SUPPLEMENT 1

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* HR was reported as 0.63 vs warfarin (95% CI: 0.53-0.74); 0.77 vs rivaroxaban (95% CI: 0.65-0.90); and 0.79 vs dabigatran (95% CI: 0.65-0.94).
† HR was reported as 0.56 vs warfarin (95% CI: 0.46-0.67); and 0.71 vs rivaroxaban (95% CI: 0.59-0.85).
# 30 mg Lixiana® vs warfarin (dose adjusted to INR of 2.0-3.0): efficacy in stroke/SEE prevention, HR=0.81 (95% CI: 0.58-1.13), p-interaction=0.85; risk of major bleeding, HR=0.63 (95% CI: 0.50-0.81), p-interaction=0.023.
^ 41% patients aged ≥75 years require dose reduction at randomization, vs 10% patients aged <65 years, 18% patients aged 65-74 years

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; INR: international normalized ratio; NOAC: non-vitamin K antagonist oral anticoagulant; SEE: systemic embolic events

References: 1. Lee SR, et al. Stroke. 2019;50:2245-2249. **2.** Chiang CE, et al. J Arrhythm. 2017;33:345-367. **3.** Hong Kong Lixiana Package Insert Sep 2016. **4.** Steffel J, et al. Eur Heart J. 2018;39:1330-1393. **5.** Ruff CT, et al. Lancet. 2015;385:2288-2295. **6.** Kato ET, et al. J Am Heart Assoc. 2016;5:e003432.

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Daiichi Sankyo Hong Kong Limited
Rm 1801, 18/F., One Hysan Avenue, Causeway Bay, Hong Kong
Tel: (852) 2868 9079 Fax: (852) 2801 4341

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26th Medical Research Conference, 16 January 2021

Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

1

Clinical characteristics in patients with non-cystic fibrosis bronchiectasis and co-existing airway diseases in Chinese population

WC Kwok, JCM Ho, TCC Tam, MSM Ip, DCL Lam
Division of Respiratory Medicine, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Bronchiectasis, asthma and chronic obstructive pulmonary disease (COPD) are common respiratory diseases among the Chinese population. Co-existing bronchiectasis with asthma or COPD are more recognised in recent years.

Methods: A cross-sectional observational study was conducted to investigate the clinical characteristics non-cystic fibrosis bronchiectasis with co-existing asthma and COPD in a Chinese population in Queen Mary Hospital. Total 350 Chinese patients were included in the study.

Results: Patients with bronchiectasis and co-existing COPD are older, more smoker, more likely to have dyspnoea, with lower FEV_1/FVC ratio and higher risk of exacerbation requiring hospitalisation compared with those with pure bronchiectasis. For patients with co-existing asthma and bronchiectasis, they are younger, diagnosed to have bronchiectasis at younger age and have lower FEV_1 compared than those with pure bronchiectasis.

Conclusion: Co-existing asthma or COPD with bronchiectasis have distinct clinical characteristics which have therapeutic and prognostic implications.

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Territory-wide epidemiology and sensitisation patterns of beta-lactam allergy in Hong Kong

PH Li[1], HHF Yeung[2], CS Lau[1], EYL Au[2]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Division of Clinical Immunology, Department of Pathology, Queen Mary Hospital, Hong Kong

Introduction: Allergy to beta-lactam antibiotics is one of the most frequently reported drug reactions. We previously identified an estimated 5% prevalence of reported beta-lactam allergy for hospitalised patients in Hong Kong, but population-based epidemiological data in Asians are lacking. Furthermore, ethnic- and region-specific sensitisation patterns for beta-lactam allergy in Chinese also remain unknown.

Methods: Anonymised electronic patient data from the Hospital Authority were obtained for a cross-sectional territory-wide study to study the prevalence and cumulative incidence of reported beta-lactam allergy from 2018 to 2019. A subgroup of these patients was referred to Queen Mary Hospital for beta-lactam allergy evaluation from the same period, were also analysed for sensitisation patterns of allergy skin testing.

Results: Complete records of 7 184 271 unique patients (representing >95% of the Hong Kong population) were analysed. 511 492 (7.1%) patients had physician-reported drug allergies, of which 143 483 (28.1%) were beta-lactam allergies. The near-point prevalence of reported beta-lactam allergy was therefore 2.0%. 8032 patients had newly reported beta-lactam allergies reported in 2018 alone, therefore the cumulative incidence was 107 per 100 000 population. 305 patients with suspected beta-lactam allergy underwent skin testing, but only 13.8% had positive skin test results. More than 50% of patients were sensitised to either benzylpenicilloyl polylysine or a minor determinant only.

Conclusion: In Hong Kong, the prevalence of reported beta-lactam allergy was 2.0% and the cumulative incidence was 107/100 000 population. Only 13.8% of patients referred for evaluation had positive skin testing. In contrast to Western populations, patients in Hong Kong had much higher rates of monosensitisation to benzylpenicilloyl polylysine and/or minor determinant, making these reagents essential in beta-lactam allergy skin testing. This unique finding warrants further studies into whether this specific phenomenon pertains to the Chinese ethnicity or Asia-Pacific region.

Prevalence of mild behavioural impairment: a systematic review and meta-analysis

3

Y Pan[1]*, YF Shea[2]*, S Li[1], R Chen[1], HKF Mak[3], PKC Chiu[2], LW Chu[2], YQ Song[1]
[1]School of Biomedical Sciences, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[3]Department of Diagnostic Radiology, The University of Hong Kong, Hong Kong

* The first two authors contributed equally to the work.

Introduction: Mild behavioural impairment (MBI) is a neurobehavioral syndrome characterised by later-life emergent neuropsychiatric symptoms (NPS). The prevalence of MBI varies among studies, but there has been no systematic review or meta-analysis.

Methods: A search of the literature on MBI in mild cognitive impairment (MCI), cognitively normal (CN), and subjective cognitive impairment (SCI) and cognitively normal but at risk (CN-AR) subjects published between 1 January 2003 and 4 September 2020 was conducted. Meta-analysis using a random-effects model was performed to determine the pooled estimate of the prevalence of MBI. Meta-regression was performed to identify factors contributing to the variance of prevalence rate. A systematic review was also performed to study the impact of MBI in cognitive outcomes and its correlation to pathology and genetics of Alzheimer's disease (AD).

Results: Seven studies conducting among 1358 MCI subjects were subjected to meta-analysis revealing a pooled prevalence at 45.5% (95% confidence interval [CI]=36.1%-55.3%). Four studies conducting among 13153 CN subjects were subjected to meta-analysis revealing a pooled prevalence at 17% (95% CI=7.2%-34.9%). Five studies conducting on 1158 SCI or CN-AR subjects were subjected to meta-analysis revealing a pooled prevalence at 35.8% (95% CI=21.4%-53.2%). Systematic review of 13 studies showed MBI has a significant impact on cognitive deterioration, and it's associated with pathology and genetics of AD.

Conclusion: MBI is common in MCI, CN, and SCI and CN-AR subjects. Our finding is potentially useful in planning future clinical trials.

First report of pathogenic mutations and complete C6 deficiency in Chinese pedigree

4

JMH Li, PH Li
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Objectives: Complete C6 deficiency (C6Q0) is a rare primary immunodeficiency leading to increased susceptibility to recurrent *Neisseria* infections. Patients with C6Q0 have mostly been reported in individuals of African ancestry previously, but never in Chinese. We identify the first Chinese patients with C6Q0 through family screening of an index case presenting with recurrent *Neisseria* meningitis with septicaemia and performed extensive clinical, serological investigations.

Methods: Two variants in C6 were identified by next-generation sequencing and confirmed by Sanger sequencing in an index case of C6Q0. Immunological investigations, complement haemolytic assays (CH50/AH50), C6 gene sequencing and quantification of serum C6 levels were performed for all available members of his non-consanguineous family.

Results: Three C6Q0 patients were identified with near-absent C6 levels, absent CH50/AH50 activity and compound heterozygous for two nonsense mutations in the C6 gene: NM_000064.4:c1786C>T (p.Arg596Ter) and NM_000065.4:c.1816C>T (p.Arg606Ter). Neither mutations have been reported to be pathogenic previously. Two other family members who were heterozygous for either p.Arg596Ter or p.Arg606Ter had intermediate C6 levels but preserved CH50/AH50 activity. These two loss-of-function mutations showed a strong genotype-phenotype correlation in C6 levels.

Conclusion: We report on two compound heterozygous mutations in C6, p.Arg596Ter and p.Arg606Ter inherited in three patients of the first recorded Chinese pedigree of C6Q0. Neither mutations had been reported to be pathogenic previously. We demonstrate that heterozygous family members with subtotal C6 levels had preserved complement haemolytic function and demonstrate a threshold effect of C6 protein level.

5

Statins associated with better clinical outcomes in patients achieving HBsAg seroclearance: a long-term follow-up study

KS Cheung[1], LY Mak[1], J Fung[1], F Liu[2], WK Seto[1], MF Yuen[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Gastroenterology and Hepatology, The First Affiliated Hospital, Sun Yat-Sen University, China

Introduction: Hepatitis B surface antigen (HBsAg) seroclearance is a clinical event that occurs either spontaneously or during treatment with nucleos(t)ide analogue (NA) therapy or interferon. We aimed to describe the long-term clinical course after HBsAg seroclearance, and to identify factors that modify disease outcomes, as clinical studies on these aspects are lacking.

Methods: Chronic hepatitis B patients with HBsAg seroclearance occurring between 1986 and 2017 were recruited. Primary outcome was cirrhosis/hepatocellular carcinoma (HCC), and secondary outcomes were hepatic decompensation, liver-related death/transplantation, and all-cause mortality. Multivariable Cox model included demographics, prior antivirals, comorbidities, drugs (statins, metformin, proton-pump inhibitors, non-selective beta-blockers), and laboratory parameters (anti-HBs, platelet, liver function test, prothrombin time, and alpha-fetoprotein [AFP]). Statin users were propensity score matched (PSM) with non-users (1:2 ratio) for survival analysis of all outcomes.

Results: Of 913 patients with HBsAg seroclearance (613 male [67.1%]; median age 53.4 years [range, 18.5-87.0]), 129 (14.1%) were statin users. During median follow-up of 7.7 years (up to 29.1 years), 64/833 (7.7%) developed cirrhosis, 25/905 (2.8%) developed HCC, 3/913 (0.3%) underwent transplantation, and 76/913 (8.3%) died. Statins were associated with lower cirrhosis/HCC risk (adjusted hazard ratio [aHR]=0.44; 95% confidence interval [CI]=0.20-0.96; aHR for every 1-year increase in use: 0.85; 95% CI=0.75-0.97). Statin users had no hepatic decompensation or liver-related death/transplantation (vs 18/778 [2.3%] and 18/784 [2.3%] cases in statin non-users, respectively). Statins also associated with lower all-cause mortality risk (aHR=0.21; 95% CI=0.08-0.53). PSM yields consistent results for beneficial effects of statins (log-rank $P<0.05$ for all outcomes). Other factors for cirrhosis/HCC included increasing age (aHR=1.06), diabetes (aHR=2.03), higher creatinine (aHR=1.008), gamma-glutamyl transferase >50 U/L (aHR=3.25) and AFP >9 ng/mL (aHR=10.14).

Conclusion: Long-term survival in patients with HBsAg seroclearance is good. However, liver-related adverse outcomes still develop, necessitating further investigations on beneficial effects of statins.

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Neurosensory rehabilitation and olfactory network recovery in coronavirus disease 2019–related olfactory dysfunction

TWH Chung[1], H Zhang[2], FKC Wong[3], S Sridhar[1,4,5], KH Chan[1], VCC Cheng[1], KY Yuen[1,4,5,6], IFN Hung[4,7], HKF Mak[2,8,9]
[1]Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Diagnostic Radiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[3]Department of Ear, Nose and Throat Surgery, Pamela Youde Nethersole Eastern Hospital, Hong Kong
[4]State Key Laboratory of Emerging Infectious Diseases, The University of Hong Kong, Hong Kong
[5]Carol Yu Centre for Infection, Hong Kong
[6]The Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, China
[7]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[8]State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong
[9]Alzheimer's Disease Research Network, The University of Hong Kong, Hong Kong

Introduction: Non-conductive olfactory dysfunction (OD) is an important extra-pulmonary manifestation of coronavirus disease 2019 (COVID-19). Prolonged COVID-19-related OD is a serious neurosensory disability. Treatment for the restoration of smell is urgently needed.

Methods: Two patients presenting with prolonged COVID-19-related OD underwent structural and resting-state functional magnetic resonance imaging (rs-fMRI) brain scans. Two healthy controls were recruited for radiological comparison. One patient received olfactory treatment (OT) by the combination of oral vitamin A (VitA) and novel smell training diffuser technology.

Results: Olfactory bulb (OB) volume loss and olfactory network functional connectivity (FC) defects were identified in patients having prolonged COVID-19-related OD. After 4 weeks of OT, clinical recuperation of smell was correlated with interval increase of bilateral OB volumes (right: 22.5 mm^3 to 49.5 mm^3 [120%], left: 37.5 mm^3 to 42 mm^3 [12%]), suggesting active neurogenesis. Robust neuroplasticity and functional network remodulation were demonstrated in the enhancement of mean olfactory FC (0.09 to 0.15 [66.6%]) at the completion of OT.

Conclusion: Olfactory network functional defects and OB volume loss were identified in patients presenting with prolonged COVID-19-related OD. Preliminary evidence demonstrated that the combination of oral VitA and ST may induce robust neurogenesis at the olfactory apparatus and achieve olfactory neurosensory rehabilitation.

Piperacillin-tazobactam allergies: an exception to usual penicillin allergy

7

CYJ Wong, PH Li
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction/Objective: The majority of penicillin allergy labels are false and skin tests (ST) have high negative predictive value (NPV) of around 90%. Piperacillin-tazobactam (PT) allergy has been suspected to be an exception to this, but existing literature is scarce. We investigate the epidemiology, clinical characteristics, testing outcomes and predictive value of ST in patients referred for suspected PT allergies.

Methods: The records of all patients referred for suspected PT allergy testing and prescription rates of PT in all Hong Kong public hospitals (2015-2019) were analysed.

Results: There was an increase in PT prescriptions and number of newly reported PT allergies between 2015 and 2019. The majority (91.1%) of patients with suspected PT allergy had at least one underlying medical comorbidity or immunosuppressant use leading to increased risk of infections. Thirty-six patients with suspected PT allergy completed ST. Two patients had positive ST, and 32/34 patients with negative ST underwent drug provocation testing (DPT). Nine of these patients were diagnosed with PT allergy based on positive DPT. Overall, 11/34 (32.4%) were diagnosed with PT allergy and the NPV of ST was 71.9%.

Conclusion: There is growing utilisation of PT and corresponding cases of suspected allergies. The majority of suspected PT allergics had increased risk for recurrent infections. Unlike other penicillin allergy, there is a high rate of genuine PT allergy (32.4%) and poor NPV of ST (71.9%). DPT remains the gold standard for accurate diagnosis and all patients with a suspected allergy should undergo thorough allergy workup.

Identification of a novel therapeutic target for cerebral ischaemia injury: role of branched chain amino acids catabolism in ischaemic stroke

8

B Liao, L Geng, RLC Hoo, A Xu
Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Stroke has been the fourth leading cause of death in Hong Kong. Increasing studies demonstrate that impaired branched chain amino acids (BCAAs) catabolism and high BCAAs accumulation have adverse effects on diabetes, cardiovascular diseases (CVD), and neurological diseases. However, the exact role of BCAAs catabolism in mediating the ischaemic stroke outcome is still unknown.

Methods: Eight-week-old C57/BL6J mice will be subjected to middle cerebral artery occlusion (MCAO) surgery for 1h followed with 24h reperfusion. Mice will be administered with branched chain ketoacid dehydrogenase kinase (BCKDK) inhibitor BT2 for 7 days before the surgery. The cerebral and serum BCAAs in mice will be measured by high-performance liquid chromatography (HPLC). Infarct volume will be measured by triphenyl tetrazolium chloride (TTC) staining. The mRNA levels of key enzymes in BCAAs catabolism will be quantified by qPCR while the protein expression levels will be measured by Western blot.

Results: BCAAs catabolism has been impaired by MCAO induced cerebral ischaemia accompanied with increased expression of critical kinase BCKDK. Reversing the impaired BCAA catabolism induced by ischaemia alleviates cerebral ischaemia injury, including reduced infarct volume and cerebral oedema, improved neurological score, and increased survival rate. Moreover, oxygen glucose deprivation (OGD) experiment showed lower glutamate release when BCKDK was inhibited suggesting ischaemia-induced accumulation of BCAAs potentially aggravates cerebral ischaemia injury via enhancing glutamate excitotoxicity.

Conclusion: We propose that cerebral ischaemia upregulates the expression of BCKDK and impairs BCAAs catabolism in brain tissue during ischaemic stroke. Then, accumulated BCAAs in the infarct core leads to enhanced glutamate excitotoxity and cerebral ischaemia injury.

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Associations of seasonal variations and meteorological parameters with incidences of upper and lower gastrointestinal bleeding in older adults

CG Guo, L Tian, F Zhang, KS Cheung, WK Leung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Previous studies have demonstrated the seasonal variations of non-variceal upper gastrointestinal bleeding (UGIB), especially peptic ulcer bleeding, but there is no data on seasonal variations of lower gastrointestinal bleeding (LGIB). Ageing is changing the epidemiology of gastrointestinal bleeding (GIB). There is paucity of data on the association of seasonal variations of GIB in older patients, who are at highest risk of bleeding. We aimed to investigate the seasonal variations of UGIB and LGIB, and their associations with various meteorological parameters in different age-groups in Hong Kong over a 10-year period.

Methods: We included all patients hospitalised for UGIB and LGIB between 2009 and 2018 in Hong Kong. The monthly age- and sex-standardised GIB incidences were fitted to meteorological data including average temperature (AT), maximum temperature (MaxT), minimum temperature (MinT), temperature range (TR), average precipitation, average atmospheric pressure (AtomP) and average relative humidity after adjusting for prescriptions of aspirin, proton pump inhibitors and *Helicobacter pylori* eradication therapy using the autoregressive integrated moving average (ARIMA) model.

Results: Despite a gradual decline in UGIB incidences, the median incidences of UGIB were still higher in winter months. The incidences of both UGIB and LGIB were higher in the older age-groups, especially those ≥80 years. The seasonality was only identified in those ≥60 years for UGIB, and only in those ≥80 years for LGIB. UGIB incidence was inversely associated with AT, MaxT and MinT, but positively associated with TR and AtomP. LGIB was also significantly associated with AT, MaxT, MinT and AtomP.

Conclusion: Despite the change in GIB incidences, the seasonal patterns of GIB were most marked in the elderly. With the ageing population, the impacts of seasonal variations on GIB incidences could be considerable.

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Impact of childhood pneumococcal conjugate vaccine immunisation on all-cause pneumonia admissions: a 14-year population-based interrupted time series analysis

QY Yu[1], X Li[1,2], M Fan[1], LW Tian[3], CSL Chui[1], PH Li[2], LKW Lau[1], EW Chan[1], P Ip[4], TY Lum[5], IFN Hung[2], BJ Cowling[3], ICK Wong[1]
[1]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Hong Kong
[3]School of Public Health, The University of Hong Kong, Hong Kong
[4]Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong
[5]Department of Social Work and Social Administration, The University of Hong Kong, Hong Kong

Abstract not available.

Tumour suppressive role of sirtuin 4 in induction of G2/M arrest and apoptosis in HBV-related hepatocellular carcinoma

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FY Huang, DKH Wong, WK Seto, LY Mak, MF Yuen
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Hepatocellular carcinoma (HCC) is developed from uncontrolled cell growth after malignant transformation. The hepatitis B virus (HBV) HBx protein is associated with mitochondrial dysfunction and hepatocarcinogenesis. Recent studies suggested a tumour suppressor role of mitochondrial sirtuin 4 (SIRT4) in cancers. However, little is known about its effect on hepatocarcinogenesis. We aimed to investigate the clinical significance and functional role of SIRT4 in HBV-related HCC.

Methods: We analysed SIRT4 expression in paired HBV-associated HCC tissues and cell-lines using qPCR and Western blot. SIRT4 expression and its correlation with patient survival were validated using The Cancer Genome Atlas (TCGA) database. The effects of HBx on cancer cell growth were assessed by cell proliferation and colony formation assays. Interaction of SIRT4 and HBV on apoptosis and cell cycle progression, and cell senescence were examined by flow cytometry and β-galactosidase assay, respectively.

Results: SIRT4 expression was significantly downregulated in HCC cell lines. Downregulation of SIRT4 was observed in HCC tumour and adjacent non-tumour tissues compared with normal liver tissues. Analysis of TCGA data indicates SIRT4 levels were downregulated in patients with HBV infection but positively associated with better survival in patients with HCC. Stable HBx transfection suppressed SIRT4 expression in HCC cell lines. Ectopic SIRT4 overexpression could induce cellular senescence through arresting cell-cycle progression at G2/M, and inducing cell apoptosis in HCC cancer cells. Mechanistically, SIRT4 upregulated cell-cycle governing genes p16 and p21 protein expression, suppressed CyclinB1/Cdc2 and Cdc25C which normally induce cell-cycle progression, and suppressed survivin to induce apoptosis.

Conclusion: These findings demonstrate SIRT4 is involved in G2/M checkpoint control and genomic stability in hepatocarcinogenesis, which could be targeted for future anticancer strategies.

Novel role of GDF15 in non-alcoholic steatohepatitis

12

X Yan, Z Huang, R Yang, L Xu, A Xu
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Growth differentiation factor (GDF) 15, a divergent member of the transforming growth factor-β superfamily, is synthesised as an inactive precursor, which is subsequently cleaved and secreted as a disulphide-linked mature protein with a molecular weight of 24.5 kDa. GDF15 is known as a stress-induced cytokine and is correlated with cancer, cardiovascular and kidney diseases. However, the association of GDF15 with non-alcoholic steatohepatitis (NASH) remains unclear and the function of GDF15 during the development of NASH is unidentified.

Methods: We established two animal models for NASH with the use of choline deficient and methionine restricted L-amino acid diet with 60 kcal% fat (CDAHF60) and a genetically apoE deficient mice fed with high-fat high-cholesterol diet (HFHCD). Dynamic changes in serum GDF15 levels during the development of NASH were measured. The tissue source and cell source of GDF15 induction under NASH was explored. The potential target cell with expression of its receptor, GFRAL and co-receptor, RET is identified by flow cytometry.

Results: (1) Serum GDF15 level was increased stepwise during the progression of NASH; (2) Serum GDF15 level is positively associated with liver injury markers and non-alcoholic fatty liver disease (NAFLD) activity score; (3) Liver is the major tissue source of GDF15 expression and secretion under NASH; (4) Hepatocytes contribute to the majority of induced GDF15 expression as compared with non-parenchymal cells; (5) Fc-fusion GDF15 treatment alleviated NASH mainly through inhibition of inflammation, and (6) Kupffer cell is the potential target cell of GDF15 actions under NASH which mediates the anti-inflammatory effects of GDF15.

Conclusion: GDF15 has a protective role during the development of NASH through Kupffer cell-mediated anti-inflammatory effects.

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Comparative effectiveness on remission, risk of Graves' ophthalmopathy and hypothyroidism of treatments for Graves' diseases: a systematic review and network meta-analysis

X Liu, CKH Wong, Y Wei, WWL Chan, YC Woo, CLK Lam, BHH Lang
Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Introduction: Anti-thyroid drug (ATD), radioactive iodine (RAI) and thyroidectomy are common treatments for patients with Graves' disease (GD). Comparisons of effectiveness and adverse effects among the therapies could help give guidance in clinical practice. To evaluate the comparative remission rates after the first-line and second-line treatments of ATD, RAI, and thyroidectomy, and risks of hypothyroidism and Graves' ophthalmopathy (GO), a systematic review and network meta-analysis was conducted.

Methods: Cohort studies or randomised controlled trials (RCT) comparing at least two treatments (ATD, RAI, or thyroidectomy) among patients with GD were searched through Ovid Medline, Ovid Embase, and the Cochrane Library database for literature published from January 2012 to May 2020. By applying PRISMA, two independent reviewers read through the literature, extracted data, assessed the risk of bias and qualities of studies. Random-effects models were used to pool the data and to achieve direct and indirect (network) comparisons.

Results: Twelve eligible studies (three RCTs and nine cohort studies) were included in the qualitative synthesis. Seven studies were qualified for the estimation of first-line remission rate involving 7657 participants. Compared with first-line ATD and RAI, thyroidectomy showed a higher remission rate in pooled analysis (odds ratio [OR]=25.68, 95% confidence interval [CI]=11.26-58.52; OR=2.73, 95% CI=1.20-6.25, respectively). Surgery as second-line treatment was observed with a higher remission rate than ATD (OR=45.22, 95% CI=13.74-148.84) and RAI (OR=5.56, 95% CI=1.92-16.08). Differences in GO and hypothyroidism risks were not significantly different among the three groups. Thyroidectomy was associated with an increased risk for hypothyroidism in direct pairwise comparison with RAI (OR=1.89, 95% CI=1.29-2.78).

Conclusion: This study demonstrates that thyroidectomy is a better treatment option than ATD or RAI in maintaining remission over time. RAI is associated with a higher remission rate than ATD. However, relative to ATD and RAI, thyroidectomy results in a higher risk of permanent hypothyroidism.

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Thyroid dysfunction in relation to immune profile, viral load, disease status and outcome in 191 patients with COVID-19

DTW Lui[1], CH Lee[1], WS Chow[1], ACH Lee[1], AR Tam[1], CHY Fong[1], CY Law[2], EKH Leung[1], KKW To[3], KCB Tan[1], YC Woo[1], CW Lam[4], IFN Hung[1], KSL Lam[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Division of Chemical Pathology, Queen Mary Hospital, Hong Kong
[3]Department of Microbiology, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[4]Department of Pathology, The University of Hong Kong, Hong Kong

Introduction: SARS-CoV-2-related thyroiditis is increasingly recognised. The role of thyroid autoimmunity and SARS-CoV-2 viral load in SARS-CoV-2-related thyroid dysfunction is unclear. We evaluated the thyroid function of a cohort of COVID-19 patients, in relation to their clinical features, biochemical, immunological and inflammatory markers.

Methods: Consecutive adult patients, without known thyroid disorders, admitted to Queen Mary Hospital for COVID-19 from 21 July to 21 August 2020 were included. Serum levels of thyroid-stimulating hormone (TSH), free thyroxine, free triiodothyronine (fT3) and anti-thyroid antibodies were measured on admission.

Results: Among 191 patients with COVID-19 (mean age 53.5±17.2 years; 51.8% male), 84.3% were mild, 12.6% were moderate, and 3.1% were severe. 13.1% had abnormal thyroid function. Ten patients had isolated low TSH, suggestive of subclinical thyrotoxicosis due to thyroiditis, although the contribution of autoimmunity was likely in two of them. Autoimmune thyroiditis probably also contributed to subclinical hypothyroidism in another patient. Ten patients had isolated low fT3, likely representing non-thyroidal illness syndrome. Lower SARS-Cov-2 PCR cycle threshold values and elevated C-reactive protein were independently associated with occurrence of low TSH (P=0.030) and low fT3 (P=0.007), respectively. A decreasing trend of fT3 with increasing COVID-19 severity (P=0.032) was found. Patients with low fT3 had more adverse COVID-19-related outcomes, including dexamethasone and/or oxygen requirement (P=0.003), prolonged hospital stay (P=0.018), and clinical deterioration (P<0.001).

Conclusion: Around 15% of patients with predominantly mild to moderate COVID-19 had thyroid dysfunction. There may be a direct effect of SARS-CoV-2 on thyroid function, potentially leading to exacerbation of pre-existing autoimmune thyroid disease. Low fT3, associated with systemic inflammation, may have a prognostic significance.

Predicting incident hip fractures in Chinese type 2 diabetic individuals using A to G'S

15

DTW Lui, CH Lee, WS Chow, CHY Fong, DCW Siu, YC Woo, KSL Lam
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: FRAX underestimates hip fracture risk in type 2 diabetes (T2D). We developed and validated a Chinese hip fracture risk prediction tool (CHFx) using a Chinese T2D cohort and compared its performance with a recently published Caucasian hip fracture risk equation from Fremantle Diabetes Study Phase I (FDS1).

Methods: 84359 Chinese T2D individuals aged 60 to 85 years who completed diabetic complication assessments during 2008 to 2012 were identified from electronic health records in Hong Kong. Incident hip fractures were recorded till 31 May 2018. The cohort was randomly divided into the training set (80%, n=67488) for the development of CHFx and the testing set (20%, n=16871) for internal validation. CHFx was developed by using multivariable Cox regression of incident hip fractures with variables selected based on Bayesian information criterion (BIC). The discrimination and calibration of CHFx was assessed by C-statistics, Greenwood-Nam-D'Agostino statistics, and calibration plot, in comparison with the FDS1 risk equation.

Results: Upon median follow-up of 6.9 years, 2432 individuals had incident hip fractures. Individuals who had incident hip fractures were more likely women, older, smokers, had longer duration of diabetes, lower BMI and eGFR, more history of severe hypoglycaemia, fall, fractures, cardiovascular diseases and stroke (all P<0.001). Based on BIC, CHFx comprised age, BMI, cigarette smoking, duration of diabetes, EGFR, history of fall, gender and history of stroke (mnemonic: ABCDEFG-S or A to G'S). CHFx predicted mean 5-year incident hip fracture risk at 1.6% with good discrimination (C-statistics 0.744, 95% confidence interval [CI]=0.733-0.754) and calibration (chi^2=7.995, P=0.535) in the training set. CHFx had a better C-statistics (0.754, 95% CI=0.733-0.776) than the FDS1 risk equation (0.729, 95% CI=0.706-0.752) in the testing set (P<0.001).

Conclusion: CHFx consists of eight readily available parameters (A to G'S) and more accurately predicts incident hip fractures among Chinese T2D individuals than the Caucasian FDS1 risk equation. CHFx may help to identify high-risk T2D individuals for a more aggressive approach to optimise their bone health.

Machine learning model in predicting the minimal endoscopy services requirement for gastrointestinal cancer diagnosis in Hong Kong during various phases of COVID-19

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TKL Lui, WK Leung
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: The ongoing COVID-19 outbreak has severely affected the healthcare service delivery, including routine endoscopy services. We have previously shown a 37% to 46% drop in gastrointestinal cancers diagnosed during the initial phase of COVID-19 in Hong Kong. As the situation would unlikely to resolve soon, we have to develop a new strategy to monitor and predict our endoscopic service requirement, in order to provide robust guidance on optimal endoscopy volume to minimise the delay in gastrointestinal cancers diagnosis.

Methods: We retrieved from the CDARS of the Hospital Authority the number of patients who had upper and lower endoscopy and the number of new cases of gastrointestinal cancers diagnosed, as well as the real-time reproductive number of local COVID-19 case and the number of new COVID-19 cases from the School of Public Health dashboard. The number of patients with potential delay in cancer diagnosis was estimated with the autoregressive integrated moving average (ARIMA) model. Six different machine learning models: traditional linear regression (LR), random forest (RF), support vector machine (SVM), stochastic gradient boosting (SGB), neural network (NN) and extreme gradient boosting (XGBoost) were used to estimate the requirement of endoscopy service for gastrointestinal cancer diagnosis during different phases of COVID-19 in Hong Kong.

Results: There were a total of 337903 upper endoscopies and 254588 lower endoscopies performed between October 2016 and June 2020. The model with the best performance in terms of prediction of minimal upper and lower endoscopy volume without delay in diagnosis of gastric and colorectal cancer is the XGBoost (MAPE±95% confidence interval [CI]=3.0±2.6 and 2.4±0.01, respectively). The minimal average weekly number of upper endoscopy to be performed in the subsequent month is 1781±149 (mean±95% CI), which is still significantly lower than usual upper endoscopy volume in the pre-COVID-19 period (1974±818, P<0.01). Accordingly, the minimal average weekly number of lower endoscopy required is 1115±386 as compared with usual lower endoscopy volume of 1330±456 (P<0.01).

Conclusion: Machine learning model, particularly the XGBoost, can be applied in the prediction of minimal number of endoscopy service required to minimise delay in gastrointestinal cancer diagnosis during the ongoing COVID-19 outbreak in Hong Kong.

Aspirin use and risk of colorectal cancer among older adults

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CG Guo[1,2], W Ma[2], WK Leung[1], AT Chan[2]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, United States

Introduction: Aspirin is considered the most established agent for chemoprevention of colorectal cancer (CRC) and is recommended by the United States Preventive Services Task Force (USPSTF) for adults aged 50 to 59 years. But recent data from a randomised controlled trial suggest a lack of benefit and even possible harm among older adults. We aimed to examine the association between aspirin use and the risk of incident CRC among older adults.

Methods: We included participants aged ≥70 years from two large prospective cohort studies, the Nurses' Health Study and Health Professionals Follow-up Study. Our primary exposure was regular aspirin use, using twice or more per week, at age ≥70. Person-time started from the age of 70 until the date of diagnosis of CRC, death, or the end of follow-up on 1 June 2014. Cox proportional hazards models stratified on age and calendar time (2-year intervals) were used to calculate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CRC.

Results: Among 94 540 participants, including 67 223 women and 27 317 men, aged ≥70, we documented 1431 incident cases of CRC over 996 463 person-years of follow-up. After adjustment for other covariates, regular use of aspirin at age ≥70 was associated with a lower risk of CRC compared with non-regular use (HR=0.80, 95% CI=0.72-0.90). However, the inverse association was only evident among aspirin users who initiated aspirin use before age 70 (HR=0.80, 95% CI=0.67-0.95). In contrast, initiating aspirin use at age ≥70 was not significantly associated with lower risk of CRC (HR=0.92, 95% CI=0.76-1.11).

Conclusion: Initiating aspirin at an older age was not associated with lower risk of CRC. In contrast, continuing using aspirin if initiated at a younger age appeared to derive continued benefit for CRC risk reduction.

Trends in cardiovascular risk in the United States 1999 to 2018

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HL Li, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: As guidelines evolve, lifestyle changes and new drugs are introduced, and the long-term trends in cardiovascular risk in the general population are of interest. We evaluated the AHA-ACC-ASCVD risk score (ASCVD-RS) in the United States population in the last 20 years.

Methods: Participants in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2018 aged 40 to 79 years were included. Pregnant participants and those with missing relevant laboratory/self-reported data were excluded. Temporal trends in ASCVD-RS and its components, and the proportions of participants at high risk (score ≥10%) were characterised using linear regression, adjusted for age, sex, and ethnicity. Data analysis was performed using the R statistical package "survey" (version 3.6.3).

Results: Altogether 12744 NHANES participants (mean age 56.4 years; 55.9% male) were analysed. From 1999 to 2018, the proportion of people with diabetes and taking antihypertensives increased significantly (both P<0.001), while total cholesterol level decreased significantly (P<0.001). Levels of high-density lipoprotein cholesterol (HDL), and the proportion of smokers and individuals with systolic blood pressure ≥120 mmHg remained static. The mean±standard error of ASCVD-RS significantly increased from 11.4±0.7% in 1999 to 2000 to 12.5±0.5% in 2017 to 2018 (P=0.014), and the proportion of high-risk participants increased from 39.1% to 44.1% (P=0.020).

Conclusion: Cardiovascular risk in the United States population increased slightly in the past 20 years. Despite the increased treatment rate of hypertension and the decrease in total cholesterol, the prevalence of diabetes doubled. More effort should be directed at preventing diabetes through weight control and regular physical activity.

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Obesity is a major risk factor for severe COVID-19 illness

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HL Li, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Conditions including obesity, diabetes mellitus (DM), chronic kidney disease (CKD), heart disease, and chronic obstructive pulmonary disease (COPD) predispose individuals to severe illness from COVID-19. We estimated the prevalence of these risk factors in the United States population.

Methods: Participants in the National Health and Nutrition Examination Survey (NHANES) 2011 to 2016 aged ≥20 years were included. Pregnant participants and those with missing relevant laboratory/examination/self-reported data were excluded. The prevalence of obesity, DM, CKD, heart disease, and COPD were calculated. Subgroups according to age (<50 and ≥50 years), sex, and ethnicity were compared. Data analysis was performed using the R statistical package "survey" (version 3.6.3).

Results: Altogether 7744 NHANES participants (mean age 49.5 years; 49.4% male) were analysed. Obesity was the most common risk factor (41.0%) followed by DM and CKD. Whereas DM, CKD, heart disease, and COPD were more common in people aged ≥50 years, obesity was almost equally common in either age-group. Overall, the prevalence of ≥1 risk factor was 58.9% In people aged ≥50, 69.5% had one or more risk factors, compared with 47.9% in people aged <50 years. In the latter age-group, the prevalence of obesity was 38.9%, making it the leading risk factor. The prevalence of one or more risk factors was around 60% across people of different sex and ethnicity, except in Asians (39.5%), in whom both obesity and DM are the leading risk factors.

Conclusion: More than half of adult Americans are at risk from severe COVID-19 illness. Obesity is the major risk factor. COVID-19 is a threat to people across all age-groups, sexes, and ethnicities. Individuals with increased risk should strictly follow social distancing and personal hygiene measures, as well as adopt lifestyle modifications for weight control.

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Aspirin is associated with higher mortality in patients with infective endocarditis

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HL Li, SSY Yu, PF Wong, ASY Yu, YK Tse, LY Lam, CKY Leung, KY Li, MZ Wu, QW Ren, KH Yiu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Despite improvement in diagnostic methodology and treatment modalities, patients with infective endocarditis (IE) remain to have a high mortality rate. It has been hypothesised that aspirin could reduce inflammation and embolism, but previous small-scale studies have shown conflicting evidence. We aimed to clarify the association between aspirin and mortality in patients with IE.

Methods: Data were retrieved from Clinical Data Analysis and Reporting System (CDARS), a territory-wide database in Hong Kong. Patients diagnosed with IE from 1996 to 2019 with at least 1-year follow-up were included. Data on the duration of use of aspirin and cause of death were extracted. Pre- and post-admission use of aspirin were defined as using aspirin for ≥90 days in 1 year before admission, and for ≥3 days starting within 1 day after admission, respectively. Patients were compared using inverse probability weighting of the covariate balancing propensity score, which included age, sex, causative organism, Charlson Comorbidity Index, underlying heart conditions, and baseline medication use as covariates. The outcomes of interest included 30-day and 1-year all-cause mortality. Statistical analysis was performed using R (version 3.6.3).

Results: Altogether 6929 patients (mean age 56.2 years; 63.1% male) were included. There were 949 and 787 patients with pre- and post-admission use of aspirin. After adjustment for post-admission aspirin use, pre-admission aspirin use was associated with a higher 1-year mortality (hazard ratio [HR]=1.21, 95% confidence interval [CI]=1.07-1.38, P=0.003) but not 30-day (HR=0.98, 95% CI=0.84-1.14, P=0.813) mortality. After adjustment for pre-admission use of aspirin, post-admission use of aspirin was associated with a higher 30-day (HR=1.24, 95% CI=1.06-1.45, P=0.096) but not 1-year (HR=1.02, 95% CI=0.90-1.15, P=0.802) mortality. Among pre- or post-admission aspirin users who died within 1 year, bleeding-related death was the main cause of death followed by IE and pneumonia, compared with sepsis-related death in non-aspirin users.

Conclusion: The use of aspirin appeared to be associated with a higher mortality in patients with IE, possibly due to higher bleeding tendency. While patients with previous use of aspirin admitted for IE require closer monitoring, our results suggest that aspirin should not be initiated in patients with IE.

Apabetalone reduces cardiovascular risk: a meta-analysis

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HL Li, Y Fei, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Epigenetic inhibition of bromodomain and extra-terminal protein (BET) is a rapidly emerging therapeutic approach in reducing residual cardiovascular risk. Apabetalone is a novel drug that reduces inflammation and thrombosis through selective BET inhibition. Three phase II trials suggested benefits while the recent phase III BETonMACE trial did not. To reconcile these inconsistencies, we performed a meta-analysis of all trials of apabetalone.

Methods: We searched MEDLINE, EMBASE, Cochrane Library, and ClinicalTrials.gov for randomised controlled trials of apabetalone up to 5 May 2020. The outcomes of interest were cardiovascular events (major adverse cardiovascular events [MACE] and hospitalisation for heart failure) and inflammatory markers (alkaline phosphatase [ALP] and C-reactive protein [CRP]), and lipid parameters (high-density lipoprotein cholesterol [HDL]), low-density lipoprotein cholesterol (LDL), apolipoprotein A-I (apoA-I), and apolipoprotein B (apoB). Pooled risk ratios (RRs) or mean differences (MD) and 95% confidence intervals (95% CIs) in a fixed-effects model were generated using the "meta" package in R (version 3.6.3).

Results: Four trials with altogether 3223 patients were included. All patients had coronary artery disease and received standard statin therapy. Apabetalone significantly reduced MACE (RR=0.78, 95% CI=0.63-0.96), hospitalisation for HF (RR=0.48, 95% CI=0.33-0.70) and ALP (MD= -9.35%, 95% CI= -12.17 to -6.53), and significantly increased HDL (MD=4.43%, 95% CI=2.74-6.13) and apoA-I (MD=2.82%, 1.36-4.28). No significant differences were observed for CRP (MD= -0.32%, 95% CI= -1.42 to 0.77), apoB (MD= -0.42%, 95% CI= -3.61 to 2.76), and LDL (MD= -0.10%, 95% CI= -0.41 to 0.22). There was no significant heterogeneity.

Conclusion: Our meta-analysis shows that apabetalone reduces cardiovascular events and inflammation, and improved lipid profiles. While BET inhibition shows promising potential in eliminating residual cardiovascular risk, larger outcome trials are urgently needed to investigate the cardiovascular benefits and underlying mechanisms of BET inhibition.

Prevalence of childhood obesity in the United States 1999 to 2018: a 20-year analysis

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HL Li, MF Tsoi, Q Feng, CL Cheung, TT Cheung, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Obesity is a public health crisis in the United States. Childhood obesity is associated with multiple comorbidities in adulthood, including metabolic syndrome, cardiovascular diseases, and premature death. This study estimated the prevalence of obesity and severe obesity in United States children and adolescents.

Methods: From the United States National Health and Nutrition Examination Survey from 1999 to 2018, 35907 children aged 2 to 19 years with body mass index (BMI) data were included. Prevalence of obesity and severe obesity, defined as BMI ≥95th percentile and ≥120% of 95th percentile of United States Centers for Disease Control and Prevention growth charts, respectively. Trends in prevalence of obesity and subgroup analyses according to age-group, sex, ethnicity, language used in interview, household education level, and household income level, were analysed. Data analysis was performed using the R statistical package "survey" (version 3.6.3).

Results: The prevalence of obesity and severe obesity increased from 14.7 (95% confidence interval [CI]=12.9%-17.0%) to 19.2 (17.2%-21.0%) and 3.9 (2.9%-5.0%) to 6.1 (4.8%-8.0%) in 1999 to 2018, respectively (P=0.001 and P=0.014 for obesity and severe obesity, respectively). In 2017 to 2018, the prevalence of obesity among children from Spanish-speaking households was 24.4 (22.4%-27.0%), higher than children from English-speaking households (P=0.027). Children from households with high education level and high-income level had a lower prevalence of obesity compared with those with low education level and low-income level (P=0.003 and P=0.002 for education level and income level, respectively).

Conclusion: The prevalence of childhood obesity in America kept increasing during the period 1999 to 2018 despite various public health initiatives. The problem is worse in children with lower socioeconomic status, and in children from Spanish-speaking households. Public health interventions are urgently needed to halt the rising trend of childhood obesity, and measures specifically catering to children from Spanish-speaking families should be put in place.

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Outcomes and microbiology in patients with infective endocarditis in Hong Kong 1996 to 2019

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HL Li, SSY Yu, PF Wong, ASY Yu, YK Tse, LY Lam, MZ Wu, QW Ren, KH Yiu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Infective endocarditis (IE) is associated with high mortality rate and morbidity despite improvements in guidelines and management. Limited data exist regarding the characteristics of IE in the Asian population. We aimed to describe the epidemiological characteristics, microbiology, and outcomes in IE patients in Hong Kong.

Methods: From the Clinical Data Analysis and Reporting System (CDARS), a territory-wide database in Hong Kong, patients diagnosed with IE from 1996 to 2019 with ≥1-year follow-up were included. Temporal trends in 30-day and 1-year mortality and surgery rate were characterised using linear regression. Factors associated with higher mortality rate were identified using multivariate logistic regression, adjusted for age, sex, Charlson Comorbidity Index (CCI), and other relevant comorbidities including prosthetic valve and implanted cardiac device. Statistical analysis was performed using R (version 3.6.3).

Results: Altogether 6929 patients (mean age 56.2 years; 63.1% male) were included. Small reductions in 30-day (P=0.025) and 1-year mortality (P=0.001) were observed, and they remained at around 16.9% and 43.6%, respectively. There were significant increases in 30-day (0.6% per year, P<0.001) and 1-year surgery rates (1.0% per year, P<0.001). Compared with culture-negative IE, 30-day mortality was higher in Staphylococcal IE (hazard ratio [HR]=2.13, 95% confidence interval [CI]=1.80-2.52, P<0.001) and was lower in Streptococcal IE (HR=0.72, 95% CI=0.58-0.89, P=0.003). Methicillin resistance, advanced age, and male sex were associated with higher 30-day mortality (P<0.001, P<0.001, and P=0.020, respectively). Additional factors associated with higher 1-year mortality included higher CCI (P<0.001), history of myocardial infarction (P=0.039), and ulcer disease (P=0.045), and pre-admission use of antibiotics (P<0.001) and diuretics (P=0.002).

Conclusion: This is the first and largest report to comprehensively evaluate the trends and outcomes of IE in Hong Kong. The mortality rate remained high despite improvements in management and changes in guidelines. Methicillin resistance, Staphylococcal infection, advanced age, and male sex were associated with poorer prognosis. Novel strategies are urgently needed to eliminate the residual risk of death in patients with IE.

Factors associated with sleep apnoea prevalence in patients with stroke: a systematic review and meta-analysis

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XD Liu, DCL Lam, HY Chan, MSM Ip, GKK Lau
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Recent meta-analyses have noted a high prevalence (~70%) of sleep disordered breathing in patients with transient ischaemic attack (TIA) and stroke. However, heterogeneity between studies was high and did not appear to be accountable by phase of stroke. We conducted an updated meta-analysis and aimed to explore whether stroke characters could account for some of the unexplained heterogeneity.

Methods: We searched Medline, Embase, CINAHL and Cochrane Library (until 1 July 2020) for clinical studies in English that have reported the prevalence of sleep apnoea in TIA/stroke patients using polysomnography devices. We used a random-effects model to calculate the pooled prevalence by apnoea hypopnea index (AHI) ≥5/h, 10/h and 15/h. We performed meta-analysis and subgroup analysis to evaluate the impact of stroke characters on overall prevalence.

Results: We included 75 studies describing 8753 stroke patients in this meta-analysis. The pooled prevalence of sleep apnoea was 72.7% (95% confidence interval [CI]=67.5%-77.4%) by AHI ≥5/h, 68.3% (95% CI=64.9%-71.5%) by AHI ≥5 to 15/h, and 26.7% (95% CI=23.1%-30.7%) by AHI ≥30/h. The high heterogeneity is partially explained by stroke subtype (1.8%) and stroke phase (6.0%). Overall prevalence defined by AHI ≥5 to 15/h was higher in patients with haemorrhagic than ischaemic stroke (82.7% [95% CI=64.4%-92.7%] vs 67.5% [95% CI=63.2%-71.5%]), higher in supratentorial stroke than infratentorial stroke (69.0% [95% CI=57.8%-78.3%] vs 51.1% [95% CI=42.2%-60.0%]), higher in strokes due to cardioembolism (74.0% [95% CI=56.5%-86.2%]) than other etiological subtypes. Prevalence in infratentorial stroke was homogenous (I2=0) compared with supratentorial stroke (I^2=76%).

Conclusion: Stroke subtype, phase, location and aetiology may play important roles in the mechanism linking sleep apnoea with stroke. These factors are recommended to be reported in future cohort studies.

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Pilot study of smartphone-based applications in assessing motor and gait disability in Parkinson's disease

KK Yam, SYY Pang, SL Ho
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: It is unknown how phone-based kinematic tests are compared to the standard Unified Parkinson's Disease Rating Scale (UPDRS) in idiopathic Parkinson's disease (IPD).

Methods: Patients with IPD were recruited from out-patient clinics of Queen Mary Hospital and Tung Wah Hospital. A full rating of UPDRS (Part III motor) was performed by a trained clinician, followed by supervised use by patients of a novel smartphone application called EncephalogClinic™, which obtained objective measurements based on inbuilt motion sensors of smartphones using the timed up and go test (TUGT), finger tap test (FTT) and tests for tremor.

Results: 65 IPD patients (mean age 65 years, median UPDRS part III score 27, and median Hoehn and Yahr stage II) and 65 control subjects were recruited. There was strong correlation between 5-metre TUGT standup time (r=0.82, P<0.001), moderate correlation between 5-metre TUGT total time (r=0.53, P=0.001) and UPDRS gait subscore; moderate correlation between total tremor signals and UPDRS tremor subscore (r=0.54, P<0.001); moderate correlations between total number of finger taps (r= -0.53, P=0.02), average time between finger taps (r=0.58, P=0.03) and UPDRS bradykinesia subscore. Average stride length in 5-metre TUGT could distinguish IPD patients from normal subjects with AUC 0.821 (95% confidence interval=0.744-0.898, P<0.001).

Conclusion: These phone-based tests could serve as alternative objective assessment tools of motor features and potential screening tool for IPD. As they are simple to use and do not require administration by healthcare professional, they can be useful for home and remote patient monitoring. This is especially relevant during COVID-19 pandemic when patients may not be able to attend out-patient follow-up.

Acknowledgement
This research utilises a free phone-based application called EncephalogClinic™, designed by Montfort Brain Monitor LTD (https://www.mon4t.com) company which designs smartphone-based neurological tests.

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Reduced hepatic steatosis is associated with higher risk of hepatocellular carcinoma in chronic hepatitis B infection

LY Mak[1,2], RWH Hui[1], J Fung[1,2], F Liu[3], DKH Wong[1,2], KS Cheung[1,4], MF Yuen[1,2], WK Seto[1,2,4]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]State Key Laboratory for Liver Research, The University of Hong Kong, Hong Kong
[3]Department of Gastroenterology and Hepatology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China
[4]Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

Introduction: Concomitant chronic hepatitis B infection (CHB) and non-alcoholic fatty liver disease (NAFLD) is common, but the implications of NAFLD on clinical outcomes of CHB, including hepatocellular carcinoma (HCC), are not well investigated.

Methods: CHB patients (both treatment-naïve and treated with nucleos(t)ide analogues [NA]) were recruited for transient elastography assessment for liver stiffness, and controlled attenuation parameter (CAP), a non-invasive quantification of hepatic steatosis, and were prospectively followed up for development of HCC. Steatosis and severe steatosis were diagnosed by CAP ≥248 dB/m and ≥280 dB/m, respectively, and advanced fibrosis/cirrhosis was diagnosed by liver stiffness ≥9 kPa.

Results: Among 2403 CHB patients (55.6% male, median age 55.6 years, 57.1% NA-treated, median ALT 26 U/L), 48 patients developed HCC during a median follow-up of 46.4 months. Multivariate Cox regression analysis showed increased CAP to be inversely associated with HCC development (hazard ratio=0.994, 95% confidence interval=0.989-0.999). The cumulative probability of HCC was 2.88%, 1.56% and 0.71%, respectively for patients with no steatosis, mild-to-moderate steatosis, and severe steatosis (P=0.01). The risk of HCC increased from 1.56% to 8.89% in patients without severe steatosis if advanced fibrosis/cirrhosis were present (P<0.001).

Conclusion: Reduced hepatic steatosis was significantly associated with a higher risk of incident HCC in CHB patients. Routine CAP and liver stiffness measurements can be important for risk stratification, especially in on-treatment patients.

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Persistently detectable serum HBV DNA and HBV pgRNA is associated with hepatocellular carcinoma development in chronic hepatitis B patients receiving long-term nucleoside analogue therapy

LY Mak[1,2], Q Huang[3], DKH Wong[1,2], LM Stamm[3], KS Cheung[1,4], KL Ko[1], R Yan[3], L Ouyang[3], J Fung[1,2], WK Seto[1,2,4], MF Yuen[1,2]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]State Key Laboratory for Liver Research, The University of Hong Kong, Hong Kong
[3]Assembly Biosciences, Inc.
[4]Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

Introduction: Hepatocellular carcinoma development is not completely prevented in patients with chronic hepatitis B infection (CHB). We aimed to assess whether residual hepatitis B virus (HBV) viraemia is associated with HCC development.

Methods: This is a case-control study of 104 patients (52 HCC and 52 non-HCC [matched with age, sex, cirrhosis and treatment duration]) on ≥3 years entecavir (ETV) with unquantifiable HBV DNA by Cobas TaqMan assay v2.0 (Roche Diagnostics; lower limit of quantification [LLOQ] 20 IU/mL). Serial sera within 1, 1-2, and >2 years prior to HCC diagnosis or last follow-up (LFU) were measured for HBV DNA and pre-genomic (pg) RNA using a highly sensitive semi-quantitative PCR assay with lower limit of detection of 10 IU/mL and LLOQ of 51.5 IU/mL, respectively.

Results: Among the 104 patients (80.8% male, median age 61.2 years, 38.5% cirrhosis, median duration of ETV 45.5 months), 38.5% and 9.6% HCC patients had undetectable serum DNA and pgRNA, respectively compared with 65.4% and 36.5% in non-HCC patients; P=0.005 and 0.001, respectively at the time of HCC diagnosis/LFU. Detectable HBV DNA and pgRNA was associated with a higher 2-year risk of HCC development (hazard ratio [HR]=2.79, 95% confidence interval [CI]=1.424-5.468 and HR=4.544, 95% CI=1.07-19.289, respectively).

Conclusion: More than 50% CHB patients on ETV with HBV DNA <LLOQ by standard assay had persistent viraemia as determined by a more sensitive assay. Detectable HBV DNA and/or pgRNA by more sensitive assays was associated with HCC development. More potent viral suppression is required to further reduce the risk of HCC.

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PAR-1 antagonist vorapaxar protects against kidney injury and tubulointerstitial fibrosis in the progression of acute kidney injury to chronic kidney disease

SWY Lok, WH Yiu, LYY Chan, JCK Leung, KN Lai, SCW Tang
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Protease-activated receptor-1 (PAR-1) has been reported as a coagulation regulator in the pathophysiology of acute kidney injury (AKI). Beyond its function in normal haemostasis, aberrant PAR-1 signalling may lead to the development of tubulointerstitial fibrosis, and subsequently chronic kidney disease (CKD).

Methods: We investigated whether the administration of PAR-1 antagonist vorapaxar, an FDA-approved drug for reducing thrombotic cardiovascular events, has renoprotective effect on a robust kidney fibrotic murine model of chronic kidney disease following unilateral ischaemia-reperfusion injury (UIRI), as well as in hypoxia-induced cultured rat proximal tubular epithelial cells (NRK-52E).

Results: Vorapaxar ameliorates kidney injury as evidenced by the reduction in morphological abnormalities and tubular injury marker KIM-1 in UIRI kidneys. Mice treated with vorapaxar showed alleviated kidney fibrotic changes with less accumulation of ECM proteins including fibronectin, α-smooth muscle actin and collagen 1 via TGF-β/Smad signalling after UIRI. IR-induced endothelial dysfunction and macrophage infiltration were also decelerated by vorapaxar treatment. In NRK-52E cells, PAR-1 expression was activated during hypoxic condition associated with the upregulation of TGF-β-induced ECM proteins accumulation.

Conclusion: Vorapaxar diminishes renal fibrosis through TGF-β/Smad signalling in UIRI model and protects against tubular injury during the process of AKI to CKD. This PAR-1 targeted strategy by vorapaxar mandates further investigation into therapeutic potential in CKD in human.

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Intractable hypoglycaemia induced by the antibody against exogenous insulin in a Chinese patient with type 1 diabetes

L Geng[1,2], X Diao[3], X Zhao[1,2], J Yu[1,2], Y Chen[3], W Liang[3], A Xu[1,2,4]
[1]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Hong Kong
[3]Department of Endocrinology, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China
[4]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: A 25-year-old Chinese woman with 13-year history of type 1 diabetes (T1D) was periodically hospitalised for recurrent abdominal pain and vomiting alternating with spontaneous hypoglycaemia in the last 3 years. She was treated short-acting insulin Lispro via an insulin pump. Although the insulin dosage had been reduced from 10.9 U/day to 3.2 U/day, she gained 32 kg body weight and her haemoglobin A1c level decreased from 10.9% to 5.9% after the occurrence of hypoglycaemia. This study aimed to investigate why this patient with T1D developed obesity and recurrent hypoglycaemia.

Methods: A comprehensive biochemical and immunological analysis was performed to measure the levels of circulating factors involved in regulation of glucose homeostasis and insulin actions.

Results: Physical examination and imaging diagnosis with computed tomography, gastroenteroscopy and magnetic resonance imaging did not observe any abnormality. The glutamate decarboxylase 65 (GAD65) autoantibody was extremely high (20 000 U/mL) while C-peptide was undetectable (<0.01 ng/mL). During one episode of hypoglycaemia, the blood glucose level was 2.34 mM while insulin was almost undetectable (<0.2 uU/mL) by Elecsys insulin assay, which can only detect human endogenous insulin. The IGF-1 level was normal and anti-insulin receptor autoantibody was negative. In contrast, an extremely high titre of anti-insulin antibody (21.85%, normal 0%-5%) was detected in the patient. Notably, after disruption of antibody-antigen interaction with acid followed by polyethylene glycol precipitation, high levels of free insulin (9.50 uU/mL) and total insulin (60.72 uU/mL) were detected using an immunoassay, which can detect both endogenous insulin and insulin analogues, even 12h after stopping injection with insulin.

Conclusion: Frequent hypoglycaemia in this patient with T1D is attributed to the existence of anti-exogenous insulin antibody, which acts as a buffer system to extend the half-life of insulin. The presence of extremely high titres of GAD65 autoantibody after 13 years of T1D suggests the potential existence of autoimmune disease in the central nervous system, contributing to cyclic abdominal pain and vomiting in this patient.

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Shifts in gut antibiotic resistance genes after the exposure to different *H pylori* eradication therapies

LL Wang[1], HB Yao[2], T Tong[1], KS Lau[1], A Chan[3], JWK Ho[2], SY Leung[3], WK Leung[1]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]School of Biomedical Sciences, The University of Hong Kong, Hong Kong
[3]Centre for PanorOmic Science, The University of Hong Kong, Hong Kong

Introduction: Antibiotics used in *H pylori* eradication therapies could alter the gut microbiota as well as ARGs, thus increasing the risk of antibiotic resistance. We aimed to investigate the relationship between antibiotic use and subsequent gut ARGs patterns after *H pylori* eradication therapy.

Methods: Adult patients (n=44) diagnosed with active *H pylori* infection were recruited. Patients were divided according to their treatment into primary treatment with clarithromycin-based triple therapy (CLA; n=21); retreatment with levofloxacin-based quadruple therapy (LEVO; n=10) or other combinations (OTHER; n=13). Consecutive stool samples were collected before current eradication therapy, at 4 to 8 weeks and 6 months after completing the therapy. All stool samples were sequenced on the Illumina NovaSeq 6000 System (Illumina, USA, PE 150bp) and qualified reads were assembled into contigs using MEGAHIT. ARGs were identified against the Comprehensive Antibiotic Resistance Database (CARD).

Results: The total ARG abundance increased at 4 to 8 weeks compared with baseline (662.05 to 857.87, P=0.002), and continued to 6 months (887.26, P=0.028). In the CLA group, the relative abundance of MLS resistance gene increased (24.33% to 31.42%, P=0.02) at 4 to 8 weeks, especially ErmF and tetO. In the LEVO group, the relative abundance of fluoroquinolone, multidrug, and nitroimidazole resistance genes increased, while the relative abundance of MLS and beta-lactam resistance genes decreased at 4 to 8 weeks. Specifically, 28 unique ARGs were found to have a slight increase in abundance at 4 to 8 weeks, which restored at 6 months in the LEVO group. In the OTHER group, no significant difference in ARGs was found at 4 to 8 weeks or 6 months.

Conclusion: Antibiotic used in various *H pylori* eradication therapies had a significant impact on the total gut ARGs abundance, which last for at least 6 months. However, short-term changes in specific ARGs are more prevalent after treatment with levofloxacin-based therapy.

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Delineating interferon-alpha mediated AIM2 inflammasome response in systemic lupus erythematosus

JX Chow, CS Lau, VSF Chan
Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of diverse aetiologies, characterised by a breakdown of tolerance to self-antigens. Elevated serum levels of type I interferons (IFN-I) and pro-inflammatory cytokines interleukin-1beta (IL-1beta) and IL-18 positively correlate with SLE disease activity and lupus nephritis. Upon infection, caspase-1 dependent AIM2 inflammasome oligomerises in the cytosol following detection of dsDNA to produce IL-1beta and IL-18. We additionally demonstrated that AIM2 inflammasome response was highly augmented in the SLE context as well. It was proved that serological IFN-I in SLE serum were responsible for elevating AIM2 inflammasome activity. This study aimed to elucidate the molecular mechanisms underlying the observed AIM2-associated dysregulation in SLE patients.

Methods: Untreated healthy (HC) monocytes (group A); IFN-alpha treated HC monocytes (group B); HC serum treated HC monocytes (group C); and SLE serum treated HC monocytes (group D) were submitted for RNA-sequencing (RNA-Seq). Transcriptome analysis and gene set enrichment analysis (GSEA) were used to screen for potential molecular factors (mediated by IFN-alpha) that regulate AIM2 inflammasome. Q-PCR and western blot were used to confirm our RNA-Seq findings.

Results: RNA-Seq revealed a total of 396 differentially expressed, overlapping genes between group A versus B and group C versus D. Interferon signalling pathways were predominantly mobilised upon treatments. GSEA identified signal transducer and activator of transcription 1 (STAT1), STAT2 and Interferon Regulatory Factor 9 (IRF9) as potential upstream modulators of AIM2. STAT1 and STAT2 protein were highly expressed and phosphorylated in SLE monocytes (vs HC). SLE serum treated HC monocytes showcased elevated mRNA levels of STAT1 and STAT2 in strong positive correlation to AIM2 gene expression.

Conclusion: STAT1/2-associated transcription factors could potentially regulate AIM2 inflammasome response. Chromatin immunoprecipitation will be employed to validate the associations between STAT1 and STAT2 with AIM2 promoter regions in SLE versus HC serum cultured monocytes. Knockdown assays will be used as well.

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Dysregulation of interleukin-18 receptor accessory protein in neutrophils of patients with systemic lupus erythematosus

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J Ma, IKY Lam, CS Lau, VSF Chan
Division of Rheumatology and Clinical Immunology, Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Systemic lupus erythematosus (SLE) is a female-biased, chronic systemic autoimmune disorder. Cytokine dysregulation is a typical characteristic of SLE. The proinflammatory cytokine, interleukin-18 (IL-18), plays a pathological role in the development of SLE. IL-18 receptor (IL-18R) consists of two subunits where the alpha-chain (IL-18Ralpha) has a weak affinity for IL-18 binding. Upon binding of IL-18 to IL-18Ralpha, the other subunit IL-18 receptor accessory protein (IL18RAP) is recruited to form a heterotrimeric complex for high-affinity binding. IL-18 is capable of stimulating a variety of leukocytes expressing IL-18R including T cells, NK cells and neutrophils. In a screening assay, we observed an elevated expression of IL18RAP in peripheral leukocytes of lupus nephritis (LN) patients and its expression level was highly correlated with neutrophil-associated genes. So far, the functional significance of IL18RAP in mediating IL-18 driven response in myeloid cells in SLE remains largely unexplored. This study aimed to investigate the expression and function significance of IL18RAP in neutrophils of SLE patients.

Methods: Expression level of IL18RAP in neutrophils was compared between normal controls and SLE patients by qRT-PCR and Western Blotting. Modulation of IL18RAP expression in neutrophils was assayed by in vitro culture with patient sera and interferon-alpha. Neutrophils' ability to produce reactive oxygen species (ROS) upon stimulation was evaluated in combination with recombinant IL-18 and IL18RAP blocking antibodies.

Results: Increased expression of IL18RAP was observed in neutrophils from SLE patients at both mRNA and protein level, particularly those with history of nephritis. IL18RAP expression was negatively correlated with complement 3, while positively correlated with SLE disease activity. Its expression could be upregulated by SLE sera with high interferon level or by recombinant interferon-alpha. IL-18 can enhance fMLP-mediated ROS generation in neutrophils. SLE neutrophils exhibited higher enhancement of ROS production in an IL18RAP expression-dependent manner. The observed enhancement could be neutralised by the anti-IL18RAP antibody.

Conclusion: IL-18 could contribute to SLE pathogenesis through mediating neutrophil dysfunction via the upregulated IL18RAP expression.

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Haploidentical haematopoietic stem cell transplant outcomes from Queen Mary Hospital

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YZ Ng, JPY Sim, AKW Lie, YL Kwong
Department of Medicine, Queen Mary Hospital, Hong Kong

Introduction: Queen Mary Hospital is the only centre in Hong Kong that provides Haploidentical haematopoietic stem cell transplant (haplo-HSCT) service for adult patients. This study reported the outcomes of our haplo-HSCT.

Methods: Data of haplo-HSCT patients with at least 6 months post-transplant follow-up were retrospectively collected and analysed. First four earlier patients received ATG-based modified BuCy as per PUPH protocol and the remaining patients received post-transplant cyclophosphamide (PTCy)-based conditioning.

Results: 38 haplo-HSCT were performed from December 2014 to February 2020 with a median 427 days of follow-up. Median age at transplant was 46 (range, 20-62). 15 of them were male. 16 of them were lymphoid and 22 of them were myeloid. 19 of them received reduced intensity conditioning. Four patients were at CR2 or above at transplant. 36 patients achieved neutrophil engraftment with median 17 days and 35 achieved platelet engraftment with median 22 days. Seven patients developed grade II-IV acute graft-versus-host disease (GVHD) and none of them had grade III or above acute GVHD. Nine patients developed chronic GVHD. Relapse occurred in 15 patients. Overall and progression-free survivals at 1 year were 78.9% and 53%, respectively. There were nine mortalities, five were due to relapse, three were due to transplant-related mortality and one was due to GVHD from donor lymphocyte infusion (DLI). One-year overall survival (OS) in myeloablative conditioning (MAC) group was 83.5% and in reduced intensity conditioning (RIC) group was 71.1% (P=0.251). One-year progression-free survival (PFS) in MAC group was 61% and in RIC group was 45.6% (P=0.345).

Conclusion: The outcomes of our centre is encouraging and comparable to outcomes from haplo-HSCT studies by other international institutions. It demonstrated haplo-HSCT is effective and safe with good tolerability in high-risk group patients. In our report, MAC group is associated with a statistically insignificantly higher OS and PFS than RIC group.

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Lactococcus lactis as a faecal biomarker predicting the development of non-alcoholic fatty liver disease: evidence from a human microbiota-associated rodent model

S Zhang[1], HM Tun[2], CH Lee[1], HT Chau[1], D Zhang[2], S Liang[2], FY Huang[1], DKH Wong[1,3], KSL Lam[1,4], MF Yuen[1,3], WK Seto[1,3]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]School of Public Health, The University of Hong Kong, Hong Kong
[3]State Key Laboratory for Liver Research, The University of Hong Kong, Hong Kong
[4]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong

Introduction: Gut microbiota dysbiosis is increasingly linked to the development of non-alcoholic fatty liver disease (NAFLD). We aim to investigate whether this relationship is causal via faecal microbiota transplantation (FMT) in a human microbiota-associated rodent model.

Methods: We obtained human faeces (n=8 each group) from obese NAFLD, lean NAFLD, and healthy controls, and performed FMT combined with high-fat diet feeding without pooling on the same number of C57BL/6J mice. NAFLD was diagnosed using controlled attenuation parameter (CAP) measurements ≥248 dB/m via transient elastography (Fibroscan, Echosens, Paris). We assessed the histology, lipid metabolism, hepatic inflammation and intestinal barrier function at 12 weeks and performed shotgun metagenomic sequencing to analyse the microbiome.

Results: Obese NAFLD donors had a significantly higher median BMI and CAP than lean NAFLD and healthy controls. Compared with FMT-healthy mice, FMT-obese NAFLD mice had significantly higher plasma and intrahepatic triglyceride content (P<0.01); increased hepatic lipid accumulation and adipocyte size (P<0.05); but lower ileal expression of zonula occludens-1, an intestinal barrier marker (P=0.03). No difference was observed between FMT-healthy versus FMT-lean mice. Biomarker analysis confirmed a higher mean abundance of *Lactococcus lactis* in FMT-healthy mice (43.50% vs 36.65% in FMT-lean mice vs 24.82% in FMT-obese mice, P=0.0351). *Lactococcus lactis* was correlated positively with biotin biosynthesis pathway (rho=0.53, P=0.0075), but correlated negatively with plasma triglyceride levels (rho= -0.45, P=0.0273).

Conclusion: In this study, stool microbes from healthy human donors prevented the development of NAFLD in mice, signifying a potentially causal relationship. The faecal presence of *Lactococcus lactis* as a biomarker was associated with a reduced risk of NAFLD development.

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Thyroid immune-related adverse events in cancer patients treated with anti-PD1/anti-CTLA4 immune-checkpoint inhibitor combination: clinical course and outcomes

DTW Lui[1], CH Lee[1], V Tang[1], CHY Fong[1], ACH Lee[1], JWY Chiu[1], RCY Leung[1], GGW Kwok[1], BCW Li[1], TT Cheung[2], YC Woo[1], KSL Lam[1], T Yau[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Thyroid immune-related adverse events (irAEs) have been reported to have prognostic significance among cancer patients treated with anti-PD1 and anti-PDL1 monotherapies. We evaluated the clinical course and predictors of thyroid irAEs, in relation to outcomes of advanced cancer patients treated with combination anti-PD1/anti-CTLA4.

Methods: We conducted a territory-wide study and identified advanced cancer patients who received ≥1 cycle of combination anti-PD1/anti-CTLA4 between 2015 and 2019 in Hong Kong. Thyroid function tests (TFTs) were monitored every three weeks. Thyroid irAE was defined by ≥2 abnormal TFTs after initiation of combination anti-PD1/anti-CTLA4 in the absence of other causes.

Results: One hundred and three patients were included (median age 59 years; 71.8% male). About 45% had prior anti-PD1 exposure. Upon median follow-up of 6.8 months, 17 patients (16.5%) developed thyroid irAEs, where six initially presented with thyrotoxicosis (overt, n=4; subclinical, n=2), and 11 with hypothyroidism (overt, n=2; subclinical, n=9). Eventually, ten patients (58.8%) required continuous thyroxine replacement. Systemic steroid was not required in all cases. Prior anti-PD1 exposure (odds ratio [OR]=3.67, 95% confidence interval [CI]=1.19-11.4, P=0.024) independently predicted thyroid irAEs. Multivariable Cox regression analysis revealed that occurrence of thyroid irAEs was independently associated with better overall survival (adjusted hazard ratio=0.39, 95% CI=0.19-0.79, P=0.009).

Conclusion: Thyroid irAEs are common in routine clinical practice among advanced cancer patients treated with combination anti-PD1/anti-CTLA4 and might have potential prognostic significance. Regular TFT monitoring is advised for timely treatment of thyroid irAEs to prevent potential morbidities.

Soluble interleukin-6 receptor determines exercise responsiveness in term of insulin sensitivity and glycaemic control

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Y Wang[1,2], JM Wu[1,2], Y Liu[1,2], AM Xu[1,2]
[1]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Exercise is an effective non-pharmacological approach for diabetes management. However, highly interpersonal responsiveness in exercise and the lack of predictive biomarkers for exercise response restrain its current clinical implementation. Our clinical study demonstrated about 30% participants failed to improve insulin sensitivity and glycaemic control after 12 weeks of exercise training.

Methods: The dynamic changes of serum cytokines and hormones levels of volunteers before and after exercise intervention were measured by ELISA or MESO Scale Discovery electrochemiluminescence technology (MSD).

Results: Exercise responders (R) had significantly decreased circulating levels of soluble interleukin-6 receptor (sIL-6R), by contrast, it increased in exercise non-responders (NR). Importantly, the alternation of sIL-6R tightly associated with exercise responsiveness to fasting insulin and HOMA-IR index. sIL6R recombinant protein treatment abolished exercise-improved glucose homeostasis in obese mice.

Conclusion: sIL-6R is a novel biomarker for exercise responsiveness to insulin sensitivity and glycaemic control. Targeting sIL-6R might provide a potential therapeutic strategy to maximise therapeutic efficacy of physical exercise for diabetes prevention.

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Adipocyte-derived lactate potentiates obesity-evoked adipose macrophage inflammation

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TS Feng[1,2], AM Xu[1,2,3], HXY Hui[1,2]
[1]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Hong Kong
[3]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: Obesity is characterised by mobilisation of macrophage inflammation, which represents the major events of obesity-associated adipose tissue inflammation. On the other hand, lactate accumulation in adipose tissue long been observed. However, whether elevation of lactate plays an essential role in adipose inflammation is not known. In this study, we sought to examine the intermediary role of lactate in macrophage polarisation and adipose inflammation upon obesity.

Methods: Lactate level and activity of lactate dehydrogenase (LDH), the key enzyme of lactate production, were measured by biochemical assays. Adipocyte- and macrophage-specific *Ldha* knockout mice were constructed by cre-LoxP system to study the physiological role of lactate in diet-induced obesity. Macrophage polarisation and inflammation were examined by western blotting and Q-PCR.

Results: Lactate and LDH activity were selectively upregulated in adipose tissues of obese mice. Adipocyte-, but not macrophage-selective deletion of LDHA, led to a significant improvement of adipose inflammation and metabolic dysfunctions. In vitro experiments showed that the lactate promoted M1 polarisation through direct interaction and inhibition of the PHD2, which subsequently stabilises HIF-1alpha. In addition, a positive correlation between adipose lactate level and adipose tissue inflammation was found in obese patients.

Conclusion: In obese condition, increased production of lactate from adipocytes enhances adipose tissue inflammation by promoting the proinflammatory polarisation of adipose macrophages.

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Long-term pharmacological inhibition of mutant leucine-rich repeat kinase 2 hyperactivity reduced alpha-synuclein serine-129 phosphorylation and oligomer levels in mouse brains

EES Chang, HF Liu, CT Leung, Y Malki, YK Choi, SYY Pang, PWL Ho, SL Ho
Division of Neurology, Department of Medicine, The University of Hong Kong, Hong Kong

Background: Leucine-rich repeat kinase 2 (LRRK2) mutations which confer genetic risk for Parkinson's disease (PD) shows aberrant hyper-kinase activity. Alpha-synuclein aggregation in form of Lewy body deposits is a pathological hallmark of PD. We previously showed that aged LRRK2^{R1441G} knock-in mutant mice developed more alpha-synuclein aggregates in the brain than the age-matched wild-type controls. The majority of alpha-synuclein in Lewy bodies is phosphorylated at serine-129 (pSer129), and Ser129 phosphorylation is associated with increased alpha-synuclein aggregation. So far, the potential interplay between Ser129 phosphorylation and mutant LRRK2 hyper-kinase activity in PD remains unexplored. Thus, we aimed to determine whether long-term administration of a brain-penetrable LRRK2 kinase inhibitor, GNE7915, can reduce Ser129 phosphorylation and thereby reduce the formation of toxic alpha-synuclein oligomers in the brain of aged LRRK2^{R1441G} knock-in mutant mice.

Methods: A 14-month-old LRRK2^{R1441G} knock-in mice and wildtype controls were injected subcutaneously with either vehicle or GNE-7915 (100 mg/kg) twice a week for 18 weeks. Mice were sacrificed for immunoblotting and ELISA of pSer129 and oligomeric alpha-synuclein levels in cortex and striatum. Reduction in T73-Rab10 phosphorylation in the lung reflects GNE-7915-induced LRRK2 kinase inhibition.

Results: GNE-7915 injection for 18 weeks significantly reduced T73-Rab10 phosphorylation in lung indicating inhibition of LRRK2 kinase activity. Levels of pSer129 alpha-synuclein and its oligomers in striatum were higher in aged LRRK2 mutant compared with wild-type mice, which were ameliorated by long-term treatment of GNE-7915.

Conclusion: An 18-week subcutaneous injection of GNE-7915 reduced both pSer129 and oligomer levels in brains of LRRK2^{R1441G} mutant mice. These results highlight a potential therapeutic link between LRRK2 kinase inhibition and pSer129 in synucleinopathies of PD.

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Clinical outcome following percutaneous coronary intervention in stable coronary artery disease based on a novel index: computational pressure-flow dynamics derived fractional flow reserve

LY Lam[1], CKL Leung[1], KY Li[1], ASY Yu[2], MZ Wu[2], QW Ren[2], PF Wong[2], YK Tse[1], SSY Yu[1], HL Li[1], KH Yiu[2]
[1]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Computational pressure-flow dynamics derived fractional flow reserve (caFFR) is a novel index to assess myocardial ischaemia of coronary artery disease (CAD), without the need of invasive pressure wire and hyperaemic stimulus measured by conventional fractional flow reserve (FFR). Nonetheless, the clinical value of caFFR is uncertain. This study evaluated the clinical outcome of patients with and without percutaneous coronary intervention (PCI) in patients with ischaemia defined by caFFR.

Methods: A total of 442 patients (mean age 66.0±10.7 years; 73.1% male) with stable CAD and functional ischaemia defined as caFFR ≤0.80 were identified. Patients were subsequently stratified into those with PCI (n=320) and without PCI (n=122). The primary endpoint was defined as a composite of all-cause mortality, myocardial infarction or any repeat revascularisation at 3 years.

Results: The number of obstructive lesions was 2.6±1.5 in patients with PCI and 2.3±1.4 in those without PCI (P=0.203) and the severity of CAD assessed by SYNTAX score was similar between the two groups (19.8±10.6 vs 17.8±9.5, P=0.072). The rate of primary end point was significantly lower in those with PCI compared with those without PCI (8.1% vs 18.0%; adjusted hazard ratio [HR]=0.49; 95% confidence interval [CI]=0.28-0.88; P=0.016). Recurrent angina was also significantly less in patients with PCI compared with those without PCI (10.3% vs 20.5%; adjusted HR=0.54; 95% CI=0.32-0.92; P=0.005).

Conclusion: In CAD patients with myocardial ischaemia defined by caFFR ≤0.80, PCI significantly reduces the rate of the composite end-point and recurrent episode of angina compared with those without PCI.

Pioglitazone ameliorates motor impairments and spinal cord pathologies in a mouse model of neuromyelitis optica spectrum disorders

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LW Yick, C Wong, KH Chan
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Neuromyelitis optica spectrum disorders (NMOSD) are central nervous system inflammatory demyelinating diseases characterised by recurrent optic neuritis and myelitis. Binding of pathogenic aquaporin-4 autoantibodies (AQP4-IgG) to AQP4 on astrocytes triggers lesion development that is driven by astrocyte-microglia interaction. Pioglitazone exerts neuroprotective effects through suppressing microglia activation in various models of CNS insults. Here we examined whether pioglitazone ameliorates motor impairments and pathologies in mice which received human AQP4-IgG.

Methods: Mice with disrupted blood-brain barrier received passive transfer of purified IgG from AQP4-IgG-seropositive NMOSD patients. Pioglitazone was administered by oral gavage. Motor impairments were assessed by beam walking test. Spinal cord pathologies were examined by immunofluorescence and ELISA.

Results: Oral administration of pioglitazone ameliorated the motor impairments induced by AQP4-IgG. Pioglitazone profoundly reduced AQP4 and astrocyte loss, demyelination and axonal loss in the spinal cord of mice which received AQP4-IgG. The protective effects of pioglitazone were associated with suppression of neuroinflammation, with decrease in microglia activation and reduction in levels of proinflammatory cytokines including interleukin-1 beta (IL-1 beta), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha).

Conclusion: Our findings support that microglia activation plays an important role in the pathophysiologies of NMOSD and highlight the potential of pioglitazone as a therapeutic agent in NMOSD acute attacks.

Age-related expression and activity profile of glucocerebrosidase in brain and the association with phosphorylated alpha-synuclein implicated in Parkinson's disease

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Y Malki, YK Choi, PWL Ho, HF Liu, CT Leung, EES Chang, SYY Pang, SL Ho
Division of Neurology, Department of Medicine, The University of Hong Kong, Hong Kong

Objectives: The aggregation and inter-neuronal propagation of misfolded alpha-synuclein determine the progression and severity of Parkinson's disease (PD). Reduced lysosomal enzyme glucocerebrosidase (GCase) activity may be linked to alpha-synuclein accumulation in PD. Different brain regions may have varied susceptibility to developing alpha-synuclein pathology, due to the difference in cellular composition and proteomes. Here, we aimed to establish a brain region profile for the levels of phosphorylated serine-129 (pSer129) alpha-synuclein, the fibril promoting form of alpha-synuclein, as well as GCase expression and activity, in both young and aged mouse brains.

Methods: Total lysates from freshly isolated brain regions (olfactory bulb, cortex, striatum, hippocampus, midbrain, cerebellum, and spinal cord) of young (3-month-old) and aged (26-month-old) wild-type mice were subjected to immunoblotting. GCase activity was measured through an established fluorescence assay. Tyrosine hydroxylase (TH) expression was used to determine dopaminoceptive regions of the brain.

Results: The levels of pSer129/total alpha-synuclein in the olfactory bulb and cortex of both young and aged mice were higher, compared with other brain regions; while only aged mice had a marked increase of pSer129 alpha-synuclein in the striatum. GCase activity was the lowest in the striatum, followed by cortex, and highest in the olfactory bulb. The GCase activity was generally lower in aged mice compared with young mice.

Conclusion: Our findings indicate that varied levels of pSer129/total alpha-synuclein and GCase activity exist in different brain regions, possibly in age and cell-type dependent manner. The age-dependent accumulation of pSer129 alpha-synuclein, and relatively lower GCase activity specifically in the striatum may underlie its selective vulnerability to neurodegeneration in PD.

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CRISPR-targeted genome editing of human induced pluripotent stem cells–derived hepatocytes for treatment of Wilson's disease

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R Wei[1,2*], J Yang[1,2*], WI Ho[1,2], CW Cheng[1,2], N Li[1,2], WH Lai[1,2], YL Tse[1,2], KM Ng[1,2], HF Tse[1,2]
[1]The Cardiology Division, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Hong Kong-Guangdong Stem Cell and Regenerative Medicine Research Centre, The University of Hong Kong and Guangzhou Institutes of Biomedicine and Health, Hong Kong

* The first two authors contributed equally to the work.

Background and Aims: Wilson's disease (WD) is a monogenic disorder of liver metabolism characterised by copper accumulation in the liver and other organs. The available pharmacological therapies for WD have the limitations of long-term side-effects, life-long adherence, and are ineffective in WD patients with acute liver failure. Liver transplantation could cure WD but it is hampered by the scarcity of donors and patients have to suffer the long-term adverse effects of immunosuppressive agents. Recent advances in the human induced pluripotent stem cells (iPSCs) and genome editing may enable the development of autologous cell replacement therapy for WD.

Methods: In this study, we corrected the homozygous ATP7B R778L variants, one of the common variants in Chinese WD patient, in WD iPSCs using CRISPR/Cas9 and ssODNs, evaluated the recovery of ATP7B function in iPSC-derived hepatocytes (iHeps) after gene correction, and further tested the therapeutic potential of iHeps in WD mouse models.

Results: The WD iHeps regained normal ATP7B subcellular localisation as well as copper exportation function after gene correction. Moreover, transplantation of gene-corrected WD iHeps attenuated the disease phenotypes of WD mouse models.

Conclusion: We confirmed that correction of one allele of variants was sufficient to rescue the disease phenotype in the iPSC-derived hepatocytes (iHeps) in vitro and in vivo. Our results provide a comprehensive proof-of-principle for employing CRISPR/Cas9 to obtain genetically corrected iHeps for autologous cell-based therapies for WD and other inherited liver diseases.

Clinical consequences of gestational diabetes mellitus in Ho Chi Minh City, Vietnam

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SRB Yue[1,2], DP Le[3], KVT Thi[4], E Kestelyne[4], THN Bui[3], TD Trong[4], T Quang[3], JE Hirst[2]
[1]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Nuffield Department of Women's and Reproductive Health, University of Oxford, United Kingdom
[3]Tu Du Hospital, Ho Chi Minh City, Vietnam
[4]Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

Introduction: Women of South-East Asian ethnicity are at high risk for Gestational Diabetes Mellitus (GDM), yet many populations are relatively lean and the perinatal consequences of GDM are less well characterised.

Methods: This was a secondary analysis of a prospective, hospital-based, cohort study in Ho Chi Minh City (Vietnam Preterm Birth Biomarkers Project). GDM was diagnosed between 24 to 28 weeks (IADPSG criteria). The comparison group was women without GDM. Outcomes assessed were: large for gestational age (LGA), primary c-section, hypertensive disorders of pregnancy (HDP), and a composite adverse neonatal outcome. Multivariable logistic and linear regression was performed presenting adjusted odds ratios (aOR), with body mass index (BMI) assessed for effect modification.

Results: Among 4949 women, 903 (18%) developed GDM. GDM women gave birth to heavier babies than non-GDM women (weight z-score 0.16 vs 0.09, P=0.027), with 16% increased odds of having an LGA baby (aOR=1.16, 95% confidence interval [CI]=0.90-1.48). After adjustment for maternal BMI and age, there was no increased risk of primary c-section (aOR=1.01, 95% CI=0.85-1.19), HDP (aOR=0.97, 95% CI=0.66-1.45), or adverse neonatal outcomes (aOR=1.01, 95% CI=0.75-1.38). C-section rates were 43% in non-GDM and 47% in GDM women, with the most common indications being previous c-section, post-term, and cephalo-pelvic disproportion. Outcomes associated with GDM were not modified by BMI.

Conclusion: GDM has a high prevalence in urban Vietnam; highlighting the importance of universal screening. Notably high c-section rates in the baseline group may potentially conceal any increased adverse outcomes from GDM. Likewise, whilst the perinatal consequences of GDM appeared less frequently than reported in western cohorts, GDM is likely to be associated with longer term consequences for these women and babies.

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Clinical outcome following percutaneous coronary intervention in non-ischaemic stable coronary artery disease based on a novel index: computational pressure-flow dynamics derived fractional flow reserve

CKL Leung[1], LY Lam[1], KY Li[1], ASY Yu[2], MZ Wu[2], QW Ren[2], PF Wong[2], YK Tse[1], SSY Yu[1], HL Li[1], KH Yiu[2]
[1]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Computational pressure-flow dynamics derived fractional flow reserve (caFFR) is a novel index to assess the degree of myocardial ischaemia in patients with coronary artery disease (CAD), without the need of invasive pressure wire and hyperaemic stimulus as required in conventional fractional flow reserve (FFR) measurement. In this study, we evaluate the clinical outcome of patients with and without percutaneous coronary intervention (PCI) in patients without functional myocardial ischaemia defined by caFFR.

Methods: A total of 266 patients (mean age 66.7±11.2 years; 71.1% male) with stable CAD without functional myocardial ischaemia defined by caFFR >0.8 were identified and included in this study. Patients were then stratified into those with PCI (n=218) and those without PCI (n=48). The primary endpoint was defined as a composite of all-cause mortality, myocardial infarction or any repeat revascularisation at 3 years.

Results: The number of obstructive lesions was 1.8±1.0 in patients with PCI and 1.5±0.9 in patients without PCI (P=0.032), and the severity of CAD based on SYNTAX score assessment was similar across two groups (12.3±8.0 vs 10.4±7.2, P=0.529). The primary endpoint rate was similar in patients with PCI compared with those without PCI (11.5% vs 10.4%; adjusted hazard ratio [HR]=0.89; 95% confidence interval [CI]=0.33-2.40; P=0.821). Rate of recurrent angina episodes at 3 years was also similar in patients with PCI compared with those without PCI (17.0% vs 18.8%; adjusted HR=0.88; 95% CI=0.42-1.85; P=0.734).

Conclusion: In CAD patients without functional myocardial ischaemia, as defined by caFFR >0.8, PCI does not alter the clinical outcome in terms of the composite endpoint and recurrent angina episodes.

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Association between contrast-induced nephropathy after percutaneous coronary intervention and major adverse cardiac events

AKY Ng[1], PY Ng[2,3], A Ip[1], CW Siu[4]
[1]Cardiac Medical Unit, Grantham Hospital, Hong Kong
[2]Department of Adult Intensive Care, Queen Mary Hospital, Hong Kong
[3]Division of Respiratory and Critical Care Medicine, Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[4]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Contrast induced nephropathy (CIN) after percutaneous coronary intervention (PCI) has established association with worse long-term mortality and renal outcomes. However, the association between CIN and the long-term major adverse clinical events (MACE) had not been well described. We aimed to determine whether patients who developed CIN after PCI has increased risks of long-term MACE.

Methods: This was a retrospective cohort study from 14 hospitals under the Hospital Authority between 1 January 2004 and 31 December 2017. Participants were patients who underwent first-ever PCI, previously not on regular dialysis and survived for >30 days after PCI. CIN was defined as a rise in serum creatinine of >25% from baseline value, or an absolute rise of >44 μmol/L within 30 days after PCI. Severe CIN was defined as a rise in serum creatinine of >50% from baseline value, or an absolute rise of >88 μmol/L, or requiring dialysis within 30 days after PCI. The primary endpoint was MACE, defined as a composite outcome of all-cause mortality, non-fatal myocardial infarction after hospital discharge, stroke and any unplanned coronary revascularisation, as a time-to-first-event analysis up to 5 years after PCI. The secondary endpoints were individual components of MACE and death from cardiovascular cause.

Results: Among the 34 589 patients analysed, 6343 (18.3%) developed CIN after PCI. After adjustment for baseline and procedural characteristics, CIN was associated with higher risks of MACE (hazard ratio [HR]=1.28; 95% confidence interval [CI]=1.22-1.35; P<0.001). CIN was associated with increased all-cause mortality (HR=1.56; 95% CI=1.45-1.69; P<0.001), myocardial infarction after hospital discharge (HR=1.29; 95% CI=1.20 to 1.39; P=0.001), stroke (HR=1.42; 95% CI=1.32-1.52; P<0.001) and similar risks of any unplanned coronary revascularisation (HR=1.22; 95% CI=1.12-1.33; P<0.001). CIN was also associated with increased death from cardiovascular cause (HR=1.62; 95% CI=1.42-1.84, P<0.001). Severe CIN was associated with higher risk of MACE compared with non-severe CIN (HR=1.59; 95% CI=1.29-1.95; P<0.001).

Conclusion: Among patients undergoing first-ever PCI, CIN was associated with a significant increase in risks of MACE for up to 5 years, driven by increase in all-cause mortality, myocardial infarction and stroke. Severe CIN was associated with additional increase in MACE.

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Lipopolysaccharide induces nuclear paraspeckle assembly transcript 1 expression in acute kidney injury via TLR4/NF-κB signalling

R Xue[1], WH Yiu[1], SWY Lok[1], LYY Chan[1], JCK Leung[1], KN Lai[1], HY Lan[2], SCW Tang[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Medicine and Therapeutics, and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong

Background: Toll-like receptor 4 (TLR4)/Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) have been implicated in the pathogenesis of acute kidney injury (AKI). Nuclear paraspeckle assembly transcript 1 (NEAT1) is a long non-coding RNA that plays key roles in a variety of biological processes and is involved in many other diseases. Beyond its fundamental role of maintaining function of the nucleus, it remains unknown whether interaction between TLR4/NF-κB signalling and NEAT1 is involved in the process of the development of AKI.

Methods: Septic AKI model was established with injection of lipopolysaccharide (LPS) into mice. Mouse tubular cells were stimulated with LPS for the study of tubular inflammation. The role and upstream regulatory mechanisms of NEAT1 in the inflammatory processes were studied by using signalling inhibitors.

Results: In LPS-induced AKI, NEAT1 expression was upregulated in tubular cells, accompanied by elevated TLR4/NF-κB signalling in vitro, mouse tubular cells treated with LPS also showed increase in NEAT1, prior to the production of proinflammatory cytokines including IL-6 and CCL-2, whereas treatment with an inhibitor of TLR4 or NF-κB signalling suppressed LPS-induced NEAT1 expression.

Conclusion: NEAT1 expression was induced in LPS-induced AKI model via TLR4/NF-κB signalling, suggesting its potential role in the inflammatory process. Our findings open the door to exploit NEAT1 expression as a potential novel therapeutic approach for AKI and other inflammation-related renal diseases.

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Outcomes of allogeneic haematopoietic stem cell transplant for acute lymphoblastic leukaemia/lymphoma in Hong Kong: a retrospective study

TH Lam, YM Cheung, JPY Sim, AKW Lie, YL Kwong
Division of Haematology, Department of Medicine, Queen Mary Hospital, Hong Kong

Introduction: The optimal treatment for ALL is evolving, particularly for B-ALL with the introduction of minimal residual disease (MRD) monitoring, bispecific T-cell engager, and CAR-T therapy. Our unit historically offers all adult ALL patients with suitable donors to undergo allogeneic haematopoietic stem cell transplant (allo-HSCT) in first complete remission (CR1). Here we retrospectively reviewed the outcomes of 70 patients undergoing allo-HSCT between June 2016 and February 2020.

Methods: Clinical records of 70 consecutive patients undergoing 1st allo-HSCT for ALL during the study period were reviewed and analysed. All had at least 6 months follow-up at last data cut-off.

Results: The overall survival (OS) and disease-free survival (DFS) at 24 months were 75% and 53%, respectively. Patients transplanted in >CR1 had worse DFS (median 44 months vs 6 months, P=0.00). Twenty-six patients had pre-transplant MRD tested: 11 positive and 15 negative. Patients who were tested negative had a trend towards better DFS (83% vs 60%, P=0.078). None of the pre-HSCT clinical factors determined MRD status at transplant. Re-emergence or persistence of MRD positivity predicts relapse (P<0.001). Blinatumomab was used in five patients pre-HSCT, two in MRD-positive CR1 with one successful MRD eradication. One patient achieved MRD-negative CR2 pre-HSCT but developed morphological relapse at 5 months post-HSCT.

Conclusion: HSCT performed at CR1 with the aid of MRD detection predicts the best outcome in terms of DFS and OS. The best treatment for MRD eradication needs further studies.

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Neurological observation assistant in healthcare: classifying postures and estimating disability of neurological in-patients using wearable inertial sensors

S Waibel[1], C Auepanwiriyakul[2], EHL Yeung[1,3], P Bentley[1], AA Faisal[2]
[1]Division of Brain Sciences, Imperial College London, Charing Cross Hospital, London, United Kingdom
[2]Department of Computing, Imperial College London, London, United Kingdom
[3]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Introduction: In-patient behavioural monitoring provides key insights about their cognitive and motor functional performance. Current behavioural observations rely on intermittent and labour-intensive assessments conducted by healthcare professionals. Significantly, the assessments have inter-rater variability and use patient self-reports, which are subject to recall bias. Using standard wearable consumer smartwatches, our team developed an automated method to record clinical behaviours. Our solution addresses the challenges of optical motion tracking methods, such as cost, practicality, usability, and patient privacy.

Methods: We recruited a sample of patients admitted to Charing Cross Hospital stroke unit with capacity to consent and full cognitive function. Participants wore smartwatches on their four limbs for an 'in-wild' (free-living) task. Video ground truth was used to generate behaviour labels. We used this data to train a deep convolutional long-short term memory (DeepConvLSTM) model to classify whether the in-patient is in bed, sitting in chair, standing, and walking. Subsequently, we used the DeepConvLSTM predicted percentage time spent in each behaviour, as well as patient age, weight, and height to train a logistic regression model to predict (1) functional disability (modified Rankin Score ≥3), and (2) clinical deterioration within two weeks of the inertial sensor recording. All models are tested using leave-one-out cross-validation for each subject in turn and the average performance across all subjects was calculated.

Results: 44 subjects completed the protocol with the following demographics: age (median 63 years, interquartile range [IQR]=54-77), sex (23 male, 21 female), and NIHSS score at admission (median 2, IQR=1-4). The DeepConvLSTM model achieved a weighted F1-score of 0.93±0.02 for classifying the four behaviours. The functional disability model achieved area under the curve (AUC) of 0.73 (95% confidence interval [CI]=0.64-0.91), similar to a recent prediction study using computerised tomography brain scans. The early clinical deterioration model achieved an AUC of 0.73 (95% CI=0.64-0.81).

Conclusion: Our findings support our method for automatic and reliable classification of the four behaviours, functional performance, and clinical deterioration in stroke-in patients. Ongoing studies are developing models to classify more complex every-day functional behaviours, such as eating and drinking.

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Role of adipocyte fatty acid-binding protein in left ventricular remodelling and diastolic function in type 2 diabetes: a prospective echocardiography study

MZ Wu, CH Lee, Y Chen, SY Yu, YJ Yu, QW Ren, HY Fong, PF Wong, HF Tse, SL Lam, KH Yiu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: The relationship between adipocyte fatty acid-binding protein (AFABP) and cardiac remodelling has been reported in cross-sectional studies. Type 2 diabetes mellitus (T2DM) is associated with left ventricular (LV) hypertrophy and diastolic dysfunction, as well as elevated circulating AFABP levels. We investigated prospectively the role of AFABP in the longitudinal changes of cardiac remodelling and diastolic dysfunction in T2DM.

Methods: Circulating AFABP levels were measured in 176 T2DM patients without cardiovascular diseases (CVD) at baseline. All participants received transthoracic echocardiography both at baseline and after 1 year. Multivariable linear and Cox regression analyses were used to evaluate the associations of circulating AFABP levels with changes in echocardiography parameters and incident major adverse cardiovascular events (MACE), respectively.

Results: The median duration between baseline and follow-up echocardiography assessments was 28 months. Higher sex-specific AFABP quartiles at baseline were associated with increase in LV mass and worsening of average E/e' (all P<0.01). Multivariable linear regression demonstrated that AFABP in the highest quartile was independently associated with both increase in LV mass (beta=0.89, P<0.01) and worsening of average E/e' (beta=0.57, P<0.05). Moreover, multivariable Cox regression analysis showed that elevated baseline circulating AFABP level independently predicted incident MACE (hazard ratio=2.65, 95% confidence interval=1.16-6.05, P<0.05) after adjustments for age, sex, body mass index, glycated haemoglobin, hypertension, dyslipidaemia and presence of chronic kidney disease.

Conclusion: Circulating AFABP level at baseline predicted the development of LV hypertrophy, diastolic dysfunction and MACE in T2DM patients without CVD.

Antineoplastic impact of thymoquinone from Nigella Sativa on Small Cell Lung Cancer

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M Khan, SK Lam, JCM Ho
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Small cell lung cancer (SCLC) comprises 15% of all lung cancer cases and has a 5-year survival rate of a mere 7%. The recalcitrant malignancy is defined by poor prognosis, rapid growth, widespread metastasis, frequent relapse and high mortality rates. Recently, increased attention and resources have been invested in studying medicinal herbs for alleviation of the enervating side-effects of chemotherapy. My project investigates the anticancer effects of Thymoquinone (TQ), a naturally occurring compound found in black cumin (*Nigella sativa*).

Methods: MTT Assay was used to assess relative cell viability in response to varying concentrations of TQ over time, in five SCLC cell lines: H69-Adherent, DMS79 (Suspension), H446 (Mixed Adherent and Suspension), H841-Adherent and SW1271 (Adherent),

Results: The average IC_{50} of all cell lines across 24h, 48h and 72h were noted: H446 was the most sensitive with 6, 4 and 3 μM ; the next three cell lines were similar to one another: H69-Adherent with 18, 15 and 17 μM; H841 with 19, 16 and 17 μM; and SW1271 with 15, 12, and 12 μM; for DMS79, the replicates are ongoing, and exact IC_{50} values to be confirmed.

Conclusion: Increasing concentrations of TQ dose-dependently decreased the relative cell viability over time across all cell lines. The results show the anticancer potential TQ exerts on SCLC. Future directions include the role of TQ on apoptosis, cell cycle and ROS.

Interleukin-9 triggers strong antitumour immune response thus inhibiting lung cancer growth

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Y Feng, S Yan, SK Lam, JCM Ho
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Lung cancer is still the leading cause of cancer-related death. Mounting evidence indicated that interleukin (IL)-9 was linked to cancer. However, its role in lung cancer is still controversial. In this study, we aimed to explore the therapeutic role of IL-9 in lung cancer and to elucidate its mechanism.

Methods: Mouse lung cancer cell lines (LLC cells and CMT167 cells), and human lung cancer cell lines (H1975, A549, HCC827) were purchased from ATCC. Western blot was used to detect the IL-9 receptor expression. MTT assay was conducted to explore the effect of IL-9 on human lung cancer cell lines. CMT167 mouse model was established by subcutaneous injection of CMT167 cells. Mice were randomised into control and IL-9 group, which were treated with PBS and IL-9, respectively. Tumour volume and weight were measured with size calliper and balance each other day. Immune responses in tumours were analysed by flow cytometry.

Results: IL-9 receptor was found in human lung cancer cell lines and CMT167 cells, but not in LLC. In vitro, IL-9 had no much effect on cell viability in lung cancer cells. In CMT167 mouse model, tumour volume and weight in IL-9 treated mice were significantly smaller. T cells, especially the CD8+ T cells percentage were significantly higher in tumours of IL-9 group. Furthermore, CD25 expression on CD8+ T cells was much higher in the IL-9 group. Enhanced dendritic cell (DC) recruitment was also found in tumours of IL-9 group. However, NK cells had no difference between the two groups.

Conclusion: IL-9 could inhibit tumour growth in CMT167 mouse model via enhancing antitumour immune responses in the tumour microenvironment, especially through CD8+ T cells recruitment and activation. The recruitment of DC induced by IL-9 may account for the antitumour activity of CD8+ T cells. However, the underlying mechanisms remain to be further elucidated.

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Bioproduction and reconstruction of anti-C-reactive protein monoclonal antibody

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JX Peng, X Jiang, CK Wong, A Xu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: C-reactive protein (CRP) is an annular pentameric protein synthesised by the liver and sent into the bloodstream in response to inflammation. Measuring the serum CRP level can provide useful information for determining disease progress. Consequently, there is a large demand of high-quality CRP antibody for immunoassay, which cannot be fulfilled by traditional method produced from hybridoma cells. Here, we developed a method to express anti-CRP antibody with high quantity and quality.

Methods: Using next-generation sequencing, the sequence information was obtained from a previously established anti-CRP hybridoma cell line. The anti-CRP plasmid was reconstructed with recombinant mouse IgG1 Fc region for heavy chain and Igκ for light chain, respectively. After confirmation of the sequence accuracy, the plasmids were transiently transfected into ExpiCHO cells for anti-CRP antibody expression. After affinity purification using protein G beads, the amount of the anti-CRP antibody was determined by BCA, and the binding activity of anti-CRP measured by ELISA.

Results: Medium was collected for purification at day 9 as the viability of transfected cells dropped to 60%-70%. The yield of anti-CRP antibody in ExpiCHO expression system was 93.6 mg/L, which was around 2 to 3 times higher than that of hybridoma cells, and the affinity was similar to hybridoma cells.

Conclusion: The recombinant anti-CRP antibody expression plasmids were successfully constructed based on variable region sequences obtained from hybridoma cell line 7E12. Using ExpiCHO expression system, the expression yield of newly recombinant anti-CRP antibody was >90 mg/L, which was higher than that from hybridoma cell line (30-40 mg/L), with comparable antibody functional affinity. This method will provide fundamental materials for diagnostic assay and therapeutic drug development.

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Using an artificial neural network to identify the population at risk of obesity in the United States

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Y Fei, Q Feng, LYF Wong, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Obesity is an escalating problem in the United States. Artificial neural network (ANN), a machine learning method has been increasingly used in disease classification and prediction. We therefore aimed to build an obesity classifier and identify novel predictors of obesity risk using this method.

Methods: Participants of the United States National Health and Nutrition Examination Survey 2013 to 2016 aged ≥20 years with records of body mass index were used to develop the multilayer perceptron ANN model in R. The demographic, clinical, and questionnaire data were used to build an ANN model for identifying patients with high obesity risk. Obesity was defined as BMI ≥30 kg/m^2.

Results: There were 3836 (40.2%) obese and 5701 (59.8%) non-obese people in the final dataset. Our ANN model achieved a sensitivity of 87.6%, a specificity of 89.4%, an accuracy of 88.7% (95% confidence interval=87.3%-89.9%), and a measured area under the curve of 0.88 in obesity classification. In a decreasing order of importance, waist circumference, education level, sex, diabetes mellitus, smoking, time spent on watching TV, dietary quality, sleep hours, having meals not home-prepared, and time spent using a computer were identified as the 10 leading predictors of obesity in the model established.

Conclusion: ANN is useful in risk stratification of obesity. Our model identified several lifestyle risk factors associated with obesity that can be used to improve intervention programmes. Modifying these lifestyle factors would be effective, safe and inexpensive.

Change in cardiovascular disease risk between the two Hong Kong Population Health Surveys

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BYC Sung[1], EHM Tang[2], L Bedford[2], CKH Wong[2,3], ETY Tse[2], EYT Yu[2], BMY Cheung[1], CLK Lam[2]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Family Medicine and Primary Care, The University of Hong Kong, Hong Kong
[3]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: The Framingham Risk model estimates a person's 10-year cardiovascular disease (CVD) risk. We aimed to calculate the change in sex-age specific Framingham CVD risk in the Hong Kong Population Health Survey (PHS) 2014/15 in comparison with the previous survey conducted in 2003-05 (PHS2003/2004 and Heart Health Survey (HHS) 2004/2005).

Methods: Subjects aged 30 to 74 years from PHS2014/15 (n=1662) and PHS2003/2004/HHS2004/2005 (n=818) with complete data for the calculation of Framingham CVD predicted risk were included. The sex-specific CVD risks of participants were calculated based on their age, total cholesterol and high-density lipoprotein, mean systolic blood pressure, smoking habits, diabetic status, and treatment for hypertension. The mean sex-age specific CVD risks were then compared by independent t tests.

Results: An insignificant decrease in 10-year CVD risks from 2003-2005 to 2014/15 was observed (10.8% vs 10.6%, P=0.38). By adjustment to the WHO standard population, the age-standardised predicted CVD risk was lower in 2014/15 compared to that of 2003/04 (8.8% vs 9.8%). Analysed by age-group, more participants aged 65 to 74 years were classified as high risk in 2003/04 (PHS2003/2004HHS2004/2005: 66.8% vs PHS14/15: 53.1%, P<0.05).

Conclusion: During the period of 2003/04 to 2014/15, the difference in predicted 10-year risk for CVD was not statistically significant. However, the proportion of low-risk participants are higher in older age-groups in PHS14/15 compared to PHS03/HHS04. More aggressive CVD prevention strategies and primary care intervention are needed to manage CVD risk factors.

Novel therapeutic effects and mechanisms of Polo-like kinase 4 inhibition in acute myeloid leukaemia

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CC Dang, KL Ng, AY Leung
Department of Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong

Introduction: Acute myeloid leukaemia (AML) is a heterogeneous disease with distinct clinicopathologic, cytogenetic and genetic features. Induction and consolidation chemotherapy and allogeneic haematopoietic stem cell transplantation (HSCT) are the mainstays of treatment, but the outcome has remained unsatisfactory. Polo-like kinase 4 (PLK4) has been shown to regulate centrosome duplication and play a critical role in oncogenesis. We examined the effects of PLK4 inhibition and investigated its mechanisms of action in AML.

Methods: Eight AML cell lines representative of the diverse driver events in leukaemogenesis, were used. Antileukaemic effects of PLK4 inhibitors (PLK4i) were evaluated based on cellular proliferation, apoptosis and cell-cycle analysis. Effects on centriole duplication were examined by immunofluorescence and confocal microscopy.

Results: Cellular responses to PLK4 inhibition were cell-line and time-dependent. The eight AML cell lines showed distinct in vitro responses to 3-day treatment of PLK4i CFI-400945, CFI-400437 and centrinone. IC50 (half-maximal inhibitory concentration) of CFI-400945 ranged from 7.5 nM (ML-2) to 64 nM (Nomo-1). THP-1 and K562 did not respond at the doses tested. Similar differential responses were seen with other PLK4 inhibitors. CFI-400945 induced an increase in apoptosis in the PLK4i sensitive ML-2 but not resistant THP-1. The number of centrosomes was also increased in ML-2 upon exposure to CFI-400945. Despite an apparent lack of cellular response in THP-1, the latter showed a progressive increase in polyploidy (>4N) upon treatment with CFI-400945, up to 22% of cells on day 4 of treatment. The effects on ML-2 were modest (7% on Day 4). The observations led us to examine the effects of prolonged PLK4i treatment. Intriguingly, on Day 12 of CFI-400945 treatment, THP-1, hitherto resistant to shorter term treatment, became sensitive, with IC50 of 1.1 nM, which was not different from that of ML-2.

Conclusion: PLK4i showed different effects on AML cell lines and in some cell lines (eg, THP-1), the antileukaemic effects were only apparent with prolonged treatment. The mechanisms underlying these observations, the effects of PLK4 gene knockout, as well as the in vivo effects of PLK4i, are being examined in our laboratory.

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Predictors of favourable neurological outcomes in a territory-first extracorporeal cardiopulmonary resuscitation programme

ACC Li, S Fang, JCR Lin, A Ip, PY Ng
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Extracorporeal cardiopulmonary resuscitation (E-CPR) is an alternative resuscitation method that has been associated with better survival and neurological outcomes in both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) compared with conventional cardiopulmonary resuscitation (CPR). This study aimed to report the results of the territory-first E-CPR programme at Queen Mary Hospital, and identify factors that predict favourable patient outcomes.

Methods: This is a single centre, retrospective analysis of all patients who had OHCA or IHCA and were managed with E-CPR from 2012 to 2020. The outcome measures were survival with good neurological outcome, defined as Cerebral Performance Categories 1 or 2 at 3 months, and 30-day survival.

Results: From 2012 to 2020, a total of 102 patients received E-CPR: 48 (47.1%) were patients who had OHCA, and 54 (52.9%) from IHCA. 63 (61.8%) patients were diagnosed with myocardial infarction, and 11 (10.8%) were diagnosed with acute myocarditis. The overall hospital survival was 24.5% (n=25), while intensive care unit survival was 31.4% (n=32). 19 (18.6%) patients survived with favourable neurological outcome. Having a shockable arrest rhythm at presentation was the strongest predictor of good neurological outcome in both univariate (P<0.001) and multivariate analysis (odds ratio=7.84; 95% confidence interval=1.63-37.60; P=0.010). Patients with good neurological outcome were also more likely to have received defibrillation during E-CPR (P=0.006), lower aspartate aminotransferase (AST) levels within 24 hours after E-CPR (P=0.003), myocardial infarction as the cause of cardiac arrest (P=0.026), and percutaneous coronary intervention (PCI) after E-CPR (P=0.007).

Conclusion: Hong Kong's first territory-wide E-CPR programme achieved a favourable survival with good neurological outcome of 18.6%, which is comparable to internationally reported outcomes. Patients who had a shockable rhythm at presentation, defibrillation during E-CPR, low AST values in the first 24 hours, myocardial infarction as the cause of cardiac arrest, or PCI after E-CPR had better neurological outcomes.

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Trends in use and outcomes of extracorporeal membrane oxygenation in Hong Kong from 2010 to 2019

JCR Lin, S Fang, ACC Li, A Ip, PY Ng
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Background: Extracorporeal Membrane Oxygenation (ECMO) usage has increased globally as the technology and training have become more accessible, and ECMO outcomes have improved considerably over the past several years. However, evaluations of ECMO trends across Hong Kong are limited. This study aimed to describe the characteristics and outcomes of patients on ECMO admitted to general intensive care units (ICUs) in Hong Kong public hospitals and analyse the trends over the past decade.

Methods: Patients on ECMO admitted to general ICUs in Hong Kong from 1 January 2010 to 31 December 2019 were identified from Hong Kong's public healthcare system electronic health record database. Data including APACHE scores and hospitalisation outcomes were collected and analysed.

Results: There were 901 patient episodes of ECMO admitted to a general ICU. Over the 10-year study period, annual ECMO usage in general ICUs increased from 19 to 156 cases per year. The mean age of ECMO patients increased from 41 to 56 years old, and the APACHE IV predicted risk of death increased from 43% to 53%. The median ICU length of stay over the study period decreased from 15 to 8 days, and the median hospital length of stay decreased from 28 to 16 days. ICU mortality in ECMO cases increased from 12.5% to 40.4%, hospital mortality increased from 15.6% to 46.8%.

Conclusion: There has been a drastic increase in the number of ECMO cases in Hong Kong over the past 10 years. As hospitals in Hong Kong gain more experience in managing ECMO patients, the eligibility and indications for ECMO broadens. Older and patients with higher disease severity scores are considered for ECMO. The mortality rate on ECMO remains high, and more research is needed to evaluate which patients should receive ECMO and explore if the centralisation of ECMO care is favourable.

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Prognostic value of right ventricular remodelling and function in patients undergoing concomitant mitral and aortic valve surgery

YK Tse, YJ Yu, MZ Wu, ASY Yu, HL Li, PF Wong, QW Ren, SSY Yu, LY Lam, KY Li, CKL Leung, KH Yiu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Patients who undergo concomitant mitral and aortic valve surgery have poor postoperative clinical outcomes. Whilst current guidelines focus on left ventricular function and dimension as indications for surgery, little is known regarding the importance of right ventricular (RV) remodelling in patients undergoing concomitant mitral and aortic valve surgery. This study aims to evaluate the predictive value of RV remodelling on long-term survival following concomitant mitral and aortic valve surgery.

Methods: RV remodelling was characterised by preoperative transthoracic echocardiography in 160 patients who underwent concomitant mitral and aortic valve replacement (n=122) or aortic valve replacement (AVR) and mitral valve repair (MV Repair) [n=38]. Patients were divided into four RV remodelling patterns: normal RV size and systolic function (type 1); dilated RV (tricuspid annulus diameter >35 mm) with normal systolic function (type 2); RV systolic dysfunction (tricuspid annular plane systolic excursion <17 mm) with normal RV size (type 3); dilated RV with systolic dysfunction (type 4). Adverse event was defined as the composite of hospitalisation for heart failure (HHF) and all-cause death.

Results: Overall, 33%, 20%, 29%, and 18% of patients were classified as type 1, 2, 3, 4, respectively. Patients with advanced RV remodelling more frequently had heart failure, atrial fibrillation, and had larger left and right atria. During a median follow-up of 43 months, a total of 42 adverse events (23 heart failure hospitalisation and 19 deaths) occurred. Kaplan-Meier analysis showed that patients with more advanced patterns of RV remodelling were associated with an increased risk of adverse outcome (log-rank χ^2 14.09; P=0.003). Compared with type 1 RV remodelling, type 2 (hazard ratio [HR]=4.08, 95% confidence interval [CI]=1.39-11.94, P<0.05) and 4 (HR=4.597, 95% CI=1.60-13.25, P<0.05) were associated with adverse events, even after adjustment for age and EuroSCORE II.

Conclusion: In patients undergoing concomitant mitral and aortic valve surgery, RV remodelling is frequent and is associated with poorer outcomes. Our study underlines the importance of preoperative assessment of RV remodelling and function in patients undergoing combined left heart valve surgery.

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Ipilimumab and nivolumab/pembrolizumab in advanced hepatocellular carcinoma refractory to prior immune checkpoint inhibitors

SLJ Wong[1], GW Kwok[1], V Tang[1], CW Li[1], R Leung[1], J Chiu[1], KW Ma[2], WH She[2], J Tsang[1], TT Cheung[2], T Yau[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Programmed cell death protein 1 (PD-1) pathway blockade with immune checkpoint inhibitors (ICI) is a standard therapy in advanced hepatocellular carcinoma (HCC) nowadays. No strategies to overcome ICI resistance have been described. We aimed to evaluate the use of ipilimumab and anti-PD-1 ICIs (nivolumab or pembrolizumab) combinations in advanced HCC patients with progression on prior ICIs.

Methods: Advanced HCC patients with documented tumour progression on prior ICIs and subsequently received ipilimumab with nivolumab/pembrolizumab were analysed. Objective response rate (ORR), median duration of response (DOR), time-to-progression (TTP), overall survival (OS), and treatment-related adverse events (TRAEs) were assessed.

Results: Twenty-five patients were included. The median age was 62 years (range, 51-83). 68% were of Child-Pugh (CP) grade A and 48% had primary resistance to prior ICI. At median follow-up of 37.7 months, the ORR was 16% with a median DOR of 11.5 months (range, 2.76-30.3). Three patients achieved complete response. The median TTP was 2.96 months (95% confidence interval [CI]=1.61-4.31). Median OS was 10.9 months (95% CI=3.99-17.8) and the 1-year, 2-year and 3-year survival rates were 42.4%, 32.3% and 21.6%, respectively. The ORR was 16.7% in primary resistance group and 15.4% in acquired resistance group (P=1.00). All responders were of CP grade A and albumin-bilirubin (ALBI) Grade 1 or 2. CP and ALBI grades were significantly associated with OS (P=0.006 and P<0.001, respectively). Overall, 52% of patients experienced TRAEs and 12% experienced grade 3 or above TRAEs.

Conclusion: Ipilimumab and nivolumab/pembrolizumab can achieve durable antitumour activity and encouraging survival outcomes with acceptable toxicity in patients with advanced HCC who had prior treatment with ICIs.

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Single-agent nivolumab or pembrolizumab in patients with advanced hepatocellular carcinoma in a real-world setting

SLJ Wong[1], GW Kwok[1], V Tang[1], CW Li[1], R Leung[1], J Chiu[1], KW Ma[2], WH She[2], J Tsang[1], TT Cheung[2], T Yau[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Immune checkpoint inhibitors (ICI) targeting the programmed-cell death protein 1 (PD-1) pathway have been established in first and second-line settings for the systemic treatment of patients with inoperable, advanced hepatocellular carcinoma (HCC). However, there is limited evidence for their use in real-world, non-trial populations.

Methods: Advanced HCC patients who received single-agent nivolumab or pembrolizumab between May 2015 and December 2019 were analysed. Objective response rate (ORR), duration of response (DOR), time-to-progression (TTP), overall survival (OS) and treatment-related adverse events (TRAE) were assessed.

Results: 104 patients were included. The median age was 59 years (range, 28-83). 54.8% of patients were of Child-Pugh (CP) Grade A. At median follow-up of 31.8 months, the ORR was 8.0%, median TTP was 2.04 months (95% confidence interval [CI]=1.77-2.30) and median DOR was 5.09 months (range, 2.27-19.1). All responders had a CP score of 8 or below. Overall, the median OS was 5.42 months (95% CI=2.83-8.02). CP and albumin-bilirubin grades were significantly associated with OS (P=0.001 and P<0.001, respectively). Among patients with hepatitis B–related HCC, commencement of HBV antiviral agents at least 1 year prior to HCC diagnosis was significantly associated with better overall survival (P=0.018). 34.6% and 6.7% of patients experienced TRAEs of any grade and of grade 3 or above, respectively.

Conclusion: Single-agent nivolumab or pembrolizumab can demonstrate promising anti-tumour activity and acceptable safety profile in patients with advanced HCC in a real-world setting.

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Association of aspirin with lung carcinoma in patients with chronic obstructive pulmonary disease

SY Yu, MSM Ip, X Li, KS Cheung, QW Ren, HL Li, PF Wong, HF Tse, KH Yiu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Patients with chronic obstructive pulmonary disease (COPD) is associated with a high risk of lung carcinoma. The effect of low-dose aspirin use (≤160 mg) among patients with COPD on incidence of lung carcinoma and the risk of bleeding is nonetheless unknown.

Methods: Using a territory-wide clinical information registry, aspirin use was ascertained among all eligible COPD patients from 2005 to 2018. Inverse probability of treatment weighting was used to balance baseline covariates between aspirin non-users (35 049 patients) with new aspirin users (7679 patients). Competing risk regression with Cox proportional hazards models were performed to estimate the risk subdistribution hazard ratio (SHR) of lung carcinoma with low-dose aspirin (≤160 mg daily) and the associated bleeding events associated with aspirin use.

Results: Of all eligible subjects, 1779 (4.2%) were diagnosed with lung carcinoma. Aspirin use was associated with a 25% lower risk of lung carcinoma (SHR=0.75, 95% confidence interval [CI]=0.65-0.87). Subgroup analysis reveals that aspirin is beneficial regardless of whether above or below the age of 75, but is also beneficial among populations who are male, non-diabetic, and non-hypertensive. Aspirin was associated with lower small cell carcinoma risk (SHR=0.53, 95% CI=0.30-0.95) but not non-small cell carcinoma. Aspirin use was not associated with an increased risk of upper gastrointestinal bleeding (UGIB) [SHR=1.19, 95% CI=0.94-1.53], but was associated with an increased risk of haemoptysis (SHR=1.96, 95% CI=1.73-2.23).

Conclusion: Our study suggests that low-dose aspirin use was associated with a lower risk of lung carcinoma, in particular small cell carcinoma, among COPD patients. Whilst aspirin was not associated with an increased risk of UGIB, the risk of haemoptysis was elevated.

Association of statin with 1-year mortality in patients with infective endocarditis

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SSY Yu, HL Li, PF Wong, ASY Yu, YK Tse, CKL Leung, KY Li, LY Lam, MZ Wu, QW Ren, HF Tse, KH Yiu
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Statin's anti-inflammatory effects lead to hypotheses about their potential protective effect in infectious diseases. The effect of statin use in infective endocarditis (IE) patients is, however, unknown.

Methods: Patients diagnosed with IE from 1996 and 2019 were identified from a territory-wide clinical information registry. We analysed the effect of pre-admission use, and subsequently the effect of post-admission statin use censoring events in the first week, via Cox proportional hazards regression. Propensity score analytics were used to balance baseline covariates between users and nonusers, including comorbidities, bacterial culture, proxy variables for socioeconomic status, and concurrent drug uses (including prior statin use for analysing post-admission use). We also investigated cause-specific mortality by Fine and Gray competing risk regression.

Results: Of 6929 IE patients (mean age 56.2 years; 63.1% male), 771 and 629 patients had pre- and post-admission statin use. Pre-admission users had a 29% lower risk of mortality (hazard ratio [HR]=0.71, 95% confidence interval [CI]=0.59-0.84) compared with nonusers. Post-admission users had a 34% lower risk of mortality (HR=0.66, 95% CI=0.49-0.87), pre-admission use had no significant effect on mortality upon adjusting for post-admission use (HR=0.84, 95% CI=0.60-1.18). Subgroup analyses shows significant protective effect in post-admission statin use for patients who are culture-negative (HR=0.51, 95% CI=0.27-0.98) or have methicillin-resistant staphylococcus aureus (HR=0.53, 95% CI=0.28-0.99). Post-admission atorvastatin and rosuvastatin use were significantly protective (HR=0.56, 95% CI=0.35-0.90; HR=0.45, 95% CI=0.22-0.94). Statin use was associated with a lower mortality caused by IE (subdistribution HR=0.49, 95% CI=0.25-0.94), but not with other causes of death including cerebrovascular or renal causes.

Conclusion: The post-admission use of statin was associated with a lower risk of mortality in IE patients.

Prognostic value of cirrhotic features detected by ultrasound in patients undergoing tricuspid annuloplasty

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SY Yu[1], Y Chen[1], YJ Yu[1], MZ Wu[1], QW Ren[1], YC Ho[2], KH Yiu[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Radiology, Queen Mary Hospital, Hong Kong

Introduction: Cardiohepatic syndrome describes the interaction between the heart and liver in patients with cardiac disease. The prognostic role of cardiohepatic syndrome in patients undergoing valvular heart surgery is however uncertain. This study investigated the prognostic value of ultrasound derived features of liver cirrhosis in patients undergoing valvular surgery.

Methods: Consecutive patients (n=570) referred for preoperative assessment for valvular surgery were recruited. Detailed echocardiography and liver stiffness assessed by transient elastography were performed. Patients with transient elastography >7 kPa, indicating significant liver stiffness, were referred for detailed hepatobiliary system ultrasound to determine features of liver cirrhosis.

Results: A total of 214 patients who had significant liver stiffness received ultrasonography of the hepatobiliary system. Ultrasonography features of liver cirrhosis were observed in 11 patients, 12 patients with splenomegaly and 14 patients with ascites. Upon follow-up (median 16.4 months), 49 patients developed adverse outcome (28 hospitalisations for heart failure and 31 mortalities). Patients who developed adverse outcome had a higher frequency of ultrasound features of cirrhosis (12.2% vs 3.03%, P=0.05), splenomegaly (16.3% vs 2.4%, P<0.01) and ascites (20% vs 2.4%, P<0.01). Multivariable Cox regression confirmed that ultrasound features of cirrhosis (hazard ratio [HR]=5.309, 95% confidence interval [CI]=1.502-18.766, P=0.01), splenomegaly (HR=8.78, 95% CI=2.358-32.685, P<0.01) and ascites (HR=10.142, 95% CI=2.899-35.488, P<0.01) were independently predictive of adverse outcome in patients undergoing valvular surgery.

Conclusion: Patients undergoing valvular surgery had a high prevalence of cirrhotic changes, splenomegaly and ascites detected by ultrasound. Importantly, presence of cirrhotic feature, splenomegaly and ascites provide important prognostic value, supporting the use of ultrasound assessment of liver for risk stratification, in patients undergoing valvular surgery.

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Redefining prognostication of de novo cytogenetically normal acute myeloid leukaemia in young adults

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SP Tsui[1,2], HW Ip[2], A Javed[3], AY Leung[1], on behalf of 31 co-authors
[1]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pathology, Queen Mary Hospital, Hong Kong
[3]School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Introduction: Cytogenetically normal acute myeloid leukaemia (CN-AML) is the single largest cytogenetic subgroup of AML, occurring in 50% of cases. It is heterogeneous with diverse mutations and prognoses. The European LeukemiaNet (ELN) guideline categorised AML into favourable, intermediate and adverse risk groups based on cytogenetic and mutation features but its application in CN-AML has not been formally tested.

Methods: Young patients (≤60 years old) with de novo CN-AML diagnosed between 2003 and 2019 were recruited. Treatment entailed induction and consolidation chemotherapy and allogeneic haematopoietic stem cell transplantation (allo-HSCT). Mutations at diagnosis and their clonal architectures were identified by next-generation sequencing (NGS). The clinical and genetic data formed a databank from which prediction model was built by machine learning.

Results: 459 patients were recruited. 436 patients have received induction chemotherapy ("7+3": 96%; Other regimens: 4%). 396 patients (91%) achieved complete remission (CR) [1 induction=283 patients (65%) and >1 inductions in 113 patients (26%)]. 181 patients received allo-HSCT. Each AML carried a median of three mutations (range, 0-7 mutations). *NPM1*, *FLT3* and *DNMT3A* mutations were the most common, occurring in 30% to 40% cases. Univariate and multivariate analyses were performed. On aggregate, superior survivals were associated with *NPM1* mutation (event-free EFS and leukaemia-free LFS) and allo-HSCT at first CR (EFS, LFS and overall survival [OS]). Inferior EFS, LFS and OS were associated with *FLT3* and *DNMT3A* mutations. Prognostic impacts of DNMT3A mutation overrode those of *NPM1* and *FLT3* mutations and when incorporated as an adverse risk factor, it improved prognostication by ELN. Machine learning resulted in a predication model (https://redefiningprognosis.shinyapps.io/denovo_cnaml/) that might inform clinical decision with respect to allo-HSCT at CR1. Based on concordance index, its performance compared favourably with that of ELN prediction, both in our cohort as well as in a validation cohort in TCGA (The Cancer Genome Atlas).

Conclusion: NGS and machine learning are powerful tools that have shed light to the mutation landscape of AML and improved our ability to predict outcome and inform clinical decision. The prediction model described herein might provide personalised guidance for AML patients.

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Association between antibiotic use and colorectal cancer development: a territory-wide study

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KS Cheung[1], EW Chan[2], WK Seto[1], ICK Wong[1,3], WK Leung[1]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
[3]School of Pharmacy, University College London, London, United Kingdom

Introduction: Recent studies suggested that antibiotics may modulate colorectal cancer (CRC) risk due to gut dysbiosis. We aimed to investigate the specific and temporal effects of different antibiotics on CRC development in older subjects.

Methods: This is a retrospective cohort study using a territory-wide electronic healthcare database in Hong Kong including patients aged ≥60 years who had undergone colonoscopy between 2005 and 2013. Exclusion criteria included inflammatory bowel disease, prior colectomy, prior CRC and CRC detected within 6 months of index colonoscopy. The primary outcomes were CRC diagnosed >6 months after index colonoscopy. The adjusted hazard ratio (aHR) of CRC with antibiotics (defined as any antibiotic use up to 5 years before index colonoscopy) was derived by multivariable Cox proportional hazards model with adjustment for other covariates (including patient's demographics, history of colonic polyps/polypectomy, concurrent drug usage [aspirin, NSAIDs, COX-2 inhibitors and statins] and endoscopy centre's performance [polypectomy rate and colonoscopy volume]). Eleven classes of antibiotics were included: penicillins, cephalosporins, macrolides, carbapenems, quinolones, tetracyclines, aminoglycosides, nitroimidazoles, glycopeptides, sulpha/trimethoprim, and others (clindamycin, nitrofurantoin, linezolid, rifampicin, rifaximin, and daptomycin). Stratified analysis was performed according to cancer location and nature of antibiotics.

Results: Among 97 162 eligible patients (52.3% male), 1026 (1.1%) patients developed CRC after colonoscopy (proximal: 171 [16.7%], distal: 254 [24.8%], and rectal: 601 [58.6%]). The median age of cancer diagnosis was 79.1 years (interquartile range=72.9-85.0). There were 58 704 (60.4%) antibiotic users. Antibiotic use was associated with lower rectal cancer risk (adjusted hazard ratio [aHR]=0.64; 95% confidence interval [CI]=0.54-0.76), but higher proximal colon cancer risk (aHR=1.63; 95% CI=1.15-2.32). Th effect was neutral on distal colon cancer development (aHR=0.99; 95% CI=0.76-1.30). These effects varied according to anti-anaerobic/anti-aerobic activity, broad-/narrow-spectrum, and route of administration of antibiotics. Notably, penicillins were associated with a lower CRC risk (aHR=0.83; 95% CI=0.73-0.96), while aminoglycosides were associated with a higher risk (aHR=1.53; 95% CI=1.05-2.25).

Conclusion: Antibiotic use was associated with divergent effects on CRC development in older patients, with respect to cancer location, class of antibiotics, and route of administration.

67 Combination effect of dichloroacetate and niclosamide in malignant pleural mesothelioma cells

SK Lam, S Yan, Y Feng, M Khan, C Chen, JCM Ho
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Inhaling asbestos fibres is the commonest cause of malignant pleural mesothelioma (MPM). Although the use of asbestos has been restricted, the incidence of MPM is still rising due to a long lag time in malignant transformation. In 2004, the United States Food and Drug Administration approved a combination of pemetrexed with cisplatin for treatment of unresectable MPM. However, overall prognosis is still extremely poor. As such, development of novel therapeutic options is urgently needed. The anticancer effect of dichloroacetate or niclosamide has been demonstrated in different cancer types. This study aimed to disclose the combination effect of dichloroacetate and niclosamide in MPM.

Methods: The combination effect of dichloroacetate and niclosamide was studied using a panel of MPM cell lines. The effect of dichloroacetate and/or niclosamide on cell viability was studied by MTT assay. Mitochondrial transmembrane potential was monitored with JC-1 staining by flow cytometry.

Results: Combination of dichloroacetate (D) and niclosamide (N) reduced cell viability in H28 (IC_{50}: D: 10 mM, N: 1 μM, synergism), 211H (IC_{50}: D: 7.5 mM, N: 0.75 μM, synergism), H226 (IC_{50}: D: 8 mM, N: 0.8 μM, synergism), H2052 (IC_{50}: D: 8 mM, N: 0.8 μM, synergism) and H2452 (IC_{50}: D: 10.5 mM, N: 1.1 μM, synergism) cells. Niclosamide alone increased mitochondrial transmembrane potential which was further enhanced when combined with dichloroacetate in H28 and 211H cells. Niclosamide alone increased mitochondrial transmembrane potential which was comparable with combination of dichloroacetate and niclosamide in H226, H2052 and H2452 cells.

Conclusion: Combination of dichloroacetate and niclosamide synergistically reduced cell viability which was partially mediated by elevation of mitochondrial transmembrane potential in MPM cells.

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68 Concurrent docetaxel, epirubicin and cyclophosphamide is effective and safe neoadjuvant therapy for early high-risk Her2-negative breast cancers

BCW Li, JWY Chiu, RCY Leung, GGW Kwok, JWY Tsang, TCC Yau
Department of Medicine, Queen Mary Hospital, Hong Kong

Introduction: Anthracyclines and taxanes are the two most effective chemotherapeutic agents in breast cancers. Concurrent docetaxel, epirubicin and cyclophosphamide (TEC) is an effective, efficient, and regime of short duration. However, tolerance and toxicities were concerns, especially in Asian populations. Here we report the clinical experience of this regime in a tertiary academic referral centre for breast cancer in Hong Kong.

Methods: All patients with Her2-negative breast cancers who received neoadjuvant TEC from January 2013 to December 2019 were reviewed. Pathological reviews were done in a local laboratory.

Results: 71 patients, of which 57 had clinical luminal B disease and 14 had triple-negative disease, received neoadjuvant TEC. The pCR rate was 26.8% (n=19) overall. There was no difference between the subtypes. With median follow-up of 46 months, 3-year disease-free survival was 85.9%. and 3 years overall survival was 89.6%. Overall survival (OS) and progression-free survival (PFS) were not significantly different between groups of whether pCR (P=0.503) were achieved or not. Among those with residual disease, one eighth had change in Her2 status, and all did not have any recurrence when given adjuvant Herceptin. The most common grade3/4 haematological toxicity was neutropenia (26.8%), despite routine use of prophylactic granulocyte stimulating factor (GCSF). Neutropenic fever was not common (12.7%). Half of the patients had at least one dose reductions. The side-effects were all manageable. There was no grade 4 non-haematological toxicity. All patients completed the intended number of cycles.

Conclusion: TEC is an effective chemotherapy regime for neoadjuvant therapy for Her2-negative breast cancers with more than one quarter of patients achieving pCR irrespective of hormonal status. The outcome of patients with change of Her2 status after neoadjuvant therapy, when given Herceptin adjuvant therapy, was excellent. The regime is generally well tolerated and safe. Neutropenia remained the most significant toxicity despite routine use of prophylactic GCSF. Many patients needed dose reduction which did not affect the efficacy.

69 A combination of sorafenib, capecitabine and oxaliplatin as neoadjuvant therapy in patients with locally advanced hepatocellular carcinoma, a phase 2 study

BCW Li, JWY Chiu, RCY Leung, GGW Kwok, JWY Tsang, TCC Yau
Department of Medicine, Queen Mary Hospital, Hong Kong

Background: The combination of capecitabine, oxaliplatin and sorafenib (SECOX) has shown early clinical outcomes as the first-line treatment of advanced hepatocellular carcinoma (HCC). We aimed to evaluate the efficacy and safety of using SECOX in treating locally advanced HCC patients as neoadjuvant therapy.

Methods: Eligible locally advanced HCC patients with unresectable disease received four 2-week cycles of SECOX regimen: oxaliplatin 85 mg/m^2 on day 1 only; capecitabine 850 mg/m^2 orally twice daily from day 1 to day 7 only; and sorafenib 400 mg orally twice daily from day 1 to day 14. The primary endpoint was resectability assessed by designated hepatobiliary surgeons. Secondary endpoints were overall tumour response rate, progression-free survival, overall survival and exploratory biomarkers. Response was evaluated by the investigators according to RECIST 1.1.

Results: 15 patients were recruited. The trial was terminated early due to futility. The median age was 53 years (range, 38-69) and all patients were in ECOG performance status 1. In total, 80% of patients were chronic hepatitis B carriers and all patients had Child A cirrhosis. Among these 15 patients, nine patients completed four cycles of neoadjuvant SECOX. No patient became resectable after treatment. The overall objective response rate was 13% with only two partial responses. Median progression-free survival was 3.2 months (95% CI=0.5-22). Median overall survival was 8.9 months (95% CI=1.9-22). Rash (47%), diarrhoea (40%) and malaise (40%) were the most commonly encountered toxicities.

Conclusion: Neoadjuvant SECOX did not improve resectability or survival of locally advanced HCC.

70 Effectiveness of urinary catheter care programme in minimising catheter-associated urinary tract infection

TC Chan[1], HY Lam[2], OYF Lin[1], JKH Luk[1]
[1]Department of Medicine and Geriatrics, Fung Yiu King Hospital, Hong Kong
[2]Department of Nursing, Fung Yiu King Hospital, Hong Kong

Background: Nosocomial catheter-associated urinary tract infection (CAUTI) is common. Common causes are low percentage of planned urinary catheter removal, lack of reminder system to remind the doctor to review indication of a urinary catheter, and lack of regular surveillance. A new urinary catheter care programme was launched in September 2019 in Fung Yiu King Hospital (FYKH).

Objective: To investigate if a new urinary catheter care program can effectively reduce CAUTI.

Methods: The new programme included: (1) Use of an infection control team designed yellow label to serve as a reminder for reviewing urinary catheter indication, for any patients with a urinary catheter; (2) Frontline knowledge updates for urinary catheter through multiple identical forums, and (3) Implementation of regular surveillance for nosocomial CAUTI. The new programme was started on 1 September 2019. After implementation of a new urinary catheter care programme, three surveillance studies were performed in 3 different days of September 2019.

Results: Point prevalence of patient having urinary catheter reduced from 12.5% to 8.0%. Point prevalence of nosocomial CAUTI reduced from 2.6% to 0%. Monthly prevalence of nosocomial CAUTI after the programme was 0 per 1000 catheter days. The new urinary catheter care programme in FYKH successfully minimise nosocomial CAUTI.

71 Prevalence of foot problems in Hong Kong long-term care facility residents

TC Chan[1], YK Kwok[2], CSY Leung[2], FHW Chan[1], JKH Luk[1]
[1]Department of Medicine and Geriatrics, Fung Yiu King Hospital, Hong Kong
[2]Department of Podiatry, Queen Mary Hospital, Hong Kong

Introduction: Foot problems are common in long-term care facility (LTCF) residents. There is little data regarding its prevalence in Hong Kong LTCF residents.

Methods: This is a cross-sectional study in three LTCFs located in Hong Kong West Cluster from November 2019 to December 2019. Residents of the three LTCFs were assessed by the same podiatrist.

Results: 103 LTCF residents were assessed. The mean age of the patients was 84 years. 39.5% were male and 60.5% were female. For foot conditions, three patients had pressure injury. No patient was recorded with cellulitis, ulceration, or ingrown toenails. For skin integrity, 13.0% had different kinds of skin problems including eczema, anhidrotic, fissure and bruises. For the toenails pathology, 65.1% of the patients had different forms of toenails pathologies, including 44.0% of onychomycosis; 34.9% onychauxis; 15.6% of onychocryptosis. For the onychomycosis, 81.2% of the patients had multiple fungal toenail infections and 19.3% had tinea pedis as well. For the toe deformity, 9.2% of the patients had hallux valgus deformity and 8.3% had lesser toe deformity.

Conclusion: 72.5% of patients had foot problems that required further podiatric care to optimise foot condition.

72 In situ simulation training of donning personal protective equipment and cardiopulmonary resuscitation for nurses during COVID-19 in a district general hospital

TC Chan[1], KK Lam[2], PL Cheung[2], S Law[2], HY Lam[2], FHW Chan[1], JKH Luk[1]
[1]Department of Medicine and Geriatrics, Fung Yiu King Hospital, Hong Kong
[2]Department of Nursing, Fung Yiu King Hospital, Hong Kong

Introduction: Donning personal protective equipment (PPE) and performing cardiopulmonary resuscitation (CPR) during COVID-19 pandemic is stressful for healthcare professionals.

Methods: This is a pretest-posttest analysis to assess the effectiveness of a training course for a group of nurses at a district general hospital. Each nurse attended (1) whole class lecture and (2) simulation training for donning PPE and performing CPR. CPR knowledge, self-confidence of donning PPE and performing CPR were assessed before training, after the lecture, and after simulation training.

Results: Fifty nurses attended the lecture and simulation training. There was significant improvement in CPR knowledge. For both self-confidence of donning PPE and performing CPR, there was significant enhancement after simulation training.

Conclusion: In-situ simulation training of donning PPE and performing CPR for nurses significantly improved their knowledge and confidence in district general hospital during COVID-19.

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Malignancies in spondyloarthritis with and without concomitant psoriasis, and the effect of disease-modifying antirheumatic drugs

HY Chung[1], SCW Chan[1], ACT Cheung[2], ETF Chui[1], TCC Yau[3], CS Lau[1]
[1]Division of Rheumatology and Clinical Immunology, The University of Hong Kong, Hong Kong
[2]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[3]Division of Medical Oncology, The University of Hong Kong, Hong Kong

Objectives: To determine the risk of six types of malignancies in patients with spondyloarthritis (SpA), with and without psoriasis (PsO) and on disease-modifying antirheumatic drugs (DMARDs) when compared with those with non-specific back pain (NSBP).

Methods: Medical records were retrieved. Patients with SpA, with and without PsO were identified and compared with those with NSBP. Clinical data; follow-up duration; comorbidities; dates and types of cancer diagnosed; types and duration of DMARDs used were collected. Propensity score adjustment was used to compare the risks of malignancies between SpA, SpA with and without PsO, and NSBP. Cox regression analysis was used to determine the risk of malignancy with the use of DMARDs.

Results: A total of 3020 patients with SpA and 2527 patients with NSBP were studied. The mean follow-up duration in patients with SpA and NSBP was 9.6 years and 13.5 years, respectively. Incidence and risk of malignancies were compatible between patients with SpA and NSBP. Subgroup analysis showed higher incidence of colorectal carcinoma (1.37 per 1000 patient-years), carcinoma of pancreas (0.30 per 1000 patient-years), carcinoma of stomach (0.30 per 1000 patient-years), and lymphomas (0.91 per 1000 patient-years) in SpA patients with PsO. Risk of colorectal carcinoma (hazard ratio [HR]=2.46; P=0.03) and lymphomas (HR=2.86; P=0.04) was also increased in the group. DMARD use was not associated with increased risks of malignancies after adjustment for confounding factors.

Conclusion: Risk of malignancy was increased in SpA with PsO but not with other subtypes of SpA or the use of DMARDs.

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Risk of community-acquired pneumonia requiring hospitalisation in patients with spondyloarthritis

HY Chung[1], LS Tam[2], SCW Chan[3], JPY Cheung[4], PY Wong[5], CO Ciang[6], HY Ng[7], MY Law[8], TL Lai[5], CH Wong[2]; Hong Kong Society of Rheumatology, HE Lau[9], JC Fok[9]
[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong
[3]Division of Rheumatology and Clinical Immunology, The University of Hong Kong, Hong Kong
[4]Department of Orthopedics and Traumatology, The University of Hong Kong, Hong Kong
[5]Department of Rheumatology, Tseung Kwan O Hospital, Hong Kong
[6]Department of Medicine, Queen Elizabeth Hospital, Hong Kong
[7]Division of Rheumatology, Caritas Medical Centre, Hong Kong
[8]Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Hong Kong
[9]Faculty of Medicine, The University of Hong Kong, Hong Kong

Aims: To compare the risk of community-acquired pneumonia (CAP) requiring hospitalisation in spondyloarthritis (SpA) and non-specific back pain (NSBP) and to identify the risk factors for CAP in SpA.

Methods: A total of 2984 patients with SpA from 11 rheumatology centres and 2526 patients with NSBP from orthopaedic units were reviewed from the centralised electronic database in Hong Kong. Incidence of CAP requiring hospitalisation and demographic data including age, sex, smoking and drinking status, use of sulfasalazine, individual biological-disease modifying antirheumatic drugs (DMARDs) used, micro-organisms, other immunosuppressants or immunosuppressive states, use of steroid for >1/2 year, and comorbidities were identified. Risks of CAP in SpA were compared with those in NSBP using propensity score regression method. Multivariate Cox regression model was used to identify the risk factors in SpA.

Results: CAP requiring hospitalisation was found in 183 patients with SpA and 138 patients with NSBP. Increased risk for CAP was found in the following groups with SpA: all subgroups (hazard ratio [HR]=2.14, P<0.001), without use of DMARDs (HR=2.64, P<0.001), without psoriasis and not taking DMARDs (HR=2.38, P<0.001). Infliximab (HR=2.55, P=0.04), smoking (HR=1.68, P=0.003), comorbid psoriasis (HR=1.67, P=0.003), and use of steroid for >1/2 year (HR=1.94, P=0.003) were found to associate with CAP after adjustments for traditional risk factors.

Conclusion: Risk of CAP is increased in patients with SpA. Our data favour universal influenza and pneumococcal vaccination programmes in the population. Rheumatologists should also advise smoking cessation and avoid long term steroid therapy.

Risk of tuberculosis in patients with spondyloarthritis: data from a centralised electronic database in Hong Kong

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NCO Ciang[1], SCW Chan[2], CS Lau[2], ETF Chiu[2], HY Chung[2], HM Lam[3], CPY Lee[3], CY Chan[3]
[1]Division of Rheumatology, Department of Medicine, Queen Elizabeth Hospital, Hong Kong
[2]Division of Rheumatology and Clinical Immunology, The University of Hong Kong, Hong Kong
[3]Faculty of Medicine, The University of Hong Kong, Hong Kong

Background/Objective: To determine the crude incidence rate of and risk factors for tuberculosis (TB) in spondyloarthritis (SpA).

Methods: Clinical data of 2984 patients with SpA from 11 rheumatology centres were reviewed. This included demographics, duration of follow-up, comorbidities including diabetes, chronic kidney disease, chronic heart disease, chronic lung disease, stroke and malignancies, date of diagnosis of tuberculosis, use of non-steroidal anti-inflammatory drugs, duration of glucocorticoid therapy for >6 months, conventional (cDMARD) and biological (bDMARD) disease-modifying antirheumatic drug therapies. Crude incidence rates were reported. Cox regression models were used to determine the risk factors for TB in patients with SpA.

Results: Forty-three patients had TB, of which four (9.3%) were extra-pulmonary. The crude incidence rate of TB was 1.57 in patients with SpA, compared with 0.58 in the general population in Hong Kong. Independent risk factors identified from the multivariate Cox regression model was: alcohol use (hazard ratio [HR]=2.62; P=0.03), previous TB (HR=13.62; P<0.001), chronic lung disease (HR=3.39; P=0.004), duration of glucocorticoid therapy greater than 6 months (HR=3.25; P=0.01) and infliximab therapy (HR=5.06; P<0.001). Age was associated with decreased risk (HR=0.93; P<0.001).

Conclusion: Incidence of TB was higher in patients with SpA. Glucocorticoid therapy beyond 6 months and infliximab therapy increased the risk of TB. Rheumatologists should avoid prolonged use of glucocorticoids and consider DMARDs other than infliximab in the treatment of at-risk patients.

Liposome-embedded curcumin alleviates liver injury in Atp7b-/-Wilson disease mouse model

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WI Ho, JY Yang, R Wei, CW Cheng, N Li, WH Lai, KW Au, LY Wong, WL Tsang, HF Tse
Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Wilson disease (WD) is a rare inherited genetic disorder caused by diverse mutations in the *ATP7B* gene located on chromosome 13. Impaired ATP7B protein causes accumulation of copper in a variety of tissues especially liver and brain, which leads to severe physiological disorders such as hepatitis, progressive cirrhosis, acute liver failure, impairment of blood-brain barrier, and other neuropsychiatric dysfunctions. Curcumin, a natural polyphenolic compound extracted from *Curcuma longa* plants, has been studied extensively and proofed to have anti-inflammatory, antioxidant, hepatoprotective even neuroprotective activities. However, poor bioavailability of this hydrophobic compound has limited its beneficial roles on different diseases. Previous studies have shown that liposome-embedded curcumin can successfully enhance bioavailability in vitro and in vivo.

Methods: Liposome-embedded curcumin was injected in 8-week-old *Atp7b*$^{-/-}$ WD mouse model twice a week for 8 weeks, to investigate the treatment efficacy of Wilson disease.

Results: liposome-embedded curcumin can improve liver function, reduce inflammation and fibrosis.

Conclusion: We confirmed that liposome-embedded curcumin as an effective treatment of Wilson disease, and more mechanistic studies will be performed.

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Phase II single-arm open-labelled study evaluating combination of quizartinib and omacetaxine mepesuccinate in newly diagnosed or relapsed/refractory acute myeloid leukaemia carrying Fms-like tyrosine kinase 3

GMK Leung[1], CX Zhang[2], J Sim[1], YL Kwong[2], AYH Leung[2]
[1]Department of Medicine, Queen Mary Hospital, Hong Kong
[2]LKS Faculty of Medicine, The University of Hong Kong, Hong Kong

Introduction: Acute myeloid leukaemia (AML) with internal tandem duplication of Fms-like tyrosine kinase 3 (FLT3-ITD) is associated with a high relapse risk and inferior outcome. A single-arm, phase 2 study evaluated efficacy and safety of combining FLT3 inhibitor quizartinib with a protein translation inhibitor omacetaxine mepesuccinate (OME) [QUIZOM].

Methods: Relapsed/Refractory FLT3-ITD AML patients aged ≥18 years or newly diagnosed patients aged ≥65 years old were recruited. Treatment comprised quizartinib 30 mg daily and OME (2 mg daily for 7 days in cycle 1 and for 5 days in subsequent cycles) every 21 to 28 days, until disease progression or allogeneic haematopoietic stem cell transplantation (HSCT). Quizartinib was given as post HSCT maintenance after engraftment at doses ranging from 30 mg weekly to 30 mg daily, depending on blood counts. Primary endpoint was composite complete remission (CRc) defined by CR+CRi (CR with incomplete haematological recovery). Secondary endpoints were leukaemia-free (LFS) and overall survival (OS). Molecular responses were evaluated by FLT3-ITD based on PCR and NPM1 variant allele frequency (VAF) based on droplet digital PCR (ddPCR). Mutation profiling of patients was performed by MiSeq Next Generation Sequencing (NGS).

Results: Forty-two patients (R/R=36; newly diagnosed=6) were recruited between November 2017 and October 2020. Forty patients completed at least one course of QUIZOM (median 3 courses, range 1-20 courses) of whom 34 (R/R=31; newly diagnosed=3) achieved CR/CRi (CR=2 [5%]; CRi=32 [80%], CRc=34 [85%]), three patients showed partial remission (PR) and three did not respond. All 13 patients with prior FLT3 inhibitors exposure (sorafenib=3, midostaurin=10) achieved CR/CRi. Median LFS and OS after CR/CRi were 6.9 and 13 months. Twelve patients received allogeneic HSCT and 11 of them remained in remission as of 30 November 2020 (OS=6.3 to 35.4 months). One patient died during HSCT. Deep molecular responses (DMR) as defined by FLT3-ITD VAF ≤0.1% and NPM1 VAF ≤0.001% were accomplished in 73% and 31% patients. Grade 3/4 cytopenia was the major adverse effects. Two patients succumbed before commencement and on day 1 of QUIZOM due to pneumonia and intracranial haemorrhage. None of recurrently mutated genes was significantly associated with treatment responses in this cohort.

Conclusion: QUIZOM is effective and safe for newly diagnosed and R/R FLT3-ITD AML.

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Clinical outcomes in stable coronary artery disease treated with optimal medical therapy alone based on a novel index: computational pressure-flow dynamics derived fractional flow reserve

KY Li[1], LY Lam[1], CKL Leung[1], ASY Yu[2], MZ Wu[2], QW Ren[2], PF Wong[2], YK Tse[1], SSY Yu[1], HL Li[1], KH Yiu[2]
[1]Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Computational pressure-flow dynamics derived fractional flow reserve (caFFR) is a novel method to determine the fractional flow reserve (FFR) in patients with coronary artery disease, without the need for invasive pressure wire and hyperaemic stimulus. The study aimed to evaluate the prognostic role of caFFR in patients with stable coronary artery disease (CAD) who were treated by optimal medical therapy alone.

Methods: A total of 284 stable CAD patients (mean age 67.0±11.0 years; 71.8% male) with ≥1 coronary lesion detected by coronary angiogram were included. All of them did not undergo percutaneous coronary intervention and were treated with optimal medical therapy alone. Patients were classified into four groups according to their caFFR value; caFFR ≤0.7 (n=95), caFFR=0.71-0.8 (n=32), caFFR=0.81-0.9 (n=112), caFFR=0.91-1.0 (n=45), with a lower caFFR indicating a greater magnitude of myocardial ischaemia. The primary endpoint was defined as a composite of all-cause mortality, myocardial infarction, or any unplanned revascularisation at 3 years.

Results: During a median follow-up of 36 months, 48 composite events occurred, including 23 all-cause mortality, six myocardial infarction, and 19 unplanned revascularisation. The measurement of myocardial ischaemia by caFFR, as a continuous parameter, showed a significant inverse relationship with composite endpoints (adjusted hazard ratio [HR]=0.043; 95% confidence interval [CI]=0.01-0.23; P<0.01), cardiac death or myocardial infarction (adjusted HR=0.01; 95% CI=0.01-0.21; P=0.005) and all-cause mortality (adjusted HR=0.02; 95% CI=0.01-0.15; P<0.01). Using caFFR=0.91-1.00 as reference, the risk of primary endpoint was highest in patients with caFFR ≤0.7 (adjusted HR=4.45; 95% CI=1.33-14.89; P=0.015), followed by caFFR=0.71-0.8 (adjusted HR=4.30; 95% CI=1.11-16.72; P=0.035). The risk of primary endpoint was nonetheless similar between caFFR=0.91-1.00 and caFFR=0.81-0.9 (adjusted HR=0.94; 95% CI=0.24-3.63, P=0.92).

Conclusion: In patients with stable CAD who were otherwise treated with optimal medical therapy alone, those with significant myocardial ischaemia (caFFR <0.8), had the highest risk of adverse events. The finding supports the use of this novel index to quantify the severity of myocardial ischaemia and improve risk stratification in patients.

Homoharringtonine overcame drug resistance and showed synergism with venetoclax in the treatment of acute myeloid leukaemia

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TH Kwok, AY Leung, CH Man
Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Introduction: Acute myeloid leukaemia (AML) is one of the most lethal cancers worldwide. In young and fit patients, chemotherapy and allogeneic haematopoietic stem cell transplantation are the mainstays of treatment. In elderly and unfit patients, the outcome is dismal. Venetoclax, a BCL-2 inhibitor, when used in combination with a hypomethylating agent, is effective in inducing remission and improve survival. Leukaemia relapse may be caused by emergence of alternative anti-apoptotic proteins and is a major cause of treatment failure. We hypothesised that protein synthesis inhibitor, homoharringtonine (HHT) may overcome venetoclax resistance and combination of venetoclax and HHT will enhance the therapeutic effects of venetoclax.

Methods: Ten AML cell lines representative of distinct driver events in leukemogenesis were screened for their sensitivities to venetoclax. Selected cell lines were treated in vitro with a combination of venetoclax and HHT to demonstrate synergism. Some were transduced with luciferase and transplanted into NOD.Cg-*Prkdc*^{scid}*Il2rg*^{tm1Wjl}/SzJ (NSG) mice via tail vein and once engraftment has been confirmed by bioluminescence, recipient animals were gavaged with venetoclax and intraperitoneally injected with HHT. Western Blot was performed to examine the underlying therapeutic mechanisms.

Results: Venetoclax showed differential effects on different AML cell lines with IC50 (half maximal inhibitory concentration) ranging from 5.83 nM (MV-4-11 cell line) to over 1000 nM (THP-1 and OCI-AML3 cell line etc). OCI-AML3 and THP1 were resistant at the doses tested. Intriguingly, the latter two cell lines showed significant synergism upon combination treatment with venetoclax and HHT, as shown by growth inhibition as well as the Excess Over Bliss. At doses relevant to peak plasma concentrations in patients, the synergism and leukaemia inhibitory effects were significantly higher than those of venetoclax and cytarabine as well as venetoclax and azacitidine combination, which are regimens currently approved by the United States Food and Drug Administration. Combination of venetoclax and HHT also significantly inhibited OCI-AML3 growth in vivo. Mechanistically, HHT suppressed short-lived proteins, including anti-apoptotic protein MCL-1, HOXA9.

Conclusion: HHT may overcome drug resistance to venetoclax in AML and should be explored as potential therapeutic partners with venetoclax to improve its clinical efficacy.

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Benefit and risk of lower follow-up blood pressure after intracerebral haemorrhage

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KC Teo, CYW Leung, C Yeung, YK Wong, KH Chan, RTF Cheung, SL Ho, KK Lau
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Intracerebral haemorrhage (ICH) survivors are prone to recurrent ICH, and blood pressure (BP) control is the sole modifiable risk for ICH recurrence. It remained unclear whether a more intensive BP target during follow-up would be beneficial, with the concern of increased mortality. Hence, we aimed to study the benefit and risks of lower follow-up BP in ICH survivors

Methods: We studied the follow-up data of 501 primary ICH survivors from the prospective stroke registry of The University of Hong Kong, who were admitted from January 2011 to March 2019. Follow-up data were retrieved from the electronic patient record system or written medical notes. Our primary end-points were recurrent ICH, cardiovascular mortality, and all-cause mortality. The adjusted hazard ratios (HR) for each BP categories during follow-up were derived using multivariate Cox regression.

Results: During a median FU of 4.2 years (interquartile range=2.2-6.1), there were 39 recurrent ICHs. When compared with systolic BP (SBP) of <120 mmHg, higher SBP categories were associated with an increasing risk of recurrent ICH (HR=4.5 for SBP 120-139 mmHg, 95% confidence interval [CI]=1.1-19.1; HR=10.4 for SBP 140-159 mmHg, 95% CI=2.1-50.8; HR=46.6 for SBP ≥160 mmHg, 95% CI=7.7-283.1). Similarly, the recurrent ICH risk increased with higher diastolic BP (DBP) categories. There was a J-shape relationship between SBP and all-cause mortality (HR=1.7 for SBP <120 mmHg, 95% CI=1.1-2.6; HR=2.0 for SBP 140-159 mmHg, 95% CI=1.1-3.3; HR=4.3 for SBP ≥160 mmHg, 95% CI=1.6-12.0), but not for cardiovascular mortality. No J-shape relationship was observed between DBP and all-cause mortality. In the subgroup analysis of patients aged ≤70 years, lower BP did not heighten all-cause mortality risk.

Conclusion: A more intensive BP target of below 120/70 should be considered in ICH survivors, especially in patients aged ≤70 years.

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Effect of cigarette smoke on airway inflammation, mucus hypersecretion and endoplasmic reticulum stress in a three-dimensional co-culture model of airway epithelium and smooth muscle

R Chen[1], MSM Ip[1], JCW Mak[1,2]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Introduction: Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally, in which cigarette smoke (CS) is the major risk factor. To investigate CS-induced effects, two-dimensional (2D) submerged culture model was widely performed as the model for primary airway cells research, which could not reproduce the characteristics of respiratory tract in vivo. In addition, the interaction between airway epithelium and smooth muscle in response to CS is still unclear. Therefore, there is a need for setting up a robust and reliable three-dimensional (3D) model to study the interaction between airway epithelium and smooth muscle recapitulating comparable characteristic of respiratory tract in vivo for CS exposure. We aimed to investigate CS-induced airway inflammation, mucus hypersecretion and endoplasmic reticulum (ER) stress in the well-differentiated co-culture model.

Methods: Primary normal human bronchial epithelial cells (HBECs) differentiated at the air-liquid interface (ALI) for 28 days were co-cultured with normal human airway smooth muscle cells (HASMCs). Cigarette smoke medium (CSM) was directly applied to the apical side of well-differentiated HBECs for 24 hours (n=4). The inflammatory, mucin and ER stress markers were assessed by qPCR, ELISA and Western blot assays.

Results: A functional multilayer epithelium consisting of basal cells, goblet cells and ciliated cells was successfully developed under ALI culture. Co-culture of well-differentiated airway epithelium and smooth muscle showed higher sensitivity in response to CS, with significantly increase in airway inflammation and mucus hypersecretion in comparison with single cell culture model. CS could also cause induction of ER stress via activation of the unfolded protein response (UPR) pathway activating transcription factor 6 (ATF6) in the co-culture model.

Conclusion: The current findings provide evidence of interaction between airway epithelium and smooth muscle, leading to greater responses in CS-induced airway inflammation and mucus hypersecretion via regulation of UPR-ATF6 pathway.

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Statin use is associated with lower cancer risk and cancer-related mortality in patients with heart failure: a territory-wide study

QW Ren[1,2], SY Yu[2], X Li[2], KS Cheung[1,2], MZ Wu[1,2], HL Li[2], PF Wong[2], HF Tse[1,2], CSP Lam[3,4], KH Yiu[1,2]
[1]Cardiology Division, Department of Medicine, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China
[2]Cardiology Division, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[3]Duke-NUS Medical School, Singapore
[4]Department of Cardiology, National Heart Center, Singapore

Background: Patients with heart failure (HF) is associated with a high risk of cancer. The effect of statin use among patients with HF on cancer risk and cancer-related mortality is nonetheless unknown.

Methods: Using a territory-wide clinical information registry, statin use was ascertained among all eligible patients with HF (n=87102) from 2003 to 2015. Inverse probability of treatment weighting was used to balance baseline covariates between statin nonusers (50926 patients) with statin users (36176 patients). Competing risk regression with Cox proportional hazards models was performed to estimate the risk of cancer and cancer-related mortality associated with statin use.

Results: Of all eligible subjects, 11052 (12.7%) were diagnosed with cancer. Statin use was associated with a 16% lower risk of cancer incidence (multivariable-adjusted subdistribution hazard ratio [SHR]=0.84; 95% confidence interval [CI]=0.80-0.89). This inverse association with risk of cancer was duration-dependent; as compared with short-term statin use (3 months to <1 year), the adjusted SHR were 0.97 (95% CI=0.88-1.07) for 1 to <3 years of use, 0.78 (95% CI=0.70-0.88) for 3 to <5 years of use, and 0.52 (95% CI=0.46-0.60) for ≥5 years of use. Ten-year cancer-related mortality was 3.3% among statin users and 4.8% among nonusers (absolute risk difference, -1.5 percentage points [95% CI= -1.7% to -1.2%]; adjusted SHR=0.74; 95% CI=0.67-0.81).

Conclusion: Our study suggests that statin use is associated with a significantly lower risk of cancer incident and cancer-related mortality and appears to be duration-dependent.

Using an artificial neural network to identify the population at risk of type 2 diabetes mellitus in the United States

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Y Fei, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Prevention of type 2 diabetes mellitus (T2DM) is now believed to be possible. We aimed to construct an artificial neural network (ANN) to classify the risk of T2DM in a general population and to identify novel predictors of T2DM.

Methods: The demographic, clinical, and questionnaire data on the participants aged ≥20 years in the United States National Health and Nutrition Examination Survey 2007 to 2010 were used to develop the multilayer perceptron ANN model in R. The diagnosis of T2DM was based on self-reported history. The analysis excluded pregnant women and participants diagnosed with diabetes mellitus at age <30 years requiring insulin therapy. We randomly selected the same number of people without T2DM as those with T2DM as controls.

Results: In the final dataset, there were 576 T2DM and 576 control participants. Our ANN model achieved a sensitivity of 74.4%, specificity of 72.4%, accuracy of 73.4% (95% confidence interval=67.9%-78.4%), and area under the curve of 0.73 in T2DM classification. In decreasing order of importance, waist circumference, age, race, LDL level, diet quality, close relatives having diabetes mellitus, education level, calcium level, marital status, and hypertension were identified as the 10 leading predictors of T2DM in the model.

Conclusion: ANN is a novel method of identifying the risk of T2DM in the general population. Although the predictors are population-specific, the availability of big data allows rapid model construction for different populations.

Comparison of the characteristics of people with hypertension in China and the United States

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XP Liang, ZY Lin, MY Cheung
Division of Clinical Pharmacology and Therapeutics, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: The characteristics of people with hypertension in western populations have been well studied. China has a population of 1.4 billion, among whom, 300 million are hypertensive. We therefore compared the hypertensive populations in these two countries.

Methods: We used data from the China Hypertension Survey (CHC) and the United States National Health and Nutrition Examination Survey (NHANES) 2013 to 2016. We included participants aged >18 years and excluded participants without blood pressure (BP) measurements. Systolic BP ≥130 mmHg/or diastolic BP ≥80 mmHg was considered as hypertension. Body mass index 24.0-27.9 and ≥28.0 were considered as overweight and obesity, respectively.

Results: 451755 CHC (mean age 43.7 years) and 12105 NHANES participants (mean age 47.8 years) were included for analysis. The prevalence of obesity, smoking (including current and past smoking), and consumption of alcohol was, respectively, 12.1%, 23.1%, 15.8% in CHC and 50.1%, 37.1%, 42.5% in NHANES. There were 209615 CHC and 5524 NHANES participants who had hypertension. The overall hypertension prevalence was 46.4% in CHC and 45.6% in NHANES. The prevalence of hypertension among overweight, obesity, current smokers and alcoholics was, respectively, 56.3%, 70.2%, 54.4%. 58.3% in CHC, and 43.4%, 55.7%, 48.1%, 46.5% in NHANES.

Conclusion: Hypertension, a major risk factor for stroke and coronary heart disease, is as prevalent in China as in the United States, despite a lower prevalence of obesity, smoking and alcohol consumption.

Myocardial strain analysis in uncomplicated COVID-19 survivor

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M Zhou, CW Siu, CK Wong
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: A number of studies were reported the impact of COVID-19 infection on the cardiovascular (CV) system, however, few data focused on the subclinical myocardial damages in uncomplicated COVID-19 survivors after hospital discharge.

Methods: We enrolled 195 uncomplicated COVID-19 survivors in this study after their immediate hospital discharge. Comprehensive cardiac screening algorithm was recommended to those patients, including electrocardiogram (ECG), echocardiography, and cardiac biomarkers. Patients were divided into T wave abnormalities group, elevated troponin T levels group, and no cardiac abnormalities group according to the aforementioned screening results. Strain echocardiography was performed to investigate the subclinical myocardial damages among those patients.

Results: A total of 18 (9.2%) patients with T wave abnormalities, and 13 patients were detected with elevated troponin T level. Patients with cardiac abnormalities were relatively older and had a deteriorated left ventricular (LV) systolic and diastolic function, a higher level of NTproBNP and a higher rate of CV risk factors compared with those patients without cardiac abnormalities. Strain analysis indicated that segmental longitudinal strain in the basal and middle level of the interventricular septum (IVS), Peak circumferential strain of endomyocardial from basal to the middle level of the LV, and the segmental circumferential strain in IVS were significantly decreased in patients with cardiac abnormalities compared with those patients without cardiac abnormalities.

Conclusion: Uncomplicated COVID-19 survivors with T wave abnormalities or elevated Troponin T levels presented with decreased longitudinal and circumferential strain compared with those patients without cardiac abnormalities.

Predictors of early death and long-term survival of acute promyelocytic leukaemia in the real-world setting: a territory-wide study

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PK Yip, HT Chu, E Lee, Y Yung, YL Kwong, H Gill
Division of Haematology, Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Acute promyelocytic leukaemia (APL) is a distinct form of acute myeloid leukaemia (AML) characterised by *PML-RARA* gene fusion. Despite therapeutic advances with the use of arsenic trioxide in combination with all-trans-retinoic acid (ATRA) and chemotherapy, early death remains a significant factor predicting patient outcome.

Methods: We performed a territory-wide analysis of all patients with newly diagnosed APL in Hong Kong between 1 January 2013 and 30 April 2020. The impact of sex, age, presenting white blood cell (WBC) count, presenting platelet count, and presenting fibrinogen level on early deaths and long-term survival were determined. Prognostic factors for early death were determined using univariable and multivariable logistic regression analysis. Prognostic factors for overall survival (OS) were determined using log-rank test and Cox proportional hazards regression.

Results: Between January 2013 and April 2020, 219 patients (96 men, 123 women) with a median age of 49 years were diagnosed with APL. Twenty-eight patients (13%) died within the first 30 days of admission. On univariable analysis, male sex (P=0.001), presenting WBC ≥10 × 10^9/L (P=0.001) and presenting fibrinogen concentration <1.5 g/L (P=0.02) were associated with a higher risk of early deaths within 30 days of admission. On multivariable analysis, male sex (P=0.01), presenting WBC ≥10 × 10^9/L (P=0.02) remained significant. Taking into account early deaths, the 5-year OS was 67.7%. Prognostic factors for worse OS included male sex (P=0.01), age ≥65 (P=0.008) and presenting WBC ≥10 × 10^9/L (P<0.001). On multivariable analysis, all these factors remained significant prognostic factors for OS.

Conclusion: Sex and presenting haematological parameters (WBC, platelet count and fibrinogen concentration) are important factors predicting early deaths in APL. Efforts have to be made in correcting the adverse haematological parameters at presentation.

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Polo-like kinase 4 inhibitor suppresses hepatocellular carcinoma through inducing extensive polyploidy and activating STING pathway

CY Chan[1], VW Yuen[1], DK Chiu[1], C Goh[1], K Thu[2], DW Cescon[2], I Soria-Bretones[2], DC Law[1], JW Cheu[1], D Lee[1], AP Tse[1], KV Tan[3], MS Zhang[1], BP Wong[1], PL Khong[3], IO Ng[1,4], TC Yau[4,5], MR Bray[2], TW Mak[2], CC Wong[1,4]
[1]Department of Pathology, The University of Hong Kong, Hong Kong
[2]The Campbell Family Institute for Breast Cancer Research, Princess Margaret Cancer Center, Toronto, Canada
[3]Department of Diagnostic Radiology, The University of Hong Kong, Hong Kong
[4]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong
[5]Department of Medicine, The University of Hong Kong, Hong Kong

Introduction: Aneuploidy is a typical feature in cancer cells, including hepatocellular carcinoma (HCC). A centrosome duplication regulator, polo-like kinase 4 (PLK4), is overexpressed in HCC, and is closely associated with mutations/deletions in p53 and phosphatase and tensin homolog (PTEN). Dysregulation of these two cell cycle checkpoint regulators leads to chromosome mis-segregation and aneuploidy. CFI-400945, a novel orally available PLK4 inhibitor, was shown effective in suppressing growth of other solid tumour types, including breast and pancreatic cancer. We are interested to know its effectiveness in HCC model.

Methods: Cell cycle profiles were analysed by flow cytometry analysis using propidium iodide (PI) staining. Liver specific p53/PTEN knockout HCC models were established by hydrodynamic injection of plasmids encoding CRISPR-Cas9 and transposon systems. Infiltrated immune cell populations in tumours were analysed by flow cytometry. Transcription factors were identified by ChIP assay. Expression of senescence-associated secretory phenotypes (SASPs) was studied by transcriptome sequencing, RT-qPCR, and ELISA.

Results: CFI-400945 selectively targeted proliferating HCC cells by blocking centrosome duplication, causing severe aneuploidy, DNA damage, and senescence. Interestingly, CFI-400945 suppressed cell division without stopping DNA replication, leading to a large amount of cytosolic DNA accumulation which elicits cytosolic DNA sensing pathway DDX41-STING-IRF3/7-NFkappaB, thereby driving the transcription of SASPs which are the secretory factors that recruit immune cells. CFI-400945 significantly impeded HCC tumour growth in vivo and altered the immune landscape inside tumours, increased tumour infiltration of CD4+, CD8+ T cells, macrophages and natural killer cells. The effect of CFI-400945 in tumour suppression was alleviated in STING-knockout HCC. Due to the increased number of immune infiltrates caused by CFI-400945, combination therapy of CFI-400945 with anti-PD-1 or anti-PD-L1 antibody further prolonged survival of HCC-bearing mice.

Conclusion: CFI-400945 dramatically suppressed HCC progression through deregulating the cell cycle and activation of the STING pathway, which is originally an integral component of the antiviral immune response. We demonstrated a novel therapeutic approach by targeting a centrosome regulator to activate the cytosolic DNA sensing mediated immune response. It will directly benefit the development of clinical trials involving CFI-400945 in HCC treatment.

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Fibroblast growth factor 21-Sirtuin3 mediates cardioprotective effects of exercise by governing mitochondrial integrity in diabetic mice

LG Jin[1,2], LL Geng[1,2], L Ying[2,3], RY Yang[1,2], X Jiang[1,2], WH Woo[2,3], AM Xu[1,2,3]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong
[3]State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Hong Kong

Introduction: Although exercise is an effective non-pharmacological strategy for the prevention and treatment of DCM, the underlying molecular mechanisms remain poorly understood. Fibroblast growth factor 21 (FGF21), a peptide hormone with multiple salutary effects on cardiometabolic complications, has been identified as an exercise-responsive factor. Nevertheless, the roles of FGF21 in cardiac function under exercise intervention have not yet been explored. This study aimed to investigate whether FGF21 signalling is involved in exercise-induced improvement in cardiac function in diabetic mice.

Methods: Global FGF21 knockout (KO) and wild-type (WT) diabetic mice were subjected to treadmill running for 6 weeks. Cardiac mitochondria were isolated after measurement of heart function. Muscle-specific beta-klotho (KLB, the co-receptor of FGF21) knockout and WT diabetic mice were also performed exercise training to address the role of FGF21 signalling in the protective effects of exercise on diabetic hearts.

Results: Treadmill exercise significantly alleviated diabetes-induced impairments of cardiac function in WT mice, whereas such a cardiac protective role of exercise was abrogated in FGF21 KO mice. Histological and biochemical analyses additionally revealed that exercise improved diabetes-induced mitochondrial dysfunctions in the hearts of WT mice, whereas FGF21 KO mice were resistant to such beneficial effects of exercise on mitochondrial integrity. Furthermore, muscle KLB KO mice were also refractory to the cardio-protective effects of exercise on diabetic heart, suggesting FGF21 signalling is essential for exercise-induced improvement of diabetic cardiomyopathy. We next identified the critical mitochondrial deacetylase Sirtuin3 (SirT3) was selectively downregulated in FGF21 KO mice under exercise intervention. Restoration of cardiac Sirt3 by using adeno-associated virus 9 (AAV9) vectors alleviated mitochondrial dysfunction and diabetic cardiomyopathy in FGF21 KO mice, which suggests cardiac Sirt3 is obligatory for beneficial effects of FGF21 on cardiac function.

Conclusion: Our study uncovers a novel role of FGF21-SirT3 signalling cascade for exercise-induced cardiac benefits via improvements of mitochondrial integrity.

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90 Effect of fine particulate matter (PM2.5) collected in Hong Kong on mitochondrial permeability transition pore in human airway epithelial cells

YM Liang[1,2], PH Chu[1], LW Tian[3], KF Ho[4], MSM Ip[1,2], JCW Mak[1,2,5]
[1]Department of Medicine, The University of Hong Kong, Hong Kong
[2]Shenzhen Institute of Research and Innovation, The University of Hong Kong, Hong Kong
[3]School of Public Health, The University of Hong Kong, Hong Kong
[4]Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong
[5]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong

Background: Air pollution has been considered as the most significant environmental risk factor to human health. Fine particulate matter with aerodynamic diameter <2.5 μm (PM2.5) can penetrate into the lung reaching the large and small airways and even alveoli, causing adverse effect on the respiratory system. Our previous findings demonstrated the mitochondrial toxicity induced by PM2.5 exposure in airway cells. Recently, strong evidence is emerging that mitochondrial permeability transition pore (mPTP) may be important in certain physiological conditions and in the processes of cell damage and death. Thus, we aimed to study the effect of PM2.5 on mPTP in BEAS-2B cells.

Methods: Atmospheric PM2.5 samples were collected by 47-mm Teflon filters using Desert Research Institute portable mid-volume samplers in the road site of Hong Kong. Human bronchial epithelial cell line BEAS-2B cells were cultured until 80% confluent. After arrest, cells were treated with different concentrations of PM2.5 samples to examine the ultracellular structure, intracellular calcium content, protein expressions of mPTP and apoptosis.

Results: PM2.5 exposure caused mitochondrial swelling and structural damage on cristae from TEM images. In parallel, PM2.5 treatment significantly increased intracellular calcium content in a dose-dependent manner, which was accompanied by the upregulation of the major mPTP component voltage-dependent calcium channel (VDAC) expression as well as cell apoptosis.

Conclusion: The current data suggest that exposure to PM2.5 collected in Hong Kong may cause mitochondria-mediated apoptosis via promoting mPTP opening.

Acknowledgement
This study was supported by the Hong Kong Lung Foundation Research Grant Award (2017-2018) and National Natural Science Grant of China Grant (NSFC 81870038).

91 Nicotinic acetylcholine receptor subunit alpha 7 mediates cigarette smoke-induced PD-L1 expression in human bronchial epithelial cells

HH Kwok[1], B Gao[2], NCM Lee[1], J Deng[1], MSM Ip[1], JD Minna[2], DCL Lam[1]
[1]Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[2]Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center at Dallas, Texas, United States

Introduction: Tobacco smoking is the top risk factors for lung cancer. Nicotine in cigarette smoke can induce addiction, and its derivatives could be potent carcinogens after metabolic activation. Lung cancer from smokers usually showed higher PD-L1 expression levels and appeared to be more responsive than non-smokers to immune-checkpoint inhibitors. This study aimed to investigate whether activation of nicotinic acetylcholine receptor subunit α7 (nAChRα7) expression would induce PD-L1 expression.

Methods: Expression levels of nAChRα7 and PD-L1 in eight human bronchial epithelial cell lines (HBECs) were measured after treatment with cigarette smoke extract (CSE) or nicotine derivative.

Results: nAChRα7 was highly expressed in lung squamous cell carcinoma tissue as well as in normal lung tissue from smokers. PD-L1 expression levels increased in HBECs after exposure to CSE and nicotine derivative. This induction of PD-L1 expression by CSE could be diminished by nAchRα7 small-interfering RNA, with relevant signalling mediated via STAT3 phosphorylation or NRF2 expression. This study demonstrated the linkage on the well-known nicotine derivative-activated nAChRα7-induced STAT3/NRF2 pathways and revealed PD-L1 as the downstream signalling target in normal lung epithelial cells.

Conclusion: This may provide insight into the possible mechanism of cigarette smoke-induced pre-cancerous immune invasion mediated through nicotine and its derivative, with activation of nAChRα7-induced STAT3/NRF2 pathways leading to cellular growth and proliferation.

Acknowledgement
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CMF-019 elevates neuronal insulin sensitivity: an implication of therapeutic potential of Alzheimer's disease

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OKF Ma, KH Chan, RCL Ng
Department of Medicine, The University of Hong Kong, Laboratory Block, Hong Kong

Introduction: Increasing evidence has demonstrated the association between neuronal insulin resistance and Alzheimer's Disease (AD) pathogenesis. Neuronal insulin resistance not only enhances the activity of γ-secretase, A β production and secretion, but also induces the activation of GSK3β, which associates with Tau phosphorylation and aggregation. Recent studies have reported that Apelin can increase glucose uptake by promoting GLUT4 translocation and restore insulin sensitivity of TNFα-induced insulin resistance via activating PI3K/AKT and ERK1/2 signalling pathways. Hence, we will study if a novel invented Apelin receptor (APJ) agonist, CMF-019 can restore the neuronal insulin sensitivity and its potential effects as a therapeutic treatment of AD.

Methods: For in vitro study, insulin-induced insulin resistance (IR) hippocampal cells (HT22) were pre-treated with CMF-019 for 2 hr and cultured with 10 nmol/L insulin for 30 min. Insulin-signalling molecules and its corresponding phosphorylation were measured by western blot analysis. For in vivo study, the pharmacokinetics of CMF-019 was quantitatively determined in the mice plasma and brain after feeding each mouse orally with CMF-019.

Results: The results showed that CMF-019 pretreatment alleviated the insulin sensitivity of insulin-induced IR HT22 cells by increasing the level of Akt phosphorylation. However, the level of pERK1/2 did not show any significant difference upon CMF-019 pre-treatment. CMF-019 was able to be detected by the LC-MS/MS in the plasma and the brain of CMF-019-oral administrated mice.

Conclusion: APJ agonist, CMF-019, elevated insulin sensitivity through PI3K/AKT activation, but not ERK1/2 signalling pathway. In addition, the penetration of CMF-019 across the blood-brain-barrier may implicate the therapeutic potential of CMF-019.

Acknowledgement
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Serum beta-2 microglobulin level and the risk of cardiovascular events in Hong Kong Chinese patients

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RYH Leung, LYF Wong, KCY Kong, CL Cheung, EYT Chan, SH Tsui, SW Lee, BMY Cheung
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: Beta-2 microglobulin (B2M) is a marker of renal dysfunction and inflammation. We previously showed a significant association between serum B2M and acute coronary syndrome (ACS)[1]; whether serum B2M level predicts future cardiovascular events remained to be demonstrated. In this prospective cohort study, we aimed to investigate the relationship between serum B2M levels and the risk of cardiovascular events.

Methods: 127 Hong Kong Chinese patients (64 ACS and 63 control subjects; 88 men and 39 women; mean age±standard deviation, 66±12 years) were enrolled between 2015 and 2016.[1] Cardiovascular events were ascertained using the Hong Kong Hospital Authority Clinical Data Analysis and Reporting System. Serum B2M was measured at baseline, and its association with incident cardiovascular events was evaluated using multivariable Cox proportional hazards regression.

Results: During 561.3 person-years of follow-up (median 4.6 years), 45 participants had a cardiovascular event, including two cardiovascular-related deaths. The mean serum B2M level was 2.23±1.12 μg/mL. Age-sex-adjusted Cox proportional hazards regression showed that serum B2M levels were associated with increased risk of cardiovascular events (hazard ratio [HR]=1.40; 95% confidence interval [CI]=1.14-1.73). The association remained statistically significant after further adjustment for hypertension, diabetes, hyperlipidaemia, stroke, renal function and smoking (HR=1.17; 95% CI=1.10-2.66). A similar association was observed in ACS patients in the age-sex-adjusted and fully adjusted model (HR=1.36; 95% CI=1.04-1.72 and HR=2.53; 95% CI=1.141-5.591, respectively). In control subjects, a significant association was only observed in the age-sex adjusted model (HR=2.48; 95% CI=1.33-4.61) but not in the fully adjusted model.

Conclusion: Increased serum beta-2 microglobulin was significantly associated with incident cardiovascular events in Hong Kong Chinese. We have shown that this familiar marker has a novel use as a marker of cardiovascular risk.

Acknowledgement
This study was supported by a Seed Funding for Basic Research Grant from The University of Hong Kong.

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Serum adipocyte fatty acid-binding protein level predicts heart failure hospitalisation in type 2 diabetes: a prospective cohort study

AKC Kan, CH Lee, DTW Lui, CHY Fong, MMA Yuen, WS Chow, YC Woo, A Xu, KSL Lam
Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong

Introduction: The association between circulating adipocyte fatty acid-binding protein (AFABP) levels and heart failure (HF) in type 2 diabetes has not been clearly defined. We conducted this prospective study to evaluate the association of circulating AFABP levels with incident HF hospitalisation in type 2 diabetes, and its relationship to the use of sodium glucose co-transporter 2 inhibitors (SGLT2i).

Methods: Baseline serum AFABP levels were measured in 3322 participants without known cardiovascular diseases or HF recruited from the Hong Kong West Diabetes Registry. The association of baseline serum AFABP levels and incident HF hospitalisation was evaluated using multivariable Cox regression analysis, with the use of SGLT2i included as a time-dependent covariate.

Results: Over a median follow-up of 8 years, 176 (5.3%) participants developed HF hospitalisation, while 731 (22%) were commenced on SGLT2i during the study period. In multivariable Cox regression analysis, baseline log-transformed serum AFABP level was significantly associated with incident HF hospitalisation (hazard ratio [HR]=1.39; P=0.015), independent of the use of SGLT2i and other conventional HF risk factors. High cumulative defined daily dose of SGLT2i was protective of incident HF hospitalisation (HR=0.10, P=0.019), and a dose-dependent reduction in cumulative incidence of HF hospitalisation in response to SGLT2i was more clearly observed in participants with a higher baseline AFABP level above the sex-specific median (P for trend <0.01).

Conclusion: Circulating AFABP level is independently associated with incident HF hospitalisation in type 2 diabetes and could potentially be used as a biomarker for better risk stratification for the prevention of HF hospitalisation.

Acknowledgement
This work was supported by the Health and Medical Research Fund (Ref. 14150781).

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Relationship of HLA-B*15:11 allele in carbamazepine-induced cutaneous adverse drug reactions in HLA-B*15:02-negative patients

SM Wong[1], P Ip[2], WHS Wong[2], GT Chua[2], HHL Chan[1], CK Yeung[1], DYH Yap[3], JSY Kwok[4]
[1]Division of Dermatology and Venereology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong
[2]Department of Paediatrics and Adolescent Medicine, Department of Medicine, The Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[3]Division of Nephrology, Department of Medicine, The Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong
[4]Division of Transplantation and Immunogenetics, Department of Pathology, The University of Hong Kong, Queen Mary Hospital, Hong Kong

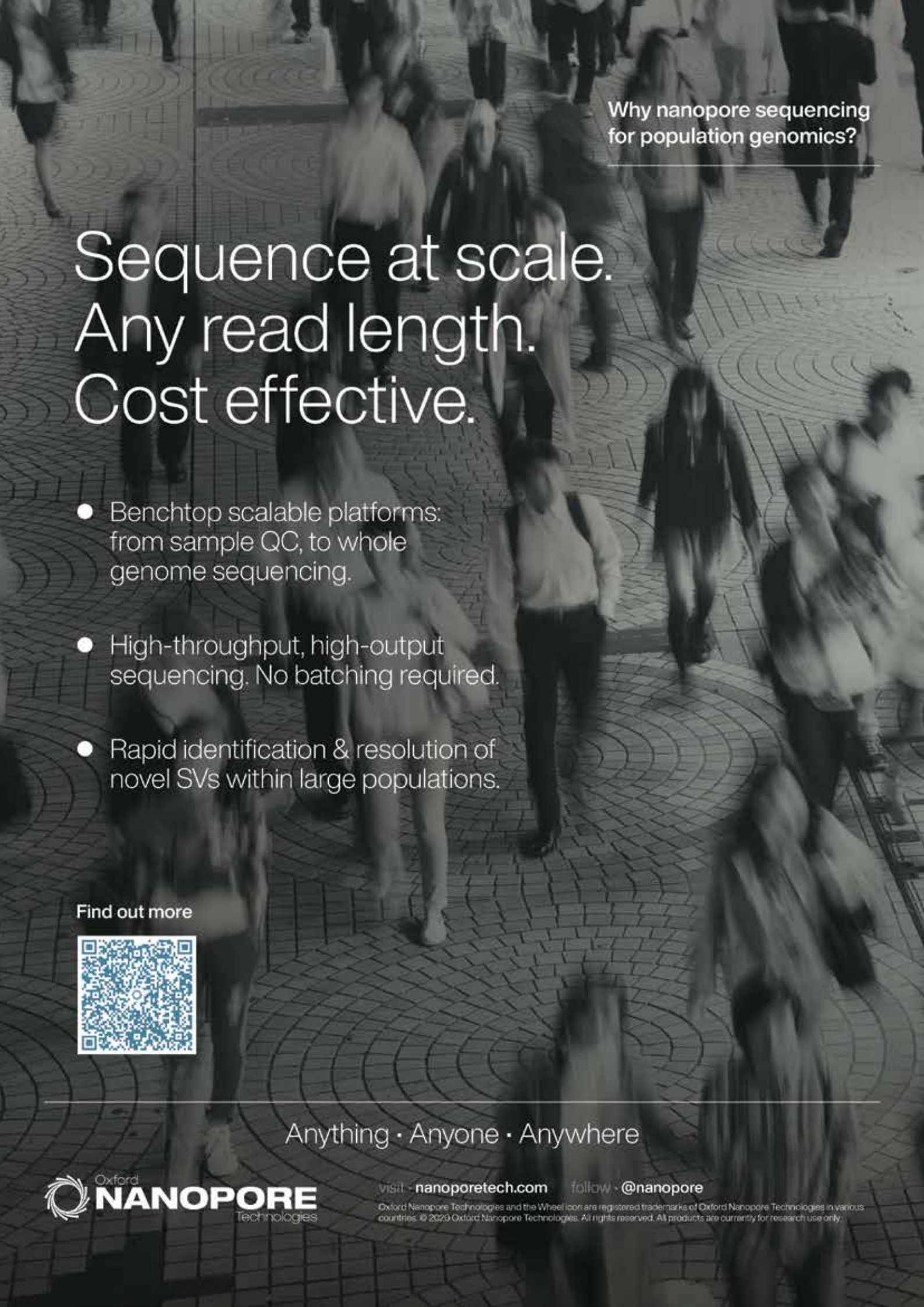
Introduction: HLA-B*15:02 showed a strong link with carbamazepine (CBZ)-induced SJS/TEN in Han Chinese population. Despite avoidance of carbamazepine in HLA-B*15:02-positive patients are advised, CBZ-induced cutaneous adverse drug reactions (cADRs) are still observed in those HLA-B*15:02-negative individuals. It is worth to examine whether cADRs can be related to other genetic predisposition. The presence of HLA-B*15:11 allele has been reported with CBZ-induced SJS/TEN in other populations. This study aimed to study the incidence of cADRs in HLA-B*15:02-negative Chinese patients and its relationship with other HLA allele, in particular, HLA-B*15:11 status and CBZ consumption.

Methods: Blood samples collected from Chinese patients between 2014 and 2019 for HLA-genotyping before CBZ prescription were further screened for B*15:11 status. Electronic medical records were reviewed and the incidence of cADRs was compared between patients who had or had not been prescribed CBZ.

Results: 8328 blood samples were analysed: 1416 (17%) and 6912 (83%) were HLA-B*15:02-positive and -negative, respectively, and 71/6912 (1.03%) were HLA-B*15:11-positive. Of these 71 HLA-B*15:11 carriers, one non-Chinese sample was excluded, 23 (32.4%) patients were given CBZ and 47 (66.2%) patients were given AEDs other than CBZ. In CBZ group, four (17.4%) patients developed CBZ-induced cADRs. One SJS and 1 DRESS with generalised maculopapular exanthema (MPE), deranged liver function and eosinophilia, one MPE and one urticaria were identified. The mean duration of CBZ use before onset of rash was 11.8 days. The median hospital stay was 7 days. Among 47 patients given AEDs other than CBZ, one (2.13%) patient developed MPE after phenytoin use. HLA-B*15:02-negative Chinese patients with HLA-B*15:11-positivity is more likely to develop adverse cutaneous reaction with CBZ consumption than the control group without (P=0.019; OR=9.68 [95% confidence interval=1.02-92.4; P=0.039*, two-tailed]).

Conclusion: Determination of HLA-B*15:11 status shall be performed before use of CBZ in HLA-B*15:02-negative Chinese patients to minimise the possible risk of cADRs.

AUTHOR INDEX



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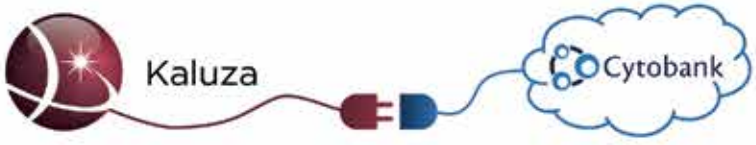

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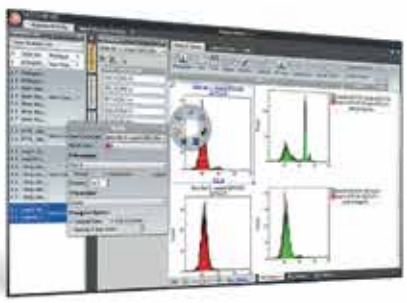

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Reference: 1. Zinman B, et al. N Engl J Med. 2015;373(22):2117-2118. **2.** Jardiance Hong Kong Prescribing Information. **3.** Davies MJ, D'Alessio DA, Fradkin J,et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018.

† JARDIANCE demonstrated RRR in CV death in adult patients with insufficiently controlled type 2 diabetes (baseline HbA1c 7-10%) and established CV disease (coronary artery disease, peripheral artery disease, or a history of myocardial infarction or stroke).

‡ Standard of care included CV medications and glucose-lowering agents given at the discretion of physicians.[1]

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