112 年年會 海報論文展示：原著論文

目錄

原著論文　112_A 1

膽結石患者之糞便微菌叢與代謝物之變化

The alteration of fecal microbial and metabolic profile in gallstone patients

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Background

Gallstone disease is a prevalent health concern leading to numerous cholecystectomies. Cholesterol stones (CS) and pigment stones (PS) are two primary types of gallstones. CS is associated with metabolic disorders and high biliary cholesterol, while PS is mainly related to calcium hydrogen bilirubinate. The exact role of gut microbiota in gallstone formation is still being studied. We aim to explore the crosstalk between gut microbiota, gut metabolomic, and metabolic parameters in gallstone patients compared to controls.

Method

From March 2019 to February 2021, we recruited gallstone and healthy participants. Fresh stool samples were collected before cholecystectomy and frozen. 16s rRNA sequencing was performed, followed by differential abundance analyses. UHPLC-MS/MS was used for quantifying fecal short-chain fatty acids (SCFAs) and bile acids.

Results

20 gallstone patients and 30 healthy subjects for control group were enrolled. A total of 777 Operational Taxonomic Units (OTUs) at 97% sequence identity. The control group manifested abundance of *Faecalibacterium* and *Prevotella 9*, whereas *Desulfovibrionaceae* and *Bacteroides uniformis* were notably present in CS group and more *Escherichia-Shigella* in PS group (Figure 1, Table 1). In metabolite analysis (18 qualified participants), only n-butyric acid displayed significant higher level in controls than gallstones group ($p < 0.01$). Specific bile acids, including 3α-hydroxy-12 ketolithocholic acid, deoxycholic acid, and cholic acid showed no intergroup differences (Figure 2).

Conclusion

We identified certain bacterial taxa that are different between PS, CS and control group, n-butyric acid may serve as the biomarker for differentiate gallstones patients. However, future research is still needed to establish the correlation between the gut microbiota and the metabolites.

reported by LEfSe

LEfSe (LDA > 4.0)	Control	CS	PS
Phylum			*Fusobacteria* *Actinobacteria*
Class			*Fusobacteriia*
Order			*Enterobacteriales* *Fusobacteriales*
Family	*Ruminococcaceae*		*Bacteroidaceae* *Enterobacteriaceae* *Fusobacteriaceae*
Genus	*Prevotella_9* *Faecalibacterium* *Prevotella_2*	*Fusobacterium*	*Bacteroides* *Acidaminococcus*
Species	*Bacteroides plebeius DSM_17135*	*Bacteroides uniformis* *Bacteroides fragilis*	

Table 1. Dominant families in each group

Figure 1. Known taxa abundance reported by linear discriminant analysis effect size (LEfSe) in the bacterial community.
C: control; CS: cholesterol stones; PS: pigment stones

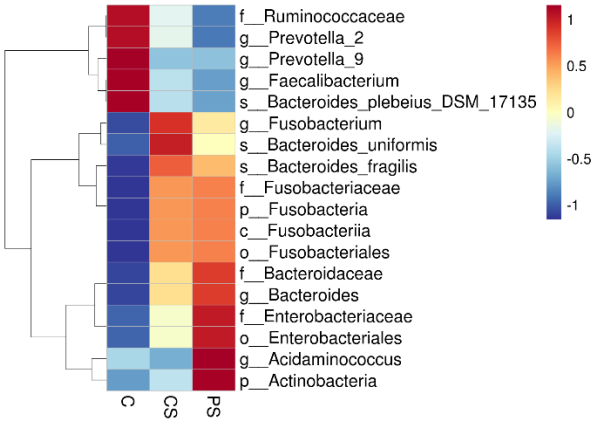
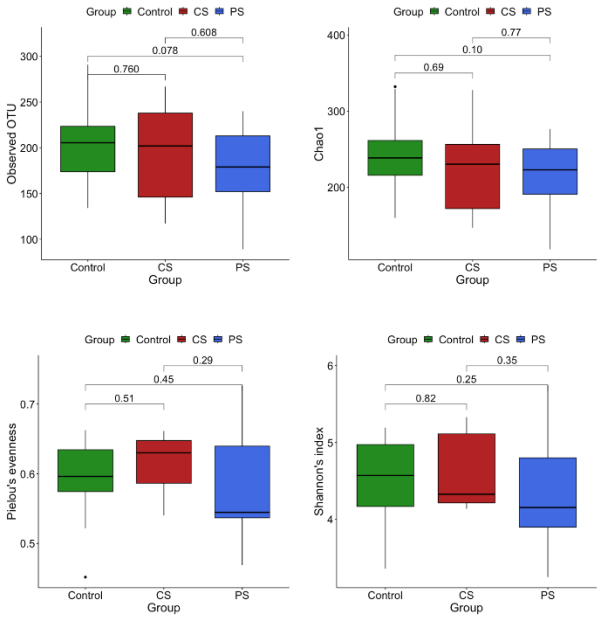


Figure 2. Measurements of SCFAs and bile acids.
12-keto LCA: 3α-hydroxy-12 ketolithocholic acid; DCA: deoxycholic acid; CA: cholic acid



原著論文　112_A 2

B 型肝炎相關肝癌射頻消融術後局部與遠處復發之預測因子

Distinct predictors of local and distant recurrence in patients with HBV-related hepatocellular carcinoma receiving radiofrequency ablation

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Background

In patients with hepatocellular carcinoma (HCC) receiving radiofrequency ablation (RFA), tumor, viral and host factors may play distinct prognostic roles in local tumor progression (LTP) and intrahepatic distant recurrence (IDR). Especially, the role of quantitative HBsAg in predicting recurrence of HBV-related HCC after RFA remains unclear. We aim to evaluate the tumor, viral and host factors, including HBsAg, in predicting LTP and IDR among patients with HBV-related HCC undergoing RFA.

Methods

Consecutive 397 patients with radiologically confirmed complete tumor ablation after RFA for HBV-related HCC were retrospectively enrolled. Factors associated with LTP and IDR were evaluated.

Results

With a median follow-up period of 50.4 months, 146 (36.8%) and 225 (56.7%) patients developed LTP and IDR respectively. By multivariate analysis, tumor size >2 cm (hazard ratio (HR)=1.859, p<0.001) and tumor adjacent to major blood vessel (HR=1.454, p=0.036) were independent predictors of LTP. FIB-4 >3.25 (HR=1.427, p=0.010), multiple tumors (HR=1.829, p=0.001) and AFP>20 ng/mL (HR=1.313, p=0.047) were independently associated with IDR. In patients without advanced fibrosis (FIB-4 ≤3.25, n=181), HBsAg >100 IU/mL (HR=2.131, p=0.021), male sex (HR=2.297, p=0.015), multiple tumors (HR=2.713, p=0.001) and AFP >20 ng/mL (HR=1.638, p=0.044) independently predicted IDR, while in patients with advanced fibrosis (FIB-4 >3.25, n=216), age >70 years (HR=1.538, p=0.015) and FIB-4 >6 (HR=1.812, p=0.001) were independently associated with IDR.

Conclusions

In patients with HBV-related HCC receiving RFA, tumor factors are associated with LTP, while both host and tumor factors are accounted for IDR. HBsAg level strongly predicts distant recurrence in patients without advanced hepatic fibrosis.

原著論文　112_A 3

亞洲類風濕性關節炎病人使用 Janus 激酶抑制劑和腫瘤壞死因子-α 抑制劑以外的生物製劑發生主要不良心血管事件的風險

The risk of major adverse cardiovascular events of Janus kinase inhibitors and biologics other than tumor necrosis factor-α inhibitors in Asian patients with rheumatoid arthritis

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Background

Rheumatoid arthritis (RA) is the most frequent inflammatory disease that affects many tissues and organs, principally synovial joints. Biologics are medicinal products manufactured from a variety of natural sources. Several biologics, including tumor necrosis factor-α (TNF-α) inhibitors, interleukin-6 (IL-6) inhibitors, and T-cell inhibitors, such as CTLA-4 fusion protein, offer alternative options for effective treatment of RA by blocking the effects of the cytokines or inhibiting activation of effector cells. JAK inhibitors (JAKi), a class of oral medication which interfere with the JAK-STAT signaling pathway and inhibit the inflammatory response, has shown efficacy in the treatment of RA since 2012. Recently, in the ORAL surveillance trial conducted in Northern America, the risks of major adverse cardiovascular events (MACE) were 33 % higher with tofacitinib usage than with TNF-α inhibitors. It is worth noting that only 4% of enrolled patients were Asians. In addition, the data for such events between tofacitinib and biologics other than TNF-α inhibitors are limited. The aim of this retrospective study is to investigate the difference of MACE risk in RA patients with tofacitinib, IL-6 inhibitors (tocilizumab), or CTLA-4 fusion protein (abatacept) at a medical center in Taiwan.

Method

From 2005 to 2023, patients with RA using tofacitinib, IL-6 inhibitors (tocilizumab), or CTLA-4 fusion protein (abatacept) in Taipei Veterans General Hospital in Taiwan were included and retrospectively evaluated. The incidence of MACE was compared.

Results

In the current study, there were 739 patients enrolled; 87.1 percent of them were female and mean age of diagnosis for RA was 48.1 years. 78.1 percent were positive for rheumatoid factors, while 47.9 percent were positive for anti-cyclic citrullinated peptide antibody. 353 patients (47.77%) were treated with tofacitinib, 232 patients (31.39%) were treated with tocilizumab, while 218 patients (29.50%) were treated with abatacept. During 3486 person-years of follow-up (median follow-up period: 4.5 years), 22 (2.98%) patients developed MACE, with the incidence of 0.66 per 100 person-years. Among them, 6 (26.1%) patients were treated with tofacitinib, 11 (35%) with tocilizumab, and 6 (26.1%) with abatacept. (One overlapped tocilizumab/abatacept). The median intervals from the start of tofacitinib, tocilizumab, and abatacept to MACE were 3.19 (range: 0.40-5.43), 2.31 (range: 0.19–5.54), and 4.20 (range: 1.54–6.17) years, respectively. The incidence of MACE in tofacitinib, tocilizumab, and abatacept groups were 0.51, 0.76, and 0.55 per 100 patient-years, respectively. Importantly, no significant increases in MACE were observed among patients using tofacitinib when compared to those receiving tocilizumab and abatacept treatment.

Conclusion

The use of tofacitinib among RA patients is not significantly related to increased incidence of MACEs over a median follow-up of 4.5 years. However, randomized studies of larger scales may be required to better determine the relationship among Asian patients.

原著論文　112_A 4

機器學習用於預測幹細胞收集成功率：單一醫學中心研究經驗

Machine learning assist predicting successful stem cell harvesting: a single medical central experience

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Background

High dose chemotherapy followed by autologous stem cell transplantation (ASCT) is an important and potential curative treatment option for certain hematologic and non-hematologic malignancies. For successful engraftment, adequate hematopoietic stem cell (HSC) collection is necessary. Thus, HSC mobilization need to be performed before stem cell harvest, accomplished by hematopoietic growth factor administration or cytotoxic chemotherapy. Currently, a minimum of 2x10^6 CD34+ cells/kg HSCs is considered appropriate in most scenarios to proceed to ASCT, but there are 15–30% patients fail to yield an optimal HSC dose under above-mentioned strategy. Although some factors related to poor mobilization were known in previous studies, including advanced age, platelet count before mobilization, bone marrow infiltration by primary disease, it's worth to identify more factors relevant to successful mobilization by new technology.

Artificial intelligence predicts outcomes by machine learning patterns and relationship with data. They analyze big dataset, identify relevant features and use algorithms to make prediction based on these patterns. In this study, we have collected data from a series of patients experiencing stem cell harvesting in a single medical center, trained machine to analyze data and obtained a formula to estimate the possibility of harvest success.

Method

We retrospectively reviewed the clinical data from patients undergoing stem cell harvesting during 2021/01~2023/07. Clinically relevant information, such as age, sex, diagnosis, peripheral blood cell count before apheresis, and stem cell amount were obtained from medical chart and the definition of successful stem cell harvesting is the number of CD34+ cell higher than 2x10^6 CD34+ cells/kg.

In preview of data, the successful rate of this cohort is approximately 92%, resulting in imbalance data in the frequency of the observed class labels and consequently impairing algorithms classification performance. To take the imbalance problem into account, we developed a random forest q*-classifier, a type of quantile classifier. This q^*-classifier provides the maximized sum of the sensitivity and specificity rates. In this study, we trained the tuning parameters by applying the Monte-Carlo cross validation via 1000 machines by repeatedly splitting 70% training data and 30% test data. Each machine contained 3000 trees with area under curve (AUC) as the splitting rule. For the tuning parameters, the considered numbers of features splitting at each node are probably 4~9, while the minimum sizes of terminal node are 1~3. Each trained machine calculated the AUC, G-mean and Youden index

of the prediction of failure/success in HSC collection in the test data. The Monte-Carlo cross validation determined the optimal tuning parameters by choosing the one which had the minimum average AUC, G-mean and Youden index calculated from 1000 machines. Based on the chosen optimal tuning parameters, we constructed the final random forest q^*-classifier based on the whole data. The feature importance was evaluated by conducting permutation in each node.

Results

A total of 213 independent subjects were reviewed and 18 of them got harvesting failure. The most common diagnosis as stem cell harvesting are high grade B cell lymphoma (36.6%) and plasma dyscrasia (35.2%). By choosing optimal tuning parameters in our study, the number of features in a node for splitting was 11, and the minimum size of terminal node was 3. It produced average AUC for the test data set was 0.87 (standard deviation, SD=0.06), G-mean was 0.77 (SD=0.10) and Youden index was 0.71 (SD=0.12). Based on the chosen optimal tuning parameters, we constructed the final random forest q*-classifier based on the whole data. The Variable importance (VIMP) plot indicated that Hematopoietic progenitor cell (HPC) number, Monocyte percent and segment percent were the top three important features in this study. (Figure 1). The proposed classifier contained 3000 trees (Figure 2). The proposed classifier's performance, assessed with out-of-bag data yielded the following results, specificity at 0.76, sensitivity at 0.72, an AUC of 0.87 and G-mean of 0.74.

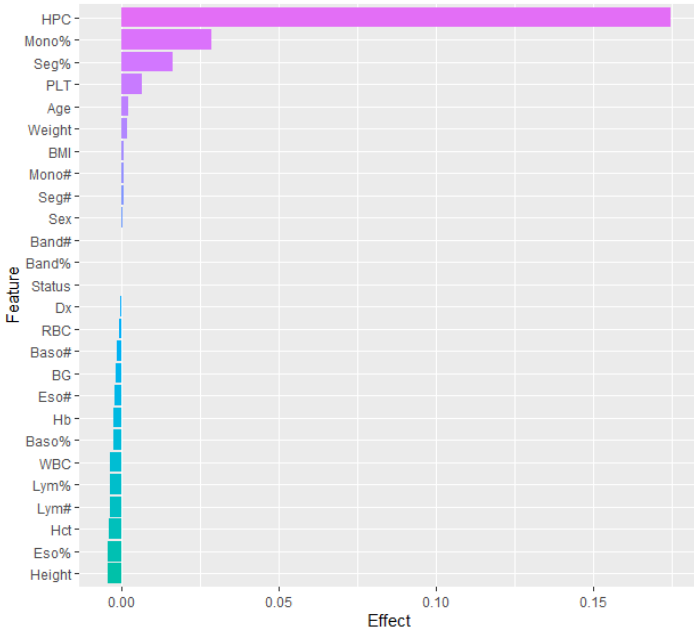

Figure 1. The Variable importance plot demonstrated the HPC number, Monocyte percent and segment percent were the top three important features. The performance is measured by the G -mean.

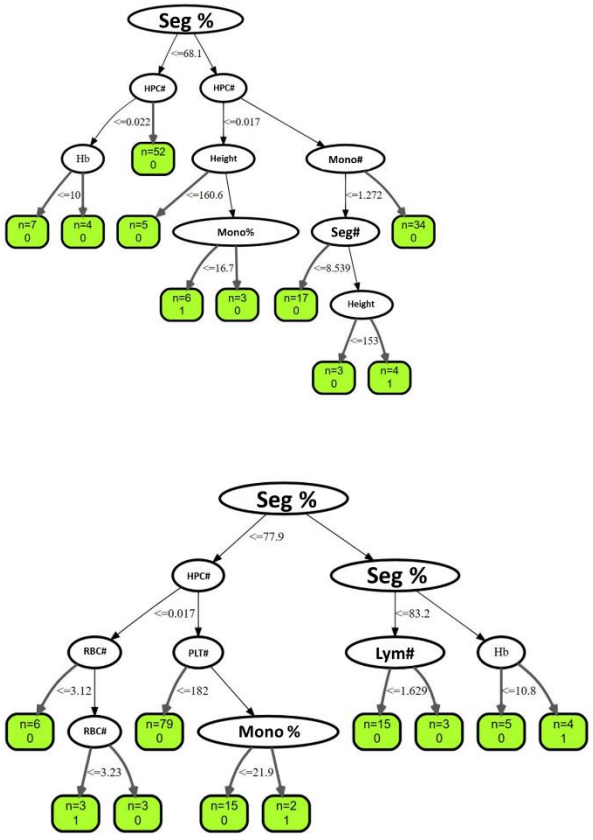

Figure 2. Tree 2 and tree 6 in the developed machine using the whole data.

Conclusion

Based on the machine learning trained by our cohort, the feature importance was evaluated by conducting permutation in each node and performance was measured by the G -mean. The VIMP plot indicated that HPC number, Monocyte percent and segment percent were the top three important features in this study. Consequently, the new case is predicted to be failure or success by comparing the estimated frequency with the empirical relative frequencies of the two classes.

原著論文　112_A 5

水果命名測驗: 簡單可信用以篩檢台灣華人輕度肝性腦病變的工具

Fruit Naming Test (FNT): a Simple and Reliable tool that can be used in the Screening for Minimal Hepatic Encephalopathy (MHE) in Chinese patients with Liver Cirrhosis in Taiwan

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Background

Hepatic encephalopathy (HE) produces a spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma. Minimal hepatic encephalopathy (MHE) represents the mildest form of HE, characterized by trivial neuropsychiatric symptoms without disorientation or asterixis, and is a predictor of overt hepatic encephalopathy (OHE) and mortality.

Several tools are useful for the detection of MHE; the Psychometric Hepatic Encephalopathy Score (PHES), quantified electroencephalography, the critical flicker frequency, and computerized tests. All these techniques require some kind of equipment. PHES is now the golden standard in detecting MHE and requires only a simple pencil-and-paper form to be completed, and it is time-consuming and requires regional standardization. Animal Naming Test (ANT) has been proven to facilitate rapid and reliable evaluation of MHE. ANT demonstrates its prognostic value regarding the risk of OHE and mortality.

However, the people in Taiwan and other Asian countries are usually very familiar with the Chinese Zodiac, a customary classification scheme that ascribes an animal to each year in a 12-year cycle. This may lead to potential bias when it comes to naming as many animal names in a one minute as in the ANT. We postulated that naming of fruits instead of animals can reduce this bias. Hence, we performed a study to (1) determine the cut-off point of the Fruit Naming Test (FNT) for detection of PHES-defined MHE, and (2) assess the prognostic value of the FNT in a group of Chinese patients with liver cirrhosis in Taiwan.

Methods

1. We performed a prospective cohort study at a tertiary 2,700-bed referral center. The inclusion criteria were patients with liver cirrhosis diagnosed by liver biopsy, endoscopic findings, fibroscan, or ultrasonography. Enrolled patients were followed up from March 2013 to February 2023 for prognostic analysis.
2. FNT: Patients were instructed to list as many different types of fruits as they could within 60 seconds. We counted all responses, excluding incorrect names and repetitions.
3. PHES: The patients then underwent a PHES, within which there are five neuropsychological tests. The scores are tabulated, and the differences in each subtest of PHES in multiples of the standard deviation (SD) were tabulated as Z scores; this ranged from -15 to +5. MHE was defined in patients with a total PHES of < -4.
4. Statistical analysis: Receiver operating characteristic (ROC) curve analysis and Liu method were employed to determine the optimal cutoff value in differentiating MHE. Kaplan-Meier analysis and Cox proportional hazard model analysis were used to assess the prognostic outcomes of the occurrence of OHE and all-cause mortality. Sensitivity analysis was

performed with subgroup analyses according to the Child-Turcotte-Pugh (CTP) score and the Model for End-stage Liver Disease (MELD) score.

Results

1. Seventy-one patients with liver cirrhosis were enrolled. The demographic data and baseline characteristics are presented in Table 1.
2. ROC curve analysis for the FNT in determining the discriminative power of PHES-defined MHE is shown in Figure 1. We found FNT of 10 to be the optimal cutoff point with an Area-Under-Curve (AUC) value of 0.754 [95% CI: 0.611-0.896], having a sensitivity of 94.6% and a specificity of 33.3%. FNT correlated well with PHES (r = 0.45, p = 0.0001).
3. The cirrhotic patients who scored < 10 on FNT developed OHE earlier [70.8 months (IQR, 26.9-106.8)] as compared to those patients who scored higher (≥ 10) on FNT. (Figure. 2) The patients with FNT < 10 were associated with higher risk of OHE development [Hazard Ratio (HR) = 3.05 (95% CI: 1.01-9.23, p=0.048)] as compared to those patients with FNT ≥ 10. (Table 2)
4. In the subgroup analysis, cirrhotic patients with FNT < 10 were associated with a significantly higher risk of OHE development in both CTP class A [HR: 4.59 (95% CI: 1.24-17.03) p=0.022] or MELD < 15 group [HR: 3.64 (95% CI: 1.16-11.43), p=0.027] (Table 2). Such sensitivity analyses further confirm the usefulness of FNT in predicting OHE in patients with compensated liver cirrhosis.

Conclusion

1. FNT is a simple and reliable verbal frequency test for screening for MHE in Chinese patients with liver cirrhosis in Taiwan.
2. Cirrhotic patients with FNT < 10 have a higher risk of developing OHE as compared with those with FNT ≥ 10.

原著論文　112_A 6

溝槽胰臟炎與溝槽胰臟癌之臨床鑑別

Clinical differentiation between groove pancreatitis and groove pancreatic carcinoma

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Background

The pancreato-duodenal groove is a small space bordered by pancreatic head, duodenum, and common bile duct. Although the incidence of groove pancreatic lesion is scarce, it is important to distinguish groove pancreatitis (GP) from groove pancreatic carcinoma (GC) owing to the remarkably different prognosis and clinical managements. However, the complexity of this space makes differential diagnosis challenging.

Method

A case series study was retrospectively performed in patients diagnosed with GP (n = 9) and GC (n = 5) in Taipei veterans general hospital between January 2002 and December 2012. Clinical presentations, laboratory data, imaging studies, and pathology reports were analyzed. Five GP patients and all GC patients underwent Whipple operation.

Results

Both GP and GC patients were male predominant. However, the patients with GC were significantly younger at diagnosis (median age: 45.0 vs 56.0 years old, p = 0.028). Besides, less GC patients had excessive drinking problem (40% vs 100%, p = 0.027); and the serum level of carbohydrate antigen 19-9 (CA 19-9) was significantly higher in patients with GC (128.94 vs 29.24 U/L, p = 0.042). As to the radiologic findings, peri-pancreatic vascular encasement, particularly the gastroduodenal artery, could be observed more in GC patients (60% vs 0%, p = 0.027). According to these clinical features, a new "groove cancer score" was developed that consists of age > 55, CA 19-9 > 35 U/mL, no problem with heavy drinking, and the presence of peri-pancreatic vascular encasement. A higher score 2 is highly suggestive of groove pancreatic carcinoma.

Conclusion

A new "groove cancer score" was proposed in this case series to assist the clinical differentiation between GP and GC. Further comprehensive investigation with larger sample size is needed for detailed analysis and validation.

原著論文　112_A 7

免疫檢查點抑制劑在骨肉瘤治療的臨床療效

The clinical efficacy of immune checkpoint inhibitors in treating bone and soft tissue sarcoma

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Background and Aims

Immune checkpoint inhibitors (ICIs) have emerged as a pivotal therapeutic approach in oncology, offering promise against various cancer types. However, their efficacy in treating bone and soft tissue sarcomas remains are limited. Past investigations highlighted a modest response of ICIs in a subset of soft tissue sarcomas, while the efficacy in bone sarcomas seems to be marginal. Considering this context, our study aims to further investigate and elucidate the clinical efficacy of ICIs in patients with both osteosarcoma and soft tissue sarcoma. Through a comprehensive analysis, we sought to provide clearer insights into the therapeutic potential of ICIs in these challenging sarcoma types.

Method

We conducted a retrospective cohort study involving 13 patients diagnosed with either osteosarcoma or soft tissue sarcoma. Patients' demographics, type of sarcoma, etiology, previous systemic therapies, and treatment responses were thoroughly recorded. Treatment response metrics, including objective response rate (ORR) and disease control rate (DCR), were evaluated using the Chi-Square test. Progression-free survival (PFS) and overall survival (OS) were analyzed for both sarcoma types using the Kaplan-Meier method, with the significance of differences assessed by the log-rank test. Furthermore, a univariate analysis was employed to determine potential factors on study outcomes, such as age, gender, sarcoma type, etiology, tumor location, disease staging, and the combination of treatment.

Results

A cohort of 13 patients was assessed in our study, including 4 patients with osteosarcoma and 9 with soft tissue sarcoma, with a median age of 43 years (IQR: 22-73 years) and a male predominance (8 males, 61.5%). Regarding the etiology, primary sarcoma was dominant with 76.9% (10 out of 13). Previous systemic therapies were administered in 61.5% (8 out of 13) of the patients. ICI monotherapy was administered to 61.5% of patients (9 out of 13), while combination therapy was given to 38.5% (5 out of 13). Of those receiving combination therapy, three out of five were combined with tyrosine kinase inhibitors, and two out of five were combined with chemotherapy.

In evaluating the treatment response between osteosarcoma and soft tissue sarcoma, we applied the Chi-Square test to assess the ORR and DCR. For the OGS group (N=4), the ORR was 25%, and the DCR was 50%. Meanwhile, in the STS group (N=9), the ORR was slightly lower at 22.2%, with a DCR of 44.4%. There was no significant difference between the two groups in terms of ORR (p=0.91) and DCR (p=0.85).

Two out of four (50.0%) patients with osteosarcoma and five out of nine (55.6%) with soft tissue sarcoma experienced disease progression during the follow-up period. The PFS of osteosarcoma and soft tissue sarcoma was 2.5 months (95% CI na.) and 2.3 months (95%

CI 1.9-2.6), respectively, with no statistically significant difference (p=0.66).
Two out of four patients (50.0%) in the osteosarcoma and five out of nine (55.6%) in the soft tissue sarcoma died. The OS of osteosarcoma and soft tissue sarcoma was 9.9 months (95% CI: 1.7-18.0) and 9.3 months (95% CI: 0-52.6), respectively, with no statistically significant difference (p=0.85).
In a univariate analysis that included a variety of factors—such as median age, gender, sarcoma type, etiology, tumor location, disease staging, and treatment approach—none emerged as statistically significant contributors to disease progression or death.

Conclusion

Our study highlights that ICI showed some therapeutic efficacy in both soft tissue and bone sarcomas, which has not been previously documented. This necessitates further research to optimize ICIs use and identify sarcoma patient subgroups most likely to benefit from this treatment.

原著論文　112_A 8

前瞻性研究分析身體質量指數動態改變對心血管疾病死亡風險的影響

Modification of risk for all-cause and cardiovascular disease-related mortality with changes in the body mass index: A prospective cohort study with 12 years follow up

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Background & Aims

The longitudinal impact of changes in body mass index (BMI) on the risk of all-cause and cardiovascular disease (CVD)-related mortality has not been extensively studied. We examined whether changes in BMI status over time are associated with risk of all-cause and CVD-related mortality.

Methods

This longitudinal study recruited 90,258 adults between 2002-2008 from the Taiwan MJ cohort who underwent repeated BMI measurements at an interval of 3.3 years and were followed up for all-cause and CVD-related mortality over 12.1 years. Cox proportional hazard and Fine-Gray sub-distribution hazard models with death from non-CVD causes as the competing risk were used to determine the impact of changes in BMI status on the risk of all-cause or CVD-related mortality, respectively.

Results

Over 1,094,606 person-years of follow-up, 2,084 participants died, including 391 (18.8%) CVD-related deaths. After adjusting for other covariates, >10% increase (adjusted hazard ratio [aHR], 1.36; 95% confidence interval [CI], 1.09-1.70) or >10% decrease of BMI (aHR, 1.86; 95% CI, 1.43-2.43) was significantly associated with higher risk of all-cause mortality, compared with stable BMI. Participants with obesity at baseline who had BMI increase of >10% during the follow-up period had a significantly higher risk of all-cause (aHR = 2.30; 95% CI:1.38-3.85) and CVD-related mortality (aHR = 3.44; 95% CI:1.33-8.89).

Conclusion

A >10% increase in BMI in individuals with obesity was significantly associated with a higher risk of all-cause and CVD-related mortality. Our findings suggest that individuals with adiposity should adopt measures to reduce body weight to prevent premature mortality.

原著論文　112_A 9

腎細胞癌的亞型，分期，腫瘤組織分級和職業暴露

Subtypes, Stages, Grades and Occupational Exposures of Renal Cell Carcinoma

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Background

The aim of our study was to assess the differences between clinical profiles of metastatic and non-metastatic clear cell renal cell carcinoma(ccRCC). We also discuss occupational exposure, subtypes, grades, and stages of RCC.

Method

A univariate analysis study was performed on the clinical data retrieved from The Cancer Image Archive with two categories of the presence or absence of distant metastases of patients with ccRCC. In addition, PubMed, Google Scholar and ProQuest Medical Database were searched for literature review on occupational exposure, subtype, nuclear grade and TNM staging of RCC.

Results

Patients with ccRCC with distant metastases demonstrated larger tumors, higher serum calcium level, and high two-tiered nuclear grade than those without distant metastases. A literature review found that Paner chromophobe tumor grading system and WHO/ISUP grading system were validated for prediction of outcomes of chromophobe RCC and papillary RCC, respectively.

Conclusion

The dichotomous high nuclear grade and larger Tumor size are easier to distinguish the metastatic or non-metastatic groups of ccRCC by literature review and univariate analysis.

IRB:TCHIRB-11003006-E [Wang]

原著論文　112_A 10

單細胞蛋白體識別不同的表觀遺傳變化以預測急性骨髓性白血病與骨髓化生不良症對去甲基化藥物 Azacitidine 之反應

Single cell proteomics identifies distinct epigenetic perturbations and biomarkers to predict responsiveness to azacitidine in MDS and AML

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Background
While genetic mutations have been widely studied in MDS and AML, the epigenetic landscape regarding the leukemic blasts and immune cells in the bone marrow microenvironment remains largely unknown. In this study, we aim to decipher the epigenetic perturbations of MDS and AML at single cell level.

Methods
Primary bone marrow samples from 5 healthy controls, 19 MDS and 13 AML patients at initial diagnosis were obtained. Single cell proteomics was conducted by Mass cytometry to profile the epigenetic landscape, including methylation, histone modifiers, and histone marks.

Results
Our data revealed lineage-specific chromatin modification in hematopoietic cells. In healthy controls, myeloid lineage cells were characterized by higher expression of H3K36me3, but lower expression of H3K27me3 than lymphoid lineage cells. These lineage-specific chromatin modifications were disrupted in MDS and AML. Compared to healthy controls, patients with AML were characterized by downregulation of HDAC1 and LSD1 in T cells, hypomethylation in T cells and myeloblasts, and hypermethylation in innate immune cells. On the contrary, HDAC1 and LSD1 were upregulated in T cells in MDS.
To identify biomarkers that predict response to azacitidine, we compared the epigenetic properties between responders (n=9) and non-responders (n=6). Responders had significantly higher levels of H3K27me3, H3K36me3 and global hypermethylation. In paired sample analysis, azacitidine decreased the expression of enhancer marks (H3K27ac and H3K4me1) especially in T and NK cells of responders.

Conclusion
Dysregulated epigenetic landscapes are hallmarks for MDS and AML. Our data clearly shows the epigenetic crosstalk between methylation and chromatin modification and identifies biomarkers to predict response to azacitidine.

原著論文　112_A 11

僵直性脊椎炎病人罹患脊椎及髖骨骨折的危險因子相關研究

Risk of spinal and hip fractures in patients with ankylosing spondylitis: a nationwide population-based study in Taiwan

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Objectives

A small but significant proportion of patients with ankylosing spondylitis (AS) suffered from fractures during the disease course, causing severe disability and functional impairment. We aimed to study the prevalence and risk factors of spinal fracture and hip fracture of the AS population in Taiwan.

Methods

This population-based, retrospective cohort study used claim-based National Health Insurance dataset from 2006 to 2017, identifying newly diagnosed patients with AS. The risk of developing spinal and hip fracture in the AS group was compared with those of an age- and sex-matched non-AS group. A Cox proportional hazard regression analysis was performed to examine the risk factors for developing spinal and hip fractures.

Results

87,248 eligible patients newly diagnosed of AS were matched with a non-AS control group during the study period. The AS group had a higher risk of developing spinal fracture than the non-AS control with the adjusted hazard ratio (aHR) being 1.97 (95% CI 1.91 - 2.17, P < 0.0001), however the risk of developing hip fracture was not significantly increased (aHR 0.97, 95% CI 0.98 - 1.16, P > 0.05). Risk factors for spinal fracture in the AS group were advanced age and female sex. Patients ever treated with anti-tumor necrosis factor agents (Anti-TNF) or sulfasalazine showed no statistical difference in the risk of developing spinal fracture compared with non-users (aHR 0.94, 95% CI 0.67 - 1.31, P > 0.05; aHR 0.96, 95% CI 0.85 - 1.08, P > 0.05, respectively), but non-steroidal anti-inflammatory drugs (NSAIDs) ever-users had a significantly decreased risk of spinal fracture compared with non-NSAID users (aHR 0.31, 95% CI 0.27 - 0.35, P < 0.0001).

Conclusions

Patients with AS had a higher risk of spinal fracture compared with the control group. NSAIDs show a protective effect on the development of spinal fracture in patients with AS.

原著論文　112_A 12

使用抗骨吸收藥物（雙磷酸鹽和 Denosumab）的患者發生藥物相關頜骨壞死的風險

The risk of Medication related osteonecrosis of the jaw (MRONJ) among patients with anti-resorptives (bisphosphonates and denosumab)

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Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but severe adverse event of antiresorptive agents. The study aimed to analyze the risk of medication related osteonecrosis of the jaw (MRONJ) among patients with anti-resorptives (bisphosphonates and denosumab).

Methods

The study used data from the National Health Insurance Research Database (NHIRD) and Major Illness/Injury Database from 2006 to 2017. The target population were included and excluded by criteria. The study identified comorbidities that increased the risk of MRONJ and used a flow chart for study design. Outcomes were defined as osteonecrosis of the jaw with three diagnosis records within eight weeks. Subgroup analysis of patients with osteoporosis and oncology were also included.

Results

The study reported the Hazard Ratios (HR) of the osteoporosis and cancer group compared with the comparison group in ONJ. The crude HR of the osteoporosis group was 1.42, indicating that the osteoporosis group had a 42% higher risk of developing ONJ than the comparison group. The adjusted HR of the osteoporosis group was also 1.42, which was statistically significant. The crude HR of the cancer group was 2.75, indicating that the cancer group had a 175% higher risk of developing ONJ than the comparison group. The adjusted HR of the cancer group was also 2.98, which was statistically significant.

Conclusion

The study found that the incidence of MRONJ was higher in patients with oncology than in those with osteoporosis. The study's findings provide important insights into the risk factors for MRONJ and can help healthcare providers make informed decisions when prescribing anti-resorptives to patients with osteoporosis and oncology.

原著論文　112_A 13

Association of Dipeptidyl Peptidase-4 Inhibitor Use for Type 2 Diabetes and Incidence of OA in Taiwan

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Background
Cellular senescence is involved in osteoarthritis (OA) development. Dipeptidyl Peptidase-4 (DPP4) is associated with senescence in OA chondrocytes. It is uncertain whether DPP4 inhibitor use is associated with reduced risk of OA in patients with type 2 diabetes mellitus. We aimed to establish whether DPP4 inhibitor use was associated with a reduced risk of OA among these patients.

Methods
We selected patients with type 2 diabetes mellitus that was diagnosed between 2008 and 2018 from the Taiwan National Health Insurance Research Database. We used Individual Matching (1:1), age ±1, same gender, same index year, same Diabetes Compilations Severity Index to balance potential confounders between DPP4 inhibitor users and nonusers. We assessed the risks of incident OA using Cox proportional hazards regression between DPP4 inhibitor users and nonusers.

Results
We included 166,987 participants who were not treated with DPP4 inhibitor and 166,987 who were treated with DPP4 inhibitor (mean age 58.60 yr, standard deviation 9.53 yr; 56.07% were men). In the DPP4 inhibitor use cohort, 5953 patients developed OA during a median follow-up of 3.61years (Table 1). Compared with participants who did not use DPP4 inhibitor, those who used DPP4 inhibitor had lower risks of incident OA (adjusted hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.42~0.45(Table 2). Furthermore, the use of concurrent medications, such as Glucagon-like peptide-1receptor agonist (GLP-1RA; 0.22 [0.15~0.31]) and Corticosteroid (0.66 [0.64~0.68]), was associated with a lower OA risk (Table 3). We observed no relationship between a dose-dependent effect of DPP4 inhibitor use and OA(Table 3).

Conclusions
DPP4 inhibitor use in patients with type 2 diabetes mellitus was associated with a significantly reduced risk of OA. Randomized controlled clinical trials in patients with osteoarthritis are warranted to determine whether DPP4 inhibitor is effective in decreasing the incidence of OA.

原著論文　112_A 14

紅斑性狼瘡患者增加罹患隱球菌腦膜炎之風險：利用台灣健保資料庫之回溯性研究

High risk of Cryptococcal Meningitis infection in patients with systemic lupus erythematosus in Taiwan: a nationwide population-based study

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Background

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the formation of autoantibodies, complement activation, and immune complex deposition. This condition increases vulnerability to opportunistic infections. While central nervous system (CNS) infections are relatively rare in SLE (0.53-2.25% incidence), they have a high mortality rate, with over 40% reported. Cryptococcus meningitis (CM) is particularly concerning, as it often presents with an indolent disease course and delayed diagnosis. Despite insufficient evidence regarding the risk of CM in SLE patients, this nationwide population-based study aimed to evaluate this risk and identify related factors.

Methods

This retrospective cohort study was conducted using Taiwan's National Health Insurance (NHI) Research Database (NHIRD) from 2005 to 2018. The study identified 11,472 SLE patients and compared their incidence rate of CM with 57,360 non-SLE controls matched by age, sex, and the same index day at a 1:5 ratio. A multivariable Cox proportional hazards model was employed to evaluate the risk of CM in the systemic lupus erythematosus cohort.

Results

After a mean follow-up of over six years, the SLE cohort had a significantly higher incidence rate of cryptococcal meningitis compared to the matched control cohort (10.98 vs. 1.02 per 100,000 person-years; Hazard ratio [HR]: 10.64, p=0.0001, Table 3). Kaplan-Meier analysis demonstrated a similar trend of higher cumulative incidence of CM in the SLE cohorts (Figure 2, p<0.001). Multivariate Cox regression analysis of the SLE and control cohorts revealed that SLE remained a significant risk factor even after adjusting for other variables (adjusted hazard ratio [HR] 7.73, 95% confidence interval [CI] 2.13-28.05, p=0.0019, Table 3). Additionally, older age (>65 years) in SLE patients was a significant risk factor for cryptococcal meningitis (adjusted HR 6.35, 95% CI 1.11-36.25, p=0.0377, Table 3). Subgroup analysis showed that the risk of CM was significantly higher in female, young (age <50) SLE patients without comorbidities such as chronic kidney disease, heart failure, or ischemic heart disease (Table 4). Finally, Cox regression analysis with Stepwise model selection revealed that a history of stroke and intravenous (IV) steroid use were significantly associated with a high risk of CM in SLE patients (Table 5).

Conclusion

The study found a higher risk of cryptococcal meningitis in systemic lupus erythematosus patients. Risk factors for CM in the SLE cohort included older age, a history of stroke, and IV steroid therapy.

原著論文　112_A 15

台灣全身性紅斑狼瘡患者患細菌性腦膜炎的風險：以全國人口為對象之研究

Risk of bacterial meningitis in patients with systemic lupus erythematosus in Taiwan: a nationwide population-based study

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Background

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by organ damage and a variety of clinical complications. Involvement of the central nervous system (CNS) in SLE can lead to noninfectious complications such as aseptic meningitis, cerebrovascular disease, and demyelinating syndromes. The dysregulated immune system and long-term use of immunosuppressants in SLE patients contribute to an increased susceptibility to infections. CNS infections account for a small percentage of all SLE infections (0.53-2.25%) and are primarily caused by viruses or bacteria. Bacterial meningitis (BM) and brain abscess (BA) are potentially life-threatening CNS infections, with reported mortality rates ranging from 26.3% to 52.2%. However, specific risk factors for bacterial meningitis in SLE patients have not been extensively studied. This nationwide population-based cohort study conducted in Taiwan from 2006 to 2018 aims to investigate the incidence, mortality trends, and potential risk factors associated with bacterial meningitis among SLE patients. The objective of this research is to address the knowledge gap and enhance our understanding of this particular infectious complication in SLE patients.

Method

We retrospectively identified systemic lupus erythematosus (SLE) patients from the National Health Insurance research-oriented database and compared the incidence rate of bacterial meningitis with that of non-SLE controls. To assess the risk of bacterial meningitis in the SLE cohort, we utilized a Cox multivariable proportional hazards model.

Results

A total of 11,460 patients diagnosed with systemic lupus erythematosus (SLE) and 57,300 non-SLE individuals were included in this study. The mean age of the participants had a mean age of 42.36 years (standard deviation: 16.66 years), with 85.43% being female. Following a mean follow-up period of over six years, the incidence rate of bacterial meningitis was significantly higher in the SLE cohort compared to the control cohort (45.33 vs. 1.53 per 100,000 person-years, hazard ratio [HR] 29.14, 95% confidence interval [CI] 12.21–69.55, p<0.0001; Table 3). Kaplan–Meier analysis (Figure 2) further confirmed a substantially higher cumulative incidence of bacterial meningitis among SLE patients compared to the matched controls (p<0.0001). Multivariate Cox regression analysis, adjusting for other variables, demonstrated that SLE remained a significant independent risk factor (adjusted hazard ratio [HR] 22.59, 95% confidence interval [CI] 9.18–55.62, p<0.0001; Table 3). Additionally, Cox

multivariate proportional hazards analysis (Table 5) revealed several independent risk factors for bacterial meningitis among patients with systemic lupus erythematosus. Female (adjusted HR 2.96, CI 1.42–6.19), comorbidity with chronic kidney disease (adjusted HR 2.69, CI 1.16–6.23), predisposing factors with sepsis (adjusted HR 2.96, CI 1.14–7.66), or receiving a mean prednisolone dose >7.5 mg (adjusted HR 92.41, CI 31.42–271.76) were all identified as significant risk factors associated with bacterial meningitis in this specific population.

Conclusions

Systemic lupus erythematosus (SLE) patients exhibited a significantly increased risk of bacterial meningitis. Risk factors associated with bacterial meningitis in the SLE cohort included female gender, comorbidity with chronic kidney disease, predisposing factors with sepsis, and receiving a mean prednisolone dose greater than 7.5 mg.

原著論文　112_A 16

羥氯奎寧降低 B 型肝炎患者罹患肝細胞癌之風險：回溯性研究

Hydroxychloroquine Reduced the Risk of Hepatocellular Hydroxychloroquine Reduced the Risk of Hepatocellular Carcinoma in patients with hepatitis B virus infection: A retrospective cohort study

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Background

This study investigated the association between Hydroxychloroquine (HCQ) usage and the risk of hepatocellular carcinoma (HCC) in patients with newly diagnosed HBV infection. The study used a retrospective cohort design and analyzed data from the National Health Insurance Research Database in Taiwan from 2005 to 2018. The study found that HCQ usage was associated with a lower risk of HCC in patients with newly diagnosed HBV infection. The protective effect of HCQ was dose-dependent, with higher doses associated with a lower risk of HCC. The study highlights the importance of monitoring the safety of drugs and the need for ongoing research to improve our understanding of their effects on human health.

Method

The study used a retrospective cohort design to investigate the association between Hydroxychloroquine (HCQ) usage and the risk of hepatocellular carcinoma (HCC) in patients with newly diagnosed HBV infection. The study used data from the National Health Insurance Research Database in Taiwan from 2005 to 2018. The target group was patients with newly diagnosed HBV infection between January 1, 2006, and December 31, 2016. HCQ usage was identified using the ATC code P01BA02, and exclusion criteria were applied to ensure the validity of the results. Comorbidities such as cirrhosis were identified using ICD-9-CM and ICD-10 codes. The study analyzed the data using statistical methods, including incidence rates, crude hazard ratios, and adjusted hazard ratios. The study also used subgroups based on the duration of HCQ usage and the dose of HCQ to investigate the dose-response relationship between HCQ usage and the risk of HCC. The study had some limitations, including the lack of information on lifestyle factors and the possibility of unmeasured confounding variables. However, the study provides valuable insights into the potential risks and benefits of HCQ usage in patients with newly diagnosed HBV infection.

Results

This study investigated the association between Hydroxychloroquine (HCQ) usage and the risk of hepatocellular carcinoma (HCC) in patients with newly diagnosed HBV infection. The study used a retrospective cohort design and analyzed data from the National Health Insurance Research Database in Taiwan from 2005 to 2018. Our study found that HCQ usage was associated with a lower risk of HCC in patients with newly diagnosed HBV infection. The incidence rate of HCC was 173.7 per 100,000 person-years in HCQ users compared to 359.6 per 100,000 person-years in HCQ non-users. The crude hazard ratio (HR) for HCC in HCQ users was 0.48 (95% CI: 0.35-0.67) compared to HCQ non-users. After adjusting for

confounding variables, the adjusted HR for HCC in HCQ users was 0.47 (95% CI: 0.32-0.69) compared to HCQ non-users. The study also found that the protective effect of HCQ was dose-dependent. The incidence rate of HCC was 140.0 per 100,000 person-years in HCQ users with a cumulative defined daily dose (cDDD) of 28-65.12, and 200.7 per 100,000 person-years in HCQ users with a cDDD of 65.12-162.02. The crude HR for HCC in HCQ users with a cDDD of 28-65.12 was 0.39 (95% CI: 0.19-0.78), and the adjusted HR was 0.42 (95% CI: 0.21-0.85). The crude HR for HCC in HCQ users with a cDDD of 65.12-162.02 was 0.56 (95% CI: 0.30-1.04), and the adjusted HR was 0.46 (95% CI: 0.22-0.96).

Conclusion

Hydroxychloroquine (HCQ) usage was associated with a reduced risk of hepatocellular carcinoma (HCC) in patients newly diagnosed with HBV infection. The protective effect of HCQ was dose-dependent, with higher doses correlating to a decreased risk of HCC. The study provides evidence suggesting that HCQ usage may confer a protective effect against hepatocellular carcinoma in patients newly diagnosed with HBV infection. However, the study had some limitations, including a lack of information on lifestyle factors and the potential presence of unmeasured confounding variables. Further research is required to validate these findings and enhance our understanding of the impact of HCQ on human health.

原著論文　112_A 17

Corrected QT Interval and Clinical Outcomes in Dialysis Patients with Peripheral Artery Disease

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Objectives

Peripheral artery disease (PAD) is common and associated with a higher risk of cardiovascular morbidity and mortality in dialysis patients. A longer corrected QT (QTc) interval was associated with adverse cardiovascular events and mortality in the general population and patients with end-stage kidney disease. However, little evidence is available on the predictive value of QTc in dialysis patients with PAD.

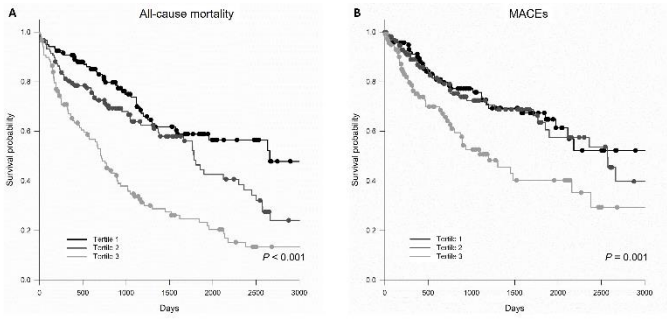
Methods

We conducted a prospective cohort study of 356 dialysis patients with symptomatic PAD undergoing endovascular therapy. We performed the resting 12-lead electrocardiogram (ECG) at baseline. Cox regression analyses were used to assess the association of QTc with all-cause mortality and major adverse cardiovascular events (MACEs), defined as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death.

Results

The mean age was 67.3 ± 11.5 years; 41.6% of participants were women. The median QTc was 471 (interquartile ranges 448–491) milliseconds (ms). During a median follow-up of 2.2 years, 188 (52.8%) patients died, and MACEs occurred in 119 (33.4%) patients. In multivariable-adjusted models, patients in tertile 3 of QTc levels had a significantly greater risk of all-cause mortality (hazard ratio [HR] 2.41, 95% confidence intervals [CI] 1.58–3.69) and MACEs (HR 1.90, 95% CI 1.15–3.13) than those in tertile 1. Similarly, each 10-ms increase in the baseline QTc predicted a higher risk of all-cause death (HR 1.15, 95% CI 1.09–1.21) and MACEs (HR 1.15, 95% CI 1.07–1.23).

Figure1 Kaplan-Meier survival curves for (A) all-cause mortality and (B) MACEs. MACE, major adverse cardiovascular event.



Conclusions

QTc prolongation was independently associated with adverse outcomes among dialysis patients with PAD requiring endovascular therapy.

Table 1 Baseline characteristics according to tertiles of QTc[1]　　**Table 2 Baseline characteristics as determinants**

of QTc interval

Characteristic	QTc Tertile 1 (n = 119)	Tertile 2 (n = 118)	Tertile 3 (n = 119)	*P* Value
Demographic data				
Age (yr)	65.7±11.8	67.4±11.7	68.9±10.8	0.096
Male sex, n (%)	42(35.3%)	60(50.8%)	46(38.7%)	0.038
Current smoking, n (%)	31(26.1%)	24(20.3%)	26(21.8%)	0.554
Dialysis method, n (%)				
Hemodialysis	112(94.1%)	113(95.8%)	109(91.6%)	0.406
Peritoneal dialysis	7(5.9%)	5(4.2%)	10(8.4%)	
Dialysis vintage (yr)	6.0(2.5–10.0)	5.2(2.4–8.0)	3.3(1.6–7.5)	0.009
Body mass index (kg/m^2)	23.8±3.1	23.8±3.7	24.5±4.1	0.226
Comorbidity, n (%)				
Diabetes mellitus	102(85.7%)	93(78.8%)	102(85.7%)	0.257
Hypertension	104(87.4%)	102(86.4%)	101(84.9%)	0.850
Coronary artery disease	63(52.9%)	57(48.3%)	79(66.4%)	0.014
Congestive heart failure	22(18.5%)	22(18.6%)	34(28.6%)	0.098
Cerebrovascular disease	24(20.2%)	20(16.9%)	20(16.8%)	0.747
Atrial fibrillation	8(6.7%)	18(15.3%)	18(15.1%)	0.073
Medication, n (%)				
Antiplatelet	110(95.7%)	113(97.4%)	111(95.7%)	0.722
Cilostazol	77(67.0%)	71(61.2%)	71(61.2%)	0.579
RAASi	35(30.4%)	38(32.8%)	35(30.2%)	0.896
CCB	45(39.1%)	44(37.9%)	34(29.3%)	0.234
β-Blocker	58(50.4%)	57(49.1%)	56(48.3%)	0.947
Statins	21(18.3%)	33(28.4%)	29(25.0%)	0.182
Laboratory data				
Potassium (mmol/L)	4.0(3.5–4.7)	3.8(3.4–4.4)	3.8(3.4–4.3)	0.055
Albumin (g/dl)	3.4±0.7	3.6±0.6	3.2±0.7	<0.001
Total cholesterol (mg/dl)	153(131–173)	159(138–196)	141(124–168)	0.002
Triglycerides (mg/dl)	122(90–165)	127(88–191)	133(94–194)	0.338
HDL (mg/dl)	36(27–44)	39(31–48)	34(26–42)	0.007
LDL (mg/dl)	90(70–109)	88(72–114)	80(65–96)	0.013
Hematocrit (%)	31.9±5.1	32.5±5.8	31.3±5.0	0.248
Creatinine (mg/dl)	7.0±2.7	6.7±2.4	6.7±2.7	0.652
HbA1c (%)	7.0(6.0–8.5)	6.7(5.7–7.8)	6.8(5.9–8.0)	0.283
CRP (mg/dL)	2.0(0.4–8.2)	1.6(0.6–6.4)	3.4(1.1–11.5)	0.006

Abbreviations: CCB, calcium channel blocker; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RAASi, renin-angiotensin-aldosterone system inhibitor.
[1]Tertile 1: 369–458 ms; Tertile 2: 459–484 ms; Tertile 3: 485–568 ms.

Variables	Univariate β (SE)	Univariate *P* value	Multivariate[1] β (SE)	Multivariate[1] *P* value
Age (yr)	0.31(0.14)	0.025	–	–
Male sex	1.00(3.28)	0.761	–	–
Dialysis vintage(yr)	-0.76(0.32)	0.019	-1.03(0.35)	0.004
BMI(kg/m^2)	0.45(0.44)	0.311	–	–
Diabetes mellitus	0.83(4.34)	0.848	–	–
Hypertension	-1.85(4.69)	0.694	–	–
Coronary artery disease	7.12(3.23)	0.028	7.62(3.4)	0.025
Congestive heart failure	7.83(3.88)	0.044	–	–
Cerebrovascular disease	-5.41(4.20)	0.198	–	–
Atrial fibrillation	6.74(4.89)	0.169	–	–
Potassium(mmol/L)	-4.10(4.69)	0.050	–	–
Albumin(g/dl)	-5.85(2.45)	0.017	-7.76(2.63)	0.003
Total cholesterol(mg/dl)	-0.06(0.04)	0.135	–	–
HDL(mg/dl)	-0.10(0.14)	0.442	–	–
LDL(mg/dl)	-0.12(0.06)	0.028	–	–
CRP(mg/dL)	0.37(0.23)	0.116	–	–

BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[1]Stepwise method using all covariates in univariate analyses (adjusted R^2= 0.07).

Table3 Associations between QTc and clinical outcomes

Outcome	Unadjusted HR(95% CI)	Unadjusted *P* value	Model 1 HR(95% CI)	Model 1 *P* value	Model 2 HR(95% CI)	Model 2 *P* value
All-cause mortality						
QTc, continuous						
Per 10-ms increment	1.17(1.12–1.23)	<0.001	1.16(1.11–1.22)	<0.001	1.15(1.09–1.21)	<0.001
QTc, categorical[1]						
Tertile 1	Reference		Reference		Reference	
Tertile 2	1.63(1.09–2.42)	0.016	1.58(1.05–2.38)	0.030	1.64(1.06–2.55)	0.028
Tertile 3	3.14(2.16–4.56)	<0.001	2.84(1.90–4.24)	<0.001	2.41(1.58–3.69)	<0.001
MACEs						
QTc, continuous						
Per 10-ms increment	1.1(1.07–1.32)	<0.001	1.13(1.06–1.20)	<0.001	1.15(1.07–1.23)	<0.001
QTc, categorical[1]						
Tertile 1	Reference		Reference		Reference	
Tertile 2	1.20(0.75–1.91)	0.440	1.16(0.72–1.87)	0.551	1.19(0.71–1.98)	0.516
Tertile 3	2.12(1.36–3.32)	0.001	1.79(1.11–2.86)	0.016	1.90(1.15–3.13)	0.012

原著論文　112_A 18

末期腎病患者的透析方式與中風發生之關聯

Dialysis Modality and Stroke Incidence among patients with End-Stage Kidney Disease

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Background

Patients with end-stage kidney disease undergoing dialysis are at significant risk of stroke. However, the association between dialysis modality and the incidence of cerebrovascular disease is still unclear. This study compared the risk of stroke incidence in patients undergoing peritoneal dialysis and hemodialysis.

Methods

39542 patients, with no history of stroke, who were started on dialysis from 1 January 2010 to 31 December 2014 were retrospectively studied using the Taiwan's National Health Insurance Research Database. We matched 3809 patients undergoing peritoneal dialysis (mean age 59±13 years; 46.5% women) and 11427 patients undergoing hemodialysis (mean age 59±13 years; 47.3% women) with a propensity score of 1:3 ratio, and then followed them up until 31 December 2015. The primary outcome was the incidence of acute ischemic stroke. The secondary outcomes included hemorrhagic stroke, acute coronary syndrome, and all-cause mortality. Cox proportional hazard models were conducted to determine the hazard ratios of clinical outcomes according to the dialysis modality.

Results

During a median follow-up period of 2.59 (interquartile range 1.50–3.93) years, acute ischemic stroke, hemorrhagic stroke, and acute coronary syndrome occurred in 783 (5.1%), 376 (2.5%), and 1350 (8.9%) patients, respectively. In a multivariable Cox model that accounted for the competing risk of death, acute ischemic stroke occurred more frequently in the peritoneal dialysis group than in the hemodialysis group (subdistribution hazard ratio [sHR], 1.32 [CI, 1.13–1.54]; P=0.0005). There were no significant treatment-related differences in the risk of hemorrhagic stroke (sHR, 0.89 [CI, 0.70–1.14]; P=0.3571) and acute coronary syndrome (sHR, 0.99 [CI, 0.88–1.12]; P=0.9080). Patients undergoing peritoneal dialysis were more likely to die from any cause than patients undergoing hemodialysis (adjusted HR, 1.24 [CI, 1.15–1.33]; P<0.0001).

Conclusion

Peritoneal dialysis was associated with a significantly higher risk of acute ischemic stroke compared to hemodialysis. Further studies are needed to clarify whether more aggressive cerebrovascular preventive strategies might mitigate the increased risk for ischemic stroke among patients receiving peritoneal dialysis.

原著論文　112_A 19

由每日單次糖德仕®同劑量轉換成每日單次諾怡得®可改善血糖控制

Improving glycemic control with equal dose conversion from once-daily insulin Toujeo® to once-daily insulin Ryzodeg®

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Background

Increasing frequency of insulin injection is a significant barrier in type 2 diabetes mellitus (T2DM) patients who fail to reach the glycemic goal under basal insulin treatment. Ryzodeg® is a composite of insulin degludec and insulin aspart and can mimic effect of basal plus one insulin injection without increasing injection times a day. Also, equal dose conversion is the simplest and reasonable way for this clinical practice. We evaluated the efficacy and hypoglycemia risk of equal dose switching from once-daily basal insulin therapy (Toujeo®) to once-daily pre-meal injection insulin Ryzodeg® in T2DM patients with uncontrolled glycemic target.

Methods

Between 2022 to 2023, the T2D patients with HbA1c > 7% under once-daily insulin Toujeo® for at least 3 months were enrolled. We shifted insulin Toujeo® to insulin Ryzodeg® with equal doses and injected from at bedtime to at supper. The fasting glucose levels, HbA1c, and body weight before and 3 months after this shifting and the number of hypoglycemia episodes were evaluated.

Results

A total 27 patients, mean age 56 ± 12 years old, were collected for analysis. The mean duration of diabetes was 9.5± 5.0 years and the average insulin dose was 22 ± 10 unit (0.3 unit per kilogram of body weight). After shifting to insulin Ryzodeg®, the mean of fasting sugar improved from 141mg/dL to 116mg/dL (p=0.011) and the average of HbA1c decreased from 8.4% to 7.7% (p<0.01). The change in body weight did not reach statistically significant. A total of two episodes of hypoglycemia (7.4%) in two patients were recorded but no any episode of severe hypoglycemia was found.

Conclusion

Equal dose conversion once-daily insulin from Toujeo® to Ryzodeg® showed favored fasting sugar and HbA1c control without increasing body weight. However, education for hypoglycemia treatment should be introduced because of increasing risk of hypoglycemia.

原著論文　112_A 20

北台灣單一醫學中心呼吸道融合病毒感染之流行病學及臨床特徵

Epidemiology and clinical characteristics of hospitalized adults with respiratory syncytial virus infection at a medical center in northern Taiwan

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Background

Human respiratory syncytial virus (RSV) has been recognized as a major pathogen of acute lower respiratory tract infection in preschool children globally.[1] In recent years, growing evidence has revealed that RSV infection among vulnerable adult populations may cause serious complications that lead to subsequent hospitalization and even death.[2] Risk factors for hospitalization due to RSV-related infection include old age and chronic cardiopulmonary disease.[3,4] The disease burden caused by RSV among at-risk adult populations may be driven not only by the infection itself but also by the exacerbation of underlying illness, causing increased healthcare utilization.[5] In Taiwan, compared to the pediatric population, there have been few studies on the adult population with RSV infection. In two studies on the prevalence of respiratory tract pathogens among the adult population in Taiwan, the incidence of RSV infection is approximately 2%.[6,7] Those two studies were conducted before the coronavirus disease (COVID 19) pandemic, and local prevalence rates of RSV may change during and after the pandemic period. Moreover, there remains a gap in the information regarding the clinical characteristics of the adult population infected with RSV. Therefore, this study aimed to describe the clinical characteristics, disease burden, and local epidemiology of RSV infections in hospitalized adults at a medical center in northern Taiwan.

Method

This retrospective cohort study was conducted at the Tri-Service General Hospital between January 2021 and February 2023. During the study period, all patients aged over 18 years had laboratory-confirmed RSV infection, which was defined as positive RSV antigen tests (Capilia™ RSV Neo; Becton-Dickinson, Japan) and/or reverse transcription polymerase chain reaction using a FilmArray respiratory panel (BioFire Diagnostics, USA) or a pneumonia panel (BioFire Diagnostics) were included. Those aged <18 years with RSV infections were excluded from the study. Epidemiological data including the date of onset and season of occurrence were recorded. The clinical data of the included cases were retrieved from electronic medical records. Demographic data, including age, sex, and living conditions, were recorded. The body mass index and smoking status were also documented. Underlying diseases, including cardiovascular diseases (coronary artery disease, valvular heart disease, arrhythmia, and heart failure), chronic lung diseases (chronic obstructive pulmonary disease, asthma, and bronchiectasis), cerebrovascular disease, diabetes mellitus, liver disease, kidney disease, malignancy, and autoimmune diseases, were also recorded. Moreover, initial symptoms at onset, disease severity presented with sequential organ failure assessment (SOFA) Score, complications of respiratory co-infection, and clinical outcomes were documented. Continuous variables are presented as medians and interquartile ranges (IQRs), and categorical variables are expressed as numbers and percentages.

Results

Between January 2021 and February 2023, 2149 samples were collected from hospitalized adult patients with respiratory symptoms screening for RSV infection. Specimens were collected from intensive care units (1011 samples, 47.0%), respiratory centers (12, 0.5%), ordinary wards (976, 45.4%), and emergency departments (150, 7.0%). Nineteen patients with RSV infection were identified. The overall positivity rate was 0.9%. Only 3 cases of RSV infection occurred between January 2021 and August 2022 during the COVID 19 pandemic period. The number of RSV-positive cases surged in autumn 2022 and winter 2023, with incidences being up to 2.3% and 1.8%, respectively.

The 19 adult patients with a positive RSV result had an approximately equal sex distribution, with 10 (52.6%) of cases in men. Most infected patients were aged > 65 years, with a median age of 79 years (IQR: 66–83 years). Most infected patients were from the community, with only one patient residing in a long-term care facility. All the included patients had one or more coexisting underlying diseases. The major underlying disease was cardiovascular disease (10/19, 52.6%). Diabetes mellitus, chronic lung disease, and obesity (defined as body mass index >30) took the second place (all 5/19, 26.3%). Among those with cardiovascular disease, eight had valvular heart disease and two had congestive heart failure. Three patients with valvular heart disease also had coronary artery diseases. At the disease onset, the most common presenting symptoms include fever, cough, and dyspnea. The median SOFA score as an indication of the disease severity among infected patients at onset was 4.5 (IQR: 2–8.5). Lower respiratory tract complications occurred in 14 patients (12 had pneumonia and 2 had acute exacerbation of chronic pulmonary disease), and five infected patients had cardiac complications with acute decompensated heart failure. Co-infection with other respiratory pathogens was observed in 11 patients. One patient had a *Chlamydia pneumoniae* infection, one had a *Mycobacterium avium* complex infection, and the others had a bacterial infection. Five patients infected with RSV required mechanical ventilation and were admitted to the intensive care unit. In-hospital death was 26.3%, and the median duration of overall hospital stay was 10 days among survivors. Among those discharged alive (n=14), three were readmitted within 30 days. The reasons for readmission were pneumonia (n=2) and acute exacerbation of chronic pulmonary disease (n=1).

Conclusion

In conclusion, our study described the clinical characteristics and revealed substantial disease burden of RSV infection in an adult population in Taiwan. To further validate the study results, a prospective multicenter study across Taiwan is warranted. Guidance regarding antiviral therapy and vaccination against RSV infection for at-risk adults is urgently needed to improve outcomes and decrease the disease burden on the healthcare system.

原著論文　112_A 21

Ceftazidime-avibactam 治療對 carbapenem 具抗藥性之克雷白氏肺炎菌感染：一個單中心回溯性研究

Ceftazidime-avibactam for the Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infection, a Retrospective, Single Center Study

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Introduction

Ceftazidime-avibactam (CZA), a novel beta-lactam/beta-lactamase inhibitor, plays an important role in the threat of emerging carbapenem-resistant Enterobacteriaceae (CRE) infection. We aim to analyze the clinical efficacy and factors of treatment response in applying CZA for carbapenem-resistant Klebsiella pneumoniae.

Methods

From February 2020 to December 2021, patients with carbapenem-resistant Klebsiella pneumoniae infection treated by ceftazidime-avibactam were enrolled in this retrospective, single-centered study in Taiwan. The primary outcome was 28-day survival. The secondary outcomes were 14-day survival, clinical success, and microbiological cure. Multivariate regression analysis was used to evaluate variables associated with 28-day survival.

Results

A total of 142 patients with ceftazidime-avibactam alone (n=82) or combination therapy (n=60) were included. We found 28-day survival rate, 14-day survival rate, clinical success, and microbiological cure rate were 78% (111/142), 88% (125/142), 86% (87/101), and 48% (63/132), respectively. In multivariate analysis, there were no significant differences in 28-day survival between the monotherapy group and the combination therapy group (P=0.424). Higher SOFA scores were associated with poorer 28-day survival rate (P=0.001, aOR: 0.63, 95% C.I: 0.49-0.83) and 14-day survival rate (P<0.001, aOR: 0.51, 95% C.I:0.36-0.71) respectively. Solid tumor was associated with less clinical success (P=0.017, aOR: 0.34, 95% C.I:0.14-0.82). A relatively lower rate of microbiological cure can be observed in lower respiratory tract infections from univariate analysis (P=0.07). In addition, significantly better survival was observed in patients with CCr≥50 than CCr<50 (P=0.005) according to Kaplan-Meier survival curve.

Fig 1. Distribution of agents that were prescribed with ceftazidime-avibactam as a combination therapy aFluoroquinolones (ciprofloxacin and levofloxacin). bCarbapenems (meropenem, doripenem, imipenem, ertapenem). cAminoglycosides (amikacin, gentamicin, tobramycin). dOther agents include ampicillin/

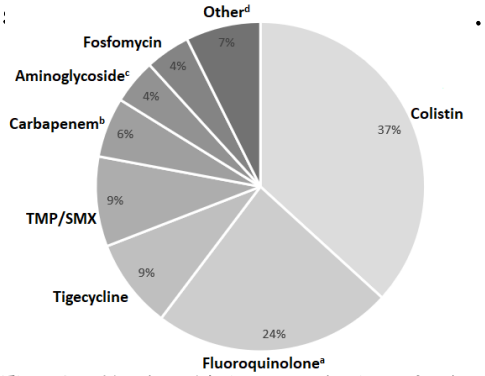
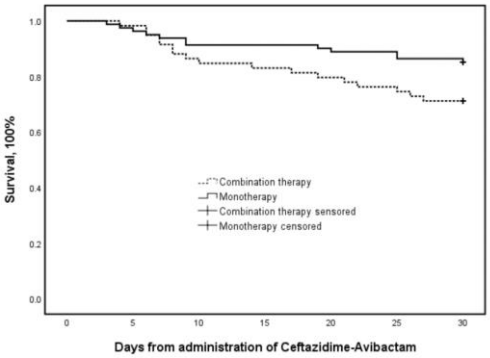


Fig 2. Kaplan-Meier analysis of the impact of monotherapy or combination therapy on 30-day survival. Significantly higher survival was observed in patients with monotherapy versus combination therapy (P=0.046).



Conclusion

Ceftazidime-avibactam is an effective and important treatment option for carbapenem-

resistant K. pneumoniae infection even when it is treated as monotherapy. Patients with impaired renal function was found to be associated with poor survival so that more research is needed for optimal renal dose adjustment.

Table 1. Characteristics Of Patients And Infection Site

	All infection (n=142)	Bactere mia (n=29)	Non-bacteremia (n=113)	P Value (Bactere mia vs Non-bactere mia)	LRTI (n=65)	UTI (n=26)	IAI (n=15)	SSTI (n=7)
Males	83 (58%)	15 (52%)	68 (60%)	0.16	42 (65%)	11 (42%)	9 (60%)	6 (86%)
Ages,median (IQR), yrs	74 (65-81)	74 (62-84)	74 (65-81)	0.57	76 (67.5-82.5)	76 (64.75-81.5)	68 (58-76)	58 (51-65)
Combine with CRPA infection	5 (4%)	1 (3%)	4 (4%)	0.98	2 (3%)	0	1 (7%)	1 (14%)
Comorbidities								
Mechanical ventilation	78 (55%)	15 (52%)	63 (56%)	0.7	46 (71%)	8 (31%)	7 (47%)	2 (29%)
Septic shock	25 (18%)	13 (45%)	12 (11%)	<0.001	10 (15%)	1 (4%)	1 (7%)	0
Severity of illness								
INCREMENT, median (IQR)	3 (3-7)	10 (6-12)	3 (3-3)	<0.001	3 (3-7)	3 (3-3)	3 (3-3)	3 (3-3)
INCREMENT>=8	26 (18%)	16 (55%)	10 (9%)	<0.001	7 (11%)	2 (8%)	1 (7%)	0
Charlson comorbidity index, median (IQR)	6 (4-7)	7 (4.5-8.5)	6 (4-7)	0.07	6 (5-7)	6.5 (4-9)	6 (4-8)	6 (3-7)
SOFA, median (IQR)	4 (2-7)	5 (3-12)	4 (2-6)	0.001	5 (3-7)	3 (1.75-4.5)	2 (1-5)	4 (0-10)
Renal function								
CCr>=50	67 (47%)	7 (24%)	60 (53%)	0.005	33 (51%)	14 (54%)	9 (60%)	4 (57%)
50>CCr>=10	45 (32%)	14 (48%)	31 (27%)	0.03	20 (31%)	7 (27%)	3 (20%)	1 (14%)
CCr<10 (without dialysis)	2 (1%)	0	2 (2%)	0.47	1 (2%)	1 (4%)	0	0
Dialysis	28 (20%)	8 (28%)	20 (18%)	0.23	11 (17%)	4 (15%)	3 (20%)	2 (29%)
CCr<30	50 (35%)	17 (59%)	33 (29%)	0.003	18 (28%)	10 (38%)	4 (27%)	1 (14%)
Therapy								
Time to active antibiotics, median (IQR),days	4 (1.75-5)	4 (1.5-5)	4 (1.5-5)	0.32	4 (1.5-5)	4 (0.75-5)	4 (0-6)	4 (4-8)
Time to CTZ-AVI, median (IQR), days	4 (4-6)	4 (3.5-6)	4 (4-6)	0.17	4 (4-6.5)	4 (3-5)	6 (4-8)	4 (4-8)
Therapy duration, median (IQR), days	14 (8-18)	15 (7-18)	14 (8-17.5)	0.74	14 (10.5-17)	8 (5.75-15)	18 (13-22)	13 (11-29)
Monotherapy	82 (58%)	17 (59%)	65 (58%)	0.92	33 (51%)	21 (81%)	7 (47%)	4 (57%)
Combination therapy	60 (42%)	12 (41%)	48 (42%)	0.92	32 (49%)	5 (19%)	8 (53%)	3 (43%)
Combine 1 agent	52 (37%)	9 (31%)	43 (38%)	0.48	27 (42%)	5 (19%)	8 (53%)	3 (43%)
Combine 2 agents	8 (6%)	3 (10%)	5 (5%)	0.22	5 (8%)	0	0	0
Combine with Colistin	24 (17%)	4 (14%)	20 (18%)	0.62	16 (25%)	1 (4%)	3 (20%)	0
Outcome								
In-hospital mortality	36 (25%)	14 (48%)	22 (19%)	0.002	15 (23%)	3 (12%)	3 (20%)	1 (14%)
14-day survival	125 (88%)	20 (69%)	105 (93%)	<0.001	60 (92%)	24 (92%)	14 (93%)	7 (100%)
28-day survival	111 (78%)	17 (59%)	94 (83%)	0.002	52 (80%)	24 (92%)	12 (80%)	6 (86%)
microbiological cure[a]	87 (86%)	24 (96%)	63 (83%)	0.1	39 (80%)	13 (93%)	6 (75%)	5 (100%)
clinical success[b]	63 (48%)	9 (33%)	54 (51%)	0.09	36 (56%)	13 (62%)	4 (29%)	1 (17%)
AKI	23 (20%)	7 (30%)	16 (17%)	0.15	15 (27%)	0	1 (8%)	0

COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; AKI, acute kidney injury; LRTI, lower respiratory tract infection; UTI, urinary tract infection; IAI, intra abdominal infection; SSTI, skin and soft tissue infection; CCr, creatinine clearance rate; IQR, interquartile range; CRPA, Carbapenem-resistant Pseudomonas aeruginosa

原著論文　112_A 22

高機械功率會增加急性呼吸窘迫症候群的發生

High mechanical power increases the development of acute respiratory distress syndrome

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Background

The impact of ventilatory settings on the onset of acute respiratory distress syndrome (ARDS) in non-ARDS patients with respiratory failure is not thoroughly understood. This study sought to pinpoint respiratory parameters associated with ARDS development in mechanically ventilated patients without an initial ARDS diagnosis.

Method

Using the Medical Information Mart for Intensive Care IV (MIMIC-IV) v1.0 database, we analyzed data from 117 patients with respiratory failure but without ARDS. Selection criteria were clearly defined. After propensity score matching for cohort comparability, 108 patients were considered for detailed analysis. A multivariate logistic regression then identified significant risk determinants.

Results

Of the 108 matched participants, 36 evolved into ARDS, while 72 did not. For the individual records (n = 1,417 for non-ARDS; n = 648 for ARDS), we noted significant differences in respiratory rate, tidal volume, driving pressure (DP), and mechanical power (MP) between the two groups. However, when the settings were averaged for each patient (n = 72 for non-ARDS; n = 36 for ARDS), only the MP showed a significant difference between the two groups. The regression pinpointed that DP exhibited a significant association with ARDS development ($p < 0.001$) at the individual record level. Conversely, when settings were averaged per patient, only MP demonstrated a significant relationship with ARDS development ($p = 0.035$) in the ventilated cohort.

Conclusion

MP emerges as a prominent predictor of ARDS onset, outperforming its constituent components in patients initially not diagnosed with ARDS. Incorporating MP-focused ventilatory strategies could mitigate the progression from a non-ARDS state to ARDS.

原著論文　112_A 23

糖尿病腹膜透析患者血清纖維母細胞生長因子 23 值跟主動脈脈波傳播速率有關

Serum Fibroblast Growth Factor 23 Level Is Associated with Aortic Pulse Wave Velocity in Diabetic Peritoneal Dialysis Patients

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Background

Derangement of serum chronic kidney disease-mineral and bone disorder (CKD-MBD) biomarkers in patients with end-stage renal disease (ESRD) is tightly linked to vascular dysfunction and calcification. However, few studies evaluate whether the association of serum CKD-MBD biomarkers on aortic stiffness differs between diabetes mellitus (DM) and non-DM PD patients. We aimed to explore the relationship of four CKD-MBD biomarkers, including intact parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), soluble α-Klotho, and Fetuin-A, with aortic stiffness among ESRD patients undergoing PD, comparing those with DM and non-DM.

Method

A total of 213 prevalent PD patients (mean age 58 ± 14 years), comprising 81 (38.0%) DM and 132 (62.0%) non-DM, were enrolled. We measured aortic pulse wave velocity (PWV) using pressure applanation tonometry and quantified serum levels of intact PTH, FGF23, α-Klotho, and fetuin-A levels using commercial enzyme-linked immunosorbent assay kits.

Results

DM patients had significantly higher aortic PWV than non-DM patients ($p < 0.001$). The four CKD-MBD biomarkers were comparable between two groups, except that FGF23 levels were significantly lower in DM group ($p = 0.028$). Among four CKD-MBD biomarkers, log-FGF23, but not the other biomarkers, independently predicted aortic PWV in our PD patients but only in those with DM ($\beta = 0.61$; 95% CI = 0.06-1.16, $p = 0.029$ in DM group; $\beta = 0.10$; 95% CI = -0.24-0.45, $p = 0.546$ in non-DM group; interaction $p = 0.016$).

Conclusion

In our study, the DM status significantly modified the association between FGF23 and aortic PWV among PD participants.

原著論文　112_A 24

血清類血管生成素 3 濃度跟血液透析患者內皮功能失調有關

Serum Angiopoietin-Like Protein 3 Level Is Associated with Endothelial Dysfunction in Patients Undergoing Hemodialysis

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Background

Angiopoietin-like protein 3 (ANGPTL3) plays important roles in lipid and lipoprotein trafficking and metabolism and has demonstrated a positive correlation with cardiovascular risk assessment parameters of carotid and femoral artery intima-media thickness. We evaluated the association between serum ANGPTL3 levels and endothelial function in chronic hemodialysis (HD) patients.

Method

Blood samples were obtained from 116 chronic HD patients. We measured the endothelial function—represented by the vascular reactivity index (VRI)—via non-invasive digital thermal monitoring, and serum ANGPTL3 concentrations by using commercial enzyme-linked immunosorbent assay.

Results

Seventeen (14.7%), 50 (43.1%), and 49 (42.2%) patients had poor (VRI < 1.0), intermediate (1.0 ≤ VRI < 2.0), and good (VRI ≥ 2.0) vascular reactivity. As the VRI decreased, the serum alkaline phosphatase (ALP, $p = 0.025$) and ANGPTL3 ($p < 0.001$) levels significantly increased. Serum log-transformed ALP (log-ALP, $r = -0.187$, $p = 0.045$) and log-ANGPTL3 ($r = -0.319$, $p < 0.001$) were negatively associated with VRI values by univariate linear regression analysis. After applying multivariate stepwise linear regression analysis adjustment, the significantly negative association of log-ANGPTL3 (standardized $\beta = -0.319$, adjusted R^2 change = 0.094; $p < 0.001$) with VRI values in chronic HD patients remained.

Conclusion

Our results indicated that ANGPTL3 concentration was negatively associated with VRI values and modulated endothelial function in chronic HD patients.

原著論文　112_A 25

血清硫酸吲哚酚跟第二型糖尿病病人中樞動脈硬度有關

Serum Indoxyl Sulfate is Associated with Aortic Stiffness in Patients with Type 2 Diabetes Mellitus

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Background

Indoxyl sulfate (IS), a uremic toxin derived from tryptophan, which plays crucial roles in oxidative stress, inflammation, and atherosclerosis. The present study aimed to evaluate the relationship between serum total IS levels and aortic stiffness in type 2 diabetes mellitus (T2DM) patients.

Method

General characteristics and serum IS concentrations were measured in 80 persons with T2DM. Serum total IS levels were determined by high-performance liquid chromatography–mass spectrometry. A carotid-femoral pulse wave velocity (cfPWV) value >10 m/s, as determined using the SphygmoCor system, was defined as an indicator of aortic stiffness.

Results

Among the 80 participants with T2DM, 30 participants (37.5%) were classified in the aortic stiffness group. The rates of hypertension ($p = 0.037$) as well as older age ($p = 0.007$), systolic blood pressure ($p = 0.002$), the serum levels of triglyceride ($p = 0.023$), fasting glucose ($p = 0.025$), glycated hemoglobin ($p = 0.013$), blood urea nitrogen ($p = 0.013$), creatinine ($p = 0.047$), urine albumin-to-creatinine ratios ($p = 0.005$), C-reactive protein ($p = 0.029$) and IS ($p < 0.001$) were higher, while estimated glomerular filtration rates ($p = 0.003$) were lower in the aortic stiffness group than in the control group. Multivariate logistic regression analysis with additional variables also noted IS level (odds ratio: 2.565, 95% confidence interval: 1.145–5.748, $p = 0.022$) was an independent predictor of aortic stiffness in T2DM. Multivariate forward stepwise linear regression analysis also showed that logarithmically transformed IS levels (log-IS, $\beta = 0.261$, adjusted R2 change = 0.051, $p = 0.019$) were positively associated with cfPWV values in T2DM.

Conclusion

Serum IS level is an independent predictor of aortic stiffness and is positively associated with cfPWV values in T2DM.

原著論文　112_A 26

血清對硫甲酚跟非透析慢性腎臟病患者以中心脈波傳導速率測量中樞動脈硬度有關

Increased Serum P-Cresyl Sulfate Level Is Associated with Aortic Stiffness Measured by Carotid-Femoral Pulse Wave Velocity in Patients with Non-Dialysis Chronic Kidney Disease

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Background

The *p*-cresyl sulfate (PCS) is a uremic toxin with pro-inflammatory and cytotoxic effect on proximal tubular epithelial cells, which leads to cardiovascular injury and the progression among chronic kidney disease (CKD) patients. Aortic stiffness (AS) has been estimated via a non-invasive method of measuring the carotid-femoral pulse wave velocity (cfPWV) which is regarded as a valuable predictor for cardiovascular events in general population. The study aimed to investigate the correlation between serum PCS level and AS measured by cfPWV values in patients with CKD.

Method

We had obtained baseline characteristics and fasting blood samples from 165 patients of CKD. AS was defined as above 10.0 m/s of any side of cfPWV value measured with cuff-based volumetric displacement. High-performance liquid chromatography–mass spectrometry was used to assay the serum PCS level.

Results

Among 165 CKD patients, 50 patients (30.3%) were in the AS group. When compared to those in the control group, the AS group had high prevalence of diabetes mellitus ($P = 0.036$), older age ($P < 0.001$), higher systolic blood pressure ($P = 0.016$), fasting glucose ($P = 0.008$), urine protein–creatinine ratio ($P = 0.048$), and higher serum PCS level ($P = 0.001$). Multivariate logistic regression analysis of the factors significantly associated with AS revealed that serum PCS levels (odds ratio (OR): 1.097, 95% confidence interval (CI): 1.024–1.175, $P = 0.008$) and age (OR: 1.057, 95% CI: 1.025–1.090, $P < 0.001$) were the independent predictors of AS in CKD patients. Multivariate forward stepwise linear regression analysis also showed that logarithmically transformed PCS level (log-PCS, $\beta = 0.181$, adjusted R^2 change = 0.032, $P = 0.007$) was an independent predictor of cfPWV values in patients with CKD.

Conclusion

In addition to older age, increased serum PCS levels were independently predictive of AS in patients with non-dialysis CKD.

原著論文　112_A 27

血清蝕骨細胞抑制因子跟高血壓病人內皮功能失調有關

Serum Osteoprotegerin is Associated with Endothelial Dysfunction in Patients with Hypertension

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Background

Osteoprotegerin (OPG), a soluble glycoprotein found in serum, has been associated with both the presence and severity of atherosclerosis. Due to endothelial dysfunction, hypertension patients (HTN) had higher mortality rates. To better understand the connection between endothelial dysfunction in patients with HTN, serum OPG levels were examined in this study.

Method

There are 102 patients with HTN included. For the purpose of determining the levels of OPG, a commercial enzyme-linked immunosorbent test kit was applied. The vascular reactivity index (VRI), which is assessed by the digital thermal monitoring test, provides information on endothelial function. In this study, we classified VRI values between 1.0 and 2.0 as moderate and good vascular reactivity, respectively. VRI values below 1.0 were classified as poor vascular reactivity.

Results

Ten patients with HTN (9.8%) were classified as having poor vascular reactivity (VRI < 1.0), 46 HTN patients (45.1%) as having intermediate vascular reactivity (1.0 VRI < 2.0), and 46 HTN patients (VRI <2.0) were classified as having high vascular reactivity. A greater serum OPG level ($p < 0.001$) and older age ($p = 0.022$) were linked to impaired vascular reactivity. The estimated glomerular filtration rate ($r = 0.196$, $p = 0.048$) was positively correlated with VRI values in patients with HTN, while advanced age ($r = -0.222$, $p = 0.025$) and the logarithmically converted blood OPG level (log-OPG, $r = -0.357$, $p < 0.001$) were negatively correlated with VRI. Serum log-OPG level was shown to be strongly and independently correlated with VRI values in HTN individuals after multivariable forward stepwise linear regression analysis ($\beta = -0.357$, adjusted R2 change = 0.119, $p < 0.001$).

Conclusion

In patients with HTN, serum OPG levels were adversely correlated with VRI and probably had a role in endothelial dysfunction.

原著論文　112_A 28

探討拔管後病人使用高流量濕化氧氣經鼻導管失敗原因分析

Discussion on the failure of high flow nasal cannula in patients after extubation

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Background

高流量濕化氧氣經鼻導管(High Flow Nasal Cannula, HFNC)可提供高流速氣體在鼻咽產生 3-5cmH_2O 的氣道正壓(Positive End Expiratory Pressure, PEEP)及穩定溫度 31℃-37℃與相對濕度 100%之氣體，可有效濕化痰液。多篇研究都在探討拔管後使用 HFNC 可有效降低低血氧及再次插管機率，但有研究指出 HFNC 對拔管後的再次插管率並無影響。也有研究顯示 HFNC 可提供良好舒適性及降低再次插管機率，與非侵襲性呼吸器(Non-Invasive Ventilation, NIV)相比並無顯著差異。因兩者儀器設備所提供之功能性不同，且較少針對再次插管之個案進行相關性研究分析。因此進行某區域教學醫院移除氣管內管病人使用 HFNC 失敗原因進行分析。

Method

本研究採電子病例回溯性調查設計。以電子病歷搜尋方式列出某區域教學醫院 2021 年 1 月 1 日至 2022 年 12 月 31 日(共 2 年)住院病人中拔管後使用 HFNC 之個案共 120 人。將其分為成功脫離之個案有 81 人，失敗再次插管之個案有 39 人，進行探討失敗原因分析，所有數據以 SPSS for windows 25.0 版進行分析。

Results

本研究中拔管後使用 HFNC 共 120 人，年齡平均為 70.01 歲(*SD*=13.83)，HFNC 平均使用天數為 3.67 天(*SD*=3.67)。拔管後使用 HFNC 成功脫離病人有 81 人(佔 67.5%)，再次插管病人有 39 人(佔 32.5%)，因呼吸衰竭使用 NIV 病人有 22 人(佔 56.4%)。拔管後使用 HFNC 再次插管與成功脫離兩組，65 歲以上合併心肺疾病(20.8% vs 11.7%；*p* 值<0.001)、呼吸器使用天數大於 7 天(25.8% vs 6.7%；p 值=0.021)之比率皆顯著差異。再次插管住院中死亡有 13 人(佔 33.3%)。如表一

Conclusion

拔管後使用 HFNC 再次插管機率仍有三成以上。由本文數據分析顯示屬於高風險者，如 65 歲以上合併心肺疾病、呼吸器使用天數大於 7 天，應審慎評估使用。此外仍需更多臨床數據並納入統計分析，以提供更有力的相關證據，來提升醫療及呼吸照護品質。

變項	成功脫離 (n=81)	再次插管 (n=39)	p-value
65 歲以上合併心肺疾病			<0.001*
無	59(72.8)	14(35.9)	
有	22(27.2)	25(64.1)	
呼吸器使用天數>7 天			0.021*
無	34(42)	8(20.5)	
有	47(58)	31(79.5)	
拔管前 PaCO2≧45mmHg			0.814
無	65(80.2)	32(82)	
有	16(19.8)	7(18.0)	
再次插管前 PaCO2≧45mmHg			<0.001*
無	81(100)	22(56.4)	
有	0(0)	17(43.6)	
體重(BMI≧27)			0.486
無	53(65.4)	28(71.8)	
有	28(34.6)	11(28.2)	
住院中死亡			<0.001*
無	81(100)	26(66.7)	
有	0(0)	13(33.3)	

表一 拔管後使用 HFNC 失敗原因比較

原著論文　112_A 29

第二型糖尿病患者使用二肽基肽酶 4 抑制劑與發生周邊動脈阻塞疾病之相關性：28 篇隨機對照試驗統合分析

Utilization of DPP-4 inhibitors and the incidence of peripheral arterial occlusive disease in type 2 diabetic patients: a meta-analysis of 28 randomized controlled trials

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Background

Dipeptidyl peptidase-4 (DPP-4) inhibitors have attracted increased attention within the population of individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) due to their notable advantage of posing less risk of hypoglycemia and not causing weight gain. DPP-4 inhibitors have demonstrated efficacy in managing blood glucose levels and enhancing cardiovascular and renal function in certain randomized controlled trials. However, the clinical evidence regarding its functional significance in reducing the risk of cardiovascular illnesses is not entirely conclusive. Peripheral artery occlusive disease (PAOD) is a revalent and consequential consequence of T2DM that impairs the circulation of blood to the lower extremities. PAOD has been found to be associated with an elevated risk of cardiovascular events, including myocardial infarction and stroke. These events are recognized as a major cause of mortality among individuals with T2DM. The estimated prevalence of PAOD in people with T2DM is considerable, with a greater mortality risk compared to individuals without diabetes. Hence, the prevention and management of PAOD hold significant importance in enhancing the overall well-being and longevity of individuals diagnosed with T2DM. Therefore, we performed a systematic review of randomized controlled trials and conducted a meta-analysis to evaluate the incidence of peripheral arterial occlusive disease among individuals diagnosed with type 2 diabetes mellitus who underwent DPP-4 inhibitor treatments as compared to those who were given placebo or alternative oral hypoglycemic medications.

Methods

The study followed the PRISMA standards and conducted a comprehensive search of the PubMed, Cochrane Library, and ClinicalTrials.gov databases to identify relevant articles published up until January 1, 2023. The study included comparative analyses of DPP-4 inhibitors and alternative control drugs, with a focus on evaluating the incidence of diseases associated with PAOD, all-cause mortality, cardiovascular death, and hospitalization due to heart failure. Studies involving individuals with severe renal illness, heart failure, or type 1 diabetes were excluded. The quality of the included studies was assessed using the Cochrane Risk of Bias tool. Funnel plots and Egger's test were employed to identify potential publication bias, while forest plots were utilized to visually represent the relative risk associated with each outcome. In addition, we ran subgroup analyses to look at the impact of individual types of DPP-4 inhibitors. Furthermore, a meta-regression analysis was performed to investigate the relationship between various study variables, including age, baseline changes in T2DM indicators, duration of T2DM, and the effects of DPP-4 intervention in the meta-analysis.

Results

A total of twenty-eight randomized controlled trials were included for the metaanalysis, with

nine studies investigating the use of Sitagliptin, seven focusing on Linagliptin, five examining Saxagliptin, five exploring Alogliptin, and one study have both Vildagliptin and Omarigliptin as intervention medicines. The studies were published between the period of 2007 to 2020, with the study sample sizes varying from 133 to 16,492 participants. The median length after the diagnosis of T2DM was 6.25 years, while the median follow-up period for the included trials was 52 weeks. Metformin appeared as the predominant background treatment, with a higher frequency of use compared to pioglitazone, insulin, and other hypoglycemic interventions.

Our study revealed that the use of DPP-4 inhibitors did not yield a statistically significant reduction in the incidence of PAOD, all-cause mortality, or cardiovascular mortality when compared to the control group. However, the use of Saxagliptin had a statistically significant protective benefit against peripheral artery occlusive disease (relative risk [RR] = 0.59, 95% confidence interval [CI]: 0.37–0.96). However, it is important to note that this finding was not resilient to sensitivity analysis, suggesting a need for further investigation. No significant correlations were seen between the study variables and the risk ratio of the four research outcomes in the meta-regression analysis.

Conclusion

Based on our comprehensive meta-analysis of randomized controlled trials conducted until January 2023, it is evident that the use of DPP-4 inhibitors does not yield a statistically significant reduction in the risk of developing PAOD, all-cause mortality, cardiovascular death, and hospitalization due to heart failure. Further research is required to substantiate the efficacy of saxagliptin in reducing the incidence of PAOD.

原著論文　112_A 30

葡萄糖轉運蛋白抑制劑對於癌症患者在房顫的保護效應

Protective effects of sodium–glucose cotransporter 2 inhibitors on incident atrial fibrillation in patients with cancers

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Background

This study was to assess the ability of sodium-glucose cotransporter-2(SGLT2) inhibitors in predicting new-onset atrial fibrillation (AF) among patients with cancer.

Method

Patients with newly diagnosed cancer between 1 January, 2016 and 31 December, 2019, from the Taiwan Nationwide Database, were defined as the study cohorts. Each cohort contained 20,339 participants. Cox model was applied and subgroup analysis with age-, sex-, comorbidity- and medicaiton- substratification was emplyed in the analysis.

Results

SGLT2 inhibitors cohort conferred (adjusted HR = 0.64, 95 % CI = 0.60-0.68) a significantly lower risk of new onset AF than controls among patients with cancer. Among cancer types, patients with uteri cancer had the lowest risk of AF with the adjusted HR of 0.41, and 95 % CI = 0.25-0.66.

Conclusion

SGLT2 inhibitors was found to have a significantly lower risk of incident AF among cancer patients.

原著論文　112_A 31

血管張力素受體-腦啡肽酶抑制劑在末期腎臟疾病心衰患者臨床預後探討

Impact of ARNI(angiotensin receptor-neprilysin inhibitor) on adverse clinical events in heart failure with end-stage renal disease patients

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Background

The authors tried to define the association of adverse cardiovascular(CV) events, such as acute myocardial infarction (AMI), heart failure (HF) requiring admission and CV death among patients with HF+ end stage renal disease (ESRD) using ARNI(angiotensin receptor-neprilysin inhibitor).

Method

This data came from Taiwan National Health Insurance Research Database(NHIRD). Propensity scoring (PS)matching was used. Univariable cox proportional hazard model was applied to calculate hazard ratio (HR) and 95% confidence interval(CI) for adverse events among these two groups.

Results

After propensity score matching, among HF+ESRD patients, 714 receiving ARNI whereas the other 714 patients did not. Compared to patients who did not receive ARNI, patients with ARNI were more likely to suffer AMI readmission (aHR= 1.86, 95% CI = 1.43–2.42), HF readmission (aHR = 2.07, 95% CI = 1.82–2.35) and CV death (aHR = 1.71, 95% CI = 1.32–2.22) after the index year matching. After PS matching, patients with ARNI were more likely to suffer AMI readmission (aHR =1.68, 95% CI = 1.18–2.41) and HF readmission (aHR = 1.94, 95% CI = 1.62–2.32).

Conclusion

Among HF+ESRD patients, those taking ARNI have a higher risk of adverse clinical CV events.

原著論文　112_A 32

使用人工智能來偵測腹膜透析患者的出口部位感染

Detection of exit site infection with artificial intelligence in peritoneal dialysis patients

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Background

Peritoneal dialysis (PD) requires the placement of a catheter that traverses the patient's abdominal wall and extends into the peritoneal cavity. Infections can occur at the catheter exit site, tunnel, and peritoneum, potentially leading to morbidity, mortality, and catheter removal. Patients need to inspect the exit site daily to detect infections early. The purpose of this study is to utilize artificial intelligence (AI) to assist in the detection of exit site infections in PD patients.

Method

Patients or medical personnel took photos of the abdominal catheter exit site using a smartphone camera. Abnormal exit site features were defined as redness, swelling, crusting, and discharge. These photos were reviewed by medical personnel and classified as normal or abnormal images. The no-code development platform AIDMS, established by Leadtek Company, was used for image classification and object detection with adopting image classification models including ResNet, Inception, and MobileNet series, and object detection models including Yolo, DETR-transformer, and Resnet series.

Results

Medical personnel reviewed a total of 220 images, of which 150 were classified as abnormal and 70 as normal. Object annotations were also performed separately. The ratios of adopted training, validation, and testing were 7:1:2. For image classification prediction, the best performance was achieved using Inception-V3, with an accuracy of 0.89 and an area under the curve (AUC) of 0.934. At a probability threshold of 0.9, the positive accuracy was 0.964. In object detection, the best performance was achieved using Yolo v4, with an AP50 of 0.805 at an intersection over union (IOU) of 0.5. If object detection results were used to determine image classification, the model had an accuracy of 0.911, an AUC of 0.864, and a positive accuracy of 0.935 at a probability threshold of 0.81.

Conclusion

Given the higher accuracy, precision, and AUC, AI can be used to assist in the detection of exit site infections in PD patients. Moreover, since object detection results are more intuitive and have only slightly lower performance than image classification, object detection technology may be employed in the future to aid in the interpretation of exit site infections in patients.

原著論文　112_A 33

探討抗發炎的微小核糖核酸 146a-5p 和微小核糖核酸 200b-3p 用於改善糖尿病傷口的癒合的角色

Investigating the role of anti-inflammatory microRNA-146a-5p and microRNA-200b-3p in diabetic wound healing improvement

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Background

Diabetic foot ulcer (DFU) constitutes a major health burden with a lifetime risk developing a foot ulcer as high as 25% among diabetic patients. Wound healing is a complex overlapping sequence of cellular and molecular processes, including hemostasis, inflammation, cell proliferation, angiogenesis, collagen deposition, and re-epithelization. Diabetes is a chronic inflammatory process. The non-healing DFUs are partially attributed to the diabetes-induced pro-inflammatory wound, a hostile healing environment that impairs the normal healing processes. Previously, we reported that both miR-146a-5p and miR-200b-3p decreased endothelial inflammation in human aortic endothelial cells and db/db diabetic mice. In this study, we demonstrated local injections of miR-146a-5p and miR-200-3p hold promise in accelerating wound healing process in a wound model of db/db diabetic mice.

Methods

Twelve-week-old male db/db mice were used in all experiments. Mice were anesthetized with inhaled isoflurane. The dorsal skin of mouse was carefully shaved, depilated, and sterilized before wounding. Each mouse underwent two dorsal full-thickness wounds with an 8-mm biopsy punch at its left and right back at day 0. Immediately after wounding, four intradermal injections equally spaced in a radial pattern at the wound edge in a total volume of 20 μL (5 μL per injection) using a Hamilton syringe at day 0. A total dose of 100 ng miR-146a-5p mimic, miR-200b-3p mimic, and miR-negative control (NC) per wound was injected. The mouse in each treatment group received full-thickness skin area harvests of all the wounded area at post-wounding day 14 for real time PCR and immunohistochemistry (IHC) examinations. Photographs were obtained every day up to day 14. ImageJ software was used to calculate the wound area of each mouse every day.

Results

Owing to the hypercatabolic state of wound healing process, all db/db mice gradually lost their body weight. However, the mean body weight reduction between the day 0 to day 14 was most apparent in the miR-NC group, as compared to miR-146a-5p and miR-200b-3p groups. At day 14, miR-200b-3p showed most significant healing improvement among these three groups. Regarding to the inflammation modulation, both miR-146a-5p and miR-200b-3p groups were associated with slightly decreased IL-6 and significantly decreased IL-1β gene expression, as compared to miR-NC group. Regarding to the collagen deposition modulation, both miR-146a-5p and miR-200b-3p groups were associated with slightly increased COL1A2 and significantly increased COL3A1 gene expression, as compared to miR-NC group. TGF-β1 is a pleiotropic cytokine in cutaneous wound healing and its level increases in the acute wound healing process, but it decreases in chronic wound condition. At day 14, our data

showed that TGF-β 1 gene expression levels had the following sequence: miR-NC > miR-146a-5p > miR-200b-3p, suggesting that the acute, non-healing miR-NC-treated wound was attenuated to a more chronic, healing wound in the miR-146a-5p-treated and miR-200b-5p-treated groups. CD68 is a known marker of the tissue macrophages. At day 14, IHC staining showed that the immunoreactivities of CD68 were significantly decreased in miR-146a-5p and miR-200b-3p groups, as compared to miR-NC group. CD31 is known marker for endothelial cells. At day 14, IHC staining showed that the immunoreactivities of CD31 were significantly increased in miR-146a-5p and miR-200b-3p groups, as compared to miR-NC group. Finally, the granulation tissue thickness at day 14 was significantly increased in miR-146a-5p and miR-200b-3p groups, as compared to miR-NC group. Our data support local injections of microRNAs are a viable approach in improving wound healing process in db/db diabetic mice.

Conclusion

Targeting the defective inflammatory process with miR-200b-3p shows the most promising result by improved wound healing in db/db diabetic mice, suggesting a strategy aiming to correct the deregulatory inflammation with anti-inflammatory microRNA injections in diabetic wounds holds promise in the management of patients with DFUs in future.

原著論文　112_A 34

比較兩種微生物鑑定與藥物敏感性自動化系統與標準瓊脂擴散法於台灣地區無菌部位分離之金黃色葡萄球菌基因型與表現型的關聯性 (2011 年至 2021 年)

Comparative analysis of two commercial automated systems with agar dilution for antibiotic susceptibility and their association with genotypes of invasive *Staphylococcus aureus isolates* (2011-2021)

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Background

Determining oxacillin susceptibility is crucial for treating invasive infections caused by *Staphylococcus aureus*. Commercial automated systems efficiently determine antibiotic susceptibility. This study compares two automated systems with the reference method and correlates them with genotypes of invasive *S. aureus*.

Methods

Non-duplicate *S. aureus* isolates from patients with invasive infections were collected from a 11-year longidutinal study conducted in a medical center. Methicillin-resistant *S. aureus* (MRSA) was confirmed with *mecA* existence, and the genotype was determined using SCC*mec* with multiplex PCR. Antimicrobial susceptibility was performed using agar dilution and two automated systems (BD Phoenix™ 100 and Vitek® 2) for oxacillin and cefoxitin according to the Clinical and Laboratory Standards Institute (CLSI). The correlation of SCC*mec* types with antibiotic susceptibility using two automated systems and agar dilution was analyzed.

Results

In total, 842 invasive *S. aureus*, including 443 *mecA*+MRSA and 399 *mecA*-MSSA types were identified. The susceptibility rates of oxacillin determined by two automated systems and agar dilution were 68.8% (76.8% for Phoenix™ 100 and 57.6% for Vitek® 2) and 54.0%, respectively. When compared with agar dilution, the oxacillin sensitivity for Phoenix™ 100 and Vitek® 2 were 46.9% and 85.7%, respectively ($p < 0.001$). There were 143 isolates determined as oxacillin-susceptible *S. aureus* (OSSA) using automated systems but assigned as oxacillin-resistant *S. aureus* (ORSA) using agar dilution (false negative). Among them, those with molecularly community-associated MRSA (CA-MRSA, including SCC*mec* IV, V, and V_T,) surpassed healthcare-associated MRSA (HA-MRSA, including SCC*mec* I, II, and III) (99 vs. 34, $p < 0.001$).

Conclusion

The categorical agreement of Vitek® 2 in determining oxacillin susceptibility and predicting *mecA* existence is comparable with agar dilution, whereas Phoenix™ 100 is not. Most ORSA determined by agar dilution but misinterpreted as OSSA by automated systems are categorized as CA-MRSA.

原著論文　112_A 35

2011 年至 2021 年台灣地區對苯唑西林具敏感性但對甲氧西林具抗藥性的無菌部位分離之金黃色葡萄球菌基因型與表現型的關聯性

Invasive oxacillin-susceptible mecA+ methicillin-resistant Staphylococcus aureus (OS-MRSA) is strongly associated with community-associated MRSA (CA-MRSA) in Taiwan (2011-2021)

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Background

Invasive infections caused by *Staphylococcus aureus*, including methicillin susceptible (MSSA) and methicillin resistant *S. aureus* (MRSA), lead to significant morbidity and mortality. Genotyping using the staphylococcal cassette chromosome *mec* (SCC*mec*) has been universally used for MRSA. OS-MRSA has been identified for decades with *mecA* gene and susceptibility to oxacillin (oxacillin MIC ≦ 2 mg/L). The goal of this study was to delineate the molecular typing results of OS-MRSA and to correlate these with antibiotic susceptibility.

Methods

Non-duplicate *S. aureus* isolates from patients with invasive infections were collected from a 11-year longidutinal study conducted in a medical center. Methicillin-resistant *S. aureus* (MRSA) was confirmed with *mecA* existence, and the genotype was determined using SCC*mec* with multiplex PCR. Antimicrobial susceptibility was performed using agar dilution for MIC determination of vancomycin, oxacillin, and cefoxitin according to the Clinical and Laboratory Standards Institute (CLSI). The correlation of SCC*mec* types with antibiotic susceptibility was analyzed.

Results

In total, 842 invasive *S. aureus*, including 443 *mecA*+MRSA and 399 *mecA*-MSSA types were identified. Six (1.4%) vancomycin-intermediate *S. aureus* (VISA) isolates with vancomycin MIC of 4 mg/L were identified, but no vancomycin-resistant *S. aureus* (VRSA) was found. The sensitivity/specificity of cefoxitin and oxacillin with agar dilution in predicting *mecA* existence were similar (87.1%/95.0% vs. 84.2%/96.5%). The categorical agreements among the agar dilution and *mecA* existence for oxacillin and cefoxitin were comparable (0.799 vs. 0.815). There were 70 *mecA*+ OSSA (OS-MRSA) using agar dilution, among which 42 harboring SCC*mec* types, were predominantly categorized as CA-MRSA (38, $p < 0.001$), and their distribution and proportion stratified by oxacillin MICs were as follows: MIC≤0.25 mg/L, 13.4% (9/67); MIC = 0.5 mg/L, 13.6% (30/220); MIC = 1 mg/L, 14.6% (19/130); and MIC = 2 mg/L, 31.6% (12/38).

Conclusion

Genotyping MRSA with SCC*mec* can differentiate MRSA isolates for epidemiological purpose. OS-MRSA is closely related to CA-MRSA and centralizes at an oxacillin MIC of 2 mg/L, raising concerns about the treatment efficacy for invasive OS-MRSA infections using semi-synthetic penicillins and β-lactams.

原著論文　112_A 36

新綠原酸透過 miR-145 調控 Ras 表現對血管平滑肌細胞增生和轉移之機制研究

Mechanisms of neochlorogenic acid in regulating Ras via miR-145 and impact on vascular smooth muscle cell proliferation and migration

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Background

In our previous study, we utilized ApoE$^{-/-}$ mice fed a high-fat diet (HFD). Treatment with neochlorogenic acid (nCGA) proved effective in mitigating cardiovascular lipid accumulation, reducing the rate of weight gain, and improving serum concentrations induced by the high-fat diet. Consequently, in the present experiment, we investigated the mechanistic aspects of nCGA's impact on vascular endothelial cells under conditions of high sugar and high lipid content.

Methods

We assessed cell proliferation and cell death using MTT and flow cytometry, respectively. Cytoskeletal alterations were observed through F-actin fluorescent staining. Furthermore, we conducted quantitative analyses of relevant protein expression and microRNA changes using Western blotting and Real-Time PCR.

Results

The experimental data demonstrates that in cell experiments simulating a high-sugar and high-lipid environment mimicking diabetes, we performed quantitative analysis using Western blotting for migration-related proteins such as Integrin β3 and p-FAK, as well as proliferation-related proteins like Ras and p-AKT. These analyses substantiate that treatment with nCGA led to reduced expression of proteins involved in both migration and proliferation pathways.

Conclusion

Based on the comprehensive findings of this experiment, nCGA has the potential to regulate miR-145, subsequently modulating the Ras signal pathway. This regulatory effect contributes to the alleviation of vascular smooth muscle cell proliferation and migration induced by high glucose and high lipids.

原著論文　112_A 37

前導性化學治療在嚴重型口腔癌(clinical T4 staging)的角色

The role of induction chemotherapy in advanced T4 staging oral cavity squamous cell carcinoma

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Background

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer globally and the fifth most common cancer in Taiwan. Oral cavity squamous cell carcinoma (OCSCC) is the largest subgroup of HNSCC. Although induction chemotherapy did not prolong overall survival (OS) in HNSCC, the role of induction chemotherapy in advanced OCSCC remained uncertain, especially in those who had borderline resectable lesions.

Methods

From January 2010 to December 2018, a total of 205 OCSCC patients with clinical T4 staging were retrospectively enrolled at Chung Shan Medical University Hospital. All of them underwent curative surgery. And induction chemotherapy, before curative surgery, was administered according to the consensus of the head and neck multidisciplinary conference. And all of the enrolled patients were divided into patients with and without induction chemotherapy. Clinicopathological variables, independent factors for OS, and survival outcomes between these two groups were analyzed.

Results

Among the clinical T4 staging OCSCC, one-fourth (24.9%, 51/205) of all were treated with induction chemotherapy. The patients with induction chemotherapy had more primary sites of cheek mucosa (41.2% vs. 23.0%, $P = 0.011$), more smokers (86.0% vs. 71.7%, $P = 0.029$), and advanced nodal status (76.5% vs. 49.3%, $P = 0.001$) than those without. Three-year locoregional-free survivals between the patients with and without induction chemotherapy were 67% and 64.5% ($P = 0.567$), with a hazard ratio (HR) (95% confidence intervals [CI]) of 0.825 (0.427–1.596). Although the 5-year OSs of both groups were insignificant (62.7% and 53.2%, $P = 0.123$), with a HR (95% CI) of 0.669 (0.400–1.119), the trend showed that the patients with induction chemotherapy had a better OS than those without.

Conclusion

The trend suggested that induction chemotherapy might prolong OS in advanced T4 OCSCC. Future warranted studies were needed.

原著論文　112_A 38

衛教演講場的睡眠調查

Sleep survey in a lecture venue

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Background

Obstructive sleep apnea (OSA) is characterized by intermittent pauses in airflow due to the collapse of the upper airway during sleep. Polysomnography (PSG) is considered the gold standard for diagnosing OSA. However, PSG is time-intensive and difficult to access for diagnosing OSA. Previous studies have indicated that the prevalence of OSA may have been underestimated. Therefore, we conducted a field study to investigate OSA prevalence among participants attending a lecture venue.

Methods

The cross-sectional study evaluated participants aged ≥ 20 years who attended a lecture venue called "Cherish Your Family" on May 20, 2023. Participants completed a STOP-Bang questionnaire that included information about their sex, age, body height, body weight, snoring, tiredness, observed apnea, high blood pressure, and neck circumference. The STOP-Bang score was then used to categorize participants into low, intermediate, or high risk for OSA. A total score of ≤ 2 indicated a low risk of OSA, while a score of 3 or 4 indicated an intermediate risk. A high risk of OSA was defined as a total score greater than 5.

Results

A total of 75 participants took part in the sleep survey, comprising 27 males and 48 females. The average age and body mass index (BMI) of the participants were 43.0 ± 13.5 years and 24.2 ± 3.4 kg/m², respectively. Among them, 15 (20%) participants reported experiencing loud snoring, 41 (54.7%) reported daily tiredness, 5 (6.7%) participants had a history of observed apnea, and 9 (12%) participants had a neck circumference of ≥ 40 cm. A total of 55 (73.3%) participants were categorized as having a low risk of OSA, while 11 (14.7%) and 9 (12%) were classified as having intermediate and high risks of OSA, respectively.

Conclusions

The results of the cross-sectional study indicated that 20 (26.7%) participants at the lecture venue were found to potentially have intermediate and high risks of OSA.

原著論文　112_A 39

精神科病人惡性症候群的發生率與風險

Risk and incidence of neuroleptic malignant syndrome in patients with psychiatric disorders

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Background

Neuroleptic malignant syndrome (NMS) is a severe condition marked by fever, rigidity, changes in mental state, and dysfunction of the autonomic nervous system. There is a lack of extensive research on the occurrence of NMS in individuals with psychiatric disorders. Our objective was to explore the frequency and potential risk of NMS among patients with psychiatric disorders in Taiwan.

Methods

We conducted a retrospective cohort study involving a total of 674,755 individuals, including 134,951 patients with psychiatric disorders and 539,804 patients without psychiatric disorders. The data were sourced from the Taiwan National Health Insurance Research Database. The case cohort was composed of patients diagnosed with schizophrenia, paranoia, or bipolar disorder. To ensure comparability, we employed a 1:4 matching strategy, matching each case with four control individuals based on sex, age, and index date. Patients with a prior diagnosis of rhabdomyolysis or neuroleptic malignant syndrome before the index date – defined as the date of initial diagnosis of the psychiatric disorder and commencement of antipsychotic medication were excluded from the analysis.

Results

The overall incidence rates of NMS were 7.5 and 0.7 per 10,000 person-years in the case cohort and control cohort, respectively. After accounting for potential covariates, patients with psychiatric disorders displayed a significantly elevated risk of NMS, with a 2.93-fold higher risk compared to the non-psychiatric cohort (adjusted hazard ratio [aHR]: 2.93, 95% confidence interval [CI]: 2.48-3.45). It was observed that men carried a higher risk of NMS than women (aHR: 1.17, 95% CI: 1.05-1.29).

Conclusions

Patients with psychiatric disorders exhibited a significantly elevated risk of NMS compared to patients without psychiatric disorders.

原著論文　112_A 40

土木香內酯於角質形成細胞之抗發炎效果

The anti-inflammatory effect of Alantolactone in keratinocytes

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Introduction

Psoriasis is an immune-mediated inflammatory disease with activation of keratinocytes. Alantolactone, a sesquiterpene lactone, was isolated from Inula helenium and Radix inulae, and have several biological effects including antifungal, anthelmintic, antimicrobial, anti-inflammatory, antitrypanosomal, and anti-cancer activities. This study aimed to evaluate the anti-psoriatic potential of alantolactone in keratinocytes and explore underlying mechanisms.

Methods

To the experimental design, first, we will examine the effect of alantolactone on the proliferation and pro-inflammatory cytokines production expression in M5 (IL-17A, IL-22, oncostatin M, IL-1 α , and TNF- α) stimulated HaCaT keratinocytes by CCK-8 and qPCR assay. In addition, we will investigate whether the inhibitory effect of alantolactone on keratinocyte activation were associated with STAT3, and NF- κ B pathway.

Results

2.5 and 5 uM alantolactone significantly inhibited the proliferation of M5 cytokines-induced HaCaT cells at 72 hr. These cytokines of TNF- α , IL-6, IL-1 β , and IL-8 mRNA expressions were significantly decreased by alantolactone. M5 cytokines significantly induced STAT3 phosphorylation and decreased I- κ B α expressions, which could be recovery in the presence of alantolactone.

Conclusion

Alantolactone had the effect of anti-proliferation of keratinocytes and decreasing proinflammatory cytokines. The inhibitory effect of alantolactone was associated with STAT3 and NF- κ B pathway.

原著論文　112_A 41

急性白血病患者接受半吻合與非親屬完全吻合異體造血幹細胞移植之預後：台中榮總回溯性研究

Haploidentical Versus Matched Unrelated Donor Allogeneic Hematopoietic Stem Cell Transplantation for Acute Leukemia: A Retrospective Study

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Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the standard post-remission therapies and a potentially curative treatment for acute leukemia. The use of hematopoietic stem cell from a human leukocyte antigen (HLA) - matched sibling donor (MSD) is generally preferred for allo-HSCT due to the low incidence of graft-versus-host disease (GVHD) and transplant-related mortality. However, the availability of an HLA-MSD is often limited, with more than 70% of patients lacking such a donor. In the absence of an HLA-MSD, HLA-matched unrelated donors (HLA-MUD) are commonly sought as an alternative source of allogeneic hematopoietic stem cells. In recent years, haploidentical HSCT (haplo-HSCT) has also gained popularity as a viable option because finding a suitable HLA-MUD can still be challenging. Whether the outcomes of haplo-HSCT and MUD-HSCT are comparable is unclear. This retrospective study aims to compare overall survival (OS) and leukemia-free survival (LFS) in patient with acute leukemia who underwent haplo-HSCT and MUD-HSCT.

Method

We retrospectively reviewed the medical records of adult patients with acute leukemia who underwent their first MUD-HSCT or haplo-HSCT between January 2010 and December 2021 at Taichung Veterans General Hospital. We collected the patients' characteristics, pre-transplant disease status, conditioning regimen, and treatment response. The data from the two groups were collected and compared, including overall survival, leukemia-free survival, and incidence of GVHD.

Results

A total of 85 adult patients underwent their first MUD-HSCT (n = 33) or haplo-HSCT (n = 52) during the period. As for underlying hematologic malignancy, 56 patients had acute myeloid leukemia (AML), 27 patients had acute lymphoblastic leukemia, and 2 patients had mixed-phenotype acute leukemia. The median follow-up time was 20.8 months. Sex distribution, median age at diagnosis and Charlson comorbidity index were comparable between two groups.

Median OS period was not reached in the haplo-HSCT group, whereas it was 29.8 months in the MUD-HSCT group (P = 0.211). The median LFS periods were 52.6 months for haplo-HSCT group and 12.7 months for MUD-HSCT group (P = 0.212). Univariate analysis indicated that haplo-HSCT was not associated with a high risk of worse LFS. The incidence rates of acute GVHD in the haplo-HSCT and MUD-HSCT groups were 57.7% and 48.5%, respectively (P = 0.282).

Conclusion

We found no significant differences in OS or LFS between patients with acute leukemia who underwent haplo-HSCT and who underwent MUD-HSCT. Haplo-HSCT may be used alternatively for treating acute leukemia instead of MUD-HSCT, with comparable survival outcomes.

原著論文　112_A 42

預測台灣幽門螺桿菌感染一線治療含鉍劑四合一療法根除失敗的獨立危險因素

Independent risk factors predicting eradication failure of standard bismuth quadruple therapy for the first-line treatment of *Helicobacter pylori* infection in Taiwan

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Background

Bismuth quadruple therapy is recommended as the choice treatment for *H. pylori* infection in areas of either low or high clarithromycin resistance in the Maastricht VI/Florence Consensus Report. However, the optimal treatment duration and drug dosages of bismuth quadruple therapy remain unclear.

Aim

to search the independent risk factors predicting eradication failure of standard bismuth quadruple therapy in the first-line treatment of *H. pylori* infection.

Methods

From July 2014 to June 2022, 274 *H. pylori*-infected patients who received 10-day or 14-day bismuth quadruple therapy containing a proton pump inhibitor, bismuth, tetracycline and metronidazole were included for the study. Post-treatment *H. pylori* status was assessed at least 4 weeks after completion of treatment. The relationships between eradication rate and 13 clinical parameters were analyzed by univariate and multivariate analyses.

Results

The eradication rates of standard bismuth quadruple therapy were 93.8% and 94.2% by intention-to-treat and per-protocol analyses, respectively. Univariate analysis revealed that patients harboring metronidazole-resistant strains had a lower eradication rate than those harboring metronidazole-susceptible strains (88.7% [55/62] *vs.* 96.7% [148/153]). The other factors including smoking, treatment duration and drug adherence were not significantly associated with cure rate. Multivariate analysis revealed that metronidazole resistance of *H. pylori* was the only independent risk factors related to eradication failure of standard bismuth quadruple therapy with an odds ratio of 3.8 (95% CI: 1.2 to 12.4).

Table 1 Demographic Data of the patients receiving standard bismuth quadruple therapy in the first-line treatment of *H. pylori* infection

Variables	Patient characteristics (n = 274)
Age (yr) (mean ± SD)	55.2 ± 13.3
Gender (male / female)	130/144
Smoking	53/274 (19.3%)
Alcohol consumption	32/274 (11.7%)
Ingestion of coffee	117/274 (42.7%)
Ingestion of tea	104/274 (38.0%)
NSAID use	7/274 (2.6%)
Underlying disease	94/274 (34.3%)
Endoscopic Findings	
Gastritis	250/274 (91.2%)
Peptic ulcer	24/274 (8.8%)
Antibiotic resistance [a]	
Clarithromycin	45/215 (20.9%)
Amoxicillin	0/215 (0%)
Metronidazole	62/215 (28.8%)
Tetracycline	0/215 (0%)
Duration of treatment	
10-day therapy	123/274 (44.9%)
14-day therapy	151/274 (55.1%)

Table 2 The major outcome of standard bismuth quadruple therapy in Taiwan

Variables	Outcomes
Eradication rate	
Intention-to-treat	257/274 (93.8%)
Per-protocol	245/260 (94.2%)
Adverse events	118/274 (43.0%)
Drug adherence	260/274 (94.9%)

Table 3. Univariate analysis for factors affecting eradication rates of standard bismuth quadruple therapy in the first line treatment of *H. pylori* infection in the intention-to-treat population

Characteristics	Patient number	Eradication rate	*P* value
Sex			0.639
Male	130	121 (93.1%)	
Female	144	136 (94.4%)	
Age			0.544
< 60 years old	158	147 (93.0%)	
≧60 years old	116	110 (98.4%)	
Cigarette smoking			0.086
Yes	53	47 (88.7%)	
No	221	210 (95.0%)	
Alcohol drinking			0.116
Yes	32	28 (87.5%)	
No	242	229 (94.6%)	
Coffee consumption			0.058
Yes	117	106 (90.6%)	
No	157	151 (96.2%)	
Tea consumption			0.778
Yes	104	97 (93.3%)	
No	170	160 (94.1%)	
NSAID use			1.000
Yes	7	7 (100.0%)	
No	267	250 (93.6%)	
Underlying disease			
Yes	94	90 (95.7%)	
No	180	167 (92.8%)	
Peptic ulcer			0.665
Yes	24	23 (95.8%)	
No	250	234 (93.6%)	
Metronidazole resistance			0.020*
Susceptible	153	148 (96.7%)	
Resistant	62	55 (88.7%)	
Tetracycline resistance			
Susceptible	215	203 (94.4%)	—
Resistant	0	—	
Duration of treatment			0.379
10-day therapy	123	119 (96.7%)	
14-day therapy	151	138 (91.4%)	
Drug adherences			0.212
Good	14	12 (85.7%)	
Poor	260	245 (94.2%)	

Table 4. Multivariate analysis for independent risk factors predicting eradication failure of standard bismuth quadruple therapy in Taiwan

Risk factors	Coefficient	Standard Error	Odds ratio (95% CI)	*P*-value
Metronidazole resistance	1.326	0.606	3.8 (1.2–12.4)	0.029
Smoking	0.851	0.657	2.3 (0.6 – 8.5)	0.195
Coffee consumption	0.629	0.619	1.9 (0.6-6.3)	0.309

Conclusion

Metronidazole resistance is an independent risk factor predicting eradication failure of standard bismuth quadruple therapy in the first-line treatment of *H. pylori* infection. There is no difference in eradication efficacy between 10-day and 14-day bismuth quadruple therapies in Taiwan.

原著論文　112_A 43

Comparison of real-world treatment for ulcerative colitis between doctors practicing in northern and southern Taiwan

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Introduction
Currently, the doctors in Asia face unique challenges in the treatment of ulcerative colitis including various therapeutic targets and a growing number of drug options.

Aims
To investigate the differences in the real-world treatment of ulcerative colitis between doctors practicing in northern and southern Taiwan.

Methods
A questionnaire focusing on the treatment target, therapeutic strategies, and medicine use for the patients with different severities of ulcerative colitis was distributed to the doctors who attended the Taiwan Digestive Disease Week 2023 on March 25–26. The options of the treatment target, therapeutic strategy and medicine use for the treatment of ulcerative colitis of the doctors practicing in southern and northern Taiwan were compared.

Results
A total of 234 doctors from the southern (n = 98) and northern Taiwan (n = 136) participated in the ulcerative colitis treatment survey. Among them, the top three therapeutic targets for the treatment of ulcerative colitis were steroid-free mucosal healing, histological healing and mucosal healing (27.4%, 26.5% and 19.7%, respectively). However, the leading therapeutic target in the doctors from southern Taiwan was histological healing (63.3%), and that in the doctors from northern Taiwan was mucosal healing (33.8%). There were significantly differences in the therapeutic targets between groups ($P < 0.001$). With regard the real-world practice, the most commonly adopted strategy for the treatment of moderate to severe ulcerative colitis in all the participants was top-down approach (57.7%). Nonetheless, the most commonly adopted strategy for the treatment of moderate to severe ulcerative colitis in the doctors from southern Taiwan was top-down approach (100%) and that of the doctors from northern Taiwan was step-up approach (72.8%). In this survey, the most commonly used biological agent in doctors from southern Taiwan was integrin blockers (100%), while that in the doctors from northern Taiwan was ere TNF-α blocker (100%). Differences in the most commonly used biological agents existed between groups ($P < 0.001$).

Conclusions
The leading therapeutic target for the treatment of ulcerative colitis among the doctors in Taiwan is steroid-free mucosal healing. Significant differences in the preferred therapeutic

targets and most commonly adopted biological agents for the treatment of ulcerative colitis exist between the doctors from southern and northern Taiwan.

原著論文　112_A 44

台灣不吸菸者早期肺癌的過度診斷

Possible overdiagnosis of early-stage lung adenocarcinoma among never-smokers in Taiwan

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Background

Overdiagnosis in cancer screening denotes the detection of cancer that does not cause premature mortality. We hypothesized that adenocarcinoma in situ (AIS), bronchioloalveolar carcinoma (BAC), and minimally invasive adenocarcinoma (MIA) with tumor sizes >2 cm are unlikely to be overdiagnosed. We attempted to corroborate our hypothesis by comparing the survival of never-smoking patients with that of matched referents.

Methods

This is a retrospective matched cohort study. Data of all patients with stage 0/IA lung adenocarcinoma aged 50-80 and had never smoked were collected from the Taiwan Cancer Registry database (2011-2019). Each patient was matched with ten referents based on age, sex, calendar year at diagnosis, and quintiles of working salaries. Additionally, both patients and referents were free from catastrophic illnesses. Both patients and referents were linked to the National Mortality Registry database and followed up until the end of 2020 for death information. We applied the Kaplan-Meier method to estimate survival and compared patient and referents' survival using a log-rank test. Cox proportional hazards regression was performed to identify the predictors of mortality.

Results

A total of 8,990 patients with stage 0/IA lung adenocarcinoma were identified. Irrespective of tumor size, patients with AIS/BAC/MIA did not experience excess mortality compared to the referents up to 10 years of follow-up. After adjusting for comorbidities, the adjusted hazard ratio of patients versus referents was 0.76 (95% confidence intervals [CI]: 0.45 to 1.29) for patients with >2 cm AIS/BAC/MIA. The 10-year survival rates of patients with other invasive IA adenocarcinoma >1 but ≤2 cm and >2 cm were inferior to those of the referents (log-rank tests, $p<0.001$).

Conclusion

In conclusion, we failed to prove that AIS/BAC/MIA detected in never-smokers with a tumor size >2 cm is unlikely to be overdiagnosed. However, other invasive IA adenocarcinomas with tumor sizes of >1 cm seem to corroborate this hypothesis.

原著論文　112_A 45

影響原發性高醛固酮症患者姿勢刺激測試準確度的變因

Variables influencing the accuracy of postural stimulation testing in patients with primary aldosteronism

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Background

Primary aldosteronism (PA) is the most common cause of secondary hypertension, associated with higher risks of hypokalemia, and cardiovascular complications. Once PA is confirmed, subtype classification is needed because unilateral diseases are potentially curable by unilateral adrenalectomy, whereas bilateral diseases require lifelong treatment with mineralocorticoid receptor antagonists. Despite being the least invasive and most convenient among subtyping tools, postural stimulation testing (PST) is limited by its variable protocols and different sensitivity and specificity. However, factors affecting the accuracy of PST remain obscure. In this study, we retrospectively reviewed the patients receiving PST and conducted a review of the related literature.

Methods

We reviewed a retrospective observational study of patients confirmed with PA from January 2012 to July 2023 in a medical center in Southern Taiwan. The screening, confirmation, subtype classification, and treatment were all based on Endocrine Society Clinical Practice Guideline. The final subtype classification primarily relied on the gold standard, adrenal vein sampling (AVS). In cases where AVS was deemed unfeasible, NP-59 SPECT/CT was employed for subtyping determination. Every patient underwent a 4-hour PST. After an overnight supine, the plasma aldosterone was measured at 8 o'clock in the morning and after 4 hours (at noon) of continued erect posture. The optimal cutoff for the percentage change in aldosterone for diagnosing unilateral PA was optimized by using receiver operating characteristics (ROC) analysis. The "accuracy" group was defined as those was diagnosed as unilateral PA with aldosterone change percentage fell below the established threshold and those was diagnosed as bilateral PA with aldosterone change percentage exceeding the threshold. Patients not meeting these criteria were assigned to the "error" group. Comparative analysis of baseline characteristics and laboratory data was conducted between the accuracy and error groups.

Results

A cohort of 29 patients, with a median age of 54 years, was encompassed in the study, comprising 19 individuals with unilateral PA and 10 with bilateral PA. The optimal threshold for the percentage change in aldosterone was determined at 0%, yielding the highest Youden index. Utilizing a criterion of a 0% or greater reduction in aldosterone concentration after four hours in an upright position, the PST demonstrated a sensitivity of 95.7% at a specificity of 50.0% for identifying unilateral cases (area under the curve, AUC = 0.76; 95% CI, 0.56-0.95; P = 0.03). Within this cohort, 23 patients were classified into the accuracy group (comprising 18 with unilateral PA and 5 with bilateral PA), while 6 were designated into the error group (comprising 1 with unilateral PA and 5 with bilateral PA). Notably, the accuracy group exhibited significantly higher pre-test serum potassium levels (3.2 ± 0.5 mmol/L vs 2.6

± 0.4 mmol/L, P = 0.01) in comparison to the error group. It is worth mentioning that in our cases, the PST was always correctly subtyping when serum potassium levels exceeded 3.1 mmol/L. There were no statistically significant differences observed in other characteristics or laboratory data.

Conclusion

In conclusion, the optimal threshold for the percentage change in aldosterone was established at 0% based on the highest Youden index in this study. This cutoff value was compatible with previous studies. Additionally, we found that lower pre-test serum potassium levels were significantly associated with the wrong subtyping in PST. It may be caused by the suppressive effect of hypokalemia on aldosterone secretion. To our knowledge, this is the first study to elucidate the interplay between potassium levels and the accuracy of PST. This revelation potentially illuminates the disparities in cutoff values and accuracy of aldosterone changes observed in prior studies, which encompassed varying proportions of hypokalemia. Consequently, our findings advocate for the enough potassium supplementation, or at least exceeding 3.1 mmol/L in refractory cases, prior to undertaking PST, to enhance its diagnostic accuracy.

原著論文　112_A 46

醫學中心敗血症病人的預後

Outcome of Septic Patients in a Medical Center

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Background

Sepsis, a condition where the body responds improperly to an infection, can lead to septic shock, the most severe complication with high mortality rates. This study aimed to identify associated factors and outcomes for sepsis patients admitted to the intensive care unit (ICU).

Methods

Between January 2017 and December 2021, we conducted a prospective study involving adult sepsis patients across five ICUs (95 beds) at Chi-Mei Medical Center. We gathered demographic and clinical data, laboratory results, co-morbidities, severity scores, as well as mortality and lengths of stays for both ICU and hospital. Our analysis focused on ICU mortality and its predictors.

Results

Out of the 926 patients included, 39.3% (364/926) was expired in the ICU. The average age was 68.7 years, with males comprising 63.1% of the cohort. Of these patients, 38.1% (353/926) experienced septic shock. In comparison to the survival group, those who passed away had comparable ICU stays and total hospital costs. Multivariate analyses revealed the following predictors of ICU mortality: higher Body Mass Index (odds ratio, OR=1.078), number of organ failures (OR=1.608), elevated lactate levels (OR=1.122), and increased bilirubin levels (OR=1.065). Conversely, lower hemoglobin levels were associated with higher odds of mortality (OR=0.963). Additionally, the presence of pneumonia (OR=1.866), chest failure (OR=1.281), and septic shock (OR=3.463) were significant indicators of increased mortality risk.

Conclusions

This cohort study identified critical predictors of mortality among ICU patients with sepsis. Physicians should communicate these risk factors to families, enabling more informed decisions, including considerations for palliative care.

原著論文　112_A 47

鋅補充對於肝硬化併發輕微肝腦病變患者的臨床效益

The clinical efficacy of zinc supplementation for patients with liver cirrhosis complicated by minimal hepatic encephalopathy

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Background

Hepatic encephalopathy (HE) is a severe but prevalent complication in individuals with cirrhosis, representing a significant concern in chronic liver diseases. HE can be classified into minimal HE (mHE) and overt HE (oHE) based on clinical manifestations. The former, despite lacking obvious clinical neuropsychiatric symptoms, could still impact the daily life and work capability of patients. Minimal HE can be diagnosed through neuropsychological tests or psychomotor tests. For example, the number connection test (NCT) is a widely used tool for diagnosing mHE. It consists of two variations: NCT-A and NCT-B. Both variations require the connection of a sequence of numbers or letters; however, NCT-B is more complex than NCT-A as it includes more elements. According to the recommendations of the AASLD guidelines, lactulose is the preferred treatment for episodic overt hepatic encephalopathy and for preventing recurrent episodes of hepatic encephalopathy after the initial episode. Rifaximin and oral branched-chain amino acids are also recommended as adjunctive therapies for patients with recurrent or refractory HE. Additionally, the clinical efficacy of nutritional supplements has long been explored, such as acetyl-L-carnitine and zinc. Zinc deficiency is common in patients with liver cirrhosis, and several studies provided the link between zinc and HE.

Based on the EASL guidelines, routine zinc supplementation is not recommended for patients with hepatic encephalopathy. However, the JSGE guidelines suggest supplementing with zinc preparations for patients with HE who may have zinc deficiency. Although previous literature indicate that zinc supplementation may improve HE by increasing the efficiency of the urea cycle, and the alterations in zinc's antioxidant activity could contribute to overall improvement in liver function, the effectiveness of zinc for patients with cirrhosis complicated by HE remains an issue of debate. This study aimed to collect data from relevant trials and assess the clinical effectiveness of adjunctive zinc supplementation in patients with liver cirrhosis complicated by HE.

Methods

A systematic search was performed for only randomized controlled trials (RCTs) in PubMed, Embase, Cochrane Library, and Airiti Library from inception to August 02, 2023. No publication year and language limitation were applied. RCTs involving patients with cirrhosis complicated by HE and receiving zinc supplementation were included. The primary outcome was the severity of encephalopathy, which was assessed through performance on neuropsychometric tests such as the NCT-A, NCT-B, and the digit symbol test (DST); the secondary outcome were serum ammonia levels. The results were expressed as the risk ratio (RR) or mean difference (MD) and 95% confidence intervals (CI), which used a random-effects model to pool effect sizes.

Results

A total of nine RCTs involving 475 subjects were included. Four studies with the primary outcome were analyzed, all of which used additional zinc supplementation as the intervention. The control group was not administered zinc supplementation; the treatment included placebo, standard therapy, branched-chain amino acids (BCAAs), or lactulose. The pooled results showed significant effects on the performance of NCT-A, with low heterogeneity across studies identified (MD -8.10, 95% CI -10.06 to -6.15, $p < 0.001$; $I2 = 0\%$). In contrast, there is no statistical significance in the performance of NCT-B (MD -8.95, 95% CI -20.96 to 3.06, $p = 0.14$; $I2 = 0\%$). However, a marginal improvement was observed in the results of DST (SMD 0.35, 95% CI 0.00 to 0.69, $p = 0.05$; $I2 = 35\%$). As for the secondary outcome, three studies evaluating serum ammonia levels as outcome were pooled in the meta-analysis. A significant reduction was revealed in the serum ammonia levels between the intervention and control groups (MD -9.55, 95% CI -17.85 to -1.25, $p = 0.02$; $I2 = 11\%$). None of the included studies found serious adverse effects attributable to zinc supplementation.

Conclusion

Adjunctive zinc supplementation demonstrated a significant difference in the performance of NCT-A and serum ammonia levels compared to the control group. Nonetheless, it did not demonstrate a notable difference in the performance of NCT-B and only exhibited a marginal improvement in DST. Although the results of this study suggest that zinc supplementation may improve the clinical presentation of HE in patients with liver cirrhosis, further research is warranted to elucidate the clinical efficacy for such patients.

原著論文　112_A 48

在表面抗原陰轉的病人中，肝炎對 B 型肝炎表面抗原下降速度的影響

Hepatitis flares promote rapid HBsAg decline in chronic Hepatitis B patients achieving HBsAg loss, a long term follow-up study

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Background

Hepatitis B surface antigen (HBsAg) loss, a milestone often referred to as "functional cure", is the ultimate goal in the treatment of chronic Hepatitis B (CHB). However, decline rates of HBsAg are reported to be as low as 0.1 log10 IU/mL, and seroclearance rates at 1% per year. Our study demonstrates the long term kinetics and different patterns of HBsAg levels in patients who achieved HBsAg seroclearance. We aim to identify factors associated with increased HBsAg decline rates in these patients. We also investigated the relationship between hepatitis flares and annual reductions of HBsAg.

Method

In a retrospective analysis from 2011 to 2022, this study identified patients who attained HBsAg seroconversion, substantiated by a documented series of HBsAg measurements conducted at least nine times over a five-year timeframe. Patients with HBsAg data gaps exceeding one year were excluded from the study cohort. Univariate and multivariate analyses were conducted to identify potential associations between HBsAg decline rates and baseline characteristics. Annual HBsAg decline rates were then calculated for each hepatitis flare that occured.

Results

During a median follow up of 7.5 years, 41 patients demonstrated HBsAg seroclearance with complete HBsAg documentation. We will demonstrate the kinetics of individual and median HBsAg in figure form, and present the median HBsAg levels at 5, 3 and 1 year prior to seroclearance. Univariate and multivariate analysis with baseline characteristics revealed that hepatitis flares with ALT levels over 200 IU/L (hazard ratio [HR],1.35;P= 0.012) was an independent predictive factor of HBsAg decline rates. 17 hepatitis flares with ALT levels over 200 IU/L were identified among 9 patients, and average annual HBsAg decline rates during hepatitis flare was 0.79 log10 IU/mL, with 10 (59%) leading to rapid HBsAg decline (>0.5log10 IU/mL).

Conclusion

Hepatitis flares promoted rapid HBsAg declines and greater annual HBsAg decline rates in patients with HBsAg seroclearance.

原著論文　112_A 49

腎臟功能減退之成年人其久坐式生活型態與全死因死亡及特定原因死亡風險之相關性

Association of sedentary lifestyle with all-cause and cause-specific mortality in adults with reduced kidney function

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Background

Sedentary behavior, which involves activities with low energy expenditure, is associated with an increased risk of cardiovascular disease (CVD), cancer, and overall mortality in the general population, even when adjusted for physical activity. Individuals with chronic kidney disease tend to exhibit sedentary behavior and decreased physical activity, both of which are independent predictors of mortality in the general population. While physical inactivity is linked to adverse health outcomes in patients with reduced kidney function, it is unclear whether this relationship remains significant for sedentary behavior that represents a distinct domain from physical inactivity. The aim of this study is to assess the association between sedentary lifestyle and the risk of mortality in individuals with impaired renal function.

Method

The study population consisted of adult participants from the 2007-2016 National Health and Nutrition Examination Survey (NHANES) aged 20 to 79 years with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or self-reported receiving dialysis therapy (N=1,419). Sedentary lifestyle was defined as self-reported sedentary time >6 hours per day. The outcomes of interest included all-cause mortality and death from CVD or cancers. Survival status was determined by linking NHANES data to death records from the National Death Index through probabilistic matching and death certificate review. Death from specific causes were ascertained using International Classification of Diseases–Tenth Revision codes; death from CVD was defined by leading causes of death codes I00-I09, I11, I13, I20-I51 and from cancer as C00-C97. The follow-up period for each participant was the period between the NHANES baseline examination date and the participant's date of death or last date of follow-up (December 31, 2019), whichever occurred first. We performed survival analysis using the Kaplan-Meier method and log-rank test to plot the survival curves. Cox regression analysis was performed to explore the association between sedentary lifestyle and mortality risks with adjustment for age, sex, race/ethnicity, body mass index, diabetes mellitus, hypertension, smoking status, educational level, family income to poverty ratio, and level of kidney function.

Results

The mean age of the study population was 65.8±0.4 years old and 41.5% of them was male, with race/ethnicity distribution of 67.5% Whites, 20.7% Blacks, and 7.3% Hispanics. We observed that nearly half of the population had sedentary lifestyle, similar in males (49.2%) and females (43.7%). When stratified by age groups, we found that more than half (52.4%) of people aged ≤65 years had sedentary lifestyle, with a lower prevalence (41.8%) among people >65 years. In addition, while the prevalence of sedentary lifestyle in whites and blacks was close to 50%, it was lower in Hispanics and other races/ethnicities. By logistic regression,

we showed that the factors associated with sedentary lifestyle included younger age, non-Hispanic whites, single, higher BMI, diabetes, disability in activity of daily living (ADL), and mobility disability.
During a median follow-up of 99 (interquartile range 70 to 128) months, 458 participants died, of whom 120 died from CVD and 92 died from cancer. The crude analyses showed that individuals with sedentary lifestyle were at higher risk for all-cause (hazard ratio [HR]: 1.65; 95% confidence interval [CI]: 1.26-2.16) and CVD-related mortality (HR: 2.00; 95% CI: 1.27-3.14) but not cancer-related mortality (HR: 0.78; 95% CI: 0.42-1.44). After adjusting for potential confounders, our results showed that sedentary lifestyle correlated to greater risk of all-cause (HR: 1.64; 95% CI: 1.26-2.12) and CVD-related mortality (HR: 1.66, 95% CI: 1.03-2.67). In the stratified analyses, we observed a significant association between sedentary lifestyle and risk of all-cause mortality (HR: 1.80; 95% CI 1.35-2.40) or CVD-related mortality (HR: 1.74; 1.02-2.99) in people >65 years old, but not in those aged ≤ 65 years. When stratified by sex, our results demonstrated that sedentary lifestyle was associated with increased risk of all-cause mortality in both males (HR: 1.58; 95%CI: 1.09-2.29) and females (HR: 1.66; 95% CI: 1.23-2.25); the risk of CVD-related death also increased in both sexes, but did not reach statistical significance. Additionally, the association between sedentary lifestyle and all-cause mortality was significant among those with BMI ≥ 30, with or without diabetes, and with lower (≤ high school) or higher (≥ some college) educational attainment. Furthermore, we observed a significant association between sedentary lifestyle and CVD-related mortality among those with diabetes, and with higher educational attainment.
When dividing the participants by sedentary time into 4 groups, we showed that individuals with sedentary time 6 to 8 hours (HR: 1.58; 95% CI 1.10-2.26) and more than 8 hours per day (HR: 1.63; 95% CI 1.05-2.52) had higher risk of all-cause mortality when compared with those with sedentary time less than 4 hours per day, but the association in CVD- or cancer-related mortality was not significant.

Conclusions

Our study suggested that sedentary lifestyle was associated with increased risk of all-cause and CVD-related mortality among individuals with reduced kidney function. In addition, we observed that non-Hispanic Whites, and individuals with younger age and higher BMI were more likely to have sedentary lifestyles. Our findings have practical importance for public health, as interventions aimed at individuals with risky behaviors may help mitigate adverse health outcomes.

原著論文　112_A 50

重金屬曝露與慢性腎臟病及隨後的長期死亡風險之相關性：美國以群體為基礎之世代研究

Association of heavy metal exposure with risk of chronic kidney disease and subsequent long-term mortality: a population-based cohort study in the United States

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Background

Human exposure to heavy metals is increasing through a variety of sources, including contaminated air, drinking water, food, folk prescription or remedies, and occupational exposure. Several cross-sectional studies have shown an association between low-level heavy metal exposure and chronic kidney disease (CKD). However, there are relatively few longitudinal studies on the relationship between heavy metal exposure and health outcomes in individuals with reduced renal function. Therefore, we conducted a population-based cohort study using a nationally representative sample from the United States (U.S.) to evaluate the association between low levels of heavy metals and the risk of CKD and subsequent long-term mortality.

Method

We merged 5 discrete 2-year cycles (2003-2004 through 2011-2012) of the U.S. National Health and Nutrition Examination Survey (NHANES) to create the study population. We included 24,810 adult participants aged 18 years or older who had their blood tested for creatinine, lead, and cadmium levels. We used the CKD-EPI Creatinine Equation (2021) to calculate estimated glomerular filtration rate (eGFR); CKD was defined as eGFR < 60 ml/min/1.73 m^2. Blood lead level ≥ 2 ug/dL and cadmium level ≥ 0.4 ug/L were respectively defined as elevated blood levels. The survival status was ascertained by linking NHANES data to death records from the National Death Index through probabilistic matching and death certificate review. Participants were followed from the NHANES baseline interview until the participant's death or end of follow-up date (December 31, 2019), whichever came first.

Results

In weighted analyses of 24,810 participants, 3.9% had CKD (unweighted n=1,309). The weighted mean (± SE) estimates of lead level were 2.14 (± 0.05) ug/dL and 1.58 (± 0.02) ug/dL (p < 0.001), respectively, in those with and without CKD, and cadmium levels were 0.60 (± 0.02) ug/L and 0.53 (± 0.01) ug/L (p < 0.01), respectively. Compared with those without CKD, participants with CKD were more likely to have elevated blood lead level (44.3% vs. 22.8%, p < 0.001) and elevated cadmium level (54.8% vs. 39.7%, p < 0.001). By weighted logistic regression with adjustment for age and sex, we showed that elevated blood lead level was significantly associated with increased risk of CKD (OR: 1.28, 95% CI 1.07-1.53, p < 0.01). However, the association between elevated blood cadmium level and CKD was not significant.

Among the 1,309 participants with CKD, 602 individuals died during a median follow-up of 145 months (interquartile range: 116-171 months), a crude death rate of 4.2 per 1,000 person-months. By Kaplan-Meier method, we showed that both elevated blood lead and cadmium levels were associated with an increased risk of death (Log Rank test p < 0.05 and

$p < 0.001$, respectively). By multivariable Cox regression with adjustment for age and sex, we showed that the risk of death was 1.29 (95% CI: 1.00-1.66, $p < 0.05$) and 1.91 (95% CI: 1.46-2.50, $p < 0.001$) times higher in individuals with elevated blood lead and cadmium levels, respectively. After further adjusting for race, body mass index, eGFR, diabetes, hypertension, cardiovascular disease, previous stroke, smoking status, educational level, marital status, and family income, the association between elevated blood cadmium level and mortality remained significant (HR: 1.42, 95% CI: 1.07-1.88, $p < 0.05$), but the association between elevated blood lead level and mortality attenuated.

Conclusion

Elevated blood lead level was a significant risk factor of CKD in the U.S. general population. In addition, in individuals with CKD, elevated blood cadmium level was a predictor of long-term mortality, but elevated blood lead level was not. However, the causal relationship needs to be examined.

原著論文　112_A 51

台灣、韓國與日本的肝硬化疾病負擔及 1990-2019 年趨勢：2019 年全球疾病負擔研究的系統分析

Burden and trend of cirrhosis in Taiwan, South Korea, and Japan, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019

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Background

Cirrhosis and other chronic liver diseases (below collectively referred to as cirrhosis) are a major cause of morbidity and mortality, although the burden and underlying causes differ across locations and demographic groups. We reported the results from the Global Burden of Diseases (GBD) Study 2019 on the burden of cirrhosis and its trends since 1990 by cause and sex in Taiwan, South Korea, and Japan, which are similar in geographical locations and socio-demographic indices.

Method

GBD modelled the prevalence of cirrhosis based on hospital and claims data and estimated mortality based on data from vital registrations, vital registration samples, and verbal autopsies. Disability-adjusted life-years (DALYs) were calculated as the sum of years of life lost due to premature death and years lived with disability. Estimates are presented as numbers and age-standardized rates per 100,000 population, with 95% uncertainty intervals (UIs). All estimates are presented for five causes of cirrhosis: hepatitis B, hepatitis C, alcohol-related liver disease, non-alcoholic fatty liver disease (NAFLD), and other causes. The causes grouped in the "other chronic liver diseases" category mainly included autoimmune hepatitis, toxic liver diseases, other inflammatory liver diseases, chronic hepatitis not specified, and other diseases of the liver.

Results

In Taiwan, there were 7840719.5 (95% UI: 7278117.6 to 8510254.3) cirrhosis in 2019 [3790502.9 (95% UI: 3497225.5 to 4166834.3) in females and 4050216.6 (95% UI: 3765009.5 to 4386625.0) in males], with an age-standardized point prevalence of 23913.8 per 100,000 population (95% UI: 22156.6 to 26060.6) [22149.9 (95% UI: 20377.0 to 24334.0) in females and 25674.9 (95% UI: 23758.2 to 27870.2) in males, respectively]. The age-standardized point prevalence of cirrhosis was lower in Japan [10745.9 (95% UI: 9856.2 to 11700.5) per 100,000 population] and Korea [10883.4 (95% UI: 9990.7 to 11886.1) per 100,000 population]. From 1990 to 2019, the age-standardized prevalence rate of cirrhosis decreased by 12.6% (95% UI: 9.7% to 15.6%) and 18.0% (95% UI: 14.7% to 21.2%) in Taiwan and Korea, respectively, while it remained unchanged [0.4% (95% UI: -1.1% to +1.7%)] in Japan. In the three decades, the age-standardized prevalence rate of cirrhosis due to hepatitis B, hepatitis C, alcohol use, and other causes decreased by 48.5% (95% UI: 46.3% to 50.4%), 40.4% (95% UI: 33.4% to 47.5%), 24.4% (95% UI: 12.2% to 36.4%), and 22.7% (95% UI: 11.2% to 32.8%), respectively, while cirrhosis caused by non-alcoholic fatty liver disease (NAFLD) increased by 20.8% (95% UI: 16.1% to 25.4%) in Taiwan. The trends were similar in Japan and Korea, except that cirrhosis due to alcohol use had a steady age-standardized prevalence rate in Japan.

In 2019, cirrhosis caused 7287.1 (95% UI: 5735.7 to 9264.2) deaths [2324.2 (95% UI: 1803.0 to 2931.1) in females and 4962.9 (95% UI: 3871.1 to 6399.5) in males] and 199865.3 DALYs (95% UI: 157575.7 to 257236.8) [45484.5 (95% UI: 34920.0 to 58302.5) in females and 154380.8 (95% UI: 121246.2 to 198521.2) in males], with an age-standardized death rate of 19.3 per 100,000 population (95% UI: 15.3 to 24.6) [10.9 (95% UI: 8.4 to 13.8) in females and 28.2 (95% UI: 22.1 to 36.2) in males, respectively] and an age-standardized DALY rate of 562.3 per 100,000 population (95% UI: 444.6 to 722.0) [227.6 (95% UI: 175.7 to 292.6) in females and 908.9 (95% UI: 716.1 to 1163.8) in males, respectively] in Taiwan. The age-standardized death rate of cirrhosis was lower in Japan [7.6 (95% UI: 6.9 to 8.2) per 100,000] and Korea [11.9 (95% UI: 10.6 to 13.8) per 100,000] in 2019. The age-standardized DALY rate of cirrhosis was also lower in Japan [192.9 (95% UI: 182.9 to 202.8) per 100,000] and Korea [326.6 (95% UI: 292.3 to 365.2) per 100,000]. In Taiwan, the age-standardized death rate decreased by 46.8% (95% UI: 31.9% to 57.9%) and DALY rate decreased by 43.1% (95% UI: 26.4% to 55.1%) from 1990 to 2019. The age-standardized death rate decreased by 50.4% (95% UI: 47.5% to 53.3%) and 74.9% (95% UI: 68.7% to 77.9%) in Japan and Korea, respectively, and the age-standardized DALY rate decreased by 51.3% (95% UI: 49.5% to 53.0%) and 77.6% (95% UI: 73.2% to 80.2%), respectively. The age-standardized death and DALY rates decreased for all five causes of cirrhosis, but the smallest decline was seen for cirrhosis due to NAFLD.

Conclusion

While the burden of cirrhosis due to hepatitis B and C continues to decline due to the advent of effective preventive and therapeutic interventions, the impact of NAFLD is expanding. While viral hepatitis is of widespread public health concern, strategies are needed to achieve early diagnosis and prevent NAFLD-induced cirrhosis.

原著論文　112_A 52

血管張力素受體-腦啡肽酶抑制劑於晚期慢性腎臟疾病及透析病人的使用效益及安全性

The Efficacy and Safety of Angiotensin Receptor Neprilysin Inhibitor in Heart Failure Patients with Advanced Chronic Kidney Disease and End-stage Renal Disease

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Background

Sacubitril/Valsartan is an angiotensin receptor neprilysin inhibitor, known for its capability to inhibit the renin-angiotensin-aldosterone system and neprilysin, has demonstrated improved heart function and outcomes. The PARADIGM trial showed its benefits in patients with heart failure and reduced ejection fraction (HFrEF). However, the treatment effects on patients with advanced chronic kidney diseases (CKD) or end-stage renal diseases (ESRD) remain under-explored due to the eGFR<30 ml/min/1.73m² exclusion in most major trials. To fill this knowledge gap, we conducted a systematic review and meta-analysis to evaluate the treatment effects on these patients.

Method

A systematic review was conducted through searching for key words in four databases including PubMed, Cochrane, Embase, and ClinicalTrials.gov without restriction on language or geographic locations. To qualify, studies had to focus on adults with advanced CKD or ESRD on maintenance dialysis, receiving sacubitril/valsartan treatment, and report on outcomes such as all-cause mortality, heart failure hospitalization (HHF), and specific pre- and post-treatment metrics. Eligible studies were assessed for quality using the Newcastle-Ottawa Scale for observational studies. Heterogeneity among the included studies was evaluated using the I^2 statistic. We employed a random-effects model to pool the data due to the anticipated clinical and methodological diversity across studies. The presence of publication bias was assessed using funnel plots and the Egger's regression asymmetry test. Sensitivity analyses were conducted by sequentially omitting individual studies to assess the robustness of the results.

Results

Our systematic review and meta-analysis synthesized findings from 11 observational studies, emphasizing primary outcomes like HHF and all-cause mortality among HFrEF patients with advanced CKD or ESRD. Analysis from four studies involving 4,329 such patients yielded a pooled odds ratio of 0.54 [95% CI: 0.25-1.18, P=0.12], indicating no significant association in favor of the sacubitril/valsartan group. When examining data by patient subgroup, the odds ratio for ESRD patients was 0.67 [95% CI: 0.17-2.70, P=0.58], based on findings from 1,378 individuals, whereas the CKD subgroup, encompassing 1,267 patients, presented an odds ratio of 0.64 [95% CI: 0.25-1.66]. Furthermore, evaluation of heart failure hospitalization from three studies with 2,644 patients showed a combined odds ratio of 0.70 [95% CI: 0.28-1.73, P=0.44]. Notably, the odds ratio for all-cause mortality was neutral at 0.86 [95% CI: 0.50-1.46, P=0.57] for the combined cohort, although data from the CKD subgroup did hint at a potential benefit of sacubitril/valsartan with an odds ratio of 0.68 [95% CI: 0.50-0.91]. The ESRD subgroup's odds ratio for this metric stood at 0.86 [95% CI:

0.62-1.19, P=0.37].
Transitioning to secondary outcomes, our analysis revealed that in the ESRD patient group, sacubitril/valsartan was associated with notable improvements in several parameters. From seven studies with 790 patients, the pooled mean difference in LVEF variation was a significant 4.10% [95% CI: 2.69-5.51, P<0.001]. Blood pressure insights from five studies indicated a pronounced reduction in SBP by 7.13 mmHg [95% CI: -12.37 to -1.88, P=0.008], although DBP effects were less clear. Data from four studies, involving 525 patients, showed a remarkable association of sacubitril/valsartan with reduced NT-proBNP levels, with a mean difference of -7098 [95% CI: -13215 to -980, P=0.02]. For left heart chamber remodeling, the mean differences in left ventricular end-diastolic diameter and left atrial diameter variations were -2.64 mm [95% CI: -5.73 to 0.46, P=0.09] and -2.60 mm [95% CI: -5.00 to -0.20, P=0.03], respectively. In terms of safety outcomes for ESRD patients, sacubitril/valsartan group didn't show a heightened risk for hyperkalemia, with an odds ratio of 0.98 [95% CI: 0.45-2.15, P=0.97], and the odds ratio for hypotension was a non-significant 1.22 [95% CI: 0.38-3.90, P=0.74].

Conclusion

In our systematic review and meta-analysis of observational studies, we assessed the efficacy and safety of sacubitril/valsartan in real-world HFrEF patients with advanced CKD and ESRD. Our findings did not demonstrate a significant association between sacubitril/valsartan use and reductions in HHF or all-cause mortality. However, we observed a potential improvement in LVEF among HFrEF patients with ESRD, suggesting some benefits of sacubitril/valsartan. Notably, using sacubitril/valsartan in the ESRD group does not appear to increase the risks of hyperkalemia or hypotension. Given the inherent limitations in establishing causality in observational studies, there is a pressing need for randomized controlled trials to conclusively evaluate the efficacy and safety of sacubitril/valsartan in this patient population.

原著論文　112_A 53

台灣一大型研究發現短期空氣汙染暴露與腎功能下降有關

Association between short-term ambient air pollutants and kidney function in a large Taiwanese population study

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Background

The associations between kidney function and air pollutants remain poorly defined. Therefore, the aim of this study was to evaluate associations among air pollutants, including particulate matter (PM) with a diameter ≦ 2.5 μm ($PM_{2.5}$), PM_{10} (PM with a diameter ≦ 10 μm), carbon monoxide (CO), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), sulfur dioxide (SO_2), and ozone (O_3) with kidney function.

Methods

We used the Taiwan Biobank databases to gather data on individuals residing in Taiwan communities. The exposure levels to major outdoor air pollutants, including $PM_{2.5}$, PM_{10}, NO_2, NO_x, SO_2, CO, and O_3, were estimated using Kriging's interpolation, which was based on data from 76 nationwide air pollution monitoring stations, linked to residency information at the township or district level during the baseline interview.

Results

We enrolled 114,439 participants. Multivariable analysis showed that increasing short-term exposure to $PM_{2.5}$, PM_{10}, O_3, SO_2 (all $p < 0.001$), CO ($p = 0.005$) and NO_2 ($p < 0.014$) were significantly correlated with decline of estimated glomerular filtration rate (eGFR).

Conclusions

Short-term exposure to $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, and O_3 were associated with decline of renal function. The findings of this study have important implications for public health and environmental policy.

原著論文　112_A 54

汽車內二氧化碳滯留研究

Study on CO2 Retention Inside Vehicles

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Background
The influence of indoor carbon dioxide (CO2) concentration on human health is a pivotal concern, particularly in environments with limited ventilation. Mild CO2 exposure may manifest as symptoms such as headache and drowsiness, while higher levels may result in headache, dizziness, inattention, tiredness or even chest tightness. This study aims to investigate CO2 concentration levels within automobiles.

Method
Vehicles were categorized into two groups: air recirculation mode and fresh air mode, to evaluate the condition of CO2 retention during a long-distance drive. A portable CO2 sensor was used to record CO2 concentration inside a vehicle. Data were collected for each driving session, including air circulation mode, driving duration, the number of passengers, and CO2 concentrations (ppm). The mean CO2 concentration, CO2 range, and average rate of CO2 rise were calculated.

Results
This study showed that the CO2 concentrations in the group of air recirculation mode are dramatically higher than in those utilizing fresh air mode (average CO2: 1654~4972ppm vs. 668~969ppm; maximum CO2: 2334~7813ppm vs. 708~1306ppm) (Table 1). Furthermore, an increase in the number of passengers correlates with a higher mean CO2 concentration and higher rate of CO2 rise (Figure 1). Conversely, in the group of fresh air mode, the CO2 range maintained at a low level (Figure 2). The study also showed that transient opening the doors led to a modest reduction of CO2 concentration (Figure 3). In contrast, switch from air recirculation mode to fresh air mode was much more effective to improve the CO2 retention inside a vehicle (Figure 4).

Conclusion
In conclusion, CO2 retention inside a vehicle could be severe during a long-distance drive with air recirculation mode. Ensuring adequate ventilation during a vehicle driving is crucial for passenger's comfort and overall well-being.

原著論文　112_A 55

鈣化尿毒血管病變患者使用硫代硫酸鈉治療的臨床結果：一世代研究

Clinical Outcomes Associated with Sodium Thiosulfate Therapy in Patients with Calcific Uremic Arteriolopathy: a Cohort Study

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Background

Calcific uremic arteriolopathy (CUA), also called calciphylaxis, is a rare, but often fatal condition in end-stage renal disease (ESRD) patients with no effective treatment so far. There is limited report concerning the effect of sodium thiosulfate (STS) therapy in this population.

Methods

The study included 24 ESRD patients who had CUA between 2013 and 2023 at Kaohsiung Veterans General Hospital. Demographic data, laboratory data, co-morbidity and type of therapy were collected for analysis. The association between STS therapy, all-cause mortality, and lesion progression was evaluated.

Results

Eighty percent of patients were diagnosed clinically and 20% of patients had received skin biopsy. Nine (37.5%) patients with CUA received STS therapy during the study period. The baseline characteristic was similar between the two groups in terms of age, diabetes mellitus, dialysis modality, previous trauma history, body weight, albumin, calcium, phosphate, alkaline phosphatase, parathyroid hormone, C-reactive protein and white cell count. The skin lesion in STS group had lower rate of progression as compared with control group (67% versus 80%, p=0.036). In Kaplan-Meier survival analysis, there is a trend toward lower mortality rate in STS group, but no reach statistically significance (33% versus 47%, p =0.678).

Conclusion

Sodium thiosulfate therapy was associated with less lesion progression but not better survival in ESRD patients with calcific uremic arteriolopathy.

原著論文　112_A 56

腎上腺素注射術併用氬氣電漿凝固術或併用止血夾兩者對於消化性潰瘍出血的止血療效之隨機控制試驗

The Randomized Controlled Trial of the Combined Use of Adrenaline Injection with Argon Plasma Coagulation or Hemoclip Application for the Hemostatic Efficacy in Gastrointestinal Ulcer Bleeding

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Introduction
This randomized controlled trial investigates the efficacy of two distinct endoscopic treatment modalities for high-risk peptic ulcer bleeding. High-risk peptic ulcer bleeding poses a substantial clinical challenge, and the choice of treatment can significantly impact patient outcomes.

Background
Nonvariceal upper gastrointestinal bleeding is a common and often urgent clinical scenario, necessitating prompt intervention for initial hemostasis. Various endoscopic techniques have been developed to achieve hemostasis in bleeding ulcers. However, the specific benefits of argon plasma coagulation (APC) following endoscopic injection therapy has not been widely investigated. The study aim is to compare APC plus diluted adrenalin injection (APC group) with clipping plus diluted adrenalin injection (Clip group) in treating high-risk peptic ulcer bleeding.

Study Design and Methods
Conducted from January 2019 to October 2022, this study enrolled consecutive patients with high-risk bleeding ulcers, characterized by active bleeding, non-bleeding visible vessels, or adherent clots. Eligible patients were prospectively randomized into two treatment groups: one receiving APC therapy plus diluted adrenalin injection (APC group) and the other undergoing hemoclipping plus diluted adrenalin injection (Clip group). Additionally, pantoprazole infusion was administered during the fasting period post-endoscopy, and oral therapy was continued for 8 weeks to facilitate ulcer healing. Rebleeding episodes were addressed using endoscopic combination therapy, and patients unresponsive to retreatment were considered for emergency surgery or arterial embolization. Statistical analyses were conducted using appropriate tests, with significance set at $p < 0.05$.

Results
The study included a total of 138 eligible patients, with 68 in the APC group and 70 in the Hemoclip group. Both groups exhibited similar baseline characteristics. Initial hemostasis was achieved in nearly all patients in both groups (98.5% in APC vs. 98.6% in Clip, $p = 1.000$). Rates of rebleeding were comparable (7.4% in APC vs. 8.6% in Clip, $p = 1.000$), as were the rates of surgery and mortality ($p = 1.000$ for both). Hospital stay and transfusion requirements also showed no significant differences between the two groups.

Conclusion

this study provides valuable insights into the management of high-risk peptic ulcer bleeding. The findings suggest that endoscopic therapy with APC plus diluted adrenalin injection is equally effective as hemoclipping plus diluted adrenalin injection in preventing rebleeding. Furthermore, both approaches appear to be equally safe during therapeutic endoscopy.

原著論文　112_A 57

比較 10 天反轉式混合療法與 10 天三合療法合併鉍劑對於胃幽門桿菌之除菌效益

10-day reverse hybrid therapy versus 10-day standard triple therapy plus bismuth for *Helicobacter pylori* infection

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Background

In Taiwan, both the 14-day reverse hybrid therapy and the 10 to 14-day bismuth quadruple therapy are recommended as first-line regimens for *Helicobacter pylori* eradication. The 14-day reverse hybrid therapy has proven effective, and shortening its duration to a 12-day regimen showed a similar eradication rate (95.7%) with better drug compliance (96.8%). On the other hand, the 10-day bismuth quadruple therapy (PPI + bismuth + tetracycline + metronidazole, PBTM) achieved an eradication rate of 91.6%. Comparatively, the standard triple therapy plus bismuth (PPI + bismuth + clarithromycin + amoxicillin, PBCA) displayed a similar eradication rate (95.3%) with fewer adverse effects and higher compliance than traditional PBTM under a 14-day regimen in previous studies. However, the effect of a 10-day reverse hybrid therapy and a 10-day standard triple therapy plus bismuth remains uncertain.

Given the uncertainty surrounding the efficacy of 10-day regimens, this study aimed to compare the eradication rate, adverse events, and drug compliance of 10-day reverse hybrid therapy and 10-day standard triple therapy plus bismuth in southern Taiwan.

Method

Patients infected with *H. pylori* (≥ 20 years old) were randomly assigned to receive either a 10-day reverse hybrid therapy (a 7-day quadruple regimen with pantoprazole 40 mg twice daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily, and metronidazole 500 mg twice daily, followed by a 3-day dual regimen with pantoprazole 40 mg twice daily, amoxicillin 1 g twice daily) or a 10-day triple therapy plus bismuth (pantoprazole 40 mg twice daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily, and tripotassium dicitrato bismuthate 600 mg twice daily for 10 days). Adverse events were assessed on the 14th day after therapy initiation. *H. pylori* status was determined by urea breath test 6 weeks after the end of treatment.

Results

A total of 272 *H. pylori*-infected participants were randomized, with 137 in the reverse hybrid group and 135 in the triple plus bismuth group. The eradication rate of the 10-day reverse hybrid therapy was 89.8%, compared to 87.4% in the triple plus bismuth group by intention-to-treat analysis (P = 0.538). Per-protocol analysis also yielded similar results (89.3% vs. 88.3%, P = 0.792). Although more adverse events were observed in the 10-day reverse hybrid therapy group, there was no significant difference (26.3% vs. 17.8%, P = 0.091). Both groups demonstrated high drug compliance (95.6% vs. 94.8%, P = 0.755).

Conclusion

In southern Taiwan, both the 10-day reverse hybrid therapy and the 10-day triple therapy plus bismuth demonstrated acceptable eradication effects. There was no significant difference in adverse events between the two treatment groups. Additionally, both groups exhibited high drug compliance. These findings provide valuable information for clinicians when selecting treatment regimens for *H. pylori* infection in this region.

原著論文　112_A 58

針對南臺灣免疫缺陷病人於暴露前使用 Evusheld 預防 SARS-CoV-2 感染的效果研究

Effectiveness of pre-exposure administrated Evusheld for prevention of SRAS-CoV-2 infection in immunocompromised patients in Taiwan

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Background

The immunocompromised persons or those contraindicated of SARS-CoV-2 vaccination were at risk of severe disease progression[1]. Evusheld, composed of two SARS-CoV-2–neutralizing monoclonal antibodies (tixagevimab and cilgavimab), has been suggested to help preventing SARS-CoV-2 infection[2]. In this study, our aim was to investigate the incidence of SARS-CoV-2 infection in immunocompromised patients in Taiwan after the administration of pre-exposure Evusheld. We also checked the levels of anti-SARS-CoV-2 spike (S) protein receptor binding domain (RBD) antibodies before and after Evusheld injection.

Methods

We included the immunocompromised patients visiting clinic at Kaohisung Chang Gung Memorial Hospital who were eligible for Evusheld injection according to Taiwan Centers for Disease control. We recorded the patient's information including serum anti-SARS-CoV-2 S protein RBD antibody levels and nucleocapsid protein values at different timings, vaccination history, and SARS-CoV-2 infection history, etc. We measured the serum concentration of the total anti–SARS-CoV2 S protein RBD antibody (Roche Elecsys) for assessing immunity confronting SARS-CoV-2 virus. In addition, we measured the antinucleocapsid antibody (Roche Elecsys; predominantly immunoglobulin) levels (cutoff index, <1.0, for nonreactive samples) to check the SARS-CoV-2 infection status of patient.

Results

A total of 50 patients were included. The administration time points of Evusheld ranged from September 2022 to May 2023. The median age of patients was 54 years old (IQR: 47.5-61). Among them, 31 patients were male. The median of vaccination dosage was 3 (IQR: 1-3). Fourteen patients had history of liver transplantation, 11 patients had history of renal transplantation, and 8 patients had history of autologous transplantation. Nine patients reported having history of SARS-CoV-2 infection and 13 patients showed positive finding of nucleocapsid protein values before the administration. Twenty-six patients showed further elevated serum antibody concentration one month after Evusheld administration (geometric mean: 7217.4, standard deviation: 3432.1). At present, 7 patients told suffering from new SARS-CoV-2 infection after Evusheld administration, and 6 patients showed nucleocapsid protein value converting from negative to positive after Evusheld administration.

Conclusion

For immunocompromised patients, Evusheld efficiently boosted the patient's serum levels of antibody against SARS-CoV-2 virus within one month. Due to emerging omicron variants，Evusheld is unable to prevent the immunocompromised host from SARS-CoV-2 infection.

Reference

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原著論文　112_A 59

臺灣南部一家醫學中心對馬內菲氏徽菌感染的案例研究分析

A case series of *Talaromyces marneffei* infection in a tertiary center in southern Taiwan

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Background

Talaromyces Marneffei, formerly known as *Penicillium Marneffei*, is a thermally dimorphic fungus capable of causing life-threatening infections in endemic regions, notably Southeast Asia and southern China. Incidence of *T. marneffei* infection was infrequent prior to the emergence of the acquired immunodeficiency syndrome (AIDS) pandemic, with the initial case reports surfacing in Thailand in 1984. However, a notable surge occurred, with over 6,000 reported cases between 1984 and 2004. Moreover, during the mid-1990s, it ranked as the third most prevalent opportunistic infection in HIV-infected individuals in northern Thailand. While *T. marneffei* infections are predominantly observed in patients with human immunodeficiency virus (HIV)/AIDS and those manifesting functional impairments in cellular immunity, it is imperative to acknowledge that this pathogen is also capable of causing disseminated disease in individuals, regardless of detectable immunocompromise. *T. marneffei* has been recovered from bamboo rats (*Rhizomys sinensis*), among other species of bamboo rats, and the soil surrounding their burrows. Nevertheless, the precise nature of the relationship between these rats and human infections remains unknown. The first documented case of *T. marneffei* infection in Taiwan was published in 1998, with only sporadic cases reported to date. The principal objective of this study is to present a comprehensive report on talaromycosis cases diagnosed at Kaohsiung Chang Gung Memorial Hospital (KCGMH), contributing to a better understanding of the recent epidemiological data pertaining to this infection in Taiwan.

Method

We obtained cases with culture-proven *T. marneffei* infection from the clinical microbiology laboratory report at KCGMH from 2004 to 2022.

Results

There were 10 patients (seven males and three females) diagnosed as talaromycosis with mean age of 47.5 years old. There were no autochthonous cases have been reported since 2017. Among the cases, six patients (60%) were HIV-infected, two (20%) had a history of solid cancer, and the remaining two (20%) denied the presence of systemic underlying diseases. It is notable that one patient who denied any systemic underlying disease exhibited low absolute CD4 T helper cell counts (67 cells/uL). The presenting symptoms exhibited by these patients varied and included fever, cough, shortness of breath, sore throat, skin lesions, lymphadenopathy, and even asymptomatic cases. The diagnosis of talaromycosis was confirmed through culture, with five cases (50%) isolated from blood specimens, five cases (50%) from skin tissue specimens, and four cases (40%) from bronchoalveolar lavage fluid. Among the patients, seven individuals (70%) received antifungal treatment, which encompassed intravenous amphotericin B, intravenous liposomal amphotericin B, or oral itraconazole. Regrettably, two patients (20%) succumbed during hospitalization, one due to

T. marneffei pneumonia, with a history of nasopharyngeal cancer, and the other to disseminated *T. marneffei* infection, who was HIV-infected. Additionally, one HIV- infected patient experienced a relapse of skin lesions six months after completing initial therapy.

Conclusion

In conclusion, talaromycosis has exhibited low prevalence in our hospital between 2004 and 2022, with the majority of cases occurring in individuals who were either HIV-infected or immunocompromised. Notably, no locally acquired cases have been documented since 2017. The clinical manifestations of talaromycosis were diverse among patients, although the presence of skin lesions and a history of systemic underlying diseases served as valuable diagnostic clues. Encouragingly, patients who received appropriate antifungal treatment demonstrated a favorable prognosis.

原著論文　112_A 60

The Association of Gut Microbiota with Treatment Response in Hepatocellular Carcinoma

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Background & aim
Gut microbiota can influence systemic immune responses, and immune responses are directly related to the efficacy of tumor treatment. Research has shown that gut microbiota is also associated with tumor development and treatment response. Our study primarily investigates the differences in gut microbiota among different treatment responses in patients with hepatocellular carcinoma (HCC).

Methods
This is a prospective study at Kaohsiung Chung-Gung memorial hospital, Taiwan, from October 2019 and September 2021. We recruited patients with advanced HCC (BCLC stage C) receiving target therapy (sorafenib, lenvatinib, or regorafenib). Fecal samples were collected before target treatment. The taxonomic composition of gut microbiota was determined using 16S ribosomal RNA gene sequencing of stool samples.

Results
A total of 35 patients with advanced HCC were included in the study. Out of these patients, 21 presented with progression disease (PD), while the remaining 14 had stable disease (SD) at the 3-month mark. The alpha diversity indices did not show a significant difference between the two groups, but the beta-diversity indices exhibited a significant difference ($p<0.001$). Among the PD group and the SD group, Patients who positively responded to targeted therapy (SD group) exhibited significantly higher abundances of Barnesiella, Subdoligranulum, and Intestineibacter, whereas patients with progressive disease (PD group) demonstrated elevated levels of Oribacterium.

Conclusions
There is variation in gut microbiota among different populations that exhibit different responses to target therapy. However, further research is needed to support the use of gut microbiota as a predictive factor for treatment response.

原著論文　112_A 61

比較肝細胞癌患者手術前後腸道菌群的變化

Comparing Gut Microbiota in Hepatocellular Carcinoma Patients Pre- and Post-Resection

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Background

Emerging evidence links gut microbiota to various human diseases including hepatocellular carcinoma (HCC) initiation and development. However, limited research has been conducted on the longitudinal changes in gut microbiota in HCC patients after resection. The aim of this study was to compare the changes in gut microbiota before and after HCC resection.

Method

A total of 69 HCC patients who underwent resection at Chang Gung Hospital in Kaohsiung from September 2021 to June 2023 were enrolled. Stool samples were collected before the surgery and one year after the surgery for analysis of gut microbiota. The taxonomic composition of the gut microbiota was determined by sequencing the 16S ribosomal RNA gene in the stool samples.

Results

The average age of the 69 HCC patients was 61 years, with 18 (53%) being over 60 years old. The distribution of BCLC stages was as follows: 6 patients in stage 0, 35 patients in stage A, and 28 patients in stage B. Analysis of the gut microbiota showed no significant differences in the alpha-diversity and beta-diversity before and one year after HCC resection. After a median follow-up of 14 months, 8 patients had HCC recurrence. The depletion of Megamonas_rupellensis and Phocaeicola_coprophilus appears to be linked to the recurrence of HCC.

Conclusion

The removal of HCC did not result in significant changes in the composition of the gut microbiota. Fecal microbiota was associated with HCC recurrence. These findings highlight the potential role of gut microbiota as biomarkers to predict outcomes of HCC after resection.

原著論文　112_A 62

慢性 B 型肝炎病人停止貝樂克或惠立妥治療後的相位轉變和表面抗原消失的發生率

Incidences of phase transition and HBsAg loss after cessation of entecavir or tenofovir cessation in patients with chronic hepatitis B

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Background

Phase transition remains unknown after cessation of nucleot(s)ide analogues (NA) therapy in patients without clinical relapse. This study investigated the incidences of phase transition and HBsAg loss in patients who did not experienced clinical relapse in the first 2 years after nucleos(t)ide analogues (NA) cessation.

Method

A total of 367 patients who did not experience clinical relapse or receive retreatment in the first 2 years after cessation of entecavir or TDF were enrolled in this study. All patients met the stopping criteria for antiviral agents based on the 2012 guidelines of the Asian Pacific Association for the Study of the Liver.

Results

Inactive phase (phase I) was defined as persistent HBV DNA <2000 IU/mL and persistent normal alanine transaminase (ALT) <40 U/mL; phase II and phase III, as HBV DNA>2000 IU/mL and persistent ALT <40 U/L (phase II) or persistent or intermittent ALT 40–80 IU/mL (phase III); active phase (phase IV), as HBV DNA >2000 IU/mL and ALT >80 U/mL. Of the 367 patients, 233 were in phase I, 87 in phase II, and 47 in phase III in the first 2 years after NA cessation. Of the 233 patients in the inactive phase, 201 (86.3%) remained in the same phase and 17 (7.3%) transitioned to phase IV after the first 2 years. Multivariate analysis showed that older age, genotype B, higher ALT levels at initial treatment and higher HBsAg levels at 2 years after entecavir or TDF cessation were factors independently associated with phase I, II or III transition to phase IV beyond 2 years after entecavir or TDF cessation. Of the 134 patients in phase II or III, 35 (26.1%) and 44 (32.8%) transitioned to phase I and phase IV, respectively. The cumulative incidences of HBsAg loss at 10 years after entecavir or TDF cessation in patients in phase I who remained in phase I and phase II or III patients who transitioned to phase I were 57.8% and 58.3% (P=0.339), respectively. No patients experienced hepatic decompensation upon clinical relapse or died during follow-up.

Conclusion

Our study showed that 86.3% of patients in the inactive phase during the first 2 years after cessation of entecavir or TDF remained in the inactive phase during follow-up. In contrast, 26.1% of patients who experienced viremia without clinical relapse (phase II or phase III) transitioned to the inactive phase (phase I). The incidence of HBsAg loss was high for patients who remained in the inactive phase or transitioned to the inactive phase after cessation of entecavir or TDF. Therefore, closely monitored patients with CHB who do not meet the criteria for retreatment in the first 2 years after cessation of entecavir or TDF achieve favorable

clinical outcomes if antiviral treatment is initiated when patients transition to a more active phase.

原著論文　112_A 63

Denosumab 在洗腎病人中的心血管風險

Denosumab and the risk of cardiovascular events in end stage kidney disease patients

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Background

Osteoporosis and cardiovascular diseases (CVD) have become the major problems of the aging population, especially in end stage kidney disease (ESKD) patients. Denosumab, a receptor activator of nuclear factor-κB ligand (RANKL) inhibitor, is increasingly used as an anti-resorptive agent. Denosumab was proven to be an effective anti-osteoporosis agents but its effects on CVDs remain unclear. In this study, we aimed to investigate the correlation of denosumab and the risk of cardiovascular events in end stage kidney disease (ESKD) patients on regular hemodialysis.

Method

We identified 388 patient who received denosumab therapy for osteoporosis from 19,400 ESKD patients follow up in Chang Gung Memorial Hospital between Janunary 1, 2003 and December 31, 2018. The Kaplan–Meier analysis and Cox regressions were performed to assess the effect of denosumab treatment on the cardiovascular events in ESRD patients on regular hemodialysis.

Results

The data recorded 388 of the patients who received denosumab therapy and 12,563 of the comparison subjects between Janunary 1, 2003 and December 31, 2018. After a propensity score matching, there were 162 patients in the denosumab group and 324 patients without denosumab use. The incidence rate of CVDs (myocardial inarction (MI), ischemic stroke and congestive heart failure) significantly lower in the denosumab group than the non-denosumab group. (HR = 0.58, 95 % CI = 0.37-0.92, p = 0.0195). However, the secondary outcome including myocardial infarction, ischemic stroke, congestive heart failure and In-hospital death from any cause had a lack of statistical significance. In the subgroup analysis, denosumab is associated with lower risk of CVD in female and patients with higher Ca*P product, hypertension and hyperlipidemia.

Conclusion

Denosumab therapy was associated with lower risk of cardiovascular events in ESRD patients. Denosumab has lower risk of CVD in female and patients with higher Ca-P product, hypertension and hyperlipidemia.

原著論文　112_A 64

多次新冠疫苗追加劑在感染新型冠狀病毒之血液透析患者的臨床效果

Clinical effectiveness of multi-dose SARS-CoV-2 vaccine boosters in patients with COVID-19 undergoing hemodialysis

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Background

Individuals undergoing hemodialysis (HD) are at an increased risk of coronavirus disease 2019 (COVID-19) infection due to their underlying diseases, compromised immunity, and regular visits to dialysis facilities. Additionally, vaccine hesitancy among patients undergoing HD is widely observed. While the effectiveness of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine booster has been documented, the benefits of multi-dose vaccine boosters have yet to be clarified in the HD population, particularly in those with COVID-19 and receiving antiviral medications. In this retrospective study, we assessed the real-world effectiveness of multi-dose SARS-CoV-2 vaccine boosters in patients with COVID-19 undergoing HD.

Method

We enrolled adult patients (≥ 20 years of age) undergoing maintenance HD who were diagnosed of COVID-19 in the Kaohsiung Chang Gung Memorial Hospital between April 2022 and July 2023. The study protocol was approved by the Institutional Review Board and Ethics Committee of Chang Gung Medical Foundation, Taipei, Taiwan (IRB No. 202301145B0) and adhered to the principles of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective design. The outcomes of interest in this study were COVID-19-associated hospitalization and mortality within 30 days of COVID-19 onset. To evaluate the effectiveness of SARS-CoV-2 vaccine boosters, we categorized the study cohort into three groups based on their COVID-19 vaccination status: those who did not receive any booster dose, those who received the first booster dose, and those who received the second or subsequent booster doses, respectively. Baseline characteristics, the utilization of antiviral agents, and the risks of COVID-19-associated hospitalization and mortality were compared among groups. Categorical variables are presented as numbers (*n*) with percentages and were analyzed using the chi-squared test. Continuous variables are expressed as medians with interquartile ranges (IQRs), and the Kruskal–Wallis test was employed for univariate analysis. The probabilities of survival within 30 days after disease onset were plotted as Kaplan–Meier curves and compared among groups using the log-rank test. To assess the effects of SARS-CoV-2 vaccine boosters on the risks of COVID-19-associated hospitalization and mortality, multivariate logistic regression analysis and multivariate Cox regression analysis were conducted respectively, adjusting for age, sex, body mass index, diabetes, hypertension, HD duration, antiviral agent usage, and covariates with a *p*-value of <0.1 in univariate analyses. Statistical significance was set at a *p*-value of <0.05. Statistical Product and Service Solutions software (version 22.0; IBM, Armonk, NY, USA) was used for all the analyses.

Results

In this study, 521 patients undergoing HD were enrolled for analysis. The median age of the cohort was 66 years (IQR, 58–72), and women accounted for 50.1% of the study population. Of the enrolled patients, 124 (23.8%), 212 (40.7%), and 185 (35.5%) received no more than two vaccine doses, three vaccine doses (two-dose primary series with one booster), and at least four vaccine doses (two-dose primary series with two or more boosters), respectively. Most enrolled patients (96.7%) received adequate antiviral treatments according to the guidelines of Taiwan Centers for Disease Control. Compared with those receiving no more than two vaccine doses, patients received three or more vaccine doses had significantly lower risks of COVID-19-associated hospitalization (19.4% vs. 8.0% vs. 7.0%, $p = 0.001$), and the risks of hospitalization were not significantly different between patients receiving three or at least four vaccine doses. Additionally, the probabilities of death within 30 days after disease onset in patients receiving at least four vaccine doses were slightly lower than in those receiving three vaccine doses (0.5% vs. 2.8%, $p = 0.084$) and significantly lower than in those receiving no more than two vaccine doses (0.5% vs. 5.6%, $p = 0.006$). In the multivariate logistic regression analysis, booster vaccination was independently associated with a lower risk of COVID-19-associated hospitalization after adjust for covariates (odds ratio [95% confidence interval, CI], 0–2 vs. 3 vaccine doses, 0.406 [0.188–0.875], $p = 0.022$; 0–2 vs. 4 or more vaccine doses, 0.393 [0.169–0.913], $p = 0.030$). Furthermore, only multi-dose vaccine boosters significantly reduced the risk of COVID-19-associated mortality in the multivariate Cox regression analysis after adjusting for covariates (hazard ratio [95% CI], 0–2 vs. 3 vaccine doses, 0.354 [0.100–1.260], $p = 0.109$; 0–2 vs. 4 or more vaccine doses, 0.097 [0.011–0.869], $p = 0.037$).

Conclusion

SARS-CoV-2 vaccine boosters effectively reduce the risk of hospitalization in patients undergoing HD with COVID-19 and receiving antiviral treatment. Moreover, multi-dose SARS-CoV-2 vaccine boosters provide additional benefits in lowering the risk of COVID-19-associated mortality in the HD population. Our findings highlight the benefits of extensive COVID-19 booster vaccination in this vulnerable population.

原著論文　112_A 65

利用血清發炎指標來預測接受免疫檢查點抑制劑治療的轉移性膀胱上皮癌患者的存活情況

Leveraging serum inflammatory markers for prognostication of survival in patients with metastatic urothelial carcinoma undergoing treatment with immune checkpoint inhibitors

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Background

Numerous serum inflammatory markers have been extensively examined for their potential to predict the outcomes of immune checkpoint inhibitor (ICI) treatment in solid cancer. Nevertheless, studies exploring the ideal threshold and clinical validation of these inflammatory markers are lacking specifically in the context of metastatic urothelial carcinoma (mUC).

Method

In our retrospective study, we analyzed patient data from two Taiwan medical centers: Linkou Chang Gung Memorial Hospital (training cohort) and Kaohsiung Chang Gung Memorial Hospital (validation cohort). The serum biomarkers of our interest were white blood cell counts (WBC), hemoglobin levels, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and the systemic immune-inflammation index (SII). The optimal cutoff values for PLR and SII were established through analysis of the training cohort data using X-tile software.

Results

In total, 123 patients in the training cohort and 69 in the validation cohort were enrolled. The cutoff values for the inflammatory markers were as follows: WBC (10,000), NLR (5), Hemoglobin (10), PLR (194.84) and SII (2205). In the training cohort, patients experienced significantly poorer survival rates when their inflammatory marker levels exceeded the defined threshold: median OS for WBC (22.6 vs 2.6 months, $p < 0.0001$), NLR (Not reached vs. 2.9 months; $p < 0.0001$), hemoglobin (18.0 vs. 2.9 months; $p = 0.006$), PLR (not reached vs 4.9 months; $p = 0.0001$) and SII (22.6 vs. 1.9 months; $p < 0.0001$). In the validation cohort, patients with elevated NLR (18.9 vs. 4.5 months; $p = 0.002$), PLR (18.9 vs. 7.0 months; $p = 0.02$), SII (15.4 vs. 4.4' $p = 0.02$), and lower levels of hemoglobin (17.5 vs. 7.5 months; $p = 0.02$) demonstrated unfavorable OS. In the multivariate Cox regression analysis, certain factors emerged as independent prognostic indicators: visceral metastasis (hazard ratio [HR]: 2.06; 95% confidence interval [CI]: 1.40–3.0; $p < 0.001$), ECOG performance status ≥ 2 (HR 2.35; 95% CI: 1.51-3.70; $p < 0.001$), hemoglobin levels > 10 mg/dL (HR 0.61; 95% CI: 0.41 – 0.90; $p = 0.014$), and NLR > 5 (HR 2.15; 95% CI: 1.18–3.90; $p = 0.012$).

Conclusion

Integrating serum inflammatory markers with clinicopathologic factors forms a practical and accessible prognostic tool for assessing survival in mUC patients.

原著論文　112_A 66

比較埃索美拉唑基礎和拉百樂唑基礎高劑量雙重療法在首線幽門螺旋桿菌的根除治療效果- 台灣多中心實際研究報告

The Multicenter Real-World Report of the Efficacies of 14-Day Esomeprazole-Based and Rabeprazole-Based High-Dose Dual Therapy in First-Line Helicobacter pylori Eradication in Taiwan

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Background

Because of the rising antibiotics resistances of *Helicobacter pylori (H. pylori)*, 14-day high-dose dual therapy (HDDT) using proton-pump inhibitors (PPI) and amoxicillin attracted attention for its simplicity and lower adverse event profile. Besides, vonoprazan is not available worldwide. This real-world study aims to compare the efficacy of esomeprazole-based and rabeprazole-based HDDT regimens and to identify clinical factors influencing outcomes.

Methods

A retrospective study enrolled 346 *H. pylori*-infected naïve patients from January 2016 to August 2023. Patients were assigned to either a 14-day esomeprazole-based HDDT (EA-14; esomeprazole 40 mg t.i.d. and amoxicillin 750 mg q.i.d. for 14 days, n=173) or a 14-day rabeprazole-based HDDT (RA-14; rabeprazole 20 mg and amoxicillin 750 mg q.i.d. for 14 days, n=173).

Results

Five patients from the EA-14 group and 10 from the RA-14 group were lost to follow-up, resulting in 168 and 163 patients for the per-protocol (PP) analysis, respectively. Eradication rates for the EA-14 and RA-14 groups were 90.2% and 80.9% (P=0.014) in intention-to-treat (ITT) analysis; and 92.9% and 85.9% (P=0.039) in PP analysis. Adverse event rates were similar between the two groups (11.9% vs 11.7%, P=0.944). Smoking and age≧60 were associated with eradication failure in the EA-14 group (P=0.007 and P=0.039, respectively), but not in the RA-14 group. Hence, the antibiotic resistance rates were amoxicillin (2.3%), clarithromycin (14.7%), metronidazole (40.3%), and dual resistance to clarithromycin and metronidazole (7.0%).

Conclusions

Esomeprazole-based HDDT regimen achieved over 90% eradication rates, significantly outperforming the rabeprazole-based regimen, which failed to achieve such high eradication rates.

原著論文　112_A 67

結節性硬化症病人之腎臟血管肌肉脂肪瘤於使用癌伏妥後的容積變化

The Effect of everolimus on the volume changes in renal angiomyolipoma associated with tuberous sclerosis complex

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Background

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder, caused by pathogenic variants in the TSC1 or the TSC2 genes, which results in overactivation of the mTOR pathway. It is characterized by benign tumors in multiple organs, including renal angiomyolipoma, cardiac rhabdomyoma, subependymal giant cell astrocytoma and skin angiofibroma. This study aims to investigate the changes in the size of renal angiomyolipoma after use of everolimus.

Method

In this retrospective study, we identified patients with diagnosis of tuberous sclerosis complex, renal angiomyolipoma, and use of everolimus between years 2013 and 2022. Patients without CT or MRI imaging or with history of nephrectomy or transcatheter arterial embolization were excluded. From each CT or MRI image, we used software to calculate the cross-sectional area of the AML and then times the image thickness (4~6mm). The total AML volume was obtained by the addition of areas from serial image slides. We calculated the AML volumes from 4 different time points: 2 before and 2 after starting everolimus.

Results

We analyzed data from six patients (3 females and 3 males, mean age 28.7, 19-47year-old), and 13 AMLs. Four patients had TSC2 genotype, and four patients had SEGA and seizure history. AML volume was significantly reduced from 10.7ml (IQR 4.9-22.3) before starting everolimus, to 8.8ml (2.2-14.6) after 10.7 (5.2-11.9) months of treatment (p=0.011) with volume reduction rate 45.3% (1-67%). The AML size remained stable at 12.1ml (1.5-13.6) after 24.1 (12.7-33.9) months of treatment (p=0.563, vs. 10.7 months). In three patients, the AML volumes changed differently. Specifically, in the same patient, one tumor may reduce volume 17-64%, while the other tumors increased volume 1.5~9%.

Conclusion

In this preliminary analysis, the volume of TSC-associated AMLs reduced significantly after 10.7 months of everolimus treatment, and remained stable at 24 months. However, AMLs in the same patient may have divergent responses to everolimus. These results need to be confirmed in larger study.

原著論文　112_A 68

單顆肝細胞癌無微小血管侵犯接受手術切除的病患腫瘤大小並不影響整體存活期

Tumor size does not affect overall survival of patients undergoing resection for a single hepatocellular carcinoma without microscopic vascular invasion

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Background

Whether tumor size affects the survival of patients undergoing liver resection(LR) for a single hepatocellular carcinoma(HCC) without microscopic vascular invasion(MVI), i.e., pathological T1N0M0, is controversial. We aimed to clarify this issue.

Method

We enrolled 626 patients with HCC of pathological stage T1N0M0 of the 7th edition of American Joint Committee of cancer staging who underwent LR between 2011 and 2021 at our institution. The overall survival (OS) of patients with T1N0M0 HCC >5.0 cm and those with T1N0M0 HCC ≤5.0 cm was compared using the Kaplan–Meier estimator and log-rank test both before and after propensity score matching (PSM).

Results

Ninety-two (14.7%) patients had T1N0M0 HCC >5.0 cm. The proportion of patients with cirrhosis was lower in the T1N0M0 HCC >5.0 cm group than in the T1N0M0 HCC ≤5.0 cm group (16.3% vs 41.2%, p<0.001). The former also had a lower proportion of patients showing anti-HCV positivity than the latter (17.4% vs 33.9%, p=0.002). Five- year OS did not differ significantly between the two groups before PSM (82% vs 84%, p=0.857) or after PSM (82% vs 92%, p=0.274).

Conclusion

Tumor size did not affect the OS of patients undergoing LR for T1N0M0 HCC.

原著論文　112_A 69

腎臟科醫師執行經皮腹膜透析導管植入手術：高通暢率和低併發症率的新選擇

Nephrologist-initiated Percutaneous Peritoneal Catheter Insertion: A Promising Approach with High Technical survival and Low Complication Rates

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Background

Peritoneal dialysis (PD) plays a pivotal role in renal replacement therapy for end-stage kidney disease (ESKD). Previous articles (1-3) have advocated for the adoption of percutaneous PD catheter insertion by nephrologists. This technique offers several advantages, such as simplicity, minimal wound size, shorter procedure duration, and cost-effectiveness (3). Therefore, it deserves increased attention. However, this technology remains relatively unfamiliar in Taiwan. In this report, we share our experience with PD catheter insertion by nephrologists at Kaohsiung Chang Gung Memorial Hospital (KCGMH).

Method

We retrospectively gathered data from patients aged 18 and older with ESKD who underwent percutaneous PD catheter insertion by a nephrologist at KCGMH between June 2020 and June 2022. Each case was monitored for 12 months or until the catheter was removed.
For our primary outcome, we followed the guidelines established by the International Society for Peritoneal Dialysis (ISPD) (4). Catheter patency was defined as the percentage or probability of catheter survival at 12 months post-placement without requiring removal, replacement, or intervention (surgical or radiological) due to flow dysfunction or unmanageable drain pain.
All PD catheters were also evaluated for early infections and early mechanical complications within 30 days for secondary outcome. Mechanical complications were broadly divided into extrinsic compression of the catheter tip, internal luminal obstruction, poor positioning and/or migration, tissue attachment, peri-catheter leakage, abdominal wall hernias, and pleuroperitoneal connection or fistula development (5).
Infectious outcome includes peritonitis, exit-site infections, and tunnel infections (5). Exit-site infection was defined as exit-site edema, erythema, and purulent discharge. Ultrasound examinations were performed when tunnel infection was suspected. Peritonitis was identified as turbid dialysate with more than 100 white blood cells per cubic millimeter, with at least 50% being polymorphonuclear, with or without a positive effluent culture (5). We also sampled dialysate culture for the organisms of infectious complication while peritonitis was diagnosed.

Results

In this study, total 30 patients were included. Table 1 summarizes the baseline characteristics of these patients. The mean age was 59.2 ± 16.4 years old , with approximately 36.7% being elderly (≧65 years old).
The overall catheter patency rate at the 12th month was 90%, surpassing the recommended threshold of >80% according to the ISPD guideline at the 12th month (4). Figure 1 provides a visual representation of Kaplan-Meier curve of catheter cumulative survival rate. Three

cases resulted in catheter failure, with two cases attributed to refractory peritonitis despite receiving appropriate antibiotic treatment (one occurring in the 4th month due to a Citrobacter freundii complex infection and the other in the 1st month due to an Escherichia coli infection), while the third case experienced early catheter leakage in the 1st month.
During the initial 30 days post-operation, early complications were noted in four cases (Table 2), and the incidence rates for all these complications align with the recommendations of the ISPD guideline (4). Among these cases, two were linked to early mechanical complications - one resulting from hernia and the other from early peri-catheter leakage. The hernia case was further complicated by peritonitis, leading to both patients transitioning to hemodialysis after the initial complication episode. In addition, two cases were associated with early infectious complications, specifically peritonitis (Table 2). Both cases successfully recovered with antibiotic treatment. We also conducted organism sampling, with the culture results detailed in Table 2. It's worth noting that in one case, cultures revealed the presence of three different organisms.

Table 1 Demographic characteristics of study patients

Number of catheters	30	
Gender	Male	15(50%)
	Female	15(50%)
Age	Mean	59.2±16.4yrs
	Range	28.7~90.8yrs
	≧65yrs	11(36.7%)
	≦75yrs	7(23.3%)
Causes of ESKD	CGN	14(46.7%)
	DM	10(33.3%)
	HTN	2(6.7%)
	Others	4(13.3%)
Comorbidity	HTN	28(93.3%)
	Dyslipidemia	20(66.7%)
	DM	11(36.7%)
	CAD	10(33.3%)
	Heart failure	6(20.0%)
	Malignancy	5(16.7%)
	CVA	3(10.0%)
	Arrythmia	3(10.0%)

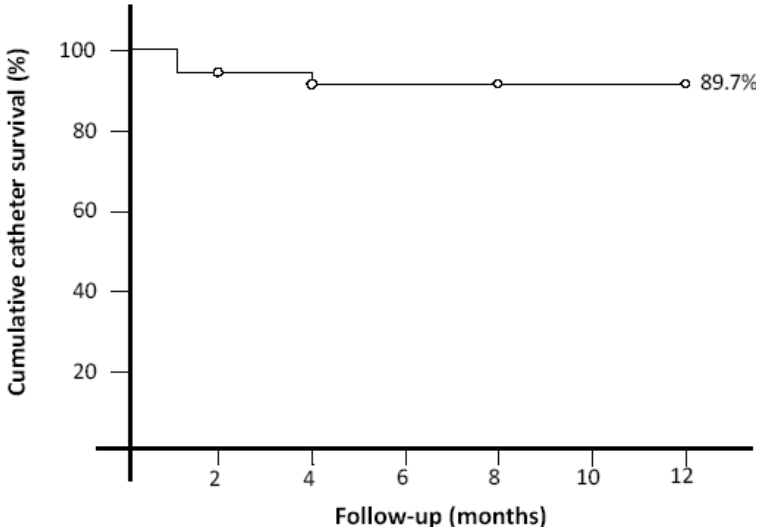
CGN- Chronic Glomerulonephritis(Clinical diagnoses, without pathology); DM- Diabetes mellitus; HTN- Hypertension; CAD- Coronary artery disease; CVA- Cerebral Vascular Accident

Table 2 Early complications(≦30 days)post PD catheter insertion

Infections	Mechanical		
Peritonitis	2(6.7%)	Abdominal wall hernias	1(3.3%)
Escherichia coli	1	Peri-catheter leakage	1(3.3%)
Enterobacter cloacae complex	1*	Poor positioning/Migration	0
Morganella morganii	1*	Tissue attachment	0
Candida glabrata	1*	Extrinsic compression	0
Exit-site infection	0	Internal Luminal obstruction	0
		Pleuroperitoneal connection or fistula	0
Tunnel infection	0		

*Cultures of one case revealed 3 different organisms

Figure 1 Kaplan-Meier curve of catheter cumulative survival rate



Conclusion

In this retrospective study, percutaneous PD catheter insertion by nephrologists featured with high catheter patency rate, alone with low early mechanical complication rate and low early infectious complication rate.
In our study, over one-third of the participants are elderly, and we believe that this technique also can provide a safer and more effective option of PD catheter implantation for older patients. With advantages mentioned above, this new era technique indeed needs more emphasis. However, this study is small-scale and not compared with placement of PD catheter via surgeon. Further research would be needed in the future.

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原著論文　112_A 70

比較膠囊內視鏡及單氣囊小腸鏡作為第一線探查大量不明原因消化道出血之應用價值

Comparison of video capsule endoscopy and single-balloon enteroscopy for first-line exploration of massive obscure gastrointestinal bleeding

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Background

The position of video capsule endoscopy (VCE) relative to single-balloon enteroscopy (SBE) in the diagnostic algorithm of massive obscure gastrointestinal bleeding (OGIB) is unclear, as previous studies involved the use of both techniques in all patients. The aim of this study was to compare the diagnostic yield and clinical outcomes of the two approaches.

Methods

We retrospectively enrolled patients who had undergone VCE or SBE for massive OGIB between January 2017 and March 2023 at a tertiary referral academic center. The alternative method was only used if the first-line method revealed no definite bleeding source, or if required for clinical reasons during follow-up. We analyzed the diagnostic yield of VCE and SBE, therapeutic intervention rate and long-term rebleeding rate.

Results

VCE and SBE, used as the first-line exploration, identified a bleeding source in 30 of 40 patients and 34 of 49 patients, respectively (75% vs 69.4%; *P* =0 .639). The most frequent positive findings at VCE were erosions/ulceration (15 patients, 37.5 %) followed by angiodysplastic/vascular lesions (9, 22.5%). The most frequent findings at SBE were angiodysplastic/vascular lesions (20 patients, 40.8%) followed by erosions/ulceration (12, 24.5%). Therapeutic intervention was performed in 55% and 65.3% of patients in the VCE and SBE groups, respectively (P=0.385). In patients with OGIB, the overall rebleeding rate was 32.5% (13/40) in VCE group and 38.8% (19/49) in SBE group during a median follow-up of 12 months (range 6-64 months). Multivariate analysis showed that only hemoglobin ≤7 g/dL before OGIB study (hazard ratio [HR] 2.543, 95% confidence interval [CI] 1.236-5.196, P = 0.011) was independent risk factor associated with rebleeding.

Conclusions

High detection rates of the causes of massive OGIB are feasible with VCE-first and SBE-first approaches. The ulceration and angiodysplasia were two common findings for OGIB. Rebleeding is common during the long-term follow-up of patients with OGIB. Careful follow-up is required for these patients after hospital discharge.

原著論文　112_A 71

針對末期瀰漫性冠心症患者以冠狀動脈內注輸 CD34+細胞治療和優化藥物治療的超長期預後比較

Comparison of long-term clinical outcomes between intracoronary CD34+ cell therapy and optimal medical treatment for end-stage diffuse coronary artery disease

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Background

Patients with end-stage diffuse coronary artery disease (EnD-CAD) have multiple and severely diffuse coronary artery stenosis. Vast majority of EnD-CAD patients are unsuitable for coronary intervention due to too small epicardial vessels and poor distal coronary circulation. They usually express intractable angina, present with low exercise capacity, and have high risk for adverse clinical events. Cumulative evidence has shown that application of stem cell therapy in the EnD-CAD patients not only reduce angina and dyspnea but also improve left ventricular ejection fraction (LVEF) and functional capacity. However, long-term follow-up data for this kind of high-risk patients undergoing intracoronary (IC) CD34+ cell therapy is still lacking.

Objective

We sought to investigate and compare long-term clinical outcomes between IC CD34+ cell therapy versus optimal medical treatment (OMT) in the EnD-CAD patients.

Methods

This retrospective analysis were comprised of phase I ((2011-2014, ISRCTN72853206) and phase II (2013-2017, ISRCTN26002902) clinical trials. Stem cell therapy (SCT) group included a total of 68 EnD-CAD patients receiving IC CD34 cell therapy (n=38 in the phase I and n=30 in the II trial). Additionally, OMT group included 30 EnD-CAD patients only treated with guideline-directed medical therapy. All 98 patients in both groups took strict clinical surveillance and follow-up. Data were collected from electronic medical records and telephone contact for judicious scrutiny of clinical events. Clinical symptoms including dyspnea and angina scores, change of LVEF on 3D-echocardiography, and adverse clinical events were compared between the SCT and OMT groups. All data were censored till July 2023.

Results

Baseline characteristics did not differ between both groups with mean age of 65 years and LVEF around 54% on average. More than 70% of patients were male. Eighty-seven percent of EnD-CAD patients had history of surgical and percutaneous coronary intervention, including left main disease in 35% of them. After a 6.8-year mean follow-up period with longest period of 11.6 years, the all-cause mortality rate was 37.3% vs 30.0% in the SCT and OMT group, respectively (p=0.485). A composite of adverse clinical events occurred in more than 80% of the frail EnD-CAD patients of both groups. Although higher rate of bailout myocardial revascularization for refractory angina was noted in the SCT than OMT group (46.3% vs 33.3%, p=0.233), both groups had a similar rate of major adverse cardiovascular and cerebrovascular events (MACCE, 25.4% vs 23.3%, p=0.830). Among the survivors at the

end of follow-up, LVEF was insignificantly higher in the SCT than OMT group (54.2% vs 52.9%, p=0.652). Notably, SCT group suffered from twice episodes of hospitalization for heart failure (26.9% vs 13.3%) and sepsis (26.9% vs 10.3%) as compared with OMT group, but they did not reach statistical significance.

Conclusions

The long-term follow-up study demonstrates that compared with optimal medical treatment for EnD-CAD, IC CD34+ cell therapy might slightly improve LV systolic function but did not reduce death and adverse clinical events. Furthermore, it deserves further investigation for why cell therapy group expressed higher rates of unexpected hospitalization for heart failure and sepsis.

原著論文　112_A 72

不同病因所致之肺高壓病人長期存活率分析：單一醫學中心案例回顧

Long term survival in pulmonary arterial hypertension with different etiologies: A single center review

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Background

Pulmonary artery hypertension (PAH) is a rare disease, which is a common but fatal complication of connective tissue disease (CTD) and congenital heart disease (CHD). Other diseases that may associated with pulmonary arterial hypertension included infection of human immunodeficiency virus (HIV), portal hypertension. It also can be an idiopathic disease in some cases. This study is aimed to evaluate the long-term survival rate of patients who had the different etiologies, specific comorbidities, and received different PAH-target medication.

Method

We collected 98 patients who receiving echocardiogram with tricuspid regurgitation pressure gradient (TRPG) greater than 31mmHg in Kaohsiung Chang Gung Memorial Hospital. After excluding patients who had not meet the current diagnostic criteria of pulmonary arterial hypertension, the remained 47 patients with final diagnosis of PAH by cardiac catheterization were enrolled. We classified those patients into different groups according to the leading cause of PAH. The survival of these patients was estimated by the Kaplan-Meier method. Other comorbidities which may affect the long-term survival and therapeutic effectiveness of different PAH-specific medication were also reviewed.

Results

In this study, 98 patients receiving echocardiogram with TRPG greater than 31mmHg were screened initially. After excluded the patients who meet the excluding criteria (no cardiac catheterization for diagnosis; the pulmonary arterial wedge pressure greater than 15 mmHg; mean pulmonary artery pressure less than 20; and received echocardiogram for only one time), 51 patients were excluded from our study. For the remaining 47 patients, mean age of PAH diagnosis of enrollment was 52.2 (SD 16.6) years, and the female to male ratio was 29:18. The most common disease that leads to PAH is CTD, followed by CHD, portal hypertension, HIV infection; 15 patients of them were idiopathic. Of these 47 patients, 3 patients didn't have medical treatment due to intolerance of the side effect of PAH-target medication. 44 patients received Sildenafil as PAH-target medication, in which 20 patients had combined therapy (12 patients with Macitentan and 8 patients with Bosentan). The whole 1-, 3-, and 5- year survival rate of the enrolled patients were 97.9, 81.5, and 77.8%, respectively. Among those underlying disease, CTD had the poorest outcome that the 1-, 3-, and 5- year survival rate were 92.9, 55.7, and 41.7, respectively. Using dual PAH-target therapy had better 1-, 3-, and 5- year survival rate but the choice of the second medication (Macitentan or Bosentan) had no significant difference. The most common comorbidity of the patients is systemic hypertension, which was found to be relevant to higher mortality rate, but also had no statistical significance.

Conclusions

PAH is a rare disease that occurred in patients with CTD, CHD, portal hypertension, HIV infection, while partial of them were idiopathic. Among these patients, the choice of medication was limited and the efficiency was unsatisfactory. Systemic hypertension may be a predictor risk factor of higher mortality rate. The overall 5-year survival rate of our patients after PAH diagnosis was 77.8%.

原著論文　112_A 73

糖尿病患者握力低下的相關因子：肌少症的可能風險

Factors Associated with Low Hand Grip Strength in Patients with Diabetes Mellitus: Implications for Sarcopenia Risk

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Background

Sarcopenia is a degenerative skeletal muscle condition characterized by the progressive loss of muscle mass, strength, and function, primarily seen in older adults. Sarcopenia can significantly impact an individual's quality of life, leading to reduced mobility, increased risk of falls, and a higher likelihood of morbidity and mortality. Hand grip strength (HGS) is often used as a simple and reliable measure to assess muscle function and overall frailty in these individuals. This study was aimed to investigated the associated contributing to low HGS in patients living with diabetes mellitus (DM).

Method

A total of 1468 patients with diabetes mellitus (DM) who was attending endocrinology clinic in Kaohsiung Chang Gung Memorial Hospital was recruited in this study. Low HGS was defined as handgrip strength <28 kg for men and <18 kg for women according to 2019 Asian Working Group for Sarcopenia (AWGS) consensus. Patients' characteristics, anthropometric parameters, laboratory data, use of medications and comorbidities were collected for analyzing the difference between normal HGS and low HGS. Odds ratios (OR) for proposed parameters were calculated using bivariate logistic regression analysis.

Results

For the purpose of our analysis, the study participants were stratified into two groups based on handgrip strength (HGS): those with normal HGS (N=959) and those with low HGS (N=509). Notably, individuals exhibiting low HGS were observed to be of older age (66.4 ± 10.7 vs. 59.1 ± 11.5 years, $p < 0.001$) and presented an extended duration of Diabetes Mellitus (DM) (12.83 ± 8.00 vs. 10.67 ± 7.21 years, $p < 0.01$) in comparison to their counterparts with normal HGS. Additionally, the low HGS group displayed a lower body mass index (BMI) (25.8 ± 4.21 vs. 27.0 ± 4.8 kg/m², $p < 0.001$), elevated levels of total cholesterol (160.27 ± 31.67 vs. 167.20 ± 33.70 mg/dl, $p < 0.001$), and reduced levels of low-density lipoprotein (87.01 ± 25.77 vs. 92.39 ± 27.89, $p < 0.001$) as contrasted with those with normal HGS. Furthermore, individuals within the low HGS category exhibited higher proportions of utilizing anti-hypertensive agents (59.5% vs. 50.9%, $p = 0.002$), presenting cardiovascular disease (17.3% vs. 12.0%, $p = 0.005$), retinopathy (50.9% vs. 39.4%, $p < 0.001$), and chronic kidney disease (30.6% vs. 15.7%, $p < 0.001$) in comparison to their counterparts with normal HGS. In the context of multivariable analysis, diminished HGS was notably linked to several factors. These encompassed age (Odds Ratio [OR] 1.046, 95% Confidence Interval [CI]: 1.032-1.061, $p < 0.001$), BMI (OR 0.888, 95% CI: 0.842-0.936, $p < 0.001$), waist circumference (OR 1.038, 95% CI: 1.015-1.061, $p < 0.001$), total cholesterol (OR 0.888, 95% CI: 0.991-0.982, $p = 0.04$), and chronic kidney disease (OR 1.681, 95% CI: 1.126-2.508, $p = 0.011$).

Conclusion

In conclusion, our study underscores the significant correlation between age, obesity, and CKD with reduced HGS in individuals diagnosed with DM. These results emphasize the importance of heightened vigilance in clinical settings towards monitoring the progression of diminished muscular strength and potential onset of sarcopenia among patients exhibiting these specific attributes.

原著論文　112_A 74

以海博刀執行之內視鏡黏膜下剝離術治療早期食道腫瘤的臨床療效:南台灣單一醫學中心回溯性研究

Clinical outcomes of endoscopic submucosal dissection with Hybridknife® for early esophageal neoplasms: A single-center experience in South Taiwan

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Background

Endoscopic submucosal dissection (ESD) is accepted as the major treatment modality for early gastrointestinal neoplasm including the esophagus. It is an advanced and risky endoscopic procedure with highly technically demand. Hybridknife emerged as a new endoscopic knife with high pressure needle-free injection, which can decrease ESD procedure time. We aimed to analyze the clinical outcomes of ESD with Hybridknife for early esophageal neoplasms in our hospital, retrospectively.

Method

From January 2019 to June 2023, 126 patients with diagnosis of early esophageal neoplasms and received ESD procedure with Hybridknife are enrolled in this study. All patients underwent chromoendoscopy with narrow-band imaging and Lugol staining before ESD for peripheral margin detection. Endoscopic ultrasound or magnified endoscopy were also performed for invasive depth evaluation.

Results

A total of 163 lesions in 126 patients were enrolled. There were 4 patients with loss follow-up and 8 patients haven't received surveillance endoscopy yet. 114 patients were men (90%). The mean age was 57.93±7.82 years. The mean size of tumors was 12.89±8.70 cm2. En bloc resection rate was 98.8%. R0 resection rate was 84.7%. The mean operation time was 47.07±34.27 minutes. Average ESD speed, defined as tumor size(cm2) divided by operation time(mins), was 0.314±0.167. There were 104 lesions of esophageal squamous cell carcinoma(ESCC), 1 lesion of adenocarcinoma of esophagus, 33 lesions of high grade dysplasia(HGD), 21 lesions of low grade dysplasia(LGD), respectively. There were 52 ESD-related delayed complications, including 45 with post-ESD stricture, 6 with post ESD wound bleeding and 1 immediate ESD-related complication with intra-procedure perforation. 9 patients received additional esophagectomy due to submucosal invasion of esophageal neoplasms. During a mean of 7.37 months of follow-up, there were 2 local recurrence, and 16 metachronous recurrence (9.8%) were noted. There was no procedure-related mortality. Tumor size and circumference of the lumen were associated with longer procedure time. Otherwise, tumor size greater than 10 cm2 and circumference of the lumen greater than 75% were associated with post-ESD stricture.

Conclusion

ESD with Hybridknife is an effective and relatively safe treatment for early esophageal neoplasms. Larger tumor size and circumference of the lumen were associated with longer procedure time and should be aware of post-ESD stricture.

原著論文　112_A 75

合併使用急性腎損傷的尿液及血中肌酸酐診斷標準可改善預測重症患者的腎臟病預後

Combination of Urine Output and Serum Creatinine Criteria for Acute Kidney Injury may improve Prediction of Renal Outcomes in Patients with Critical Illnesses

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Background

Acute kidney injury (AKI) is a common complication which can lead to short and long-term morbidity and mortality in patients with critical illnesses. The KDIGO classification of AKI is based on an acute increase in serum creatinine (SCr) level or decrease in urine output (UO< 0.5 ml/kg/hr for 6 hours). We modified the urine output criteria to 8 hours, which are more compatible with the practice of 8-hour shift in our intensive care units (ICU). We aim to investigate the roles of combining urine output and serum creatinine criteria in predicting the outcomes of critically ill patients.

Method

We collected the clinical data of patients admitted to our medical intensive care units (MICUs) from 1st September, 2022 to 30th September, 2022. Patients were excluded if they have end-stage renal disease, under maintenance renal replacement therapy, confirmed COVID-19 cases transferred from Surgical department for quarantine observation, or stay less than 48 hours. Urine output was recorded every 8 hours in our ICUs.

Results

Forty patients (24 male) were analyzed and their average age is 66 (±16) years old. ICU stay is 12.3 (±10.9) days and the hospital stay is 24.7 (±21.4) days. Twenty-one patients expired or discharged under critical condition. Six patients needed renal replacement therapy during ICU stay, none needed after discharge. Thirty patients had AKI_{UO} according to UO criteria: 28 patients with UO < 0.5 ml/kg/hr for 8 hours and 15 patients with UO < 0.5 ml/kg/hr for over 24 hours. Based on the SCr criteria, 22 patients had AKI_{Cr}. Compared to the non-AKI_{Cr} group, AKI_{Cr} group had significantly higher admission SOFA scores and SCr levels 30 days after ICU admission. Combining both the SCr and UO criteria, 20 patients fulfilled both criteria (AKI_{CrUO}), and the others fulfilled one or none of the two criteria (non-AKI_{CrUO}). Compared to the non-AKI_{CrUO} group, AKI_{CrUO} group had significantly higher SCr levels 30 and 90 days after ICU admission.

Conclusion

From this preliminary study, patients with AKI based on both serum creatinine and urine output criteria had significantly higher serum creatinine level at 30 days and 90 days after ICU admission, suggesting higher risk of progressing to acute and chronic kidney disease (AKD, CKD). Further confirmation is warranted in order to validate the importance of modified urine output criteria in AKI patients, potential integration into our daily clinical practices.

原著論文　112_A 76

糖尿病周邊神經病變風險因素：回顧性橫斷研究

Risk Factors of Diabetic Peripheral Neuropathy in Patients with Diabetes Mellitus: A Retrospective Cross-Sectional Study

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Introduction

Diabetic peripheral neuropathy (DPN) is a significant and widespread complication of diabetes, and it makes a significant public health challenge. DPN affects the peripheral nerves, particularly in the hands and feet, and can lead to symptoms such as tingling, numbness, pain, and weakness. It can also result in foot ulcers, infections, and even amputations. The impact of DPN is not only physical but also has social and economic consequences. Thus, identifying the risk factors of DPN and managing it at an early stage are crucial to reduce the burden of this condition on individuals, families, and healthcare systems.

Methods

This is a cross-sectional retrospective study. A total of 1672 participants living with diabetes mellitus (DM) who was attending metabolism clinics from 2016/05-2019/10 in Kaohsiung Chang Gung Memorial Hospital was included in this study. Quantitative sensory testing (QST), which offers a noninvasive and user-friendly approach to assess sensory neuropathy was used for test of presence of DPN. The QST-based neural test measured parameters of vibration perception threshold (VPT), cold perception threshold (CPT), and warming perception threshold (WPT). We defined the diagnosis of DPN as positive findings in CPT and WPT of lower limbs. Patient's characteristics, anthropometric parameters, laboratory data, use of medications and comorbidities were collected for analysis.

Results

A total of 1672 patients were included in the analysis, among which 297 individuals (17.8%) exhibited DPN. The patients displaying DPN were notably older (mean age 67.7 ± 9.1 vs. 61.8 ± 10.5 years, $p < 0.001$) and presented an extended duration of DM (mean duration 14.7 ± 9.1 vs. 11.9 ± 8.2 years, $p < 0.01$) in comparison to those without DPN. Furthermore, individuals with DPN exhibited reduced levels of total cholesterol (median 159.7 vs. 168.8 mg/dl, $p < 0.001$), high-density lipoprotein cholesterol (HDL-C) (median 46.6 vs. 49.1 mg/dl, $p = 0.003$), and low-density lipoprotein cholesterol (LDL-C) (median 85.6 vs. 92.8 mg/dl, $p < 0.001$) as contrasted with their counterparts lacking DPN. Notably, a higher proportion of individuals with DPN presented with hypertension (48.2% vs. 39.7%, $p = 0.007$). Multivariate analysis was conducted to discern the independent associations between DPN and various factors. The presence of DPN exhibited a positive correlation with male gender (Odds Ratio [OR]: 1.91, 95% Confidence Interval [CI]: 1.44-2.54, $p < 0.001$), age (OR: 1.07, 95% CI: 1.05-1.08, $p < 0.001$), and duration of DM (OR: 1.02, 95% CI: 1.00-1.03, $p = 0.014$). Additionally, the presence of DPN displayed a negative association with HDL-C (OR: 0.99, 95% CI: 0.974-0.998, $p = 0.019$) and LDL-C (OR: 0.99, 95% CI: 0.978-0.998, $p = 0.014$).

Conclusions

Male gender, older age, and longer duration of diabetes emerged as positive predictors of DPN, highlighting the interplay between demographic and disease-related variables. Furthermore, low levels of HDL-C and LDL-C were identified as negative contributors to the presence of DPN. These results collectively emphasize the multifactorial nature of DPN, implicating metabolic and clinical factors in its etiology. Enhanced awareness of these associations can inform targeted interventions aimed at mitigating the risk and impact of DPN in individuals with DM.

原著論文　112_A 77

毛地黃對於持續性心房顫動接受導管消融後使用抗心律不整藥仍然復發的病人回復竇性心律的效果

The Impact of Digoxin in Restoring Sinus Rhythm in Patients with Persistent Atrial Fibrillation Who Have Atrial Tachyarrhythmia Recurrence Despite Catheter Ablation and Antiarrhythmic Drugs Therapy

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Background

Early rhythm control is beneficial for clinical outcomes in patients with paroxysmal and persistent atrial fibrillation (AF). However, some patients, particularly those with persistent AF, experienced a high rate of recurrence of atrial tachyarrhythmia even after catheter ablation (CA) and the administration of antiarrhythmic drugs (AADs). The purpose of this investigation was to assess the efficacy of digoxin in restoring sinus rhythm (SR) in patients with recurrent atrial tachyarrhythmia following CA who were already taking AADs and rate-control medication.

Method

This retrospective cohort study included 8 patients presenting with recurrent AF or atrial tachycardia (AT), all of whom were treated with digoxin after failing to achieve SR restoration with at least one type of AAD and one type of rate-control medication following CA for persistent AF. These patients were divided into two distinct categories. Those who successfully converted to SR in response to digoxin therapy composed the 'digoxin-effective group,' while those who did not comprise the 'non-effective group.' The differences between the two groups in terms of baseline characteristics, comorbidities, medications, and echocardiographic parameters were evaluated.

Results

A total of 2 (25%) of the 8 patients were males, and the average age was 65 ± 6 years. The duration of AF or AT recurrence after CA was 30 (5.3-36) days. In 5 cases (62.5%), recurrent arrhythmias manifested as AF, whereas AT was observed in 37.5% of patients. Notably, 5 patients (62.5%) were categorized into the 'digoxin-effective group,' whereas 3 patients (37.5%) were assigned to the 'non-effective group.' The left atrial size was smaller in the digoxin-effective group than in the non-effective group (40.4 ± 3.1 vs. 47.3 ± 2.9 mm; P = 0.019). In terms of baseline characteristics, comorbidities, medication, CA-associated parameters, and other echocardiographic parameters, there were no discernible differences between the two groups. Within the digoxin-effective group, recurrent arrhythmias consisted of AT (60%) and AF (40%). The duration of SR recovery after digoxin use was 28 (17-175) days. No serious side effect was observed in both groups.

Conclusion

This study demonstrated that digoxin has promising results in restoring SR in patients with persistent AF who experienced recurrence of tachyarrhythmia after treatment with CA and AADs, particularly in patients with smaller left atrial size. Further research is required to assess the efficacy of digoxin in restoring SR in these patients and to determine the underlying mechanism.

原著論文　112_A 78

於住院當日檢測嗜中性球與淋巴球比例更優於 NT-proBNP 來預測無論何種原因造成收縮性心衰竭病患的一年預後

Checking neutrophil-to-lymphocyte ratio on admission is better than NT-proBNP for the prediction of one-year adverse clinical outcomes in systolic heart failure with either ischemic or nonischemic cardiomyopathy

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Background

Although N-terminal pro B-type natriuretic peptide (NT-proBNP) is an acute biomarker for evaluating severity of heart failure (HF), its role on the prediction of long-term adverse clinical outcomes remains inconclusive.

Objective: We intended to identify a useful easily available biomarker from laboratory test on admission to predict long-term clinical outcomes in patients with heart failure with reduced ejection fraction (HFrEF, defined as LVEF <40% on echocardiography).

Methods

This was a prospective single-center clinical trial conducted from January 2019 to August 2022. A total of 162 patients diagnosed with HFrEF receiving optimization of anti-HF medications were consecutively enrolled. All study subjects were regularly followed up for at least one year. All-cause mortality, hospitalization for heart failure (HHF), sepsis, and major adverse cardio-/cerebro-vascular events (MACCE: cardiovascular death, myocardial infarction, and stroke) were analyzed among HFrEF population. Aside from NT-proBNP, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and eosinophil-to-neutrophil (ENR), three indictors of acute/chronic inflammation, were tested for the correlation with aforementioned long-term adverse outcomes.

Results

Of these HFrEF patients with mean age of 56 years, 82% of them were male. The average LVEF was 28.7%. Sixty-nine percent of HFrEF were resulted from ischemic cardiomyopathy (ICM) and remaining 31% of HFrEF were belong to nonischemic dilated cardiomyopathy (DCM). By Pearson correlation analysis, NLR was significantly correlated with all one-year clinical outcomes, including death from any cause (r=0.449), HHF (r=0.160), sepsis (r=0.228) and MACCE (r=0.169)(all p-values <0.05). In particular, NLR was modestly related to long-term all-cause mortality (r=0.633, p<0.001) and MACCE (r=0.466, p<0.001) in DCM-related HFrEF. The level of NLR >4.0 could also be moderately predictive of long-term adverse outcomes in ICM-related HFrEF (p<0.05). On the contrary, for those patients with DCM-related HFrEF, neither NT-proBNP, PLR, nor ENR lost correlation with long-term adverse events. NT-proBNP could only be used to predict one-year death in the ICM group.

Conclusions

NLR, an easily available inflammatory index, has a great correlation with long-term clinical

outcomes in the both ICM-related and DCM-related HFrEF. Based on limited role of NT-proBNP on predicting HF outcomes in the DCM subgroup, we suggest calculating NLR on admission rather than only checking NT-proBNP before the etiology of HF is clarified.

原著論文　112_A 79

肌少症可以預測無法切除肝癌病人使用一線樂衛瑪的預後

Pre-Sacropenia predicts the outcome in patients with Unresectable Hepatocellular Carcinoma undergoing first line Lenvatinib

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Background
Muscle volume loss (Pre-sarcopenia) is linked to an unfavorable prognosis in individuals diagnosed with hepatocellular carcinoma (HCC). The psoas muscle index (PMI) serves as a straightforward and quick indicator for assessing muscle atrophy. It may potentially serve as a dependable predictor for HCC patients undergoing treatment. Hence, we conducted this study to elucidate the clinical importance of pre-sarcopenia in patients receiving lenvatinib as first-line treatment for unresectable HCC in real world.

Method
We retrospectively evaluated patients with unresectable HCC who had undergone lenvatinib treatment between January 2018 and Dec 2021. Patients were excluded if they had previously received other systemic therapy or had become lost to follow-up during treatment. Pre-sarcopenia was diagnosed based on a previously reported cut-off value calculation formula [psoas muscle area at level of middle of third lumbar vertebra (cm2)/height (m)2]. Treatment response was assessed by radiologic imaging according to the Response Evaluation Criteria in Solid Tumors vesions 1.1. (RECIST1.1)

Results
A total of 171 patients (Male/Female: 124/47, mean age: 65.9 years) were recruited including 52 (30.4%) patients with pre-sarcopenia and 119 (69.6%) patients with non pre-sacropenia. The Kaplan-Meier estimate of overall survival (OS) and progression free survival (PFS) was 18.2 months and 6.5 months, respectively. The overall objective response rate (ORR) and disease control rate (DCR) was 18.4% and 70.7%, respectively. Pre-sarcopenia group had a significant poorer PFS (4.7 vs 6.8 months, p=0.026) and OS (7.6 vs 22.4 months, p<0.001) than Non pre-sacropenia group. Also, at the time of lenvatinib termination, higher percentage of patients without pre-sacropenia could maintain a better liver function reserve to afford sequential therapies than those with pre-sacropenia (58% vs 26.5%, p <0.001). Moreover, multivariate analysis showed pre-sarcopenia (Hazard Ratio: 2.025, 95% Confidence Interval (1.222–3.335); p = .006) was associated with mortality after adjusting post-treatment and alpha-fetoprotein.

Conclusion
In real world practice, pre-sarcopenia was shown to be a significant prognostic factor in patients treated with first-line lenvatinib for unresectable HCC.

原著論文　112_A 80

利用新的代謝性脂肪肝定義與命名法重新分析脂肪肝世代族群

Using the new definition and nomenclature of steatotic liver disease from Delphi consensus in the analysis of fatty liver disease cohort

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Background

The novel definition and nomenclature proposed from Delphi consensus introduced the comprehensive interpretation of steatotic liver disease (SLD). The new diagnostic and classification algorithm are more overarching for various etiologies of steatosis and pathophysiology. It is important to emphasize that the term nonalcoholic fatty liver disease (NAFLD), previously known as metabolic dysfunction-associated fatty liver disease (MAFLD), has been rebranded as metabolic dysfunction-associated steatotic liver disease (MASLD).

Objective

The aim of this study was to compare the different definition between NAFLD, MAFLD and MASLD applying in fatty liver disease cohort.

Materials and Methods

A total of 906 patients who were diagnosed with fatty liver disease by abdominal sonography at Chang Gung Hospital in Kaohsiung from July 2022 to September 2023 were enrolled. The patients' characteristics, comorbidities, social habit, and medications were retrieved from medical record. Biochemistry data was collected within one week of abdominal sonography.

Results

The average age of the 906 patients with fatty liver was 56 years. A total of 565 patients were defined as NAFLD and 770 patients as MAFLD by previous concept of fatty liver disease. A total of 894 (98.7%) patients in our cohort were classified into defined SLD group by the diagnostic criteria proposed from Delphi consensus. There were 711 (78.5%) patients defined as MASLD, 72 (7.9%) patients defined as MASLD with alcoholism (MetALD), 4 patients defined as Alcohol associated liver disease (ALD) and 107 (11.8%) patients defined as cryptogenic SLD. The patients of MetALD had highest FIB-4 index (1.73 ±0.18, $p<0.001$) and fatty liver index (47.7 ±4.1, $p<0.001$).

Conclusion

Using the new definition and diagnostic criteria of steatotic liver disease from Delphi consensus classified the most of patients in our cohort into specific SLD groups. It also emphasized the importance of alcoholism on the metabolic dysfunction associated liver disease, which had been shown with poor outcome in previous studies. More SLD patients will benefit from further clinical trials and studies by using the new definition and classification of steatotic liver disease in the future.

原著論文　112_A 81

慢性病患者他汀類藥物強化控制與非強化控制腸道微生物群特徵的比較分析

A Comparative Analysis of Gut Microbiota Profiles in Statin Intensive Control *vs.* Non-Intensive Control in Patients with Chronic Disease

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Background

G Several studies have shown that persons with hyperlipidemia have altered gut flora structure and function. However, limited research exists on the effects of statin therapy on the gut microbiome, and there is a lack of discussion regarding potential variations in the gut microbiome based on different low-density lipoprotein cholesterol (LDL-C) targets. Therefore, our study aims to investigate the changes and differences in the gut microbiome among patients with chronic diseases under different LDL-C target under statin treatment.

Methods

A total of 125 patients (77 males and 48 females) diagnosed with chronic diseases, specifically diabetes mellitus (87%), hypertension (74%), and chronic kidney disease (48%), were recruited for participation in this study. Fecal samples were collected from the participants to analyze the composition of the gut microbiota using Illumina sequencing of the 16S ribosomal ribonucleic acid gene.

Results

The patients were divided into 2 groups according to LDL-C level including 57 patients with intensive statin control group (LDL-C < 70 mg/dL), 68 patients with non-intensive statin control (LDL-C ≥ 70 mg/dL). There was no significant difference in microbial species diversity (Chao1 index and Shannon index), beta diversity and microbial dysbiosis index between 2 groups. However, A distinct microbial community structure was found in patients with intensive statin control group (LDL-C < 70 mg/dL), with a decreased abundance at genus level of the *Barnesiella, Coprococcus 1, Flavonifractor, Odoribacter* and *Coprobacter*.

Conclusion

In comparison to the non-intensive statin control group, the intensive statin control group with a lower LDL-C target did not exhibit significant differences in terms of alpha diversity, beta diversity, and microbial dysbiosis index. However, it was associated with a significant reduction in short-chain fatty acids producing bacteria, including taxa *Barnesiella, Coprococcus 1, Flavonifractor* and *Odoribacter*.

原著論文　112_A 82

空氣汙染為胰臟癌和膽管癌潛在危險因子

Air pollution as a potential a risk factor for pancreatic cancer and cholangiocarcinoma in Taiwanese patients

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Background and Aim

Air pollution is a risk factor for many cancers. However, the effect of air pollution on the risk of pancreatic cancer (PCA) and cholangiocarcinoma (CCA) in Taiwanese patients with remains unclear.

Methods

This cross-sectional study recruited 370 patients who were tested for serum hepatitis B surface antigen (HBsAg) and and hepatitis C virus (anti-HCV) in 2020. The diagnosis of PCA and CCA diagnosis was based on pathology. Daily estimates of air pollutants were aggregated into mean estimates for the previous year based on the date of recruitment or PCA and CCA diagnosis.

Results

Out of 370 patients, 16 patients had PCA (4.3%) and 18 patients had CCA (4.9%). The patients with PCA and CCA were older (73.4 years vs 50.9 years; P<0.001) and had higher levels of $PM_{2.5}$ (19.3 μg/m^3 vs 18.2 μg/m^3; P=0.03). Logistic regression analysis revealed that the factors associated with PCA and CCA were age (Odd ration [OR]: 1.09; confidence interval (CI): 1.06–1.13; P<0.001) and $PM_{2.5}$ (OR: 1.33; CI: 1.00–1.76; P=0.05). The best cut-off value for $PM_{2.5}$ level associated with HCC was 18.7 μg/m^3 (AUROC, 0.63; P=0.01). We defined high level of $PM_{2.5}$ as 20 μg/m^3. We put $PM_{2.5}$ > 20 μg/m^3 and age > 50 years as a covariant and logistic regression analysis revealed that the factors associated with PCA and CCA were age > 50 years (OR: 24.77; CI: 3.29-86.10; P=0.002) and $PM_{2.5}$ > 20 μg/m^3 (OR: 2.98; CI: 1.30–6.83; P=0.01)

Conclusions

In this study, we demonstrated that $PM_{2.5}$ were associated with PCA and CCA occurrence.

原著論文　112_A 83

對於急性肢體缺血使用 Rotarex 裝置進行機械性血栓抽吸治療：台灣單一醫學中心的 2 年追蹤

Percutaneous Mechanical Thrombectomy Using Rotarex Device in Acute Limb Ischemia : a 2-year follow up at single Taiwan medical center

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Background

Acute limb ischemia (ALI) is a medical emergency, occurs when there is a sudden halt of blood flow to the arm or leg, mostly owing to thrombosis or emboli. If left untreated, it can threaten the viability of the limb, followed by infection, necrosis, limb loss and ultimately, death[1].

Open surgical approaches have historically been used to address immediately threatened limbs. However, the development of rheolytic, mechanical, and aspiration thrombectomy techniques allows for rapid endovascular revascularization in more severe cases of ischemia[2]. Rotarex mechanical thrombectomy (RMT) is a useful treatment option that has a marked potential for reduced morbidity and mortality in comparison with studies of primary lytic or surgical treatment[3]. However, this equipment has just been introduced to Taiwan in recent years. To date, our peripheral endovascular team has successfully completed over 70 cases of RMT. In this research, we examined 47 RMT-treated patient performed at our hospital and assessed the amputation outcomes at 30-day, 1-year, and 2-year.

Methods

Study subjects

We conducted a retrospective study at Kaohsiung Medical University Hospital (KMUH) on patients with ALI who underwent RMT between January 2016 and July 2021. We excluded cases of Rutherford stage 3 and cases without 2- year follow-up. Finally, 47 cases were enrolled for analysis. We collected and analyzed the baseline data as Table 1included percentage of ALI involving lower extremities, and etiology of ALI (embolism or thrombosis). The research protocol was approved and registered by the ethics committee (KMUH IRB).

Outcomes evaluated in our study

The major outcomes evaluated in our study were major amputation, minor amputation, and all-cause mortality. We assessed the 30-day, 1-year, and 2-year major outcomes. Composite endpoints included major amputation, minor amputation, and all-cause mortality.

Results

Among the 47 RMT-treated cases, the average age was 69 ± 15 years, and the average time from clinical symptoms/signs to emergency room was 4.7 ± 4.3 days. One-year outcomes revealed 1 major amputations (2.1%), 2 minor amputations (4.3%), 4 all-cause deaths (8.5%), and 6 cases with composite endpoints (12.7%). Two-year outcomes revealed 1 major amputations (2.1%), 2 minor amputations (4.3%), 6 all-cause deaths (12.8%), and 7 cases with composite endopoints (14.9%). Table 1 shows the baseline characteristics of patients. Table 2 shows the 30-day, 1-year, and 2-year outcomes of major amputation, minor amputation, all-cause mortality, and composite endopoints. In our study, the 30-day

outcomes of major amputation, minor amputation, all-cause mortality and composite endopoints were 2.1%, 2.1%, 8.8% and 10.6%. And the 1-year outcomes were 2.1%, 4.3%, 8.5% and 12.7%. The 2-year outcome were 2.1%, 4.3%, 12.8% and 14.9%.

Table 1. Baseline Characteristics of patients

Baseline Characteristics	N = 47
Age (yr)	69 ± 15
Male gender (%)	68.1%
ALI duration (day)	4.7 ± 4.3
Rutherford stage	
Stage 1	21.3%
Stage 2a	27.7%
Stage 2b	51.1%
Diabetes (%)	36.2%
Hypertension (%)	61.7%
Dyslipidemia (%)	27.7%
CVD (%)	19.1%
CAD (%)	27.7%
CKD (%)	42.6%
Heart failure (%)	23.4%
Atrial fibrillation (%)	40.4%
Body mass index (kg/m^2)	25.2 ± 4.1
Lower extremities (%)	85.1%
Etiology	
Embolism	40.4%
Thrombosis	59.6%
Treatment Strategy	
Rotarex (RMT) + CDT	78.7%
Rotarex (RMT) only	21.3%

Table 2. 30 days, 1 year, and 2 year outcome of major amputation, minor amputation, all-cause mortality, and composite endopoint (EP)

Outcomes	30 days	1year	2 year
Major amputation	2.1%	2.1%	2.1%
Minor amputation	2.1%	4.3%	4.3%
All-cause mortality	8.5%	8.5%	12.8%
Composite EP	10.6%	12.7%	14.9%

Conclusion

Our research is the pioneering investigation into the application of RMT for ALI in Taiwan. We assessed the results at 30-day, 1-year, and 2-year intervals employing RMT and revealed its efficacy and safety in treating ALI, which reveal relatively good outcomes at 30 days, 1 year, and 2-year on major and minor amputation, along with the all-cause mortality. For limitation, our sample size was relative small, and further multi-center registries should be performed to have more detailed data of RMT in Taiwan.

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原著論文　112_A 84

經導管主動脈瓣置換（TAVR）術後心臟超音波之追蹤與臨床預後的性別差異

Sex Differences in Post-TAVR Echocardiographic Follow-up and Clinical Outcomes

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Background

TAVR with a self-expanding aortic bioprosthesis has been proven to be a well-established procedure for patients with severe aortic stenosis (AS), which has been performed in Kaohsiung Medical University Hospital (KMUH) since 2013.

Methods

This study investigated sex-related differences in clinical and hemodynamic outcomes of TAVR in the first 100 cases of KMUH that had been performed between December 2013 and December 2021. Data from these cases were retrospectively reviewed and analyzed. The baseline characteristics, procedural outcomes, mortality rates, and baseline and follow-up echocardiographic parameters were analyzed and compared between sexes.

Results

Among the 100 patients, male (46%) and female (54%) were of similar age (mean age, male 86.0 vs. female 84.5 years, p= 0.6405) and had the same severity of AS (mean pressure gradient, male 47.5 ± 16.0 mmHg vs. female 45.7 ± 19.2 mmHg, p= 0.0615) at the time of TAVR. Women had greater hypertension rate (90.7% vs. men 71.7%, p< 0.001), and smaller aortic valve areas calculated by continuity equation VTI (0.8 ± 0.3 cm2 vs. 0.7 ± 0.2 cm2, P< 0.001). In addition, women had better left ventricle ejection fraction (59.6 ± 14.0% vs. men 54.7 ± 17.2%, p< 0.01) before the procedure. In the post-TAVR follow-up, regression of left ventricle hypertrophy was better in women than in men. None of the patients died within 30 days after the procedure, and the overall mortality rate was 28% at a follow-up of over 8.3 year. Women tended to have a more favorable survival rate than men (all-cause mortality, women 22.2% vs. men 34.8%, p=0.6385).

Conclusion

Our study suggests that sex-related differences exist after TAVR based on echocardiologic parameters. Women had better LVEF and LVMI than men. The clinical outcome demonstrated that there were no differences but a favorable influence on the long-term survival of women. Collectively, TAVR is a reliable procedure, with exceptional outcomes in elderly patients with severe AS.

原著論文　112_A 85

登革熱感染時唾液酸含量減少對內皮細胞醣萼層潛在影響

Decreased serum sialic acid concentration in dengue viral infection and its possible impact in endothelial glycocalyx

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Background

Dengue fever is the most prevalent and important mosquito-borne disease. The hyperpermeability of endothelial glycocalyx layer (EGL) leading to plasma leakage is a major pathogenesis of severe dengue infection. Sialic acid (Sia) is one of the main components of EGL presenting as terminal residues of glycoproteins or glycolipids on the cell surface. Degradation of Sia related to increased permeability in dengue nonstructural protein 1 treated endothelial cells and association of serum Sia level with disease severity in murine model have been reported. This study aimed to investigate the altered Sia content in dengue infection.

Method

We enrolled dengue patients during 2014-2015 outbreak in southern Taiwan. Serum total sialic acid levels were measured in dengue patients (n=118) and health controls (n=30). The samples collected were divided into febrile phase (day 0-2), critical phase (day 3-5), and recovery phase (day >7) based on the day of symptoms onset. Human microvascular endothelial cell (HMEC-1) was infected with dengue virus serotype 2 (DENV2) at a multiplicity of infection of 5 for 24 hours, and total sialic acid on cells were stained by wheat germ agglutinin. Futher, in animal study, tissues of skin and intestine were obstained from AGB mices infected with DENV2. Immunohistochemical staining using Maackia amurensis lectin II and Sambucus nigra lectin were conducted to show the expression of α2,3-linked and α2,6-linked Sia.

Results

The total sialic acid level in dengue patients was significantly lower than health controls (p= 0.0129). The total sialic acid levels decreased by days, that were lowest during critical phase (p= 0.0006, compared with health controls), and restored on recovery phase. The expression of sialic acid on cell surface decreased in HMEC-1 infected with DENV2. Meanwhile, the sialic acid synthesis site in the cytoplasm became fragmented and the density reduced after dengue infection. Reduced and dispersed patterns of total sialic acid and α2,6-linked Sia were observed in the intestine of mice with dengue infection, and these patterns were restored in mice treated with IM7 (anti-CD44 antibody).

Conclusion

Taken together, our findings suggest that the decrease of sialic acid in dengue patients as well as endothelial cell and murine model. The synthesis of sialic acid may be affected during dengue infection. Considering the important role of sialic acid in human physiology and

maintenance of EGL integrity, further studies on altered sialylation during dengue infection and potential derived treatment for dengue were required.

原著論文　112_A 86

高齡對食道鱗狀細胞癌患者存活的影響

Impact of old age on survival in patients with esophageal squamous cell carcinoma

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Background

Esophageal squamous cell carcinoma (ESCC) predominantly occurs in middle-aged and elderly people. Chemoradiotherapy (CRT) and esophagectomy are the mainstay treatment for ESCC. Numerous patients aged 65 or older are traditionally excluded from clinical trials and receive sub-standard treatment, considering the increased comorbidities associated with age. Management of the elderly became therapeutically challenging. The aim of this study was to investigate the prognosis in elderly patients with ESCC.

Methods

A retrospective study of 474 patients with pathologically confirmed ESCC in the divisions of Gastroenterology at Kaohsiung Medical University Hospital between 2011 and 2022 was conducted. Patients were divided into 3 age groups (<50, 50–65, and >65 years). We analyzed the association of age groups with clinicopathologic factors and 2 quality of life questionnaires of the European Organization for Research and Treatment of Cancer (EORTC). The impact of the factors on overall survival and progression-free survival were analyzed using the IBM SPSS Statistics 25.

Results

Among the 474 cases, 110 (23.2%) were older than 65 years old. Compared with other two groups, group >65 years was exposed to less risk factors including alcohol, smoking and betel nuts use (p<0.001) and has no different Eastern Cooperative Oncology Group (ECOG) (p=0.46) or quality of life status (p=0.41 and 0.23, respectively), however, receiving less standard treatment (82.4% vs. 90% vs. 80%; p=0.02, respectively). There was no significant difference in overall survival (p=0.32) and progression-free survival rate (p=0.08) between the 3 age groups.

Conclusion

Chronological age was not predictive of poorer outcomes in patients with ESCC.

原著論文　112_A 87

分析接受同步化學放射治療的食道鱗狀細胞癌患者身體組成在電腦斷層 T12 與 L3 的相關性

The correlation of body components at T12 and L3 levels of computed tomography in esophageal squamous cell carcinoma patients undergoing chemoradiotherapy

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Background

Esophageal cancer is the eighth most common cancer worldwide. In Taiwan, esophageal squamous cell carcinoma (ESCC) has increased substantially during the past three decades. Sarcopenia and malnutrition are associated with the prognosis in patients with ESCC after radiotherapy or chemoradiotherapy. The CT (computed tomography) scan can evaluate different parameters of body compositions to represent the clinical indexes of sarcopenia and these parameters can help clinical doctors conveniently evaluate the condition of patients before and after chemoradiotherapy. Traditional chest CT protocol does not cover L3 which is the standard level used to calculate body composition. We used ESCC patients with chest CT covering the low neck to L3 to calculate the correlation between muscle thickness and fat component at T12 and L3 levels.

Method

Patients ≥20 years old with pathologically confirmed ESCC were enrolled between March 2017 and December 2021. A patients underwent computed tomography of the chest before and 4-6 weeks after the completion of chemoradiotherapy were recruited. The sarcopenia and nutrition-related parameters, including skeletal muscle index (SMI), skeletal muscle radiodensity (SMA), intramuscular adipose tissue content (IMAC), and visceral-to-subcutaneous adipose tissue area ratio (VSR) were measured at the level of T12 and L3 to examine for their correlation and the association with treatment response and patients' outcome.

Results

In total, 78 patients (99 person-times) with complete computed tomography of the chest covering the levels of T12 and L3 were analyzed. The median age at diagnosis was 59 years and 96.15% of patients in this study were male. 82.05% of patients had stage III-IV diseases and 80.77% of them had the Eastern Cooperative Oncology Group (ECOG) performance status grade 1. We found a moderate correlation between the body components (muscle mass and fat component) at the L3 and T12 levels. The Pearson correlations and p values were 0.63 and <0.01 for SMI, 0.46 and <0.01 for SMA, 0.48, <0.01 for VSR and 0.13, 0.19 for IMAC.

Conclusion

Our study suggested we can estimate the SMI, SMA, and VSR at L3 by CT images from T12, which will be used to calculate clinical indexes of sarcopenia. Such measurement will be helpful in ESCC patients who underwent chest CT, not always covering the L3 level.

原著論文　112_A 88

南臺灣某醫學中心新診斷合併易酮病型糖尿病的臨床特徵

Clinical Characteristics of Newly-Diagnosed and Ketosis-Prone Diabetes in a Medical Center in Southern Taiwan

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Background

Diabetic ketoacidosis (DKA) is a multifaceted metabolic condition defined by hyperglycemia, ketonemia and metabolic acidosis, which is traditionally thought to be the typical presentation at the onset of type1 diabetes. Growing incidence of DKA in newly-diagnosed type 2 diabetes was reported worldwide, which prompted the naming of the atypical diabetes as ketosis-prone diabetes (KPD). At current, the Aβ classification, distinguishing KPD into four subgroups based on the presence/absence of autoantibodies and β cell function measured by fasting C-peptide level, is considered the most accurate method to predict treatment outcome. However, there were no literature reports regarding the epidemiology of KPD in Taiwan. Our study was conducted to analyze the clinical manifestation of KPD in southern Taiwan.

Method

A retrospective study was conducted to screen for newly-diagnosed adult diabetes patients discharged from the endocrinology and metabolism ward between January 2018 and December 2022 in a medical center of southern Taiwan. By reviewing the electronic medical records, newly-diagnosed diabetes were identified at first and then recruited if met all the inclusion criteria: 1.presented with ketoacidosis 2.underwent testing for glutamic acid decarboxylase (GAD) autoantibodies and fasting C-peptide. Then subjects were classified by the Aβ classification based on the presence/absence of GAD and fasting C-peptide at the cutoff of 1ng/ml. The anthropometric and biochemical data were collected at the onset of diabetes.

Results

Among the 158 newly-diagnosed diabetes identified from our retrospective study, 72 individuals without ketoacidosis and 54 subjects not undergoing tests for GAD and C-peptide were excluded. The remaining 32 patients were further classified into four groups of A-β+ (N=11), A+β- (N=12), A-β- (N=8), and A+β+ (N=1). Of the four groups, the A-β+ had significantly higher weight and body mass index (BMI) and the A+β- exhibited significantly higher HbA1c along with more severe ketonemia. Borderline-significantly higher microalbuminuria was also observed in the A-β+ group. In addition, the A-β- shared similar characteristics as the A-β+ including higher weight, BMI, and proportions with comorbidity of hypertension and less severe ketonemia. There were no significant differences in terms of age, lipid profile, renal function, or length of hospitalization among the four groups of KPD.

Conclusion

This was the first study in Taiwan to highlight the heterogeneity within KPD patients. As the Aβ classification is currently the most reliable method to predict long-term clinical outcomes

including β-cell function, the baseline characteristics identified in our study may help clinicians to decide the necessity of maintaining insulinization when encountering newly-diagnosed diabetes with KPD. Further study about the serial follow-up of our subjects will be conducted to elucidate the predictability by Aβ classification of KPD patients in Taiwan.

原著論文　112_A 89

白血球數與血清鐵蛋白量與台灣血液透析患者全因性和心血管死亡相關：2615 名患者追蹤 10 年的世代研究

Leukocyte Count and Ferritin Levels Were Associated with All-Cause and Cardiovascular Mortality in Hemodialysis Recipients: A Cohort Study of 2615 Patients for 10 Years in Taiwan

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Background

Taiwan had the highest incidence and prevalence of end stage renal disease (ESRD) in the world as the 2022 annual report of the United States Renal Database System. The patients with chronic kidney disease (CKD) revealed an 83% higher all-cause mortality and 100% higher cardiovascular diseases compared with general population. Protein energy wasting (PEW) is prevalent among individuals with CKD and exhibits a robust association with unfavorable clinical outcomes, particularly among those undergoing dialysis. Abundant evidence demonstrated that systemic inflammation is the major predictor of cardiovascular and all-cause mortality in the ESRD population. However, previous studies showed inconclusive results for the association between white blood cell (WBC) count and ferritin with mortality in the ESRD population. Therefore, this investigation aims to assess the hypothesis whether high ferritin and WBC count are associated with all-cause and cardiovascular mortality within the ESRD population undergoing hemodialysis.

Methods

We conducted a cohort study including 2615 incident patients of hemodialysis to investigate the association between WBC count and ferritin with all-cause and cardiovascular mortality. Of these patients, 50.4% were woman, 17.0% had cardiovascular disease, 70.6% had hypertension, 48.7% had DM, and 13.7% had hepatitis. The mean age of dialysis is 59.1 ± 14.5 years, mean weight before dialysis is 58.9 ± 12 Kg and mean WBC was 7.0 ± 2.3 (x1000/μl). The participants were further stratified in high and low albumin groups (cutoff for albumin is 3.78 [g/dL]). The model was adjusted for female, age at dialysis, entry year, hepatitis, heart failure, body weight before dialysis, ultrafiltration – body weight ratio, Kt/V (Daugirdas), normalized protein catabolic rate, hemoglobin, albumin, cholesterol log, glucose, total Calcium and phosphorus.

Results

In the fully adjusted Cox regression model, a positive association between WBC count with all-cause mortality was found: WBC Q5 (HR: 1.33 [1.09-1.61]); meanwhile, a U-shaped association between ferritin with all-cause mortality was noticed: ferritin Q2 (HR: 1.27 [1.03-1.56]) and Q5 (HR: 1.42 [1.18-1.73]). WBC count and ferritin were not associated with cardiovascular mortality. After stratification by albumin, high WBC count and ferritin were still associated with all-cause mortality: WBC Q5 (HR: 1.40 [1.15-1.70]) and ferritin Q5 (1.27 [1.05-1.53]). Interestingly, a positive association between WBC with cardiovascular mortality was noticed after stratification by albumin: WBC Q3 (HR: 1.36 [1.01-1.83]) and WBC Q5 (HR: 1.27 [1.05-1.53]). Ferritin was not associated with cardiovascular mortality after

stratification.

Conclusion

We concluded that a positive association between WBC count and all-cause mortality, and a U-shaped association between ferritin and all-cause mortality. Only after stratification by albumin, high WBC count was associated with cardiovascular mortality.

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南臺灣某醫學中心新診斷合併易酮病型糖尿病最終治療不需依賴胰島素的相關因素

Factors Associated with the Treatment Outcome of Insulin Independence in Newly-Diagnosed and Ketosis-Prone Diabetes in a Medical Center in Southern Taiwan

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Background

Unlike the traditional concept of diabetic ketoacidosis (DKA) occurring at the onset of classical type 1 diabetes, ketosis-prone diabetes (KPD) represents a complex subtype of diabetes with overlapping characteristics of both type 1 and type 2 diabetes. The Aβ classification has been proposed to distinguish four subgroups of KPD based on the presence/absence of glutamic acid decarboxylase (GAD) antibodies and fasting C-peptide levels, recognized as a strong predictor to assess insulin discontinuation. Increasing prevalence of KPD has been observed worldwide. Besides the exploration on the risks for DKA occurrence and the factors associated with subsequent insulin discontinuation, there were no reported literature regarding the epidemiology and long-term treatment outcomes of KPD in Taiwan. Our study aimed to compare KPD patients by Aβ classification, and to investigate clinical parameters related to long-term treatment needs with insulin or oral antidiabetic agents.

Method

By reviewing the electronic medical records, a retrospective study was conducted to screen for newly diagnosed adult diabetes patients discharged from the endocrinology and metabolism ward between January 2018 and December 2022 in a medical center of southern Taiwan. First, newly-diagnosed diabetes were identified. Second, subjects were excluded if no ketoacidosis at the onset of diabetes. Third, patients who did not undergo testing for glutamic acid decarboxylase (GAD) autoantibodies or fasting C-peptide were further excluded. Finally, patients who did not follow up in the outpatient department were also excluded. Then we classified the remaining KPD patients by the Aβ classification. The anthropometric and biochemical data were collected at the onset of diabetes and the treatment modality of insulin/oral antidiabetic agents (OAD) at the last outpatient follow-up as of Aug 31, 2023 were recorded. We then classified subjects into 3 groups according to the final treatment modality of (1) insulin, (2) insulin plus OAD, and (3) OAD for analysis.

Results

Among the 158 newly-diagnosed diabetes identified by reviewing medical records, 72 individuals without ketoacidosis, 54 subjects not undergoing tests for GAD and C-peptide, and 4 patients not return to the outpatient department after discharge were excluded. The remaining 28 patients were further classified into four groups of A-β+ (N=7), A+β- (N=12), A-β- (N=8), and A+β+ (N=1). Specifically, there were totally six patients (2 in the A-β+ group and 4 in the A-β- group) who did not require insulin for glycemic control throughout the follow-up period. Notably, the A-β+ group exhibited an earlier average time to insulin independence compared to other groups. For the three groups with different treatment

modality, there were statistically significant differences in three key aspects including lower body weight in insulin group, lower GAD values in OAD group, and higher presence of hypertension in OAD group.

Conclusion

Our study is the first in Taiwan to analyze the treatment outcome of KPD patients by Aβ classification. The results demonstrated that patients classified as GAD-negative had a higher likelihood of achieving insulin independence. Furthermore, certain baseline factors such as body weight, GAD values, and the presence of hypertension may serve as potential predictors for this outcome. However, it is essential to acknowledge the limitations of this study, primarily the small sample size, which may limit the generalizability of these findings. Further research with a larger and more diverse cohort is necessary to validate and expand upon these preliminary observations.

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血液透析病人的大腦白質負荷與認知功能有關

Cerebral white matter burden is linked to cognitive function in patients undergoing hemodialysis

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Background

Chronic kidney disease is related to neurodegeneration and structural changes in the brain, which might lead to cognitive decline. The Fazekas scale for assessing white matter hyperintensities (WMHs) was associated with poor cognitive performance. Therefore, this study investigated the associations between the mini-mental status examination (MMSE), Montreal cognitive assessment (MoCA), cognitive abilities screening instrument (CASI), and Fazekas scale in patients under hemodialysis (HD).

Method

The periventricular (PV) WMHs and deep WMHs (DWMHs) in brain magnetic resonance images of 59 patients under dialysis were graded using the Fazekas scale. Three cognition function tests were also performed, and then multivariable ordinal regression and logistic regression were used to identify the associations between cognitive performance and the Fazekas scale.

Results

There were inverse associations between the three cognitive function tests across the Fazekas scale of PVWMHs ($p = 0.037$, 0.006, and 0.008 for MMSE, MoCA, and CASI, respectively), but the associations were attenuated in the DWMHs group. In CASI, significant differences were identified in short-term memory, mental manipulation, abstract thinking, language, spatial construction, and name fluency in the PVWMHs group. However, DWMHs were only significantly correlated with abstract thinking and short-term memory.

Conclusion

An inverse correlation existed between the Fazekas scale, predominantly in PVWMHs, and cognition in patients with HD. The PVWMHs were associated with cognitive performance assessed by MMSE, MoCA, and CASI, as well as with subdomains of CASI such as memory, language, and name fluency in patients with HD.