

screening potential mortality predictors, in order to as early as possible stratify the mortality risk in anti-MDA5 positive DM patients before making therapeutic strategies.

**Objectives:** To investigate the baseline independent risk factors for predicting 6-month mortality of anti-MDA5-positive DM patients and develop a matrix prediction model formed by these risk factors.

**Methods:** This was a real-world prospective observational study. The hospitalized patients with DM were included if they fulfilled the criteria including: aged over 18 years old; diagnosed as having DM according to the criteria proposed by Bohan and Peter or the modified Sontheimer definitions; and positive anti-MDA5 which was determined by both line immunoassay testing and enzyme-linked immunosorbent testing. The primary outcome was all-cause 6-month mortality after enrolment. A matrix prediction model was built with the mortality risk probability.

**Results:** There were 82 DM patients enrolled (mean age of onset  $50 \pm 11$  years and 63% female), with 40 (49%) showing positive anti-MDA5. Gottron sign/papules (OR: 5.135, 95%CI: 1.489–17.708), arthritis (OR: 5.184, 95%CI: 1.455–18.467), interstitial lung disease (ILD, OR: 7.034, 95%CI: 1.157–42.785), and higher level of C4 (OR: 1.010, 95%CI: 1.002–1.017) were independent associators with positive anti-MDA5 in DM patients. Anti-MDA5-positive DM patients had significant higher 6-month all-cause mortality than those with anti-MDA5-negative (30% vs. 0%). Among anti-MDA5-positive DM patients, compared to the survivors, non-survivors had significantly advanced age of onset ( $59 \pm 6$  years vs.  $46 \pm 9$  years), higher rates of fever (75% vs. 18%), positive carcinoma embryonic antigen (CEA, 75% vs. 14%), higher level of ferritin (median 2858  $\mu\text{g/L}$  vs. 619  $\mu\text{g/L}$ , all  $p < 0.05$ ). Multivariate COX regression showed ferritin  $\geq 1250 \mu\text{g/L}$  (HR: 10.4, 95%CI: 1.8–59.9), fever (HR: 11.2, 95%CI: 2.5–49.9), and positive CEA (HR: 5.2, 95%CI: 1.0–25.7) were independent risk factors of 6-month mortality.

According to the matrix prediction model, anti-MDA5-positive DM patients could be stratified into three subgroups based on various probabilities of predicted mortality: (i) High-risk: eight patients with two of the above three features (including fever, serum ferritin  $\geq 1250 \mu\text{g/L}$ , and positive CEA) had high predicted mortality probability with 64%–85% (three red grids in Figure 1A), and the actual mortality was 75% ( $n=6$ ) with 60%, 100%, and 100% respectively in three red grids (Figure 1B). Five patients with all of three features had extremely high predicted mortality probability with 97% (95%CI: 70%–100%), the dark red grid of Figure 1A), and the actual mortality was 100% in Figure 1B; (ii) Moderate-risk: nine patients with one of the above three features had moderate predicted mortality probability with 11%–29% (three yellow grids in Figure 1A), and the actual mortality was 11% ( $n=1$ ) with 0%, 0%, and 17% respectively in three yellow grids (Figure 1B); (iii) Low-risk: eighteen patients with none of the above three features had low predicted mortality probability with 2% (95%CI: 0.2%–20%), the green grid in Figure 1A), and the actual mortality was 0% in the green grid (Figure 1B).

**Conclusion:** Baseline characteristics of fever, positive CEA, and ferritin  $\geq 1250 \mu\text{g/L}$  are risk factors for 6-month all-cause mortality in anti-MDA5-positive DM patients. A novel matrix prediction model composed of these three clinical indicators is firstly proposed to provide a chance for exploration of individual treatment strategies in anti-MDA5-positive DM subgroups with various probabilities of mortality risk.

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## Translational and Clinical Research in Crystal Arthritis

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### A POPULATION-BASED, PROSPECTIVE METABOLOMICS STUDY IN THE UK BIOBANK IDENTIFIES GLYCOPROTEIN ACETYLS AS A NOVEL BIOMARKER OF INCIDENT GOUT

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**Background:** Serum urate (SU) level is the strongest known causal predictor of clinical gout, but only ~20% with prolonged hyperuricemia develop

gout, motivating the need for additional biomarkers for risk prediction and stratification. The metabolome represents a compelling intermediate trait between genome and phenome to elucidate disease mechanisms. Multiple cross-sectional studies of prevalent gout from men in Asia have been conducted, but no prospective data for incident gout (prediagnostic metabolome) are available.

**Objectives:** Our objectives were to (1) conduct a discovery-based metabolome-wide study to identify novel biomarkers of incident gout; and (2) replicate novel metabolomic biomarkers of gout in independent samples.

**Methods:** We conducted a prospective cohort analysis of 105,703 UK Biobank (UKB) participants (46% males, mean age 57.2 years) with targeted NMR metabolomic profiling ( $N=168$  metabolites, including routine lipids and amino acids) available from baseline samples (2006–10), and no prior diagnosis of gout or urate lowering therapy use. Incident cases of gout were documented from linked medical records until gout diagnosis, death, or end of study period (Dec 31/19). We used Cox proportional hazard models to obtain hazard ratios (HR) and 95% confidence intervals (CIs) per standard deviation (SD) increase in each of the 168 metabolites to determine associations with incident gout.

To replicate our findings, we assessed association of metabolome-wide significant metabolites in a replication set, restricted to 4,804 non-overlapping participants who provided blood in the repeat assessment visit (2012–13).

**Results:** During a median 10.4 years follow-up, we documented 1,367 cases of incident gout in the discovery set. After correction for multiple comparisons, glycoprotein acetyls (GlycA) were positively associated with risk of incident gout (multivariable HR per 1SD increase = 1.34 (1.27 to 1.41),  $P = 9.04 \times 10^{-28}$ ) after adjusting for age, sex, and lifestyle and clinical covariates (Table 1). This association persisted even after SU adjustment (HR 1.07,  $P = 0.0091$ ). In the replication set, among 4,804 participants followed for a median of 6.8 years, we documented 22 cases. In this dataset, we replicated GlycA association with incident gout (multivariable HR per 1SD increase = 1.56 (1.08 to 2.25),  $P = 0.017$ ).

**Conclusion:** In this large-scale, prospective metabolomics study, we identified and independently replicated our findings that plasma levels of GlycA are associated with incident gout in UKB participants. GlycA is novel for gout, though this pro-inflammatory biomarker has predicted risk of other cardiometabolic-inflammatory phenotypes, independent of CRP.<sup>1</sup> These findings may provide insight into the metabolic-inflammatory pathogenesis of gout, with implications for risk prediction, even beyond SU, but call for further investigation with more extensive metabolome profiling and external replication.

**Table 1. Association of glycoprotein acetyls (GlycA) with risk of incident gout in the UK Biobank**

Model	Univariable HR, (95% CI)	P	Multivariable HR, (95% CI)	P
<b>Discovery (N= 105,703)</b>				
Per Standard deviation: GlycA, per SD	1.48 (1.41 to 1.60)	$3.7 \times 10^{-59}$	1.34 (1.27 to 1.41)	$9.04 \times 10^{-28}$
<b>Categorized as quintiles:</b>				
GlycA, Q1	1.0 Ref		1.0 Ref	
GlycA, Q2	1.43 (1.13 – 1.80)	0.002	1.30 (1.03 – 1.64)	0.0252
GlycA, Q3	2.06 (1.66 – 2.56)	$4.88 \times 10^{-11}$	1.73 (1.39 – 2.15)	$7.64 \times 10^{-07}$
GlycA, Q4	2.53 (2.05 – 3.12)	$4.15 \times 10^{-18}$	1.98 (1.60 – 2.45)	$3.96 \times 10^{-10}$
GlycA, Q5	3.70 (3.02 – 4.52)	$3.21 \times 10^{-37}$	2.63 (2.12 – 3.23)	$2.01 \times 10^{-19}$
<b>Replication (N= 4804)</b>				
Per Standard deviation: GlycA, per SD	1.65 (1.19 to 2.29)	0.0027	1.56 (1.08 to 2.25)	0.0172

<sup>1</sup> Hazard ratios (HR) and 95% confidence intervals (CIs) obtained after adjusting for the first 4 genomic principal components (controlling for population stratification), age, sex, fasting (<4 hrs, 4–8 hrs and  $\geq 8$  hrs), smoking (never, former, current), freq of alcohol, BMI, diabetes (yes/no) and hypertension at baseline (yes/ no).

## REFERENCES:

[1] Kettunen; PMID 30571186

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