

ORIGINAL ARTICLES

Factors associated with methotrexate-related gastrointestinal intolerance and toxicity in rheumatoid arthritis and psoriatic arthritis

Campinho Ferreira C*¹⁵, Borges I*², Pinheiro M¹, Gonçalves H¹, Pereira P¹, Costa E¹**ABSTRACT**

Background: Methotrexate (MTX) is the cornerstone therapy for rheumatoid arthritis (RA) and psoriatic arthritis (PsA), yet gastrointestinal adverse events (GIAE), including intolerance and hepatotoxicity, remain major causes of treatment modification and discontinuation. Identifying baseline predictors of these reactions is essential to optimizing treatment safety and persistence.

Objectives: To identify clinical and laboratory predictors of MTX-related GIAE and to compare risk profiles between RA and PsA.

Methods: Retrospective observation study including MTX-treated patients with RA or PsA. Baseline demographics, comorbidities, laboratory results, MTX characteristics, and concomitant medications were extracted from medical records. GIAE comprised either gastrointestinal (GI) intolerance or toxicity. Associations were assessed through univariate tests followed by multivariable logistic regression. Kaplan-Meier curves evaluated treatment survival according to administration route and disease type.

Results: Among 369 patients (62.6% female; mean age 57.5 ± 12.6 years), 50.9% developed GIAE. GI intolerance occurred in 127 patients, mainly presenting as nausea (68.5%). GI toxicity occurred in 75 patients, with baseline alanine transaminase (ALT) significantly higher in affected patients. Independent predictors of GIAE were diabetes mellitus (aOR 2.22), female sex (aOR 1.82), and PsA (aOR 1.67). Predictors of GI intolerance included higher baseline ALT (aOR 1.02), concomitant leflunomide (aOR 1.91), and female sex (aOR 2.08). Predictors of GI toxicity included diabetes (aOR 2.98), alcohol consumption (aOR 2.79), and baseline ALT (aOR 1.03). Survival analysis showed earlier MTX-related GIAE in patients receiving the subcutaneous formulation across diseases ($p < .001$).

Conclusions: MTX-related GIAE are frequently and largely driven by metabolic comorbidities, lifestyle exposures, sex, and baseline ALT. These routinely available parameters allow early identification of high-risk patients and may guide personalized MTX initiation and monitoring strategies.

Keywords: Predictors; Rheumatoid arthritis; Spondyloarthropathies (including psoriatic arthritis); Methotrexate; Adverse event.

INTRODUCTION

Methotrexate (MTX) is a folate antagonist drug with anti-inflammatory, anti-proliferative, and anti-metabolic properties, primarily exerting its effects through the inhibition of deoxyribonucleic acid (DNA) synthesis¹. It is currently considered the first-line treatment for several chronic rheumatic diseases, including rheumatoid arthritis (RA)² and psoriatic arthritis (PsA)³, due to its low cost, wide availability, and well-established efficacy,

making it the cornerstone treatment for the diseases^{4,5}.

Despite its therapeutic benefits, MTX is associated with several adverse effects, mainly involving the liver, kidneys, hematological system, mucous membranes, and gastrointestinal (GI) tract, which often lead to treatment discontinuation⁶. GI adverse events (GIAE) are among the most prevalent, occurring in 20-70% of patients, and typically include nausea, vomiting, gastroesophageal reflux, diarrhea, and anorexia. These manifestations are generally dose-dependent. The underlying pathophysiological mechanism involves multiple organs, and evidence suggests a correlation between their occurrence and changes in plasma homocysteine levels⁷. Furthermore, genetic factors, such as the SLC19A1 80G allele variant, have been linked to a greater predisposition to MTX-induced GI events⁸.

Strategies to minimize toxicity include switching the route of administration from oral to subcutaneous,

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which has been shown to reduce GI symptoms⁷. In addition, folic acid supplementation has proven effective in mitigating these effects, contributing to better treatment adherence and tolerance⁹.

Hepatotoxicity is the main concern in patients receiving MTX, potentially affecting 15 to 50% of patients within the first 2 to 4 years of treatment. There are some well-established risk factors associated with an increased risk of hepatotoxicity, including alcohol consumption, pre-existing liver disease, obesity, diabetes mellitus, dyslipidemia, high cumulative doses of MTX, and concomitant use of other hepatotoxic drugs, including other disease-modifying antirheumatic drugs (DMARDs)¹⁰. Furthermore, substantial evidence indicates that PsA is particularly associated with metabolic comorbidities, as well as a high prevalence of liver enzyme abnormalities and liver disease¹¹.

Given the long-term use of MTX in chronic therapeutic regimens, the characterization and management of its adverse events are crucial in clinical practice. GI events are highly prevalent and compromise patients' quality of life and disease control. Therefore, a deeper knowledge of the risk factors contributing to these adverse reactions is needed, focusing on the study of clinical and laboratory predictors.

The main objective of this project is to investigate and characterize potential baseline risk predictors for the development of MTX-induced GIAE, with the ultimate goal of improving therapeutic management and patient outcomes.

Objectives

The main goal of this study was to identify clinical factors at the start of MTX treatment that may be associated with GIAE: GI intolerance or GI toxicity. For that, the following specific objectives were set:

- a) Explore the association between baseline, pre-MTX exposure, factors, and GI intolerance and toxicity.
- b) Compare different toxicity profiles between RA and PsA.

MATERIALS AND METHODS

Population and Sample

This research was designed as a retrospective observational study.

The study population comprised all individuals with a previous or current history of MTX treatment who had an appointment at the Rheumatology Service of ULS Braga between January and December 2024.

The sample was limited to individuals from the defined population who fulfil the inclusion criteria: (1) patients with RA according to the EULAR² criteria and

at least one positive result for rheumatoid factor or anti-citrullinated peptide antibodies; or patients with PsA according to the CASPAR³ criteria; (2) patients with a previous or current history of oral or subcutaneous MTX treatment; and who do not meet the exclusion criteria: (1) missing data greater than 50%. Data were collected from patients' medical records using *SClinico*[®] software.

Statistical Analysis

Recent research on sample size estimation for predictive modelling indicates that a sample size of N=369 would be required for our model, assuming an outcome prevalence of 40%¹¹⁻¹⁵.

Data were analysed using IBM SPSS[®] software (version 29.0.2.0). Statistical significance was set at a p-value < .05, with a 95% confidence interval (CI).

Descriptive statistical analysis was performed to characterize the sample. Quantitative variables were described using the mean and standard deviation (SD) for normally distributed data, and the median and interquartile range (IQR) for non-normally distributed data. Qualitative variables were described using absolute (n) and relative frequencies (%).

For normally distributed data, differences between continuous variables were analysed using *Student's t-test* for two groups. In cases where normality was not met, the *Mann-Whitney U* nonparametric test was used. Associations were investigated using the *Chi-square test*, or *Fisher's exact test* when assumptions were not fulfilled. Effect sizes were measured using *Cohen's d* (d), *Rosenthal's r* (r), *Phi coefficient* (φ), and *Odds Ratio* (OR) for contingency tables 2x2. The others were evaluated using *Cramér's V* (φc).

Logistic regression analyses were performed to identify potential predictors. Additionally, *Kaplan-Meier* survival analysis was performed to assess MTX treatment duration without adverse reactions between oral and subcutaneous administration routes, stratified by disease type. Differences in survival distributions were assessed using the *log-rank* (*Mantel-Cox*).

Two composite variables were defined for this analysis: (1) GIAE, the primary outcome, comprising the occurrence of either GI intolerance or GI toxicity, and reflecting the overall tolerability profile of MTX treatment; (2) Metabolic syndrome, defined by the presence of two or more of the metabolic syndrome core clinical components. GI toxicity was defined as a persistent elevation of liver enzymes greater than two times the upper limit of normal.

Ethical Procedures

The study protocol was approved by the Data Protection Office and the Ethics Committee of the Unidade

Local de Saúde de Braga, in accordance with the principles of the Declaration of Helsinki.

RESULTS

Sample Characterization

The study comprised 369 patients undergoing MTX treatment, including 231 females (62.6%), with an average age of 57.5 ± 12.6 years and a mean body mass index (BMI) of 27.84 ± 5.31 kg/m². Based on clinical records, 190 patients (70.1%) had obesity or overweight. Among the patients, 215 (58.3%) had seropositive RA, while 154 patients (41.7%) had PsA. Baseline demographic and clinical characteristics, and laboratory workup are detailed in Table I. Overall, 48.2% and 45.8% of the patients presented with dyslipidemia and hypertension, respectively. Alcohol and tobacco consumption were reported in approximately a fifth and a quarter of the patients, respectively. The mean initial MTX dose was 12.4 ± 2.6 mg. The oral route was the preferred initial method of administration, used in 290 patients (78.6%). Concomitant medications included prednisolone (74.3%), nonsteroidal anti-inflammatory drugs (NSAID, 62.9%), and proton pump inhibitors (PPI, 57.5%). The mean initial MTX dose was 12.4 ± 2.6 mg. The oral route was the preferred method of administration, used in 290 patients (78.6%).

GIAE were observed in 188 patients (50.95%), including 127 cases of GI intolerance and 75 cases of GI toxicity, with a mean MTX dose of 17.9 ± 4.8 and 17.8 ± 4.4 mg per week, respectively. Fourteen patients experienced both GI intolerance and toxicity. The most frequently reported GI symptom was nausea (n=87, 68.5%), followed by general malaise (n=54, 42.5%), vomiting (n=11, 8.7%), diarrhea (n=10, 7.9%), anticipatory phenomena (n=5, 3.9%), and anorexia (n=5, 3.9%). Some patients reported more than one GI symptom. In managing GIAE, adjustments such as switching the route of administration (18.1%) or reducing the dose (39.4%) were usually effective in maintaining MTX therapy. However, 80 patients (42.5%) ultimately discontinued treatment despite optimization strategies (Table II).

Patients' Characteristics Related to GIAE

The type of disease ($p=.045$; $\phi=.094$) and the presence of hypertension ($p=.040$; $\phi=.097$), diabetes mellitus ($p=.004$; $\phi=.146$), metabolic syndrome ($p=.027$; $\phi=.105$), and higher alanine aminotransferase (ALT) levels ($p=.024$; $r=.02$) were significantly associated with a higher frequency of GIAE. When analysing the disease type, patients with PsA presented a higher frequency of GIAE (56.5%) compared to those with RA

(47.0%), although the effect size was small ($\phi=.094$). Among the comorbidities, the association with diabetes mellitus demonstrated the strongest statistical relationship – Table I.

Patients' Characteristics Related to GI Intolerance

Smoking, alcohol consumption, route of MTX administration, higher ALT levels, and concomitant use of leflunomide and PPI showed statistically significant associations with GI intolerance to MTX. Tobacco use ($p=.003$; $\phi=.145$), alcohol consumption ($p<.001$; $\phi=.167$), and use of PPI ($p=.005$; $\phi=.139$) were associated with a higher frequency of GIAE, although the effect sizes were small. The route of MTX administration ($p=.014$; $\phi=.123$) also demonstrated a significant but small association, with patients receiving MTX orally being more likely to experience GI symptoms compared to those on subcutaneous administration. Similarly, concomitant leflunomide use ($p=.047$; $\phi=.096$) was associated with these adverse effects – Table III.

Patients' Characteristics Related to GI Toxicity

Alcohol consumption demonstrated the strongest association ($\chi^2=29.014$; $\phi=.280$), followed by diabetes mellitus ($\chi^2=19.368$; $\phi=.229$) to GI toxicity, with moderate effect sizes. Dyslipidemia ($p=.004$; $\phi=.146$) and the presence of at least two components of metabolic syndrome ($p=.009$; $\phi=.129$) were also significantly associated with GI toxicity, although with smaller effect sizes. The underlying inflammatory disease ($p=.016$; $\phi=.119$) was significantly associated as well, with patients with PsA showing a higher frequency of toxicity compared to those with RA – Table IV.

Predictors of GIAE

Following the identification of factors associated with GIAE, multivariate logistic regression was performed to evaluate potential predictors, including variables selected based on clinical relevance, statistical significance, or evidence from the literature (ALT, initial dose, route of administration, leflunomide, diabetes mellitus, sex, underlying disease, alcohol, dyslipidemia, and hypertension). The multivariable logistic regression model was statistically significant ($\chi^2=28.317$; $p=.002$) and identified diabetes mellitus ($p=.020$; aOR 2.217), female sex ($p=.023$; aOR 1.818), and PsA ($p=.029$; aOR 1.672) as independent predictors of GIAE. Higher baseline ALT levels, although within the normal range, and initial MTX dose did not reach statistical significance in the model but approached significance ($p=.068$ and $p=0.099$, respectively).

Predictors of GI Intolerance

When analysing only the patients who developed GI

TABLE I. Baseline demographic and clinical characteristics.

Characteristics	Overall Cohort (n=369)	No GIAE (n=181)	GIAE (n=188)	p-value	Effect Size
Female	231 (62.6)	108 (59.7)	123 (65.4)	.253	-.059
Age (yr), mean ± SD	57.5 ± 12.6	57.9 ± 12.9	57.1 ± 12.2	.568	.060
Disease					
Rheumatoid Arthritis	215 (58.3)	114 (63.0)	101 (53.7)	.045	.094
Psoriatic Arthritis	154 (41.7)	67 (37.0)	87 (46.3)		
Height (cm), mean ± SD	163.2 ± 10.1 (n=99)	162.7 ± 9.1 (n=45)	163.7 ± 10.9 (n=54)	.623	-.101
Weight (kg), mean ± SD	74.2 ± 16.2 (n=276)	72.5 ± 14.7 (n=133)	75.5 ± 17.4 (n=143)	.111	-.197
BMI (kg/m ²), mean ± SD	27.84 ± 5.31 (n=99)	27.31 ± 5.77 (n=45)	28.24 ± 4.95 (n=54)	.414	-.176
BSA (m ²), mean ± SD	1.83 ± .24 (n=99)	1.80 ± .22 (n=45)	1.85 ± .26 (n=54)	.275	-.226
Comorbidities					
Dyslipidemia	78 (48.2)	85 (47.0)	93 (49.5)	.353	-.025
Hypertension	169 (45.8)	74 (40.9)	95 (50.5)	.040	.097
Diabetes mellitus	54 (14.6)	17 (9.4)	37 (19.7)	.004	.146
Hyperuricemia	46 (12.5)	28 (15.5)	18 (9.6)	.060	-.089
Hepatic Steatosis	18 (5.0) (n=363)	6 (3.4) (n=178)	12 (6.5) (n=185)	.130	.072
Chronic liver disease	4 (1.1) (n=367)	3 (1.7) (n=180)	1 (.5) (n=187)	.297	.054
Chronic kidney disease	9 (2.4)	6 (3.3)	3 (1.6)	.233	.056
Smoking	93 (25.2)	51 (28.2)	42 (22.3)	.121	-.067
Alcohol	75 (20.3)	35 (19.3)	39 (21.3)	.370	.024
Metabolic Syndrome	189 (51.2)	83 (45.9)	106 (56.4)	.027	.105
Medications					
Methotrexate					
Initial dose (mg/week), mean ± SD	12.4 ± 2.6	12.1 ± 2.6	12.7 ± 2.6	.026	-.233
Route of administration					
Oral	290 (78.6)	147 (81.2)	143 (76.1)	.140	.063
Subcutaneous	779 (21.4)	34 (18.8)	45 (23.9)		
Prednisolone	274 (74.3)	133 (73.5)	141 (75.0)	.415	.017
NSAID	232 (62.9)	117 (64.2)	115 (61.2)	.280	.036
Proton pump inhibitor	212 (57.5)	98 (54.1)	114 (60.6)	.124	.066
Statin	150 (40.7)	70 (38.7)	80 (42.6)	.257	.039
Leflunomide	63 (17.1)	27 (14.9)	36 (19.1)	.173	.056
Antidiabetic	46 (12.5)	16 (8.8)	30 (16.0)	.027	.108
Laboratory workup					
Hemoglobin (g/dl), mean ± SD	13.7 ± 1.4 (n=368)	13.7 ± 1.3	13.6 ± 1.5 (n=187)	.570	.059
MCV (fl), mean ± SD	89.3 ± 5.4 (n=367)	89.6 ± 5.0	89.1 ± 5.7 (n=186)	.334	.101
ALT (U/L), median (IQR)	25.0 (14) (n=367)	24.0 (11) (n=180)	27.0 (17) (n=187)	.024	.12
GGT (U/L), median (IQR)	23.0 (21) (n=360)	22.5 (19) (n=178)	24.5 (24) (n=182)	.125	.08
Urea (mg/L), median (IQR)	37.0 (15) (n=353)	36.0 (15) (n=174)	37.0 (15) (n=179)	.663	.02
Creatinine (mg/L), median (IQR)	.80 (.2) (n=366)	.80 (.2) (n=179)	.80 (.3) (n=187)	.699	.02

Data are presented as n (%) unless otherwise indicated. *Classification based on clinical records. ALT – Alanine aminotransferase; BMI – Body mass index; BSA – Body surface area; GGT – Gama glutamyl transferase; IQR – Interquartile range; MCV – mean corpuscular volume; NSAID – non-steroidal anti-inflammatory drugs; SD – Standard deviation; yr – years.

TABLE II. Methotrexate treatment information at the adverse event.

MTX treatment information on the adverse event	GIAE* (n=188)	GI Intolerance (n=127)	GI Toxicity (n=75)
Dose (mg /week), mean \pm SD	17.9 \pm 4.6	17.9 \pm 4.8	17.8 \pm 4.4
Route			
Oral	111 (57.5)	67 (52.8)	46 (61.3)
Subcutaneous	82 (42.5)	60 (47.2)	29 (38.7)
Adjustment performed			
Rout change		34 (18.1)	
Dose reduction		74 (39.4)	
Discontinuation		80 (42.5)	

Data are presented as n (%) unless otherwise indicated. *Some patients had more than one adverse effect. GI – Gastrointestinal. GIAE – Gastrointestinal adverse event; MTX – Methotrexate; SD – standard deviation.

Table III. Patients' characteristics related to GI intolerance.

Characteristics	No GI Intolerance (n=242)	GI Intolerance (n=127)	p-value	Effect Size
Smoking	72 (29.8)	21 (16.5)	.003	.145
Alcohol	61 (25.2)	14 (11.0)	<.001	.167
Administration Route				
Oral	199 (82.2)	91 (71.7)	.014	.123
Subcutaneous	43 (17.8)	36 (28.3)		
Leflunomide	35 (14.5)	28 (22.0)	.047	.096
Proton pump inhibitor	127 (52.5)	85 (66.9)	.005	.139
ALT (U/L), median (IQR)	26.0 (15)	24.0 (13)	.008	21.011

Data are presented as n (%) unless otherwise indicated. ALT – Alanine aminotransferase; GI – Gastrointestinal; IQR – interquartile range.

intolerance, a significant logistic regression model was obtained ($\chi^2=28.511$; $p<.001$). Within this subgroup, higher baseline ALT levels ($p=.038$; aOR 1.020), concomitant use of leflunomide ($p=.031$; aOR 1.910), and female sex ($p=.005$; aOR 2.077) emerged as independent significant predictors.

Predictors of GI Toxicity

When analysing only the patients who developed GI toxicity, a significant logistic regression model was obtained ($\chi^2=62.308$; $p<.001$). The model identified diabetes mellitus ($p=.020$; aOR 2.980), alcohol consumption ($p=.003$; aOR 2.786), and higher baseline ALT levels ($p<.001$; aOR 1.029) as independent predictors of GI toxicity. The model achieved an overall accuracy of 80.7%. Despite a low sensitivity of 21.3%, it demonstrated a high specificity of 95.9%, indicating that it is particularly effective at correctly identifying patients who do not develop GI toxicity.

GIAE by Disease

When GIAE were stratified according to disease type

(RA or PsA), relevant differences were observed between groups. In patients with RA (n=215), but not in those with PsA, the presence of metabolic syndrome ($p=.008$) was more frequently associated with GIAE occurrence. Conversely, among PsA patients, concomitant leflunomide use ($p=.043$) and higher baseline ALT levels ($p=.029$) were linked to an increased likelihood of GIAE.

Drug Survival until GIAE by Route of Administration and Disease Type

A Kaplan-Meier survival analysis was performed to compare MTX treatment duration without adverse reactions between oral and subcutaneous administration routes, stratified by disease type. The average treatment duration was 1405 ± 1304 days. No significant differences were observed in the mean MTX dose associated with the occurrence of GIAE between patients on oral and on subcutaneous treatment – Table I.

Regardless of the underlying disease, patients receiving subcutaneous MTX had earlier GIAE compared to those on the oral formulation, suggesting better

TABLE IV. Patients' characteristics related to GI toxicity.

Characteristics	No GI Toxicity (n=294)	GI Toxicity (n=75)	p-value	Effect Size
Diabetes mellitus	31 (10.5)	23 (30.7)	<.001	.229
Dyslipidemia	131 (44.6)	47 (62.7)	.004	.146
Metabolic syndrome	141 (48.0)	48 (64.0)	.009	.129
Disease				
Rheumatoid arthritis	180 (61.2)	35 (46.7)	.016	.119
Psoriatic arthritis	114 (38.8)	40 (53.3)		
Alcohol	43 (14.6)	32 (42.7)	<.001	.280
ALT (U/L), median (IQR)	24.0 (11)	35.0 (26)	<.001	20.204

Data are presented as n (%) unless otherwise indicated. ALT – Alanine aminotransferase; GI – Gastrointestinal; IQR – interquartile range.

TABLE V. MTX survival until GIAE by route of administration and disease type.

Administration route	Rheumatoid arthritis		Psoriatic arthritis	
	Oral	Subcutaneous	Oral	Subcutaneous
MTX survival until GIAE (days), mean ± SE	2649 ± 174	1440 ± 255	2633 ± 216	1382 ± 346
MTX 5-year survival probability until GIAE (%)	55.0	46.0	52.0	22.0

GIAE – Gastrointestinal adverse event; MTX – Methotrexate; SE -Standard error.

tolerability – Table V. The log-rank (Mantel-Cox) test confirmed a statistically significant difference between administration routes ($\chi^2=12.360$, $p<.001$). When the same route of administration was considered, GIAE behaved similarly in both diseases.

At five years (1826 days), the estimated probability of RA patients remaining on MTX without adverse reactions was 55% for oral administration and 46% for subcutaneous administration. In PsA patients, the corresponding probabilities were 52% and 22%, respectively. Oral MTX showed longer mean survival times overall, in both AR and PsA subgroups – Table V and Figure 1.

DISCUSSION

In this retrospective cohort of 369 MTX-treated patients with RA and PsA, GIAE were common, affecting approximately half of the population, of whom 67.5% experienced GI intolerance and 39% presented GI toxicity. This prevalence of GIAE aligns with previously reported rates in retrospective studies^{7,10}, reinforcing the clinical relevance of identifying patients at risk of GIAE.

GI intolerance is the most frequent adverse reaction to MTX, reported in 20-70% of patients⁷, while GI toxicity has been described as potentially affecting 15 to 50% of patients^{6,10}. The prevalence of GI intolerance in our population (34.4%) was slightly lower than the rate reported in a study conducted in the Netherlands (42.3%)¹⁶, which assessed the prevalence of MTX intolerance in both RA and PsA. However, comparisons with our results should be made cautiously, as they are limited by methodological differences, particularly the use of the MTX Intolerance Severity Score (MISS). The demographic and metabolic profiles of our population, namely age, sex, and high burden of metabolic comorbidities, including obesity, hypertension, dyslipidemia, and diabetes mellitus, were also aligned with previously published real-world MTX-treated cohorts, supporting the external validity of our findings.

GIAE were more frequent in patients with PsA, hypertension, diabetes mellitus, and metabolic syndrome. In multivariate analysis, diabetes mellitus, female sex, and PsA emerged as independent predictors of overall MTX-related GIAE. These findings are consistent with prior research identifying metabolic comorbidities and female sex as contributors to MTX GIAE¹⁷⁻¹⁹. Diabetes

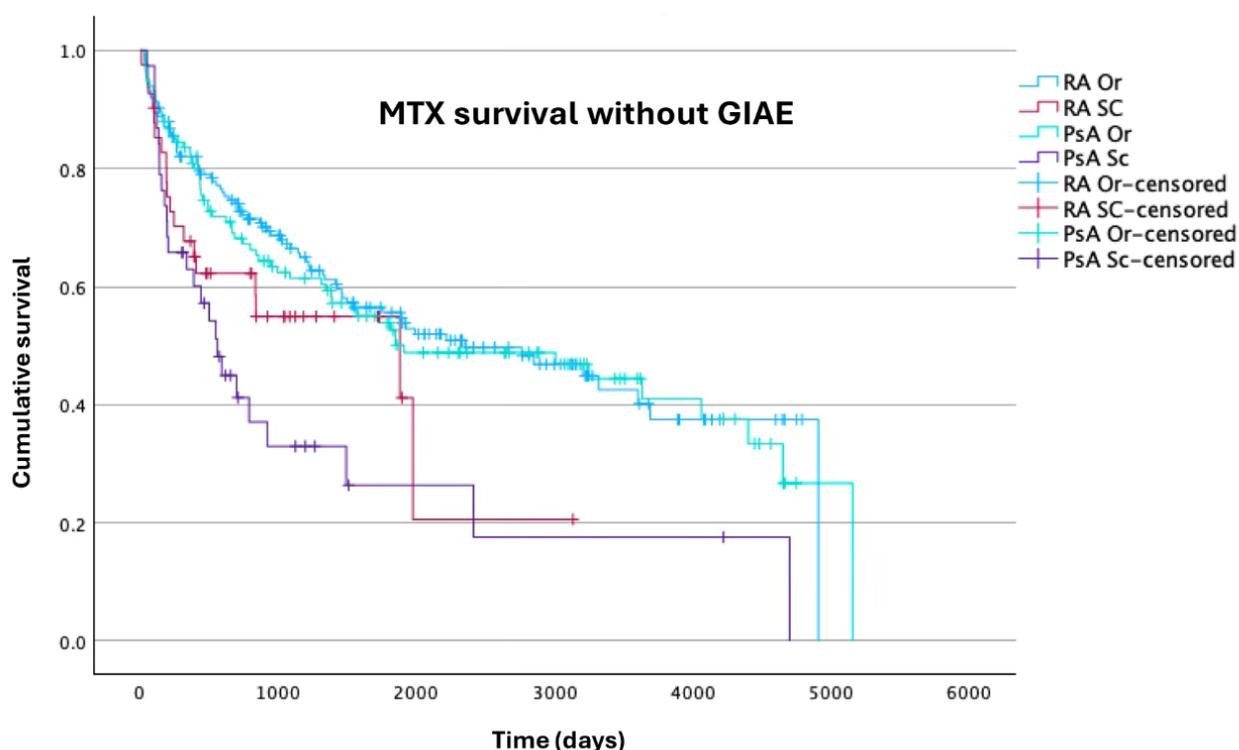


Figure 1. Kaplan-Meier estimates of MTX survival until GIAE according to route of administration and disease type.

mellitus showed the strongest association, conferring approximately a twofold increase in the risk of developing GIAE, which may reflect underlying metabolic dysregulation in diabetic patients¹⁷. The increased susceptibility observed in patients with PsA may relate to the higher prevalence of metabolic syndrome and liver disease described in patients with psoriasis and PsA^{11,20}. Although higher baseline ALT and initial MTX dose did not reach statistical significance in the multivariable model, both variables trended towards significance, supporting their biological plausibility as contributors to GIAE, as described in previous predictive models^{21,22}.

MTX-related GI intolerance is a complex phenomenon that extends beyond direct physical symptoms, such as nausea and vomiting, after drug administration. It also encompasses anticipatory symptoms, occurring before MTX intake, and associative symptoms, triggered merely by thinking about the medication²³. Nausea was the most frequently reported symptom, consistent with prior research^{6,7}. Current evidence suggests that the two main mechanisms underlying MTX-related GI intolerance are increased sensitivity of the gastrointestinal epithelium to this drug and stimulation of the chemoreceptor trigger zone in the brain, which detects circulating emetogenic substances^{18,19}. Tobacco use, alcohol consumption, oral route of MTX administration, higher baseline ALT levels, and both PPI and lefluno-

mide use were associated with GI intolerance. However, in multivariate analysis, only higher baseline ALT values, concomitant leflunomide therapy, and female sex were independent predictors of GI intolerance. The relevance of lifestyle factors is noteworthy, given that approximately one-quarter of our cohort reported smoking or alcohol intake, highlighting the need to systematically address lifestyle counselling when initiating MTX. Concomitant medications, specifically leflunomide and PPI, were also associated with increased GI intolerance risk, potentially due to drug-drug interactions and the reduced MTX clearance potentiated by PPI, respectively^{24,25}. Baseline ALT levels, even within the normal range, also predicted GI intolerance, suggesting that subclinical hepatic vulnerability may increase susceptibility to early GI symptoms. Several studies have reported an association between female sex and MTX intolerance^{18,23}. This finding is thought to be partially explained by a lower renal elimination rate of MTX in women compared with men, even after adjusting for body weight and creatinine clearance, which may promote drug accumulation and increase the risk of GI intolerance^{18,19}.

GI toxicity was more frequent in patients with diabetes mellitus, alcohol consumption, dyslipidemia, metabolic syndrome, and PsA. In multivariate analysis, independent predictors of GI toxicity included diabe-

tes mellitus, alcohol consumption, and higher baseline ALT levels. These results align with the mechanistic view that metabolic syndrome, which includes diabetes mellitus and dyslipidemia, and alcohol consumption are established contributors for non-alcoholic fatty liver disease, impaired folate metabolism, and consequently MTX-associated hepatotoxicity^{10,17,26}. Previous research has explored the cumulative impact of the number of metabolic syndrome features on GI toxicity^{27,28}. Patients presenting two metabolic syndrome-related conditions had an increased likelihood of elevated liver enzymes. Shetty et. al¹⁷ similarly reported that the probability of this elevation increased progressively with the number of metabolic syndrome components present. The limited availability of height and weight data for each patient hindered the calculation of BMI, a variable identified as relevant for GI toxicity and suggested as an important factor in determining individualized MTX dosing²⁷. Given this limitation, the authors decided not to include this variable in the logistic regression models. PsA patients demonstrated a higher frequency of toxicity compared to RA patients. This is consistent with prior research showing a greater hepatotoxic risk in PsA²⁰, potentially reflecting the higher burden of metabolic comorbidities in his patients¹⁷.

Stratified analysis showed that in RA patients, but not in PsA patients, metabolic syndrome was associated with higher GIAE risk, a finding somewhat discrepant from prior reports where metabolic syndrome was typically linked to PsA GI toxicity^{11,21,27}. This may be explained by the slightly younger age of PsA patients and the predominance of RA in our cohort, which may have increased the statistical weight of GIAE in this group. In PsA, leflunomide use and higher baseline ALT emerged as risk factors for GIAE.

Kaplan-Meier analysis showed that patients receiving subcutaneous MTX had GIAE earlier, compared to patients receiving oral MTX. Literature on this topic presents a dual pattern: some studies report that oral MTX is better tolerated¹⁶, whereas others describe fewer GIAE with subcutaneous administration^{7,29,30}. This discrepancy may result from higher treatment adherence rates with subcutaneous compared to oral therapies³¹ and its bypass of intestinal absorption, leading to higher systemic drug concentrations³². In our cohort, MTX dose at the time of GIAE did not differ significantly between administration routes, suggesting that factors other than dose may underline route-specific differences.

The three multivariable logistic models developed in this study demonstrated good internal validity and identified clinically accessible parameters that can stratify GIAE risk during pre-MTX consultations. Variables such as sex, diabetes mellitus, alcohol consumption, ALT levels, concomitant leflunomide use, and disease

type can be readily assessed in routine consultations and may guide decision-making. Nevertheless, the modest predictive strength of individual variables and their combination underscores the multifactorial nature of MTX GI intolerance and toxicity, suggesting that additional unmeasured factors may also influence susceptibility. From a clinical perspective, these models can guide personalized MTX therapy by identifying patients at higher baseline risk of GIAE, allowing clinicians to decide if MTX is the best treatment option, adjust starting doses, concomitant medications, and administration routes to improve adherence, quality of life, and treatment persistence.

An additional strength of our work lies in its broader analytical scope. Most previous studies have focused on homogeneous rheumatic populations, analysing patients with RA and PsA separately, and have typically addressed GI intolerance and toxicity, the main causes of MTX discontinuation, in isolation^{6,11,21,27}. In contrast, we combined RA and PsA patients into a single cohort to simultaneously model the risks of both GI intolerance and toxicity, leveraging their shared MTX exposure. This integrated approach may have allowed us to capture a more comprehensive and clinically relevant pattern of predictors across the spectrum of MTX-related GIAE.

Despite these strengths, our study also had some limitations that should be acknowledged. Its retrospective design resulted in missing or incomplete data. Additionally, the heterogeneity of medical reports was also a limiting component in the collection and subsequent analysis of the data, namely in the reporting of specific GI symptoms. Finally, the single-center nature may reduce generalizability to different populations.

In future studies, it would be relevant to include psychological comorbidities and fibromyalgia as variables of interest. Roberto et al.⁶ found that the presence of fibromyalgia was associated with the development of GI intolerance. However, they were unable to determine whether this was due to the confounder effect of the concomitant drugs, as some of the adjuvant treatments in patients with fibromyalgia are associated with GI intolerance, and could have influenced the results. This study was also unable to assess the influence of depression and anxiety on MTX side effects. To date, it is known that MTX treatment tends to reduce symptoms of anxiety and depression³³, and that psycho-behavioural mechanisms can impact intolerance¹⁹. However, depression has never been specifically studied as a potential predictor. Prospective multicentre studies incorporating standardized symptom assessment and validated intolerance scales are warranted. Such studies would allow more precise modelling of GIAE risk and could support the development of a robust clinical prediction tool.

CONCLUSIONS

GIAE were common in this real-world cohort of MTX-treated patients with RA and PsA, affecting approximately half of the population. Diabetes mellitus, female sex, and PsA were independent predictors of overall GIAE, with diabetes conferring nearly a twofold increase in risk. When intolerance and toxicity were examined separately, GI intolerance was independently associated with higher baseline ALT levels, concomitant leflunomide therapy, and female sex, whereas GI toxicity was predicted by diabetes mellitus, alcohol consumption, and elevated baseline ALT. These findings underscore the multifactorial nature of MTX-related GIAE and highlight clinically accessible characteristics that can help stratify risk and guide personalized therapeutic decisions, ultimately aiming to improve MTX adherence and treatment persistence.

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