Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19: Precision Medicine and Vascular Endothelium

To The Editor: We read with care and interest the original article from Pereira et al on the development of a precision medicine approach to the COVID-19 pandemic.[1] We appreciate very much the specialist explanation about the demographic (such as age, race, ethnicity, sex) and biological variables (such as angiotensin converting enzyme 2 expression, immune regulation, body mass index, and genetics) that may characterize the high-risk patient and can serve for optimizing hospitalization, vaccination and targeted drug therapy.

However, "predictive algorithms may help in individualizing targeted therapy including hospitalization and assist in the logistics of vaccine administration" only if all key factors are included. In our opinion, it is of paramount importance to introduce the vascular endothelium into the discussion.[2] In fact, endothelial damage to various organs was highlighted by autopsy outcomes,[3] and severe SARS-CoV-2 infection could have a more complete and significant interpretation evaluating integrity of endothelial glycocalyx.[4]

In conclusion, the recognition of the whole COVID-19 host/genetic factors that contribute to COVID-19 susceptibility and subsequent pathogenesis advocates the use of precision medicine in better designing clinical trials and in treatment of the disease.[5]

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In reply—COVID-19: Precision Medicine and Vascular Endothelium

To The Editor: We appreciate the kind comments provided by Travagli et al regarding our article on interindividual variability[1] and fully agree with their statement that recognition of coronavirus disease 2019 (COVID-19) host/genetic factors should inform the design of precision clinical trials in this disease. We also acknowledge that inflammatory changes in the vascular endothelium are an important component of the response to COVID-19 infection. However, the studies cited by the authors do not provide evidence of interindividual variability in these processes (small vessel endotheliitis, vascular endothelial glycocalyx levels, or neutrophil extracellular trap formation and/or dysregulation) that could contribute to the variability observed in COVID-19 susceptibility, severity, and outcome. The question also arises whether the endothelial changes that occur in COVID-19 are a downstream change to variability observed in upstream processes that involve angiotensin-converting enzyme 2, transmembrane serine protease 2, toll-like receptors, and other factors as described in our article. We do look forward to future agnostic multi-omic (proteomic, transcriptomic, and metabolomic) studies that could explore the role of such pathways and find their association, or lack thereof, with interindividual variation in COVID-19.

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Lack of Marked Association Between Gastrointestinal Symptoms and COVID-19 Mortality: An Updated Meta-analysis Based on Adjusted Effect Estimates

To the Editor: Recently, a meta-analysis by Tariq et al has reported

TABLE. Characteristics of the Included Studies[a,b,c]

Author	Country	No. of cases	Age (y)	Male	Study design	Outcomes	Adjusted effect estimate (95% CI)	Confounders
Yan X	China	1004	60.98±14.97	493 (49.1)	R	Mortality	OR 39.463 (3.851-404.357)	NLR >11.75, hs-CRP, BUN, hypertension, respiratory failure, NT-proBNP, cerebrovascular disease
Magleby R	United States	678	67.05±16.65	414 (61.1)	R	Mortality	OR 0.5 (0.21-1.19)	Age, race, CAD, CHF, cerebrovascular disease, hypertension, COPD, days of symptoms before admission, symptoms on admission (fever, cough, headache, myalgias, altered mental status, aguesia), oxygen by nasal cannula, oxygen by a non-rebreather mask, high-flow nasal cannula or noninvasive mechanical ventilation, mechanical ventilation, Chest radiography findings (unilateral infiltrates, bilateral infiltrates), viral load by nasal pharyngeal swab (medium viral load [Ct, 25-30], high viral load [Ct, <25])
Zhang L	China	409	65 (56-71)	234 (57.2)	R	Death	OR 1.547 (1.029-2.325)	Neutrophil count, lymphocyte count
Knopp P	United Kingdom	217	80±6.8	134 (62)	P	Mortality	HR 0.45 (0.11-1.91)	Age, sex, CFS, cough, fever, dyspnea, imaging abnormalities, falls, reduced mobility, delirium, CRP, NLR
Russell B	United Kingdom	156	65.18±14.80	90 (57.70)	A	Death	HR 1.44 (0.64-3.26)	Age, sex, SES, ethnicity, number of comorbidities, smoking history, cancer type, treatment paradigm, time since cancer diagnosis, performance status, symptoms (cough, fever, dyspnea), time between first symptom and diagnosis, CRP, lymphocytes, albumin
Ioannou GN	United States	10,131	63.6±16.2	9221 (91.0)	A	Mortality	HR 1.02 (0.77-1.35)	Age, sex, race, ethnicity, COVID-19–related deaths per million residents, urban vs rural, BMI at index date, diabetes, cancer, hypertension, CAD, CHF, cerebrovascular disease, dialysis, CKD, cirrhosis, asthma, COPD, obstructive sleep apnea, obesity hypoventilation, alcohol dependence, hyperlipidemia, smoking, Charlson Comorbidity Index score, fever, cold, chills, myalgia, fatigue, cough, dyspnea, sore throat, nausea, abdominal pain, headache

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TABLE. Continued

Author	Country	No. of cases	Age (y)	Male	Study design	Outcomes	Adjusted effect estimate (95% CI)	Confounders
de Azambuja E	Belgium	13,594	68.29±16.81	6584 (48.4)	R	Mortality	OR 1.44 (0.93-2.24)	Age, sex, number of comorbidities, comorbidities (CVD, hypertension, diabetes, CKD, CLD, chronic lung disease, chronic neurological disease, cognitive disorder, immunosuppression including HIV), smoking history (noncurrent smoker, current smoker), timing of symptoms onset (before or at the day of admission, during hospitalization), symptoms at diagnosis (systemic symptoms, respiratory symptoms, neurological symptoms), number of symptoms at diagnosis, signs at diagnosis (temperature <38°C, temperature ≥38°C, respiratory signs, neurological signs), number of signs at diagnosis, evolution during hospitalization (pneumonia at imaging examination, ARDS), treatment during hospitalization (hydroxychloroquine, azithromycin, corticosteroids, specific treatment of COVID-19, no treatment reported)
Rozaliyani A	Indonesia	4052	45.8±16.3	2169 (53.5)	R	Death	OR 0.79 (0.52-1.21)	Age, sex, registered address, symptoms (cough, fever, malaise, dyspnea, headache, sore throat, chills, pneumonia), comorbidity (hypertension, diabetes, heart disease, renal disease, immunological disorder)
Aksel G	Turkey	168	59.5 (48.3-76)	90 (53.6)	P	Mortality	HR 0.97 (0.19-4.91)	Age, dyspnea, presence of any comorbid disease, pulse O_2 saturation, WBC, CRP
Abayomi A	Nigeria	2175	43.0±16.0	1436 (65.8)	R	Death	OR 1.12 (0.31-4.02)	Fever, cough, weakness, loss of appetite, headache, difficulty in breathing, throat irritation, loss of taste/smell, other symptoms
Raines AM	United States	440	60.76±13.82	393 (89.3)	R	Death	OR 0.81 (0.47-1.39)	Age, sex, race, BMI, immunodeficiency syndromes, pulmonary diseases, oncological diseases, renal diseases, hematologic diseases, endocrine diseases, CVD, neurological problems, lifetime tobacco user

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TABLE. Continued

Author	Country	No. of cases	Age (y)	Male	Study design	Outcomes	Adjusted effect estimate (95% CI)	Confounders
Ramos-Rincon JM	Spain	2772	86.3 (83.2-89.6)	1367 (49.4)	R	Mortality	OR 0.83 (0.62-1.34)	Age, sex, degree of dependence, comorbidities (non-ASCVD, ASCVD, dementia, moderate-severe renal disease), symptoms (shortness of breath, anorexia), physical examination (oxygen saturation <90%, temperature ≥37.8°C, pulmonary rales, q-SOFA score ≥2), chest radiography, laboratory findings (neutrophils ≥7.5 × 10^3/μL, lymphocytes <0.800 × 10^3/μL, eosinophils <0.030 × 10^3/μL, monocytes <0.500 × 10^3/μL, glucose >126 mg/dL, eGFR <45 mL/min per 1.73 m^2, lactate dehydrogenase ≥500 U/L, CRP ≥80 mg/L)
de Souza CD	Brazil	9807	70.21±8.37	4662 (47.5)	R	Mortality	OR 0.83 (0.54-1.29)	Sex, age ≥75 y, initial symptoms reported (cough, fever, fatigue, headache, myalgia, odynophagia, dyspnea), comorbidities (diabetes, CVD, hypertension, chronic lung disease, CKD, obesity)
Peng X	China	49	63 (53-73)	32 (65)	R	Death	OR 13.4 (1.9-94.8)	Lymphocytes <1.1 × 10^9/L, fasting blood glucose ≥7.0 mmol/L
Elimian KO	Nigeria	10,517	37.2±1 5.7	7070 (66.7)	R	Death	OR 1.18 (0.62-2.28)	Age, male, geopolitical zone (south-west, south-south, south-east, north-central, north-west, north-east), occupation (housewife, trader/business, health worker, farmer, religious/traditional leader, transporter, other), vomiting, travel history, abdominal pain, chest pain, chills/sweat, confusion, cough, breathing difficulty, fatigue, fever, joint pain, malaise, nausea, rapid breathing

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TABLE. Continued

Author	Country	No. of cases	Age (y)	Male	Study design	Outcomes	Adjusted effect estimate (95% CI)	Confounders
Jain AC	India	426	49 (21-77)	313 (73.38)	R	Mortality	OR 0.65 (0.08-5.03)	Age, sex, weight, travel, visit: hotspots, contact, fever, symptoms, duration of illness >5 d, sore throat, cough, sputum production, shortness of breath, headache, myalgia/arthralgia, comorbidities, diabetes, hypertension, CKD, CAD/IHD, malignancy, hypothyroidism, medication for chronic disease, SBP, effusions, DBP, temperature, respiratory rate, SpO_2, pulse rate, bilateral patchy shadows, local patchy shadows
Guglielmetti L	Italy	218	68 (59-76)	172 (79)	R	Death	HR 0.31 (0.13-0.72)	Sex, presence of bilateral disease at computed tomography scan, treatment with corticosteroids, age >65 y at admission, ≥1 comorbidity, severe ARDS at admission, platelet count $<197 \times 10^3/\mu L$ at admission, LDH >440 U/L at admission
Lee J	Korea	770	NR	453 (58.8)	R	Death	OR 0.6 (0.28-1.21)	Age, SBP, heart rate, dyspnea at presentation, mental disturbance at presentation, comorbidity (treating cancer, diabetes, hypertension, chronic cardiac disease, chronic pulmonary disease, chronic renal disease, dementia), hemoglobin, Absolute lymphocyte counts (group II, ≥500 to $<1000/mm^3$; group I, $<500/mm^3$), platelet counts $<100,000/mm^3$

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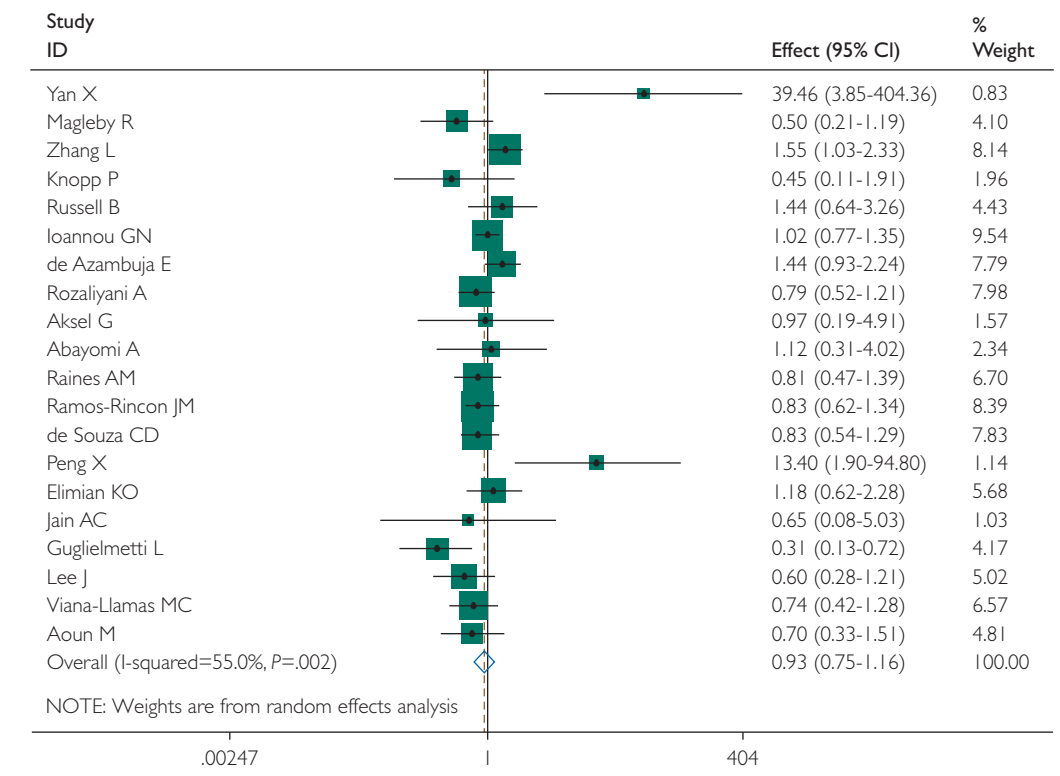
TABLE. Continued

Author	Country	No. of cases	Age (y)	Male	Study design	Outcomes	Adjusted effect estimate (95% CI)	Confounders
Viana-Llamas MC	Spain	609	71 (58-82)	367 (60.3)	R	Mortality	OR 0.735 (0.422-1.281)	Sex, BMI, symptoms on admission (dyspnea, dysgeusia/anosmia, arthralgia/myalgia, asthenia, cough, high temperature, vomiting), vital signs on admission (blood O_2 saturation <92%, tachypnea >22 beats/min, disorder of consciousness, SBP <90 mm Hg or/and DBP <60 mm Hg, q-SOFA score ≥2), chest radiography on admission (bilateral infiltration), laboratory findings on admission (albumin <34 g/L, lymphocytes ≤800/μL, creatinine, D-dimer >0.49 ng/dL, hs-CRP >8 mg/L, lactate dehydrogenase >250 U/L, hemoglobin, leukocyte count, platelet count, fibrinogen, sodium, AST, ferritin), adverse events (ARDS, sepsis, acute respiratory failure, bilateral pneumonia, acute kidney injury, MAS, acute heart failure, bleeding events, embolic events)
Aoun M	Lebanon	231	61.46±13.99	128 (55.4)	R	Death	OR 0.705 (0.33-1.51)	Age, sex, dialysis vintage, multimorbidities, smoking, diabetes, obesity, heart failure, CAD, lung disease, cancer, history of stroke, dementia, fever, dyspnea, hypotension, pneumonia, CRP, admission to hospital

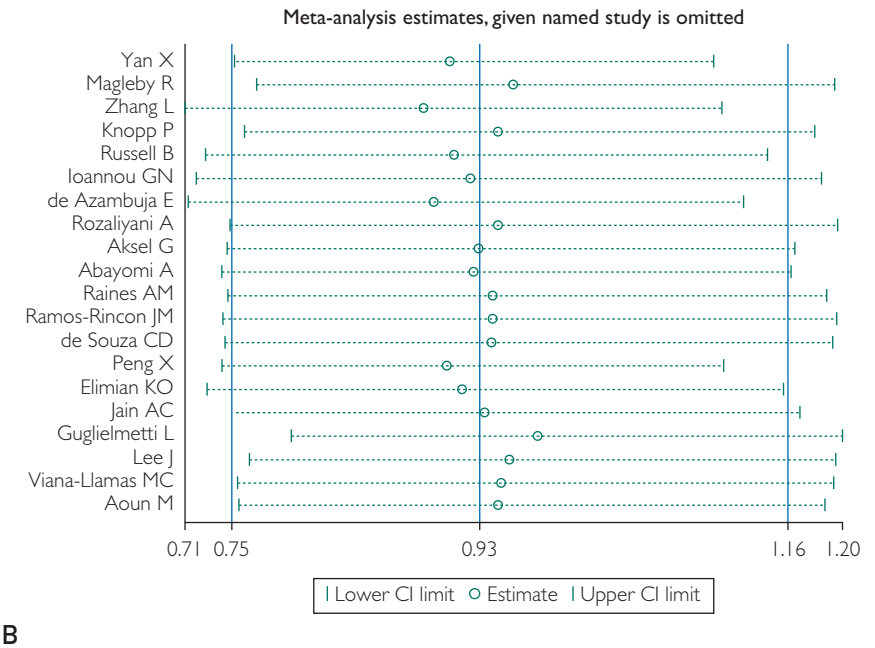
[a]A, ambispective study; ARDS, acute respiratory distress syndrome; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CFS, clinical frailty scale; CHF, congestive heart failure; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Ct, cycle threshold; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; NLR, neutrophil-to-lymphocyte ratio; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; P, prospective study; q-SOFA, quick sequential organ failure assessment; R, retrospective study; SBP, systolic blood pressure; SES, socioeconomic status; SpO_2, saturation of pulse oxygen; WBC, white blood cell.

[b]SI conversion factors: To convert ng/dL values to mg/L, divide by 100000; to convert g/L values to mg/L, multiply by 1000; to convert mg/dL values to mmol/L, multiply by 0.055551 (glucose); to convert g/L values to mol/L, multiply by 0.000015 (albumin).

[c]The values of age are mean ± SD or median (interquartile range); the values of male are n (%).

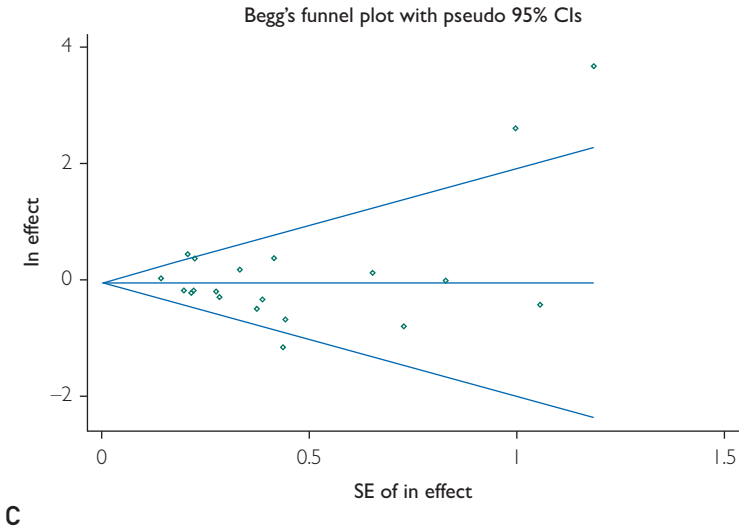


A



B

FIGURE. A, The forest plot depicted that gastrointestinal symptoms were not markedly associated with coronavirus disease 2019 mortality on the basis of adjusted effect estimates. B, Sensitivity analysis indicated that our results were stable and robust. C and D, Publication bias was evaluated using the Begg test (panel C) and Egger test (panel D).



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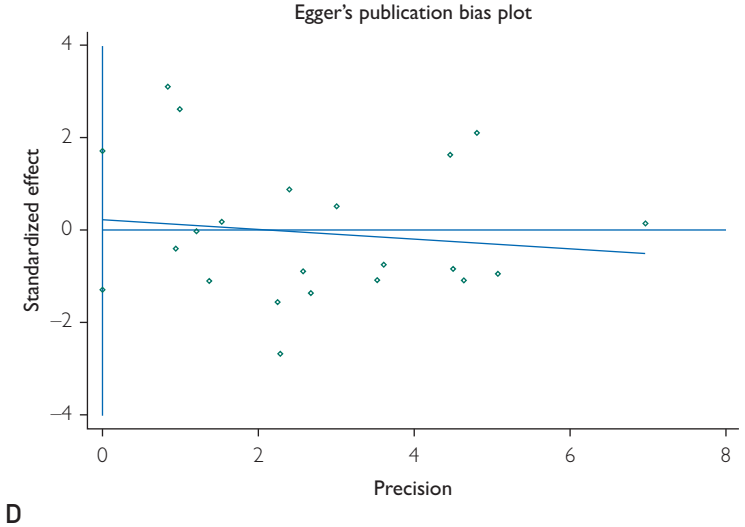

D

FIGURE. (*continued*).

that the mortality of patients with coronavirus disease 2019 (COVID-19) and gastrointestinal (GI) symptoms (0.4%; 95% CI, 0% to 1.1%) was similar to the overall mortality (2.1%; 95% CI, 0.2% to 4.7%).[1] This is an extremely interesting study. However, their findings were based on limited sample sizes. Moreover, the pooled effects of the study by Tariq et al were based on crude effect estimates. Various factors such as age, sex, and comorbidities (such as diabetes, hypertension, and cerebrovascular disease) affected the clinical outcomes of patients with COVID-19,[2-5] suggesting that these factors might influence the relationship between GI symptoms and COVID-19 mortality. So, an updated meta-analysis based on adjusted effect estimates is needed to clarify the association between GI symptoms and COVID-19 mortality.

We carried out an electronic search in PubMed, Web of Science, and EMBASE until March 9, 2021. The following keywords were used: (*COVID-19 or 2019-nCoV or SARS-CoV-2 or coronavirus disease 2019*) *and* (*GI or gastrointestinal symptoms*) *and* (*mortality or death or fatality or deceased or non-survivor or died*). All peer-reviewed studies written in English investigating the relationship between GI symptoms and COVID-19 mortality on the basis of adjusted effects were included. We excluded reviews, case reports, duplicated papers, and studies without complete data. All data analyses were performed using STATA

11.2 (StataCorp, College Station, TX).

The main characteristics of the included studies are presented in the Table. We observed that there was not a significant association between GI symptoms and COVID-19 mortality on the basis of 20 studies with 58,423 patients with COVID-19 reporting adjusted effect estimates (pooled effect size, 0.93; 95% CI, 0.75 to 1.16; P=.535; random effects model) (Figure A). We observed consistent results in the subgroup analyses by effect estimates (pooled odds ratio, 0.97; 95% CI, 0.75 to 1.26 and pooled hazard ratio, 0.78; 95% CI, 0.45 to 1.36), region (Asia: pooled effect size, 1.25; 95% CI, 0.69 to 2.24; Americas: pooled effect size, 0.90; 95% CI, 0.73 to 1.11; Europe: pooled effect size, 0.83; 95% CI, 0.55 to 1.27; and Africa: pooled effect size, 1.17; 95% CI, 0.65 to 2.09), study design (retrospective studies: pooled effect size, 0.92; 95% CI, 0.70 to 1.21; prospective studies: pooled effect size, 0.63; 95% CI, 0.22 to 1.84; and ambispective studies: pooled effect size, 1.06; 95% CI, 0.81 to 1.38), sample size (≤2000 cases: pooled effect size, 0.92; 95% CI, 0.60 to 1.40 and >2000 cases: pooled effect size, 0.98; 95% CI, 0.83 to 1.15), age (≤65 years old: pooled effect size, 1.13; 95% CI, 0.81 to 1.57 and >65 years old: pooled effect size, 0.81; 95% CI, 0.59 to 1.11), and percentage of male patients (≤60%: pooled effect size, 1.04; 95% CI, 0.77 to 1.40 and >60%: pooled effect size, 0.81; 95% CI, 0.58 to 1.15). Sensitivity analysis indicated that our results were reliable and robust (Figure B). Publication bias was not found in the Begg test and Egger test (Figure C and D).

In summary, our findings based on adjusted effect estimates suggested that GI symptoms were not markedly associated with COVID-19 mortality. Further well-designed studies with large sample sizes are needed to confirm our conclusions.

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In reply—Lack of Marked Association Between Gastrointestinal Symptoms and COVID-19 Mortality: An Updated Meta-analysis Based on Adjusted Effect Estimates

We appreciate the interest of Li et al[1] in our systematic review and meta-analysis evaluating the prevalence of gastrointestinal (GI) symptoms and the association with mortality in patients with coronavirus disease 2019 (COVID-19).[2] Li et al performed an updated meta-analysis with a larger sample size to explore the effect of GI symptoms on mortality associated with COVID-19. On the basis of adjusted effect estimates (controlling for potential confounders), they found no association between GI symptoms and mortality (pooled effect 0.93; 95% CI, 0.75 to 1.16; P=.535). The results remain consistent in multiple subgroup analyses. Because of the lack of risk of bias assessment of the included studies, it is hard to ascertain the quality of included evidence. Moreover, different follow-up duration of the included studies could affect mortality estimates.

The results of their pooled meta-analysis are similar to our study with some differences.[2] Because of the lack of reporting of uniform data on confounders and comorbidities, our findings were based on crude estimates. Since then, additional studies have been published, with COVID-19 being a widely researched topic. We completely agree that certain risk factors, including age, sex, and comorbidities could affect the mortality in patients with COVID-19.[3]

Another similar meta-analysis suggested an increased risk of severe COVID-19 with GI symptoms compared with those without GI symptoms (odds ratio, 3.97; 95% CI, 1.49 to 10.62; P=.006).[4] Patients with GI symptoms conceivably had delayed COVID-19 diagnosis, which may have led to severe COVID-19 and worse outcomes. A recent study found that despite the presence of severe acute respiratory syndrome coronavirus 2 antigens in the intestinal tissue, the inflammatory