



Review Article

Digestive Cancer Mortality in the U.S.: Recent Trends and the Influence of COVID-19

Young Eun Chon^{1*}, Mohammad Saeid Rezaee-Zavareh^{2*}, Xindi Huang^{3*}, Sikai Qiu⁴, Zhanpeng Yang⁵, Yajing Bo³, Yuxin Guo³, Xin Liu³, Kai Qu^{6,7}, Xinyuan He³, Chang Liu^{6,7}, Yan Yin⁴, Yee Hui Yeo⁸, Cristina Ferrone⁹, Amit G Singal¹⁰, Fanpu Ji^{3,7,11,12#}, Ju Dong Yang^{8,9,13#}

¹Department of Gastroenterology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea;

²Middle East Liver Diseases (MELD) Center, Tehran, Iran;

³Department of Infectious Diseases, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China;

⁴Department of Gastroenterology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China;

⁵School of Mathematics and Statistics, Xi'an Jiaotong University, Xi'an, China;

⁶Department of Hepatobiliary-Pancreatic and Liver Transplantation, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.

⁷Key Laboratory of Surgical Critical Care and Life Support (Xi'an Jiaotong University), Ministry of Education, Xi'an, Shaanxi, China.

⁸Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, United States;

⁹Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA, United States;

¹⁰Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, United States;

¹¹Key Laboratory of Environment and Genes Related to Diseases (Xi'an Jiaotong University), Ministry of Education of China, Xi'an, China;

¹²Shaanxi Provincial Clinical Medical Research Center of Infectious Diseases, Xi'an, China;

¹³Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, United States.

*Young Eun Chon, Mohammad Saeid Rezaee-Zavareh, and Xindi Huang equally contributed as co-first authors.

#Fanpu Ji and Ju Dong Yang equally contributed as co- corresponding authors.

***Corresponding author:** Fanpu Ji, Department of Hepatology, The Second Affiliated Hospital of Xi'an Jiaotong University, No. 157 Xi Wu Rd, Xi'an 710004, Shaanxi, China.

Yang JD, Karsh Division of Gastroenterology and Hepatology, Comprehensive Transplant Center Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center 8900 Beverly Blvd, Los Angeles 90048, CA, USA.

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Abstract

Background: A comprehensive analysis of the trends in mortality of digestive cancers over the past decades in the U.S. is lacking. This study investigates U.S. mortality trends for digestive cancers during the pandemic and assesses the impact of COVID-19. **Methods:** Using data from the National Vital Statistics System and CDC WONDER (2006–2023), age-standardized all-cause mortality (ASACM) rates for digestive cancers were analyzed by joinpoint analysis with annual percentage changes (APC). The percentage of COVID-19-related deaths and the proportion of COVID-19-related deaths among the predicted excess mortality were calculated. **Results:** Between 2018 and 2023, there were 1,089,603 digestive cancer deaths in U.S. adults. The ASACM for digestive cancer decreased significantly from 2006 to 2018 (APC, -0.81%, 95%CI: -1.37, -0.64%), then plateaued from 2018 to 2023 (APC, 0.25%, 95%CI: -0.40, 1.84). The ASACM was stable at approximately 71 per 100,000 persons between 2018 and 2020, increased to 72.5 per 100,000 persons in 2021, and then declined back to baseline in 2022. The percentage of COVID-19-related deaths among decedents with digestive cancer rose between 2020 and 2022 (1.6%→2.0%→2.2%) and then declined in 2023 (0.8%). The proportion of COVID-19-related deaths was higher in men, older individuals, and American Indian/Alaska Native populations. **Conclusions:** The COVID-19 pandemic temporarily reversed the decreasing trend of digestive cancer mortality. The impact of COVID-19 on cancer-related mortality is underestimated by the proportion of COVID-related deaths, likely related to indirect effects from delays in screening and treatment.

Keywords: Digestive Cancer; Colorectal Cancer; Hepatocellular Carcinoma; Pancreatic Cancer; Mortality.

Introduction

According to the Global Cancer Observatory 2022, most gastrointestinal (GI) cancers are among the top ten cancer for incidence and mortality worldwide, contributing to over 25% of all cancer deaths in the United States (U.S.). Colorectal cancer (CRC) (9.3%), liver cancer (7.8%), and gastric cancer (6.8%) were the second, third, and fifth leading causes of cancer death in 2022 [1-3].

COVID-19 has caused a high number of deaths globally, including a profound impact in the U.S. Between June 2021 and March 2022, the U.S. death rate was 2-4 times higher than that of 20 similar countries for both COVID-19-related and overall excess mortality [4-9]. In addition to direct mortality from COVID-19 infections, indirect effects by shut downs, health systems being overwhelmed with COVID-19 cases, and patients avoiding healthcare systems resulted in screening and treatment delays [10-12]. Studies consistently reported missed cancers and an increase in late-stage GI cancers during the pandemic [13].

Several studies have examined digestive cancer-related mortality during the COVID-19 pandemic [14-17]. The overall age-adjusted mortality rate of digestive cancer decreased from 46.7 in 1999 to 38.4 in 2020 per 100,000, with an average annual percent change (APC) of -0.9% [18]. When stratified by cancer type, mortality rates decreased for esophageal, gastric, colon, rectal, and gallbladder cancers, while increases were noted for small intestine, anal, pancreatic, and hepatic cancers. However, most studies focused on mortality during the initial years of the COVID-19 pandemic.

In contrast to the early phases of the COVID-19 pandemic, later phases were characterized by improvements in medical responses. Conversely, delayed presentations may have resulted in increased late-stage incidence and mortality in later years [19-22]. Therefore, it is essential to investigate the entire COVID-19 pandemic period for a comprehensive understanding of mortality trends. Herein, we aimed to investigate the mortality trends of all digestive cancers, including the proportion of COVID-19 related deaths, before and during the COVID-19 pandemic period.

Materials and Methods

Study Design and Data Source

In this population-based cross-sectional study, we extracted data from the National Vital Statistics System (NVSS) via the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database. Each death certificate listed one primary cause of death as the underlying cause of death (UCD), and up to 20 contributing factors classified as multiple causes of death (MCD). Data were reported using the International Classification of Diseases, Tenth Revision (ICD-10). We analyzed the NVSS database from 2006 to 2023, which covers over 99% of the U.S. death. The MCD data were final only through 2022, with the data for 2023 being provisional. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [23]. As all the data was de-identified and publicly available, Institutional Review Board approval was not obtained.

Study Population and Operational Definitions

We evaluated GI cancer mortality in U.S. adults aged 25 years or older between 2006 and 2023, focusing on the following

cancers (ICD-10 code): malignant neoplasms of digestive organs (C15-C26), esophagus (C15), gastric (C16), colorectum (colon: C18, rectum: C19–C20, and anus: C21), HCC (C22.0 and C22.9), ICC (C22.1), gallbladder (C23), extrahepatic cholangiocarcinoma (ECC) (C24.0), and pancreas (C25). Deaths were considered COVID-19-related if COVID-19 (U07.1) was recorded as the cause of death (UCD or MCD) on the death certificate. The COVID-19 pandemic period was defined as 2020 to 2023.

Study Outcomes

First, we investigated the number of all-cause deaths (referred to as MCD), UCD, and COVID-19-related deaths among all and each digestive cancer-related death from 2018 to 2023. Age-standardized all-cause mortality (ASACM) and underlying cause mortality (ASUCM) for all and each digestive cancer from 2006 to 2023 were also explored. ASACM, ASUCM, and the percentage of COVID-19-related deaths were analyzed by gender (men and women), age groups (young, 25–44; middle, 45–64; and old age group, ≥ 65 years), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Non-Hispanic Asian/Pacific Islander [PI], Non-Hispanic American Indian/Alaska Native [AI/AN], and Hispanic). The CDC WONDER database added the “more than one race” category in 2020, with few cases. This category was included for baseline characteristics but excluded from further analysis due to its small sample size. Second, we evaluated both observed and predicted ASACM for all and each digestive cancer during the COVID-19 pandemic, with subgroup analyses by gender, age, and race/ethnicity.

Statistical Analysis

ASACM (/100,000 persons) was calculated using the 2000 U.S. Census Standard Population [24]. Mortality trends were analyzed using Joinpoint regression and the Monte Carlo permutation test to identify the best-fit segments. Changes in trend lines were reported as APC with a 95% confidence interval (CI). For the prediction of ASACM, the observed mortality rates were obtained from the CDC WONDER database, and the expected mortality rates for 2020 to 2023 were projected from the linear regression analysis to fit the trends of ASACM from 2006 to 2019. Excess ASACM percentage was calculated by subtracting predicted ASACM from observed ASACM, dividing by predicted ASACM, and multiplying by 100. The percentage of excess deaths attributable to COVID-19 was also reported, accounting for annual COVID-19-related deaths during the pandemic. A two-tailed p-value of ≤ 0.05 was considered statistically significant. Analyses were conducted using Joinpoint Trend Analysis software (version 4.9.1.0; National Cancer Institute, Bethesda, MD), PyCharm 3.9.0 for prediction and modeling, and R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) for other analyses.

Results

Baseline Characteristics

We identified 1,089,603 digestive cancer-related deaths among U.S. adults aged ≥ 25 years (2018–2023) in the CDC WONDER database. Baseline characteristics for all digestive cancer types are provided in Supplementary Table 1. The most frequent causes of death among digestive cancer-related deaths were CRC (n=378,085), pancreatic cancer (n=300,429), and HCC (n=137,887). Digestive cancer-related deaths were more prevalent in old age group (71.6%), men (58.1%), and White individuals (72.6%).

When stratified by age group, gastric cancer (4.8%) exhibited the highest proportion of mortality in the young age group, HCC (29.3%) in the middle age group, and gallbladder cancer (75.7%) in the old age group. Cancers with a higher proportion of deaths in men included esophageal cancer (79.7%) and HCC (72.1%), while gallbladder cancer was the only one with a higher proportion of deaths in women (66.7%). The cancer with the highest proportion of deaths among white individuals was esophageal cancer (84.2%), while the lowest was gastric cancer (55.6%). In contrast, among Black, Asian/PI, and Hispanic individuals, gastric cancer had the highest proportion of death, and esophageal cancer had the lowest. Among AI/AN individuals, HCC resulted in the highest proportion of deaths.

Age-Standardized All-Cause Mortality Rates and COVID-19-Related Deaths

All Digestive Cancers

Table 1 shows ASACM, ASUCM, and the percentage of COVID-19-related deaths for digestive cancers in U.S. adults aged ≥ 25 years (2018–2023). For all digestive cancers, the ASACM for digestive cancer decreased significantly from 2006 to 2018 (APC, -0.81%, 95% CI: -1.37–-0.64%), then plateaued from 2018 to 2023 (0.25%, 95% CI: -0.40–1.84) (Table 3). From 2018 to 2023, the ASACM declined from 71.04 in 2018 to 70.51 per 100,000 persons in 2019 and then increased to 70.83 and 72.5 in 2020 and 2021, respectively. The ASACM then slightly dropped to 71.11 and 71.73 in 2022 and 2023, respectively. (Supplementary Figure 1A). From 2018 to 2023, the trends in digestive cancer-related ASACM among men and women closely mirrored the trend observed in the overall patient population (Table 1). Additionally, the percentage of COVID-19-related deaths increased from 2020 to 2022 and then decreased in 2023 (Supplementary Figure 1B), remaining higher in men than in women each year except for 2023. When examined by age groups, the ASACM trend in the young age group showed a decrease in 2019, followed by a persistent rise from 2019 to 2022 and a slight decrease in 2023. The old group showed a similar ASACM trend to the overall population. The middle age group

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exhibited a decline trend from 2018 to 2023. The old age group had the highest percentage of COVID-19-related deaths. When analyzed by race/ethnicity, the percentage of COVID-19-related deaths was highest among racial/ethnic minorities (AI/ANs, Hispanics, Blacks).

Population	Parameter	Year					
		2018	2019	2020	2021	2022	2023
Overall	MCD, n	174420	176667	180967	183817	186008	187240
	UCD, n	159992	161828	163268	165545	166845	169728
	COVID-19 death, n (%)	0 (0)	0 (0)	2896 (1.6)	3750 (2)	4179 (2.2)	1487 (0.8)
	ASACM rate	71.04	70.51	70.83	72.5	71.11	71.73
	ASUCM rate	65.21	64.63	63.96	65.26	63.83	64.92
Sex							
Men	ASACM rate	91.98	91.24	91.56	92.58	90.95	91.58
	ASUCM rate	83.93	83	82.04	82.6	81.09	82.31
	COVID-19, n (%)	0 (0)	0 (0)	1761 (1.7)	2258 (2.1)	2510 (2.4)	890 (0.8)
Women	ASACM rate	53.59	53.13	53.52	55.56	54.53	55.18
	ASUCM rate	49.49	49.11	48.76	50.51	49.28	50.27
	COVID-19 death, n (%)	0 (0)	0 (0)	1135 (1.5)	1492 (1.9)	1669 (2.1)	597 (1.1)
Age (year)							
25-44	ASACM rate	4.69	4.63	4.75	4.85	4.89	4.85
	ASUCM rate	4.54	4.45	4.52	4.62	4.64	4.57
	COVID-19 death, n (%)	0 (0)	0 (0)	43 (1.1)	56 (1.2)	80 (1.8)	13 (0.3)
45-64	ASACM rate	54.03	53.76	53.66	52.72	52.9	52.35
	ASUCM rate	51.04	50.76	50.02	48.78	49.04	48.97
	COVID-19 death, n (%)	0 (0)	0 (0)	561 (1.2)	900 (1.9)	946 (2)	252 (0.5)
>65	ASACM rate	240.79	238.78	240.36	250.49	243.01	247.24
	ASUCM rate	217.61	215.43	213.42	222.32	214.5	220.19
	COVID-19 death, n (%)	0 (0)	0 (0)	2292 (1.8)	2794 (2.1)	3153 (2.4)	1222 (0.9)
Race/Ethnicity							

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White	ASACM rate	69.45	69.21	69.59	71.99	70.77	71.78
	ASUCM rate	63.6	63.34	62.83	64.77	63.43	64.84
	COVID-19 death, n (%)	0 (0)	0 (0)	1807 (1.3)	2562 (1.9)	2955 (2.2)	1130 (0.8)
Black	ASACM rate	90.19	88.72	88.46	89.05	86.75	87.14
	ASUCM rate	83.38	81.65	80.03	80.22	78.23	79.15
	COVID-19 death, n (%)	0 (0)	0 (0)	462 (2)	528 (2.3)	543 (2.4)	177 (0.7)
Asian/PI	ASACM rate	57.18	57.45	56.78	60.46	57.11	56.5
	ASUCM rate	53.53	53.59	52.16	55.57	51.7	51.94
	COVID-19 death, n (%)	0 (0)	0 (0)	111 (1.5)	103 (1.3)	148 (1.9)	64 (0.8)
Hispanic	ASACM rate	69.4	67.44	68.32	68.14	68.4	67.35
	ASUCM rate	64.06	62.22	61.67	61.4	61.9	61.5
	COVID-19 death, n (%)	0 (0)	0 (0)	480 (2.8)	497 (2.8)	487 (2.6)	103 (0.5)
AI/AN	ASACM rate	72.68	71.66	76.49	75.37	70.95	70.68
	ASUCM rate	65.58	63.54	67.23	66.9	63.4	63.21
	COVID-19 death, n (%)	0 (0)	0 (0)	36 (2.8)	38 (3.1)	31 (2.8)	7 (0.6)
<p>Abbreviations: MCD, multiple cause of death; UCD, underlying cause of death; ASACM, age-standardized all cause mortality; ASUCM, age-standardized underlying cause of mortality; PI, Pacific Islander; AI/AN, American Indians/Alaska Natives. *All ASACM and ASUCM rates in this table are expressed per 100,000 persons.</p>							

Table 1: Age-standardized mortality and COVID-19-related deaths for digestive cancers.

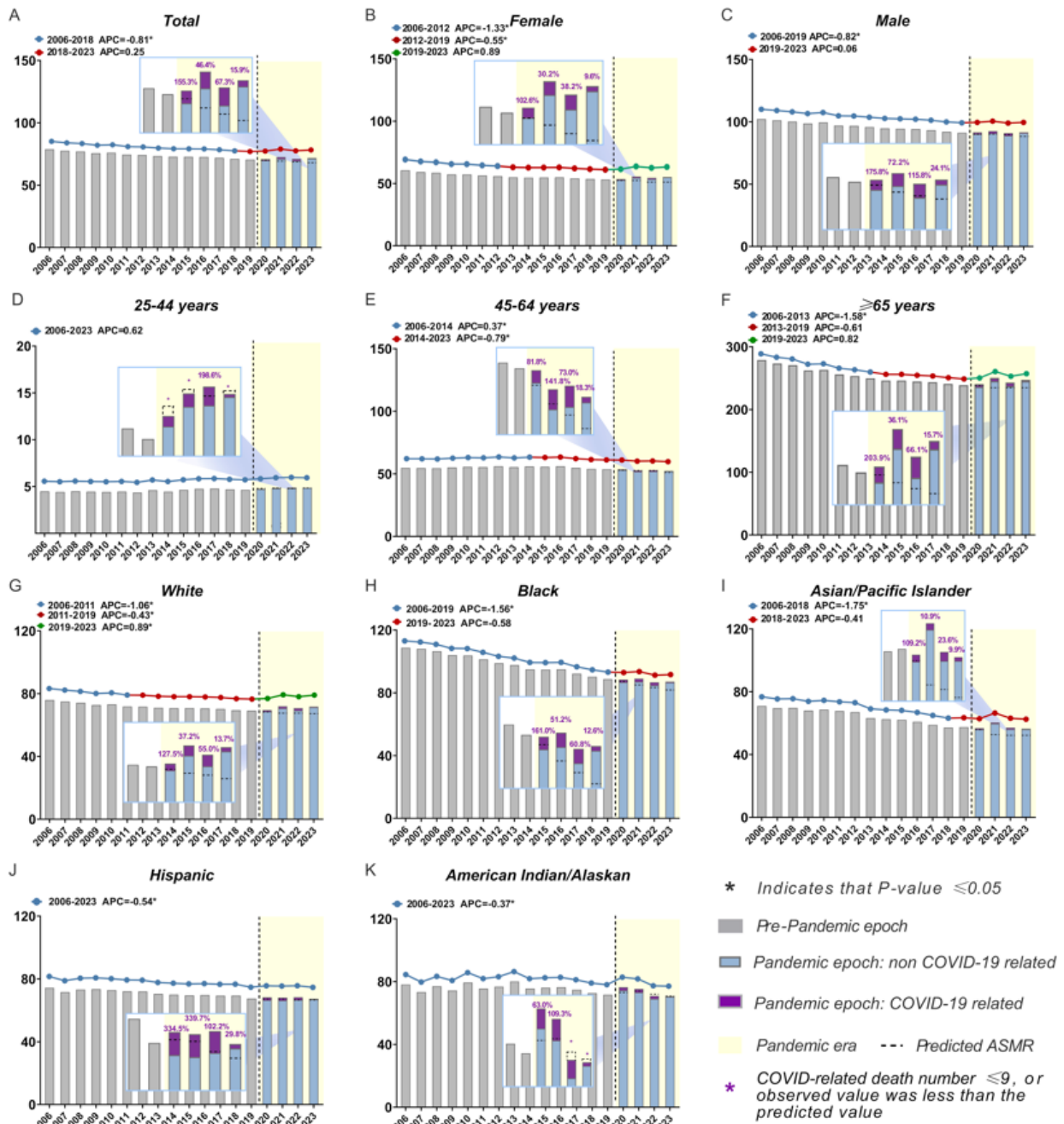


Figure 1: Age-standardized all cause-mortality rate from 2006 to 2023 and predicted mortality during COVID-19 pandemic for digestive cancer.

Colorectal Cancer, Pancreatic Cancer, and Hepatocellular Cancer

Table 2 presents ASACM, ASUCM, and the percentage of COVID-19-related deaths (2018–2023) for CRC, pancreatic cancer, and HCC, the leading causes of digestive cancer mortality.

For CRC, the ASACM showed significantly declining trend in 2006–2013 (APC, -2.87%; 95% CI, -3.87--2.51) and 2013–2019 (-1.49%, -2.32--0.73), and then plateaued from 2019–2023 (0.39%, -0.40-2.03) (Table 3). From 2018 to 2023, ASACM decreased in 2019 compared to 2018, increased from 2019 to 2021, and then declined in 2022 and 2023. The percentage of COVID-19-related deaths in CRC rose from 2020 to 2021, decreased in 2022, and dropped further in 2023 (Table 2). For pancreatic cancer, the ASACM rose non-significantly from 2006–2014 (APC,0.09%; 95% CI, -0.91-0.36) and significantly from 2014–2023 (0.56%, 0.31-1.53) (Table 3). From 2018 to 2023, the ASACM exhibited a steady increase from 2018 to 2021, followed by a decline in 2022, and a subsequent rise in 2023. The percentage of COVID-19-related deaths in pancreatic cancer increased from 2020 to 2022 and decreased in 2023 (Table 2). For HCC, the ASACM significantly increased from 2006–2012 (APC, 3.30%; 95% CI, 2.86-4.04), rose non-significantly from 2012–2015 (1.54%, -1.14-2.80), and significantly decreased from 2015–2023 (-1.01%, -1.50-0.56) (Table 3). From 2018 to 2023, the ASACM declined from 2018 to 2022 and increased in 2023. The percentage of COVID-19-related deaths in HCC increased from 2020 to 2022 and decreased in 2023 (Table 2).

Colorectal Cancer							
Population	Parameter	2018	2019	2020	2021	2022	2023
Overall	All cause death, n	61265	61233	62801	64027	64423	64336
	Underlying cause of death, n	53141	53041	53099	54149	54311	54934
	ASACM rate	25.31	24.85	25.09	25.96	25.28	25.18
	ASUCM rate	22.01	21.58	21.29	21.96	21.38	21.59
	COVID-19 death, n (%)	0 (0)	0 (0)	1425 (2.2)	1820 (2.8)	1784 (2.7)	637(1.0)
Men	ASACM rate	30.54	29.89	30.42	30.99	30.22	30.22
	ASUCM rate	26.32	25.57	25.46	25.8	25.26	25.63
	COVID-19 death, n (%)	0 (0)	0 (0)	841 (2.5)	1047 (3.1)	1009 (2.9)	336(1.0)
Women	ASACM rate	21.05	20.68	20.7	21.76	21.16	21.01
	ASUCM rate	18.42	18.19	17.78	18.66	18.06	18.14
	COVID-19 death, n (%)	0 (0)	0 (0)	584 (1.9)	773 (2.6)	775 (2.6)	301(1.0)
25-44	ASACM rate	2.27	2.18	2.39	2.46	2.41	2.08
	ASUCM rate	2.2	2.1	2.28	2.34	2.29	2.29
	COVID-19 death, n (%)	0 (0)	0 (0)	18 (0.8)	27 (1.2)	41 (2.1)	8(0.4)
45-64	ASACM rate	18.58	18.66	19.22	19.15	19.61	18.5
	ASUCM rate	17.4	17.46	17.59	17.4	17.9	17.9
	COVID-19 death, n (%)	0 (0)	0 (0)	241 (1.4)	414 (2.4)	378 (2.2)	96(0.5)
>65	ASACM rate	85.91	83.64	83.28	87.67	83.4	82.96
	ASUCM rate	71.72	69.67	67.54	71.23	67.38	67.38
	COVID-19 death, n (%)	0 (0)	0 (0)	1166 (2.7)	1379 (3.1)	1365 (3)	533(1.2)
White	ASACM rate	25.48	25.04	25.18	26.37	25.8	25.76
	ASUCM rate	22.02	21.62	21.29	22.21	21.73	21.73
	COVID-19 death, n (%)	0 (0)	0 (0)	921 (1.9)	1292 (2.7)	1316 (2.7)	503(1.0)
Black	ASACM rate	32.54	32.04	32.65	33.04	31.58	31.7
	ASUCM rate	29.02	28.38	28.15	28.4	27.23	27.23
	COVID-19 death, n (%)	0 (0)	0 (0)	231 (2.8)	255 (3.1)	224 (2.8)	62(0.8)

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Asian/PI	ASACM rate	16.62	16.7	17.05	18.12	17.62	16.89
	ASUCM rate	14.84	15.11	14.79	15.87	15.08	15.08
	COVID-19 death, n (%)	0 (0)	0 (0)	45 (2)	38 (1.6)	53 (2.2)	24(1.1)
Hispanic	ASACM rate	20.96	20.13	20.78	21.32	21.09	20.69
	ASUCM rate	18.51	17.9	17.83	18.36	18.22	18.22
	COVID-19 death, n (%)	0 (0)	0 (0)	209 (4.1)	208 (3.8)	176 (3.2)	43(0.8)
AI/AN	ASACM rate	25.11	25.57	26.35	25.97	24.95	25.65
	ASUCM rate	22.04	20.96	22.23	21.24	21.75	21.75
	COVID-19 death, n (%)	0 (0)	0 (0)	19 (4.4)	14 (3.3)	11 (2.9)	4(0.9)
Pancreatic cancer							
		2018	2019	2020	2021	2022	2023
Overall	All cause death, n	47287	48313	49739	50973	51611	52506
	Underlying cause of death, n	44959	45948	46820	47954	48368	49352
	COVID-19 death, n (%)	0 (0)	0 (0)	454 (0.9)	659 (1.3)	884 (1.7)	308(0.6)
	ASACM rate	19.04	19.04	19.18	19.8	19.41	19.75
	ASUCM rate	18.11	18.12	18.06	18.62	18.2	18.56
Men	ASACM rate	22.06	22.02	22.26	22.81	22.61	22.8
	ASUCM rate	20.87	20.85	20.86	21.34	21.09	21.3
	COVID-19 death, n (%)	0 (0)	0 (0)	235 (0.9)	367 (1.4)	472 (1.8)	170(0.6)
Women	ASACM rate	16.49	16.5	16.55	17.24	16.8	17.19
	ASUCM rate	15.76	15.76	15.66	16.29	15.8	16.26
	COVID-19 death, n (%)	0 (0)	0 (0)	219 (0.9)	292 (1.2)	412 (1.7)	138(0.5)
25-44	ASACM rate	0.64	0.69	0.65	0.69	0.68	0.61
	ASUCM rate	0.6	0.65	0.62	0.65	0.65	0.57
	COVID-19 death, n (%)	0 (0)	0 (0)	2 (0)	7 (1.5)	11 (1.5)	1(0.2)
45-64	ASACM rate	13	13.29	13.04	13.02	13.14	13.05
	ASUCM rate	12.44	12.75	12.38	12.33	12.4	12.38
	COVID-19 death, n (%)	0 (0)	0 (0)	100 (0.8)	155 (1.3)	210 (1.8)	55(0.5)
>65	ASACM rate	68.82	68.14	69.4	72.51	70.33	72.35
	ASUCM rate	65.29	64.59	65.13	68.03	65.73	67.78
	COVID-19 death, n (%)	0 (0)	0 (0)	352 (1)	497 (1.3)	663 (1.7)	252(0.6)
White	ASACM rate	19.27	19.29	19.49	20.27	19.91	20.35
	ASUCM rate	18.36	18.36	18.42	19.11	18.71	19.15
	COVID-19 death, n (%)	0 (0)	0 (0)	294 (0.8)	473 (1.2)	649 (1.7)	241(0.6)
Black	ASACM rate	23.88	23.97	23.63	24.52	23.99	24.24
	ASUCM rate	22.6	22.76	22.13	22.82	22.27	22.6
	COVID-19 death, n (%)	0 (0)	0 (0)	72 (1.2)	112 (1.8)	121 (1.9)	45(0.7)

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Asian/PI	ASACM rate	12.85	12.69	13.11	14.32	13.13	13.27
	ASUCM rate	12.24	12.13	12.31	13.52	12.22	12.62
	COVID-19 death, n (%)	0 (0)	0 (0)	19 (1.1)	12 (0.6)	23 (1.3)	11(0.6)
Hispanic	ASACM rate	15.72	15.62	15.83	15.68	15.81	15.67
	ASUCM rate	14.82	14.83	14.63	14.69	14.71	14.77
	COVID-19 death, n (%)	0 (0)	0 (0)	64 (1.5)	57 (1.4)	83 (1.9)	10(0.3)
AI/AN	ASACM rate	14.14	13.93	15.65	14.59	15.56	14.74
	ASUCM rate	13.12	13.04	14.49	13.69	14.79	13.75
	COVID-19 death, n (%)	0 (0)	0 (0)	5 (1.6)	2 (1.1)	5 (1.9)	0(0)
Hepatocellular Carcinoma							
		2018	2019	2020	2021	2022	2023
Overall	All cause death, n	22539	22536	23036	23110	23320	23346
	Underlying cause of death, n	20176	20066	20180	20081	20260	20345
	COVID-19 death, n (%)	0 (0)	0 (0)	388 (1.7)	473 (2)	523 (2.2)	168(0.7)
	ASACM rate	9.05	8.83	8.82	8.8	8.63	8.66
	ASUCM rate	8.1	7.86	7.73	7.65	7.49	7.55
Men	ASACM rate	14.39	14.1	13.87	13.68	13.4	13.44
	ASUCM rate	12.88	12.51	12.15	11.9	11.63	11.7
	COVID-19 death, n (%)	0 (0)	0 (0)	276 (1.7)	317 (1.9)	363 (2.2)	125(0.8)
Women	ASACM rate	4.45	4.3	4.51	4.56	4.51	4.58
	ASUCM rate	3.99	3.87	3.95	3.96	3.91	3.98
	COVID-19 death, n (%)	0 (0)	0 (0)	112 (1.8)	156 (2.4)	160 (2.4)	43(0.6)
25-44	ASACM rate	0.3	0.31	0.3	0.31	0.3	0.3
	ASUCM rate	0.28	0.27	0.25	0.28	0.25	0.25
	COVID-19 death, n (%)	0 (0)	0 (0)	8 (3.3)	2 (0)	5 (3.4)	1(0.4)
45-64	ASACM rate	8.68	7.95	7.46	6.94	6.58	6.22
	ASUCM rate	7.67	7.04	6.55	5.96	5.66	5.4
	COVID-19 death, n (%)	0 (0)	0 (0)	97 (1.3)	129 (2)	117 (2)	29(0.5)
>65	ASACM rate	27.66	27.99	28.96	29.88	29.77	30.68
	ASUCM rate	24.92	25	25.36	26.11	25.97	26.79
	COVID-19 death, n (%)	0 (0)	0 (0)	283 (1.8)	342 (2.1)	401 (2.4)	138(0.8)
White	ASACM rate	7.68	7.6	7.64	7.73	7.58	7.74
	ASUCM rate	6.86	6.76	6.69	6.73	6.58	6.73
	COVID-19 death, n (%)	0 (0)	0 (0)	189 (1.2)	251 (1.7)	306 (2)	114 (0.7)
Black	ASACM rate	12.35	12.04	11.22	10.87	10.5	10.79
	ASUCM rate	11.21	10.81	9.86	9.45	9.26	9.53
	COVID-19 death, n (%)	0 (0)	0 (0)	74 (2.4)	72 (2.4)	73 (2.4)	18 (0.6)

Asian/PI	ASACM rate	10.75	10.57	10.59	10.74	9.77	9.73
	ASUCM rate	9.91	9.57	9.52	9.56	8.73	8.59
	COVID-19 death, n (%)	0 (0)	0 (0)	22 (1.6)	18 (1.3)	24 (1.7)	16 (1.2)
Hispanic	ASACM rate	14.51	13.19	13.44	13.08	13.22	12.56
	ASUCM rate	12.88	11.72	11.66	11.18	11.38	10.88
	COVID-19 death, n (%)	0 (0)	0 (0)	96 (2.8)	123 (3.5)	106 (2.9)	19 (0.6)
AI/AN	ASACM rate	15.3	13.96	16.23	14.14	14.1	12.28
	ASUCM rate	12.73	11.82	13.69	12.48	11.37	9.83
	COVID-19 death, n (%)	0 (0)	0 (0)	7 (2.7)	7 (3.1)	10 (4.3)	0 (0)
Abbreviations: MCD, multiple cause of death; UCD, underlying cause of death; ASACM, age-standardized all case mortality; ASUCM, age-standardized underlying cause of mortality; PI, Pacific Islander; AI/AN, American Indians/Alaska Natives. *All ASACM and ASUCM rates in this table are expressed per 100,000 persons							

Table 2: Age-standardized mortality rates and COVID-19-related deaths for colorectal cancer, pancreatic cancer, and hepatocellular carcinoma, 2018 to 2023.

The ASACM trends of CRC, pancreatic cancer, and HCC from 2018 to 2023 according to gender, age, race/ethnicity were presented in Table 2. Men, old age group, AI/ANs and Hispanics had the highest percentage of COVID-19-related deaths in CRC. Men and AI/AN, Hispanic, and Black populations were most significantly affected by COVID-19-related deaths in pancreatic cancer. The percentage of COVID-19-related deaths was higher in women, AI/AN, Hispanic populations in HCC.

Esophageal Cancer, Gastric cancer, Intrahepatic and Extrahepatic Cholangiocarcinoma, and Gallbladder Cancer

The ASACM, ASUCM, and the percentage of COVID-19-related deaths of esophageal cancer, gastric cancer, ICC, ECC, and gallbladder cancer are listed in Supplementary Table 2. From 2018 to 2023, the overall ASACM trends declined in esophageal cancer, gastric cancer, and gallbladder cancer, whereas they increased in ICC and ECC. The percentage of COVID-19-related deaths was relatively higher in the old age group and among AI/ANs for gastric cancer, in the old age group for ECC, and among men, Hispanics, and Blacks for gallbladder cancer.

Observed, and Predicted Values for ASACM During the COVID-19 Pandemic

For all digestive cancers, based upon the ASACM trend for digestive cancers from 2006 to 2019 (the ASACM in 2006, 78.77; in 2019, 70.51 /100,000 years), the ASACMs from 2020 to 2023 were predicted (Tables 3 and 4). The excess percentage of ASACM

remained positive from 2020 to 2023, particularly from 4.59% in 2021 to 5.16% in 2023. The excess percentage of ASACM was relatively higher in women, in the old age group, and in Asian/PI populations (Table 4). The percentage of the expected increase attributable to COVID-19 was 155.3% in 2020, 46.4% in 2021, 67.3% in 2022, and 15.9% in 2023, showing the highest share in 2020 (Figure 1). For CRC, the percentage of the expected increase attributable to COVID-19 ranged 11.9–92.7% between 2020 and 2023, with the highest value recorded in 2020. (Supplementary Figure 2A). The excess percentage of ASACM for CRC in the overall population from 2020 to 2023 ranged from 2.45% to 8.83%, with the highest values around 8% from 2021 to 2023 (Table 3 and Supplementary Table 3). The excess percentage of ASACM was relatively higher in women, the old age group, and in Asian/PI populations. For pancreatic cancer, the percentage of the expected increase attributable to COVID-19 ranged from minus in 2020 to 339.7% in 2022 (Supplementary Figure 2B). The excess percentage of ASACM for pancreatic cancer in overall population was negative (-0.59) in 2020 and reached the highest value of 2.9% in 2021 (Table 3 and Supplementary Table 3). This was relatively higher in Asian/PI populations. For HCC, the percentage of the expected increase attributable to COVID-19 ranged from minus in 2020 to 523.1% in 2021 (Supplementary Figure 2C). The excess percentage of ASACM for HCC in overall population ranged from -0.2% to 2.6% from 2020 to 2023 (Table 3 and Supplementary Table 3). This was relatively higher in women, in old age group, and in Asian/PI populations.

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	Age-Standardized Mortality Rate (per 100,000 persons)						Trend segment		
	2006	2019	2020(Pandemic epoch 1)	2021(Pandemic epoch 2)	2022 (Pandemic epoch 3)	2023 (Pandemic epoch 4)	Year	Annual Percentage Change (95% CI)	P-Value
	Observed	Observed	Observed & Predicted (Excess %)	Observed & Predicted (Excess %)	Observed & Predicted (Excess %)	Observed & Predicted (Excess %)			
All digestive cancers	78.77	70.51	70.83 & 70.11 (1.03)	72.50 & 69.32 (4.59)	71.11 & 68.74 (3.44)	71.73 & 68.21 (5.16)	2006-2018	-0.81 (-1.37, -0.64)	0.006
							2018-2023	0.25 (-0.40, 1.84)	0.376
Colorectal cancer	33.58	24.85	25.09 & 24.49 (2.45)	25.96 & 23.95 (8.40)	25.28 & 23.55 (7.33)	25.18 & 23.14 (8.83)	2006-2013	-2.87 (-3.87, -2.51)	0.001
							2013-2019	-1.49 (-2.32, -0.73)	0.006
							2019-2023	0.39 (-0.40, 2.03)	0.267
Pancreatic cancer	18.55	19.04	19.18 & 19.29(-0.59)	19.80 & 19.24 (2.90)	19.41 & 19.32 (0.51)	19.75 & 19.43 (1.63)	2006-2014	0.09 (-0.91, 0.36)	0.771
							2014 -2023	0.56 (0.31, 1.53)	0.031
Hepato-cellular carcinoma	7.38	8.83	8.82 & 8.84 (-0.18)	8.80 & 8.77 (0.39)	8.63 & 8.57 (0.69)	8.66 & 8.45 (2.55)	2006-2012	3.30 (2.86, 4.04)	< 0.0001
							2012-2015	1.54 (-1.14, 2.80)	0.165
							2015-2023	-1.01 (-1.50, 0.56)	0.015
Esophageal cancer	7.92	6.93	6.75 & 6.72 (0.42)	6.84 & 6.60 (3.62)	6.77 & 6.59 (2.81)	12.60 & 6.52 (93.22)	2006-2018	-1.12 (-2.24, 0.13)	0.053
							2018-2023	-0.35 (-1.16, 1.24)	0.422
Gastric cancer	6.53	4.88	4.93 & 4.78 (3.32)	4.87 & 4.60 (5.95)	4.71 & 4.51 (4.34)	4.72 & 4.41 (7.11)	2006-2018	-2.19 (-3.02, -1.98)	0.002
							2018-2023	-1.18 (-1.88, 0.56)	0.126
Intra-hepatic cholangio-carcinoma	2.08	3.32	3.34 & 3.42 (-2.34)	3.61 & 3.54 (1.98)	3.63 & 3.64 (-0.27)	3.95 & 3.74 (5.61)	2006-2023	3.72 (3.53, 3.92)	< 0.0001
Extra-hepatic cholangio-carcinoma	0.38	0.44	0.45 & 0.47 (-4.26)	0.46 & 0.49 (-6.12)	0.54 & 0.51 (5.88)	0.51 & 0.53 (-3.77)	2006-2009	-6.64 (-11.85, -2.27)	0.007
							2009-2013	-0.38 (-2.96, 9.29)	0.753
							2013-2023	5.82 (0.68, 9.37)	0.042
Gallbladder Cancer	1.13	0.91	0.95 & 0.88 (7.95)	0.9 & 0.89 (1.12)	0.87 & 0.87 (0.00)	0.90 & 0.84 (7.14)	2006-2023	-1.39 (-1.64, -1.16)	< 0.0001

Abbreviations: CI, confidence interval.

Table 3: Observed and predicted age-standardized all-cause mortality rates during the COVID-19 pandemic for all digestive cancers and by cancer type.

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	2006	2019	2020 (Pandemic epoch 1)			2021 (Pandemic epoch 2)			2022 (Pandemic epoch 3)			2023 (Pandemic epoch 4)		
	observed	observed	observed	pre- dicted	excess	observed	pre- dicted	excess	observed	pre- dicted	excess	observed	pre- dicted	excess
Overall	78.77	70.51	70.83	70.11	1.03%	72.5	69.32	4.59%	71.11	68.74	3.44%	71.73	68.21	5.16%
Female	60.62	53.13	53.52	52.75	1.46%	55.56	52.02	6.80%	54.53	51.49	5.89%	55.18	51.03	8.13%
Male	102.16	91.24	91.56	90.68	0.97%	92.58	89.83	3.06%	90.95	89.11	2.07%	91.58	88.37	3.63%
25-44	4.48	4.63	4.75	4.79	-0.84%	4.85	4.87	-0.41%	4.89	4.84	1.03%	4.85	4.87	-0.41%
45-64	54.74	53.76	53.66	52.9	1.44%	52.72	52.01	1.37%	52.9	51.45	2.82%	52.35	50.8	3.05%
≥65	278.94	238.78	240.36	238.25	0.89%	250.49	235.74	6.26%	243.01	234.35	3.70%	247.24	233.05	6.09%
White	75.97	69.21	69.59	68.86	1.06%	71.99	68.31	5.39%	70.77	67.96	4.14%	71.78	67.59	6.20%
Black	108.66	88.72	88.46	87.34	1.28%	89.05	85.02	4.74%	86.75	83.36	4.06%	87.14	81.8	6.52%
Asian/ PI	70.92	57.45	56.78	56.01	1.38%	60.46	53.26	13.51%	57.11	52.58	8.61%	56.5	51.77	9.14%
His- panic	74.34	67.44	68.32	67.76	0.83%	68.14	67.59	0.81%	68.4	66.64	2.64%	67.35	66.07	1.93%
AI/AN	78.17	71.66	76.49	73.06	4.70%	75.37	73.22	2.93%	70.95	71.8	-1.19%	70.68	71.07	-0.54%

* Age-standardized all-cause mortality rates are expressed per 100,000 persons.

Table 4: Observed and predicted age-standardized all-cause mortality rates during the COVID-19 pandemic for all digestive cancers by subgroups.

Discussion

The ASACM in digestive cancers, which had been on a continuous downward trend from 2006 to 2019, reversed to an upward trend from 2019 to 2023, likely due to the negative impact of the COVID-19 pandemic. For most types of digestive cancers, the ASACM demonstrated an upward trend during pandemic with the ASACM of pancreatic cancer, ICC, and ECC increasing significantly. Previously significant decreasing trends became non-significant (gastric cancer) or shifted to non-significant increases (digestive cancer overall and CRC), and non-significant decreases for esophageal cancer slowed. Only exception was observed for gallbladder cancer, where the mortality rate slightly increased in 2020 compared to 2019, but subsequently returned to a decreasing trend from 2021.

Although the proportion of COVID-19-related deaths during the pandemic was relatively low, ranging from 1.3% to 3.5%, the indirect effects of the pandemic, both short-term and long-term, which are complex and multifactorial, may have led to this worsening trend. These effects profoundly impacted healthcare systems, leading to disruptions in cancer diagnosis, delays in treatment, and reduced access to medical facilities [25, 26]. The temporary drop in ASACM observed in 2022 may be attributed to the adaptation and recovery of the healthcare system during the later stages of the COVID-19 pandemic. However, further complete observation, including years after the pandemic, is needed to assess whether the ongoing increase in ASACM in 2023 is mainly due to COVID-19 pandemic. In fact, the percentage of COVID-19-related deaths increased continuously from 2020 to 2022 but declined sharply in 2023. The higher proportion of

COVID-19-related deaths observed in men, the older age group, and the AI/ANs and Hispanics suggests that these populations should have receive specialized care in public health crisis in the future.

Since CRC accounts for the highest number of deaths among digestive cancers, it drives the overall ASACM trend. The ASACM of CRC, which decreased from 2006 to 2019, shifted to a stable or slightly increasing trend after 2020, likely reflecting the negative effects of COVID-19. A recovery trend was observed in 2022 and 2023 as COVID-19 mortality gradually decreased. These CDC WONDER database-based findings align with previous studies [27], which used the Surveillance, Epidemiology, and End Results (SEER), National Center for Health Statistics (NCHS), and Global Burden of Diseases (GBD) databases. Similarly, a previous CDC WONDER analysis for CRC ASACM (1999–2022) reported a significant pre-pandemic decline and a non-significant increase from 2020 to 2022 [28]. Regarding the negative impacts of COVID-19 on CRC, screening volumes were significantly reduced during the early pandemic period [29], leading to an increase in diagnoses at advanced stages [30]. Additionally, studies have shown an increase in emergency room visits among CRC patients [31]. The ASACM increased across all ages, genders, and race/ethnicity groups in 2020 and 2021 compared to 2019, but decreased in nearly all subgroups in 2022 and 2023, reflecting a recovery from the impact of COVID-19. Additionally, mortality trends continued to decline in most subgroups in 2023, but increased in Black and AI/AN populations, suggesting a delayed recovery in CRC management and treatment for these groups.

Pancreatic cancer mortality has shown an increasing trend from 2006 to 2023. This trend is also corroborated by another study based on the CDC WONDER database, which demonstrated a 0.2% increase in the APC from 1990 to 2020 [32]. Despite advancements in early diagnostic tests and systemic treatments for pancreatic cancer, these developments have not yet been associated with a reduction in mortality among the elderly, highlighting the challenges in this age group. Our study results highlight that mortality rates for pancreatic cancer are higher among Blacks, likely attributed to factors such as limited access to effective treatment, as well as higher rates of risk factors, including obesity and smoking in the Blacks population [33]. The percentage of COVID-19-related deaths increased consistently from 2020 to 2022, with higher rates observed in AI/AN and Black populations, highlighting the need for targeted management in these race/ethnicities.

HCC mortality showed a significant decreasing trend from 2015 to 2023, with a slower decline from 2019 to 2022, followed by a slight increase in 2023. Similarly, Kim et al. also reported a significant decline in ASACM for HCC from 2018 to 2023 [34]. Subgroup

analysis of our study revealed similar decreasing trends in men, the middle age group, and the Black, Asian/PI, and Hispanic groups, which were likely the key contributors to the overall decline. Meanwhile, this study highlights the increasing HCC mortality in women, individuals aged 65 and older, and the White population, underscoring the need to investigate the underlying causes of this trend and to offer tailored management in these subgroups. The percentage of deaths from COVID-19 among HCC patients averaged 1.7%, similar to the average for all digestive cancers. Unlike other cancers, the impact of COVID-19 on mortality was notably higher in women and younger individuals.

Among all digestive cancer mortalities, COVID-19-related deaths disproportionately affected men, the old age group, and AI/AN and Hispanic populations, while excess deaths were highest among women, the old age group, and Asian/PI populations. Despite this, COVID-19-related deaths comprised only about 2% of all digestive cancer fatalities. It is likely that the changes in cancer mortality rates were due to a combination of factors such as diagnostic delays, restricted access to treatment, and insufficient management of critically ill patients during the COVID-19 pandemic [25, 35, 36]. Furthermore, although predicted to be highest in 2020, the proportion of COVID-19-related deaths in digestive cancers and specific cancer types steadily increased from 2020 to 2022. This can be interpreted as an increase in the reporting of COVID-19-related deaths, which represents the cumulative impact of the pandemic on ASACM over time.

Our study has several strengths. First, it provides trends for overall digestive cancer mortality as well as mortality trends for each of the eight individual cancers, extending through 2023, and offers a comprehensive analysis of mortality throughout the entire COVID-19 pandemic period. To the best of our knowledge, this is the first that analyzing GI cancer mortality during the entire span of the COVID-19 pandemic. Second, it is the first study to directly calculate the proportion of deaths attributed to COVID-19 for each type of cancer. The trends were compared throughout the entire pandemic period, revealing no significant differences across various digestive cancer types. Third, the study presents the trends of each digestive cancer by gender, age, and race/ethnicity. Through subgroup analyses, we were able to identify mortality disparities and pinpoint vulnerable group during the COVID-19 pandemic. Lastly, by prediction analyses, this study identified the cancer types and cancer subgroups that deviated most significantly from previous mortality trends due to COVID-19. This information can provide valuable insights into where improvements should be made in healthcare systems to address the vulnerabilities exposed during the pandemic.

Our study has several inherent limitations associated with the use of big data analysis. First, the cause of death in cancer patients

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may have been misclassified, or COVID-19-related deaths may have been underestimated. Second, the CDC data is anonymized, which restricts access to information such as social determinants of health, treatment rates, and comorbidities, all of which can influence mortality. Third, we did not account for differences across U.S. states, where variations in risk factors and healthcare access could impact mortality trends for different cancers.

In conclusion, the COVID-19 pandemic temporarily reversed the decreasing trend of digestive cancer mortality. Although the proportion of COVID-19-related deaths during the COVID-19 pandemic was relatively low, the indirect impacts of COVID-19 on the healthcare environment for cancer patients may have played a significant role in the shift in mortality within this population. The observed disparities in mortality trends by gender, age, and race/ethnicity suggest the critical need for targeted interventions.

Authors' Contributions:

Concept and Design: YEC, MSR-Z, FJ, JDY

Data Acquisition and/ or Interpretation: XH, SQ, ZY, YB, YG, XL, KQ, XH, CL, YY, YEC, MSR-Z, YHY, CF, AGS, FJ, JDY.

Drafting the Manuscript: YEC, MSR-Z, XH.

Critical Revision: XH, SQ, ZY, YB, YG, XL, KQ, XH, CL, YY, YHY, CF, AGS, FJ, JDY.

Final Approval and Agreement: All Authors.

Conflict of Interest: JDY provides a consulting service for AstraZeneca, Eisai, Exact Sciences, Exelixis, Fujifilm Medical Sciences. FJ provides speaking services for Gilead Sciences, MSD, and Ascleptis, and consulting/advisory board services for Gilead and MSD. AGS has served as a consultant or on advisory boards for Genentech, AstraZeneca, Bayer, Eisai, Exelixis, Merck, Elevar, Boston Scientific, Sirtex, HistoSonics, Fujifilm Medical Sciences, Exact Sciences, Glycotest, Abbott, Roche, Freenome, and GRAIL. Other authors declare no conflict of interest.

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