ARTÍCULO ORIGINAL

Risk factors for thiopurine-related toxicity in Latin American inflammatory bowel disease patients

Factores de riesgo para toxicidad a tiopurinas en pacientes latino americanos con enfermedad inflamatoria intestinal

Belén Giacaman[1,a], Francisca Grandón[1,a], Magdalena Ibacache[2,b], Valeria Granzotto[2,b], José Miguel Ortega[3,c], Constanza Norambuena[3,c], Ignacia Sepúlveda[1,d], Tamara Pérez-Jéldres[1,4,a], Javier Chahuán[1,4,a], Manuel Álvarez-Lobos[1,4,a], Carolina Pavez[1,4,a], Cristian Hernandez-Rocha[1,4,a]

[1] Department of Gastroenterology, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.
[2] Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile.
[3] Department of Medicine, Faculty of Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile.
[4] Instituto de Medicina, Red Salud UC Christus, Santiago, Chile.
[a] Gastroenterologist
[b] Medical Student
[c] Internal Medicine Specialist
[d] Nurse

Received: 17/03/2026
Peer-reviewed
Accepted: 17/08/2026
Online: 12/09/2026

Author contribution
BG: acquisition of data, data curation, analysis and interpretation of data. FG: acquisition of data, data curation, analysis and interpretation of data. MI: acquisition of data, data curation. VG: acquisition of data, data curation. JMO: acquisition of data, data curation. CN: acquisition of data, data curation. IS: acquisition of data, data curation. TPJ: Writing - review & editing. JC: Writing - review & editing. MAL: Writing - review & editing. CP: Writing - review & editing. CHR: conception and design of the study, acquisition of data, analysis and interpretation of data; Writing - review & editing.

Conflict of interest
None.

Funding
This work was supported by The Chilean National Agency of Research and Development (ANID). Grant number [FONDECYT regular 1230757 to C. H-R.] and [FONDECYT regular 1211344 to M.A-L.].

Data availability statement
The data underlying this article will be shared on reasonable request to the corresponding author.

Cite as
Giacaman B, Grandón F, Ibacache M, Granzotto V, Ortega JM, Norambuena C, *et al.* Risk factors for thiopurine-related toxicity in latin american inflammatory bowel disease patients. Rev Gastroenterol Peru. 2026;46(3). doi: 10.47892/rgp.2026.463.2237.

Correspondencia:
Dr. Cristian Hernández-Rocha
E-mail: cristian.hernandez.rocha@gmail.com

ABSTRACT
Objectives: Thiopurines continue to play a role in inflammatory bowel disease (IBD) treatment, particularly in resource-limited countries. However, there are scarce data from Latin America regarding thiopurines-associated AE. We aim to describe the thiopurine-associated AE and determine risk factors for its occurrence. **Materials and methods:** Clinical data from IBD patients treated with thiopurines in a Chilean tertiary centre were retrospectively collected including AE that required thiopurine withdrawal and weight-based thiopurine dose. A multivariable model was fitted to determine independent risk factors of thiopurine-related AE. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. **Results:** A total 163 out of 587 (27.7%) patients discontinued thiopurine treatment due to AE including myelosuppression, hepatitis, pancreatitis, and gastrointestinal intolerance. Multivariate analysis showed that older age (OR: 1.02; 95% CI: 1.01-1.04; p=0.01) and lower body weight (OR: 0.97; 95% CI: 0.95-0.99; p=0.01) were independent risk factors for thiopurine-associated AE. **Conclusions:** Discontinuation of thiopurines due to AE is frequent in Latin IBD patients. Particular caution should be exerted in older and low-weight IBD patients starting thiopurine treatment.
Keywords: *Inflammatory Bowel Diseases; Immunosuppressive Agents; Latin America (source: MeSH NLM).*

RESUMEN
Objetivos: Las tiopurinas continúan jugando un rol en el tratamiento de la enfermedad inflamatoria intestinal (EII) particularmente en países con recursos limitados. Sin embargo, hay escasos datos latinoamericanos relacionados a los efectos adversos (EA) asociados a tiopurinas. Nuestro objetivo en este estudio es describir los EA más frecuentes a tiopurinas y determinar los factores de riesgo para su desarrollo. **Materiales y métodos:** Datos clínicos de pacientes con EII tratados con tiopurinas en un centro terciario chileno fueron retrospectivamente recolectados incluyendo EA que requirieron suspensión de tratamiento y dosis de tiopurinas por Kg. Un modelo multivariable fue utilizado para determinar los factores de riesgo independientes para el desarrollo de EA a tiopurinas. Odds ratios (OR) e intervalos de confianza del 95% (IC 95%) fueron calculados. **Resultados:** Un total de 163 de los 587 pacientes evaluados (27,7%) discontinuaron el tratamiento con tiopurinas debido a EA, principalmente mielosupresión, hepatitis, pancreatitis e intolerancia gastrointestinal. En el análisis multivariable, una mayor edad (OR: 1,02; IC 95%: 1,01-1,04; p=0,01) y menor peso corporal (OR: 0,97; IC 95%: 0,95-0,99; p=0,01) se asociaron de manera independiente con un mayor riesgo de EA relacionados con tiopurinas. **Conclusiones:** La suspensión de tiopurinas debido a EA es frecuente en pacientes latinos con EII. Se debe ejercer particular precaución en pacientes de mayor edad y menor peso que inician tratamiento con tiopurinas.
Palabras clave: *Enfermedades Inflamatorias del Intestino; Inmunosupresores; América Latina (fuente: DeCS BIREME).*

INTRODUCTION

Inflammatory bowel diseases (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) are chronic conditions characterized by frequent relapse and debilitating course. A steady increase of IBD has been seen in the past decades in Latin American countries [1]. Although biologics and new small molecules have revolutionized the pharmacological treatment of IBD and modified its progressive trajectory, conventional therapies, such as thiopurines, continue to play a central role in the management of IBD, particularly in resource-limited countries [2,3]. Thiopurines, including azathioprine (AZA) and 6-mercaptopurine (6-MP), are oral antimetabolites and immunomodulators that have been proven to be effective in maintaining remission in patients with steroid-dependent, moderate-to-severe CD and UC [4,5]. Nonetheless, thiopurines has been associated with many different presentations of toxicity, some of which are immunosuppression-related, some are dose-related and some are idiosyncratic [6]. Several clinical and genetic risk factors, as well as ethnic differences for thiopurine-induced toxicity have been reported [7-9], highlighting the need for safety data of thiopurine use from different regions. Nonetheless, data from Latin American populations, where AZA and 6-MP are frequently used [10-13], has not been reported. In this study, we aimed to analyse a large retrospective cohort of Chilean IBD patients exposed to thiopurines and evaluate independent risk factors for thiopurine-related toxicity.

MATERIALS AND METHODS

Study design and data collection

We conducted a retrospective observational study. Adult patients with confirmed CD, UC or IBD-unclassified (IBDU) attending the Clinical Hospital at the Pontificia Universidad Católica of Chile, who were treated with thiopurines between 2000 and 2024, were identified from our database. This database registers all the IBD patients attending our institution. Demographic and clinical data were retrospectively extracted from electronic chart review. Clinical data including age at thiopurine initiation, sex, smoking status, IBD phenotype, and other medications were collected. Thiopurine dose and weight was extracted from charts to calculate maximum weight-based dose of AZA and 6-MP used by the patient. The following adverse events (AE) of interest were searched retrospectively throughout standardized chart review: myelosuppression, hepatitis, pancreatitis, infections, alopecia, flu-like symptoms, non-melanoma skin cancer, and lymphoma. Myelosuppression was defined as leukocyte count $<3.0\times10^9$/L, an absolute neutrophil count $<1.0 \times 10^9$/L or a platelet count $<100\times10^9$/L. Hepatotoxicity was defined as AST or ALT >2× the upper limit of normal. AE that necessitated discontinuation of thiopurine therapy were differentiated from those that did not require treatment withdrawal. Given the retrospective design of our study, we did not establish causality between the AE and thiopurine use, but this was inferred from the attending physician record.

Data on Thiopurine S-methyltransferase (TPMT) activity were obtained when available. TPMT enzymatic activity and thiopurine metabolites have been measured in our institution as part of the clinical practice since January 2008. TPMT activity is measured using high-performance liquid chromatography (HPLC) with fluorometric detection [11]. TPMT is expressed as nmol of 6-methyl thioguanine (6-MTG)/g haemoglobin/hour and categorized as deficient (<5), low (6-24), normal (25-55) and high (>55) [14].

All the data were collected in RedCap [15] and anonymized.

Statistical analysis

Descriptive statistics were used to summarize patient demographics and clinical characteristics. Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) according to their distribution, while categorical variables are presented as frequency and percentages. Between-group differences were analysed using Wilcoxon rank sum test or t-test and Chi-square test or Fisher's exact test, as appropriate, for continuous and categorical variables, respectively. To enable a join analysis of AZA and 6-MP, the dose of AZA was converted to 6-MP equivalent dose dividing by a conversion factor of 2.08 as per previous publications [16]. Odds ratios (OR) and 95% confidence intervals were calculated. A logistic regression was conducted to determine the risk factors associated with AE. Variables with a p-value < 0.1 were included in the multivariable analysis. Only AE that resulted in permanent discontinuation of thiopurine therapy were considered for case classification and regression analysis. Missing data were not imputed. Multivariable models were constructed using all available information for each variable, allowing for optimal use of the dataset.

All data was prepared and analysed with R software v4.1.1 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

Ethical considerations

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee (Approval number #230113002; March 9th, 2023). Informed consent for each participant was not obtained; however, waiver of consent was approved by the institution's human research committee.

RESULTS

Population characteristics

A total of 587 IBD patients treated with thiopurines were identified, with a median age at thiopurine initiation of 35 years (IQR 25-47) and a median of thiopurine exposure of 3 years (IQR 1-7 years). Of these, 338 (57.6%) were

 https://doi.org/10.47892/rgp.2026.463.2237

female and 316 (53.8%), 237 (40.4%) and 34 (5.8%) had CD, UC and IBDU, respectively. AZA was the thiopurine used on 542 (92.3%) patients with the remaining using 6-MP. Clinical characteristics of the whole cohort and stratified by diagnosis, are shown in Table 1. A total of 208 IBD patients (35.4%) presented AE of interest with the following specific frequencies (Table 2): myelosuppression (n=71, 12.1%); gastrointestinal intolerance (n=65, 11.1%); hepatitis (n=31, 5.3%); pancreatitis (n=17, 2.9%); infections (n=6, 1.0%); flu-like symptoms (n=6, 1.0%); non-melanoma skin cancer (n=6, 1.0%); alopecia (n=5, 0.9%), lymphoma (n=1; 0.2%). Most of these patients (163/208; 78.4%) had to permanently stop thiopurines. The remaining had dose adjustment or transient suspension.

Table 1. Clinical characteristics of the whole cohort and stratified by diagnosis.

	CD (n = 316)	UC (n = 237)	IBDU (n = 34)	Total (n = 587)
Sex, female	182 (57.6)	136 (57.4)	20 (58.8)	338 (57.6)
Age at thiopurine initiation, years	36.5 (25.0 - 51.8)	34.0 (25.0 - 42.0)	31.0 (25.5 - 47.8)	35.0 (25.0 - 47.0)
Missing data	46 (14.6)	27 (11.4)	8 (23.5)	81 (13,8%)
Smoking				
Current	49 (15.5)	20 (8.4)	6 (17.6)	75 (12.8)
Former	50 (15.8)	45 (19)	7 (20.6)	102 (17.4)
Never	192 (60.8)	165 (69.6)	19 (55.9)	376 (64.1)
Missing data	25 (7.9)	7 (3)	2 (5.9)	34 (5.8)
UC extent				
E1		23 (9.7)	0	
E2		57 (24.1)	8 (23.5)	
E3	-	145 (61.2)	25 (73.5)	-
Missing data		12 (5.1)	1 (2.9)	
CD location				
L1	46 (14.6)			
L2	140 (44.3)			
L3	122 (38.6)	-	-	-
Missing data	8 (2.5)			
CD location L4	17 (5.4)	-	-	-
CD Behaviour				
B1	171 (54.1)			
B2	67 (21.2)			
B3	49 (15.5)	-	-	-
Missing data	29 (9.2)			
Perianal disease	117 (37.0)	-	-	-
Missing data	3 (1)			
EIM	175 (55.4)	99 (41.8)	15 (44.1)	289 (49.2)
Missing data	8 (2.5)	3 (1.3)	1 (2.9)	12 (2.0)
Thiopurine type				
AZA	290 (91.8)	222 (93.7)	30 (88.2)	542 (92)
6-MP	26 (8.2)	15 (6.3)	4 (11.8)	45 (7.7)
Thiopurine duration, years	3.0 (1.0 - 2.3)	3.0 (0 - 6.0)	3.0 (1.00 - 6.7)	3.0 (1.0 - 7.0)
Missing data	68 (21.5)	41 (17.3)	12 (35.3)	121 (20,6%)
AZA dose (mg/kg/day)*	1.9 (1.2 - 2.3)	1.8 (1.3 - 2.2)	1.7 (0.7 - 2.3)	1.8 (1.2 - 2.2)
Missing data	85/290 (29.3)	63/222 (28.4)	9/30 (30.0)	157/542 (29.0)
6-MP dose (mg/kg/day)*	1.0 (0.6 - 1.2)	0.9 (0.6 - 1.3)	0.6 (0.5 - 0.7)	0.9 (0.6 - 1.2)
Missing data	13/26 (50.0)	2/15 (13.3)	1/4 (25.0)	16/45 (35.6)
Aminosalicylates use at thiopurine initiation	234 (74.1)	219 (92.4)	32 (94.1)	485 (82.6)
Anti-TNF use at thiopurine initiation	37 (11.7)	16 (6.8)	3 (8.8)	56 (9.5)

Categorical variables are shown as n (%) and continuous variables as median (interquartile range). CD, Crohn's disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; EIM, extraintestinal manifestations; AZA, azathioprine; 6-MP, 6-mercaptopurine; TNF, tumor necrosis factor. *The total of patients differs from the n showed in the Table header and is shown as denominator.

Table 2. Adverse events developed in the total cohort and stratified by patients who discontinued or remained on treatment due to adverse events.

	Remained on thiopurine (n = 424)	Discontinued thiopurine (n = 163)	Total (n = 587)
Myelosuppression	19 (4.5)	52 (31.9)	71 (12.1)
Gastrointestinal intolerance	12 (2.8)	53 (32.5)	65 (11.1)
Hepatitis	2 (0.5)	29 (17.8)	31 (5.3)
Pancreatitis	1 (0.2)	16 (9.8)	17 (2.9)
Infections	1 (0.2)	5 (3.1)	6 (1.0)
Flu-like symptoms	1 (0.2)	5 (3.1)	6 (1.0)
Non-melanoma skin cancer	4 (0.9)	2 (1.2)	6 (1.0)
Alopecia	2 (0.5)	3 (1.8)	5 (0.9)
Lymphoma	0	1 (0.6)	1 (0.2)

Variables are shown as n (%)

Clinical variables associated with permanent treatment discontinuation due to adverse events

The analysis of the 163 IBD patients permanently stopping thiopurines due to AE (Table 2) revealed that most of the patients discontinued medication due to gastrointestinal intolerance (n=53, 32.5%), myelosuppression (n=52, 31.9%), hepatitis (n=29, 17.8%) and pancreatitis (n=16, 9.8%). The univariable analysis showed that older age at thiopurine initiation and lower weight were associated ($p<0.05$) with thiopurine-related AE (Table 3). Thiopurine treatment duration was shorter ($p<0.05$) and there was a trend ($p<0.1$) to have lower BMI and thiopurine dose (mg/Kg/day) in patients who discontinued medication in our univariable analysis. The multivariable analysis including age at thiopurine initiation, weight, thiopurine dose and duration demonstrated that older age (OR = 1.02; 95% CI 1.01-1.04) and lower weight (OR = 0.97; 95% CI 0.95-0.99) were independent predictors of AE preventing

Table 3. Univariable analysis of variables associated with thiopurine discontinuation due to adverse events.

	Remained on thiopurine (n = 424)	Discontinued thiopurine (n = 163)	P- value
Sex, Female	238 (56.1)	100 (61.3)	0.26
Age at thiopurine initiation, years	34.0 (25.0 - 45.0)	37.5 (27.8 - 54.3)	0.003
Missing data	58 (13.7)	23 (14.1)	
Weight, Kg	67.0 (57.6 - 79.0)	63.0 (55.0 - 72.0)	0.008
Missing data	83 (19.6)	34 (20.9)	
BMI, weight (kg)/height (m2)	24.7 (21.3 – 28.3)	22.8 (21.2 – 24.9)	0.06
Missing data	308 (72.6)	129 (79.1)	
Smoking			0.37
Current	51 (12.0)	24 (14.7)	
Former	79 (18.6)	23 (14.1)	
Never	271 (63.9)	105 (64.4)	
Missing data	23 (5.4)	11 (6.7)	
Diagnosis			0.15
CD	218 (51.4)	98 (60.1)	
UC	179 (42.2)	58 (35.6)	
IBDU	27 (6.4)	7 (4.3)	
EIM	202 (47.6)	87 (53.4)	0.30
Missing data	11 (2.6)	1 (0.6)	
Thiopurine Type			0.73
Azathioprine	390 (92.0)	152 (93.3)	
Mercaptopurine	34 (8.0)	11 (6.7)	
Thiopurine dose (mg/Kg/day)*	0.9 (0.6 - 1.1)	0.8 (0.5 - 1.0)	0.08
Missing data	111 (26.2)	62 (38.0)	
Split dose	40 (9.4)	14 (8.6)	0.8
Missing data	15 (3.5)	10 (6.1)	
Thiopurine duration, years	4.00 (1.0 - 8.0)	1.0 (0 - 2.0)	< 0.001
Missing data	85 (20.0)	36 (22.1)	
Aminosalicylates use at thiopurine initiation	350 (82.5)	135 (82.8)	1
anti-TNF use at thiopurine initiation	41 (9,7)	15 (9.2)	1

Categorical variables are shown as n (%) and continuous variables as median (interquartile range). CD, Crohn's disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified; BMI, body mass index; EIM, extraintestinal manifestations; TNF, tumor necrosis factor. *Azathioprine doses were adjusted to 6-mercaptopuine equivalents using a conversion factor of 2.08

 https://doi.org/10.47892/rgp.2026.463.2237

Table 4. Multivariable analysis of clinical factors associated with thiopurine discontinuation due to adverse events.

Predictors	Odds ratio	95% confidence interval	p-value
Age thiopurine (year)	1.02	1.01- 1.04	0.008
Weight (kg)	0.97	0.95 - 0.99	0.007
Thiopurine dose (mg/kg/day)*	0.42	0.17- 0.99	0.04
Thiopurine duration (months)	0.81	0.74- 0.88	< 0.001

CD, Crohn's disease; UC, ulcerative colitis; IBDU, inflammatory bowel disease unclassified. *Azathioprine doses were adjusted to 6-mercaptopuine equivalents using a conversion factor of 2.08.

thiopurine continuation (Table 4). When analysing IBD patients with AE including only myelosuppression, hepatitis and pancreatitis; older age at thiopurine initiation (OR 1.02, 95% CI 1.01-1.04) and lower weight (OR 0.97, 95% CI 0.97-0.99) remained significantly associated with these AE. The analysis by age ranges demonstrated that 49 out of 196 (25%) patients aged 30 years or younger; 87 out of 245 (35.5%) patients aged 31-60 years and 30 out of 59 (50.8%) patients over 60 years old had either myelosuppression, hepatitis or pancreatitis that required thiopurine discontinuation. The multivariable analysis using age ranges showed that age at thiopurine initiation between 31-60 (OR 1.83, 95% CI 1.02-3.34) and older than 60 years (OR 2.71, 95% CI 1.22-6.02) significantly increased the probability of AE requiring discontinuation compared to patients younger than 30, independent of weight-based thiopurine dose and treatment duration. There were no differences in the rate of AE between patients using AZA compared to those using 6MP, nor between those who were or were not concomitantly treated with aminosalicylates or anti-TNF.

TPMT activity

A total of 272 (46.3%) IBD patients had TPMT activity evaluated before starting thiopurine treatment. Only 8 (2.9%) had low activity, while 257 (94.5%) and 7 (2.6%) had normal and high enzyme activity, respectively. None of the patients had deficient activity. Myelosuppression was observed in 2 patients with low activity (25.0%), 33 patients with normal activity (12.8%) and 1 patient with high TPMT activity (14.3%).

DISCUSSION

Thiopurines remain an important medication in the IBD therapeutic arsenal in many Latin American countries where penetration of biological therapy is still low, or health regulatory agencies make mandatory the use of immunomodulators before starting biologics. Data related to the safety of IBD therapy have been reported in regions different to Latin America; therefore, data on thiopurine-related toxicity in our population is needed. In this large cohort of 587 IBD patients exposed to thiopurines from a tertiary centre, one third had to permanently discontinue thiopurines mainly due to AE. This proportion is concordant with the highest rates reported in the literature (10%-30%) [17-23].

Thiopurine-induced myelotoxicity

Thiopurine-induced myelotoxicity is one of the most serious thiopurine-induced side effects and the most frequently reported in our cohort (12.1%), usually requiring drug suspension. Myelotoxicity is reported between 1.7% and 11% of IBD patients exposed to thiopurines in previous studies [18,19,21-25]. Myelosuppression is related to higher thiopurine dose, genetics and ethnical factors [9,26]. Genetic polymorphisms in metabolizing enzymes for thiopurines, specifically Nudix hydrolase 15 (NUDT15) and TPMT increase predisposition to develop myelosuppression [27]. Interestingly, a recent study found that NUDT15 and TPMT variants were rare in the Hispanic population, except for rs116855232 variant in NUDT15, which was common only in alleles of Amerindian origin [10]. The high Amerindian contribution to the Chilean genetic structure [28-31] could explain this high proportion of patients experiencing myelosuppression despite the small number of patients with low TPMT activity (2.9%). However, the lack of TPMT activity measurement in a great proportion of our cohort could introduce bias and make difficult a correct interpretation of the role of TPMT activity in preventing thiopurine toxicity in our cohort. Our findings support that the frequency of NUDT15 variants should be explored in Latin America, and testing should become standard clinical practice before prescribing thiopurines in individuals with Amerindian background such as Latin American IBD patients [9].

Other adverse events

We observed thiopurine-Induced hepatotoxicity in 5.3% of our cohort and the rates vary between 0.3% and 14% in previous reports [19,21-23,32,33]. In our study, 2.9% of the patients treated with thiopurines had pancreatitis, which is similar to previous publications, where this percentage varies from 1 to 5% [19,21-23,34,35]. Gastrointestinal intolerance was identified in 11.1% of our patients and although this is not usually considered a severe adverse effect, it resulted in a significant percentage of drug suspension. Nausea, vomiting or abdominal pain are frequent and have been also related to polymorphisms of TPMT [36] and switching treatment from AZA to 6MP can curb some of these side effects [37].

Although we found infectious complications in only 6 patients (1.0%), some of them were serious infections conducting to therapy suspension such as a case of

disseminated cytomegalovirus with concomitant use of anti-TNF and corticosteroids and one case of fungal ear infection. Thiopurines and anti-TNF has been associated with a mild increased risk of serious and opportunistic infections which is higher with combination therapy [38]. Flu-like symptoms and alopecia were uncommon (cumulative rate ~1%). We search for non-melanoma skin cancer and lymphoma cases because they have been previously associated with thiopurine use [39]. We found six cases of non-melanoma skin cancer and four of these cases continued thiopurines after resection, particularly in cases diagnosed before 2015 where access to biologic therapy was limited in our country. Only one case of lymphoma was observed in our cohort and thiopurine treatment was discontinued. This low frequency of non-melanoma skin cancer and lymphoma is in agreement with recent studies showing no increased risk of these type of neoplasia on thiopurine users [40-42].

Clinical factors associated with thiopurine toxicity

Given the frequent occurrence of thiopurine-related AE in our population, it is important to identify those IBD patients at-risk. Our multivariable analysis showed that older age and lower weight are significantly associated with AE independent of weight-based dose, sex, type of diagnosis (CD or UC) and treatment duration. Notably, 50% of IBD patients in our cohort starting thiopurines after 60 years old had AE (myelosuppression, pancreatitis or hepatitis) obligating thiopurine withdrawal compared to 25% of those starting thiopurines before 30 years old with almost 3-fold higher risk. A previous report by the ENEIDA registry showed that in elderly IBD patients, thiopurines are associated with an increased risk of non-infectious and non-neoplastic AE [43]. These findings are of relevance because the elderly population with IBD is increasing due to the worldwide rising of IBD and ageing [44]. Therefore, clinicians should be particularly cautious when starting therapy with thiopurines in elderly IBD patients or use alternative medications that have shown a better risk profile in this group, when available [45].

We found that lower weight was also independently associated with thiopurine toxicity. A diminished BMI was also numerically associated with higher thiopurine toxicity, however, excessive missing data due to lack of height data in our registers prevented the inclusion of BMI in our multivariable analysis. It has been previously shown that lower BMI is associated with higher 6-thiogunanine nucleotide levels, which is the active metabolite of thiopurines related to myelotoxicity [46]. Additionally, a reduced weight/BMI could reflect a poorer nutritional and health status which could make IBD patients more susceptible to drug-related AE.

We finally also identified that a lower dose per Kg and a longer duration of thiopurine treatment were associated with lower rate of AE. An incapacity to reach an appropriate dose in patients experiencing AE could explain the association of AE with a lower thiopurine dose. Similarly, most of the AE usually occur within the first months of therapy initiation; therefore, patients who tolerate treatment with no AE will remain on treatment longer.

Study limitations

To our knowledge, this is the largest and the first cohort of IBD patients from Latin America reporting thiopurine toxicity. However, our study has a number of limitations including the retrospective design that could produce bias on clinical data extracted; particularly, anthropometric data and AE recording. We also had a significant proportion of missing data in some relevant variables that prevented the inclusion of several cases in our multivariable analysis. Therefore, our results should be taken with caution. Future prospective studies with standardize data collection might confim our findings. Similarly, we were not able to include other parameters such as disease activity and therapy response in our analysis that could influence AE rates. Given the data was collected from a tertiary centre, IBD patients with more severe disease could be included which could explain a high proportion of patients discontinuing thiopurines. These findings should be confirmed in largest and prospective multicentric cohorts in our region.

In conclusion, we have identified older age and lower weight as independent risk factors for thiopurine toxicity in a large Latin American population from Chile. Thiopurines should be initiated with caution in IBD patients older than 60 years old and other options should be explored in this age group, when possible.

REFERENCES

1. Kotze PG, Underwood FE, Damião AOMC, Ferraz JGP, Saad-Hossne R, Toro M, *et al*. Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean: A Systematic Review. Clin Gastroenterol Hepatol. 2020;18(2):304-12. doi: 10.1016/j.cgh.2019.06.030.
2. Sousa P, Ministro P, Armuzzi A, Dignass A, Høivik ML, Acosta MB, *et al*. Thiopurines: Use them or lose them? International survey on current and future use of thiopurines in inflammatory bowel disease. Dig Liver Dis. 2021;53(12):1571-9. doi: 10.1016/j.dld.2021.05.038.
3. Queiroz NSF, Martins C de A, Quaresma AB, Olivera Sendra PA, Ernest-Suarez K, Kotze PG. IBD barriers across the continents: a continent-specific analysis: Latin America. Ther Adv Gastroenterol. 2023;16:17562848231167953. doi: 10.1177/17562848231167953.
4. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2015;(10):CD000067. doi: 10.1002/14651858.CD000067.pub3.
5. Timmer A, Patton PH, Chande N, McDonald JWD, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016;(5):CD000478. doi: 10.1002/14651858.CD000478.pub4.
6. de Boer NKH, Peyrin-Biroulet L, Jharap B, Sanderson JD, Meijer B, Atreya I, *et al*. Thiopurines in Inflammatory Bowel Disease: New Findings and Perspectives. J Crohns Colitis. 2018;12(5):610-20. doi: 10.1093/ecco-jcc/jjx181.
7. Bastida G, Nos P, Aguas M, Beltrán B, Rubín A, Dasí F, *et al*. Incidence, risk factors and clinical course of thiopurine-

induced liver injury in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2005;22(9):775-82. doi: 10.1111/j.1365-2036.2005.02636.x.

8. van Gennep S, Konté K, Meijer B, Heymans MW, D'Haens GR, Löwenberg M, *et al*. Systematic review with meta-analysis: risk factors for thiopurine-induced leukopenia in IBD. Aliment Pharmacol Ther. 2019;50(5):484-506. doi: 10.1111/apt.15403.
9. Balarajah S, Martinez-Gili L, Alexander JL, Mullish BH, Perry RW, Li JV, *et al*. A large-scale comparison of clinical outcomes to IBD therapies in White and South Asian ethnicities. EClinicalMedicine. 2025;90:103644. doi: 10.1016/j.eclinm.2025.103644.
10. Ioannou S, Beecham A, Gomez L, Dauer R, Khakoo N, Pascual L, *et al*. Ancestral Diversity in Pharmacogenomics Affects Treatment for Hispanic/Latine Populations With Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2025;23(6):1008-1018.e7. doi: 10.1016/j.cgh.2024.07.032.
11. Jorquera A, Solari S, Vollrath V, Guerra I, Chianale J, Cofré C, *et al*. [Phenotype and genotype of thiopurine methyltransferase in Chilean individuals]. Rev Med Chil. 2012;140(7):889-95. doi: 10.4067/S0034-98872012000700009.
12. Gallardo-Cóndor J, Naranjo P, Atarihuana S, Coello D, Guevara-Ramírez P, Flores-Espinoza R, *et al*. Population-Specific Distribution of TPMT Deficiency Variants and Ancestry Proportions in Ecuadorian Ethnic Groups: Towards Personalized Medicine. Ther Clin Risk Manag. 2023;19:1005-18. doi: 10.2147/TCRM.S432856.
13. Suarez-Kurtz G, Araújo GS de, de Sousa SJ. Pharmacogeomic implications of population diversity in Latin America: TPMT and NUDT15 polymorphisms and thiopurine dosing. Pharmacogenet Genomics. 2020;30(1):1-4. doi: 10.1097/FPC.0000000000000388.
14. Ford LT, Cooper SC, Lewis MJ, Berg JD. Reference intervals for thiopurine S-methyltransferase activity in red blood cells using 6-thioguanine as substrate and rapid non-extraction liquid chromatography. Ann Clin Biochem. 2004;41(Pt 4):303-8. doi: 10.1258/0004563041201617.
15. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, *et al*. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019;95:103208. doi: 10.1016/j.jbi.2019.103208.
16. Maeda T, Sakuraba H, Hiraga H, Yoshida S, Kakuta Y, Kikuchi H, *et al*. Long-term efficacy and tolerability of dose-adjusted thiopurine treatment in maintaining remission in inflammatory bowel disease patients with NUDT15 heterozygosity. Intest Res. 2022;20(1):90-100. doi: 10.5217/ir.2020.00133.
17. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. Gut. 2002;50(4):485-9. doi: 10.1136/gut.50.4.485.
18. Chaparro M, Ordás I, Cabré E, Garcia-Sanchez V, Bastida G, Peñalva M, *et al*. Safety of Thiopurine Therapy in Inflammatory Bowel Disease: Long-term Follow-up Study of 3931 Patients. Inflamm Bowel Dis. 2013;19(7):1404-10. doi: 10.1097/MIB.0b013e318281f28f.
19. Martínez F, Nos P, Pastor M, Garrigues V, Ponce J. Adverse effects of azathioprine in the treatment of inflammatory bowel disease. Rev Esp Enferm Dig. 2001;93(12):769-78.
20. Saibeni S, Virgilio T, D'Incà R, Spina L, Bortoli A, Paccagnella M, *et al*. The use of thiopurines for the treatment of inflammatory bowel diseases in clinical practice. Dig Liver Dis. 2008;40(10):814-20. doi: 10.1016/j.dld.2008.03.016.
21. Present DH, Meltzer SJ, Krumholz MP, Wolke A, Korelitz BI. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. Ann Intern Med. 1989;111(8):641-9. doi: 10.7326/0003-4819-111-8-641.
22. Warman JI, Korelitz BI, Fleisher MR, Janardhanam R. Cumulative experience with short- and long-term toxicity to 6-mercaptopurine in the treatment of Crohn's disease and ulcerative colitis. J Clin Gastroenterol. 2003;37(3):220-5. doi: 10.1097/00004836-200309000-00006.
23. López-Martín C, Chaparro M, Espinosa L, Bejerano A, Maté J, Gisbert JP. Adverse events of thiopurine immunomodulators in patients with inflammatory bowel disease. Gastroenterol Hepatol. 2011;34(6):385-92. doi: 10.1016/j.gastrohep.2011.03.023.
24. Solbach P, Chhatwal P, Woltemate S, Tacconelli E, Buhl M, Gerhard M, *et al*. BaiCD gene cluster abundance is negatively correlated with Clostridium difficile infection. PLoS One. 2018;13(5):e0196977. doi: 10.1371/journal.pone.0196977.
25. Gisbert JP, Gomollón F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. Am J Gastroenterol. 2008;103(7):1783-800. doi: 10.1111/j.1572-0241.2008.01848.x.
26. Luber RP, Honap S, Cunningham G, Irving PM. Can We Predict the Toxicity and Response to Thiopurines in Inflammatory Bowel Diseases? Front Med (Lausanne). 2019;6:279. doi: 10.3389/fmed.2019.00279.
27. Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui C-H, Stein CM, *et al*. Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on and 15 Genotypes: 2018 Update. Clin Pharmacol Ther. 2019;105(5):1095-105. doi: 10.1002/cpt.1304.
28. Eyheramendy S, Martinez FI, Manevy F, Vial C, Repetto GM. Genetic structure characterization of Chileans reflects historical immigration patterns. Nat Commun. 2015;6(1):6472. doi: 10.1038/ncomms7472.
29. Pérez-Jeldres T, Magne F, Ascui G, Alvares D, Orellana M, Alvarez-Lobos M, *et al*. Amerindian ancestry proportion as a risk factor for inflammatory bowel diseases: results from a Latin American Andean cohort. Front Med (Lausanne). 2023;10:1258395. doi: 10.3389/fmed.2023.1258395.
30. Bustos BI, Miquel JF, Hernández-Rocha C. Letter to the Editor Regarding Ioannou *et al*. Clin Gastroenterol Hepatol. 2026;24(5):1471-1472. doi: 10.1016/j.cgh.2025.06.008.
31. von Muhlenbrock C, Estay C, Covarrubias N, Miranda J, Venegas M. The c.415C>T polymorphism in NUDT15 is more frequent than the polymorphisms in TPMT in Chilean patients who use thiopurine drugs. Pharmacogenet Genomics. 2023;33(7):161-3. doi: 10.1097/FPC.0000000000000503.
32. Gisbert JP, González-Lama Y, Maté J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. Am J Gastroenterol. 2007;102(7):1518-27. doi: 10.1111/j.1572-0241.2007.01187.x.
33. Bastida G, Nos P, Aguas M, Beltrán B, Rubín A, Dasí F, *et al*. Incidence, risk factors and clinical course of thiopurine-induced liver injury in patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2005;22(9):775-82. doi: 10.1111/j.1365-2036.2005.02636.x.
34. Bermejo F, Lopez-Sanroman A, Taxonera C, Gisbert JP, Pérez-Calle JL, Vera I, *et al*. Acute pancreatitis in inflammatory bowel disease, with special reference to azathioprine-induced pancreatitis. Aliment Pharmacol Ther. 2008;28(5):623-8. doi: 10.1111/j.1365-2036.2008.03746.x.
35. Weersma RK, Peters FTM, Oostenbrug LE, van den Berg AP, van Haastert M, Ploeg RJ, *et al*. Increased incidence of azathioprine-induced pancreatitis in Crohn's disease compared with other diseases. Aliment Pharmacol Ther. 2004;20(8):843-50. doi: 10.1111/j.1365-2036.2004.02197.x.
36. Ansari A, Arenas M, Greenfield SM, Morris D, Lindsay J, Gilshenan K, *et al*. Prospective evaluation of the pharmacogenetics of azathioprine in the treatment of inflammatory bowel

disease. Aliment Pharmacol Ther. 2008;28(8):973-83. doi: 10.1111/j.1365-2036.2008.03788.x.

37. Kennedy NA, Rhatigan E, Arnott IDR, Noble CL, Shand AG, Satsangi J, *et al*. A trial of mercaptopurine is a safe strategy in patients with inflammatory bowel disease intolerant to azathioprine: an observational study, systematic review and meta-analysis. Aliment Pharmacol Ther. 2013;38(10):1255-66. doi: 10.1111/apt.12511.
38. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2018;155(2):337-346.e10. doi: 10.1053/j.gastro.2018.04.012.
39. Wewer MD, Letnar G, Andersen KK, Malham M, Wewer V, Seidelin JB, *et al*. Thiopurines and the Risk of Cancer in Patients With Inflammatory Bowel Disease and Reference Individuals Without Inflammatory Bowel Disease: A Danish Nationwide Cohort Study (1996-2018). Clin Gastroenterol Hepatol. 2025;23(6):1030-8. doi: 10.1016/j.cgh.2024.08.006.
40. Schaik FDM van, Oijen MGH van, Smeets HM, Heijden GJMG van der, Siersema PD, Oldenburg B. Risk of Nonmelanoma Skin Cancer in Patients With Inflammatory Bowel Disease Who Use Thiopurines Is Not Increased. Clin Gastroenterol Hepatol. 2011;9(5):449-450.e1. doi: 10.1016/j.cgh.2011.01.021.
41. Ranjan MK, Kante B, Vuyyuru SK, Kumar P, Mundhra SK, Golla R, *et al*. Minimal risk of lymphoma and non-melanoma skin cancer despite long-term use of thiopurines in patients with inflammatory bowel disease: A longitudinal cohort analysis from northern India. J Gastroenterol Hepatol. 2022;37(8):1544-53. doi: 10.1111/jgh.15880.
42. Kobayashi T, Uda A, Udagawa E, Hibi T. Lack of Increased Risk of Lymphoma by Thiopurines or Biologics in Japanese Patients with Inflammatory Bowel Disease: A Large-Scale Administrative Database Analysis. J Crohns Colitis. 2020;14(5):617-23. doi: 10.1093/ecco-jcc/jjz204.
43. Calafat M, Mañosa M, Cañete F, Ricart E, Iglesias E, Calvo M, *et al*. Increased risk of thiopurine-related adverse events in elderly patients with IBD. Aliment Pharmacol Ther. 2019;50(7):780-8. doi: 10.1111/apt.15458.
44. Everhov ÅH, Halfvarson J, Myrelid P, Sachs MC, Nordenvall C, Söderling J, *et al*. Incidence and Treatment of Patients Diagnosed With Inflammatory Bowel Diseases at 60 Years or Older in Sweden. Gastroenterology. 2018;154(3):518-528.e15. doi: 10.1053/j.gastro.2017.10.034.
45. Ananthakrishnan AN, Nguyen GC, Bernstein CN. AGA Clinical Practice Update on Management of Inflammatory Bowel Disease in Elderly Patients: Expert Review. Gastroenterology. 2021;160(1):445-51. doi: 10.1053/j.gastro.2020.08.060.
46. Poon SS, Asher R, Jackson R, Kneebone A, Collins P, Probert C, *et al.* Body Mass Index and Smoking Affect Thioguanine Nucleotide Levels in Inflammatory Bowel Disease. J Crohns Colitis. 2015;9(8):640-6. doi: 10.1093/ecco-jcc/jjv084.