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Program

08:15 – 09:00	Poster Presentation
09:00 – 09:10	Opening Ceremony
09:10 – 09:50	**Plenary Lecture I: Genomic Medicine for Kidney Diseases and Beyond** **Prof Ali GHARAVI** *Columbia University, United States*
09:50 – 10:10	Break

Scientific Session I

10:10 – 10:35	**Optimizing Cholesterol Treatment with Statins in Patients with Type 2 Diabetes** **Dr Eric WAN** *Department of Family Medicine and Primary Care &* *Department of Pharmacology and Pharmacy, HKUMed*
10:35 – 11:00	**Update on the Treatment and Prevention of COVID-19 Infection** **Prof Ivan HUNG** *Department of Medicine, School of Clinical Medicine, HKUMed*
11:00 – 11:25	**Inflammation-Driven Diseases: Insights from Drosophila** **Dr Jung KIM** *School of Biomedical Sciences, HKUMed*

Scientific Session II

11:25 – 11:50	**Press-N-Go Wearable Sensors for Continuous Healthcare Monitoring** **Prof Xi YAO** *Department of Biomedical Sciences, City University of Hong Kong*
11:50 – 12:15	**Targeting Unhealthy Vascular Endothelium** **Prof Yu HUANG** *Department of Biomedical Sciences, City University of Hong Kong*
12:15 – 12:40	**Combating Immune Checkpoint Blockade Resistance: Exploring Mechanism and Novel Targets** **Dr Heidi LING** *School of Biomedical Sciences & Department of Medicine,* *School of Clinical Medicine, HKUMed*
12:40 – 13:50	Lunch
13:50 – 14:25	Best Abstract Award Presentation
14:25 – 15:05	**Plenary Lecture II: Translating Genomic Research to Clinical Practice – Haematology Perspective** **Dr Hein THAN** *Duke-NUS Medical School, Singapore*

Program

15:05 – 15:45	**Plenary Lecture III: Advancing Evidence-Based Coronary Interventions: The Asan Experience with Randomized Controlled Trials** **Prof Duk-Woo PARK** *University of Ulsan College of Medicine, South Korea*
15:45 – 16:00	Break

Scientific Session III

16:00 – 16:25	**AI in Radiology** **Prof K. Ty BAE** *Department of Diagnostic Radiology, School of Clinical Medicine, HKUMed*
16:25 – 16:50	**Multi-omics and Artificial Intelligence in Medical Research** **Dr Joshua HO** *School of Biomedical Sciences, HKUMed*
16:50 – 17:15	**Exploring the Future of Gastrointestinal Healthcare: The Integration of Artificial Intelligence in Colonoscopy Procedures** **Dr Thomas LUI** *Department of Medicine, School of Clinical Medicine, HKUMed*

Scientific Session IV

17:15 – 18:10	✧ **Genetically Encoded Multiphase Droplet for Drug Delivery** **Prof Anderson SHUM** *Department of Mechanical Engineering, HKU* ✧ **Multiplexed Digital PCR for Disease Diagnosis** **Prof David A. WEITZ** *Harvard University, United States* ✧ **Structure Switching Aptamers for Sepsis Biomarker** **Prof Julian A. TANNER** *School of Biomedical Sciences, HKUMed* ✧ **Cell-omics** **Prof Kevin TSIA** *Department of Electrical and Electronic Engineering, HKU* ✧ **Inhalable Nanoagglomerate for Respiratory Application** **Dr Aviva CHOW** *Department of Pharmacology and Pharmacy, HKUMed* ✧ **Organoide in Droplets** **Prof Andreas BAUSCH** *Technical University of Munich, Germany*
18:10 – 18:15	Closing Remarks

Plenary Lecture

Genomic Medicine for Kidney Diseases and Beyond

Prof Ali GHARAVI

Ali Gharavi, M.D., is the Jay Meltzer M.D. Professor of Nephrology and Hypertension and serves as Chief of the Division of Nephrology, Director of the Center for Precision and Genomics in the Department of Medicine and Interim Chair of the Department of Medicine. After receiving his medical degree from George Washington University, Dr. Gharavi completed residency in internal medicine and fellowships in hypertension and nephrology at the Mount Sinai Medical Center. He then completed a postdoctoral fellowship in human genetics at Yale University and joined Columbia University in 2003. Dr. Gharavi's research is focused on the molecular genetics of kidney diseases and his work has led to the discovery of genes and loci for IgA nephropathy and congenital defects of the kidney and urinary tract. His research has demonstrated the utility of clinical sequencing in the diagnosis and management of patients with kidney disease and he is extending this work to other adult constitutional disorders. His goal is to bring personalized genomic medicine from the laboratory into patient care. He is the principal investigator of multiple scientific projects funded by the National Institute of Health, including the All of Us grant, the national precision medicine initiative. He was elected to the American Society of Clinical Investigation and the American Association of Physicians. He is a recipient of the Judson Daland Prize for Outstanding Clinical Investigation from the American Philosophical Society, the National Medical Award, from the Kidney and Urology Foundation of America and the Homer Smith Award from the American Society of Nephrology. He also received the mentor of the year award at Columbia University.

Translating Genomic Research to Clinical Practice – Haematology Perspective

Dr Hein THAN

Dr Than Hein is a Senior Consultant Haematologist at Singapore General Hospital and National Cancer Centre Singapore, and a Clinical Assistant Professor at the Duke-NUS Medical School Singapore. He is a fellow of the Royal College of Pathologists (UK) and the Academy of Medicine Singapore. His clinical interest focuses on myeloproliferative neoplasm, leukaemia, and haematopoietic stem cell transplantation. His research on leukaemia genomics was supported by SingHealth Health Manpower Development Plan Award and National Medical Research Council Singapore. He is a winner of Nurturing Clinician Scientist Scheme Award from SingHealth Duke-NUS Medicine Academic Clinical Programme. He is currently the Lead for Diagnostics at SingHealth Duke-NUS Blood Cancer Centre.

Plenary Lecture

Advancing Evidence-Based Coronary Interventions: The Asan Experience with Randomized Controlled Trials

Prof Duk-Woo PARK

Dr. Duk-Woo Park was a Professor in the Cardiovascular Medicine Division at Asan Medical Center, Seoul, Korea, and an Instructor in Medicine at the University of Ulsan College of Medicine.

Dr. Duk-Woo Park graduated from Kyoung-Hee Medical College and received medical degree from Kyoung-Hee Medical College and received M.S., Ph.D., degree from University of Ulsan College of Medicine. Dr. Duk-Woo Park subsequently did his Internal Medicine residency, Chief Residency, and Cardiology fellowship at the Asan Medical Center.

Dr. Duk-Woo Park's primary research interest has been in coronary revascularization treatments (PCI or CABG), PCI for left main disease, TAVR, antiplatelet therapies, biomarker, and stent studies. Dr. Duk-Woo Park has been the Investigator of many clinical trials conducted in the Asan Medical Center, Seoul, Korea. Dr. Duk-Woo Park was the first author on the primary results paper (REAL-LATE and ZEST-LATE trial) that was presented at ACC 2010 and published in the New England Journal of Medicine 2010 and the MAIN-COMPARE registry results paper that was presented at ACC 2008 and published in New England Journal of Medicine 2008. Dr. Duk-Woo Park has also authored or coauthored over 350 original, peer-reviewed research articles. Especially, Dr. Duk-Woo Park has major contributions as the principal (first or corresponding) authors in top medical journals (2 NEJM, 1 JAMA, 25 JACC, 5 Circulation, 2 EHJ) within last 20 years. By the remarkable academic achievements, Dr. Duk-Woo Park was awarded with Douglas P. Zipes Distinguished Young Scientist Award at the 2012 ACC (American College of Cardiology), Chicago, IL, United States.

Dr. Duk-Woo Park has now a particular interest in revascularization strategy (PCI vs. CABG for multivessel and left main disease), antiplatelet/antithrombotic strategy, transcatheter valve interventions (TAVR), major clinical trials or registries studies (drugs, stents, revascularization strategy), biomarkers, and medical statistics.

Dr. Duk-Woo Park is now a Deputy Editor in JACC Asia.

Scientific Session I

Optimizing Cholesterol Treatment with Statins in Patients with Type 2 Diabetes

Dr Eric WAN

Dr Eric Wan holds the position of Assistant Professor at the Department of Family Medicine and Primary Care, as well as the Department of Pharmacology and Pharmacy, at The University of Hong Kong. He is a skilled epidemiologist and medical statistician, with more than 150 published articles in renowned international journals such as Annals of Internal Medicine, Lancet Infectious Disease, The Lancet Healthy Longevity, Journal of the American College of Cardiology, Cardiovascular Research, Diabetes Care, and Hypertension. His expertise lies in using big data analytics for research in health and health services. Dr Wan was awarded the Health and Medical Research Fund Research Fellowship by the Health Bureau of Hong Kong SAR Government as a visiting scholar at Harvard University. His achievements have been recognized by funding bodies such as the National Natural Science Foundation of China (NSFC) Excellent Young Scientists Fund (Hong Kong and Macau), and awards such as the HKU Faculty Outstanding Research Output Award.

Update on the Treatment and Prevention of COVID-19 Infection

Prof Ivan HUNG

Professor Ivan Fan Ngai HUNG is currently Chair of Infectious Diseases, Ru Chien and Helen Lieh Professor in Health Science Pedagogy, Chief of the Division of Infectious Diseases, Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong, and Honorary Consultant in Queen Mary Hospital, Hong Kong. He is also Chair Professor and Chief-of-Service of the Department of Infectious Diseases and Clinical Microbiology at the HKU-Shenzhen Hospital.

Professor Hung has published more than 370 international peer reviewed original articles, including research articles in the Lancet, Nature, the Lancet Infectious Diseases and the Clinical Infectious Diseases. He has pioneered the use of the triple combination of interferon beta-1b, lopinavir/ ritonavir and ribavirin in the treatment of hospitalized COVID-19 patients, resulting in significantly faster clinical alleviation and viral load suppression. He and his team also pioneered the application of topical imiquimod before intradermal influenza vaccination, which results in protection against heterologous non-vaccine and antigenically drifted viruses. He is ranked as HKU Scholars in the world top 1% in 2013, 2018-2023. He is the world-leading expert in the field of antiviral and vaccinology for influenza and COVID-19 infection. He is Associate Editor of the medical journals, Vaccine, Diagnostics.

Scientific Session I

Inflammation-Driven Diseases: Insights from Drosophila

Dr Jung KIM

Dr. Kim joined the School of Biomedical Sciences at the University of Hong Kong in September 2022 as an Assistant Professor investigating the impact of tumor-driven systemic inflammation on host morbidity and mortality using Drosophila melanogaster as a model system. Dr. Kim received his BSc and MSc degrees from Korea University, South Korea and obtained his PhD degree from the University of Minnesota, USA. Dr. Kim then worked as a postdoc fellow at the University of California-Berkeley, USA. Currently, Dr. Kim and his team at HKU are focusing on mechanisms by which tumor-secreted cytokines disrupt host organs, including the blood-brain barrier and the renal tubule.

Scientific Session II

Press-N-Go Wearable Sensors for Continuous Healthcare Monitoring

Prof Xi YAO

Prof. Yao is currently a Professor and Assistant Head at Department of Biomedical Sciences, City University of Hong Kong. Prior to joining the university in 2014, he received the PhD degree in Chemistry from Institute of Chemistry, Chinese Academy of Sciences (CAS) in Beijing, and postdoc training at School of Engineering and Applied Sciences and Wyss Institute of Biologically Inspired Engineering at Harvard University, working on the bioinspired surface engineering.

Prof. Yao's research interest lies at the interface of polymer chemistry, biomaterials, and wearable devices. His current research projects include the bioinspired manipulation of microdroplets for pathogen control and biosensing, the development of supramolecular biomaterials for tissue engineering, and the development of wearable devices for healthcare monitoring, by using interdisciplinary approaches in the areas of molecular engineering, nanotechnology, and artificial intelligence.

Prof. Yao received the Outstanding Research Award for Junior Faculty from the University in 2020, and was admitted as a Fellow of Royal Society of Chemistry in 2022. In the past five years, his corresponded research papers include those in PNAS, Nature Communications, Science Advances, Advanced Materials, Angew Chemie, ACS Nano and STTT.

More information can be found at:
http://staffweb1.cityu.edu.hk/xiyao7

Targeting Unhealthy Vascular Endothelium

Prof Yu HUANG

HUANG Yu received his BSc from Fudan University Shanghai Medical College and his PhD from the University of Cambridge. He joined CUHK in late 1993 and served as Chair Professor of Biomedical Sciences (2010-2021) and Founding Director (Basic Sciences) of the Heart and Vascular Institute (2007-2021) in CUHK. He is currently Chair Professor of Biomedical Sciences and Vascular Biology, Jeanie Hu Professor of Biomedical Sciences and Head of the Department of Biomedical Sciences at CityU. He is Vice President of both the Chinese Section of the International Society for Heart Research (ISHR) and the Chinese Association for Physiological Sciences. He is an elected Fellow of both ISHR and the International Union for Physiological Sciences. He received the Inaugural Hong Kong RGC-Senior Research Fellow Award (2020). He is an Associate Editor of Circulation Research. His team aims to elucidate cellular and molecular events in the initiation and progression of endothelial cell dysfunction in hypertension, obesity and diabetes, to uncover novel biomarkers of vascular pathogenesis, and to develop ways to reverse vascular dysfunction in animal models of cardiometabolic disease. He has co-authored 494 SCI publications with over 33,600 citations.

Scientific Session II

Combating Immune Checkpoint Blockade Resistance: Exploring Mechanism and Novel Targets

Dr Heidi LING

Dr Heidi GS Ling is an Assistant Professor in the School of Biomedical Sciences and the Department of Medicine, School of Clinical Medicine at the University of Hong Kong (HKU). She obtained her BSc and PhD at HKU and did her postdoctoral training at Imperial College London. She starts her own group in 2019 and her primary research interest lies in understanding the mechanisms behind immune dysregulation in various chronic inflammatory diseases, particularly those that contribute to inflammation-driven cancers. Her laboratory employs the emerging technologies from the field of immunometabolism to assess the effects of sustained inflammation on exhausted T cell differentiation as well as the implications of tumor-immune co-evolution on the efficacy of cancer immunotherapy.

Scientific Session III

AI in Radiology

Prof K. Ty BAE

Kyongtae Ty Bae, PhD, MD, MBA, is Clinical Professor and Head of the Department of Diagnostic Radiology and Global STEM Professor at the University of Hong Kong. He is also the Director of the Jockey Club STEM Lab of Innovative Medical Imaging Research. He was Professor and Chairman of the Department of Radiology and Associate Dean at the University of Pittsburgh, USA. He was also a Professor of Bioengineering and the Director of the Imaging Biomarker Lab at the University of Pittsburgh. He graduated from Seoul National University with a BS in Chemical Engineering. He received a MS in Chemical Engineering from the University of Iowa, MS and PhD in Bioengineering from the University of Pennsylvania, and a MD from the University of Chicago. Dr. Bae did his Radiology residency and fellowship training at the Mallinckrodt Institute of Radiology, Washington University in St Louis and rose through the academic ranks before moving to University of Pittsburgh. He also received MBA from Wharton School of Business at University of Pennsylvania.

Dr. Bae's JC STEM Lab of Innovative Medical Imaging Research at HKU specializes in developing novel image-guided intervention, developing and analyzing morphological and functional imaging biomarkers from medical images, and improving the quality and efficiency of radiology practice by use of AI and machine learning.

Dr. Bae has published over 680 papers, proceedings, and abstracts including over 272 peer reviewed journal publications (H-index 83). Dr. Bae has received numerous research awards throughout his academic career, including the 2021 Lillian Jean Kaplan International Prize for Advancement in the Understanding of Polycystic Kidney Disease.

Multi-omics and Artificial Intelligence in Medical Research

Dr Joshua HO

Dr Joshua Ho is a bioinformatics and digital health researcher at the School of Biomedical Sciences at HKU, in which he serves as an Associate Professor. He completed a BSc (Hon) and PhD in Bioinformatics at the University of Sydney and a postdoctoral fellowship at Harvard Medical School. His research focuses on developing and using advanced single cell analysis, metagenomics, and artificial intelligence (AI) techniques to address key issues in cancer biology, gut microbiome, and digital health, resulting in over 138 publications. At HKUMed, he is also the Programme Co-Director of BSc (Bioinformatics), Deputy Director of Educational Technology (AI), Academic Lead (Bioinformatics Core) at the Centre for PanorOmic Sciences, and Lead Scientist at the Laboratory of Data Discovery for Health ($D^2$4H).

Scientific Session III

Exploring the Future of Gastrointestinal Healthcare: The Integration of Artificial Intelligence in Colonoscopy Procedures

Dr Thomas LUI

Dr Thomas Lui was awarded a distinction in medicine upon graduating in 2004 and subsequently completed his specialist training in Gastroenterology and Hepatology in 2011. He further honed his skills by receiving advanced endoscopy training at Kobe University in Japan under the tutelage of Dr Takashi Toyonaga in 2014 and 2017. Dr Lui also earned the title of Honorary Research Fellow at Kobe University in 2014. With over 500 cases of experience in advanced endoscopic surgery, Dr Lui's expertise encompasses image-enhanced endoscopy, endoscopic submucosal dissection, per-oral endoscopic myotomy, full-thickness endoscopic resection, and submucosal tunnelling endoscopic resection. He currently serves as the specialist in charge at the HKU Endoscopic Centre. In addition to his proficiency in advanced endoscopy, Dr Lui's research interests include the application of artificial intelligence and machine learning in gastroenterology and endoscopy. He has published multiple original articles as the first author in leading journals, including Gastroenterology and Gastrointestinal Endoscopy. At present, Dr Lui holds the position of Clinical Associate Professor in the Department of Medicine, Li Ka Shing Faculty of Medicine at the University of Hong Kong.

Scientific Session IV

Genetically Encoded Multiphase Droplet for Drug Delivery

Prof Anderson SHUM

Ir Prof. Ho Cheung (Anderson) Shum is currently a Professor in the Department of Mechanical Engineering and Associate Vice-President (Research and Innovation) at HKU, also serving as the Director of the ABIC. His research interests include emulsion, biomicrofluidics, biomedical engineering, and soft matter.

Prof. Shum is highly recognized for his pioneering contributions and received numerous international scientific honors, including but not limited to the inaugural Hong Kong Engineering Science and Technology Award 2022, Croucher Senior Research Fellowship 2020, Rising Star Award by Ton Duc Thang University (Vietnam) 2019, NSFC Excellent Young Scientist Fund 2019, Young Scientists Award in Microsystems and Nanoengineering Summit 2019, IEEE Nanomed New Innovator 2018, and Early Career Award by the Research Grants Council of Hong Kong in 2012. He was selected as Fellow of Hong Kong Institution of Engineers in 2023, Member of Global Young Academy (First in Hong Kong) in 2021, Founding Member (2018) and President (2021) of Hong Kong Young Academy of Sciences, and Fellow of Royal Society of Chemistry (RSC) in 2017. He serves as an Associate Editor for Biomicrofluidics (American Institute of Physics), Editorial Board Member for Microsystems and Nanoengineering (Springer Nature) and Scientific Reports (Springer Nature), and Editorial Advisory Board Member for Lab-on-a-Chip (RSC).

Multiplexed Digital PCR for Disease Diagnosis

Prof David A. WEITZ

Prof David A. Weitz received his PhD in physics from Harvard University and then joined Exxon Research and Engineering Company, where he worked for nearly 18 years. He then became a professor of physics at the University of Pennsylvania and moved to Harvard at the end of the last millennium as professor of physics and applied physics. He leads a group studying soft matter science with a focus on materials science, biophysics and microfluidics. Several startup companies have come from his lab to commercialize research concepts. He is a member of the Advanced Biomedical Instrumentation Center at HKU. He is also a member of the National Academy of Sciences and the National Academy of Engineering in the US and is a foreign member of the Chinese Academy of Engineering.

Scientific Session IV

Structure Switching Aptamers for Sepsis Biomarker

Prof Julian A. TANNER

Julian Tanner is a Professor in the School of Biomedical Sciences, HKUMed, and is also the Director of the Common Core of the University of Hong Kong. He is also a Co-PI of the Advanced Biomedical Instrumentation Centre (ABIC) at the Hong Kong Science Park. His research field is in nucleic acids, particularly in directed evolution of aptamers, in DNA nanotechnology, and in translational applications of nucleic acids in diagnostics and therapeutics. In 2024, he published the second edition of his interdisciplinary textbook "Essentials of Chemical Biology" (Wiley). Currently his team is developing aptamer-based electrochemical diagnostic technologies for a variety of disease areas including sepsis, pancreatic cancer and malaria. The team is also developing fluorescent RNA tools, and is using CryoEM to investigate a new class of facet-based geometric nucleic acid nanostructures. In education and research, he is highly committed to transdisciplinarity, bringing together creative ideas across all disciplines of the University.

Cell-omics

Prof Kevin TSIA

Kevin Tsia is currently a Professor in the Department of Electrical and Electronic Engineering and the Program Director of the Biomedical Engineering Program at The University of Hong Kong. His research interest covers a broad range of subject matters including ultra-fast optical imaging for imaging flow cytometry and high-speed in-vivo brain imaging, bioinformatics approaches for single-cell analysis. He is currently the HK Research Grants Council (RGC) Research Fellow (2020). He received Early Career Award 2012-2013 by RGC in Hong Kong. He also received the Outstanding Young Research Award 2015 at HKU as well as 14th Chinese Science and Technology Award for Young Scientists in 2016. He holds 11 granted and pending US patents on ultrafast optical imaging technologies. He is a co-founder of start-up company commercialising the high-speed microscopy technology for cancer screening and treatment monitoring applications. It was among the top 10 finalists in Falling Walls Venture in 2019.

Scientific Session IV

Inhalable Nanoagglomerate for Respiratory Application

Dr Aviva CHOW

Dr. Aviva Chow is an Assistant Professor in the Department of Pharmacology and Pharmacy at the University of Hong Kong (HKU). He is also a Project Leader and Co-principal Investigator at the Advanced Biomedical Instrumentation Centre funded by the InnoHK Programme. He obtained his bachelor degree in Chemical & Bioproduct Engineering and PhD in Pharmacy from the Hong Kong University of Science and Technology and Chinese University of Hong Kong, respectively. Prior to his appointment at HKU, he worked as a Technical Lead and Scientist in a HKEX-listed company for drug development. Dr. Chow's research focuses on the crystal and particle engineering of pharmaceutical materials for advanced drug delivery. He has published over 40 peer-reviewed articles in the leading journals in Pharmacology & Pharmacy and Crystallography. Dr. Chow's professional leadership also extends to the community via engaging as a committee member in the Pharmacy and Poisons (Manufacturers Licensing) Committee and Committee on Research and Development of Chinese Medicines under the Department of Health and Innovation and Technology Commission, respectively.

Organoide in Droplets

Prof Andreas BAUSCH

Prof. Andreas R. Bausch targets a quantitative understanding of the mechanical properties of cells, active matter and the mechanisms of self-organization in molecular and organoid systems. After his Ph.D. in physics at Technical University of Munich (TUM) and his postdoctoral stay at Harvard University he accepted the Chair position at the Technical University in 2008.

He received an ERC Starting, Advanced Grant and Synergy Grant. He is founder of two start-up companies and spin offs. He is founding director of two research buildings and centers: the Center of Functional Protein Assemblies (2014) and Center for Organoid Systems (2021).

Abstract

Abstract

Abstract

Abstract

A prospective one-year follow-up of glycaemic status and C-peptide levels of COVID-19 survivors with dysglycaemia in acute COVID-19 infection

1

DTW Lui[1], CH Lee[1], Y Wong[1], CHY Fong[1], KH Tsoi[1], YC Woo[1], KCB Tan[1]

[1]*Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong*

Introduction: Population-based studies have suggested increased risks of incident diabetes among COVID-19 survivors, but individuals included in these retrospective observational population-based studies were not systematically evaluated for glycaemic status. Also, data are limited regarding the insulin secretory capacity of COVID-19 survivors. We evaluated systematically the evolution of glycaemic status and insulin secretory capacity among COVID-19 survivors who had dysglycaemia at baseline.

Methods: COVID-19 survivors who had dysglycaemia (defined by HbA1c 5.7-6.4% or random glucose ≥10.0 mmol/L) in acute COVID-19 were recruited from a major COVID-19 treatment centre from September to October 2020. Non-COVID controls matched for age, sex, BMI and HbA1c were recruited from community. 75-gram oral glucose tolerance test (OGTT) were performed at baseline (six weeks after acute COVID-19) and one year after acute COVID-19, with HbA1c, insulin and C-peptide measurements. Insulin sensitivity was assessed by HOMA-IR (derived from fasting glucose and insulin) and Matsuda index (derived from glucose and insulin levels during OGTT at baseline and 2 hours). Progression in glycaemic status was defined by progression from (i) normoglycaemia to prediabetes/diabetes, or (ii) prediabetes to diabetes.

Results: Fifty-two COVID-19 survivors were recruited (age: 61.2±8.8 years; 50% men; BMI: 24.6±3.1 kg/m^2; HbA1c 5.5±0.3%). Compared with non-COVID controls (n=50), they had higher C-peptide (0.66 nmol/L [IQR: 0.56-0.83] vs 0.52 [0.45-0.66], p<0.001) and trend towards higher HOMA-IR (p=0.065). Forty-three COVID-19 survivors attended one-year reassessment. HbA1c increased from 5.5±0.3% to 5.7±0.2% (p<0.001), with increases in glucose on OGTT at fasting (p=0.089), 30-minute (p=0.126), 1-hour (p=0.014) and 2-hour (p=0.165). At baseline, 19 subjects had normoglycaemia, 23 had prediabetes, and 1 had diabetes. Over one year, 10 subjects (23.8%; of 42 non-diabetes subjects at baseline) had progression in glycaemic status. C-peptide levels remained unchanged (from 0.67 nmol/L [IQR: 0.54-0.84] to 0.67 [0.54-0.92], p=0.835). Matsuda index decreased (p=0.007) and there was a trend of BMI increase from 24.4±2.7kg/m^2 to 25.6±5.2 (p=0.083). Subjects with progression in glycaemic status had more severe COVID-19 illness than non-progressors (p=0.030).

Conclusion: Subjects who had dysglycaemia in acute COVID-19 were characterised by insulin resistance. Over one year, a quarter had progression in glycaemic status, especially those with more severe COVID-19. Importantly, there was no significant deterioration in insulin secretory capacity.

Acknowledgement: The study received funding support from the Diabetes Care Research Fund of Diabetes Hongkong (RF202201). DTWL is a recipient of Li Ka Shing Medical Fellowship for Internal Medicine (2023).

Analysis of all-cause hospitalization and death among nonhospitalized patients with type 2 diabetes and SARS-CoV-2 infection treated with molnupiravir or nirmatrelvir-ritonavir during the Omicron wave in Hong Kong

2

DTW Lui[1], MSH Chung[2], EHY Lau[3], KTK Lau[2], ICH Au[2], CH Lee[1], YC Woo[1], CKH Wong[2,3], BJ Cowling[3]

[1]*Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong*
[2]*Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong*
[3]*Laboratory of Data Discovery for Health, Hong Kong Science Park, Hong Kong*

Introduction: Type 2 diabetes is a common comorbidity in patients with acute COVID-19 and is a key determinant of COVID-19 prognosis. Molnupiravir and nirmatrelvir-ritonavir are oral antiviral medications recently approved for nonhospitalized patients with mild to moderate COVID-19, following demonstration of their efficacies in reducing adverse outcomes of the disease. We aimed to evaluate the effectiveness of molnupiravir and nirmatrelvir-ritonavir in a contemporary population-based cohort comprising exclusively nonhospitalized patients with type 2 diabetes and SARS-CoV-2 infection.

Methods: This retrospective cohort study was performed using population-based electronic medical record data for patients in Hong Kong with type 2 diabetes and confirmed SARS-CoV-2 infection between February and October 2022. Each patient was followed up until death, outcome event, crossover of oral antiviral treatment, or end of the observational period (October 30, 2022), whichever came first. Outpatient oral antiviral users were divided into molnupiravir and nirmatrelvir-ritonavir treatment groups, respectively, and nontreated control participants were matched through 1:1 propensity score matching. The primary outcome was a composite of all-cause mortality and/or hospitalization. The secondary outcome was in-hospital disease progression. Hazard ratios (HRs) were estimated with Cox regression.

Results: This study identified 22098 patients with type 2 diabetes and COVID-19 (3390 patients received molnupiravir and 2877 received nirmatrelvir-ritonavir in the community setting). After applying exclusion criteria and 1:1 propensity score matching, this study comprised 2 groups. One group included 921 molnupiravir users (52.9% men, mean age: 76.7 years), and 921 control participants (52.3% men, mean age: 76.6 years). The other group included 793 nirmatrelvir-ritonavir users (50.6% men, mean age: 71.7 years), and 793 control participants (49.8% men, mean age: 71.9 years). At a median follow-up of 102 days (IQR, 56-225 days), molnupiravir use was associated with lower risk of all-cause mortality and/or hospitalization (HR, 0.71 [95% CI, 0.64-0.79]; P<0.001) and in-hospital disease progression (HR, 0.49 [95% CI, 0.35-0.69]; P<0.001) compared with nonuse. At a median follow-up of 85 days (IQR, 56-216 days), nirmatrelvir-ritonavir use was associated with lower risk of all-cause mortality and/or hospitalization (HR, 0.71 [95% CI, 0.63-0.80]; P<0.001) and nonsignificantly lower risk of in-hospital disease progression (HR, 0.92 [95% CI, 0.59-1.44]; P=0.73) compared with nonuse.

Conclusion: These findings suggest that both molnupiravir and nirmatrelvir-ritonavir oral antiviral medications were associated with a lower risk of all-cause mortality and hospitalization among patients with COVID-19 and type 2 diabetes. Further studies in specific populations, such as individuals in residential care homes and individuals with chronic kidney disease, are suggested.

Annexin A8 exacerbates diet-induced obesity through its central and peripheral actions **3**

Q Wang[1,2], BL Wang[1,2], J Liu[1,2], QX Hu[1,2], LY Cheong[1,2], AM Xu[1,2,3]

[1]*State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong*
[2]*Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong*
[3]*Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong*

Introduction: Obesity is caused by the imbalance between energy intake and energy expenditure. The excessive energy intake is stored in white adipose tissues (WAT), while energy expenditure is mediated by lipolysis, thermogenesis and physical activity. Our previous transcriptomic analyses have identified a dramatic upregulation of Annexin A8 (AnxA8) in WAT of diet-induced obese (DIO) mice. AnxA8, a calcium-dependent phospholipid-binding protein, has been shown to exert functions in the regulation of membrane-trafficking and is closely associated with various types of cancers. However, its functions in metabolic diseases have never been investigated.

Methods: AnxA8 global knockout (KO), adipocyte-specific AnxA8 knockout (Adn-AnxA8 KO, generated by crossing $AnxA8^{flox/flox}$ mice with adiponectin-Cre mice), hypothalamus-specific AnxA8 knockout (Hypo-AnxA8 KO, generated by intracerebroventricular injection of AAV-CMV-Cre into $AnxA8^{flox/flox}$ mice) and wild-type (WT) mice were fed with either standard chow (STC) or high-fat diet (HFD) for 24 weeks and then subjected to metabolic characterization of basic metabolic parameters, including body weight, food intake, fat content (determined by Bruker LF90 Minispec Body Composition Analyzer), lipid profile, oxygen consumption and locomotor activity (determined by Columbus Laboratory Animal Monitoring System), *etc.*

Results: AnxA8 was first validated to be significantly upregulated in the adipocyte fractions of WAT in DIO mice compared to lean mice. Both AnxA8 global KO and Adn-AnxA8 KO mice displayed obvious weight loss, reduced adiposity and enhanced oxygen consumption under both STC and HFD feeding conditions. SVF isolated from AnxA8 global KO mice showed similar adipogenic capacity as WT SVF, but obviously smaller size of lipid droplets. Histological analysis also revealed that AnxA8 depletion led to decreased size of adipocytes. Further analyses showed that ablation of AnxA8 resulted in enhanced lipolysis, as evidenced by increased free fatty acid (FFA) and glycerol levels in both serum and culture medium collected from SVF-derived adipocytes or WAT explants. Mechanistically, AnxA8 may regulate lipolysis by inhibiting the activity of hormone-sensitive lipase (HSL) and modulate the size of lipid droplet by upregulating *Plin1* and *Cidea* expression. On the other hand, increased locomotor activity was observed in AnxA8 global KO mice, but not in Adn-AnxA8 KO mice. AnxA8 was found to be abundantly expressed and markedly upregulated in the hypothalamus of DIO mice. Similar to AnxA8 global KO mice, AAV-mediated Hypo-AnxA8 KO mice also displayed lower body weight, increased locomotor activity and oxygen consumption, suggesting that the hypothalamic actions of AnxA8 also contributes to the regulation of energy homeostasis.

Conclusion: Our study uncovers the indispensable role of AnxA8 in the development of obesity by exerting dual actions in WAT and hypothalamus, suggesting that AnxA8 might be a novel therapeutic target for obesity and its related metabolic complications.

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Association between triglyceride with all-cause and cardiovascular outcomes among patients with heart failure: A population-based study **4**

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Introduction: Remnant cholesterol, identified by triglyceride-rich lipoprotein, is increasingly acknowledged as a significant causal risk factor for ischemic heart diseases. The association with cause-specific outcomes in heart failure (HF) settings remains unexplored. This study aims to determine the association between triglyceride levels with all-cause mortality and cardiovascular outcomes among patients with HF.

Methods: 127124 eligible patients with HF from 2000 to 2020 were enrolled. Triglyceride levels associated with risk of mortality were evaluated on a continuous scale using restricted cubic spline curves and by categories using Cox proportional hazards regression model. The outcomes included Atherosclerotic cardiovascular disease (ASCVD), HF, cardiovascular death (CVD) and all-cause mortality.

Results: The mean age was 71.4±12.2 years, 51.8% were male. Notably, when we investigated the association of triglyceride levels with admission or death for ASCVD, a positive relationship was seen in high triglyceride levels and ASCVD admission or death while neutral in low triglyceride levels. Conversely, when we investigated the association with readmission or death for HF, an inverse relationship was found where lower triglyceride levels were associated with higher risks of HF readmission or death. Together, the association between triglyceride levels and the risk of all-cause mortality and CVD was a U-shaped curve. The risk of adjusted all-cause mortality reached a nadir between triglyceride levels of 1.2 to 3.0 mmol/L and was lowest at 1.95 mmol/L.

Conclusion: In the HF population, low and high triglyceride levels were associated with increased risks of all-cause mortality and CVD compared with those with intermediate levels. Triglyceride was positively associated with ASCVD while inversely associated with HF admission or death. A better understanding of the role and contribution of triglyceride levels to adverse outcomes in patients with HF is needed.

Atrial fibrillation-related complications following short-term use of antibiotics in patients receiving NOAC or warfarin **5**

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Introduction: To study the association of antibiotics with ischaemic stroke/systemic embolism (IS/SE) in patients with atrial fibrillation (AF) receiving anticoagulants.

Methods: This retrospective population-based cohort study applied electronic health data from a territory-wide medical database in Hong Kong. Data were collected for patients with AF who were prescribed non-vitamin K antagonist oral anticoagulants (NOAC) or warfarin between January 1, 2010 and December 31, 2018. We further identify the patients with and without use antibiotics (any classification of antibiotics with prescription period within 7 days) during the NOAC/warfarin treatment period. The primary outcome is IS/SE and the secondary outcomes including hemorrhagic stroke (HS) and all-cause mortality. Patients were followed up for a median of 3.7 years. A self-control case crossover design was adopted to compare the short-term association between use of antibiotics and outcomes of interest among NOAC and warfarin group.

Results: This study included 40221 patients, consisted of 30617 NOAC users and 9826 warfarin users, while 9604 patients in NOAC group and 3325 patients in warfarin group had concurrent antibiotics use. At baseline, 46.1% of patients in NOAC group were male and the mean (SD) age was 77.4 (9.8) years, and 56.2% of patients in warfarin group were male and the mean (SD) age was 73.8 (11.3) years. Short-term use of antibiotics is associated with increased risk of IS/SE, HS and all-cause mortality in both NOAC and warfarin groups (NOAC vs. warfarin group: IS/SE: hazard ratio [HR]:3.41 [95% CI, 2.78-4.18]; HR: 2.51 [95% CI, 2.00-3.14]; HS: HR: 2.22 [95% CI, 1.78-2.78]; HR: 2.53 [95% CI, 1.86-3.43]; mortality: HR: 1.96 [95% CI, 1.85-2.08]; HR: 1.87 [95% CI, 1.73-2.02]; all P<0.001).

Conclusion: The findings of the present study suggest that the short-term antibiotics use was associated with an increased risk of IS/SE, HS and all-cause mortality among patients in both NOAC and warfarin group. These findings further suggest that use of antibiotics may indicate a higher risk of IS/SE, HS and death for patients with AF, even when receiving NOAC/warfarin and that further investigation is warranted.

Changes in etiology and clinical outcomes of pleural empyema during the COVID-19 pandemic **6**

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Introduction: Pleural infection, especially complicated parapneumonic infection including pleural empyema, is a clinical problem associated with high mortality and morbidity. Healthcare-seeking behavior changed during the COVID-19 pandemic and might alter the epidemiology of pleural empyema.

Methods: Territory-wide retrospective study on patients admitted to public hospitals under the Hospital Authority for pleural infection with positive pleural culture results. The incidence, etiology and outcomes of patients admitted for pleural empyema in Hong Kong in the pre-COVID-19 (January 2015 – December 2019) and post-COVID-19 (January 2020 – June 2022) periods were compared.

Results: Overall, *Streptococcus pneumoniae* was the predominant organism in <18-year-old patients, while *Streptococcus anginosus*, anaerobes and polymicrobial infections were more frequent in adults. In the post-COVID-19 period, a marked decline in the incidence of pleural empyema in children was observed (pre-COVID-19, 18.4 ± 4.8 vs. post-COVID-19, 2.0 ± 2.9 cases per year, p=0.036), while the incidence in adults remained similar (pre-COVID-19, 189.0 ± 17.2 vs. post-COVID-19, 198.4 ± 5.0 cases per year; p=0.23). In the post-COVID-19 period, polymicrobial etiology increased (OR 11.37, p<0.0001), while *S. pneumoniae* etiology decreased (OR 0.073, p<0.001). In multivariate analysis, clinical outcomes (length of stay, ICU admission, use of intrapleural fibrinolytic therapy, surgical intervention, death) were not significantly different in pre- and post-COVID-19 periods.

Conclusion: An increase in polymicrobial pleural empyema was observed during the pandemic. We postulate that this is related to the delayed presentation of pneumonia to hospitals.

Characteristics and outcomes of direct oral anticoagulant-associated intracerebral haemorrhage

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Introduction: Direct oral anticoagulants (DOAC) are currently the preferred anticoagulant over warfarin. With its increasing use, DOAC-associated intracerebral haemorrhage (DOAC-ICH) is a common clinical encounter. Whether DOAC-ICH is less severe and associated with better outcomes than warfarin-associated ICH (warfarin-ICH) remains debatable. We therefore aimed to compare the clinical, radiological characteristics and outcomes between DOAC-ICH, warfarin-ICH, and non-anticoagulant associated ICH (non-AC ICH).

Methods: We retrospectively analyzed data from the HKU stroke registry. Consecutive anticoagulant-associated ICH (AC-ICH) retrieved from the registry included patients admitted to Queen Mary Hospital from 2011-2022 and with the addition of three other hospitals (Ruttonjee Hospital, Yan Chai Hospital, and Princess Margaret Hospital) from 2020-2022. As controls, we included non-AC ICH patients from Queen Mary Hospital from 2011-2018. Outcomes of interest include hematoma expansion (absolute hematoma increase >6ml or relative increase >33%), 1-month and 6-month mortality, and 6-month poor outcome (modified Rankin Scale 4-6). We performed multivariate logistic regression to investigate the association between DOAC and ICH outcomes.

Results: There were a total of 167 AC-ICH. Compared to non-AC ICH, AC-ICH patients were older, with the mean age of DOAC-ICH, warfarin-ICH, and non-AC ICH being 80, 71, and 69 years respectively ($p<0.001$), and occurred less at deep hypertensive ICH sites (55.1% vs. 68.5%; $p=0.001$). The 1-month, 6-month mortality and 6-month poor outcome rates were comparable between DOAC-ICH and warfarin-ICH (45.6% vs. 37.7%; 54.4% vs. 42.2%; 78.6% vs. 69.7%; all $p>0.05$) but were significantly higher than non-AC ICH. Warfarin was associated with a higher risk of hematoma expansion (aOR 2.69, 95% CI 1.18-6.17), 6-month mortality (aOR 2.17, 95% CI 1.01-4.68), and poor outcome (aOR 2.74, 95% CI 1.21-6.20), but not DOAC (all $p>0.2$).

Conclusion: DOAC-ICH is attributed to both hypertensive arteriopathy and cerebral amyloid angiopathy, and its high mortality and morbidity was likely driven by age.

Clinical characteristics, densitometric parameters and treatment outcomes of patients with atypical femoral fractures related to bisphosphonate treatment for osteoporosis

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Introduction: We described the clinical and densitometric characteristics and treatment outcomes of patients who developed atypical femoral fractures (AFF) while on bisphosphonate for osteoporosis.

Methods: We performed a retrospective cohort study including all adults aged ≥50 years who developed AFF while on bisphosphonates between 1 January 2008 and 31 December 2020, and subsequently managed in the Osteoporosis Centre at Queen Mary Hospital in Hong Kong. A control group of patients who developed fragility hip fractures while on bisphosphonates in the same period was included for comparison. We compared the clinical and densitometric characteristics between the two groups, and described the clinical outcomes for the AFF group.

Results: In total, 75 patients were included (AFF: n=35; fragility hip fracture: n=40). All were related to oral bisphosphonates. The AFF group was characterised by a longer duration of bisphosphonate use (median of 5 years), higher bone mineral density (BMD) and more acute neck-shaft angle (all $p<0.05$). Following AFF, 8 patients (22.9%) did not receive any subsequent bone-active agents: due to refusal to use an injectable, or BMD out of osteoporotic range. Most of those who received bone-active agents were given teriparatide, followed by raloxifene, and achieved stable BMD. However, subsequent fragility risk remained high. Nonetheless, AFF did not confer excess morbidity and mortality.

Conclusion: AFF was characterised by usually long duration of bisphosphonate use, higher BMD and more acute neck-shaft angle. AFF did not confer significant impairment in mobility or mortality. Nonetheless, further research work is necessary to optimise bone health among patients who develop AFF.

Clinical frailty scale as a predictor of two-year mortality in elderly diabetic patients

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Introduction: Frailty and diabetes are two important medical conditions in the elderly. The prevalence of frailty is higher among diabetics than those without diabetes. Frailty in diabetes has been shown to increase mortality and hospitalization. There is no local study using the Rockwood Clinical Frailty Scale (CFS) to study mortality among elderly diabetic patients.

Methods: A retrospective cohort study was conducted. Community-dwelling patients who were at least 65 years old and diagnosed with diabetes before the index admission were identified from the discharged patients enrolled in the Integrated Care and Discharge Support program between 1 August 2018 and 31 December 2019. Patients were excluded if they died during the index admission, had exclusive medical follow-up in the private sector, or were discharged directly to residential care homes. A two-year follow-up record was retrieved from the electronic patient record since the recruitment into the study. The primary outcome was all-cause mortality. A Kaplan-Meier survival analysis with log-rank test was performed comparing frail and non-frail patients. Frailty status was assessed based on CFS. Baseline characteristics including demographics, functional status, comorbidities, and laboratory parameters were retrieved and compared between the survival group and the mortality group. Univariate and multivariate Cox proportional hazards regressions were conducted.

Results: Of the 670 elderly patients with diabetes, 154 patients (23%) died within the two-year period. The median age of the patients was 81 years old. Patients who died were older, had lower body weight and BMI, and were more likely to be educated. They also had lower scores on Abbreviated Mental Test, Modified Functional Ambulatory Category, Barthel Index-20, and CFS. They had lower levels of lymphocytes, creatinine, albumin, and a higher level of albuminuria. They had a higher Charlson Comorbidity Index (CCI), and a history of ischemic heart disease, congestive heart failure, malignancy, and polypharmacy. Kaplan-Meier survival analysis showed that CFS predicted mortality ($p<0.001$). Multivariate Cox models, adjusting for age, frailty, cognitive function, nutrition and comorbidities, showed that higher risk of mortality was associated with a higher CFS score (HR 1.224, 95% CI 1.001-1.497, $p=0.049$), higher creatinine level (HR=1.002, 95% CI 1.001-1.003, $p<0.001$), history of ischemic heart disease (HR=1.682, 95% CI 1.078-2.263, $p=0.022$) history of congestive heart failure (HR=2.084, 95% CI 1.168-3.363, $p=0.011$) and history of malignancy (HR 2.9, 95% CI 1.819-4.624, $p<0.001$); while higher BMI and albumin levels were associated with a lower mortality (HR=0.946, 95% CI 0.903-0.990, $p=0.018$ and HR=0.928, 95% CI 0.900-0.957, $p<0.001$, respectively). Further risk stratification of mortality showed that CFS 5 had a hazard ratio (HR) of 1.692 (95% CI 1.114–2.569, $p=0.014$) compared to CFS 1-4. CFS 6 had a HR of 2.299 (95% CI 1.52–3.477, $p<0.001$). CFS 7-8 had a HR of 5.108 (95% CI 2.963–8.806, $p<0.001$). Age was insignificant after adjustment.

Conclusion: The clinical frailty scale can predict mortality within as short as two years among community dwelling elderly patients with diabetes.

Comparison of glycated albumin, 1,5-anhydroglucitol and glycated hemoglobin on detection and risk prediction of diabetes in Chinese

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Introduction: Glycated hemoglobin A1c (HbA1c) is considered as the gold standard for monitoring chronic glycemia of diabetes patients. However, HbA1c and blood glucose levels do not always match, and this discordant information often makes clinical interpretation difficult. Therefore, this study aimed to compare the performances of two alternative biomarkers, glycated albumin and 1,5-anhydroglucitol with glycated hemoglobin on detection and risk prediction of diabetes.

Methods: 318 age and sex matched serum samples from the Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS) were used to compare the performances of these biomarkers on diabetes prediction. 474 serum samples from obese individuals at baseline, 1 month, 3 months and 6 months after bariatric surgery were used to evaluate their performances on prediabetes detection and glycemic monitoring respectively.

Results: In the CRISPS cohort, both glycated albumin and 1,5-anhydroglucitol showed better performances on diabetes prediction than glycated hemoglobin. When adding glycated albumin and 1,5-anhydroglucitol to a traditional diabetes prediction model comprising sex, age, waist, circumference, fasting glucose, hypertension and BMI, the AUROC on diabetes prediction had improved from 0.726 (95% CI 0.671-0.781) to 0.817 (95% CI 0.771-0.863). In obese individuals, glycated albumin exhibited a satisfactory correlation to both fasting glucose level and glycated hemoglobin. It also exhibited a comparable performance to glycated hemoglobin on detection of prediabetes (AUROC: 0.838, Sensitivity: 80.9%, Specificity: 71.6%). Besides, the concordance rate between glycated albumin and fasting glucose level on both diabetes and prediabetes detection were significantly higher than that between glycated hemoglobin and fasting glucose level. Moreover, glycated albumin was superior to glycated hemoglobin in monitoring the dynamic changes after bariatric surgery.

Conclusion: Glycated albumin is a robust biomarker on detection and risk prediction of diabetes. On diabetes prediction, addition of glycated albumin and 1,5-anhydroglucitol can significantly improve the performances of the traditional diabetes prediction model. Glycated albumin is also superior to glycated hemoglobin with a higher concordance rate to fasting glucose level on prediabetes and diabetes detection and a better matching to fasting glucose level on glycemic monitoring.

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Concomitant aortic stenosis and left ventricular mass predict postoperative adverse outcomes regardless of valvular morphology in patients with aortic regurgitation **11**

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Introduction: Bicuspid aortic valve (BAV) predicts adverse cardiac remodelling and postoperative heart failure in patients with severe aortic stenosis. It remains unclear if BAV predicts left ventricle (LV) remodelling and adverse outcomes in aortic regurgitation (AR) patients undergoing aortic valve replacement (AVR). Using clinical, laboratory, echocardiographic, and surgical data, we explored the preoperative and surgical differences between BAV and tricuspid aortic valve (TAV) patients with AR, and differences in postoperative adverse outcomes.

Methods: Three-hundred twenty-three patients with moderate to severe AR without severe AS undergoing AVR were included, with either BAV (n=70) or TAV (n=253). Baseline clinical, laboratory, medication, and echocardiographic data, as well as surgical data, were analysed. Follow-up data was collected and analysed for adverse events, defined as the composite outcome of all-cause mortality and heart failure rehospitalization. Kaplan-Meier and interaction analyses were performed, as well as Cox regression analysis adjusted for age, sex, diabetes, hypertension, euroSCORE II, LV ejection fraction (LVEF) and LV end-systolic dimension (LVESD).

Results: Patients with BAV were a decade younger ($p<0.001$) and had more concomitant AS ($p<0.001$). They also had lower surgical risk scores ($p<0.001$) and shorter aortic cross-clamp durations during AVR ($p=0.036$). AV morphology significantly interacts with LVESD on LVEF, where patients with TAV showed greater LVEF decline with LVESD elevation (Pinteraction= 0.004). Patients with BAV experienced less adverse events than those with TAV (HR: 0.50 (1.07-3.80), log-rank P=0.03). After multivariable Cox regression analysis, significant predictors of adverse events were indexed aortic valve area (AVAi) ($p=0.042$), indexed left ventricular mass (LVMi) ($p=0.013$), and indexed left atrial volume (LAVi) ($p=0.031$). The presence of BAV or TAV did not independently predict adverse outcomes.

Conclusion: Patients with BAV were younger and had more concomitant AS, as well as better surgical characteristics and less postoperative adverse events than those with TAV. Systolic function was more preserved in patients with BAV with LV dilation. However, adverse outcomes were significantly predicted by the degree of concomitant aortic stenosis, LV hypertrophy, and left atrial dilation, rather than aortic valve morphology. Earlier AVR should be considered in patients with significant aortic regurgitation if concomitant aortic stenosis is present.

Diagnostic performance of penicillin allergy testing and post-delabelling outcomes among Hong Kong Chinese: the Prospective Assessment of Penicillin Allergy (PAPA) cohort study **12**

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Introduction: Incorrect penicillin 'allergy' labels predispose patients to adverse outcomes but are under-recognised in many Asian countries. Studies on performance and post-delabelling outcomes of penicillin allergy evaluation among Chinese remain scarce. In view of that, we conducted the first study to evaluate the diagnostic performance of allergy testing and post-delabelling outcomes among Chinese patients in a prospective penicillin allergy cohort – Prospective Assessment of Penicillin Allergy (PAPA).

Methods: All adult patients (age ≥ 18 years) who underwent penicillin allergy evaluation between January 2020 and December 2021 at the Allergy Clinic at Queen Mary Hospital/Hospital Authority Hong Kong West Cluster (Hong Kong's only adult allergy centre in the public sector) were recruited and prospectively reviewed by both medical records and individual interviews at least 6 months after delabelling or allergy confirmation.

Results: Out of 372 patients who completed penicillin allergy evaluation, 335 (90%) patients were delabelled. The overall negative predictive value of penicillin skin testing was 95%, but lower for patients with non-immediate type reactions (88%). History of non-immediate symptom onset (OR=4.501 [95% CI = 2.085-9.716], $p<0.001$) and duration since index reaction (OR=0.942 [95% CI = 0.899-0.987], $p=0.012$) were associated with positive skin testing. After at least 6 months, 60 (18%) of de-labelled patients had received penicillins again without any adverse reactions. Fluoroquinolone-use was significantly lower among delabelled patients compared to those with penicillin allergy (38[11%] vs 11[30%], $p=0.004$).

Conclusion: After at least 6 months, one in six delabelled patients already received penicillins again safely, with significantly lower fluoroquinolone usage. None experienced adverse reactions. History of non-immediate onset and shorter duration since index reaction were associated with genuine allergy. In patients with severe non-immediate reactions, skin tests should be supplemented with thorough clinical history and adjunct diagnostic evaluations.

Early intervention with biosimilars compared with leflunomide in established rheumatoid arthritis: A cost-effectiveness analysis in Hong Kong

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Introduction: Among patients with rheumatoid arthritis (RA) who had inadequate response or intolerance to methotrexate, leflunomide is frequently recommended before biological disease-modifying antirheumatic drugs (bDMARDs), as the incremental monetary cost of using bDMARDs outweighs the improved clinical efficacy it provides. Biosimilar DMARDs share comparable efficacy and safety to the reference biologics with a 50 - 80% price reduction, providing an opportunity for early use of bDMARDs. We aim to evaluate the cost-effectiveness of biosimilar DMARDs versus leflunomide to inform formulary listing decisions for biosimilars.

Methods: From an institutional perspective in Hong Kong, a Markov disease transition model was developed to simulate the lifetime disease progression of patients with RA who failed with methotrexate. The model contains three competing treatments: biosimilar infliximab (CT-P13), biosimilar adalimumab (ABP-501), and leflunomide. Model inputs were sourced from local population-based electronic health records databases, landmark clinical trials, and meta-analyses. Probabilistic and deterministic sensitivity analyses were conducted to address parameter uncertainties.

Results: The lifetime healthcare cost and quality-adjusted life years (QALYs) for leflunomide, CT-P13, and ABP-501 are USD 118,316, 11.63; USD 113,850, 12.00; USD 107,311, 12.16, respectively. Both biosimilars demonstrated lower costs and greater QALYs compared to leflunomide. CT-P13 is associated with greater healthcare cost (USD 6539) but lower QALY gain (-0.16) compared to ABP-501. At the willingness-to-pay threshold USD 48,555/QALY gain (local GDP per capita in 2022 year), the probability of leflunomide, CT-P13, and ABP-501 being cost-effective out of 2,000 iterations was 0%, 10%, and 90%.

Conclusion: Biosimilar DMARDs are likely to be the cost-effective alternatives to leflunomide in the management of patients with RA who failed initial methotrexate treatment in Hong Kong. Local reimbursement agencies should give full consideration to the early use of biosimilars given the fact that none of the reference bDMARDs are reimbursed at present.

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Effect of hematoma location and its interaction with initial volume in predicting hematoma expansion in intracerebral hemorrhage

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Introduction: Hematoma expansion (HE) is among the few modifiable factors for intracerebral hemorrhage (ICH) outcomes. As HE only occurs in 13-32% of ICH, improving HE prediction may guide patient selection for hemostatic therapies. Reports on location differences in HE were conflicting, and its interaction with volume in HE prediction was unclear. We hypothesized that a location-specific volume may offer better predictive value because the caliber of the bleeder varies by location. In this study, we aimed to delineate the interaction between haematoma location and volume in HE prediction.

Methods: We retrospectively analyzed consecutive primary ICH patients admitted to Queen Mary Hospital (2011-2022), and Ruttonjee Hospital, Yan Chai Hospital and Princess Margaret Hospital (2020-2022), with first computer tomography (CT) brain ≤12 hours of symptom-onset/last-seen-well and reassessment CT within 72 hours. Patients on anticoagulants were excluded. HE was defined as >33% or >6mL volume increase. Multivariate logistic regression was performed to determine predictors of HE. The sensitivity and specificity of location-specific volumes in predicting HE were determined using receiver operating characteristic curves.

Results: HE occurred in 34.3% (192/559) of patients, more common in lobar (adjusted odds ratio (aOR) 1.63, p=0.047) and brainstem (aOR 2.78, p=0.016) and less in deep (aOR 0.62, p=0.021). Male, ischemic heart disease, initial haematoma volume, time from symptom-onset/last-seen-well to initial CT brain and location were independently associated with HE, and a significant interaction between location and volume was observed (p=0.005). Subgroup analyses by location showed that initial volume only predicts HE in lobar ICH (p<0.0005**)** but not other locations, with a C statistic of 0.745. A lobar-specific cut-off of >27mL predicts HE with 0.88 sensitivity and 0.55 specificity.

Conclusion: HE is more common in lobar and brainstem and less in deep ICH. Previously reported predictive power of initial volume may be primarily driven by lobar ICH. A lobar-specific cut-off predicts HE with high sensitivity and low specificity.

Effect of venous thromboembolism on brain cortical structure: a Mendelian randomization study

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Introduction: Emerging evidence suggests an association between vascular risk factors and changes in brain cortical structure and function. However, the relationship between venous thromboembolism (VTE) and brain cortical remodeling remains unclear, impeding further research on brain cortical dysfunction.

Methods: We performed a two-sample Mendelian randomization (MR) study using summary statistics obtained from genome-wide association studies (GWAS). Data from the UK Biobank Consortium which included 361,194 and 462,933 individuals separately, were utilized for identifying genetic proxies of pulmonary embolism (PE) and deep vein thrombosis (DVT). Data from the FinnGen Biobank Consortium which comprised 218,792 participants, were used to distinguish genetically proxied VTE. Further, we analyzed data from the ENIGMA Consortium, which enrolled 51,665 individuals, to investigate the relationship between PE, DVT, VTE and cortical structural changes. Magnetic resonance imaging (MRI)-based measures of brain cortex including surface area (SA) and thickness (TH) were collected both globally and across 34 regional gyri. All participants were of European descent. Data analysis was conducted between June 2023 and September 2023.

Results: Globally, cortical TH was consistently reduced in patients with PE, DVT and VTE (PE: beta = -0.344mm, 95% CI: -0.654mm to -0.033mm, *P*=0.030; DVT: beta = -0.150mm, 95% CI: -0.298mm to -0.002mm, *P*=0.047; VTE: beta = -0.003mm, 95% CI: -0.006mm to -0.0003mm, *P*=0.029). Regionally, DVT specifically caused a decrease in cortical TH in the paracentral gyrus (beta = -0.438mm, 95% CI: -0.647mm to -0.229mm, Bonferroni-corrected $P=4.02\times10^{-5}$). This decrease persisted even after global adjustment (beta = -0.281mm, 95% CI: -0.434mm to -0.126mm, Bonferroni-corrected $P=3.49\times10^{-4}$). No pleiotropy or heterogeneity was detected.

Conclusion: Our study shows a causal effect of genetically proxied VTE on brain cortical thinning. This finding supports previously established epidemiological associations between VTE and brain dysfunctions and offers mechanistic insight.

Elucidating the role of classical memory B cells, exhausted memory B cells and related genes in lupus nephritis

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Introduction: Various B cell abnormalities have been implicated in the pathogenesis of lupus nephritis (LN), and our previous studies have demonstrated memory B cells assume pathogenic relevance in disease relapse. Memory B cell exhaustion is a B lymphocyte abnormality reported in chronic human immunodeficiency virus (HIV) infection and autoimmune conditions, but the pathogenic roles of classical (CD19+CD21+CD27+) and exhausted (CD19+CD21-CD27-) memory B cells in disease relapse of LN patients remain elusive. Our preliminary studies showed that patients with multiple relapses showed higher percentage of circulating exhausted memory B cells than patients who never relapsed, and further bioinformatics analyses identified aberrant expression of STAT1, XAF1, MX1, IFI44L in exhausted and classical memory B cell of LN patients. We shall perform bioinformatics analyses using domain datasets to elucidate the relationships of STAT1, XAF1, MX1, IFI44L in exhausted and classical memory B cells and pertinent immune pathways. To validate our bioinformatics findings, I will compare the expression levels of STAT1, XAF1, MX1 and IFI44L in classical and exhausted memory B cells isolated from LN patients and healthy controls.

Methods: To identify the pathogenic genes in LN, we first obtained the GSE135779 dataset from the NIH, which included 8 SLE patients and 6 healthy donors. The LN raw single-cell RNA-seq dataset was obtained from a published article, which was deposited in dbGAP. We identified the pathogenic genes by separately identifying the disease-associated genes in SLE compared to healthy controls and in LN compared to healthy controls. The differential analysis was performed using the "FindMarkers" function from the Seurat package and differentially expressed genes with adjust $p<0.05$ and log2fold change (FC)>0.25 were saved. We shall isolate classical and exhausted memory B cells from LN patients (n=10) and healthy controls (n=10). RNA will be extracted from exhausted B cell and memory B cell using ReliaPrepTM RNA Miniprep.mRNA will be converted to cDNA and the levels will be quantified by qPCR.

Results: STAT1, XAF1, MX1, IFI44L, EPSTI1, LCP1, OAS1, NEAT1, IFI16, IFI44 in exhausted B cells and XAF1, MX1, IFI44L in memory B cells play a pathogenic role in LN patients. SLN patients also show increased proportion of exhausted B cells compared to healthy control and the expression of STAT1, XAF1, MX1 and IFI44L correlate positively with the proportion of exhausted B cells.

Conclusion: Our results suggested that altered expression of STAT1, XAF1, MX1 and IFI44L in memory and exhausted B cells may have pathogenic significance in LN.

Enhancing outcome prediction of intracerebral hemorrhage with detailed clinical and radiological analysis using machine-learning

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Introduction: Intracerebral hemorrhage (ICH) is a deadly and disabling disease. Effective treatment has remained elusive due to the heterogeneity of ICH outcomes because of differing patient and hematoma characteristics, which confound therapeutic effects. A thorough understanding of ICH's natural history and outcome is vital in selecting patients who benefit best from treatment. The most widely used ICH prediction score, the ICH score comprises five components (age, Glasgow Coma Scale [GCS], location [supratentorial vs. infratentorial], hematoma volume, and presence of intraventricular hemorrhage). However, recent studies demonstrated that a more detailed clinical and radiological analysis would better predict outcomes. With the recent advances in machine learning in the medical field, we aim to use machine learning to study whether adding more detailed clinical and radiological characteristics will enhance outcome prediction in ICH.

Methods: Using machine learning techniques, we developed a random forest model for 6-month outcome prediction using 80% of the patient data as training data from 533 ICH patients of the University of Hong Kong stroke registry, who presented from January 2011 to December 2018. The remaining 20% were used for validation. The 6-month neurological outcome was categorized as good (mRS 0-2), poor (mRS 3-5), and death (mRS 6). The enhanced outcome prediction model consisted of additional characteristics, which include individual components of GCS, worse limb power of the affected side, specific ICH location (lobar, putamen, internal capsule, thalamus, brainstem, cerebellum), laterality, and Graeb score; and was compared with a conventional model derived from components of the ICH score.

Results: The enhanced outcome prediction model has precision rates of 78% (good prognosis), 71% (poor prognosis) and 85% (death), and recall rates of 88% (good prognosis), 71% (poor prognosis), and 73% (death). Compared to the conventional model, the enhanced model had a significantly higher accuracy (78% vs 68%, paired two-sided t-test p-value = 0.015). Using recursive feature elimination, we found that the most predictive individual features include maximum hematoma size, patient age, lower and upper limb power of the affected side, individual components of the GCS, and blood pressure.

Conclusion: This study demonstrates that it is not only possible to use machine learning to predict the 6-month outcome of ICH patients, but a more detailed clinical and radiological analysis can enhance the predictive power over the conventional ICH prognosis system. We also identified which clinical or radiological features can be used to build such a prognosis model.

Estimation of the impact of neurosurgical intervention for intracerebral hemorrhage using a counterfactual machine learning approach

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Introduction: Intracerebral hemorrhage (ICH) is a deadly and disabling disease. Neurosurgical intervention, including clot evacuation and external ventricular drainage, improves survival, but it is unclear if it confers functional outcome benefits to patients. This is due to the significant outcome heterogeneity of ICH based on location and volume, confounding therapeutic effects. With the recent advances in machine learning and causal inference, we aim to use a causal machine learning approach to quantitatively estimate how neurosurgical intervention can modify the outcome of ICH and to discover which ICH characteristic would yield the best therapeutic benefit.

Methods: We analyzed 589 consecutive ICH patients enrolled in the University of Hong Kong prospective stroke registry from January 2011 to December 2018. Patients with premorbid modified Rankin Scale (mRS) >2 were excluded. The 6-month neurological outcome was categorized as good (mRS 0-2), poor (mRS 3-5), and death (mRS 6). A total of 518 patients who did not undergo neurosurgical intervention were utilized to derive a random forest model to predict the 6-month outcome of ICH patients. This model was applied to counterfactually predict the outcome of 71 patients who underwent surgery if surgery was not performed. By comparing the actual 6-month outcomes against the predicted non-surgical outcomes of these patients, we obtained a counterfactual estimate of the impact of the surgery.

Results: Of the 71 ICH patients who underwent surgery, 11 had a good outcome at 6 months (15%), 48 had a poor outcome (68%), and 12 died (17%). The random forest machine learning model predicted that the 6-month outcomes of these patients would have been: 9 good outcomes (13%, 95% confidence interval [CI] 11.8 - 13.5), 33 poor outcomes (46%, 95% CI 44.4 - 48.2), and 29 deaths (41%, 95% CI 39.4 - 42.6). Notably, among the 11 patients who had a good outcome after surgery, 7 (63%) were predicted to have had a poor outcome or death if surgery was not performed.

Conclusion: Our counterfactual machine learning approach demonstrated that the net benefit of neurosurgical intervention for ICH was shifting mortality (from 41% to 17%) to poor outcomes (from 46% to 68%), which is compatible with the findings of clinical trials. This illustrates the possibility of using a machine-learning-based causal inference framework to estimate the effect of neurosurgical intervention using retrospective observational data, and with a larger dataset, we can identify patients who will best benefit from surgery to achieve good outcomes.

Fatty acid binding protein 4 mediates atherosclerosis by disrupting gut microbiota and immunity **19**

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Introduction: Atherosclerosis is a chronic inflammatory arterial disease and is currently one of the most common causes of cardiovascular morbidity and mortality worldwide. Therefore, there is an urgent need to discover new therapeutic targets for treatment of this fatal chronic disease. Fatty acid binding protein 4 (FABP4), a pro-inflammatory adipokine that links obesity with its related metabolic diseases, has been implicated in the development of atherosclerosis. This study aims to investigate whether FABP4 potentiates atherosclerosis by mediating the crosstalk between gut microbiota and immunity and to explore whether targeting FABP4 is therapeutically effective for treatment of this disease.

Methods: FABP4$^{+/+}$ApoE$^{-/-}$ and FABP4$^{-/-}$ApoE$^{-/-}$ mice were generated for the study and fed with high fat and high cholesterol diet (HFHC) for 12 weeks. Biochemical, immunological, flow cytometry and metagenomic analysis were conducted to determine the pathophysiological roles of FABP4 in potentiating diet-induced atherosclerosis by altering gut microbiota and immunity. Fecal microbiota transplantation (FMT) were performed The FABP4 chemical inhibitor BMS309403 was used to evaluate the effects of FABP4 inhibition in alleviating atherosclerosis. to further investigate the role of FABP4 in atherosclerosis mediated through microbiota.

Result: The aortic trees stained with Oil Red and the sections of aortic roots analyzed by H&E staining exhibited significantly reduced atherosclerosis in FABP4$^{-/-}$ mice. Likewise, FMT of FABP4$^{-/-}$ feces to FABP4$^{+/+}$ mice significantly attenuated the development of atherosclerosis. DGGE analysis of fecal DNA showed that the pattern of bacterial phyla was obviously changed in FABP4$^{-/-}$ mice comparing to their FABP4$^{+/+}$ littermates. These changes in FABP4$^{-/-}$ mice were accompanied by significantly increased expression of zona occuldens protein-1 (ZO-1) and occluding in intestinal villa, suggesting that FABP4 may enhance the intestinal permeability in mice in response to HFHC diet. Furthermore, FABP4 promoted macrophage infiltration and the polarization of macrophage from M0 to pro-inflammatory M1 subtype in the intestine of mice. Treatment with the FABP4 inhibitor BMS309403 dramatically alleviated the inflammatory response in the gut and atherosclerotic plaque formation, and elevated the intestinal expression of ZO1 and occludin in FABP4$^{+/+}$ mice.

Conclusion: FABP4, which is elevated during obesity, alters the composition of gut microbiota and intestinal permeability by creating a pro-inflammatory microenvironment, leading to endotoxinemia and subsequently contributing to the development of atherosclerosis. Targeting FABP4 with small-molecule inhibitors such as BMS303409 is a promising therapeutic strategy for treatment and prevention of atherosclerosis by modulating gut microbiota and intestinal immunity.

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Fracture risks associated with sodium-glucose cotransporter-2 inhibitors in type 2 diabetes patients across eGFR and albuminuria categories: A population-based study in Hong Kong

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Introduction: As sodium-glucose cotransporter-2 inhibitors (SGLT2i) are increasingly popular in the management of diabetes comorbid with heart failure and chronic kidney disease, it is imperative to evaluate the fracture risks across different eGFR and albuminuria categories. We evaluated major osteoporotic fracture (MOF) risk among type 2 diabetes patients treated with SGLT2i across eGFR and albuminuria categories.

Methods: A population-based cohort of adults with type 2 diabetes who were initiated on either SGLT2i or dipeptidyl peptidase-4 inhibitors (DPP4i) between March 2007 (the earliest DPP4i prescription recorded in the database) and December 2020 was identified from Hong Kong Hospital Authority database. The index dates in the SGLT2i and DPP4i groups were defined as the dates of initiation of SGLT2i and DPP4i, respectively. Patients were followed up from the index date to the occurrence of study outcomes, death, treatment crossover, or end of the observation period (31 December 2020), whichever came first. We excluded patients with (i) a history of end-stage kidney diseases (ESKD) (eGFR < 15 mL/min/1.73 m^2, dialysis, or renal transplantation), (ii) follow-up duration less than one month, and (iii) co-initiation of SGLT2i and DPP4i in the same month. One-to-one propensity score matching was applied to match each SGLT2i user with one DPP4i user. The primary outcomes were 180- and 365-day risks of MOF (which include hip, clinical vertebral, and upper limb fractures identified with validated ICD-9-CM codes). Cox proportional hazard regression models were used to estimate hazard ratios (HR).

Results: A total of 28,696 patients (14,348 in each group) were included (mean age: 60.5 years, 63.6 % were men, mean baseline HbA1c: 8.4 %, mean duration of diabetes: 10.7 years). Over 180-day follow-up, MOF occurred in 25 (0.17 %) SGLT2i users and 24 (0.17 %) DPP4i users (incidence of 4.07 and 3.63 per 1,000 person-years, respectively). At 365 days, MOF occurred in 43 (0.30 %) SGLT2i users and 44 (0.31 %) DPP4i users (incidence of 4.16 and 3.64 per 1,000 person-years, respectively). Risks of MOF were comparable between two groups at both 180 days (HR=1.13, 95 % CI 0.65-1.98, P=0.67) and 365 days (HR=1.15, 95 % CI 0.75-1.75, P=0.52). Subgroup analyses were consistent across age, sex, eGFR, albuminuria, or KDIGO categories.

Conclusion: Our study did not reveal a statistically significant increased fracture risk with SGLT2i use compared with DPP4i use among type 2 diabetes patients, consistent across eGFR and albuminuria categories. Our results may reassure clinicians to prescribe SGLT2i to patients with type 2 diabetes to optimise their cardiorenal profiles.

Generation of a stem-cell derived and patient-specific disease model for mechanistic study of lupus nephritis

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Introduction: Lupus nephritis (LN) is a prevalent and life-threatening manifestation of System Lupus Erythematosus (SLE), affecting around 50% of the patients in Hong Kong. LN flares are unpredictable, and repeated nephritic flares causing irreversible kidney damage have been observed in some patients. Conventional immunosuppressants and steroid-based therapeutics are not specific for LN management, and patients often experience side-effects upon prolonged usage. Understanding LN immunopathology is important for development of personalised treatments, but there is no human-based model for deciphering the mechanism of immune cell-mediated nephritis in situ. This study aims to develop a patient-specific disease model using pluripotent stem cells for mechanistic study of LN.

Methods: Peripheral blood mononuclear cells (PBMCs) were obtained from consented healthy individuals, LN patients and SLE patients without nephritis histories. Expanded potential pluripotent stem cells (EPSC) were generated by Sendai viral reprogramming of PBMC-expanded erythroid progenitors. EPSCs from patients and healthy individuals were differentiated into macrophages and kidney organoids for constructing the LN disease model.

Results: All the viral vector-free EPSC lines expressed pluripotent markers (TRA-1-60, OCT4, SOX2) and were able to undergo trilineage differentiation. EPSC differentiated macrophages expressed specific markers (CD68, CD86, CD163, HLA-DR), and were functionally competent as illustrated by the ability of phagocytosing *E.coli* bioparticles and the release of pro-inflammatory factors (IL-6, TNF-alpha) in response to lipopolysaccharides (LPS). EPSCs were also able to undergo differentiation into kidney organoids, all cell lines followed a similar developmental trend with downregulation in pluripotent factors *OCT4* and *SOX2*, transient upregulation of primitive streak markers *MIXL1* and *Brachury*, and enrichment of kidney cell markers in the organoids. Concordantly, kidney organoids expressed markers of podocyte (NPHS1), mesangial (PDGFRA), endothelial (KDR1), basement membrane (Laminin 1), proximal tubule (lotus tetragonolobus lectin) and collecting duct (PAX2).

Conclusion: Functional macrophages and kidney organoids were generated from EPSCs of patients and healthy individuals. This builds up the basis for studying the interplay between macrophages and kidney cells in the SLE microenvironment.

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Global health inequality analysis of premature mortality related to peptic ulcer disease: a systematic analysis based on global burden of disease

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Introduction: Despite the declining incidence and mortality rates of peptic ulcer disease (PUD) over the past three decades, there remains an uneven distribution of disease burden in countries with varying sociodemographic levels. This updated systematic analysis was conducted to investigate the association between changes in sociodemographic-related health inequalities and PUD premature mortality from 1990 to 2019.

Methods: We performed a secondary analysis by extracting cross-sectional data on PUD from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019. The age-standardized years of life lost (YLLs) were utilized to reflect premature mortality attributed to PUD. As recommended by the WHO, the slope index of inequality (SII) and the health concentration index were calculated to quantitatively measure absolute and relative changes in health inequalities, taking into account the socio-demographic indexes (SDI) level. The data was further analysed across different sexes, age groups, and six WHO regions, and re-validated using the health-care access Index (HAQI).

Results: Global YLL of PUD premature mortality declined from 181.4 per 100,000 in 1990 to 69.2 per 100,000 in 2019. Countries with the lower 50% level of sociodemographic status accounted for 59.3% and 73.8% of the global PUD premature mortality in 1990 and 2019, respectively. Although the absolute cross-national inequality (SII) of YLL fell from -197.4 (95% CI: -227.6 to -167.2) in 1990 to -145.5 (95% CI: -164.9 to -126.2) in 2019, the relative inequality (concentration index) for global PUD premature mortality significantly increased from 1990 (−0.246, 95% CI: −0.306 to −0.187) to 2019 (−0.339, 95% CI: −0.394 to −0.285). The observed increase in relative health inequity was statistically significant for both sexes and age groups, with consistently larger effects observed among women and the elderly when compared to men and younger individuals. The African region demonstrated a significant increase in both absolute and relative health inequality of PUD premature mortality, while the Southeastern Asia region exhibited improvements in both measures. The findings were similar in terms of the healthcare access perspective.

Conclusion: Although there has been a decline in the global PUD premature mortality burden over the past three decades, this decline has been comparatively slower among female, elderly, and low SDI countries. The implementation of intervention measures is still imperative to effectively reduce the global burden of PUD premature mortality.

Hemoptysis - How far should we workup and who should we follow?

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Introduction: Hemoptysis is a common presenting respiratory complaint. In Hong Kong, lung cancer is the commonest cancer and the annual rate of tuberculosis is 0.6/1000. This study aimed to examine the etiology patterns of patients with first episode hemoptysis in Hong Kong, and to analyze the risk factors for subsequent diagnosis of lung cancer.

Methods: Territory-wide retrospective cohort study by retrieval of hospitalisation records from the Hospital Authority's electronic record database. All adult patients presented with first episode of hemoptysis to public hospitals over five-year were included. Descriptive analysis on demographics and etiology identified in one-year was performed, followed by multinomial logistic regression for possible risk factors including age, sex, smoking history and recurrent hemoptysis, for subsequent diagnosis of lung cancer.

Results: 18,954 subjects (M:F 10,994:7,960) were admitted with mean age 61+/-17.6. In 6,875 subjects, possible etiologies were identified. The commonest causes were pneumonia (11.13%), active lung cancer (6.93%), bronchiectasis (5.03%) and tuberculosis (3.56%). Among 16,443 patients with follow-up, the rate of lung cancer diagnosed after 2-year was 6.99 per 1000 patients. Male gender (OR 3.09) and smoking history (OR 4.04) were risk factors in those with non-cancer etiology made at the time of hemoptysis. Age>65 (OR 2.57) was the only risk factor among those with previously established cryptogenic hemoptysis. For non-workup group (bronchoscopy+/-axial imaging), risk factors include age>60 (OR 3.76), smoking history (OR 3.67) and recurrent hemoptysis (OR 2.82).

Conclusion: In this territory-based study on patients presenting with first episode of hemoptysis, the epidemiology and risk factors for subsequent lung cancer diagnosis were identified.

Hereditary angioedema in the Asia-Pacific region: an international multicentre study on the epidemiology, real-world practice and treatment access

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Introduction: Hereditary angioedema (HAE) is associated with substantial morbidity and mortality. Many countries in the Asia-Pacific region lack access to diagnostic facilities and treatment modalities for HAE. Asia-Pacific region epidemiological data are urgently needed to formulate regional or country-specific guidelines that improve standards of care. In view of that, we studied the prevalence, needs and potential interventions for HAE in the Asia-Pacific region. To our knowledge, this is the largest epidemiological study on HAE to date and the first to be conducted on the Asia-Pacific region, which represents nearly half of the world's population.

Methods: A structured questionnaire consisting of 28 country- and centre-specific questions was distributed to representative experts from member societies of the Asia Pacific Association of Allergy, Asthma and Clinical Immunology (APAAACI) from 1st June to 31st July 2022. Patient profiles and the presence of diagnostic facilities, regional HAE guidelines and patient support groups were reported and compared amongst member countries.

Results: There were completed questionnaires by 14 representatives on behalf of 12 APAAACI member countries/regions, representing 46% of the world's population in 2022. Overall minimal Asia-Pacific prevalence of HAE was 0.02 per 100,000 population, with substantial patient heterogeneity across different centres (Figure 1). Only half and one-third of countries had registered on-demand and prophylactic medications respectively. Few Asia-Pacific countries had patient support groups (58%) or regional guidelines (33%), and their existence were associated with availability of HAE-specific medications (p=0.015 and p=0.018, respectively). Availability of C1 inhibitor antigen (C1inhA) level testing was associated with a lower youngest age of diagnosis (4.0 years [2.0-10.0] vs 25.0 years [13.0-25.0], p=0.017).

Conclusion: Epidemiology of HAE in the Asia-Pacific region appears to differ from that of Western populations. HAE-specific medications were only registered in the minority, but countries with patient support groups or regional guidelines were more likely to have access to HAE-specific medications. Asia-Pacific region-specific consensus and guidelines are urgently needed.

High-sensitivity C-reactive protein level in stable-state bronchiectasis predicts exacerbation risk

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Introduction: Elevation of systemic inflammatory markers were found to correlate with increased disease extent, reduced lung function and higher risk of future severe exacerbations in patients with bronchiectasis. Although a significant correlation of circulating hs-CRP (high-sensitivity C-reactive protein) levels with HRCT scores and resting oxygen saturation in patients with stable-state non-cystic fibrosis (CF) bronchiectasis was suggested, there is little data on the relationship between hs-CRP and the prognosis of bronchiectasis and a lack of data on the role of hs-CRP in predicting bronchiectasis exacerbation.

Methods: A prospective study was conducted on Chinese patients with non- CF bronchiectasis from 1st October to 31st December 2021. Baseline serum hs-CRP were obtained at stable-state. The follow-up period lasted for one year. Co-primary endpoints were the development of any bronchiectasis exacerbation and hospitalized bronchiectasis exacerbation.

Results: Totally 123 patients were included. Higher hs-CRP was associated with increased risk to develop any bronchiectasis exacerbation, adjusted odds ratio (aOR) of 2.254 (95% CI = 1.040-4.885, p=0.039), and borderline significantly increased hospitalized bronchiectasis exacerbation with aOR of 1.985 (95% CI = 0.922-4.277, p=0.080).

Conclusion: Baseline serum hs-CRP level at stable-state can predict risk of bronchiectasis exacerbation, which is reflecting chronic low-grade inflammation in bronchiectasis.

Hong Kong Drug Allergy De-labelling Initiative – a protocol of penicillin allergy evaluation featuring triage by trained nurses: effectiveness, safety and clinical outcomes

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Introduction: Misdiagnosed penicillin allergy is common, and it is associated with a variety of adverse outcomes. With the devastating burden of false penicillin allergy labels and shortage of allergy specialists, novel de-labelling strategies are urgently needed. In view of that, we developed and investigated the effectiveness and clinical outcomes of a nurse-triaged protocol of penicillin allergy evaluation – Hong Kong Drug Allergy De-labelling Initiative (HK-DADI), which has shortened the waiting time for a routine penicillin allergy consultation from over 7 years to around 1 year. This is the first comparative study on the real-world outcomes after allied health professional-triaged penicillin allergy de-labelling.

Methods: Patients with suspected penicillin allergy who were referred to the Allergy Clinic of Queen Mary Hospital/Hospital Authority Hong Kong West Cluster (Hong Kong's only adult allergy centre in the public sector) were included in this study. Allergy and post-de-labelling clinical outcomes of patients evaluated via HK-DADI and those who underwent traditional allergist evaluation were compared.

Results: A total of 312 patients completed penicillin allergy evaluation, among which 84 (27%) were evaluated via HK-DADI and 228 (73%) via traditional allergist evaluation. Overall, 280 (90%) penicillin allergy labels were removed (i.e., de-labelled). De-labelling rates were similar between HK-DADI and traditional allergist evaluation (90% vs. 89%, p=0.80). Among patients who underwent the HK-DADI pathway, low-risk patients had significantly higher de-labelling rate compared to non-low-risk patients (97% vs. 77%, p=0.01). Skin tests did not have additional diagnostic value in low-risk patients, as all (100%) low-risk patients with confirmed penicillin allergies were diagnosed with positive drug provocation test following negative skin test; on the contrary, 83% of non-low-risk patients with confirmed penicillin allergies had positive skin testing and only 1 patient had positive drug provocation test following a negative skin test. In both pathways, none of the patients developed any severe/systemic reactions during evaluation. Upon a follow-up of 6-12 months (median: 10 months) after de-labelling, 123 (44%) patients had suffered from infections which needed antibiotics, and 63 (23%) had used penicillin after de-labelling. This proportion was significantly greater in those who were de-labelled via HK-DADI than the traditional pathway (32% vs. 19%, p=0.03).

Conclusion: HK-DADI, a nurse-triaged evaluation protocol was effective in penicillin allergy de-labelling. HK-DADI resulted in a higher rate of penicillin use after de-labelling and could minimise the need of unnecessary skin testing in low-risk patients.

Hyperandrogenism-associated central obesity and metabolic disorders are related to mesothelial cell loss and adipose remodeling in visceral adipose tissue

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Introduction: Hyperandrogenism is an important diagnostic criteria in polycystic ovary syndrome, which is usually accompanied with central obesity and metabolic disorders. But the link between these metabolic disorders and high levels of androgens remains unclear.

Methods: In this study, we established a hyperandrogenic mouse model with chronic dihydrotestosterone (DHT) infusion. The metabolic phenotypes, including body weight, food intake, glucose tolerance, insulin resistance, adipose tissue weight, and adipose tissue pathology were measured. The non-immune fraction in gonadal adipose stromal vascular cells were isolated and subjected to 10x single-cell sequencing. Mesothelial cells were isolated using cell sorting and production of stable cell lines to verify cell counts. ER stress levels were tested by qPCR. Downstream pathways of androgen receptor in adipose tissue were studied by Cut&Tag. White adipose tissue organoids were cultured to verify the absence and secretory role of mesothelial cells by Sirius red staining.

Results: Mice with hyperandrogenism had higher body weight and gonadal adipose weight, and exhibited exacerbated glucose intolerance and insulin resistance, compared to the control mice. In gonadal adipose tissue, adipocyte was enlarged in size, and inflammatory markers were elevated, while the extracellular matrix (ECM) content was significantly lower in these mice. By single-cell sequencing, we found the number of mesothelial cells was reduced by 50% upon hyperandrogenism, which was experimentally verified by flow cytometry and immunofluorescent staining. Pathway enrichment analysis and TUNEL staining demonstrated that hyperandrogenism induced apoptosis in mesothelial cells. Mesothelial androgen receptor (AR) Cut&Tag results showed that *Inmt* was an AR downstream gene to activate ER stress and promote apoptosis. In visceral adipose organoids, mesothelial cell deletion caused loss of ECM, and supplementation with mesothelial cells conditioned medium restored this loss. Proteomics analysis on mesothelial cell conditioned medium revealed Decorin (DCN) as a secreted factor by mesothelial cells. Furthermore, DCN expression was reduced in mesothelial cells of DHT mice. Neutralization of DCN in mesothelial cell conditioned medium abolished its effect to enhance ECM formation in organoid culture, demonstrating the key role of DCN in linking mesothelial cell function and ECM formation.

Conclusion: Chronic hyperandrogenism leads to central obesity, systemic metabolic disorder and adipose tissue inflammation, with significant loss of extracellular matrix in visceral adipose tissue. Mechanistically, hyperandrogenism enhances *Inmt* expression in mesothelial cells which in turn induces apoptosis. Both the absence of mesothelial cells and the reduced DCN expression in mesothelial cells result in reduced DCN in adipose tissue and impaired ECM assembly, leading to ECM loss. This event eventually culminates in central obesity and metabolic disorders.

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Impact of Lactobacillus, lactate, and pH fluctuations on the regulation of human endometrial receptivity and potential to predict pregnancy outcomes

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Introduction: WHO 2020 estimated that 48 million couples and 186 million individuals are living with infertility globally. Recent studies suggested that the microbiome, especially the Lactobacillus-dominant (LD) environment in the uterus affects embryo implantation and pregnancy outcome in IVF patients. Lactobacilli produce bacteriocins, lactic acid and hydrogen peroxide to suppress the growth of some pathogenic bacteria, re-establishes the normal microbiota and normal vaginal pH. To understand the mechanism of the pH and lactates inside the uterus on embryo implantation, we conducted experiments on Ishikawa and BeWo cells which resemble endometrium and embryos.

Methods: In this study, we used various methods to investigate the role of lactate (D- & L-form) and pH on embryo implantation using the spheroid-endometrial co-culture model and studied the invasion and cytokine production of the endometrial epithelial cells. Concurrently, we employed Next-Generation Sequencing (NGS) analysis to investigate the composition and characteristics of uterine fluid and vaginal fluid samples obtained from the patients.

Results: We demonstrated that high lactate concentrations (>20mM) inhibit the cell viability and proliferation of the human endometrial epithelial Ishikawa and trophoblastic BeWo cells. Culture media at pH 6.1 (acidic), 7.2-7.4 (neutral), and 8.1 (alkaline) conditions did not affect the spheroid attachment on the treated Ishikawa cells. Moreover, high lactate concentrations (>20mM) inhibited the invasion of trophoblastic BeWo by the treated Ishikawa cells, as well as tube formation (angiogenesis) in the treated human endothelial HUVEC cells. D- & L-lactate induce the production of cytokines including TIMPs, MMPs, IL6, IL6R, and Th1 and Th2 cytokines. Taken together, our in vitro studies suggested that high lactate concentrations, but not pH6.1-8.1, did not favour spheroid attachment.

Conclusion: To sum up, our in vitro studies suggested that Lactobacillus and Bifidobacteriaceae is most abundant bacteria inside uterine and vaginal fluid. However, high lactate concentrations, but not pH 6.4-8.1, do not significant effect on spheroid attachment. The underlying molecular mechanism of how the LD microenvironment favour pregnancy outcome could be due to changes in cytokines and secretome that modulate endometrial receptivity and immune responses in pregnancy.

Incidence of diabetes following COVID-19 vaccination and SARS-CoV-2 infection: a population-based cohort study

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Introduction: The risk of incident diabetes following Coronavirus Disease 2019 (COVID-19) vaccination remains to be elucidated. Also, it is unclear whether the risk of incident diabetes after Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is modified by vaccination status or differs by SARS-CoV-2 variants. We evaluated the incidence of diabetes following mRNA (BNT162b2), inactivated (CoronaVac) COVID-19 vaccines, and after SARS-CoV-2 infection.

Methods: In this population-based cohort study, individuals without known diabetes were identified from an electronic health database in Hong Kong. The first cohort included people who received ≥1 dose of COVID-19 vaccine and those who did not receive any COVID-19 vaccines up to September 2021. The second cohort consisted of confirmed COVID-19 patients and people who were never infected up to March 2022. Both cohorts were followed until August 15, 2022. A total of 325,715 COVID-19 vaccine recipients (CoronaVac: 167,337; BNT162b2: 158,378) and 145,199 COVID-19 patients were 1:1 matched to their respective controls using propensity score for various baseline characteristics. We also adjusted for previous SARS-CoV-2 infection when estimating the conditional probability of receiving vaccinations, and vaccination status when estimating the conditional probability of contracting SARS-CoV-2 infection. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident diabetes were estimated using Cox regression models.

Results: In the first cohort, we identified 5,760 and 4,411 diabetes cases after receiving CoronaVac and BNT162b2 vaccines, respectively. Upon a median follow-up of 384 to 386 days, there was no evidence of increased risks of incident diabetes following CoronaVac or BNT162b2 vaccination (CoronaVac: 9.08 versus 9.10 per 100,000 person-days, HR=0.998 [95% CI 0.962-1.035]; BNT162b2: 7.41 versus 8.58, HR=0.862 [0.828-0.897]), regardless of diabetes type. In the second cohort, we observed 2,109 cases of diabetes following SARS-CoV-2 infection. Upon a median follow-up of 164 days, SARS-CoV-2 infection was associated with significantly higher risk of incident diabetes (9.04 versus 7.38, HR=1.225 [1.150-1.305])—mainly type 2 diabetes—regardless of predominant circulating variants, albeit lower with Omicron variants (p for interaction=0.009). Subgroup analysis revealed no evidence of increased risk of incident diabetes among fully vaccinated COVID-19 survivors.

Conclusion: There was no evidence of increased risks of incident diabetes following COVID-19 vaccination. The risk of incident diabetes increased following SARS-CoV-2 infection, mainly type 2 diabetes. The excess risk was lower, but still statistically significant, for Omicron variants. Fully vaccinated individuals might be protected from risks of incident diabetes following SARS-CoV-2 infection.

Increased circulating neutrophil is associated with higher risk of cardiovascular mortality among adults with diabetic kidney disease: a cross-sectional and longitudinal study

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Introduction: Previous studies have reported the correlations between neutrophils, cardiovascular inflammation, and outcomes of cardiometabolic diseases, but the relationship of circulating neutrophil counts with cardiovascular disease (CVD) and all-cause mortality in patients with type 2 diabetes mellitus (T2DM) and diabetic kidney disease (DKD) remains unclear.

Methods: This prospective cohort study was performed based on 44,494 participants in the National Health and Nutrition Examination Surveys (NHANES) from 2005 to 2020. The association of peripheral neutrophils count with kidney functions in DKD and CVD mortality were further explored using logistic regression and Cox proportional hazards models. Clinical predictive models and risk scores for long-term mortality were constructed.

Results: Among 44,332 patients [18% T2DM and 82% without T2DM] were included. 2,220 patients had DKD and 775 died (31.5% related to CVD) during a follow-up of 6.18 (range: 5.94-6.42) years. The weighted mean of peripheral neutrophil count level (×109 /L) in DKD participants was 4.98. When compared with those in the lowest neutrophil count quintile, the highest quintile in DKD had the positive relationship with urine albumin-creatinine ratio (uACR) and negative association with estimated glomerular filtration rate (eGFR). In the multivariate logistic regression analysis with RCS, circulating neutrophil counts showed a U-shaped association with CVD mortality. Neutrophil counts of 3.68×10^9/L and 3.69×10^9/L were associated with the lowest risk of CVD mortality and all-cause mortality respectively in DKD patients. Clinical predictive models showed good diagnostic performance for 5- and 10-year CVD mortality-free survival (all ROC AUC values >0.80).

Conclusion: In this cohort study, higher peripheral neutrophil count was associated with an increased risk of cardiovascular mortality in DKD individuals. Clinical predictive models can help predict long-term mortality risk among patients with DKD.

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Insomnia and increased incidences of adverse cardiovascular outcomes among heart failure patients: a population-based study

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Introduction: Heart Failure (HF) represents a substantial worldwide health issue, affecting over 60 million individuals globally. Previous research has established a link between insomnia and an increased risk of developing HF, yet the influence of insomnia on existing HF patients' outcome remains underexplored. Given the large number of the HF demographic, this study aims to investigate the relationship between insomnia and negative HF outcomes in the already vulnerable HF population, as well as to assess the potential advantages of treating insomnia pharmacologically to mitigate these risks.

Methods: Data were obtained using a territory-wide database developed by the Hong Kong Hospital Authority for a population-representative sample of 202,585 patients diagnosed with HF between 2001 and 2020. Propensity score matching (PSM) was implemented, pairing previously treated individuals with their corresponding control subjects. Competing risk regression with Cox proportional-hazard models was performed to estimate the incidences of composite outcome of HF rehospitalization and cardiovascular death, HF rehospitalization, cardiovascular death (CVD), and all-cause mortality associated with insomnia.

Results: Over a median follow-up of 10.5 years [interquartile range 5.7-15.8 years], 135,928 HF rehospitalizations and 147,534 all-cause deaths were documented. Insomnia correlated with a 19% increase in the composite outcome (multivariable adjusted subdistribution hazard ratio [SHR]: 1.19, 95% confidence interval [CI]: 1.17-1.21), a 23% increase in HF rehospitalization incidence (SHR: 1.23, 95% CI: 1.20-1.26), an 11% increase in CVD (SHR: 1.11, 95% CI: 1.07-1.15), and a 13% increase in all-cause mortality incidence (HR: 1.13, 95% CI: 1.10-1.16). The insomnia cohort was further stratified based on medication usage, revealing increased all-cause mortality risks in non-medicated (HR: 1.14, 95% CI: 1.12-1.17) versus medicated patients (HR: 1.05, 95% CI: 1.01-1.09), a pattern consistent across other HF outcomes. This association with incidences of adverse HF outcomes was duration dependent; as compared with short-term insomnia medication use (1 to 30 days), the adjusted HR for all-cause mortality rose to 1.10 (95% CI, 1.05-1.16) for 30 to 180 days of use, and 1.16 (95% CI, 1.10-1.22) for use beyond 180 days of use.

Conclusion: Our findings suggest an association between insomnia and increased incidences of adverse HF outcomes. The importance of public awareness campaigns and regular screening protocols for insomnia in HF patients must not be underestimated in future healthcare practices.

Lipidomic study discovered specific triacylglycerol, diacylglycerol, and lyso-phosphatidylcholine species as promising predictors for type 2 diabetes and phospholipase A2 group VII as potential therapeutic target: from bed to bench

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Introduction: Bioactive lipids play an important role in insulin secretion and sensitivity, contributing to the pathophysiology of type 2 diabetes (T2D). This study aimed to identify novel lipid species associated with incident T2D and explore the potential roles of these lipid species in T2D.

Methods: Plasma samples from 196 incident T2D cases and 196 age- and sex-matched non-T2D controls recruited from the Hong Kong Cardiovascular Risk Factor Prevalence Study (CRISPS) were first analyzed using untargeted lipidomics. Potential predictive lipid species selected by the Boruta analysis were then verified by targeted lipidomics. The associations between these lipid species and incident T2D were assessed. Effects of novel lipid species on insulin secretion in mouse islets were investigated. The effect of their synthetic enzyme on glucose metabolism was investigated using mice over-expressing the enzyme induced by adeno-associated virus.

Results: A total of 301 lipid species were detected after excluding 47 lipid species with relative standard deviation > 30% in QC samples. Boruta analysis then identified 16 potential lipid species. After adjustment for body mass index (BMI), triacylglycerol/high-density lipoprotein (TG/HDL) ratio and the presence of prediabetes, triacylglycerol (TG) 12:0_18:2_22:6, TG 16:0_11:1_18:2, TG 49:0, TG 51:1 and diacylglycerol (DG) 18:2_22:6 were independently associated with increased T2D risk, whereas lyso-phosphatidylcholine (LPC) O-16:0, LPC P-16:0, LPC O-18:0 and LPC 18:1 were significantly associated with a decreased risk of T2D. Addition of the identified lipid species to the clinical prediction model significantly increased the area under the receiver operating characteristics curve from 0.785 to 0.823 (improved by 3.8%, p=0.0026). LPC O-16:0 and LPC O-18:0 significantly potentiated glucose induced insulin secretion (GSIS) in a dose-dependent manner. The overexpression of phospholipase A2 group VII (PLA2G7), the synthetic enzyme of LPC O-16:0 and LPC O-18:0, was induced by adeno-associated virus. While fed with standard chow, mice over-expressing PLA2G7 showed no difference in glucose tolerance during glucose tolerance test (GTT) compared to the luciferase control. However, diet-induced obese mice over-expressing PLA2G7 showed improved glucose intolerance demonstrated by GTT, as well as lower body weight and fed glucose.

Conclusion: Addition of the lipid species substantially improved the prediction of T2D beyond the model based on clinical risk factors. Decreased levels of LPC O-16:0 and LPC O-18:0 may contribute to the development of T2D via reduced insulin secretion. PLA2G7 may be a potential therapeutic target that ameliorates T2D via increasing LPC O-16:0 and LPC O-18:0 levels.

Long-term glycemic instability does not affect the effectiveness of SGLT2 inhibitors vs DPP-4 inhibitors in patients with type 2 diabetes

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Introduction: Sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy reduces the risk of cardiovascular and renal adverse events. However, whether the benefit varies with differences in long-term glycemic homeostasis is unknown.

Methods: This territory-wide cohort study prospectively analyzed patients with type 2 diabetes initiating SGLT2 inhibitors or dipeptidyl-peptidase 4 (DPP-4) inhibitors in Hong Kong between 2015 and 2022. Hemoglobin A1c variability score (HVS) was calculated to represent the long-term glycemic variability in 3 years prior to the drug initiating date. Patients were divided into two subgroups according to HVS and 1:1 propensity score matching (PSM) was performed separately in each subgroup. Cox regression analysis was used to compare the risk of outcomes between SGLT2 inhibitors users and DPP-4 inhibitors users. The interactive effect of baseline HVS and the mediation effect of HVS variation after the therapy were evaluated.

Results: A total of 60865 eligible adults with T2D initiating SGLT2 inhibitors (n=18217) or DPP-4 inhibitors (n=42648) were identified. Overall, 26218 eligible patients were 1:1 propensity score-matched: 12334 with a baseline HVS less than 50 and 13884 with a baseline HVS greater than 50. The initiation of SGLT2 inhibitors vs DPP-4 inhibitors was associated with a reduction in the risk of major cardiovascular events (MACE) (IR per 1000 person-years 23.67 vs 31.60; HR 0.747; 95% CI 0.685-0.814) and serious renal outcomes (SRE) (IR per 1000 person-years 28.61 vs 59.77; HR 0.475; 95% CI 0.445-0.507), with no treatment effect heterogeneity across baseline HVS. SGLT2 inhibitors treatment was associated with a more drastic reduction in HVS (-9.05±30.87 vs -3.33±31.10, p<0.001). HVS variation mediated 6% of the total effect of SGLT2 inhibitors treatment on MACE and 4% on SRE.

Conclusion: In patients with type 2 diabetes, SGLT2 inhibitors vs DPP-4 inhibitors treatment reduced the risk of MACE and SRE regardless of baseline HVS. The protective effect of SGLT2 inhibitors is partially mediated by reducing the long-term variability of blood hemoglobin A1c level.

Lupus low disease activity state complements renal response in predicting lupus nephritis relapse free patients

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Introduction: Lupus nephritis (LN) is a significant comorbidity affecting approximately up to 50-60% of patients with systemic lupus erythematosus (SLE). Complete renal response (CRR) and partial renal response (PRR) have been recommended as treatment targets in LN. Lupus low disease activity state (LLDAS) is an important target associated with improved clinical outcome in SLE. Its role in patients in LN has not been fully evaluated. This study aims to investigate the attainment rate, predictors and outcomes associated with LLDAS attainment in patients with LN.

Methods: Patients with biopsy-proven LN during 2010-2020 in Queen Mary Hospital were included. Baseline demographics, blood parameters and urinalysis results were recorded. Renal response and LLDAS attainment were assessed at 12 months after LN diagnosis. CRR was defined as proteinuria ≤0.5g/day with normal estimate glomerular filtration rate (eGFR); PRR was defined as a reduction in proteinuria by ≥50% with near normal eGFR. LLDAS was attained by meeting: (1) SLE Disease Activity Index ≤4 with no major organ activity; (2) no new lupus disease; (3) physician global assessment ≤1; (4) prednisolone dose ≤7.5mg; (5) standard maintenance immunosuppressants. Treatment response was defined as proteinuria reduction of ≥50% or to sub-nephrotic range. Relapse was defined as a biopsy-proven active LN on histology after an initial treatment response. Time-to-relapse survival analysis was performed to compare the significance of CRR/PRR and LLDAS attainment.

Results: A total of 143 LN patients were included with a median follow-up duration of 10.4 years. At 12 months, 57 (40%), 14 (10%) and 69 (48%) patients achieved CRR, PRR and LLDAS, respectively. Although 39 (27%) patients attained both CRR/PRR and LLDAS, a significant number of 30 (21%) patients reached LLDAS without meeting CRR/PRR. Among 136 patients who achieved the pre-defined treatment response, 30 (22%) patients developed LN relapse after a median of 2.98 years. Patients reaching either CRR/PRR or LLDAS had a significantly lower risk of relapse (CRR/PRR: HR = 0.34, p=0.02; LLDAS: HR = 0.28, p=0.003). The attainment of both CRR/PRR and LLDAS was associated with the lowest risk of relapse.

Conclusion: We advocate LLDAS as a target for LN patients as LLDAS attainment lowers the risk of future relapse.

Machine learning-based subgroup identification of hypertensive patients with hypokalemia and predicting mortality risk, United States National Health and Nutrition Examination Survey 1999-2018

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Objectives: Hypokalemia frequently occurs in hypertensive patients, but its underlying causes can vary widely. We aimed to use unsupervised machine learning to discover more precise and homogeneous subgroups within hypertensive patients with hypokalemia and evaluate the mortality risk among these distinct clusters.

Methods: We analyzed data from the United States National Health and Nutrition Examination Survey (NHANES) from 1999 to 2018. We applied consensus clustering analysis to create clinical phenotypes in adult hypertensive patients with hypokalemia. Variables included demographic information, examination details, medical history, medication usage, and laboratory tests. We then evaluated cumulative survival probabilities for all-cause and cardiovascular disease (CVD) mortality across the identified clusters and examined their association with mortality outcomes.

Results: Our analysis included 1456 hypertensive patients with hypokalemia, yielding three distinct clusters. Cluster 1 patients were younger, had fewer comorbidities, lower serum sodium, bicarbonate, and calcium levels, but higher estimated glomerular filtration rate (eGFR). Cluster 2 patients were older, had the highest blood pressure, CVD prevalence and renin angiotensin system inhibitors usage, but lower education levels and economic status. Cluster 3 patients were older, had more comorbid arthritis and cancer, used more diuretics, methylxanthines, and glucocorticoids but lower eGFR. Compared to cluster 1, both cluster 2 and cluster 3 exhibited significantly higher hazard ratios for all-cause (6.19 [95% CI, 3.66-10.49] vs 5.28 [95% CI, 3.35-8.35]) and CVD mortality (8.67 [95% CI, 3.49-21.53] vs (8.69 [95% CI, 3.69-20.47]).

Conclusion: Our study applied a consensus clustering algorithm to hypertensive patients with hypokalemia, categorizing their baseline clinical characteristics into three distinct clusters, each associated with varying mortality risks.

Metabolic dysfunction-associated steatotic liver disease is a risk factor for lower vaccine immunogenicity against SARS-CoV-2 omicron variant among three-dose BNT162b2 recipients

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Background: We aimed to investigate the effect of metabolic dysfunction-associated steatotic liver disease (MASLD) on different COVID-19 vaccine platforms to SARS-CoV-2 omicron variant.

Methods: Adult recipients of three doses of COVID-19 vaccine (BNT162b2 or CoronaVac), either homologous or heterologous, were prospectively recruited from vaccination centers between May and December 2021. Serology of neutralising antibody by live virus microneutralization (vMN) to SARS-CoV-2 omicron variant were measured at baseline, day180 and day360 after first dose. Outcome of interest was seroconversion (MN titre $\geq$10) at one year after first dose. Exposure of interest was MASLD, defined as hepatic steatosis (controlled attenuation parameter $\geq$248dB/M on transient elastography) plus at least one of five cardiometabolic risk factors. Exclusion criteria included immunocompromised status, inflammatory bowel disease, history of gastrointestinal surgery and those with COVID-19 infection prior to one-year follow up. Adjusted odds ratio of seroconversion with MASLD by adjusting for age, sex, antibiotic and proton pump inhibitor use was calculated by multivariable logistic regression model.

Results: 247 three-dose vaccine recipients (BNT162b2:148[59.9%]; CoronaVac:44[17.8%]; heterologous:55[22.3%]) were recruited. The median time from first to third dose was 8.2 months (IQR:7.4-8.9). The median time from day180 to third dose and third dose to day360 was 2.4 months (IQR:1.5-3.1) and 3.9 months (IQR:3.0-4.6), respectively. Only 7(2.8%) (BNT:4[2.7%]; CoronaVac:1[2.3%], heterologous:2[3.6%]) was seropositive on day180. Of 148 BNT162b2 recipients (32.4% male; median age 51.0 years, 48[32.4%] had MASLD). Subjects with MASLD had lower seroconversion rate than non-MASLD (89.6%vs99.0%; p=0.007). On multivariate analysis, MASLD was the only independent risk factor of this outcome (aOR:0.051; 95% CI:0.002-0.440; p=0.022). On subgroup analysis, MASLD subjects had significantly lower seroconversion rate (76.9%vs97.4%, p=0.016) and vMN geometric mean titer (13.06[IQR:7.69-22.20] vs 33.49[IQR:24.05-46.53], p=0.004) than non-MASLD subjects after 4 months from third dose but not within 4 months. Of 44 CoronaVac recipients (40.9% male; median age 52.1 years, 17[38.6%] had MASLD) and 55 heterologous vaccine recipients (41.8% male; median age 53.7 years, 28[50.9%] had MASLD), there were no difference in seroconversion rate between MASLD and non-MASLD to SARS-CoV-2 omicron variant (CoronaVac: 41.2%vs40.7%; p=0.977; Heterologous: 82.1%vs81.5%; p=0.949). Findings are consistent regardless of sequence of vaccine platform (two-dose CoronaVac followed by third dose BNT162b2: 76.2%vs85.7%; p=0.490; two-dose BNT162b2 followed by third dose CoronaVac: 100%vs76.9%; p=0.148).

Conclusion: MASLD is a risk factor for poorer immunogenicity to omicron variant with a more pronounced waning effect among three-dose BNT162b2 recipients, but not among CoronaVac nor heterologous vaccine recipients.

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More exacerbations of bronchiectasis after recovery from mild-to-moderate COVID-19 in patients with non-cystic fibrosis bronchiectasis

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Introduction: Respiratory viral infection is one important trigger for acute exacerbation of bronchiectasis. While there is no regional exemption from the global impact of severe COVID-19, its effect on bronchiectasis in intermediate- to long-term outcome has been lacking.

Methods: A retrospective cohort study was conducted a major regional hospital in Hong Kong, to assess bronchiectasis exacerbation frequency post-recovery from mild-to-moderate COVID-19.

Results: A total of 234 adult patients with bronchiectasis were recruited in which 52 (24.4%) were classified as the COVID-19 group. Patients with COVID-19 had significantly increased annual bronchiectasis exacerbation frequency (in both total exacerbation and hospitalized exacerbation) from baseline (using 2019 and 2019 to 2021 for comparison respectively) with follow-up period up to 1 year. The total exacerbation frequency reduced by 0.1 +/- 0.51 per year among non-COVID-19 group and increased by 0.68 +/- 1.09 per year among COVID-19 group, with p-value < 0.001 by suing 2019 to 2021 as comparison. It reduced by 0.14 +/- 0.79 per year among non-COVID-19 group and increased by 0.76 +/- 1.17 per year among COVID-19 group, with p-value < 0.001, using 2019 as comparison. The annual hospitalized bronchiectasis exacerbation frequency increased by 0.01 +/- 0.32 per year among non-COVID-19 group and increased by 0.39 +/- 1.06 per year among COVID-19 group, with p-value < 0.001 using 2019 to 2021 for comparison. It remained unchanged by 0 +/- 0.43 per year among non-COVID-19 group and increased by 0.38 +/- 1.12 per year among COVID-19 group, with p-value < 0.001, using 2019 for comparison.

Conclusion: Mild-to-moderate COVID-19 in bronchiectasis patients were associated with increase in total and hospitalized bronchiectasis exacerbation frequency after recovery.

Neutrophil to lymphocyte ratio and systemic immune-inflammation index in predicting hospitalized COPD exacerbation risks

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Introduction: Chronic obstructive pulmonary disease (COPD) is characterized by chronic neutrophilic inflammation. Blood neutrophil to lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) are readily available biomarkers in COPD. While there were more studies on the role of NLR, the evidence on SII is relatively less, especially among patients with different phenotypes.

Methods: A prospective study on patients with COPD was conducted in two major regional hospitals and tertiary respiratory referral centres in Hong Kong, to investigate the association between baseline inflammatory state (NLR and SII) and hospitalized COPD exacerbation (AECOPD) risks including requirement of ventilatory support. The baseline NLR and SII were collected in the year 2021.

Results: There were 305 Chinese patients with COPD recruited. 84 had hospitalized AECOPD in the follow-up period and 14 with respiratory failure requiring non-invasive or invasive ventilatory support. Higher NLR or SII was associated with increased risks of hospitalized AECOPD, with adjusted odds ratios (aOR) of 1.197 (95% CI = 1.023-1.400, p-value = 0.025) for NLR and aOR of 1.310 (95% CI = 1.000-1.714, p-value = 0.050) for 1 SD increase in SII. NLR and SII were also associated with increased risks of hospitalized AECOPD in respiratory failure requiring ventilatory support, with aOR of 1.460 (95% CI = 1.130-1.886, p-value = 0.004) for NLR and aOR of 1.757 (95% CI = 1.114-2.770, p-value = 0.015) for 1 SD increase in SII. Similar findings were also observed in patients with either eosinophilic or non-eosinophilic phenotype. Baseline NLR was found to have weak negative association with baseline FEV1 (in litre and percentage predicted) and FVC in litre; and weak positive association with baseline mMRC score. Baseline SII was found to have weak negative association with FEV1 in litre and FVC in litre; and weak positive association with baseline mMRC score with Pearson coefficient of 0.161 (p-value < 0.001).

Conclusion: Baseline NLR and SII may serve as biomarkers to predict the risks of hospitalized AECOPD and correlate with different clinical parameters in COPD, among patients with either eosinophilic or non-eosinophilic phenotype.

Non-pharmacological treatments of postpolio syndrome: a systematic review

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Introduction: Poliomyelitis (often called polio) is a highly contagious disease caused by a poliovirus. It was believed that after recovery from acute paralytic polio, the physical conditions of survivors would remain stable for the rest of their lives. However, up to 40% of polio survivors may develop what has been called postpolio syndrome (PPS) approximately 15 to 40 years after the original paralytic polio infection. Symptoms of PPS include increasing muscle weakness, muscle fatigue, general fatigue, muscle and joint pain, muscle loss, respiratory problems, sleep disturbance, swallowing difficulties, and cold intolerance. These PPS symptoms can affect the polio survivors' daily functioning, mobility, quality of life, and psychological well-being. There are unmet needs of polio survivors with PPS for effective rehabilitation programs in Hong Kong. Therefore, it is important to gain some insight on how to help guide this particular population, their caregivers, and healthcare professionals in managing PPS. This systematic review may serve as a background search for developing future clinical trials and rehabilitation protocols for individuals with PPS in Hong Kong. This review aimed to systematically review the evidence from randomized and quasi-randomized controlled trials for the effect of any form of non-pharmacological treatment for individuals with prior paralytic poliomyelitis with or without a diagnosis of PPS, in comparison of placebo, usual care or no treatment.

Methods: Systematic search of MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Library, PubMed and Web of Science for published and unpublished RCTs and quasi-randomized trials over the past 20 years. Selection criteria included polio survivors with or without a diagnosis of PPS and any form of non-pharmacological treatment. Placebo, usual care or no treatment were used as control in the relevant trials. Each study had its own outcome measures of interest.

Results: There has been an earlier Cochrane review on the treatment for PPS published in 2011 and later updated in 2015. In this review, we identified four new non-pharmacological studies published after the 2015 review and two previously reviewed studies on non-pharmacological intervention.

Conclusion: Due to insufficient good-quality data and insufficient high-quality randomized studies, it was impossible to draw definite conclusions about the effectiveness of interventions for PPS. Results indicated that anthroposophic multimodal treatment on chronic pain and interactive video games on upper limb motor function may be beneficial but need further investigation to clarify whether any real and meaningful effect exists.

Omics-driven discovery and multicentric validation of soluble CDCP1 as a robust non-invasive diagnostic biomarker for NASH

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Introduction: Non-alcoholic steatohepatitis (NASH), the advanced form of non-alcoholic fatty liver disease (NAFLD), associates with an increased risk of progression to liver-related mortality. However, the definitive diagnosis of NASH relies on invasive and labour-intensive liver biopsy. This study aimed to identify novel circulating biomarkers for NASH and to develop a personalized non-invasive test for identification and risk stratification of NASH.

Methods: Serum samples from a discovery cohort comprising 238 individuals with biopsy-based histological assessment and total RNA from liver biopsies of 98 paired cases were subjected to Olink-based proteomics and transcriptomics analysis, respectively. A top-ranked serum biomarker for NASH was selected by machine learning, and its diagnostic potential was verified by quantitative ELISA in multiple cross-sectional cohorts (n=489 in main cohort and 135 in multicentric validation cohort) and a longitudinal cohort including 151 cases after bariatric surgery. The diagnostic algorithm for predicting NASH was constructed based on logistic bootstrap. Algorithm performance in diagnosing fibrotic NASH was also evaluated and compared with existing clinical tests.

Results: Quantitative proteomics analysis for 1104 proteins identified the soluble CUB Domain Containing Protein 1 (sCDCP1) as the best performer in identifying NASH. Both its circulating concentration and mRNA abundance in liver were markedly elevated in NASH patients and closely correlated with each histological feature. Similar results were observed in both the main cohort and the multicentric validation cohort; the decline in serum sCDCP1 closely paralleled decreases in liver enzymes after bariatric surgery. The C-DAG model established by the combination of sCDCP1 with diabetes, AST and gender showed a AUROC of 0.893 (95% CI 0.859-0.927) in the pooled validation cohort, and significantly outperformed cytokeratin-18 and other tests for NASH. Cut-offs of C-DAG were 0.393 for NASH rule-in (sensitivity 72.5%, specificity 81.5%, and positive predictive value 69.3%) and 0.235 for NASH rule-out (sensitivity 90.8%, specificity 71.4% and negative predictive value 93.1%), with an indeterminate zone of 12.8%. Moreover, the C-DAG score demonstrated high accuracy in identifying fibrotic NASH and was significantly superior to existing non-invasive tests.

Conclusion: sCDCP1 is a robust circulating biomarker for NASH and the C-DAG score is a promising non-invasive test for personalized early diagnosis and risk stratification of NASH in obese individuals, thus avoiding unnecessary liver biopsy in low-risk individuals.

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Performance of GPT-4 and GPT-3.5 in generating accurate and comprehensive diagnoses across medical subspecialties

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Introduction: The proficiency of Generative Pre-trained Transformer 4 (GPT-4) in diagnosing complex medical cases across various subspecialties, as compared to its predecessor GPT-3.5, remains underexplored. The implications of GPT-4's performance in diagnosing patients with infections, rheumatic diseases, adverse drug reactions, and cognitive impairment need further investigation.

Methods: Two hundred and ten case records from the New England Journal of Medicine (NEJM) were screened, and 81 cases across the subspecialties of "cognitive impairment" (CI), "infectious disease" (ID), "rheumatology" (RH) and "drug reactions" (DR) were selected. Clinical information was inputted along with instructions for the chat-bots to provide the primary diagnoses, differential diagnoses and investigations to establish diagnoses. GPT-4's diagnostic accuracy in each subspecialty was compared against its combined performance in the remaining subspecialties. A novel scoring system was proposed to assess the diagnostic accuracy and comprehensiveness of the differential diagnoses of GPT-3.5 and GPT-4.

Results: GPT-4's primary diagnostic accuracy was 38.3%, which improved to 71.6% after including the suggested differential diagnoses. GPT-4 was superior in making the primary diagnosis in the DR category (odds ratio 7.26, 95% confidence interval 1.08-90.28) and providing differential diagnoses that accounted for the primary diagnosis in the ID category (odds ratio 2.89, 95% confidence interval 1.05-7.45). However, it underperformed in providing a differential diagnosis in the CI category (odds ratio 0.26, 95% confidence interval 0.08-0.89). The mean scores achieved by GPT-3.5 and GPT-4 were 8.72 and 12.59, respectively ($p < 0.001$).

Conclusion: The GPT-4 exhibits diagnostic accuracy comparable to previous studies and shows promise in dealing with complex medical diagnoses. It particularly excels in the subspecialties of infectious diseases and drug reactions, but less favorably in cognitive impairment. The results recommend further evaluation of AI performance across different stages of diagnosis, and the potential of AI, particularly GPT-4, in supporting patient management.

Prevalence and risk factors of frailty in community-dwelling elderly patients with type 2 diabetes mellitus

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Introduction: Frailty is a condition commonly seen in older adults and is associated with adverse health outcomes such as higher in-hospital mortality, increased readmission rates, and increased institutionalization. Previous studies showed that frailty status could be reversed. Since frailty is reversible, early identification and intervention of these risk factors could reverse the frail state.

Objectives: To study the local prevalence of frailty and to identify risk factors predicting frailty status among community-dwelling diabetic elderly.

Methods: A retrospective cross-sectional study was conducted. Community-dwelling diabetic patients at least 65 years old were identified from the discharged patients enrolled in the Integrated Care and Discharge Support program between August 2018 and December 2019. Frailty status was assessed using the Clinical Frailty Scale (CFS). Patients with CFS 1-4 were grouped as "non-frail", while those with CFS 5 or above were grouped as "frail". Binary and ordinal multivariate regression analyses were performed using frailty as the outcome.

Results: Of 670 diabetic elders, 51.3% were frail (CFS>=5) and 48.7% were non-frail. The distribution of frailty showed that most patients had a CFS score of 4 (29.9%), i.e. living with very mild frailty. This was followed by patients with a CFS score of 5 (25.1%), then 6 (21.3%), and 3 (18.7%). After adjusting for age, sex, hemoglobin level, creatinine level, presence of urinary incontinence and rheumatological diseases, and total number of medications, the risk of frailty significantly increased with age (OR:1.055; 95% CI: 1.029-1.081; p<0.001), being female (OR:1.428; 95% CI: 1.002-2.034; p=0.048), presence of cognitive impairment (OR:3.437; 95% CI: 1.691-6.986; p<0.001) and history of fracture (OR:1.764; 95% CI:1.048-2.97; p=0.033). Frailty was also associated with low levels of albumin (OR:0.961; 95% CI: 0.933-0.99; p=0.009) and HbA1c (OR: 0.856. 95% CI: 0.762-0.961, p=0.008). Further analysis using original logistic regression analysis was performed using CFS score as the dependent variable. Across all models, age, albumin level, HbA1c, and the AMT score consistently remained to be significant predictors of CFS. Both Modified functional Ambulatory Category and Bartel Index-20 were persistently predictive of CFS when either functional score were used.

Conclusion: Frailty was common among the diabetic elderly, with 51.3% of the patients being classified as frail according to the CFS. Age, sex, cognitive impairment, history of fracture, lower levels of albumin and HbA1c, and functional scores including MFAC and BI-20 were significant predictors of frailty. Implementation of screening and early intervention targeting at the modifiable risk factors may reverse frailty.

Prognostic implication of coronary angiography-derived fractional flow reserve in patients with non-obstructive coronary artery disease

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Introduction: Non-obstructive coronary artery disease (NOCAD) is proved to have high association with rate of major adverse cardiovascular events (MACE) in recent studies, yet there is lack of risk assessment to stratify it. A novel index named caFFR exhibits remarkable accuracy in correlation with FFR measurements in coronary arteries using coronary angiography. While importance of FFR has been established in coronary artery disease patients, its relevance in NOCAD patients has yet to be explored. Therefore, our objective is to evaluate the clinical implications of caFFR on MACE in NOCAD patients.

Methods: From 2014 to 2017, we enrolled patients with ≤ 50% diameter stenosis and underwent successful caFFR measurement with a value ≥ 0.8 in all three coronary arteries on coronary angiography. The sum of caFFR values in the three vessels was calculated for each patient. We grouped the patients based on the following criteria: single vessel analysis (median value of left anterior descending artery (0.92), left circumflex artery (0.94), and right coronary artery (0.94)), multi-vessel analysis (the number of arteries with a value less than the median of all coronary arteries (0.93)), and the median value (2.78) of the total 3-vessel (3V). 3V-caFFR reflects the total physiologic atherosclerotic burden. The primary endpoint of this study was rate of MACE at 5 years, defined as a composite of cardiac death, myocardial infarction, and ischemia-driven revascularization.

Results: In this study, a total of 490 NOCAD patients (mean age 64.39 ± 11.16, 55.5% male) were included, 31 individuals had MACE events during the 5-year follow-up period. In single-vessel analysis, the MACE rate between the low and high caFFR groups were found to be statistically insignificant. In multi-vessel analysis, the MACE rate was higher in the multi low-caFFR group (with 2-3 vessels lower than median value of all coronary arteries) compared with the single low-caFFR group (with only 0-1 vessel) (3.32% vs. 8.60%, hazard ratio [HR] 2.648, 95% confidence interval [CI] 1.141 - 6.145, P=0.023). In 3V analysis, patients in the low 3V-caFFR group indicated a higher MACE rate than those in the high 3V-caFFR group (8.5% vs. 3.6%, HR 2.43, CI 1.087 - 5.433, P=0.031).

Conclusion: Among NOCAD patients, those with a higher number of vessels with low caFFR value and lower 3V-caFFR values exhibited increased clinical outcomes at a 5-year rate of MACE. Unlike single-vessel caFFR, both multiple-vessel and 3V caFFR measurements serve as valuable prognostic indicators for NOCAD patients.

Prognostic implications of iron deficiency and supplementation in patients undergoing valvular heart surgery

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Introduction: Iron deficiency is common in patients with cardiovascular diseases, present in up to 60% of patients with coronary artery disease or heart failure. Its role in valvular heart disease, including its determinants and prognostic implications, remains unclear. The present study aimed to evaluate the prognostic significance of iron deficiency in patients undergoing valvular heart surgery.

Methods: Pre-operative haematology and iron profiles were retrospectively collected in all patients undergoing valvular heart surgery in Hong Kong between 2010 and 2021. Iron deficiency was defined referencing the ESC 2021 guidelines as a ferritin level <100 ng/mL or a transferrin saturation <20% with a ferritin level of 100 to 299 ng/mL. Logistic regression analyses were conducted to determine variables associated with guideline-defined iron deficiency. Stepwise Cox proportional hazards regression was applied to identify predictors of 5-year mortality. The impact of iron supplementation on outcomes was estimated in iron-deficient patients, modelled by inverse probability of treatment-weighted (IPTW) logistic regression.

Results: Our study included 578 patients; the median age was 62 (interquartile range 54-70) years, and 47.4% were males. Iron deficiency was present in 324 (56.1%) patients. Independent correlates of iron deficiency were age, male sex, diabetes mellitus, atrial fibrillation, heart failure, diuretics and warfarin use, aortic stenosis, and tricuspid regurgitation (all P<0.05). Death from any cause occurred in 99 patients over five years of follow-up, of which 45 were due to cardiovascular events. Iron deficiency was associated with a two- to three-fold excess risk of all-cause (hazard ratio [HR] 1.89, 95% CI 1.23-2.90; P=0.004) and cardiovascular mortality (HR 2.84, 95% CI 1.23-2.90; P=0.004). Results were consistent in multivariable models incorporating comorbidities, medications, type of valvular intervention, and cardiac surgery risk-scoring systems, even after adjustment for haemoglobin levels (HR 1.58, 95% CI 1.02-2.44; P=0.039 for all-cause mortality; HR 2.36, 95% CI 1.15-4.82; P=0.019 for cardiovascular mortality). For individual components of the guideline criteria, transferrin saturation <20% and ferritin <300 ng/mL were associated with worse all-cause and cardiovascular mortality. Among 324 patients with iron deficiency, 61 (18.8%) received iron supplementation before valvular surgery. Iron supplementation was associated with a 58% lower risk of death in multivariable models with IPTW (HR 0.42; 95% CI, 0.19-0.99; P=0.047).

Conclusion: Iron deficiency is associated with worse survival in patients undergoing valvular heart surgery. This elevated risk may be mitigated by iron supplementation before valvular surgery.

Prognostic implications of pulmonary vascular resistance based on echocardiography in patients undergoing tricuspid annuloplasty

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Introduction: Across the spectrum of left-sided valvular heart diseases, increased pulmonary artery pressure and pulmonary vascular resistance (PVR) portends worse clinical outcomes. The prognostic roles of PVR derived from echocardiography have not been investigated in patients undergoing concomitant tricuspid annuloplasty (TA) during left-sided valvular surgery.

Methods: Data of 235 TA patients (mean age: 63.8±9.3 years; 37.4% male) were obtained from a prospective registry to determine the impact of PVR on the composite outcome (including all-cause mortality and heart failure hospitalization). PVR was defined as the ratio of peak tricuspid regurgitation velocity to the time-velocity integral of the right ventricular outflow tract.

Results: Mean PVR was 2.06±0.78 WU and a threshold of 2 WU determined by spline curve was used to dichotomize the cohort. Compared to those with PVR<2WU, patients with increased PVR were older, had more male and higher EuroScore II. Higher tricuspid regurgitant volume and larger right ventricular dimensions were also observed in PVR≥2WU group. During a median follow-up of 5.2 (IQR 2.2-8.2) years, 56 adverse events occurred including 26 deaths and 30 heart failure. PVR≥2WU was independently associated with increasing risk of combined event on the multivariable Cox regression model (adjusting baseline variables, right ventricular dilation, tricuspid annular plane systolic excursion and EuroScoreII) (HR 3.15, 95% CI 1.74-5.70, P<0.001).

Conclusion: PVR measured on echocardiography is an independent determinant of clinical outcomes in patients received tricuspid annuloplasty. A further study investigating the pathophysiological mechanisms of PVR in the setting of functional tricuspid regurgitation is warranted.

Prognostic value of computational pressure-flow dynamics derived fractional flow reserve among non-ST-elevation myocardial infarction and unstable angina patients **46**

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Introduction: Computational pressure-flow dynamics derived fractional flow reserve (caFFR) is a novel index to assess the severity of coronary artery stenoses without requirement of invasive pressure wire and hyperaemic stimulus in fractional flow reserve (FFR) measurement. Non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) is the most and second most common acute coronary syndrome, respectively. The clinical value of caFFR in patients presenting with NSTEMI and UA has not been validated. The aim of this study is to investigate the prognostic value of caFFR among NSTEMI and UA patients.

Methods: A total of 1449 vessels in 483 patients that presented with NSTEMI or UA (mean age=67.0±12.3, 67.9% male) from Queen Mary Hospital, Hong Kong were analysed and caFFR was calculated for the vessels. Patients had undergone PCI according to the angiographic and clinical data available at the time. Vessels were said to be adherent to caFFR if ischemic vessels, defined by caFFR≤0.8 were treated with PCI and non-ischemic vessels, defined by caFFR>0.8 were not treated by PCI. Otherwise, they were considered non-adherent to caFFR. The primary endpoint was the vessel-oriented composite endpoint (VOCE), defined as vessel-related cardiovascular mortality, vessel-related myocardial infarction (MI) and unplanned revascularisation at median 4.4 years follow-up. Survival curves were constructed using Kaplan-Meier estimates and differences between groups were tested using the log-rank test. Cox proportional hazards model was used to evaluate the association of adherence-to-caFFR with the risk of VOCE, with parameters with P<0.1 upon univariate analysis entered into multivariable Cox model.

Results: Among the 1449 vessels, caFFR was analysable in 1020 (70.4%) vessels, with 801 (78.5%) vessels receiving treatment adherent to caFFR and 219 (21.5%) vessels receiving treatment non-adherent to caFFR. Adherent vessels had significantly lower incidence rates of VOCE (8.6% vs 17.4%; P<0.001), cardiovascular mortality (3.0% vs 7.3%, P=0.004) and MI (2.0% vs 9.1%, p<0.001) compared to non-adherent vessels. After multivariate adjustment, adherent vessels had a significantly lower risk than non-adherent vessels in terms of VOCE (HR 0.47; 95% CI 0.32-0.70; P<0.001), vessel-related cardiovascular mortality (HR 0.40; 95% CI 0.21-0.76; P=0.005) and vessel-related MI (HR 0.22; 95% CI 0.11-0.42; P<0.001).

Conclusion: In both NSTEMI and UA patients, revascularization adherent to caFFR guidelines significantly reduces the risk of VOCE. The findings support the potential use of caFFR in treatment guidance of NSTEMI and UA patients.

Proteomic profiling identifies biomarker signature for incident diabetic kidney disease **47**

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Objectives: Diabetic kidney disease (DKD) is one of the main causes of diabetes-related mortality. The ability of current serum creatinine-based renal function tests to stratify type 2 diabetes (T2D) patients with a high risk of developing DKD in early stage is limited. Here, we systematically profiled the Olink-based proteome to identify novel DKD prognostic biomarkers and construct a DKD risk prediction model among T2D patients.

Methods: Circulating concentrations of 357 proteins in 4 Olink panels (inflammation, immune response, cardiovascular disease, and metabolism) at baseline were analysed in a nested case-control study involving 132 incident DKD cases and 132 age, sex, estimated glomerular filtration rate (eGFR) and diabetes duration-matched non-DKD controls recruited from the Hong Kong West Diabetes Registry (HKWDR). Features that comprised the protein model were selected by Lasso regression, Boruta, support vector machine, and extreme gradient boosting. Stepwise selection was utilized to identify the best clinical model. Prognostic performance of the selected biomarkers was then evaluated. A similar case-control study nested within UK Biobank was conducted to independently validate the model performance.

Results: Among the 321 proteins that passed quality check, defined as those been detected in at least 75% of samples, 8 were identified as important predictors for incident DKD by at least 2 out of 3 of the machine learning methods. The baseline levels of the 8 proteins showed significant associations with the declining trajectory of eGFR observed in longitudinal data (linear mixed-effects model p<0.05). Subsequently, a model was constructed using the 8-protein panel to predict the onset of DKD. The model demonstrated strong prognostic performance, with annualized AUC values ranging from 0.77 to 0.85 within 10 years follow-up in the HKWDR. It was superior to the clinical model comprised of hemoglobin A1c (HbA1c) and systolic blood pressure (protein+clinical vs clinical AUC[95% CI]=0.87[0.83-0.92] vs 0.70[0.64-0.76]; DeLong p=2.18e-08). An acceptable AUC of 0.76 was yielded in the external validation cohort.

Conclusion: Eight proteins were identified as significant predictors of incident DKD in T2D patients. The baseline concentrations of these proteins demonstrated a strong correlation with eGFR trajectory during follow-up. A panel composed of these 8 proteins exhibited good performance for predicting DKD risk in both an Asian cohort and an independent validation cohort with diverse ethnic backgrounds.

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Real-world efficacy and safety of naltrexone-bupropion therapy in Chinese patients with obesity: a single-centre experience

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Introduction: Naltrexone-bupropion has shown efficacy and safety in large randomised controlled trials, predominantly consisting of Caucasians. Data are limited in the Asian populations. We carried out a retrospective case-control study of Chinese patients with obesity to evaluate the efficacy and safety of naltrexone-bupropion in real-world clinical practice.

Methods: We performed a retrospective case-control study of Chinese patients with obesity managed in the Obesity Clinic of Queen Mary Hospital in Hong Kong between December 2015 and December 2021. Electronic health records of patients treated with naltrexone-bupropion were retrieved for body weight, height and hip circumference, obesity-related metabolic parameters including glycated haemoglobin, lipid profile and liver enzymes, and adverse events over a 12-month period. Additionally, patients were invited to undergo vibration-controlled transient elastography (VCTE) at baseline and 12 months for controlled attenuation parameter (CAP) and liver stiffness (LS) measurements for assessment of non-alcoholic fatty liver disease. Age- and sex-matched controls from the Obesity Clinic who were on self-directed lifestyle management only were identified for comparison of weight changes. General linear models were used to analyse the change in body weight over 12 months.

Results: Thirty-seven patients treated with naltrexone-bupropion were included (mean age 42.2±8.4 years, 54.1% men, baseline body mass index 37.3±4.6 kg/m2), with their characteristics comparable with the 37 age- and sex-matched controls. Among the 37 naltrexone-bupropion-treated patients, 18 (48.6%) and 13 (35.1%) of them continued treatment by 6 months and 12 months. They achieved mean weight loss of 9.2±5.2% at 6 months and 9.7±8.1% at 12 months, significantly more than the controls ($p<0.001$). When expressed in percentage of body weight lost, the naltrexone-bupropion treatment group achieved a mean of around 25% at 6 months and 28% at 12 months. There were concomitant improvements in the obesity-related parameters over 12 months, namely glycated haemoglobin ($p=0.044$), low-density lipoprotein ($p=0.048$), alanine transaminase ($p=0.024$) and aspartate transaminase levels ($p=0.017$). For patients who had undergone VCTE, there was also a statistically significant decrease in CAP ($p=0.008$) and LS ($p=0.013$) measurements. Ten patients (27.0%) discontinued naltrexone-bupropion due to side effects such as neurological and gastrointestinal manifestations, all within the first 12 months.

Conclusion: We demonstrated the real-world efficacy and safety of naltrexone-bupropion among Chinese patients with obesity.

Recapitulating and repairing STAT1 gain-of-function using patient-derived expanded potential stem cells: a proof-of-concept of using a personalized stem cell platform to study inborn errors of immunity

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Introduction: Inborn errors of immunity (IEI) often lack specific disease models and personalized management. Signal transducer and activator of transcription (STAT)-1 gain-of-function (GoF) is such example of an IEI with diverse clinical phenotype with unclear pathomechanisms and unpredictable response to therapy. Limitations in obtaining fresh samples for functional testing and research further highlights the need for patient-specific *ex-vivo* platforms. Using STAT1-GoF as an example IEI, we investigated the potential of patient-derived expanded potential stem cells (EPSC) as an *ex-vivo* platform for disease modelling and personalized treatment.

Methods: We generated EPSC derived from individual STAT1-GoF patients. *STAT1* mutations were confirmed with Sanger sequencing. Functional testing including STAT1 phosphorylation/ dephosphorylation and gene expression with or without Janus-kinase inhibitors (JAKi) were performed. Functional tests were repeated on EPSC lines with GoF mutations repaired by CRISPR/Cas9 editing.

Results: EPSC were successfully reprogrammed from STAT1-GoF patients and expressed the same pluripotent makers as controls, with distinct morphological differences. Patient-derived EPSC recapitulated the functional abnormalities of index STAT1-GoF patients with STAT1 hyperphosphorylation and increased expression of *STAT1* and its downstream genes (*IRF1, APOL6,* and *OAS1)* following IFN-gamma stimulation. Addition of ruxolitinib and baricitinib inhibited STAT1 hyperactivation in STAT1-GoF EPSC in a dose-dependent manner, which was not observed with tofacitinib. Corrected STAT1 phosphorylation and downstream gene expression were observed among repaired STAT1-GoF EPSC cell lines.

Conclusion: This proof-of-concept study demonstrates the potential of our patient-derived EPSC platform toward modelling STAT1-GoF. We propose this platform toward researching, recapitulating and repairing other IEI in the future.

Respiratory assessment of chronic lung disease patients using electrical impedance tomography, spirometry, and computational tomography **50**

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Introduction: Electrical impedance tomography (EIT) is a radiation-free and non-invasive biomedical imaging modality. EIT can provide lung function assessment owing to its relatively high frame rate as well as structural lung assessment by virtue of its dynamic tomographic images. Yet, the literature lacks comparison between EIT and gold standard lung assessment modalities such as Spirometry and CT. Here, we aim to compare the results from EIT, spirometry and CT scans in order to evaluate the diagnostic screening capacity of EIT.

Methods: Simultaneous EIT and spirometry measurements were performed on N=88 subjects of whom 47 had respiratory disorders including ILD (N=13), asthma (N=10), COPD (N=8), bronchiectasis (N=8), and others (N=8) such as pneumonectomy, lung tumor, lymphangioleiomyomatosis, motor neuron disease, heart failure, myopathy, and bronchiolitis obliterans syndrome. CT scans available for 20 subjects were collected and analysed. EIT measurements are combined with subject's anthropometric to compute the global spirometry indicators and the regional amplitude mapping [1].

Results: EIT-derived spirometry indicators are significantly correlated with spirometry indicators with a Pearson correlation coefficient (ρ) of 0.73 ($p<0.001$) for FVC, 0.71 ($p<0.001$) for FEV1 and 0.55 ($p<0.001$) for FEV1/FVC. Regional EIT amplitude mapping qualitatively showed consistency with the CT scans. For instance, a structural deterioration observed in the CT scan of one patient with pneumonectomy and one patient with COPD were also observed in EIT amplitude mapping.

Conclusion: EIT shows consistency with gold standard lung assessment modalities, hence it has potential diagnostic screening capabilities of lung diseases.

Risks of incident major osteoporotic fractures following SARS-CoV-2 infection among older individuals: a population-based cohort study in Hong Kong **51**

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Introduction: There is a lack of population-based epidemiological studies on the risk of fractures in the post-acute phase of COVID-19 infection among older adults. We performed a retrospective population-based propensity-score matched cohort study in Hong Kong to examine the risk of incident major osteoporotic fractures following COVID-19 infection among individuals aged ≥50 years, compared to individuals without COVID-19.

Methods: This was a retrospective, propensity-score matched, population-based cohort study of COVID-19 patients and non-COVID individuals identified from the electronic database of the Hong Kong Hospital Authority from January 2020 to March 2022. The primary outcome was a composite of major osteoporotic fractures (hip, clinical vertebral, and upper limb). COVID-19 patients were 1:1 matched to controls using propensity-score according to age, sex, vaccination status, medical comorbidities and baseline medications. To enhance the robustness of our results, we assessed the association between COVID-19 and a negative control outcome (diseases of sebaceous glands). Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models.

Results: In total, 429,459 COVID-19 patients were included, 1:1 matched to non-COVID individuals. Upon median follow-up of 11 months, COVID-19 patients had higher risks of major osteoporotic fractures (5.08 vs 3.95 per 1000 persons; HR 1.22, 95% CI 1.15-1.31), hip fractures (2.71 vs 1.94; HR 1.33, 95% CI 1.22-1.46), clinical vertebral fracture (0.42 vs 0.31; HR 1.29, 95% CI 1.03-1.62) and fall (13.83 vs 10.36; HR 1.28, 95% CI 1.23-1.33). Subgroup analyses for major osteoporosis fractures revealed no significant interaction by age, sex, presence of diabetes, vaccination status and the periods of COVID-19 pandemic. We observed a significantly higher risk of major osteoporosis and hip fractures in the dexamethasone-treated group (HR=1.36, 95% CI 1.07-1.74, p=0.012). In line with a priori expectation, there was no relationship between COVID-19 and the negative control outcome (HR=1.07, 95% CI 0.93-1.23, p=0.348). When specifically evaluating the acute (within 30 days) and post-acute phases (beyond 30 days) following SARS-CoV-2 infection, we consistently observed a significant increase in the risks of fractures and falls.

Conclusion: Our study demonstrated increased risk of major osteoporotic fractures following SARS-CoV-2 infection both in acute and post-acute phase among older adults. The increased risk of fall following SARS-CoV-2 infection could contribute to the increase in fracture risk. Our results would call for clinicians' awareness of musculoskeletal health of COVID-19 survivors. Further studies with longer follow-up and on the bone density of COVID-19 survivors are warranted.

Risks of stroke, its subtypes and atrial fibrillation associated with glucagon-like peptide 1 receptor agonists versus sodium-glucose cotransporter 2 inhibitors: A real-world population-based cohort study in Hong Kong

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Introduction: There are limited data on head-to-head comparative risk of stroke between sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RA). We compared risk of stroke with its subtypes and incident atrial fibrillation (AF) between them.

Methods: A population-based, retrospective cohort of patients with type 2 diabetes between 2008 and 2020 were identified from the electronic health records of Hong Kong Hospital Authority. The index date of each patient was set at the date of SGLT2i or GLP-1RA initiation. Patients who were aged <18 years, had end-stage kidney disease (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73m^2, dialysis or kidney transplantation) on or before the index date, or had co-initiation of SGLT2i and GLP-1RA at index date were excluded from the study. Patients who received SGLT2i or GLP-1RA were matched pairwise by propensity score for demographics, clinical parameters, comorbidities, and baseline use of medications. The primary outcome was all events of stroke, consisting of hemorrhagic and ischemic stroke. Secondary outcomes included hemorrhagic stroke, ischemic stroke, incident AF, and cardioembolic stroke. All included patients were observed from the index date until (i) the occurrence of events; (ii) death; (iii) addition or switching of treatments to another study exposures; or (iv) the date of the end of study 31 December 2020), whichever was earlier. Risks of stroke and AF were evaluated by hazard ratios (HRs) from the Cox proportional hazard regression models.

Results: A total of 5840 patients (2920 SGLT2i users; 2920 GLP-1RA users) were included (mean age 55.5 years, 56.1% men, mean HbA1c 8.9% and duration of diabetes 13.7 years). Upon median follow-up of 17 months, there were 111 (1.9%) events of stroke (SGLT2i: 62, 2.1%; GLP-1RA: 49 1.7%). SGLT2i users had comparable risk of all stroke as GLP-1RA users (HR 1.46, 95% CI 0.99-2.17, p=0.058). SGLT2i users had higher risk of ischemic stroke (HR 1.53, 95% CI 1.01-2.33, p=0.044) but similar risk of hemorrhagic stroke compared to GLP-1RA users. Although SGLT2i was associated with lower risk of incident AF (HR 0.43, 95% CI 0.23-0.79, p=0.006), risk of cardioembolic stroke was similar.

Conclusion: Our real-world study demonstrated that GLP-1RA use was associated with lower risk of ischemic stroke, despite the association between SGLT2i use and lower risk of incident AF. There was no significant difference in hemorrhagic stroke risk. GLP-1RA may be the preferred agent for patients with type 2 diabetes at risk of ischemic stroke.

Single-cell atlas of the peripheral cytotoxic lymphocytes immune characteristics associated with HBsAg seroclearance in CHB patients

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Introduction: Chronic hepatitis B (CHB) is a major global health concern due to its association with significant liver-related morbidity and mortality. HBsAg seroclearance represents a primary endpoint in antiviral treatment for CHB. Investigating peripheral immune characteristics in the context of HBsAg seroclearance is essential for understanding the pathophysiological mechanisms underlying recovery from chronic viral infections and informing the development of novel therapeutic strategies.

Methods: We recruited four patients with a history of CHB, including two with documented spontaneous HBsAg seroclearance and two HBeAg-negative treatment-naïve patients as controls. Peripheral blood mononuclear cells (PBMCs) from these patients were subjected to single-cell RNA sequencing (scRNA-seq), yielding an UMI count expression matrix of 36,601 genes across 57,506 cells. Dimensionality reduction and clustering were performed using principal component analysis (PCA), UMAP, and the graph-based clustering with Louvain algorithm. Differentially expressed genes were identified using the Wilcoxon rank-sum test, and cell types were annotated using SingleR and fgsea. Focused analysis on T and NK cell compartment led to the identification of distinct cell clusters, including NK/NKT cells, effector CD8+ T cells, central memory CD8+ T cells, and CD4+ T cells. Cytotoxic lymphocytes (NK/NKT cells, effector CD8+ T cells, central memory CD8+ T) were further analyzed for differential gene expression between cases and controls using Wilcoxon rank-sum test.

Results: The pro-inflammatory cytokine CCL3 was found to be upregulated in cytotoxic lymphocytes from the case group, while genes associated with T cell receptor function (TRGC2, CD8A, and CD8B) were downregulated. Analysis of CD16+ (NK cells) and CD3+ (T cells) subsets revealed a significant reduction in CD3+ CD16+ cells (NKT cells) in the peripheral immune system of recovered patients. Focusing on the central memory CD8+ T cells, we also find upregulation of HLA-DRB1, HLA-DRA, and ERAP2k, suggesting improved antigen processing and presentation capabilities.

Conclusion: Our findings suggest that a more efficient and responsive immune system contributes to the successful elimination of CHB infection. Recovery of NK cell-mediated cytotoxicity may indicate reduced HBsAg-mediated inhibition of NK cell activity. Additionally, the decreased presence of NKT cells in recovered patients suggests a diminished requirement for immunomodulation following successful viral clearance. The direct elimination of virally infected cells from CD8+ T cells and NK cells was recovered.

The association of diabetes mellitus control with outcomes of intracerebral haemorrhage

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Background: Various epidemiological studies on diabetes mellitus [DM] and intracerebral haemorrhage [ICH] have demonstrated conflicting conclusions on their association. Considering DM is a prevalent and manageable disease in Hong Kong, we aimed to study the association between the outcome of ICH and DM, including DM control and use of insulin sensitizer.

Methods: We performed a retrospective analysis of consecutive primary ICH patients recruited to the University of Hong Kong's stroke registry from 2011-2018. Patients with premorbid modified Rankin scale (mRS) >2 were excluded. The primary outcomes were 6-month mortality and poor outcome (mRS 4-6). Inadequately controlled DM was defined as admission HbA1c of >7%. Pre-ICH insulin sensitizer use included use of metformin and thiazolidinedione. The associations between DM and ICH outcomes were determined using multivariate logistic regression, and subgroup analysis among DM patients for DM medication and ICH outcome was performed.

Results: 653 ICH patients were identified, of which 158 (24.2%) had DM. Compared to non-DM patients, DM patients had a higher rate of poor outcome after ICH (52.5% vs. 42.0%, p=0.021), but the 6-month mortality rate was similar (27.8% vs. 26.1%, p=0.658). Although DM was not associated with 6-month mortality risk (adjusted odd ratio [AOR] 1.03, 95% confidence interval [CI] 0.53-2.91, p=0.935), DM patients had a higher risk of poor outcome after ICH (AOR 2.13, 95% CI 1.24-3.65, p=0.006). The risk was explicitly observed in patients with inadequately controlled DM (AOR 2.36, 95% CI 1.12-4.98, p=0.025). In subgroup analysis, pre-ICH use of insulin sensitizer was independently associated with a lower risk of mortality (AHR 0.10, 95% CI 0.02-0.66, p=0.017) but not poor outcome (AHR 0.88, 95% CI 0.31-2.46, p=0.805), and it remained significant even after adding eGFR <30 into the model.

Conclusion: DM, especially inadequately controlled DM, were associated with poor outcome in ICH. Pre-ICH insulin sensitizer use reduced mortality risk. Adequate glycaemic control of DM and use of insulin sensitizer could potentially improve outcome of ICH in DM patients.

The Hong Kong Drug Allergy Delabelling Initiative: a multicentre, territory wide implementation of penicillin allergy delabelling by non-allergist

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Introduction: Penicillin allergies are prevalent but are largely over-diagnosed. To overcome the magnitude of penicillin labels and the lack of specialists, there is increasing interest for non-allergists to perform allergy testing in low-risk cases. Under the Hong Kong Drug Allergy Delabelling Initiative (HK-DADI), a multidisciplinary team consisting of the allergists and non-allergists corroborated on a set of consensus statements for allergy testing by non-allergists for low-risk penicillin allergies. HK-DADI have previously demonstrated the safety and effectiveness of a nurse-led, protocol-driven evaluation in penicillin allergy delabelling. To assess the role of non-allergists in the implementation of HK-DADI, a "Hub-and-Spokes" model was adopted whereby nurses triaged patients with penicillin allergies into low-risk and non-low risk. Low-risk cases were seen at a nurse-led clinic, with either an allergist on site at the "Hub", or a non-allergist at a "Spoke". The aim was to compare the effectiveness and safety of penicillin delabelling under this model.

Methods: A multicentre, cross-sectional study was conducted at four tertiary hospitals (one Hub and three Spokes) in Hong Kong. Patients triaged into low-risk penicillin allergies underwent complete allergological workup. Demographics and clinical outcomes were compared between the Hub-and-Spokes.

Results: Among 244 patients with penicillin allergy labels, 228 (93.4%) completed workup; 75 (32.9%) from the Hub and 153 (67.1%) from the Spoke. Only fourteen (6.1%) patients were diagnosed with a genuine penicillin allergy. Delabelling rates of Hub and Spokes were similar (94.7% vs 94.1%, p=0.867). The duration of carrying an allergy label were similar between the Hub-and-Spokes (10.4±5.7 vs 8.9±7.2 years, p=0.278, respectively). No patients developed severe or systemic reactions during evaluation. On multivariate analysis, patients assessed at the Spokes had more concomitant drug allergies (76.0% vs 36.6%, p<0.013), encountered more difficulties in prescription of antibiotics (86.7% vs 39.9%, p<0.001) and required more clinic attendances (2.07±0.71 vs 1.15±0.40, p<0.001) compared to the Hub. Duration between referral and first consultation (i.e., clinic waiting time) was significantly shorter at the Spokes compared with Hub (0.67 vs 15.7 months, p>0.001).

Conclusion: The HK-DADI Hub-and-Spokes model proved penicillin allergy delabelling to be safe and effective, with comparable outcomes between non-allergists and allergist. This robust model should be adopted in low-risk cases as it safely mitigated the need for all drug allergy assessments to be carried out by an allergist and significantly cut specialist clinic waiting time.

The impact of bronchiectasis and its severity on long-term renal outcomes

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Introduction: Bronchiectasis, characterized by chronic airway and systemic inflammation, is associated with adverse cardiovascular outcomes; but data regarding its impact on long-term renal outcomes is lacking.

Methods: We reviewed all bronchiectasis patients who were followed at Queen Mary Hospital (QMH) in 2017 and examined their clinical/renal outcomes in the subsequent five years. The relationships between severity of bronchiectasis (as defined by FACED scores) and adverse renal outcomes were evaluated.

Results: Three hundred and fifteen bronchiectasis patients were included [162 (49.1%), 108 (34.3%) and 45 (14.3%) patients with mild, moderate, and severe bronchiectasis respectively. Seventy-five patients (23.8%) showed renal progression. Baseline FACED score showed a positive correlation with renal progression over 5 years of follow up [adjusted odds ratio (aOR) 1.277 (95% CI 1.041-1.566), p=0.019]. Patients with moderate-to-severe bronchiectasis (FACED score ≥3) showed an increased risk of renal progression [aOR of 1.891 (95% CI 1.059-3.377), p=0.031] and more rapid eGFR decline than those with mild disease (-4.77±4.19 mL/min/1.73m2/year vs. -3.49±3.94 mL/min/1.73m2/year, p=0.006). Patients who developed renal progression had higher risk of death [adjusted hazard ratio (aHR) 2.545 (95% CI 1.159-5.588), p=0.020] and subsequent rates of hospitalization (1.56 ± 2.81 episodes/year vs. 0.60 ± 1.18 episodes/year; p<0.001) compared to those without renal progression.

Conclusion: Progressive renal function deterioration is prevalent amongst bronchiectasis patients, and the severity of bronchiectasis is a robust predictor for renal progression. Bronchiectasis patients with renal progression showed increased risk of mortality and higher subsequent rates of hospitalization.

The pathogenic role of Complement 5a/Complement 5a receptor axis in AKI-to-CKD transition

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Introduction: Activation of Complement 5a/Complement 5a receptor (C5a/C5aR) axis contributes to the pathogenesis of acute kidney injury (AKI). However, whether it plays a role in the transition to chronic kidney disease (CKD) after AKI remains unclear. In this study, we investigated the chronic effects of bilateral ischemia-reperfusion injury on C5aR deficient mice and dissected C5aR-dependent mechanisms during AKI-to-CKD transition.

Methods: Wild type $C5aR^{+/+}$ and knockout $C5aR^{-/-}$ mice were subjected to bilateral ischemia and sacrificed at day 3 and 7 after reperfusion. Kidney damage was assessed by evaluating kidney function, histopathological changes and expression levels of pro-inflammatory, fibrotic, oxidative and injury markers.

Results: Compared to the $C5aR^{+/+}$ controls, $C5aR^{-/-}$ mice showed significant decrease in serum creatinine and reduced expressions of Kim1 and Ngal in both the 3-day and 7-day BIRI models. The improvement in kidney injury in BIRI $C5aR^{-/-}$ mice was further confirmed by PAS staining. The expression levels of MCP-1, TNF-alpha, IL-6 and IL-1b were significantly decreased in $C5aR^{-/-}$ mice after BIRI. In particular, there was decreased infiltration of M1 macrophages with an increase in M2 macrophage number in $C5aR^{-/-}$ mice on day 7 after reperfusion. Sirius red and Masson Trichrome staining demonstrated a progressive development of interstitial fibrosis in $C5aR^{+/+}$ mice after BIRI, which were suppressed in $C5aR^{-/-}$ mice with less deposition of collagen 1 and collagen 3 in the post-ischemic kidneys. Moreover, the oxidative stress markers NOX2 and 8-OHdG were significantly reduced in $C5aR^{-/-}$ mice after BIRI.

Conclusion: C5aR deficiency protected mice from kidney inflammation and fibrosis by reducing oxidative stress during AKI-to-CKD transition.

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The potential role of L-Arginine in the management of type 2 diabetes: from clinical discovery to molecular mechanism **58**

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Introduction: Type 2 diabetes (T2D), characterized by hyperglycemia, is a chronic disease that primarily results from insulin resistance and relative insulin deficiency. Improper management of T2D can lead to serious complications. Therefore, early diagnosis of T2D and development of novel therapeutic targets for T2D are imperative. L-Arginine is a semi-essential amino acid that involved in the synthesis of proteins, urea, and nitric oxide. Cumulating clinical and experimental evidences have shown that L-Arginine supplementation can reduce obesity, improve insulin sensitivity and restore glucose homeostasis. However, it is still controversial whether L-Arginine can be used as a nutrient supplement to prevent and/or relieve T2D.

Methods: Untargeted metabolomics profiling of a discovery cohort including plasma samples of 178 Chinese subjects (59 lean subjects, BMI≤24 kg/m^2; 60 obese non-diabetic and 59 obese diabetic subjects, BMI≥30 kg/m^2) were conducted to determine the association between circulating L-Arginine level and T2D. Adipocyte-specific MDM2 KO (Adipo-MDM2 KO) mice and their wild-type (WT) littermates were supplemented with L-Arginine in drinking water (6 g/L) to assess the impact of L-Arginine supplementation on glucose and systemic metabolism. Arginase activity in serum and liver was measured using a colorimetric Arginase Activity Assay Kit (Sigma-Aldrich).

Results: Metabolomics analyses showed that the circulating level of L-Arginine was significantly decreased in obese diabetic subjects, while ornithine (the direct downstream product of L-Arginine) was markedly increased in both obese non-diabetic and obese diabetic subjects compared to the lean controls. Consistent with the findings in obese diabetic subjects, the lipodystrophic mouse model Adipo-MDM2 KO mice with severe hyperglycemia and hyperlipidemia displayed dramatically lower serum level of L-Arginine and higher level of ornithine than their WT controls. Transplantation of subcutaneous white adipose tissue into Adipo-MDM2 KO mice could significantly reverse the lower L-Arginine and higher ornithine levels, accompanied by alleviated hyperglycemia and hyperlipidemia. L-Arginine supplementation could largely improve feeding glucose level, glucose tolerance, insulin sensitivity and gluconeogenesis in Adipo-MDM2 KO mice. Mechanistically, arginase activity was significantly upregulated in the serum but downregulated in the liver of Adipo-MDM2 KO mice, suggesting the potential leakage of arginase from liver to the circulation, where the circulating L-Arginine was rapidly degraded.

Conclusion: Circulating L-Arginine level, as controlled by arginase activity in the circulation, is negatively associated with the incidence of T2D in both human and mice. L-Arginine supplementation could be an inexpensive alternative way to prevent or alleviate T2D.

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The utility of an amplicon-based liquid biopsy platform for metastatic carcinoma: 4-year experience at a tertiary oncology center in Hong Kong

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Introduction: Next generation sequencing-based tumor molecular profiling (MP) is an important tool to personalize oncological therapy. While this can be performed on tumor tissue, the capture and interrogation of circulating tumor DNA (ctDNA) by liquid biopsy (LB) have gained momentum in recent years. FDA-approved assays such as the Guardant-360 enable targeted-therapy identification, real time treatment response monitoring, and subclinical disease detection while overcoming the difficulties of limited tissue availability. There is little knowledge how LB contributes to cancer care in Asia, specifically in the translation of actionable mutations to therapy.

Methods: To investigate the utility of a Medicare-covered amplicon-based LB platform in patients with advanced carcinomas, we analyzed the clinical and molecular findings of 54 consecutive patients who underwent a commercial ctDNA assay covering 80 cancer related genes, 10 fusions, and 6 microsatellite loci between September 2019 and November 2023 (Lucence HALLMARK v.4). Clinical data were obtained from an electronic clinical management system while molecular findings from test reports were validated by 2 independent investigators.

Results: Between 2019 and 2023, 54 patients (33 women and 21 men) with metastatic carcinoma underwent one or more LB at a median of 63.5 years (range 35-88). 1 patient each with cholangiocarcinoma and colorectal carcinoma repeated testing on separate occasions, leading to 56 LB samples in total. Cholangiocarcinoma (n=16, 28.6%), non-small cell lung cancer (n=12, 21.4%), pancreatic cancer (n=7, 12.5%), breast cancer (n=5, 8.9%), and hepatocellular carcinoma (n=4, 7.1%) were common tumors in the cohort. Of 147 molecular alterations, 103 (70.1%) and 13 were missense and frameshift (8.8%) mutations respectively. 13 tests reported no alterations. Commonly mutated genes included TP53 (n=37), EGFR (n=13), BRCA2 (n=13), MAP2K1 (n=11), APC (n=9), KRAS (n=9), NRAS (n=9), BRAF (n=5), CDKN2A (n=5), and CTNNB1 (n=4). All patients had microsatellite stable phenotype. Importantly, one or more FDA-approved targeted therapies specific to tumor type were found in 16 cases (28.6%), of which 8 (50%) were not used in prior treatments. One biliary cancer patient who progressed on 2 prior chemotherapy regimens had sustained partial response to combination BRAF and MEK inhibition for 8 months before retesting at progression showed features suggestive of clonal evolution. Incidentally, suspected germline BRCA1/BRCA2 variants of unknown significance were found in melanomas and cholangiocarcinomas.

Conclusion: Our LB series with diverse tumor types showcase the broad clinical utility of LB in metastatic carcinomas. We report a 28.6% pickup rate for FDA-approved therapies and reveal clonal evolution and molecular mechanisms of treatment resistance.

Therapeutic targeting of cancer-associated fibroblasts prevents regional lymphatic spread in non-small cell lung cancer (NSCLC)

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Introduction: Cancer-associated fibroblasts (CAFs) represent a pivotal component within the milieu of the tumor microenvironment. Yet, the biological function of lung CAFs, particularly in the context of tumor lymphangiogenesis and regional lymph node metastasis in non-small cell lung cancer (NSCLC), remains unknown. Our study endeavors to address this critical knowledge gap, employing an orthotopic xenograft model as an investigative tool.

Methods: The experimental design entailed the inoculation of NSCLC cells, both in the presence and absence of lung CAFs, into the left lung of nude mice to establish an orthotopic xenograft model. This model was leveraged for the purpose of assessing tumor lymphangiogenesis and mediastinal lymph node metastasis. Concurrently, micro-computed tomography (CT) was employed to monitor tumor formation and size over the course of the study. Furthermore, the administration of an inhibitor targeting CAFs (ABT-199) (Bcl inhibitor) via oral gavage was carried out, allowing for a comparative analysis with control groups.

Results: Inoculation of cancer cells in conjunction with lung CAFs yielded the successful development of desmoplastic and lymphangiogenic lung tumors within the left lung of nude mice. Notably, these tumors exhibited heightened peritumoral lymphangiogenesis and an augmented incidence of mediastinal lymph node metastasis when compared to tumors derived from NSCLC cells alone. The administration of ABT-199 yielded a discernible reduction in lung CAFs, subsequently mitigating tumor-associated lymphangiogenesis and mediastinal lymph node metastasis.

Conclusion: Lung CAFs promote lymphangiogenesis and facilitate regional lymph node metastasis. Our study posits that ABT-199, as therapeutic agents targeting lung CAFs, hold promise in the suppression of NSCLC mediastinal lymph node metastasis, thus offering potential avenues for clinical exploration and intervention.

Ticagrelor was associated with lower fracture risk than clopidogrel in the dual anti-platelet regimen among patients with acute coronary syndrome treated with percutaneous coronary intervention

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Introduction: Patients with coronary artery disease have increased fracture risks. P2Y12 inhibitors may impact on fracture risks by reducing osteoblastic activity and new bone formation. We compared the fracture risks associated with ticagrelor and clopidogrel in the dual antiplatelet therapy (DAPT).

Methods: We identified all adults who underwent first-ever percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) between 2010 and 2017 from a territory-wide PCI registry in Hong Kong. Following 1:1 propensity-score matching for baseline characteristics, patients were followed up till event occurrence, death, or 30 June 2022. Outcomes of interest were major osteoporotic fractures (MOF) identified by validated ICD-9-CM codes. Cox proportional hazards regression was used to compute the hazard ratio (HR) for MOF associated with ticagrelor versus clopidogrel use.

Results: 3,018 ticagrelor users and 3,018 clopidogrel users were identified after propensity-score matching (mean age: 61.4 years; 84.1% men). Upon median follow-up of 6.5 years, 59 ticagrelor users and 119 clopidogrel users sustained MOF (annualized fracture risks: 0.34% and 0.56%, respectively). Ticagrelor use was associated with lower risks of MOF (HR 0.60, 95% CI 0.44-0.83; p=0.002). Consistent HRs were observed for fractures over vertebrae, hip and upper limbs. Subgroup analyses showed no interaction according to age, sex, presence of diabetes, presence of chronic kidney disease and prior fracture history.

Conclusion: Among adults who underwent first-ever PCI for ACS, ticagrelor use in the DAPT was associated with a lower risk of MOF compared with clopidogrel. Our results support the use of ticagrelor in the DAPT from the perspective of bone health.

Translocator protein (TSPO) mediates tubulointerstitial fibrosis and kidney inflammation after unilateral ureteral obstruction

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Introduction: Tubulointerstitial fibrosis is a hallmark of chronic kidney disease (CKD) and predicts progression to kidney failure. A better understanding of its pathogenetic mechanisms is required for designing novel and effective treatments for this irreversible pathological process. Translocator protein (TSPO), located on the outer mitochondrial membrane, is associated with renal tubular cell death and regeneration in acute kidney injury. However, the role of TSPO in progressive CKD remains unknown.

Methods: Unilateral ureteral obstruction (UUO) or sham operation were performed on C57BL/6J mice to establish progressive tubulointerstitial fibrosis. TSPO antagonist PK11195 or vehicle was administrated daily to UUO mice for 7 days starting on the day of surgery. Kidneys were harvested for histology, inflammation and fibrosis.

Results: Histopathologically, tubular damage induced by UUO was reversed by PK11195 treatment. Induction of TNF-alpha, CCL-2 and IL-1beta mRNA in the UUO kidney was reduced in PK11195 group compared to vehicle control. UUO-induced collagen deposition, as demonstrated by Masson's Trichrome and Picrosirius Red staining, was decreased after PK11195 treatment, and immunohistochemical analysis further confirmed significant reduction of Col-1 and Col-3 expression. Furthermore, PK11195 treatment downregulated UUO-induced fibronectin, alpha-SMA, vimentin and TGF-beta levels by Western blotting.

Conclusion: We provided novel data to show that blockade of TSPO activity could alleviate kidney fibrosis and inflammation in murine UUO, suggesting that TSPO could play an important role in regulating progressive kidney disease.

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Triple anti-hypertensive medication prediction after intracerebral hemorrhage (The TRICH Score) 63

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Background: Most intracerebral hemorrhage (ICH) survivors have uncontrolled hypertension, which leads to elevated long-term cardiac and cerebrovascular risk. As many ICH survivors require ≥3 anti-hypertensive medications for blood pressure (BP) control, upfront triple anti-hypertensive medication in ICH survivors would improve therapeutic inertia and consequent better BP control. However, excessive BP lowering with triple anti-hypertensive remains a concern, especially in older people. Hence, we aim to develop and test a score to predict the need for ≥3 anti-hypertensive for BP control three months post-ICH.

Methods: We analyzed consecutive ICH survivors admitted from 2011-2020 who were enrolled in the prospective HKU stroke registry. Clinic BP record and the number of antihypertensive agents prescribed three months post-ICH were reviewed. Patients with uncontrolled hypertension (systolic BP >130mmHg) while on <3 antihypertensive were considered undertreated and excluded. Baseline predictors of the need for ≥3 antihypertensive agents were derived using multivariate logistic regression, and a prediction score (TRICH score) was created based on the beta coefficients.

Results: At three months post-ICH, 43.7% (181/414) of patients were prescribed ≥3 antihypertensive medications. Age <60 (adjusted odds ratio (aOR) 1.72, 95% confidence interval (CI) 1.10-2.69), higher admission systolic BP (190-220mmHg: aOR 2.38, 95% CI 1.50-3.76; >220mmHg: aOR 4.19, 95% CI 2.08-8.44), male sex (aOR 2.38, 95% CI 1.51-3.75) and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73^2 (aOR 2.19, 95% CI 1.23-3.88) were independently associated with the need for ≥3 antihypertensives. The 5-point TRICH score (1 point for age <60, 1 point for male, 1 point for eGFR <60 mL/min/1.73^2, 1 point for systolic BP 190-220mmHg, and 2 points for >220mmHg) has a c statistic of 0.70. A dichotomized score (TRICH score ≥2) predicts the need for ≥3 antihypertensive with 0.69 sensitivity and 0.66 specificity.

Conclusion: TRICH score had good discrimination ability, yet a larger sample size would likely improve its strength. Further study and validation of the TRICH score would be helpful for generalizability.

Vitamin D deficiency in older adults living in residential care homes in Hong Kong 64

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Introduction: Currently, about six percent of older adults in Hong Kong are living in the residential care homes (RCHEs). These elderly are susceptible to vitamin D deficiency due to decreased synthesis from skin, decreased dietary intake and limited sunlight exposure. Vitamin D deficiency was associated with increased risk of frailty, sarcopenia, falls, fractures, dementia and infection. There is no local study on vitamin D deficiency in this population to date.

Methods: Most Hong Kong West Cluster RCHE residents were under the care of the Hong Kong West Cluster Community Geriatric Assessment Team (HKW CGAT). Serum essay of vitamin D (total 25OH-D) was performed by HKW CGAT if these residents showed risks or clinical features (e.g. falls, frailty, sarcopenia or history of fractures) of vitamin D deficiency. A retrospective review of their laboratory and clinical data was performed.

Results: 381 RCHE residents were tested for 25OH-D from May 2022 to April 2023. They had a mean age of 83.6 years and 205 (53.8%) were females, and the mean length of stay in RCHEs was 19.4 months. Their mean 25(OH)D level was 51nmol/L. 204 (53.5%) residents had vitamin D deficiency (25OH-D <50nmol/L). Among them, 47.8%, 42.5% and 9.7% had mild (30-49nmol/L), moderate (12.5-29nmol/L) and severe deficiency (<12.5-29nmol/L) respectively. Alkaline phosphatase (ALP) was significantly higher, while adjusted calcium and phosphate level were significantly lower in the vitamin D deficient group when compared with the sufficient group. Multivariate analysis showed male gender (odds ratio 1.2, 95% CI:1.08 to 2.6, p=0.03) and not on vitamin D (calcichew D3, vitamin D3 or daily 1 plus) replacement (Odds ratio 45.8, 95% CI: 13.8 to 152, p<0.001) were significant risk factors of vitamin D deficiency.

Conclusion: Vitamin D deficiency is common in RCHE residents. Targeted testing of 25OH-D levels for those with clinical features and risk factors was useful in identifying those with vitamin D deficiency. Replacement by usual preparations of vitamin D can maintain the serum vitamin D level within the normal range. Further study is needed to examine the prevalence and clinical impact of vitamin D deficiency in this vulnerable group.

Acknowledgement

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MSD

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Reference: 1. molnupiravir US EUA Product Insert.

MOLNUPIRAVIR Selected Safety Information

Authorized Use

1. Molnupiravir is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults:
   - with positive results of direct SARS-CoV-2 viral testing, and
   - who are at high risk for progression to severe COVID-19, including hospitalization or death, and
   - for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate
2. Molnupiravir is not approved for any use, including the treatment of COVID-19, but is authorized for emergency use by the FDA under an Emergency Use Authorization (EUA).
3. The emergency use of molnupiravir is only authorized for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under Section 564(b)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1) unless the declaration is terminated or authorization revoked sooner.

Limitations of Authorized Use

4. Molnupiravir is not authorized:
   - for use in patients who are less than 18 years of age
   - for initiation of treatment in patients hospitalized due to COVID-19. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19
   - for use for longer than 5 consecutive days
   - or pre-exposure or post-exposure prophylaxis for prevention of COVID-19
5. Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives).

Contraindications

6. No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA.

Warnings and Precautions

7. There are limited clinical data available for molnupiravir. Serious and unexpected adverse events may occur that have not been previously reported with molnupiravir use.
8. Molnupiravir is not recommended for use during pregnancy. Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
9. Molnupiravir is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and the potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual.
10. Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently during treatment with molnupiravir and for 4 days after the final dose.
11. Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated.
12. Hypersensitivity reactions, including anaphylaxis, have been reported with molnupiravir. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue molnupiravir and initiate appropriate medications and/or supportive care.
13. Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. The safety and efficacy of molnupiravir have not been established in pediatric patients.

Adverse Reactions

14. The most common adverse reactions occurring in ≥1% of subjects in the molnupiravir treatment group in the Phase 3 double-blind MOVe-OUT study were diarrhea (2% versus placebo at 2%),nausea (1% versus placebo at 1%), and dizziness (1% versus placebo at 1%) all of which were Grade 1 (mild) or Grade 2 (moderate). Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) of the subjects receiving molnupiravir and 12 (2%) of subjects receiving placebo.

Drug Interactions

15. No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild to moderate COVID-19, have been conducted.

Breastfeeding

16. There are no data on the presence of molnupiravir or its metabolites in human milk. It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production. Based on the potential for adverse reactions in the infant from molnupiravir, breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir.

Males of Reproductive Potential

17. Nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of molnupiravir. The risk beyond three months after the last dose of molnupiravir is unknown.

Before prescribing, please consult the full prescribing information.

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