Association of digestive symptoms with severity and mortality of COVID-19: a protocol for systematic review and meta-analysis

Zhang, Y¹; Ma, P²; Zhang, X³; Pei, Z⁴; Wang, H⁵; Dou, X⁶.

**Review question / Objective:** To assess whether digestive symptoms are associated with COVID-19 severity and mortality.

**Condition being studied:** Gastrointestinal manifestations are common in patients with COVID-19, but the association between specific digestive symptoms and COVID-19 prognosis remains unclear. This study aimed to assess whether digestive symptoms are associated with COVID-19 severity and mortality.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 September 2020 and was last updated on 13 September 2020 (registration number INPLASY202090055).

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**Corresponding author:** Xinman Dou

**3441828719@qq.com**

**Author Affiliation:** Department of Nursing, Lanzhou University Second Hospital, Lanzhou, China

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**Review Stage at time of this submission:** Preliminary searches.

**Conflicts of interest:** None.
study aimed to assess whether digestive symptoms are associated with COVID-19 severity and mortality.

METHODS

Participant or population: Patients diagnosed with COVID-19 by a laboratory test.

Intervention: The prevalence of digestive symptoms in infected patients with severe illness, or non-survivors.

Comparator: Patients with non-severe illness or survivors.

Study designs to be included: Clinical studies comparing ≥ 20 COVID-19 patients with severe or non-severe disease, or non-survivors and survivors, and presenting non-overlapping data.

Eligibility criteria: Our meta-analysis will include clinical studies that met the following criteria: (1) patients should be diagnosed with COVID-19 by a laboratory test; (2) provided the prevalence of at least one specific digestive symptom in infected patients; (3) compared patients with the severe or non-severe disease or between non-survivors and survivors; (4) written in English or Chinese; (5) with a sample size of larger than 20 patients. We will exclude studies with following characteristics: (1) did not provide the prevalence of digestive symptoms; (2) only provided the overall prevalence of digestive symptoms without a detailed digestive symptom; (3) without comparisons (e.g. non-survivors versus survivors); (4) involved suspected cases; (5) reviews, abstracts, and editorials.


Main outcome(s): The association between digestive symptoms and the severity of COVID-19.

Additional outcome(s): The association between digestive symptoms and mortality in COVID-19 patients.

Data management: We will develop a standardized data extraction form using Microsoft Excel 2016 (Microsoft Corp, Redmond, WA, http://www.microsoft.com) through discussions with the review team and will revise the content after piloting on a random of five studies. We will extract the following information from included studies: first author, country of the first author, journal name, year of publication, publication language, study setting, recruitment time frame, age and sex of patients, sample size; prevalence of digestive symptoms, including diarrhea, nausea, vomiting, anorexia, abdominal pain, bloating, and constipation; number of sever cases, non-severe cases, non-survivors, and survivors.

Quality assessment / Risk of bias analysis: The Newcastle-Ottawa quality assessment scale (NOS) will be used to assess the quality of included studies [15]. We will consider studies with more than 7 stars as high quality, 5-7 stars as moderate quality, and lower than 5 stars as low quality. Two independent reviewers (YFZ, PFM, XZ, or ZXP) will conduct data extraction and quality assessment and a third reviewer checked the data (HXW). Discrepancies were resolved by consensus or by the discussion with a third reviewer (XMD).

Strategy of data synthesis: We will perform meta-analyses to calculate the odds ratio.
(OR) and 95% confidence interval (CI) to estimate the association between digestive symptoms and COVID-19 severity and mortality using the inverse variance method. Owing to heterogeneity within and between studies, meta-analyses will be conducted using the random-effects model. The Cochran's Q test and I² statistic will be used to assess the statistical heterogeneity, I² values of 50% will be considered as low, moderate, and high degrees of heterogeneity, respectively. If substantial heterogeneity was identified among studies, we will conduct subgroup analyses, sensitivity analyses, and meta-regression analyses to explore the sources of heterogeneity. All statistical analyses will be performed with Stata (13.0; Stata Corporation, College Station, Texas, USA Stata) and the statistical level of significance was set at \( P < 0.05 \).

**Subgroup analysis:** Subgroup analyses will be conducted for outcomes between different countries to explore the potential sources of heterogeneity. We will further perform univariate meta-regression analyses to assess if either the outcomes or the heterogeneity is associated with the sample size of studies included.

**Sensibility analysis:** Sensitivity analyses will be conducted by excluding studies published in Chinese or studies with high risk of bias to assess the stability of results.

**Country(ies) involved:** China.

**Keywords:** COVID-19; SARS-CoV-2; Gastrointestinal symptoms; Severity; Mortality; Meta-analysis.

**Contributions of each author:**
Author 1 - Yufang Zhang.
Author 2 - Peifen Ma.
Author 3 - Xiu Zhang.
Author 4 - Zhuoxi Pei.
Author 5 - Haixia Wang.
Author 6 - Xinman Dou.