

Non-invasive markers of liver fibrosis for monitoring of long-term methotrexate therapy: A multi-centre longitudinal cohort study

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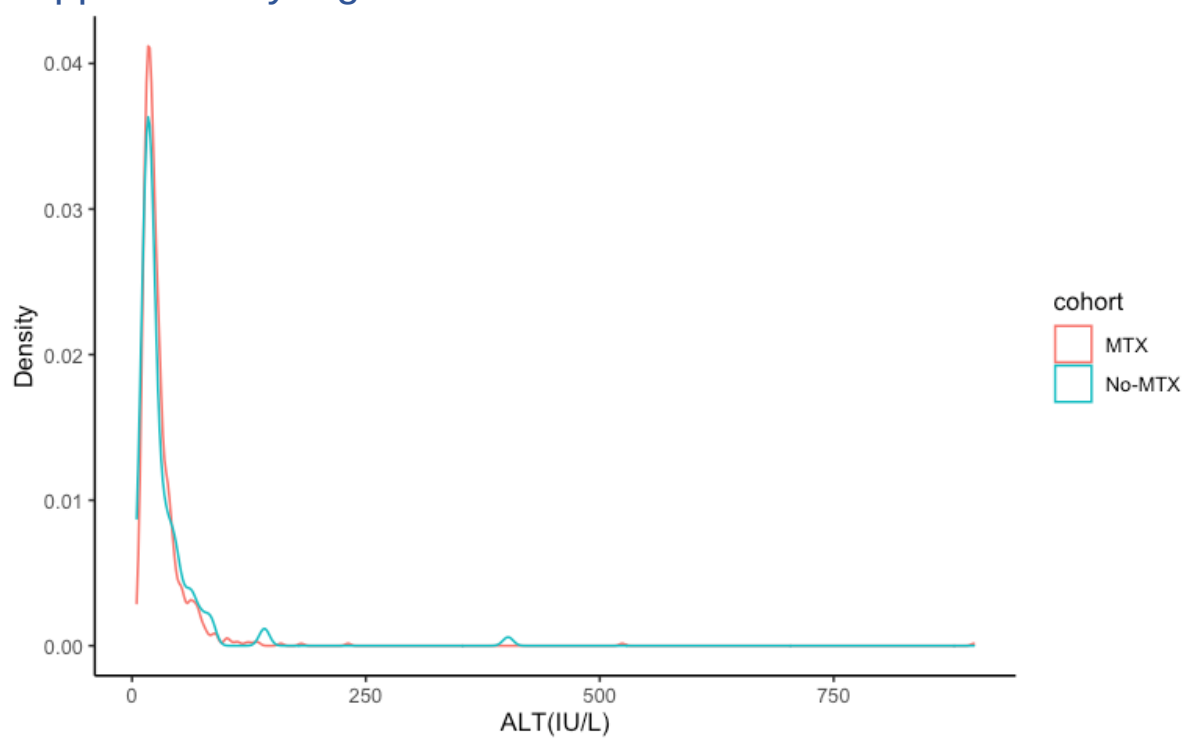
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Supplementary Figure 1. Kernel density plot of ALT in exposed (MTX) and unexposed (no-MTX) cohorts

Supplementary Tables

Supplementary Table 1. Distribution of patients recruited across sites

Site	Number of participants	Age (years), mean (SD)	Female, n (%)
Bradford	359	61.7 (12.3)	231 (64.3)
Brighton	17	58 (9.6)	13 (76.5)
Cornwall	425	62.1 (11.1)	258 (60.7)
Nottingham	146	56.8 (12.7)	88 (60.3)
Portsmouth	46	56.8 (13.1)	29 (63)
Sussex	6	62.6 (9.7)	3 (50)

Supplementary Table 2. Summary of medications taken per group

Medications, n (%)	MTX (n = 876)	No-MTX (n = 123)	P
NSAIDs	170 (19.4)	36 (29.3)	0.01
Steroids	53 (6.1)	9 (7.3)	0.59
Statins	168 (19.2)	23 (18.7)	0.9
Sulfasalazine	134 (15.3)	25 (20.3)	0.15
Hydroxychloroquine	136 (15.5)	11 (8.9)	0.054
Etanercept	34 (3.9)	1 (0.8)	0.11*
Adalimumab	35 (4.0)	2 (1.6)	0.30*
Rituximab	26 (3.0)	0	0.06*
Metformin	47 (5.4)	13 (10.6)	0.02
Gliclazide	14 (1.6)	5 (4.1)	0.07*
Dapagliflozin	2 (0.2)	2 (1.6)	0.08*
Gliptin	5 (0.6)	3 (2.4)	0.06*
Insulin	8 (0.9)	2 (1.6)	0.35*
Glitazone	4 (0.5)	0	1*

Supplementary Table 2. P values were derived from the Chi-square test. *Fisher's Exact Test was applied because one or more expected cell counts in the cross-tabulation were less than 5.

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs.

Supplementary Table 3. Factors associated with elevated ALT > ULN

Factors	Adjusted OR	95% CI	P
MTX cumulative dose	0.94	0.89 – 1.00	0.05
Age	0.96 ***	0.94 – 0.98	<0.001
Sex (Male)	1.19	0.72 – 1.96	0.49
Psoriatic arthritis	1.43	0.75 – 2.58	0.25
BMI	1.04 *	1.00 – 1.07	0.046
Diabetes	1.24	0.58 – 2.47	0.56
Alcohol > 14 units/week	1.19	0.52 – 2.45	0.66
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 3. Multivariable logistic regression model of ALT > ULN (45IU/L) in patients with arthritis on MTX (MTX cumulative dose was used as the independent variable). **Abbreviations:** alanine transaminase, BMI: body mass index, CI: confidence interval, MTX: methotrexate, OR: odds ratio, ULN: upper limit of normal.

Supplementary Table 4. Factors associated with elevated liver stiffness ≥ 7.9 kPa

Factors	Unadjusted OR	P	Adjusted OR	95% CI	P
MTX duration	0.997*	0.04	0.999	0.996 – 1.002	0.44
Age	1.003	0.63	1.02 *	1.00 – 1.04	0.04
Sex (Male)	1.56*	0.01	1.61 *	1.07 – 2.44	0.02
Psoriasis	1.74 **	0.003	1.52	0.99 – 2.32	0.06
BMI	1.13***	<0.001	1.13 ***	1.10 – 1.17	<0.001
Type 2 Diabetes	5.25***	<0.001	3.16 ***	1.93 – 5.15	<0.001
Hyperlipidaemia	1.97***	<0.001	1.23	0.77 – 1.94	0.38
Hypertension	2.33***	<0.001	1.34	0.87 – 2.07	0.18
Alcohol (> 14 units/week)	0.76	0.37	0.68	0.33 – 1.31	0.27
* p<0.05 ** p<0.01 *** p<0.001					

Supplementary Table 4. Univariable and multivariable logistic regression model of liver stiffness ≥ 7.9 kPa in the whole population (MTX duration was used as the independent variable).

Abbreviations: BMI: body mass index, CI: confidence interval, MTX: methotrexate, OR: odds ratio.

Supplementary Table 5. Factors associated with elevated liver stiffness ≥ 7.9 kPa

Factors	Unadjusted OR	P	Adjusted OR	95% CI	P
MTX cumulative dose	0.96	0.06	0.97	0.93 – 1.01	0.17
Age	1.003	0.63	1.01	1.00 – 1.03	0.14
Sex (Male)	1.56*	0.01	1.48 *	1.02 – 2.14	0.04
Psoriasis	1.74 **	0.003	1.76 **	1.19 – 2.60	0.004
MAFLD	3.00***	<0.001	2.73 ***	1.58 – 5.08	<0.001
Alcohol (>14 units/week)	0.76	0.37	0.70	0.36 – 1.28	0.28
* p<0.05 ** p<0.01 *** p<0.001					

Supplementary Table 5. Univariable and multivariable logistic regression model of liver stiffness ≥ 7.9 kPa in the whole population (MTX cumulative dose was used as the independent variable).

Abbreviations: BMI: body mass index, CI: confidence interval, MAFLD: metabolic dysfunction-associated fatty liver disease MTX: methotrexate, OR: odds ratio.

Supplementary Table 6. Factors associated with elevated liver stiffness ≥ 7.9 kPa

Factors	Unadjusted OR	P	Adjusted OR	95% CI	P
MTX duration	0.997*	0.04	1.00	0.99 – 1.00	0.06
Age	1.003	0.63	1.01	1.00 – 1.03	0.10
Sex (Male)	1.56*	0.01	1.47 *	1.02 – 2.13	0.04
Psoriasis	1.74 **	0.003	1.78 **	1.20 – 2.62	0.004
MAFLD	3.00***	<0.001	2.70 ***	1.56 – 5.01	<0.001
Alcohol (>14 units/week)	0.76	0.37	0.69	0.35 – 1.26	0.25
* p<0.05 ** p<0.01 *** p<0.001					

Supplementary Table 6. Univariable and multivariable logistic regression model of liver stiffness ≥ 7.9 kPa in the whole population (MTX duration was used as the independent variable).

Abbreviations: BMI: body mass index, CI: confidence interval, MAFLD: metabolic dysfunction-associated fatty liver disease, MTX: methotrexate, OR: odds ratio.

Supplementary Table 7. Factors associated with elevated ELF ≥ 9.8

Factors	Unadjusted OR	P	Adjusted OR	95% CI	P
MTX duration	1.003**	0.002	1.002	1.000 – 1.004	0.08
Age	1.06***	<0.001	1.07 ***	1.05 – 1.09	<0.001
Sex (Male)	1.17	0.30	1.16	0.83 – 1.60	0.39
Psoriasis	0.63**	0.007	0.84	0.58 – 1.21	0.36
BMI	1.003	0.72	1.03 *	1.007 – 1.06	0.01
Type 2 Diabetes	1.49	0.07	1.24	0.77 – 1.97	0.37
Hyperlipidaemia	1.27	0.14			
Hypertension	1.66***	<0.001	1.09	0.77 – 1.54	0.62
Alcohol > 14 units	0.74	0.24	0.76	0.44 – 1.28	0.32
Regular NSAIDs	1.47*	0.02	1.75 **	1.20 – 2.55	0.003
* p<0.05 ** p<0.01 *** p<0.001					

Supplementary Table 7. Univariable and multivariable logistic regression model of ELF score ≥ 9.8 in the whole population (MTX duration was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio.

Supplementary Table 8. Factors associated with elevated ELF ≥ 9.8 in patients with RA

Factors	Adjusted OR	95% CI	P
MTX cumulative dose	1.05 **	1.02 – 1.09	0.005
Age	1.07 ***	1.05 – 1.09	<0.001
Sex (Male)	1.26	0.86 – 1.84	0.23
BMI	1.04 **	1.01 – 1.08	0.008
Diabetes	0.98	0.55 – 1.71	0.94
Hypertension	0.95	0.63 – 1.41	0.78
Alcohol > 14 units/week	0.58	0.28 – 1.09	0.10
Regular NSAIDs	1.73 *	1.13 – 2.64	0.01
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 8. Multivariable logistic regression for ELF ≥ 9.8 in patients with RA (MTX cumulative dose was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio, RA: rheumatoid arthritis.

Supplementary Table 9. Factors associated with elevated ELF ≥ 9.8 in patients with RA

Factors	Adjusted OR	95% CI	P
MTX duration	1.004 **	1.001 – 1.006	0.007
Age	1.06 ***	1.044 – 1.088	<0.001
Sex (Male)	1.29	0.878 – 1.879	0.19
BMI	1.04 **	1.012 – 1.077	0.007
Diabetes	0.98	0.545 – 1.715	0.93
Hypertension	0.96	0.644 – 1.432	0.85
Alcohol > 14 units/week	0.57	0.283 – 1.090	0.10
Regular NSAIDs	1.72 *	1.123 – 2.626	0.01
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 9. Multivariable logistic regression for ELF ≥ 9.8 in patients with RA (MTX duration was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio, RA: rheumatoid arthritis.

Supplementary Table 10. Factors associated with elevated ELF ≥ 9.8 in patients with psoriasis

Factors	Adjusted OR	95% CI	P
MTX cumulative dose	0.99	0.92 – 1.05	0.69
Age	1.07 ***	1.03 – 1.11	<0.001
Sex (Male)	0.78	0.38 – 1.59	0.50
BMI	1.01	0.96 – 1.06	0.75
Diabetes	2.14	0.90 – 4.97	0.08
Hypertension	1.70	0.82 – 3.50	0.15
Alcohol > 14 units/week	1.50	0.58 – 3.68	0.39
Regular NSAIDs	2.11	0.88 – 4.97	0.09
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 10. Multivariable logistic regression for ELF ≥ 9.8 in patients with psoriasis (MTX cumulative dose was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio.

Supplementary Table 11. Factors associated with elevated ELF ≥ 9.8 in patients with psoriasis

Factors	Adjusted OR	95% CI	P
MTX duration	1.00	0.99 – 1.00	0.38
Age	1.07 ***	1.04 – 1.11	<0.001
Sex (Male)	0.78	0.37 – 1.59	0.50
BMI	1.01	0.96 – 1.06	0.78
Diabetes	2.06	0.87 – 4.81	0.1
Hypertension	1.75	0.84 – 3.61	0.13
Alcohol > 14 units/week	1.47	0.57 – 3.59	0.41
Regular NSAIDs	2.19	0.90 – 5.19	0.08
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 11. Multivariable logistic regression for ELF ≥ 9.8 in patients with psoriasis (MTX duration was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio.

Supplementary Table 12. Factors associated with elevated ELF ≥ 9.8

Factors	Unadjusted OR	P	Adjusted OR	95% CI	P
MTX cumulative dose	1.05***	<0.001	1.04 *	1.00 – 1.07	0.03
Age	1.06***	<0.001	1.07 ***	1.05 – 1.08	<0.001
Sex (Male)	1.17	0.30	1.15	0.83 – 1.58	0.40
Psoriasis	0.63**	0.007	0.91	0.62 – 1.31	0.61
MAFLD	1.02	0.9	1.21	0.82 – 1.81	0.34
Alcohol > 14 units	0.74	0.24	0.76	0.44 – 1.27	0.30
Regular NSAIDs	1.47*	0.02	1.68 **	1.16 – 2.43	0.006
* p<0.05 ** p<0.01 *** p<0.001					

Supplementary Table 12. Multivariable logistic regression for ELF ≥ 9.8 (MTX cumulative dose was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MAFLD: metabolic dysfunction-associated fatty liver disease, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio.

Supplementary Table 13. Factors associated with elevated ELF ≥ 9.8

Factors	Unadjusted OR	P	Adjusted OR	95% CI	P
MTX duration	1.003**	0.002	1.00	1.00 – 1.00	0.18
Age	1.06***	<0.001	1.07 ***	1.05 – 1.08	<0.001
Sex (Male)	1.17	0.30	1.15	0.83 – 1.59	0.40
Psoriasis	0.63**	0.007	0.88	0.60 – 1.26	0.48
MAFLD	1.02	0.9	1.21	0.82 – 1.80	0.35
Alcohol > 14 units	0.74	0.24	0.77	0.45 – 1.28	0.33
Regular NSAIDs	1.47*	0.02	1.68 **	1.16 – 2.43	0.006
* p<0.05 ** p<0.01 *** p<0.001					

Supplementary Table 13. Multivariable logistic regression for ELF ≥ 9.8 (MTX duration was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MAFLD: metabolic dysfunction-associated fatty liver disease, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio.

Supplementary Table 14. Factors associated with liver stiffness in the exposed (MTX) group

MTX/ group

Factors	Estimates	95% CI	P
(Intercept)	0.7476 ***	0.6619 – 0.8333	<0.001
MTX cumulative dose	-0.0001	-0.0023 – 0.0020	0.89
Age	0.0011 *	0.0001 – 0.0021	0.03
Sex (Male)	0.0271 *	0.0050 – 0.0491	0.02
Psoriasis	0.0221	-0.0020 – 0.0462	0.07
BMI	0.0068 ***	0.0051 – 0.0085	<0.001
Type 2 Diabetes	0.0845 ***	0.0498 – 0.1192	<0.001
Hyperlipidaemia	0.0224	-0.0036 – 0.0483	0.09
Hypertension	-0.0034	-0.0277 – 0.0209	0.78
Alcohol (>14 units/week)	0.0150	-0.0204 – 0.0505	0.40
R ² / R ² adjusted	0.143 / 0.133		
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 14. Multivariable linear regression model of liver stiffness in cases (MTX cumulative dose was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate.

Supplementary Table 15. Factors associated with liver stiffness in the exposed (MTX) group

MTX group			
Factors	Estimates	95% CI	P
(Intercept)	0.7493 ***	0.6638 – 0.8347	<0.001
MTX duration	-0.0001	-0.0002 – 0.0001	0.48
Age	0.0012 *	0.0002 – 0.0022	0.02
Sex (Male)	0.0270 *	0.0050 – 0.0490	0.02
Psoriasis	0.0225	-0.0015 – 0.0465	0.07
BMI	0.0067 ***	0.0050 – 0.0084	<0.001
Diabetes	0.0838 ***	0.0491 – 0.1184	<0.001
Hyperlipidaemia	0.0225	-0.0034 – 0.0484	0.09
Hypertension	-0.0032	-0.0274 – 0.0211	0.80
Alcohol (>14 units/week)	0.0152	-0.0201 – 0.0506	0.40
R ² / R ² adjusted	0.144 / 0.134		
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 15. Multivariable linear regression model of liver stiffness in the exposed cohort (MTX duration was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate.

Supplementary Table 16. Factors associated with ELF score in the exposed (MTX) group

MTX) group

Factors	Estimates	95% CI	P
(Intercept)	1.10577 ***	1.09249 – 1.11905	<0.001
MTX cumulative dose	0.00058 ***	0.00025 – 0.00091	<0.001
Age	0.00111 ***	0.00096 – 0.00126	<0.001
Sex (Male)	0.00232	-0.00097 – 0.00561	0.17
Psoriasis	-0.00282	-0.00654 – 0.00090	0.14
BMI	0.00056 ***	0.00030 – 0.00082	<0.001
Diabetes	0.00426	-0.00093 – 0.00945	0.11
Hyperlipidaemia	0.00087	-0.00300 – 0.00473	0.66
Hypertension	0.00145	-0.00218 – 0.00508	0.43
Alcohol (>14 units/week)	-0.00315	-0.00842 – 0.00213	0.24
Regular NSAIDs	0.00520 *	0.00120 – 0.00921	0.01
R ² / R ² adjusted	0.301 / 0.291		
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 16. Multivariable linear regression model of ELF score in the exposed cohort (MTX cumulative dose was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs.

Supplementary Table 17. Factors associated with ELF score in the exposed (MTX) group

Factors	Estimates	95% CI	P
(Intercept)	1.10640 ***	1.09312 – 1.11968	<0.001
MTX duration	0.00004 **	0.00001 – 0.00006	0.002
Age	0.00110 ***	0.00094 – 0.00125	<0.001
Sex (Male)	0.00240	-0.00090 – 0.00570	0.15
Psoriasis	-0.00335	-0.00707 – 0.00036	0.08
BMI	0.00057 ***	0.00031 – 0.00083	<0.001
Diabetes	0.00430	-0.00090 – 0.00951	0.10
Hyperlipidaemia	0.00100	-0.00287 – 0.00487	0.61
Hypertension	0.00143	-0.00221 – 0.00507	0.44
Alcohol > 14 units/week	-0.00279	-0.00806 – 0.00249	0.30
Regular NSAIDs	0.00510 *	0.00107 – 0.00912	0.01
R ² / R ² adjusted	0.298 / 0.289		
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 17. Multivariable linear regression model of ELF score in the exposed cohort (MTX duration was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs.

Supplementary Table 18. Factors associated with liver stiffness in the unexposed (no-MTX) group

Factors	Estimates	95% CI	P
(Intercept)	0.7447 ***	0.5182 – 0.9711	<0.001
Age	0.0003	-0.0022 – 0.0029	0.79
Sex (Male)	0.0232	-0.0380 – 0.0843	0.45
Psoriasis	0.0184	-0.0419 – 0.0787	0.55
BMI	0.0075 ***	0.0032 – 0.0118	<0.001
Diabetes	0.1118 *	0.0241 – 0.1995	0.01
Hyperlipidaemia	-0.0424	-0.1191 – 0.0343	0.28
Hypertension	0.0235	-0.0510 – 0.0980	0.53
Alcohol (>14 units/week)	-0.0105	-0.0852 – 0.0642	0.78
R ² / R ² adjusted	0.256 / 0.202		
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 18. Multivariable linear regression model of liver stiffness in the unexposed cohort. **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate.

Supplementary Table 19. Factors associated with ELF in the unexposed (no-MTX) group

MRX) group

Factors	Estimates	95% CI	P
(Intercept)	2.2585 ***	2.0543 – 2.4628	<0.001
Age	0.0058 ***	0.0035 – 0.0081	<0.001
Sex (Male)	0.0285	-0.0287 – 0.0857	0.32
Psoriasis	0.0257	-0.0295 – 0.0809	0.36
BMI	0.0009	-0.0029 – 0.0046	0.64
Diabetes	-0.0110	-0.0917 – 0.0698	0.79
Hyperlipidaemia	-0.0653	-0.1334 – 0.0028	0.06
Hypertension	0.0449	-0.0235 – 0.1133	0.20
Alcohol (>14 units/week)	-0.0580	-0.1277 – 0.0118	0.10
Regular NSAIDs	0.0441	-0.0131 – 0.1014	0.13
R ² / R ² adjusted	0.286 / 0.217		
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 19. Multivariable linear regression model of ELF in the unexposed cohort. **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs.

Supplementary Table 20. Factors associated with elevated liver stiffness ≥ 7.9 kPa in patients with arthritis on MTX

Factors	Adjusted OR	95% CI	P
MTX Cumulative dose	1.00	0.95 – 1.05	0.92
Age	1.02	0.99 – 1.05	0.16
Sex (Male)	1.34	0.82 – 2.19	0.24
Psoriatic arthritis	1.60	0.82 – 3.02	0.16
BMI	1.13 ***	1.08 – 1.17	<0.001
Type 2 Diabetes	2.93 ***	1.60 – 5.30	<0.001
Hyperlipidaemia	1.28	0.76 – 2.13	0.35
Hypertension	1.31	0.76 – 2.22	0.33
Alcohol (>14 units/week)	0.81	0.32 – 1.81	0.63
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 20. Multivariable logistic regression model of liver stiffness ≥ 7.9 kPa in patients with arthritis on MTX (MTX cumulative dose was used as the independent variable). **Abbreviations:** BMI: body mass index, CI: confidence interval, MTX: methotrexate, OR: odds ratio.

Supplementary Table 21. Factors associated with elevated ELF ≥ 9.8 in patients with arthritis on MTX

Factors	Adjusted OR	95% CI	P
MTX cumulative dose	1.07 ^{***}	1.03 – 1.11	<0.001
Age	1.07 ^{***}	1.05 – 1.09	<0.001
Sex (Male)	1.16	0.80 – 1.68	0.43
Psoriatic arthritis	0.79	0.44 – 1.36	0.40
BMI	1.04 [*]	1.01 – 1.07	0.02
Type 2 Diabetes	1.14	0.65 – 1.97	0.65
Hypertension	1.00	0.67 – 1.47	0.99
Alcohol > 14 units	0.58	0.29 – 1.10	0.11
Regular NSAIDs	1.56 [*]	1.02 – 2.38	0.04
* p<0.05 ** p<0.01 *** p<0.001			

Supplementary Table 21. Multivariable logistic regression model of ELF score ≥ 9.8 in patients with arthritis on MTX (MTX cumulative dose was used as the independent variable). Abbreviations: BMI: body mass index, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio.

