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Case fatality rate of the adult in-patients with COVID-19 and digestive system tumors
A systematic review and meta-analysis

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Abstract

Background: During the coronavirus disease 2019 (COVID-19) pandemic, endoscopic screening for gastrointestinal tumors was suspended or delayed in most countries. Thus, our study aimed to quantify the impact of COVID-19 on the clinical outcomes of patients with digestive system tumors through a systematic review and meta-analysis.

Methods: We systematically searched the PubMed, Web of Science, Cochrane Library, and Embase databases as of March 7, 2021 to identify the case fatality rate (CFR) of COVID-19 patients diagnosed with digestive system tumors. A random-effects model was used for meta-analysis, I^2 was used to assess heterogeneity, and funnel plot was used to assess publication bias.

Results: A total of 13 studies were included, involving 2943 tumor patients with COVID-19, of which 871 were digestive system tumors, and the CFR was 24% (95% CI, 18%–30%; $I^2 = 55.7\%$). The mortality rate of colorectal cancer was 21% (95% CI, 14%–27%; $I^2 = 0.0\%$), gastric cancer was 25% (95% CI, 6%–45%; $I^2 = 0.0\%$), and hepatobiliary cancer was 29%. In general, there was no significant difference in the CFR of digestive system tumors.

Conclusion: The combined CFR of digestive system tumors and COVID-19 patients was 24%, which is much higher than that of the general population. Under the premise of fully complying with the international guidelines to limit the spread of COVID-19, we call for the resumption of endoscopic screening programs and selective surgery as soon as possible.

Registration information: PROSPERO registration no. CRD42021248194.

Abbreviations: ACE-2 = angiotensin-converting enzyme-2, CFR = the case fatality rate, CI = confidence interval, COVID-19 = the coronavirus disease 2019, CTC = computed tomography colonography, CTSL = cathepsin L, ES = effect size, FIT = fecal immunochemical test, ICU = intensive care unit, NOS = Newcastle-Ottawa Scale, OR = odds ratio, PRISMA = Preferred reporting items for systematic reviews and meta-analyses, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SD = standard deviation, TMPRSS2 = transmembrane protease serine 2, WHO = the World Health Organization.

Keywords: case fatality rate, COVID-19, digestive system tumors, mortality, SARS-CoV-2, systematic review and meta-analysis

1. Introduction

COVID-19 is a new respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] On March 11, 2020, the World Health Organization (WHO) announced that COVID-19 was a global pandemic, and it has now ben constituted a public health emergency of international concern. According to the real-time statistics of the global COVID-19 epidemic, as of February 14, 2022, more than 412 million COVID-19 cases have been confirmed worldwide, and the cumulative number of deaths has reached 5.83 million. Compared with the general population, cancer patients are more susceptible to COVID-19. Liang et al observed that COVID-19 patients with cancer have a higher risk and frequency of serious events compared with those who have no cancer.[2] In addition to the fact that the tumor itself and the anti-tumor treatment will directly lead to the damage of the immune system, the overall age of tumor patients is older and they also have coexisting multiple comorbidities, which may be potential risk factors for an increased risk of COVID-19 infection and poor prognosis.[3–6]

Due to the COVID-19 pandemic, endoscopic screening has been suspended or delayed in most countries, causing the diagnostic rate of digestive system tumors to drop to half.[7] A delay in the endoscopic diagnosis of colorectal cancer in patients with positive clinical manifestations, including positive fecal occult blood tests and suspicious radiological findings, will increase the risk of tumor progression and metastasis. Even if screening is resumed, the impact of this delay on disease progression is still irreversible. In addition, some studies have found that there are coronavirus-like particles in the cytoplasm or surface of intestinal cells in the appendix, colon, or rectum of some patients with COVID-19, indicating that the virus productively infects human gut enterocytes.[8,9] Therefore, it is imperative to conduct a comprehensive assessment of patients with digestive system tumors on the premise of complying with the guidelines for prevention and control of the epidemic situation of COVID-19.

Here, we conducted a systematic review and meta-analysis of patients with digestive system tumors infected with COVID-19 to assess the overall mortality rate and potential risk factors of this population and provide a reference for the clinical treatment of cancer patients under the background of the COVID-19 pandemic.

2. Methods

2.1. Search strategy

We conducted a systematic search of four databases, namely PubMed, Web of Science, Cochrane Library, and Embase. Combining MeSH terms and keyword strategies, we used the following search terms: ([COVID-19] OR [coronavirus disease-19] OR [novel coronavirus] OR [new coronavirus] OR 2019 novel coronavirus) OR (2019-nCoV) OR (nCoV-2019) OR (novel coronavirus) OR (novel coronavirus pneumonia) OR (coronavirus disease 2019) OR (severe acute respiratory syndrome coronavirus 2) OR (SARS-CoV-2) AND ([cancer] OR [neoplasm] OR [oncology] OR [malignancy] OR [tumor] OR [carcinoma]). Considering the time of the COVID-19 outbreak, the publication date was limited from December 2019 to March 7, 2021. We pre-specified the search results for studies written in or translated into English. There were 10,727 articles in total. In addition, we manually searched the references of the

selected articles to obtain all possible relevant studies. Our report was based on the PRISMA statement of systematic reviews and meta-analyses. EndNote X9 software was used to manage the records and eliminate duplicates. This research proposal was submitted to the PROSPERO database (CRD42021248194) for registration and approved by the Medical Ethics Committee of Nanjing Pukou Central Hospital (NPEC-2020-019).

2.2. Article selection

After eliminating duplicate data, two authors (GW, LP) independently extracted all eligible studies and determined their final eligibility based on the inclusion and exclusion criteria. Only original research articles meeting the following criteria were included in the study:

1. Included patients who had been diagnosed with cancer and subsequently confirmed to be infected with COVID-19 by the laboratory;
2. Study type was original research article;
3. The clinical characteristics and outcome information of the patients were reported.

The exclusion criteria were as follows:

1. Non-original research (reviews, clinical guidelines, expert consensus, letters, plans, news, or comments);
2. Research on the death outcome of cancer patients infected with COVID-19 was not reported;
3. Animal research;
4. Molecular biology research;
5. Case report;
6. Clinical trials;
7. Research where the data is incomplete or the full text cannot be retrieved; and,
8. Research where the research object is medical staff.

In cases of studies with overlapping data, the study with a larger sample size was used.

2.3. Data extraction

Two authors (LP and JZ) screened and extracted the data according to the pre-designed form of the Excel spreadsheet. All differences were resolved by consensus and further adjudicated by a third author (WC). The extracted information included the first author, publication time, study design, cohort name, study period, single/multi center, country, region, cancer patients with COVID-19, median age, male percentage, percentage of patients in the intensive care unit (ICU), proportion of severe cases, percentage of patients with ventilator support, comorbidities, therapy, cancer stage, tumor type, and clinical outcome.

2.4. Literature quality evaluation

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies. Based on the scores, the risk of bias in the studies were categorized into low (7–9), moderate (4–6), and high (1–3).

2.5. Data analysis

The data are presented as mean and standard deviation (SD) for numerical data, and proportions for categorical data. The CFR

was defined as the number of patients with cancer who died divided by the number of patients with a known hospital outcome (death or discharged alive) after the diagnosis of COVID-19. The results are presented as forest plots. Chi-square test and I^2 statistics were used to assess the heterogeneity of the results (25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively). If $P > .1$ and $I^2 < 50\%$, a fixed-effects model was used for meta-analysis; otherwise, a random-effects model was used for meta-analysis. We used a random-effects model to calculate the CFR of patients with digestive tract tumors infected with COVID-19. Publication bias was assessed using funnel plot. Odds ratio (OR) was used to measure the strength of association, while a 95% confidence interval (CI) was used to measure the accuracy of estimation. Stata/SE 15.1 for Windows (College Station, TX) was used for data analysis.

3. Results

3.1. Literature search

The flow diagram in Figure 1 shows the detailed literature search steps. Through comprehensive literature retrieval, we retrieved 10,723 articles from PubMed, Web of Science, Cochrane Library, and EMBASE, and four additional records identified through other sources. After excluding duplicate documents, 4753 articles were screened by title and abstract, and 525 full-text articles were assessed for eligibility. According to our inclusion and exclusion criteria, 472 articles were excluded, and 53 articles were included in the qualitative review. Forty articles were excluded because they did not report the death outcome of patients with digestive system tumors. Finally, 13 articles were included in the meta-analysis,[8,10–21] one of which was a prospective cohort study, and the rest were retrospective cohort studies.

3.2. Study characteristics and quality evaluation

We analyzed the data from six countries (China 6, UK 1, USA 1, Japan 1, Italy 2, France 1) and an international cohort study. A total of 2943 patients with COVID-19 were enrolled, including 871 patients with digestive system cancer. The digestive system tumors in the studies refer to tumors that originated in the esophagus, stomach, duodenum, jejunum, ileum, appendix, colon and rectum, liver, biliary tract, pancreas, etc. The pathological types include cancer, sarcoma, and neuroendocrine tumors. The sample size of each study ranged from 6 to 1289, while the sample size of digestive system tumors ranged from 2 to 470, and the CFR ranged from 0% to 100.00%. The median age
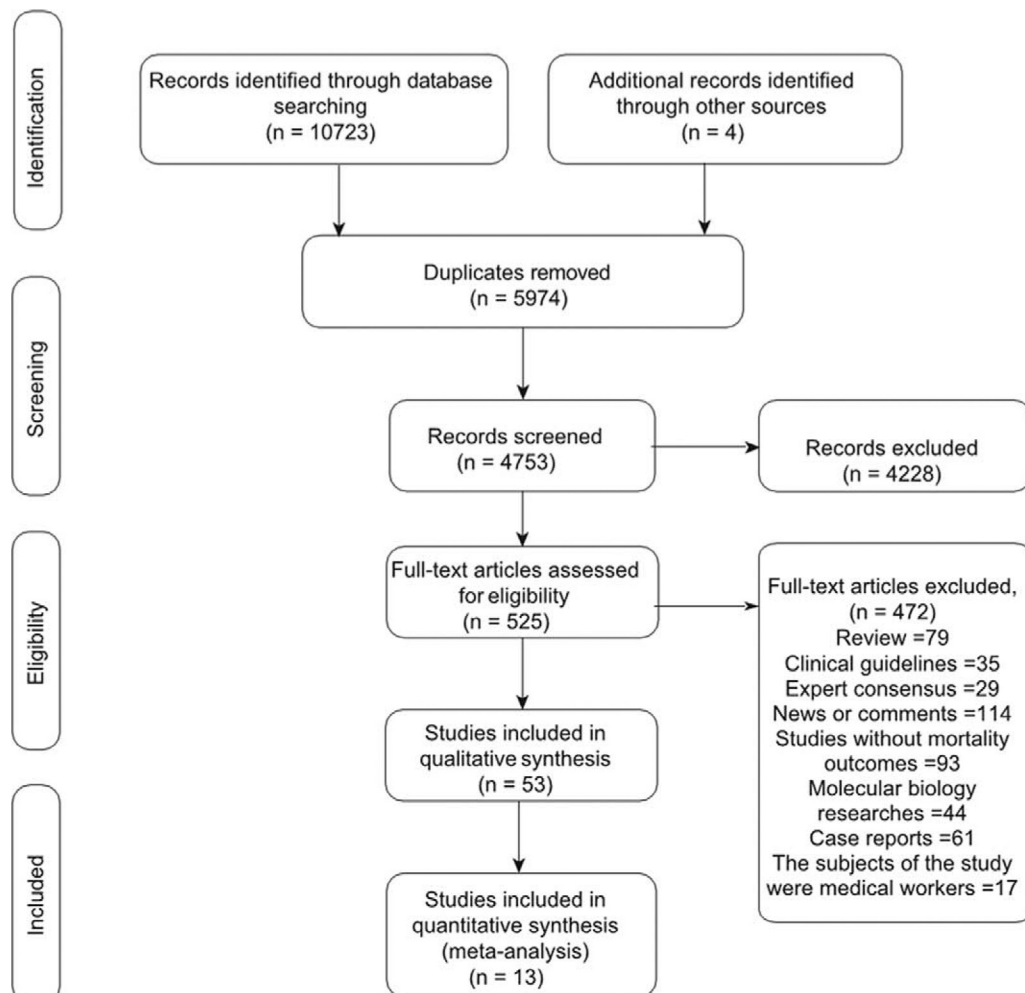

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study inclusions and exclusions.

Table 1

The 13 studies selected for the Systematic Review and Meta-analysis.

Reference	Author	Regione	Multicenter	Study design	Cancer patients with COVID-19	Median age of patients	Male %
10	Yang KY (2020)	Hubei, China	1	Retrospective cohort study	205	63.0	47
11	Lee LYW (2020)	UK	2	Prospective cohort study	800	69.0	56
8	Liu YL (2020)	Wuhan, China	2	Retrospective cohort study	6	65.0	33.3
12	Mehta V (2020)	New York, USA	1	Retrospective cohort study	218	Alive: 66.0 Deceased: 76.0	58
13	Yang F (2020)	Wuhan, China	2	Retrospective cohort study	52	63.0	54
14	Pinto C (2020)	Italy	1	Retrospective cohort study	14	79.0	64
15	Lie'vre A (2020)	France	1	Retrospective cohort study	1289	67.0	62
16	Dai MY (2020)	Hubei, China	1	Retrospective cohort study	105	64.0	55
17	Zhang HY (2020)	Wuhan, China	1	Retrospective cohort study	107	66.0	56
18	Stroppa EM (2020)	Italy	2	Retrospective cohort study	25	71.64	80
19	Bhangu MA (2020)	International	1	Retrospective cohort study	78	NA	NA
20	Yu J(2020)	Wuhan, China	2	Retrospective cohort study	12	66.0	83
21	Nakamura S (2020)	Japan	2	Retrospective cohort study	32	74.5	69

			Case fatality rate of different tumors					
Reference	Author	Digestive cancer	Non-digestive cancer	Colorectal cancer	Gastric cancer	Hepatobiliary cancer	Pancreatic cancer	Esophageal cancer
10	Yang KY (2020)	9/40 (22.50%)	22/143 (15.38%)	6/28 (21.43%)	3/12 (25.00%)	NA	NA	NA
11	Lee LYW (2020)	42/150 (28.00%)	124/481 (25.78%)	NA	NA	NA	NA	NA
8	Liu YL (2020)	1/6 (16.67%)	NA	1/5 (20.00%)	0/1 (0.00%)	NA	NA	NA
12	Mehta V (2020)	15/39 (38.46%)	26/82 (31.71%)	8/21 (38.10%)	NA	2/7 (28.57%)	2/3 (66.67%)	NA
13	Yang F (2020)	2/16 (12.50%)	8/35 (22.86%)	0/13 (0.00%)	1/2 (50.00%)	NA	NA	NA
14	Pinto C (2020)	2/2 (100.00%)	3/12 (25.00%)	2/2 (100.00%)	NA	NA	NA	NA
15	Lie'vre A (2020)	146/470 (31.06%)	224/817 (27.42%)	NA	NA	NA	NA	NA
16	Dai MY (2020)	3/28 (10.71%)	5/67 (7.46%)	1/9 (11.11%)	0/7 (0.00%)	0/3 (0.00%)	0/1 (0.00%)	1/6 (16.67%)
17	Zhang HY (2020)	7/20 (35.00%)	5/21 (23.81%)	NA	NA	NA	NA	NA
18	Stroppa EM (2020)	0/8 (0.00%)	7/13 (53.85%)	NA	NA	NA	NA	NA
19	Bhangu MA (2020)	15/78 (19.23%)	NA	15/78 (19.23%)	NA	NA	NA	NA
20	Yu J (2020)	1/3 (33.33%)	2/9 (22.22%)	0/2 (0.00%)	NA	NA	1/1 (100.00%)	NA
21	Nakamura S (2020)	2/13 (15.38%)	6/12 (50.00%)	1/5 (20.00%)	1/5 (20.00%)	0/1 (0.00%)	NA	0/2 (0.00%)

COVID-19 = the coronavirus disease 2019, NA = not available, UK = the United Kingdom, USA = the United States of America.

of the patients included in the study ranged from 63 to 79 years, and the percentage of men ranged from 33% to 83%. The details of the 13 included studies are presented in Table 1. The NOS scores of the selected studies are shown in Table 2. Two of the 13 studies had a low risk of bias, and 11 studies had a moderate risk of bias. Overall, the risk of bias in the articles included in the analysis was not significant.

3.3. Meta-analysis results

First, we conducted a separate analysis of 871 patients with digestive system tumors in the included 13 studies. The overall mortality rate was 24% (95% CI, 18%–30%; $I^2 = 55.7\%$), which was obtained through a random effects meta-analysis. In contrast, the mortality rate of patients with non-digestive tract tumors was 24% (95% CI, 18%–30%; $I^2 = 80.2\%$). A forest plot is shown in Figure 2.

Next, we assessed whether there was a relationship between the tumor location and prognosis. We divided the studies that reported mortality from tumors of the digestive tract in different locations into appropriate subgroups. The results (Fig. 3) show that the CFR of colorectal cancer, gastric cancer, and

hepatobiliary tumors were 21% (95% CI, 14%–27%; $I^2 = 0.0\%$), 25% (95% CI, 6%–45%; $I^2 = 0.0\%$), and 29% (95% CI, −5% to 62%), respectively. In addition, pancreatic cancer patients had the highest mortality rate, 67% (95% CI, 13%–120%), while esophageal cancer patients had the lowest mortality rate of approximately 17% (95% CI, −13% to 46%). Due to the limited data collected on pancreatic, hepatobiliary, and esophageal tumors in the studies we included, the CFR of these tumors may not have a clear reference value, but the data may be updated in the future for further research. In general, there was no significant difference in the CFR among the different parts of the digestive tract tumors.

When these studies were divided into subgroups according to single/multicenter studies, the CFR of the single-center study group was 25% (95% CI, 17%–33%; $I^2 = 71.5\%$) and the multicenter group was 24% (95% CI, 17%–30%; $I^2 = 5.0\%$) (Fig. 4). We then conducted a subgroup analysis of the study design and found that the CFR of the retrospective study group was 23% (95% CI, 16%–30%; $I^2 = 59.9\%$), while the CFR of the prospective study group was 28% (95% CI, 21%–35%) (Fig. 5). Overall, there was little difference in mortality between the single/multicenter and retrospective/prospective subgroups.

Table 2

The Newcastle-Ottawa Scale scores of the selected studies in the systematic review.

		Selection					Outcome			
Reference	Author	Exposed cohort	Non-exposed cohort	Ascertainment of exposure	Outcome of interest	Comparability	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total
10	Yang KY	1	1	1	1	0	1	0	1	6
11	Lee LYW	1	1	1	1	0	1	1	0	6
8	Liu YL	1	1	1	1	1	1	0	1	7
12	Mehta V	1	1	1	0	1	1	0	0	5
13	Yang F	1	1	1	0	0	1	0	0	4
14	Pinto C	1	1	1	1	0	1	0	0	5
15	Lie'vre A	1	0	1	1	0	1	0	0	4
16	Dai MY	1	1	1	1	1	1	0	1	7
17	Zhang HY	1	0	1	1	0	1	1	1	6
18	Stroppa EM	1	0	1	1	0	1	1	1	6
19	Bhangu MA	1	1	1	1	0	1	1	0	6
20	Yu J	1	0	1	1	0	1	0	1	5
21	Nakamura S	1	0	1	1	0	1	1	1	6

Based on the scores, the risk of bias in the studies were categorized into low (7–9), moderate (4–6), and high (1–3).
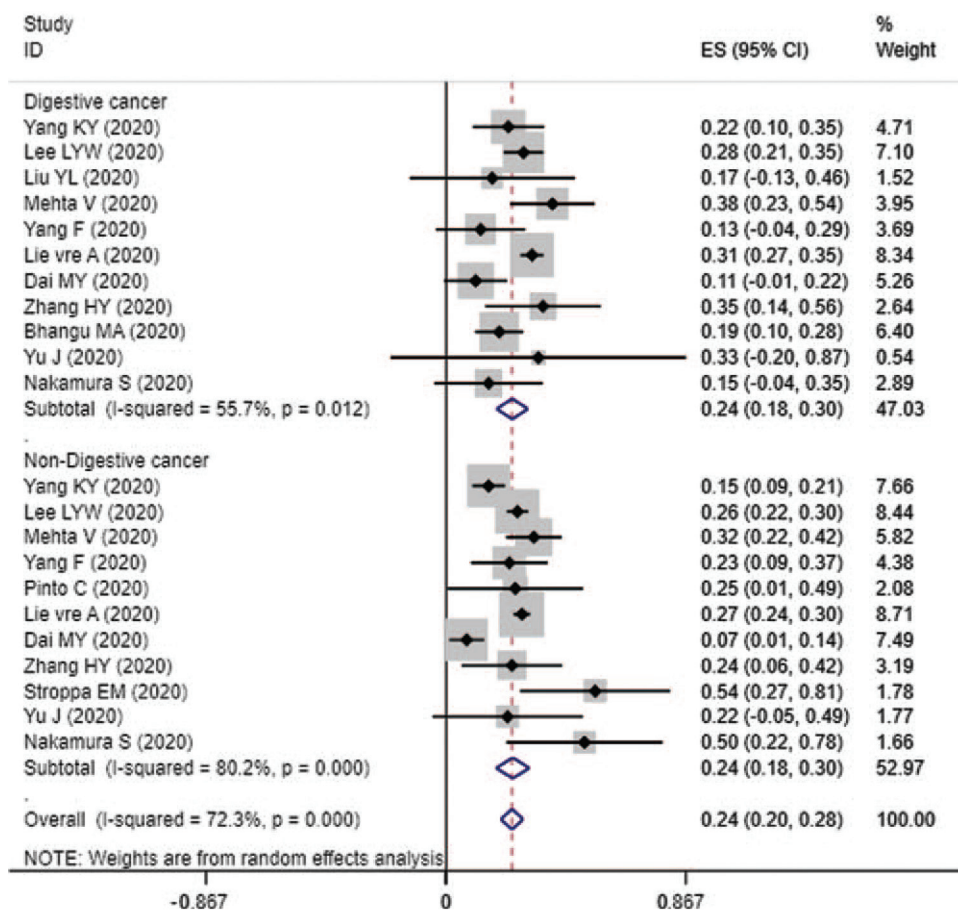

Figure 2. Forest plot of the CFR of digestive system tumors and non-digestive system tumors with COVID-19. CFR = the case fatality rate, COVID-19 = the coronavirus disease 2019.
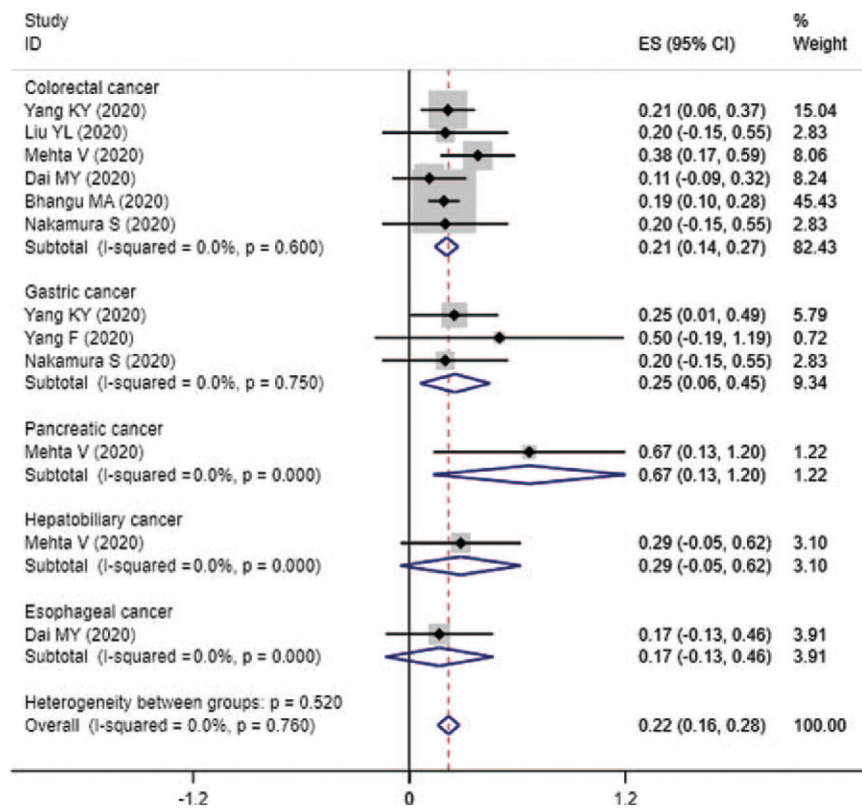
Figure 3. Forest plot of the CFR of digestive tract tumors in different locations with COVID-19. CFR = the case fatality rate, COVID-19 = the coronavirus disease 2019.
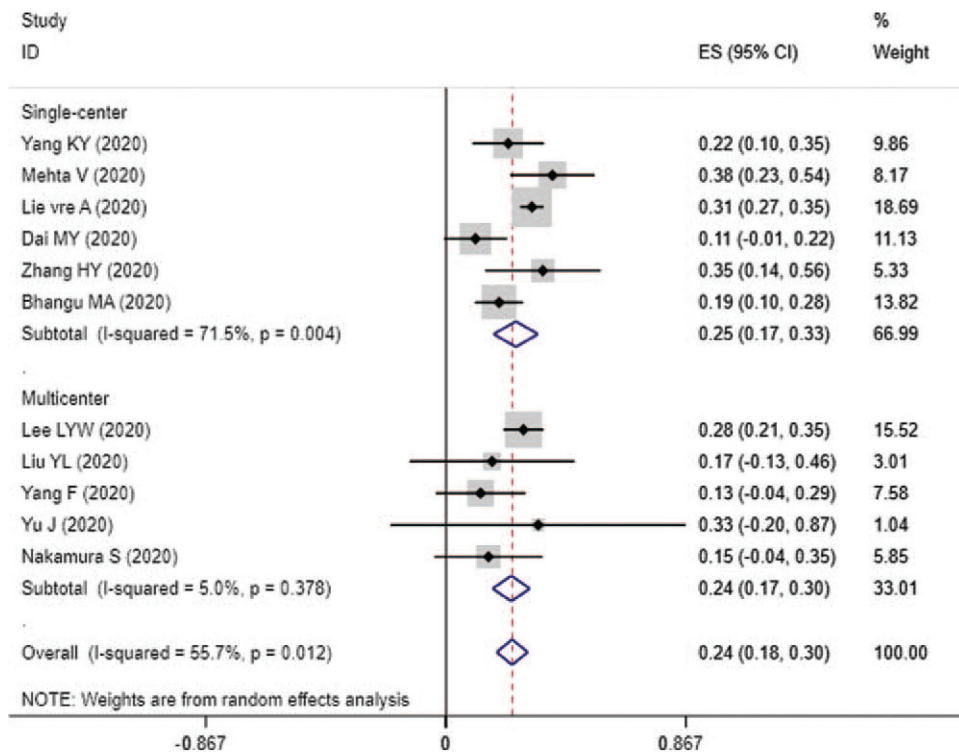

Figure 4. Forest plot of CFR for single/multicenter study subgroup analysis of digestive system tumors with COVID-19. CFR = the case fatality rate, COVID-19 = the coronavirus disease 2019.
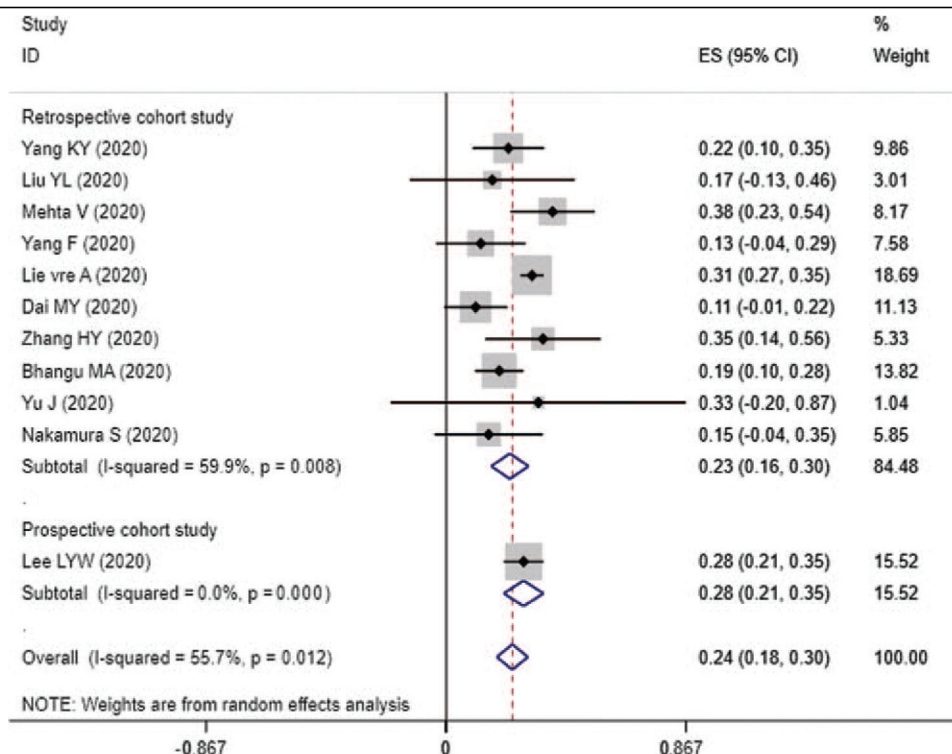
Figure 5. Forest plot of CFR for retrospective/prospective study subgroup analysis of digestive system tumors with COVID-19. CFR = the case fatality rate, COVID-19 = the coronavirus disease 2019.

3.4. Publication bias

A funnel plot of the selected studies is shown in Figure 6. The plot was symmetrical on visual inspection, suggesting a low risk of publication bias.

4. Discussion

COVID-19 has become a threat to global health care because of its high infectivity and human-to-human transmission. Cancer patients are usually characterized by older age, impaired immune system, and a variety of chronic diseases (such as coronary heart

Figure 6. Funnel plot of the selected studies.

disease, hypertension, chronic obstructive pulmonary disease, and diabetes), which places them at high risk of being infected by COVID-19.[22] During the pandemic, the management mode of cancer patients was forced to be adjusted in many aspects. Telemedicine was advocated instead of face-to-face consultation, and intravenous chemotherapy was shifted to oral chemotherapy to reduce the potential risk of hospital-acquired infection.[22–24]

A recent meta-analysis conducted by Cao et al showed that the CFR of COVID-19 in the general population was 6.8% (CI, 0.04–0.09),[25] while a single-center retrospective study by Ma et al found that the mortality rate of COVID-19 in cancer patients was 13.5%.[26] Yang et al analyzed the clinical characteristics of patients with COVID-19 in Hubei, China, and found that the mortality rates of lung cancer, breast cancer, and thyroid cancer were 25%, 7.5%, and 6.25%, respectively.[10] It is well known that digestive system tumors are the second leading cause of cancer-related deaths. According to the 2018 Global Cancer Statistics Report released by the World Health Organization, the mortality rates of colorectal cancer, gastric cancer, and liver cancer were 9.2%, 8.2%, and 8.2%, respectively.[27] However, against the current background of viral epidemics, the impact of COVID-19 on the prognosis of patients with digestive system tumors has rarely been studied. In our systematic review and meta-analysis, we observed that the overall mortality of patients with digestive system tumors and COVID-19 was 24%, which was much higher than the mortality rate reported in the 2018 Global Cancer Statistics.

In the clinical practice of gastrointestinal tumors, the COVID-19 pandemic has put incredible pressure on the screening and
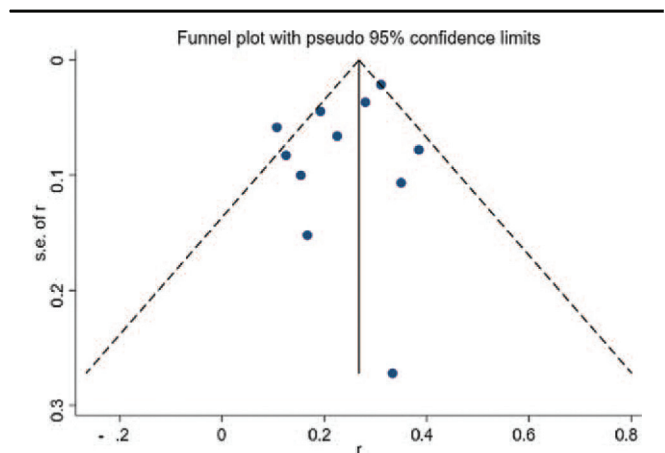
diagnostic procedures for gastrointestinal tumors. Similar to chemotherapy, radiotherapy, and targeted therapy, surgery can also lead to systemic immunosuppression. Patients with cancer undergoing surgery are more susceptible to various bacterial and viral infections than the general population.[28,29] On March 13, 2020, the American College of Surgeons recommended minimizing, postponing, or canceling elective surgery during a pandemic.[8] To reduce the risk of virus exposure, difficult cases cannot be discussed by a multidisciplinary team, and many non-advanced patients lose the opportunity for follow-up surgery because they cannot receive neoadjuvant radiotherapy and chemotherapy.

In addition to emergency endoscopic surgery, endoscopy in non-emergency situations has been postponed or even suspended in many countries and regions. In Italy, 49 of 121 hospitals (47%) suspended their endoscopic screening programs for colorectal cancer during the COVID-19 pandemic.[30] In North America, colonoscopy was delayed in 71 (97%) of 73 digestive endoscopy centers.[31] In Hong Kong, the number of endoscopies decreased by more than 50%, resulting in a 49.1% and 38.1% decrease in the diagnostic rate of gastric cancer and colorectal cancer, respectively.[7] This is alarming, with the number of delayed examinations increasing every day, which may lead to saturation of the digestive department at the end of the pandemic, and the consequences for patients cannot be recovered from the accumulated delays. European guidelines for quality assurance in colorectal cancer screening and diagnosis recommend colonoscopy within one month of a positive fecal occult blood test.[32] When colonoscopy is delayed for more than 6 months, the risk of advanced colorectal cancer with distant metastasis is high.[33] It can be predicted that the longer the lag time, the more advanced the lesions and the higher the mortality of tumor patients (far more than 24%).

Holshue et al confirmed for the first time that SARS-CoV-2 is present in the patient's feces.[34] Subsequently, Zhang et al proposed that coronaviruses may be transmitted through the fecal-oral route.[35] Studies have successively reported that the viral RNA test results in the stool samples of COVID-19 patients ranged from 6.5% to 66.67%.[36–38] This clinical evidence indicates that the intestine may be another important target organ for SARS-CoV-2.

Hoffmann et al proved that SARS-CoV-2 binds to the angiotensin-converting enzyme-2 (ACE-2) receptor, enters the endoplasmic body of the host cell, and is cleaved and activated by cathepsin L (CTSL). In addition, transmembrane protease serine 2 (TMPRSS2) and ACE-2 are co-expressed on the cell membrane and can stimulate spike viral proteins, thereby activating the fusion of the virus with the membrane lipid layer and promoting its entry into host cells. Therefore, the coronavirus receptors ACE2 and TMPRSS2 have been considered to play a key role in SARS-CoV-2 infected cells.[39]

Wang et al evaluated the expression of infection core genes ACE2 and TMPRSS2 in different types of cancer using the GEPIA database and found that the mRNA expression of ACE2 and TMPRSS2 in colorectal cancer was higher than that in other types of cancer.[40] Liu et al found coronavirus-like particles in the cytoplasm or surface of enterocytes from the appendix, colon, or rectum of 5 patients and confirmed considerable ACE2 expression in SARS-CoV-2 infected enterocytes by immunofluorescence and fluorescent ISH. This is the first report to show the presence of active SARS-CoV-2 in the appendix, colon, and rectum of an infected patient.[8] ACE2 was highly expressed not only in the absorptive enterocytes from the colon, but also in stratified epithelial cells of the upper esophagus. Guan et al also detected SARS-CoV-2 in cases of esophageal erosion and in the bleeding sites of patients with peptic ulcer.[41] These results may explain why SARS-CoV-2 can be isolated from feces and spread through the fecal-oral route.

From another perspective, SARS-CoV-2 may contribute to the deterioration of tumor patients. Related pathophysiological studies have found that SARS-CoV-2 infection is characterized by continuous activation of T cells leading to a state of exhaustion,[42,43] which leads to a weakened cellular immune response necessary for COVID-19 patients to effectively eliminate the virus. Therefore, in laboratory examinations, many patients show lymphopenia.[44–46] Cytokine release syndrome is an important aggravating mechanism of COVID-19. SARS-CoV-2 induces self-injury of tissues and organs through excessive production of pro-inflammatory cytokines.[47,48] The potential immunosuppressive microenvironment caused by abnormal immune cell functions is an important pathogenesis of malignant tumors.[49] In addition, advanced age, multiple comorbidities, radiotherapy, chemotherapy, and other cytotoxic treatments have led to further damage to the immune system of cancer patients. When faced with additional insults (such as COVID-19), cancer patients may not have enough immunity to fight the infection. As the pandemic progresses, cancer populations show more severe cases.

Huang et al reported the clinical characteristics of 41 confirmed patients in Wuhan for the first time. In addition to typical respiratory symptoms, patients have various degrees of gastrointestinal dysfunction.[50] A systematic literature review on the digestive system manifestations of COVID-19 reported that about 3% to 40.7% of patients have gastrointestinal symptoms, manifesting as nausea, diarrhea, anorexia, vomiting, abdominal pain, belching, bloating, and gastrointestinal bleeding.[41] Further pathological studies revealed that in infected patients with gastrointestinal symptoms, the digestive system will have a series of manifestations such as necrosis, atrophy, congestion, hemorrhage, and infarction.[51] In the process of clinical diagnosis and treatment, many cases initially showed atypical respiratory symptoms such as nausea and diarrhea, leading to delayed diagnosis. This also contributed to the poor prognosis of patients with gastrointestinal cancer to a certain extent.

It is necessary to make adjustments for the current crisis of patients with gastrointestinal cancer. Under the premise of fully complying with the international guidelines to limit the spread of COVID-19, we call for the resumption of endoscopic screening programs and selective surgery as soon as possible. Multi-target stool fecal immunochemical test (FIT)-DNA detects DNA mutations in fecal exfoliated cells. This is combined with a FIT to form an individual comprehensive risk score. Subjects whose comprehensive score exceeds a preset threshold are defined as high-risk groups and require colonoscopy. A prospective validation study involving 9989 subjects conducted in the United States and Canada reported that the sensitivity of this multi-target stool FIT-DNA test for colorectal cancer and advanced adenoma was 92.3% and 42.4%, respectively.[52] Based on this research, this detection technology has been approved by the U.S. Food and Drug Administration and recommended by the U.S. Colorectal Cancer Screening Guidelines for colorectal cancer screening. At present, China also has multi-target FIT-DNA testing products approved by the

National Medical Products Administration. The China Guideline for the Screening, Early Detection, and Early Treatment of Colorectal Cancer (2020, Beijing) systematically evaluated the diagnostic accuracy of colorectal cancer and corresponding precancerous lesions screened by computed tomography colonography (CTC). The results of the meta-analysis showed that the sensitivity and specificity of CTC in screening colorectal cancer were 0.95 and 0.98, respectively, and the sensitivity and specificity of CTC in screening precancerous lesions were 0.88 and 0.95, respectively.[53] Therefore, in some countries and regions that do not have the conditions for open endoscopic screening and surgery, multi-target stool FIT-DNA detection, CTC, barium meal imaging, and capsule endoscopy can also be used as alternative measures to alleviate the pressure caused by long-term interrupted endoscopy and surgery in patients with digestive tract tumors to a certain degree. Vaccination is the most effective way to prevent and control the COVID-19 pandemic. A variety of 2019-nCoV vaccines produced in China have been certified by the WHO for safety, effectiveness, and quality, providing more options and powerful weapons for controlling the global epidemic as soon as possible.

Our study had some limitations. Because the collected data were not comprehensive enough, we did not further analyze the correlation between the clinical characteristics and prognosis of cancer patients. Many studies have reported that elderly patients, men, and those with comorbidities, such as hypertension, chronic lung disease, diabetes, and cancer, have a higher incidence and mortality risk. We encourage future researchers to further explore whether these covariates are consistent with the characteristics of mortality in patients with gastrointestinal cancer. With the rapid development and spread of the pandemic, the research data we included may not be able to reflect the actual situation of infection and mortality in real time because our research data came from different countries and regions in the world. Moreover, it is unclear if the deaths are caused by COVID-19 or cancer. Some patients who died out of the hospital or had an asymptomatic infection may be missed, resulting in high or low mortality. Therefore, the combined mortality we obtained should be interpreted with caution (Supplemental Table, original material of Table 1.xlsx, http://links.lww.com/MD2/B48).

In conclusion, the COVID-19 pandemic has caused tremendous and profound changes in the diagnosis and treatment of gastrointestinal cancers. The fatality rate of patients with gastrointestinal tumors is increasing with the delay of endoscopic screening and surgery, and this will lead to a series of unpredictable consequences. Therefore, the relevant public health centers should formulate a standardized and active restart plan to actively respond to the huge challenges posed by COVID-19 within a controllable range and, to a certain extent, balance the adverse effects of this vulnerable group due to delays in diagnosis and treatment.

Author contributions

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Methodology: Wensen Chen.
Project administration: Wensen Chen.
Resources: Guoqun Wang.
Software: Guoqun Wang, Wensen Chen.
Supervision: Wensen Chen, Xiaofeng Chen.
Validation: Wensen Chen.
Writing – original draft: Guoqun Wang.
Writing – review & editing: Guoqun Wang, Wensen Chen, Xiaofeng Chen, Poshita kumari Seesaha.

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