



The prognostic and therapeutic significance of polyunsaturated fatty acid-derived oxylipins in ST-segment elevation myocardial infarction

Zhiyong Du ^{1#}, Yingyuan Lu ^{3#}, Ying Ma ^{2#}, Yunxiao Yang ¹, Wei Luo ¹, Sheng Liu ¹, Ming Zhang ¹,
Yong Wang ⁴, Lei Li ^{5*}, Chun Li ^{6,7*}, Wei Wang ^{7*}, Hai Gao ^{1*}

¹ Beijing Anzhen Hospital, Capital Medical University, Beijing, China

² China Academy of Chinese Medical Sciences, Beijing, China

³ School of Pharmaceutical Sciences, Peking University, Beijing, China

⁴ Dongzhimen Hospital of Beijing University of Chinese Medicine, Beijing, China

⁵ Peking University Third Hospital, Beijing, China

⁶ State Key Laboratory of Traditional Chinese Medicine Syndrome, Guangzhou, China

⁷ Beijing University of Chinese Medicine, Beijing, China

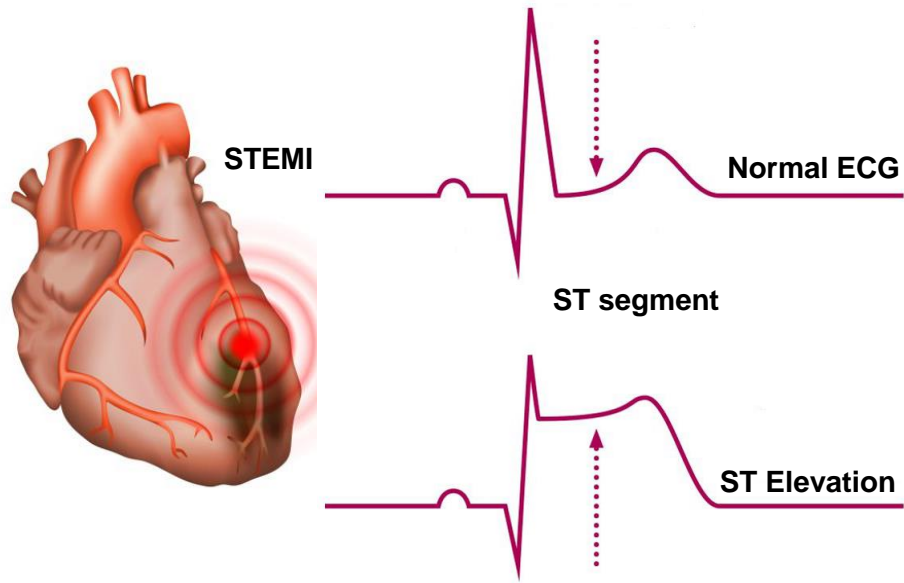


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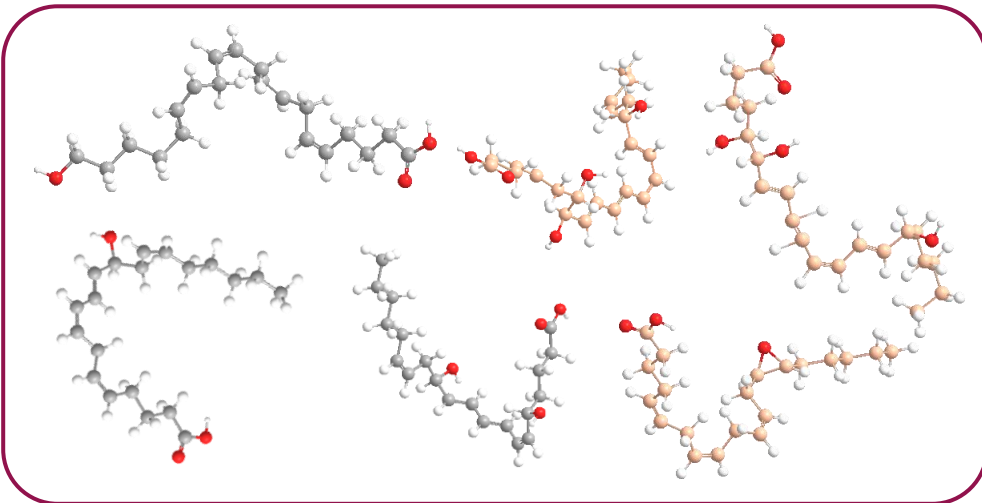
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Introduction



PUFA-derived Oxylipins

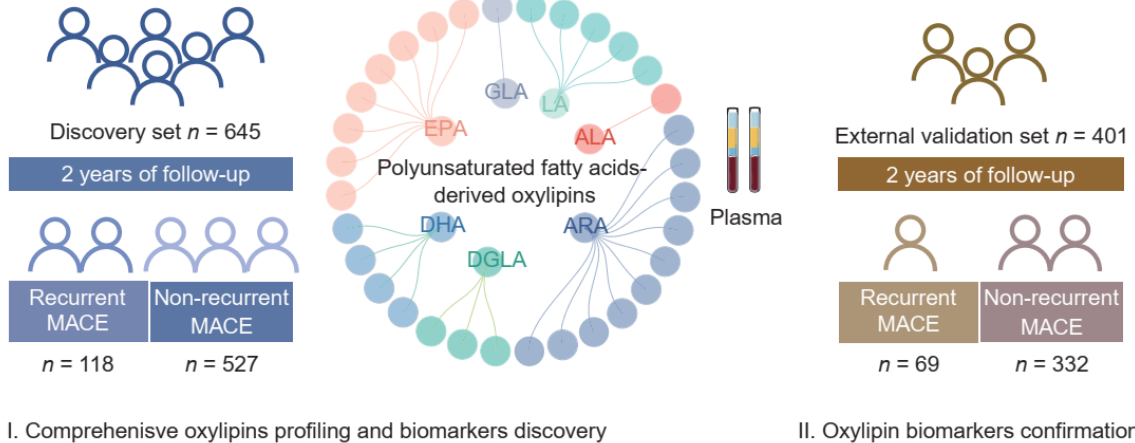


- ❑ The recurrent major adverse cardiovascular event (MACE) rates after ST-segment elevation myocardial infarction (STEMI) still remain unacceptably high.
- ❑ There is a great need to understand the exact mechanisms by which inflammatory progression contributes to adverse cardiovascular outcomes and discover novel risk markers for prognostic management after STEMI.
- ❑ Limited clinical data exist on the prognostic value of pro-inflammatory and anti-inflammatory oxylipins in the STEMI population.
- ❑ We aimed to investigate the association of oxylipin profiles with recurrent MACE the roles of the key oxylipin predictors.



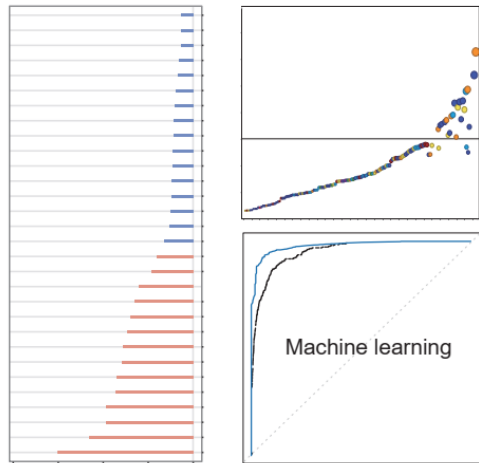
Highlights

1046 patients with ST-segment elevation myocardial infarction enrolled from two hospitals

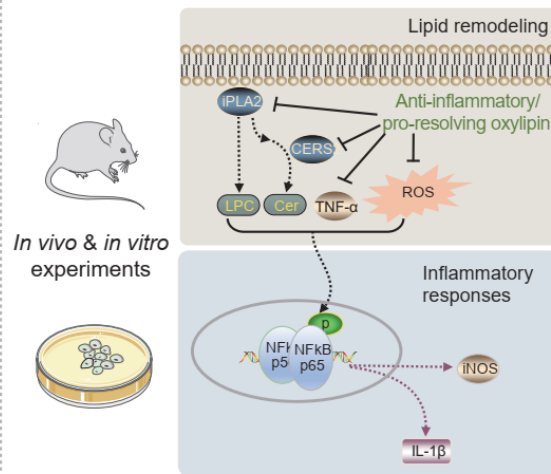


I. Comprehensive oxylipins profiling and biomarkers discovery

II. Oxylipin biomarkers confirmation



III. Oxylipin-based accurate risk model for forecasting recurrent major adverse cardiovascular events



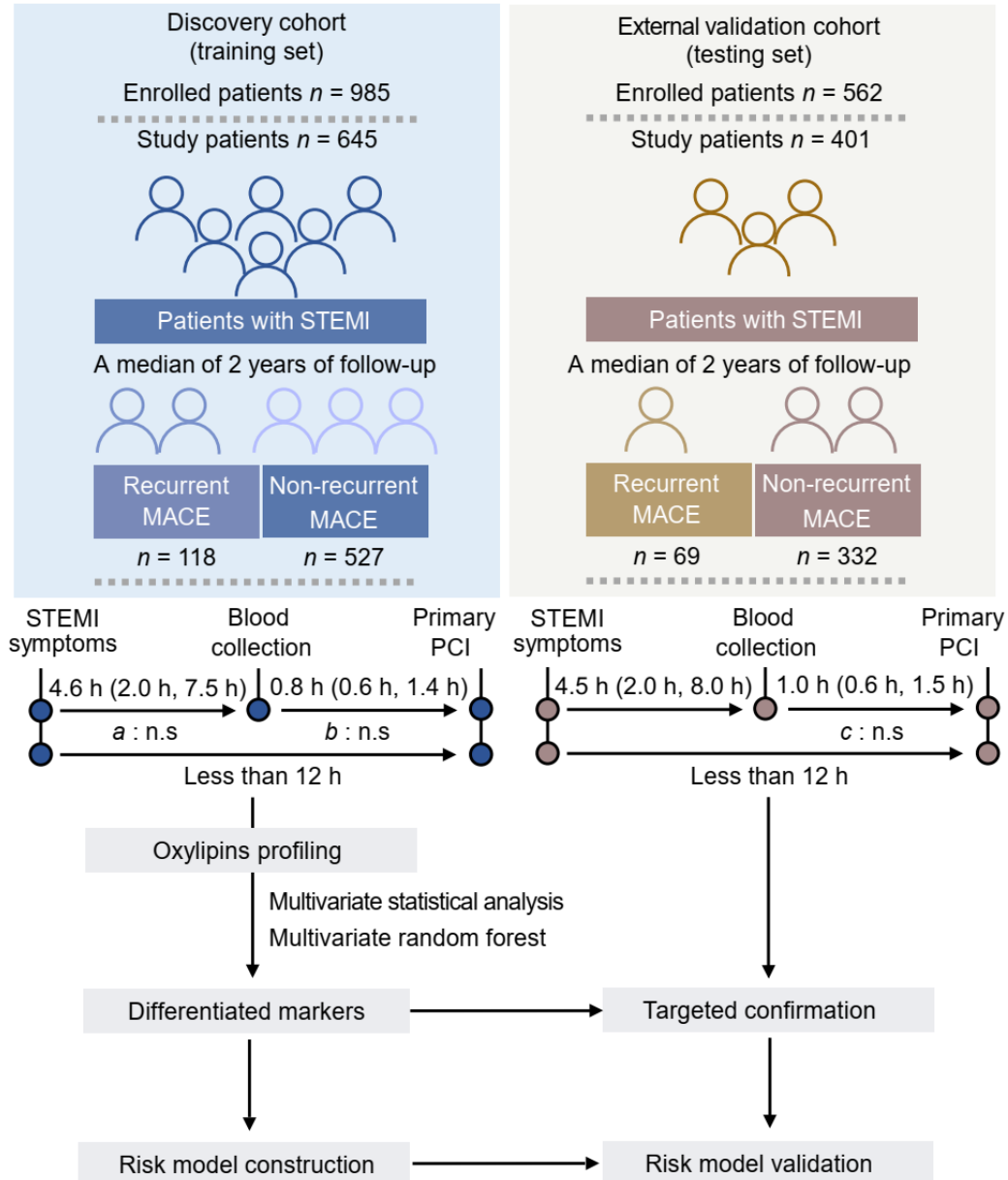
IV. Effects of the key bioactive oxylipin predictors on myocardial ischemia-reperfusion injury

- ❑ Polyunsaturated fatty acid-derived oxylipins regulate systemic inflammation and exert cardiovascular effects, however, their role in ST-segment elevation myocardial infarction (STEMI) remains unclear.
- ❑ We constructed an oxylipin-based prediction model that showed powerful performance in predicting recurrent major adverse cardiovascular events in two independent cohorts of 1046 STEMI patients.
- ❑ We also demonstrated that six anti-inflammatory/pro-resolving oxylipin combination had synergistic and cardioprotective effects against myocardial ischemia-reperfusion injury.



Clinical study

(A)



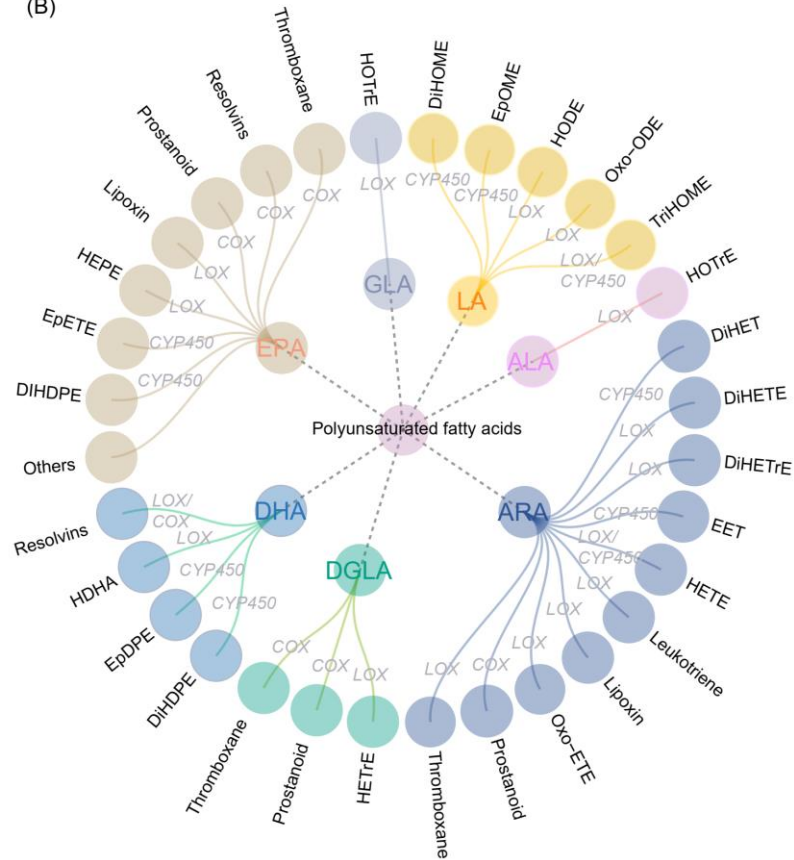
□ A total of 645 subjects from 985 patients with ST-segment elevation myocardial infarction (STEMI) who were enrolled at Beijing Anzhen Hospital were included in the discovery cohort. Another 401 patients from the Peking University Third Hospital-built external cohort consisting of 562 STEMI patients were included as the independent validation set.

□ Targeted metabolomics and machine learning algorithms were performed to develop an oxylipin-based risk model to accurately predict recurrent major adverse cardiovascular events (MACE) after STEMI in the two prospective cohorts with two years of follow-up.

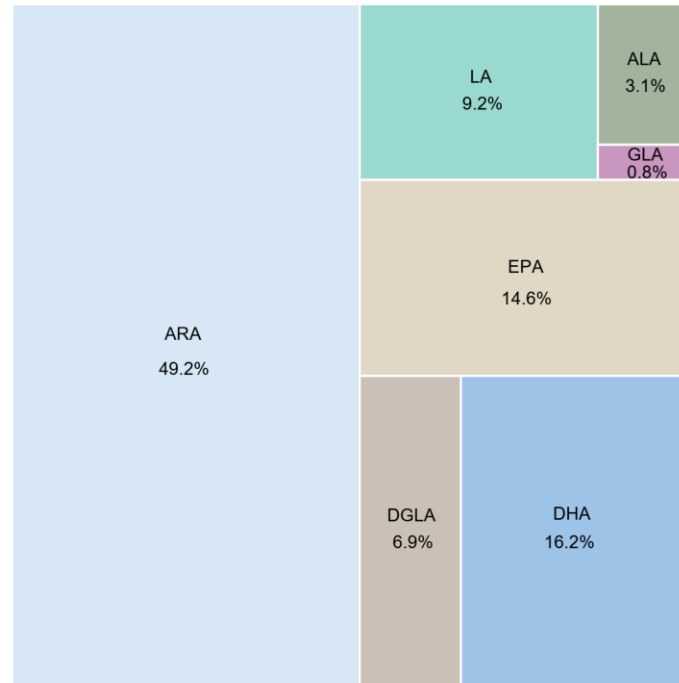


Polyunsaturated fatty acid-derived oxylipins detection

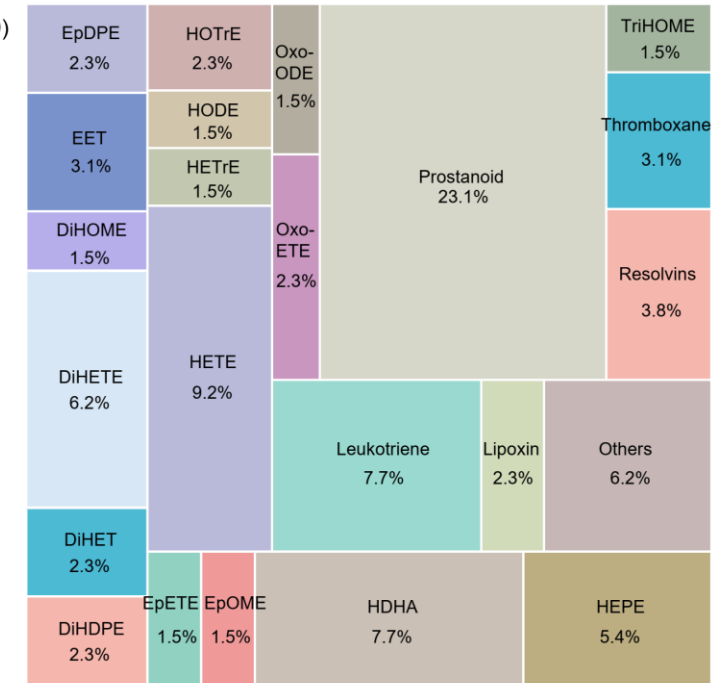
(B)



(C)



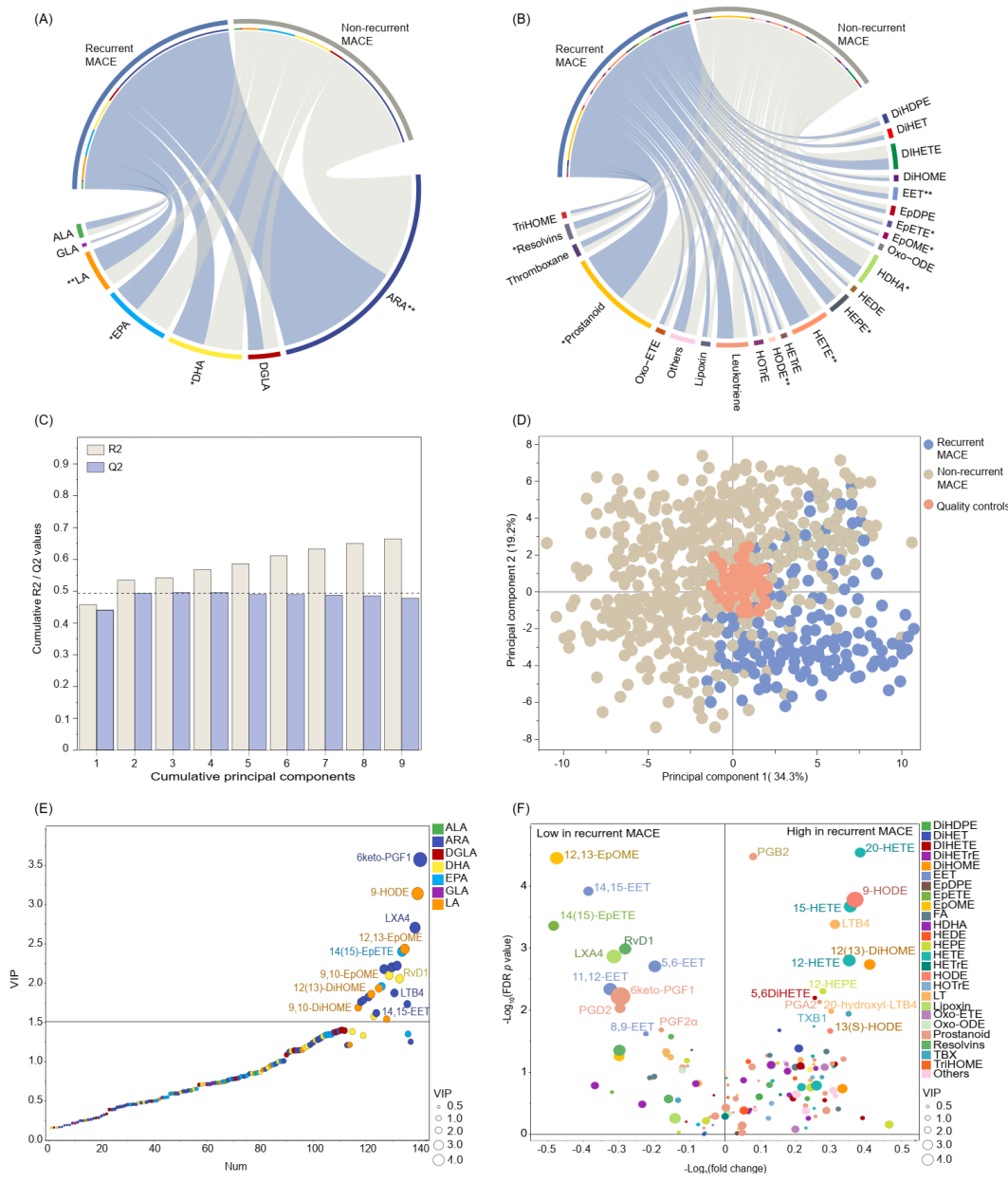
(D)



Targeted metabolomics: Seven prototype polyunsaturated fatty acid (PUFA) precursors and 130 species of oxylipin products metabolized by cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome P450s (CYP450s).

Various oxylipin subclasses were associated with recurrent MACE

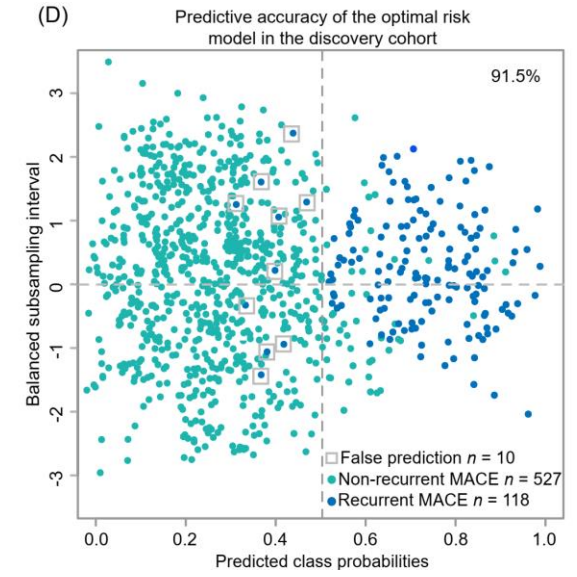
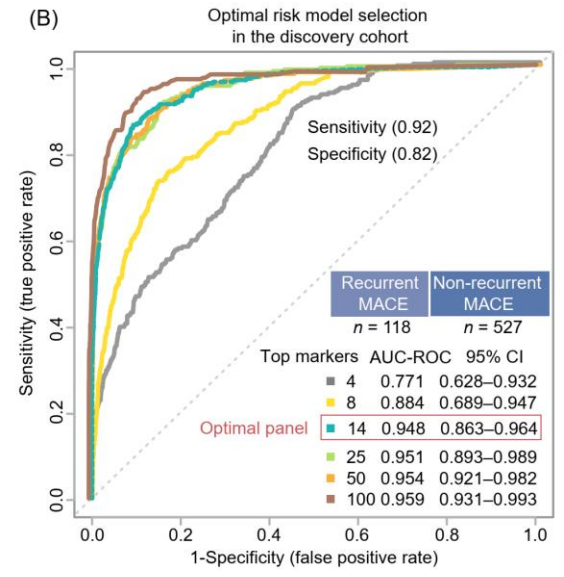
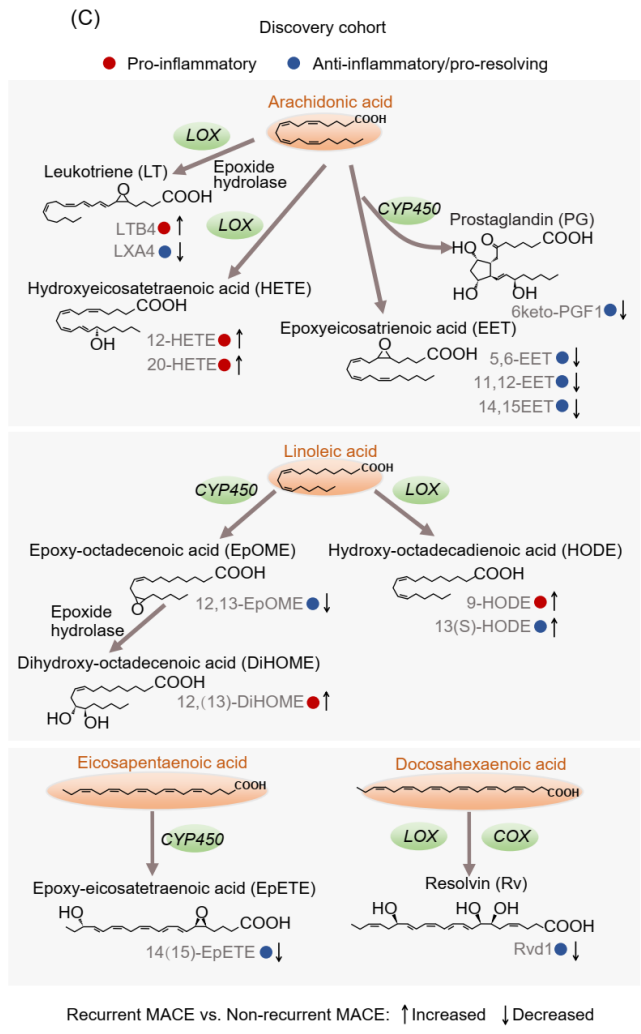
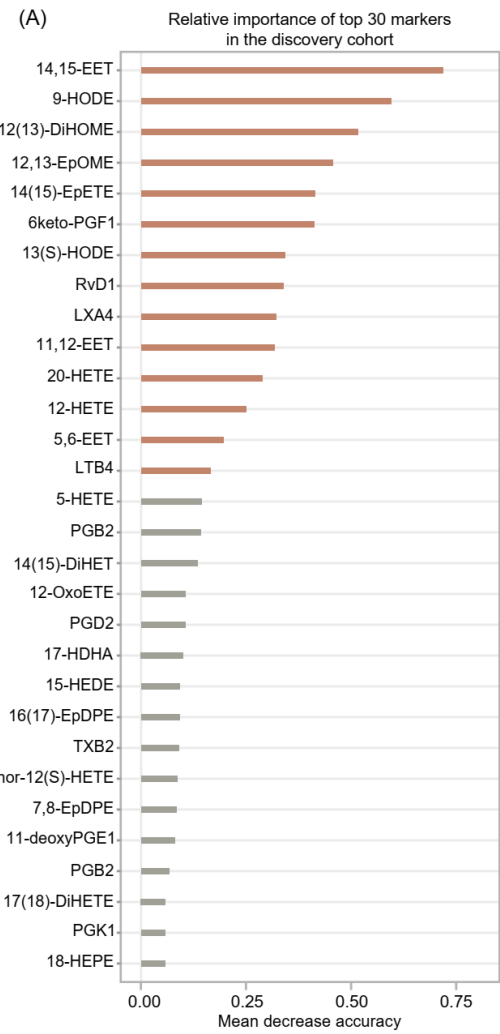
Discovery cohort



□ The differentiated oxylipins between the recurrent MACE and non-recurrent MACE groups were mainly derived from arachidonic acid, eicosapentaenoic acid, and linoleic acid.

□ The differentiated oxylipin mainly included nine subclasses, namely hydroxy-eicosatetraenoic acid, prostanoid, epoxy-eicosatrienoic acid, resolvins, hydroxy-octadecadienoic acid, epoxy-eicosatetraenoic acid, epoxy-octadecenoic acid, hydroxy-eicosapentaenoic acid, and hydroxy-docosahexaenoic acid.

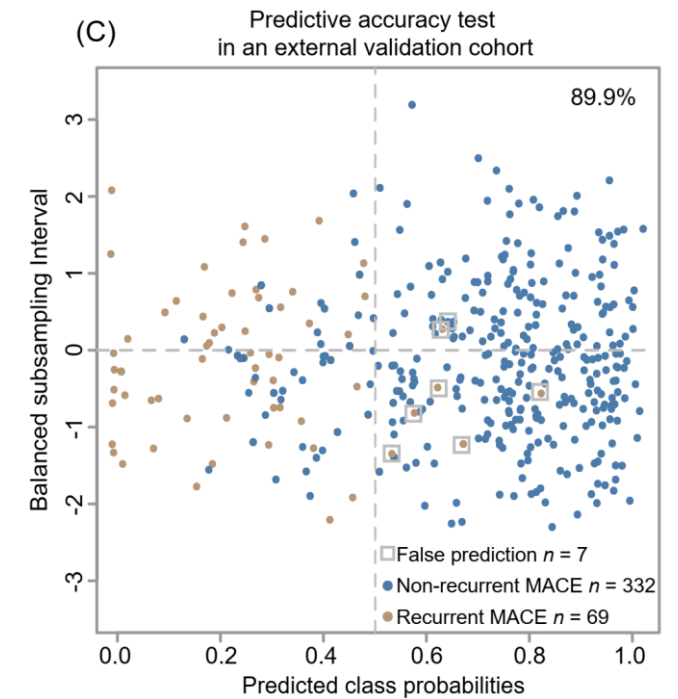
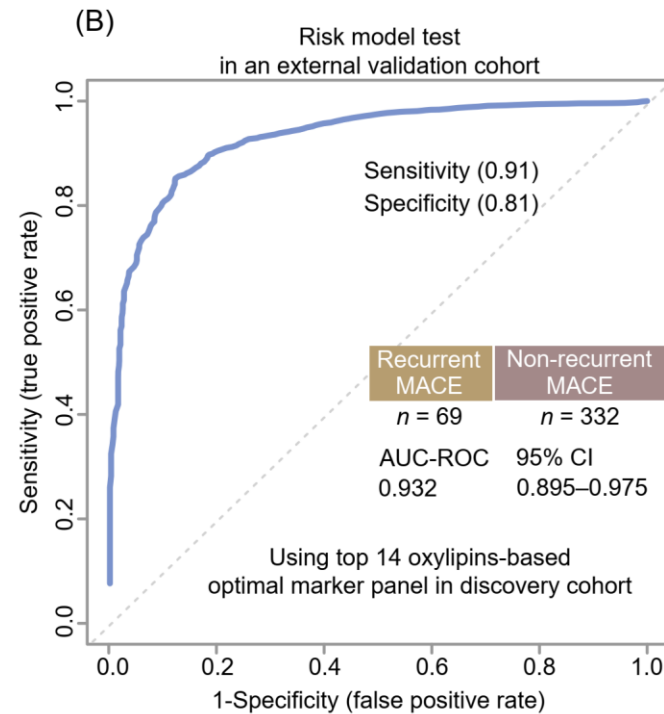
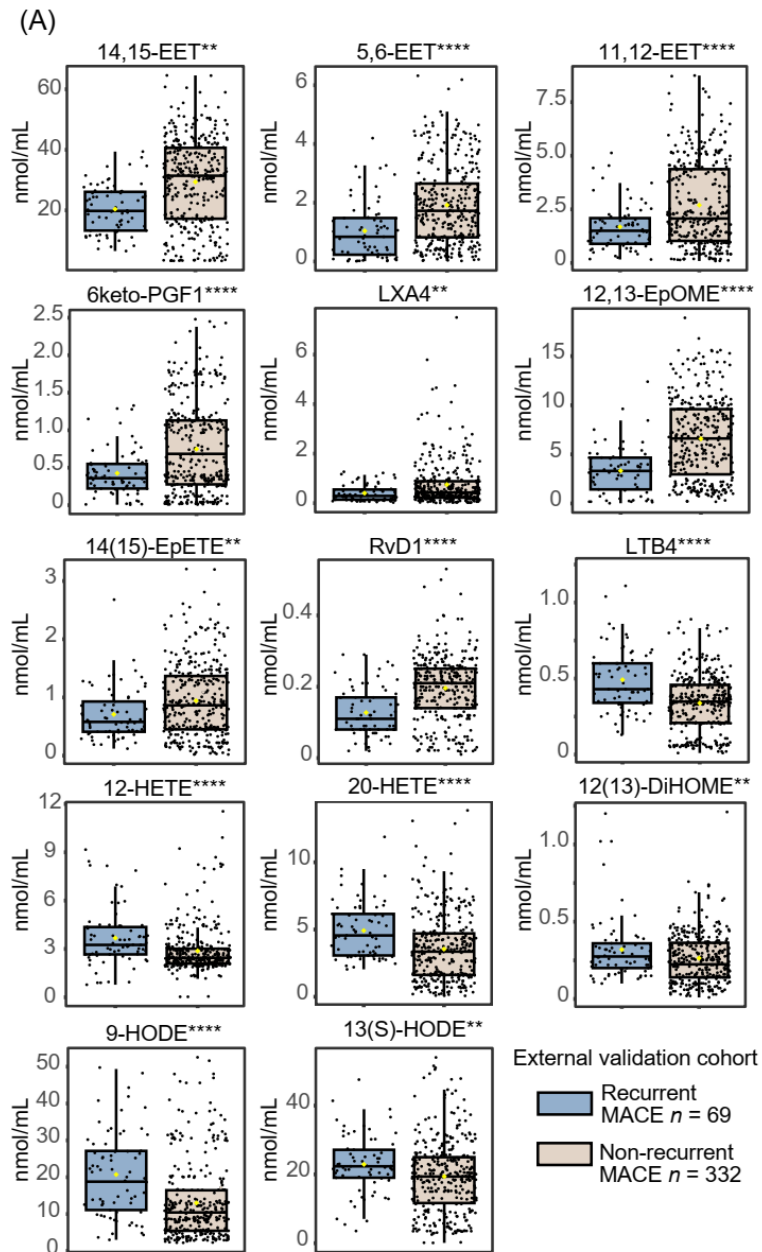
Discovery cohort: Oxylipin-based risk model construction



Random forest algorithm identified an optimal panel consisting of fourteen oxylipins that showed significant performance in predicting recurrent MACE with significant predictive accuracy (91.5%).



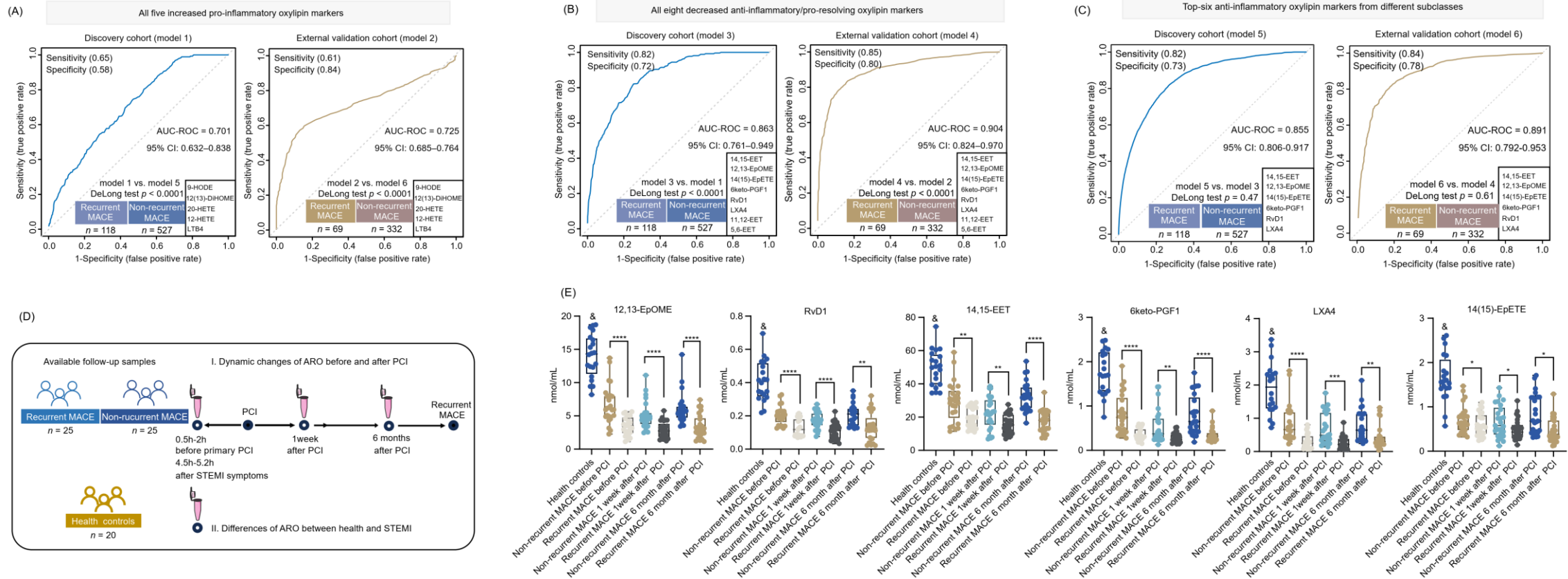
The risk model was confirmed in an external cohort



- The quantitative levels of fourteen oxylipin markers from the discovery cohort was confirmed in an external cohort.
- The predictive accuracy of risk model in the external validation cohort was also highlighted with a significantly accurate prediction rate (89.9%).

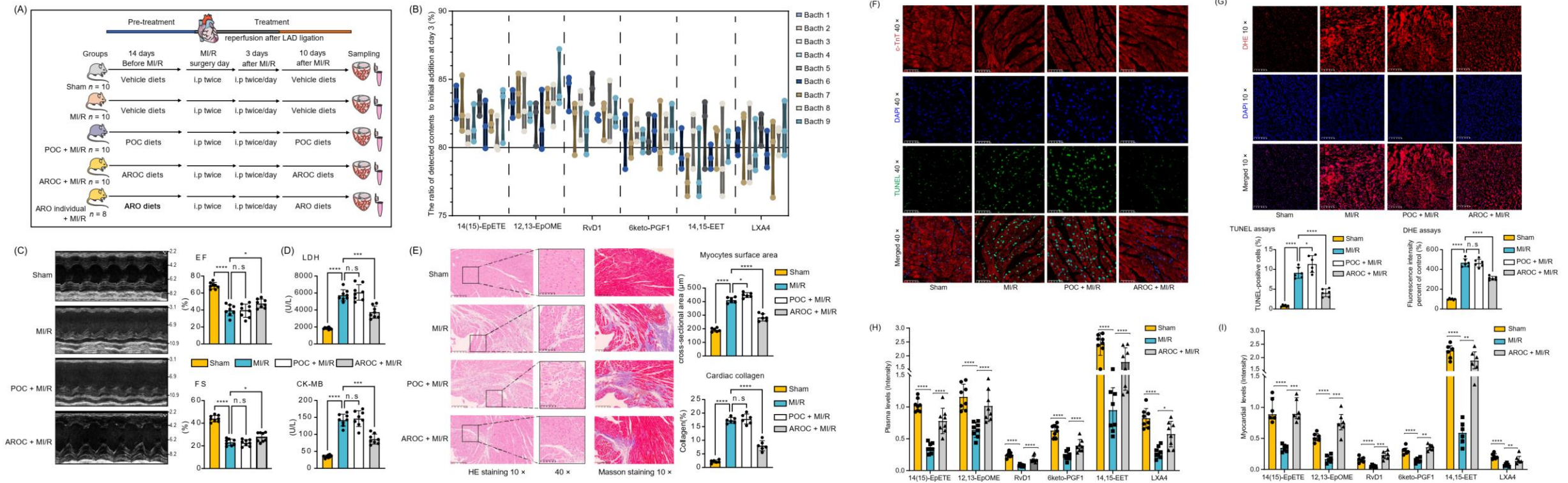


AROs exhibited greater prognostic values than POs



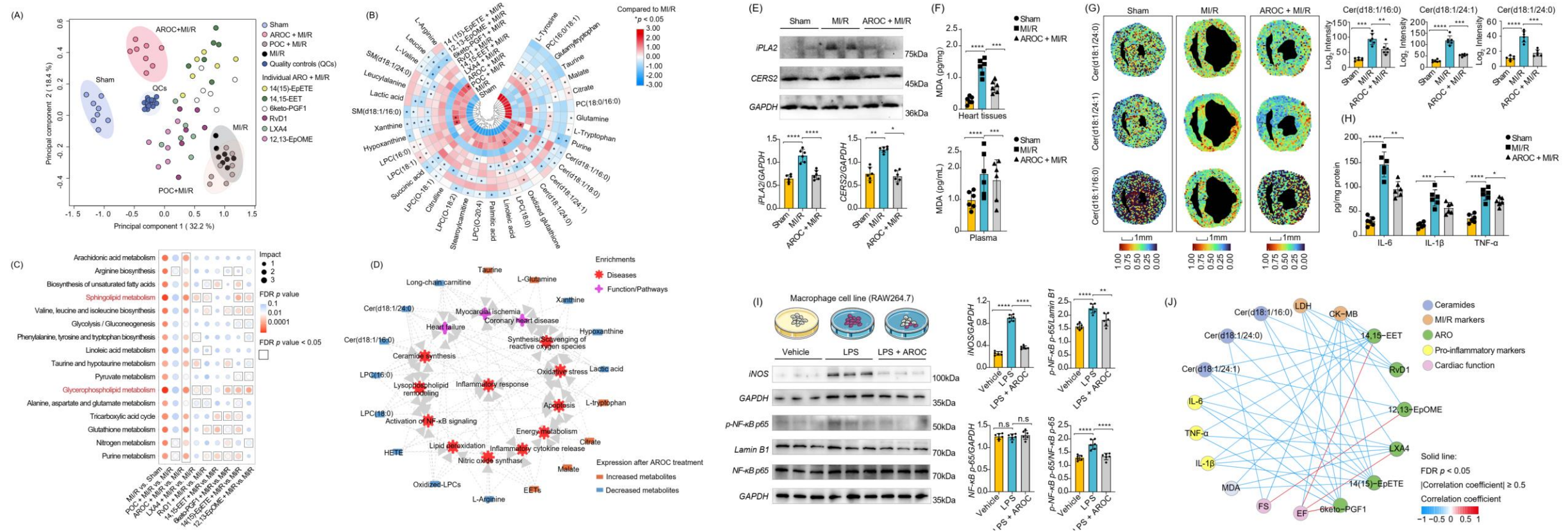
- Top-six anti-inflammatory/pro-resolving oxylipin (ARO) combination showed better predictive performances in differentiating recurrent MACE and non-recurrent MACE than the other top-ARO combination and proinflammatory oxylipins (POs).
- The plasma levels of AROs in healthy individuals were higher than those in STEMI patients with and without recurrent MACE.

AROC exhibited significant cardiac effects on MI/R mice



- Proinflammatory oxylipin combinations (POC) did not alter myocardial injury in myocardial ischemia-reperfusion (MI/R) mice.
- Anti-inflammatory/pro-resolving oxylipin combination (AROC) significantly protected against MI/R-induced abnormalities.
- AROC treatment significantly elevated the plasma and myocardial concentrations of ARO in MI/R mice.

AROC showed synergistic actions on improving metabolic remodeling



□ Different types of anti-inflammatory/pro-resolving oxylipin (ARO) showed various effects on the metabolite profile and pathways in myocardial ischemia-reperfusion (MI/R) mice.

□ AROC significantly inhibited the ceramide and lysophospholipid synthase, and ameliorated their downstream pro-inflammatory signaling, including the nuclear factor-kappa B activation and nitric oxide synthase.



Conclusions

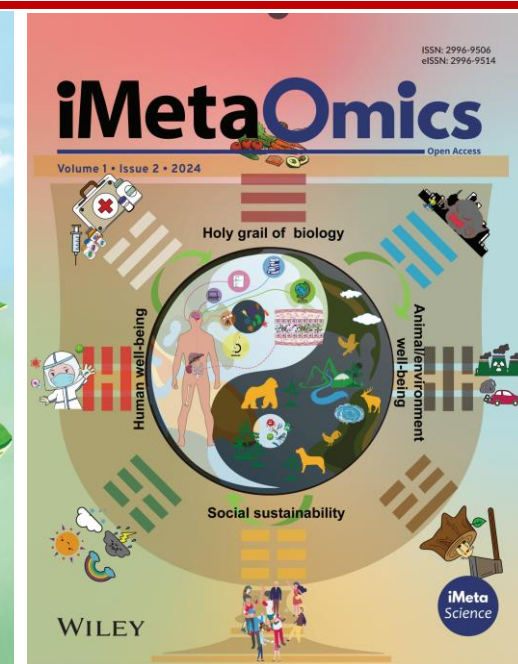
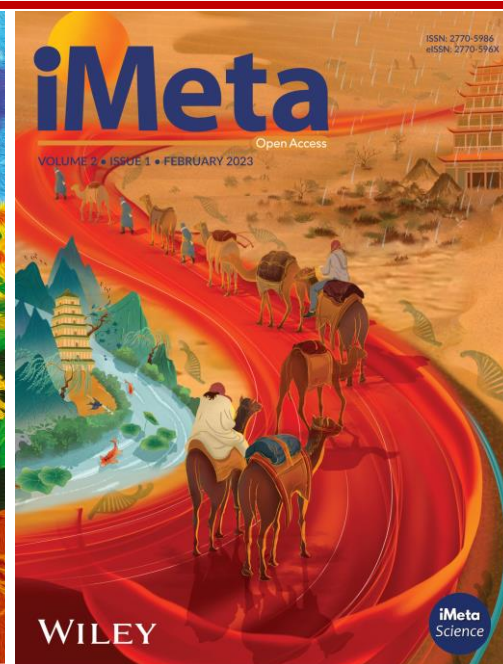
- ❑ In conclusion, the present study demonstrated that a variety of polyunsaturated fatty acid-derived oxylipins serve as residual risk markers for prognosis after ST-segment elevation myocardial infarction (STEMI) .
- ❑ The oxylipin-based risk model exhibited powerful performance in predicting recurrent major adverse cardiovascular event after STEMI.
- ❑ Our study opens a new range of possibilities for the design of bioactive oxylipin agents as intervention points to mitigate post-myocardial infarction pathogenesis with significant therapeutic potential for improving adverse clinical outcomes after STEMI.

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 office@imeta.science
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