Research Article

International Journal of Clinical Rheumatology

Risk of upper gastrointestinal adverse events in Malaysian rheumatic patients on long-term non-steroidal anti-inflammatory drugs

Lydia Say Lee Pok[*1], Fatiha Hana Shabaruddin[2], Maznah Dahlui[3], Sargunan Sockalingam[1], Mohd Shahrir Said[4], Azmillah Rosman[5], Ing-Soo Lau[5], Liza Mohd Isa[6], Heselynn Hussein[6], Chin Teck Ng[7,8] & Sanjiv Mahadeva[1]

[1]Department of Medicine, Faculty of Medicine, University of Malaya, Malaysia

[2]Department of Pharmacy, Faculty of Medicine, University of Malaya, Malaysia

[3]Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Malaysia

[4]Department of Medicine, Faculty of Medicine, University Kebangsaan Malaysia, Malaysia

[5]Department of Medicine, Selayang Hospital, Malaysia

[6]Department of Medicine, Putrajaya Hospital, Malaysia

[7]Department of Rheumatology and Immunology, Singapore General Hospital, Malaysia

[8]I-NUS Medical School, Singapore

*Author for correspondence:
lydiapok@gmail.com

Background: Non-steroidal anti-inflammatory drug (NSAID)-induced upper gastrointestinal (GI) adverse events are well-described in the Western population but data is lacking in Asian patients. This study aims to describe the incidence and predictive factors for NSAID-induced upper GI complications in a cohort of multi-ethnic patients in Malaysia.

Methods and Findings: A retrospective cohort study was conducted in adult patients with rheumatoid arthritis (RA) and/or osteoarthritis (OA) from 2010-2013 in four main rheumatology centres in Malaysia with computerized clinical and pharmaceutical records. Clinical, pharmaceutical and demographic data over a 24-months follow-up period were analysed in subjects who were prescribed long-term NSAID therapy (defined as a minimum duration of four weeks). 634 patients were included in the final analysis with the following characteristics: mean age 53.4 ± 12.5 years, 89.9% female, diagnosis: RA 59.5%, OA 10.2% and RA/OA combination 30.3%. 371 (58.5%) patients received non-selective NSAIDs and 263 (41.5%) patients received COX-2 inhibitors. There were a total of 84 GI adverse events during the period of study, giving an incidence rate of 66.2 per 1000 person-years and a risk of 13.2%. The majority of upper GI adverse events was dyspepsia (92.9%), and only 7.1% with peptic ulcer disease/ upper GI bleeding. Multivariate analysis showed that the only independent predictive factor of upper GI adverse event in this cohort was a history of upper GI disease (O.R. 2.073, 95% C.I. 1.029 – 4.176). COX-2 inhibitor showed a trend towards, but not independently predictive of, GI protection in this analysis (OR 0.643; 95% C.I. 0.397 – 1.043).

Conclusion: Malaysian rheumatic patients on long-term NSAID therapy, managed at referral centres, have a 13.2% risk of upper GI adverse events, with dyspepsia being the commonest complication. Patients with a history of upper GI disease were twice as likely to develop further upper GI adverse events with the use of long-term NSAIDs.

Keywords: gastrointestinal • osteoarthritis • rheumatoid arthritis • non-steroidal anti-inflammatory drugs

Abbreviations: ARAMIS- Arthritis, Rheumatism and Aging Medical Information System; CLASS- Celecoxib Long-term Arthritis Safety Study; GI- Gastrointestinal; H2RA- Histamine2 Receptor Antagonist; NSAID- Non-steroidal Anti-inflammatory Drug; OA- Osteoarthritis; PPI- Proton Pump Inhibitor; PUD- Peptic Ulcer Disease; RA- Rheumatoid Arthritis; SPSS- Statistical Package for the Social Science; SUCCESS-I- Successive Celecoxib Efficacy and Safety Study I; TARGET- Therapeutic Arthritis Research and Gastrointestinal Event Trial; UGIB- Upper Gastrointestinal Bleeding

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used medications worldwide [1,2]. More than 30 million NSAIDs are prescribed every day in the United States [2] and they are also widely available as an over-the-counter medication. The efficacies of their anti-inflammatory and analgesic effects are well-established [3] and NSAIDs are recommended in the management of rheumatic diseases such as rheumatoid arthritis (RA) [4] and osteoarthritis (OA) [5-7].

Despite the recognised benefits and availability of NSAIDs, they are also known to cause

a spectrum of adverse events involving the gastrointestinal (GI), cardiovascular and renal systems. The most common of these adverse events are gastrointestinal, with a reported prevalence of 15-36.7% for dyspepsia [8-10], 4.36-6.19% for peptic ulcer disease (PUD) [11] and 0.21–3.6% for upper GI bleeding (UGIB) [11,12]. These adverse events have important clinical implications, contributing to patient morbidity, mortality and increased healthcare utilisation and costs.

One of the strategies to limit these adverse events includes identifying predictive factors for these adverse events among long-term NSAID users. Established GI risk factors include age ≥ 65 years [13], upper GI history [14], concomitant medications (e.g. prednisone, aspirin, non-aspirin anti-platelet and anticoagulant) [15,16] and H. pylori infection [17]. It is crucial for the prescribing clinician to identify high-risk patients, in whom specific options can be clinically beneficial and cost-effective, such as prescribing more GI-favourable COX-2 specific inhibitor versus traditional NSAID, adding a GI protective agent (e.g. proton pump inhibitor) or avoiding NSAIDs altogether. There is a paucity of information in Asian patients on long-term NSAID therapy. A previous community-based survey in Malaysia has revealed that over-the-counter purchases for NSAIDs for prolonged duration were not uncommon [18]. Another study from Northern Malaysia revealed that 35,944 prescriptions for NSAIDs per 100,000 patients were administered annually from a single institution [19], indicating the common usage of NSAIDs among Asians.

As NSAIDs are commonly prescribed on a long-term basis for patients with chronic rheumatological conditions, this study aimed to identify the incidence and predictive factors of NSAID-induced upper GI adverse events in Malaysian patients with chronic rheumatic diseases.

Methods

Study population

A retrospective, multi-centre, cohort study was conducted at four large public hospitals with rheumatology units in the Klang Valley, an area with the highest population density in Malaysia of almost 7 million people [20].

Study protocol

Electronic prescription data in the respective hospitals were accessed to determine long-term NSAID users (defined as at least four weeks prescriptions of any type of NSAID) among patients diagnosed with RA and/or OA who were on active rheumatology clinic follow up in 2010 or 2011 in the four hospitals. These patients were followed up for 24 months via manual review of the medical records to determine whether any upper GI adverse event(s) developed in the 24 months follow up period. The exclusion criteria were incomplete prescription data, patients who defaulted follow-up and GI adverse event within 6 months prior to recruitment in the study.

Data collection

A retrospective, multi-centre, cohort study was conducted at four large public hospitals with rheumatology units in the Klang Valley, an area with the highest population density in Malaysia of almost 7 million people [20].

Data analysis

Data was analysed using the Statistical Package of Social Sciences (SPSS) version 23. Descriptive statistics was used for demographic data analysis and frequencies of each type of GI adverse events. The incidence rate (per 1000 person-years) was calculated using the formula=(number of new cases of upper GI adverse events × 1000)/(total number of RA/OA patients observed × 2 years of observation). Each concomitant medication (prednisone, aspirin, non-aspirin anti-platelet and anticoagulant) was considered an individual GI risk factor (one point each) in the analysis. Pearson chi-square test was used to determine significant associations for categorical variables with a p-value of <0.05 indicating statistical significance. The odds ratio for the calculation of risk of upper GI events was determined using logistic regression for the multivariate test.

Results

1679 patients with an RA and/or OA diagnosis on regular rheumatology clinic follow up in 2010 or 2011 at the four hospitals were screened. 634 of these patients received long-term NSAID therapy and the medical records of these patients were followed up for 24 months from the date of the NSAID prescription.

Demographic data

The demographic data of the included patients (N=634) are described in Table 1. Their mean age was 53.4 ± 12.5 years and the majority of patients (83.0%) were under the age of 65 years. Most patients were female (89.9%). Almost half

Table 1. Demographic and clinical data.

Demographic data	Number (%) (N=634)
Patients from each centre	
UMMC	201 (31.7%)
HUKM	92 (14.5%)
Selayang Hospital	141 (22.2%)
Putrajaya Hospital	200 (31.6%)
Age	
Mean ± SD (years)	53.4 ± 12.5
Age group	
Non-elderly (<65 years)	526 (83.0%)
Elderly (≥ 65 years)	108 (17.0%)
Sex	
Male	64 (10.1%)
Female	570 (89.9%)
Race	
Malay	253 (39.9%)
Chinese	168 (26.5%)
Indian	202 (31.9%)
Others	11 (1.7%)
Rheumatic disease	
Rheumatoid arthritis (RA)	377 (59.5%)
Osteoarthritis (OA)	65 (10.3%)
RA and OA	192 (30.3%)
Gastrointestinal (GI) history	
No GI disease	561 (88.5%)
Dyspepsia	64 (10.1%)
Peptic ulcer disease	9 (1.4%)
Concomitant medications	
Prednisone	286 (45.1%)
Aspirin	53 (8.4%)
Other antiplatelets (Clopidogrel, Ticlopidine)	11 (1.7%)
Anticoagulant	8 (1.3%)
No. of GI risk factors*	
0	217 (34.2%)
1	311 (49.0%)
2	91 (14.4%)
3	14 (2.2%)
4	1 (0.2%)
Concomitant GI prophylaxis	
Yes	234 (36.9%)
Co-morbidities	
Diabetes mellitus	111 (17.5%)
Hypertension	260 (41.0%)
Dyslipidaemia	232 (36.6%)
Ischaemic heart disease	22 (3.5%)
Chronic kidney disease	2 (0.3%)

*Established GI risk factors [7-10]: age ≥ 65 years, upper GI history, concomitant medications (prednisone, aspirin, non-aspirin anti-platelet and anticoagulant [one point for each concomitant medication]). UMMC, University of Malaya Medical Centre; HUKM, Hospital Universiti Kebangsaan Malaysia.

of the patients (45.1%) were on concomitant prednisone, while aspirin was concomitantly prescribed in only 8.1% of patients. A small proportion of patients were on other antiplatelet agents (1.7%) and anticoagulants (1.3%). 88.5% of patients had no history of upper GI disease and there were no patients with a history of upper gastrointestinal bleeding. We determined that 371 (58.5%) of the 634 patients received NSAIDs prior to the start of the 24 months follow-up in this study. There were 371 (58.5%) patients in the non-selective NSAIDs group, comprising of 267 patients who received non-selective NSAIDs and 104 patients who received combination of non-selective and COX-2 inhibitors. 263 (41.5%) patients were prescribed only COX-2 inhibitors.

Incidence of upper GI adverse events

A total of 84 upper GI adverse events occurred during the 24 months follow up, translating to an incidence of 66.2 per 1000 person-years and a risk of 13.2%. These upper GI adverse events consisted of 78 patients with dyspepsia, five patients with PUD and one patient with upper GI bleeding.

Upper GI adverse events were higher in the COX-2 group (43/263, 16.3%) compared to the non-selective NSAID group (41/371, 11.1%) but this did not reach statistical significance (Chi-square p=0.053). 16 (39.0%) of the 41 patients with upper GI adverse events in the non-selective NSAID group took a combination of selective and non-selective NSAIDs in the 24 months follow up period.

Predictive factors of upper GI adverse events

Univariate analysis Table 2 revealed that variables that were associated with upper GI adverse events were a gastrointestinal history, number of GI risk factors (0 and 1-2 risk factors) and GI prophylaxis. The type of NSAID, 3-4 GI risk factors and concomitant prednisone did not reach statistical significance in this analysis. Age group and concomitant aspirin were not associated with upper GI adverse events. There was no significant difference in upper GI adverse events when comparing the type of rheumatic disease (RA/RA with OA *vs*. OA alone).

Multivariate analysis, analysed using logistic regression analysis Table 3, subsequently revealed that a previous history of upper GI disease (OR 2.073, 95% C.I. 1.029– 4.176) was independently predictive of GI adverse event. Gender (male), concomitant prednisone and GI

Table 2. Univariate analysis of variables associated with upper GI adverse event.

Variable	No adverse events	Adverse event	p-value
Age >65			
No	456 (86.7%)	70 (13.3%)	0.923
Yes	94 (87.0%)	14 (13.0%)	
Sex: Male			
No	490 (86.0%)	80 (14.0%)	0.082
Yes	60 (93.7%)	4 (6.3%)	
Disease			
RA / RA with OA	495 (87.0%)	74 (13.0%)	0.592
OA	55 (84.6%)	10 (15.4%)	
GI history			
No	497 (88.6%)	64 (11.4%)	<.001
Yes	53 (72.6%)	20 (27.4%)	
Number of GI risk factors			
0	199 (91.7%)	18 (8.3%)	0.006
1 or 2	341 (84.8%)	61 (15.2%)	0.004
3 or 4	10 (66.7%)	5 (33.3%)	0.069
Prednisone			
No	310 (89.1%)	38 (10.9%)	0.056
Yes	240 (83.9%)	46 (16.1%)	
Aspirin			
No	504 (86.7%)	77 (13.3%)	0.993
Yes	46 (86.8%)	7 (13.2%)	
Type of NSAID			
Non-selective	330 (88.9%)	41 (11.1%)	0.053
COX-2	220 (83.7%)	43 (16.3%)	
Number of NSAIDs			
1	438 (87.8%)	61 (12.2%)	0.143
>1	112 (83.0%)	23 (17.0%)	
GI prophylaxis			
No	357 (89.3%)	43 (10.7%)	0.015
Yes	193 (82.5%)	41 (17.5%)	
Other antiplatelet (Ticlopidine and Clopidogrel)			
No	545 (87.5%)	78 (12.5%)	0.001
Yes	5 (45.5%)	6 (54.5%)	
Anticoagulation			
No	543 (86.7%)	83 (13.3%)	0.949
Yes	7 (87.5%)	1 (12.5%)	

GI, gastrointestinal; RA, rheumatoid arthritis; OA, osteoarthritis; NSAID, non-steroidal anti-inflammatory drug

prophylaxis were not independent predictors in this analysis. The number of GI risk factors was also not an independent predictor as this did not reach statistical significance although there was a trend towards higher risk of GI adverse events with increasing number of GI risk factors. COX-2 inhibitor showed a trend towards, but not independently predictive of, GI protection in this analysis (OR 0.643; 95% C.I. 0.397–1.043).

Discussion

This study has described the incidence and predictive factors of NSAID-induced upper GI adverse events in Malaysian patients with RA and OA. The incidence rate was 66.2 per 1000 person-years and dyspepsia was the most common adverse effect. The risk of upper GI adverse events found in this study (13.2%) is similar to a North America study of 1921 patients with RA from the ARAMIS (Arthritis, Rheumatism and Aging Medical Information System) centres, which reported a risk of 15%.

Predictive factors of upper GI adverse events

Among the various recognised risk factors for GI adverse events in long-term NSAID users, only a prior history of GI disease was identified as an independent predictive factor in this study. A previous meta-analysis demonstrated that a prior history of complicated or uncomplicated ulcers (pooled RR 15.4 [95% CI 12.6-18.9] and RR 5.9 [95% CI 5.2-6.7] respectively) [21] was a strong predictor of risk of GI events. A large, prospective, double-blinded GI outcomes trial of 8076 patients with rheumatoid arthritis additionally reported that a history of GI disease increases the risk of GI events by approximately 2- to 4-fold [14]. Furthermore, patients with prior history of NSAID-related dyspepsia have been reported to have an increased risk of ulcer complications (OR 8.7, 95% CI 4.0-18.9) when consuming long-term NSAIDs [22]. However, we are not able to determine whether prior history of NSAID-related dyspepsia was a predictor of upper GI events as the aetiology of prior upper GI disease was not available from the patient's medical records.

Other factors, such as concomitant usage of anti-platelet agents [15,23,24], anti-coagulants [25-27] and steroids [16,28,29] have been shown to increase the risk of NSAID-associated GI complications but these factors were not found to be predictive in this study. We were not able to explore the role of Helicobacter pylori infection

Table 3. Multivariate analysis of independent predictive factors of upper GI adverse event.

Variable	Odds ratio	95% C.I.	p-value
Sex (Male)	2.192	0.764– 6.287	0.144
Gastrointestinal history	2.073	1.029– 4.176	0.041
Prednisone	1.402	0.740– 2.665	0.3
GI prophylaxis	1.331	0.805– 2.200	0.265
No. of GI risk factors 1-2	1.328	0.613– 2.878	0.472
No. of GI risk factors 3-4	1.979	0.447– 8.752	0.368
Type of NSAID COX-2 inhibitor	0.643	0.397– 1.043	0.074

[17,30] or higher doses of NSAIDs [2,31] and multiple NSAID use [28], which are recognised causes of NSAID-associated GI complications as this information was not available for all patients in this study.

Although each GI risk factor has different odds or risk ratio for GI adverse events, there is no widely accepted algorithm to aid in quantifying and combining multiple risk factors for upper GI adverse events due to NSAIDs. However, a large randomised double-blinded study of over 34,000 patients [13] showed that the rate of GI events increased with increasing number (0,1,2,3 and 4) of the four major risk factors (age ≥ 65 years, prior upper GI clinical event, low-dose aspirin use and systemic corticosteroid use). In this study, we combined the number of risk factors in our study into groups of increasing numbers for analysis (0, 1-2 and 3-4 risk factors).

Limitations and Strengths

One of the limitations of this retrospective study was the complete reliance on medical records and as such, some patients may not have reported their GI symptoms during routine clinic visits, thus affecting the true incidence of GI adverse events in this patient population and subsequently further analysis on the predictive factors. Secondly, patients with GI risk factor(s) may have been preferentially prescribed a COX-2 inhibitor or GI prophylaxis, potentially confounding the results of this study. Additionally, only double-dose H2RAs have been shown to reduce upper GI adverse events [9,32] and all patients prescribed with H2RAs for GI prophylaxis in this study were given standard doses of H2RAs. Another possible confounder is over-the-counter usage of NSAID, which is common among Malaysian adults [18]. It is possible that rheumatic patients prescribed COX-2 inhibitors alone may have additionally consumed non-selective NSAID by purchasing over-the-counter medications. Similarly, our data on patients using GI protective agents may have been inaccurate, as over-the-counter availability and usage of H2RAs and PPIs are also quite common in the local community [33]. Another limitation was the fact that this study was not sufficiently powered to calculate for differences in GI adverse events between classes of NSAID. This may be the reason why COX-2 inhibitors did not significantly confer protection in this study whereas several large randomised clinical trials (CLASS, TARGET and SUCCESS-I) [10,34,35] have shown otherwise. For possibly the same reason, GI prophylaxis was not found to be protective in this study, in contrast to the findings of other large studies [32,36].

The data in this study is robust for several reasons. Firstly, the upper GI effects in this study have been observed in a uniform group of patients (i.e. patients with rheumatic diseases) and there are unlikely to be other confounders for GI complications in these patients apart from their concomitant treatment for the rheumatic diseases. However, we acknowledge that other minor confounders such as diet, short-term medications (e.g. antibiotics) and alcohol history may have existed. Secondly, the study subjects were fairly representative of most Malaysian patients with rheumatic diseases as the public healthcare system in Malaysia manages the majority of adults with complex, chronic diseases. The Malaysian healthcare system is generally divided into public and privately funded health institutions [37]. Nationally, patients mostly rely on the publicly-funded healthcare system for the management of complex chronic disease. Due to the chronic and costly treatment of rheumatology disorders, particularly RA that often has relatively early onset and peaking at age 30-55 years old [38], it is estimated that the majority of rheumatology patients in Malaysia are treated within the public healthcare system. Furthermore, there was comprehensive data on all medication prescriptions as this was available electronically in all four centres. Our data may not be representative of patients on long-term NSAID managed in non-referral centres. Nevertheless, this study provides useful clinical

information for patients managed in tertiary care referral centres.

Conclusion

The risk of upper GI adverse events in our Malaysian cohort of patients (13.2%) is comparable to the Western population. Prior upper GI disease was the only independent predictive factor identified in this study and the rheumatic patients on long-term NSAIDs with this risk factor were twice as likely to develop further upper GI events. Judicious prescription of NSAIDs in patients with this risk factor is recommended. Future studies that are adequately-powered, suitably-designed and incorporate rheumatology patients in non-referral centres and primary care are needed to determine the role of COX-2 selective inhibitors and GI protective agents in Asian patients in reducing the risk of upper GI adverse events in Asian patients on long-term NSAID.

Ethics approval

Ethical approval was granted to conduct this research within the following centres:

- University Malaya Medical Centre (Medical Ethics Committee of UMMC, MREC ID 1087.46)
- Selayang Hospital and Putrajaya Hospital (Medical Research & Ethics Committee of the Ministry of Health Malaysia, NMRR-14-1659-23298)
- National University of Malaysia (Research Ethics Committee of the National University of Malaysia, UKM 1.5.3.5./244/FF-2015-054)

Competing and conflicting interests

All authors have no competing and conflicting interests to declare.

Funding

This study received an Investigator Initiated Research Grant from Pfizer Pharmaceuticals, no. WI194385

References

1. Breivik H, Collett B, Ventafridda V *et al*. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur. J. Pain*. 10(4), 287–333 (2006).
2. Singh G. Gastrointestinal complications of prescription and over-the-counter nonsteroidal anti-inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. *Am. J. Ther*. 7(2), 115–21 (2000).
3. Bjordal JM, Ljunggren AE, Klovning A *et al*. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ*. 329(7478), 1317 (2004).
4. Luqmani R, Hennell S, Estrach C *et al*. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). *Rheumatology (Oxford)*. 48(4), 436–9 (2009).
5. Hochberg MC, Altman RD, April KT *et al*. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis. Care. Res (Hoboken)*. 64(4), 465–74 (2012).
6. Zhang W, Doherty M, Arden N *et al*. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis*. 64(5), 669–81 (2005).
7. Zhang W, Moskowitz RW, Nuki G *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis. Cartilage*. 16(2), 137–62 (2008).
8. Larkai EN, Smith JL, Lidsky MD *et al*. Dyspepsia in NSAID users: the size of the problem. *J. Clin. Gastroenterol*. 11(2), 158-62 (1989).
9. Singh G, Ramey DR, Morfeld D *et al*. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. *Arch. Intern. Med*. 156(14), 1530–6 (1996).
10. Silverstein FE, Faich G, Goldstein JL *et al*. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 284(10), 1247–55 (2000).
11. Rostom A, Muir K, Dube C *et al*. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. *Clin. Gastroenterol. Hepatol*. 5(7), 818–28 (2007).
12. Chan FK, Lanas A, Scheiman J *et al*. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. *Lancet*. 376(9736), 173–9 (2010).
13. Laine L, Curtis SP, Cryer B *et al*. Risk factors for NSAID-associated upper GI clinical events in a long-term prospective study of 34 701 arthritis patients. *Aliment. Pharmacol. Ther*. 32(10), 1240–8 (2010).
14. Laine L, Bombardier C, Hawkey CJ *et al*. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology*. 123(4), 1006–12 (2002).
15. Dubois RW, Melmed GY, Henning JM *et al*. Risk of Upper Gastrointestinal Injury and Events in Patients Treated With Cyclooxygenase (COX)-1/COX-2 Nonsteroidal Antiinflammatory Drugs (NSAIDs), COX-2 Selective NSAIDs, and Gastroprotective Cotherapy: An Appraisal of the Literature. *J. Clin. Rheumatol*. 10(4), 178–89 (2004).

16. Piper JM, Ray WA, Daugherty JR *et al.* Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann. Intern. Med.* 114(9), 735–40 (1991).

17. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet*. 359(9300), 14–22 (2002).

18. Chua SS, Paraidathathu T. Utilisation of non-steroidal anti-inflammatory drugs (NSAIDs) through community pharmacies in Malaysia. *Asia. Pac. J. Public. Health*. 17(2), 117–23 (2005).

19. Dhabali AA, Awang R, Hamdan Z *et al.* Associations between prescribing nonsteroidal anti-inflammatory drugs and the potential prescription-related problems in a primary care setting. *Int. J. Clin. Pharmacol. Ther*. 50(12), 851–61 (2012).

20. Department of Statistics M. Population and Demography 2017, 6 March 2018.

21. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. *Arch. Intern. Med.* 160(14), 2093–9 (2000).

22. Hansen JM, Hallas J, Lauritsen JM *et al.* Non-steroidal anti-inflammatory drugs and ulcer complications: a risk factor analysis for clinical decision-making. *Scand. J. Gastroenterol*. 31(2), 126–30 (1996).

23. Masclee GM, Valkhoff VE, Coloma PM *et al.* Risk of upper gastrointestinal bleeding from different drug combinations. *Gastroenterology.* 147(4), 784–92 (2014).

24. Rafaniello C, Ferrajolo C, Sullo MG *et al.* Risk of gastrointestinal complications associated to NSAIDs, low-dose aspirin and their combinations: Results of a pharmacovigilance reporting system. *Pharmacol. Res*. 104, 108–14 (2016).

25. Johnsen SP, Sørensen HT, Mellemkjoer L *et al.* Hospitalisation for upper gastrointestinal bleeding associated with use of oral anticoagulants. *Thromb. Haemost.* 86(2), 563–8 (2001).

26. Lanas A, García-Rodríguez LA, Arroyo MT *et al.* Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *Am. J. Gastroenterol*. 102(3), 507–15 (2007).

27. Penning-van Beest F, Erkens J, Petersen KU *et al.* Main comedications associated with major bleeding during anticoagulant therapy with coumarins. *Eur. J. Clin. Pharmacol*. 61(5-6), 439–44 (2005).

28. Garcia Rodriguez LA, Hernandez-Diaz S. The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. *Arthritis. Res*. 3(2), 98–101 (2001).

29. Masclee GM, Valkhoff VE, van Soest EM *et al.* Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily clinical practice? *Aliment. Pharmacol. Ther*. 38(2), 178–89 (2013).

30. Sostres C, Carrera-Lasfuentes P, Benito R *et al.* Peptic Ulcer Bleeding Risk. The Role of Helicobacter Pylori Infection in NSAID/Low-Dose Aspirin Users. *Am. J. Gastroenterol*. 110(5), 684–9 (2015).

31. Garcia Rodriguez LA, Barreales Tolosa L. Risk of upper gastrointestinal complications among users of traditional NSAIDs and COXIBs in the general population *Gastroenterology*. 132(2), 498–506 (2007).

32. Rostom A, Muir K, Dube C *et al.* Prevention of NSAID-related upper gastrointestinal toxicity: a meta-analysis of traditional NSAIDs with gastroprotection and COX-2 inhibitors. *Drug. Health. Patient. Saf*. 1, 47–71 (2009).

33. Mahadeva S, Yadav H, Everett SM *et al.* Economic impact of dyspepsia in rural and urban malaysia: a population-based study. *J. Neurogastroenterol. Motil.* 18(1), 43–57 (2012).

34. Schnitzer TJ, Burmester GR, Mysler E *et al.* Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. *Lancet*. 364(9435), 665–74 (2004).

35. Singh G, Fort JG, Goldstein JL *et al.* Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. *Am. J. Med*. 119(3), 255–66 (2006).

36. Regula J, Butruk E, Dekkers CP *et al.* Prevention of NSAID-associated gastrointestinal lesions: a comparison study pantoprazole versus omeprazole. *Am. J. Gastroenterol*. 101(8), 1747–55 (2006).

37. Yu CP, Whynes DK, Sach TH. Equity in health care financing: The case of Malaysia. *Int. J. Equity. Health*. 7, 15 (2008).

38. Bathon JTC, Klippel SJ, Crofford LJ *et al.* Rheumatoid arthritis clinical and laboratory manifestations, (2008).