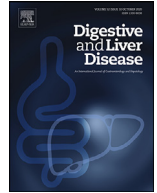




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Oncology

Changes in digestive cancer diagnosis during the SARS-CoV-2 pandemic in Italy: A nationwide survey



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ABSTRACT

Background: The SARS-CoV-2 pandemic has had a huge impact on healthcare systems, resulting in many routine diagnostic procedures either being halted or postponed.

Aims: To evaluate whether the diagnoses of colorectal, gastric and pancreatic cancers have been impacted by the SARS-CoV-2 pandemic in Italy.

Methods: A survey designed to collect the number of histologically-proven diagnoses of the three cancers in gastroenterology services across Italy from January 1 to October 31 in 2017–2020. Non-parametric ANOVA for repeated measurements was applied to compare distributions by years and macro-areas.

Results: Compared to 2019, in 2020 gastric cancer diagnoses decreased by 15.9%, CRC by 11.9% and pancreatic by 9.9%. CRC distributions showed significant differences between all years, stomach cancer between 2018 and 2020 and 2019–2020, and pancreatic cancer only between 2017 and 2019. The 2019–2020 comparison showed fewer CRC diagnoses in the North (-13.7%), Center (-16.5%) and South (-4.1%), fewer stomach cancers in the North (-19.0%) and South (-9.4%), and fewer pancreatic cancers in the North (-14.1%) and Center (-4.7%), with an increase in the South (+12.3%). Distributions of CRC and gastric cancer were significantly different between all years in the North.

Conclusions: This survey highlights the concerning effects of the COVID-19 pandemic on the diagnostic yield of gastroenterology services for stomach, colorectal and pancreatic cancers in Italy.

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1. Introduction

The SARS-CoV-2 pandemic has had a rapid and dramatic effect on healthcare systems around the world. Due to the critical need to divert healthcare efforts to absorb the rapidly increasing number of COVID-19 patients, many activities have had to be

quickly reorganized or reduced in order to accommodate the influx of patients. In Italy, during the first wave of the pandemic, which occurred between 1 March and 30 June 2020, many activities related to routine diagnostic procedures were either halted or postponed. In a recently published survey, up to 3% of routine endoscopic procedures were completely stopped, while the remaining ones were converted to emergency or oncological patient follow-ups [1]. A significant disruption in colon cancer screening programs occurred, including a complete suspension of both first (fecal immunochemical test) and second (colonoscopies) levels in some areas [2]. Furthermore, 13% excess mortality was registered in Italy between January and November 2020. Importantly, how-

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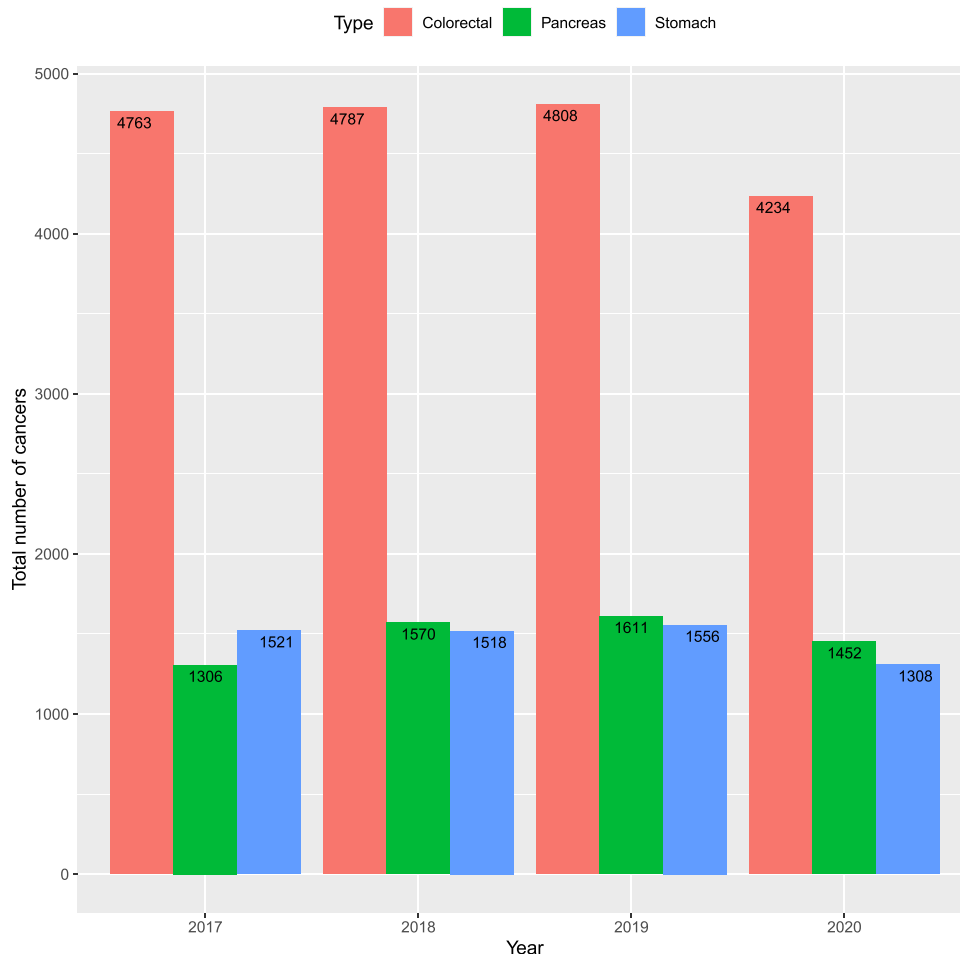


Fig. 1. Distribution (across centers) of the number of cancers separated by year and type.

Table 1

Summary statistics (across all 49 centers) aggregated by type of cancer and year (min, max, average, standard deviation – SD -, total, absolute and relative percentage variation) and Friedman test for the number of colorectal, stomach and pancreatic cancer diagnoses per year.

Type of cancer	Year	Min [§]	Max [§]	Average [§]	SD [§]	Total	D	Δ	Post-hoc Friedman test p-values [#]
Colorectal	2017	0	331	97.20	81.34	4763			2017 vs 2020 ($p = 0.045$); 2018 vs 2020 ($p = 0.001$); 2019 vs 2020 ($p = 0.003$)
	2018	2	320	97.69	73.19	4787	24	0.50	
	2019	0	297	98.12	74.82	4808	21	0.44	
	2020	6	308	86.41	74.66	4234	-574	-11.94	
Pancreas	2017	0	171	27.79	33.79	1306			2017 vs 2019 ($p = 0.034$)
	2018	0	266	33.40	45.70	1570	264	20.21	
	2019	0	211	34.28	41.75	1611	41	2.61	
	2020	0	141	30.89	33.58	1452	-159	-9.87	
Stomach	2017	0	105	31.04	26.33	1521			2018 vs 2020 ($p = 0.014$); 2019 vs 2020 ($p = 0.010$)
	2018	1	126	30.98	25.80	1518	-3	-0.20	
	2019	0	116	31.76	26.29	1556	38	2.50	
	2020	1	101	26.69	20.60	1308	-248	-15.94	

[§] Min, Max, Average refer to minimum, maximum, average and SD of number of cancers computed across all 49 centers with respect to the specific type of cancer at specific year;

^D is the absolute variation in the total number of cases compared to the previous year

^Δ is the percentage relative variation in the total number of cases compared to the previous year.

[#] the p-values are adjusted for Bonferroni correction.

ever, during the early months of the first wave of the pandemic (March-April), the number of deaths from any cause was 48,761 as opposed to 28,000 registered deaths from COVID-19 [3], indicating that excess deaths from any cause were far higher than those directly attributed to COVID-19.

Digestive cancers represent a huge burden in Europe as well in Italy [4]. Recent estimates indicate that cancer of the colorectum, stomach and pancreas represent the second, sixth and seventh most frequent tumors, respectively, in both sexes in Italy in 2020 [5].

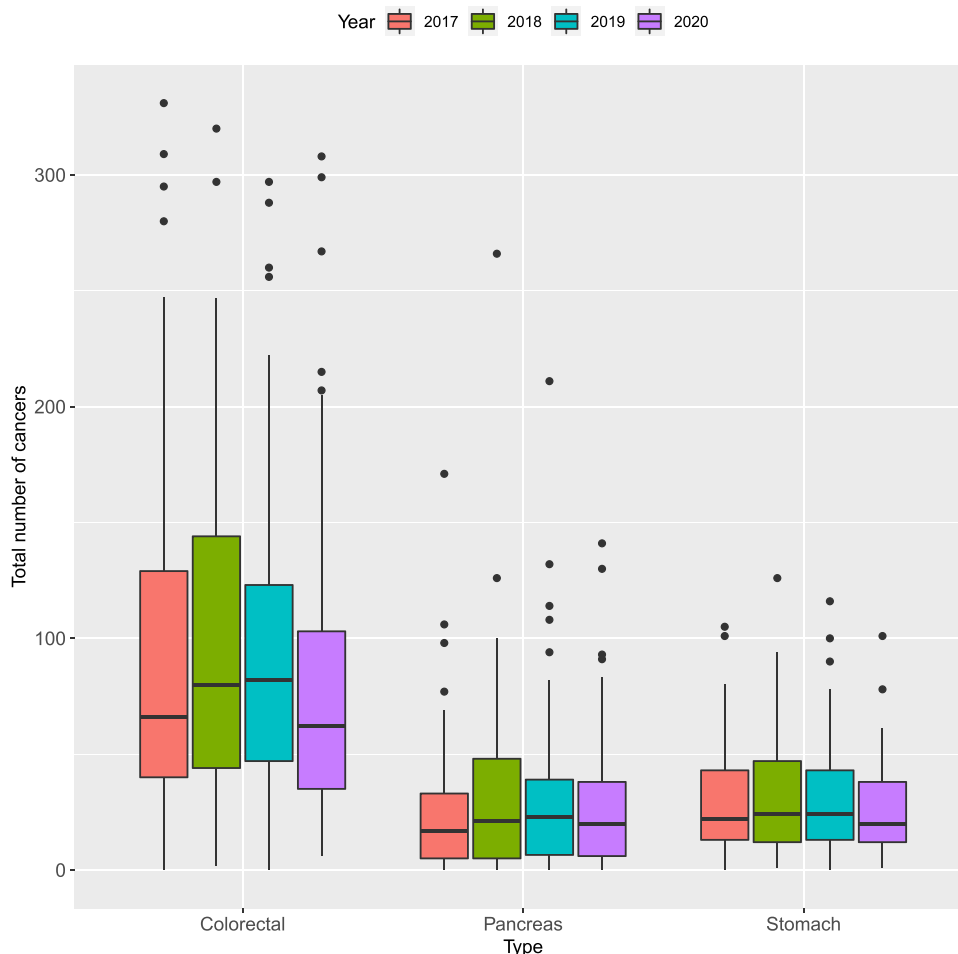


Fig. 2. Total number of cancers by year and type.

In this work we investigated whether in Italy the diagnosis of the three most incidental digestive cancers was impacted by the SARS-CoV-2 pandemic, by comparing the number of diagnoses made from January to October 2020 to those made during the same 10-month period in the previous three years.

2. Methods

We developed a web-based survey designed to assess the number of histologically-proven diagnoses of colorectal, gastric and pancreatic adenocarcinomas made in gastroenterology (GE) services across Italy.

The working group that formulated the survey was composed of the executive board of FISMAD (Italian Federation of Gastroenterological Societies) which included the presidents of the Italian Society of Gastroenterology and Digestive Endoscopy (SIGE, AB), the Italian Society of Digestive Endoscopy (SIED, LP), the Italian Association of hospital gastroenterologists and digestive endoscopists (AIGO, FM) together with the FISMAD president (EB) and one board member (LR).

A 9-question questionnaire (see supplementary information) was designed by the working group and administered through SurveyMonkey to the GE services across the country. The link to access the survey was emailed to all members affiliated to AIGO, SIED and SIGE.

The survey questions were aimed at assessing the number of diagnosed gastric, colorectal and pancreatic adenocarcinomas from January 1 to October 31 in 2017, 2018, 2019 and 2020. Ethics com-

mittee approval was not required for this type of survey. Data collection took place between 1 November 2020 and 22 January 2021.

2.1. Statistical analysis

The distributions of the number of diagnosed cancers were analyzed by plots (boxplots and bar charts), whereas summary statistics, across all 49 centers, were reported as the minimum, maximum, average, standard deviation and total number of cases aggregated by year (from 2017 to 2020) and by type (colorectal, gastric and pancreatic) of cancer. Similarly, a second descriptive analysis was conducted separately for each macro-area (North, Center and South).

In order to compare the distributions of the number of diagnoses across years, we applied the non-parametric ANOVA for repeated measurements (Friedman test, *p*-values adjusted for Bonferroni correction), separately for each type of tumor and then for each macro-area. All statistical analyses were performed using R software (version 4.0.3).

3. Results

A total of 61 GE services replied to the survey (representing approximately 35% of all services in Italy) [6], with complete datasets available from 49. The distribution of the replies was: 32 from the North (65.3%), 6 from the Center (12.2%), and 11 from the South (22.4%).

Table 2

Summary statistics (across all 49 centers) aggregated by type of cancer and year (min, max, average, standard deviation – SD –, total, absolute and relative variation) and Friedman test for the number of colorectal, stomach and pancreatic cancer diagnosis per year and macro-area.

Macro Area	Type of cancer	Year	Min \$	Max \$	Average \$	SD \$	Total	D	Δ	Post-hoc Friedman test p-values [#]
North	Colorectal	2017	38	331	116.31	86.89	3722			2017 vs 2020 ($p=0.015$); 2018 vs 2020 ($p<0.001$); 2019 vs 2020 ($p=0.003$)
		2018	35	320	114.63	75.25	3668	-54	-1.45	
		2019	31	297	110.13	71.17	3524	-144	-3.93	
		2020	31	299	95.06	70.83	3042	-482	-13.68	
	Pancreas	2017	0	171	35.93	38.67	1078			
		2018	0	266	43.93	53.42	1318	240	22.26	
		2019	0	211	43.73	48.22	1312	-6	-0.46	
		2020	0	141	37.57	37.85	1127	-185	-14.10	
	Stomach	2017	6	105	40.63	26.43	1300			
		2018	5	126	40.34	26.09	1291	-9	-0.69	
		2019	4	116	39.78	25.60	1273	-18	-1.39	
		2020	4	101	32.22	21.43	1031	-242	-19.01	
Center	Colorectal	2017	0	100	39.50	36.86	237			
		2018	2	121	41.17	44.79	247	10	4.22	
		2019	0	178	53.50	65.27	321	74	29.96	
		2020	6	107	44.67	38.09	268	-53	-16.51	
	Pancreas	2017	0	25	7.67	9.50	46			
		2018	0	24	9.00	9.59	54	8	17.39	
		2019	0	41	10.67	15.63	64	10	18.52	
		2020	1	31	10.17	11.11	61	-3	-4.69	
	Stomach	2017	0	17	8.67	7.00	52			
		2018	1	26	12.00	9.65	72	20	38.46	
		2019	0	22	10.67	8.98	64	-8	-11.11	
		2020	2	18	9.67	5.82	58	-6	-9.38	
South	Colorectal	2017	4	210	73.09	62.15	804			
		2018	6	205	79.27	62.84	872	68	8.46	
		2019	5	256	87.55	85.21	963	91	10.44	
		2020	6	308	84.00	95.85	924	-39	-4.05	
	Pancreas	2017	0	55	16.55	16.97	182			
		2018	0	50	18.00	18.29	198	16	8.79	
		2019	1	70	21.36	19.14	235	37	18.69	
		2020	0	73	24.00	22.92	264	29	12.34	
	Stomach	2017	0	60	15.36	16.51	169			
		2018	1	55	14.09	15.04	155	-14	-8.28	
		2019	0	90	19.91	24.87	219	64	41.29	
		2020	1	59	19.91	16.59	219	0	0.00	

^s Min, Max, Average refer to minimum, maximum, average and SD of number of cancers computed across all 49 centers with respect to the specific type of cancer at specific year;

^D is the absolute variation in the total number of cases compared to the previous year.

^Δ is the percentage relative variation in the total number of cases compared to the previous year.

[#] the p-values are adjusted for Bonferroni correction.

Fig. 1 shows the cancer distribution across centers by year and type. For all the years, CRC was the most prevalent with also the largest variability across centers; gastric and pancreatic cancer distributions were more similar in terms of median level and variability (see also Table 1). Fig. 2 reports the total number of cases per year and separated by type. Between January 1 and October 31 2020, a total of 4234, 1308 and 1452 center-reported diagnoses of adenocarcinomas of the colorectum, stomach and pancreas, respectively were recorded.

As reported in Table 1, compared to 2019, in 2020 the total number of stomach cancer diagnoses showed the highest reduction across Italy (-15.9%), followed by CRC (-11.9%) and pancreatic cancer (-9.9%).

When comparing the number of cases (of the 49 centers) across years, separately for each type of tumor, the following distributions were significantly different (see Table 1): for CRC, 2017 vs 2020 ($p=0.045$), 2018 vs 2020 ($p=0.001$) and 2019 vs 2020 ($p=0.003$); for stomach cancer 2018 vs 2020 ($p=0.014$) and 2019 vs 2020 ($p=0.01$); and for pancreatic cancer, 2017 vs 2019 ($p=0.034$).

We then considered the three major Italian macro-areas: the North, Center and South. The total number of cases by year, type

and macro-area are reported in Fig. 3. Compared to 2019, the total number of diagnoses for colorectal cancer decreased in all three areas (see Table 2): North -13.7%, Center -16.5%, and South -4.1%. Stomach cancer, which had the highest diagnosis reduction at a national level in 2020 compared to 2019 (-15.9%, see Table 1), showed a different behavior when analyzed separately for each macro-area: while no changes were recorded in the South, in the North and Center 19.0% and 9.4% reductions, respectively were recorded. When considering pancreatic cancer, compared to 2019, in 2020 a 12.3% increase in diagnoses was recorded in the South, and 14.1% and 4.7% reductions were recorded in the North and Center, respectively.

By comparing the distributions across years separately for each type and macro-area, no significant differences were found in both the Center and Southern Italy for all cancer types (see Table 2). On the other hand, for northern Italy the following significant results were found: for CRC 2017 vs 2020 ($p=0.015$), 2018 vs 2020 ($p < 0.001$) and 2019 vs 2020 ($p=0.003$); for stomach cancer 2017 vs 2020 ($p=0.011$), 2018 vs 2020 ($p < 0.001$) and 2019 vs 2020 ($p=0.001$). No significant changes were found for pancreatic cancer in the North.

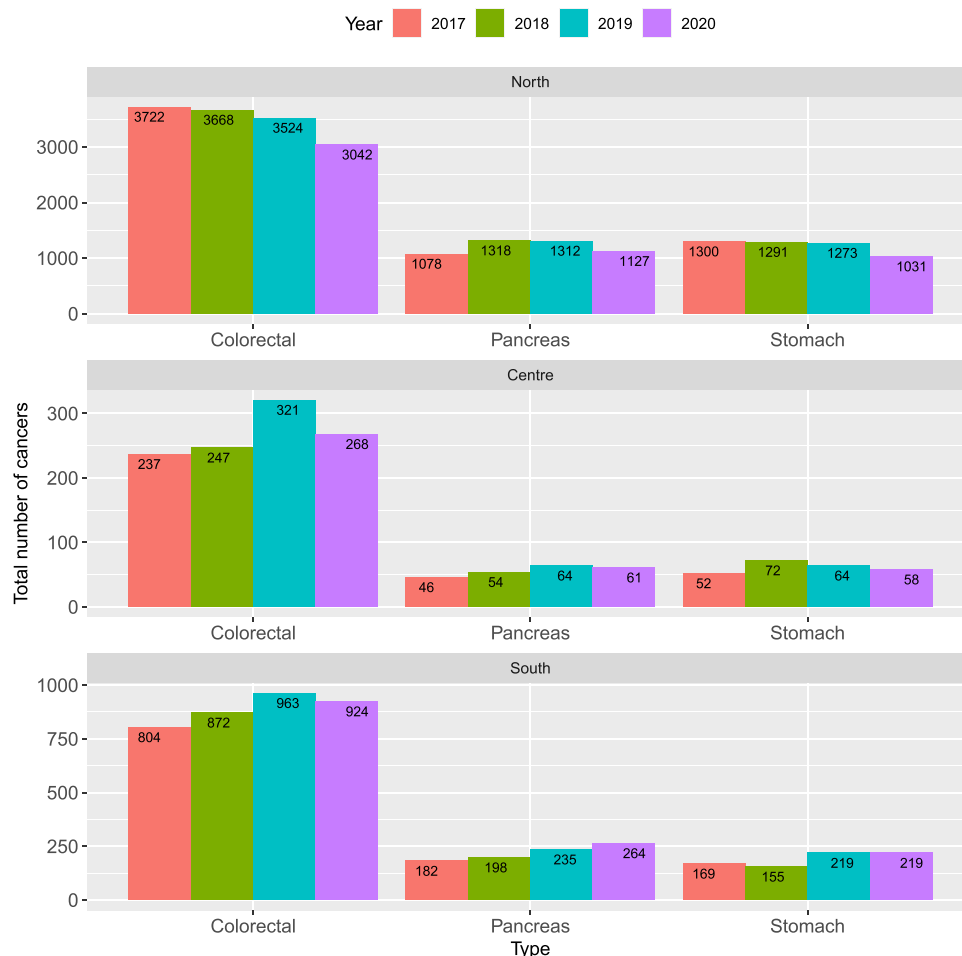


Fig. 3. Total number of cancers by year, type and macro-area.

4. Discussion

The aim of our study was to assess whether under the SARS-CoV-2 pandemic, the diagnoses of digestive cancers with a high impact on the population such as colorectal, stomach and pancreatic adenocarcinomas, had been affected. Compared to 2019, in 2020 we found a 11.9% reduction in the total number of diagnoses of CRC, a 15.9% reduction in stomach cancer diagnoses, and 9.9% reduction in pancreatic cancer diagnoses. Importantly, at a national level CRC and stomach cancer showed significant differences when comparing data between 2020 and 2019 and 2018. Considering data from the three macro-areas, we found that in northern Italy, compared to 2019, the total number of CRC, stomach and pancreatic cancer diagnoses decreased by 13.7%, 19.0% and 14.1%, respectively. Comparing the diagnosis distributions across years, in 2020 in the North, only CRC and stomach cancer were significantly different from the previous years, while no differences were found in the Center and South for any cancer.

Our analysis might reflect differences in the areas that were affected by COVID-19, in particular during the first phase of the pandemic in which the North had a dramatic spread of infection associated with a high mortality, while in the Center-South the spread was much lower [7]. Importantly, during the early months (March-April) of the first phase of the epidemic, the greater impact of mortality in the cities in Northern Italy was only partially (66%) explained by the deaths notified as COVID-19 [8].

Our data confirm the anticipated negative effect that the SARS-CoV-2 pandemic has had on highly-impacting diseases such as cancers. There were fewer diagnoses of CRC throughout the country, which were more pronounced and significant in the North. Data on CRC also reflect the difficulties of screening programs which had to be halted across Italy. Data published by the Italian National Screening Observatory (ONS) and including information from 1 January 2020 to 30 September 2020, estimated a 4.7 standard month screening delay across the country with peaks of 7.1 and 8.4 months (Lombardy and Calabria, respectively). Importantly, the ONS estimated that 1168 CRC and 6700 advanced adenomas had not been carried out across the country, though under normal circumstances they would have been [2].

The fact that these diagnoses were not carried out could have an impact on disease stage and mortality. In fact, recent data on delays from colorectal cancer screening showed a possible 12% increase in mortality for delays beyond 12 months [9]. This was also echoed by two different studies from Hong Kong and the UK, indicating that missing diagnoses due to surges in SARS-CoV-2 would lead to increased mortality [10,11].

The data presented show how reductions in the volume of specialized GE diagnostic activities due to the COVID-19 pandemic have led to a substantial number of diagnoses not being carried out of the three “big killers”, namely stomach, colorectal and pancreatic cancers. These effects of the COVID-19 pandemic could drastically impair the protective effect of CRC screening that has been accumulated over two decades, and reverse the positive trends observed for colorectal and stomach cancers. In fact,

between 2008 and 2016, 1.4 and 1.2% reductions were recorded in colorectal cancer incidence in men and women annually, respectively. In addition, considering the colorectal cancer screening age-target (50–69 years), 4.1% and 3.0%, yearly reductions were recorded respectively, highlighting the important effect of screening programs on colorectal incidence; a lower trend has also been recorded for stomach cancer (–1.9% and –1.4% in men and women) [5].

Data from the present survey highlight the need for an urgent response to this critical situation by decision-makers at different institutional levels, with adequate actions aimed at restoring the level of activity necessary to meet the epidemiological needs and make up for the accumulated delay, both in routine GE diagnostic activity and CRC screening program.

The GE workforce was already inadequate to meet the needs of specialized health care in 2014 [6]. Consequently, with the COVID-19 pandemic, it is imperative that an appropriate, efficient and stable allocation of resources is carried out, which is truly commensurate with healthcare needs.

We acknowledge some limitations. First of all, our study does not cover the entire Italian healthcare system. However, considering that according to Ministry data in 2014 there were 174 gastroenterology services in Italy [6], our survey captured data from approximately one third of them. We thus believe that our sample provides a significant nationwide representation of the diagnostic activities of digestive cancers during the COVID-19 pandemic. Furthermore, our study does not assess the impact of the COVID-19 pandemic on the cancer-related mortality. We can reasonably assume that the significant proportions of missed diagnoses will affect the disease stage and, in turn, the number of deaths (as discussed above), but more studies will be needed in the near future to assess this aspect.

In conclusion, this survey highlights the concerning effects of the COVID-19 pandemic on GE diagnostic activities related to stomach, colorectal and pancreatic cancers. These data should support appropriate and timely decision making and planning of support for GE in the months and years to come.

Declaration of Competing Interest

The authors of the manuscript and the researchers involved in the study declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.dld.2021.02.021](https://doi.org/10.1016/j.dld.2021.02.021).

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