TITLE: Systemic matrix metalloproteinases (MMPs) are associated with disease severity in chronic respiratory diseases: a national registry–based study.

AUTHORS:

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ABSTRACT:

Matrix metalloproteinases (MMP) are endogenous proteases involved in airway inflammation and lung tissue remodelling, key drivers of chronic respiratory diseases pathophysiology. Evidence on the clinical implications of the activity of single proteases remains limited and heterogenous, limiting their use as biomarkers of disease severity.

We conducted a cross-sectional study including patients with asthma and chronic obstructive pulmonary diseases enrolled in a national patient registry. Disease severity was assessed using a set of clinical and patient-reported outcomes including pulmonary function, number of pulmonary exacerbations, hospitalizations and emergency department (ED) visits in the previous year, therapy, Saint George Respiratory Questionnaire score (SGRQ), Asthma Control Test score (ACT), and Medical Research Council (MRC) dyspnoea scale. Associations between MMPs and disease severity were assessed using multivariable statistical models adjusted for relevant confounders.

The study included 367 patients (median age, 63 years, range: 18-92; 222 with asthma,136 with COPD, and 9 patients with both conditions). Serum levels of MMP3 and MMP9 were associated with increased rates of exacerbations (rate ratio per one standard deviation increase in serum concentration, RR: 1.39, 95% CI: 1.18-1.64), hospitalizations (RR: 2.10, 95% CI: 1.64-2.70), ED visits (RR: 1.83, 95% CI: 1.47-2.28), as well as use of inhaled triple therapy (odds ratio: 1.62, 95% CI: 1.14-2.32). High circulating levels of MMP3 and MMP9 are associated with increased disease severity in individuals with asthma and COPD, supporting their potential role as biomarkers and therapeutic targets in chronic respiratory diseases.

TABLES AND FIGURES

Table 1: Patients' characteristics

Characteristic	N = 367[a]
Male sex	185 (50.4%)
Age (years)	63.0 (53.0; 72.0)
White-European descents	342 (93.2%)
BMI (Kg/m2)	25.2 (22.1; 28.8)
Unknown	128
BMI category	
Underweight	12 (5.0%)
Normal weight	103 (43.1%)
Overweight	80 (33.5%)
Obesity	44 (18.4%)
Unknown	128
Smoking status	
Current	62 (16.9%)
Former	176 (48.0%)
Never	129 (35.1%)
Pack-years of cigarettes	
0	129 (35.1%)
<11	54 (14.7%)
11-20	37 (10.1%)
21-40	58 (15.8%)
40+	89 (24.3%)
Asthma	231 (62.9%)
COPD	145 (39.5%)
Any circulatory disease	71 (19.3%)
Myocardial infarction	22 (6.0%)
Angina	14 (3.8%)
Heart failure	16 (4.4%)
Atrial fibrillation	30 (8.2%)
Stroke	16 (4.4%)
Diabetes	42 (11.4%)
Cirrhosis	3 (0.8%)
Chronic renal failure	12 (3.3%)
Neoplastic disease	53 (14.4%)
MMP1 (ug/mL)	11.7 (7.2; 17.4)
MMP2 (ug/mL)	193.0 (160.4; 232.3)
MMP3 (ug/mL)	54.3 (28.6; 88.3)
MMP7 (ug/mL)	26.6 (18.2; 37.8)
MMP9 (ug/mL)	276.4 (174.2; 448.5)
MMP10 (ug/mL)	0.7 (0.5; 1.0)
TIMP1 (ug/mL)	110.1 (90.9; 131.8)
TIMP2 (ug/mL)	52.2 (43.3; 65.3)

BMI: Body mass index. COPD: Chronic obstructive pulmonary disease. LAMA: Long-acting muscarinic antagonist. MMP: Metalloproteinase. $ppFEV_1$: Percent predicted forced expiratory volume in one second. TIMP: Tissue inhibitor of metalloproteinases.

[a] Data are summarised as frequency (%) or median (25^{th} – 75^{th} percentile)

Table 2: Disease severity and therapies.

Clinical outcome/therapy	N = 367[a]
$ppFEV_1$	82.0 (64.0; 97.0)
Unknown	60
SGRQ score	34.2 (17.0; 55.2)
Unknown	41
ACT score	20.0 (14.0; 24.0)
Unknown	34
MRC dyspnoea scale	
0	115 (33.4%)
1	112 (32.6%)
2	47 (13.7%)
3	52 (15.1%)
4	18 (5.2%)
Unknown	23
Number of EXAC over the previous year	
0	188 (51.2%)
1	97 (26.4%)
2	48 (13.1%)
3	17 (4.6%)
4	6 (1.6%)
5	2 (0.5%)
6	5 (1.4%)
8	1 (0.3%)
10	3 (0.8%)
Number of HOSP over the previous year	
0	310 (84.5%)
1	43 (11.7%)
2	11 (3.0%)
3	3 (0.8%)
Number of ED visits over the previous year	
0	288 (78.5%)
1	58 (15.8%)
2	17 (4.6%)
3	2 (0.5%)
4	2 (0.5%)
SABA	27 (7.4%)
LABA	20 (5.4%)
LAMA	85 (23.2%)
ICS	18 (4.9%)
LABA/LAMA/ICS	50 (13.6%)
OCS	30 (8.2%)
Biologic therapy	53 (14.4%)
Oxygen therapy	
No	320 (87.2%)
Only maintenance	36 (9.8%)
Only on demand	5 (1.4%)
Both maintenance and on demand	6 (1.6%)

ACT: Asthma control test. ED: Emergency department. EXAC: Pulmonary exacerbation. HOSP: Hospitalization for pulmonary exacerbation. ICS: Inhaled corticosteroid. LABA: Long-acting β_2-agonist. LAMA: Long-acting muscarinic antagonist. MRC: Medical Research Council. OCS: Oral corticosteroid. SABA: Short-acting β_2-agonist. SGRQ: St. George's respiratory questionnaire.
[a] Data are summarised as frequency (%) or median (25^{th} – 75^{th} percentile)

FIGURES

Figure 1: Flowchart of patient exclusion.

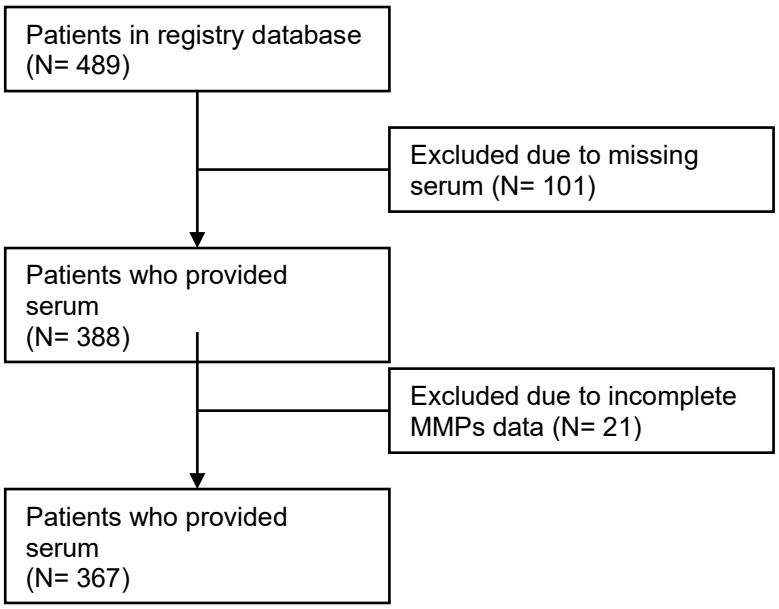


Figure 2: Estimated changes in median ppFEV$_1$ (a), SGRQ score (b), and ACT score (c) per one–standard deviation increase in MMPs and TIMPs. Estimates are colour-coded with grey indicating changes that were not statistically significant after adjustment for multiple testing. Error bars denote 95% confidence intervals.

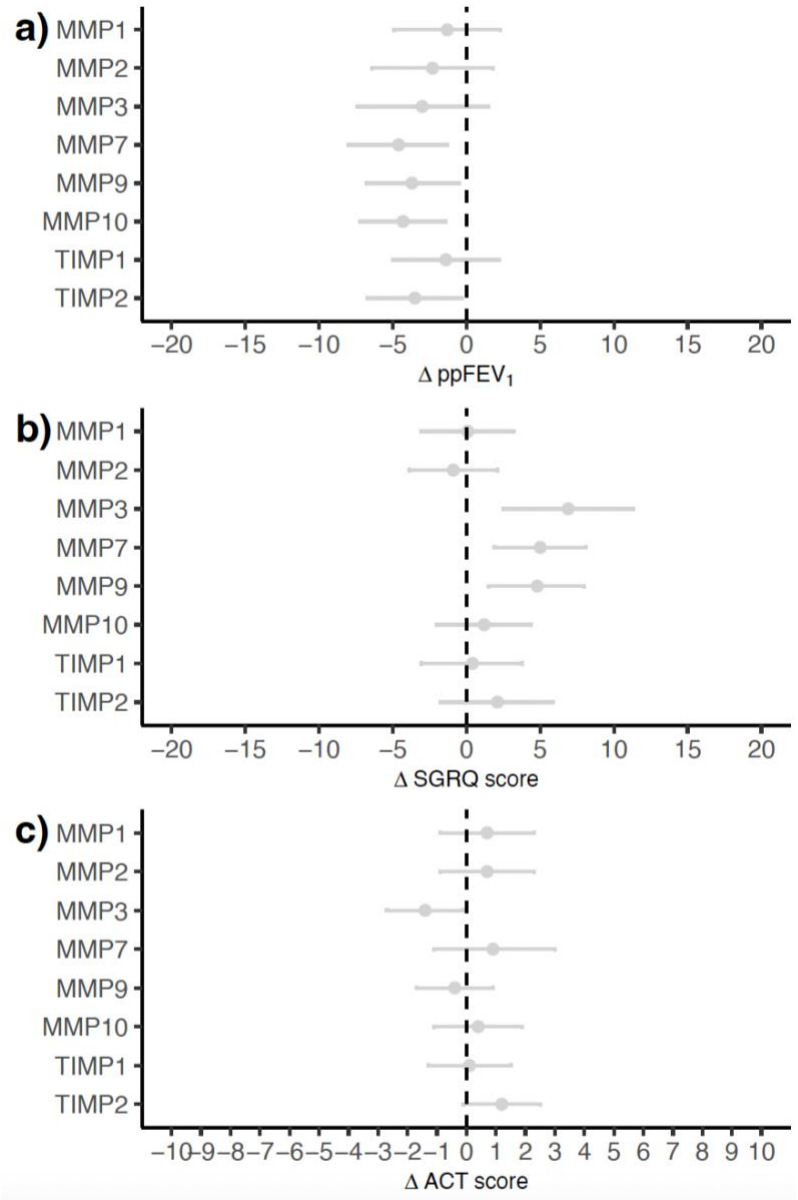


Figure 3: Estimated odds ratios (ORs) for increased MRC dyspnoea score (a) and rate ratios (RRs) for pulmonary exacerbations (EXAC) (b), hospitalisations (HOSP) (c), and emergency department (ED) visits (d) per one–standard deviation increase in MMPs and TIMPs. Estimates are colour-coded, with grey indicating non-statistically significant results after adjustment for multiple testing and blue indicating statistically significant results. Error bars represent 95% confidence intervals.

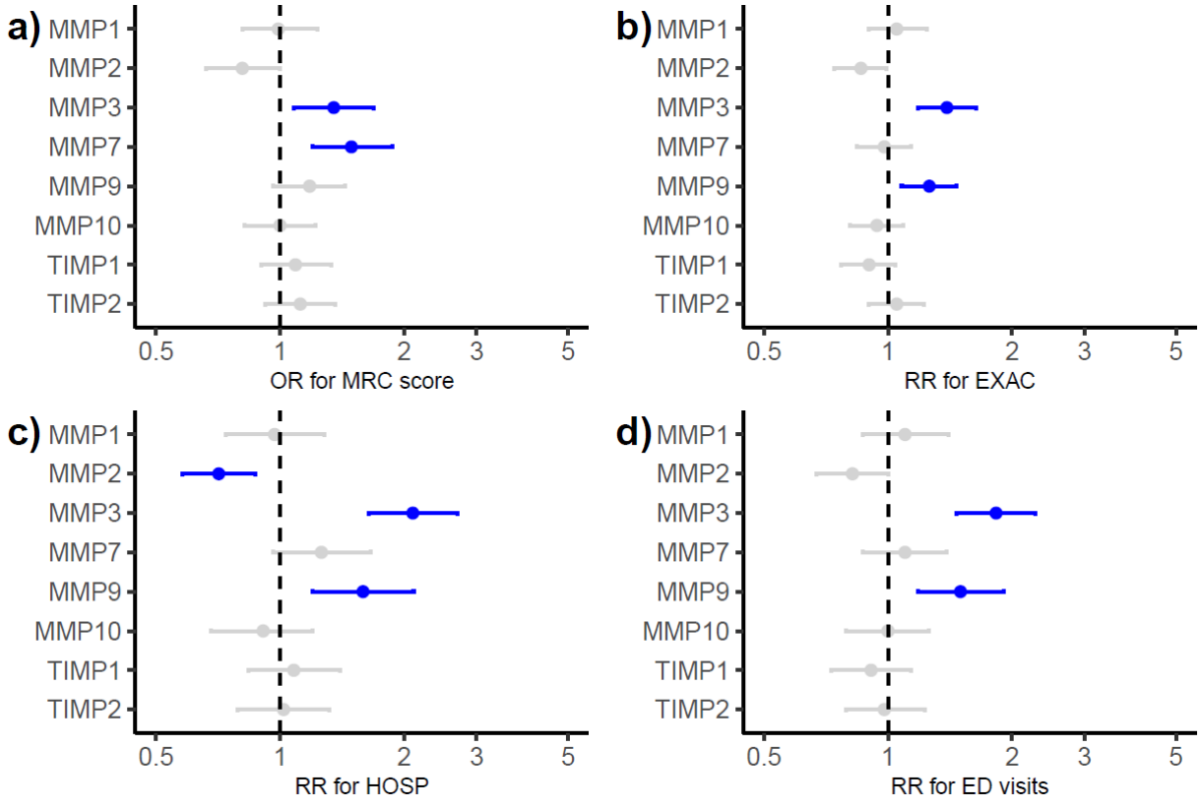


Figure 4: Estimated odds ratios (ORs) for LABA/LAMA/ICS triple therapy use (a) biologic therapy (b), OCS (c), and any oxygen supplemental therapy (d) per one–standard deviation increase in MMPs and TIMPs. Estimates are colour-coded, with grey indicating non-statistically significant results after adjustment for multiple testing and blue indicating statistically significant results. Error bars represent 95% confidence intervals.

