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ISSN: 2056-5623 (Online) Journal homepage: www.tandfonline.com/journals/ifso20

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To cite this article: Aigerim Japparkulova, Ainash Oshibayeva, Gulnaz Nuskabayeva, Karlygash Sadykova, Jamilya Kaibullayeva & Nursultan Nurdinov (2025) A systematic review of inflammatory bowel disease in Kazakhstan: prevalence, risk factors, and genetic insights, Future Science OA, 11:1, 2567152, DOI: 10.1080/20565623.2025.2567152

To link to this article: https://doi.org/10.1080/20565623.2025.2567152

Published online: 29 Sep 2025.

FUTURE SCIENCE OA
2025, VOL. 11, NO. 1, 2567152
https://doi.org/10.1080/20565623.2025.2567152

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REVIEW ARTICLE

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A systematic review of inflammatory bowel disease in Kazakhstan: prevalence, risk factors, and genetic insights

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ABSTRACT

Background: Inflammatory bowel disease is a chronic condition characterized by immune mediated inflammation and primarily includes Crohn's disease and ulcerative colitis.
Objective: There is an increase rate of incidence of the disease in Kazakhstan. Therefore, it is important to determine the prevalence of the condition in to improve diagnosis and the treatment for the local population.
Method: They current manuscript is a systematic review of the literature that focuses on IBD from Kazakhstan with a focus on prevalence, risk factors including genetic predisposition, disease mechanism, diagnosis and treatment.
Results: The prevalence of IBD is higher in urban regions, and more prevalent in individuals under the age of 40 years. Genetic studies reported that familial IBD is quite rare in Kazakhstan, suggesting an environmental cause rather than a genetic reason that is driving the increase of prevalence.
Conclusion: There are IBD-associated variants linked to immune function and inflammation pathways that may serve as noninvasive biomarkers for disease diagnosis and severity. However, the mechanisms of disease development and drug response may differ across different populations, therefore, there might be a need implement genetic testing to improve therapy and disease management in Kazakhstan.

ARTICLE HISTORY
Received 4 August 2025
Accepted 24 September 2025

KEYWORDS
Inflammatory bowel disease; Crohn's disease; ulcerative colitis; prevalence; systematic review

1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract characterized by a variable and often progressive clinical course [1]. It is primarily classified into two main subtypes: Crohn's disease (CD) and ulcerative colitis (UC) [2]. Crohn's disease typically involves the terminal ileum, colon, cecum, and perianal region, although it can affect any part of the gastrointestinal tract in a discontinuous, patchy manner, with areas of inflammation (skip lesions) separated by segments of healthy tissue [3]. CD is distinguished by transmural inflammation, which affects all layers of the intestinal wall and may1 result in complications such as fistulae, strictures, and abscesses [1]. In contrast, UC is limited to the colon, beginning at the rectum and extending proximally in a continuous pattern. While UC is characterized by inflammation confined to the mucosal and submucosal layers, without involvement of the deeper layers of the intestinal wall, and commonly includes the region surrounding the appendix, CD often causes non-bloody diarrhea resulting from deeper tissue involvement [4].

The etiology of IBD remains incompletely understood, with current evidence suggest a multifactorial pathogenesis involving genetic susceptibility, impaired integrity of the intestinal mucosal barrier, changes in the composition of gut microbiota, dysregulated immune responses, as well as the influence of environmental and lifestyle factors [3,4].

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Given the chronic nature of IBD and its relatively low mortality rate, the prevalence of the condition has increased substantially over time. According to recent global estimates, approximately 4.9 million individuals were living with IBD in 2019 [5]. Traditionally it is more prevalent in Western countries, a pattern largely associated with lifestyle-related factors and extensive urbanization. For example, IBD is reported to affect approximately 0.3% of the population in both North America (around 2.2 million individuals) and Europe (estimated at 2.5–3 million individuals) [6,7]. However, the incidence of IBD is now rising markedly in newly industrialized regions across Africa, South America, and Asia. This shift is thought to be influenced by environmental changes linked to urban development and the increasing adoption of Westernized dietary and lifestyle practices [8]. For instance, incidence rates in Taiwan have risen from 0.6 to 3.9 per 100,000 population, and in South Korea from 7.6 to 30.9 per 100,000 [9,10].

However, the numbers from Kazakhstan, a developing country Central Asian country of more than 20 million people, have been inconsistent [11]. In light of massive urbanization and adaptation of western diet in Kazakhstan, we hypothesized that IBD is more common among Kazakh citizens than the reported figures. Therefore, it is important to estimate the prevalence of IBD in Kazakhstan and determine the influencing factors. Hence, the aim of this systematic review is to comprehensively synthesize and critically evaluate the existing literature on the prevalence and etiological factors of IBD in Kazakhstan. The review aims to elucidate disease distribution, genetic predisposition, and lifestyle risk factors to guide disease management and future research directions.

2. Methods

2.1. Literature search

The present study is a systematic review performed following the methodological framework and reporting standards specified in the PRISMA 2020 statement, as established by Page et al. [12]. To identify studies related to IBD prevalence, distribution and causes in Kazakhstan, an extensive literature search conducted across four primary electronic databases including; Scopus, PubMed, EMBASE-Elsevier, and ScienceDirect. Due to the limited availability of publications in English on this topic, no restrictions were imposed on the initial publication date; however, the search was confined to articles published up to June 20, 2025. The search strategy employed the following key terms: Inflammatory Bowel Disease in Kazakhstan; Ulcerative Colitis in Kazakhstan; Crohn Disease in Kazakhstan; Genetic Susceptibility of Asians to IBD; and treatment of IBD.

2.2. Study selection and data extraction

The literature search, article screening, and quality assessment were independently performed by A.J., O.A., K.S., and J.K. Subsequently, the selected studies were compared, and discrepancies were resolved through consensus discussions involving G.N. and N.N.S. The methodological quality of the included studies was evaluated using the GRADE framework, which appraises the overall strength and reliability of the evidence. Initially, titles and abstracts were screened for eligibility, followed by a comprehensive full-text review based on predefined inclusion criteria.

Extracted data encompassed the first author's name, publication year, study design, and principal findings.

2.3. Assessment of research bias and limitations

The objectives of this study are to investigate the prevalence, etiological factors, and geographic distribution of IBD within Kazakhstan. Accordingly, only studies presenting epidemiological data or pertinent analyses were included. It is important to acknowledge that the reported rates and prevalence figures do not represent the entirety of documented cases. Furthermore, multiple manuscripts were excluded from the review due to subject overlap, language barriers, publication formats (such as book chapters, abstracts, presentations, and clinical trials), or restricted availability of full-text articles.

2.4. Study outcome

The primary outcome of interest was the determination of prevalence, distribution, and causes of IBD in Kazakhstan.

3. Results

The search yielded thirty-two articles, of which 10 were duplicates and hence removed. The remaining 22 articles underwent full-text review. A further 13 articles were then excluded; four articles were inaccessible, six articles were in languages other than English, and three articles were not from Kazakhstan. Therefore, only nine studies met the inclusion criteria and, thus, included in this review (Figure 1). The descriptions of each study and key findings presented in Table 1.

3.1. Disease prevalence and distribution

The incidence and prevalence of IBD other gastrointestinal disorders are increasing in many developing countries. However, the estimated prevalence in developing regions, particularly in Asia, ranges from 5.3 to 63.6 per 100,000 individuals, whereas in North America, the estimates are significantly higher and ranges from 37.5 to 238 per 100,000 population [13].

While there is a lack of epidemiological data on IBD in Kazakhstan, a nationwide cross-sectional study by Kaibullayeva and colleagues titled "Prevalence and patient awareness of inflammatory bowel disease in Kazakhstan" aimed to estimate the prevalence of IBD and patient awareness among Kazakhstani adults [14]. The study used a self-administered questionnaire, and for suspected cases with positive disease, symptoms were confirmed by laboratory testing. The study involved more than 115,000 participants, of whom 128 cases of IBD were confirmed (92 patients with UC, and 36 with CD), yielding an age- and sex-adjusted prevalence of 113.9 per 100,000 population (84.4 for UC and 29.5 for CD) (Figure 2). In terms of disease distribution, they study reported that IBD is more prevalent among urban areas, particularly in the Eastern region of the country than remote areas. Interestingly, analysis of the age distribution of the disease showed that disease is more common among people less than 40 years old with UC observed mostly in individuals aged 30–39 years, and CD more prevalent among those aged 18–29.

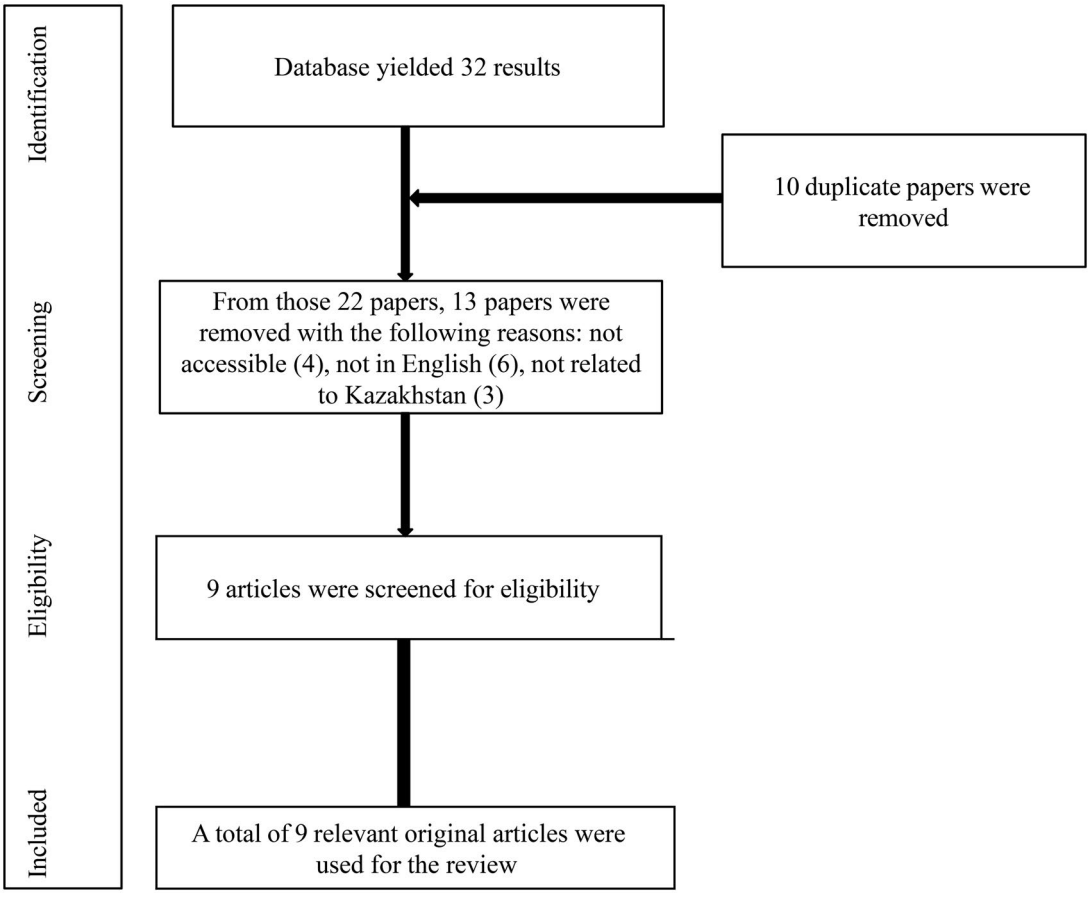

Figure 1. Selection process following the PRISMA guidelines.

Table 1. Summary of findings from the included articles.

#	Title	Author	Publication year	Design	Relevant findings
1	Expression profile of the matricellular protein periostin in pediatric inflammatory bowel disease	Coelho et al. [18]	2021	Clinical study	Disease etiology, risk factors and treatment
2	Prevalence and patient awareness of inflammatory bowel disease in Kazakhstan: a cross-sectional study	Kaibullayeva et al. [14]	2020	Cross-sectional study	Prevalence
3	The Role of Immunopathology: As Predictor Factors in Patients with Inflammatory Bowel Diseases	Kemelbekov et al. [17]	2020	Prospective cross-sectional study	Treatment
4	Alterations of the Gut Microbiome and TMAO Levels in Patients with Ulcerative Colitis	Laryushina et al. [21]	2024	Clinical study	Etiology and diagnosis
5	Association of TMAO levels with indicators of ulcerative colitis activity	Laryushina et al. [22]	2025	Observational cross-sectional comparative study	Etiology and diagnosis
6	Role of periostin in inflammatory bowel disease development and synergistic effects mediated by the CCL5–CCR5 axis	Mukanova et al. [19]	2022	Laboratory based animal study	Etiology and treatment
7	Pediatric Ulcerative Colitis in Kazakhstan: First Case Series from Central Asia and Current Clinical Management	Poddighe et al. [15]	2020	Retrospective case series	Genetic variations and treatment
8	*Cytokine profile: recent advances in pathogenesis of inflammatory bowel diseases*	Doszhan et al. [20]	2018	Retrospective case series	Diagnosis and treatment
9	Real world practice of medical treatment for moderate and severe inflammatory bowel diseases in Russian Federation, Republic of Belarus and Republic of Kazakhstan: intermediate results of the INTENT study	Knyazev et al. [25]	2021	Retrospective cohort study	Genetic variation, prevalence, and treatment

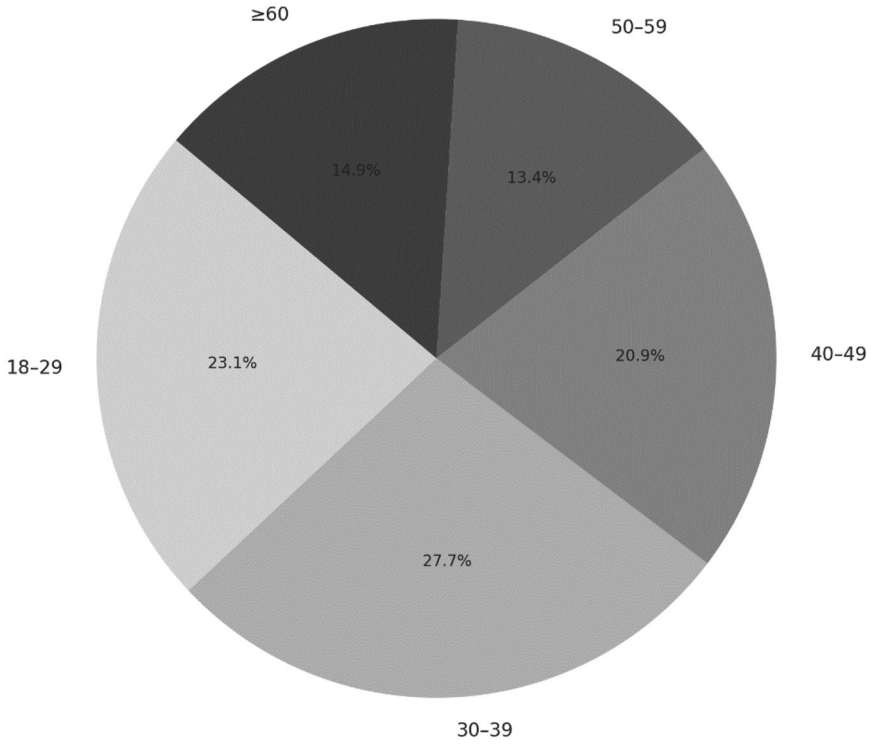

Figure 2. Prevalence of IBD per 100,000 population by age group in Kazakhstan.

However, these numbers might be significantly higher due to underdiagnoses or delayed as claimed by Poddighe et al., which investigated pediatric ulcerative colitis in Kazakhstan. In their retrospective analysis of more than 25 cases, they noted that the disease usually go undiagnosed or more often reported delayed diagnosis [15]. They also reported that the disease was more predominant in males than females (64% vs. 36%).

3.2. Risk factors and genetic predisposition

Although genetic predisposition was identified as a major risk factor IBD, Kazakhstanis and possibly other Central Asian countries have no reports or very few cases of familial IBD [16]. This suggests that IBD in

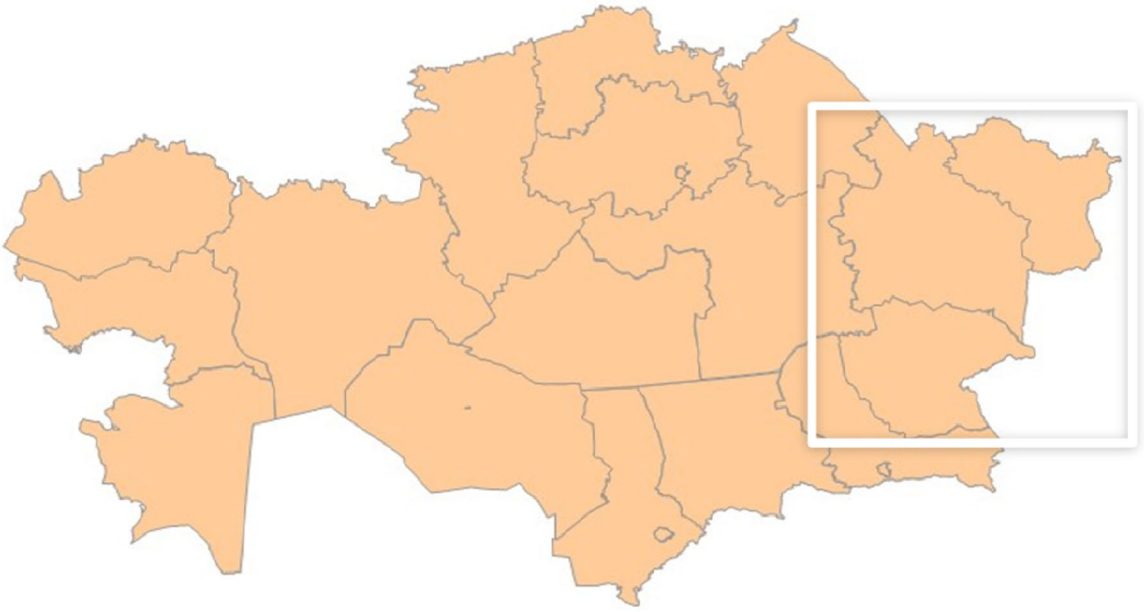

Figure 3. Map of the Republic of Kazakhstan.

Kazakhstan is likely due to environmental rather than genetic risk factor. However, genetic studies of several Asian countries, including Kazakhstan, identified a number of variants linked to immune regulation, epithelial barrier function, microbial recognition, autophagy, and cytokine signaling pathways such as interleukin-23 (IL-23) and tumor necrosis factor (TNF) related genes [13]. For example, in their study titled "The role of immunopathology as predictor factors in patients with inflammatory bowel diseases", Kemelbekov and colleagues evaluated the immunopathological markers of more than 40 newly diagnosed IBD patients to identify predictors of disease activity and progression [17]. They quantified cellular immune markers including $CD4^+$, $CD8^+$ T cells and $CD16^+$ NK cells, and assessed mucosal expression of toll-like receptors (TLR-2 and TLR-4) in the colon. The results showed an upregulation of TLR-2 and TLR-4 genes, suggesting that they may initiate or amplify mucosal inflammatory responses (Figure 3).

Similarity, Coelho et al investigated the role of periostin, an inflammatory protein in pediatric inflammatory bowel disease from Kazakhstani patients. The authors measure plasma level of the protein 144 pediatric IBD patients to identify its role in disease development and progression.

The results showed that plasma periostin levels were significantly elevated during clinical remission compared to active Crohn's disease, suggesting its possible role in the inflammation process as well as potentially in tissue repair and mucosal remodeling [18]. Thus, they concluded that periostin might not only be involved as an inflammation-related biomarker, but also as a candidate marker for repair and remodeling in pediatric IBD.

In a follow up study Mukanova and colleagues which aimed to better understand or explore how periostin interacts with chemokine axis to mediate inflammation process in IBD, suggested that periostin interacts with CCL5–CCR5 signaling axis, a signaling pathway that plays a critical role in regulating immune cell trafficking and inflammation in IBD [19]. The authors compared inflammation between periostin-deficient mouse model with chemically induced colitis to that wild type. The authors claimed that periostin-deficient mice exhibited significantly reduced inflammation, while administration of recombinant periostin exacerbated disease severity, confirming its pro-inflammatory role. In addition, they reported that periostin deficiency animals reduced the recruitment of CCR5-expressing immune cells to the gut mucosa, which is a key component of inflammatory cell infiltration in IBD [19]. To confirm this finding, they reported that the use of CCR5 antagonist, maraviroc inhibited colitis in these models, suggesting that targeting of both periostin and the CCL5–CCR5 axis as a potential therapy target.

3.3. Disease diagnosis

Furthermore, Doszhan and colleagues aimed to evaluate cytokines concentrations and fecal calprotectin during various stages of IBD [20]. They quantified serum IL-6, IL-8, TNF-α, and fecal calprotectin levels across varying

clinical and endoscopic disease phases of 41 Kazakhstani patients with IBD (78% with UC, 22% and with CD). Most patients had chronic relapsing disease with moderate activity, while among CD patients more than half presented with mild disease and the remainder moderate severity based on Crohn's Disease Activity Index (CDAI) [20]. Cytokine levels were significantly elevated above reference ranges. For example, IL-6 averaged 20–25 pg/mL in UC and 18–22 in CD; IL-8 reached more than 80 pg/mL; TNF-α measured nearly 30 pg/mL in UC and 32 pg/mL in CD. There was higher levels of IL-8 in more sever cases compared to moderates, and the higher the inflammatory activity, the greater the concentration of IL-6, IL-8, and TNF-α. Fecal calprotectin was found to correlate with lesion location and inflammatory severity, suggesting that it could be used as a suitable noninvasive disease biomarker. The authors also claimed that the vast majority of patients have no genetic predisposition, further confirming external stimuli.

Laryushina and colleagues investigated the microbiota status and trimethylamine-N-oxide (TMAO) metabolite levels in patients with UC in a study titled "Alterations of the Gut Microbiome and TMAO Levels in Patients with Ulcerative Colitis" [21]. They performed microbiome metagenomic sequencing, measured plasma TMAO levels in 31 patients with UC, and compared to analysis of 15 healthy individuals. Analysis from patients with UC exhibited significant gut dysbiosis, characterized by a marked reduction in beneficial genera such as *Bacteroides*, *Parabacteroides*, and *Prevotella*, along with an increased abundance of *Actinomyces*, *Klebsiella*, *Limosilactobacillus*, *Streptococcus*, and *Escherichia-Shigella*. In comparison to control, patients with UC showed significantly lower TMAO concentration, and levels declined in parallel with increasing clinical and endoscopic disease severity, which suggest that altered microbiome composition and reduced TMAO production correlate with UC severity. The authors concluded that this finding could serve as informative noninvasive biomarkers for Kazakh populations.

The same group, Laryushina and colleagues conducted a follow up observational cross-sectional study titled "Association of TMAO levels with indicators of ulcerative colitis activity" where they evaluated plasma TMAO levels in 63 patients with UC and compared to thirty-eight healthy volunteers [22]. Their aim in the follow up study was to determine the relationship between TMAO concentrations and clinical, laboratory, and endoscopic markers of UC activity. In agreement with their previous finding, they showed that the median TMAO levels were significantly lower in the UC group compared to controls. They also showed that UC patients with clinically active disease had noticeably reduced TMAO compared to patients in remission. Furthermore, the results showed no significant differences in TMAO when grouped by endoscopic lesion extent or activity, which suggest that reduced plasma TMAO may serve as a noninvasive biomarker of UC presence and clinical severity in the Kazakh population.

3.4. Treatment peculiarities

In the retrospective study by Poddighe et al., described the treatment strategy for pediatric patients with UC as closely adhering to international guidelines. The authors mentioned that **t**hiopurine immunomodulators such as azathioprine were also used according to the joint consensus of the European Crohn's and Colitis Organization (ECCO) and European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), particularly for steroid-dependent or refractory patients [15]. However, azathioprine and their active metabolite 6-mercaptopurine (6-MP) were shown to exert both cytotoxic and immunosuppressive effects [23], as well as having several adverse effects, notably hepatotoxicity, pancreatitis, myelosuppression, a potentially life threatening complication [24]. However, a one-year follow- up data demonstrated significant improvements hemoglobin levels at one year, and that histopathological remission was achieved in only 28% of patients [15].

Interestingly, an observational study titled "Real world practice of medical treatment for moderate and severe inflammatory bowel diseases in Russian Federation, Republic of Belarus and Republic of Kazakhstan: intermediate results of the INTENT study" by Knyazev et al., that analyzed the clinical management of moderate to severe IBD across different countries including Kazakhstan [25]. The analysis showed that in Kazakhstan, the use of biologics was relatively limited and delayed, often following prolonged steroid use, which contradicts the ECCO/ESPGHAN recommendations. While the study found discrepancies in the clinical practice of IBD management, they also suggested the potential might be related to genetic variabilities between the involved patients, particularly from Kazakhstan [15,25].

4. Discussion

IBD is a chronic condition of the gastrointestinal tract characterized by inappropriate and sustained immune responses to intestinal microbiota. Although IBD is predominantly reported in Western populations, newly industrialized regions in Asia and Eastern Europe have witnessed an increase in disease burden. Thus, the current systematic review aimed to determine the prevalence of IBD in Kazakhstan as well as to investigate the genetic predisposition, environmental factors as well as treatment modalities for ethnic Kazakhstanis.

Despite the increase in disease prevalence, a major lack of published literature about IBD in Kazakhstan, which stems partly from a historically low prioritization of gastroenterological research within the national scientific agenda, and low integration into international research networks [14,16]. However, the cross sectional study by Kaibullayeva et al appears to one of the very few large-scale investigations into IBD within the Kazakhstan. The study suggested that the prevalence of IBD is nearly 114 per every 100,000 people. These figures are significantly higher than previously reported national estimates of approximately 13.5 average yearly incidence rate for every 100,000 people (95% CI: 9.4–17.5) [26]. The governmental numbers are likely to be based on hospital records, hence the discrepancies in the prevalence, but could also suggest a significant under-diagnosis of IBD in Kazakhstan.

Interestingly, official data from the MoH and research suggest that the disease is prevalent among young people less than 40 years old, and those from urban areas [14,26]. This finding is agreement with other studies from the regions. For example, a study from Japan titled "Trends in the prevalence and incidence of ulcerative colitis in Japan and the US" claimed that the disease is more prevalent among young Japanese people [27]. This could suggest that industrialization related change of diet is quite common among younger individuals, thus the prevalence of IBD is more common among this population. While the characteristics of patients with IBD differ between different countries, there is strong evidence suggest that genetic variability can influence the risk of developing IBD [8].

Genetic studies have revealed notable differences in the susceptibility loci associated with IBD across different populations [28]. While several risk loci such as IL23R and ATG16L1 are shared across populations, their effect often varies [ref], and some key genes such as NOD2 that strongly linked to CD are commonly found in Europeans, but almost absent in Asians [28,29]. This could explain the high prevalence of IBD in Western countries compared to Asians [28]. In addition, studies identified different polymorphisms in disease susceptibility variant genes such as TNFSF15, IL17REL, and HLA-DQA1 to be more prevalent among East Asian cohorts [13].

Despite the low disease susceptibility among Asians, there is an increase in the reported numbers of IBD among this population, which suggest that IBD is shaped by both inherited variation and environmental interaction. The most likely causative factor is the adaption of Western diet that is increasing in popularity in Asia, particularly among the youths. This could not only explain the increase in prevalence, but also the age group of Asian patients with IBD, as suggested by many to be less than 40 year of age [30]. This is also confirmed by the study by Yamazaki et al., which showed that IBD is almost absent among older Japanese people [27], which is also the case in Kazakhstan as confirmed by Kaibullayeva et al., that claimed the disease is common among young Kazakhstanis people, but not the older counterparts [14].

Another concerning point is the clinical management of IBD in Kazakhstan that predominantly relies on immunomodulatory drugs such as azathioprine [15], which is a known drug that causes various side effects including the potentially fatal complication myelosuppression [13].

The drug is metabolized into active and inactive metabolites through complex processes that involves three enzymes, thiopurine S-methyltransferase, hypoxanthine-guanine phospho-ribosyl transferase, and xanthine oxidase that regulate the balance between active and inactive metabolites [31,32]. The activity of thiopurine S-methyltransferase is reduced in Asian patients due to allele polymorphism that can significantly affect the drugs' efficacy and toxicity. For instance, myelosuppression is estimated to occur in 2–7% of European patients [23], but could reach up to half of Asian patients even at doses lower than those in Western countries [33]. Thus, it is important to determine the suitability of Kazakhstani patients in using azathioprine, particularly in those who may carry genetic polymorphisms to reduce the risk of severe myelosuppression.

5. Limitations

This is study aimed to estimate the prevalence of IBD in Kazakhstan while also exploring potential genetic variations related to disease mechanisms and response to treatment. One of the major drawbacks in the

current study is the limited search for English-language publications only, potentially excluding relevant research published in other languages. Another drawback is the lack of published research focusing specifically on the Kazakhstani population. This resulted in the inclusion of various study types and drawing a conclusion from the results of different research settings and designs such as human-based studies, in vivo and in vitro. Despite this, the current review attempted to provide valuable insight into the burden of IBD in the country and highlights key gaps in the current literature.

6. Conclusion

There is a potential variation in the mechanism of disease development and response to drug therapy among different populations. Therefore, optimizing treatment strategies through genetic screening or pharmacogenetic testing might be needed to improve disease management and therapeutic outcomes. The current results warrant further research into the genetic make-up of Kazakhstani people to determine their IBD susceptibility and response to therapy.

Authors contribution

A.J., A.O., K.S., and J.K. performed data extraction, validation, and manuscript editing. G.G., N.N., developed the methodology, performed formal analysis, and drafted the original manuscript, conducted the literature search, curated data, and contributed to validation and manuscript revision. All authors read and approved the final manuscript.

Disclosure statement

The authors declare the absence of any conflict of interest.

Funding

This research is funded by the Program-targeted financing project: Development of innovative technologies and creation of modern infrastructure for sustainable development of the South Kazakhstan region (Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan) (No. BR24992814).

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