INPLASY PROTOCOL

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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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None.

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

Zhang, Y[1]; Ma, P[2]; Zhang, X[3]; Pei, Z[4]; Wang, H[6]; Dou, X[6].

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).

INTRODUCTION

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

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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.

Information sources: We will search PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify clinical studies. The following search terms will be used: "coronavirus disease-19", "coronavirus disease 2019", "COVID-19", "2019-nCoV", "novel corona virus", "novel coronavirus", "new coronavirus", "nCoV-2019", "novel coronavirus pneumonia", "2019 novel coronavirus", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "clinical characteristic", "clinical feature", "risk factor", "prognosis", "nausea", "vomiting", "diarrhea", "digestive symptom", and "gastrointestinal symptom". The searches will be conducted in September 2020. We will also manually search reference lists of eligible studies and relevant systematic reviews to identify additional potentially eligible studies.

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.