Circulating blood matrix metalloproteinase (MMP)-10 can accurately predict and track mucosal healing in UC in a prospective, longitudinal cohort study

Cartlidge P[1,2,4], Lau P[1], Hodge M[1], Chuah CS[1,2], Hall R[1,2,4], Ong S[1,2], Le Saint-Grant A[1,2,5], Brownson E[3], Campbell I[3], Whelan R[1], Shafi L[6], Poulose B[1,2], Oddy A[1,2], Mowat C[4], MacDonald J[3], Seenan JP[3], Nowak J[7], Ho GT[1,2], Kalla R[1,5]
[1]Centre for Inflammation Research, University of Edinburgh [2] Western General Hospital, NHS Lothian [3] Queen Elizabeth University Hospital, NHS Greater Glasgow & Clyde [4] Ninewells Hospital, NHS Tayside [5] Royal Infirmary of Edinburgh, NHS Lothian, [6] Leeds Immunogenomics Facility, [7]Poznan University of Medical Sciences

Background

Complete mucosal healing (CMH) is a key prognostic indicator of long-term remission in IBD. We **aim to develop a non-invasive, patient-centred tool, for monitoring IBD activity**.

Methods

Patients with Ulcerative colitis (UC) or Crohn's disease (CD) from the multi-centre, **prospective, observational, longitudinal, MUSIC study** (www.musicstudy.uk) were included. [Figure 1]

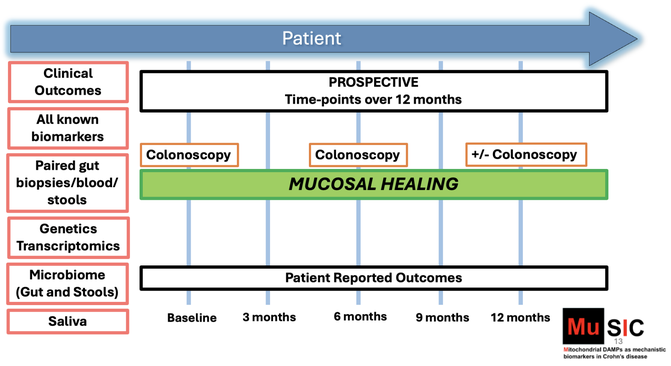


Figure 1: MUSIC Study

CXCL9	OSM	IL6
HGF	CSF1	SCF
IL1RA	CXCL8	MMP10
MMP12	TNF	IL18
GZMB	CXCL11	IFNB1
CXCL10	THPO	ANG1
EMMPRIN	MMP1	TGFA

Figure 2: Protein Panel

A **custom selected 21-protein marker Olink Flex panel** [Figure 2] was applied to **blood plasma samples** collected at timepoint 1 (month 0), timepoint 2 (month 3) and timepoint 3 (month 6).

The Olink proteomics platform uses a **unique proximity extension assay** for highly specific and sensitive quantification of low-abundance proteins. It requires **minimal sample volume (1µl) and is easily scalable.**

All patients had **prospective endoscopic assessment of disease activity at baseline and during follow-up,** with CMH defined by a Mayo score of 0 in UC and SES-CD of 0 in CD.

Statistical analysis was performed using R, adjusting for age, gender and sample batch.

Results

479 samples from 160 IBD patients were analysed in 2 batches [Table 1].

Complete mucosal healing was achieved in 39% of patients at follow-up colonoscopy.

Cohort characteristics	
IBD Type	64 UC / 96 CD
Gender	95 M/ 65 F
Mean age	39.5 years old
Diagnosis <2 years	N=61 (39%)
Advance therapy	N= 123 (77%)
Mean baseline Calpro	635µg/g
Mean baseline UCEIS	4
Mean baseline MES	2
Mean baseline SES-CD	11
Achieved CMH	N=62 (39%)
Mean endoscopy interval	5.5 months

Table 1: Cohort Characteristics

MMP10, MMP 12 and CXCL9 levels are associated with mucosal healing at 6 months in UC and CD combined using differential expression analysis (FDR adjusted p = 0.006, 0.016 and 0.016). [Figure 3]

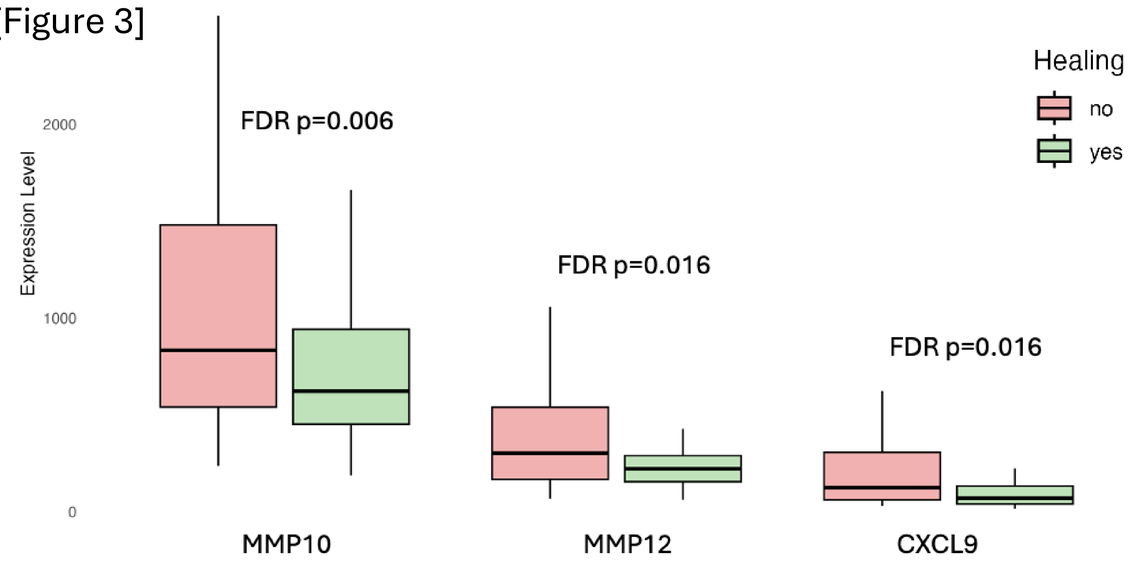


Figure 3: Significant Proteins at timepoint 3

MMP10, MMP12 and CXCL9 individually and combined are significant in UC and CD alone using logistic regression analysis. [Table 2]

Group	Protein	Coefficient	p-value	AUC	N
UC	MMP10	–0.00130	0.0070	0.762	64
UC	MMP12	–0.00230	0.0407	0.750	64
UC	CXCL9	–0.00478	0.0400	0.737	64
UC	MMP10 + MMP12 + CXCL9	—	0.0105	0.770	64
CD	MMP10	–0.00170	0.0077	0.692	95
CD	MMP12	–0.00430	0.0175	0.668	95
CD	CXCL9	–0.00436	0.0424	0.688	95
CD	MMP10 + MMP12 + CXCL9	—	0.0150	0.725	95

Table 2: AUC of Proteins for mucosal healing

MMP10 levels significantly declined over time in UC healers

In UC, the **reduction in MMP10 levels across timepoints 1, 2 and 3 using linear mixed effects model, was associated with CMH** (P = 0.005), but not in CD.

MMP12 and CXCL9 showed no significant dynamic change over time in UC or CD alone. [Figure 4]

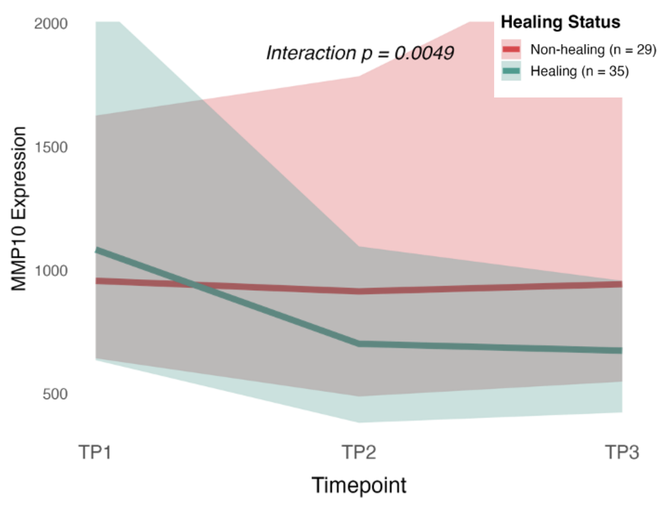
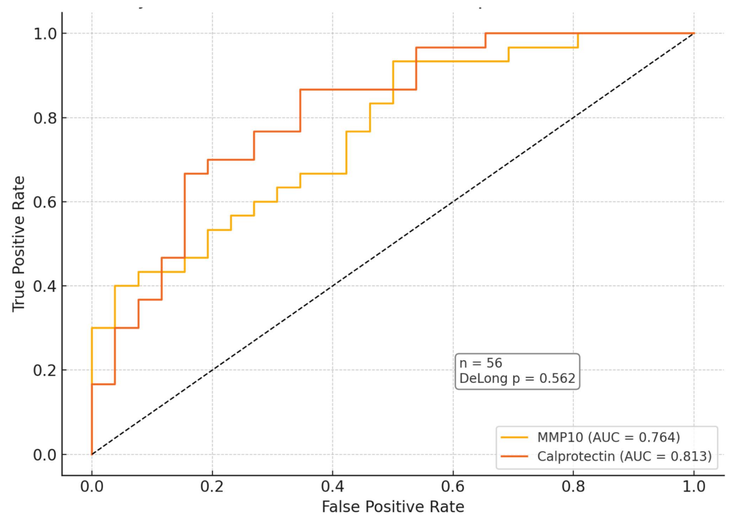


Figure 4: MMP10 change over time

Biomarker performance of MMP10 is comparable to faecal calprotectin in UC



Receiver operator curve (ROC) performance of **MMP 10 (AUC 0.76) is comparable to faecal calprotectin (AUC 0.81) in UC at timepoint 3 in predicting mucosal healing** (DeLong's test p=0.56). [Figure 5]

Figure 5: ROC curves for MMP10 and calprotectin

We conducted an **online IBD patient survey** (N=77). **Patients prefer a blood test over stool test** (p=0.03) when ranking their preferred method of IBD monitoring (from 1 to 5, with 1 being the most preferred). [Figure 6]

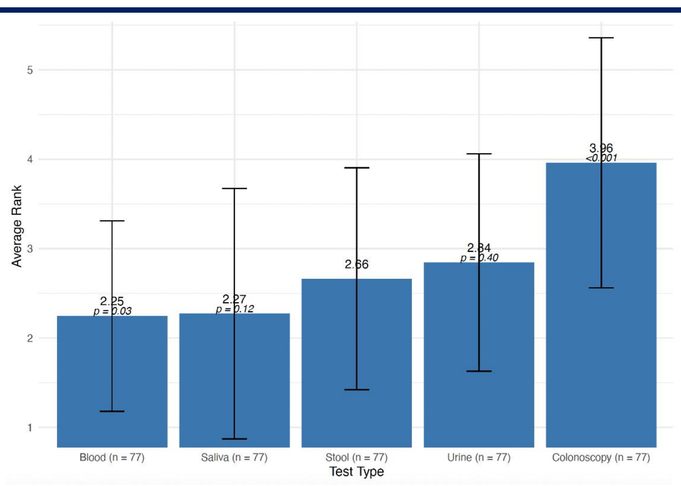


Figure 6: average rankings of IBD monitoring tests

Conclusion

Our study, using minimal blood levels, identifies **MMP-10 protein as a strong and dynamic biomarker for CMH in UC, on par with faecal calprotectin.**

MMP-10 is involved in the tissue degradation and remodelling process of inflamed mucosa. This may explain the decreased levels observed in the blood as inflammation resolves.

Patients highlight a **preference for blood tests over stool** tests for monitoring IBD activity.

Further validation work is being undertaken in phase 2 of this study.

The authors have no potential conflict of interest to disclose
Contact e-mail: pcartlid@ed.ac.uk