The impact of the COVID-19 pandemic on the diagnosis of cutaneous melanoma: a multicenter study in Portugal

O impacto da pandemia COVID-19 no diagnóstico de melanoma cutâneo: um estudo multicêntrico em Portugal

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Abstract

Objective: Malignant melanoma (MM) is among the most lethal skin cancers, with early diagnosis being essential for timely treatment and favorable prognosis. The coronavirus disease 19 (COVID-19) pandemic-related disruptions in global healthcare systems affected cancer screening and treatment. The aim of this study was to investigate the potential impact of the COVID-19 pandemic on the diagnosis and prognosis of MM. **Methods:** A retrospective analysis of all histopathology-confirmed MMs diagnosed between 2019 and 2022 was conducted in three dermatology departments in Lisbon. Histopathology reports and medical records of included patients were reviewed and data of interest analyzed. Data from the pandemic period (2020 and 2021) were compared to the pre and post-pandemic ones (2019 and 2022, respectively). **Results:** During the study period, a total of 644 MMs were diagnosed. When compared to the post-pandemic period, we observed a significant association between the pandemic group and a higher median Breslow thickness, ulcerated tumors, locoregional metastases, and more advanced stages (≥ T1B, final staging ≥ IIB) (p < 0.05). **Conclusion:** With the pandemic group being associated with unfavorable prognostic factors, we believe that restricted access to healthcare during the COVID-19 pandemic may have had a negative impact on the morbimortality of patients with MM.

Keywords: Malignant melanoma. Coronavirus disease 19 pandemic. Breslow thickness.

Resumo

Objetivo: O melanoma maligno representa um dos cancros de pele mais letais, sendo o diagnóstico precoce essencial para um tratamento atempado e um prognóstico favorável. As alterações nos sistemas de saúde relacionadas com a pandemia COVID-19 afetaram negativamente o rastreio e o tratamento do cancro. O objetivo deste estudo foi investigar o potencial impacto da pandemia COVID-19 no diagnóstico e prognóstico do melanoma maligno. **Métodos:** Foi realizada uma análise retrospetiva dos melanomas malignos confirmados histologicamente, diagnosticados entre 2019 e 2022 em três departamentos de dermatologia em Lisboa. Foram revistos os relatórios de histopatologia e os registos clínicos dos doentes incluídos e analisados os dados de interesse. Os dados do período pandémico (2020 e 2021) foram comparados com os pré e pós-pandemia

(2019 e 2022 respetivamente). **Resultados:** No período estudado foram diagnosticados 644 melanomas malignos. Quando comparado ao período pós-pandemia, observamos uma associação significativa entre o grupo pandémico e maior espessura de Breslow média, tumores ulcerados, metástases locorregionais e estadios mais avançados (≥ T1B, estadio final ≥ IIB) (p < 0.05). **Conclusão:** Estando o grupo pandémico associado a fatores prognósticos desfavoráveis, acreditamos que o acesso restrito aos cuidados de saúde durante a pandemia COVID-19 pode ter tido um impacto negativo na morbimortalidade dos doentes com melanoma maligno.

Palavras-chave: Melanoma maligno. Pandemia COVID-19. Espessura de Breslow.

Introduction

Malignant melanoma (MM) is a malignant tumor that arises from melanocytes, most commonly originating on the skin. Its incidence is rising worldwide, while data show a stabilization or even decrease in mortality[1-3]. The annual incidence increase varied globally between 3% and 7% over recent decades, while Alves da Costa et al. reported a stabilized incidence in the south region of Portugal in recent years[2,4]. MM represents one of the most lethal cutaneous neoplasms, accounting for more than 90% of deaths from skin cancer. Prognosis hinges heavily on MM's stage at diagnosis, highlighting the importance of its early detection. Breslow depth (i.e., MM thickness) is the strongest prognostic predictor, correlating with disease-specific 10-year survival rate. Together with the presence of ulceration on histological examination, higher Breslow depth predicts a more aggressive clinical course, with a greater risk of locoregional and distant metastases[5-7]. Although most melanomas are detected by self-examination, identification by clinicians is associated with thinner lesions[8,9].

In December 2019, in Wuhan, China, the first case of coronavirus disease 19 (COVID-19), an acute respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was diagnosed[10]. The virus was first detected in Portugal on March 2, 2020, and due to its rapid global dissemination, the World Health Organization declared the COVID-19 outbreak a pandemic on March 11. This led to drastic organizational changes and restrictions in various sectors of society on a worldwide scale, to contain the propagation of the virus. There were major changes in the workflow of healthcare systems, with a reduction in hospital activity in non-urgent and non-COVID-19 cases, and a mobilization of material and human resources to manage COVID-19 patients. In Portugal, there were significant reductions in primary care and hospital outpatient appointments, elective surgeries, and emergency department activity[11-13]. Official reports show a decrease in face-to-face activity between March and May 2020, compared to the homologous period in 2019, highlighting a 58% reduction in scheduled surgeries, 44% in emergency department activity, and 40% of the first hospital medical appointments. Conversely, a significant increase in teleconsultation was registered, which represented 65% of all assistance activity in primary care centers in the referred period[14].

These pandemic-related disruptions in global healthcare systems had a major impact on cancer screening and treatment, with concerns raised regarding the delay in the diagnosis and management of MM and the consequent increase in patients' morbidity and mortality. Teledermatology platforms were widely implemented during this period, in an attempt to follow patients with chronic dermatological conditions or a history of skin cancer, and to evaluate suspicious skin lesions[15,16]. However, examination through video or still images has a reduced diagnostic accuracy when compared to in-person observation, using in-office diagnostic tools such as manual and computerized dermoscopy. Several studies focusing on the impact of COVID-19 pandemic in MM reported a significant reduction in MM diagnoses during this period, with thicker lesions and more advanced stages at diagnosis[17-29]. Notably, a recent study on the health economic consequences of COVID-19-related delay in MM diagnosis in Europe estimated additional costs of $7.65 billion USD, with indirect treatment costs accounting for 94.5% of the total[28]. Conversely, some studies have indicated that MM thickness remained unaffected by the pandemic[30-34].

Further understanding the influence of the recent pandemic on MM burden can elucidate its true effects on Dermatology Departments' functioning and management of skin cancer patients. This multicenter study conducted in Lisbon, Portugal, focuses on the potential impact of the COVID-19 pandemic on the diagnosis and prognosis of MM.

Methods

A multicenter, retrospective, and observational study was conducted in three hospital Dermatovenereology Departments in Lisbon, Portugal, to analyze and compare the characteristics of MM diagnosed from January 2019 to December 2022. All excised and histologically confirmed MMs were identified from the Dermatopathology databases of each Department and included in the study. MM were divided into 3 groups, depending on the date of diagnosis: pre-pandemic period (2019), pandemic period (2020 and 2021), and post-pandemic period (2022). Medical records and histopathology reports of included MM were reviewed and patients' demographic data (age, gender, and Fitzpatrick phototype) and clinical information (personal and familial history of MM and non-MM skin cancer, immune status) as well as MM location, histopathological characteristics (subtype, Breslow depth, ulceration, mitotic index, regression, inflammatory infiltrate, perineural, and perivascular invasion), and staging were retrieved and analyzed. Due to differences in histopathological reports between centers, *in situ* cutaneous MM was classified as such regardless of their subtype, whereas all other subtypes described refer to invasive MM (thickness beyond the epidermis). Staging was based on the melanoma staging criteria of the American Joint Committee on Cancer 2017 8th edition[7].

Data collection and analysis were performed using Microsoft Excel 2021 and IBM Statistical Package for the Social Sciences Version 29, respectively. Descriptive statistics were employed to summarize the demographic and clinical characteristics of the study population. Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages. The normality of data distribution was assessed using the Shapiro–Wilk test. For comparisons between groups, analysis of variance was used to test differences between continuous and categorical variables at a significance level of 0.05. When significant differences were found, *post hoc* multiple comparisons were performed using Tukey's test.

Results

From January 2019 to December 2022, a total of 644 MM were diagnosed in our Departments, with an average of 161 ± 23.3 cases identified per year. The number of MM diagnoses remained relatively stable throughout 2019 and the pandemic period (n = 153, 142 and 154 in 2019,

2020, and 2021 respectively), with a significant increase in diagnoses in the post-pandemic period (n = 195).

The 644 MM diagnosed correspond to 607 patients, with 28 (4.6%) having more than one diagnosis of MM during the study period. Approximately 1% of the patients (n = 6) had synchronous diagnosis of multiple primary cutaneous MM. There was a slight predominance of males, corresponding to 50.7% (n = 308) of the population under analysis, with a mean age of 66.6 years (range: 26-103). There were no significant differences with regard to sex and age of the patients between the three groups. Causes of immunosuppression were identified in about 4% (n = 25) of the subjects, with solid organ transplant being the most common one (36%, n = 9), followed by conventional systemic immunosuppressor therapy (32%, n = 8). Of the 536 patients in whom we were able to obtain data regarding personal and family history of skin cancer, 4.1% (n = 22) had a positive MM family history, 21.6% (n = 116) had a personal history of non-melanoma skin cancer, and 14.6% (n = 78) had had a previous diagnosis of melanoma.

The clinic-histological data collected are summarized in table 1 and distributed accordingly to each study group. Concerning the anatomical topography of the 644 lesions, the trunk was the most common location of MM (46.6%, n = 300), followed by the lower limbs (14.9%, n = 96), face (14.3%, n = 92) and upper limbs (12.6%, n = 81). No significant differences were found in the body location of MM between the different groups.

Regarding the histological characteristics of MM, superficial spreading MM was the most common subtype (44.3%, n = 285), with MM *in situ* corresponding to 36.2% (n = 233) of the lesions. No statistically significant differences were found in terms of histological subtype between the years under study. Considering only invasive MM, the mean Breslow depth was 2.35 mm, being significantly higher in the pandemic period (3.10 mm), as opposed to 2022 (1.61 mm) (p < 0.05).

With regard to histological features, the pandemic cohort more frequently presented with MM with classification ≥ T1b (34.6%, n = 102) compared to the pre (30.9%, n = 47) and post-pandemic (29.2%, n = 57) periods, with a statistically significant difference between the pandemic and post-pandemic groups (p < 0.05). The pandemic group was associated with the presence of ulceration (18.2%, n = 54), when compared to both pre and post-pandemic ones (9.2% and 5.6%, respectively) (p < 0.05). The proportion of patients with locoregional lymph node metastases was significantly higher

Table 1. MM anatomical topography, histological features, and staging, accordingly to each study group

	Pre-pandemic	Pandemic	Post-pandemic	Global
MM topography (%)				
Trunk	48.4	41.9	52.1	46.6
Lower limbs	13.1	16.9	13.4	14.9
Face	13.7	16.6	11.3	14.3
Upper limbs	11.1	12.8	13.4	12.6
Feet	7.2	4.7	4.6	5.3
Scalp	3.3	4.4	2.1	3.4
Nail	0.7	1.4	0.5	0.9
Neck	1.3	0.7	1.0	0.9
Hands	1.3	0.3	1.0	0.8
Genitalia	0.0	0.3	0.5	0.3
MM subtype (%)				
Superficial spreading	50.3	36.5	51.3	44.3
In situ	32.7	37.2	37.4	36.2
Nodular	6.5	14.2	5.6	9.8
Lentigo	2.6	4.7	3.1	3.7
Acral lentiginous	3.9	3.7	1.0	3.0
Spitzoid	0.7	1.4	0.5	0.9
Nevoid	0.7	0.3	0.0	0.3
Desmoplasic	0.0	0.0	0.5	0.2
NOS	2.6	2.0	0.5	1.7
Histological characteristics				
Breslow index (mm)	1.27	1.93	1.00	1.49
Ulceration (%)	9.2	18.2	5.6	12.3
T ≥ 1B (%)	30.9	34.6	29.2	31.9
Locoregional lymph node metastasis (%)	9.6	13.5	4.9	9.5
Distant metastasis (%)	4.7	5.9	3.7	4.7
Staging ≥ IIB (%)	16.6	22.3	9.7	16.9
Route of referral (%)				
Primary care center	47.7	44.3	51.8	47.4
Dermatology	26.1	27.0	19.5	24.5
Other specialties	12.4	8.1	6.2	8.5
Emergency department	2.0	3.4	3.6	3.1
Other	11.8	17.2	19.0	16.5

NOS: non otherwise specified; MM: malignant melanoma.

during the pandemic period, compared to 2022 (13.5% vs. 4.9%, $p < 0.05$). Furthermore, distant metastases were more common in the pandemic group (5.9%, n = 17), but the differences between groups did not reach the significance threshold. MM staging at diagnosis ≥ IIB was significantly more frequent in the pandemic group (22.3%, n = 66) than the post-pandemic one (9.7%, n = 19) ($p < 0.05$).

Finally, considering the route of referral, 47.4% (n = 305) of the MM were from patients referred from primary healthcare centers. Dermatology appointments (24.5%) were associated with a significantly lower MM thickness (mean Breslow depth = 0.4 mm), compared with referral from the emergency department (3.1%; mean thickness = 8.1 mm). No significant differences were found in the route of referral among the study groups.

Discussion

As previously mentioned, the measures implemented to control the spread of the SARS-CoV-2 virus significantly impacted the healthcare services provided to the population. Among all cancer patients, those with skin tumors experienced the highest rate of missed appointments, with an analysis of the North of England Cancer Network showing a 68.6% decrease in diagnoses in the first lockdown compared to the same period in the previous year[35,36]. While the European Academy of Dermatology and Venereology advised that skin cancer screening for individuals at higher risk of MM could be postponed by no more than 2-3 months during the COVID-19 pandemic, the International Dermoscopy Society noted a 75% reduction in work activity among its members during the lockdown, with over half

reporting virtually no MM diagnoses during this period[37,38]. In fact, several studies have demonstrated a significant reduction in newly diagnosed MM during the pandemic and immediate post-pandemic periods, with Jeremić et al., for instance, finding a 58.2% reduction in annual MM diagnoses compared to previous years[18,19-29,34]. Our study revealed a relatively stable incidence of MM during the pandemic period and the year before, which aligns with a Swiss study by Kostner et al.[23]. We verified a statistically significant increase in MM diagnoses in 2022, in contrast to the post-pandemic decrease found in other studies[39,40]. These conflicting findings across studies may be influenced by variable definitions and durations of pandemic and post-pandemic periods as well as diverse levels of restrictions and state regulations which result in different levels of impact on healthcare systems between different regions and countries. Furthermore, the increment in MM diagnoses can potentially be explained by a greater demand for dermatological observation during the post-pandemic period from patients who complied with isolation measures and/or actively avoided healthcare due to fear of contagion and who realized the potential impact of the pandemic on the diagnosis and treatment of conditions such as skin cancer. Our data reveal an association between the pandemic period and the occurrence of thicker and ulcerated tumors, a higher proportion of MM classified as $\geq$ T1B, locoregional metastases, and more advanced stages ($\geq$ IIB), reaching the significance threshold only in the comparison with the post-pandemic group. Most studies focusing on this topic demonstrate an association between the COVID-19 pandemic and the diagnosis of thicker lesions, tumor ulceration, and more advanced stages[17-24,26-29]. A study conducted in 2020 by Lallas et al. verified a significantly higher-than-expected proportion of MM with a staging at diagnosis $\geq$ IIC[21]. Similarly, Molinier et al. reported an association between the pandemic period and clinically occult lymph node involvement and indication for adjuvant therapy[22].

Finally, the variability of MM thickness depending on the referral route of patients, with Dermatology appointments being significantly associated with thinner MM at diagnosis, reinforces the importance of effective access to specialized healthcare for recognition of suspicious skin lesions and early MM diagnosis. These data are in accordance with a study conducted in a pigmented lesion clinic in New York, where patients already followed up at the clinic had more *in situ* and thinner invasive newly diagnosed MM compared with new patients referred from other departments[41].

Conclusion

To the best of our knowledge, no comparable studies focusing on the impact of COVID-19 pandemic in the diagnosis of MM have been performed in Portugal. In our study, we verified an association between the pandemic period and the diagnosis of thicker and more advanced MM. Taking these data into consideration, and knowing that early detection and excision of thin lesions is the key to reduce MM-related morbidity and mortality, we believe that restricted access to healthcare during the pandemic may have had an impact on the prognosis of patients with MM. The increase in MM diagnosis in the post-pandemic period, with less aggressive histological features and staging compared to the pandemic group, may reflect the prompt normalization of hospital activity and Dermatology Departments' reestablished efficiency.

This study is strengthened by its multicenter design, incorporating data spanning 4 years and a large sample size. However, it is important to acknowledge its limitations, including its retrospective nature and inherent biases. In addition, patient evaluations were conducted by diverse medical teams, and MM analyses were performed by different dermatopathologists.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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