HKU Med School of Clinical Medicine
Department of Medicine
香港大學內科學系

30th MEDICAL RESEARCH CONFERENCE

Interdisciplinary Collaboration, Innovation and Technology Transfer

November 30, 2024

WELCOME MESSAGE

We are delighted to invite you to the 30th Medical Research Conference (MRC) taking place at the New World Millennium Hong Kong Hotel on November 30, 2024. This year's theme, "Interdisciplinary Collaboration, Innovation and Technology Transfer", emphasizes the significance of collaboration across disciplines, promotes innovation, and translates research into practical applications. Our Organizing Committee has specially designed a comprehensive program with various hot topics of interest to the healthcare profession, which will be delivered by distinguished speakers from the University Medical Center Groningen (Netherlands), Peking University Institute of Hematology (Beijing, China), Westlake University (Hangzhou, China), Angsana Health, The University of Hong Kong and City University of Hong Kong.

Moreover, the conference will feature two named lectures: the AJS McFadzean Distinguished Lecture and Rosie Young Lecture, and the "Award for Excellence" presentation ceremony recognizing outstanding staff in medical research. The oral and poster presentation session will provide a platform for researchers and postgraduates to present their work and establish meaningful connections.

Lastly, we would like to extend our sincere appreciation to our esteemed speakers, session chairs, delegates and industry partners for their invaluable contributions and unwavering support in making this event a success. We hope you will find the event rewarding and enlightening.

Professor Hung-Fat Tse
Chairperson,
Department of Medicine,
School of Clinical Medicine,
HKUMed

Professor Gary Lau
Chairman,
Organizing Committee of
the 30th Medical Research
Conference

ORGANIZING COMMITTEE

Chairman
Professor Gary Lau

Members (in alphabetical order of surnames)
Professor Paul Lee
Professor Philip Li
Professor Shirley Li
Professor Heidi Ling
Professor Loey Mak
Professor David Montero
Professor Kay-Cheong Teo
Professor Emmanuel Wong
Professor Susan Yung

GENERAL INFORMATION

About Medical Research Conference

The Medical Research Conference (MRC) is an annual event organized by the Department of Medicine, School of Clinical Medicine, The University of Hong Kong. Its objective is to provide a unique opportunity for knowledge exchange, networking and fostering research collaborations among faculty members, researchers, scientists, clinicians and medical students.

Format & Language

The event will take place in a physical format. The official language is English.

E-Certificate of Attendance

Participants who have attended the whole event will receive an e-certificate of attendance via e-mail. Please be informed that physical copies of the certificate will not be issued.

Photos & Recordings

The Organiser will take photos and videos during the event for any purposes in connection with the promotion, marketing or record of MRC. However, participants' identification will not be revealed without prior consent.

Disclaimer

Whilst every attempt has been made to ensure that all aspects of the MRC announced will take place as scheduled, the Organizing Committee reserves the right to make changes at any time should the need arise. All views and opinions expressed during the event are from the individuals' and do not reflect those of the Organizer or imply endorsement.

Conference Secretariat

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ACCREDITATIONS

Continuing Medical Education (CME) / Continuing Nursing Education (CNE) / Continuous Professional Development (CPD) have been awarded by the following Colleges of the Hong Kong Academy of Medicine and other accrediting bodies in Hong Kong.

Continuing Medical Education (CME)	November 30, 2024 (Saturday)	Category
The Hong Kong College of Anaesthesiologists	4.5	PP-NA
Hong Kong College of Community Medicine	4.5	PP-PP
The College of Dental Surgeons of Hong Kong	Pending	Pending
Hong Kong College of Emergency Medicine	4.5	CME-PP
The Hong Kong College of Family Physicians	5.0	OEA-5.02
The Hong Kong College of Obstetricians and Gynaecologists	4.5	PP-PN
The College of Ophthalmologists of Hong Kong	4.0	CME-PP
The Hong Kong College of Orthopaedic Surgeons	5.0	PP-B
The Hong Kong College of Otorhinolaryngologists	4.5	OT-5
Hong Kong College of Paediatricians	6.0	E-PP
The Hong Kong College of Pathologists	4.5	CME-PP
Hong Kong College of Physicians	4.0	PP-PP
The Hong Kong College of Psychiatrists	4.5	PP-OP
Hong Kong College of Radiologists	4.5	B-PP
The College of Surgeons of Hong Kong	4.5	CME-PP
MCHK CME Programme (HKMA, HKDU, HKAM, DH)	5.0	--

Continuing Nursing Education (CNE)	November 30, 2024 (Saturday)	Category
The Nursing Council of Hong Kong	4.5	--

Continuous Professional Development (CPD)	November 30, 2024 (Saturday)	Category
Hong Kong Dietitians Association	5.0	Non-core
Hong Kong Physiotherapy Association	Pending	Pending
Medical Laboratory Technologists Board	Pending	Pending
Occupational Therapists Board	Pending	Pending
Department of Pharmacology and Pharmacy, HKU	10.0	CPE

PROGRAM

Venue: Grand Ballroom, 2/F, New World Millennium Hong Kong Hotel

Time	Event
08:45 – 09:30	**Poster Presentation** (Chairmen: Professor Iris Tang & Professor David Montero) **Venue:** 2/F Foyer, New World Millennium Hong Kong Hotel
09:00 – 09:35	**Best Abstract Award Presentation** (Chairmen: Professor Susan Yung & Professor Herbert Kwok)
09:35 – 09:45	**Opening Ceremony**
Scientific Session I (Chairman: Professor WK Seto)	
09:45 – 10:10	**Pursuing the Nature of Intelligence** **Professor Yi Ma** School of Computing and Data Science & Musketeers Foundation Institute of Data Science, The University of Hong Kong
10:10 – 10:30	**Coffee Break**
Scientific Session II (Chairmen: Professor Sydney Tang & Professor Heidi Ling)	
10:30 – 11:00	**The Future of The Treatment of Chronic Kidney Disease. What's Next After SGLT2i?** **Professor Hiddo Lambers Heerspink** University Medical Center Groningen, Netherlands
11:00 – 11:25	**Endogenous Retrotransposable Element Expression as Biomarkers for Health and Disease** **Professor Jason Wong** School of Biomedical Sciences, The University of Hong Kong
11:25 – 11:35	**Break**
Scientific Session III (Chairmen: Professor Philip Li & Professor Shirley Li)	
11:35 – 12:05	**High Resolution Profiles of Antibody Responses at Proteome-scale** **Professor Ren Sun** Westlake University, Hangzhou, China
12:05 – 12:30	**Photoresponsive Nanomedicine for The Treatment of Various Diseases** **Professor Weiping Wang** Department of Pharmacology and Pharmacy & Dr. Li Dak-Sum Research Centre, The University of Hong Kong
12:30 – 13:40	**Lunch**

PROGRAM

Venue: Grand Ballroom, 2/F, New World Millennium Hong Kong Hotel

Time	Event
13:40 – 14:05	**"Award for Excellence" Presentation Ceremony**
Rosie Young Lecture (Chairmen: Professor CS Lau & Professor Karen Lam)	
14:05 – 14:35	**Towards Better Cardio-Kidney-Metabolic (CKM) Health – The Key to Longevity?** **Professor Paul Lee** Department of Medicine, School of Clinical Medicine, The University of Hong Kong
Scientific Session IV (Chairmen: Professor Gary Lau & Professor KC Teo)	
14:35 – 15:00	**The Perfect Time Is Now: The First Three Steps to Healthcare Innovation for Researchers** **Dr. Swee-Kheng Khor** Angsana Health
15:00 – 15:25	**Assessing Brain and Heart Health for Cerebro-Cardiovascular Disease Management** **Professor Kannie Chan** Hong Kong Centre for Cerebro-cardiovascular Health Engineering (COCHE) & Department of Biomedical Engineering, City University of Hong Kong
15:25 – 15:40	**Coffee Break**
Scientific Session V (Chairmen: Professor Paul Lee & Professor KH Chan)	
15:40 – 16:05	**AI-enabled e-Skin and Conformal Sensors for TCM-Based Diagnostics** **Professor Wen-Jung Li** Department of Mechanical Engineering, City University of Hong Kong
16:05 – 16:30	**Hydrogel Electronics for Implantable and Wearable Therapeutic Systems** **Professor Peng Shi** Department of Biomedical Engineering, City University of Hong Kong
AJS McFadzean Distinguished Lecture (Chairman: Professor TK Chan)	
16:30 – 17:05	**The New Era of Hematopoietic Stem Cell Transplantation** **Professor Xiaojun Huang** Peking University Institute of Hematology & Peking University People's Hospital, Beijing, China
17:05 – 17:10	**Closing Remarks**

PROFESSOR YI MA

Director, School of Computing and Data Science &
Director, Musketeers Foundation Institute of Data Science,
The University of Hong Kong

PURSUING THE NATURE OF INTELLIGENCE

In this talk, we will try to clarify different levels and mechanisms of intelligence from historical, scientific, and computational perspective. From the evolution of intelligence from phylogenetic, to ontogenetic, to communal, and to artificial intelligence, we will try to shed light on how to understand precisely what the seemingly dramatic advancement in machine intelligence in the past decade has truly accomplished. This includes to provide a principled mathematical explanation to the practice of deep learning from the perspective of compressive data encoding and decoding. This reveals limitations of the current practice and suggests natural ways to develop more correct and complete learning systems. Eventually, we will clarify the difference and relationship between knowledge and intelligence, which may guide us to pursue the goal of developing truly autonomous intelligent systems.

PROFESSOR HIDDO LAMBERS HEERSPINK

Professor of Clinical Trials and Personalized Medicine,
Department of Clinical Pharmacy and Pharmacology,
University Medical Center Groningen, Netherlands

THE FUTURE OF THE TREATMENT OF CHRONIC KIDNEY DISEASE. WHAT'S NEXT AFTER SGLT2I?

Patients with chronic kidney disease face a high risk of kidney failure, cardiovascular complications and premature death. ACE-inhibitors or Angiotensin Receptor Blockers, sodium glucose co-transporter 2 inhibitors (SGLT2i) and the non-steroidal mineralocorticoid receptor antagonist finerenone are registered and recommended by guidelines to slow CKD progression. Despite the use of these agents, the risk of kidney failure and cardiovascular complications remains high in many patients which is associated with high residual albuminuria. Novel therapies are thus desired to augment kidney and cardiovascular protection.

Several promising combination of novel drugs are currently tested in ongoing clinical trials. The efficacy and safety of the GLP-1 receptor agonists semaglutide has recently been established in the FLOW trial in patients with type 2 diabetes and CKD. The efficacy of the combined GLP-1/GIP receptor agonist tirzepatide is also assessed in phase 3 clinical trials. Post-hoc analyses from cardiovascular safety trials have suggested that tirzepatide may markedly reduce the progression of kidney function decline. This effect remained present when these agents were added to SGLT2 inhibitors. Other potential promising therapies include aldosterone synthase inhibitors, endothelin receptor antagonists and soluble glucanyl cyclase activators. The challenge for the future will be to tailor the optimal medication (or combination) to each patient.

PROFESSOR JASON WONG

Professor, School of Biomedical Sciences,
The University of Hong Kong

ENDOGENOUS RETROTRANSPOSABLE ELEMENT EXPRESSION AS BIOMARKERS FOR HEALTH AND DISEASE

Human endogenous retroviruses (HERVs) are remnants of ancestral viral infections that had incorporated into human genomes. While all HERVs are believed to be no longer infectious, there are numerous examples where HERV sequences have been co-opted for other physiological functions. In cancer, HERV has gained increasing attention for their role in tumorigenesis and tumour immunity. In this talk, I will give recent examples of HERVs as biomarkers. I will then focus on our study of the regulation of one specific copy of HERV, *ERVK-7*, which is up-regulated in lung adenocarcinoma and a factor in immunotherapy response. We dissect the regulation of *ERVK-7* in normal and tumour cells, highlighting the complexities underlying its apparent over-expression in RNA-seq studies.

PROFESSOR REN SUN

Chair Professor & Director,
Center for Infectious Disease Research,
Westlake University, Hangzhou, China

HIGH RESOLUTION PROFILES OF ANTIBODY RESPONSES AT PROTEOME-SCALE

Professor Ren Sun takes systems biology approaches to address critical interactions between virus and host. One of his research interests is to systematically define the immunome of infection, vaccination and immune-related diseases. His team has developed a high-throughput technology platform to map epitope-specific antibody responses, and built antigen peptide libraries covering commonly seen human viruses and human proteome. They have applied this method for profiling antibody targets and immune signatures of SARS-CoV-2 infection and multiple autoimmune diseases.

PROFESSOR WEIPING WANG

Associate Professor,
Department of Pharmacology and Pharmacy &
Dr. Li Dak-Sum Research Centre, The University of Hong Kong

PHOTORESPONSIVE NANOMEDICINE FOR THE TREATMENT OF VARIOUS DISEASES

Photoresponsive drug delivery can enhance the accumulation of drugs at targeted sites where light is applied, thereby increasing therapeutic efficacy and reducing side effects. Currently, this strategy faces challenges in clinical applications, such as limited light penetration depth in biological tissues. In this talk, I will present our research on the development of simple photoresponsive drug delivery systems for the treatment of various diseases, including cancer and eye diseases. Additionally, I will discuss the approaches we have developed to overcome the challenge of limited light penetration within the body. By exploring these advancements and solutions, we aim to further the potential of photoresponsive nanomedicines and improve their overall efficacy in treating a wide range of diseases through interdisciplinary collaborations.

November 30 | 14:05 – 14:35

ROSIE YOUNG LECTURE 2024

PROFESSOR ROSIE YOUNG

GBM, GBS, CBE, JP, MD (HK), DSc (Hon), D Soc Sc (Hon), FRCP, FRACP, FHKAM (Hon), FHKCP (Hon)

Professor Rosie Young holds an MBBS and an MD from the University of Hong Kong (HKU). She joined the Department of Medicine in 1954, and was appointed Professor of Medicine in 1974. In 1983, Professor Young became Dean of the Faculty of Medicine, the first woman to hold the position. From 1985-1993, she served as Pro-Vice-Chancellor and Senior Pro-Vice-Chancellor of the University. She is now Emeritus Professor and Honorary Clinical Professor in the Department of Medicine, HKU.

Professor Young is a world-renowned medical educationist and researcher, and one of the foremost authorities on endocrinology globally. She had made immense contributions to research in diabetes mellitus, carbohydrate metabolism in liver disease, thyrotoxicosis and thyrotoxic periodic paralysis.

Professor Young was the first Hong Kong medic to qualify for Membership of both Royal Colleges of Physicians in London and Edinburgh in 1959. She subsequently contributed to the profession and by 1995, she had served as Chairman of, *inter alia*, the Medical Council of Hong Kong, the Working Party in Primary Health Care in Hong Kong, the Hospital Governing Committee of Princess Margaret Hospital, and the Education Commission.

The Rosie Young Lecture has been established in 2024 to honour the remarkable contributions of Professor Rosie Young. This lectureship aims to uphold the high standards of teaching, clinical practice and research in Internal Medicine.

PROFESSOR PAUL LEE

Assistant Dean (Student Wellness and Engagement) &
Clinical Associate Professor, Faculty of Medicine,
The University of Hong Kong

TOWARDS BETTER CARDIO-KIDNEY-METABOLIC (CKM) HEALTH – THE KEY TO LONGEVITY?

Biography:

Professor Paul Lee graduated in 2006 from the University of Hong Kong (HKU) and became an endocrinologist in 2013. He obtained the Croucher Foundation Fellowship in 2017 and received his Doctor of Medicine degree from HKU in 2022 with the Sir Patrick Manson Gold Medal. He is now a Clinical Associate Professor and the Assistant Dean (Student Wellness and Engagement) of the Faculty of Medicine, HKU.

Professor Lee's research focuses on type 2 diabetes (T2D) and its complications, particularly in the contribution of adipokines and novel biomarkers that enhance risk stratification in the clinical management of diabetes and its complications. Professor Lee also has special interests in studying metabolic dysfunction-steatotic liver disease (MASLD) in T2D and initiated the *Hong Kong West Diabetes NAFLD Cohort* to investigate the risk factors of liver fibrosis progression in T2D. He is an editorial board member of *JCEM and Diabetes & Metabolism Journal*. Over the years, his research has been published in high-impact peer-reviewed journals, and received awards including the Investigator Award by the Asian Association for the Study of Diabetes in 2021, the Faculty Outstanding Research Output Award by HKU, the Young Investigator Outstanding Research Paper Award in 2022 and the Richard Yu Lectureship by the Hong Kong College of Physicians (HKCP) in 2023.

Abstract:

The American Heart Association (AHA) has recently established the Cardiovascular-Kidney-Metabolic (CKM) syndrome, a new entity that highlights the multiple inter-related connections among excess adiposity, adipose tissue dysfunction, metabolic conditions, chronic kidney disease (CKD), atherosclerotic cardiovascular diseases (ASCVD), atrial fibrillation (AF), heart failure (HF), as well as other important adverse health outcomes. Despite changes in health literacy and standard of care over the last two decades, our local CKM burden, as in other parts of the world, remains substantial. Higher CKM stages are associated with increased mortality outcomes in the long term. The framework advocates screening of CKM risk factors, staging, and emphasizes the importance of early identification of high-risk individuals for timely management to improve their CKM health. Adipokines and biomarkers of CKM health are eagerly required. Notably, type 2 diabetes is an important stage in the CKM framework, and the presence of metabolic dysfunction-associated steatotic liver disease (MASLD) further enhances the risks of adverse CKM health. Therefore, proactive management to maintain optimal CKM health, including weight reduction, glycaemic control and use of cardio-renal protective medications, is important to prevent CKM syndrome progression, mortality, and ultimately translate to better CKM health and longevity in the global community in future.

DR. SWEE-KHENG KHOR

Chief Executive Officer, Angsana Health

THE PERFECT TIME IS NOW: THE FIRST THREE STEPS TO HEALTHCARE INNOVATION FOR RESEARCHERS

The urgency for healthcare innovation has never been greater. Fortunately, the opportunities for healthcare innovation have also never been greater, with abundant government grants and venture funding, strong innovation infrastructure, and a higher stature for start-up founders in a traditionally conservative Asia. This session will describe three critical steps for researchers to start innovation. First, to psychologically adopt a “parallel approach” of prototyping an idea or a company as a “side project” while enjoying the benefits of a full-time role. Secondly, to build a multidisciplinary team comprising scientists and non-scientists. Thirdly, prioritize patient-centric design, ensuring innovations address actual wants and needs. This session will describe practical, realistic, and achievable micro-steps that can be taken by the ambitious researcher, not just provide guiding principles.

PROFESSOR KANNIE CHAN

Associate Dean, College of Engineering,
City University of Hong Kong & Director, Hong Kong Centre for Cerebro-cardiovascular Health Engineering (COCHE)

ASSESSING BRAIN AND HEART HEALTH FOR CEREBRO-CARDIOVASCULAR DISEASE MANAGEMENT

Cardiovascular diseases (CVDs) are one of the leading causes of death that killed over 17 million people every year, and yet early and timely identification of high-risk subjects remains challenging. Many early neuropathology can be imaged by advanced MRI approaches, and the rapid development of accessible sensing technologies and AI empower us to develop a sustainable and efficient healthcare system for CVD. In this presentation, I will talk about the capability of CEST-MRI to detect related neuropathologies, such as altered glucose uptake, utilization and clearance, myelin and aquaporin abnormalities, and image-guide drug delivery to the brain. The exchange processes detected by CEST-MRI are intrinsically sensitive to local environment like temperature and pH, which enables the imaging of intriguing in vivo events in stroke, Alzheimer's disease, Parkinson's disease and multiple sclerosis. This facilitates a totally non-invasive assessment of brain health. Moreover, I will showcase some accessible and non-invasive technologies to measure related risk factors for CVDs, such as carotid artery, ejection fraction, blood glucose and blood pressure, which are essential for assessing the heart health. With these developments, we can work together to build a health assessment system to identify high-risk subjects in an accessible and efficient manner.

PROFESSOR WEN-JUNG LI

Vice-President (Talent and International Strategy) &
Chair Professor, Department of Mechanical Engineering,
City University of Hong Kong

AI-ENABLED E-SKIN AND CONFORMAL SENSORS FOR TCM-BASED DIAGNOSTICS

Traditional Chinese Medicine (TCM) relies on non-conventional diagnostic tools, such as visual inspection, auscultation/olfaction, inquiring, and palpation, instead of Western medicine's advanced apparatus such as electrocardiograms, magnetic resonance imaging, and X-ray computed tomography. One such TCM technique, known as sphygmopalpation, has been practiced since the Han Dynasty, where TCM practitioners decode 28 basic pulse patterns using their fingertips on specific locations of the wrists. Although pulse-based diagnosis is gaining popularity as a low-cost, non-invasive method, it requires skilled practitioners and can lack objectivity. This lecture explores the potential of emerging conformal sensor technologies, such as electronic skin (e-skin) and epidermal electronic systems, to digitize and enhance TCM evaluations. Several examples utilizing 3D additive-printing technology to develop flexible e-skin and 3D-conforming sensors for digitalizing physiological signals based on TCM diagnostic concepts will be presented.

We will discuss the application of a skin-like arterial pulse sensing array and artificial neural network to demonstrate the consistency and repeatability of certain pulse patterns identified by TCM practitioners across different test subjects. Additionally, a personalized 3D contour-conforming device for real-time multipoint auricular electric skin impedance (AESI) monitoring will be introduced. The 3D spatiotemporal AESI data shows individual uniqueness and consistent variations during similar exercise sequences. The lecture further investigates how e-skin and conformal sensors can be specifically employed in TCM diagnostics. Objective characterization of pulse waveforms, spatial mapping of pulse pressure across wrist arteries, and detection of subtle variations in skin mechanical properties during palpation will be discussed. The integration of sensor data with machine learning algorithms holds the potential to automate diagnosis, standardize evaluations, and reveal new biophysical insights into TCM-based diagnostics.

PROFESSOR PENG SHI

Professor, Department of Biomedical Engineering,
City University of Hong Kong

HYDROGEL ELECTRONICS FOR IMPLANTABLE AND WEARABLE THERAPEUTIC SYSTEMS

Bioelectronics is undergoing tremendous developments with soft and flexible construction, improved electronic performance and multifunctional capability. The technical innovation relies on the development of conductive hydrogels to forge novel bioelectronic devices for various biomedical applications. Our first demonstration is an in vivo gene editing system to create engineered immune cells to enhance cancer immunotherapy. A wearable electronic patch is created for transdermal cancer vaccination, which involves subcutaneous delivery of neoantigen gene to dendritic cells for subsequent T cell activation. Implantable bioelectronics is also created for in vivo generation of genetically engineered T-cells by direct gene-editing lymph nodes with a CRSPR-cas9 vector. The second demo is a multifunctional Hydrogel Electronics for Closed-loop Antiepileptic Treatment, which enables the smart anti-seizure management by combining electrical and pharmacological intervention. The device was made of conductive hydrogels and fabricated as a flexible array of microneedle electrodes, each of which can be individually addressed for electrical recording and chemical releasing with sophisticated spatial and temporal control in vivo. The recorded neural spiking signal acts as closed-loop feedback to trigger a voltage-driven drug release in detected pathological conditions, where seizure occurrence is predicted by real-time electrophysiology analysis.

November 30 | 16:30 – 17:05

AJS MCFADZEAN DISTINGUISHED LECTURE 2024

PROFESSOR ALEXANDER JAMES SMITH MCFADZEAN (1914-1974)

MBChB (Glasgow) MD (Glasgow) FRCP (Edin, Lond) FRACP FACP OBE FRS (Edin) Hon DSc (HK) Hon FRCS (Edin) JP

Professor AJS McFadzean (1914 - 1974) was the longest serving Professor and Head of the Department of Medicine (1948 - 1974) at the University of Hong Kong. This Distinguished Lecture and Visiting Professorship was established in 2015 to honour and commemorate Professor McFadzean's achievements and contributions to the development of modern medicine in Hong Kong.

Professor McFadzean was born on 28th January 1914 in Troon, Ayrshire on the west coast of Scotland. He studied medicine at the University of Glasgow and graduated in 1936 with MBChB with Honours and was awarded the Brunton Memorial Prize as the most distinguished graduate of medicine that year. In 1959, the University of Glasgow further awarded him the MD with Honours and the Bellahouston Gold Medal for his thesis, On the production of plasma fibrinolytic activity within veins.

Having worked in the Glasgow Royal Infirmary, Hawkhead Mental Hospital in Paisley, and Anlaby Road Hospital in Hull until the outbreak of World War II, Professor McFadzean was appointed Lecturer and later Senior Lecturer in the Muirhead Department of Medicine, University of Glasgow from 1945 to 1948. In 1948, he was appointed Professor of Medicine, University of Hong Kong and Consultant in Medicine to the Hong Kong Government. He also served as Vice-Chancellor for a year in 1965 and as Dean of Medicine from 1967 to 1972.

During his 26 years tenure at the University of Hong Kong, Professor McFadzean had shaped the way medicine was taught and practised locally. As Consultant to the Hong Kong Government, he also played an important role in improving the healthcare system in Hong Kong. Professor McFadzean was distinguished for his work on liver, thyroid and blood disorders. With his clinical acumen, he offered countless patients hopes of recovery, and inspired generations of physicians to continue his legacy in putting Hong Kong on the world map of excellence in medicine. His insistence in understanding the scientific basis of health and disease has laid the foundation of medical education and research in Hong Kong.

PROFESSOR XIAOJUN HUANG

Chairman, Peking University Institute of Hematology &
Director, Department of Hematology,
Peking University People's Hospital, Beijing, China

THE NEW ERA OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

Biography:

Professor Xiaojun Huang, who graduated from Sun Yat-sen University with an MD and Peking University with a PhD, is a renowned hematologist specialized in hematopoietic stem cell transplantation, cellular therapy and malignant hematological diseases. He has been serving as the Head of Peking University Institute of Hematology and the Director of the hematology department of Peking University People's Hospital since 2005. He is also the academician of Chinese Academy of Engineering, the fellow of Chinese Academy of Medical Sciences, and the foreign corresponding academician of French National Academy of Medicine.

Since 1996, Professor Huang has pioneered the exploration of haploidentical hematopoietic stem cell transplantation (haplo-HSCT). With persistent efforts, he established a series of key techniques of non T-cell depleted haploidentical transplantation, which gradually developed into the novel G-CSF/ATG-based "Beijing Protocol", increasing the 3-year survival rate from approximately 20% to about 70% in haploidentical transplantation treating leukemia. This system has made significant strides in overcoming the global challenge of donor scarcity, achieving in a new era where "everyone has a donor". Nowadays, the "Beijing Protocol" techniques have been adopted in over 190 centers in China. The protocol has also been extended to countries worldwide and holds a dominant position globally in the field of haploidentical stem cell transplantation.

Professor Huang received worldwide attention and appreciation for his groundbreaking work. He has won numerous prizes, including the second prize of the National Award for Progress in Science and Technology in 2014 and 2017, as well as international awards, such as the prestigious annual Center for International Blood and Marrow Transplant Research (CIBMTR) "Distinguished Service Award" and the "International Collaboration Award" from International Academy for Clinical Hematology.

Abstract:

The shortage of donors for hematopoietic stem cell transplantation (haplo-HSCT) has long been a significant challenge. To address this worldwide challenge, Professor Xiaojun Huang and his team from the National Clinical Research Center for Hematologic Disease at Peking University People's Hospital developed the non-in vitro T-depleted haplo-matched hematopoietic stem cell transplantation technology system, being named the "Beijing Program" by the Worldwide Network for Blood & Marrow Transplantation (WBMT). This technology system has brought hope of life to countless leukemia patients.

This innovative protocol uses granulocyte colony-stimulating factor (G-CSF) and anti-thymocyte globulin (ATG) to enhance graft engraftment and reduce graft-versus-host disease (GVHD). It has not only improved haplo-SCT outcomes but also established it as a viable first-line treatment for acute leukemia. Internationally, the Beijing Protocol increased the success rate of haploidentical transplantation from 20% to 70%, achieving results comparable to chemotherapy and HLA-matched SCT, with outcomes equal to or even better than chemotherapy.

The Beijing Protocol is noted for inducing T-cell tolerance through the upregulation of suppressor of cytokine signaling 1 (SOCS1), a mechanism that mitigates GVHD. Additionally, Huang's team identified N-acetylcysteine (NAC) as a method to address poor graft function, further enhancing SCT success rates. The protocol's impact is evident in the rapid expansion of haplo-SCT in China, reflected in the significant increase in transplant centers and annual cases. However, there are still areas in the Beijing Protocol that could be further optimized in the future.

This breakthrough has transformed the global landscape of transplantation, making groundbreaking contributions to the field of allogeneic HSCT, particularly in the development and refinement of haploidentical SCT. Their research has expanded the donor pool and set a global benchmark for SCT, optimized transplant outcomes and making the procedure more accessible to a broader patient population.

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24-hour Diastolic Blood Pressure Variability is Independently Associated with Impaired White Matter Microstructure in Middle-aged Adults Without Hypertension

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Introduction: Blood pressure variability (BPV) is associated with white matter (WM) loss, reduced brain volume and dementia. However, whether BPV is similarly associated with impaired WM integrity in normotensive individuals is unknown. The objective of this study is to examine the association of BPV with impaired WM integrity in normotensive individuals, using advanced neuroimaging techniques and tractography analysis.

Methods: We recruited 262 community-dwelling middle-aged Chinese without known hypertension during 2021-2024. All participants received 24-hour ambulatory blood pressure monitoring (ABPM) to determine their mean 24-hour BP and BPV [reflected using coefficient of variation (COV)], brain magnetic resonance imaging to assess WM integrity [fractional anisotropy (FA) of 42 WM tracts], fasting blood tests and arterial stiffness measurement. Amongst individuals who were normotensive on ABPM (BP<130/80mmHg), we then assessed the association of BPV with FA in models adjusting for age, sex, education, body mass index, 24-hour systolic and diastolic BP, fasting glucose, triglycerides, low- and high-density lipoprotein, smoking, alcohol intake and mean pulse wave velocity (PWV).

Results: Amongst 152/262 normotensives (65% females, aged 54±6 years old[mean±SD]), their mean 24-hour BP was 115±7 / 71±6mmHg, COV 13/18mmHg, and PWV 13.8±1.8m/s. After adjusting for covariates, 24-hour diastolic BPV was independently associated with decreased FA in superior longitudinal fasciculus, dorsal cingulum bundle and frontal aslant tract (all $p<0.05$). Daytime diastolic BPV was independently associated with decreased FA in middle cerebellar peduncle, whilst nighttime diastolic BPV was independently associated with decreased FA in superior longitudinal fasciculus ($p<0.05$). In univariate analysis, 24-hour systolic BPV was associated with decreased FA in middle longitudinal fasciculus; similar for daytime systolic BPV with middle cerebellar peduncle, and nighttime systolic BPV with superior longitudinal fasciculus, middle longitudinal fasciculus and corpus callosum body ($p<0.05$), but not after multivariate adjustment.

Conclusion: Diastolic BPV is independently associated with impaired microstructure of WM tracts in normotensives. While the bidirectional relationship between WM loss and vascular control cannot be excluded, clinical attention should be given to this subclinical middle-aged population with high diastolic BPV.

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Adiponectin Deficiency Exacerbates Cerebrovascular Dysfunction in Alzheimer's Disease

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Introduction: Cerebrovascular damage and dysfunction are increasingly recognized as critical components in the pathophysiology of Alzheimer's disease (AD). Adiponectin (APN), an adipocyte-secreted hormone, has been demonstrated to be neuroprotective against cytotoxicity induced by Amyloid beta (Abeta), while little is known about its impact on cerebrovascular dysfunction in AD.

Methods: *In vivo* study: APN-deficient AD mice (5xFAD;$APN^{-/-}$) were generated by crossbreeding 5xFAD mice with APN knockout mice ($APN^{-/-}$). Cerebrovascular integrity was assessed through cerebral blood flow (CBF), neurovascular coupling (NVC), cerebral amyloid angiopathy (CAA), blood-brain barrier (BBB) permeability, and expression levels of tight junction proteins (TJPs) in cerebral endothelial cells. *In vitro* study: Primary mouse brain endothelial cells were treated with human Abeta40 oligomers in the presence or absence of APN to examine whether APN enhances TJP expression and improves endothelial barrier integrity.

Results: Longitudinal study using laser speckle contrast imaging in mice aged 6 to 9 months revealed that 5xFAD;$APN^{-/-}$ mice showed more severe NVC impairment than 5xFAD mice as early as 6 months, whereas significantly reduced resting CBF in these mice was not observed until 9 months. Fluorescein sodium salt penetration assay revealed that 5xFAD;$APN^{-/-}$ mice exhibited increased BBB permeability at 3, 6, and 9 months of age compared to 5xFAD mice. Immunofluorescence staining confirmed greater endogenous IgG extravasation into the brain parenchyma in 5xFAD;$APN^{-/-}$ mice compared to 5xFAD mice. Higher amount of Abeta was deposited within the cerebral vessels of 5xFAD;$APN^{-/-}$ mice compared to that of 5xFAD mice at 6 months of age, indicating aggravated CAA pathology. Reduced expression of TJPs, including claudin-5 and occludin, was observed in both 5xFAD and $APN^{-/-}$ mice, with the most significant decrease seen in 5xFAD;$APN^{-/-}$ mice. Western blot analysis on primary endothelial cells demonstrated that Abeta40 reduced the expression of TJPs. Furthermore, Abeta40 compromised endothelial barrier integrity, as evidenced by the rhodamine dextran permeability assay. Importantly, pre-treatment with APN significantly mitigated TJP loss and barrier disruption induced by Abeta40.

Conclusion: Our results indicate that APN deficiency exacerbates CBF reduction, NVC impairment, CAA pathology, BBB leakage, and TJP loss in AD mice. APN protects brain endothelial cells from Abeta40 toxicity by preserving TJP integrity and maintaining barrier function. These findings suggest that enhancing APN signalling may be a promising therapeutic strategy for cerebrovascular dysfunction in AD.

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Adiponectin Deficiency Exacerbates Tauopathy and Neuroinflammation in A Human Tau Mutation Mouse Model

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Introduction: Tauopathy is characterized by intraneuronal accumulation of hyperphosphorylated tau proteins, which form insoluble neurofibrillary tangles and lose the homeostatic function of stabilizing intracellular microtubules. It is one of the pathological hallmarks of several neurodegenerative diseases including Alzheimer's disease. Adiponectin (APN) is an adipokine secreted from adipocytes. It regulates glucose metabolism by enhancing insulin sensitivity and exerts anti-inflammatory effects. Low molecular weight APN has been shown to cross the blood-brain barrier and promote hippocampal neurogenesis. However, whether APN contributes to tau-mediated neurodegeneration remains unknown. In this study, we hypothesize that APN deficiency exacerbates tauopathy with enhanced microgliosis and aggravated neuronal loss.

Methods: To study the impact of APN deficiency on tauopathy development, APN knockout ($APN^{-/-}$) mice were crossbred with human tau P301S mutation transgenic (Tau^{P301S}) mice to generate APN-deficient tau (Tau^{P301S}; $APN^{-/-}$) mice. The anxiety-like behaviour, cognitive function, and memory and learning function of 9-month-old wildtype, $APN^{-/-}$, Tau^{P301S}, and Tau^{P301S}; $APN^{-/-}$ mice were assessed by open field test, novel object recognition test, and Morris water maze test, respectively. Immunofluorescent staining was performed to examine hyperphosphorylated tau accumulation, microgliosis, and neuronal loss in the brain. The plasma level of the proinflammatory cytokine interleukin-6 (IL-6) was quantified by enzyme-linked immunosorbent assay (ELISA).

Results: The immunoreactivity of hyperphosphorylated tau (AT8) in the hippocampus and cortex of Tau^{P301S}; $APN^{-/-}$ mice was significantly elevated compared with wildtype, $APN^{-/-}$, and Tau^{P301S} mice. The immunoreactivity of the microglia marker ionized calcium-binding adaptor molecule 1 (Iba1) was significantly higher in Tau^{P301S}; $APN^{-/-}$ mice than that in other groups. Tau^{P301S}; $APN^{-/-}$ mice showed significantly less neuronal nuclei (NeuN) positive neurons than Tau^{P301S} mice. The plasma level of IL-6 in Tau^{P301S}; $APN^{-/-}$ mice was significantly higher than in wildtype mice. However, there were no significant differences in the behavioural test results among the groups.

Conclusion: APN deficiency aggravates tauopathy with increased hyperphosphorylated tau accumulation, microgliosis, and neuronal loss. Since the adiponectin receptor is a promising therapeutic target for tau-mediated neurodegeneration, future experiments will be conducted to examine whether an adiponectin receptor agonist can improve tauopathy.

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Assessment of Cardiopulmonary Function in Fabry Patients Using Cardiopulmonary Exercise Test

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Introduction: Using cardiopulmonary exercise test (CPET) to evaluate the cardiopulmonary function of patients with Fabry disease and analyze its characteristics, further analyzing the relationship between CPET cardiac function indices and echocardiography.

Methods: Twenty patients aged ≥18 years (10 males and 10 females) diagnosed with Fabry disease at The University of Hong Kong-Shenzhen Hospital from July 2022 to July 2024 were selected as the Fabry group, and 20 healthy adults (10 males and 10 females) served as the control group. Both groups underwent comprehensive cardiopulmonary exercise test (CPET) and echocardiography. Those with positive treadmill test results further underwent coronary CTA examination. Small airway dysfunction was defined as having two of the following three indices below 65%: the percentage of maximum mid-expiratory flow (MMEFpre) to predicted value, the percentage of forced expiratory flow at 75% of vital capacity (FEF75%pre) to predicted value, and the percentage of forced expiratory flow at 50% of vital capacity (FEF50%pre) to predicted value, all in the absence of ventilatory dysfunction.

Results: There were no statistically significant differences in age, gender composition, BMI, and smoking history between the Fabry group and the control group ($p>0.05$). In cardiac function assessment, the Fabry group showed significantly lower values in maximal oxygen consumption (VO_{2max}), anaerobic threshold (AT), peak oxygen pulse (O_2/HR), and metabolic equivalents (METs) compared to the control group, with respective values of 22.68±4.46ml·kg^{-1}·min^{-1} vs. 29.49±6.61ml·kg^{-1}·min^{-1}, 16.31±3.80ml·kg^{-1}·min^{-1} vs. 20.49±5.25ml·kg^{-1} min^{-1}, 9.01±1.62ml/beat vs. 12.82±3.57ml/beat, and 6.80 (5.70, 7.88) vs. 7.65 (7.30, 9.25). These differences were statistically significant ($p<0.05$). Four patients (20%) in the Fabry group had positive treadmill test results, but coronary CTA examination did not reveal coronary stenosis, suggesting possible microcirculatory disturbances. Regarding lung function parameters, although both groups had normal forced expiratory volume in 1 second (FEV1%pre) within the normal range (92.08±7.32% vs. 101.7±5.06%, $p<0.05$), up to 65% of patients in the Fabry group exhibited small airway dysfunction. The Fabry group had significantly lower values in MMEFpre, FEF75%pre, FEF50%pre, and FEF25% pre-compared to the control group, with respective values of 63.84±29.05% vs. 87.80±13.32%, 76.59±21.05% vs. 110.8±16.9%, 66.33±27.29% vs. 100.4±15.33%, and 56.70±32.13% vs. 74.70±16.06%. These differences were statistically significant ($p<0.05$). Pearson correlation analysis revealed a negative correlation between VO_{2max} and left ventricular hypertrophy in Fabry patients ($r=-0.579$, $p<0.05$).

Conclusion: The cardiac function assessed by CPET in Fabry disease patients was significantly lower than that of healthy adults, with VO_{2max} negatively correlated with left ventricular thickness. The impairment of lung function was mainly manifested as small airway dysfunction.

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Association Between Metabolic Syndrome Traits and The Risk of Hip Fracture in A Territory-Wide Cohort of 165,289 Individuals with Type 2 Diabetes

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Introduction: Type 2 diabetes (T2D) is associated with increased risk of fragility fractures. While obesity may protect against fractures, T2D patients often exhibit other metabolic syndrome (MetS) traits. The cumulative effects of additional MetS traits in people with T2D on fracture risks are not well delineated, which carries implication in managing cardiovascular-kidney-metabolic overlap in T2D from the perspective of bone health. Here, we evaluated the role of these MetS traits and their synergistic implications in predicting hip fractures in T2D.

Methods: Patients with T2D who had no history of major osteoporotic fractures were identified from the territory-wide electronic health records of Hong Kong between 1997 and 2018. MetS traits included obesity (body mass index ≥25 kg/m^2), hypertension, low HDL-cholesterol levels, hypertriglyceridemia, and albuminuria. Hip fractures were identified by ICD-9-CM code 820. The cohort was followed up till the occurrence of hip fractures, death or 31 December 2020, whichever was earlier. Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for hip fractures were calculated using multivariate Cox regression models stratified by obesity status, accounting for various cardiometabolic and osteoporotic risk factors.

Results: In total, 165,289 patients (median age 60.0 years; 54.2% men) were identified with median duration of diabetes only 1 year. Upon median follow-up of 5.3 years, 966 (0.58%) developed incident hip fractures. Among individual MetS trait, albuminuria had the strongest association with hip fractures (aHR=1.47, 95% CI 1.26–1.71) in both obese and non-obese T2D patients. In non-obese patients, the risk of hip fractures increased progressively with number of MetS traits at baseline (aHR=1.12 per added trait, 95% CI 1.03–1.22, p=0.006) and with subsequent acquisition of additional MetS traits upon follow-up. Among obese patients, the dose-response relationship between number of MetS traits and hip fractures became less significant (aHR=1.11 per added trait, 95% CI 0.998–1.24, p=0.054). Sensitivity analysis revealed that poor glycemic control (HbA1c ≥8%) was an independent risk factor for hip fractures only in patients with diabetes duration ≥5 years, but not in the entire cohort with short duration of diabetes.

Conclusion: Albuminuria is an important predictor of hip fracture risk in patients with diabetes, particularly among recently diagnosed diabetes, even before hyperglycemia sets in as the risk factor later. Additional MetS traits compound the risk, especially in non-obese T2D patients. These findings could be instrumental in shaping screening initiatives for fracture risk optimization in T2D. Comprehensive management of cardiovascular-kidney-metabolic overlap is beneficial from the perspective of bone fragility in T2D.

Association of Blood Lead and Cadmium with Subclinical Cardiovascular Disease

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Introduction: This study investigates the association between blood levels of lead and cadmium and subclinical cardiovascular disease, as indicated by elevated high-sensitivity cardiac troponin (hs-cTnT) or N-terminal pro b-type natriuretic peptide (NT-proBNP) among a cohort of U.S. adults without overt cardiovascular disease (CVD).

Methods: We included 10,197 participants from the U.S. National Health and Nutrition Examination Survey (NHANES) from 1999 to 2004, all without diagnosed CVD. The cut-offs for elevated hs-cTnT and NT-proBNP were 19 ng/L and 125 pg/mL, respectively. Logistic regression models were employed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the association of metal levels with elevated hs-cTnT and NT-proBNP.

Results: The mean age of participants was 48.8±18.2 years, with 50.3% being female. Elevated hs-cTnT and NT-proBNP were observed in 5.3% and 19.4% of the cohort, respectively. After adjusting for confounders, elevated blood lead was associated with an OR (95% CI) of 1.46 (1.02, 2.11) for elevated hs-cTnT and 1.25 (1.02, 1.53) for elevated NT-proBNP. The corresponding OR (95% CI) for elevated blood cadmium were 1.52 (1.12, 2.06) and 1.61 (1.33, 1.96). The effect of blood lead on NT-proBNP was particularly pronounced among non-Hispanic Blacks and individuals with impaired kidney function. No significant interactions were observed between blood cadmium and demographic or clinical variables with the studied biomarkers.

Conclusion: This study substantiates significant associations of elevated blood lead and cadmium with biomarkers of subclinical cardiovascular disease. These findings underscore the potential for targeted preventive strategies to mitigate cardiovascular risk factors, enhancing overall cardiovascular health.

Association of Spatial Tumor Immuno-Phenotyping Score (STIPscore) with Patient Survival in Malignant Pleural Mesothelioma

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Introduction: Malignant pleural mesothelioma (MPM) is a highly aggressive cancer that affects the mesothelial lining of the pleura and is typically associated with asbestos exposure. With advancements in sequencing technology, recent characterizations of the genomic and tumor-immune profiles of MPM tumor samples suggest that the majority of MPM cases promote tumor cell growth by fostering a 'cold' tumor microenvironment (TME) characterized by the presence of M2 macrophages and elevated TGFB1 expression. However, subsets of MPM may respond well to immune checkpoint therapy due to a 'hot' TME. A prognostic tool that provides a quantitative description of the TME in MPM patients would facilitate timely risk stratification and treatment planning.

Methods: Using a novel automatic cyclic staining imaging platform, we established a highly multiplex immunofluorescence panel to acquire the spatial phenotype of a cohort (n=17) of resected MPM formalin-fixed paraffin-embedded tissues. The comprehensive and quantitative spatial patterns of the samples were analyzed using a graph neural network-based approach powered by machine learning.

Results: We established a multiplex panel consisting of 40 immune cell markers and 2 mesothelioma markers. The deep tumor-immune profiles of the samples were obtained using this multiplex panel. Preliminary analysis suggested that a T-cell enriched TME favours MPM patient survival. Further characterization of spatial patterns for the formulation of the STIPscore is warranted.

Conclusion: Our research uncovers vital cell-to-cell interactions that could impact the immune response to malignant mesothelioma tumors, possibly explaining the varied behaviours observed in MPM. Quantitative analysis of spatial patterns in the TME would allow the establishment of a composite score associated with patient survival, thereby improving the clinical management of MPM.

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Cardiovascular-kidney-metabolic (CKM) Health and Mortality Outcomes – Insights from Two Population-Based Studies Over Two Decades Apart

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Introduction: In 2023, the American Heart Association (AHA) established the cardiovascular-kidney-metabolic (CKM) syndrome and defined the different stages of adverse CKM health. Here, we evaluated the prognostic significance of CKM stages with mortality outcomes, and their changes in prevalence over time.

Methods: The prospective associations of CKM stages with mortality outcomes at 10, 15 and 20 years were evaluated in 1912 participants of the Hong Kong Cardiovascular Risk Factors Prevalence Study (CRISPS) using Cox proportional hazard regression analysis. The changes in CKM health over years were assessed by comparing the age-standardized prevalence of different CKM stages in 1739 CRISPS participants (recruited in 2000-2004) with 2382 New-CRISPS (NRCISPS) participants (recruited in 2019-2023).

Results: Higher CKM stages 3 and 4 were associated with all-cause mortality at 15- and 20-years but not at 10-year. At 20-year, the adjusted hazard ratios (HR) for all-cause mortality were 3.8 ($p<0.001$ and 3.7 ($p=0.002$) for stages 3 and 4, respectively, whereas HRs for cardiovascular mortality were 9.0 ($p=0.034$) and 11.1 ($p=0.029$) for stages 3 and 4, respectively. Over the last two decades, the age-standardized prevalence of CKM stage 4 had doubled from 2% to 4%. Although the rates of CKM stages 0 to 2 remained similar, the prevalence of excess adiposity and metabolic dysfunction had significantly increased.

Conclusion: Adverse CKM health was associated with long-term mortality risks up to 20 years. The burden of CKM health burden is large and maintaining individuals at their early CKM stages is important to prevent the progression to mortality.

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Changes in The Incidence, Clinical Features and Outcomes of Tuberculosis During COVID-19 Pandemic

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Introduction: COVID-19 pandemic has disrupted tuberculosis (TB) services in many countries, but the impacts on sites of involvement, drug susceptibility, smear positivity and clinical outcomes, and clinical outcomes of co-infection with influenza and COVID-19 remain unclear.

Methods: Descriptive epidemiological study using episode-based and patient unique data of tuberculosis from Hospital Authority's territory-wide electronic medical record database, comparing baseline (January 2015-December 2019) and COVID-19 period (January 2020-December 2022), followed by univariate and multivariate analyses. Effects of co-infection with influenza and COVID-19 were investigated.

Results: The study included 10,473 episodes of laboratory-confirmed TB, with 6,818 in baseline period and 3,655 during COVID-19 period. During COVID-19 period, TB patients had a lower proportion of smear positivity (49.2% vs. 54.7%, p<0.001), and fewer cases of extrapulmonary TB (7.0% vs. 8.0%, p=0.078) and multidrug resistant TB (1.0% vs. 1.6%, p=0.020). Mortality was higher in TB patients with COVID-19 co-infection (OR 1.7, p=0.003) and influenza co-infection (OR 2.6, p=0.004). During COVID-19 period, there were higher rates of treatment delay (20.5% vs. 15.5%, p<0.001) and episodic death (15.1% vs. 13.3%, p=0.006). Factors associated with higher mortality included age ≥70 years (OR 7.24), treatment delay (OR 2.16), extrapulmonary TB (OR 2.13), smear positivity (OR 1.71) and Charlson comorbidity index score ≥3 (OR 1.37). Higher mortality was observed with co-infection by influenza (OR 1.18) and COVID-19 (OR 1.7).

Conclusion: The epidemiology and outcomes of TB were changed during COVID-19 period. Mortality was higher during COVID-19 period and with co-infection by influenza and COVID-19.

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Clinical Outcomes of Mild-To-Moderate Mixed Aortic Valve Disease Versus Isolated Aortic Stenosis

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Introduction: Aortic regurgitation (AR) imposes additional volume overload to left ventricle in patients with aortic stenosis (AS), however, a direct comparison of outcomes between mild-to-moderate mixed aortic valve disease (MAVD) and isolated AS has not been performed, there are limited data for evidence-based recommendations to be made in patients with mild-to-moderate MAVD. Hence, the aim of this article is to compare the clinical outcomes between patients with mild-to-moderate MAVD and those with isolated mild-to-moderate AS.

Methods: This was a retrospective observational cohort study, which included patients with mild-to-moderate native tricuspid AS (defined as aortic valve area between 1.0 and 2.0 cm^2) and preserved left ventricular ejection fraction ≥50% from QMH between 2003 and 2021. Mild-to-moderate MAVD was defined as a combination of mild-to-moderate AS and mild-to-moderate AR (grade 2). All patients were divided into those with MAVD and those with isolated AS. All-cause mortality, aortic valve replacement (AVR), and major adverse cardiovascular events (MACE) were analyzed as endpoints and compared between two groups.

Results: We included 1590 patients (mean age, 75±12 years and 45% men), of whom 227 had mild-to-moderate MAVD. At baseline, patients with MAVD were younger (73.17 vs. 75.69 years; p=0.004) and less frequently had diabetes mellitus (14 vs. 23%; p=0.003) compared to those with isolated AS. In terms of LV remodelling, the presence of MAVD led to an increase in LV end-diastolic diameter (4.39 vs. 4.15 cm; p<0.001) and a reduction in LV ejection fraction (62.38 vs. 63.10%; p=0.2), in which the reduction in LVEF was especially significant when patients with moderate AS developed AR (61.42 vs. 63.35%; p=0.043). Patients with MAVD were similar in all-cause mortality but had a higher risk of AVR (HR: 1.58; 95% CI: 1.12–2.24; p=0.009) and MACE (aHR: 1.28; 95% CI: 1.02, 1.60; p=0.035).

Conclusion: Patients with mild-to-moderate MAVD had a higher risk of AVR and MACE compared to those with isolated AS, and they are associated with faster progression and worse clinical outcomes. In MAVD, presence of coexisting AR adds additional volume load, leading to a different LV remodelling. Closer surveillance is warranted in this population to optimize patient care.

Clinical Outcomes of Total Knee Replacement in People with Type 2 Diabetes After Achieving Satisfactory Glycemic Control: The Role of Diabetes Chronicity

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Introduction: With the implementation of a program aiming for stringent optimization of pre-operative glycemic control, we evaluated the clinical outcomes and their predictors among patients with type 2 diabetes who had achieved excellent glycemic control prior to total knee replacement (TKR).

Methods: We included patients with type 2 diabetes who underwent TKR during the implementation of the pre-operative glycemic optimization program from 2016–2021. Clinical characteristics, anthropometric measurements, knee score and function score at one-year post-operation, post-operative complications and mortality were retrieved. Multivariable regression analyses were performed to identify independent factors associated with various post-operative outcomes.

Results: In total, 382 knees (in 294 patients) were included (mean age 72.1±8.5years, 34.8% men, body mass index 28.5±4.6kg/m2, HbA1c 6.6±0.6%, duration of diabetes 10.1±8.6years). 95.5% achieved pre-operative glycated hemoglobin (HbA1c) ≤7.5%. Coronary artery disease independently predicted lower likelihood of satisfactory one-year knee score (adjusted odds ratio [aOR] for knee score≥90 =0.48, p=0.026). Older age (≥65years) (aOR=0.40, p=0.002), long duration of diabetes (≥10 years) (aOR=0.54, p=0.008) and diabetic retinopathy (aOR=0.54, p=0.049) all independently predicted lower likelihood of achieving fair one-year function score (≥56). Rates of periprosthetic joint infection and all-cause revision were only 1.6% and 2.4% respectively. Long duration of diabetes (adjusted hazard ratio [aHR]=2.50, p<0.001) and CAD (aHR=2.10, p=0.018) were independent predictors of all-cause mortality. Glycemic control was no longer a significant predictor of all the above outcomes.

Conclusion: Among type 2 diabetes patients with excellent pre-operative glycemic control before TKR, more intensive glycemic control might not be associated with further improvement in outcomes. Residual post-operative risks were characterized by presence of chronic diabetes-related microvascular and macrovascular complications.

Comparison of Mesenchymal Stem Cells Derived from Induced Pluripotent Stem Cells (iPSC-MSCs) and Umbilical Cord (UC-MSC) in Immunomodulatory Functions

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Introduction: Mesenchymal stem cell (MSC) therapy is currently being actively investigated in clinical trials. Their anti-inflammatory activities and abilities to home to damaged tissue allow wide applications in different diseases. With their confirmed abilities to suppress the immune system, MSC was first applied in clinical trials in treating graft-versus-host disease (GvHD). MSCs from different sources have their uniqueness and can behave very differently. Among those, MSCs derived from traceable cell sources such as induced pluripotent stem cells (iPSCs) are preferably considered in clinical cases, due to the ease of mass production, unlimited cell sources supply, and better quality-control when translating into good manufacturing practice (GMP)-compliant cell therapeutic products compared to tissue-derived MSCs. We previously reported that iPSC-MSCs have advantages over bone marrow MSCs such as their higher proliferation capacity, and they can better promote angiogenesis in the ischemia hindlimb mouse model. To further assess the potential use of iPSC-MSCs over tissue-derived MSCs, we aim to compare iPSC-MSCs with umbilical cord (UC)-MSCs.

Methods: We first studied their similarities and differences by both bulk RNA sequencing and single-cell RNA sequencing analysis and pinpointed their immunoregulatory characteristics. We also examined their immunomodulatory effects by assessing their abilities to suppress T-cell proliferation in vitro and compared the RNA expression levels of common immunoregulatory proteins after co-culture studies.

Results: From both aspects, we found that both iPSC-MSCs and UC-MSCs have comparable immunosuppression potential.

Conclusion: With the advantage of being differentiated from pluripotent stem cells, we believe that iPSC-MSCs is a better alternative of UC-MSCs in terms of immunomodulation for different autoimmune diseases in clinical applications.

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Consumption and Expenditure of WHO Essential Medicine for Cancer: Drug Utilisation Analysis of 40 Countries and Regions Between 2012 To 2022

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Introduction: To address the escalating global cancer burden, the World Health Organization introduced the Model List of Essential Medicines (EML) for neoplasm. This multinational drug utilization study aimed to evaluate international patterns in the consumption and expenditure of EML-listed cancer drugs.

Methods: For each year from 2012 to 2022, we adopted the MIDAS database, which captures monthly sales volume by IQVIA global auditing, to measure annual consumption in standard units (SU) sold per 1,000 capita and expenditure in US dollars adjusted by inflation rate for the selected drugs of 40 countries. Changes in consumption and expenditure were estimated using the average annual growth rate (AAGR). Lorenz curve and concentration index were adopted for visualization and quantification of health equalities. Panel regression was used to assess the associations between consumption, national/regional income levels, disability-adjusted life-years (DALYs), and regional Gini index. Drug expenditure and consumption patterns with overall survival (OS) benefit evidence were further analyzed for targeted therapies and immunomodulators.

Results: By 2022, median consumption (SU) per 1,000 capita was comparable between high-income (427.65 [Interquartile range (IQR): 709.02]) and middle-income economies (603.15 [IQR: 486.52]). Over the 11-year study period, middle-income economies showed increased consumption trends (AAGR: 13.56%, compared to 1.31% in high-income, $p<0.05$) and increased expenditure (AAGR: 7.72%, compared to -0.4% in high-income, $p<0.05$). The consumption inequalities have gradually improved over the past decade. However, per 1,000 capita expenditure disparities were evident (middle-income economies: USD 2,540.84 [IQR: 2,033.71], high-income expenditures: USD 12,747.11 [IQR: 18,918.57]). Consumption positively correlated with DALYs ($p<0.05$) and Gini index ($p<0.05$). Furthermore, Middle-income economies spent more on drugs without proven clinical benefits compared to high-income economies (74.63% vs. 55.84%, chi-squared $p<0.05$).

Conclusion: Consumption disparities for essential cancer drugs were improved in the past decade, driven by increased consumption and controlled expenditure in middle-income economies. As expected, consumption of essential cancer drugs was correlated with disease burden and social inequality and was less sensitive to national income. Notably, high-income economies allocate more fundings towards drugs with clinical benefits.

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Derivation of A New Clinical Score to Predict Late Seizures After Intracerebral Hemorrhage and Validation of The CAVE and CAVE2 Scores

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Introduction: Intracerebral hemorrhage (ICH) survivors are at high risk of late seizures, which are indicative of post-stroke epilepsy (PSE). As PSE is associated with poorer long-term outcomes, accurate prediction of late seizures is essential in advancing treatment, particularly in selecting patients for long-term prophylactic antiseizure medications (ASM). Therefore, we aim to validate the CAVE and CAVE2 scores (current validated scores to predict late seizures after ICH) from our ICH cohort and derive a new prediction score for late seizures following ICH.

Methods: Consecutive ICH patients from the HKU ICH registry from 2011 to 2022 were retrospectively analyzed to identify potential predictors of late seizures following ICH. Patients who died within six months of ICH were excluded. Independent factors associated with late seizure were identified using multivariate logistic regression, and the new prediction (CLoVE) score was created based on the β-coefficients. The discriminative ability of the CAVE, CAVE2, and CLoVE was compared using the receiver operating characteristic curve analysis. The cut-off for the CloVE score was determined to maximize specificity (>0.95).

Results: Among 845 ICH survivors, 82 (9.7%) had late seizures. The 8-point CLoVE score (Creatinine clearance (estimate glomerular filtration rate, mL/min/1.73m^2) <15=3, 15.0–29.9=2, 30.0–44.9=1; Lobar=1; Volume (mL) 10.0–31=1, >31=2; Early Seizure=2) predicted post-ICH late seizure with a c-statistics of 0.757 (95% CI 0.702–0.812). The CAVE and CAVE2 score had lower discriminative ability in our cohort (c-statistic: 0.669 [95% confidence interval (CI) 0.604–0.735]; 0.688 [0.622–0.754], respectively). A CLoVE score of ≥4 had a specificity of 0.98 to predict late seizures but the sensitivity and positive predictive values were low (0.18 and 0.45).

Conclusion: The current CAVE and CAVE2 scores had low discriminant ability in our ICH cohort. The newly derived CLoVE score had better discriminative ability. Further external validation and work are warranted to study the clinical application of the CLoVE score for long-term prophylaxis ASM following ICH.

Development and Validation of A Novel Algorithm Integrating Circulating TSP2 and PIIINP for Identification of Advanced Fibrosis

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Introduction: The Enhanced Liver Fibrosis (ELF) test is a well-established non-invasive diagnostic tool for the identification of advanced liver fibrosis. Recent studies have identified thrombospondin-2 (TSP2) as a promising biomarker for fibrosis. This study aims to compare the diagnostic performance of TSP2 with the components of the ELF test and to develop a novel biomarker-based algorithm for detecting advanced fibrosis in patients with non-alcoholic fatty liver disease (NAFLD).

Methods: Circulating levels of TSP2 and the components of the ELF test were quantified in a derivation cohort of type 2 diabetes (T2D) patients diagnosed with NAFLD via vibration-controlled transient elastography (VCTE). Validation was performed using a cohort of morbidly obese patients with biopsy-confirmed NAFLD and an additional community-based cohort of T2D patients with VCTE-confirmed NAFLD. The diagnostic accuracy was assessed using receiver operating characteristic (ROC) analysis. A multivariate logistic regression model was employed to construct an algorithm based on TSP2 and procollagen 3 N-terminal peptide (PIIINP). A dual cut-off strategy was implemented to define rule-in and rule-out thresholds.

Results: Both TSP2 (AUC [95% CI]: 0.844 [0.810–0.878]) and PIIINP (AUC [95% CI]: 0.843 [0.807–0.875]) demonstrated excellent diagnostic performance and were utilized to formulate the biomarker-based algorithm in the derivation cohorts. The TSP2-PIIINP algorithm (AUC [95% CI]: 0.900 [0.874–0.925]) significantly outperformed ELF, FIB-4, and NFS, exhibiting high specificity (85.16%), sensitivity (78.62%), and negative predictive value (NPV) (95.06%) at the optimal cut-off. Implementing rule-out and rule-in thresholds of <0.132 and ≥0.289, respectively, the algorithm resulted in fewer indeterminate results compared to ELF. It also demonstrated robust diagnostic performance in the validation cohorts. Decision curve analysis confirmed the clinical utility of the TSP2-PIIINP algorithm.

Conclusion: The TSP2-PIIINP algorithm exhibited superior diagnostic accuracy compared to the ELF test and has the potential to be developed into a novel non-invasive diagnostic tool for advanced liver fibrosis.

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Diabetes Mellitus Control and Clinical Outcomes in Intracerebral Hemorrhage

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Introduction: Previous population studies on diabetes mellitus (DM) and intracerebral hemorrhage (ICH]) have demonstrated conflicting conclusions on their association. These discrepancies may be due to the lack of accounting for glycemic control. Additionally, pre-ICH use of metformin had been associated with better functional outcomes. Therefore, we aimed to evaluate the association of admission glycaemic control and the types of diabetic medication use with ICH outcomes.

Methods: We retrospectively analyzed ICH patients enrolled in The University of Hong Kong prospective stroke registry from January 2011 to December 2022. Patients with recurrent stroke within six months of ICH or those 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 >6.5%. The associations between DM control and medication use with ICH outcomes were determined using multivariate logistic regression.

Results: Among the 948 ICH patients included, 206 (21.7%) had DM, in which 69.9% had inadequately controlled DM. DM was found to be independently associated with poor outcomes (adjusted odds ratio (aOR) 1.76, 95% confidence interval (CI) 1.11–2.80). When patients were stratified based on DM control, only inadequately controlled DM was linked to poor outcomes (aOR 1.78, 95% CI 1.05–2.99). There were no significant differences in 6-month mortality between patients with and without DM (aOR 1.26, 95% CI 0.74–2.16), and the risk of mortality did not differ according to DM control (both p>0.05). In the subgroup analysis among patients with DM, no specific class of diabetic medications was demonstrated to be associated with mortality and functional outcome, including metformin (all p>0.05).

Conclusion: Around two-third of ICH patients with DM had inadequately controlled DM, increasing their risk of poor outcome after ICH.

Exosomes from Human Induced Pluripotent Stem Cell–Derived Mesenchymal Stem Cells Alleviate Liver Fibrosis in A Mouse Model of Wilson's Disease

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Introduction: Wilson's Disease (WD) is a hereditary disorder of liver metabolism due to ATP7B gene mutation characterized by copper accumulation and hepatic dysfunction. Mesenchymal Stem Cells (MSCs) exosomes are increasingly used as cell-free therapies in liver diseases. As such, in this study, we aimed to investigate the in vivo therapeutic potential of exosomes isolated from human induced pluripotent stem cell derived -MSCs (hiPSC-MSCs-Ex) in a WD mouse model.

Methods: The DiR-labeled hiPSC-MSCs-Ex were injected intravenously into the ATP7B -/- WD mouse model every two weeks for 8 weeks, and the hepatic functions were evaluated after systematic administration.

Results: Our results showed that hiPSC-MSCs-Ex was successfully targeted to the injured liver and maintained in the liver after systematic administration. Functionally, compared to the untreated group, hiPSC-MSCs-Ex-treated mice showed reduced liver fibrosis as indicated by a decrease in collagen accumulation, enhanced liver functionality, and alleviation of inflammation.

Conclusion: These results demonstrated that hiPSC-MSCs-Ex could reduce inflammation and ameliorate hepatic fibrosis in a liver disease mouse model, which may provide an allogeneic cell-free MSC therapy for chronic liver fibrosis.

Global Landscape of Stroke Rehabilitation and Telerehabilitation: Current Situations, Perceptions, and Future Directions

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Introduction: Timely and adequate stroke rehabilitation is crucial in facilitating post-stroke recovery. Telerehabilitation bloomed up as an innovative approach to delivering services remotely, yet no consensus has reached with various solutions and practices available. This study aimed to understand the current landscape and barriers of conventional stroke rehabilitation and telerehabilitation in hope of guiding future improvement in stroke care pathway.

Methods: An online global survey was developed and validated by a panel of stroke experts from the World Stroke Organization Future Leaders Program and distributed worldwide, aimed at stroke care providers, affiliated societies, and partner organizations. Countries with at least ten responses were included in subsequent country-based analyses. Chi-square analysis was used to analyze differences in survey responses between countries.

Results: Between January and July 2024, 526 responses were received from 63 countries, covering six continents. Majority of respondents are physicians (67%) and physio- and occupational therapists (20%) with over 10 years of experience in stroke care (66%). Conventional rehabilitation services are only available to 33.5% of eligible stroke patients globally, and as low as 22% in low-middle income countries. Challenges to conventional rehabilitation faced by respondents' sites include limited availability to rehabilitation facilities or post-discharge care (59%), lack of trained rehabilitation professionals (42%), and patients' lack of awareness about the importance of rehabilitation (40%). There is a significant knowledge gap on telerehabilitation (p=0.007**); 29% of responders (n=153) have not heard of telerehabilitation, including Romania (56%), India (42%), China (37%), and Malaysia (32%). Among all respondents, only 14.8% sites (n=56) offer stroke telerehabilitation with diverse practice. Notably, only 46% of them have relevant protocol or guideline in place, 34% (n=19) of which were synthesized locally, and 19% (n=7) adapted or followed international protocol. The most commonly reported barriers to providing telerehabilitation include the lack of suitable electronic devices (12.9%), limited internet connectivity (12.9%), leading to poor quality of the sessions (10.4%), and lack of clear guidelines and protocols (9.2%). Despite the challenges, majority of the respondents agreed that telerehabilitation still has a role after the coronavirus-19 pandemic (83%), improves access to services (88%), and is an acceptable approach (72%). However, a significant proportion of respondents (39%) do not feel comfortable delivering telerehabilitative services.

Conclusion: This study provides a comprehensive overview of global practices and availability of post-stroke rehabilitation and telerehabilitation services, highlighting the burden, limitations, and challenges to be tackled in future enhancement and incorporation of telerehabilitative technologies into stroke care pathway.

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Glycemic Control is A Modifiable Risk Factor for Pancreatic Cancer Development in Patients with Diabetes Mellitus: A Population-Based Cohort Study

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Introduction: Diabetes mellitus (DM) is a risk factor of pancreatic cancer (PC). However, whether glycemic control influences PC development among patients with long-standing Type 2 DM (T2DM) (> three years) remains unclear.

Methods: We identified adults (age ≥18 years) newly diagnosed with T2DM between 2001 and 2015 from a territory-wide healthcare registry in Hong Kong. T2DM was diagnosed by (i) the American Diabetes Association criteria with two abnormal HbA1c results of ≥6.5% or fasting glucose levels ≥7 mmol/L, (ii) use of anti-diabetic medications, or (iii) international classification of diseases (ICD-9) coding. Exclusion criteria included prior history of PC, pancreatic cyst, IgG4 disease, or pancreatectomy. To minimize reverse causality, patients who developed PC within three years of DM diagnosis were excluded. The primary outcome was PC development. Glycemic control was assessed using time-weighted mean HbA1c throughout the observation period, categorized into optimal (HbA1c <7%) and suboptimal (HbA1c ≥7%) control. Propensity score (PS) matching with multivariable Cox regression was used to estimate the adjusted hazards ratio (aHR) of PC with optimal glycemic control. Covariates included age, sex, smoking, alcohol use disorder, chronic or acute pancreatitis, acute cholangitis or cholecystitis, dyslipidemia, cardiovascular factors, chronic renal failure, cirrhosis, use of concurrent medications (including aspirin, NSAIDs, statins), and anti-diabetic medications. The Fine-Gray competing risk analysis was used to derive the subdistribution hazard ratio (SHR) and 95% CI, considering all-cause mortality as a competing event for PC. Subgroup analyses stratified by PC risk by age (<65 vs. ≥65 years), sex, BMI (<25 vs. ≥25 kg/m^2), smoking status, diabetes-related complications and medication use.

Results: Among 312,404 T2DM patients (mean age:58.7±11.6 years, 50.4% male), 1,042 (0.33%) developed PC over a median follow-up of 10.5 years (interquartile range:7.7–14.6 years). The mean time-weighted HbA1c was 7.1±1.0%. Optimal glycemic control was associated with a lower PC risk (aHR:0.49; 95% CI:0.43–0.56) compared to suboptimal control. Competing risk analysis indicated that optimal glycemic control was associated with a lower risk of PC (SHR:0.48; 95% CI:0.41–0.55). The 15-year cumulative incidence of PC in the optimal glycemic control group (0.36%) was significantly lower than suboptimal glycemic control group (0.69%). This beneficial effect persisted across age, sex, BMI, smoking, DM-related complications, and most medications, but wasn't statistically significant for insulin users.

Conclusion: Glycemic control was independently associated with PC risk in long-standing T2DM patients. The finding could guide PC risk stratification and provides an additional oncopreventive strategy.

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Gut Microbiota Predicts Treatment Response to Empagliflozin Among Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Patients Without Diabetes Mellitus

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Introduction: Empagliflozin (an SGLT2 inhibitor) was shown to be effective in reducing hepatic steatosis in metabolic dysfunction-associated steatotic liver disease (MASLD) patients without diabetes mellitus (DM). We aimed to investigate whether baseline gut microbiota profile could predict treatment response to empagliflozin among MASLD patients without DM.

Methods: We prospectively followed up non-diabetic MASLD patients who used empagliflozin 10mg daily. Clinical, anthropometric and laboratory assessments were performed serially from baseline to week 52 (EOT) and magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at baseline and EOT. Baseline stool samples before treatment were collected for the empagliflozin group, and shotgun DNA metagenomic sequencing was performed to profile microbiome. Primary outcome was treatment response to empagliflozin at EOT, defined as MRI-PDFF decline ≥30%. Linear discriminant analysis [LDA] effect size analysis was used to identify putative bacterial species and metabolic pathways. Multivariable logistic regression was used to derive adjusted odds ratio (aOR) of outcome with bacterial species by adjusting for clinical factors including baseline body weight, diet and alanine aminotransferase (ALT) ≥40U/L.

Results: Among 49 empagliflozin users, 45 with sufficient DNA concentration in stool samples were included. 22 (48.9%) achieved treatment response to empagliflozin at EOT. There was a significant difference in alpha diversity (Shannon index:$p<0.001$; Simpson index:$p=0.001$) and beta diversity ($p=0.048$) in baseline microbiome between treatment response and non-response groups. Faecalibacterium prausnitzii (log10LDA score=4.27), Lachnospira pectinoschiza (log10LDA score=3.99), Anaerostipes hadrus (log10LDA score=3.98), Roseburia faecis (log10LDA score=3.97), Roseburia inulinivorans (log10LDA score=3.58), and Agathobaculum butyriciproducens (log10LDA score=2.77) were enriched in treatment response group. L. pectinoschiza (aOR:34.1; $p=0.015$), A. hadrus (aOR:35.0; $p=0.032$) and A. butyriciproducens (aOR:22.3; $p=0.023$) were associated with treatment response, but not clinical factors. These three species collectively distinguished treatment response from no response with AUROC of 0.89 (95% CI:0.80–0.99). A. hadrus correlated with pathways that produced metabolites beneficial to alleviating hepatic steatosis, including acetyl-CoA fermentation to butanoate II pathway ($r=0.47$; $p=0.024$) as well as superpathway of L-lysine, L-threonine and L-methionine biosynthesis II ($r=0.44$; $p=0.035$). F. prausnitzii and A. butyricidproducens correlated with L-arginine biosynthesis I pathway (F. prausnitzii:$r=0.71$, $p<0.001$; A. butyriciproducens:$r=0.45$, $p=0.027$), L-arginine biosynthesis II pathway (F. prausnitzii:$r=0.71$, $p<0.001$; A. butyriciproducens:$r=0.45$, $p=0.031$) and superpathway of L-cysteine biosynthesis (mammalian) (F. prausnitzii:$r=0.86$, $p<0.001$; A. butyriciproducens:$r=0.43$, $p=0.036$).

Conclusion: Baseline abundance of certain gut bacterial species, particularly combination of A. hadrus, L. pectinoschiza and A. butyriciproducens, may predict treatment response to empagliflozin in MAFLD patients without DM.

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HPK1 Inhibition and Venetoclax Combination Suppressed AML by Enhancing Cytotoxic T-cell Response to Leukaemia

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Introduction: Immune escape is one of the major causes of treatment failure in cancer therapy and modulation of immune cell function has become an emerging therapeutic strategy. Haematopoietic progenitor kinase 1 (HPK1) is a negative regulator of T cell signaling and its inhibition promotes T cell function. Venetoclax, a BCL2 inhibitor, has become a standard of care for unfit or elderly patients with acute myeloid leukaemia (AML) and may enhance anti-leukaemic effector T-cell function. We hypothesize that HPK1 inhibitor (HPK1i) may synergize with venetoclax and improve treatment outcome in AML by co-activating cell-death pathway and T cell immunity.

Methods: Human T cells were activated by anti-CD3/CD28 antibodies in vitro. Proliferation, cytokine production, T-cell subsets and exhaustion were examined by flow cytometry after 3-day treatment of HPK1i. Recipient mice engrafting with MLL-AF9 AML were treated with HPK1i singly or in combination with venetoclax. Leukaemic burden, apoptosis and T cell functions and exhaustion were examined.

Results: In vitro, HPK1i treatment of activated human T-cells induced cellular proliferation and expression of TNF-α and INF-γ. It increased effector memory T-cell (CD62L-CD45RA-) and decreased naïve T-cell population (CD62L+CD45RA+). Furthermore, it reduced exhaustion markers including PD-1 and TIM3. In vivo, HPK1i and venetoclax combination significantly decreased the burden and induced apoptosis of leukaemic cells on 18th DPT (days post transplantation), and prolonged survival of non-irradiated mice that were transplanted with donor mouse MLL-AF9 AML cells. Cytotoxic T-cells were activated, associated with increase in TNF-α and INF-γ expression and increase in the effector memory T cell subset. There was a decrease in naïve T cell population and T cell exhaustion marker PD-1.

Conclusion: HPK1i and venetoclax reduced the leukaemic burden and enhanced the anti-leukemic ability of T cells in MLL-AF9 AML mouse model.

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Immunotherapy for the Treatment of Alzheimer's Disease: A 2024 Update on Clinical Trials

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Introduction: Alzheimer's disease is the most common form of dementia characterized by the accumulation of extracellular amyloid-beta and intracellular neurofibrillary tangles. Since the introduction of anti-amyloid immunotherapies, significant advances have been made in recent years in altering neurodegeneration and progression in dementia.

Methods: We conducted a literature search in PubMed up to July 2024. Randomized controlled trials studying the efficacy and safety of anti-amyloid immunotherapies were included.

Results: Passive immunotherapies with third-generation anti-amyloid-beta monoclonal antibodies have demonstrated the most success. Aducanumab (EMERGE, ENGAGE trials), Lecanemab (Clarity-AD) and Donanemab (TRAILBLAZER-ALZ2) have been approved by the FDA. Aducanumab was able to decrease amyloid burden on positron emission tomography (PET), with a difference in adjusted mean change of standardized uptake value ratio (SUVR) between high-dose group and placebo of -0.278 (95% Confidence Interval [CI], -0.306 to -0.250, $p<0.0001$) for EMERGE and -0.232 (95% CI, -0.256 to -0.208, $p<0.0001$) for ENGAGE. However, Aducanumab failed to show statistically significant amelioration in cognitive decline. Meanwhile, both Lecanemab and Donanemab were able to reduce amyloid burden on PET and improve clinical cognitive outcomes, with a difference of -0.45 (95% CI -0.67 to -0.23, $p<0.001$) in adjusted least-squares mean change in Clinical Dementia Rating-Sum of Boxes [CDR-SB] between Lecanemab and placebo whereas Donanemab shows 35.1% slowing of disease progression (95% CI, 19.9% to 50.23%). Amyloid-related imaging abnormalities (ARIA), including cerebral edema (ARIA-E) and cerebral microhemorrhage (ARIA-H) were reported in all trials. Further research with real-world data is warranted to optimize patient selection, risk stratification, and monitoring strategies. Active immunotherapies, including tau-directed vaccines (AADvac1 and ACI-35), have shown promising results in phase II trials, which demonstrated safety, high tolerability and immunogenicity. More data is required to ascertain their efficacy in improving functional outcomes. Over-reactivity may lead to neuroinflammation, and immunosenescence in advanced ages may result in failure to elicit immunogenicity.

Conclusion: Passive immunotherapies, Aducanumab, Lecanemab and Donanemab are effective to reduce amyloid burden on PET scan and ameliorate cognitive decline in early Alzheimer's disease patients. However, ARIAs were reported as adverse events and warrant further investigation in monitoring strategies. Active immunotherapies are currently under research to ascertain their clinical efficacy.

Impact of Biologics Use on Asthma-Related Hospitalization – An Epidemiological Study in Hong Kong

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Introduction: Severe asthma is defined as asthma requiring treatment with high dose inhaled glucocorticoids plus a second controller and/or systemic glucocorticoids for 50 percent or more of the year to prevent asthma from becoming uncontrolled or that which remains uncontrolled despite this therapy. Severe asthma remains a major health care problem and is associated with significant morbidity and mortality. The development of biologics for patient with asthma revolutionized the treatment paradigm in severe asthma. Initially, biologics that were developed were exclusively for those with Th2 asthma, while anti-thymic stromal lymphopoietin, Tezepelumab also works for non-Th2 asthma. Although the biologics for severe asthma have not been compared in head-to-head trials, indirect comparisons found similar improvements in terms of exacerbation rates and asthma control. While the individual effect of biologics in asthma is well demonstrated in clinical trials and real-world studies, whether the impact of the use of biologics have an impact on overall asthma-related hospitalization in population-based level have not been reported.

Methods: This is a territory-wide epidemiological study conducted in Hong Kong. Adult patients with asthma managed in Hong Kong Hospital Authority (HKHA) of Hong Kong from 2014 to 2023 were included. This study utilized electronic health records from the Clinical Data Analysis and Reporting System (CDARS) managed by the HKHA. HKHA is a public healthcare service provider that manages 43 hospitals and institutions, and 122 outpatient clinics, that covers more than 90% of the Hong Kong population since 1993. The CDARS captures medical information including diagnosis, drug prescription details, demographics, admissions, medical procedures, and laboratory results. The asthma diagnostic code for CDARS was validated with positive predictive value (PPV) of 85.0% (95% CI 80.1−89.9%). The inclusion criteria include adult patients with asthma age at or above 18 years old. Patients with asthma was identified by International Classification of Diseases, 9th Revision (ICD-9) code of 493 (493.0, 493.1, 493.2, and 493.9) from CDARS. Patients with co-existing ICD-9 code of 496, which suggest the co-existing diagnosis of chronic obstructive pulmonary disease were excluded. The demographics (Age, gender, age of diagnosis of asthma, Charlson co-morbidity index (CCI), baseline blood eosinophil count (BEC), medication for asthma, the severity of asthma based on GINA steps as in version 2024) were retrieved from CDARS. The number of asthma-related hospitalizations were retrieved from CDARS, from 1st January 2014 to 31st December 2023.

Results: There were total of 101,521 adult patients with asthma included in this study. The weekly asthma-related hospitalizations number was 96 at the start of the study period and 78 at the end of the study period. There was a significant reduction of asthma-related hospitalization associated with biologics usage with the estimated risk ratio of 0.993 (95% CI=0.991–0.996, p-value <0.05). The estimated break-point for the change in asthma-related hospitalization was at week number 169 (95% CI=130.3–207.7), which was the week of 19/3/2017 to 25/3/2017. The slope before and after the break-point were 0.022 and -0.191 (p=1.000) with the difference in the two slope estimates is significant (p< 0.001) according to the Davies' test. This suggested that beyond week 169, there was a trend of significant reduction in asthma-related hospitalization. The estimated break-point is right before the introduction of the mepolizumab, the mostly commonly used asthma biologics for Th2-asthma, in Hong Kong.

Conclusion: Increase in biologics prescription is associated with significant and sustained reduction in asthma-related hospitalizations.

Impact of Hepatic Steatosis on Risk of Acute Liver Injury in People with Chronic Hepatitis B and SARS-CoV-2 Infection

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Introduction: SARS-CoV-2 infection was known to be associated with higher risk of liver impairment in people with chronic hepatitis B infection (CHB). However, evidence regarding the impact of concomitant hepatic steatosis (HS) on the risk of liver disease among people with CHB and SARS-CoV-2 infection is lacking. We investigated the impact of concomitant HS on people with CHB suffering from SARS-CoV-2 infection.

Methods: This retrospective cohort study was performed using an electronic health database for people in Hong Kong with CHB and confirmed SARS-CoV-2 infection between 1st January 2020 and 31st January 2023. People with HS diagnosis (HS+CHB+COVID-19) were identified and matched 1:1 by propensity-score with those without (CHB+COVID-19). Each person was followed up until death, outcome event, or 31st January 2023. Study outcome was incidence of acute liver injury (ALI) within first 28 days since COVID-19 diagnosis. Severity of ALI and comparison of ALI risk stratified by the presence of CHB infection and HS were also analyzed. Incidence rate ratios (IRRs) were estimated by Poisson regression models.

Results: Of 52,259 COVID-19 patients with CHB infection in the cohort, 15,391 people with HS+CHB+COVID-19 and 15,391 people with CHB+COVID-19 were included after matching. HS+CHB+COVID-19 was associated with increased risk of ALI (IRR:1.41,95% CI:1.05–1.90, p=0.023), compared to CHB+COVID-19. Over 99% ALI cases were mild to moderate severity and there were no differences in the severity of ALI between HS+CHB+COVID-19 and CHB+COVID-19 (p=0.127).

Conclusion: Concomitant HS was associated with increased risk of ALI among people with CHB infection suffering from SARS-CoV-2 infection.

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Impact on Mortality, Respiratory and Kidney Outcomes Among Adults – A Territory-Wide Study Comparing Respiratory Syncytial Virus (RSV) and Seasonal Influenza and Identifying Risk Factors for Severe RSV Infections

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Introduction: Respiratory syncytial virus (RSV) and seasonal influenza viruses are important pathogens causing respiratory diseases in both children and adults. Influenza A and B viruses cause acute respiratory illness within outbreaks and epidemics worldwide, mainly during the winter season. According to a global modeling study in 33 countries, the estimated mean annual influenza-associated mortality rates range from 0.1–6.4 per 100,000 individuals to 17.9–223.5 per 100,000, with higher mortality among elderly patients. Patients aged below 5 (especially below 2), aged at or above 65 and patients with comorbidities are at risk of complications from seasonal influenza. RSV was reported to be the third commonest identified respiratory viruses causing hospitalization. In adult patients, apart from upper respiratory tract disease, RSV can cause a spectrum of lower respiratory tract disease ranging from pneumonia to bronchitis, as well as exacerbations of asthma or chronic obstructive pulmonary disease (COPD). Severe in-hospital complications are also common among adult patients hospitalized with RSV infections with 10–31% of the patients requiring intensive care unit (ICU) admission and 3–17 % requiring invasive mechanical ventilation (IMV). Underlying medical comorbidities such as cardiopulmonary diseases, stroke, diabetes mellitus (DM) and chronic kidney diseases (CKD) were reported to be important risk factors for severe RSV infections. Compared to other common respiratory viruses such as COVID-19 and seasonal influenza, RSV infection appeared to cause more respiratory complications. Indeed, previous literature had suggested that patients hospitalized with RSV were more likely to receive standard flow oxygen, high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV), and ICU admission than those hospitalized with COVID-19 or seasonal influenza. Comment on some shortcomings of earlier studies and thus why we want to compare again. Earlier reports in Hong Kong suggested that RSV can cause severe lower respiratory complications in older adults, resulting in respiratory failure, prolonged hospitalization, and high mortality similar to seasonal influenza. Similarly, a study conducted in the United States also suggested that RSV infection may result in greater morbidity and mortality among older hospitalized adults than influenza.

Methods: This was a territory-wide retrospective study to compare mortality and serious in-hospital outcomes in adult patients hospitalized for RSV and seasonal influenza infections. The study will also examine the important risk factors for mortality and serious clinical outcomes in adult patients hospitalized for RSV infection. Adult patients (age 18 years) who were admitted to public hospitals in Hong Kong for RSV infection and seasonal influenza during the period of 1st January 2016 to 30th June 2023 were included. Patients were identified from Clinical Data Analysis and Reporting System (CDARS) of Hospital Authority by International Classification of Diseases, Ninth Revision code of 487.8 for seasonal influenza and 079.6 for RSV infections, and all patients had laboratory confirmation of RSV or seasonal influenza infections. This is a retrospective study without active patient recruitment while the data was already de-identified.

Results: A total of 41206 and 3565 adult patients were hospitalized for seasonal influenza and RSV infections to public hospitals in Hong Kong during the period of 1st January 2016 to 30th June 2023. Patients with RSV infections were older and had higher proportion of male and other medical comorbidities than those with seasonal influenza infection. Patients admitted for RSV infection showed significantly higher risk of in-patient mortality, SRF, secondary bacterial pneumonia, ICU admission and AKI compared those with seasonal influenza ($p<0.001$, for all), and the results were consistent with patients aged ≥ 60, <60 and 50–59. End-stage kidney disease (ESKD) requiring renal replacement therapy (RRT) was a robust independent risk factors for in-patient mortality and serious respiratory outcomes in RSV infection across different age groups ($p<0.001$, for all).

Conclusion: Adults hospitalized for RSV infection was associated with significantly increased risk of in-patient mortality and adverse respiratory and kidney outcomes than those with seasonal influenza. The findings are consistent across various age groups, and the results call for update on RSV vaccination recommendations in adults, especially for the vulnerable subjects such as those with ESKD, irrespective of their age.

Improves Hepatic Differentiation from Induced Pluripotent Stem Cells by The Suppression of Epithelial-Mesenchymal Transition

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Introduction: Induced pluripotent stem cells (iPSCs) induced hepatocytes (iHeps) have been widely used in modeling human liver diseases and as a potential cell source for replacement therapy. However, most iHeps are relatively immature and hard to maintain for long-term in-vitro.

Methods: We optimized the differentiation protocol by addition of a combination of small molecules to inhibit iHeps from epithelial-mesenchymal transition (EMT, iHeps EMTi), and further characterized their function both by in-vitro and in-vivo analysis.

Results: Inhibition of EMT could extend the in-vitro culture of iHeps EMTi from Day-24 up to Day-60. In-vitro analysis revealed that iHeps EMTi exhibit significantly higher expression levels of hepatic functional markers, and enhance hepatocyte functions, including lipid accumulation, glycogen storage, albumin secretion and urea acid metabolism. Moreover, the molecular profiles of iHeps EMTi are closer to those of primary human hepatocytes (PHHs). In addition, the in-vivo engraftment efficiency of iHeps EMTi in chimeric mice model was also improved as compared to iHeps alone.

Conclusion: We established a robust protocol to generate human iHeps with improved function and capable of long-term in-vitro culturing via the suppression of EMT. Moreover, those iHeps with EMT suppression have improved engraftment in human chimeric mice.

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Improving Coronary Artery Disease (CAD) Risk Stratification: CT Coronary Angiogram Radiomics

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Introduction: Cardiovascular disease (CVD) remains a leading cause of mortality globally. This study aimed to evaluate the predictive performance of various machine learning models for identifying patients at high risk of major adverse cardiovascular events (MACE) using coronary CT angiography (CTA) features.

Methods: A retrospective cohort of patients undergoing CTA at QMH Hospital between 2010 and 2019 was analyzed. Clinical data, including age, sex, and vital CTA-derived features, were extracted from the Clinical Data Analysis and Reporting System (CDARS). Quantitative plaque volumes were extracted for every coronary artery, including total volume, calcium volume, fibrous volume, lipid volume, and fibrolipid volume. Other parameters extractd include fractional flow reserve (FFR) and fat attenuated index (FAI). Machine learning models, including XGBoost, CatBoost, LightGBM, Random Forest, and Multilayer Perceptron (MLP), were developed to predict MACE, defined as all-cause mortality, acute coronary syndrome. Logistic regression was used as a comparator. Model performance was assessed using accuracy, sensitivity, specificity, F1-score, and area under the receiver operating characteristic curve (AUC). Feature importance was evaluated using Shapley Additive explanations (SHAP) values.

Results: In total, 3414 patients who had CTA between 2014 and 2019 in Queen Mary Hospital were included (47% male; mean age 62.6±14.20). XGBoost, CatBoost, LightGBM, and Random-Forest outperformed logistic regression predicting MACE. XGBoost achieved the highest F1-score [0.9119] and AUC [0.9679], followed closely by LightGBM [F1-score: 0.9082, AUC: 0.9676], and Random Forest [F1-score: 0.9095, AUC: 0.9675]. MLP had the lowest performance [F1-score: 0.8792, AUC: 0.9254]. SHAP analysis revealed age, calcium plaque volumes, CT-FFR, and FAI as the most influential features in predicting cardiovascular outcomes. The confusion matrix for XGBoost demonstrated high specificity (93.6%) and sensitivity (92.6%), and the ROC curve confirmed its superior predictive power.

Conclusion: The findings show that, compared to conventional logistic regression, the XGBoost, CatBoost, LightGBM, and Random-Forest models offer better prediction accuracy for cardiovascular events. These results support the integration of advanced machine learning models into clinical workflows for personalized risk stratification based on comprehensive CTA features, including quantitative plaque volumes, CT-FFR, and FAI.

Inhibition of Bruton's Tyrosine Kinase Suppresses B Cell Expansion and Alleviates Pathologies in An Autoimmune Model of Neuromyelitis Optica Spectrum Disorders

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Introduction: Neuromyelitis optica spectrum disorders are autoimmune inflammatory demyelinating disorders of the central nervous system (CNS). IgG autoantibodies targeting aquaporin-4 water channel (AQP4-IgG) are the pathogenic effector of NMOSD. B cells are crucial in NMOSD pathogenesis, and Bruton's tyrosine kinase (BTK) is an enzyme involved in B-cell activation, differentiation and maturation. BTK inhibitors (BTKi), such as evobrutinib, have been shown to suppress B-cell activation without depletion of pan-B cells. BTKi are being developed as therapeutic agents for multiple sclerosis; their potential for treating NMOSD remains unknown. The aim of this study is to assess disease progression in a mouse model of NMOSD with AQP4 autoimmunity and to examine the therapeutic potential of evobrutinib using this model.

Methods: A mouse model of NMOSD with AQP4 autoimmunity was established using *in vivo* DNA electrotransfer. AQP4 immunized mice were treated with evobrutinib or vehicle. Beam walking test was employed to assess motor impairments. Flow cytometry was used to examine B cell responses in secondary lymphoid organs. Immunofluorescent staining was performed to study NMOSD-like pathologies.

Results: Beam walking test revealed that at day 7 and 14, AQP4 immunized mice did not display motor weakness compared to controls. At day 28, 42 and 90, AQP4 immunized mice took a longer time and slipped more frequently than control mice to cross a 1.2 × 80 cm (width × length) beam. Similar findings were observed with a narrower 0.6 × 80 cm beam. At day 42, flow cytometry analysis found that AQP4 immunization caused an increase in the frequency of splenic $CD19^{+}CD80^{+}PD\text{-}L2^{+}$ memory B cells and $CD19^{-}CD138^{+}IgG^{+}$ plasma cells. Immunofluorescence analysis showed prominent NMOSD-like pathologies, including loss of AQP4 and glial fibrillary acidic protein (GFAP), demyelination, and axonal loss in the spinal cord of AQP4 immunized mice compared to that of controls. Notably, preliminary data showed that treatment with evobrutinib ameliorated NMOSD-like pathologies in AQP4 immunized mice associated with a significant reduction in the frequency of $CD19^{+}CD86^{+}$ antigen-presenting B cells.

Conclusion: Our results demonstrate that AQP4 immunization via electrotransfer leads to motor impairments in mice for up to 90 days. These mice display B-cell expansion and NMOSD-like pathologies. Additionally, preliminary data suggest that treatment with evobrutinib suppresses antigen-presenting B cells and ameliorates pathologies in AQP4 immunized mice.

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Insights from the Secular Trend of Major Osteoporotic Fractures, Glycemic Control and Osteoporosis Management in People With and Without Diabetes: A 15-Year Population-Based Study in Hong Kong (2009-2023)

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Introduction: Type 2 diabetes is associated with increased fracture risks. With the advancements in glycemic control and osteoporosis management, we evaluated how diabetes-specific excess risk of major osteoporotic fractures (MOF) evolved over a 15-year period, which would provide valuable information to inform public health policy regarding prioritizing the management of bone fragility in diabetes.

Methods: Between 2009 and 2023, individuals aged ≥40 years who sustained MOF were identified from a territory-wide electronic health database, stratified by diabetes status. Key parameters including HbA1c, hypoglycemic episodes, and osteoporosis screening and treatments were retrieved. Ratios of rates between people with and without diabetes were calculated to reflect the disparity between two groups. Secular trends were reported in average annual percentage change (AAPC) using joinpoint regression.

Results: During the 15-year observation, we recorded 91429 hip fractures (mean age: 81.9±10.0 years; 67.5% female; 33.1% comorbid with diabetes), 24473 clinical vertebral fractures (mean age: 71.7±14.8 years; 66.8% female; 25.5% comorbid with diabetes) and 118510 upper limb fractures (mean age: 68.6±14.0 years; 70.6% female; 22.7% comorbid with diabetes). Annual number of hip fractures steadily increased from 5595 in 2009 to 6613 in 2023, with increasing proportion comorbid with diabetes. Although annual age-standardized incidence of hip fractures decreased, rate ratios between diabetes and non-diabetes remained static at 5.4 for women (AAPC +0.59%, p=0.06) and 3.3 for men (AAPC +0.32%, p=0.053), suggesting persistent gap of diabetes-specific excess fracture risk. This gap was similarly observed for clinical vertebral and upper limb fractures. Age-standardized mean HbA1c improved (from 7.5% to 7.0%) with significantly fewer severe hypoglycemic episodes, contributed by increasing use of novel anti-diabetic medications. Prevalence of individuals with screening dual-energy x-ray absorptiometry performed increased, more so in women with diabetes (ratio between diabetes and non-diabetes: AAPC +2.12%, p<0.001). Anti-osteoporosis medication prescriptions increased in both diabetes and non-diabetes, but the ratio between diabetes and non-diabetes dropped, especially in women (AAPC -1.10%, p<0.001).

Conclusion: The persistence of a diabetes-specific excess fracture risk, despite improved glycemic control, highlights a significant gap in current osteoporosis prevention and management practices. Despite increasing efforts of osteoporosis screening in diabetes, this has not translated into more aggressive treatment of bone fragility in diabetes. To address this, public health programs should incorporate more aggressive osteoporosis screening and treatment protocols for people with diabetes. This may include lowering the intervention threshold for bone mineral density in type 2 diabetes patients and ensuring better access to anti-osteoporosis medications.

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Investigation of the Function of β-Klotho in the Progression of Non-Alcoholic Fatty Liver Disease

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Introduction: β-Klotho (KLB) is a transmembrane protein that serves as an essential coreceptor for the endocrine hormone FGF21, playing a key role in FGFR signaling. Recent studies have enhanced our understanding of KLB's function in the liver, adipose tissue, brain, and pancreas, suggesting it offers protection against metabolic diseases. There may also be a soluble form of KLB, similar to KLA, but its existence remains to be confirmed. KLB is involved in bile acid synthesis, indicating its role in lipid homeostasis and potential therapeutic applications for non-alcoholic fatty liver disease (NAFLD), a condition marked by fat accumulation in the liver. However, the mechanisms by which KLB protects the liver from lipotoxicity are not yet clear. This project aims to investigate: (1) how hepatocyte KLB protects against NAFLD and the underlying mechanisms; (2) whether soluble β-Klotho (sKLB) exists and how it is produced; (3) whether sKLB can alleviate NAFLD.

Methods: To investigate the therapeutic role of KLB in NAFLD, this project consists of three parts: (1) a gain-of-function study to restore KLB protein in NAFLD mice; (2) a loss-of-function study using NAFLD mice with the Klb gene deleted in hepatocytes to assess metabolic and liver phenotype changes; (3) an in vitro experiment to identify the presence of a soluble KLB form and its potential to modulate FGF21 activity.

Results: The KLB protein expression levels in Klb^{Alb} mice liver were decreased obviously comparing with those in $Klb^{F/F}$ mice liver, and the Klb^{Alb} mice showed higher fat mass level than that of the $Klb^{F/F}$ mice. The soluble form of mouse KLB could be detected in the serum of the mice from the 4th week up to the 20th week following the AAV injection. The HEK293T cells that have been stably transfected with the full-length mouse (m) and human (h) Klotho-beta (KLB) genes have been validated to detect the soluble forms of mKLB and hKLB in a responsive manner, when cultured in the conditional medium.

Conclusion: Targeted deletion of the Klb gene in hepatocytes may negatively influence the progression of NAFLD. Moreover, the soluble form of KLB is detectable in vitro and may also exist in vivo, acting as a regulatory factor in lipid and glucose metabolism.

Knockdown of Translocator Protein (TSPO) Retards AKI to CKD Transition through Regulating Mitochondrial Dysfunction

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Introduction: Acute kidney injury (AKI) has been widely recognized as an important risk factor for the occurrence and development of chronic kidney disease (CKD). Recent studies suggest that mitochondrial dysfunction emerges as a pivotal contributor to the transition from AKI to CKD. Translocator protein (TSPO), located on the outer mitochondrial membrane, is associated with renal tubular cell death and regeneration in AKI. However, the role of TSPO in AKI to CKD transition remains unknown.

Methods: Renal tubule-specific TSPO knockout (Tubule-$TSPO^{-/-}$) mice were created by crossing TSPO floxed ($TSPO^{flox/flox}$) mice on a C57BL/6J background with tamoxifen inducible Ksp-CreERT2 mice. Unilateral ischemia-reperfusion injury (uIRI) for different timepoints was performed on both Tubule-$TSPO^{-/-}$ and $TSPO^{flox/flox}$ wildtype mice to establish AKI to CKD transition. Kidneys were harvested for histology, inflammation, fibrosis and mitochondria function measurements.

Results: Both TSPO mRNA and protein levels were increased at day 1 and lasted for at least 14 days after uIRI. Histopathologically, uIRI-induced tubular damage was reversed by knockdown of TSPO at day 7 and day 14. Induction of fibronectin, Col-1, TNF-α, CCL-2 and IL-1β mRNA in the uIRI kidney was reduced in knockout group compared to control. In 14 day-uIRI mice, immunohistochemical analysis further confirmed significant reduction of Col-1 and Col-3 expression by TSPO deficiency. Furthermore, PGC1-α, the master regulator of mitochondria function, was significantly increased after knockdown of TSPO. Electron microscope images demonstrated higher number of mitochondria and improved mitochondrial ultrastructure with TSPO deficiency. Reduction of mitochondrial DNA copy number by uIRI was also reversed by knockdown of TSPO.

Conclusion: Knockdown of TSPO in tubular cells could alleviate kidney inflammation and fibrosis in murine uIRI models, increasing mitochondria number and improving mitochondria structure. The results suggested that TSPO could play an important role in regulating mitochondrial functions during AKI to CKD transition progress.

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Large Language Model-Based Knowledge Representation from EHR Data and Prediction of Hepatocellular Carcinoma through Trajectory Modelling of Previous Liver Disease Progressions

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Introduction: The prediction of hepatocellular carcinoma (HCC) development in patients with chronic liver disease is crucial for early diagnosis and improving their survival. However, this task poses significant challenges due to significant heterogeneity in disease manifestation and natural course. In this study, we propose a non-invasive, cost-effective large language model (LLM)-based method for the prediction of HCC, which only utilized the diagnoses history of individuals.

Methods: We evaluated the utility of several LLMs, including BERT, GPT2, MedBERT, and MedGPT2, in a two-stage training process involving pretraining and finetuning. In pretraining, we used the comprehensive diagnostic history of 136,801 patients (males: 45.6%, age: 65.8 [Interquartile range: 52.5–76.0] years old at initial admission between Jan 1, 2000 and Dec 31, 2003, and were followed up until Dec 31, 2023) from the Hong Kong Hospital Authority (HA). For finetuning, we used patients' diagnostic history to train these models to predict future HCC development. Additionally, we applied the GradientSHAP method to investigate the models' interpretations. We tested model performance on two cohorts: a retrospective cohort of 3,672 HCC-diagnosed patients (males: 53.5%, age: mean 78.1 [Interquartile range: 71.4–85.5] at initial HCC diagnosis) and an equal number of matched non-HCC controls with sex and date of birth, and an independent validation cohort (males: 46.9%, age: mean 63.8 [Interquartile range: 54.8–77.5] at initial admission between Jan 1, 2008 and Dec 31, 2009, and were followed up until Dec 31, 2023) with 7,028 HCC-diagnosed patients (males: 65.0%, age: mean 67.5 [Interquartile range: 57.0–78.5] at initial HCC diagnosis) and matched controls. Notably, these HCC-diagnosed and non-HCC individuals were not part of the pretraining population. In the sensitivity analysis, a bootstrapping statistical test with 1,000 iterations was employed to test metrics such as AUROC and AUPRC for median score significance. The robustness of these models was further validated by excluding recent diagnosis history prior to HCC (e.g., 1, 3, and 6 months) in additional experiments.

Results: Among the LLMs, GPT2 demonstrated superior performance in predicting HCC based on patients' historical disease trajectories. It achieved an area under the receiver operating characteristic (AUROC) of 0.830 (0.826–0.834) and 0.863 (0.860–0.866) on the retrospective and the independent validation cohort datasets, respectively. This performance significantly surpassed traditional machine learning models (BOW, MLP, and GRU), improving the AUROC by 5.06% compared to the next best model (GRU). We further found that a shorter, more recent diagnostic history (3 months) was more predictive for HCC identification, yielding an AUROC of 0.836 (0.835–0.838). Excluding longer recent diagnosis history significantly reduced GPT2's performance, decreasing by 6.57%, 12.64%, and 17.46% when excluding the recent 1, 3, and 6 months, respectively. The GradientSHAP method applied to the GPT2 model showed a strong alignment between the interpretations derived from GPT2 and clinical evidence. Specifically, GPT2 considers the history of ‘Unspecified disorder of lipoid metabolism’ (ICD-9: 272.9), ‘Overweight and obesity’ (ICD-9: 278), and ‘Sleep disturbances’ (ICD-9: 780.5) as the top-3 predictive factor for HCC, which is consistent with current clinical observations.

Conclusion: Large language model-based knowledge representation derived from electronic health records (EHR) data demonstrates exceptional performance in the early detection of HCC in liver disease patients. This approach holds significant promise for practical clinical applications.

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Measurable Residual Disease Detection on Day 30 Post Haematopoietic Stem Cell Transplantation Predicts Clinical Outcome in Acute Myeloid Leukaemia

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Introduction: Relapse after allogeneic haematopoietic stem cell transplantation (allo-HSCT) is a major cause of treatment failure in acute myeloid leukaemia (AML). The role of measurable residual disease (MRD) detection in AML has been well established on the prediction of post-chemotherapy relapse and it informs post-remission treatment options. However, its role in post-HSCT is less studied. In this study, the prognostic value of MRD detection during early post HSCT was investigated, to allow possible modulation of graft-versus-leukaemia effect.

Methods: Adult AML patients diagnosed after 2003 with allo-HSCT performed at complete remission in Queen Mary Hospital were studied. MRD detection was performed from archival samples by droplet digital PCR (ddPCR) at 9 recurrent hotspot mutations, including *NPM1* Type A, *DNMT3A* R882H, *IDH1* R132H/C/S, *IDH2* R140Q/R172K, *FLT3* D835Y and *NRAS* G12D, or at patient-specific mutations on bone marrow (BM) samples at defined timepoints post-HSCT. The study was approved by the Institutional Review Board (IRB) of Hospital Authority /HKU (HKU/HA HKW UW14-430 and UW14-639).

Results: Day 30 post-HSCT BM samples were available in 123 AML patients undergoing allo-HSCT from unrelated (N=49) and related (N=74) donors. Conditioning regimens were myeloablative and reduced intensity in 79 and 44 patients, respectively. MRD monitoring was performed at the 9 recurrent hotspots in 116 patients (*NPM1* Type A, N=70; *DNMT3A* R882H, N=33; *IDH1* R132, N=15; *IDH2* R140Q/R172K, N=27; *FLT3* D835Y, N=11; *NRAS* G12D, N=14) and at patient-specific mutations in 7 patients. Forty-eight patients had more than 1 MRD markers, detectable mutations identified in any one marker were considered MRD positive. MRD was positive in 37 (30%) patients. Post-HSCT Day 30 MRD positivity was associated with inferior post-HSCT leukaemia free survival (LFS) and overall survival (OS). MRD positivity was predictive of post-HSCT 3-year relapse risk in both NPM1 and non-NPM1 markers. Multivariate analysis was performed to investigate factors that affect post-HSCT LFS and OS, including post-HSCT Day 30 MRD status, patient clinical and demographic information, European LeukemiaNet (ELN) 2022 risk stratification and status at HSCT. Post-HSCT Day 30 MRD positivity was the only statistically significant factor associated with inferior post-HSCT LFS and OS.

Conclusion: MRD positivity at day 30 post-HSCT BM sample is predictive of early relapse within 3 years for both *NPM1* and non-*NPM1* mutations. This study demonstrated the role of MRD detection early post-HSCT on identifying patients who are at risk of early post-HSCT relapse and allows future investigation of early interventions to prevent post-HSCT relapse.

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Multimodal Multiphasic Deep-Learning for Risk Stratification in Hepatocellular Carcinoma

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Introduction: Hepatocellular carcinoma (HCC) recurrence frequently occurs after curative surgery. Histological microvascular-invasion (MVI) predicts recurrence but cannot provide pre-operative prognostication, whereas clinical prediction scores have variable performances.

Methods: Recurr-NET, a multimodal multiphasic residual-network random survival forest deep-learning model incorporating pre-operative CT and clinical parameters, was developed to predict HCC recurrence after curative surgery. Pre-operative triphasic CT scans were retrieved from patients with resected histology-confirmed HCC from four centers in Hong Kong (Internal-cohort). The internal-cohort was randomly divided in an 8:2 ratio into training and internal-validation. External-testing was performed in an independent cohort from Taiwan.

Results: Among 1231 patients (Age 62.4, 83.1% male, 86.8% viral hepatitis, median follow-up 65.1 months), cumulative HCC recurrence at years 2 and 5 after surgery were 41.8% and 56.4% respectively. Recurr-NET achieved excellent accuracy in predicting recurrence from years 1–5 (Internal cohort AUROC 0.770–0.857; External AUROC 0.758–0.798), significantly out-performing MVI (Internal AUROC 0.518–0.590; External AUROC 0.557–0.615) and the Early-Recurrence-After-Surgery-for-Liver-Tumor pre-operative (ERASL-PRE) score (Internal AUROC 0.523–0.559; External AUROC: 0.524–0.545) respectively (all $p<0.001$). In survival analysis, Recurr-NET was superior to MVI in stratifying recurrence risks at year 2 (Internal: 72.5% vs. 50.0% in MVI; External: 65.3% vs. 46.6% in MVI) and year 5 (Internal: 86.4% vs. 62.5% in MVI; External: 81.4% vs. 63.8% in MVI) (all $p<0.001$). Recurr-NET was also superior to MVI in stratifying liver-related and all-cause mortality (all $p<0.001$). The performance of Recurr-NET remained robust in subgroup analyses.

Conclusion: Recurr-NET accurately predicted HCC recurrence, out-performing MVI and the ERASL-PRE score respectively, highlighting its potential in pre-operative prognostication.

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New Stem Cell-Derived Mesenchymal Stem Cells (A-MSCs) Subpopulations: Functional Identification and Therapeutic Potential for Kidney Regenerative Medicine

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Introduction: Mesenchymal stem cells (MSCs) are multipotent stem cells with the potential for self-renewal and multidirectional differentiation, which provide significant possibilities, such as anti-inflammatory, tissue repairment and immunomodulation promotion. MSCs have been intensively investigated in both pre-clinical and clinical studies. However, the therapeutic efficacy varies resulting from the heterogenicity of MSCs. We aim to target the specific subpopulation in a new stem cell-derived Mesenchymal Stem Cells (A-MSCs) based on the scRNA-seq analysis, purify the specific MSC subpopulation with defined functions, and further investigate the efficacy and safety of A-MSCs in therapeutic applications associated with kidney regeneration.

Methods: 1) Define, characterize and compare the functional differences of the subpopulation of A-MSCs. 2) Single-cell RNA sequencing and bulk RNA sequencing analysis are performed to identify the potential therapeutic advantages of the defined subpopulation. 3) The therapeutic applications associated with kidney disease of the purified MSCs will be assessed in vitro and in vivo.

Results: 1) Generation and Characterization of A-MSCs from the new stem cell. 2) The single-cell RNA sequencing analysis provided a comprehensive analysis of MSCs derived from three different sources: umbilical cord, induced Pluripotent Stem Cell (iPSC) and advanced pluripotent stem cell (Cell A). From the analysis of the differential expressed genes, we found the Gene B, known for its essential role in mammalian kidney development, which is prominently expressed in specific subpopulations, indicating its importance in distinguishing A-MSCs and potentially contributing to their unique therapeutic properties. 3) Check the Gene B expression level in different MSCs, and separate the Gene B + subpopulation by magnetic sorting.

Conclusion: We aim to elucidate the functional differences between A-MSC subpopulations and identify those with the highest therapeutic potential for use in regenerative medicine and immunotherapy.

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Non-Steroidal Anti-Inflammatory Drug Allergy Labels Associated with Mortality and Cardiovascular Outcomes in Stroke

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Introduction: (Mis)labelled drug 'allergy' can restrict future prescriptions and medication use, but its prevalence and impact among stroke patients remain unknown. This longitudinal study investigated the prevalence of the most commonly labelled drug allergies, their accuracy and impact among a large cohort of stroke patients.

Methods: In this combined retrospective, longitudinal and cross-sectional study, longitudinal data of patients diagnosed with acute ischemic stroke between 2008 and 2014 were analyzed. Prevalence of drug allergy labels was compared with the general population. Outcomes between patients with or without the most commonly reported drug allergy were compared, followed by confirmatory allergy testing.

Results: Compared to the general population, stroke patients had disproportionally more drug allergy labels to 'cardiovascular & haematopoietic system' (OR=2.401 [95% CI=1.740–3.315], p<0.001) and 'radiographic & diagnostic agents' (OR=4.818 [95% CI=2.556–9.082], p<0.001) – among the most common being non-steroidal anti-inflammatory drugs (NSAID), with a prevalence of 1.8%. Patients with labelled NSAID allergy were significantly less likely to be prescribed aspirin following acute stroke (OR=0.235 [95% CI=0.092–0.604], p=0.003) and on follow-up (OR=0.217 [95% CI=0.084–0.556], p=0.002). They also experienced significantly higher mortality (OR=7.472 [95% CI=2.437–23.182], p=0.001), peripheral vascular disease (PVD) (OR=9.718 [95% CI=1.977–47.767], p=0.005) and major adverse cardiovascular events (MACE) (OR=6.265 [95% CI=2.040–19.243], p=0.005). The majority (80%) of evaluated NSAID allergy labels were incorrect and were delabelled after provocation testing.

Conclusion: NSAID allergy labels were significantly more prevalent among stroke patients, associated with mortality, PVD and MACE. Given the high rate of mislabelled allergy, multi-disciplinary neuro-allergy interventions could be of potential in improving patient outcomes.

Opportunistic Drug Allergy Delabelling Through COVID-19 Vaccine Allergy Evaluation: Effectiveness and Impact on Quality of Life

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Introduction: Mislabelling of drug 'allergies' (e.g. antibiotics, non-steroidal anti-inflammatory drugs) imposes a significant healthcare burden, compounded by limited access to allergy delabelling services. Although concerns about COVID-19 vaccine allergies have reduced, vaccine allergy services have not only allowed patients (mis)labelled with drug allergies to confidently receive vaccinations, but also offer new opportunities for drug allergy delabelling, as a novel approach to expand its access. In view of that, we conducted the first study to investigate the effectiveness of opportunistic drug allergy delabelling through COVID-19 vaccine allergy safety evaluation and explore its impact on health-related quality of life (HRQoL).

Methods: Vaccine allergy safety (VAS)-Track was the only officially designated referral pathway for suspected COVID-19 vaccine allergy in Hong Kong, which was set up in Hospital Authority Hong Kong West Cluster. Patients evaluated under VAS-Track between 2021 and 2022 and had at least one non-COVID-19 vaccine drug allergy label in their medical records were invited and consented to join the study. Data on demographics, comorbidities, drug allergy labels, COVID-19 vaccination and infection outcomes, and delabelling rates were collected. HRQoL was measured before and after evaluation in a subgroup of patients.

Results: Among 652 patients, 1,456 drug allergy labels were identified, with anti-infectives being the most common (606 [41.6%]), followed by non-steroidal anti-inflammatory drugs (354 [24.3%]). Beta-lactam antibiotics accounted for (334 [55.1%]) of anti-infective labels. Almost all patients (648 [99.4%]) safely continued COVID-19 vaccinations, with increased number of doses conferring better protection. There were 228 (35.0%) patients who underwent drug allergy investigations, with opportunistic drug allergy delabelling being successful in 223 (97.8%), removing 317 (21.8%) incorrect labels, of which 173 (51.8%) were beta-lactams. Subgroup analysis of 45 patients showed improved serial HRQoL following delabelling (DrHy-Q 45.0 vs. 33.3, p<0.001).

Conclusion: Opportunistic allergy delabelling through COVID-19 vaccine allergy evaluation achieved a success rate of 97.8% among those investigated. It is an effective approach to expand the access to drug allergy evaluation services.

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Osteoporosis Management After Occurrence of Medication-Related Osteonecrosis of Jaw

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Introduction: We aimed to investigate the osteoporosis management strategies and clinical outcomes after occurrence of medication-related osteonecrosis of jaw (MRONJ), a rare but potentially serious side effect of anti-resorptive.

Methods: We retrospectively studied individuals diagnosed to have MRONJ during treatment for osteoporosis, managed in Osteoporosis Centre or Oral Maxillofacial Surgery & Dental Unit at Queen Mary Hospital in Hong Kong between 2010 and 2022. We investigated the subsequent osteoporosis management plan, fracture events and bone mineral density (BMD). We also compared the clinical outcomes between individuals who did and did not continue anti-osteoporosis management.

Results: In total, 36 individuals were included (mean age: 78.5 years; 94.4% women). All had bisphosphonate exposure while 7 had denosumab exposure before MRONJ. Dental extraction was the trigger in 41.7% of the cases. Following MRONJ, only 14 individuals continued anti-osteoporosis treatment. Higher fracture probability at the time of MRONJ (indicated by FRAX) was associated with higher likelihood of continuing anti-osteoporosis treatment. For the 14 patients who continued anti-osteoporosis treatment, 8 were put on teriparatide-raloxifene sequence and 3 were on strontium. The two patients on strontium maintained subsequent BMD. Regarding the patients treated with teriparatide-raloxifene, three achieved stable BMD, four achieved improving BMD, and one had a mixed response (improved lumbar spine BMD and decreased total hip BMD). Interestingly, the patient with mixed BMD response had been treated with denosumab. Among the remaining three patients who restarted bisphosphonate or denosumab after MRONJ, one suffered from recurrence of MRONJ.

Conclusion: MRONJ represents a clinical challenge as patients who remain at high fracture risk requires discontinuation of antiresorptive agents. Teriparatide followed by raloxifene may be a reasonable strategy for BMD control and fragility fracture prevention.

Parallel Suppression of Tumor and Cachexia by Targeting LETMD1

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Introduction: Preventing cachexia, a metabolic disorder characterized by energy wasting and involuntary loss of body weight, is crucial for cancer therapy, but targeted strategies are very limited. Activated thermogenesis of brown adipose tissue (BAT) contributes to cachexia pathogenesis in cancer patients. LETMD1, a protein restrictively expressed in various tumor tissues and BAT, is a potential factor associated with both oncogenesis and thermogenesis. This project aims to investigate whether LETMD1 could be developed into a therapeutic target for both tumor progression and cancer cachexia, and to explore the underlying mechanisms.

Methods: Adipocyte-specific LETMD1 knockout mice and their control littermates were subcutaneously injected with 5×10^5 B16 cancer cells for 2 weeks to induce melanoma. The LETMD1-deficient B16 stable cell line was established via lentivirus infection. B16 proliferation was evaluated by cell counting, colony formation assay, and BrdU incorporation assay. Mitochondrial morphology was observed by fluorescence staining and electron transmission microscope. Co-IP/mass spectrometry (MS) was performed to explore the interactive proteins of LETMD1.

Results: shRNA-mediated knockdown of *Letmd1* inhibited B16 cancer cell proliferation in vitro, as revealed by decreased cell number, cell colonies and BrdU-positive cell population, while also retarded B16 melanoma growth in mice. Injection of B16 cancer cells into mice enhanced browning of subcutaneous WAT and BAT, accompanied by increased expression of LETMD1. Adipocyte-specific deletion of LETMD1 alleviated the development of cachexia in mice with B16-induced melanoma. Besides, our data showed that LETMD1 was predominantly localized in the mitochondria, with the transmembrane domain (79–100 amino acid) essential for its mitochondrial localization. LETMD1 decreased maximal respiration and ATP production and induced elongated mitochondria with sparse cristae in B16 cells. Co-IP/MS analysis revealed that LETMD1 interacted with mitochondrial protein VDAC2. LETMD1 deficiency decreased the ubiquitination level of VDAC2, thereby maintaining the VADC2 oligomerization and inducing the release of mitochondrial DNA into the cytosol.

Conclusion: LETMD1 inhibition has the potential to simultaneously suppress cancer cell growth and alleviate cancer cachexia by modulating mitochondrial morphology and function, offering a promising anti-cancer therapy.

Perturbed Pathways of Lipid Metabolism in Patients with Chronic Hepatitis B Infection After Cessation of Long Term Nucleos(T)Ide Analogue

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Introduction: The 'stop-to-cure' approach is a potential strategy to achieve finite duration of nucleoside analogue (NUC) in patients with chronic hepatitis B (CHB) infection. We examined the serial serum metabolomic profiles among flared compared to non-flared CHB patients who had stopped NUCs, followed by *in silico* data mining to identify relevant pathways.

Methods: Patients with HBeAg-negative non-cirrhotic CHB on ≥3 years of NUC were recruited. NUCs were stopped and they were prospectively followed up every 6 weeks for virological relapse (VR: serum HBV DNA rise from undetectable to >2000 IU/mL) and/or clinical flare (VR plus alanine aminotransferase [ALT] >2 times upper limit of normal), with serial blood sampling for metabolomic profiling at week 0, at NUC resumption (for flare patients, or non-flare patients with VR or HBeAg sero-reversion), and at ALT normalization following NUC resumption among flare patients. A total of 8 patients (4 flare [among which 2 later developed HBsAg seroclearance, SC], 4 VR or HBeAg sero-reversion) were included in this interim analysis. Serum metabolomics data was acquired with 1D 1H-Nuclear magnetic resonance spectroscopy. Metabolomics data was analyzed with MetaboAnalyst 6.0. Multiple unpaired t test is performed with GraphPad Prism with threshold p-value <0.05. GEO datasets was analyzed with GEO2R.

Results: Metabolites involved in lipid metabolism (triglyceride and total fatty acid) were significantly downregulated in flare patients compared to non-flare patients at NUC resumption. Among flare patients, succinic acid is significantly downregulated in flare-SC compared to flare-no-SC patients upon ALT normalization. Dimethylsulfone involved in triacylglycerol degradation is upregulated in flare-SC patients, compared to flare-no-SC and non-flare patients, at all timepoints. Compartment specific *in silico* data mining based on GEO DataSets showed genes involved in fatty acid synthesis (FAR1, FASN), fatty acid elongation in mitochondria (NDUFAB1), fatty acid elongation in endoplasmic reticulum (ELOVL1, ELOVL5) were significantly increased in the liver of CHB patients (GSE230397) compared to control, but not in peripheral blood CD8 T cells (GSE217838), indicating a compartment specific imbalance of lipid metabolism. In HBV-ACLF patients, fatty acid beta-oxidation associated genes ACSL1 and ACSL4 were significantly downregulated in the PBMCs of the survival group compared to patients who died (GSE168049).

Conclusion: We demonstrated alterations of lipid metabolism in CHB patients with post-NUC cessation flare that were associated with clinical outcomes. Fatty acid metabolism is perturbed in patients with CHB and is inferred to be associated with survival in those with severe HBV flare based on *in silico* datasets analysis. Our work reveals an imbalance in lipid metabolism in CHB both in spatial location and molecular signature.

Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis was An Independent Risk Factor of Pancreatic Cancer Development in Patients with Type 2 Diabetes

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Introduction: Acute pancreatitis and diabetes mellitus (DM) are established risk factors for pancreatic cancer (PC) development. However, the role of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) as an independent risk factor for PC remains underexplored.

Methods: Adults newly diagnosed with T2D (age ≥18) from January 1993 to December 2020 in Hong Kong's electronic healthcare database were studied. T2D was identified by (i) two abnormal HbA1c ≥6.5% or fasting glucose ≥7 mmol/L, (ii) anti-DM medications use, or (iii) International Classification of Diseases Ninth Revision (ICD-9) code 250. Patients with history of PC, pancreatic neuroendocrine tumor, serous cystadenoma, and chronic pancreatitis were excluded. Index date was set three years post-T2D diagnosis to avoid reverse causality, as new onset diabetes (NOD) may indicate pre-existing PC. Primary outcome was PC development. Primary exposure was PEP, indicated by amylase or lipase levels three times the upper limit of normal more than 24 hours and within 7 days after ERCP. The cohort was categorized into three groups: (i) no ERCP before index date [ERCP(-)], (ii) history of ERCP without PEP [ERCP(+)/PEP(-)], and (iii) history of PEP [ERCP(+)/PEP(+)]. Comparing ERCP(+)/PEP(+) with ERCP(+)/PEP(-) addresses indication bias, which can increase PC risk. Covariates included age, sex, lifestyle factors, metabolic disorders, time-weighted mean HbA1c, cardiovascular diseases, other anti-DM medications, non-aspirin non-steroidal anti-inflammatory drugs, statins, and episode of history of acute pancreatitis. Adjusted hazard ratios (aHRs) for PC were derived using multivariable Cox regression models.

Results: We identified 772,549 T2D patients (mean age: 60.6±12.4 years; 50.3% male). Among these patients, 751,184 (97.2%) was ERCP(-) group , 20,990 (2.7%) ERCP(+)/PEP(-) group, and 375 (0.05%) ERCP(+)/PEP(+) group. 2,128 (0.3%) incident PC cases were recorded during a mean follow-up of 9.1 (±5.9) years, resulting in an incidence rate of 3.0 per 10000 person-years. The crude incidence rates for PC were 0.22, 4.47 and 4.76 per 10,000 person-years for ERCP(-), ERCP(+)/PEP(-) and ERCP(+)/PEP(+) groups, respectively. Compared to ERCP(-), both ERCP(+)/PEP(-) and ERCP(+)/PEP(+) were associated with a higher PC risk, with aHR of 16.8 (95% CI:15.5–18.3) and 28.0 (95% CI:15.7–50.2), respectively. Compared with ERCP(+)/PEP(-), the aHR of PC was 1.94 (95% CI:1.08–3.48) with ERCP(+)/PEP(+).

Conclusion: In a large population of T2D patients, PEP was an independent risk factor for the development of PC. Our findings highlight the necessity of reducing PEP incidence to mitigate short-term complications from acute pancreatitis and lower the risk of PC development.

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Predicting Disease Progression and Mortality Among Patients with Prostate Cancer: An Application of Real-World Data-Driven, Time-inhomogeneous Markov Model

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Introduction: Understanding the progression and mortality risk of prostate cancer is important for optimized patient management and informed medical decisions. Multistate models, such as the Markov model, depict the progression process utilizing various health states, but overlook the influence of prior conditions due to the Markovian assumption. This study aims to develop a time-inhomogeneous Markov model that accounts for progression history. Using population-based real-world data, the model estimates prostate cancer progression probabilities and predicts 10-year mortality risks utilizing baseline characteristics.

Methods: We developed a time-inhomogeneous Markov model with four states related to prostate cancer (localized hormone-naive, localized progression, metastasis progression, and death). Using local electronic medical database, Clinical Data Analysis and Reporting System, we estimated real-world transition probabilities based on a 10-year follow-up of patients diagnosed between 2010 and 2012. Age, Charlson Comorbidity Index (CCI), and Prostate-Specific Antigen (PSA) were considered for fitting the time-varying transition probability. Model performance was assessed using the annual time-dependent Area Under Curve (AUC) of metastasis and death prediction over a 10-year period post-diagnosis in the evaluation cohort of incident patients in 2013. A sensitivity analysis compared this model to a more complex seven-state version to assess the impact of transition complexity. Population mortality until 2033 was projected using the weighted average of the transition probabilities and the forecasted new diagnoses.

Results: We identified 4050 incident patients with prostate cancer between 2010 and 2012, with 2282 deaths and 653 metastases recorded during the 10-year follow-up. The annual AUC for metastasis prediction declined from 0.984 in the first year to 0.737 in the tenth year, and for overall survival, from 0.989 to 0.743, showing good predictive performance even at year 10. The seven-states model, the year-10 AUC values are 0.773 for the metastasis and 0.780 for the death predictions. The predicted mortality risk of patients in the mild risk group (aged <65 years at diagnosis, CCI of 0, PSA <=20 ng/mL) at one, five, and ten years were 3.8%, 24.1%, and 46.2%, respectively. Severe patients (aged >80, CCI >= 3, and PSA >= 58 ng/mL) faced significantly higher risks, with a death probability of 20.3% at year one, 64.3% at year five, and 90.2% at year ten. By 2033, there will be 3,740 deaths among patients with prostate cancer in Hong Kong.

Conclusion: The real-world time-varying Markov model can mimic the disease progression in actual clinical practice. Although the seven-state model is more complex, it provides better predictions for metastasis and death compared to the four-state model. This model can be used for future disease forecasting and health economic evaluations to inform healthcare decisions.

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Prevalence and Incidence of Adult Bronchiectasis in Hong Kong From 2008–2023: A Population-Based Cohort Study

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Introduction: While the incidence and prevalence of bronchiectasis was reported to be increasing in different parts of the world, the epidemiological data on adult bronchiectasis in Hong Kong is lacking. We aim to investigate the incidence and prevalence of adult bronchiectasis patients in Hong Kong, and to assess the changes in trends over time.

Methods: The study population was identified through the Clinical Data Analysis and Reporting System (CDARS) of Hospital Authority, Hong Kong. Patients aged 20 or above with the diagnostic code of bronchiectasis managed in all public hospitals and clinics in Hospital Authority, Hong Kong from 2008 to 2023 were retrospectively recruited. Joinpoint regression was employed to analyze trends in prevalence and incidence, estimating the average annual percent change (AAPC).

Results: The overall prevalence of adult bronchiectasis in Hong Kong has been steadily rising from 2008 to 2023. The prevalence increased from 119.79 per 100,000 population (95% CI 116.93 to 122.65) in 2008 to 202.14 per 100,000 population (95% CI 198.67 to 205.60) in 2023, with AAPC 3.52 (95% CI 3.44 to 3.60). The overall bronchiectasis incidence rate remained relatively stable from 12.38 per 100,000 population to 17.02 per 100,000 population from 2008 to 2023. In 2019, the incidence of bronchiectasis peaked at 20.42 per 100,000 population (95% CI 17.06 to 23.78).

Conclusion: The prevalence of adult bronchiectasis has been increasing from year 2008 to 2023 in Hong Kong, with a largely stable incidence. The results concur with other epidemiological studies in other countries.

Prevalence, Clinical Characteristics and Prognosis of Vascular Disease in Valvular Heart Surgery: A Multi-Centre Study

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Introduction: Atherosclerotic disease, which often occurs in more than one vascular bed, is associated with increased morbidity and mortality. The prevalence and clinical significance of atherosclerotic vascular disease affecting more than one vascular bed, i.e. polyvascular disease, in patients undergoing valvular heart surgery have not been fully investigated. Our study aims to describe the prevalence, clinical characteristics and the prognostic value of vascular disease and polyvascular disease in patients receiving valvular heart surgery.

Methods: From January 2010 to December 2021, 3843 patients (mean age: 58 years, SD: 13 years; 52% male) receiving valvular heart surgery from 2 tertiary centres in Hong Kong were included. The presence of vascular disease in 3 major vascular beds, including coronary artery disease (CAD), ischaemic cerebrovascular accidents (CVA), and peripheral vascular disease (PVD), were collected. Polyvascular disease was defined as the presence of atherosclerotic disease in ≥2 vascular beds. Data on demographics, comorbidities, medications, and surgical evaluation were retrieved. Follow-up data were analyzed for major adverse cardiac events (MACE) and all-cause mortality.

Results: 1266 patients (33%) had vascular disease in ≥1 vascular beds, of whom 207 had polyvascular disease (5.4%). Patients with vascular disease were older with more comorbidities, higher surgical risk, longer operations, and more aortic stenosis. During a median follow-up period of 6.37 years (IQR: 3.40 years–9.54 years), rates of MACE were highest in patients with polyvascular disease (univariable HR: 3.24 (95% CI: 2.62–4.01)), followed by those with monovascular disease (univariable HR: 2.12 (95% CI: 1.83–2.46)), then by those with no vascular disease. Both monovascular and polyvascular disease independently predicted mortality and MACE after stepwise adjustment for demographics, comorbidities, medications, and surgical risk factors. Compared with patients with CAD, those with extracardiac vascular disease also had independently greater risk of MACE (HR 1.37 (95% CI: 1.08–1.73)).

Conclusion: Patients undergoing valvular heart surgery exhibit a high prevalence of vascular disease. The risk of adverse outcomes rises with both the presence and extent of vascular disease, and extracardiac vascular disease also confers greater risk of adverse events compared to CAD.

Prognostic Impact of SGLT2 Inhibitors in Diabetes Mellitus Patients with Coronary Ischemia

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Introduction: Diabetes mellitus (DM) patients with coronary ischemia face an exceptionally elevated risk, and the achievement of complete revascularization (CR) within this population is significantly arduous. The impact of SGLT2 inhibitors on the prognosis of individuals with DM and residual coronary ischemia remains to be conclusively determined. This study aimed to evaluate the prognostic impact of SGLT2 inhibitors in DM patients with coronary ischemia.

Methods: DM Patients and confirmed to have coronary ischemia based on coronary angiography and retrospective coronary angiography-derived fractional flow reserve (caFFR) analysis between January 2014 and December 2016 were included. The successful revascularization of all major coronary artery branches experiencing functional ischemia was defined as complete revascularization (CR). Patients were divided into two groups based on whether they had been prescribed for SGLT2 inhibitors. Subgroup analysis was then performed based on whether CR was achieved. The primary study endpoint was major adverse cardiac events (MACE), with all-cause mortality as the secondary endpoint. Kaplan-Meier analysis and Cox proportional hazards regression modeling assessed the influence of SGLT2 inhibitors on endpoint events occurrence.

Results: Among 671 DM patients with coronary ischemia, there were 484 (72.1%) achieved CR, and 206 (30.7%) SGLT2 inhibitors users. During a mean 36 months follow-up, 100 MACE and 89 all-cause mortality occurred. SGLT2 inhibitor users demonstrated lower rates of MACE (8.3% vs. 17.8%; p=0.002) and all-cause mortality (6.3% vs. 16.3%; p<0.001) compared to non-users. Subgroup analysis indicated that SGLT2 inhibitors were equally beneficial in both the CR and ICR groups ($P_{interaction}$=0.804 for MACE and 0.730 for all-cause mortality). After adjusting for confounding factors in multivariable Cox analysis, SGLT2 inhibitors still showed an association with a reduced risk of MACE both in the CR and ICR subgroups (HR, 0.498; 95% CI, 0.246–0.938; p=0.040 and HR, 0.341; 95% CI, 0.123–0.805; p=0.023, respectively).

Conclusion: SGLT2 inhibitors were associated with a reduced risk of 3 years MACE and all-cause mortality in DM patients with coronary ischemia, with significant effects observed regardless of whether CR was achieved.

Prognostic Value of Concomitant Inflammation and Malnutrition Among Coronary Artery Disease Patients

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Introduction: Coronary artery disease (CAD) is the leading cause of death globally. Prognostic nutritional index (PNI) is an index of nutritional status and calculated by the formula: 10 x serum albumin concentration + 0.005 x total lymphocyte count. Inflammation can be represented by the neutrophil-to-lymphocyte ratio (NLR), which divides the total absolute neutrophil count by the total absolute lymphocyte count. Both indices are simple, economical, and have emerged as key prognostic determinants in CAD. However, no study has reported the phenotype of concomitant inflammation and malnutrition in CAD patients. The aim of this study is to investigate the prognostic value of concomitant inflammation and malnutrition in a CAD population.

Methods: This was a retrospective cohort study of 2003 patients diagnosed with CAD (median age=66.0±11.6, 73.1% male) from Queen Mary Hospital, Hong Kong. 3 groups were defined based on inflammation (NLR) and malnutrition (PNI): absence of inflammation and malnutrition (normal), inflammation or malnutrition alone (mild), and concomitant inflammation and malnutrition (severe). The primary endpoint was all-cause mortality at median 4.5 years follow-up, and secondary endpoints were heart failure (HF) hospitalization and adverse outcomes, defined as the composite of all-cause mortality and HF hospitalization. Survival curves were constructed using Kaplan-Meier estimates and differences tested using log-rank test. Multivariable Cox proportional hazards model was used to evaluate the association of mild and severe status with the risk of adverse events. The Fine-Gray model accounted for mutually exclusive endpoints, considering all-cause mortality as a competing risk for HF hospitalization.

Results: 48.9%, 35.4%, and 15.6% of patients were classified into normal, mild, and severe groups, respectively. There was a graded increase in incidence rates of mortality (6.5% vs. 12.5% vs. 41.5%, log-rank p<0.001), HF hospitalization (4.9% vs. 8.3% vs. 16.6%, log-rank p<0.001), and adverse outcomes (9.9% vs. 17.7% vs. 47.9%, log-rank p<0.001) from normal to mild to severe groups. After multivariate adjustment, mild and severe groups had a significantly higher risk than the normal group in terms of mortality (hazard ratio [HR] 1.63, 95% CI 1.17–2.2, p=0.004 and HR 2.35, 95% CI 2.00–2.77, p<0.001 respectively), heart failure hospitalization (subdistribution hazard ratio [SHR] 1.63, 95% CI 1.10–2.42, p=0.015 and SHR 1.69, 95% CI 1.35–2.12, p<0.001), and adverse outcomes (HR 1.55, 95% CI 1.19–2.04, p=0.001 and HR 2.05, 95% CI 1.78–2.36, p<0.001), with a clear step-up in incidence rates and risks for the severe group.

Conclusion: In patients with CAD, concomitant inflammation and malnutrition is common and is strongly associated with increased mortality and heart failure hospitalization.

Prognostic Value of Coronary Microvascular Dysfunction Assessed by Coronary Angiography-Derived Index of Microcirculatory Resistance in Chronic Kidney Disease Patients with Chronic Coronary Syndrome

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Introduction: The Coronary Angiography–Derived Index of Microcirculatory Resistance (CaIMR) is a novel and effective method to assess coronary microvascular dysfunction (CMD), however its prognostic values in patients with chronic kidney disease (CKD) and Chronic Coronary Syndrome (CCS) are still yet to be determined. This study investigates the prognostic value of CMD, as measured by CaIMR, on the cardiac outcomes in patients suffering from CKD and CCS.

Methods: This is a retrospective observational study, which recruited CCS patients who performed coronary angiography for angina suspected by physicians at Queen Mary Hospital between January 2014 and December 2016. Diagnosis of CCS were made with reference to 2019 European Society of Cardiology diagnosis and management of CCS guideline. Clinical and demographics data, and data regarding details of coronary angiography are acquired via electronic patient records.

Results: We have recruited 1073 patients. The median follow-up time was 5 years. Among 1073 CCS patients, 100 major adverse cardiac events (MACE) were noted during the follow-up period. Compared with non-CMD patients (CaIMR < 25), patients with CMD (CaIMR ≥ 25) have a significantly higher rate of MACE (10.3% vs. 6.1%, p=0.017). In CKD patients, patients with CaIMR ≥ 25 have a noticeably higher rate of MACE than patients with CaIMR < 25 (15.3% vs. 9.5% p=0.05). However, in non-CKD patients, the difference in the incidence rate of MACE between CaIMR ≥ 25 and CaIMR < 25 is not significant (4.6% vs. 3.3%, p=0.522). In the total CCS population, CMD (CaIMR ≥ 25) patients have a notably poorer survival than non-CMD (CaIMR < 25) patients (log-rank P=0.016). In the CKD population, patients with CMD (CaIMR ≥ 25) have a significantly poorer survival than patients without CMD (CaIMR < 25) (log-rank P=0.049).

Conclusion: This study shows that CMD, assessed by CaIMR, can effectively prognosticate MACE in patients suffering from CKD and CCS. This result potentially allows the timely redirection of resources to patients who have the highest risk of MACE.

Proteomic Analysis of Plasma Exosomes: A Novel Method to Identify Potential Therapeutic Targets for Chronic Hepatitis B

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Introduction: Chronic hepatitis B (CHB) is characterized by an exhausted immune response against the virus. A possible mechanism is communication between hepatitis B virus (HBV)-infected hepatocytes and the host's immune system via exosomes, contributing to immune-dysregulation in CHB. However, studies of the role of exosomes in CHB are scarce and do not consider the different CHB disease phases. We aimed to investigate the changes in plasma proteome in CHB patients and healthy controls.

Methods: We recruited treatment-naïve CHB patients of different disease phases and healthy controls. Exosomes were isolated from plasma using ultracentrifugation method. Data-independent acquisition (DIA) mass spectrometry was performed to detect the dynamic profiles of exosome proteins. Bioinformatics and annotation analyses of differentially expressed proteins (DEPs) were performed using Geno ontology (GO) Enrichment Analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) Analysis. The types and proportions of infiltrating immune cells were detected by immune filtration analysis using CIBERSORT.

Results: In this interim analysis involving 10 healthy controls and 30 CHB patients (10 HBeAg-positive, 10 HBeAg-negative, and 10 CHB patients with hepatitis B surface antigen [HBsAg] seroclearance), 2142 exosome proteins were identified, of which 128 proteins were significantly altered in CHB vs. healthy controls (fold change > 2 or < 0.5, $p<0.05$). The most significant DEPs were observed with CIT, KRTDAP, KRT16 and HM13 (fold change=176.422, 13.774, 0.123 & 0.078 respectively, $p<0.05$). When comparing HBsAg-positive patients with patients achieving HBsAg seroclearance, 95 significant DEPs (87 downregulated and 8 upregulated proteins) were detected. GO analyses revealed these DEPs to be enriched in multiple immune-related processes; KEGG analyses showed their involvement in the estrogen signaling pathway. When compared to HBsAg-positive patients, patients with HBsAg seroclearance, had a significantly increased fraction of activated dendritic cells (0.006±0.010 vs. 0.028±0.027, $p=0.026$) and eosinophils (0 vs. 0.002±0.004, $p=0.047$), while resting dendritic cells were significantly decreased (0.041±0.019 vs. 0.024±0.021, $p=0.045$). No significant difference was observed between patients with HBsAg seroclearance and healthy controls through immune infiltration.

Conclusion: Plasma exosomes of CHB patients contain proteins associated with host immune response. The estrogen signaling pathway may potentially be associated with HBsAg seroclearance. Annotation of exosomes can potentially identify serum markers in different CHB disease phases and effectors that trigger immunity against HBV. This can be a potential method of identifying novel CHB therapeutic targets.

Risk of Seizure Aggravation after COVID-19 Vaccinations in Patients with Epilepsy

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Introduction: Concerns regarding post-vaccination seizure aggravation (PVSA) have contributed to a notable vaccination gap in persons with epilepsy (PwE). The objective of this single-centre, retrospective cohort study is to assess the early (7-day) and delayed (30-day) risk of PVSA and identify clinical predictors of PVSA among PwE.

Methods: Adult epilepsy patients aged ≥18 years without a history of COVID-19 infection were recruited from a specialty epilepsy clinic in early 2022. Data on demographics, epilepsy characteristics and vaccination status were extracted from a centralized electronic patient record. Seizure frequency pre- and post-vaccination, and vaccination-related adverse effects were collected through a structured questionnaire, completed in person or over phone interviews. Statistical analyses were performed using SPSS version 26.0.

Results: Out of 786 PwE recruited, 27.0% were drug-resistant, and 74.6% had received at least one dose of COVID vaccine. Vaccinated subjects had lower seizure frequency ($p<0.0005$), were on less anti-seizure medications ($p=0.004$), and were less likely to be drug-resistant ($p=0.001$). No change in seizure frequency was observed at 7 days post-vaccination compared to baseline, whereas seizure frequency was reduced in the 30 days after vaccination (1.31 vs. 1.89, $t=3.436$; $p=0.001$). This reduction was consistent across both vaccine types (BNT162b2 and CoronaVac) and in patients with drug-resistant epilepsy. Only 5.3% (26/786) participants experienced PVSA. Predictive factors for PVSA included a pre-vaccination seizure frequency of ≥1 per week (OR 3.01, 95% CI 1.05–8.62; $p=0.04$) and drug-resistant status (OR 3.32, 95% CI 1.45–7.61; $p=0.005$), while seizure freedom over the 3 months prior to vaccination was associated with a lower risk for PVSA (OR 0.11, 95% CI 0.04–0.28; $p<0.0005$).

Conclusion: No significant increase in seizure frequency was observed in the early phase (7 days) and delayed phase (30 days) after vaccination in our cohort. Seizure aggravation is most common in those with poor baseline seizure control, suggesting that optimizing seizure control for at least three months before vaccination may reduce this risk.

Risk of Serotonin Syndrome in the Combined Use of Selective Monoamine Oxidase B Inhibitors and Serotonin-acting Antidepressants

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Introduction: Depression is a common and disabling non-motor symptom of Parkinson's disease (PD) and may require treatment with serotonin reuptake inhibitors. Selective monoamine oxidase B (MAO-B) inhibitors are used extensively in Parkinson's disease (PD) to increase synaptic dopamine availability and improve motor symptoms. Higher doses were shown to lead to co-inhibition of MAO-A, resulting in potentiation of serotoninergic neurotransmission and theoretical risk of serotonin syndrome. Nevertheless, evidence is scarce on the exact magnitude of this risk, and the safety of combining MAO-B inhibitors and serotonin-acting antidepressants is unclear.

Methods: Electronic health records were retrieved from the Clinical Data Analysis and Reporting System (CDARS) under Hospital Authority. Patients with a prescription record of the two available MAO-B inhibitors (rasagiline, selegiline) between October 2014 and December 2023 under all public hospital in Hong Kong were first identified. These patients were then checked for concurrent prescription record of serotonin-acting antidepressants and any inpatient episodes with International Classification of Diseases Ninth Revision (ICD-9) code corresponding to serotonin syndrome (333.99 (4)). Patients with MAO-B inhibitor use within 8 weeks before date of admission for serotonin syndrome were classified as possible MAO-B inhibitor-related serotonin syndrome.

Results: A total of 4969 patients (3095 rasagiline, 2496 selegiline) were prescribed a MAO-B inhibitor during the study period, with a total prescription time of 17721.26 patient-years (9586.58 rasagiline, 8134.68 selegiline). Of these, 625 (12.6%) patients (374 (12.1%) rasagiline, 290 (11.6%) selegiline) had a concurrent prescription of serotonin-acting antidepressants. Only three cases of possible MAO-B inhibitor-related serotonin syndrome were identified, with two on concurrent rasagiline and antidepressants (escitalopram and sertraline respectively) and one on selegiline without antidepressant use. Estimated total incidence rate of serotonin syndrome was 1 per 5907 patient-years for MAO-B inhibitor use (1/4793 for rasagiline and 1/8135 for selegiline), with an estimated risk of 0.32% in those with concurrent serotoninergic antidepressant use.

Conclusion: Risk of serotonin syndrome with selective MAO-B inhibitor is small, even with the concurrent use of serotoninergic antidepressants. Serotoninergic antidepressants should not be withheld if clinically indicated for PD patients on MAO-B inhibitors and vice versa.

Role of TRPV4 Inhibitor as Drug Therapy in LMNA-related DCM Patient Specific iPSC-CMs

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Introduction: LMNA-related dilated cardiomyopathy (DCM) is characterized by early-onset atrioventricular (AV) block, supraventricular and ventricular arrhythmia (VA) and progressive DCM. A defect in nuclear lamina caused by mutation in LMNA gene could not support the inner nuclear membrane and sustain the structural integrity and mechanical stability of the nuclear envelope. In addition to the impaired nuclear stability, LMNA mutation disrupts nucleo-cytoskeletal coupling and interfere transmission between nucleus and cytoskeleton which play important role in cardiac muscle mechanical signalling. Studies revealed cytoskeletal, such as actin and tubulin colocalized with the transient receptor potential vanilloid-4 (Trpv4) non-selective cation which regulate cellular volume and calcium (Ca2+) influx. Trpv4 has recently been showed in relation to cardiomyocyte Ca2+ overload following stretch that may contribute to cardiac senescence and cardiac fibrosis. Study in 2012 also found that the C-terminal domain of trpv4 within the cytoplasm could be activated/ inactivated with either actin or tubulin, to alter Ca2+ influx. Further Ca2+ inflow through Trpv4 could be activated by cell swelling and/ or membrane stretch due to the lack of LMNA. Although the role of LMNA and trpv4 in cell function have been widely investigated, the pathophysiological mechanisms of cardiac senescence and fibrosis caused by LMNA mutation are not yet fully understood.

Methods: Research is ongoing to evaluate the effect of RN1734, Trpv4 antagonism in LMNA-related DCM patient specific iPSC-CMs for LMNA and Trpv4-specific pathways. We generated iPSCs (R225X/WT) from one patient with documented LMNA-related cardiomyopathy arising from one nonsense mutations in UGA at loci R225X for disease modelling. We differentiated those iPSCs into cardiomyocytes to evaluate RN-1734 on apoptosis in cardiomyocytes and nucleus, lamin A/C protein expression, transcriptome expression and chromatin expression among R225X/WT, R225X/R225X and COR/WT in presence of stress.

Results: The condition of nuclear blebbing is also ameliorated with RN 1734 treatment under electrical stress. Moreover, RN1734 treatment not only lowered apoptosis, but also reduced senescence-associated secretory phenotypes (SASP) in presence of mechanical stress. On top of that, the chromatin remodelling was observed, along with specific open chromatin associated with aging phenotypes in LMNA p.R225X mutant. We hypothesize that the increase in SASP in mutant due to the instability of nuclear membrane which may affect the calcium influx and induce cell apoptosis.

Conclusion: Our results allow us to differentiate RN1734 responder from non-responder to enter the clinical trials through attenuation of cardiac senescence and cardiac fibrosis.

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Sarcopenic Obesity is Associated with Cardiometabolic Multimorbidity in Chinese Middle-aged and Older Adults: A Cross-Sectional and Longitudinal Study

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Introduction: Sarcopenic obesity (SO) has been found to increase the risk of metabolic disorders, however, its relationship with cardiometabolic multimorbidity (CMM) remains unexplored. This study aims to investigate the potential association between SO and CMM in the middle-aged and older population.

Methods: Our study subjects were from CHARLS. SO was defined as the combination of impaired grip strength (grip strength <28kg for men and <18kg for women) and increased body mass index (BMI ≥25 kg/m^2). CMM was defined as having two or more cardiometabolic diseases, including diabetes mellitus, stroke, and heart disease. The participants were divided into four groups according to their sarcopenia and obesity status, and logistic regression analysis was used to examine the association between SO and CMM.

Results: A total of 15,252 study subjects were included in the cross-sectional study, with an average age of 60.6 years and a male proportion of 47.4%. In the cross-sectional analysis conducted in 2015, the prevalence of CMM was highest in the SO group (9.1%), followed by the obesity (3.7%) and sarcopenia (3.5%) group. After adjustment for confounding factors, SO [OR (95% CI): 2.453 (1.742–3.455)], sarcopenia [OR (95% CI): 1.601 (1.157–2.217)], obesity [OR (95% CI): 1.446 (1.107–1.888)] were all observed to be associated with CMM, with the strongest association in the SO group. Furthermore, in the longitudinal analysis, only the SO group demonstrated a significant risk for developing CMM [OR (95% CI): 2.302 (1.239–4.228)].

Conclusion: SO was independently and positively associated with CMM in middle-aged and older population.

Sex Dependent Associations of the Gut Microbiota with Hypertension – A Prospective Cohort

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Introduction: Whilst there is emerging evidence that the associations of the gut microbiota (GM) with hypertension differ between sexes, it remains uncertain whether the GM 1) can predict blood pressure (BP) trajectories, 2) is altered with antihypertensive-use, and 3) whether these associations are also sex-dependent. We therefore aimed to determine the sex-dependent associations of the GM with baseline hypertensive state in untreated versus treated participants and BP changes over time.

Methods: A total of 451 community-dwelling middle-aged Hong Kong Chinese without symptomatic cardiovascular diseases were recruited (50% men, 14% on antihypertensive agents, mean age, 54.6±6.5 years). Shotgun metagenomic sequencing of stool samples and 24-hour ambulatory blood pressure monitoring (ABPM) were performed. The 24hr-ABPM was repeated on 139 returned subjects after 4 years. Statistical analysis was conducted with 4 covariate models that include age, sex, menopause status, body mass index (BMI), smoking, fasting glucose, triglyceride, cholesterol, sodium intake, and fatty liver status.

Results: Amongst the 389/451 subjects not on antihypertensive agents, 167/389 (42.9%) had newly diagnosed hypertension at baseline. Females drove the significantly different β-diversity of the GM composition ($p<0.01$) between the normotensives and hypertensives in the baseline study. Multiple GM species were significantly associated with hypertension. In sex stratified analysis, *Faecalimonas umbilicate* was significantly enriched in hypertensive females while *Roseburia sp Am16-25* and *Eubacterium ramulus* were enriched in hypertensive males (all $p<0.05$–0.01). When comparing the 62 treated and 167 nontreated hypertensive subjects, the GM abundance, α-, and β-diversity were not significantly different. However, there were significant GM species associated with the use of antihypertensive medication. Notably, *Lachnospiraceae bacterium* and *Flavonifractor plautii* were significantly enriched in treated and untreated individuals, respectively (all $p<0.05$–0.001). During a mean follow up of 51.2±4.5 months, 73.2% of the 71 untreated subjects remained normotensive and were associated with enriched *Bacteroides uniformis* in their baseline metagenomic data under models adjusted for age, sex, and BMI.

Conclusion: The GM displayed sex-dependent associations with hypertension within untreated and treated individuals and can potentially predict BP trajectory changes within a Chinese population.

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Sex-specific Associations Between Gut Microbiome and 24-Hour Blood Pressure Variability

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Introduction: Blood pressure (BP) variability is an independent risk factor for cardiovascular disease (CVD). BP variability has been associated with cardiovascular organ damage and is a potential therapeutic target for the prevention of CVD. Accumulating evidence suggests that gut microbiota (GM) regulates BP and gut dysbiosis may have a pathological role in hypertension. However, the association between GM and BP variability is poorly understood.

Methods: 241 community-dwelling individuals free of symptomatic CVD from Hong Kong (113 males and 128 females, mean age 54±6 years) underwent ambulatory BP monitoring and stool microbiota shotgun sequencing. BP variability was determined as systolic/diastolic BP (SBP/DBP) coefficient of variation (CoV), nighttime dipping, and morning BP surge (MBPS). The presence of hepatic steatosis was assessed using a fibroscan, and the control attenuation parameter (CAP) score was used to measure its severity. Sleep latency was estimated using 7-day Actigraphy data. Associations of BP variability with GM and its metabolites, short-chain fatty acids (SCFAs), were analyzed under statistical models adjusting for age, sex, serum glucose and lipids, sodium intake based on spot urine analysis, menopause and smoking status, fatty liver CAP score, mean BP and sleep latency.

Results: Women had a significantly higher 24-hour SBP CoV than men ($p=0.0005$), which was negatively associated with GM α-diversity (Shannon and Simpson's index, $p<0.05$) and positively associated with Firmicutes/Bacteroidetes ratio, suggesting gut dysbiosis in women with higher systolic BP variability. Several GM species and plasma SCFA levels were significantly associated with the indices of BP variability in both men and women. Notably, *Parabacteroides merdae* had a negative association with both systolic and diastolic BP CoV (all $p<0.05$–0.01). *Bacteroidetes dorei* and *Bacteroides intestinalis* were reduced in women with higher SBP CoV ($p<0.05$) and nondipping status ($p<0.01$), respectively. Sleepthrough MBPS positively correlated with plasma acetic acid in men ($p<0.05$–0.001). Further analysis indicated that *B. dorei* may mediate SBP CoV via plasma iso-butyric acid in women (bootstrapping 95% CI: -3.6 to -0.19; $p<0.05$).

Conclusion: This cross-sectional study suggests sex-specific associations between GM and BP variability, which persisted after adjusting for various confounding variables and risk factors. Higher systolic BP variability was associated with a significant reduction in potentially beneficial bacterial species, which may be explored for therapeutic potential. Most noteworthy, *B. dorei* and iso-butyric acid may alleviate BP variability in women.

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Stem Cell Laden Cryogel as Potential Therapy for Myocardial Infarction

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Introduction: Biomaterials, particularly hydrogels, have been developed and implemented for regenerative therapies to include more bio-functional capabilities. Unlike systemic diseases, the treatment of cardiac diseases usually requires a site-specific delivery of the therapeutic agents directly to the heart. This project aimed to develop cryogels, a hydrogel-based delivery system, by the direct application to the heart as a localized delivery of therapeutic agents.

Methods: Methacrylated alginate (MA-Alg) and methacrylated gelatin (GelMA) were used to engineer the cryogels. The precursor polymer solution was mixed homogeneously and poured into the prechilled silicon moulds. The frozen moulds facilitated the formation of ice crystals within the polymer matrix before polymerization, generating the porous structure. The resultant cryogel patch was able to provide a flexible scaffold for the cell incorporation. The cryogels are further explored for their ability to provide a supportive environment for stem cell delivery, enabling tissue regeneration in vivo.

Results: 3% (w/v) MA-Alg and 4% (w/v) GelMA solution were able to produce a flexible sponge-like cryogel. HepG2 cells were cultured in the cryogel scaffold for up to 12 days. Cell viability was examined by staining with Live/Dead Viability Staining kit. It showed great cell viability under confocal microscope.

Conclusion: The cryogel structures and biocompatibility assessments using HepG2 cells, have demonstrated the feasibility and potential of cryogels as a suitable carrier for stem cell delivery. Optimization of cryogel properties for stem-cell incorporation, controlled release mechanisms, and in vivo studies would be further explored for the application of cryogels.

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Systemic Administration of iPSC-MSC Derived Exosome for Cardiac Regeneration

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Introduction: Myocardial infarction (MI) is the leading cause of death all over the world. The limited regeneration capacity of adult mammal heart leads to irreversible cardiomyocytes damages, causing pathological left ventricular remodeling and heart failure (HF). Induced pluripotent stem cell derived mesenchymal stem cells (iPSC-MSC) has been reported to have better proliferative capacity, survival, more immune privilege than bone marrow (BM)-MSC, making iPSC-MSC more effective in therapeutic application in cardiac repair after MI. Mounting evidence suggests that exosomes derived from MSC can promote cardiac regeneration and repair after MI via anti-inflammatory, anti-apoptotic, anti-fibrotic, immunomodulatory, and pro-angiogenesis. In this study, we extracted exosome from iPSC-MSC and evaluated its therapeutic potential in MI.

Methods: Mice were used to establish MI model by ligating left anterior descending coronary artery and randomized into 3 groups: intravenous injection of phosphate-buffered saline (PBS) (MI group), intravenous injection of iPSC-MSC-exosome immediately after MI (MI+Exosome group), intravenous injection of iPSC-MSC-exosome immediately and weekly after MI (4 times) (MI+Exosome/week group). Echocardiographic and hemodynamic assessments were performed to evaluate cardiac function. Masson's trichrome staining was used to assess fibrosis level. Meanwhile, immunofluorescence staining with α-smooth muscle actin (α-SMA), inducible nitric oxide synthase (iNOS) and chitinase-3 like-protein-1 (Ym1) were performed to evaluate angiogenesis and anti-inflammatory effect.

Results: Echocardiography showed that in MI+Exosome/ week group, left ventricle ejection fraction (LVEF) increased significantly compared with MI group. In MI+Exosome group, LVEF increased compared with MI group at Day7 after MI, which could not be maintained in the following 4 weeks. Maximum rate of LV pressure rise (+dp/dt) in MI+Exosome and MI+Exosome/week groups were significantly increased compared with MI group. Masson's trichrome staining showed that the infarct size in MI+Exosome and MI+Exosome/week groups significantly decreased compared with MI group. Meanwhile, immunofluorescence staining with α-SMA and iNOS showed that iPSC-MSC-exosome could increase microvascular density and decrease inflammation after MI.

Conclusion: In conclusion, iPSC-MSC-exosome could improve cardiac function after MI via neovascularization, anti-fibrosis, and anti-inflammation and repeated administration has better therapeutic efficacy.

Targeting ICOS-ICOSL Signalling for The Treatment of Neuromyelitis Optica Spectrum Disorders

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Introduction: Neuromyelitis optica spectrum disorders (NMOSD) are a group of autoimmune disorders characterized by inflammation and demyelination of the central nervous system, primarily affecting the optic nerves and spinal cord. Most patients with NMOSD are seropositive for aquaporin 4 immunoglobulin G (AQP4-IgG) autoantibodies, which target the AQP4 water channels on astrocytes. Recently, the idea of disturbing the interaction between T follicular helper (Tfh) cells and B cells to remove potentially pathogenic B cells has received significant attention in the field of autoimmune diseases. Inducible co-stimulator (ICOS) is a costimulatory receptor found on T follicular helper (Tfh) cells in the germinal center, playing a crucial role in their maintenance and differentiation. However, the contribution of Tfh cells to disease activity and the therapeutic potential of targeting ICOS-ICOSL signalling in NMOSD remain unclear. In this study, we aim to investigate whether the blockade of ICOS-ICOSL signalling ameliorates disease through the disruption of Tfh cell responses in a mouse model of NMOSD with AQP4 autoimmunity.

Methods: An autoimmune model of NMOSD was established by immunizing mice against AQP4 via *in vivo* electroporation. The effects of ICOSL-deficiency, as well as treatment with anti-ICOSL antibody, on Tfh cells and germinal centre expansion were examined using flow cytometry. The serum levels of AQP4-IgG were determined by enzyme-linked immunosorbent assay (ELISA). Motor impairments were examined using beam walking test. Spinal cord pathologies were by immunofluorescence.

Results: AQP4 immunization triggered the increase in the frequency of $CD4^+CXCR5^+PD\text{-}1^+$ Tfh cells over time. This response began before germinal center expansion, with the increase in the frequency of $CD19^+CD95^{hi}CD38^{lo}$ germinal center B cells and $CD138^+B220^{lo}$ plasma cells, as well as the production of AQP4-IgG. ICOSL-deficient (B6.129P2-*Icosl*^{tm1Mak}/J) mice did not display the expansion of Tfh cells, germinal center B cells and plasma cells, and the presence of AQP4-IgG after AQP4 immunization. Furthermore, ICOSL-deficient mice showed reduced susceptibility to motor impairments and NMOSD-like pathologies, including astrocytopathy, demyelination, axonal loss, and microglial activation, following AQP4 immunization. Therapeutic treatment with anti-ICOSL antibody depleted Tfh cells and inhibited germinal center expansion in AQP4-immunized mice. Importantly, the treatment ameliorated motor impairments induced by AQP4 immunization, and this effect was associated with a reduction in NMOSD-like pathologies and neuroinflammation.

Conclusion: Our findings provide evidence that ICOS-ICOSL signalling is required for Tfh cell response, germinal centre expansion and AQP4-IgG production in NMOSD. Importantly, ICOS-ICOSL signalling may represent a potential therapeutic target in NMOSD.

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The Association of HDL-Cholesterol Levels with Incident Major Adverse Cardiovascular Events and Mortality in 0.6 million Individuals with Type 2 Diabetes: A Population-Based Retrospective Cohort Study

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Introduction: High levels of high-density lipoprotein cholesterol (HDL-C) are previously considered protective against cardiovascular diseases (CVD), but recent studies suggest an increased risk of adverse events at very high HDL-C levels in the general population. It remains to be elucidated such a relationship in diabetes, a condition with high cardiovascular risks. We examined the association of HDL-C levels with the risk of major adverse cardiovascular events (MACE) and mortality in type 2 diabetes.

Methods: This retrospective cohort study identified individuals with type 2 diabetes who had HDL-C records (2008-2020) from the electronic health record database of the Hong Kong Hospital Authority. They were classified into three groups based on their HDL-C levels: low (≤40 mg/dL), medium (>40 and ≤80 mg/dL) and high HDL-C (>80 mg/dL) groups. The primary outcome was incident MACE (composite of myocardial infarction, stroke, heart failure, and cardiovascular mortality). Cox regression model and restricted cubic spline analysis were employed to assess the relationship between HDL-C and adverse outcomes.

Results: Among 596,943 individuals with type 2 diabetes included, 168,931 (28.30%), 412,863 (69.16%), and 15,149 (2.54%) were classified as low HDL-C, medium HDL-C, and high HDL-C groups, respectively. Over a median follow-up of 79.5 months, both low and high HDL-C groups had higher risk of incident MACE compared to the medium HDL-C group (HR 1.24, 95% CI 1.23–1.26, p<0.001; HR 1.09, 95% CI 1.04–1.13, p<0.001). The spline curves revealed a U-shaped association between HDL-C levels and incident MACE (non-linear p<0.001). Similar U-shaped relationship was observed for all-cause and non-cardiovascular mortality.

Conclusion: Our study demonstrated a U-shaped association between HDL-C levels and incident MACEs and all-cause and non-cardiovascular mortality in individuals with type 2 diabetes, highlighting the need for mechanistic studies on the adverse outcomes seen at high HDL-C levels in type 2 diabetes.

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The Impact of Diabetes on Post-Hip Fracture Clinical Outcomes and Fracture Risk Management: A 10-Year Territory-Wide Cohort Study of Hong Kong

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Introduction: Type 2 diabetes is associated with higher risk of hip fracture, the hallmark complication of bone fragility. We evaluated the effect of comorbid diabetes on the length of hospitalization, mortality, risk of recurrent fracture and osteoporosis management after hip fractures.

Methods: Individuals aged ≥40 years hospitalized for hip fractures (defined by ICD-9 CM code 820) between 2011 and 2020 were identified from the territory-wide electronic health database in Hong Kong. Diabetes was defined by HbA1c ≥6.5%, history of ICD-9 CM code 250, or history of anti-diabetic agent prescriptions. Length of hospitalization, mortality, rate of recurrent fracture and prescriptions of anti-osteoporosis agents were retrieved and compared between individuals with and without diabetes. Multivariable regression analyses were performed to identify independent factors of these outcomes.

Results: In total, 57400 individuals with incident hip fractures were identified, where 33.1% had diabetes. Mean age was 84 and 63.4% were women. Individuals with diabetes had more comorbidities (p<0.001). Median length of hospitalization was 27 days (IQR: 18–37), while one-year mortality was 15.8%. Diabetes was an independent factor of long hospital stay (≥4 weeks) (adjusted OR=1.21, 95% CI 1.17–1.25, p<0.001) and an independent predictor of one-year mortality (adjusted HR=1.17, 95% CI 1.12–1.22, p<0.001) after adjustments for multiple comorbidities, consistent in both men and women. Among men, diabetes was independently associated with increased risk of recurrent fractures (adjusted HR=1.14, 95% CI 1.01–1.29, p=0.035), despite the similar rate of anti-osteoporosis treatment. Additionally, among women, those with diabetes were less likely to receive anti-osteoporosis medications (adjusted OR=0.94, 95% CI 0.89–0.996, p=0.03).

Conclusion: Individuals with diabetes had worse clinical outcomes after hip fractures than their non-diabetes counterparts. Furthermore, diabetes may impact on the subsequent fracture risk. This calls for attention to bone fragility in diabetes. The possible disparity in osteoporosis management among diabetes population compounds the concern.

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The Role of The Complement C5a/C5a Receptor Axis in High-Fat Diet-Induced Nephropathy

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Introduction: Alteration of lipid metabolism is a common pathogenic factor of diabetic nephropathy (DN). Previous studies have shown that blockade of the complement 5a/complement 5a receptor (C5a/C5aR) axis ameliorates renal lipid accumulation, inflammation, fibrosis and improves renal function in mice with diabetes, suggesting a potential therapeutic target for DN. However, the exact mechanism has not yet been fully elucidated.

Methods: Seven-week-old wild type ($C5aR^{+/+}$) and knockout ($C5aR^{-/-}$) mice were fed with a normal diet (ND) or high-fat diet (HFD) for 16 weeks. Throughout the experimental period, body weight, blood glucose and lipid levels were monitored. Kidney morphological changes were assessed by Periodic-Acid-Schiff staining and transmission electron microscopy. Renal inflammation and lipid accumulation and mitochondrial markers were analyzed by immunohistochemical staining and Western Blot.

Results: After 16 weeks of HFD, fasting blood glucose levels were significantly increased in mice compared to ND group and no difference was found between $C5aR^{+/+}$ and $C5aR^{-/-}$ mice. There was a remarkable increase in serum C5a levels in $C5aR^{+/+}$ HFD mice compared to $C5aR^{+/+}$ ND mice. A significant lower C5a level was detected in $C5aR^{-/-}$ HFD group compared to the $C5aR^{+/+}$ HFD group. In addition, $C5aR^{-/-}$ mice showed reduced serum levels of cholesterol and free fatty acids after HFD. Oil Red O staining showed a significant reduction of lipid droplets in kidney from $C5aR^{-/-}$ mice compared to $C5aR^{+/+}$ after HFD, indicating reduction of renal lipid accumulation. Kidney injury including tubular damage, thickening of glomerular basement membrane, podocyte foot process effacement and CD68-positive macrophages infiltration were greatly induced in $C5aR^{+/+}$ mice with HFD, but these abnormalities were reduced in $C5aR^{-/-}$ mice with HFD. Furthermore, mice with C5aR deficiency preserved HFD-induced loss of mitochondrial fusion protein OPA1 and the mitochondrial structural protein TIM23, resulting in improved mitochondrial morphology in $C5aR^{-/-}$ mice with HFD.

Conclusion: Our results suggested that activation of C5a/C5aR axis impaired mitochondria homeostasis and contributed to lipid accumulation in HFD-induced kidney injury. Findings from this study may provide new insights into mechanisms of lipotoxicity in the kidney.

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Triple Antihypertensive Medication Prediction Score after Intracerebral Hemorrhage (The TRICH Score)

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Introduction: Uncontrolled hypertension is prevalent among intracerebral hemorrhage (ICH) survivors. This heightens the risk of ICH recurrence and stroke, which is the highest in the first year after ICH. Prompt blood pressure (BP) lowering could be achieved by prescribing upfront triple antihypertensive medications, as many ICH survivors required ≥3 antihypertensives for BP management. However, not all would suit this approach, particularly those with cerebral amyloid angiopathy, where elevated admission BP may be due to acute hypertensive response rather than underlying hypertension. Excessive BP lowering is also a concern, especially in older patients, which has been associated with increased mortality. Hence, to facilitate individualized treatment, we developed a score (TRICH) to predict the need for ≥3 antihypertensives at three months post-ICH.

Methods: We developed the score from 462 patients from The University of Hong Kong prospective ICH registry (2011-2022) and validated it in 203 patients from three other hospitals (2020-2022) locally. Follow-up BP and medication prescriptions three months post-ICH were reviewed. Predictors of the need for ≥3 antihypertensive medications were derived using multivariate logistic regression, and the TRICH score was created using the β-coefficients.

Results: The 9-point TRICH score (1 for age<60, 1 for males, 1 for history of ischemic heart disease, 2 for admission estimated glomerular filtration rate <60mL/min/1.73m2, 2 for admission systolic BP 190-230mmHg, and 4 for >230mmHg) has a c-statistic of 0.79 (95% CI,0.75–0.83) in the development cohort; 0.76 (95% CI,0.69–0.82) for validation. A dichotomized score (≥3) predicted the need for ≥3 antihypertensives with 0.73 sensitivity and 0.76 specificity. The score performed better in patients with untreated/uncontrolled hypertension pre-ICH than controlled (c-statistic 0.81 versus 0.74, p=0.037), but did not differ for ICH location.

Conclusion: TRICH score identifies ICH patients who need ≥3 antihypertensive medications three months post-ICH with good discrimination ability. Utilizing the TRICH score for prescribing upfront triple antihypertensives would enable prompt BP control and mitigate the risk of overtreatment.

Tumor-Associated Neutrophils Attenuate the Immuno-Sensitivity of Hepatocellular Carcinoma and Curtail Immunotherapy Response

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Introduction: Metabolic dysfunction-associated steatohepatitis hepatocellular carcinoma (MASH-HCC) is the fastest growing liver cancer etiology, and is particularly resistant towards immune checkpoint blockade (ICB) therapies. Drivers of this poor prognosis for MASH-related HCC patients are not completely understood, which impairs development of tailored therapies. Tumour-associated neutrophils (TANs) are the top immune predictor of poor prognosis among solid cancers, and are increasingly implicated during immunotherapy failure. Their abundant heterogeneity within HCC patients has recently been reported, yet the mechanisms of TAN-mediated ICB resistance remain poorly understood. Uncovering the specific TAN subsets blocking ICB efficacy and eliminating them, is key to innovating improved immunotherapy regimes.

Methods: Several HCC patient datasets, tumor samples from MASH-related HCC patients, and murine MASH-related HCC models were integrated to achieve a comprehensive transcriptomic, metabolomic, and phenotypic profile of TANs within MASH-related HCC.

Results: TANs predicted poor prognosis for MASH-related HCC patients, and their depletion improved survival of MASH-related HCC models. These tumor-infiltrating neutrophils co-evolved in quantity and heterogeneity alongside MASH-related HCC tumor progression. In particular, TANs characterized by high SiglecF expression and TGFbeta production were strongly enriched in MASH-related HCC compared to other etiologies in patient datasets and mouse HCC models. These SiglecF$^+$TANs were driven by a cMYC-mediated transcriptional program induced by elevated levels of GM-CSF and linoleic acid within MASH-related HCC tumors. Functionally, these SiglecF$^+$TAN-derived TGFbeta directly promoted HCC stemness, proliferation, and migration. Crucially, these TANs also suppressed the antigenicity of HCC cells via TGFbeta. Targeting this SiglecF$^+$TAN-TGFbeta axis conferred ICB responsiveness to an otherwise resistant MASH-related HCC model.

Conclusion: SiglecF-expressing TANs were key contributors to immunotherapy resistance in MASH-related HCC. Their TGFbeta secretion drove both MASH-related HCC aggressiveness and ICB insensitivity. Targeting the development of these SiglecF$^+$TAN holds strong therapeutic potential, and a clinically bioactive drug capable of disrupting the cMYC regulon within TANs is currently under testing.

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Vonoprazan Dual Therapy vs. Vonoprazan Triple Therapy in The Treatment of Helicobacter Pylori Infection: A Randomized Controlled Trial

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Introduction: To compare the effect and incidence of adverse events of vonoprazan-dual therapy with vonoprazan-triple therapy for the treatment-naive Helicobacter pylori (*H.pylori*) infection in Shenzhen city.

Methods: A single-centre, randomized controlled trial was conducted in the outpatients from gastroenterology department at The University of Hong Kong-Shenzhen Hospital from March 2022 to August 2023. 208 patients aged 18-75 years with treatment-naive *H.pylori* infection were randomly assigned to receive one of two 14-day regimens (1:1 ratio): vonoprazan-dual group 104 patients (VPZ-dual: vonoprazan 20 mg twice daily and amoxicillin 1g thrice daily), or vonoprazan-triple group 104 patients (VPZ-triple: vonoprazan 20 mg/amoxicillin 1 g/clarithromycin 500 mg twice daily). Primary outcome was difference in *H.pylori* eradication rate, evaluated by urea breath test (UBT) 4 weeks after treatment by intention-to-treat (ITT), modified intention-to-treat (MITT) and per-protocol (PP) analysis (based on subjects who completed 14-day treatment and tested UBT again). The secondary outcome was the incidence rates of adverse events reported by patients from two groups during treatment.

Results: ITT analysis showed the eradication rates were 96.2% and 90.4% for the VPZ-dual and VPZ-triple therapy group, respectively (difference:5.8%, p=0.097). MITT analysis showed the eradication rates were 97.1% and 96.9% for the VPZ-dual and VPZ-triple therapy group, respectively (difference: 0.2%, p=0.940). PP analysis showed the eradication rates were 96.9% and 96.7% for the VPZ-dual and VPZ-triple therapy group, respectively (difference:0.2%, p=0.936). The frequency of adverse events was significantly lower in VPZ-dual therapy group compared with VPZ-triple therapy group (38.5% vs. 57.7%, p=0.006).There was no significant difference in patient's compliance between the VPZ-dual and VPZ-triple therapy group (96.2% vs. 96.2%, p=1).

Conclusion: There is no significant difference in efficacy and compliance between VPZ-dual and VPZ-triple therapies. Given the lower rate of side effects and antibiotic use, compared with VPZ-triple therapy, VPZ-dual therapy is more recommended for patients with *H.pylori* infection as the first-line treatment.

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Young Patients with Heart Failure: Incidence, Clinical Characteristics and Outcomes: A Territory-Wide Study From 2014-2023 on 19,537 Patients

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Introduction: Heart failure (HF), commonly considered a disease of the elderly, has been increasingly observed in younger individuals over recent decades. Comprehensive data on clinical attributes, outcomes, and corresponding variations over time remain scarce. Thus, this study sought to investigate temporal trends in incidence, comorbidities, shifting pattern of risk factors and outcomes among young HF.

Methods: Using Hong Kong territory-wide health registries, we identified 19,537 patients aged 18-65 years with newly diagnosed HF between 2014-2023. Subsequently, we retrieved their most recent measurements of baseline characteristics, as well as echocardiographic data, comorbidities and prescribed medications. All subjects were tracked for the occurrence of primary and secondary endpoints (including mortality, HF hospitalization and MACE) within one year, or until the end of 2023. We calculated the standardized incidence rates (IRs) of young HF annually through direct age and sex standardization. Disparities were primarily compared between two cohorts: the past (2014-2018) and the current 2019-2023 cohorts. Shifts in risk factors were determined using multivariable logistic regression. Adverse outcomes were assessed by Kaplan-Meier survival curves and Cox regression analysis.

Results: The standardized IRs of young HF progressively increased over past decade, with a predominance in men and individuals aged 45-65 years, by 20% (from 97 to 116 per 100,000 person-years; IRR 1.20, 95% CI 1.13–1.27). Concurrent with fewer comorbidities, the current cohort more often had cardiomyopathy, obesity and were more recipients of comprehensive social security assistance (CSSA) allowance, as opposed to the conventional risk factors observed in past cohort (all $p<0.001$). Despite similar abnormalities in cardiac remodeling and valvular dysfunction, the current cohort demonstrated higher adherence to standard anti-HF therapies. All-cause mortality and CV-mortality decreased in Kaplan-Meier analysis, but exhibited wider 95% CIs after multiple adjustment (HR 0.99, 95% CI 0.91–1.08; HR 0.94, 95% CI 0.84–1.05; both $p>0.05$). Non-CV mortality remained stable (HR 1.09, 95% CI 0.96–1.24) over the study period. Conversely, the rates of HF hospitalization, CV mortality or HF hospitalization, MACE and sudden death declined over time (HR 0.79, 95% CI 0.75–0.84; HR 0.81, 95% CI 0.77–0.85; HR 0.81, 95% CI 0.76–0.88; HR 0.66, 95% CI 0.56–0.78; all $p<0.05$, respectively).

Conclusion: Although the incidence of young HF surged considerably during 2014-2023, the observed reduction in comorbidities, shifting risk factors and enhanced management collectively contribute to a stagnation of declining survival rates. The identification of cardiomyopathy, obesity and recipients of CSSA allowance in disease incidence highlights a potentially preventable aspect of young HF that necessitates further attention and intervention.

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