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Research Article

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Malignant mesothelioma diagnosis and survival in the time of COVID-19 in Northeastern Italy

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Abstract

Early data suggest a decrease in the diagnosis of new cancers and, consequently, an increase in avoidable deaths during the COVID-19 pandemic. To assess the impact of the pandemic on new diagnoses of malignant mesothelioma and survival in a population-based setting, we analysed 109 patients records from the Friuli Venezia Giulia Register during the period 2019-2020. Clinical data and information on COVID-19 diagnosis were retrieved and the number of mesothelioma diagnoses recorded in 2020 was compared to those recorded in 2019. A 2019-2020 comparison was also performed for survival time. Compared to 2019, in 2020 the total number of mesothelioma diagnoses and pleural cases increased by 9.2% and 16.7%, respectively, whereas peritoneal cases decreased by 45.2%. Mesothelioma distribution by period of diagnosis in 2020 showed no significant changes during the lockdown period, compared to the same period of the previous year, with an increase (+36.36%) in June-September and a decrease (-60%) in the second wave of the pandemic. Only six patients developed COVID-19. For the period 2019-2020, median survival was 11.5 and 7 months for pleural and peritoneal mesothelioma, respectively. Younger age ($p<0.01$) and epithelioid histology improved survival. Compared to 2019, in 2020 median survival was worse for peritoneal mesotheliomas (6 versus 12.5 months) and females (6 versus 9 months). Overall, the pandemic did not affect mesothelioma diagnosis, but survival is still poor. Our data evidence the indirect impact of the pandemic control measures on delays in cancer diagnosis and treatment, which in turn may have had a major effect on survival time. This means that early diagnosis is essential to ensure the clinical management of mesothelioma patients and provide adequate support and compensation.

Keywords: Mesothelioma, COVID-19, Diagnosis, Survival, Asbestos, Pleura, Peritoneum.

Introduction

Malignant mesothelioma (MM) is a rare and aggressive cancer arising in the pleura, peritoneum or other serosal surfaces and is known for its relationship with asbestos exposure and its poor prognosis. Long-term survival is rarely seen: most of mesothelioma patients do not survive the disease beyond 12 months [1].

Patients suffering from cancer may be a particularly vulnerable population during a pandemic [2]. In the early days of the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the susceptibility of cancer patients to the adverse outcomes of viral infection has been investigated. In Hubei, China, an incidence of 25% of severe COVID-19 pneumonia and a death rate of about 20% were found in patients with cancer [3]. In general, the proportion of patients with COVID-19 and cancer varies between 0.5% and 6% [4] and the case-mortality rate for cancer patients with COVID-19 is 18% [3]. Another study in Wuhan, China, reported that in 39% of cancer patients, compared with 8% of patients without cancer, transfer to the intensive care unit was necessary, suggesting a higher risk of developing severe complications in cancer patients [5]. Male sex and chemotherapy or surgery <1 month before the onset of symptoms were important risk factors for death in patients with cancer and concurrent COVID-19 infection [2,4].

Unquestionably, mesothelioma patients, who are often older and with concurrent restrictive lung disease, are even more at risk of an unfavourable outcome where there is infection with SARS-CoV-2 [6].

There is no doubt that cancer should be diagnosed and treated without delay. Timely diagnosis might allow the cancer to be indentified at a curable stage in order to prevent complications. Early diagnosis and treatment are even more critical for those patients with asbestos-related cancer, like mesothelioma, due to its shorter outlook compared with other cancers.

As several studies have noticed, COVID-19 pandemic has had a significant negative impact on referral and procedural rates for patients with new suspected symptoms of cancer. The reasons were multifactorial. During the peak of pandemic, many health care facilities needed to focus on screening for and treating patients with known or suspected COVID-19. As a consequence, health care facilities rapidly suspended routine screening, and

decreased endoscopic and cancer surgical services to increase capacity for patients with COVID-19 complications. At the same time, patients were frightened, especially the older one, and many have chosen to delay their attendance with primary healthcare or hospital practitioners due to concern about visiting the health care facilities and the risk of contracting SARS-CoV-2 [7,8]. As a result of these pandemic control efforts, London et al. (2020) found a significant reduction in the number of new cancer identified, with a decrease of 65.2% incidence of new cancer diagnoses in April 2020 compared to 2019. Evaluating referrals by cancer type, the authors demonstrated that patients with a new diagnosis of lung cancer dropped 46.8% in April 2020 compared to 2019 [7]. In England, modeling studies estimated changes in future death rates resulting from diagnostic delays due to COVID-19 [9,10]. According to these studies, the decrease in the diagnosis of new cancers might increase the number of patients with late-stage cancers leading to decreased survival for these patients.

During the first wave of the pandemic, hospitals in Italy saw a significant reduction in many activities related to diagnostic procedures and cancer screening services [11]. This could translate into worse prognosis and reduced survival for patients if cancer was diagnosed at a later stage, making treatment more difficult. In March and April 2020, in Italy, the excess total mortality was high (i.e., a total of over 46,000 deaths) as compared to 28,000 COVID-19 registered deaths in the same period. A plausible explanation for this difference is a substantial under-certification of COVID-19 deaths, but some of these excess deaths are probably due to inadequate management and treatment of other diseases during the pandemic [12].

Early reports have suggested that concurrent COVID-19 infection with any form of lung cancer carries a poor prognosis. The effect of SARS-CoV-2 infection on 200 patients with thoracic malignancies has been investigated in a multicentre observational study (TERAVOLT registry). Only 8 (4%) of the 200 patients diagnosed with COVID-19 reported pleural mesothelioma and were included in this analysis. All 8 patients with COVID-19 and MM were hospitalized; the majority of them had comorbidities [13].

Since 1995, the Friuli Venezia Giulia Mesothelioma Register, included in the network of the Italian National Mesothelioma Register (ReNaM), records the incident cases of MM in the Region, an industrial area in the north-east of Italy with a history of extensive occupational asbestos exposure, mainly due to the existence of several shipyards in the Trieste-Monfalcone district [14].

Based on these assumptions, to assess the impact of the COVID-19 pandemic on MM diagnosis and survival in a population-based setting, we analysed patient records from the Friuli Venezia Giulia Mesothelioma Register. Specifically, we aim (1) to examine the new diagnoses of MM and survival trends for patients with mesothelioma collected between January and December 2020 compared to those collected during the same period of the previous year and (2) to evaluate the effect of COVID-19 infection on patients with MM.

Methods

Study Population

Electronic records for patients with MM, diagnosed from 1995 to 2020, were derived from the Friuli Venezia Giulia Mesothelioma Register. The register covers a region with 1,206,216 inhabitants, divided into four districts (Trieste, Gorizia, Udine, Pordenone), called provinces, according to the geographic location. Newly diagnosed MM patients are notified to the register through hospital discharge diagnoses and notes from health care institutions (especially pathology and histology departments, pneumology and chest surgery wards). After notification, the Friuli Venezia Giulia Operative Regional Centre (COR) collects data from the clinical records, including sex and age, tumor site and morphology, and date of diagnosis (i.e., the day of acquiring cytology or histology material for microscopical verification) and classifies cases according to diagnostic certainty achieved (certain, probable and possible) [15]. Data on occupational and residential history together with lifestyle habits, were reported directly from the subjects or their relatives using a standardized questionnaire administered by an occupational physician. Exposure to asbestos was classified as occupational (certain, probable, possible), household, environmental, hobbies, unlikely or unknown, following the National Guidelines [15].

All cases of MM reported among residents and diagnosed between January 2019 and December 2020, during the two 12-month periods before and after the introduction of pandemic lockdown measures, were included in the study. Exposure information and medical data were reviewed (by occupational physicians) in all cases included for analysis. The diagnosis of MM was based on the pathology report, including immunohistochemical staining documenting the presence and location of MM. Mesothelioma of the pericardium and tunica vaginalis testis were excluded, as they were all cases in which diagnosis was based on clinical and/or radiological examinations only. Demographic and clinical characteristics, including age, sex, smoking status, type of MM diagnosis, comorbidities, current treatment, COVID-19 diagnosis, and need for hospital admission for patients with COVID-19 disease were recorded. Patients were registered COVID- 19 positive when they had a positive test for SARS-CoV-2 using reverse transcription polymerase chain reaction (RT-PCR) techniques. Survival was calculated from the date of diagnosis until the date of death or censored on March 31, 2022, using present analysis. Patient's lifetime occupational history and their asbestos exposure, both occupational and non-occupational, were acquired from the questionnaire.

Statistical Analysis

The distributions of the number of diagnosed mesotheliomas were analyzed by year (2019 versus 2020), sex, age at diagnosis ($\leq$ 69, 70-79, $\geq$80), tumor site, type of diagnosis (histological, cytological, at autopsy) and morphology (epithelioid, sarcomatoid, biphasic and not specified). The number of cases was aggregated as follows: pre-lockdown (January-February), lockdown period/ first wave of the pandemic (March-May), post-lockdown (June-September) and second wave of the pandemic (October-December). In order to compare the distributions of the number of

diagnoses across years, we applied the Pearson's chi- squared test. We also analyzed survival data, comparing MM diagnosed in 2019 to those diagnosed in 2020, based upon parameters such as age at diagnosis, sex, tumor site and histological type. Prognostic factors were tested for significance using the Pearson's chi-squared test. As concerns patients with ascertained COVID-19, we considered all factors (age, smoking status, comorbidities) known from the literature to be associated with COVID-19 outcomes in the general population. All analyses were performed using R (version 4.2.0), with the level of significance set at $p<0.05$.

Results

A total of 109 patients with MM, 91 (83%) males and 18 (17%) females, have been recorded by the Friuli Venezia Giulia Mesothelioma Register in the period 2019-2020 (Table 1). Among these, 96 (88%) were certified as pleural MM and 13 (12%) as peritoneal MM. During the COVID-19 pandemic, 57 cases were diagnosed compared to 52 cases in 2019, but this difference was not statistically significance. Peritoneal MM was uncommon between 2019 and 2020 (8 versus 5) and more frequent in females (n=5, 28%) than in males (n=8, 9%). For the period 2019-2020, all MM cases were diagnosed as certain. The diagnosis was based upon tissue biopsy in most cases (92%) and 20% underwent post mortem examination, whereas cytological examination was only performed in a minority of cases (n=15, 14%). There was no significant difference in histological type between 2019 and 2020. Epithelioid tumors (49 in 2020 versus 35 in 2019) were most common than sarcomatoid tumors (2 in 2020 versus 5 in 2019) or biphasic tumors (4 in 2020 versus 8 in 2019). Most patients had a history of occupational asbestos exposure (data not shown). Men were far likely to have some direct asbestos exposure (about 90%), whereas women were more likely to have only non-occupational exposure (72%).

As reported in Table 1, compared to 2019, in 2020 the total number of MM diagnoses increased by 9.2%. The 2020 versus 2019 comparison showed an increase in the number of new pleural MM diagnoses (+16.7%). By contrast, there was a decrease in the number of newly diagnosed patients with peritoneal MM (-46.1%), but this difference was not significant. In the 91 males and 18 women the mean age at diagnosis was 76.8 years (SD 8.6), and 49% of patients were aged ≥ 80 years, while only 15% were aged ≤ 69 years, without statistical difference between the two years. MM patients aged 70-79 years were more frequently diagnosed in 2020 (+31.6%) than in 2019, but this difference did not reach statistical significance.

Table 1: Main characteristics of patients with mesothelioma.

	2019-2020		2019		2020				χ^2 test 2019 vs 2020
All	N	%	N	%	N	%	D	Delta	-
	109	100	52	48	57	52	+5	+9.17	
Sex									$\chi^2$1=1.39; p =0.237
Male	91	83.5	43	82.7	48	84.2	+5	+10.99	-
Female	18	16.5	9	17.3	9	15.8	0	0	
Age (years)									$\chi^2$1=0.38; p=0.539
≤ 69	17	15.6	9	17.3	8	14.0	-1	-11.76	-
70-79	38	34.9	16	30.8	22	38.6	+6	+31.58	
≥ 80	54	49.5	27	51.9	27	47.4	0	0	
Site									$\chi^2$1=0.77; p=0.381
Pleural	96	88.1	44	84.6	52	91.2	+8	+16.67	-
Peritoneal	13	11.9	8	15.4	5	8.8	-3	-46.15	
Morphology									$\chi^2$1=0.11; p=0.736
Not specified	6	5.5	4	7.7	2	3.5	-2	-66.67	-
Sarcomatoid	7	6.4	5	9.6	2	3.5	-3	-85.71	
Epithelioid	84	77.1	35	67.3	49	86.0	+14	+33.33	
Biphasic	12	11.0	8	15.4	4	7.0	-4	-66.67	
Type of diagnosis									-
Cytological	15	13.8	4	7.7	11	19.3	+7	+93.33	
Histological	100	91.7	49	94.2	51	89.5	+2	+4.00	
At autopsy	22	20.2	12	23.1	10	17.5	-2	-18.18	

[D] is the absolute variation in the total number of cases compared to the previous year;
[Delta] is the percentage relative variation in the total number of cases compared to the previous year;
$\chi^{2\ test}$: Chi-Squared Test, comparison 2019 versus 2020.

Performing an analysis by period of diagnosis (Table 2), the 2020 versus 2019 comparison showed that during the first two months (January-February) and the first wave of the pandemic (Italy lockdown from March to May), the number of diagnoses was similar between 2020 and 2019. In the following months, compared to 2019, the number of diagnoses showed the highest increase (+36.36%) in June-September 2020, and a substantial decrease (-60%) during the second wave of the pandemic (October-December 2020). The trend of the total number of MM cases by year and month of diagnosis is reported in Figure 1.

Table 2: Distribution of the number of mesothelioma cases by year and period of diagnosis.

	2019-2020		2019		2020				χ^2 test
Period	**N**	**%**	**N**	**%**	**N**	**%**	**D**	**Delta**	**2019 vs 2020**
January-February	13	11,9	6	11,5	7	12,3	+1	+15.38	-
March-May	32	29,4	15	28,9	17	29,8	+2	+12.50	-
June-September	44	40,4	18	34,6	26	45,6	+8	+36.36	-
October-December	20	18,3	13	25,0	7	12,3	-6	-60.00	-
									$\chi^2 1=0.41$; p=0.520

[D] is the absolute variation in the total number of cases compared to the previous year; [Delta] is the percentage relative variation in the total number of cases compared to the previous year; χ^2 test: Chi-Squared Test, comparison 2019 versus 2020.

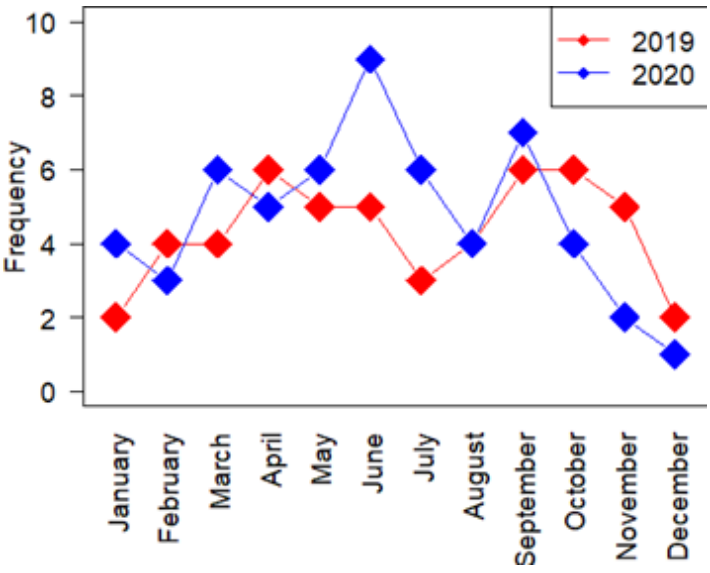

Figure 1: Total number of mesothelioma cases by year and month of diagnosis.

Information about COVID-19 diagnostic tests were available for 46 MM cases. Among these patients who had been tested for SARS-CoV-2 using RT-PCR, six (13%) patients were diagnosed with COVID-19. These patients were males and the mean age was 77 years (range 71 to 83 years). Four patients were current or former smokers and 2 patients were non-smokers. All cases with COVID-19 were pleural mesotheliomas and the most common histology was epithelioid. The diagnosis was based upon tissue biopsy in all cases. All but one were affected by metastatic tumor, and 5 (83%) patients had completed oncological treatment and were in follow-up at COVID-19 diagnosis, whereas one (17%) patient was currently under treatment (chemotherapy alone). Patients had comorbidities including hypertension and chronic obstructive pulmonary disease (COPD), which were the most common reported comorbidities in these patients. Among the 6 hospitalized patients, 4 (67%) were cured, whereas 2 (33%) patients developed complications from COVID-19 (pneumonia or pneumonitis) and died in hospital. Among the 3 (50%) patients who died, 2 deaths were listed as due to complications from COVID-19 and one as cancer disease progression (Table 3).

Table 3: Characteristics of mesothelioma patients with COVID-19.

Patient N	1	2	3	4	5	6
Sex	Male	Male	Male	Male	Male	Male
Age (years)	75	80	74	71	80	83
Smoking status	Former	Former	Never	Current	Never	Former
Site	Pleural	Pleural	Pleural	Pleural	Pleural	Pleural
Tumor type	Sarcomatoid	Epithelioid	Epithelioid	Epithelioid	Epithelioid	Epithelioid
Stage	Early	Metastatic	Early	Metastatic	Metastatic	Metastatic
Metastatic site	//	Lymph node	//	Lymph node	Lymph node, lung	Lymph node
Undergoing treatment (yes/no)	No	No	No	No	No	Yes (chemotherapy alone)
Type of comorbidities	//	Hypertension, COPD	Hypertension, dyslipidemia, arrhythmia	Hypertension, diabetes, COPD	Arrhythmia, hypertension	Hypertension, prior malignancies
Hospitalized (yes/no)	Yes	Yes	Yes	Yes	Yes	Yes
COVID-19 status	Resolved	Resolved	Resolved	Died*	Died	Died

COPD: Chronic Obstructive Pulmonary Disease; *Died of Disease Progression and not from COVID-19.

Among the 109 MM patients, 24 (22%) were still alive at the end of March 2022. Of the 85 (78%) patients who died, 45 and 40 patients were diagnosed with MM in 2019 and in 2020, respectively.

We compared the survival time of MM based upon the year of diagnosis (Table 4). There was no statistical difference in survival for pleural mesotheliomas between 2019 and 2020 (11.5 versus 12 months, respectively). Compared to 2019, in 2020 median survival was poorer for peritoneal MM (6 versus 12.5 months) and females (6 versus 9 months), but there were too few peritoneal cases and women for statistical significance. During the period 2019-2020, younger patients had a significant longer survival (14 months) compared to elderly patients (6 months). Compared to 2019, in 2020 median survival improved for patients aged ≤ 69 years (18 versus 12 months). In examining the three different histological types, median survival for patients with epithelioid MM (12 months) was better than for patients with sarcomatoid (11 months) or biphasic (8.5 months) MM, but these values were not statistically different.

Table 4: Determinants of median survival in patients with mesothelioma

	2019-2020 Median ± SD	2019 Median ± SD	2020 Median ± SD	χ^2 test Main effect	χ^2 test Interaction effect (year)
All	11.00 ± 9.69	11.00 ± 11.10	12.00 ± 8.26	$\chi^2$1=0.34; p=0.561	-
Variables					
Sex				$\chi^2$1=0.29; p=0.591	$\chi^2$2=0.30; p=0.858
Male	12.00 ± 9.80	11.00 ± 11.37	12.00 ± 8.21		
Female	8.50 ± 9.33	9.00 ± 10.21	6.00 ± 8.96		
Age (years)				$\chi^2$2=4.77;p=0.028*	$\chi^2$2=5.19; p=0.074
<=69	14.00 ± 9.75	12.00 ± 11.03	18.00 ± 8.74		
70-79	12.5 ± 8.61	12.5 ± 10.55	13.00 ± 6.84		
>=80	6.00 ± 9.95	6.00 ±11.20	6.00 ± 8.71		
Site				$\chi^2$1=0.20;p =0.6521	$\chi^2$2=0.52; p=0.769
Pleural	11.50 ± 9.66	11.50 ± 11.18	12.00 ± 8.26		
Peritoneal	7.00 ± 10.21	12.50 ± 11.41	6.00 ± 8.58		

Morphology				$\chi^2$2=0.91; p=0.635	$\chi^2$1=1.36;p=0.850
Sarcomatoid	11.00 ± 8.77	11 ± 9.02	8.00 ± 11.32		
Epithelioid	12.00 ± 9.24	12.00 ± 10.53	12.00 ± 8.19		
Biphasic	8.50 ± 12.24	7.00 ± 14.46	8.50 ± 7.59		
Median: Median Survival Months; SD: Standard Deviation; $\chi^{2\ test}$ Main effect: Chi-Squared Test For The Association between median survival and each variable; $\chi^{2\ test}$ Interaction effect (year): Chi-Squared Test For The Association Between Median Survival and the Year of Diagnosis For Each Variable; Significance codes: *p< 0.05.					

Discussion

The main purpose for this study was to evaluate the impact of the COVID-19 pandemic and related control measures on patients with MM. In a population-based series, we examined the changes in MM diagnoses and survival time under the pandemic, comparing the number of diagnoses and survival times recorded in 2020 to those recorded in the previous year.

An increase in the total number of MM diagnoses in 2020 was evident when compared to 2019. Importantly, from January 2020 to the first wave of the pandemic (Italy lockdown from March to May 2020) there was no significant changes in the number of MM diagnoses, compared to the same period of the previous year. In the following months (June-September 2020) with the gradual recovery of the diagnostic services we found the higher number of MM cases (+36.36%), compared to 2019, whereas from October to December 2020, during the second wave of the pandemic, the lower number of MM diagnoses (-60%) was recorded. As noted above, the data presented show how the pandemic did not determine a decrease in the diagnosis of pleural mesothelioma (i.e., the majority of cases in our population) after the introduction of lockdown measures. Several explanations may clarify this finding. As the most common presenting symptoms for patients with pleural MM were similar to those often reported by patients with COVID-19 disease, including shortness of breath and cough, it is possible that these patients with respiratory symptoms could have had more frequently contact with the hospital and this could have led to the detection of new pleural mesothelioma diagnoses in our region. Furthermore, most of our cases had a history of occupational asbestos exposure. Given the wide knowledge of the effects of asbestos exposure, a consistent proportion of our series may have been recognized as asbestos-related and diagnosed early. Study population differences may even explain contrasting results between our study and others. However, a recent Italian survey reported only a moderate decrease in the average number of lung cancer diagnoses in the lockdown period [16].

The results of the comparison with the previous year showed that there were fewer diagnoses of peritoneal mesothelioma (-46.1%) during the pandemic. It is known that the clinical behavior of peritoneal mesothelioma is different from that of pleural mesothelioma. The most common presenting symptoms (i.e., ascites, abdominal pain) tend to be nonspecific and tumor can be extensive at diagnosis [1]. Thus, our data on new diagnoses of peritoneal mesothelioma might also reflect the temporarily reduction of many routine diagnostic activities due to the COVID-19 pandemic. As a consequence of this, modeling studies suggest that a substantial number of missing diagnoses will probably affect the disease stage and result in worse outcomes [9,10]. The authors estimated a possible 4.8% to 5.3% increase in lung cancer deaths [9]. This negative effect of the COVID -19 pandemic (i.e., diagnostic delay) could partially explain the consistent proportion of MM cases (9%) in our series, who underwent post mortem examination.

A report from an outpatient oncology clinic in Pavia (Italy) showed a significant decrease in the number of accesses between April 2020 and April 2019-2018, which is the result not only of the treatment delays in 2020, but may also depend on the delay of follow-up visits, radiological services, and surgical interventions, reducing the number of possible new cancer diagnoses [2]. In Italy, data on delays from colorectal cancer screening showed an increase of 12% in the number of deaths beyond 12 months [17].

In order to balance the risk of infection and the benefits of cancer care, several societies and committees have released recommendations for the management of cancer patients in endemic areas. Proposed approaches to preserve the continuity of cancer care as much as possible, reducing the risk for in-hospital transmissions, include conversion to telemedicine services, postponement elective imaging procedures and modification of drug and/or radiation scheduling to reduce the frequency of cycles and/or fractions [18]. A nationwide survey underlines that such strict measures have been increased through the whole country since the COVID-19 outbreak in Italy, with the use of protective devices, limited hospital access, telephone triage, delay of non-urgent visits [19].

In Northern Italy, Friuli Venezia Giulia, a relatively small region with a high incidence rate of MM, was one of the areas with the higher incidence of COVID-19. For this reason, our study may contribute to evaluate the impact of the COVID-19 pandemic on new MM diagnoses (some mesotheliomas may not have been detected early) and patients' behaviors (patients may have been more reluctant to contact the hospital because of the fear to be infected with SARS-CoV-2).

While containment measures may have contributed to protect patients from infection, cancer patients, who were strongly motivated to continue their treatments or follow-up, have promptly adopted the government's recommendations such as social distancing and wearing face masks in the community [2]. This

could explain our data on mesothelioma patients who were infected with SARS-CoV-2. Among the 46 patients who were tested for the virus, we identified COVID-19 in six patients only. The majority of those patients had a metastatic disease and several comorbidities (such as chronic obstructive pulmonary disease and hypertension), and two patients died of complications of COVID-19 itself. The results suggest that the individual clinical features (in particular age >70 years and presence of comorbidities in our patients) can increase the risk of severe infection or death for patients with MM.

In population-based studies the median survival from MM has been poor, with a median ranged from 5 to 13.2 months [20]. A study from the Netherlands [1], including 4,464 cases with pleural mesothelioma diagnosed from 1995 to 2006, found a median survival of 8.1 months. Results from the Friuli Venezia Giulia register revealed a median survival of 11.5 months in patients with pleural mesothelioma diagnosed in the period 2019-2020. Similar to our findings, a large study from Italy reported a median survival of 9.8 months [20]. Compared to 2019, we did not find significant improvement of median survival in pleural mesotheliomas diagnosed in 2020.

Previous research suggests that younger age and epithelioid histological type are considered as beneficial prognostic factors for pleural mesothelioma [1,20]. At a younger age, patients are expected to be more able to cope with a disease, characterized by local tumor spread, due to their better performance status and eligibility for inclusion in invasive diagnostic procedures, which may prevent late-stage presentation and hence a poorer survival. Our results showing a longer survival for patients under the age of 69 years at diagnosis ($p< 0.05$) and for MM with epithelioid histology are consistent with other studies [1,20].

When we took into account peritoneal mesotheliomas, median survival was worse for patients diagnosed in 2020 than that for patients diagnosed in 2019 (6 versus 12.5 months, respectively), probably due to later diagnosis. Previous studies providing evidence for shorter survival in peritoneal mesotheliomas (5.6 months) than in pleural mesotheliomas (9.8 months) tend to be consistent with our data [20,21]. Compared to 2019, in 2020 median survival was even poorer for females (6 versus 9 months).

Some limitations of our findings should be considered. First, we recognize that this is a preliminary estimation of survival time. As the data presented here are representative of MM cases diagnosed in the period 2019-2020 and followed until March 31, 2022, we could not obtain more accurate estimates of survival time (i.e., long-term survivors). Moreover, information on treatment was available only for few patients and could not be included in survival analysis. Also, the present study, which did not have nationwide coverage, is limited by the small sample size and the potential selection bias that patients with mesothelioma were more likely to be tested for SARS-CoV-2 infection in hospitals during active cancer treatment and routine imaging for anticancer therapy or surveillance.

In conclusion, despite the introduction of pandemic control measures, our analysis evidenced that there was an overall increase in new MM diagnoses in 2020, when compared to 2019. The pandemic did not affect the diagnoses of pleural MM, probably due to its clinical presentation (i.e., respiratory symptoms were similar to those reported by patients with COVID-19) and the known causative link with asbestos exposure. On the contrary, there were fewer diagnoses of peritoneal MM, presumably related to the reduction of diagnostic and cancer surgical services during the COVID-19 pandemic. In our series, only six patients with several comorbidities developed COVID-19. It is likely that MM patients had chosen to promptly adopt containment measures, in compliance with government orders, due to concern about the consequences of the COVID-19 infection for their treatment or follow-up. During the period 2019-2020 the median survival from MM has been poor. We were unable to detect significant differences in survival time comparing mesotheliomas recorded in 2020 to those recorded in 2019. Both younger age at diagnosis ($p<0.05$) and epithelioid histological type were associated with improved survival. Compared to 2019, in 2020 the median survival for peritoneal mesotheliomas was shorter than for pleural cases, but this difference was not statistically significant. Given that women comprised 40% of peritoneal cases against 13% of pleural cases, our data support a poorer survival in females than in men. We hypothesize that our data may reflect the indirect impact of the pandemic control measures on delays in cancer diagnosis and treatment, which in turn may have had a major effect on survival times, particularly if survival is poor as in mesothelioma patients. This means that early diagnosis is essential to ensure the clinical management of MM patients, reduce suffering and provide adequate support and compensation, after confirmation of the diagnosis.

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Conflict of Interest

The authors of the manuscript declare no conflict of interest.

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