

優秀論文獎_臨床

時間：114年11月22日(星期六)10:15-11:15

地點：台中林酒店 3F 國際廳

摘要：

座長/Moderator	三軍總醫院 劉峰誠醫師
10:15-10:27	<p>Multi-omics (peptidomics and genomics) integrative approach for personalized medicine for Jaki-treated patients with rheumatoid arthritis</p> <p>Der-Yuan Chen^{1,2}, Yi-Ming Chen^{3,4}, Jeremy JW Chen^{4,5}, Po-Ku Chen^{1,2}, Shih-Hsin Chang^{1,2}, Chien-Chung Huang^{1,2}</p> <p>1Rheumatology and Immunology Center, China Medical University Hospital; Taiwan 2College of Medicine, China Medical University, Taiwan 3Department of Medical Research, Taichung Veterans General Hospital, Taiwan 4College of Medicine, National Chung Hsing University, Taiwan 5Institute of Biomedical Sciences, National Chung Hsing University, Taiwan</p> <p>綜合胜肽體學與基因體學之多質體學策略，提供JAK抑制劑治療之類風濕關節炎患者的個人化醫療</p> <p>陳得源、陳一銘、陳健尉、陳柏谷、張詩欣、黃建中 中國醫大附醫風濕免疫中心、中國醫藥大學、台中榮總醫研部、中興大學醫學院、中興大學 生醫所</p>
10:27-10:30	Q & A
10:30-10:42	<p>Identification of CNTNAP2 as a potential candidate gene in difficult-to-treat rheumatoid arthritis: A GWAS and transcriptomic study</p> <p><u>Meng-Ko Tsai</u>^{1,2,3*}, <u>Ting-Yu Hsieh</u>^{3,4*}, Yu-Tien Chang⁵, Hsiang-Cheng Chen¹, Fu-Chiang Yeh¹, Shan-Wen Lui⁶, Yi-Ming Chen^{7,8}, Deng-Ho Yang², Feng-Cheng Liu¹</p> <p><u>蔡孟格</u>^{1,2,3*}, <u>謝庭仔</u>^{3,4*}, 張雨恬⁵, 陳相成¹, 葉富強¹, 呂善玟⁶, 陳一銘^{7,8}, 楊登和¹, 劉峰誠¹</p> <p>¹ Division of Rheumatology, Immunology and Allergy, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan ² Division of Rheumatology, Immunology and Allergy, Department of Internal Medicine, Taichung Armed Forces General Hospital, Taichung, Taiwan ³ Graduate Institute of Medical Sciences, National Defense Medical University, Taipei, Taiwan ⁴ Department of Medical Education, Taichung Veterans General Hospital, Taichung, Taiwan ⁵ School of Public Health, National Defense Medical Center, Taipei, Taiwan ⁶ Department of Medical Education, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan ⁷ Department of Medical Research, Taichung Veterans General Hospital, ROC, Taichung, Taiwan ⁸ Division of Allergy, Immunology, and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, ROC, Taichung, Taiwan</p>
10:42-10:45	Q & A

<p>10:45-10:57</p>	<p>Distinct Proteomic and Cellular Signatures Predict Response to JAK Inhibitors in Rheumatoid Arthritis: An Integrated Multi-omics Analysis Yi-Ming Chen^{1,2}, Ting-Shuan Wu³, Sheng-Min Lo², Chung-Mao Kao^{1,2}, Yen-Ju Chen^{1,2}, Wen-Nan Huang¹, Tzu-Hung Hsiao² ¹ Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taiwan ² Department of Medical Research, Taichung Veterans General Hospital, Taiwan ³ Department of Biomedical Sciences, Chung Shan Medical University, Taiwan. 蛋白質體學和單細胞定序特徵預測類風濕性關節炎患者對 JAK 抑制劑反應的整合多體學分析 陳一銘, 吳亭萱, 羅聖旻, 高宗楙, 陳彥如, 黃文男, 蕭自宏 中榮過敏免疫風濕科、中榮醫研部、中山醫學大學生物醫學科學系</p>
<p>10:57-11:00</p>	<p>Q & A</p>
<p>11:00-11:12</p>	<p>Using Explainable machine learning to predict disease flare in patients with systemic lupus erythematosus 利用可解釋性機器學習預測紅斑性狼瘡病患疾病惡化 <u>Hsin-Hua Chen</u>¹, Tsu-Yi Hsieh¹, Kuo-Tung Tang¹, Yi-Ming Chen¹, Kuo-Lung Lai¹, Chia-Wei Hsieh¹, Wei-Ting Hung¹, Ching-Tsai Lin¹, Yin-Yi Chou¹, Chih-Wei Tseng¹, Yi-Da Wu¹, Yen-Ju Chen¹, Yu-Wan Liao¹, Tsai-Hung Yen¹, Yun-Wen Chen¹, Yi-Hsing Chen¹, Wen-Nan Huang¹ <u>陳信華</u>¹, 謝祖怡¹, 譚國棟¹, 陳一銘¹, 賴國隆¹, 謝佳偉¹, 洪維廷¹, 林靖才¹, 周吟怡¹, 曾智偉¹, 吳沂達¹, 陳彥如¹, 廖育婉¹, 顏在弘¹, 陳韻文¹, 陳怡行¹, 黃文男¹ ¹Division of Allergy, Immunology, and Rheumatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan ¹ 臺中榮民總醫院內科部過敏免疫風濕科</p>
<p>11:12-11:15</p>	<p>Q & A</p>

Multi-omics (peptidomics and genomics) integrative approach for personalized medicine for Jaki-treated patients with rheumatoid arthritis

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綜合胜肽體學與基因體學之多質體學策略，提供**JAK**抑制劑治療之類風濕關節炎患者的個人化醫療
陳得源、陳一銘、陳健尉、陳柏谷、張詩欣、黃建中

中國醫大附醫風濕免疫中心、中國醫藥大學、台中榮總醫研部、中興大學醫學院、中興大學生醫所

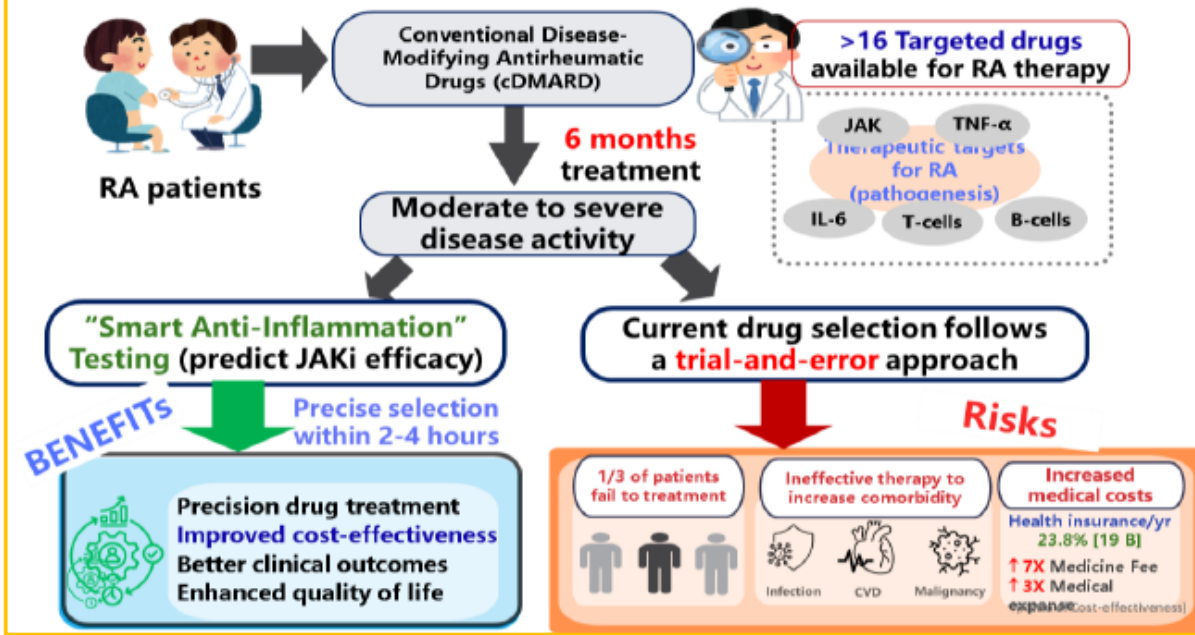
Background: To promote a treat-to-target goal of tofacitinib, one of Janus kinase inhibitors (JAKi) therapy in rheumatoid arthritis (RA) patients, there are unmet needs to predict therapeutic response. Currently, the choice of JAKi relies on a trial-and-error strategy, resulting in a poor response in 30-40% of RA patients in the first six months. Thus, there is an unmet need to identify biomarkers for predicting efficacy of JAKi in RA patients.

Methods: We enrolled (1) 106 patients, including twelve patients who underwent PhIP-Seq analysis (peptidomics) and ninety-four patients were validated with ELISA, and (2) 242 patients, including 94 patients who underwent whole exon sequencing (genomics) analysis and 148 patients were validated with RT-PCR assays or Sanger sequencing. Disease activity was assessed using the 28-joint disease activity score-erythrocyte sedimentation rate (DAS28-ESR), and therapeutic response at week 24 using EULAR response criteria, and was considered remission if DAS28-ESR < 2.6.

Results: PhIP-Seq analysis identified antibodies to sucrose non-fermenting-related kinase (SNRK) and HUWE1 (ubiquitin E3 ligase) as peptide biomarkers for discriminating good-responders (58.3%) from non-good responders. Plasma levels of anti-SNRK and anti-HUWE1 antibodies at the cut-off value of 0.381 and 0.362 revealed an accuracy of 79.8 and 70.2% ($p < 0.0001$ and $p < 0.001$), respectively. WES analysis identified ten variants of *RIN3*, *NLRC3*, and *SLX4* genes for predicting remission. Using multiplexed one-step RT-PCR assay, this panel predicts remission with a high specificity 97.0% and accuracy of 88.0%.

Conclusion: Using multi-omics technology, we have identified novel biomarkers and integrated into one-step platform (ELISA and multiplex PCR), which enables precision treatment with JAKi.

Personalized Precision Treatment Testing for JAKi-treated patients with RA



核心技術與臨床運用



Identification of CNTNAP2 as a potential candidate gene in difficult-to-treat rheumatoid arthritis: A GWAS and transcriptomic study

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Background: Rheumatoid arthritis (RA) is clinically heterogeneous, and difficult-to-treat RA (D2T RA) remains challenging due to inadequate response to standard therapies. Recent findings highlight that mechanisms beyond immune dysregulation—particularly nociception and neuro-immune interactions—may significantly influence D2T RA clinical manifestations, although these pathways remain underexplored. To investigate genetic underpinnings, we performed an exploratory genome-wide association study (GWAS) in a Taiwanese cohort and validated candidate genes using GEO transcriptomic datasets.

Methods: A case-control study was conducted at Tri-Service General Hospital under the Taiwan Precision Medicine Initiative. D2T RA was defined by the 2021 EULAR consensus: persistent disease activity despite failure of at least two b/tsDMARDs with different mechanisms, and substantial management difficulty as perceived by physician and/or patient. Candidate genes from GWAS were validated using peripheral blood transcriptomic data from the SMART cohort (GEO: GSE54629), comparing gene expression profiles between D2T RA (nonresponders) and good responders at both baseline and week 24.

Results: Among 428 participants, 29 had D2T RA. Our GWAS identified 12 SNPs associated with D2T RA, notably rs2538993 on chromosome 7 (odds ratio 6.07; 95% CI 3.12–11.80; $-\log_{10} p=5.75$) and rs2710123, both mapped to CNTNAP2. Additional mapped genes included KAZN, PRDM2, TRIM42, CCSER1, OLFM1, IRX5, and GRIN2A. Transcriptomic validation showed significant CNTNAP2 upregulation in D2T RA versus controls ($\log_{2}FC=0.095$, adj. $P=0.049$); other genes showed no significant differences.

Conclusion: Our study identifies CNTNAP2 as a novel candidate gene potentially involved in the pathogenesis of D2T RA. Further functional studies are needed to elucidate its specific role.

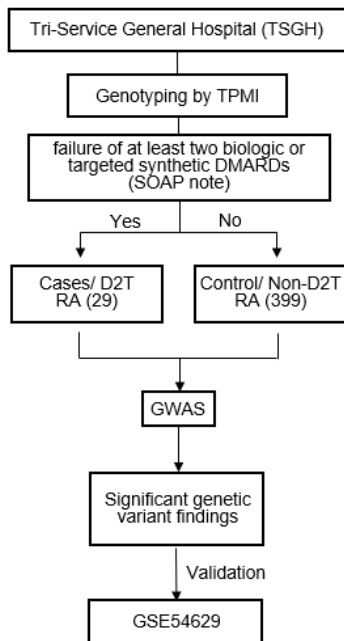


Fig. 1 Study flowchart.

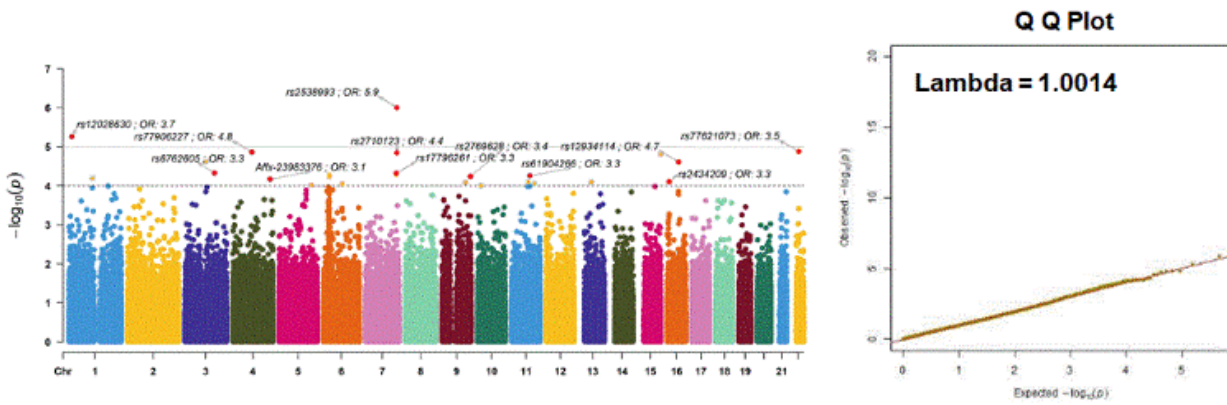


Fig. 2 The GWAS results presented as a Manhattan plot and Q-Q plot.

Distinct Proteomic and Cellular Signatures Predict Response to JAK Inhibitors in Rheumatoid Arthritis: An Integrated Multi-omics Analysis

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蛋白質體學和單細胞定序特徵預測類風濕性關節炎患者對 JAK 抑制劑反應的整合多體學分析

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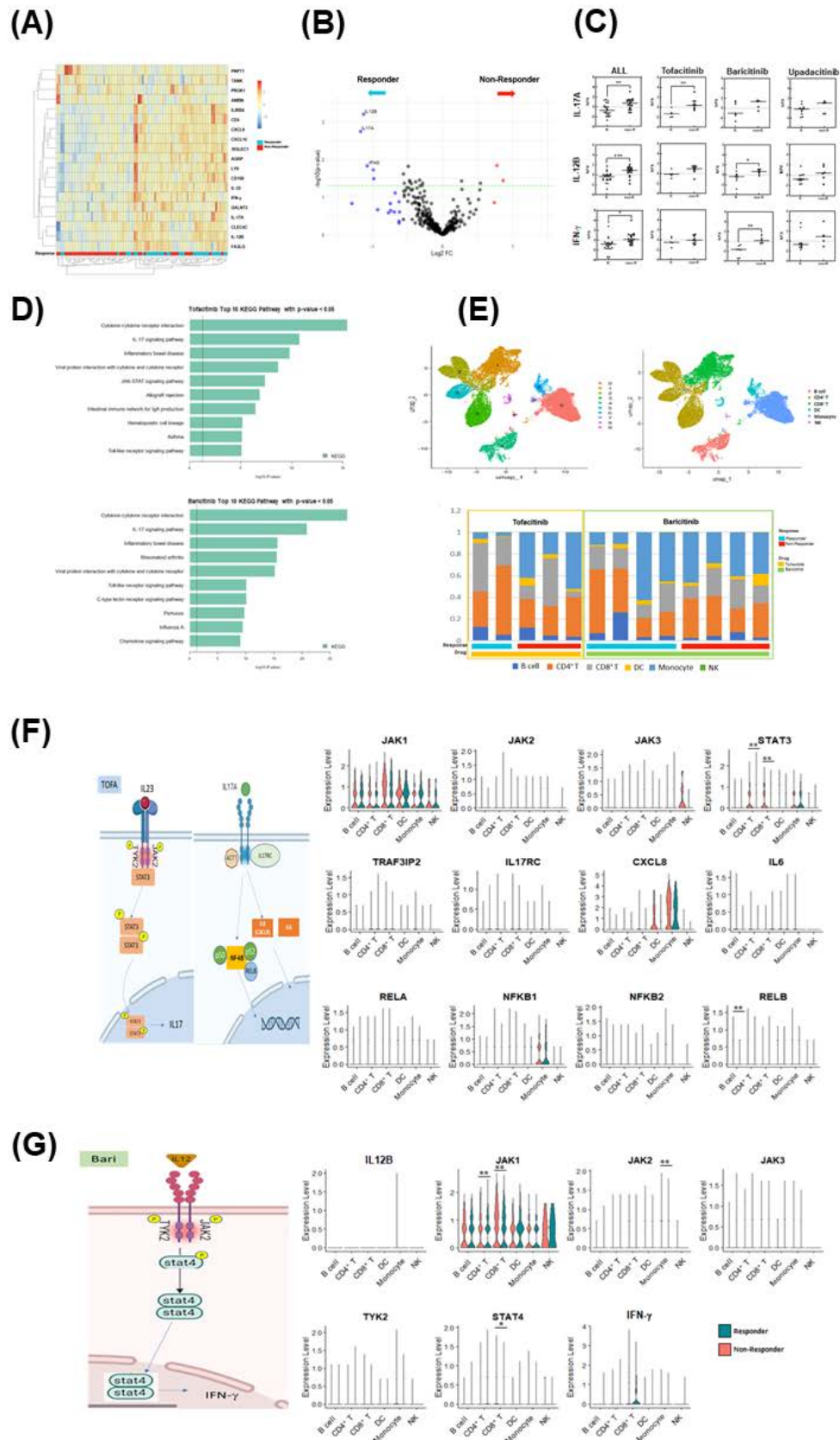
Background: Janus kinase inhibitors (JAKi) have emerged as effective therapeutics for rheumatoid arthritis (RA), yet response rates vary significantly among patients. Despite their widespread use, molecular predictors of treatment response remain poorly understood. Our objective was to discover predictive biomarkers for JAKi response using integrated multi-omics analysis and to investigate the drug-specific mechanisms of action.

Materials and Methods: In this prospective study, 42 RA patients receiving tofacitinib (n=14), baricitinib (n=12), or upadacitinib (n=16) were analyzed before treatment. We employed Olink Explore 384 proteomics platform for comprehensive protein profiling and single-cell RNA sequencing for cell-type specific transcriptional analysis. Treatment response was assessed using ACR/EULAR criteria, with patients categorized as good or non-responders.

Results: Proteomic analysis identified IL-12B, interferon-gamma (IFN- γ), and IL-17A as differentially expressed proteins across all JAKi responses, with drug-specific patterns. IL-17A levels significantly predicted response to tofacitinib, while IL-12B and IFN- γ were statistically significant predictors for baricitinib response. Single-cell transcriptomics validated these findings, showing concordant pathway activation particularly in B cells, CD4+ T cells, and CD8+. Integration of baseline proteomic and transcriptomic data revealed distinct inflammatory pathway signatures that predicted 6-month therapeutic responses, suggesting drug-specific signaling pathways for therapeutic efficacy.

Conclusion: This integrated analysis reveals a cytokine signature centered on IL-12B, IFN- γ , and IL-17A that predicts JAKi response in RA patients, with drug-specific associations. These findings offer fresh perspectives on JAKi biology in RA and could inform the selection of personalized therapies tailored to patients' molecular profiles.

Figure 1. Summary of study result. (A) - (C) Differential protein expression patterns in JAK inhibitor response; (D) Differential protein expression and pathway analysis in JAK inhibitor treatments; (E) – (G) Single-cell transcriptomic analysis



Using Explainable machine learning to predict disease flare in patients with systemic lupus erythematosus

利用可解釋性機器學習預測紅斑性狼瘡病患疾病惡化

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ABSTRACT

Background and objectives:

Systemic Lupus Erythematosus (SLE) is a common systemic autoimmune disease. Disease flares, characterized by a sudden increase in disease activity, can lead to severe complications and decreased quality of life in patients with SLE. Accurately predicting the onset and severity of flares remains a substantial clinical challenge. Using explainable machine learning, we utilized data from electronic medical records (EMR) in a medical center to develop a predictive model for SLE disease flares.

Methods:

Using EMR data of patients with SLE (ICD-9: 710.0 or ICD-10: M32) between 2012 and 2023, we analyzed clinical conditions of all ambulatory visits, which were classified into four severity categories based on medication records: non-flare; mild flare (a. initiation of any of the following: hydroxychloroquine [HCQ], an oral corticosteroid with prednisolone [Pd]-equivalent dose of ≤ 7.5 mg/day or non-steroidal anti-inflammatory drugs [NSAIDs], or b. increase dose of HCQ or NSAIDs compared with that in prior 60 days); moderate-flare (a. initiation of any of the following: an oral corticosteroid with Pd-equivalent dose > 7.5 mg/day but ≤ 30 mg/day, biologics [i.e., belimumab, rituximab, abatacept], or immunosuppressive agent other than cyclophosphamide, or b. increase dose of biologics or immunosuppressant other than cyclophosphamide); severe flare (a. initiation of any of the following: an oral glucocorticoid with Pd-equivalent dose > 30 mg/day, cyclophosphamide, or b. increase dose of cyclophosphamide) [1]. Treatment was considered to be “initiated” if there were no filled prescriptions in the prior 60 days for all medication except cyclophosphamide (denied as no cyclophosphamide prescription in prior 100 days) [1].

Features included patient demographics, laboratory results, medication usage patterns, comorbidities, and time-related derived features, such as the number of days since the last corticosteroid use and outpatient visit frequency within the past 90 days. We used EMR data from 2012 to 2022 with 5-fold cross-validation to develop explainable machine learning models, including XGBoost, LightGBM, and CatBoost, to predict four categories (non-flare, mild flare, moderate flare, severe flare) and two different binary categories (i.e., non-flare vs. mild/moderate/severe flare; non-flare/mild flare vs. moderate flare/severe flare). We used EMR datasets in 2023 to conduct testing for ML models. We performed receiver operating characteristic (ROC) analysis, calibration curve analysis, and decision curve analysis to determine the discrimination, accuracy, and applicability of the predictive ML models in the testing datasets. Bayesian optimization was used for hyperparameter tuning. Among all models, we select the model with the best AUROC in the testing datasets as the main result.

Results:

A total of 5,692 patients diagnosed with SLE were included in the analysis. After data preprocessing, medication integration, and disease flare labeling, the final dataset contained 573,592 visits. As shown in Table 1, we finally included 143 features from five domains (demographics, laboratory data, comorbidities, medication patterns, and time-dependent variables). The distribution of flare severity was 66.1% non-flare, 7.3% mild, 18.0% moderate, and 8.6% severe. Among all ML models, the LightGBM model achieves the best performance for binary classification for non-flare/mild flare and moderate flare/severe flare. As shown in Table 2, for the binary classification task (non-flare/mild flare vs. moderate flare/severe flare), the LightGBM model achieved an AUC of 90.54%, an accuracy of 85.21%, a sensitivity of 77.71%, and a specificity of 87.11% in the 2023 test set. Fig. 1A presents the feature importance rankings, highlighting the contribution of

corticosteroid and visit-related features, and Fig. 1 B shows the decision curve analysis (DCA), demonstrating the clinical utility of the LightGBM model.

Conclusion:

This study developed promising predictive models for SLE flares, particularly for identifying moderate to severe flares. The established flare classification and feature engineering provide a robust framework. The models demonstrate potential for proactive clinical flare management; however, continuous monitoring and retraining are crucial for maintaining performance, given the evolving nature of clinical practices.

Keywords: systemic lupus erythematosus; disease flare, machine learning, electronic medical records.

Reference

1. Garris C, Jhingran P, Bass D, et al. Healthcare utilization and cost of systemic lupus erythematosus in a US managed care health plan. *J Med Econ* 2013,16:667-77.

Table 1. Features used for the development of explainable machine learning prediction models for flare severity in patients with systemic lupus erythematosus at Taichung Veterans General Hospital.

Quantity	Type	Description
8 x 9 - 2 = 70	LAB statistics: mean, standard deviation, variance, maximum/minimum value, median, MAD, uniformity	C3, WBC, PLT, ALT, ESR, HGB, C4, CREAT, dsDNA (SLEDAI, IGG, CRP, and the missing values of ESR variance and standard deviation exceed 30%.)
4 x 11 = 44	Drugs: outpatient (out), emergency (em), hospitalization (hos), discharge medication (dt)	Steroid, Rituximab, Belimumab, Abatacept, Methotrexate, Leflunomide, Azathioprin, Hydroxychloroquine, CICLOSPORIN, Cyclophosphamide, MMF
17	Comorbidities	Myocardial infarction, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic pulmonary disease, Rheumatic disease, Peptic ulcer disease, Mild liver disease, Diabetes without chronic complication, Diabetes with chronic complication, Hemiplegia or paraplegia, Renal disease, Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin, Moderate or severe liver disease, Metastatic solid tumor, AIDS/HIV
2	others	Gender, Age
10	Time-related derivatives	Use of mild immunosuppressants, Use of moderate immunosuppressants, Use of severe immunosuppressants, Use of corticosteroids, Total number of other immunosuppressants used, Corticosteroid monotherapy, Days since last corticosteroid use, Number of visits within 90 days, Current immunosuppressant intensity level, Previous immunosuppressant intensity level

Table 2. Performance of LightGBM models to predict flare severity in patients with systemic lupus erythematosus (SLE), with 2023 data used for model testing.

Method	Type	Sensitivity	Specificity	Accuracy	AUC	Precision	F1-Score
Original four-class model	Test	52.15%	86.94%	66.55%	81.81%	43.92%	44.37%
Four-class model <ul style="list-style-type: none"> Time-related derived features Bayesian optimization 	Test	53.48%	88.09%	69.78%	82.91%	46.90%	46.33%
Binary classification (flare vs. no flare) <ul style="list-style-type: none"> Time-related derived features Bayesian optimization 	Test	70.91%	86.50%	82.45%	86.90%	64.84%	67.74%
Binary classification (non-flare + mild vs. moderate + severe) <ul style="list-style-type: none"> Time-related derived features Bayesian optimization 	Test	77.71%	87.11%	85.21%	90.54%	60.54%	68.06%



Fig 1A

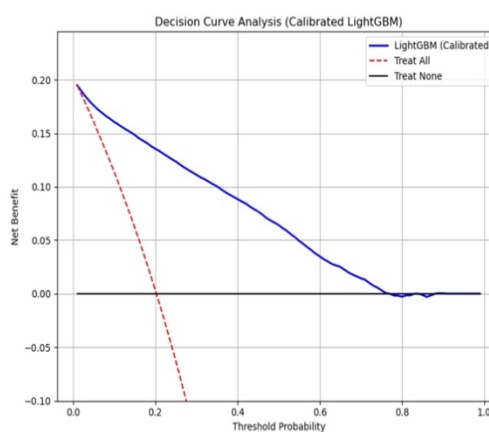


Fig 1B

Figure 1. Fig. 1A reveals the top 20 features based on the feature importance of the LightGBM model for predicting moderate to severe flares; Fig. 1 B displays the corresponding decision curve. The blue line indicates the net benefit of the LightGBM model across different threshold probabilities, compared to treating all patients (dotted red) or none (black).