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### 左心房應變於射出分率輕度減低心臟衰竭患者作為潛在臨床預後指標相關性研究

Potential Clinical and Prognostic Relevance of Left Atrial Strain in Patients with Heart Failure with Mildly Reduced Ejection Fraction (HFmrEF)

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### Background

Heart failure with mildly reduced ejection fraction(HFmrEF) shares characteristics with both HF with reduced EF(HFrEF) and HF with preserved EF(HFpEF). Identifying patients at risk of adverse outcomes is crucial for early and intensive treatment. Left atrial reservoir strain (LASr) has been shown to predict outcomes in HFrEF and HFpEF, but its impact on HFmrEF is less understood. This study explores the clinical value of LASr in predicting adverse cardiac events in HFmrEF patients.

#### Methods

The study included 1,075 patients with HFmrEF from two tertiary hospitals in Taiwan, collected between 2014 and 2021. Baseline echocardiography was reviewed, and key measures included left ventricular ejection fraction(LVEF), LV global longitudinal strain(LVGLS, described using absolute values) and LASr. LASr was derived from apical two- and four-chamber views. The primary endpoint was a composite of heart failure rehospitalization(hHF) and cardiovascular death(CVD). Secondary endpoints were all-cause death(ACD) or hHF. Follow-up duration spanned from enrollment to death, hHF, or the last follow-up date.

#### Results

The cohort of 1,075 participants had a mean LVEF of  $45\pm2\%$ , LVGLS of  $12.3\pm2.7\%$ , and LASr of  $16.9\pm6.1\%$ . Patients were stratified by LASr 18%, a cutoff derived from spline curves. Those with LASr <18%(62% of participants) exhibited more symptoms, lower LVEF, larger LA volume index(LAVi), and lower LVGLS(all p $\leq$ 0.012). Over a median follow-up of 1.42(IQR: 0.40-3.57) years, 315 patients(29%) reached the primary endpoint. After adjusting for age, sex, comorbidity, symptoms, medications, LVEF, diastolic function parameters and LVGLS, multivariable models showed that lower LASr was independently associated with primary endpoints(Hazard Ratio 0.93, 95% CI: 0.91-0.96, p<0.0001). Similar associations were found for the secondary endpoint of ACD or hFH, with LASr consistently showing prognostic value (p<0.0001).

#### Conclusion

In this large Asian cohort, lower LASr was associated with higher incidences of primary and secondary clinical endpoints, which likely indicate the pathophysiological significance of LA functional reserve among patients with HFmrEF. Our study results support using LASr for clinical risk stratification to facilitate early intervention for high-risk patients with HFmrEF.

### 使用二維心臟超音波及心臟磁振造影探討多腔室心肌縱向應變與不良後果之關聯

Direct Comparison of Multi-chamber Longitudinal Strains for the Association with Adverse Outcomes Using Two-dimensional Echocardiography and Cardiac Magnetic Resonance

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## Background

Impaired myocardial strains are associated with poor outcomes in cardiovascular diseases. While some studies have analyzed the prognostic value of left ventricular (LV), left atrial (LA), and right ventricular (RV) longitudinal strains within the same population, not all of them have conducted head-to-head comparisons of strains across the three cardiac chambers. In addition, no prior studies have compared LV, LA, and RV strains derived simultaneously from two-dimensional speckle-tracking echocardiography (2D-STE) and cardiac magnetic resonance feature tracking (CMR-FT). This is the first study to determine which chamber strain provides the strongest prognostic utility and whether the results are consistent across 2D-STE and CMR-FT.

#### Methods

We conducted a retrospective and observational study in patients who had undergone clinically indicated CMR and agreed to undergo transthoracic echocardiography on the same day between 2014 and 2022. Exclusion criteria included patients under 20 years of age, repeated examinations, and poor image quality. LV global longitudinal strain (LVGLS), LA reservoir strain (LASr), and RV free-wall longitudinal strain (RVfwLS) were analyzed using fully-automated 2D-STE, manually-edited 2D-STE, and CMR-FT. The primary endpoint was major adverse cardiovascular events (MACE), including cardiac death, heart failure hospitalization, and sustained ventricular tachyarrhythmia.

#### Results

Our cohort consisted of 550 patients (mean age:  $65\pm15$ , 66% male, 10% classified as NYHA III or IV). The most prevalent indications for CMR were ischemic heart disease (n=183, 33%) and secondary cardiomyopathy (n=163, 30%), followed by dilated cardiomyopathy (n=49, 9%) and valvular heart diseases (n=48, 9%). Over a median follow-up of 2.2 (IQR:0.9-4.2) years, 78 patients (14.3%) experienced MACE. LVGLS, LASr, and RVfwLS were independently associated with MACE after adjustment for age, sex, NYHA class, and Charlson comorbidity index.

In Kaplan-Meier analyses, we stratified patients according to previously reported cutoffs. Patients with lower LVGLS, LASr, and RVfwLS experienced significantly higher rates of MACE (p<0.004 for all modalities) after adjustment for the abovementioned parameters. Direct comparisons among LVGLS, LASr, and RVfwLS suggested that only LASr was significantly associated with MACE using 2D-STE (fully-automated: hazard ratio [HR]=0.91, 95% confidence interval [CI]: 0.87-0.95, p<0.001; manually-edited: HR=0.91, 95% CI: 0.86-95, p<0.001) and CMR-FT (HR=0.91, 95% CI: 0.86-0.96,

p=0.001), with no evidence of collinearity (variance inflation factor<2.5 for all modalities). In nested Cox models, LASr provided significant incremental value for MACE on top of models incorporating clinical factors and LVGLS, whereas adding RVfwLS did not offer further improvement. When LASr was added first to the base model, further addition of LVGLS and RVfwLS provided no incremental value. Nomogram analyses further indicated that LASr was the most robust determinant for MACE compared to LVGLS and RVfwLS, with consistent results across both 2D-STE and CMR-FT.

### Conclusion

In this large cohort with various cardiovascular diseases, we demonstrated that LASr, rather than LVGLS or RVfwLS, had the strongest association with MACE. The comparison results were consistent across 2D-STE and CMR-FT, which suggested that LASr may play an important role in determining adverse cardiovascular events. Therefore, we recommend incorporating LASr into clinical guidelines alongside LVGLS and RVfwLS for improved risk stratification in various cardiovascular diseases.

#### 於急性腎臟病期投予 SGLT2 inhibitor 及其短期和長期副作用的趨勢

Trends of Sodium-glucose Cotransporter-2 Inhibitor Prescription, and Its Short- and Long-term Adverse Events in Patients with Acute Kidney Disease

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## Background

The 2024 KDIGO guidelines advocate the prescription of sodium-glucose cotransporter inhibitor (SGLT2i) in individuals with chronic kidney disease (CKD), given their benefits in alleviating CKD progression, acute kidney injury development and extensive cardiovascular outcomes. Nevertheless, current evidence for the administration of SGLT2i in patients with acute kidney disease (AKD) remains unsettled.

### Methods

This study was conducted using the TriNetX Research Network, which encompasses data from over 250 million patients globally. A total of 128,867,568 individuals were screened between January 1, 2013, and December 31, 2023. AKD was defined as the cessation of previously acute dialysis within three months after hospital discharge. In this intention-to-treat analysis, SGLT2i users were identified based on prescriptions issued during the AKD period.

#### Results

A total of 1,225,389 patients diagnosed with AKD were included in which 1.76% of patients (n=21,586) were recognized as SGLT2i users. 36% of the those were female with a mean age of 66.6 years (standard deviation [SD], 13.3). Comorbidity rates of cerebrovascular disease (37% vs 28%), essential hypertension (91% vs 70%), heart failure (73% vs 29%) and ischemic heart disease (73% vs 38%) and concurrent administration of aspirin (81% vs 52%), renin-angiotensin system acting agents (92% vs 50%), and metformin (55% vs 17%) were significantly higher in SGLT2i users. Incident rates of adverse events like volume depletion (p-value = 0.008), diabetic ketoacidosis (p-value = 0.002) and amputation of the lower limbs (p-value = 0.028) significantly decreased over the years.

#### Conclusion

Prescription of SGLT2i in patients with AKD had significantly risen from 2013 to 2023, regardless of diabetes mellitus, heart failure, proteinuria status or HbA1c level. Incidences of short- and long-term adverse events decreased in some with the raising awareness of fluid status monitoring during prescription while others remained stable through the observation period.

使用鈉-葡萄糖協同轉運蛋白 2 抑制劑治療的糖尿病患者,初始腎絲球過濾率與蛋白尿的變化對心血管及腎臟不良效應之風險影響

Impact of the initial change in the estimated glomerular filtration rate and albuminuria on the risk of adverse cardiovascular and renal outcomes in people with diabetes treated with sodium–glucose cotransporter 2 inhibitors

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## Background

The interplay between initial changes in estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (UACR) changes, and whether early change in eGFR and UACR independently associated with risks of clinical outcomes among people with type 2 diabetes mellitus (T2D) receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, remained unclear.

#### Methods

Utilizing a large multi-center medical database in Taiwan, we retrospectively analyzed 8,222 individuals with newly diagnosed T2D with baseline and 3-month follow-up eGFR and UACR measurements available receiving SGLT2 inhibitor between June 1, 2016, and December 31, 2021. We assessed the risks of major adverse renal events (MARE), major adverse cardiovascular events (MACE), hospitalization for heart failure (HHF), and all-cause mortality using a Cox proportional hazards model, adjusting for relevant covariates.

#### Results

After initiating SGLT2 inhibitor 3 months shortly, patients were categorized into subgroups accordingly to various early changes in follow-up eGFR (no initial eGFR decline, eGFR decline 0-10%, and eGFR decline >10%) and UACR (no initial UACR reduction, UACR reduction 0-30%, and UACR reduction >30%). Among participants with no initial eGFR decline, a higher proportion experienced no initial UACR reduction compared to those with modest UACR reduction (0-30%) or UACR reduction >30%. Conversely, among those with an initial eGFR decline >10%, a greater proportion experienced an initial UACR reduction >30% compared to those with modest UACR reduction (0-30%) or no UACR reduction. Compared to patients with a modest early eGFR decline (0-10%) and UACR reduction (0-30%), those with an initial eGFR decline >10% but no UACR reduction were linked to higher risks of MARE (hazard ratio (HR):2.34;[95% confidence interval (CI):1.32–4.15]), MACE (HR:1.83;[95%CI:1.01–3.29]), and HHF/CV death (HR:1.93;[95% CI:1.05–3.55]).

#### Conclusion

Patients with profound early eGFR decline but no concordant UACR reduction receiving SGLT2 inhibitor represent a high-risk subgroup associated with worse clinical outcomes, requiring closer monitoring and potentially more aggressive therapeutic strategies.

### 轉移性胰臟癌病患使用第三線治療的臨床效益及毒性分析

The efficacy and safety profile of third line treatment in patients with metastatic pancreatic adenocarcinoma

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## Background

For metastatic pancreatic ductal adenocarcinoma (mPDAC), the median survival time of standard first-line and second-line chemotherapy is shorter than a year. Additionally, there are no established third-line chemotherapy options after initial treatment failure. Our study aimed to assess the effectiveness and safety of third-line chemotherapy in mPDAC patients who have failed prior treatment, comparing their response with those who have not received third-line chemotherapy across five Taiwanese medical centers.

#### Methods

The study retrospectively analyzed 363 mPDAC patients treated at five Taiwanese medical centers from 2018 to 2022. All patients had confirmed diagnoses pathologically or cytologically and had undergone first-line based on gemcitabine. The analysis included patients who either received or did not receive third-line chemotherapy after failing to second-line nal-IRI + 5FU/LV chemotherapy, with a focus on assessing efficacy and toxicity.

#### Results

We identified 363 mPDAC patients who underwent first-line chemotherapy with gemcitabine. Among them, 257 patients proceeded to receive second-line chemotherapy, while 77 (21.2%) underwent third-line chemotherapy. The median age of all patients was 64 years (27-86), with a median ECOG performance status of 1 (0–3). Patients who received third-line treatment had a median survival time of 4.5 months (95% CI, 3.6–5.4), whereas those who did not receive third-line treatment had a median survival time of 1.6 months (95% CI, 1.3–1.9). We identified three prognostic factors associated with poor overall survival: absence of previous pancreatectomy (HR 3.10, P=0.001), presence of liver metastases (HR=2.76, P=0.01), and an ECOG performance score of 2 or higher (HR 5.05, P<0.001). The median overall survival times for patients with none, one, two, and three of these factors were 15.9 months (95% CI, 12.3-19.6), 7.0 months (95% CI, 2.6-13.3), 4.4 months (95% CI, 3.5-5.2), and 2.0 months (95% CI, 1.7-2.2), respectively. Forty-three patients experienced at least one grade 3 or 4 toxicity. The most common toxicities were neutropenia (18%), anemia (16%), non-neutropenic fever (13%), fatigue (12%), and diarrhea (12%).

#### Conclusion

Our study demonstrated that consecutive third-line chemotherapy is appropriate for selected patients with mPDAC. Further research is needed to refine third-line chemotherapy regimens and patient selection criteria.

## 台灣東北部社區醫學世代研究 (NTCMRC)中社區健康教育對肝功能之長期影響

Long-term Impact of Community Health Education on Liver Function: Insights from the Northeastern Taiwan Community Medicine Research Cohort (NTCMRC)

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## Background

Since 2013, the Northeastern Taiwan Community Medicine Research Cohort (NTCMRC) has been enrolling participants to investigate the impact of community health education over time. In this study, we aim to evaluate the effectiveness of community health education by measuring liver function at five distinct time points. Our goal is to assess the trends in liver function changes and identify the risk factors associated with these changes as a result of community screening efforts.

#### Methods

The research data were obtained from community health activities organized by the Chang Gung Community Research Center. We retrospectively included participants from the Wanli, Ruifang, Gongliao, and Anle districts in northern Taiwan. All participants underwent physical and laboratory examinations, and completed a questionnaire assessing their demographic characteristics and lifestyle habits. To account for the correlation between repeated measurements, we utilized a Generalized Estimating Equations (GEE) model with an exchangeable correlation matrix. Continuous variables were reported as mean  $\pm$  standard deviation, and categorical variables as n (%). For comparisons of continuous data, Student's t-test was used, while categorical data were compared using the Chi-square test (X²). Statistical analyses were performed using Stata (version 15.0; StataCorp), with all tests being two-tailed and a P-value of <0.05 considered statistically significant.

#### Results

A total of 3,399 participants were recruited. The demographic and clinical characteristics of individuals with normal and abnormal baseline AST and ALT levels were analyzed. Subjects with abnormal AST or ALT levels at baseline exhibited higher rates of diabetes, metabolic syndrome, central obesity, HOMA-IR, elevated uric acid, and poorer lipid profiles. No significant differences were observed in renal function or alcohol consumption. Over time, subjects with abnormal baseline AST levels showed progressive improvement after receiving long-term community health education, while those with normal baseline AST levels maintained their values within the normal range. This pattern was consistent across untreated and treated patients with chronic HBV or HCV infection. Similarly, participants with abnormal baseline ALT levels demonstrated gradual improvement following ongoing health education, while those with normal ALT levels maintained stable values. This trend was also observed across different subgroups of patients with chronic HBV or HCV infection.

### Conclusion

In this long-term follow-up study within the NTCMRC cohort, individuals with abnormal AST or ALT levels at baseline showed significant improvement following long-term community health education interventions, regardless of their chronic HBV or HCV infection status. Additionally, participants with normal baseline AST or ALT levels were able to maintain their normal values. These findings suggest that long-term community health education is an effective strategy for improving liver function in the community.

急性膽管炎後預防性膽囊切除對長期預後之影響:一個台灣全國性之世代研究

Evaluating the Long-term Outcomes of Preventive Cholecystectomy in Patients with Acute Cholangitis: A Nationwide Cohort Study In Taiwan

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## Background

Acute cholangitis (AC), a life-threatening infection resulting from biliary obstruction, often requires urgent medical treatment, including biliary drainage and antibiotics, to prevent severe complications such as sepsis. Cholecystectomy is commonly recommended as a preventive measure to reduce the risk of recurrent biliary infections, particularly in patients with gallstones. While short-term outcomes have been well-documented, data on the long-term impact of cholecystectomy, particularly regarding survival, recurrence, and biliary complications, remain limited. This retrospective cohort study aims to address these gaps by analyzing data from the Taiwanese National Health Insurance Research Database.

#### Methods

From January 2000 to December 2013, a total of 6,532 patients with AC who underwent preventive cholecystectomy were enrolled as the study group. In contrast, 11,529 AC patients who did not undergo preventive cholecystectomy were selected as the control group. To account for potential confounding factors, such as age and sex, propensity score matching was used to balance baseline characteristics and assess long-term outcomes.

#### Results

Of the patients included in the control group, the cumulative incidences of biliary infections at 1, 3, 5, and 10 years were 4.1%, 13.3%, 25.4%, and 61%, respectively. Statistical analyses using univariate and following multivariate approaches identified older age (P<0.001), peptic ulcer disease (P=0.002), and moderate to severe liver disease (P<0.001) as significant risk factors. After 1:1 propensity score matching for age and sex, the cumulative incidences of biliary infections at 1, 3, 5, and 10 years were slightly reduced to 3.3%, 12.3%, 23.7%, and 59.5%, respectively, with the same significant risk factors: older age (P<0.001), peptic ulcer disease (P=0.043), and moderate to severe liver disease (P<0.001). When comparing overall survival between both groups, the control group showed significantly higher mortality rates (P<0.001) than the study group. This difference remained significant after propensity score matching (P<0.001). In the control group, predictors of overall mortality included male gender, older age, myocardial infarction, congestive heart failure, cerebrovascular disease, moderate to severe liver disease, hemiplegia or paraplegia, and renal disease. Similarly, in the study group, predictors of overall mortality included male gender, older age, congestive heart failure, cerebrovascular disease, dementia, mild to severe liver disease, diabetes with chronic complications, hemiplegia or paraplegia, and renal disease.

## Conclusion

This retrospective cohort study demonstrates that preventive cholecystectomy significantly reduces the incidence of biliary infections and improves overall survival in patients with acute cholangitis compared to those who do not undergo the procedure. Even after adjusting for age and sex using propensity score matching, patients who did not undergo preventive cholecystectomy had higher rates of biliary infections and mortality. The analysis identified older age, male gender, and comorbid conditions, such as congestive heart failure and liver disease, as key predictors of mortality. These findings suggest that preventive cholecystectomy is an effective strategy for improving long-term outcomes in patients with acute cholangitis.

### COVID-19 疫情期間台灣前五大癌症發生率趨勢之變化

Shifts in Cancer Incidence Trends during the COVID-19 Pandemic in Taiwan: Insights from the Top 5 Cancer Types

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## Background

The COVID-19 pandemic has significantly disrupted healthcare systems globally, including cancer screening, diagnosis, and treatment. These disruptions may have affected cancer incidence rates, particularly for cancers with established screening programs. However, the full impact of the pandemic on cancer detection remains unclear. Understanding these trends is critical for public health planning and mitigation strategies.

#### Aim

This study aims to evaluate the impact of the COVID-19 pandemic on cancer incidence trends in Taiwan, specifically examining changes in incidence rates for breast, lung, colorectal, prostate, and liver cancers. The study seeks to determine whether disruptions caused by the pandemic affected long-standing cancer trends, particularly for cancers with established screening programs.

#### Methods

We analyzed annual cancer incidence rates from the Taiwan Cancer Registry Database for the five most common cancer types—breast, lung, colorectal, prostate, and liver—spanning from 2000 to 2021. Incidence rates were age-standardized using the World Health Organization (WHO) 2000 standard population and reported per 100,000 individuals. The average annual percentage changes (AAPCs) were calculated to compare the pre-pandemic period (2000–2018) with the pandemic period (2019–2021). Welch's t-test was used to assess the statistical significance of the differences in AAPCs between these two periods, with a significance level of p < 0.05.

#### Results

Significant decreases in AAPCs were observed for breast cancer (3.91% vs 0.36%, p < 0.05), colorectal cancer (1.46% vs -6.26%, p < 0.05), and liver cancer (-1.62% vs -6.07%, p < 0.05) between the pre-pandemic and pandemic periods. The largest decline was in colorectal cancer (7.72% difference), followed by liver cancer (4.45%) and breast cancer (3.55%).

Lung and prostate cancer also showed decreases in AAPCs, though these were not statistically significant (lung cancer: 1.54% vs -1.23%, p = 0.3; prostate cancer: 4.01% vs -1.50%, p = 0.13).

#### Discussion

The significant declines in breast, colorectal, and liver cancer incidence suggest that the pandemic disrupted established cancer screening programs. Organized screenings, such as mammography for breast cancer, fecal immunochemical tests for colorectal cancer, and regular monitoring for

high-risk liver cancer patients, were likely interrupted, leading to fewer diagnoses during the pandemic.

In contrast, the non-significant decreases observed for lung and prostate cancers, which do not have widespread screening programs in Taiwan, suggest that these trends were less impacted by screening interruptions. Instead, the decreases might reflect other factors such as healthcare resource reallocation, delayed diagnostic follow-ups, and patient reluctance to seek medical care during the pandemic.

## Conclusion

Our study shows that the COVID-19 pandemic significantly impacted cancer incidence trends in Taiwan, particularly for breast, colorectal, and liver cancers. The findings emphasize the importance of ensuring that screening programs remain robust during public health emergencies to prevent delays in cancer diagnoses. Strengthening healthcare systems to maintain these critical services is essential for minimizing the long-term consequences of future crises.

新診斷第四期癌症患者靜脈血栓栓塞發生率:臺灣單一機構回溯性研究

Incidence of venous thromboembolism (VTE) in newly diagnosed stage 4 cancer patients: a single institution retrospective study in Taiwan

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## Background

The risk of VTE in cancer patients is at least two- to seven-fold higher than in the general population, with the risk peaking in the first 12 months after cancer diagnosis and varying by tumor site, stage, and treatment. A 2017 UK cohort study on VTE in patients with active cancer reported an incidence of 5.8 per 100 person-years, while a review in Asia (1995–2020) showed a lower rate of 1.85–9.88 per 1,000 person-years, though this figure may be underestimated. VTE significantly increases mortality, independent of cancer characteristics, particularly within the first year. Guidelines recommend prophylactic anticoagulation for high-risk outpatients and all hospitalized cancer patients if not contraindicated, but the application to the Asian remains unclear. This highlights the need to better understand cancer-associated VTE in high risk Asian populations.

#### Methods

Patients over 18 years old with a first-time diagnosis of stage 4 cancer between July 1, 2016, and June 30, 2021, at KFSYSCC were included in this study. Exclusions included multiple primary malignancies, VTE diagnosed more than 3 months before cancer, prior anticoagulant use, follow-up less than six months, or incomplete initial cancer data. VTE, defined as deep vein thrombosis (DVT) and pulmonary embolism (PE), was identified by ICD-10 codes and anticoagulant prescriptions, and confirmed by manual review of the image reports. Catheter-related thromboembolism and superficial venous thrombosis were excluded.

#### Results

A total of 1,603 patients were included, with 76 cases of VTE (4.7%). The overall incidence rate was 18.2 per 1,000 patient-years, with a median follow-up of 4.7 years. Pulmonary embolism occurred in 28 patients (36.8%), lower limb VTE in 31 (40.8%), upper limb VTE in 9 (11.8%), and concurrent pulmonary embolism and lower limb VTE in 8 (10.5%). The incidence of VTE per 1,000 patient-years varied by primary cancer site: hepatobiliary (67.6), pancreatic (62.4), gynecologic (49.9), lung (43.3), renal cell carcinoma (40.9), colorectal (28.8), gastric (26.3), upper tract urothelial carcinoma (20.4), breast (15.6), nasopharyngeal (6.1), head and neck (4.6), and hematologic malignancies (2.9). 3-year mortality rate was 44% in the non-VTE group (N=672) and 71% in the VTE group (N=68). Among the VTE cases, 21 patients (27.6%) died within three months, including 12 with confirmed PE, and 2 with suspected PE but unconfirmed by CT due to clinical limitations. All six VTE patients who did not receive anticoagulation died within one year.

#### Conclusion

The incidence rate of cancer-associated VTE varies greatly among different primary cancer sites.

The occurrence of VTE in cancer patients is linked to higher mortality rates despite standard antithrombotic treatment.

### 肝癌接受消融治療之復發模式與復發後存活分析

Patterns and Outcomes of Recurrence After Thermal Ablation for Hepatocellular Carcinoma

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## Background

Recurrence rates after thermal ablation for hepatocellular carcinoma (HCC) remain high, but the patterns of recurrence and their impact on outcomes are not well understood. This study aimed to investigate the recurrence patterns and long-term outcomes in patients with HCC following thermal ablation.

### Methods

A retrospective analysis was conducted on 553 of 826 patients who underwent thermal ablation for HCC between 2007 and 2023 and subsequently experienced recurrence. Recurrence patterns, post-recurrence treatments, and factors associated with post-recurrence survival were evaluated.

#### Results

Of the patients, 372 (67.3%) experienced early recurrence, while 181 (32.7%) had late recurrence. The median time to recurrence was 9.4 months for early recurrence and 38.2 months for late recurrence. Recurrence stages were distributed as follows: 46.7% at BCLC stage 0, 34.9% at stage A, 9.8% at stage B, and 8.7% at stage C. Both early and late recurrences showed similar recurrences patterns. Post-recurrence treatments included curative therapy (69.6%), transarterial chemoembolization (22.1%), and systemic therapy (1.6%). Median post-recurrence survival was 42.6 months for early recurrence and 65 months for late recurrence (p=0.001). Independent predictors of post-recurrence survival included early recurrence (HR=1.392, p=0.014), recurrence beyond Milan criteria (HR=2.047, p<0.001), AFP >10 ng/mL (HR=1.465, p=0.002), ALBI grade 2-3 (HR=1.505, p=0.037), and FIB-4 score >3.25 (HR=2.279, p<0.001) at recurrence.

#### Conclusion

Post-recurrence survival is influenced by recurrence patterns, AFP levels, liver fibrosis, and liver function at recurrence. These findings may help guide post-recurrence treatment strategies and inform the design of future clinical trials.

運用基質輔助雷射脫附游離飛行時間式質譜和機器學習模式準確預測金黃色葡萄球菌對甲氧西林具 抗藥性表現型、抗藥性基因和社區來源有關的菌株

Accurate prediction of oxacillin resistance, *mecA* gene, and community-associated isolates of invasive *Staphylococcuss aureus* using MALDI-TOF mass spectrometry and machine learning algorithm in Taiwan (2011-2022)

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## Background

Invasive infections caused by *Staphylococcus aureus*, especially methicillin resistant *S. aureus* (MRSA), lead to significant morbidity and mortality worldwide. Genotyping using the staphylococcal cassette chromosome mec (SCCmec) has been universally used for MRSA. OSMRSA has been identified for decades with mecA gene and susceptibility to oxacillin (oxacillin MIC  $\leq 2$  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 12-year longidutinal study conducted in a medical center. Oxacillin-resistance to *S. aureus* (ORSA) was determined with the breakpoint of 2 mg/L using agar dilution according to the Clinical and Laboratory Standards Institute (CLSI). Methicillin-resistant *S. aureus* (MRSA) was confirmed with mecA existence. The SCC *mec* type of each isolate was classified using multiple polymerase chain reaction (M-PCR). Molecularly community-associated MRSA (CA-MRSA) were defined as isolates with SCC *med* V and V, while the healthcare-associated MRSA (HA-MRSA) included SCC *med*, II, and III. The matrix-assisted laser desorption/ionization time-of-flight mass spectra (MALDI-TOF MS) profile of each isolate was retrieved from the the Microflex Biotyper System (Bruker Daltonics) and was analyzed using the Light Gradient Boosting Machine (LightGBM) algorithm.

#### Results

In total, 940 invasive *S. aureus*, including 502 *mecA*+MRSA and 438 *mecA*-MSSA were identified. The predictive performance for oxacillin resistance in terms of accuracy, area under receiver operating characteristic curve (AUROC), and area under the precision-recall curve (AUPRC) were 0.8256, 0.8990, and 0.8820, respectively. The accuracy, AUROC, and AUPRC for *mecA* gene existence prediction were 0.8191, 0.8488, and 0.8415, respectively. Considering the bin size of MALDI-TOF MS peaks from 1 to 10 m/z using LightGBM to predict the oxacillin resistance, the bin size of 3 m/z was found to have the best AUPRC (0.8820), while the bin sise of 8 m/z having the best AUROC (0.9075). The predictive performance for SCC *mec*III/IV in term of recall (0.8824/0.8372) was better than that of SCC *mec*II/V (0.667/0.3600). Excellent performance was also seen in predicting CA-MRSA and HA-MRSA (accuracy/AUROC/AUPR: 0.8673/0.8936/0.8014).

#### Conclusion

Machine learning algorithm, such as LightGBM, has been proved to have excellent predictive performance for oxacillin resistance of *S. aureus* and its responsible gene, *mecA* gene and molecularly CA-MRSA. Rapid and accurate predition of oxacillin resistance and the molecular types of S. aureus clinical isolates greatly help physician in selecting appropriate antibiotic regimens to treat severe sepsis successfully.

### 糖尿病性視網膜病變與急性心衰竭住院風險之探討

## Diabetic Retinopathy and the Risk of Hospitalization for Acute Heart Failure

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## Background

Diabetic retinopathy (DR) is a microvascular complication in patients with diabetes mellitus (DM) and has been strongly associated with cardiovascular disease. The relationship between DR and coronary artery disease (CAD) has been discussed in multiple studies, often leading to a complex and confusing understanding of the underlying mechanisms. Traditionally, DR is considered a microangiopathy, while CAD is viewed as a macroangiopathy, each with distinct pathogenic mechanisms linked to DM. The potential association between DR, a microvascular complication, and heart failure (HF) in the context of CAD status, a macrovascular complication, remains unclear.

### Methods

Our study includes 21,773 patients with type 2 DM who underwent color fundus photography to assess the severity of DR between 2005 and 2021. Participants were categorized into three groups based on DR severity: Group 1 (no apparent retinopathy), Group 2 (mild non-proliferative diabetic retinopathy [NPDR]), and Group 3 (moderate to severe NPDR or proliferative diabetic retinopathy [PDR]). Comorbidities were defined using the International Classification of Diseases coding systems.

### Results

Our analysis revealed a positive association between baseline congestive HF comorbidities and DR severity, with an odds ratio of 1.23 (95% CI: 1.02-1.47, p=0.033). During the follow-up period, increased DR severity was associated with a higher risk of acute HF hospitalization in patients without a baseline diagnosis of HF, independent of CAD status (Log-rank p < 0.0001). Among patients without CAD, the hazard ratio (HR) for acute HF hospitalization was 1.57 (95% CI: 1.30-1.88, p < 0.001) for DR Group 2 and 1.91 (95% CI: 1.63-2.24, p < 0.001) for DR Group 3, compared to DR Group 1. In patients with CAD, the HR for acute HF hospitalization was 1.34 (95% CI: 0.85-2.12, p = 0.212) for DR Group 2 and 1.60 (95% CI: 1.08-2.37, p = 0.018) for DR Group 3, compared to DR Group 1.

#### Conclusion

The severity of DR is associated with an increased risk of acute HF hospitalization in diabetic patients beyond CAD status. The underlying mechanisms by which DR severity influences HF may be independent of CAD and involve other pathways. Further research is needed to elucidate the pathophysiological connections between DR severity and HF development.

Empagliflozin 透過抑制細胞氧化壓力和導致纖維化的上皮間質轉化,改善高蛋白飲食誘導的心腎症 候群大鼠腎纖維化和腎功能惡化

Empagliflozin therapy suppresses the high protein diet induced propagation of renal fibrosis and deterioration of kidney function in cardiorenal syndrome(CRS) rat through inhibiting cell-oxidative-stress and fibrosis mediated epithelial mesenchymal transition(EMT)

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## Background

High protein diet(HPD) can accelerate the progression of chronic kidney disease (CKD) due to increased glomerular hyperfiltration and exacerbated hypoxia in kidneys. This study tested the hypothesis that HPD exacerbates the cell-stress/oxidative signaling pathways and represses AMPK-mediated mitochondrial biogenesis, which play a crucial role in mediating epithelial-to-mesenchymal transition (EMT) and fibrosis in cardiorenal(CRS) rats (induced by doxorubicin-5/6 nephrectomy) and early empagliflozin(EMPA) treatment potentially reverse these effects.

#### **Methods and Results**

In vitro result showed that underwent p-Cresol treatment, the NRK-52E cell viabilities, were significantly suppressed, whereas cellular levels of ROS and early/late apoptosis of these cells were significantly increased that were significantly reversed by EMPA treatment (all p < 0.001). The protein levels of the cell-stress/oxidative signaling (p-PI3K/p-Akt/p-mTOR/NOXs/p-DRP1) were significantly activated, whereas the mitochondrial biogenesis signaling (p-AMPK/SIRT-1/TFAM/PGC-1α) was significantly repressed in the cell lines treated by p-Cresol and all of these were significantly reversed by EMPA treatment (all p < 0.001). Male-adult-SD rats were categorized into groups 1 [sham-operated control (SC)]/2 [SC + high protein diet (HPD) since day 1 after CKD induction]/3 (CRS + HPD)/4 (CRS + HPD+EMPA/20 mg/kg/day) and heart/kidney were harvested by day 60. By day 63, the renal function parameters (creatinine/BUN/proteinuria)/renal artery restrictive index/cellular levels of ROS/inflammation were significantly increased in group 3 than in groups 1/2, and all of these parameters were significantly reversed by EMPA treatment in group 4(all p < 0.0001). The protein levels of inflammation/ oxidative-stress/cell-stress signalings were highest in group 3, lowest in group 1 and significantly lower in group 4 than in group 3, whereas the AMPK-mitochondrial biogenesis displayed an opposite manner of oxidative-stress among the groups (all p < 0.0001). The protein expressions p-Smad3, TGF-β, vimentin and fibronectin, four EMT biomarkers, were highest in group 3, lowest in group 1 and significantly lower in group 4 than in group 3.

#### Conclusion

EMPA treatment effectively safeguarded the kidneys from HPD-enhanced CRS damage by inhibiting ROS signaling, promoting AMPK-mediated mitochondrial biogenesis and attenuating EMT.

### 星狀神經節阻斷術於心室心律不整電風暴的輔助治療成效

The efficacy of percutaneous stellate ganglion block as an adjuvant therapy in patients with electrical storm

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## Background

The electrical storm (ES), classically defined as the occurrence of three or more episodes of ventricular arrhythmia in 24 hours, potentially causes hemodynamic instability and necessitates medication or defibrillation. The managements of ES are still extremely challenging despite using pharmacological treatments or mechanical hemodynamic support. Percutaneous stellate ganglion block (SGB), a technique focusing on autonomic modulation, is possibly to reduce arrhythmia but the evidence is still limited. This study aims to explore the role of percutaneous SGB as an adjuvant therapy for the ES patients without response to conventional treatments including medication and defibrillation.

## Methods

Between April, 2020 and August, 2024, thirteen consecutive patients with ES were enrolled. After prescription of standard medical therapy and defibrillation for at least three attempts, they all received percutaneous SGB as an adjuvant therapy. Continuous variables were tested with the Wilcoxon signed-rank test to compare the frequency of arrhythmia events one week before and 24 hours after SGB. Primary outcome was the effectiveness of a reduction of arrhythmic events with defibrillation after SGB, and secondary outcome was 30-day all-cause mortality.

#### Results

Among the 13 patients with ES, left-sided percutaneous SGB with injection of Lidocaine 2% 5 to 10 c.c. was performed at bedside under anatomic approach. In the study group, average age was  $60.5\pm15.2$  years old, while 10 patients are male gender(76.9%), 7 had hypertension(53.8%), 2 had diabetes mellitus (15.4%), 9 had heart failure with reduced ejection fraction(69.2%), 6 presented with acute coronary syndrome (46.2%), and 7 needed mechanical support(53.8%) including veno-arterial extracorporeal membrane oxygenation (VA ECMO) or intra-aortic balloon pump (IABP). After percutaneous SGB, eleven patients (11/13, 84.6%) experienced a significant reduction in ventricular arrhythmia events (p = 0.026), of them 10 patients had achieved termination of ES without significant adverse effects. Patients with the episodes of acute coronary syndrome showed better response to SGB. However, those with an ineffective response to SGB all expired in 30 days. No significant differences in underlying disease or left ventricular function was noted between the effective and ineffective groups.

### Conclusion

For ES patients unresponsive to conventional medical treatments and mechanical supports, especially during the episode of acute coronary syndrome, percutaneous SGB as an adjuvant

therapy demonstrates a promising effect in terminating ventricular arrhythmia without significant adverse events. Further randomized trials are needed to confirm its efficacy and assess safety.