CI 1.23-6.76, p = 0.015) and recreational exposure (OR 2.47, 95% CI 1.20-5.10, p = 0.014) also showed significant associations. Untreated water exposure (p = 0.163), occupational risk (p = 0.228), and outdoor activity exposure (p = 0.141), were not statistically significant. **Conclusion:** Rainy season, male gender and recreational exposure were significant determinants of laboratory-confirmed leptospirosis among reported cases in Jelebu District. These findings highlight the influence of seasonal environmental factors and gender-related exposure patterns in disease transmission. Strengthening surveillance during high-risk periods and enhancing targeted risk communication for recreational forest users, may support for effective leptospirosis prevention and control strategies.

Gut Microbiome Profile in Malaysians with Mild Cognitive Impairment: An Analysis of The Malaysian Cohort Participants

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ABSTRACT

Background: Emerging evidence suggests that gut microbiome alterations may play a role in neurodegenerative disorders, including mild cognitive impairment (MCI). However, data from Malaysian populations remain limited. This study characterised the gut microbiome profile of Malaysians with MCI and healthy controls within The Malaysian Cohort (TMC). **Methods:** Participants from TMC were screened for cognitive impairment using the Montreal Cognitive Assessment (MoCA) and categorised into MCI (n = 220) and cognitively healthy controls (CON, n = 100). DNA was extracted from the faecal samples and analysed using shallow shotgun metagenomic sequencing. Sequencing reads underwent quality control followed by taxonomic profiling. **Results:** Overall gut microbial composition was broadly similar between MCI and controls. Discriminant analysis identified five species enriched in MCI group and 16 species enriched in controls (all LDA >2, $p < 0.05$). Differential abundance analysis showed no significant genus-level differences, and only one species (*B. faecihominis*) was reduced in MCI individuals (P = 0.041); however, this association was attenuated after adjustment for age, gender and ethnicity. In multivariable analyses, *Chol.sp003480725* and *R.inulinivorans* were reduced in females (P = 0.006 and P = 0.018, respectively), while *UMGS1975 sp900546685* was reduced among Indian participants (P = 0.025). Alpha diversity was positively correlated with MoCA score (Spearman's Rs:0.137, P = 0.043) and the delayed recall cognitive domain (Rs:0.160, P = 0.017). No individual genus or species was significantly associated with MoCA score or delayed recall. **Conclusion:** In this Malaysian cohort, overall gut microbiome composition was similar between individuals with MCI and cognitively healthy controls, suggesting that microbiome composition is relatively stable during early cognitive decline. The modest associations between alpha diversity and cognitive performance warrant further investigations in longitudinal studies.

Keywords: Gut microbiome; microbiome diversity; mild cognitive impairment; shallow shotgun metagenomics; The Malaysian Cohort

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Explainable Machine Learning for Hospital Readmission Prediction: Association Rule Mining Approach

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ABSTRACT

Hospital readmission remains a major challenge in healthcare systems, contributing to increased medical costs and indicating potential gaps in patient care. While machine learning models have been widely applied to predict readmission risk, many of these models function as black boxes, limiting their interpretability and practical adoption in clinical decision-making. Some interpretable models cannot easily capture highly complex interactions between clinical variables. This study proposes an explainable machine learning framework for hospital readmission analysis using a common approach of market basket analysis, namely Association Rule Mining (ARM). In this retrospective study, the inpatient admissions with the discharged diagnosis of heart failure coded as I50 from general hospital across Malaysia were assessed. The primary outcome was time to readmission within 30 days post-discharge. In the first stage, hospital readmission prediction was developed using Logistic Regression, Random Forest and Neural Network. In the second stage, the predicted output from the black box model was transformed into transactional datasets to enable the extraction of frequent itemsets and association rules using support, confidence, and lift metrics. The findings demonstrate the comparative performance across measures where Neural Network shows the best in overall model discrimination. The rules extracted using ARM showed that the association of the elderly group with multiple past admission within six months and having a short length of stay lead to the high chance of readmission. This approach manages to identify hidden patterns and relationships among readmission factors. Finally, the proposed framework enhances explainability in predictive healthcare analytics and supports data-driven strategies for improving patient management.

Cross-Omics Convergence Reveals an LRG1-Associated Immune-Metabolic Reprogramming Axis in Colorectal Cancer

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ABSTRACT

Circulating biomarkers provide valuable insight into systemic biological processes in colorectal cancer (CRC). Leucine-rich alpha-2-glycoprotein 1 (LRG1), a multifunctional pathogenic signaling molecule, has emerged as a CRC-associated circulating factor implicated in angiogenesis, autophagy, and epithelial-mesenchymal transition. Despite extensive investigation into CRC molecular complexity, the systemic role of LRG1 as a mediator linking inflammatory signaling to metabolic reprogramming remains unclear. Here, we aimed to identify convergent pathways associated with the LRG1 protein in CRC using integrated circulating transcriptomic and proteomic network analyses. A public transcriptome dataset (N = 1751) was processed for differential gene expression analysis, followed by gene network construction and extraction of the LRG1-centered subnetwork for functional enrichment. A parallel pipeline was applied to an in-house serum proteomic dataset (N = 38) with layer-specific parameter adjustments. A transcript-protein discrepancy was observed: LRG1 protein was strongly upregulated in CRC serum (logFC = 1.796, $p = 2.3 \times 10^{-3}$), whereas LRG1 mRNA showed only modest elevation in blood transcriptome data (logFC = 0.278, $p = 1.4 \times 10^{-8}$). This suggests compartmental regulation or non-blood cellular sources of circulating LRG1. Network analysis revealed clustering of LRG1 with acute-phase inflammatory proteins, including haptoglobin (HP) and alpha-1-acid glycoprotein (ORM1), alongside inverse association with lipid transport components, suggesting LRG1 participation in a coordinated immune-metabolic reprogramming axis in CRC systemic circulation. Functional enrichment across Kyoto Encyclopedia of Genes and Genomes (KEGG), Gene Ontology and Reactome consistently demonstrated activation of innate immune pathways and suppression of translational programs, while proteome enrichment further indicated downregulation of lipid and sterol metabolic processes (NES < -1.7, $p < 0.001$). Together, cross-omics convergence supports a model of systemic immune-metabolic reprogramming in CRC blood circulation. These findings position circulating LRG1 as a potential integrative biomarker of the immune-metabolic remodeling axis and highlight new avenues for understanding metabolic vulnerabilities in CRC.

Keywords: Circulating biomarkers; colorectal cancer, LRG1; multi-omics; network analysis

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Longitudinal Shotgun Metagenomic Profiling of the Vaginal Microbiome in Pregnant and Non-Pregnant Malaysian Women

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ABSTRACT

Background: The vaginal microbiome plays an important role in women's reproductive health and may influence pregnancy outcomes. Pregnancy-associated hormonal and immunological changes can alter microbial community structure, yet population-specific data describing the vaginal microbiome in pregnant and non-pregnant Malaysian women remain limited. This study aimed to characterise and compare the vaginal microbiome of pregnant and non-pregnant Malaysian women, and to examine microbial dynamics across pregnancy trimesters. **Methods:** In this prospective longitudinal cohort study, three pregnant women were sampled across all three trimesters of pregnancy, and 13 non-pregnant women were recruited as controls. Vaginal microbial DNA was extracted and analysed using shotgun metagenomic sequencing. Microbial composition was assessed using alpha diversity (Chao1, Shannon, Simpson), beta diversity (Bray-Curtis, Jaccard), and relative abundance analyses. **Results:** Alpha and beta diversity analyses showed no statistically significant differences across trimesters ($P > 0.05$), although a modest increase in richness was observed in the third trimester. Marked inter-individual variability was observed. One pregnant participant demonstrated persistent *Lactobacillus* dominance across pregnancy (first trimester, 99.92%; second trimester, 99.56%, third trimester, 99.56%), while two participants showed high relative abundance of *Bifidobacterium,* particularly *Bifidobacterium leopoldii* and *Bifidobacterium swidsinskii*. In contrast, the non-pregnant group displayed greater overall microbial diversity and was predominantly associated with community state type (CST) IV, characterised by higher relative abundance in *Bifidobacterium vaginale* (14.29%), *Fannyhessea vaginae* (10.53%), *Bifidobacterium piotii* (8.61%) and *Streptococcus agalactiae* (8.28%). **Conclusion:** This study provides preliminary characterisation of the vaginal microbiome in pregnant and non-pregnant Malaysian women. While overall diversity did not differ significantly across trimesters, richness may increase modestly in late pregnancy, and substantial inter-individual variability was observed. These findings offer early baseline data to inform larger longitudinal studies of vaginal microbial patterns in Malaysian women.

Keywords: Dysbiosis; *Lactobacillus*; pregnancy, vaginal microbiome

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VapGaMo: A Theory-Driven Serious Game for Precision Public Health in Adolescent Vaping Prevention

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ABSTRACT

Background: Adolescent vaping is an escalating public health challenge, with early nicotine exposure increasing the risk of lifelong addiction and adverse health outcomes. Traditional health education often fails to engage digital-native youth effectively. Aligned with the principles of precision public health, i.e., delivering the right intervention to the right population at the right time, technology-enabled strategies offer new opportunities for targeted prevention. VapGaMo (Vaping Prevention Gaming Module) was developed as a theory-driven serious game designed to deliver interactive, behaviourally targeted vaping prevention among adolescents. **Methods:** VapGaMo was developed as a digital educational game guided by the Theory of Planned Behavior (TPB), targeting key determinants of behaviour including knowledge, attitude, subjective norm, perceived behavioural control, and intention. Designed for adolescents aged 10-17 years, the game consists of five progressive levels where players navigate a dystopian world, complete missions, and develop refusal skills while interacting with game elements such as "Vapester" monsters and educational artefacts. The intervention was evaluated using a cluster randomised controlled trial in eight secondary schools in Klang District, Malaysia. Outcomes measured included vaping-related knowledge, attitudes, perceived behavioural control, and intention to vape. **Results:** Of the 370 students enrolled, 325 (87.8%) completed the 3-month follow-up. Students exposed to the game showed significant reductions in vaping intention and improvements in vaping-related knowledge immediately post-intervention (β = 0.235, $p = 0.009$; $\beta = 2.00$, $p < 0.001$, respectively) and at 3-month follow-up ($\beta = 0.272$, $p = 0.006$; $\beta = 1.52$, $p < 0.001$). The intervention also produced significantly more negative attitudes toward vaping ($\beta = 4.53$, $p < 0.001$) and stronger perceived behavioural control ($\beta = 0.81$, $p < 0.001$) immediately after the intervention, although these effects were not sustained at the 3-month follow-up. User acceptability was high (97.4%) based on the Game User Experience Satisfaction Scale (GUESS-18), indicating strong engagement with the intervention. **Conclusion:** VapGaMo demonstrates the potential of serious games as scalable digital interventions for adolescent vaping prevention. By integrating behavioural theory with interactive technology, such tools may contribute to precision public health strategies targeting youth risk behaviours.

Stool Microbial Community Composition Differs Between Colorectal Cancer and Non-Cancer Patients in a Malaysian Shotgun Metagenomic Study: A Preliminary Result

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ABSTRACT

Background: Alterations in the gut microbiome have been linked to colorectal cancer (CRC) development, including tumor-associated microbial shifts. Whether these shifts are reflected in stool microbiota in Malaysian populations remains underexplored. This study aimed to investigate the microbial diversity and composition in patients with and without a diagnosis of CRC, addressing the lack of such data among the Malaysian population. **Methods**: Stool samples were obtained from 22 CRC patients and 22 non-CRC controls. Microbial DNA was extracted and subjected to shotgun metagenomic sequencing using the Illumina NextSeq 2000 platform, followed by bioinformatics analysis using the CosmosID pipeline. Alpha diversity was analysed using the Wilcoxon Rank Sum Test, while beta diversity was assessed using PERMANOVA. Differentially abundant taxa were identified using Linear discriminant analysis Effect Size software (LEfSe). **Results**: Our findings indicated a difference in the microbial composition between CRC and non-CRC. Beta diversity analysis observed a significant difference ($p = 0.024$) between the two groups. At the phylum level, Verrucomicrobiota was significantly higher in CRC compared to non-CRC. At the genus level, *Phocaeicola* and *Agathobacter* were significantly lower in CRC but higher in the control group ($p = 0.049$ and $p = 0.012$ respectively). At the species level, *Blautia_A wexlerae*, *Phocaeicola massiliensis* and *Megamonas funiformis* showed significantly lower abundance in CRC compared to non-CRC ($p = 0.013$, $p = 0.039$ and $p = 0.013$ respectively). LEfSe analysis demonstrated enrichment of *Peptostreptococcus stomatis*, *Parvimonas micra* and *Gemella morbillorum* in CRC, while *Escherichia coli*, *Blautia_A wexlerae* and *Agathobacter rectalis* were enriched in non-CRC (all LDA > 3). **Conclusion**: CRC is associated with a distinct gut microbial composition compared to non-CRC controls. Specific taxa that were decreased in CRC but higher in controls suggest potential microbial signature of CRC. These findings provide candidate taxa for biomarker development, but causal relationships require further investigation.

Keywords: Colorectal cancer; gut microbiome; Malaysia; microbial diversity; stool

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Association of Serum Trace Elements and Comorbidities with COVID-19 Severity and Mortality: A COVGEN Prospective Cohort Study

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ABSTRACT

Background: COVID-19 ranges from asymptomatic infection to critical illness. Identifying factors associated to disease severity improves clinical management. This study examined association of serum trace elements and comorbidities with COVID-19 severity and mortality in Malaysia patients. **Methods:** This prospective cohort included 1,522 patients aged 10 to 92 years from the COVGEN project at UKM Medical Molecular Biology Institute, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia and community facilities in Cheras, Kuala Lumpur, Malaysia. Patients were stratified into five categories according to Ministry of Health Malaysia COVID-19 severity classification. Serum trace element concentrations were quantified using ICP-MS. Group comparisons were performed using the Kruskal-Wallis and Mann-Whitney tests, while univariable multinomial logistic regression assessed associations between individual risk factors and disease severity, with category 1 (asymptomatic) as the reference. **Results:** Comorbidities were the strongest predictors of disease progression. Chronic kidney disease (CKD) showed the strongest association with critical illness (OR 24.42; 95% CI 3.19-186.59; $p = 0.002$), followed by hypertension (OR 10.36; 95% CI 4.54-23.64; $p < 0.001$), dyslipidemia (OR 9.33; 95% CI 2.67-32.58; $p < 0.001$), diabetes mellitus (OR 7.21; 95% CI 3.04-17.11; $p < 0.001$) and cardiovascular disease (OR 3.72; 95% CI 1.41-9.81; $p = 0.008$). Severe progression was also associated with toxic metal, particularly cadmium (Cd, OR 1.016; 95% CI 1.001-1.031; $p = 0.032$), thallium (Tl, OR 1.035; 95% CI 1.003-1.068; $p = 0.03$), and uranium (U, OR 1.021; 95% CI 1.001-1.041; $p = 0.037$). Mortality was significantly associated with Cd, Tl and U ($p < 0.001$). In contrast, selenium (Se, OR 0.989; 95% CI 0.982-0.997; $p = 0.004$) and vanadium (V, OR 0.993; 95% CI 0.989-0.997; $p = 0.002$) demonstrated modest protection against severe outcomes. **Conclusion:** In this Malaysia cohort, COVID-19 severity strongly associated with comorbidities, particularly CKD and hypertension, and serum trace elements imbalances, suggesting that both clinical and environmental or biochemical factors may contribute to disease progression and mortality.

Keywords: COVID-19 severity; comorbidities; mortality; serum trace elements

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Impact of an Information-Motivation-Behavioral Skills Based Intervention on Malaria Prevention among the Indigenous Community in Jelebu, Negeri Sembilan

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ABSTRACT

Background: While Malaysia has achieved zero indigenous human malaria cases, zoonotic malaria (*Plasmodium knowlesi*) remains a significant public health threat, particularly among indigenous (Orang Asli) communities living near forested areas. Effective prevention requires theory-driven interventions tailored precisely to this high-risk population. This study aimed to evaluate the effectiveness of a health education intervention based on the Information-Motivation-Behavioral Skills (IMB) model on the knowledge, attitude and practices (KAP) of malaria prevention among the Orang Asli in Jelebu, Negeri Sembilan. **Methods:** A quasi-experimental study with a single-group pre- and post-test design was conducted in three villages (Kampung Orang Asli (KOA) Ulu Kelaka, KOA Baner Tengkoh and KOA Dusun Kubur). The intervention integrated health talks (iInformation), risk perception enhancement (Motivation) and practical demonstrations on insecticide-treated net usage and vector identification (Behavioral Skills). **Results:** Out of 45 participants at baseline, 31 completed the post-test (31.11% attrition rate). Data were analysed using the Wilcoxon Signed-Rank test. Analysis showed significant improvements in Knowledge scores (Median increased from 6.5 to 8.0, $p < 0.001$) and Practice scores (Median increased from 4.0 to 5.0, $p < 0.001$). Attitude scores remained consistently high and positive (Median = 2.0, $p = 1.000$). Baseline analysis also revealed a significant positive correlation between age and knowledge ($p = 0.032$). **Conclusion:** The IMB-based intervention significantly enhanced malaria prevention knowledge and practical skills among the indigenous community. Culturally sensitive, theory-based health education should be integrated into national malaria control programs to ensure sustainable prevention practices in zoonotic-endemic areas.