Derivation and validation of a risk prediction score for nonsteroidal anti-inflammatory drug-related serious gastrointestinal complications in the elderly

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Abstract

Aim: Although there is a high risk of gastrointestinal (GI) bleeding in the elderly, few studies have quantified the impact of risk factors on GI complications in elderly nonsteroidal anti-inflammatory drug (NSAID) users. This study aimed to develop and validate a risk prediction score to identify high-risk elderly patients using NSAID for severe GI complications. Methods: We used the following two Korean claims datasets: customized data with an enrollment period 2016–2017 for model development, and the sample data in 2019 for external validation. We conducted a nested case-control study for model development and validation. NSAID users were identified as the elderly ([?] 65 years) who received NSAIDs for more than 30 days. Patients who experienced serious GI complications, defined as hospitalizations or emergency department visits, were diagnosed with GI bleeding or perforation. We derived a model using logistic regression and cross-validation. Results: In the external validation cohort, we identified 372 cases from 254,551 patients. We identified 8,176 cases and 81,760 controls with a 1:10 matched follow-up period in the derivation cohort. In the external validation cohort, we identified 372 cases from 254,551 patients. The risk predictors were high-dose NSAIDs, NSAID type, complicated GI ulcer history, male sex, concomitant gastroprotective agents, relevant co-medications, severe renal disease, and cirrhosis. Area under the receiver operating characteristic curves was 0.77 (95% confidence interval, 0.75–0.80) in the external validation dataset. Conclusion: The prediction model may be a useful tool for reducing the risk of serious GI complications by identifying high-risk elderly patients.

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Short running title

Model for NSAID-related GI complications

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Abstract

Aim: Although there is a high risk of gastrointestinal (GI) bleeding in the elderly, few studies have quantified the impact of risk factors on GI complications in elderly nonsteroidal anti-inflammatory drug (NSAID) users. This study aimed to develop and validate a risk prediction score to identify high-risk elderly patients using NSAID for severe GI complications. Methods: We used the following two Korean claims datasets: customized data with an enrollment period 2016–2017 for model development, and the sample data in 2019 for external validation. We conducted a nested case-control study for model development and validation. NSAID users were identified as the elderly ([?] 65 years) who received NSAIDs for more than 30 days. Patients who experienced serious GI complications, defined as hospitalizations or emergency department visits, were diagnosed with GI bleeding or perforation. We derived a model using logistic regression and cross-validation. Results: In the external validation cohort, we identified 372 cases from 254,551 patients. We identified 8,176 cases and 81,760 controls with a 1:10 matched follow-up period in the derivation cohort. In the external validation cohort, we identified 372 cases from 254,551 patients. The risk predictors were high-dose NSAIDs, NSAID type, complicated GI ulcer history, male sex, concomitant gastroprotective agents, relevant co-medications, severe renal disease, and cirrhosis. Area under the receiver operating characteristic curves was 0.77 (95% confidence interval, 0.75–0.80) in the external validation dataset. Conclusion: The prediction model may be a useful tool for reducing the risk of serious GI complications by identifying high-risk elderly patients.

What is already known about this subject

Models for predicting the risk of upper GI bleeding in overall nonsteroidal anti-inflammatory drug (NSAID) users have been developed. However, specific risk stratification schemes to quantify the risk factors for GI

complications in elderly NSAID users have seldom been evaluated even though old age is a major risk factor for GI complications in NSAID users.

Most geriatric focused criteria recommend the concomitant use of a gastroprotective agent (GPA) with NSAID. However, GPA use in the elderly might not eliminate the risk of serious GI complications in high-risk situations.

What this study adds

This study developed a clinical risk score to predict the risk of serious GI complications in elderly by using data from the entire Korean population, and demonstrated good performance through external validation.

This study identified new risk prediction factors not included in the current guidelines: male sex, very old age, and concomitant use of selective serotonin reuptake inhibitors.

Compared to the risk classification system of the current guidelines that count the number of risk factors, this newly developed risk score model included the concomitant use of a GPA as an offset factor, which enabled to capture expanded cases where use of proton pump inhibitors or H2-receptor antagonists was not sufficient to offset serious GI complications.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently used medicines to treat musculoskeletal and rheumatic diseases [1]. NSAID use is a common cause of gastrointestinal (GI) bleeding, and mortality from GI bleeding has been reported to be 5–10% worldwide [2].

Several risk factors for GI injury in patients taking NSAIDs have been reported, including a history of GI ulcer, older age, and concomitant use of low-dose aspirin (ASA), other antiplatelet agents, anticoagulants, and corticosteroids [3]. Older age is a major risk factor for serious GI complications. In Italy, the prevalence of NSAID use among the elderly was estimated at 24.7% [4], and in the United States, 40% of the elderly people were prescribed with NSAIDs at least once a year [5]. The hospitalization rate for GI complications due to NSAIDs was 12 per 1,000 person-years in the elderly compared to < 1 per 1,000 person-years in the population aged < 50 years [5].

In 2014, a model for predicting the risk of upper GI bleeding in NSAID users was developed and verified [6], and a model for predicting the incidence rate of upper GI bleeding in NSAID users using a case-control study was developed [1]. There was a report on the risk score calculated for major toxicity, including adverse cardiovascular events, major GI events, acute kidney injury, and death in NSAID users from the PRECISION trial data in 2019 [7]; however, the outcome of this study was not specific for GI complications.

Although GI bleeding in the elderly is a burden due to the high mortality and disability rates [4], there is no risk stratification scheme to quantify the risk factors for GI complications in elderly NSAID users. Most geriatric focused criteria regarding the appropriate use of medication recommend the concomitant use of a gastroprotective agent (GPA) with chronic NSAID use [8]. However, GPA use might not eliminate the risk of serious GI complications in high-risk situations [8]. Few studies have included the use of a GPA in the prediction of GI complications.

Identifying high-risk patients in the elderly population would be helpful in preventing serious GI complications; therefore, developing a predictive risk score is important. We aimed to develop a risk prediction score to identify high-risk patients for severe GI complications in the elderly using NSAIDs and to validate it externally using nationwide claims datasets.

2. Methods

2.1 Data sources

The National Health Insurance (NHI) system of the Republic of Korea covers approximately 98% of the overall Korean population [9]. The Health Insurance Review and Assessment Service (HIRA) is a government

organization that reviews and assesses all NHI claims. The HIRA database provides demographic, diagnostic, treatment, and prescription information for all inpatients and outpatients as anonymized data [9]. Our study was approved by the Institutional Review Board of Seoul National University (No. E2002/001-008) and the requirement for written informed consent was waived owing to the anonymized data.

We used two separate databases from Korea's claims data provided by the HIRA for derivation and validation cohorts. The derivation cohort included the entire population of the elderly ([?]65 years) diagnosed with arthritis between July 2016 and June 2017 in Korea (n=2,570,122) using customized HIRA research data (M20200324406). The diagnosis of arthritis was identified using ICD-10 codes applicable for rheumatoid arthritis and osteoarthritis (Table S1). This cohort was followed up until December 31, 2018 (time span, up to 30 months). For the external validation cohort, we used the HIRA sample data from 2019 (HIRA-APS in 2019), which included 10% of the total Korean elderly population (approximately 700,000 patients).

2.2 Study population

A nested case-control study was conducted on a development cohort. The inclusion criteria were patients who used NSAIDs for more than 30 consecutive days allowing for a 15–day gap from July 2016. NSAID treatment included non-selective (ns) NSAIDs and selective COX-2 inhibitors (ATC code for NSAIDs in Table S1). Patients were followed up for up to 10 days after the end of NSAID prescription. The patient selection process is described in Fig 1. Patients diagnosed with esophageal varices, GI cancer, or Mallory–Weiss syndrome within 6 months of NSAID initiation were excluded.

NSAID users in the external validation cohort included those who used NSAIDs after July 2019 for more than 30 consecutive days, allowing a 15–day gap, and were followed up for 10 days after the end of NSAID prescription. The exclusion criteria were identical to those used in the development cohort.

2.3 Definition of cases and selection of controls

Patients included those who experienced serious GI complications, defined as hospitalizations or emergency department visits, with the main diagnosis of GI bleeding or perforation. GI complications from the upper GI tract, such as the stomach, to the lower GI tract, such as the duodenum, were also included. The diagnostic codes for GI complications according to the ICD-10 codes are summarized in Table S1. The index date for cases was the date of diagnosis of serious GI complications. We randomly selected 1:10 matched controls for NSAID use duration. We assigned an index date to the controls equal to that of the corresponding cases.

2.4 Study variables

We considered the types of NSAID, high-dose NSAID use, concomitant medications, demographics, and baseline comorbidities as candidate risk factors. Baseline comorbidities and past medical history were confirmed within 6 months of NSAID initiation (see Table S1 for the diagnosis code). NSAID types were classified as selective COX-2 inhibitors or nsNSAIDs. High-dose NSAID use was defined as the total daily administration of NSAIDs, including the use of multiple NSAIDs, in excess of the daily recommended dose based on the ATC/DDD system from the World Health Organization collaborating center [10]. Medications known to affect GI complications [11] were identified by reviewing prescriptions within 30 days prior to the index date: GPA, corticosteroids, selective serotonin reuptake inhibitors (SSRI), HMG-CoA reductase inhibitors, calcium channel blockers, and oral anticoagulants, including vitamin K antagonists and direct oral anticoagulants, as well as antiplatelet agents, including ASA, $P2Y_{12}$ inhibitors, and PDE3 inhibitors. GPAs include proton pump inhibitors (PPIs), misoprostol, H2-receptor antagonists (H2RAs), rebamipide, and *Artemisia* herb soft extract [12]. Concomitant medications were considered for concomitant use with NSAIDs when used for at least 80% overlap with NSAID treatment [6].

The customized HIRA research data used as the derivative cohort included detailed age, whereas the HIRA sample data (HIRA-APS 2019) for external validation included age information as age groups in 5-year increments, and 80+ was provided as one age group.

2.5 Statistical analysis

Descriptive statistics were used to evaluate baseline characteristics of the study population. Continuous variables are presented as means with standard deviations or medians with interquartile ranges and categorical variables as numbers and percentages. We used a multivariable unconditional logistic regression model to calculate the adjusted odds ratio (OR) and 95% confidence interval (CI) for the risk of serious GI complications, considering the study variables. To apply the risk prediction model during multivariate analysis, continuous variables were converted to categorical variables [13].

2.6 GI complication risk score

The derivation cohort was randomly divided into internal training (70%) and internal hold-out validation (30%) datasets [14]. Candidate risk predictors with p>0.10 in the univariate logistic regression using the internal training dataset were included in the multivariate analysis. We performed three repeated five-fold cross-validations for predictor variable selection [14]. This was based on the principle of randomly dividing the dataset into five equal subsamples and using four subsamples for training and the remaining subsample for the test [13]. As each of the five subsamples was used once during the cross-validation process, the analysis was performed five times per cross-validation. Fifteen analyses were performed when this was repeated three times. This process has also been used for internal cross-validation [15].

After selecting the final predictors through model optimization, the regression coefficient for the risk factors in the final model was used to calculate the integer assigned to the risk prediction score [13]. The integer points closest to each regression coefficient $\times 10$ was chosen for each risk factor [6]. Individual risk was based on the sum of the weighted scores for each assigned risk factor score [13]. For use in clinical decision-making, we derived a cut-off value for the risk prediction score to distinguish between high-risk and non-high-risk groups based on the Youden index [16].

We used an internal hold-out validation and an external validation dataset to validate the final model. The discrimination of the prediction score was evaluated by calculating the Area under the receiver operating characteristic (ROC) curves (AUROC) [13]. Calibration of the model for comparing the predicted and observed risks was evaluated using the Hosmer–Lemeshow goodness-of-fit test and calibration plots [13].

After applying the prediction model to the external validation dataset, we classified patients with a risk score greater than or equal to the cut-off value as high-risk cases. We then evaluated predictors of high-risk cases.

3. Results

3.1 Study population and characteristics

After applying the eligibility criteria, the derivation cohort included 8,176 cases of serious GI complications from a total of 2,004,031 patients who used NSAIDs for more than 30 consecutive days and 81,760 matched controls (Fig 1). The prevalence and rate of serious GI complications were 0.41% and 4.85 per 1000 person-years (95% CI, 4.75–4.96), respectively, in the total derivation cohort. The mean age was 75.9 years, and 71.6% were female; 1.3% of the development cohort had a history of GI bleeding or perforation and 27.6% had a history of GI ulcer without bleeding or perforation (Table 1).

3.2 Model development and performance

The predictors included in the multivariate analysis are presented in Table S2. Predictive risk factors included in the final model after parameter selection were as follows: age, sex, high-dose NSAIDs, type of NSAIDs, GPA with NSAIDs, concomitant antithrombotic agents, glucocorticoids, SSRI, history of GI bleeding or perforation, severe renal disease, and liver cirrhosis. GPA concomitant with NSAIDs included only PPI and H2RA. Misoprostol use did not reach statistical significance due to its infrequent use. The scores and adjusted OR for each risk factor are shown in Table 2. The points from -5 to 18 were assigned for each risk factor. For the prediction of serious GI complications, the cutoff score for classifying low-risk vs. high-risk patients was 16 (Youden Index, 0.42; sensitivity, 0.66; specificity, 0.76; Table 4).

Results from the Hosmer–Lemeshow test for the total score calculated using the risk scores showed an AUROC of 0.78 (95% CI, 0.77–0.79) from the internal training dataset and 0.77 (95% CI, 0.76–0.78) from the

internal hold-out validation dataset, which considered acceptable discrimination (Table 3) [17]. The calibration curves of the internal hold-out validation dataset demonstrated highly accurate calibration (calibration slope β =1.11), and the risk of GI complications increased as the prediction scores increased (Fig S1).

3.3 External validation

After applying the eligibility criteria, the external validation dataset included 372 cases with serious GI complications and 254,179 controls without any GI complications. These control groups did not undergo a control-selection matching process (Fig 1). The Hosmer–Lemeshow test for the external validation dataset showed an AUROC of 0.77 (95% CI, 0.75–0.80), indicating acceptable discrimination (Table 3). The calibration curves of the external validation dataset showed nearly perfect calibration (calibration slope β =1.08), and the risk of GI complications increased as the prediction scores increased (Fig S1).

Based on a total risk score cut-off of 16, patients were classified into high-risk or low-risk groups. There were 237 (4.6%) and 134 (20.5%) cases of serious GI complications in the high- and low-risk groups, respectively, with a statistically significant difference ($p<0.01$, Table 4).

The top ten cases predicted based on our model are presented in Table S3. For age factors from the risk model, 85 years or older could not be applied due to data limitations (HIRA-APS 2019).

4. Discussion

We developed a clinical risk prediction score to predict the possibility of serious GI complications in elderly patients receiving NSAIDs using geriatric population data from South Korea. By demonstrating the good performance of the prediction model through external validation, we confirmed that it is not limited to patients with arthritis and can be applied to the general elderly population that uses NSAIDs. Because the factors contributing to the risk of GI bleeding are different in the elderly and young populations using NSAIDs, risk prediction models specific to the elderly population should be considered. To the best of our knowledge, this is the first study to predict GI complications associated with NSAID use in the elderly population.

In our study, high-dose NSAID use was the greatest risk factor for serious GI complications as well as a history of complicated GI ulcers. The history of complicated GI ulcers is, as already known, a potent risk factor for NSAID-induced ulcers and a critical criterion in GI ulcer prevention algorithms [17] [18]. We found that NSAID use in excess of the daily recommended dose (e.g., ibuprofen 1200 mg, naproxen 500 mg, celecoxib 400 mg) or multiple NSAID use was a risk factor similar to a history of complicated GI ulcers in the elderly population. Multiple NSAIDs may be prescribed simultaneously, which may result in patients taking high-dose NSAIDs. Multiple prescribers may prescribe different NSAIDs. Patients may use multiple pharmacies or pharmacists may not detect multiple NSAID prescriptions. Therefore, a systematic medication management system for the elderly is required.

Our study identified new risk factors not included in the current guidelines [19]: male sex, very old age, and concomitant use of SSRI. Previous risk prediction studies [1] [6] for upper GI bleeding related to NSAID use have reported risk factors similar to those identified in our study, although their study populations were not specific to the elderly. In one study, age, male sex, anemia, aspirin, and anticoagulants were identified as predictors, while GI history and co-treatment with corticosteroids and SSRIs were not [6]. In another study, age; history of GI bleeding or perforation; concomitant use of corticosteroids, SSRIs, and antithrombotic agents; and male sex were identified [1]. Although these factors were included in our analysis, they were not identified as predictors. In our study, concomitant PPI or H2RA treatment with NSAID reduced the risk of serious GI complications, whereas the use of rebamipide or *Artemisia* herb soft extract did not. According to the guidelines, PPIs are recommended to prevent NSAID-related GI damage [17], but in practice, alternative GPAs are sometimes prescribed because of concerns about the long-term safety of PPI [12]. According to our previous study that reported the pattern of GPA prescription in the elderly ([?] 65 years) using NSAIDs, PPI, H2RA, rebamipide, and *Artemisia* herb soft extract accounted for 11.4%, 24.8%, 8.0%, and 6.8% of the total GPA prescriptions in Korea, respectively [20]. In a previous study investigating whether GPAs effectively

prevent NSAID-related GI injury in patients with arthritis, mucoprotective agents such as rebamipide and misoprostol were effective in reducing the risk of GI bleeding in NSAID users as acid suppressants (PPI or H2RA) [12]. However, the population in this study who used NSAIDs were over 20 years of age, a population with a relatively low GI risk compared to the population in our study. In our evaluation of GPAs, only PPI and H2RA, which acted as offset factors that reduced the risk of serious GI complications, were included in the prediction model.

We developed a risk model for capturing expanded cases compared to the risk classification system of the current guidelines, which counts the number of risk factors [19]. All of the ten cases with high frequency predicted as high-risk patients had the following factors: age [?]75 years, male sex, concurrent use of antithrombotic agents, and concurrent use of corticosteroids. If avoidable factors, such as high-dose NSAIDs, concomitant glucocorticoids, and antiplatelets, were eliminated, all ten high-risk cases were no longer high-risk.

Our study evaluated the use of GPAs as risk prediction factors for NSAID users. PPI or H2RA use was not sufficient to offset serious GI complications in all cases. According to our prediction model, men over 75 years of age using nsNSAIDs with concomitant single antiplatelet and glucocorticoid therapy were still at high risk even though they had used PPIs. Therefore, it is important to closely monitor and eliminate avoidable risk factors, if possible, when a patient is predicted to be at high risk, even when using a PPI.

The development of a convenient risk prediction score for the safe use of commonly used medications such as NSAIDs could benefit public health. The risk prediction calculator for serious GI complications developed in our study demonstrated acceptable performance and discrimination in the external validation, even without individual laboratory tests or specific information known only to experts. It is beneficial to quickly calculate the risk scores using only the patient's prescription and severe comorbidities known to themselves. By deriving cutoff values, high-risk patients can be easily identified.

Our study had several limitations that should be considered. First, as our assessment of predictors of GI complications depends on the factors available in the claims database, there might have been unmeasured risk factors. We could not include Helicobacter pylori infection, genetic susceptibility, or social factors such as smoking and alcohol consumption. However, smoking is not a significant risk factor for GI ulcers [1], and NSAID-induced GI complications are unrelated to H. pylori infection [2]. Second, the identification of serious GI complications and risk factors from claims data might be inaccurate, as it was based on the ICD-10 diagnostic codes [21]. Third, since age information over 80 years was not provided in the external validation data, we were unable to evaluate how well our model discriminated this age group with high confidence. Fourth, our model may not be generalizable to populations other than those used to derive and validate the model [21]. Additional external validation should be conducted to generalize the results to other populations (e.g., Western countries). Fifth, some of the medications sold over the counter, including NSAIDs and H2RA, could not be identified in the claims data.

5. Conclusion

We developed and validated a risk score model that can predict the risk of severe GI complications in elderly patients using NSAIDs. Our prediction score might be a useful tool for reducing the risk of severe GI complications by identifying and closely monitoring high-risk elderly patients when an NSAID is initiated.

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Contributors

JS and YA contributed to the study conception and design. KNH, MYL and SL developed the study protocol.

JL, KNH and SL performed data management and analysis. JS, KNH, MYL and YA reviewed the study analysis and results. SL wrote the draft of the manuscript. JS conducted a critical review of the manuscript. JL provided oversight for all aspects of the study. KNH, MYL and YA reviewed and edited the manuscript. All authors read and approved the final manuscript before submission.

Competing Interests

All authors do not have any potential conflicts of interest to declare.

Data availability statement

HIRA research data (M20200324406) used in this study was provided by Health Insurance Review and Assessment Service in South Korea and is prohibited to transfer, rent or sale to any third party other than the researcher who have been officially approved for database use. However, it is possible for other researchers to request access to the data directly from the HIRA.

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Table Legends

Table 1. Baseline characteristics of the derivation and validation cohort.

Table 2. The risk score for NSAID users.

Table 3. Model discrimination by derivation and validation cohorts.

Table 4. Accuracy of the risk prediction model using the cut-off values.

Figure Legends

Fig 1. Flowchart of selection of the study population.

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