

REVIEW

for the PhD thesis of Aliya Ualiyeva

Thesis title: "Epidemiology of inflammatory bowel diseases in the Republic of Kazakhstan"
submitted for the degree of Doctor of Philosophy (Ph.D.) by specialty
6D110200 – "Public Health"

1. Relevance of the research topic

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract that can cause acute symptoms when active but can also lead to complications requiring surgical intervention. Although medical therapy has advanced considerably, responses remain suboptimal. Accordingly, its long-term impact on health-related quality of life and disability can be substantial.

The peak age of onset of IBD is in early adulthood, with substantial consequences for social and professional activity. The incidence and prevalence of IBD are increasing in many regions including Eastern Europe and Asia [Kaplan GG, 2017], which points to a strong environmental influence on its pathogenesis. Understanding the local burden of illness is important to local health planning. Understanding the epidemiology of IBD in regions where it is dynamic may also provide invaluable insight into its cause and identify opportunities for prevention and early intervention.

In Kazakhstan, unlike other regions of the world, systematic studies of the epidemiology of IBD have not been carried out, with no accurate population-based estimates of its incidence and prevalence. There has also been no analysis on its management or the organization of its medical care in Kazakhstan. The work conducted for this thesis fills this gap.

2. Scientific results within the framework of the requirements for the dissertation

This thesis addressed several questions.

- (a) Epidemiology of IBD in Kazakhstan (2015-19): Previous official estimates of incidence and prevalence were 3.5 and 9.9 per 100,000 for Crohn's disease, and 10.4 and 38.7 per 100,000 for ulcerative colitis. Using an approach of active detection, the work for this thesis found the overall prevalence of IBD in Kazakhstan to be 110.8 [95% CI: 91.5-130.1] per 100,000, of which 79.6 [95% CI: 63.2-96.1] per 100,000 are ulcerative colitis and 31.2 [95% CI: 20.7-41.6] per 100,000 are Crohn's disease. This represents a substantial and previously unrecognized burden of illness. The highest incidence and prevalence of Crohn's disease was observed in the city of Nur-Sultan and Atyrau region. The highest. Incidence and prevalence of ulcerative colitis was noted in Atyrau, Pavlodar and East Kazakhstan regions. The highest standardized prevalence of ulcerative colitis was noted in the eastern region of Kazakhstan (108.2 [95% CI: 3.6-212.9] per 100,000). The highest standardized prevalence of Crohn's disease was seen in Almaty (48.7 [95% CI: 0-98.2] per 100,000).

- (b) Factors associated with increased prevalence of IBD: The work for this thesis identified irregular food intake ($p=0.043$; OR=3.61 [95% CI:1.04-12.51]), fish and seafood consumption ($p=0.000$; OR=15.77 [95% CI:4.56-54.59]), consumption of frozen convenience foods ($p=0.018$; OR = 4.62 [95% CI: 1.3-16.4]), consumption of meat ($p=0.029$; OR = 3.2 [95% CI:1.13-9.2]), use of non-ASA NSAIDs ($p=0.031$; OR =3.79 [1.13-12.69]) and smoking ($p = 0.008$; OR= 4.93 [95% CI:1.52-15.98]). In contrast, Kazakh nationality ($p=0.011$; OR=0.18 [95% CI: 0.05-0.68]), milk consumption ($p=0.000$; OR = 0.08 [95% CI: 0, 02-0.31]), alcohol consumption ($p =0.000$; OR=0.04 [95% CI:0.01-0.16]), and childhood viral infections ($p=0.042$; OR=0.52 [95% CI:0.27-0.98]) were protective. For ulcerative colitis, a family history of IBD ($p=0.022$; OR=13.25 [1.46-120.52]) increased the likelihood of having IBD, while appendectomy ($p=0.005$; OR = 0.11 [0.02 -0.51]) and use of oral contraceptives ($p=0.005$; OR=0.11 [0.02-0.51]) were protective. Kazakh nationality and milk consumption were protective for Crohn's disease. No statistically significant associations were found between IBD and childhood antibiotics, breastfeeding, or allergy.
- (c) Challenges in healthcare delivery for IBD: The work for this thesis identified barriers to management of IBD in Kazakhstan that included no free-of-charge access to fecal calprotectin testing, MR enterography, enteroscopy, cytomegalovirus PCR, or Clostridium difficile testing. In addition, therapies such as azathioprine are not registered in Kazakhstan. There is no registry of patients with IBD to inform its disease burden, to guide procurement of medications and other health supplies, or to estimate requirements for medical insurance
- (d) IBD-related knowledge: The work undertaken for this thesis found that there is poor patient adherence to therapy due to a lack of knowledge about IBD and a lack of psychological support. The knowledge of doctors and nurses about management of IBD patients is also insufficient, with low motivation for training.

It appears that the results obtained through this scientific research meet the requirements for PhD theses and the scientific specialty 6D110200 - Public Health.

3. The degree of validity and reliability of each result (scientific position), conclusion formulated in the dissertation

The scientific work used several research designs, including a cross-sectional survey, a case-control study, and qualitative methods.

The cross-sectional study was carried out among subjects of both sexes aged 18 years and older using IBD Alert Questionnaire (CalproQuest) from January 1 to December 31, 2017, across regions of Kazakhstan. This instrument IBD Alert Questionnaire has been tested and found to be feasible for use in primary care. The questionnaires were distributed both electronically and in hard copy. Participants with positive survey results underwent fecal calprotectin testing. If this was also abnormal, further investigation including endoscopy was arranged.

The case-control study was undertaken by survey to identify environmental factors associated with IBD in Kazakhstan. Both cases and controls were over 18 years old. Cases were individuals with a confirmed diagnosis of ulcerative colitis or Crohn's disease. Controls with no IBD diagnosis were recruited by the continuous method from patients of the Research Institute of Cardiology and Internal Medicine with oral informed consent. Of 81 questionnaires distributed, 65 were returned and completely correctly for a response rate of 81.2%. The ratio cases to controls was 1:2.7.

The qualitative study of medical care for patients with IBD was carried out in 3 stages. First, a content analysis of printed resources and internet resources in Kazakhstan helped to identify problems encountered by patients with IBD while receiving medical care. Second, a focus group was conducted among gastroenterologists to identify the problems of diagnosing and treating IBD (for both patients and doctors) and to develop proposals to improve the effectiveness of IBD care. Third, a focus group was conducted among primary care physicians to identify problems in the diagnosis and treatment of IBD in the ambulatory setting.

The study received permission from the Ethics Committee of the Kazakhstan School of Public Health. The thesis contains tables and figures that communicate results well. Survey methods are well described. Appropriate steps were taken to maintain confidentiality, anonymity and voluntary participation. Analytic methods are robust.

4. The degree of novelty of each scientific result (position), conclusion formulated in the dissertation

This work is clearly novel, in that it represents the first cross-sectional attempt to define the epidemiology of IBD in Kazakhstan, risk factors for development of IBD in Kazakhstan, and the challenges with delivery of IBD care in Kazakhstan. These data are useful to an international audience, as the dynamic epidemiology of IBD in Kazakhstan may help to provide insight into its environmental determinants.

5. Assessment of the internal unity of the results obtained

The research methods are well-described and the data are summarized clearly. Accordingly, the internal validity of the work undertaken is strong.

6. The focus of the results obtained by the applicant on the solution of the relevant topical problem, theoretical and applied problem

The results address problems identified by their authors: a lack of reliable data on the epidemiology of IBD in Kazakhstan; a lack of data to inform the distribution IBD-related health resources; and a lack of structure care for IBD in Kazakhstan

7. Confirmation of sufficient completeness of publications of the main provisions, results, conclusions, and conclusions of the dissertation

The epidemiology findings of this thesis have been published in a peer-reviewed journal (Kaibullayeva J, et al. Intest Res 2020;430-7). I understand that three additional articles have been published in journals recommended by the Committee for Control in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan. Three abstracts related to this work were presented at international conferences.

8. Disadvantages in the content and design of the thesis

The work undertaken for this thesis is impressive and substantive. However, some limitations should be acknowledged:

- (a) The cross-sectional survey was widely distributed, but not to a true population-based sample. The survey sample may not be representative of the overall Kazakhstan population. There may be further participation bias among survey respondents. The survey sample was also limited to subjects 18 years of age and younger, and hence does not address the epidemiology of IBD in children.
- (b) Although the algorithm for identifying IBD among participants was robust, the sensitivities of the IBD Alert Questionnaire, the one-time fecal calprotectin assay, and the subsequent diagnostic workup are not perfect. Accordingly, cases of IBD may have been missed. Without standardized use of small bowel radiography, isolated small bowel Crohn's disease may not have been detected. Thus, the calculated prevalence of IBD in the sample may be an underestimate.
- (c) The authors noted a numerically higher prevalence of both UC and CD in urban areas. However, it is unclear whether this represents a true difference in prevalence or differences in healthcare access or socioeconomic status. A more detailed analysis of this difference would be helpful.

In conclusion, despite several limitations, this study has clinical significance because it is the first formal scientific report on the prevalence and characteristics of IBD in Central Asia. It also helps to enhance awareness of IBD in this region. This and other studies on the evolving incidence of and risk factors for IBD in increasingly industrialized and urbanized societies are expected to provide novel insights into the etiopathogenesis of IBD. The above comments and suggestions are not of a fundamental nature and do not detract from the merits of the dissertation work.

9. Conclusion

Dissertation work by Aliya Ualiyeva on the topic "Epidemiology of inflammatory bowel diseases in the Republic of Kazakhstan", submitted for the degree of Doctor of Philosophy (Ph.D.) in the specialty 6D110200 - Public Health, is a complete independent scientific work that has applied



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value in informing and improving the organization of care for patients with IBD in Kazakhstan. Considering the relevance of the dissertation research, its scientific novelty, and the practical significance of the results obtained, I believe that the presented dissertation work meets the requirements for dissertations for the degree of Doctor of Philosophy.

Yours Sincerely,

A handwritten signature in black ink, appearing to read "J. K. Marshall".

John K. Marshall MD MSc FRCPC AGAF
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Professor, Department of Medicine
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