Evidence-Based Practice Group
Answers to Clinical Questions

Causal Association Between Irritable Bowel Syndrome (IBS) and COVID-19

A Rapid Systematic Review

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WorkSafeBC

About this report

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Objectives

- The Evidence-Based Practice Group (EBPG) was asked to investigate whether there is any evidence on the (causal) association between development of irritable bowel syndrome (IBS) post covid-19 infection.

Methods

- A comprehensive and systematic literature search was conducted on January 26, 2024.
- The search was done on commercial medical literature databases, including Cochrane Database of Systematic Reviews (2005 to January 24, 2024), ACP Journal Club (1991 to January 2024), Cochrane Clinical Answers (January 2024), Cochrane Central Register of Controlled Trials (December 2023), Embase (1974 to 2024 Week 03), Ovid Medline and Medline Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Medline Daily and Medline (1946 to January 25, 2024), Joanna Briggs Institute of Evidence Based Practice Database (Current to January 17, 2024), that are available through Ovid platform.
- Combination of keywords were employed in this literature search.
- In order to identify articles on long covid, we employed keywords developed by the Canadian Agency for Drugs and Technology in Health (CADTH) as it was published in their paper entitled "CADTH Literature Search Strategy. Post-COVID-19 Condition Treatment and Management Rapid Scoping Review" and can be downloaded from https://www.cadth.ca/post-covid-19-condition-treatment-and-management-rapid-living-scoping-review (downloaded in January 3, 2024).
- The full combination of keywords employed in this search were as followed:

1. (COVID-19 Syndrome, Post-Acute) **OR** (Post Acute COVID 19 Syndrome) **OR** (Post-Acute COVID-19 Syndromes) **OR** (Long-Haul COVID) **OR** (COVID, Long-Haul) **OR** (Long Haul COVID).
2. (Long-Haul COVIDs) **OR** (Long Haul COVID-19) **OR** (COVID-19, Long Haul) **OR** (Long Haul COVID 19) **OR** (Long Haul COVID-19s) **OR** (Post-Acute Sequelae of COVID-19).
3. (COVID-19 Post-Acute Sequelae) **OR** (Post Acute Sequelae of COVID 19) **OR** (Post-Acute Sequelae of SARS-CoV-2 Infection) **OR** (Post Acute Sequelae of SARS CoV 2 Infection).
4. (Post-COVID Conditions) **OR** (Post COVID Conditions) **OR** (Post-COVID Condition) **OR** (Long COVID) **OR** (PASC Post Acute Sequelae of COVID-19).
5. (PASC Post Acute Sequelae of COVID 19) **OR** (Post Acute COVID-19 Syndrome).
6. (long COVID*) **OR** (long coronavirus*) **OR** longCOVID* **OR** longcoronavirus*.
7. (sequela* **ADJ5** (COVID* **OR** coronavirus* **OR** (corona virus*) **OR** SARS-COV-2 **OR** SARS-COV2 **OR** SARSCOV-2 **OR** SARSCOV2)).
8. ((post **OR** chronic **OR** (long term) **OR** longterm) **ADJ3** (COVID* **OR** coronavirus* **OR** (corona virus*) **OR** SARS-COV-2 **OR** SARS-COV2 **OR** SARSCOV-2 **OR** SARSCOV2) **ADJ4** (condition* **OR** sequela* **OR** syndrome* **OR** subsyndrome* **OR** (clinical syndrome*) **OR** disorder* **OR** symptom* **OR** outcome* **OR** (clinical outcome*) **OR** function* **OR** followup **OR** follow-up **OR** subtyp* **OR** sub-typ* **OR** phenotyp* **OR** complication* **OR** survivor*)).
9. ((post acute) **OR** postacute **OR** (late complication*) **ADJ3** (COVID* **OR** coronavirus* **OR** (corona virus*) **OR** SARS-COV-2 **OR** SARS-COV2 **OR** SARSCOV-2 **OR** SARSCOV2)).
10. (post-COVID* **ADJ** fatigue).
11. PASC.

12. 1 **OR** 2 **OR** 3 **OR** 4 **OR** 5 **OR** 6 **OR** 7 **OR** 8 **OR** 9 **OR** 10 **OR** 11.
13. (irritable **ADJ** bowel **ADJ** syndrome*).
14. #12 **AND** #13.

- No limitation, such as on the language or country of publication, was implemented in the literature search. It should be noted though that due to the topic of this systematic review was on Covid-19, the literature was "self-selected" to those published ≥ 2019.
- Manual search was done on the references of the articles that were retrieved in full.

Results

- Search results:
  - Forty-eight([1-48]) published studies were identified from search #14. Upon examination on the titles and abstracts of these 48([1-48]) studies, 25([4,5,11-13,15,17,18,20-25,30-32,34,35,37,39,41,42,44,45]) studies were thought to be relevant and were retrieved in full for further appraisal.
  - Five([48-52]) published studies were identified from manual searches. As such, overall, 30([4,5,11-13,15,17,18,20-25,30-32,34,35,37,39,41,42,44,45,48-52]) studies were retrieved in full for further appraisal in this systematic review.
  - Of the 30([4,5,11-13,15,17,18,20-25,30-32,34,35,37,39,41,42,44,45,48-52]) studies that were retrieved in full, 21([4,11,12,13,15,18,20,22,24,25,31,32,34,35,37,39,41,42,44,48,52]) studies did not provide relevant data/traced for the relevant primary studies/duplicitous publication of the same data/not relevant to the objective of this systematic review and will not be discussed further.
  - Hence, the results of nine([5,17,21,23,30,45,49-51]) studies providing relevant data are summarized below.
- A small (n=49) case series (level of evidence 4. Appendix 1), by Austhof[(5)] et al, reported on the development of post-infectious irritable bowel syndrome (PI-IBS) among participants enrolled in Arizona resident CoVHORT, a public health surveillance program interviewing participants following SARS-CoV-2 infection. Of the 1475 PCR conformed positive Covid-19, 499 (33.8%) had acute gastrointestinal (GI) symptoms while 976 (66.2%) did not have any. The authors followed those 499 with acute GI symptoms on which only 49 (9.8%) completed Rome IV survey for diagnosing post-infection (PI) IBS. Of the 49 participants who completed the Rome IV survey, 10 (20.4%) had persistent abdominal symptoms consistent with IBS with an onset less than 6 months, and 5 (10.2%) met the Rome IV diagnosis for PI-IBS. This resulted in an incidence of 3.0% for those with GI symptoms during acute infection. In this population, overall, PI-IBS was reported on average 6.2 months (175 days, S.D.: 61.6) from acute infection. *It should strongly be noted that in their analysis, the authors showed potential selection bias among those completed and these that did not complete the Rome IV questionnaire. Further, there was no attempt to exclude potential differential diagnosis of those with similar symptoms of IBS[(52)] in this study. Statistically, the authors also conducted multiple statistical tests without adjusting for type I error level (although this may not affect the incidence of PI-IBS).*
- A small (n=116) cross sectional study (level of evidence 4. Appendix 1), by Elmunzer et al[(17)], examined the long-term GI impact of hospitalization with COVID-19. The original study cohort comprised 1992 patients hospitalized with COVID-19 across 36 centers in the United States and Canada. However, this ancillary survey study was conducted at 18 of the 36 centers in the original cohort analysis, 12-18 months after hospitalization. At these 18 centers, 530 survivors of the 1097 hospitalized patients were invited to participate. Of these 530 survivors, 132 (24.9%) consented and 116 (87.9%) completed the survey. In this follow-up survey, based on participants' responses to the Rome IV

Diagnostic Questionnaire, 12.1% were diagnosed with IBS. The authors posted that the US population prevalence of IBS was 5.3% and concluded that the prevalence of IBS in this sample was statistically significantly higher than the US population prevalence. *It should strongly be noted that potential selection bias, based on the differences between those consented and not consented for follow-up, is strongly suspected. It should also be noted that there was no effort to conform the diagnosis of IBS by eliminating other diagnoses[52], while at the same time it is not clear whether the characteristics of this patient population was the same with the US population employed as a comparative group.*

- A small-medium size (280 cases with 264 controls) case-control (level of evidence 3. Appendix 1), reporting on the frequency and spectrum of post-infection-functional gastrointestinal disorders (PI-FGID) among hospitalized COVID-19 and historical healthy controls, matched for age and gender, and the risk factors for its development, was conducted by Ghoshal et al[21]. By employing Rome III criteria for the FGID diagnosis, telephone follow, at 1, 3 and 6 months were conducted. At 6-month follow-up, 15 (5.3%) of the 280 COVID-19 patients developed IBS while one (0.4%) of the 264 controls developed IBS using Rome III criteria ($p<0.05$). *It should strongly be noted that, with the exception on the matching variables, potentially there was an imbalance in the baseline characteristics between cases and controls that was not controlled for in the statistical tests. Further, it was not clear how cases and controls were selected and multiple comparisons were not taken into account. Further, there was no attempt to exclude differential diagnosis of IBS[52].*
- A small-medium size (cases=320 post-discharged Covid-19 hospitalized patients and two types of control groups (n=320 of age matched spouses/family members with no history of Covid-19 of the case group sharing the same dietary and environmental factors and n=280 of COVID serology negative healthcare workers at the same hospital with the cases) case-control study (level of evidence 3. Appendix 1) investigating the frequency and risk factors of post-infectious functional gastrointestinal disorders in a New Delhi hospital was reported by Golla et al[23]. The authors reported that at 1 month, 36 among the 320 cases (11.3%) developed functional gastrointestinal disorders (FGID) like symptoms. At 3 months, 27 (8.4%) persisted to have symptoms, and 9 improved. At 6 months, another 6 improved, and 21 (6.6%) had persistent symptoms. No new patients in the case group developed symptoms on follow-up. Of the various reported FGID as per Rome IV questionnaire at 3 months, 8 (2.5%) had IBS. None of the healthy controls developed FGID up to 6 months of follow-up ($P < .01$). *It should be noted that multiple comparisons, potential selection bias, absence of differential diagnostics elimination[52] for IBS (and other FGIDs) may affect the reported outcome. It should also be noted that there was no 6-month follow-up data on IBS presented.*
- A small-medium size (n=623) multicenter cohort study (level of evidence 3. Appendix 1) investigating the prevalence of gastrointestinal symptoms and post-COVID- 19 disorders of gut–brain interaction after hospitalization for SARS-CoV-2 infection in Bologna, Italy, was reported by Marasco et al[30]. In this cohort study, hospitalized patients, with or without COVID-19, were prospectively and consecutively enrolled on hospital admission, and followed up with symptom reassessment at 1, 6 and 12 months Of the 2183 patients recruited during the study period, only 883 (40.4%) patients (614 with Covid-19 and 269 without (as controls)) were included in the baseline analysis due to exclusion and incomplete/loss to follow-up of data. Further, follow-up evaluations were completed by 772 (87.4%) patients (548 covid-19 (+) and 224 covid-19 (-)) at 6 months and only 623 (70.6%) patients (435 with covid-19 and 188 without) completed the 12 months follow-up. At 6 months follow-up, two (0.9%) of Covid-19 (-) and three (0.6%) of Covid-19 (+) group developed irritable bowel syndrome (IBS) (per Rome IV criteria) ($p=0.59$); further, at 12 months follow-up, one (0.3%) of Covid-19 (-) and fourteen (3.2%) of

Covid-19 (+) group developed IBS (p=0.045). *It should be noted that potential selection bias affecting the observed outcomes exists due to included patients in the analysis as well as due to unclear patient selection. That this study also performed multiple comparisons without adjusting to their level of type I error; that there was no effort to investigate differential diagnosis associated with IBS and that there was no assessment on the impact of potential confounders, may all affect the reported outcomes.*

- A small (n=303) cross sectional study (level of evidence 4. Appendix 1) of hospitalized patients, in Karachi Pakistan, without prior history of irritable bowel syndrome (IBS), prospectively followed their discharge and were evaluated as per Rome-IV criteria for IBS, was reported by Siyal et al[45]. One hundred seventy-eight patients were males (58.7%) and the age range was 17–95 years (mean ± SD, 55.9 ± 15.8). Patients were prospectively followed post discharge in the primary care outpatient department and those patients having IBS-like symptoms were asked to follow-up in the gastrointestinal clinics at 1, 3, and 6 months. A total of 67 patients followed up in the gastrointestinal outpatient clinics with IBS-like symptoms. 61 patients had GI symptoms imitating IBS at 1 month follow-up, out of which 12 patients reported resolution of these symptoms during their visit at 3 months. Seventeen patients experienced alleviation of IBS-like symptoms before coming for 6 months outpatient department visit. On follow-up at 6 months, 32 (10.6%) patients fulfilled the Rome-IV criteria for IBS. *It should be noted that this study attempted to exclude potential differential diagnosis of IBS; however, potential selection bias as well as potential unadjusted effect of multiple comparisons cannot be excluded for in the reported outcome. Further, no data was provided on the background prevalence of IBS in this population.*
- A very large (n=154,068 Covid-19 cases), large administrative database based, investigating the risk and burden of a set of pre-specified, including on IBS, incident gastrointestinal outcomes, was reported by Xu et al[49]. The authors employed the US Department of Veterans Affairs national health care databases to build a cohort of 154,068 people who survived the first 30 days of Covid-19 with two control groups including a contemporary control of 5,638,795 who lived during the same time but had no evidence of SARS-CoV-2 infection, and a historical cohort of 5,859,621 people from the pre-pandemic era (level of evidence 3. Appendix 1). These cohorts were followed longitudinally to estimate the risks and 1-year burdens of a set of pre-specified incident gastrointestinal outcomes, including IBS, in the overall cohort and by care setting of the acute phase (whether people were non-hospitalized, hospitalized, or admitted to intensive care) of SARS-CoV-2 infection. In this study, the Covid-19, contemporary control, and historical control groups had a median follow up of 408 (interquartile range: 378–500), 409 (379–505), and 409 (379–504) days. With regard to IBS, the authors reported that, at 12 months follow-up, patients who survived the first 30 days of Covid-19 exhibited an increased risk of IBS among those hospitalized (hazard ratio (HR): 3.2; 95% CI:2.2- 4.6; burden (per 1000 person): 2.7, 95% CI: 1.9-3.8) or admitted to intensive care (HR: 5.9; 95% CI:2.9-11.9; burden 4.9, 95% CI: 2.4-9.9) and NOT among non-hospitalized (HR: 1.2; 95% CI:0.9-1.5; burden 1.0, 95% CI: 0.8-1.2). *It should strongly be noted that although this study showed a potentially positive association between hospitalized Covid-19 patient and higher risk of developing IBS at 12 months, this evidence coming from this study perhaps need to be interpreted as a hypothesis generating study only since these studies lack of hypothesis setting to guide its process in a study with such a large sample size it is theoretically possible to conduct and to prove many statistical significant testing which may be invalid. This study did conduct and reported many statistical tests; this practice triggered multiple comparison problems in which type I error levels need to be adjusted based on the number of statistical tests performed. However, given the size of the sample it is potentially possible to still detect statistical significance with the adjusted type I error level. This*

study employed an administrative database as their source of primary data. This kind of database usually lack a number of variables that may be relevant to the study such as the availability of potential confounders. Further, there was no attempt to report exclusions on differential diagnosis of the IBS while it was also not clear which criteria were employed in diagnosing IBS.

- A small-medium size (n=571) cross sectional study (level of evidence 4. Appendix 1), investigating the potential risk factors for subsequent development of irritable bowel syndrome (IBS) among SARS-CoV-2 polymerase chain reaction (PCR) conformed patients admitted to a university hospital in Tokyo, was reported by Yamamoto et al[50]. Utilizing the data available from the hospital information system, the authors identified all patients admitted due to Covid-19 from January 2020 to October 2021. 571 patients were eligible for this study and among them, 12 (2.1%) patients were diagnosed with IBS (Rome IV criteria) following recovery from Covid-19 with the median duration from admission to IBS diagnosis of 5 months. *It should be noted that there was no data on the background prevalence of IBS in this population; hence it is not possible to investigate the impact of Covid-19 infection to the development of IBS. It should also be noted that there was no attempt to exclude potential differential diagnosis of IBS while the nature of the data source (c.q. administrative database as opposed to data specifically collected to prove certain hypothesis) limited the potential investigation on the impact of confounders. Further, although it may not relate to the objective of our systematic review and this primary study reported many statistical tests without adjusting to the level of type I error.*
- A small (n total=350) case control study (level of evidence 3. Appendix 1), investigating the frequency, disease spectrum and risk factors for post-infection functional gastrointestinal disease (PI-FGID) in Covid-19 patients and healthy controls from a hospital in China, was reported by Zhang et al(51). Between July 2022 and February 2023, adult patients, with PCR positive for SARS-CoV-2 and admitted to a hospital in Hainan province, China, were recruited and, at the same time, patients with Covid-19 serology negative were also recruited as potential healthy controls. Participants were then followed up either as outpatients or over the telephone at 1, 3, and 6 months using the validated Rome III and Rome IV questionnaire. Initially, 194 patients in each group were recruited but due to incomplete questionnaires or loss to follow-up, final analysis was done on 190 cases and 160 controls. With regard to IBS (Rome III criteria), the authors reported that, at 6 months follow-up, seven (3.7%) patients among Covid-19 cases and two (1.3%) of controls developed IBS (p=0.19). It should be noted that with regard to IBS, the authors attempted to exclude other diagnoses of IBS through numerous physical, laboratory and imaging exams. However, it should also be noted to the fact of multiple comparisons, unclear participant selection and potential for selection bias due to incomplete data and loss to follow-up, this data and conclusions may not be valid.

Summary

- At present, there is some, low level and low-quality evidence, on the association of post Covid-19 infection and the development of IBS. Although some of these primary studies may show evidence on temporality, other criteria to provide causal association, such as on the size of the association and consistency of the association, may not yet be fulfilled with the available data. It should also be noted that the low-quality status of the primary studies included in this systematic review may not be able to exclude bias, chance and confounding, and may affect the reported outcome of interest.

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Appendix 1

WorkSafeBC — Evidence-Based Practice Group levels of evidence (adapted from 1-6)

1	Experimental, randomized controlled trial (RCT), systematic review RTCs with or without meta-analysis.
2	Evidence from controlled trials without randomization (quasi-experimental studies) or systematic reviews of observational studies.
3	Evidence from cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees based on scientific evidence.

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