Research Square

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# Gastrointestinal adverse events associated with Riociguat: A pharmacovigilance study based on FDA adverse event reporting system

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## Abstract

# Background

Riociguat, a soluble guanylate cyclase stimulator approved for pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), is frequently associated with gastrointestinal adverse events (GI AEs). However, comprehensive real-world evaluations focusing specifically on GI AEs remain limited.

# Methods

FAERS reports from the third quarter of 2013 to the fourth quarter of 2025 were retrospectively analyzed. Gastrointestinal AEs were identified using MedDRA preferred terms under the gastrointestinal disorders system organ class. Disproportionality analysis was performed using the reporting odds ratio (ROR), with signals defined by a lower 95% confidence interval > 1 and at least 10 reports. Comparisons between serious and non-serious cases, stratified analyses by demographic and reporting characteristics, clinical prioritization of signals, and time-to-onset analyses using Weibull shape parameter modeling were conducted.

# Results

Among 16,076,520 FAERS reports, 14,006 gastrointestinal AEs associated with riociguat were identified, involving 3,123 patients. Thirty gastrointestinal preferred terms demonstrated significant disproportionality signals, with the strongest associations observed for dyspepsia, nausea, diarrhea, and vomiting. Older age and lower body weight were significantly associated with serious GI AEs, while no sex-related differences were observed. Stratified analyses confirmed a stable association between riociguat and gastrointestinal disorders across sex, age, body weight, and reporter type. Clinical prioritization identified small intestinal obstruction as a moderate-priority signal, while most other events were classified as weak priority. Time-to-onset analysis indicated that GI AEs typically occurred early after treatment initiation, with Weibull modeling suggesting an early failure pattern.

# Conclusions

Riociguat is significantly associated with a broad spectrum of gastrointestinal adverse events in real-world clinical practice, most of which occur early during treatment and are generally mild. However, certain serious GI complications, particularly in older and lower-weight patients, warrant increased clinical vigilance. These findings provide important evidence to support risk assessment, early monitoring, and individualized management strategies for patients receiving riociguat.

# Introduction

Riociguat is a first-in-class soluble guanylate cyclase (sGC) stimulator that exerts its therapeutic effects by directly stimulating sGC and enhancing its sensitivity to endogenous nitric oxide (NO), thereby increasing intracellular cyclic guanosine monophosphate (cGMP) levels(1). This mechanism leads to vasodilation, inhibition of vascular remodeling, and improvement of endothelial function. Riociguat has been widely used for the treatment of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH)(2, 3). In 2013, the U.S. Food and Drug Administration (FDA) approved riociguat for adults with inoperable or persistent/recurrent CTEPH after surgical treatment. Subsequently, its indication was expanded to include adults with PAH, based primarily on the CHEST and PATENT clinical trials, which demonstrated significant improvements in exercise capacity, pulmonary vascular resistance, and World Health Organization functional class compared with placebo(4, 5).

With the increasing and long-term clinical use of riociguat, concerns regarding its safety and tolerability have gradually emerged. According to clinical trials and post-marketing data, the most frequently reported adverse events (AEs) associated with riociguat include hypotension, headache, dizziness, and gastrointestinal disorders. Gastrointestinal adverse events (GI AEs), such as dyspepsia, nausea, vomiting, diarrhea, and abdominal pain, are among the most common non-cardiovascular AEs leading to dose adjustment or treatment discontinuation(6, 7). From a pharmacological perspective, activation of the NO-sGC-cGMP signaling pathway may influence gastrointestinal smooth muscle tone, intestinal motility, and secretory function, providing a plausible biological mechanism for riociguat-associated GI AEs (8).

Although the pivotal randomized controlled trials comprehensively evaluated the efficacy and overall safety profile of riociguat, systematic assessments specifically focusing on gastrointestinal AEs remain limited, particularly in real-world settings(9). Clinical trials are often constrained by relatively small sample sizes, strict inclusion criteria, and limited follow-up duration, which may restrict the detection of rare, delayed, or severe adverse events(10). Post-marketing spontaneous reporting systems offer an important complementary approach for identifying potential safety signals and characterizing adverse event patterns under routine clinical practice conditions(11).

Therefore, the present study aimed to investigate gastrointestinal adverse events associated with riociguat using a disproportionality analysis based on the FDA Adverse Event Reporting System (FAERS), a global and publicly accessible pharmacovigilance database(12). Furthermore, stratified analyses, clinical priority assessment of signals, time-to-onset evaluation, and serious outcome analyses were conducted to comprehensively characterize the features of riociguat-associated gastrointestinal AEs and to provide evidence for clinical risk management and rational drug use.

# Methods

# Data collecting and processing

The FAERS data used in this study were obtained from the FAERS Quarterly Data Extract Files (https://fis.fda.gov/extensions/FPD-QDE-FAERS/ FPD-QDE-FAERS.html). Based on the FDA approval timeline for riociguat, all records documented in FAERS from the third quarter (Q3) of 2013 through the fourth quarter (Q4) of 2025 were incorporated into our analysis.

The FAERS database comprises seven core files: patient demographics (DEMO), drug-related information (DRUG), adverse event descriptions (REAC), patient outcomes (OUTC), report sources (RPSR), therapy initiation dates (THER), and drug indication details (INDI)(13). Additionally, cases removed by the FDA or manufacturers for reasons such as merging reports, were cataloged in the Deleted files. All datasets were imported into MySQL software (version 8.0; Oracle, Sweden). Prior to statistical analysis, deduplication was conducted, with the primary ID serving as the key field to link data across files(14, 15). In this study, the case ID was used as the main filter to eliminate duplicate entries.

We identified cases containing riociguat through both its generic name and trade names within the DRUG file, selecting role_cod marked as PS (Primary Suspect). Analysis of concomitant medications was also performed. Combination therapy was defined as the simultaneous use of riociguat alongside other drugs targeting PAH or CTEPH. In these instances, riociguat was classified as the PS, while additional medications were recorded as "secondary suspect," "concomitant," or "interacting" drugs. Manual verification was conducted to prioritize the highest primary ID when duplicate case IDs were encountered.

Adverse events (AEs) in FAERS were coded using preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA), which organizes data into 27 system organ classes (SOCs). Each PT can be mapped to one or more SOCs in MedDRA. For this research, MedDRA version 24.0 was employed to classify AEs into corresponding SOC levels using MySQL 8.0. All PTs under the gastrointestinal disorders SOC (code: 10017947) in the FAERS records were included in the analysis.

Detailed available clinical profiles from the reports were described, encompassing patient information such as gender, age, weight, reporting region, outcomes, and reporter types. Serious outcomes, as categorized in the data, included death, life-threatening events, hospitalizations, disabilities, and other critical conditions. Notably, the count of serious outcomes could exceed the total number of cases, as some individual reports listed multiple such outcomes. A step-by-step flowchart detailing data extraction, processing, and analysis can be found in Fig. 1.

# Statistical analysis

The reporting odds ratio (ROR) is an algorithm based on disproportionality analysis, calculated using a 2×2 contingency table. To minimize the likelihood of false-positive results, this study included only gastrointestinal AEs with at least 10 reports. Subsequently, we assessed the signal strength of reports in the FAERS database for gastrointestinal AEs associated with riociguat during treatment compared to

conventional therapies. A positive signal was defined as the lower limit of the 95% confidence interval (CI) of the ROR exceeding one(16, 17).

Additionally, we compared serious and non-serious reports to determine the severity of identified safety signals and to evaluate potential risk factors including gender, age, and body weight. Proportions were compared using Pearson's chi-square ($\chi 2$) test or Fisher's exact test. Data analysis was performed using R software (version 4.3.1), and statistical significance was set at $p < 0.05$.

To further explore the impact of different stratification variables on the association between riociguat and gastrointestinal disorders, we conducted stratified analyses. The stratification variables included gender (male and female), age (< 18 years, 18–65 years and ≥ 65 years), body weight (< 50 kg, 50–100 kg, and > 100 kg), and report source (healthcare professionals and consumers).

## Clinical prioritization of signals

A semiquantitative score was employed to prioritize disproportionality signals in four features, including clinical relevance, reporting rate, signal stability, and reported case fatality rate. A score of 0–2, 3–5, and 6–8 identified, respectively, AEs with low, moderate, or high priority(18).

## Time-to-onset analysis

Time to onset (TTO) was defined as the interval between the date of adverse event occurrence (EVENT_DT) and the initiation date of semaglutide therapy (START_DT). To ensure the accuracy of the analysis, reports with data entry errors (e.g., EVENT_DT earlier than START_DT), inaccurate date information, or missing key data were excluded(19, 20). Median values, quartiles, and the Weibull shape parameter (WSP) test were applied to assess TTO in this study.

Statistical analysis of TTO was performed using the WSP test, which allows evaluation of temporal changes in the incidence of adverse events. The Weibull distribution is characterized by two parameters: the scale parameter ($\alpha$) and the shape parameter ($\beta$). To predict whether the risk of these adverse events increased or decreased over time, we calculated the median TTO and WSP for signals with strong, moderate, or weak clinical priority following semaglutide use. The selection of analytical parameters and evaluation criteria was based on previously published studie(21, 22). All WSP analyses were conducted using Minitab statistical software (version 20.0; Minitab LLC, State College, PA, USA).

## Results

# Descriptive analysis

During the observation period, 16,076,520 adverse event (AE) reports were retrieved from the FAERS database after removal of duplicate records. Among these, 14,006 gastrointestinal AEs associated with

riociguat were identified, involving 3,123 patients. The main clinical characteristics are presented in Table 1. Sex information was available for 5,312 cases, with a higher proportion of females than males (2,283 vs. 788). Riociguat-related gastrointestinal AEs were reported more frequently in older individuals aged over 65 years (n = 1,421, 45.5%) compared with adults aged 18–65 years (n = 1,362, 43.6%). Body weight data were reported for 1,605 patients; among them, 9.3% weighed more than 100 kg, 38.9% were in the 50–100 kg range, and 3.2% weighed less than 50 kg. The most commonly reported outcomes of riociguat therapy were classified as other events and hospitalizations, accounting for 1,486 (62.04%) and 772 (43.42%) gastrointestinal AEs, respectively, as well as 2,311 (64.18%) and 1,430 (39.71%) of all AEs. Furthermore, 516 gastrointestinal AE reports (16.5%) were submitted by healthcare professionals, whereas 1,272 reports (40.7%) were provided by consumers. The majority of gastrointestinal AE reports originated from the United States (n = 2,741, 87.8%).

## Disproportionality analysis

In the FAERS database, 30 distinct preferred terms (PTs) of gastrointestinal adverse events related to riociguat were identified, each reported in no fewer than 10 cases (Fig. 2). The most commonly reported events included nausea (n = 1,036), diarrhea (n = 866), vomiting (n = 629), dyspepsia (n = 445), constipation (n = 295), abdominal bloating (n = 256), and upper abdominal pain (n = 254). The results of the disproportionality analysis for riociguat-associated gastrointestinal AEs are illustrated in Fig. 2. All 30 gastrointestinal PTs demonstrated statistically significant signal detection when compared with gastrointestinal AEs not associated with riociguat, with signal strength values (ROR025) ranging from 1.04 for melaena to 5.66 for dyspepsia.

## Serious vs. non-serious cases

As summarized in Table 2, significant differences were observed in both age ($p < 0.001$) and body weight ($p < 0.001$) between patients with severe versus non-severe gastrointestinal AEs following riociguat treatment. In contrast, the distribution of males and females was comparable between the two groups ($p = 0.352$). 13 gastrointestinal AEs showed a higher likelihood of being classified as serious, with statistical significance ($p < 0.05$), including nausea ($p < 0.001$), diarrhea ($p < 0.001$), vomiting ($p = 0.019$), and dyspepsia ($p < 0.001$). Conversely, 41 gastrointestinal AEs were more frequently reported as non-serious events ($p > 0.05$), such as constipation, upper abdominal pain, and abdominal distension.

# Stratification analysis

To enhance the robustness of the findings, four stratified analyses were conducted. As illustrated in Fig. 3, when gastrointestinal disorders at the SOC level were evaluated separately according to sex, age, body weight, and type of reporter, the lower bounds of the ROR values in all subgroups remained greater than 1. These results consistently indicate a strong and stable statistical association between riociguat use and gastrointestinal disorders across all stratification categories.

# Clinical prioritization of the disproportionality signals

As illustrated in Table 3, we adopted semiquantitative score to prioritize disproportionality signals from clinical relevance, reporting rate, signal stability, and reported case fatality rate. Based on the clinical priority assessment results, 5 (10.87%), and 41 (89.13%) AEs were identified as moderate and weak clinical priority, respectively. Small intestinal obstruction (n = 36) was classified as moderate clinical priority with the highest priority score 4.

# Time-to-onset analysis

Results of time-to-onset and WSP analysis for the moderate and weak clinical priorities signals were shown in Table 4. The median onset time of moderate and weak signals related to riociguat was 172.5 (IQR 51.25–621.5), and 93 (IQR 30–325) days respectively. The weak clinical priority signals tended to occur earlier moderate

than those moderate AEs signals. In the assessment of WSP analysis, all shape parameters β and their 95% CI upper limits were < 1, suggesting that moderate and weak clinical priority signals had early failure types.

## Discussion

In this large-scale pharmacovigilance study based on the FAERS database, we comprehensively evaluated gastrointestinal adverse events associated with riociguat in real-world clinical practice. By integrating disproportionality analysis, stratified assessments, seriousness comparisons, clinical signal prioritization, and time-to-onset evaluation, our findings provide a detailed and systematic characterization of riociguat-related gastrointestinal safety signals, thereby complementing evidence from randomized controlled trials.

Consistent with previous clinical trials and post-marketing reports, gastrointestinal disorders emerged as one of the most frequently reported non-cardiovascular adverse event categories associated with riociguat(23, 24). We identified 30 gastrointestinal PTs with statistically significant disproportionality signals, among which nausea, diarrhea, vomiting, and dyspepsia were the most commonly reported. These findings are in line with results from the PATENT and CHEST studies(5, 6), in which gastrointestinal symptoms were among the leading causes of dose adjustment and treatment discontinuation. Importantly, our study extends these observations by quantifying the strength of association in a large real-world population and by identifying both common and less frequently recognized gastrointestinal events, such as melaena and small intestinal obstruction.

From a mechanistic perspective, the observed gastrointestinal adverse events are biologically plausible. Riociguat enhances the NO–sGC–cGMP signaling pathway, which plays an essential role not only in vascular smooth muscle relaxation but also in the regulation of gastrointestinal motility, secretion, and visceral sensitivity(25–27). Increased cGMP levels may alter intestinal smooth muscle tone and

accelerate or dysregulate peristalsis, potentially contributing to symptoms such as diarrhea, abdominal distension, and abdominal pain(28, 29). Moreover, vasodilatory effects on the splanchnic circulation and mucosal blood flow may partially explain dyspepsia and, in rare cases, gastrointestinal bleeding events such as melaena.

The comparison between serious and non-serious gastrointestinal AE reports revealed that older age and lower body weight were significantly associated with severe outcomes, whereas sex was not. These findings suggest that elderly patients and those with lower body mass may be more vulnerable to clinically significant gastrointestinal toxicity during riociguat therapy. Age-related changes in gastrointestinal physiology, comorbidities, polypharmacy, and altered drug metabolism may collectively increase susceptibility to severe adverse events in older populations(30, 31). Similarly, lower body weight may lead to relatively higher drug exposure at standard doses, potentially amplifying adverse effects. These results underscore the importance of individualized dosing, careful monitoring, and early intervention in high-risk patient groups.

Stratified analyses further confirmed the robustness of the association between riociguat and gastrointestinal disorders. The persistence of significant disproportionality signals across all subgroups stratified by sex, age, body weight, and reporter type suggests that the observed association is unlikely to be driven solely by reporting bias or confounding from a specific demographic or reporting source. Notably, consistent signals from both healthcare professionals and consumers strengthen the credibility of the findings and reflect real-world clinical experiences across different settings.

Clinical prioritization of signals revealed that most gastrointestinal AEs were classified as weak priority, reflecting their relatively high frequency but generally mild or manageable nature. However, small intestinal obstruction was identified as a moderate-priority signal despite its lower reporting frequency, highlighting its potential clinical seriousness and need for heightened awareness. Although causal inference cannot be established from spontaneous reporting data, this finding suggests that clinicians should remain vigilant for severe or atypical gastrointestinal symptoms during riociguat treatment, particularly when patients present with persistent abdominal pain, vomiting, or signs of bowel obstruction.

The time-to-onset analysis demonstrated that most gastrointestinal AEs occurred relatively early after initiation of riociguat therapy, with weak-priority signals appearing earlier than moderate-priority signals(32). The Weibull shape parameter analysis indicated an “early failure” pattern for both moderate and weak signals, suggesting that the risk of gastrointestinal AEs is highest during the initial treatment phase and decreases over time(33, 34). This temporal pattern is clinically relevant, as it emphasizes the importance of close monitoring, patient education, and proactive management during the first few months of therapy to improve tolerability and adherence(35).

Several limitations should be acknowledged. First, FAERS is a spontaneous reporting system subject to underreporting, reporting bias, and incomplete clinical information, which may affect the accuracy of incidence estimation and risk quantification. Second, causality cannot be definitively established due to

the observational nature of the data and the lack of detailed information on comorbidities, dosing regimens, and concomitant medications. Third, disproportionality analysis reflects reporting associations rather than true risk, and confounding by indication cannot be fully excluded, especially in patients with advanced PAH or CTEPH who may have baseline gastrointestinal symptoms.

Despite these limitations, this study has several strengths, including a large sample size, long observation period, comprehensive analytical framework, and multiple sensitivity analyses. Together, our findings provide robust real-world evidence supporting a significant association between riociguat and a broad spectrum of gastrointestinal adverse events.

In conclusion, gastrointestinal disorders are common and clinically relevant adverse events associated with riociguat, with signals detectable across diverse patient subgroups and occurring predominantly in the early phase of treatment. While most events are mild, certain serious gastrointestinal complications warrant clinical attention, particularly in older and lower-weight patients. These results highlight the need for individualized risk assessment, early monitoring, and patient counseling to optimize the safe and effective use of riociguat in routine clinical practice.

# Declarations

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**Author contributions**

Bin Xiong: Conceptualization, methodology, formal analysis, and writing review & editing. Tong Yi: Conceptualization, methodology, and writing. Ping Che: Investigation and data curation. Ruhao Wu: Investigation and data curation. Ke Wang: Investigation and data curation. Mingwei Fan:Investigation and data curation. Jun Kong: Conceptualization, methodology, formal analysis, writing original draft. Linyan Fu: Investigation and data curation.

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**Data availability**

Data are available on reasonable request.

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**Competing interests**

The authors declare no competing interests.

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# Tables

Tables 1 to 4 are available in the supplementary files section

# Figures

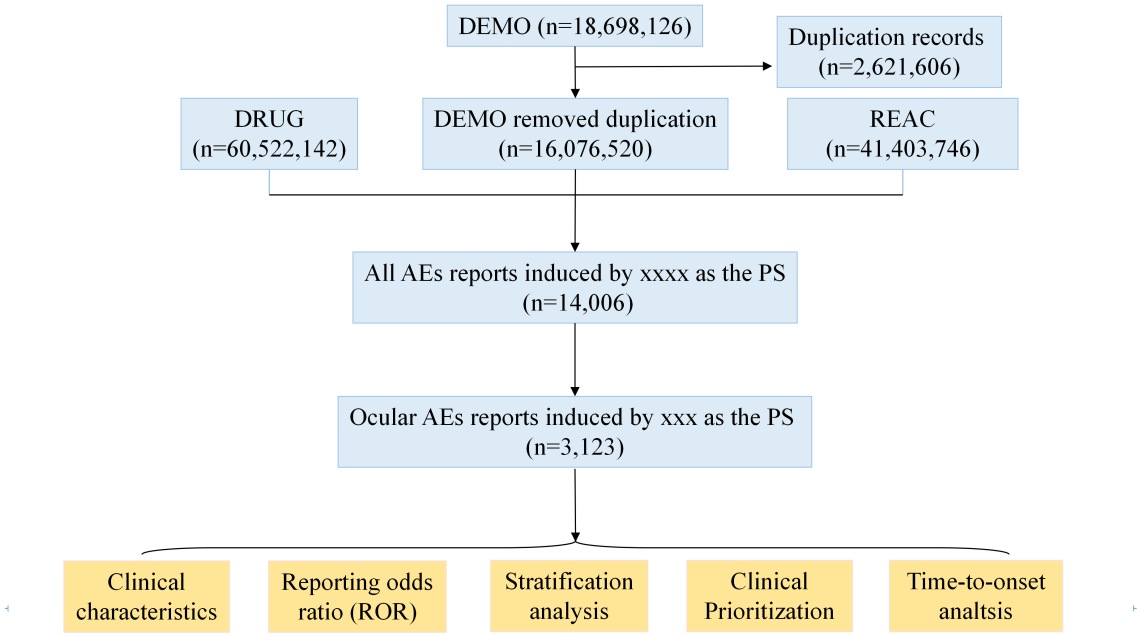



**Figure 1**

**The process of selecting riociguat-associated gastrointestinal adverse events from food and drug administration adverse event reporting database.**

| PT(Preferred Term) | Riociguat | NON−Riociguat | ROR(95% CI) |
|---|---|---|---|
| Nausea | 1036 | 507747 | 1.75(1.65~1.86) |
| Diarrhoea | 866 | 442107 | 1.68(1.57~1.79) |
| Vomiting | 629 | 294605 | 1.83(1.69~1.98) |
| Dyspepsia | 445 | 61403 | 6.21(5.66~6.82) |
| Constipation | 295 | 145296 | 1.73(1.54~1.94) |
| Abdominal Distension | 256 | 67351 | 3.24(2.87~3.67) |
| Abdominal Pain Upper | 254 | 134563 | 1.61(1.42~1.82) |
| Gastrooesophageal Reflux Disease | 250 | 49514 | 4.31(3.81~4.88) |
| Abdominal Discomfort | 239 | 119924 | 1.7(1.5~1.93) |
| Gastrointestinal Disorder | 239 | 84412 | 2.41(2.13~2.74) |
| Abdominal Pain | 216 | 146419 | 1.26(1.1~1.44) |
| Ascites | 100 | 18297 | 4.66(3.82~5.67) |
| Gastrointestinal Haemorrhage | 91 | 56376 | 1.37(1.12~1.69) |
| Flatulence | 72 | 35475 | 1.73(1.37~2.18) |
| Intestinal Obstruction | 68 | 24858 | 2.33(1.83~2.95) |
| Haematochezia | 61 | 37357 | 1.39(1.08~1.79) |
| Haematemesis | 55 | 15240 | 3.07(2.36~4) |
| Gastritis | 39 | 15490 | 2.14(1.56~2.93) |
| Retching | 38 | 13763 | 2.35(1.71~3.23) |
| Small Intestinal Obstruction | 36 | 7806 | 3.92(2.83~5.45) |
| Eructation | 28 | 11198 | 2.13(1.47~3.08) |
| Faeces Discoloured | 28 | 13623 | 1.75(1.21~2.53) |
| Melaena | 25 | 13755 | 1.55(1.04~2.29) |
| Hiatus Hernia | 20 | 7636 | 2.23(1.44~3.46) |
| Oesophagitis | 19 | 6065 | 2.66(1.7~4.18) |
| Intra−Abdominal Fluid Collection | 17 | 1644 | 8.8(5.45~14.19) |
| Oesophageal Ulcer | 12 | 2130 | 4.79(2.72~8.45) |
| Haemorrhoidal Haemorrhage | 12 | 3325 | 3.07(1.74~5.41) |
| Oesophageal Pain | 10 | 2236 | 3.8(2.04~7.08) |
| Gastrointestinal Motility Disorder | 10 | 3684 | 2.31(1.24~4.29) |




## Figure 2

## Reporting odds ratios (ROR) with 95% CI for all positive riociguat-related gastrointestinal AEs.

| Characteristies | Riociguat | NON−Riociguat | ROR(95% CI) | Bonferron_P_value |
|---|---|---|---|---|
| Overall | 6,254/42,374 | 3,453,929/37,901,189 | 1.62(1.58~1.66) | p<0.05 |
| Male | 1,504/11,563 | 1,080,038/12,647,830 | 1.52(1.44~1.61) | p<0.05 |
| Female | 4,682/30,350 | 2,022,271/20,981,149 | 1.6(1.55~1.65) | p<0.05 |
| <18 Years | 27/174 | 101,087/1,445,256 | 2.22(1.48~3.33) | p<0.05 |
| 18 ~ 65 Years | 2,921/18,715 | 1,380,262/14,447,616 | 1.63(1.57~1.7) | p<0.05 |
| >65 Years | 2,959/20,964 | 855,822/8,431,395 | 1.39(1.34~1.45) | p<0.05 |
| <50 kg | 228/1,368 | 109,072/,1049,319 | 1.6(1.39~1.84) | p<0.05 |
| 50 ~ 100 Kg | 2,672/16,375 | 7,890,22/7,123,481 | 1.47(1.41~1.53) | p<0.05 |
| >100 Kg | 650/4,818 | 1,205,09/1,227,674 | 1.37(1.27~1.49) | p<0.05 |
| Health professional | 833/5,976 | 890,973/9,962,784 | 1.56(1.45~1.68) | p<0.05 |
| Consumer | 2,459/16,358 | 1,646,243/17,445,441 | 1.59(1.53~1.66) | p<0.05 |




## Figure 3

## Stratification analysis of riociguat-induced gastrointestinal disorders.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx
- Table4.xlsx