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Clinics in Dermatology (2021) **39**, 911–919

Clinics in Dermatology

COVID-19: Important updates and developments
Edited by Franco Rongioletti, MD and Leonard J. Hoenig, MD

The Effect of the COVID-19 Lockdown on Melanoma Diagnosis in Italy

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Abstract The coronavirus disease 2019 (COVID-19) pandemic has led to lockdowns for much of the world. In Italy, all health procedures not directly related to COVID-19 were reduced or suspended, thus limiting patient access to hospitals. Any delay in cancer treatment presents the additional risk of

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https://doi.org/10.1016/j.clindermatol.2021.05.015

tumors progressing from being curable to incurable. Specifically, melanoma survival rate strictly depends on tumor thickness, which, in turn, is a function of time. To estimate the impact on melanoma progression caused by the reduction in dermatologic services during the COVID-19 lockdown, a retrospective observational cohort study was conducted. This study was designed to compare the clinical and histologic characteristics of the primary melanomas removed in the first 2 months after the end of the lockdown (May-July 2020) in 12 Italian centers characterized by different COVID-19 case frequencies. The control group was represented by the melanomas removed during the same period in the previous 3 years. Overall, 1,124 melanomas were considered: 237 as part of the study group and 887 from the control group (average, 295), with a 20% reduction. Breslow thickness, as well as high-risk histotypes and melanomas with vertical growth, increased for all melanomas. Ulcerated and high mitotic index melanomas increased, particularly in northern Italy. In Italy, the lockdown led to a significant worsening of melanoma severity, causing a staging jump, with a consequent worsening of outcomes.

Introduction

The ongoing severe acute respiratory syndrome coronavirus 2, or coronavirus disease 2019 (COVID-19), pandemic continues to be a significant concern for public health. Until May 2020, Italy was one of the countries with the largest outbreak outside of mainland China.[1] The pandemic pressure threatened health systems of all nations involved. In most countries, including Italy, the response to the pandemic was to contain the spread of the virus through immediate case detection and isolation, rigorous close contact tracing with quarantine, and the application of strict limitations to people's movements and activities.[2–4] The Italian population was confined in a lockdown from March to mid-May. This led to a reduction in ordinary hospital activities for nonurgent and non–COVID-related cases. Among hospital activities, specialized outpatient clinics were forced to comply with a marked reduction in face-to-face consultations.[5] In Italy, an 80% to 90% reduction in dermatologic consultations occurred.[5] Most hospitals postponed appointments for elective surgery and nonurgent visits to avoid any unwanted exposure in high-risk premises and crowding in waiting rooms, and to focus on the management of COVID-19. At the same time, the fear of contagion led many patients to cancel their scheduled visits. These circumstances may have led patients with medical conditions, like melanoma, to have a delay in their diagnosis and management.

Regarding outcomes of cutaneous malignant melanoma (CMM), any delay can be critical. CMM severity strictly depends on tumor thickness, which, in turn, is a function of the time to diagnosis. So far, several register-based theoretical models regarding the impact of the COVID-19 lockdown on melanoma progression have been proposed [6,7]; in addition, two single case series have been published, both showing a reduction in the number of patients undergoing melanoma excision during the lockdown period.[8,9] To date, no studies have assessed the real-world quantitative and qualitative impact of the delay induced by the lockdown in melanoma patients.

We recorded the melanoma cases referred to 12 Italian centers in different geographic locations in the 2 months immediately after the lockdown. We then compared these data with those from the same centers in the same period for the previous 3 years. The purpose of the present study was to assess the impact of the lockdown on the modification of CMM prognostic factors and other CMM characteristics for the months immediately after the lockdown in Italian geographic areas disparately affected by the pandemic.

Material and methods

Study design and data source

A prospective database of all newly diagnosed CMM cases recorded in 12 dermatologic institutions in Italy from May 1 to July 31, 2020 was collected. Centers were included according to their location (different COVID-19 case frequency areas) [10]: Brescia, Lecco, Turin, and Sassuolo for northern Italy (high COVID-19 case frequency); Chieti, Rome, L'Aquila, and Viterbo for central Italy; and Catania, Naples, Cagliari, and Cosenza for southern Italy. Centers were chosen based on the similarity of their relative workload in the respective geographic areas; high-workload centers were Brescia and Turin in the north, Rome in the center, and Naples and Catania in the south. The remaining centers had a lower patient workload but a comparable size and population rate in their respective geographic areas.

The study period coincided with the end of the lockdown imposed by the COVID-19 emergency. The control group consisted of melanoma data collected from all the centers in the same period for the previous 3 years (May 1-July 31, 2017, 2018, and 2019). Clinical and histologic characteristics were recorded. All participating centers had not stopped their surgical activities during the lockdown months. Because surgical procedures for each patient were longer during this time to allow surgeons to change their protective gear and surgery rooms to be sanitized after each patient, the number

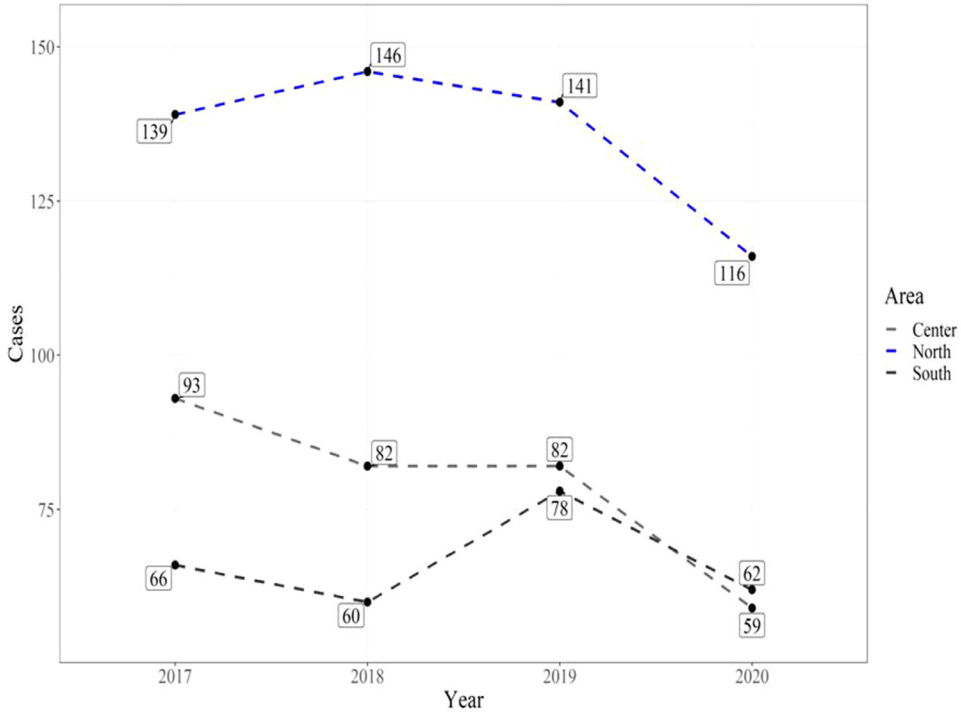

Fig. 1 **(A)** Melanoma cases that occurred during the period 2017 to 2020 in the three main geographic areas of Italy. **(B)** The absolute frequency of melanoma in 2020 and before 2020 by geographic area.

of daily surgeries was lower than before the pandemic; however, surgery for suspected melanoma was prioritized in each center over other types of skin surgery.

The wait time for melanoma surgery, set to the maximum of 2 weeks, was the same as in prelockdown. The study was approved by the various local ethics committees.

Clinical and histologic features

Patient sex, age, and tumor location (face, head, neck, chest, abdomen, back, sacrum, arm, hand, leg, foot, or genital) were evaluated. We also recorded the histologic variables of melanoma, including histologic subtype (*in situ*, superficial spreading, lentigo maligna, nodular, acral lentiginous, desmoplastic, and nevoid), Breslow thickness (mm), number of mitoses (calculated with the hot spot method/mm^2), ulceration (present versus absent), and previous mole (present versus absent).

Outcomes

The primary outcome was the detection of any quantitative and qualitative differences in melanomas removed in the different periods, plus the assessment of the impact of the lockdown measures and people's behavior during the lockdown period. The secondary outcome was the evaluation of the impact of the lockdown measures on melanoma characteristics in various geographic areas and the risk for COVID-19 infection.

Statistical analysis

Descriptive statistics included frequencies and proportions for categoric variables. Median, first, and third quartiles were reported for continuous nonnormally distributed variables. The chi-square test assessed the statistical significance in proportional differences, and the Mann-Whitney U test examined the statistical significance of the median differences between unpaired groups. All statistical tests were two-sided, with the significance level set at $P < .05$. Analyses were performed using the R software environment for statistical computing (version 3.4.1; http://www.r-project.org/).

Results

Quantitative data

Overall, 1,124 melanomas were collected from the participating centers; of these, 237 were in the study group (post–2020 lockdown period) and 887 in the control group (298 melanomas in 2017, 288 in 2018, and 301 in 2019, respectively, with an average of 295 melanomas per study period).

We found a 20% reduction in the number of melanomas excised during the study periods (previous years versus post-lockdown). Melanoma cases that occurred during the period 2017 to 2020 in the three main geographic areas of Italy are reported in Figure 1A.

Table 1 Melanoma distribution according to Gender and Age stratify for geographic Area of involved centres. The absolute frequencies before 2020 are computed as the averages of the years 2017, 2018 and 2019. P-value results from Chi-squared test.

Area	Variable		Before 2020	2020	p-value
North	Age	60.0(50.0-72.0)	59.0(51.5-75.0)	0.727	
	Gender	F	78(54.7%)	69(59.5%)	0.463
		M	64(45.3%)	47(40.5%)	
Center	Age	54.0(44.0-71.0)	58.0(50.0-72.0)	0.141	
	Gender	F	37(42.8%)	28(47.5%)	0.598
		M	49(57.2%)	31(52.5%)	
South	Age		59.0(48.0-69.5)	59.0(49.0-72.0)	0.673
	Gender	F	34(50.0%)	25(40.3%)	0.268
		M	34(50.0%)	37(59.7%)	

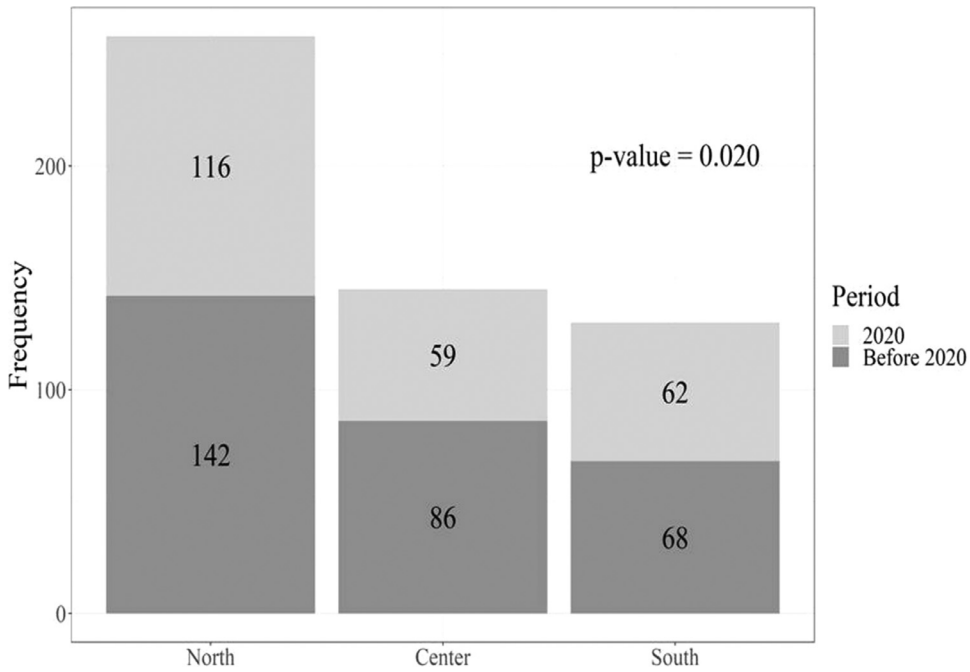

Fig. 2 **(A)** Median Breslow thickness increases after the 2020 lockdown period compared with cutaneous malignant melanomas in previous years. **(B)** A subanalysis of the data by geographic area.

The absolute frequency of melanoma in 2020 and before 2020 (average frequencies of 2017, 2018, and 2019) by geographic area (Figure 1B) illustrates how the reduction in the number of cases is mainly characteristic of the northern and central areas (chi-square test P value = .020), whereas in the south the difference is not significant. The analysis of sex and age distribution in the various areas did not show any significant differences (Table 1).

Qualitative data

As for histologic characteristics of CMM, Breslow thickness increased in the cases that occurred after the 2020 lockdown period compared with CMMs in previous years. Median increases are 0.4 to 0.5 mm (Figure 2A). A subanalysis of the data by geographic areas showed a significant increase for central Italy (0.5 mm before COVID-19 versus 1.1 mm post–COVID-19) and southern Italy (0.3 mm versus 0.9 mm), and an increase, albeit not significant, due to the presence of numerous anomalous values, for northern Italy (0.4 mm versus 0.5 mm) (Figure 2B). The presence of ulcerations also increased in the postlockdown cases, particularly in northern Italy (Table 2).

Similarly, the number of mitoses showed an overall increase in the study group with a high mitotic index (>4 mitosis/mm^2), particularly significant in northern Italy (Table 3). Analyses according to histotype were conducted, grouping the cases based on risk. High risk included nodular (NM), acral lentiginous, or other (animal type, spitzoid, nevoid), whereas low risk consisted of superficial spreading (SSM), lentigo maligna, and *in situ* melanomas. An increase in high-risk histotypes and a decrease in low-risk forms in the

Table 2 Presence and Absence of Ulceration evaluated in 2020 and Before. The Before 2020 absolute frequencies are computed as the averages of the years 2017, 2018 and 2019. P-value results from Chi-squared test.

Ulceration	2020	Before 2020	p-value
North			
Absent	75(80.6%)	100(91.7%)	0.036
Present	18(19.4%)	9(8.3%)	
Center			
Absent	43(86.0%)	55(88.7%)	0.886
Present	7(14.0%)	7(11.3%)	
South			
Absent	50(87.7%)	65(95.6%)	0.199
Present	7(12.3%)	3(4.4%)	

Table 3 Mitosis distribution in 2020 and Before. The Before 2020 absolute frequencies are computed as the averages of the years 2017, 2018 and 2019. P-value results from Chi-squared test.

MITOSIS	2020	Before 2020	p-value
North			
<1/mm2	60(66.7%)	110(74.8%)	0.020
1-4/mm2	13(14.4%)	16(15.7%)	
>4/mm2	17(18.9%)	10(9.4%)	
Center			
<1/mm2	24(48.0%)	27(52.3%)	0.645
1-4/mm2	16(32.0%)	19(36.8%)	
>4/mm2	10(20.0%)	7(10.9%)	
South			
$<1/mm^2$	10(50.0%)	13(60.0%)	0.676
$1\text{-}4/mm^2$	8(40.0%)	6(27.7%)	
$>4/mm^2$	2(10.0%)	3(12.4%)	

2020 postlockdown groups were present in all geographic areas (Figure 3A).

Evaluation of the CMM growth pattern (horizontal or vertical) showed that for all the geographic areas considered, there was an increase in vertical growth phase melanoma in the postlockdown period compared with the control period (Figure 3B). No difference regarding the presence of a previous melanocytic nevus between the two study periods was found (Table 4), nor was any difference detected in the body distribution of melanomas.

Table 4 Melanoma development on previous nevus distribution in 2020 and before. The Before 2020 absolute frequencies are computed as the averages of the years 2017, 2018 and 2019. P-value results from Chi-squared test.

Previous nevus	2020	Before 2020	p-value
North			
Absent	95(44.8%)	32(58.2%)	0.106
Present	117(55.2%)	23(41.8%)	
Center			
Absent	57(44.2%)	18(48.6%)	0.769
Present	72(55.8%)	19(51.4%)	
South			
Absent	42(37.2%)	8(26.7%)	0.392
Present	71(62.8%)	22(73.3%)	

Discussion

CMM is characterized by an extensive degree of heterogeneity in terms of clinical and histopathologic presentation [11] and genomic profile,[12–15] which makes this disorder a significant public health issue. CMM is the cause of most skin cancer–related deaths and is currently the sixth most common cancer in most European countries.[16] The most important prognostic factor for melanoma is depth (Breslow thickness), followed by ulceration and number of mitoses. Recent evidence has shown that the ratio between melanoma thickness or the mitotic index and the time to diagnosis is a strong prognostic factor.[17,18]

SSM and NM generally exhibit different growth patterns, characterized by slower versus faster, and radial growth versus vertical growth, respectively. The vertical growth phase (VGP) is defined by the focal formation of the dermal nodule within the radial growth phase (RGP). According to the linear model of progression, malignant melanocytes in SSM spread radially before invading vertically. Wallace Clark (1924-1997) called this invasion pattern [19] the VGP and defined it as the focal formation of a dermal nodule within the RGP. RGP, which is present in SSM and absent in NM, is of paramount importance in the classification of melanoma.[19–21] Up to 70% of CMMs are the superficial spreading subtype, where the initial radial growth offers a broader recognition opportunity before any vertical growth occurs to reduce the prognosis. CMMs with a VGP do not necessarily indicate NM. The CMM growing pattern is a fast-growing melanoma pattern that is characterized by a vertical growth rate exceeding 0.5 mm/mo in thickness and a slow-growing melanoma, the latter divided into two different subcategories: slow thin melanomas and very slow thin melanomas.[22] An early diagnosis and the excision of thin lesions offer the best hope of mortality reduction in the short term, whereas primary prevention may affect long-term results.[23]

We think that limited access to outpatient dermatologic clinics could have had an indirect impact on the clinical presentation and prognosis of melanoma patients in Italy. Two single-center case series from Italy demonstrated a numerical reduction in the patients undergoing melanoma excision.[8,9] In one of the studies, the authors reported a similar proportion of *in situ* CMMs in the pre-and postlockdown periods and an increase in thicker melanoma postlockdown. They concluded that health-conscious people were more likely to overcome

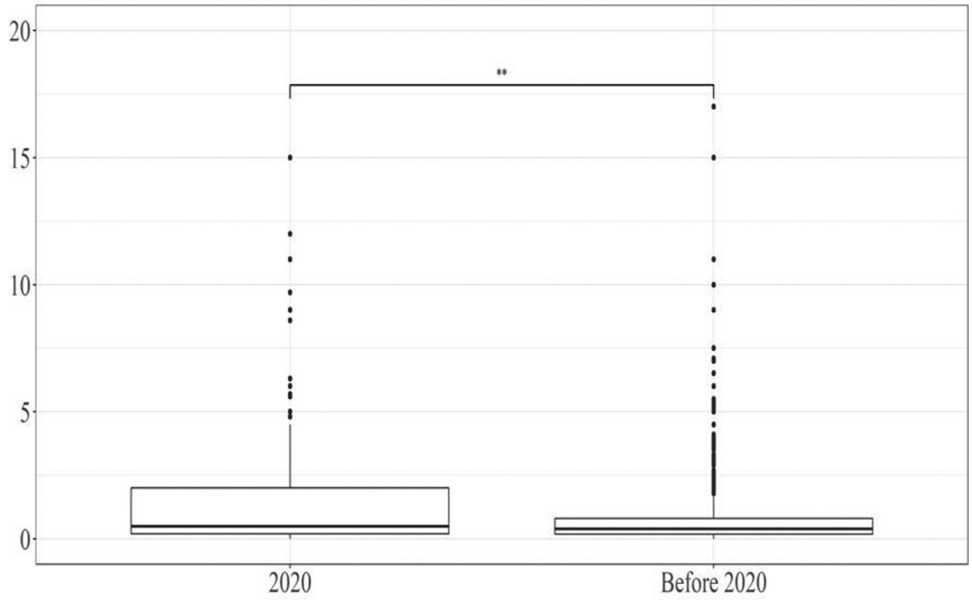

Fig. 3 **(A)** Frequency of high- and low-risk histotypes in 2020 and before 2020 by geographic area. **(B)** Evaluation of the cutaneous malignant melanoma growth pattern (horizontal and vertical) in 2020 and before 2020 period by geographic area.

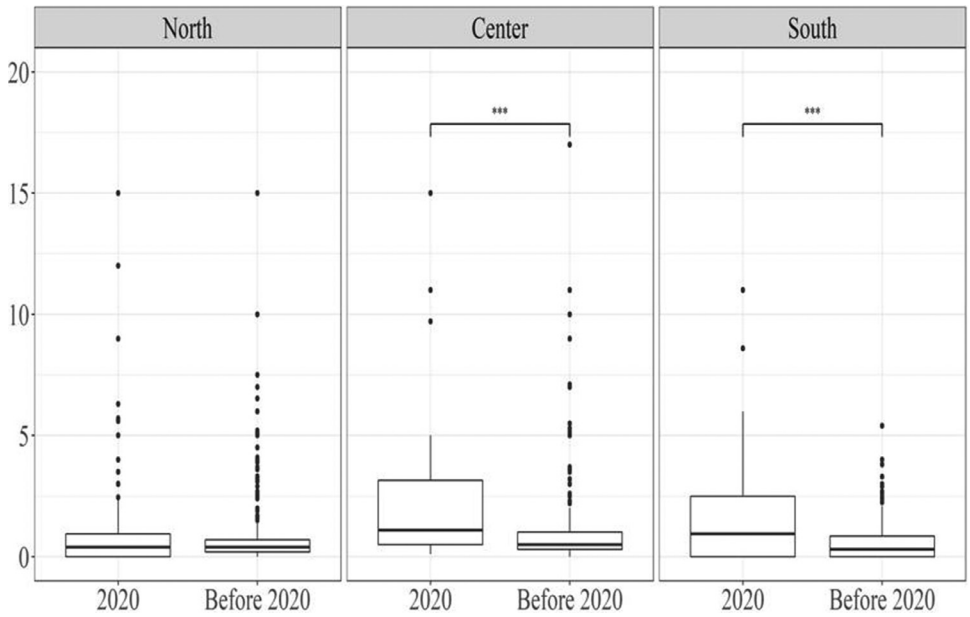

Fig. 4 Breslow median differences acording to different risk areas between 2020 and average from the three years earlier (2017-2018-2019). P-values for Mann U Whitney test results < 0.001 (***)

the lockdown limitations than patients who underestimated the severity of their lesions, leading to a delay in CMM diagnosis during lockdown.[24]

To date, some register-based theoretical models have been proposed concerning the impact of the COVID-19 lockdown on the progression of melanoma. The authors have hypothesized a considerable rise in melanoma upstaging cases because of a lack of adequate care of cancer patients.[6,7] Some observers have even hypothesized a reduction in melanoma frequency due to the limited exposure to the sun during lockdown for fair-skinned individuals confined at home.[25]

Our study provides real-world data of the effect of the lockdown on CMM clinical presentation in various parts of Italy, each characterized by different COVID-19 case frequencies and impacts. The study design allowed us to assess the postlockdown period when the limitation in movements for the population was lifted. The number of melanomas excised in this period was similar to those reported during

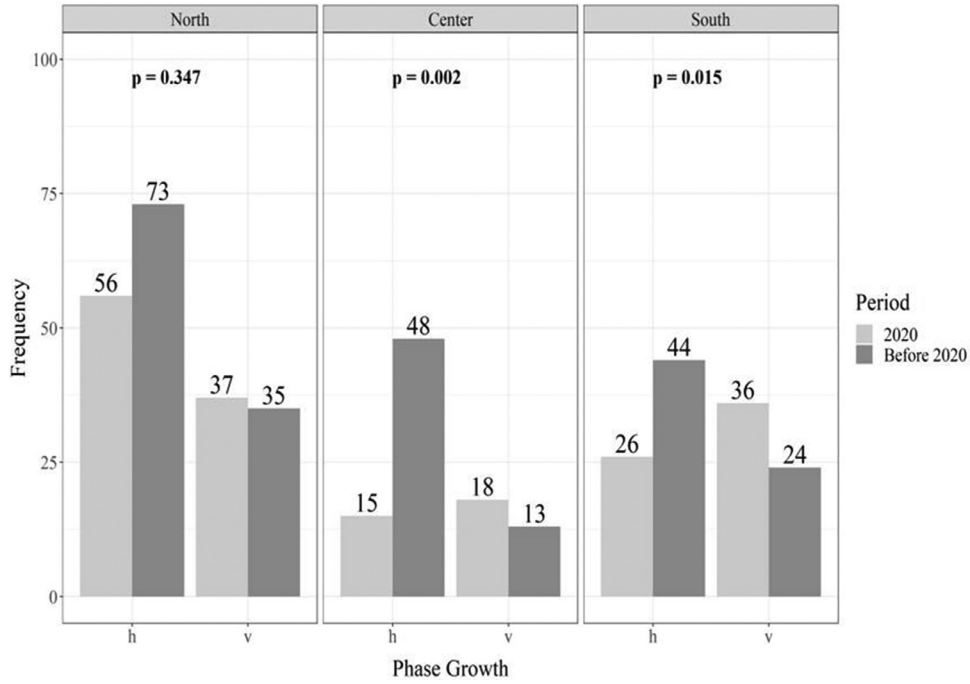

Fig. 5

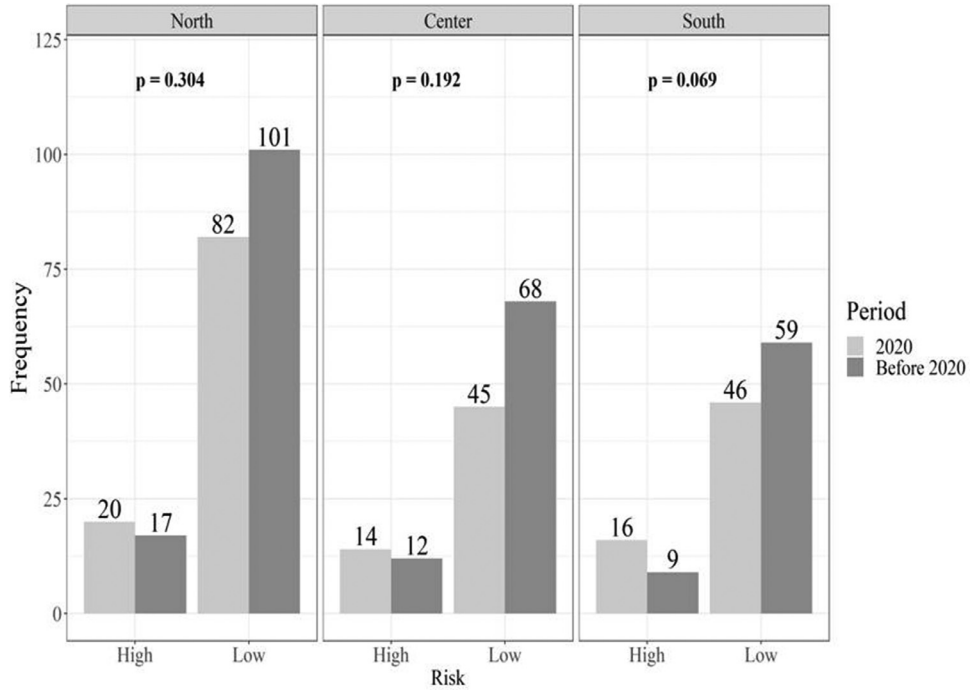

Fig. 6

the lockdown, when movement restrictions were in place, with a 20% reduction in frequency. These figures may suggest that the population was somehow still as afraid to visit hospital-based outpatient clinics just after the lockdown (May-June) as they were during the lockdown. Also, our model could be even more accurate than others, given that the well-documented phenomenon of seasonal fluctuation of melanoma diagnosis [24] cannot be a confounding bias, as in contributions comparing different months in the same year (pre- and postlockdown, ie, January versus May).[8]

The hypothesis that the reduction in the number of melanoma diagnoses after the lockdown was due to the fear of visiting hospitals is supported by the evidence that the reduction is larger in northern and central Italy, where the

incidence of severe acute respiratory syndrome coronavirus 2 was higher. We have theorized that patients from the north were more afraid to expose themselves to the high risk of the outpatient clinic environment. As a result, they would have been more likely to miss important dermatologic visits, leading to a delay in diagnosis. To the contrary, the outpatient clinics were still carrying out oncologic visits and excisions throughout the lockdown period and did not help fill the gap.

A greater reduction has been also reported in a single-center study in northern Italy,[8] in which the number of excised melanomas dropped by 30%.

We think that owing to the different models of melanoma progression, this significant decrease in the number of melanoma excisions during the lockdown period should be analyzed per the prognostic factors for melanoma.

An increase in high-risk histotypes and a decrease in low-risk forms in the 2020 postlockdown groups were present in all geographic areas. We recorded a discrepancy among the prognostic features according to COVID-19 risk areas. Low to medium COVID-19 risk areas (southern and central Italy) showed a higher Breslow thickness in the postlockdown period compared with previous years and a higher incidence, although not significant, for ulceration and the number of mitoses. On the contrary, northern Italy, an area with a higher COVID-19 frequency, showed a stronger statistical increase in the other two prognostic factors (ulceration and number of mitosis) but not in the Breslow thickness. This evidence may be explained by the presence of numerous out-of-range melanomas in the control years (2017-2019).

An analysis of the growth phases and the melanoma histologic types also showed an overall increase in the high-risk forms in the postlockdown group. We think that this evidence may still support the hypothesis that a delay in the diagnosis of melanoma and a worsening of the prognosis could be due to a combination of factors: patients missing outpatient or hospital visits during the lockdown and again after the restriction period for fear of COVID-19 infection, being homebound, and not prioritizing their regular follow-up visits.

The availability of surgery for melanoma patients was ensured during the lockdown so that, although to a lesser rate, faster-growing and more aggressive melanomas (higher mitotic rate and ulceration more identifiable by the patients as a lesion to be assessed) were preferentially excised over the slow-growing, less aggressive melanomas (slow radial growth) that are usually found in routine clinical assessment.

We did not find any significant differences between exposed and unexposed areas, nor did we find a greater number of *de novo* onset melanomas. This limited the chance that the reduction in the number of melanoma excisions after the lockdown could be due to the reduced self-diagnosis of melanoma.

All qualitative indexes of melanoma progression showed an increase as determined by the factors just mentioned. During lockdown, efforts must be made to ensure that patients have access to dermatologists so that melanoma screening and treatments are not delayed and to prevent progression of disease severity.[26]

Conclusions

Our results underscore the need, once the pandemic is over, to address the consequences of any future lockdown on the diagnosis and management of melanoma. We believe there is a need for stronger sensitization of the high-risk melanoma population, emphasizing the importance of body self-examination, as well as to provide the sense of a safe environment for melanoma outpatient clinics to encourage people to undergo screening and analysis of suspicious lesions.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

Novartis Pharma, Italy provided English-speaking editing for the manuscript.

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