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The impact of substance abuse on healthcare resource utilization: Big data analytics using the clinical data in Hong Kong

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Objectives: The study aimed to assess the differences in healthcare resource utilization between patients with and without a history of substance abuse. The number of Accident and Emergency (A&E) attendances and hospitalizations, as well as the length of hospital stay were evaluated.

Methods: A population-based cohort study using the Clinical Data Analysis and Report System (CDARS) database was conducted. Patients with a diagnosis of substance abuse, who presented to the A&E department in Hong Kong public hospitals, between 2004 and 2016 were identified. A random sample of patients without a history of substance abuse was used as a comparison group. Propensity score matching with a 1:1 ratio was performed to adjust for confounders, including sex, age, recent (≤365 days before the index date) hospital attendances, and concurrent medical conditions. T-test and Wilcoxon test were employed to assess the differences in healthcare resource utilization between the two comparison groups.

Results: Among the 8,423 patients with substance abuse, 6,627 patients were matched by propensity score. Compared to the patients without substance abuse, those with substance abuse had a higher number of A&E attendances (7.49 versus 3.07, P<0.001) and hospitalizations (8.49 versus 6.16, P<0.001), and longer length of hospital stay (27.62 days versus 8.46 days, P<0.001).

Conclusion: Substance abuse was associated with significantly greater healthcare resource utilization, including a higher number of A&E attendances and hospitalizations, and the longer length of hospital stay, compared with patients without substance abuse. Interventions to support and treat patients with substance abuse may help reduce A&E department attendances and hospitalizations in this vulnerable patient group.

Keywords: substance abuse, healthcare resource utilization, propensity score matching

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Understanding patients with substance abuse and their healthcare pathway by using bigdata approach: Towards better management in Hong Kong

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Aim/Objective: Describing the demographic and clinical profiles of patients with substance abuse in Hong Kong to provide insight for the government to guide the development of evidence-based interventions for this population.

Methods: A descriptive study was conducted using a cohort of 8,423 patients with a diagnosis of substance abuse. Patients who presented to the Accident and Emergency (A&E) department in Hong Kong public hospitals, between 2004 and 2016 were identified from Clinical Data Analysis and Report System (CDARS) databases. The demographic and clinical profiles of the patients, in addition to trends of their A&E attendances and hospitalizations due to substance abuse were described.

Results: The overall trend of substance abuse was a “M” shape curve with two peaks around year 2007 and 2012. Of all patients, 71.8% were men with mean age of 36.7 years, and 28.2% were women with mean age of 33.2 years. About 9.8% of patients were adolescents (<21 years). Among women, 5% abused substances during the period of one year prior to pregnancy and one year after delivery. The most frequently abused substance among the A&E cases were opioids (2,395 cases, 27.1%), followed by ketamine (2,177 cases, 24.6%), barbiturate/hypnotics (656 cases, 7.4%), amphetamines (592 cases, 6.7%) and cocaine (181 cases, 2%). The percent of patients with at least one substance abuse related A&E re-attendance was 19.5%. The mean number of A&E attendance for all patients was 1.93. Approximately 30% of patients with substance abuse had concurrent mental disorders. Totally, 188 patients died due to heroin and opioids abuse, which was 17.7% of total deaths.

Conclusions: Although substance abuse has been in a downward trend since 2012, it is still an issue for special groups including adolescents and childbearing age women in Hong Kong. Opioids and ketamine were the two main perpetrators of substance abused.

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The effects of more restrictive scheduling in 2018 on subsequent codeine use and harms in Australia

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Aim: Codeine is the most used opioid globally. Reports of codeine misuse, dependence, and harms, are common, particularly in countries where it is available without a prescription. In Australia, low dose codeine could be purchased over-the-counter (without prescription) until its up-scheduling to "Prescription Only" in February 2018. We aimed to evaluate the effect of this intervention on codeine use and misuse, including substitution of high-strength codeine products and other pharmaceutical opioids.

Methods: This is a retrospective study of calls to the New South Wales Poisons Information Centre (NSWPIC, captures 50% of Australia's poisoning calls), a 10% sample of dispensings subsidised through the Pharmaceutical Benefits Scheme (PBS), and national codeine sales data. We used an interrupted time series analysis to quantify the monthly change in NSWPIC cases, PBS dispensings and codeine sales. We used segmented linear regression adjusted for autocorrelation and seasonality as necessary.

Results: Prior to up-scheduling NSWPIC received a mean of 167.1 calls per month about codeine. Up-scheduling resulted in a sudden drop of 69.2 calls/month (95% CI -92.9 to -45.5, P<0.001), but no increase in calls regarding high-strength codeine products (which have always been prescription only). We found a 20.4% increase (95%CI, 17.9-22.8%) in subsidised dispensings of high-strength codeine products following the intervention, with the largest increase in females 18-64 years. There was a 2.9% increase (95%CI, 0.1-5.8%) in tramadol dispensings; but no changes in the dispensing of other pharmaceutical opioids. Sales of low strength codeine products decreased by 87.3% (95%CI, -88.5 to -85.9%), with no increase in higher strength codeine sales.

Conclusion: Codeine up-scheduling appears to have reduced use and poisonings. The modest increase in dispensing of higher strength products was not accompanied by increased overdoses with these products. These findings provide evidence of the effectiveness of this policy intervention in curbing harms from pharmaceutical misuse.

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Transition to high-dose or strong opioids: A population-based study of people initiating opioids in Australia

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Objective: To determine the rate and predictors of transitioning to high-dose or strong opioids among people initiating opioids.

Methods: People initiating opioid analgesics from July 2013-January 2018 were identified from a random 10% sample of dispensing records from Australia's Pharmaceutical Benefits Scheme. Hazard ratios (HR) and 95% confidence intervals (CIs) were estimated for the predictors of escalating to ≥50 mg OME/day (Cohort 1); ≥90 mg OME/day (Cohort 2), and transitioning to strong opioids (Cohort 3) over 12-months follow-up. Predictors included age, sex, number of comorbidities, history of cancer and depression and selected prior medication use.

Results: In total, 861,691 people initiated opioids at average doses <50mg OME/day (Cohort 1), 874,401 at <90mg OME/day (Cohort 2) and 603,884 initiated weak opioids (Cohort 3). Overall, 1.4% of people escalated to doses ≥50mg OME/day, 0.8% to doses ≥90mg OME/day, and 7.3% transitioned to strong opioids. The strongest predictors of transitioning included having cancer (Cohort 1:HR=3.19, 95%CI 3.00-3.40; Cohort 2:HR=4.19, 95%CI 3.90-4.51; Cohort 3:HR=2.07, 95%CI 1.95-2.18) and age ≥75 years (Cohort 1:HR=3.04, 95%CI 2.73-3.38, Cohort 2:HR=2.51, 95%CI 2.17-2.89; Cohort 3:HR=1.88, 95%CI 1.80-1.96). Females transitioned less rapidly (Cohort 1:HR=0.79, 95%CI 0.76-0.82; Cohort 2:HR=0.70, 95%CI 0.66-0.73; Cohort 3:HR=0.95, 95%CI 0.93-0.96).

Conclusion: More than one in every 13 people initiating weak opioids transition to strong opioids. By extrapolation, our results suggest >26,000 Australian adults initiating opioids escalate to high-doses each year. People with cancer, older people and males transition more rapidly.

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A spatial-temporal analysis of adverse drug reactions due to opioid analgesic use in New South Wales

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Aims: to investigate the geographical disparity in hospitalised adverse drug reactions (ADRs) due to opioid analgesic use.

Methods: We used the all-inclusive Admitted Patient Dataset for an Australian state (New South Wales, NSW) to select patients admitted for opioid-related ADRs over a 10-year period (July 2004 to June 2014). A space-time analysis was conducted using Kulldroff's scan statistics to identify statistically significant spatial clusters over time. Relative risk (RR) was computed with p-value based on Monte Carlo Simulation. Chi-square test was used compare proportional difference in patient clustering.

Results: During the study period, we identified four statistically significant geographic clusters during 2004-08; and seven clusters during the period 2009-14. While identified high-risk clusters primarily covered areas with convenient access to health services, those associated with socioeconomic disadvantaged residents and people with mental health disorders experienced more unmet healthcare needs of opioid analgesic safety than those from the rest of the state. Older people aged 65 year and over were more susceptible than younger people to opioid-related ADRs. While the identified clusters comprised proportionally more cancer patients during the first 5-year period, there appeared proportionally less cancer patients during the second 5-year period.

Conclusions: These results suggest that there is significant spatial-temporal variation in opioid-related ADRs, and future interventions should target vulnerable populations and high-risk geographical areas to improve safer use of pharmaceutical opioid analgesics.

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Trend in targeted therapy in patients with rheumatoid arthritis in Korea: A time-series analysis using nationwide health insurance data, 2010-2017

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Aim/Objective: With the 2013 update of the clinical guidelines for rheumatoid arthritis (RA), all biologic agents with different mechanisms of action were recommended as first-line targeted therapy on top of tumor necrosis factor inhibitors (TNFi). We aimed to describe the trend of targeted therapy for RA before and after the guidelines update.

Methods: Time-series analysis was conducted using the Health Insurance Review and Assessment Service-National Patient Samples database. RA patients who received study drugs at least once in each year between 2010 and 2017 were included. Study drugs were categorized as TNFi (adalimumab, etanercept, infliximab, and golimumab) and non-TNFi (abatacept, rituximab, tocilizumab, and tofacitinib). Trends in targeted therapy were assessed before (2010-2013) and after (2014-2017) the clinical guidelines update using the absolute difference in patients with 95% confidence intervals (CI).

Results: Of the 97,399 RA patients, 1,449 received targeted therapy (1.49%) during 2010-2017. Patients with targeted therapy for RA increased from 0.80% (98 out of 12,252 RA patients) in 2010 to 2.81% (322 out of 11,427 RA patients) in 2017. Of them, TNFi decreased from 95.38% in 2010-2013 to 62.69% in 2014-2017, whereas non-TNFi increased from 5.45% in 2010-2013 to 37.95% in 2014-2017. Decreasing trends were observed in TNFi; etanercept with absolute difference of -27.21% (95% CI, -32.14% to -22.28%) and adalimumab with -13.79% (95% CI, -17.98% to -9.60%). In contrast, non-TNFi showed increasing trends; tocilizumab with absolute difference of +20.16% (95% CI, +18.68% to 21.64%) and abatacept with +11.28% (95% CI, +9.47% to 13.08%).

Conclusion: In this time-series analysis of targeted therapy for RA from 2010 to 2017, the dramatic increase in non-TNFi beyond the generally growing trend was observed after the 2013 clinical guidelines update. Guidelines update may have affected physician's choice in selecting non-TNFi as the first targeted therapy.

Keywords: rheumatoid arthritis, drug utilization, targeted therapy, time-series

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Assessment of impact of different instructional interventions in training on inhalers amongst asthma and COPD patients

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Introduction: Asthma and COPD are the chronic respiratory diseases which effects millions of people all around the world and only 10% of patients use their inhalers correctly. This has led to poor medication adherence and reduced quality of life.

Objective: The aim of study was to assess the impact of various instructional interventions in improving proper inhaler techniques amongst asthma and COPD patients.

Methods: A randomized, interventional study was led by clinical pharmacist over a period of 9 months in the department of pulmonology in a teaching hospital. Patient information leaflets (PIL), video demonstrations were prepared in vernacular languages and validated using Bayer Able Leaflet Design scores. Pre & Post counseling checklist scores were transcribed into data collection forms. T-test and One-way ANOVA statistical methods were employed while treating the data.

Results: Out of 352 study participants screened, 210 (60%) were enrolled. Majority [95 (46%)] of patients were elderly and were on meter dosed inhalers (MDI) with spacers [125 (60%)]. These patients were randomised into three arms i.e. PIL [71 (34%)], video demonstration [57 (27%)], and clinical pharmacist counselling [82 (39%)]. There was a significant improvement in the check list scores amongst the patients who had clinical pharmacist counselling {[(MDI alone - 8.1 ± 1.6 vs. 10.8 ± 0 .4), (MDI with spacer - 7.7 ± 2.2 vs. 11.6 ± .72)]} followed by video demonstration {[(MDI alone -7.4 ± 2.0 vs 9.7 ± 1.3), (MDI with spacer 7.3 ± 2.1 vs. 10.2 ± 1.5)]} $P < 0.001$. Similarly, Rotahaler Lupihaler and Revoliser had improved utilisation with Clinical pharmacist's direct intervention (9.0 ± 0.0, 10.4 ± 0.5, and 10.0 ± 0.0 $P < 0.001$, respectively.), followed by video demonstration and PILs had least impact.

Conclusion: Pharmacist direct instruction had more impact on study participants compared to other interventions. Having CP in healthcare teams will improve adherence and improve health outcomes.

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Impact of clinical pharmacist-led education on clinical and humanistic outcome of children with Thalassemia: A randomized control study

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Aim: To assess the impact of clinical pharmacist-led education on clinical outcome, health related quality of life (HRQoL), knowledge, attitude and practice (KAP), and medication adherence of children with Thalassemia.

Methods: A prospective randomized single blind parallel group study was conducted at the Pediatric Hematology clinic of a tertiary care hospital over a period of one year. Established diagnosis of thalassemia and receipt of regular red blood cells transfusion from the study site were the inclusion criteria of the study. Thalassemia patients with any associated chronic disease were excluded. All the eligible subjects were randomized by block randomization method to intervention and control group. Baseline HRQoL using Pediatric Quality of Life (PedsQoL) questionnaire, KAP and medication adherence was assessed for all the study subjects and their treatment chart was reviewed to identify any drug related problems (DRPs). Interventional group received educational on thalassemia during the first, second (6 weeks ±3 days) and third visits (12 weeks ±3 days) using a standardized education material. During fourth visit (18 weeks ±3 days), HRQoL, KAP, Medication adherence and DRPs were reassessed.

Results: Out of 60 thalassemia patients visiting the study site, 48 children met the study criteria and were randomized into intervention (n=23) and control group(n=25). There was significant improvement in the HRQoL of all domains [physical (p=0.001), social (p=0.001), and school(p=0.001)] except emotional (p=0.34) among the intervention group. KAP and medication adherence of the intervention group also showed a significant improvement with a p value of 0.001 for each category compared to control group. The number of drug related problems was also significantly reduced in intervention group (p=0.031) when compared to control group (p=0.062).

Conclusion: Clinical pharmacist-led education can improve the clinical outcome, HRQoL, KAP and medication adherence of children with Thalassemia.

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Reducing medication burden in residential aged care: SImplification of Medications Prescribed to Long-tErm care Residents (SIMPLER) cluster randomised controlled trial

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Aim/objective: Complex and burdensome medication regimens are common in residential aged care facilities (RACFs). The objective of the SImplification of Medications Prescribed to Long-tErm care Residents (SIMPLER) cluster randomised controlled trial was to assess a structured process to consolidate the number of medication administration times.

Method: A non-blinded, matched-pair, cluster randomised controlled trial was undertaken in eight RACFs in South Australia. Trained research nurses recruited a representative sample of permanent residents. The intervention involved a clinical pharmacist applying the Medication Regimen Simplification Guide for Residential Aged CarE (MRS GRACE) in four intervention RACFs. MRS GRACE is a new five-step tool to reduce medication complexity (e.g. by administering medications at the same time, or through use of longer-acting or combination formulations). Residents in the four comparison RACFs received routine care. The primary outcome was the number of daily medication administration times four months post study entry. Analyses were undertaken using generalised linear mixed models with the RACF as a random effect.

Results: Overall, 242 residents were recruited (n=99 in the intervention arm), of whom 179 (74%) were female and the median age was 87 years. Applying MRS GRACE, the clinical pharmacist identified opportunities for medication regimen simplification for 62 (65%) residents in the intervention arm. At four months post study entry, 57 (62%) of 92 pharmacist recommendations were implemented. The mean number of resident medication administration times was reduced in the intervention arm in compared to those in the comparison arm (-0.36, 95% confidence interval (CI) -0.63 to -0.09, p=0.01).

Conclusion: Application of a new implicit 5-step tool to consolidate the number of medication administration times can reduce medication regimen complexity in RACFs.

Trial registration number. Australian New Zealand Clinical Trials Registry, ACTRN12617001060336.

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Efficacy of anti-emetic regimen in chemotherapy induced nausea vomiting and its impact on quality of life in pediatric cancer population

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Objective: Chemotherapy Induced Nausea Vomiting (CINV) is the most common side effect of cancer chemotherapy and CINV in children has a profound impact on their Quality Of Life (QoL). This study evaluated the efficacy of standard anti-emetic regimen for CINV and its impact on the QoL in paediatric cancer patients and their parents.

Methods: The study was done in the Paediatric Oncology division of a tertiary care hospital. Data was obtained from paediatric patients of either sex, in the age group of five to eighteen years, diagnosed with cancer, receiving chemotherapy and anti-emetics for management CINV, irrespective of the number of chemotherapy cycles. Pediatric Nausea Assessment Tool (PeNAT) Questionnaire was used to assess the efficacy of anti-emetics and Pediatric Quality of Life 3.0 Cancer Module (PedsQL 3.0) age appropriate child and parent versions were used to assess the QoL of the patients and its impact on their parents after obtaining authors' permissions. The effect of anti emetics and their impact on quality of life were assessed statistically considering the probability value of <0.05 as significant.

Results: Of 95 cases with male predominance, Acute Lymphoblastic Leukemia (ALL) was the most frequently diagnosed malignancy. Dexamethasone (77%) and ondansetron (52%) had a significant advantage over other standard anti-emetics with a minimal PeNAT face scores of 2 and 3 indicating mild and moderate nausea respectively. A significant association between the PeNAT score and the PedsQL scores of children and a highly significant positive correlation between the scores of PedsQL child and parent versions ($P<0.001$) were observed, implying a consequential impact of CINV on the QoL of children and their parents.

Conclusion: The study identified that Dexamethasone had a better control of CINV and also unraveled the detrimental impact of CINV on QoL, emphasizing on the need to select an appropriate anti-emetic for optimal CINV control.

Keywords: Chemotherapy, nausea, vomiting, quality of life, pediatric cancer

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A Delphi study on the development of a risk proportionality framework for the selection of risk minimisation interventions in Asia

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Aim/Objective: Risk minimisation interventions (RMIs), frequently used in the EU and US, may not be applicable to Asian countries. This study, launched through the ISoP SIG Rmin Asia, aimed at developing explicit criteria for the evaluation of risk proportionality applicable to RMIs in Asia.

Methods: Project consisted of two phases: Consultation Phase (pre-Delphi) and Modified Delphi Study. Consultation phase involved a purposeful sample of eight experts from regions of the world with the highest experience in RMIs (EU, US, Australia, Canada, Singapore, Taiwan, Japan). In-depth interviews were conducted in order to identify key factors (criteria) used in the assessment of risk proportionality and their impact on RMIs (low, medium, high stringency interventions). Using those factors, a Delphi survey, conducted in three rounds, was used to reach consensus on a structured framework, i.e., a set of explicit criteria and associated weights (scoring system) to assess risk proportionality. Delphi panel consisted of pharmacovigilance professionals representing all target groups (regulatory, academia, industry), distributed across ASEAN countries as well as East-Asia and South-Asia.

Results: In the Consultation Phase with experts (Pre-Delphi), 28 determinants of whether a RMI is needed were identified, including amongst others, the characteristics of the adverse event (AE)(seriousness and predictability), the treated population/indication, and health care setting. The Delphi survey was sent to 43 eligible stakeholders, of whom 21 (48.8%) responded (10 regulatory, 6 industry, 5 academic). All 21 also participated in Rounds 2 and 3. After three rounds, 17 (60.7%) themes achieved consensus, 3 (10.7%) partial consensus, and 8 (28.6%) no consensus. There were 9 additional criteria proposed by participants, of which 5 achieved consensus, 1 partial consensus, and 3 no consensus.

Conclusion: Criteria associated with AE characteristics and indication achieved the greatest consensus while those associated with health care setting and economic burden achieved the least.

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The association between partner bereavement and incident psoriasis or atopic eczema: A matched cohort study

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Aim/Objective: Psychological stress is commonly reported as a risk factor for psoriasis and atopic eczema. However, epidemiological evidence for the relationship is limited by small sample sizes and difficulty measuring stress. We aim to investigate the association between partner bereavement (an extreme life stressor) and psoriasis or atopic eczema.

Methods: We conducted a matched cohort study using clinical data from the United Kingdom Clinical Practice Research Datalink between 01/01/1997 and 31/07/2017. We identified opposite-sex couples using an existing algorithm. Among eligible couples, we matched up to 10 non-bereaved people to each bereaved person on age, sex and general practice. Outcomes were the first diagnosis of psoriasis or atopic eczema. We excluded partners with a history of the relevant outcome. We used Cox regression stratified by matched set to estimate hazard ratios (HR) (complete case analysis), adjusted for Charlson Comorbidity Index, smoking, body mass index, alcohol consumption and deprivation. We further examined such associations by time since bereavement (0–30, 0–90, 0–365, 0–1095 days).

Results: For psoriasis, we identified 144,873 bereaved and 1,211,218 non-bereaved people. For atopic eczema, we identified 127,477 bereaved and 946,178 non-bereaved. We found no evidence bereavement was associated with psoriasis (HR:0.97;95% CI:0.92–1.03) or atopic eczema (HR:1.01;0.98–1.04) during entire follow-up. However, we saw a possible increase in atopic eczema risk within 0-90 days following bereavement (HR:1.16;1.00–1.33) that persisted in the first year (HR:1.13;1.05–1.21) but attenuated in 3 years following bereavement (HR:1.06;1.01–1.11). We found no evidence of an increased risk of psoriasis or atopic eczema in other periods following bereavement.

Conclusions: We found evidence that partner bereavement might be associated with short-term increased atopic eczema risk. Understanding psychological stress associated with recent atopic eczema episodes could inform prevention and improve clinical care.

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Pharmacoepidemiology methods: Past, present, and advice about the future

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The current approach to drug approval has been in place for decades, and consists of preclinical studies followed by three phases of clinical studies. However, much is left unknown in the process. These gaps are opportunities for pharmacoepidemiology. Methodologically, pharmacoepidemiology applies the methods of epidemiology to the content area of clinical pharmacology. In order to study large populations very quickly, however, special logistic approaches have been developed, especially the use of large claims and more recently medical record databases. Special methodological issues arise as well, and new approaches have been developed to address them. The history of pharmacoepidemiology will be reviewed, as well as its current approaches, and new developments. Historical and recent examples will be used. Some of the dichotomies that have emerged in the development of the field will be discussed. Finally, some personal perspectives will be provided about its future.

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Antipsychotics use during pregnancy and the risk of gestational diabetes: A population-based cohort study

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Objective: To investigate whether exposure to antipsychotics during pregnancy is associated with gestational diabetes mellitus (GDM).

Methods: We conducted a population-based cohort study using data from the Hong Kong Clinical Data Analysis and Reporting System (CDARS) which includes medical records on first pregnancies from Jan 2001 to Dec 2015. The exposed group comprised nondiabetic primiparous women who received at least two prescriptions (Rx) of antipsychotics from the last menstrual period (LMP) to delivery. We compared the risk of GDM in the exposed group with the risk in women who did not receive any antipsychotics during pregnancy using logistic regression. Potential confounding factors including age, multiple pregnancy (i.e. twins), antipsychotic treatment received during 90 days before LMP, comorbidity and district of residence were adjusted using Propensity Score stratification. We also compared the risk of GDM in the exposed group with 1) the risk in women who stopped antipsychotic treatment before LMP (pre-conception users) and 2) the risk in non-gestational users but with psychiatric disorders to minimise confounding by indication.

Results: Among 217,771 first pregnancies, we identified 550 women exposed to antipsychotics (2 or more Rx) and 48 of them developed GDM (8.73%). In the non-exposed group 10,064 women (4.65%) developed GDM. Results of the adjusted analyses suggest there is strong evidence that exposure to antipsychotics in pregnancy increases the risk of GDM (adjusted Odds Ratio [OR]: 1.393, 95% Confidence Interval [CI]: 1.026-1.891). However, there is no evidence to demonstrate a similarly increased risk when the exposed group is compared to pre-conception users of antipsychotics (adjusted OR: 1.577, 95% CI: 0.697-3.569) or non-gestational users with psychiatric disorders (adjusted OR: 0.957, 95% CI: 0.527-1.735).

Conclusion: Although a nearly forty percent increased risk of GDM was found in women exposed to antipsychotics during pregnancy, this association can be partially explained by confounding by indication.

Keywords: Pregnancy, Antipsychotics, Gestational diabetes.

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Continuation of antipsychotic medication during pregnancy and the risk of gestational diabetes: A population-based cohort study

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Objective: To investigate whether exposure to antipsychotic agents during pregnancy is associated with gestational diabetes (GDM).

Methods: We conducted a population-based cohort study using data from the United Kingdom The Health Improvement Network (THIN) database. Women with a recorded live or still birth from 1990 to 2017, who received two or more prescriptions for any type of antipsychotic from a general practitioner before their first pregnancy were included in our study cohort. GDM was defined as 1) a first record diagnosis of GDM or 2) a recorded fasting plasma glucose level of 5.6 mmol/l or above or 3) a 2-hour plasma glucose level of 7.8 mmol/l or above. The exposed group comprised women who received antipsychotics from 90 days prior to the theoretical day of conception to delivery. We measured an Incidence Rate Ratio (IRR) with a 95% Confidence Interval (CI) for the association between antipsychotic use during pregnancy and GDM using a Propensity Score weighted regression model.

Results: Among 1,177,132 first-time pregnancies in THIN, 2,351 women were identified in our study cohort. 774 women (32.92%) continued their use of antipsychotics during pregnancy and 60 of them (2.55%) developed GDM. Adjusted result shows no evidence of an association between the use of antipsychotic agents during pregnancy and the onset of GDM (adjusted IRR: 0.83, 95% CI: 0.50-1.38). Adjusted results of subgroup analyses suggest there is some evidence of a decreased risk of GDM in users of typical antipsychotics (adjusted IRR: 0.54, 95% CI: 0.36-0.80) and no evidence of an association between the use of atypical antipsychotics and GDM (adjusted IRR: 1.02, 95% CI: 0.59-1.75).

Conclusion: Our results do not indicate that antipsychotic exposure during pregnancy may lead to a higher probability of GDM. The decreased risk of GDM in users of typical antipsychotics can partly be explained by channeling bias.

Keywords: Pregnancy, Antipsychotics, Gestational diabetes.

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Pharmacological treatment dynamics in people initially prescribed metformin or sulfonylurea for type 2 diabetes

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Aim: To estimate the predictors of time to anti-glycaemic medication addition and switching during the first year after initiation of metformin or sulfonylurea (SU) in people with Type 2 Diabetes (T2DM).

Methods: 109,573 individuals aged 18-99 years initiating metformin or a SU between July 2013 and April 2015 were identified from the National Diabetes Service Scheme database containing 80-90% of Australians with diagnosed T2DM linked to pharmacy dispensing data. Cox Proportional Hazards Regression was used to estimate adjusted Hazard Ratios (HRs) with 95% confidence intervals (CI) for predictors of time to an addition to or switch from the index medication during a one-year follow-up.

Results: Addition or switching occurred in 18% and 4% of metformin initiators and in 28% and 13% of SU initiators, respectively. Being a woman (HR 0.85; 95%CI 0.82-0.87) or aged ≥75 years (HR 0.56; 95%CI 0.53-0.60) delayed, while Congestive Heart Failure (CHF) (HR 1.25; 95%CI 1.13-1.39) predicted addition to metformin. Switching from metformin occurred faster in women (HR 1.44; 95%CI 1.35-1.53) and people with ≥5 comorbidities (HR 1.52; 95%CI 1.30-1.77) but slower in Australia's most remote locations (HR 0.73; 95%CI 0.56-0.95). Time to addition to SUs was longer in people aged ≥75 years (HR 0.44; 95%CI 0.37-0.51), with ≥5 comorbidities (HR 0.59 95%CI 0.48-0.73) and living in the most remote areas (HR 0.69; 95%CI 0.52-0.92). Delays of ≤2 years from diagnosis to the index medication were associated with longer time to receiving an addition to or switch from either metformin or SU.

Conclusion: Delays in initiation of metformin or SU up to two years after diagnosis reduce the likelihood of individuals receiving an addition to or switch from the initial medication within one year. People in Australia's most remote areas are less likely to receive a switch from metformin or an addition to SU.

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Bullous pemphigoid induced by dipeptidyl peptidase-4 inhibitors: A pharmacoepidemiological-pharmacodynamic assessment through an analysis of the VigiBase®

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Background: Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged recently as a putative triggering factor of Bullous pemphigoid (BP). The exact mechanism underlying this association remains unclear and needs to be elucidated.

Objective: The primary objective of the present study was to examine the potential signals of BP with DPP-4 inhibitors in VigiBase®. Secondary objective was to examine the potential role of pharmacological (pharmacodynamic/pharmacokinetic parameters) characteristics of different gliptins in the occurrence of Bullous Pemphigoid (BP). risk as a result of exposure to DPP-4 inhibitors.

Materials and Methods: Case/non-case analyses was performed in VigiBase® to examine the potential signal of BP [expressed as the reporting odds ratio (ROR) and its 95% confidence interval] for DPP-4 inhibitors. Secondly, we performed linear regression analyses to explore the association between DPP-4 inhibitor signals for BP and their affinities towards different target enzymes (DPP-2, DPP-4, DPP-8 and DPP-9) and their volume of distribution (Vd).

Results: A significant BP signal was found for DPP-4 inhibitors. The ROR for pooled DPP-IV inhibitors was 168.5 (95% CI: 156.1–181.3). Among individual DPP-4 inhibitor, the highest RORs were found for teneligliptin 898.3 (95% CI: 734.7–1098.4), omarigliptin 672.3 (95% CI: 376.7–1199.9) and lowest for saxagliptin 18.9 (95% CI: 11.5–30.9) and sitagliptin 44.4 (95% CI: 38.6–51.1). We found a marginally significant linear correlation between the BP signal and gliptin affinity at DPP-4 (slope=1.316 [-0.4385–3.21], p=0.067, R2=0.40) but not the other enzyme targets, nor for Vd.

Conclusions: BP is reported at a disproportionately higher rate with all currently clinically approved DPP-4 inhibitors, indicating a 'class effect' associated with this potentially serious disease. The results reported herein suggest a clinical relevance of gliptins selectivity for DDP-4 in the development of BP as a result of exposure to these drugs. Future preclinical and clinical studies are needed for a better understanding of this correlation.

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The use of insulin, diabetes status, and risk of progression after first episode of acute pancreatitis: A population-based cohort study

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Aim/Objective: Acute pancreatitis (AP) often progresses to recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP). The 'holistic prevention of pancreatitis' has emerged as a useful framework but there is a lack of effective strategies for primary prevention of RAP and CP. The aim was to investigate the relationship between the use of insulin and progression of pancreatitis, as well as the effect of diabetes status on it.

Methods: Using nationwide pharmaceutical dispensing data linked to hospital discharge data in New Zealand, insulin-naïve individuals were followed from their first AP admission (between January 1, 2007 and December 31, 2015). Multivariable time-dependent Cox regression analyses (adjusting for age, sex, ethnicity, social deprivation index, alcohol consumption, and tobacco smoking) were conducted in the overall cohort as well as the subgroups stratified by diabetes status, etiology, and severity of AP.

Results: A total of 10,910 insulin-naïve individuals with first episode of AP were followed for a mean of 7.0 years. Ever-use of insulin during follow-up was associated with a significantly increased risk of progression to RAP or CP in the overall cohort (adjusted hazard ratio, 1.70; 95% confidence interval, 1.31–2.20). The higher risk of the progression associated with insulin was significant among individuals with pre-existing diabetes (1.45; 1.04–2.00), those with post-acute pancreatitis diabetes mellitus (3.87; 1.20–12.46), and those without diabetes (2.80; 1.25–6.25). There was a significant dose-response relationship between insulin exposure and the risk of progression to RAP or CP ($p<0.05$).

Conclusion: This study suggests that the use of insulin during hospitalization for AP or after hospital discharge is associated with a heightened risk of progression of pancreatitis in insulin-naïve individuals, irrespective of the diabetes status. Judicious use of insulin in these individuals may be required.

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Impact of multiple cardiovascular medication on mortality after an incidence of stroke: A 10-year cohort study

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Aim: To assess the effect of multiple cardiovascular drugs on long-term survival in patients following the first diagnosis of stroke.

Methods: A cohort study was conducted using The Health Improvement Network database from 2007 to 2016. The study included 64,312 patients with their first record of stroke event and aged 45+ years. Cardiovascular drugs were categorised into seven groups: no drug, 1 (reference group), 2, 3, 4, 5, and ≥ 6 according to 1) the number of individual medicines used and 2) the number of drug classes used during the 90 days after the diagnosis of stroke. The risk of mortality was assessed using the marginal structural models to address time-varying confounders over the follow-up time.

Results: There were 7,490 patients where no drugs were prescribed, 6,235 patients with one drug, 12,516 with two drugs, 13,985 with three drugs, 11,807 with four drugs, 7,206 with five drugs and 5,073 patients with ≥ 6 drugs prescribed. The mean age was 70.9 (SD:11.9) years old and the average follow-up time was 3.5 years. Compared with patients who were prescribed one drug only, the risk ratios of mortality (95% confidence intervals) were 1.54 (1.39-1.71) for no drug, 0.79 (0.71-0.87) for two drugs, 0.59 (0.53-0.66) for three drugs, 0.59 (0.52-0.65) for four drugs, 0.57 (0.50-0.65) for five drugs and 0.60 (0.52-0.69) for ≥ 6 drugs. Similar results were found among the combination of different drug classes.

Conclusion: The results suggest that stroke patients who were on multiple drug treatment, especially with more than 3 drug treatments had a reduced risk of mortality.

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Association between relative age within school year and attention deficit hyperactivity disorder (ADHD), intellectual disability and depression

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Aim: Previous studies report an association between young relative age within the school year and increased ADHD diagnosis and medication prescription. The association between relative age and intellectual disability has been examined little and, to our knowledge, no study to date has investigated an association with depression. We aim to estimate the association between relative age and ADHD diagnosis and treatment, and diagnosis of intellectual disability and depression.

Methods: We conducted a population-based cohort study among children aged 4 to 15 years. We identified eligible children registered at UK general practices contributing data (up till January 2nd 2017) to the Clinical Practice Research Datalink. Cox regression was used to estimate the association between relative age within school year, determined by month of birth and categorised into four 3 month groups, and each of the outcomes.

Results: In total 1,042,106 children were identified of whom 532,876 (51.1%) were male and the median (IQR) age at study entry was 4.0 years (4.0-5.0). There was strong evidence of an association between relative age and all studied outcomes with children born in the last quarter of the school year (youngest in their year) at increased risk of ADHD diagnosis (HR 1.36, 95% CI 1.28-1.45) and ADHD medication prescription (HR 1.35, 1.27 - 1.45), diagnosis of depression (HR 1.31, 1.08-1.59), and diagnosis of intellectual disability (HR 1.30, 1.18-1.42) relative to those born in the first quarter.

Conclusion: Young relative age in the school year is associated with increased risk of diagnosis and treatment of ADHD, and diagnosis of intellectual disability and depression. Further research into the reasons for these associations and clinical and policy interventions to minimise these effects is warranted.

Keywords: attention deficit hyperactivity disorder, depression, intellectual disability, relative age

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Efficacy of pidotimod in children: A systematic review

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Objective: To systematically evaluate the efficacy of pidotimod in children, and provide evidence of evidence-based medicine for clinical treatment.

Methods: Databases including Pubmed, The Cochrane Library, EMbase (Ovid), CNKI, CBM, VIP and WanFang Database were searched from inception to January 2018, to collect randomized controlled trials (RCTs) about pidotimod in children. Two reviewers independently screened literature, extracted data, evaluate the quality of included studies, and meta-analysis was performed by RevMan 5.3.

Results: 318 RCTs involving 27500 children were included. The result of meta-analysis showed that compared with the control group, the pidotimod group could significantly reduce the number of respiratory tract infection[MD=-2.79, 95%CI(-3.12, -2.46),P<0.05], the time of respiratory tract infection[MD=-4.15, 95%CI(-4.72, -3.58),P<0.05], the time of fever[MD=-1.47,95%CI(-1.77,-1.17),P<0.05] in recurrent respiratory tract infection. And pidotimod could reduce the time of fever [MD= -0.25，95%CI(-0.38,-0.11),P<0.05] in mycoplasma pneumoniae pneumonia, the time of fever [RR= 1.163，95%CI(1.043,1.297，P<0.05)] in hand-foot-mouth disease, incidence of anaphylactoid purpura followed up for 6 months[RR=0.370,95%CI(0.215, 0.636),P<0.05] in anaphylactoid purpura, but there was no significant difference between the pidotimod group and the control group in the incidence of asthma followed up for 1 year[RR= 0.80，95%CI(0.60, 1.06)，P>0.05]in asthma.

Conclusions: Current evidence shows that, Pidotimod may be effective for respiratory tract infection, asthma, hand-foot-mouth disease, could reduce disease relapse and relieve symptoms related to illness. Due to limited quality included studies more strict designed and multicenter clinical researches are needed to verify the above conclusion.

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Antimicrobial resistant and prescribing pattern in children in Taiwan- TARPEC project

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Aim/Objective: Antimicrobial Resistance is a worldwide problem with the public. There is currently no global surveillance to monitor AMR in neonates and children. Thus, we setup the online surveillance system (REDCap) in Taiwan as "Taiwan Antimicrobial Resistance, Prescribing and Efficacy in Neonates and Children Project (TARPEC)" to estimate the magnitude of antimicrobial resistance in pediatrics in Taiwan.

Methods: We conducted a prospective cohort study to collect clinical data by using the online surveillance system in 4 centers. The target population are patients who are aged 18 years and younger who will be admitted into the hospital during the period of August 2017 to July 2019. The clinical data include: (1) laboratory data (2) patient demographic data (3) infectious episode data (4) hospital occupancy and admissions data (5) antimicrobial prescription data. We evaluated antimicrobial resistance among patients with blood stream infection and the 1-day point prevalence of prescription among all hospitalized neonates and pediatric patients at 8 am since at least midnight.

Results: We collected 1,729 (46.14%) children received at least one antimicrobial agent from 4 centers, including children aged 2-18 years (n=1041), followed by aged 1-24 months (n=510) and aged less than 1 month (n=178). Male to female ratio is 1.04. In total, 17% of the children had at least one comorbidities, and most of them were received one antimicrobial agent (63.3%). The most frequently prescribed antibiotics were amoxicillin and enzyme inhibitor (n=391), followed by gentamicin (n=209), azithromycin (n=199), ampicillin and enzyme inhibitor (n=190), and cefazolin (n=188). The most common indication for antibiotics was proven or probable bacterial lower respiratory tract infection (27.3%). Acinetobacter baumanii and staphylococcus aureus have gotten frighteningly resistant to many of common antibiotics.

Conclusions: Further researches focusing on identifying risk factors, high risk strains and to develop policy to ensure safe and appropriate antibiotic prescribing to prevent the future development of antibiotic resistance.

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Patterns of methylphenidate and atomoxetine use among pediatric patients with attention-deficit/hyperactivity disorder in Taiwan from 2004 to 2017

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Aim/Objective: Document the prescribing patterns of methylphenidate and atomoxetine among ADHD patients in Taiwan.

Methods: Patients who were newly diagnosed ADHD, aged between 3 to 18 years between 2004 and 2017, and ever exposed to methylphenidate or atomoxetine were included. The Health and Welfare Database served as the data source, which contains claims and registries of National Health Insurance (NHI) program in Taiwan. Prevalence of ADHD medication treatment, initial treatment for ADHD, time between the first diagnosis and the first prescription and medication-switching pattern were investigated.

Results: We began with 258,994 ADHD patients. Patients with multiple records of birthday, unknown gender or incomplete data of insurance status were excluded; 257,826 patients were included in the final cohort. Percentage of male patients was 77.7 %. Median age of first ADHD diagnosis is 7.0 years old (interquartile range 5.0-9.0). In this cohort, 153,705 (59.6 %) patients received medication treatment, with 98.1 % of them received methylphenidate and 1.9 % received atomoxetine. Atomoxetine uses increased from 0.08 % since it first entered the market in Taiwan in 2007 to 5.5 % in 2017. Median time between the first diagnosis and first prescription was 21 days (IQR 0-216). In patients initiated methylphenidate, 13,443 (8.9 %) patients switched to atomoxetine, and 53.5 % switch back to methylphenidate subsequently. Among children receiving atomoxetine as their initial treatment, 912 (31.6 %) switched to methylphenidate, and 24.2 % switched back subsequently.

Conclusion: More than half of pediatric patients with ADHD received pharmacotherapy, which methylphenidate as the predominate choice of treatment. Atomoxetine use increased considerably since it entered the market, but the utilization rate remained low overall. Medication switching was more common among patients initiated atomoxetine than methylphenidate, and the reasons behind this deserves further investigation.

Keywords: methylphenidate, atomoxetine, ADHD, prescription pattern

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Association between methylphenidate and risk of seizure: A population-based self-controlled case series study

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Objective: To investigate the association between methylphenidate and the risk of seizure.

Methods: A population-based, electronic medical records database from the Hong Kong Clinical Data Analysis & Reporting System was used to identify 30,453 individuals aged 6-25 years who were treated with methylphenidate between 2001 and 2017. Those who had incident seizure in the study period were included in the analysis. A self-controlled case series design was used to control for time-invariant characteristics of the patients. We divided patient-time into 5 windows: absence of methylphenidate (baseline), 90-day before the first methylphenidate exposure, first 30-day of methylphenidate use, first 31-180 days of methylphenidate use and subsequent methylphenidate use. Negative control analysis was conducted using skin infection as an alternative outcome. Relative incidence of seizure during different windows were compared.

Results: Among 30,453 patients with methylphenidate prescriptions, 269 had their incident seizure within the study period; of these individuals, 199 (74.0%) were male; mean (SD) age at baseline was 6.48 (1.79) years. The overall incidence of seizure during methylphenidate treatment was 4.4 per 10 000 patient-years. An increased risk of seizure was detected during the first 30-day period when methylphenidate was initiated, with an incidence rate ratio (IRR) of 3.90 (95%CI, 2.04-7.48). No increased risks were found in other windows with IRRs 1.55 (95%CI,0.85-2.81), 1.16 (95%CI,0.61-2.19) and 1.34 (95%CI,0.89-2.02) for 90-day before, 31-180 days and subsequent treatment respectively. Also, no increased risks were identified in all risk windows for the negative control analysis.

Conclusions: The incidence of seizure was higher in the short period immediately after the start of methylphenidate treatment. The risk returned to baseline levels during continuation of methylphenidate treatment. The observed higher risk of seizure reflect the possible link between methylphenidate treatment and adverse neurological outcomes immediately after the first treatment. Monitoring of neurological outcomes in methylphenidate users is essential, especially when they first started the treatment.

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Comparative effect of four antimalarial treatments on haematocrit in children in Southwest Nigeria

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Aim/Objective: Anaemia in malaria has both central (dyserythropoiesis) and peripheral causes (phagocytosis of both infected and uninfected erythrocytes and haemolysis). However, it is often difficult to disentangle the anemia effect of malaria from its treatments.

To compare the change in haematocrit following four antimalarial treatments among children of microscopically-confirmed Plasmodium falciparum infection.

Methods: Data were extracted from 313 case record forms of children that met the eligibility criteria aged 3-119 months enrolled in antimalarial clinical trials in Southwest Nigeria between 1998 and 2014. Study participants were followed up over a 28 day period according to the World Health Organization recommendation for treatment of malaria research participants. Enrollment criteria included symptoms compatible with acute uncomplicated malaria, including parasite density of at least 1000/µL and absence of chronic illness or danger signs of severe malaria. Change in haematocrit level from baseline through the treatment period and 28 days post treatment were compared among children treated with artemether-lumefantrine (82), artovaquone-proguanil (41), artesunate-amodiaquine (156) and chloroquine (34).
Repeated measures analysis was done by fitting a general linear model (GLM).

Results: The median age of the study population was 25 months and 54% were males. The mean differences (95% CI) in haematocrit from baseline were 4.7 (95% CI = 3.6, 5.8), 4.4 (95% CI = 2.7, 6.0), 3.8 (95% CI = 3.0, 4.7) and 2.4 (95% CI = 0.5, 4.4), for artemether-lumefantrine, artovaquone-proguanil and artesunate-amodiaquine and chloroquine, respectively. Using the general lineal model, repeated measure analysis showed that there were significant differences in the mean haematocrit level over the 28-day follow-up among the four treatment groups ($p<0.05$).

Conclusions: All children experienced increases in haematocrit after treatment, with artesunate-amodiaquine appearing to result in a greater increase in haematocrit than other antimalarial drugs.

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Comparative risks of cardiovascular events associated with anti-VEGF therapy in real-life patients with macular diseases in Taiwan

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Purpose: Anti-vascular endothelial growth factor (anti-VEGF) has been widely used for the treatment of age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal vein occlusion (RVO), but their cardiovascular safety remain unclear.

Methods: We conducted a retrospective cohort study using the Chang Gung Research Database which covered 1.3 million patients (6% of Taiwan's population). We included patients aged 40+ years without a history of cardiovascular event and newly received anti-VEGF (i.e., aflibercept, bevacizumab and ranibizumab) for the ophthalmic diseases (i.e., AMD, DME and RVO) from 2009 to 2018. We followed patients from the initiation of anti-VEGF until the occurrence of cardiovascular event, including all-cause cardiovascular death, myocardial infarction and ischemic stroke, or the last date of CGRD. We used multivariable Cox proportional hazard model with adjustments of patients' age, sex, co-morbidities and co-medications to compare the cardiovascular risk among anti-VEGF.

Results: We included a total of 8276 study patients (5094 bevacizumab, 1919 ranibizumab and 1263 aflibercept), and most of them were men (56.9%) and were AMD (61.6%). The mean age was 66.9 years. We found the risk of cardiovascular events was lower in ranibizumab (HR: 0.82; 95% CI: 0.63-1.07) and aflibercept (HR: 0.76; 95% CI: 0.48-1.19), compared to bevacizumab. Specifically, we found the risk of cardiovascular death (HR: 0.68; 95% CI: 0.28-1.65), myocardial infarction (HR: 0.62; 95% CI: 0.38-1.01) and ischemic stroke (HR: 0.83; 95% CI: 0.60-1.14) were lower in ranibizumab compared to bevacizumab. Aflibercept posed lower risk of cardiovascular death (HR: 0.90; 95% CI: 0.21-3.92) and ischemic stroke (HR: 0.87; 95% CI: 0.52-1.45), but had higher risk of myocardial infarction (HR: 1.56; 95% CI: 0.37-6.54), compared to bevacizumab.

Conclusions: The findings indicated Anti-VEGF posed various risk of cardiovascular events. Especially, we should pay attentions on myocardial infarction risk in patients receiving aflibercept.

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Acute kidney injury associated with non-steroidal anti-inflammatory drugs and concomitant use of renin–angiotensin system inhibitors and diuretics: A case-crossover study

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Objective: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in clinical practice. However, they are associated with an increased risk of acute kidney injury (AKI), and the concomitant use of renin-angiotensin system inhibitors (RASIs) or diuretics may further potentiate the risk. This study aimed to investigate the risk of AKI associated with NSAIDs, dual combination (NSAIDs with RASIs or diuretics), or triple combination (NSAIDs with RASIs and diuretics).

Methods: A case-crossover study was conducted using Taiwan's National Health Insurance Research Database. Patients who were newly admitted with a primary diagnosis of AKI were included as study subjects and the admission date was defined as the index date. For each subject, exposures to NSAIDs and co-exposures of RASIs and/or diuretics within the case period (1-7 days before the index date) and the control period (181-187 days before the index date) were evaluated. Multivariable conditional logistic regression models were used to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of AKI associated with NSAIDs, dual combination, or triple combination.

Results: A total of 1,284 newly diagnosed AKI patients were included in the study. Overall, NSAIDs were associated with a 3.55-fold increased risk of AKI (aOR 3.55 [95%CI 2.70-4.65]). When stratified by concomitant drug use (reference group: no exposure of NSAIDs, RASIs, and diuretics), NSAIDs use only was associated with a 3.71 fold increased risk (aOR 3.71[2.62-5.25]); dual combination with RASIs was associated with a 2.90-fold increased risk (aOR 2.90[1.47-5.70]); dual combination with diuretics was associated with a 12.68-fold increased risk (aOR 12.68[6.15-26.12]); triple combination with RASIs and diuretics was associated with the highest increased risk of AKI (aOR 29.22[12.82-66.64]).

Conclusion: NSAIDs was associated with an increased risk of AKI leading to hospitalization. Dual combination with diuretics and triple combination with RASIs and diuretics further potentiate the risk of AKI.

Keywords: acute kidney injury, NSAIDs, case-crossover study, drug-drug interaction.

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Prevalence of aspirin non-responsiveness and outcomes in patients with acute coronary syndrome undergoing percutaneous coronary intervention

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Background: Antiplatelet therapy is an indispensable part of therapy in acute coronary syndrome (ACS). Non-responsiveness to antiplatelet agents especially aspirin keeps patients at higher risk of catastrophic events. Lab assessment of platelet response to aspirin may identify patients at higher risk.

Aims/objectives: Assessment of prevalence of aspirin non-responsiveness using urinary 11-dihydroxy thromboxane B2 (UTXB2) and its correlation with major adverse cardiac events (MACE) in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) up to 180 days.

Methods: We conducted a prospective observational cohort study in a tertiary care center in South India including adult patients with ACS who underwent PTCA with drug-eluting stents. UTXB2 levels were assessed using ELISA assay. Based on UTXB2 levels aspirin responsiveness was divided into two categories; 0-1500 pg/mL shows good response and >1500 pg/mL shows poor aspirin response. The patients with poor response were labeled as 'resistance to aspirin in the lab.' MACE were observed for up to 180 days.

Results: The study included 192 patients with a mean age of 59±11.2 years of whom 72 % were males. Higher levels of UTXB2 during index admission was seen in 24 (12.5%) patients, indicating poor response to aspirin. 8 (33.3%) developed MACE. MACE occurred in 17 (8.8%) of the study population over 6-month follow-up with 8 (47.1%) events occurring in patients with abnormal response to aspirin. Patients with higher UTXB2 levels (i.e. resistance to aspirin) during index hospitalization have a significantly higher incidence of MACE compared to patients with lower levels of UTXB2 (33% vs 5.5%, P <0.001). Other factors including male gender, medication non-compliance, smoking, and alcohol were statistically significant with MACE and aspirin poor response.

Conclusions: Poor response to aspirin assessed by increased levels of UTXB2 is associated with the development of MACE. Patients 'resistance to aspirin in a lab' is at higher risk of clinical MACE.

Keywords: MACE; Thromboxane; Angioplasty; Stent thrombosis

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Statin-associated dose-dependent reductions in non-alcoholic fatty liver diseases among people without any liver disease

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Objective: We examined whether statins lower the incidence risk of NAFLD without any liver disease using real-world nationally representative data from Korea.

Method: A sample of persons (N = 683,623) without liver diseases were selected from a retrospective cohort of ~1 million individuals drawn from the Korean National Health Insurance Service data in 2002. All insurance claims for the sample persons were extracted between 2002 and 2013. Statin exposure was measured with a defined daily dose (DDD) and a cumulative defined daily dose (cDDD). The cDDDs were divided into the following groups: 0–180, 180–360, 360–720, 720–1440, and 1440 or more. Multivariate Cox proportional hazards model with statin use as time-varying variable were performed controlling for age, income level, comorbidities and medications including antidiabetics, antihypertensive drugs lipid-lowering agents as covariates.

Result: Statin use was associated with a 12% reduction in incidence risk of NAFLD (adjusted Hazard ratio (HR) 0.88, 95 Confidence interval (CI) 0.78, 0.99). Moderate-intensity statin use was associated with 15% reduction in NAFLD incidence. The NAFLD incidence according to statin cDDD showed J-shape as the adjusted HRs (95% CI) were 0.91 (0.77-1.07), 0.64 (0.49-0.84), 0.55 (0.43-0.70), 0.93 (0.74-1.16), and 1.92 (1.46-2.52) in cDDD of 0-180, 180-360, 360-720, 720-1440, and >1440. The NAFLD incidence was less likely among the statin use across all cDDD levels among those who took antidiabetic drugs as the adjusted HRs (95% CI) were 0.29 (0.13-0.65), 0.67 (0.22-1.44), 0.31 (0.14-0.71), 0.44 (0.21-0.93), and 0.69 (0.32-1.50) for cDDD of 0-180, 180-360, 360-720, 720-1440, and >1440. However, no such reduced NALFD incidence was found for those over 75 years old.

Conclusion: We demonstrate that statin use was associated with reduction in NAFLD incidence and the relationship was J-shaped. This tendency was more evident to those under 75 years old.

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Effect of early initiating statin therapy on long-term outcomes of patients with dyslipidemia after intracerebral hemorrhage

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Objective: Intracerebral hemorrhage (ICH) is higher mortality than ischemic stroke. Statin is beneficial for stroke, but high potency statin treatment has been associated with the risk of hemorrhagic stroke. The aim of this study was to assess the impact of initiating statin therapy after ICH on cardiovascular outcomes.

Methods: Dyslipidemic patients were retrieved from ICH population at the National Health Insurance Research Database in Taiwan. We retrospectively compared those patients prescribed with and without statin treatment after ICH. Outcomes of interest were mortality, myocardial infarction, ischemic stroke, and intracerebral hemorrhage during 5 years of follow-up.

Results: Of 17,980 adult patients with ICH and dyslipidemia, 8,927 were eligible for analysis over the study period, including 1,613 patients receiving statin therapy and 7,314 patients not taking statins. After propensity score matching, the mean age was 61.2±12.2 years in statin group and 61.6±13.0 years in non-statin group. Hypertension was dominance, followed by Diabetes Mellitus and the mean estimated NIHSS score was 12.9. The patients who received statin therapy were associated with lower risks of all-cause mortality (12.7% vs 21.3%; hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.45–0.65), cardiovascular death (4.0% vs 7.1%; HR, 0.54; 95% CI, 0.39–0.75) and ICH (5.4% vs 8.5%; HR, 0.62; 95% CI, 0.46–0.83) compared to those who did not receive statins.

Conclusions: Early initiating statin therapy after ICH was associated with a decreased risk of recurrent ICH and mortality for dyslipidemia patients.

Keywords: statin, intracerebral hemorrhage, cerebrovascular, mortality

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Effect of synbiotic, probiotic and prebiotic on patients with non-alcoholic fatty liver disease: A systematic review and network meta-analysis

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Aims: To compare the effect of synbiotic, probiotic and prebiotic focusing on the reduction in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in patients with NAFLD.

Methods: We searched for the articles from the electronic databases; PubMed, Embase, CLINAHL Plus, Cochrane Library and Web of Science. Searching was processed from the inception to December 19, 2018 and only English articles were selected. 19-RCT articles was met the inclusion criteria which indicated the effect of synbiotic, probiotic and prebiotic on the reduction in AST and ALT. Furthermore, the studies that showed the result in other outcomes such as waist circumference, BMI, lipid profile, HOMA-IR and fasting blood sugar were included. The risk of bias and heterogeneity were assessed. Then, we assembled the direct and indirect evidence by performing network meta-analyses (NMA) using random effect model and estimated the outcomes in weighted mean difference (WMDs) and 95% confidence intervals (CIs). Eventually, we ranked the comparative effects of three interventions with the surface under the cumulative ranking (SUCRA) probabilities.

Result: 1,015 patients were performed in 19-RCTs. There were 730 patients with non-alcoholic fatty liver (NAFL) and 285 patients with non-alcoholic steatohepatitis (NASH). The patients generally were adult (856 adults, 159 children). Qualitative assessment mostly reported in moderate risk of bias. For the outcome analyses, probiotic has the greatest effect on reduction in AST -13.71 U/L (95% CI, -20.71,-6.72; $p<0.05$) also, probiotic has the greatest effect on reduction in ALT -13.21 U/L (95% CI, -19.74,-6.68; $p<0.05$).

Conclusion: Probiotic has the greatest effect on reduction in level of AST and ALT in patients with non-alcoholic fatty liver disease.

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Does statin use change in relation to the initiation of dementia medicine? Analysis of the Australian pharmacy claims data

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Aim: This study aimed to examine the change in statin use in relation to initiating medicine for dementia.

Methods: A case-crossover study utilising data from the Australian Pharmaceutical Benefits Scheme (PBS) 10% random sample from 2005-2018 was performed. Use of statins was investigated in the 12 months pre- and post-initiation of an antidementia medicine (donepezil, galantamine, rivastigmine or memantine) or risperidone. Individuals aged ≥65 years who had their first supply of antidementia medicine or risperidone from July 2006 to June 2017 and survived ≥12 months after their first supply were included. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs) for statin use in the discordant pairs. Sub-group analyses were performed by age, sex, index medicine and index year.

Results: The cohort comprised 19,809 individuals, median age 81 years (interquartile range 76-86) and 61% female. The index medicine was antidementia medicine for 57.7%, risperidone for 41.9% and both for 0.4% of individuals. Overall, statins were significantly less likely to be used after initiating medicine for dementia (OR 0.50 [95%CI 0.45-0.55]). Females were less likely to use statins after initiating medicine for dementia than males (0.42 [0.37-0.48] vs 0.63 [0.54-0.73]). The odds of statin use decreased with increasing age (0.93 [0.75-1.16] in people aged 65-74 years vs 0.29 [0.24-0.35] in those aged ≥85). People in the risperidone group had lower odds of statin use than people in the antidementia medicine group (0.31 [0.26-0.35] vs 0.79 [0.69-0.91]). The odds of statin use after initiating medicine for dementia decreased annually over the 11-year study period from 1.21 [0.84-1.75] in 2006-7 to 0.31 [0.24-0.41] in 2016-17 (p for year*pre-post period interaction <0.0001).

Conclusion: Statin use decreases after initiating medicine for dementia, particularly in women and in people aged ≥85 years, and has decreased significantly since 2006.

Keywords: dementia, statins, drug utilization, Australia

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Benzodiazepines, Z-hypnotics and risk of dementia: Special considerations of half-lives and concomitant use

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Aim/Objective: The utilization of benzodiazepine (BZD) and z-hypnotics was substantially increased along with population aging, but the risk of BZDs and z-hypnotics in dementia development remained to be a strong concern. This study aimed to evaluate the risk of BZDs and z-hypnotics for subsequent dementia with a special consideration of the half-lives and concomitant use of medications.

Methods: People aged 65 years and older who were newly prescribed oral BZDs or z-hypnotics between 2003 and 2012 were identified from Taiwan's National Health Insurance Research Database. All BZDs were categorized into long-acting drugs (≥ 20 hours) and short-acting ones (< 20 hours) for further comparisons. Information about drug use of long-acting, short-acting BZDs and z-hypnotics during follow-up period were collected on quarterly basis, started on the first date of drug prescription and ended on the date of death, occurrence of dementia, or end of the follow-up, whichever came first. All dementia events except vascular dementia occurring during the follow-up period were identified. Generalized estimating equations (GEEs) were used to examine the associations between distinct half-lives of BZDs, z-hypnotics, concomitant use of medications and the risk of dementia.

Results: Among 260,502 eligible subjects, results of GEEs indicated that short-acting BZDs and z-hypnotics users were at greater risk for dementia than long-acting users (short-acting BZDs users: aOR =1.98, 95% CI=1.89-2.07; z-hypnotics users: aOR=1.79, 95% CI=1.68-1.91; long-acting BZDs users: aOR =1.47, 95% CI=1.37-1.58;). In addition, subjects concomitantly using two or more items of BZDs or z-hypnotics had the highest risk for dementia (aOR=4.79, 95% CI=3.95-5.81)).

Conclusions: BZDs and z-hypnotics use were strongly associated with risk of dementia development, and concomitant use of multiple agents were at the highest risk. Compared to long-acting BZDs, short-acting BZDs and z-hypnotics were at higher risk of dementia development, which deserves further intervention study to clarification.

Key word: Benzodiazepines, z-hypnotics, dementia, half-life

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Trazodone use and risk of dementia: A population-based cohort study

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Objective: This electronic health records study assessed the association between trazodone use and the risk of developing dementia in clinical practice.

Methods: We conducted a population-based cohort study using data from the United Kingdom THIN (The Health Improvement Network) database. We assessed patients aged ≥50 years who received at least two consecutive prescriptions for an antidepressant between January 2000 and January 2017. We compared the risk of dementia among patients who were prescribed trazodone to that of patients with similar baseline characteristics prescribed other antidepressants, using a Cox regression model with 1:5 propensity score matching.

Results: Patients prescribed trazodone who met the inclusion criteria (n = 4,716; 59.2% female) were older (mean age 70.9 ± 13.1 versus 65.6 ± 11.4 years) and were more likely than those prescribed other antidepressants (n = 420,280; 59.7% female) to have cerebrovascular disease and use anxiolytic or antipsychotic drugs. After propensity score matching, 4,596 users of trazadone and 22,980 users of other antidepressants were analysed. The median time to dementia diagnosis for people prescribed trazodone was 1.8 years (interquartile range [IQR] = 0.5–5.0 years). Incidence of dementia among patients taking trazodone was higher than in matched users of other antidepressants (1.8 versus 1.1 per 100 person-years), with a hazard ratio (HR) of 1.80 (95% confidence interval [CI] 1.56–2.09; $p < 0.001$). When we restricted the control group to users of mirtazapine only in a sensitivity analysis, the findings were very similar to the results of the main analysis.

Conclusion: Our results suggest that the clinical use of trazodone is not associated with a reduced risk of dementia. Whilst the incidence of dementia among patients taking trazodone was higher than that in patients taking other antidepressants, the risk differences were closer to zero with increasing duration of treatment, suggesting that people in the prodromal stage of dementia might be more likely to be prescribed trazodone.

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The association between cholinesterase inhibitors and subsequent cardiovascular events among older patients with Alzheimer's disease in Taiwan

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Aim: The aim was to investigate whether the use of cholinesterase inhibitors decreased the risk of subsequent cardiovascular events among patients aged 50 years or older with Alzheimer's disease in Taiwan.

Methods: We conducted a retrospective cohort study with the new cholinesterase inhibitor user design. A 10-year data source (2005-2014) was obtained from the Full Population Data of the Health and Welfare Data Science Center, Ministry of Health and Welfare, which contains all Taiwanese people (approximately 23 million beneficiaries) enrolled in the National Health Insurance program in Taiwan. Patients were included if they were diagnosed with Alzheimer's disease. The exposure was the use of cholinesterase inhibitors and the cumulative doses of cholinesterase inhibitors. The outcome was the diagnosis of cardiovascular events during the follow-up period. Matching and inverse probability of treatment weighting (IPTW) with the propensity score were used to adjust confounders and reduce bias. Cox-proportional hazard models with competing risk were used to estimate the hazard ratios of cardiovascular events between cholinesterase inhibitor users and nonusers as well as cholinesterase inhibitor users with different cumulative doses.

Results: The study population included 6,070 patients with Alzheimer's disease. Among them, 1,717 individuals (28.3%) reported to have at least one cardiovascular event. After adjustment, cholinesterase inhibitor users were less likely to have a cardiovascular event compared to non-users [Hazard Ratio (HR): 0.57, 95% Confidence Interval (CI): 0.51-0.62]. Among users, patients with a high cumulative dose were found to be associated with a reduced risk of a cardiovascular event when compared to patients with a low cumulative dose (HR: 0.82, 95% CI: 0.70-0.96).

Conclusion: The use of cholinesterase inhibitors had benefits of preventing cardiovascular events. The cardioprotective effect of cholinesterase inhibitors allowed physicians to have an effective treatment option especially for Alzheimer's disease patients at a high risk of cardiovascular disease.

Keywords: Cholinesterase inhibitor, cardiovascular disease, Alzheimer's disease, Taiwan

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Acetylcholinesterase inhibitors, cardiosuppresive drugs, and adverse cardiac events in patients with dementia

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Background: Acetylcholinesterase inhibitors (AChEI), widely used to treat dementia, have a theoretical chronotropic effect. Thus, patients using both AChEI and cardio-suppressive drugs (CS) can have excessive risks for bradycardia and atrioventricular (A-V) block resulting in syncope.
Objectives: To assess the effect of a single and/or combined use of AChEI and CS on syncope in patients with dementia.

Methods: We conducted a cohort study of adults aged ≥65 with dementia residing in skilled nursing facility (SNF) enrolled in Medicare Part D (7/2007-12/2013) in the US Medicare and the Minimum Data Set. We identified four groups within a cohort of dementia patients identified by validated definition; users of 1) concomitant AChEI and CS (dual), 2) AChEI only, 3) CS only (CS), and 4) none of either. The primary outcomes were syncope identified as emergency department or inpatient diagnosis. We calculated adjusted hazard ratios (HRs) in multivariable Cox proportional hazard regression models. We also estimated relative excess risk due to interaction (RERI).

Results: We identified 159,038 subjects (mean 83 year-old, 71% female). Dual users (10%) had similar characteristics as CS (24%) and none users (51%), had more heart failure, cerebrovascular, pulmonary, and renal disease compared to AChEI users (16%). Adjusted HRs (95% CI,) for syncope comparing single were 2.1 (2.0-2.3) for dual use, 1.8 (1.6-1.9) for AChEI use, and 1.6 (1.5-1.8) for CS use compared to none users. The RERI was -0.1 (95%CI,-0.6- 0.4).

Conclusions: A single user of CS or AChEI was associated with a 1.6 or 1.8 fold increase in the risk of syncope among older SNF residents even after adjusting for potential confounders including functional status. The risk was significantly higher in dual users (2.1 fold), but no evidence of additive interaction was found. Clinicians should be aware of the observed syncope risks from a single or dual use of CS and/or AChEI in older patients with dementia.

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Androgen deprivation therapy and the risk of dementia in Taiwan

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Aim/Objective: To compare the risk of dementia between patients with prostate cancer receiving androgen deprivation therapy (ADT) vs ADT-naïve patients in Taiwan.

Methods: This is a retrospective cohort study using the data of one million individuals randomly sampled from the Taiwan's National Health Insurance Research Database from 1997 to 2013. We included patients aged 40+ years and newly diagnosed with prostate cancer (ICD9: 185). We excluded patients who had a history of cancer or dementia. We classified patients based on ADT. The study outcome was dementia defined by diagnosis code (ICD9: 290, 294.1, 331.0, 331.1) and medication (ATC: N06D). Dementia occurred within 6 months after the initiation of ADT was not considered as an outcome to avoid protopathic bias. We followed patients from the initiation of ADT to the occurrence of events, death or the last day of the database. We used the Cox proportional hazard model with adjustments of age, co-morbidities and co-medications to compare the risk of dementia between patients receiving ADT vs ADT-naïve patients.

Results: We included a total of 1,197 patients (75.1 % ADT group) aged averagely 72.9 (SD: 8.67) years. Among ADT group, 43.2 % and 30.5 % of the patients used antiandrogens alone and GnRH agonist alone respectively. We found 13.1% of patients received bilateral orchiectomy and 12.7% of patients received a combination of antiandrogens and GnRH agonist. The incidence rate of dementia was 27.2 vs 24.2 cases per 1000 person-year in ADT and ADT-naïve group, respectively. We did not find an increased risk of dementia in the ADT group comparing with ADT-naïve group (hazard ratio, 0.93; 95% CIs, 0.62 - 1.39).

Conclusion: The findings indicated patients in prostate cancer receiving ADT were not associated with a higher risk of dementia compared to ADT-naïve patients.

Keywords: androgen deprivation therapy, dementia, prostate cancer

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Caveates on adjustment for additional confounders following insufficient propensity score balancing

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Aim/Objective: To show the bias arising from "partial" adjustments for distinct sets of confounders by propensity score (PS), and regression or stratification after the PS balancing such as PS matching, inverse probability weighting, and stratification or regression adjustment for PS.

Methods: We show in a hypothetical example and through causal diagrams that the stratification or regression after PS balancing causes imbalance in the confounders that have been balanced by the PS if PS-balanced confounders are ignored. We also empirically illustrate the bias in the publicly available Rotterdam Tumor Bank dataset, in which strong confounders distort the association between chemotherapy and recurrence-free survival.

Results: Despite that each covariate in the possible confounder set was conditioned in either or both of the PS or Cox models, 5-year recurrence-free survival difference estimated in PS-matched cohort varied across the combinations of PS-balanced and covariate-adjusted covariate sets. The similar discrepancy was observed in doubly robust estimates with inverse probability weighting and Cox model-based standardization.

Conclusion: If additional covariates are adjusted for after PS balancing, the covariate sets conditioned in PS should be again adjusted for, or PS should be reestimated by including the additional covariates to avoid bias owing to covariate imbalance.

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Multiple imputation for survival analysis with missing covariates using non-parametric estimation

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Objectives: Multiple imputation (MI) is frequently used for survival analysis with missing covariates in many pharmacoepidemiological studies to improve estimating efficiency. However, few studies have paid attention to the potential bias caused by the imputation model misspecification. Here, we consider both proportional and additive hazard models as analysis models. We describe novel MI procedures for survival analysis which uses non-parametric conditional probability estimation aiming to obtain consistent estimate without specification of the imputation model.

Methods: For continuous missing covariates, we firstly sample imputation values by using (possibly misspecified) parametric imputation models. Thereafter, the estimating equation of a hazard model is modified by using the ratio of the conditional density estimated non-parametrically to the conditional density calculated by the parametric imputation model. For categorical missing covariates, imputation values can be directly sampled according to the conditional probability which was estimated non-parametrically.

Simulation study: After the generation of covariates and exposure, we generated censoring time and survival time according to the proportional or additive hazard model. Thereafter, some covariates were artificially missing by missing at random mechanism. We evaluated the bias and efficiency on the hazard ratio or differences estimated by complete case analysis (CCA), MI with parametric imputation model or proposed MI procedures. We evaluate proposed MI procedures using the three simulation settings: missing of continuous covariate, missing of binary covariate, and missing of both types of covariates.

Results: Simulation studies demonstrated that the proposed MI procedures reduced the bias which is caused by the imputation model misspecification. Compared with CCA, more efficient estimates were obtained by the proposed MI procedures.

Conclusion: Proposed MI procedures can be useful methods for survival analysis with missing covariates. We will demonstrate the performance of the proposed MI procedures with a simulation study using artificial missing data generated from a real-world medical database.

Keywords: Density ratio estimation, Missing data analysis, Model misspecification

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A comparison of structural nested accelerated failure-time models and structural nested mean models for survival outcomes

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Aim: Standard methods for estimating causal effects on survival (e.g. Cox regression) may be biased in the presence of time-varying confounders themselves affected by prior exposures. This study aimed to compare two causal models for survival outcomes from a practical viewpoint.

Methods: Structural nested accelerated failure-time models (SNAFMs) usually assume a deterministic relationship between observed and potential exposure-free failure-times (Robins. Biometrika 1992). Alternatively, it is possible to model causal risk differences, risk ratios and hazard ratios under structural nested mean models (SNMMs) using pseudo-observations, a novel technique to handle censoring (Tanaka, Brookhart and Fine. Biostatistics 2019). Situations in which the assumptions for SNAFMs or SNMMs are violated were reviewed.

Results: The deterministic relationship for SNAFMs may not hold when proportional hazards assumptions are violated. In the presence of competing risks, SNAFMs estimate causal effects on survival in the hypothetical world where a subject cannot die of causes other than that of interest, while SNMMs can be used to estimate causal effects on cumulative incidence functions, which reflect the survival experience of a subject in the presence of competing risks.

Conclusion: Structural nested mean models are appealing when proportional hazards assumptions are violated.

Keywords: causal inference, g-estimation, survival analysis, time-varying exposure

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Comparison of dynamic treatment regime using inverse probability weighting for dialysis patients

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Aim/Objective: We explore how dynamic treatment regime (DTR) framework can be used to evaluate the effect of erythropoiesis-stimulating agents (ESA) using a large prospective observational study of hemodialysis patients.

Methods: DTR is one in which the treatment assigned depends upon a subject's evolving time-dependent covariate history. DTR have been used to guide treatment for chronic illnesses that require frequent monitoring and therapy changes. For hemodialysis patients, erythropoiesis-stimulating agents (ESA) are prescribed so as to manage anemia, although there is concern that ESA may be associated with increased cardiovascular mortality in patients. And so, there is great current interest in answering questions of target treatment strategies, one of the DTR, like the following: Is regime for erythropoiesis-stimulating agents (ESA) ''to target hemoglobin levels to 11g/dL'' better than ''to target hemoglobin levels to 9-10g/dL'' for dialysis patients to manage anemia? Inverse probability weighting (IPW) method may be used to compare DTR by artificially censoring subjects and then adjusting for selection bias due to censoring.

Results: IPW is a simple and useful method for comparing several DTR using the observational study. We will show the DTR framework for comparing the regimes of ESA for hemodialysis patients. Also, results for the application to the prospective observational study may be presented.

Conclusion: Applying the method of IPW, observational data makes it possible to obtain answers to questions that involve DTR.

Key words: dynamic treatment regime, erythropoiesis-stimulating agents, inverse probability weighting, observational study

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Analysis of spontaneous adverse event reports derived from real-world EMR data for prospective pharmacovigilance

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Objective: Electronic Medical Record (EMR) system is useful for evaluate post-marketing drug safety surveillance. Korea Ministry of Food and Drug Safety (MFDS) has Korea Adverse Events Reporting System (KAERS) and US Food and Drug Administration (FDA) has FDA Adverse Events Reporting System (FAERS), including information on submitted adverse events. In this study, we analyzed spontaneous reports derived from adverse drug reactions (ADRs) signals of EMR-based previous pharmacovigilance algorithm.

Methods: We compared novel ADR signals (or Positively predicted signals for unknown ADRs) of previous EMR-based algorithm with spontaneous adverse event reports. EMR-based PV algorithm named MetaLAB detected unknown ADRs using real-world EMR data. We selected two system organ class (SOC) of cardiac disorder, renal and urinary disorder and three drugs to identify unknown ADRs using KAERS and FAERS. We applied the method to study comparing the ratio of the number of ADRs to the total number of reports of each drugs.

Results: For cardiac disorder in KAERS, bisacodyl(2.36%) was more higher than naproxen(2.11%) as known ADRs of cardiac disorder and lactulose(2.26%) as unknown ADRs. Number of total reports in KAERS was 3,121,787 and cardiac disorder reports was 103,301(3.31%). In FAERS, bisacodyl was 2.39%, naproxen was 1.65% and lactulose was 1.93%. Also total cardiac disorder reports was 2.10%. For renal disorder in KAERS, sucralfate(1.90%) was higher than palonosetron(1.22%) as unknown ADRs of renal disorder, when total renal and urinary disorder reports was 74,687(2.40%), and diclofenac was 2.02%. In FAERS, sucralfate was 1.84%, diclofenac was 2.51% and palonosetron was 1.48%. And total renal disorder reports was 2.02%.

Conclusion: This study demonstrates the EMR-based computational detection signals algorithm using KAERS and FAERS. We analyzed two spontaneous reports databases and found that bisacodyl and sucralfate signals are higher than other drugs. The analysis enables to identify novel ADRs for prospective pharmacovigilance.

Keywords: pharmacovigilance, adverse events, spontaneous reports, real world data

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Evaluation of Tree-based Scan Statistic for drug safety signal detection in a Chinese healthcare database: A Plasmode simulation

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Background: The tree-based scan statistic (TreeScan) is a statistical data mining tool that has been used for signal detection in drug safety studies. However, it is unclear whether TreeScan method are applicable to combine with methods for confounding adjustment.

Objective: To conduct a plasmode simulation to evaluate the performance of the TreeScan method combined with a propensity score–matched analysis of new initiator cohorts.

Methods: The simulation framework is applied to a study of high versus low-intensity statin use and new-onset of diabetes. Simulated data is based on real data drawn from linked electronic medical records and claim data in Chengdu city, China. We constructed simulation scenarios that varying the number of outcomes affected by confounding, whether confounding moved the crude estimate toward or away from the null, and the magnitude of the true effect. For each scenario, we conducted TreeScan without confounding adjustment and TreeScan with a propensity score–matching.

Results: In multiple realistic scenarios, TreeScan with propensity score matched to adjust for confounding outperformed TreeScan in unmatched cohorts. In scenarios where the estimates were positively or negatively biased by confounding for the true hazard ratio, adjusted analyses yielded estimates nearly identical to the truth while unadjusted analyses inflated type 1 error. In scenarios where confounding moved point estimates closer to the null, adjusted analyses preserved power, whereas unadjusted analyses greatly reduced power.

Conclusion: Our findings suggested that TreeScan with propensity score matching could be considered as a promising method for detecting and prioritization potential signals of drug safety. This method could be particularly useful in the context of newly marketed drugs, where there is little experience and few hypotheses regarding the safety information.

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Medication non-adherence and its predictors among new antihypertensive initiators in Japanese working age patients

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Objective: To assesses the adherence to newly initiated antihypertensives among working age Japanese, and to identify patient and provider characteristics associated with low adherence.

Methods: We identified new initiators of oral antihypertensives aged 30 to 75 years in the database, with initiation dates in Jan.2014-Jun.2016. We measured patients' adherence in proportion of days covered (PDC) using prescription claim records. We divided the cohort into 3 groups based on the PDC: low adherence (PDC<40%), medium adherence (40≤PDC<80%) and high adherence (PDC≥80%). We extracted patients' baseline characteristics using claims recorded during the 1-year baseline period prior to antihypertensives initiation, as well as prescribers' facility information, and compared them across the PDC adherence groups. We assessed the association between patient and provider characteristics, and low adherence using multivariable logistic regression analysis with generalized estimating equations to account for provider level clustering.

Results: Among 35,192 antihypertensive initiators (mean[SD] age, 51.7[8.6] years; 13,003 female and 18,589 male) identified, 1-year median PDC was 88.5% (IQR: 41.9-98.1%). Among them, 18,701 (59.2%), 5,240 (16.6%), and 7,651 (24.2%) of patients were categorized as high, medium, and low adherence, respectively. Female sex [OR (95% confidence interval (CI)) = 1.13 (1.07-1.20)], absence of comorbidity [OR (95%CI) = 1.20 (1.11-1.28)], and use of anxiolytics and hypnotics sedatives [OR (95%CI) = 1.17 (1.08-1.27)] were significantly associated with low adherence. Those initiating anti-hypertensives at clinics showed marginally reduced risk for low adherence compared to those initiating at hospitals [OR (95%CI) = 0.93 (0.86-1.00)]. Compared with those initiated on ARBs, those initiated on beta blockers [OR (95%CI) = 4.46 (4.02-4.95)] and thiazides [OR (95%CI) = 3.82 (2.75-5.31)] were more likely to have low adherence.

Conclusion: Adherence to anti-hypertensives in working age Japanese were relatively high compared to previous reports from the US. Predictors of low adherence may aid in identifying candidates for effective improvement intervention.

Keywords: Adherence; Antihypertensives; Primary prevention; PDC, Proportion of Days Covered

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Adherence, persistence and clinical outcome between generic and brand-name statin users: Retrospective cohort study using Japanese claims database

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Objective: Statins reduce low-density lipoprotein(LDL) cholesterol levels and prevent major cardiovascular events. However, non-adherence and non-persistence to statin are common problems and therefore associated with increased risk of cardiovascular events. Lack of confidence in generic medicines may reduce patients' adherence and persistence, which lead to failures in receiving their full benefit. The study aims to evaluate adherence, persistence and clinical outcomes between patients who initiated brand-name and generic statins in Japanese population.

Methods: The retrospective cohort study was based on JMDC claims database. Adult patients who initiated statins during Jan 1, 2014 and Dec 31, 2016 were included and classified into generic and brand-name groups. Propensity score matching was applied to adjust confounding factors. Adherence was measured as proportion of days covered(PDC). Persistence was measured as proportion of non-persistent users. Major Adverse Cardiac Events(MACE) composed of all-cause mortality, acute myocardial infarction, stroke and repeat revascularization was measured as clinical outcomes. Difference in adherence values was analyzed with Mann Whitney U test. Hazard ratios(HRs) and 95% confidential intervals(CIs) of non-persistence and MACE were estimated with Cox proportional hazards regression model.

Results: A total of 50,162 patients were included, 33,306(66.4%) patients initiated generic and 16,856(33.6%) patients initiated brand-name statins. The median age of the patients was 53(IQR: 46-59) and 60.9% were male. After propensity-score matching (16,446 in each cohort), better adherence was observed in generic group(PDC: median, 91.1% vs 89.6%; difference, 1.5%; p<0.0001). Similarly, fewer patients discontinued statin treatment in generic group (23.1% vs. 26.7%; HR, 0.90; 95%CI, 0.86-0.94; p<0.0001). For clinical outcomes, a slightly large number of brand-name users had cardiovascular events but difference between groups was non-significant (6.3% vs. 6.7%; HR, 0.96; 95%CI, 0.88-1.04; p=0.32).

Conclusion: The study observed a higher adherence and persistence in generic statin recipients, while there was no significant difference in clinical outcomes.

Keywords: statins; adherence; cardiovascular events; generic

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Participation in randomized controlled trials and subsequent medication adherence and quality of treatment in patients with cardiovascular diseases

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Objective: To study the impact of previous participation in international randomized controlled trials (RCT) of patients with cardiovascular diseases (CVD) on their subsequent medication adherence, visiting health facilities and on the quality of the treatment.

Methods: The study was conducted on the basis of out-patient PROFILE register. 102 patients were enrolled in the study, 46 men, 56 women (the average age 70), who participated in international RCT since 2011 till 2018 (study group). A comparable control group includes patients who had never participated in RCT. Original questionnaires were used during consultation or telephone contact with the patient. In both groups medication adherence and adherence to follow-up in medical institutions are going to be assessed. A comparison of the quality of the treatment (according to current clinical guidelines) between patients of different groups will be considered.

Results: The vital status of 7 patients was defined as "dead." 68 patients (67%) had a higher education / degree, 86 patients (84%) participated in RCT more than 1 year ago. Among RCT participants, rates of adherence to medicines' intake and attendance of health-care facilities were significantly higher than among patients in general. 82% of patients became more interested in their own health and treatment, either taking medications or visiting healthcare providers. 77% of patients visited their attending physician at least once every six months. 68% of patients adhered to the treatment regimen developed during the RCT even years after the study ended. 82% of patients showed high and medium adherence. In 62% of cases the leading reason for participation was the proposal of the doctor.

Conclusion: Participation of patients in RCT, as an ideal model of doctor-patient interaction, has a beneficial effect on patient adherence to treatment. It is expected to improve adherence in practical health care, using a number of RCT techniques.

Keywords: randomized controlled trials, medication adherence

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Trends and evaluation of online prescription fill among adults in the United States, 2009-2017

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Objectives: Filling a prescription online has become an alternative for patients to access their medications. However, the trend and pattern of filling a prescription on the internet in the United States (U.S.) remain under-investigated. This study aimed to 1) estimate prevalence and pattern of online prescription fill and 2) identify patient characteristics associated with online prescription fill among the U.S. adult population.

Methods: We used data from the 2009 to 2017 U.S. National Health Interview Survey (NHIS) which is the most comprehensive national survey to track health status, health care access, and health resource utilization among people in the U.S. Filling a prescription online was defined as adult respondents (aged 18 and over) had ever filled a prescription on the internet in the past 12 months during the survey year. The trends of online prescription fill were reported using weighted percentages adjusted by the NHIS complex sampling design. The chi-square test was used to compare characteristics between users and nonusers. Multivariable logistic regression models were used to identify predictors of online prescription fill among adult respondents.

Results: The amount of adults reported online prescription fill increased from 13,319,877 in 2009 to 25,770,957 in 2017 ($p<0.01$).
The prevalence of online prescription fill significantly increased from 5.9% in 2009 to 10.6% in 2017($p<0.01$). Among the U.S. adults, age 45-64 years old ($p<0.05$), white ($p<0.05$), females ($p<0.05$), higher education ($p<0.05$), higher income ($p<0.05$), and with insurance coverage ($p<0.05$) were more likely to fill a prescription online.

Conclusion: An increasing trend of online prescription fill from 2009 to 2017 was observed among adults in the U.S. Health care providers need to be aware of the user trend and ensure patients understand the safety of medication use from online prescription. Future research needs to further investigate reasons and safety of online prescription fill.

Key Words: Internet, prescription, National Health Interview Survey (NHIS), trend

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Adverse drug reactions of Yunnan Baiyao capsule: A multi-center intensive monitoring study in China

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Background: Yunnan Baiyao capsule (YBC), a marketed herbal medicine in mainland China, is widely used to control bleeding. This study's aim was to determine the occurrence of YBC-related adverse drug reactions (ADRs) among users of the medicine.

Methods: This hospital-intensive monitoring study was conducted in 163 hospitals across China. Consumers who used YBC (Z53020799) between June 2015 and December 2016 were included. By face-to-face interview or telephone, the circumstances and experiences of their adverse events (AEs), during drug taking and 14 days after drug withdrawal, were recorded at follow-up and later encoded by International Conference on Harmonisation (ICH) 1997. The Naranjo Adverse Reaction Probability Scale (APS) was used to determine the likelihood of ADRs.

Results: A total of 31,556 participants were included (follow-up rate 99.40%). AEs occurred in 742 participants, of which 561 were reported as "not related with drug use" by their physician-in-charge. Based on the remaining 181 cases, the overall ADR incidence was 1.17% (intention to treat) and 0.58% (per protocol), with abnormal findings mainly concentrated in the digestive system, skin and respiratory system. The top 5 frequently reported reactions were nausea and vomiting (0.1785%, 56 cases of 31,367 participants), functional diarrhea (0.1180%, 37 of 31,367 participants), stomach discomfort (0.0893%, 28 of 31,367 participants), rash (0.0574%, 18 of 31,367 participants) and gastro-esophageal reflux (0.0383%, 12 of 31,367 participants). Among them, functional diarrhea and stomach discomfort were judged as definite ADRs of YBC.

Conclusions: In this large study, treatment of YBC was found to be associated with ADRs with an incidence of 1.17%, although most were relatively mild and not considered to be life-threatening.

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An interrupted time series analysis for use of psychoactive medicines in Japan

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Aim: Multi-drug use of psychoactive medicines is a serious problem in Japan. From 2012, prescription charges of anxiolytics and sleeping drugs began to be reduced when three or more types of these medicines were prescribed simultaneously. From 2014, charges for antidepressants and antipsychotic drugs were reduced. In the current study, we evaluated the effects of this policy using electronic healthcare records (EHRs).

Methods: We used EHR data from Kyushu University Hospital. The research subjects were patients who had been prescribed a psychoactive medication from 2008 to 2018. For four kinds of psychoactive medicine, we aggregated the number of prescriptions for each patient by day, and compiled time series data for the number of simultaneous prescriptions by month. We then conducted an interrupted time series analysis for the number of simultaneous prescriptions. In the analysis model, we used a Poisson regression model for segmented analysis, and autoregressive integrated moving average model including exogenous variables (ARIMAX). As regressors, we included the intervention, time and interaction terms of both variables to detect trend changes.

Results: The number of simultaneous prescriptions was 10932 for antipsychotic drugs, 4254 for anxiolytics, 5273 for antidepressants and 16048 for sleeping drugs. Plotting the time series revealed that the numbers of all types of drugs gradually reduced around 2013. The segmented analysis revealed that estimates of the interaction suggested significant downward trends ($p < 0.05$) for antipsychotic drugs, anxiolytics and antidepressants. ARIMAX suggested non-significant downward trends.

Conclusion: The effectiveness of the policy depended on the statistical model used, but the number of simultaneous prescriptions dropped from around the time the policy was introduced. As a forthcoming challenge, appropriate methods for interrupted time series analysis in general should be considered.

Keywords: Psychoactive medicines, Interrupted time series analysis, ARIMAX

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Development and validation of ICD-10-based disease scoring system

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Objectives: To develop and validate the International Classification of Disease 10th edition (ICD-10)-based disease scoring system using Korea health insurance claims database.

Methods: We used National Health Insurance Service-National Sample Cohort, consisted of 1,125,691 participants including 55,921 deaths. Total cohort participants were divided into training set and validation set on a one-to-one basis. We calculated mortality rate ratio (MRR) using all ICD-10 to the third digit. MRR was calculated by dividing the proportion of participants with specific ICD-10 among the total cohort participants by the proportion of deaths with specific ICD-10 among all deaths. All MRRs of ICD-10 were calculated and included in the disease scoring system using the following two criteria: 1) MRR >1 and 2) chi-square >3.84. To validate the new disease scoring system, we calculated sum of the MRR for each individual in validation set. The age and gender-adjusted hazard ratio and C-statistics were calculated.

Results: Participants in training set and validation set were 372,595 and 374,221, respectively. Selected ICD-10 codes were 164 from total 1,384 of ICD-10 by applying our predetermined criteria. In validation set, adjusted hazard ratio was 1.11 (95% confidence interval [CI]: 1.06-1.15), 1.67 (95% CI: 1.59-1.75), 2.45 (95% CI: 2.31-2.60), 3.20 (95% CI: 3.00-3.43), 4.68 (95% CI: 4.29-5.10), and 6.17 (95% CI: 5.70-6.68) in the group with 0-2, 2-4, 4-6, 6-8, 8-10, and >10 of MRR, respectively, compared with group with 0 of MRR. Adjusted C-statistic was 0.887 (95% CI: 0.884-0.890).

Conclusion: New disease scoring system which we developed may offer improvements in predicting the risk of mortality.

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Development and validation of multi-view inappropriate medication use prescription detection model

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Objectives: Develop an inappropriate medication use prescription detection model using multi-view topic modeling method combined with the topic matching method, and assess the validity of the model.

Methods： A multi-view extension of the latent Dirichlet allocation topic modeling algorithm was chosen to generate the diagnosis-medication topic models indicating the underlying health status of patients using diagnosis and medication as variables, with data from the Chinese Monitoring Network for Rational Use of Drugs (CMNRUD) database. Each topic consisted of a set of diagnoses, medications that were highly related to each topic, and the percentages for each of these. Topic mapping was used to calculate the similarities of distribution of the diagnoses and medications on the topics built in the previous step and find the inappropriate medication use prescriptions by setting a threshold. The prescription manual review result by experts in the Beijing Regional Prescription Review (BRPR) database was used as the gold standard to assess the validity of the model. We also conducted a sensitivity analysis by randomly sampling the validation prescriptions and compared the model performance.

Results: A total of 44 million prescriptions was used to generate topics using the diagnoses and medications from the CMNRUD database. A 15,000 random samples of the BRPR database were used for validation, and the model had a sensitivity of 81.84% and a specificity of 47.38%, and the positive predictive, negative predictive values were 14.46%, 96.00%, respectively. The model showed a preferable stability under different sampling proportion.

Conclusions: Multi-view topic modeling method with the topic matching method can detect inappropriate medication use prescriptions combining. Considering the mediocre specificity, with moderate sensitivity, this model can be used as a primary screening tool and will likely complement and improve manual review.

KEY WORDS： inappropriate medication use prescription, topic model, latent Dirichlet allocation, multi-view learning, prescription review

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Impact of chronological changes in propensity to be exposed a comparison validity in health insurance claim database

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Background and Objective: Using observational data for early, near real-time post-approval safety assessments is challenging. The aim of this study is to assess whether comparison validity be affected by the timing from a new drug launch because of potential chronological changes in the composition of user population.

Methods: We conducted a retrospective cohort study using Japanese health insurance claim database between January 1st 2011 and December 31st 2015. Study population was identified by dispensing records of a target drug, mirabegron (MIRA) as newly marketed drug on September 2011 and antimuscarinics (AMs) as old competitors for the treatment of overactive bladder. The earliest prescription date was selected as the index date if the target drug had not been used during 6-month lookback period. Patients characteristics was summarized and compared for the new users, MIRA and AMs in every six months during the study period. We estimated propensity score models on all eligible initiators of each target drug and investigated the chronological composition changes.

Results: The study population included 10,556 patients and of those 2,866 patients used MIRA (27.2%). The number of patients and MIRA use in each consecutive six-month period were 0 (0%), 12 (3.8%), 31 (5.8%), 105 (16.2%), 181 (22.6%), 251 (24.2%), 404 (26.8%), 473 (31.9%), 601 (33.1%), 808 (38.9%), respectively. AMs patients were more likely female, whereas MIRA patients were more male, slightly older and more likely to have abnormal findings in electrocardiogram. The difference on mean propensity score for each six intervals was decreased chronologically. With increasing market penetration, the initiators of MIRA became more similar to those initiated into treatment with AMs as indicated by increasingly overlapping propensity score distributions.

Conclusion: The comparison validity was affected by the timing from a new drug launch.

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Validity of claims based definitions for ulcerative colitis in Japan: Methodology and pilot study results from the Validate-JUC study

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Aim/Objective: In Japan, although administrative claims database epidemiological research is advancing, validation studies of claims-based definitions to define major medical conditions are lacking. We aim to review, modify and develop a claims based definition for ulcerative colitis (UC) and assess its validity against “gold standard” data from medical records by calculating positive predictive value (PPV).

Methods: This study is a cross sectional review of claims data and medical records in two large hospitals in Japan. Claims-based algorithms, gold standard definitions, and abstraction forms for UC were developed by a steering committee comprised of clinical and epidemiological experts from Japan. The cases were independently reviewed by an adjudication committee who made the final decision on the disease status. The PPV for UC was calculated based on 20 cases from each site. The abstraction form and claims-based definition were modified through this pilot chart abstract and adjudication process to create a claims-based definition with the highest validity.

Results: We identified 709 UC patients at site 1 with a mean age of 43.61 years and 43% were female; the corresponding values for site 2 were 448 patients, 45.27 years and 51% female. The initial PPV calculated was 75% at site 1 and 85% at site 2. Site 1 PPV increased to 83.33% when the algorithm was remodelled to exclude Behçet’s Disease.

Conclusion: The overall PPV of 84.17% for the claims-based algorithm for UC fell within the range of previous US (50-93%) and Canadian (81.4-97.4%) UC and inflammatory bowel disease (IBD) validation studies, and within the range obtained by an Israeli IBD validation study (82-97%). A similar PPV in the main Validate-JUC study means the algorithm developed will be considered a validated model which can be used for future Japanese database research studies, in line with the strategic aims of the Japanese regulatory agency (PMDA).

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Validity of claims-based definitions for rheumatoid arthritis, selected cancers and infectious diseases in Japan: Results from Validate-J Study

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Aim/Objective: The National Claims Database (NDB) was launched in 2011. Interest in using NDB and other large databases is mounting, especially with the growing emphasis on real world data. However, validation research of claims-based diagnoses in Japan is limited. We validated claims-based diagnoses for rheumatoid arthritis (RA), selected cancers and infectious diseases (ID) in Japan.

Methods: We designed a multi-institutional validation study using hospital claims data in Japan. We developed claims-based algorithms for RA, selected cancers and ID: herpes zoster (HZ), mycobacterium tuberculosis (MTB), non-tuberculous mycobacterium (NTM), and pneumocystis jiroveci pneumonia (PJP), and identified claims-based cases from two hospitals between 1/2012- 12/2016. Gold standard definitions and abstraction forms were developed by a steering committee of Japanese clinical and methods experts, and RA and ID cases were independently adjudicated. We calculated positive predictive values (PPV) for RA, ID and cancer, and sensitivity and specificity for cancer.

Results: Partial data generated 2,437 RA, 2,272 HZ, 161 MTB, 405 NTB, 162 PJP, and 15,860 cancers. Mean age; % female for RA, all ID, and any cancer were 63; 72%; 64; 54%, and 66; 53%, respectively. PPVs (95% confidence intervals) were RA= 77% (73-81); HZ= 76% (64-88); MTB= 92% (84-99); NTM= 80% (69-91); PJP= 32% (19-44); Colorectal= 87% (84-90); Breast=88% (86-89); Lung= 91% (88-93); Pancreas=90% (85-94); Gastric=91% (89-94); Melanoma= 46% (28-65); Lymphoma= 82% (78-86); Any malignancy= 84% (83-85). PPVs from sensitivity analyses were 7-10% higher than those in main analyses.

Conclusion: Compared to US data, PPVs for RA were similar and several cancers had better PPVs (87% - 91% (Japan) vs 60% - 82% (US)); results for most ID conditions are the first ever reported. As the Pharmaceuticals and Medical Device Agency encourages validation studies to support the validity of database research for postmarket surveillance, VALIDATE-J serves as a model.

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Identifying incident cancer cases in medicine dispensing claims: A validation study using Australia's Pharmaceutical Benefits Scheme (PBS) data

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Aim: Dispensing claims are used commonly as proxy measures in pharmacoepidemiological studies, however, their validity is often untested. We quantified the level of ascertainment and potential biases arising when using dispensing claims to identify incident cancer cases in cohort studies.

Methods: We used Department of Veterans' Affairs client data linked with the New South Wales (NSW) Cancer Registry and Repatriation and Pharmaceutical Benefits Scheme data. We included clients aged ≥65 residing in NSW between July 2004 and December 2012. We matched clients with a cancer diagnosis to clients without a diagnosis based on demographic characteristics and available observation time. We used dispensing claims for anticancer medicines dispensed between July 2004 and December 2013 as a proxy for cancer diagnosis and calculated sensitivity, specificity, positive predictive values and negative predictive values compared with cancer registry data (gold standard), overall and by cancer site. We illustrated the potential for misclassification by the proxy in a cohort of people initiating opioid therapy.

Results: We identified 15,679 incident cancer diagnoses in 14,112 clients from the cancer registry and 62,663 clients without a diagnosis. The proxy's sensitivity was 30% for all cancers and ranged from 10-67% for specific cancers. Specificity was >90% for all cancers. The proxy correctly identified 26% of people with a cancer diagnosis who initiated opioid therapy, failed to identify 74% those with a cancer diagnosis, and was most robust for clients with breast cancer (61% were correctly identified).

Conclusions: Use of anticancer medicine dispensings for identifying people with incident cancer diagnosis is a poor proxy. Excluding people with evidence of anticancer medicine dispensing from cohort studies may remove a disproportionate number of women with breast cancer. Researchers excluding or otherwise using anticancer medicine dispensing to identify people with cancer in pharmacoepidemiological studies should acknowledge the potential biases introduced to their findings.

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Anti-osteoporosis treatment pattern after hip or vertebral fractures among postmenopausal women in China

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Objective: To investigate the prescription patterns and related influencing factors for AMOs among postmenopausal women with a hip or vertebral fracture in Fuzhou, China.

Methods: This is a retrospective cohort study based on an existing electronic health record database (National Healthcare Big Data in Fuzhou, China, 37 hospitals included). Women ≥50 years old with newly diagnosed hip or vertebral fractures (index date; ICD-10 codes: S12, S22, S32, S72, T08) between Jan 1, 2010, to Dec 31, 2017 were included. Patients diagnosed with Paget's disease or malignant neoplasm, or received AOMs (Bisphosphonates; Calcitonin; Selective Estrogen Receptor Modulators (SERM); Parathyroid Hormone (PTH); RANKL) prior to the index date were excluded. Post-fracture osteoporosis therapies were summarized by fracture site. Multivariate logistic regression was performed to identify influencing factors to AOMs prescription.

Results: Data from 9,105 women of mean (SD) age of 66 (11) diagnosed with vertebral fractures, and 7,106 women of mean (SD) age of 75 (11) diagnosed with hip fractures years were extracted for analysis. Among vertebral fractures women, 1,606 (17.6%) were prescribed at least one AOMs within 2 year post-fracture. Main prescriptions were Bisphosphonare (638, 7.0%) and Calcitonin (1,296, 14.2%). In addition, 2,047 (22.5%) received Calcium and 1,870 (20.5%) received Vitamin D. Among hip fractures women, 1,815 (25.5%) were prescribed at least one AOMs within 2 year post-fracture. Main prescriptions were Bisphosphonare (413, 5.8%) and Calcitonin (1,597, 22.5%). In addition, 2,084 (29.3%) received Calcium and 2,296 (32.3%) received Vitamin D. Overall, hip fracture, pre-fracture osteoporosis diagnosis, older age, history of rheumatoid arthritis, and corticosteroids exposure prior to index date were significantly correlated to AOMs prescription within two years.

Conclusion: In a real-world setting, anti-osteoporosis treatment for postmenopausal women was suboptimal, relative to current guidelines. Adherence programs could be made into the barriers to optimize osteoporosis management in Fuzhou, China.

Keywords: Anti-osteoporosis therapy; Postmenopause; Fracture

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Changes of National Health Insurance reimbursement criteria on drug prescribing patterns and medical expenditures of osteoporotic fractures

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Aim: Since 2011, Taiwan's National Health Insurance Administration required an additional check-up of bone mineral density to qualify the reimbursement of anti-osteoporosis medications (AOMs). This study aimed to evaluate the impact of this reimbursement regulation on prescribing patterns of AOMs and subsequent fracture related medical expenditures of patients with osteoporotic fractures.

Methods: By using the National Health Insurance Research Database, patients with incident osteoporotic fracture, including hip or vertebral fracture, from 2006 to 2015 were defined as our study population. Patients younger than 50 years old or prescribed with AOMs within one year before incident fracture were excluded. The proportion of patients receiving AOMs, and subsequent osteoporotic fracture related medical expenditures within one year postfracture were evaluated. The interrupted time series study design with segmented regression model was used to quantitatively explore the impact of the policy regulation on the level (immediate) and trend (long-term) changes of these research outcomes. The evaluation interval was defined in a quarterly manner from 2006 to 2015.

Results: Our study enrolled 118,493 and 172,431 patients with incident hip or vertebral fracture, respectively. The change of reimbursement criteria was associated with a decreased in AOMs prescribing rate of patients with vertebral fracture. (Level change: -4.8%, 95% CI:-8.7%, -0.9%, p=0.0198; Trend change: -0.6%, 95% CI:-0.9%, -0.5%, p=0.0027). The prescribing rate was decreased but without significant different from that before regulation for patients with hip fracture. Noteworthy, the policy regulation was associated with an increasing trend of osteoporotic fracture related medical expenditures. (Hip: Trend change: 13 US Dollars (USD), 95% CI:8-18, p<0.001: Vertebral: Trend change: 2 USD, 95% CI:0.2-3, p=0.0394)

Conclusion: The restriction of reimbursement for AOMs decreased the prescribing rate of AOMs, while introduced higher subsequent osteoporotic related medical expenditures.

Keywords: Osteoporosis, Anti-osteoporosis medications, Osteoporotic fracture, National Health Insurance

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Osteoporotic fractures associated with the use of rivaroxaban vs warfarin or dabigatran among patients with atrial fibrillation

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Aim: To investigate the risk of osteoporotic fractures with rivaroxaban use and compare it with warfarin and dabigatran in patients with atrial fibrillation (AF).

Methods: This was a population-based cohort study using a clinical database of Hong Kong Hospital Authority that covers 7.4 million people. Patients newly diagnosed with AF during 2010-2016 and prescribed rivaroxaban, warfarin, or dabigatran were included and followed until 31 December 2017. The risk of osteoporotic hip and vertebral fracture in users of rivaroxaban was compared to warfarin and dabigatran using Poisson regression.

Results: Based on 72,373 new patients with AF, two separate propensity score weighted-cohorts were formed for the comparisons between rivaroxaban and warfarin (N=11,824) and between rivaroxaban and dabigatran (N=10,541). When compared to warfarin, rivaroxaban use was associated with a lower risk of osteoporotic fractures (incidence rate ratio [IRR]=0.48, 95% confidence interval [CI]=0.33-0.71). The association with lower risk was not statistically significant in patients with short-term use of medication (<30 days; IRR=0.82, 95%CI=0.33-2.01), but was significant in those with medium-term use (between 30 days and <1 year; IRR=0.24, 95%CI=0.10-0.57) and long-term use (≥1 year; IRR=0.57, 95%CI=0.34-0.95). When compared to dabigatran, the risk of osteoporotic fracture with rivaroxaban was similar (IRR=0.92, 95%CI=0.62-1.36). The results of all subgroup and sensitivity analyses suggested no differences in fracture risk between rivaroxaban and dabigatran.

Conclusion: Among patients with AF, the risk of developing osteoporotic fractures in those receiving rivaroxaban appears to be lower than in those receiving warfarin, but similar to those receiving dabigatran.

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A database study of clinical features and treatment patterns with biologics in patients with Crohn's disease in Japan

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Aims/Objectives: Biologics have been used to treat moderate-to-severe active Crohn's disease (CD). In Japan, infliximab was approved for reimbursement for CD treatment in 2002, adalimumab in 2010 and ustekinumab in 2017. Limited real-world information is available describing treatment patterns with ustekinumab in Japan.

Methods: This retrospective cohort study used the Japan Medical Data Center (JMDC) database to investigate biologics treatment patterns in CD patients from 01 January 2010 to 30 September2018. The JMDC is a longitudinal claims database collecting all claims information of employees and their family members, covering 4 million patients with diagnoses and treatments recorded. Patients prescribed at least one medication for treating CD were hierarchically assigned into exposure groups: ustekinumab, adalimumab, infliximab and non-biologics. The index date was the first prescription date during the study period. Eligible patients were followed-up until study end.

Results: Among 4048 patients with a diagnosis of CD (ICD-10-CM K50.x), 62.7% were male, 46% were aged 18-39 years, 116 (2.9%) received ustekinumab, 654 (16.2%) received adalimumab and 1013 (25.0%) received infliximab. Mean treatment duration respectively, was 34.1 weeks (SD 18.9), 123.1 weeks (SD 98.8), 193.7 weeks (SD 142.5), reflecting length of market availability. Among ustekinumab users, the median dose of intravenous induction therapy was 390mg and the median dose of subcutaneous maintenance therapy was 90mg. 67.2% of ustekinumab users continued treatment until study end. 38 (32.8%) ustekinumab users switched drugs, 3 to another biologic and the majority to non-biologic drugs. Among ustekinumab users, CD-related hospitalizations, surgical procedures and complications were reported in 47.6% (n=49), 21.4% (n=22), and 13.6% (n=14) patients, respectively within 12 months prior to index date, versus 21.4% (n=22), 7.8% (n=8), 8.7% (n=9) after the index date until study end.

Conclusion: CD primarily affects young men and causes substantial morbidity in Japan. Reductions in CD-related hospitalizations and complications were observed after ustekinumab treatment.

Keywords: Crohn's disease, Japan, ustekinumab, complication

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Prevalence, safety and long-term retention rates of biologics in Hong Kong from 2001 to 2015

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Aim: As biologics usage are expanding to indications beyond their original therapeutic targets, this study aimed to investigate long-term prescribing patterns and the safety of biologics in real clinical settings in Hong Kong.

Methods: This was a population-based drug utilization study in Hong Kong using a territory-wide electronic medical database Clinical Data Analysis and Reporting System (CDARS). Patients who received biologic treatments from 2001 to 2015 were identified and their corresponding demographic and clinical details retrieved from CDARS. The annual prevalence of biologic prescriptions, the long-term retention rates and incidence rates of infections associated with biologic treatments were evaluated.

Results: A total of 30,298 patients (male: 44%) prescribed biologic treatments were identified from CDARS from 2001 to 2015. The annual prevalence of biologic prescriptions increased from 0.1 to 16.1 per 100 persons for both sexes. Infliximab had the highest first year retention rate of 95.6% among all biologics and continuously attained the highest retention rate from the second to the fifth year. The overall incidence rate of serious infections was less than 5 per 100 person-years. Specifically, the incidence rate of tuberculosis, upper and lower respiratory infections and herpes zoster were 0.52, 3.24, 4.99 and 1.01 per 100 person-years respectively.

Conclusion: This population-based study revealed an increasing prevalence of biologic prescribing. Results from the study described the long-term retention rates and incidence rates of serious infections of biologic treatments for all indications and confirmed the safety of biologic treatments. Since this study provides an overview of all biologic utilization, further studies on cost-effectiveness, safety, and compliance of treatment in different patients group are still warranted.

Keywords: Biologics, drug utilization, drug safety, pharmacoepidemiology, real-world evidence, electronic medical database

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Safety regarding infectious events of biosimilars compared to other drugs in rheumatoid arthritis: A systematic review and network meta-analyses

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Objective: This network meta-analysis was to compare the relative safety performance concerning infection among the biosimilars and their reference drugs, with other available drugs for the treatment of rheumatoid arthritis (RA).

Methods: A systematic review of Medline, Embase, the Cochrane library, and clinicaltrials.gov from inception through April 22, 2018 was carried out to identify relevant randomized controlled trials (RCT). And a network meta-analysis under frequentist framework with random effect model was conducted among all the biosimilars and their reference drugs versus other biological DMARDs, conventional DMARDs, Janus kinase (JAK) inhibitors, corticosteroids or placebo in adult patients with RA. The outcomes we used were serious infectious events (SIE), which means the infection requiring intravenous antibiotics or hospitalization, upper respiratory infection (URI) and Urinary tract infection (UTI). To facilitate the interpretation, we used risk ratio (RR) as the treatment effect.

Results: 51 RCTs with 23,347 patients were included in the analyses. There was no statistically significant difference between the biosimilars and their corresponding reference drugs. For the occurrence of SIE, infliximab was the only drug showed statistically significant difference compared to placebo and other biological DMARD [RR:1.79, 95% CI:1.12-2.84; RR:4.41, 95% CI:1.29-15.06]. Regarding the UTI and URI, all the drugs did not show statistically significant difference with placebo, but what was worth noting was based on mixed comparison, rituximab showed a better behavior on occurence of UTI compared to adalimumab infliximab and their biosimilars and JAK inhibitor. According to the results of ranking, except for biosimilar of adlimumab whose results displayed a considerable imprecision, infliximab and its biosimilar showed the worst performance than other biosimilars and their reference drugs.

Conclusion: In terms of occurrence of SIE, UTI or URI, no statistically significant differences were found between all biosimilars and their corresponding drugs, among which Infliximab and its biosimilar seem to have the worst safety performance.

Keywords: Biosimilar, Rheumatoid arthritis, Safety

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Estimation of healthcare costs for multiple myeloma in Japan using a nationwide claims database

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Objective: To estimate cost trajectory of interval costs and cumulative costs up to 5 years for multiple myeloma (MM) patients in Japan, and explore factors associated with the first 3-month costs and the first-year costs for MM.

Methods: This retrospective cohort study was conducted using anonymous claims data provided by Medical Data Vision Co., Ltd. Patients with newly diagnosed MM were collected from April 1 2008 to Sep 30 2014 and followed until Sep 30 2015. We excluded patients aged younger than 18 years, or followed less than one year since diagnosis except patients who died within one year. Age, sex, charlson-comorbidity index (CCI) score, year of diagnosis, treatments, and death were considered as potential factors associated with first 3-month costs, and first year costs. The revised Basu and Manning method was used to estimate the cost trajectory up to 5 years, which considered the survival effect and the different cumulative rate on costs during different intervals. In main analysis, interval costs after patient's death was contributed to true zeros. Associated factors were conducted based on generalized linear model with log link function and gamma distribution.

Results: Finally, 482 patients were included in the analysis with a mean age of 70.4 years. Healthcare costs for MM patients were $78,514 as 5-year cumulative costs, constituted $21,091 for the first 3 months, and $43,666 for the first year. CCI score, and treatments were found highly associated with both the first 3-month costs and first year costs.

Conclusion: Healthcare costs of patients with MM were substantial. Among predisposing factors, comorbidity score and treatments were significant predictors of costs. The usefulness of claims data as the evidence for affordable healthcare systems deserved more attention.

Keywords: healthcare costs; associated factors; multiple myeloma; claims database

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Use of phosphodiesterase 5 inhibitors reduces risk of colorectal cancer in men with benign colorectal neoplasms

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Background & Aims: Phosphodiesterase 5 (PDE5) inhibitors have been proposed to have chemopreventative effects on colorectal cancer (CRC), although data are needed from population-based studies. We performed a nationwide cohort study to investigate the association between use of PDE5 inhibitors and risk of CRC in men with benign colorectal neoplasms.

Methods: We identified men who received a diagnosis of benign colorectal neoplasm from July 2005 through March 2015 that were listed in the Swedish Hospital Discharge Register. We linked data with those from other national Swedish registers to obtain information about prescription of PDE5 inhibitors and CRC diagnoses. Cox regression was used to calculate hazard ratios (HRs) and 95% CIs.

Results: A total of 4823 patients were prescribed with PDE5 inhibitors during the study period; the incidence rate of CRC was 2.64 per 1000 person-years for men prescribed PDE5 inhibitors compared to 4.46 per 1000 person-years for men without a prescription. We found a significant negative association between PDE5 inhibitor use and risk of CRC (adjusted HR, 0.65; 95% CI, 0.49–0.85); the decreased risk of CRC was associated with an increased cumulative dose of PDE5 inhibitors (P=.003). PDE5 prescription was associated with greater reduction in risk for advanced-stage CRC (adjusted HR, 0.61; 95% CI, 0.37–1.00) than early-stage CRC (adjusted HR, 0.70; 95% CI, 0.50–0.98), but the difference was not significant.

Conclusions: In a nationwide population-based study of men with a diagnosis of benign colorectal neoplasm in Sweden, we found evidence that use of PDE5 inhibitors associates with a reduced risk of CRC. Further studies are needed to confirm the observed association.

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Compare effectiveness of abiraterone and enzalutamide in patients with metastatic castration-resistant prostate cancer in Taiwan

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Background: Abiraterone and enzalutamide, new androgen receptor (AR) pathway-targeting agents, are first-line treatments for metastatic castration-resistant prostate cancer (mCRPC), but head-to-head comparisons between these medications remain unclear.

Objective: To compare the overall survival rate between abiraterone and enzalutamide in patients with mCRPC in the real-world practice.

Methods: This was a retrospective cohort study by using the electronic medical records database from the largest medical center (about 3,100 beds) in Taiwan. We included the patients with mCRPC and newly initiating abiraterone or enzalutamide between January 1, 2016 and December 31, 2018. We defined the first prescription of abiraterone or enzalutamide as the index date. The primary outcome was overall survival rate from the uses of abiraterone or enzalutamide to the all-cause death or end of observation date based on the intention-to-treat analyses. A multivariable Cox proportional hazard model was used to estimate time-to-event hazard ratio (HR) and 95% confidence interval (CI) between two groups.

Result: We enrolled 219 patients with mCRPC newly receiving either abiraterone (n=146, 67%) or enzalutamide (n=73, 33%) with the mean age of 76.0 years (SD: 8.8). A total of 137.2 person-years of abiraterone use and 39.8 person-years of enzalutamide use were included. After adjusting the age, co-morbidity, co-medication, index year, Eastern Cooperative Oncology Group (ECOG) score, Gleason score (GS) and metastatic stages, enzalutamide posed the lower risks of all-cause mortality (adjusted HR: 0.25, 95% CI: 0.08-0.76) than abiraterone.

Conclusion: Compared to abiraterone, enzalutamide provided better overall survival benefits than in patients with mCRPC. Future large-scale studies were suggested to confirm our finding.

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Comparative efficacy and safety of angiogenesis inhibitors in the treatment of non-small cell lung cancer: Systematic review and network meta-analysis

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Objectives: To comprehensively compare and rank the efficacy and safety of angiogenesis inhibitors for patients with advanced or metastatic non-small cell lung cancer (NSCLC).

Methods: We searched PubMed, Cochrane Central, Scopus and ClinicalTrials.gov systematically for the randomized control trials (RCTs) that examined efficacy and safety of angiogenesis inhibitors for patients with advanced or metastatic NSCLC. Network meta-analyses (NMA) were performed using random-effects modeling to estimate the risk ratio (RR) and 95% confidence intervals (CIs). Primary outcomes were progression-free survival (PFS) and overall hypertension. Secondary outcomes were objective response rate (ORR), severe hypertension, neutropenia, anemia and thrombocytopenia.

Results: A total of 58 studies with 18095 patients (median age 62.5 years; 60.0% male; 82.4% stage IV NSCLC) were included. NMA showed that afatinib had a potentially better efficacy in terms of PFS and ORR compared to all other angiogenesis inhibitors. Afatinib was significantly improved progression-free survival (PFS) compared to gefitinib (RR 2.46; 95% CI 1.04-5.97) and standard chemotherapy (SCMT) (RR 2.38; 95% CI 1.06-5.36). For ORR, afatinib was more effective than SCMT (RR 4.23; 95% CI 1.51-11.90). However, afatinib was associated with the highest risk of anemia compared to gefitinib (RR 7.23; 95% CI 1.11-47.31) and SCMT (RR 4.80; 95% CI 0.82-28.05). Bevacizumab was associated with a higher risk of overall hypertension (RR 4.93; 95% CI 3.14-7.74) and severe hypertension (RR 8.16; 95% CI 3.14-21.20) versus SCMT.

Conclusion: Our NMA suggests that the efficacies of afatinib in terms of PFS and ORR for advanced or metastatic NSCLC were comparatively better, whereas the toxicities of afatinib and bevacizumab were relatively higher compared to all other angiogenesis inhibitors.

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Comparing effectiveness of first-line tyrosine kinase inhibitors in advanced lung adenocarcinoma patients with EGFR mutation using real-world data

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Objective: The efficacy of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) in treating advanced lung adenocarcinoma with EGFR mutation has been demonstrated in many studies, but the effects of various EGFR TKIs have not been compared in a real-world setting. The objective was to compare the effectiveness of various EGFR TKIs in advanced lung adenocarcinoma with EGFR mutation using a retrospective cohort study design.

Methods: We extracted patients with stage IIIB/IV lung adenocarcinoma (ICD-O-3: C33 to C34) harboring EGFR mutation, who were at least 20 years old and received either gefitinib, erlotinib, or afatinib as the first-line therapy from the Taiwan Cancer Registry Database (TCRD) (2011-2015). The information of mortality and drug utilization was obtained from the Death Registry and National Health Insurance Databases. Outcome measures included all-cause and cancer-specific mortality and time to the next-treatment.

Results: After applying the inclusion and exclusion criteria, there were 5429 patients using gefitinib, 1536 patients using erlotinib, and 913 patients using afatinib as the first-line EGFR TKIs. The Kaplan-Meier estimates showed the median survival time was 19.73 months for gefitinib, 21.03 months for erlotinib, and 24.73 months for afatinib (log-rank p-value<0.0001). The adjusted hazard ratio (HR) was 0.91 (95%CI: 0.83-0.99, p-value=0.0303) for erlotinib and 0.77 (95%CI: 0.68-0.88, p-value<0.0001) for afatinib, using gefitinib as the reference with multivariable Cox regression. The median time to the next treatment was 10.80 months for gefitinib, 12.13 months for erlotinib, and 20.47 months for afatinib (log-rank p-value<0.0001). The adjusted HR of time to the next treatment was 0.81 (95%CI: 0.72~0.91, p-value=0.0003) using gefitinib as the reference.

Conclusion: This study demonstrated that afatinib and erlotinib were more effective than gefitinib in treating advanced lung adenocarcinoma. Afatinib was associated with a 23% reduction in risk of mortality and 19% reduced chance of changing to the next treatment.

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Real-world treatment trends of lung cancer: Time-series analysis using South Korea's nationwide healthcare database, 2012-2017

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Aim/Objective: Despite lung cancer therapy guidelines are being published annually, with an update, real-world evidence of lung cancer therapy in Korea remains unknown. Our objective was to assess the trends and the patterns of therapeutic options for patients with lung cancer in real-world practice.

Methods: We conducted a time-series analysis using national health insurance sampled data from 2012 to 2017. Study subjects consisted of patients who were diagnosed with lung cancer (ICD-10: C33, C34). Study therapeutic options included surgical therapy, radiotherapy, and systemic treatment. The systemic treatment regimens are categorized into platin-based chemotherapy, non-platin based chemotherapy and targeted therapy. We described the yearly treatment prevalence by dividing the sum of patients who received study therapeutic options by the number of patients with lung cancer in the respective year. We used the Cochran-Armitage trend test to assess the changes in yearly prevalence.

Results: Of 14,804 patients with lung cancer, 61.97% of the patients were over 65 years of age, and 64.77% were male. Among patients with lung cancer, 4,073 patients (27.51%) received systemic therapy, 1,713 patients (11.57%) received radiotherapy, 1,211 patients (8.18%) received surgical therapy. Among systemic treatment, the most common regimen was platin-based chemotherapy (16.70%), followed by non-platin based chemotherapy (13.62%), and targeted therapy (9.45%). From 2012 to 2017, the prevalence of patients treated with surgical therapy increased from 7.97% to 9.07% (p-for-trend<0.05). In contrast, the prevalence of radiotherapy and systemic therapy decreased from 13.27% to 9.18%, and from 29.90% to 25.28%, respectively (p-for-trend<0.001).

Conclusions: The increase in the prevalence of surgical method may indicate the increase of patients diagnosed with early-stage lung cancer over the study period. Consistent with current National Cancer Center Network (NCCN) treatment guidelines, platin-based chemotherapy was the most common regimen group among systemic treatments, which was in line with findings from US.

Keywords: Lung cancer, Real-world evidence, Healthcare database, Therapeutic options