NSAID PRESCRIPTION SURVEY IN INTEGRATED TRADITIONAL AND WESTERN MEDICINE TREATMENT: ASSESSING GASTROINTESTINAL AND CARDIOVASCULAR RISKS

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ABSTRACT

Introduction: Non-steroidal anti-inflammatory drug (NSAID) usage should be carefully considered based on gastrointestinal (GI) and cardiovascular (CV) risks. In light of restricted evidence, this study aims to assess the prescription of NSAIDs concerning the GI and CV risks in the integrated treatment of Traditional medicine (TM) and Western medicine (WM). ***Materials and method:*** A retrospective cross-sectional study was conducted on 393 medical records of inpatients using NSAIDs in 2022 at the Traditional Medicine Hospital of Ho Chi Minh City. GI and CV risks, as well as information regarding NSAID prescriptions, were recorded. A multivariable regression model was employed to identify factors associated with the prescription of NSAID groups. ***Results:*** NSAIDs were primarily prescribed for musculoskeletal and connective tissue disorders (87.28%). Approximately half of the cases exhibited moderate to high GI risk (47.59%), while for CV risk, there were 68.95% with moderate to very high risk. COX-2 inhibitors were the most commonly prescribed (94.66%), even when considering GI and CV risks separately. In the majority, NSAID prescriptions aligned with both risks according to American College of Gastroenterology (ACG) guidelines (73.79%). The prescription of NSAID groups was significantly influenced by patient gender, ailment type, and physician education ($p<0.05$), but not by GI and CV risks ($p>0.05$). ***Conclusion:*** Patients receiving NSAIDs in integrated TM and WM treatment often faced an increased GI and CV risk, with the majority adhering to ACG guidelines. However, GI and CV risks were not significantly considered for NSAID group selections. Multi-center studies should be conducted.

Keywords: *NSAID, gastrointestinal risk, cardiovascular risk, traditional medicine, integrative medicine*

I. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications for pain and inflammation. However, the use of NSAIDs is associated with various adverse events, especially those related to gastrointestinal (GI) and cardiovascular (CV) complications [1]. Consequently, regulatory bodies such as the Food and Drug Administration, the European Medicines Agency, and several scientific societies concur that the medical management of NSAID therapy should be based on the prior assessment of GI and CV risk factors in individual patients [2-6]. A study by Lanas (2011) conducted throughout the Spanish National Health System revealed that more than half of NSAID prescriptions did not adhere to the current guidelines and recommendations for patients with CV and GI risk factors [7]. This highlights the importance of proper guidance in medication use within hospital settings.

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In Traditional Medicine (TM) treatment, the effective management of pain is considered one of the significant achievements, supported by substantial evidence, and frequently applied, particularly in musculoskeletal disorders [8, 9]. Pain management in these settings often involves an integration of TM and Western medicine (WM) approaches, and as a result, includes the use of NSAIDs. However, data regarding NSAID utilization based on GI and CV risk factors in this context remains significantly limited. This study aims to assess the GI and CV risks in patients using NSAIDs and the appropriateness of their usage at integrated TM and WM treatment.

II. MATERIALS AND METHODS

2.1. Study design

A retrospective cross-sectional study was conducted by collecting information from the inpatient medical records in the year 2022 at the Traditional Medicine Hospital of Ho Chi Minh City. The study was performed in accordance with the CROSS guidelines [10].

2.2. Data collection methods

A data collection form was established to record information, comprising three sections: the first section collected patient demographic information, including sex, age, health insurance status, hospitalization duration, and disease; the second section documented GI and CV risks; and the third section gathered data regarding NSAID prescriptions, including NSAID group, the concurrent use of proton pump inhibitors (PPIs), and physician information.

GI risks and the assessment of appropriateness in prescribing NSAIDs based on GI and CV risks were classified according to the 2009 American College of Gastroenterology (ACG) guideline [11]. CV risks were categorized following the 2019 European Society of Cardiology / European Atherosclerosis Society (ESC/EAS) guidelines [12].

2.2. Sample characteristics

The study involved selecting inpatient medical records prescribed with at least one NSAID, excluding aspirin, and topical NSAIDs in 2022 at the Traditional Medicine Hospital of Ho Chi Minh City. Records with missing or inadequate information regarding NSAID prescriptions were excluded.

A simple random sampling technique was employed by first enumerating the complete list of medical records meeting the selection criteria, then assigning them random numbers generated using Microsoft Excel software. Subsequently, these medical records were sorted in ascending order of the random numbers, and selections were made in order until the required sample size was achieved.

The sample size was determined based on the formula for one proportion estimation in cross-sectional studies. To maximize the sample size, a value of p=0.5 was chosen, with a type-I error α=0.05 (95% confidence level), and an absolute precision d=0.05. The minimum required sample size was calculated to be 385 [13]. Assuming a 5% record exclusion rate, a total of 405 medical records needed to be screened.

2.3. Survey administration

During the two-month period from September to October 2023, two surveyors conducted data collection. After identifying the medical records to be accessed, these surveyors approached the medical records stored in the Traditional Medicine Hospital of Ho Chi Minh City and recorded the information based on paper data collection forms. To mitigate potential errors, the

process of recording information from medical records and data entry into Microsoft Excel was subject to dual verification by these two surveyors, and subsequently, the data was further verified by another researcher to detect any anomalies in the dataset.

2.4. Study preparation

The research team had standardized the data collection procedures before commencing to ensure the highest level of consistency between the two surveyors in data collection.

2.5. Ethical considerations

This study was approved by the Ethics Council of the University of Medicine and Pharmacy Ho Chi Minh City on August 29, 2023, according to Decision No. 769/ĐHYD-HĐĐĐ. All collected data was de-identified through identification codes, securely stored with password protection, and analyzed by a single analyst with no access to participant identities.

2.6. Statistical analysis

In this study, there were no missing data. Categorical variables were expressed as frequencies and percentages (%), while quantitative variables were presented as mean and standard deviation (SD). Multivariable logistic regression analysis was employed to assess the relationship between factors influencing the prescription of different NSAID groups. The significance level was set at a p-value of less than 0.05. Statistical analysis was conducted using R software version 4.3.0.

III. RESULTS

From September to October 2023, 405 medical records of inpatients who had used NSAIDs in 2022 were accessed. Among these, 12 records were excluded due to missing or inadequate information regarding NSAID prescriptions. Ultimately, data were collected from 393 medical records for analysis.

3.1. Patient characteristics

The majority of prescribed NSAIDs were female, with a mean age (SD) of 57.01 (14.12) years. Most had health insurance, and the hospitalization duration was relatively long (mean [SD] was 24.3 [12.8] days). Diseases of the musculoskeletal system and connective tissue received NSAIDs most frequently (87.28%). However, it is worth noting that 9.92% of NSAIDs were prescribed for conditions exclusively related to diseases of the digestive system, specifically hemorrhoids (**Table 1**).

Table 1. ***Patient characteristics***

Characteristics	Value (N=393)	Percentage (%) or standard deviation (SD)
Sex, male (n and %)	138	35.11
Age, years (mean and SD)	57.01	14.12
Health insurance status, yes (n and %)	380	96.69
Hospitalization duration, days (mean and SD)	24.30	12.80
Disease (n and %)		
- Diseases of the musculoskeletal system and connective tissue	343	87.28
- Diseases of the digestive system (conditions related to hemorrhoids)	39	9.92
- Others	11	2.80

3.2. GI & CV risk and NSAID prescription

Regarding GI risk, a substantial 47.59% demonstrated moderate to high risk. For CV risk, a noteworthy 68.95% displayed moderate to very high risk. In many cases, CV risk could not be determined due to the absence of serum cholesterol data (10.18%). When considering both GI and CV risk, 44.01% had moderate or higher levels of risk (**Table 2**).

Table 2. ***Gastrointestinal and cardiovascular risk***

	Low GI risk	Moderate GI risk	High GI risk	Total
Undetermined CV risk*	37 (9.41)	3 (0.76)	0	40 (10.18)
Low CV risk	70 (17.81)	12 (3.05)	0	82 (20.87)
Moderate CV risk	55 (13.99)	67 (17.05)	0 (0.25)	122 (31.04)
High CV risk	21 (5.34)	33 (8.40)	1 (0.25)	55 (13.99)
Very high CV risk	23 (5.85)	64 (16.28)	7 (1.78)	94 (23.92)
Total	206 (52.42)	179 (45.55)	8 (2.04)	393 (100)

Statistics are n (%).

***** due to the absence of serum cholesterol data; CV, cardiovascular; GI, gastrointestinal.*

The majority of COX-2 inhibitors were utilized (94.66%), among which, newer COX-2 inhibitors were administered approximately twice as frequently as older COX-2 inhibitors. Only a small fraction of non-selective NSAIDs were employed (5.34%). The co-administration of NSAIDs with PPIs was observed in the majority of cases (57%), with the majority of non-selective NSAIDs being paired with PPIs (80.95%) (**Table 3**).

Table 3. ***NSAID prescription***

NSAID prescription	Value (N=393)	Percentage (%)
NSAID group		
- Newer COX-2 inhibitor	253	64.38
- Older COX-2 inhibitor	119	30.28
- nsNSAID	21	5.34
NSAID + PPI	224	57.00
- Newer COX-2 inhibitor + PPI*	143	56.52
- Older COX-2 inhibitor + PPI*	64	53.78
- nsNSAID + PPI*	17	80.95
NSAID and GI & CV risk		
- Appropriate	290	73.79
- Inappropriate	65	16.54
- Unassessability#	38	9.67

** the percentage calculated within the corresponding NSAID group; # patiens with undetermined CV risk; COX, cyclooxygenase; CV, cardiovascular; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.*

The majority across all GI risk categories received COX-2 inhibitors, with most individuals at moderate and high risk being prescribed a combination of COX-2 inhibitors and PPIs. Notably, at high GI risk, exclusive use of COX-2 inhibitors occurred, predominantly newer COX-2 inhibitors (87.5%), all of which were co-administered with PPIs (**Fig 1-A**). Similarly, across all CV risk categories, the majority were prescribed COX-2 inhibitors, with most receiving newer COX-2 inhibitors (63.64-70.73%) (**Fig 1-B**). The majority of NSAID prescriptions were deemed appropriate according to the ACG guidelines, considering both GI and CV risks (73.79%). (**Table 3**).

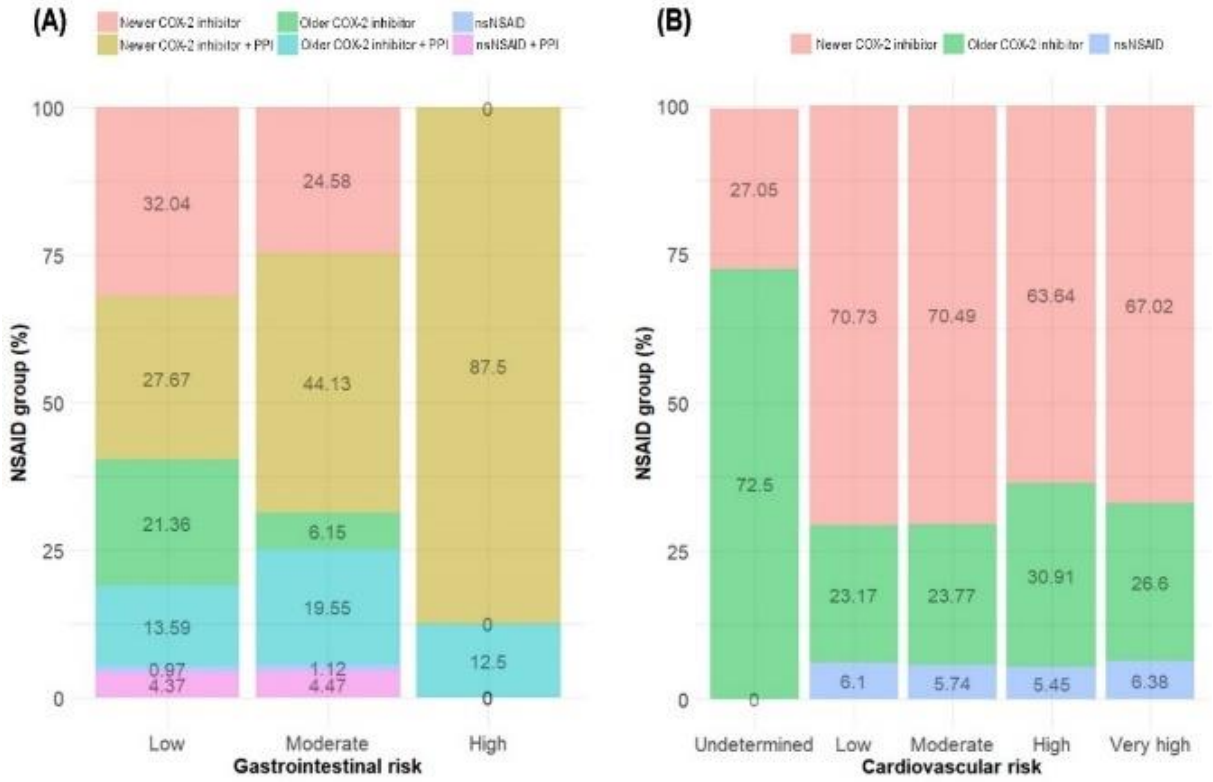

Figure 1. ***NSAID group in gastrointestinal and cardiovascular risk (N=393)***

COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

3.3. Factors related to prescribing NSAID groups

Three factors significantly associated with the prescription of different NSAID groups include patient's sex, disease, and the physician's degree. Males were more likely to receive older COX-2 inhibitors, and conversely less frequently prescribed non-selective NSAIDs (odds ratio [OR] and 95% confidence interval [95% CI]: 1.76 [1.04 - 3.00] and 0.18 [0.04 - 0.83], respectively). Patients with conditions related to hemorrhoids had a lower likelihood of being prescribed newer COX-2 inhibitors (OR [95% CI]: 0.16 [0.03 - 0.82]). Physicians with postgraduate education more frequently prescribed newer COX-2 inhibitors and less frequently prescribed older COX-2 inhibitors (OR [95% CI]: 1.77 [1.00 - 3.14] and 0.47 [0.25 - 0.86], respectively). Other factors, including GI and CV risk, did not show significant differences in the NSAID group's prescription **(Table 4)**.

Table 4. ***Factors related to prescribing NSAID groups***

	Newer COX-2 inhibitor [OR (95% CI)]	**Older COX-2 inhibitor [OR (95% CI)]**	**nsNSAID [OR (95% CI)]**
Sex of patients, male	0.83 (0.50 - 1.37)	**1.76 (1.04 - 3.00)***	**0.18 (0.04 - 0.83)***

	Newer COX-2 inhibitor [OR (95% CI)]	Older COX-2 inhibitor [OR (95% CI)]	nsNSAID [OR (95% CI)]
Age, year	1.02 (1.00 - 1.05)	0.97 (0.95 - 1.00)	1.01 (0.95 - 1.06)
Health insurance status, yes	2.69 (0.58 - 12.50)	0.25 (0.05 - 1.24)	-
Disease			
- Others	reference	reference	reference
- Diseases of the musculoskeletal system and connective tissue	0.25 (0.06 - 1.11)	3.01 (0.66 - 13.62)	-
- Diseases of the digestive system (conditions related to hemorrhoids)	**0.16 (0.03 - 0.82)***	3.29 (0.59 - 18.39)	3.42 (0.97 - 11.98)
GI risk			
- Low	reference	reference	reference
- Moderate	0.95 (0.53 - 1.71)	1.22 (0.65 - 2.29)	0.65 (0.21 - 1.97)
- High	2.48 (0.26 - 23.52)	0.75 (0.08 - 7.46)	-
CV risk			
- Low	reference	reference	reference
- Moderate	0.71 (0.31 - 1.61)	1.51 (0.61 - 3.71)	0.93 (0.20 - 4.34)
- High	0.49 (0.20 - 1.19)	2.35 (0.89 - 6.20)	0.99 (0.17 - 5.89)
- Very high	0.58 (0.25 - 1.32)	1.80 (0.74 - 4.40)	1.24 (0.26 - 5.93)
Sex of physician, male	0.92 (0.57 - 1.49)	0.93 (0.55 - 1.57)	1.66 (0.64 - 4.30)
Physician's degree, postgraduate	**1.77 (0.99 - 3.14)***	**0.47 (0.25 - 0.86)****	1.53 (0.42 - 5.58)
Physician's experience, year	0.99 (0.91 - 1.08)	0.97 (0.88 – 1.07)	1.12 (0.93 - 1.34)

** p<0.05; ** p<0.01; CI, confidence interval; COX, cyclooxygenase; CV, cardiovascular; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; OR, odds ratio.*

IV. DISCUSSION

Our findings indicated that in the context of combining TM and WM treatment, NSAIDs were primarily used in combination with other therapies for the treatment of musculoskeletal and connective tissue disorders. These conditions also represent a primary indication for NSAIDs [1, 14]. The majority of patients were females, and the relatively high average age (57.1 years) along with the extended hospitalization duration (24.3 days) were consistent with the epidemiological patterns in musculoskeletal and connective tissue diseases [15-17]. It's important to note that females are at a higher risk of experiencing GI and CV events related to NSAID use compared to men [18]. GI risk was generally low to moderate, while CV risk reached up to around 40% at high to very high-risk levels. In contrast, the differences in population may be attributed to Lanas et al., where 60.3% were defined as

having a high GI risk in Spain patients with diagnoses of osteoarthritis [7].

Current evidence suggests that all NSAIDs are associated with adverse GI and CV events, but the degree of association varies among the NSAIDs [19]. COX-2 inhibitors have been demonstrated to be safer for the GI tract than non-selective NSAIDs [19, 20]. In our study, among all GI risks, the newer COX-2 inhibitors were the most commonly prescribed. For patients with moderate and high GI risk, most received combination therapy with PPI. According to current recommendations, patients at moderate GI risk should choose COX-2 inhibitors or non-selective NSAIDs with PPI [11, 21, 22]. Those at high GI risk should avoid NSAIDs if possible, and if necessary, use COX-2 inhibitors with PPI [11, 21, 22]. Therefore, when considering only GI risk, the prescription of NSAIDs and their combination with PPIs seems to be justifiable, even taken as an excessive preventive measure. It is noteworthy that, at all CV risk, the majority of patients in our study also received COX-2 inhibitors, especially the newer COX-2 inhibitors, in contrast to the findings reported by Koffeman et al. [23]. While, COX-2 inhibitors have been reported to have an increased risk of CV events [19, 24-26]. Phueanpinit et al. also revealed that physicians typically prioritize concerns related to GI complications over those associated with renal and CV complications [27]. Current guidelines also recommend that either a non-selective NSAID or a coxib can be used in patients with moderate CV risk, with a preference for naproxen in patients with high CV risk [11, 21, 22]. Most of the NSAID group selection guidelines are based on the consideration of both GI and CV risks. Among them, the ACG guidelines are widely used. In our study, the majority of NSAID prescriptions, as well as the decision of whether or not to combine them with PPI, aligned with the ACG guidelines for both of these risks [11]. Conversely, the evaluation of prescription patterns and the appropriateness of NSAID therapy based on GI and CV risks in patients diagnosed with rheumatoid arthritis by Lanas et al. revealed that over half of patients with an increased GI and/or CV risk were not prescribed NSAIDs in accordance with current guidelines or recommendations [7].

In this study, COX-2 inhibitors were commonly prescribed regardless of GI and CV risks, almost in all cases, predominantly involving newer COX-2 inhibitors. Notably, when considering the factors influencing the choice of NSAID groups through a multivariable logistic regression model, our findings indicated that the GI and CV factors were not significantly considered in the selection of newer, older, and non-selective NSAID groups. Therefore, the appropriateness or inappropriateness of prescribing NSAIDs with GI and CV risks appeared to occur randomly, as treating physicians frequently opted for COX-2 inhibitors rather than considering these risks. Ho et al. pointed out that prescribers in the Asia-Pacific Region prefer COX-2 inhibitors to mitigate GI side effects [28]. However, they did not inquire about patients' comorbidities and concurrent medications, which may potentially increase the incidence of CV adverse events (AEs) among patients [28]. Previous data also demonstrated that healthcare professionals displayed a moderate level of awareness regarding the primary AEs associated with NSAID use [28]. Conversely, physicians who frequently prescribe NSAIDs may exhibit a higher level of AE awareness. This suggestion is supported by the findings of Phueanpinit et al., who observed that a majority of orthopedic surgeons considered patients' medical history (GI, CV, renal, NSAID

allergies, patient age) before prescribing non-selective NSAIDs [27].

Meanwhile, factors including patient's sex, disease, and the physician's degree were significantly related to the prescription of NSAID groups. An interesting and somewhat perplexing observation was that males were approximately twice as likely to receive older COX-2 inhibitors and five times less likely to receive non-selective NSAIDs when compared to females, independent of their GI and CV risk profiles. Notably, prior research conducted by Neutel et al. had shown that males are 1.4 times more likely to experience significant serious GI events than females, irrespective of NSAID usage [29]. Consequently, this prescribing pattern seemed to result in a positive outcome. Furthermore, patients with hemorrhoidal conditions appeared to be less likely to be prescribed newer COX-2 inhibitors, which could be attributed to local treatment guidelines. It was also notable that physicians with postgraduate education displayed a preference for newer COX-2 inhibitors over other NSAIDs, particularly the older COX-2 inhibitors. This preference may be linked to the easier accessibility of newer NSAIDs at higher education levels.

Our study has several limitations. Firstly, medical records may not fully document all factors related to GI and CV risk, potentially leading to an underestimation of these risks. Secondly, retrospective observations do not account for changes that may have occurred in the past year. Lastly, the study was conducted at a single hospital, thus limiting its generalizability.

V. CONCLUSION

Our findings indicate that in the integration of TM and WM treatment, NSAIDs were primarily prescribed for musculoskeletal and connective tissue disorders. Many patients had an increased risk of GI and CV events, especially CV risk. COX-2 inhibitors were prescribed very commonly, leading to a bias towards GI risk rather than CV risk. However, the majority still aligned with ACG guidelines when considering both risks. It is noteworthy that the choice of NSAID groups was not significantly influenced by GI and CV risk considerations. Multi-center studies should be conducted to further strengthen these findings.

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AUTHORS' CONTRIBUTIONS

Do Tan Khoa: Conceptualization, Methodology, Validation, Resource, Data curation, Investigation, Writing - review & editing, Supervision, Project administration. **Nguyen Thi Bich Tam**: Methodology, Data curation, Investigation, Writing - review & editing. **Tran Hoa An**: Methodology, Data curation, Formal analysis, Software, Writing - original draft, Writing - review & editing, Visualization, Project administration.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

FUNDING STATEMENT

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ETHICAL STATEMENT

This study was approved by the Ethics Council of the University of Medicine and Pharmacy Ho Chi Minh City on August 29, 2023, according to Decision No. 769/ĐHYD-HĐĐĐ.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding authors, upon reasonable request.

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