

Running head: Colchicine-induced myelosuppression in cases

Full manuscript title: Examining the Characteristics of Colchicine-Induced Myelosuppression in Clinical Cases: A Systematic Review

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Abstract

Objectives

The use of colchicine has been associated with varying degrees of myelosuppression. Despite expanded use in cardiovascular and inflammatory conditions, there remains clinician concern due to potential myelosuppressive side effects. A systematic review was conducted to explore the reported adverse myelosuppressive events of colchicine.

Methods

A systematic review was conducted using the MeSH subheading (“colchicine”) AND (“myelosuppression”, “bone*”, “marrow”, “suppression”, “aplasia”, “leukopenia/leucopenia”, “lymphopenia”, “neutropenia”) on 1 September 2020 and was updated on 30th November 2021 for PubMed, Science Direct, Scopus, EMBASE and Cochrane. The search included references from 1978 to 2020, and was limited to English language observational studies (case reports, case series, case control and cohort studies) or trial data.

Results

Three thousand, two hundred and thirty-three articles were screened, with 30 studies of 47 patients with myelosuppression from colchicine identified. Most patients with myelosuppression had comorbidities, including renal impairment (21/47,44.7%). 15/47 (31.9%) and 13/47 (27.7%) patients were reported to be concurrently taking Cytochrome P450 inhibitors (CYP3A4) and P-glycoprotein efflux transporter inhibitors (P-gp) respectively. Patients with renal impairment accounted for the majority of overall patients taking these CYP3A4 and P-gp inhibitors (8/15 [53.3%] and 8/13 [61.5%] respectively). Thirteen out of twenty-one patients with renal impairment had worsening cytopenias during colchicine use. The presentations ranged from moderate anaemia (Grade 2) to severe thrombocytopenia, neutropenia, and leukopenia (Grade 4).

Conclusion

Colchicine has few reports of myelosuppression. The majority had pre-existing renal impairment or concomitant CYP3A4 or P-gp inhibitor use. Caution should be taken in this subset of patients with increased monitoring.

1.0 Introduction

Colchicine, originally derived from the ancient plant *Colchicum autumnale*, has been used for thousands of years as a prophylaxis and treatment for gout flares and in more recent times, in inflammasome-mediated conditions such as Familial Mediterranean Fever (FMF)¹. In the last decade, it has also increasingly been recognised to have a role in managing cardiovascular disease and more recently, reduce mortality in myocardial infarction and ischaemic stroke²⁻⁴.

This has led to increased scrutiny of colchicine's safety, and therefore its pharmacology. Colchicine is a substrate for cytochrome P450 (CYP3A4 isoenzyme) and P-glycoprotein efflux transporter (P-gp)⁵. It has a long terminal half-life and a bioavailability of 24-88%⁶. It is 10-20% renally metabolised with the remainder due to hepatic metabolism^{7,8}. Peak plasma concentrations can be found 1 hour after administration and anti-inflammatory effects typically occur between 24 and 48 hours after ingestion⁷. The main mechanism of action of colchicine is the inhibition of microtubule activation in rapidly dividing inflammatory cells. It plays a vital role in the treatment of crystal arthropathies through inhibition of the release of glycopeptide crystal-derived chemotactic factor from neutrophil lysosomes after phagocytosis of monosodium urate crystals⁹. However, colchicine has shown to have relatively high concentrations in leukocytes, interacting with adhesion, mobilisation, and degranulation of lysosomes¹⁰. Colchicine's inhibition of leukocyte chemotaxis has further been shown in concentrations as low as 1×10^{-8} /L. Recent studies have further shown an inhibition of adhesion molecules on neutrophil membranes, thereby reducing neutrophil transmigration⁸.

Cases of myelosuppression have been reported in studies, particularly with cases of colchicine toxicity from overdose and drug interactions. Other known side effects of colchicine observed are gastrointestinal with nausea, vomiting, diarrhoea, neuropathy, and myopathy^{11,12}. Increased rates of infection is not a feature of colchicine use¹³.

This systematic review explores reported cases of myelosuppression with colchicine administration in rheumatic conditions, and the circumstances in which they occur. We aim to characterise the demographic and clinical factors associated with the development of myelosuppression, particularly focusing on the pre-existing comorbidities and medications that may increase its risk. As the use of colchicine has expanded to include cardiovascular and dermatological conditions, this systematic review hopes to address uncertainties around its use and potential concern over adverse myelosuppressive events. This review aims to clarify the published data to assist physicians when treating and monitoring patients with colchicine.

2.0 Methods

2.1 Search strategy

This systematic review was completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMA) as shown in Figure 1. The review was registered prospectively with PROSPERO (CRD42020205707).

A systematic review was conducted using the MeSH subheading ("colchicine") AND ("myelosuppression", "bone*", "marrow", "suppression", "aplasia", "leukopenia/leucopenia", "lymphopenia", "neutropenia") on 1 September 2020 and was updated on 30th November 2021 PubMed, Science Direct, Scopus, EMBASE and Cochrane. This included references from 1978 to 2020. The search was limited to English language observational studies (case reports, case series, case control and cohort studies) or trial data. Demographic details and clinical findings were extracted.

2.2 Eligibility criteria

The search was limited to English language observational studies (case reports, case series, case control and cohort studies) or trial data. Studies were assessed using prospective inclusion/exclusion criteria (Supplementary file 1).

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Intentional therapeutic overdoses due to the treatment of disease flares that were given above the maximum recommended daily colchicine dose were included. Two reviewers completed an initial screen of 2,705 titles and abstracts to remove exclusions and duplications, with a third moderating any conflicts. A second screen assessed 95 full-text articles for final inclusion. Two reviewers assessed these full text articles, with a third moderating any conflicts.

2.3 Data Extraction

Thirty articles for final inclusion were analysed and relevant information was extracted using a prospective data extraction form. Two reviewers were involved in the data extraction with a third moderating any discrepancies. Results are presented as number (% total), mean \pm SD or median+IQR.

Myelosuppression was defined as any one of the following: leukopenia ($<3000/\text{mm}^3$), neutropenia ($<1500/\text{mm}^3$), thrombocytopenia ($<75,000/\text{mm}^3$), and anaemia ($<10\text{g/dl}$ for females, $<13.5\text{g/dl}$ for males) ¹⁴.

Grading for myelosuppression was based on previously published scales ¹⁴

The probability of adverse drug reactions was based on the Naranjo Adverse Drug Reaction Probability scale, where each study was scaled and results were reported as: “Certain”, “Probable”, “Possible”, or “Unlikely”¹⁵.

Details from the included articles were extracted: these included demographics, comorbidities, renal function, other medications, method of diagnosis, treatment course, and outcome. Haematological outcomes measured were haemoglobin (Hb), white cell count (WCC), platelet (Plt), and neutrophil counts. These have been represented in Table 1 and 2.

3.0 Results

The initial search results yielded 2705 references. Two thousand, six hundred and ten articles were excluded and 95 included after the first review of title and abstract. After full text review, 54 references were excluded, leaving 41 articles. A further 11 articles were excluded due to qualitative data being unable to be reported adequately or studies that involved intravenous colchicine use. Thirty articles comprising of 47 patients who had myelosuppression from colchicine were included ¹⁶⁻⁴⁵.

3.1 Clinical characteristics

Out of the patients reported, 25 (53.2%) were female, 22 (46.8%) were male. These patients had a mean age of 48 ± 27 years old.

Of the 47 patients that had an indication for colchicine listed, 17 used colchicine for gout (36.2%), 16 for Familial Mediterranean Fever (FMF) (34.0%), 4 for arthralgias (8.5%), 2 for Behçet's Disease (4.3%). The remainder of indications for colchicine can be seen on Table 1.

The mean average Charlson Comorbidity Index (CCI) score was 3.2 ± 2.4 across all reported cases and 4.3 ± 2.2 in those with renal impairment. Across the data, the most commonly reported comorbidities included haematological disease, cardiovascular disease, and renal disease.

Twenty one patients were reported to have chronic renal impairment or acute kidney injury from colchicine drug interactions. Thirteen out of twenty one patients (62.0%) were reported to have worsening of their chronic renal impairment during colchicine use.

Other recorded side effects noted were diarrhoea (42.6%), abdominal pain (19.1%), vomiting (12.8%), fever (17.0%), pneumonia (4.3%), erythematous skin eruptions (4.3%), and mental

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confusion (4.3%) (Table 2). Within the renal patients, other side effects noted were diarrhoea (57.1%), abdominal pain (23.8%), vomiting (23.8%), fever (23.8%), pneumonia (9.5%), erythematous skin eruption (4.8%), and mental confusion (9.5%).

3.2 Concurrent medications

In patients regularly prescribed colchicine, 15/47 (31.9%) and 13/47 (27.7%) patients were reported to be concurrently taking CYP3A4 inhibitors and P-gp inhibitors respectively. Eight out of twenty one people who had renal impairment took both CYP3A4 and P-gp inhibitors. These renal patients accounted for the majority of overall patients taking these CYP3A4 and P-gp inhibitors (53.3% and 61.5% respectively).

3.3 Myelosuppression

The median average time to myelosuppression from initiating colchicine dosage in an addition to a different drug or a due to a cumulative dose was 7 days (IQR: 4.8-10.5) (Table 2).

3.4 Treatment and Outcomes

Presentations ranged in severity. In mild cases, discontinuation of colchicine was sufficient for recovery of cell counts (17/47, 36.2%).

In 10/47 cases (21.3%), administration of granulocyte-colony stimulating factor (G-CSF) was required for profound neutropenia. Of those 10 cases treated with G-CSF, 5 recovered (50.0%) and 5 died (50.0%).

Indications for colchicine treatment and management outcomes are indicated at Table 1 and Table 2 respectively.

Twenty four patients recovered, while 18 were deceased across 47 patients, however, within the renal impaired group, 12/21 (57.1%) patients were deceased while 6/21 (28.6%)

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recovered. Recovery rates in patients with pre-existing renal impairment were lower than those without pre-existing renal impairment (Table 2).

3.5 Treatment outcomes for renal impaired patients

Renal impairment was classified as those with stated pre-existing renal impairment (defined as: kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR or GFR < 60 mL/min/1.73m² for ≥ 3 months⁴⁶) or acute kidney injury (AKI) within each study (n=21).

Across the studies, many reports of colchicine doses taken prior to myelosuppression due to acute flares were nearly three times greater than their normal daily colchicine dose. The median cumulative colchicine dose taken prior to myelosuppression was 3.0 ± 2.9 mg while the renally impaired group took a cumulative mean average of 2.5 ± 2.4 mg. However, mean daily colchicine dose across all participants and renally impaired group was 0.8 ± 0.8 mg and 0.8 ± 0.8 mg respectively.

3.6 Haematological cell counts

Across the patients, the mean nadir haemoglobin count was 10.1 ± 2.8 (Grade 1), indicating mild anaemia. Thrombocytopenia was unremarkable across the studies as a whole, however, patients who had worsening of their pre-existing renal conditions or developed acute kidney due to colchicine toxicity had severe thrombocytopenia of $69.0 \pm 38.0 \times 10^9/L$ (Grade 4). Nadir white cell counts were $2.0 \pm 1.8 \times 10^9/L$ (Grade 2 Leukopenia), only in those with renal failure. Across the studies included, nadir neutrophil counts were at $1.2 \pm 1.6 \times 10^9/L$ (Grade 2 neutropenia), while the renal impairment group had worse neutropenia ($0.7 \pm 0.6 \times 10^9/L$ (Grade 3)). Overall, median duration of myelosuppression was 7 days (4.0-10.8) days.

None of the 30 reported studies had severe myelosuppression across all cell lines (defined as: Hb < 6.5 g/dL, platelets $< 25 \times 10^9/L$, neutrophils $< 0.5 \times 10^9/L$, leucocytes $< 1 \times 10^9/L$)¹⁴.

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A large portion of myelosuppression cases (15/47, 31.9%) were in patients who concomitantly took CYP3A4 inhibitors, such as clarithromycin and cyclosporin (Table 3). A significant number of these patients (13/47, 27.7%) also took P-gp inhibitors, such as erythromycin and amiodarone (Table 3).

3.7 Naranjo Drug Reaction Scale

Naranjo adverse drug reaction probability scales across the studies attributed colchicine causality to “possible” or “probable”. There remains uncertainty if colchicine is the main causative agent to myelosuppression (Figure 2).

An overall representation of dose of colchicine taken with or without CYP3A4 inhibitors by patients is represented in Figure 2.

4.0 Discussion

To our knowledge, this is the first systematic review to examine published cases of myelosuppression in colchicine use in the context of rheumatic conditions. We identified 30 reports of 47 patients with myelosuppression. Across the studies, there were 15/47 patients on CYP3A4 inhibitors, while 13/47 patients were on P-gp inhibitors, suggesting drug interactions contributed to myelosuppression. Within the renally impaired groups, there were 8/21 people taking CYP3A4 inhibitors while 8/21 people took P-gp inhibitors. Amongst the 30 reports, the Charlson Comorbidity Index reported a mean of 3.2 ± 2.4 (Table 2). Notably, four patients had febrile neutropenia, although two of these cases had chronic renal impairment, while one case developed septic neutropenia as a result of co-administration with anakinra.

While excluded from the study, a study by Sag et al.⁴⁷ contained paediatric cases that presented a contrast with adult cases, where a decrease in colchicine doses resolved leukopenia. Although information on concurrent medications of these patients was not

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reported, this provides a comparison to adult cases, where myelosuppression was dependent on comorbidities and other medication use.

Across the studies, none of the cases reported severe myelosuppression across all haematological cell lines. Further, cases with the most severe myelosuppression were observed to have taken a higher than recommended colchicine daily dose due to acute flares and had pre-existing renal impairment or were taking CYP3A4 inhibitors/P-gp inhibitors concomitantly with their dosage of colchicine during the time of myelosuppression (Figure 2). Colchicine has a widely acceptable safety profile within the rest of the patient population. However, there is a need for further monitoring in multi-morbid patients and those with renal impairment. Many cases represented in peer-reviewed literature based on the Naranjo adverse drug reaction scale indicated an uncertainty as to whether colchicine was the main causal agent of myelosuppression.

Due to the increasing use of colchicine in recent years, it is important to clarify as much as possible the safety of this drug. Colchicine is increasingly being used in cardiovascular conditions and in patients with other co-morbidities and who take other medications that may cause drug interactions. Numerous studies involving the use of colchicine in cardiovascular conditions have described its safety and efficacy. As discussed in a study by Andreis et al., haematological adverse events were not increased by use of colchicine, and its use was concluded to be safe ⁴⁸.

In this study, despite worsening of some cell lines across the studies, these cases of myelosuppression were particularly concentrated in those with pre-existing renal conditions or in those on other medications due to co-morbidities, specifically CYP3A4 inhibitor interaction with colchicine use such as clarithromycin and cyclosporine⁴⁹. CYP3A4 metabolism and P-gp inhibitor transportation have known interactions with colchicine's oral bioavailability, metabolism, and excretion^{49 50,51}. The use of colchicine with strong CYP3A4 inhibitors such as

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clarithromycin and P-gp inhibitors such as cyclosporine should be closely monitored, particularly when patients have co-morbidities such as renal or hepatic impairment (Table 3). However, within the general population, only minimal effects of cell counts can be attributed to the use of colchicine alone.

Due to quantitative limitations in this study, the frequency of myelosuppression caused by colchicine use could not be examined. However, the Cardiovascular Outcomes Trial (COLCOT) from Tardiff et al. examining the safety of low dose colchicine in myocardial infarction showed no serious adverse events of anaemia, leukopenia, or thrombocytopenia in the colchicine group compared to the placebo group ³. Further, in the Low Dose Colchicine (LoDoCo) trial, Nidorf et al. reported neutropenia and other disturbances to the haematological lines were uncommon in the colchicine group ⁵². The frequency of myelosuppressive events in these two studies were not significantly increased in colchicine use compared to the placebo groups, further suggesting that myelosuppressive events is uncommon and potentially due to complicating factors such as co-administration of interacting medications.

Over the past decade, there has been increasing awareness of safety concerns around the use of some anti-inflammatory medication to treat gout flares. This includes glucocorticoid toxicity and non-steroidal anti-inflammatory use (NSAID) side effects such as exacerbation of hypertension and increased cardiovascular events ⁵³. As a result, there has been an increased appreciation of the effectiveness of colchicine in the prophylaxis of gout flares preceding the initiation of urate-lowering therapy⁵⁴. As the value of colchicine in acute gout flares is increasingly recognised, there have also been exciting developments of its therapeutic use being explored in cardiovascular and dermatological conditions. With these new developments, there may be concerns amongst unfamiliar prescribers over myelosuppressive side effects of colchicine. Results from this review provide reassurance around the lack of myelosuppressive adverse events seen in this case series and other recently large randomised controlled trials.

There are limitations to this work. The main limitation is the lack of quantitative data in studies. This made quantitative data analysis challenging and as a result, a large portion of these studies were excluded for this reason. In addition, most studies included were case reports and therefore the rate of myelosuppression with colchicine use was unable to be examined.

Collating and assessing the collective experience of adverse event reports is generally considered an effective method for signal detection of rare events. However, broader pharmacoepidemiological studies using data linkage to match full blood count results with prescribing and clinical context may reveal more about the durability of such a signal, particularly as colchicine becomes more widely used in non-rheumatological indications

5.0 Conclusions

Traditionally, colchicine continues to be used as the mainstay prophylactic treatment in gout and familial Mediterranean fever, amongst other rheumatic conditions. In recent times, therapeutic uses of colchicine have expanded significantly in non-rheumatological conditions⁵⁵. However, there remains some concern in some clinicians' minds about myelosuppression with colchicine use. Our systematic review found that bone marrow suppression generally only occurred in those with pre-existing renal conditions, in patients with comorbidities where CYP3A4 and P-gp inhibitor medications were used in addition to colchicine, and in one case of anakinra interaction with colchicine. The doses taken immediately prior to myelosuppression were also higher than the usual prescribed daily doses. We were able to conclude that adverse drug reactions are likely multi-factorial.

Colchicine's expanding use and indications both in rheumatology and non-rheumatological conditions makes it a unique and important drug for the present and future. This review hopes to overcome any uncertainties over the use of colchicine and enable clinicians to use it with confidence.

6.0 Declarations of Competing Interest

BLS, BZS, MT, DFL, and PCR declare no conflicts of interest.

PCR reports personal fees from Abbvie, Atom Biosciences, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Kukdong, Novartis, UCB, Roche, Pfizer; meeting attendance support from BMS, Pfizer and UCB and grant funding from Janssen, Novartis, Pfizer and UCB Pharma.

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8.0 Table titles and Figure Legends

Table 1: Patient demographics from 30 studies of patients with myelosuppression from colchicine.

Table 2: Patient clinical presentation, and investigation results from 30 studies of patients with myelosuppression from colchicine.

Table 3: CYP3A4 and P-gp Inhibitor interacting medications with colchicine in examined cases

FIGURE 1: Prisma flow diagram of studies assessed for colchicine use and myelosuppression. 2610 articles were excluded based on title and abstract as studies did not include cases of myelosuppression after colchicine use. 54 full-text articles were excluded in the second screen as patients were put on intravenous colchicine or patients had intentionally overdosed on colchicine. an additional 11 full-text articles were excluded as data was in qualitative form and could not be extracted for quantitative analysis.

FIGURE 2: cases taken/not taken dose exceeding recommended colchicine dose, with concurrent renal impairment and use of CYP3A4 inhibitor/P-gp Inhibitor and corresponding Naranjo Adverse Drug Reaction

*patient was on concurrent azathioprine

Supplementary File 1: Inclusion and exclusion criteria of search

Table 1: Patient demographics from 30 studies of patients with myelosuppression from colchicine.

Characteristics (n=47)	Patient results
Age (years old)	48 ± 27
Sex	25 (53.2%) females, 22 (46.8%) males
Ethnicity	8 (17.0%) Caucasian 1 (2.0%) Jewish Moroccan/Syrian 1 (2.0%) Turkish 2 (4.0%) Korean 1 (2.0%) African American 1 (2.0%) Italian 33 (70.0%) Not reported
Indication for colchicine	17 (36.2%) Gout 16 (34.0%) Familial Mediterranean Fever 4 (8.5%) Arthralgias 2 (4.3%) Behcet's Disease 1 (2.1%) Renal amyloidosis 1 (2.1%) Primary biliary cirrhosis 1 (2.1%) Post-pericardiotomy 1 (2.1%) Pericarditis 1 (2.1%) Active hepatitis 1 (2.1%) Pseudogout 2 (4.3%) Chronic pain

Table 2: Patient clinical presentation, and investigation results from 30 studies of patients with myelosuppression from colchicine.

	All patients n = 47	Patients w renal impairment ¹ n=21
Naranjo Adverse Drug Reaction Probability Scale ²	“Possible” or “Probable”	“Possible” or “Probable”
Charlson Comorbidity Index (CCI) (mean±SD)	3.2±2.4 (n=47)	4.3±2.2
Investigations (mean±SD)		
Nadir Hb (g/dL)	10.1±2.8 (Grade 1)	9.7±3.2 (Grade 2)
Nadir Plt (x10 ⁹ /L)	153.1±137.8 (None)	69.0±38.0 (Grade 4)
Nadir neutrophil count (x10 ⁹ /L)	1.2±1.6 (Grade 2)	0.7±0.6 (Grade 3)
Nadir WCC (x10 ⁹ /L)	8.7±31.2 (None)	2.0±1.8 (Grade 2)
Concurrent medications	CYP3A4	CYP3A4
CYP3A4 inhibitors	Yes 15	Yes 8
P-gp Substrate	No 32	No 13
	P-gp Inhibitor	P-gp Inhibitor
	Yes 13	Yes 8
	No 34	No 13

¹ **Impaired renal function defined as: patients recorded impaired renal function based on individual study*

² *Likelihood of causality, by the Naranjo Adverse Drug Reaction Probability Scale: Probable or definite (≥5), Possible (1-4), Unlikely (≤0) 45. Diseases BMNloDaDaK. Adverse Drug Reaction Probability Scale (Naranjo) in Drug Induced Liver Injury 2019 [cited 2022 27 February]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548069/>.*

Lead time to myelosuppression (days)	Median: 7.0 IQR: 4.8-10.5	Median 7.0 IQR: 4.0-10.0
Regular daily colchicine dose (mg) ³	0.8±0.8	0.8±0.8
Colchicine dose taken prior to myelosuppression (mg) ⁴ (cumulative dose)	3.0±2.9	2.5±2.4
Duration of myelosuppression (days) (median±IQR)	Median: 7.0 IQR: 4.0-10.8	Median: 7.0 IQR: 4.0-9.0
Hypocellularity on bone marrow aspirate	14/47 (29.8%)	10/47 (21.3%)
Additional side effects	Diarrhoea 20/47 (42.6%) Abdominal pain 9/47 (19.1%) Vomiting 6/47 (12.8%) Fever 8/47 (17.0%) Pneumonia 2/47(4.3%) Erythematous skin eruptions 2/47(4.3%) Mental confusion 2/47(4.3%)	Diarrhoea 12/21 (57.1%) Abdominal pain 5/21 (23.8%) Vomiting 5/21 (23.8%) Fever 5/21 (23.8%) Pneumonia 2/21(9.5%) Erythematous skin eruption 1/21(4.8%) Mental confusion 2/21(9.5%)
Treatment		
Supportive care	5	3
Ceasing colchicine	17	8
G-CSF	10	6
Gastric Lavage and Activated Charcoal	8	0
Not reported	7	4
End Outcomes		
Recovery	24 (51.0%)	6 (28.6%)

³ Maximum dose of colchicine is <3mg/day in adults (5)

⁴ Acute colchicine dose taken during a flare immediately before myelosuppression. Some doses were above the daily recommended colchicine dosage.

Death	18 (38.0%)	12 (57.1%)
Not reported	5 (11.0%)	3 (14.3%)

Table 3: CYP3A4 and P-gp Inhibitor interacting medications with colchicine in examined cases

CYP3A4 Inhibitors used with colchicine	P-gp Inhibitors used with Colchicine
Strong	Clarithromycin Cyclosporin Erythromycin Amiodarone
Clarithromycin	
Moderate	
Diltiazem	
Erythromycin	
Unspecified potency	
Cyclosporin	
Levothyroxine	
Amiodarone	
Metformin	
Omeprazole	

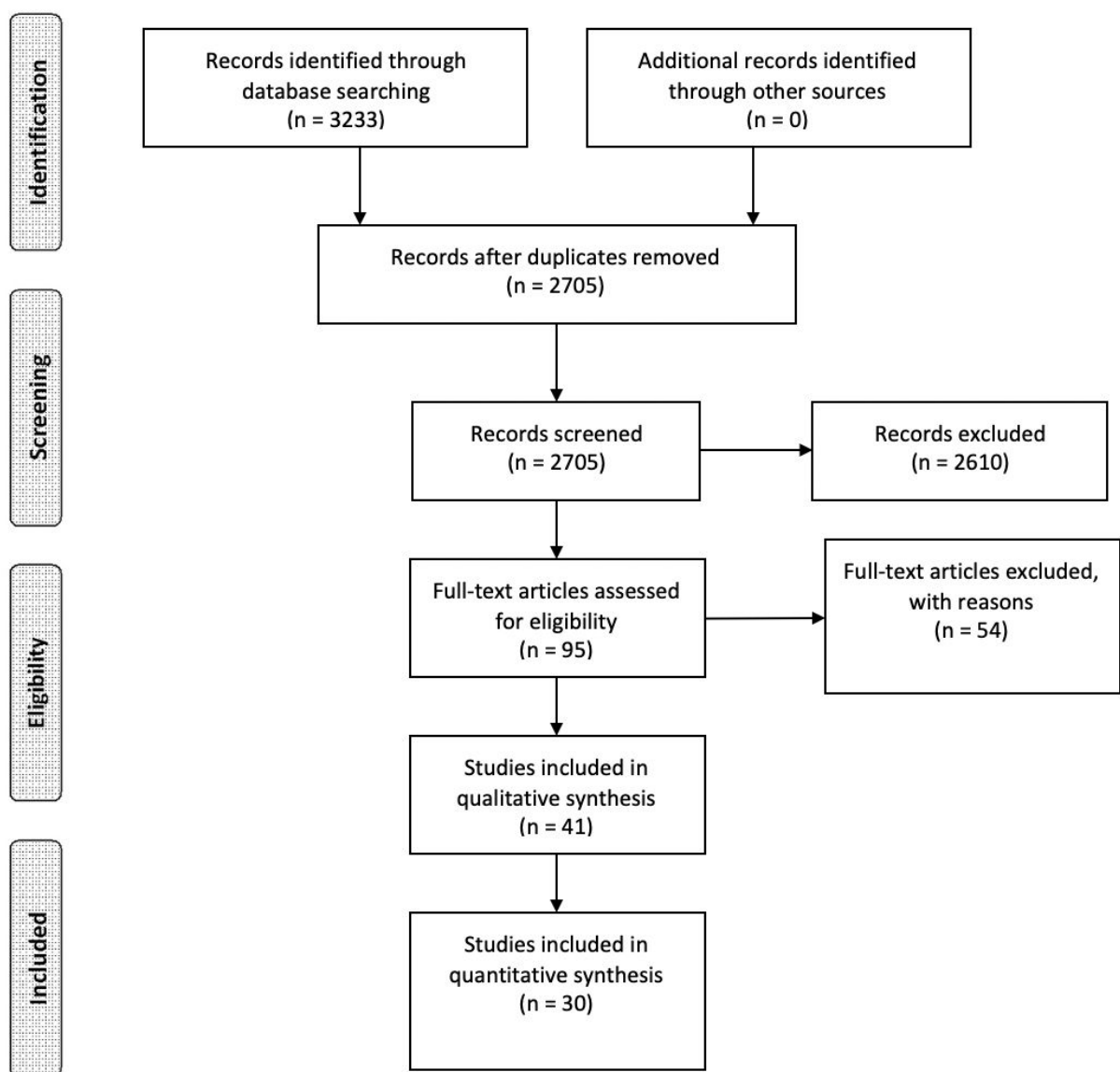


FIGURE 1

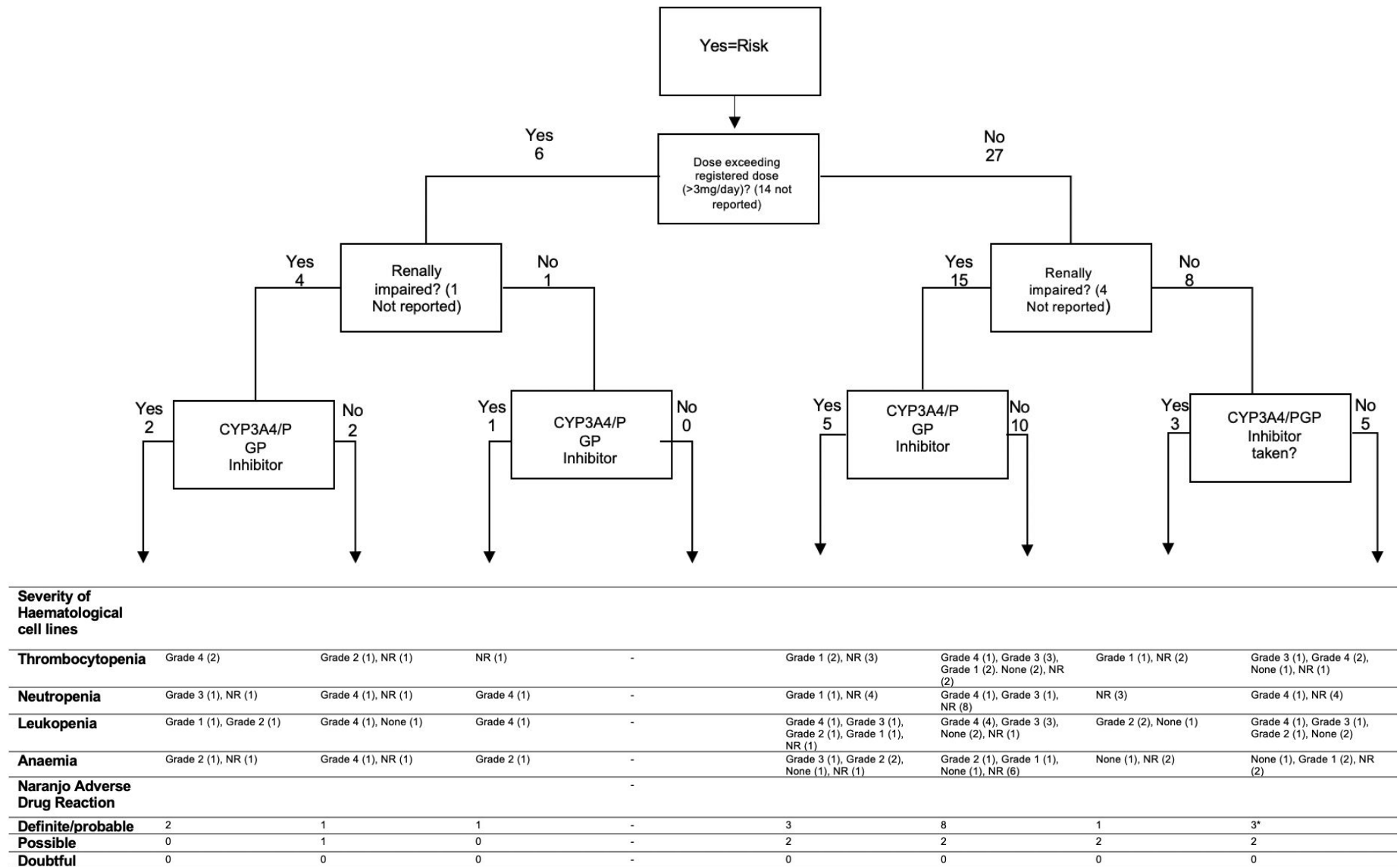


FIGURE 2