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Risk Factors for Melanoma Survival: DGCR8 as a Predictive Factor for Mortality in Young Patients

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MicroRNA-processing enzymes – Dicer and DGCR8 – have been found to be dysregulated in melanoma. This study investigated whether these microRNA-processing enzymes could be used as risk factors for mortality. A retrospective cohort including medical history and samples of 74 patients was reviewed. Clinical and pathological variables were compared with mortality. Percentage of immunoreactive tumour cells (%IRC) for each enzyme was evaluated using immunohistochemistry. A dichotomous breakdown of DGCR8 and Dicer expression (negative or positive test) was performed using a cut-off of 80% IRC. The 5-year survival rate of stage 0–I–II was 89.5% and stage III–IV was 18.5%. In the bivariate analysis, variables associated with lower survival were: aged over 42 years, histologic subtypes, Breslow thickness ≥0.8mm, ulceration, vascular invasion, metastatic melanoma, positive sentinel node, more than 1 positive node, LDH >200 IU/L, distant metastasis, and stage III–IV. In the multivariate Cox model, the analysis for stage III–IV showed a significantly lower survival curve in patients with a positive DGCR8 test and aged ≤42 years ($p=0.0152$, Wald test). The Cox proportional hazards model showed that a positive DGCR8 test was a predictive factor for mortality in patients aged ≤42 years (HR=14.3, 95%CI 1.5–140, $p=0.024$). This study highlights a potential biomarker for melanoma survival and its utility in stratifying high-risk patients.

Key words: DGCR8; melanoma; survival; age; mortality.

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SIGNIFICANCE

Malignant melanoma accounts for the majority of skin cancer-related deaths, so to find additional tools that can identify high-risk patients with more aggressive behaviour is warranted. We evaluated the association between microRNA-processing enzymes – Dicer and DGCR8 – and melanoma patient mortality. In the multivariate analysis, a positive DGCR8 test was a predictive factor for mortality in young patients for stage III–IV. This result provides valuable insights into a potential biomarker for identifying high-risk patients who may benefit from additional interventions.

Malignant melanoma is an aggressive skin cancer with a high mortality rate. It accounts for the majority of skin cancer-related deaths. Before the new era of novel therapies for advanced melanoma, immunotherapy and targeted therapy, the 5-year overall survival rate was 17%, which has significantly improved to 50% with combination immunotherapy (1–3). However, disease recurrence and progression are still an issue to overcome. On the other hand, the incidence of malignant melanoma among young adults has been increasing over time and some contributing factors such as increased surveillance, exposure to ultraviolet radiation, and personal risk factors (e.g., immunosuppression) have been involved (4, 5). Wojcik et al. (6) reported that adolescent and young adult patients had worse survival than older adults with stage IV melanoma. Melanomas occurring at younger ages are thought to be more aggressive with more mitotically active tumours (6–8). Pathological parameters such as ulceration, Breslow thickness, and mitotic rate have been associated with poor prognosis, so to find additional tools that can identify high-risk patients with more aggressive behaviour is warranted in order to achieve better outcomes. As such, the DiGeorge syndrome critical region gene 8 (DGCR8) and Dicer, which are microRNA (miRNA)-processing enzymes, have been found overexpressed in malignant melanoma (9–11). DGCR8 and Dicer participate in the miRNA biogenesis pathway, being essentials for miRNA maturation. miRNAs are small (approximately 22 nucleotides) and noncoding RNAs that play an important role in several biological processes such as angiogenesis, apoptosis, cell proliferation, and differentiation (12). In melanoma patients, DGCR8 and Dicer expression have been associated with clinicopathological parameters such as histologic subtype, ulceration, Breslow tumour thickness, mitotic rate, metastasis status, and stage (9–11). Studies have shown that DGCR8 plays an important role in cell proliferation and differentiation (13, 14). Indeed, the

inactivation of DGCR8 results in a dramatic antiproliferative response, with the acquisition of a senescent phenotype (14). On the other hand, overexpression of Dicer decreases anti-tumour immune response in melanoma cells and has been correlated with poor survival in patients with colorectal and breast cancer (15–17). In a previous study, we found that Dicer and DGCR8 were overexpressed in melanoma and had potential utility as diagnostic tools to differentiate cutaneous melanomas from other melanocytic skin lesions (10). Here, we have evaluated whether these miRNA-processing enzymes could be used as risk factors for mortality in primary cutaneous melanomas and metastatic melanomas in a long-term follow-up.

MATERIALS AND METHODS

Samples and immunohistochemistry

A retrospective cohort study was carried out based on the analysis of medical records and samples from patients with primary cutaneous melanoma and metastatic melanoma diagnosed between 2007 and 2012. The samples were obtained from the pathology archives and the study protocol was approved by the local Ethics Committee. A total of 74 samples including 42 primary cutaneous melanomas and 32 metastatic melanomas were analysed. The formalin-fixed paraffin-embedded (FFPE) samples were used for construction of the tissue microarray (TMA). From each biopsy, tissue cores of 2 mm in diameter were spotted on TMA blocks, which were assembled using the Tissue Microarrayer Platform Galileo TMA CK3600 Computer Driven (Integrated Systems Engineering S.r.l., Padua, Italy). A Leica BOND Automated Immunostainer (Leica Biosystems, Nussloch, Germany) was used for immunohistochemistry (IHC). We used the anti-Dicer antibody (1/20 dilution, ab259327, Abcam, Cambridge, MA, USA) and anti-DGCR8 antibody (1/200 dilution, ab90579, Abcam, Cambridge, MA, USA). The BOND Polymer Refine Red Detection kit was then used (DS9390). Testicular seminoma was used as positive control.

Dicer and DGCR8 immunostaining were graded according to the percentage of immunoreactive tumour cells (% IRC). The nuclear staining of DGCR8 and cytoplasmic staining of Dicer were recorded on a scale from 0 to 100% (0 = absence of immunopositive tumour cells; 100 = all tumour cells expressed the stain, **Fig. 1**).

Clinical and pathological variables

The following variables were evaluated and compared with mortality: age (≤42 years, >42 years; according to NCCN Guidelines) (18, 19), sex (female, male), ethnicity (Mapuche, non-Mapuche), photo-exposed area (yes, no), histologic subtype (superficial spreading melanoma, nodular melanoma, acral lentiginous melanoma, lentigo maligna melanoma), anatomic location (upper limbs, lower limbs, head, trunk), invasive melanoma (yes, no), Breslow thickness (<0.8mm, ≥0.8mm) (18), ulceration (yes, no), mitotic rate (≥2/mm^2, <2/mm^2) (18, 19), vascular invasion (yes, no), tumour-infiltrating lymphocytes (yes, no), metastatic melanoma (yes, no), sentinel node (positive, negative), number of positive nodes (1 node, more than 1 node), lactate dehydrogenase (LDH) (>200 IU/L, ≤200 IU/L), metastasis location (lymph nodes, distant metastasis), tumour stage (0–I–II, III–IV). For the evaluation of miRNA-processing enzymes, a

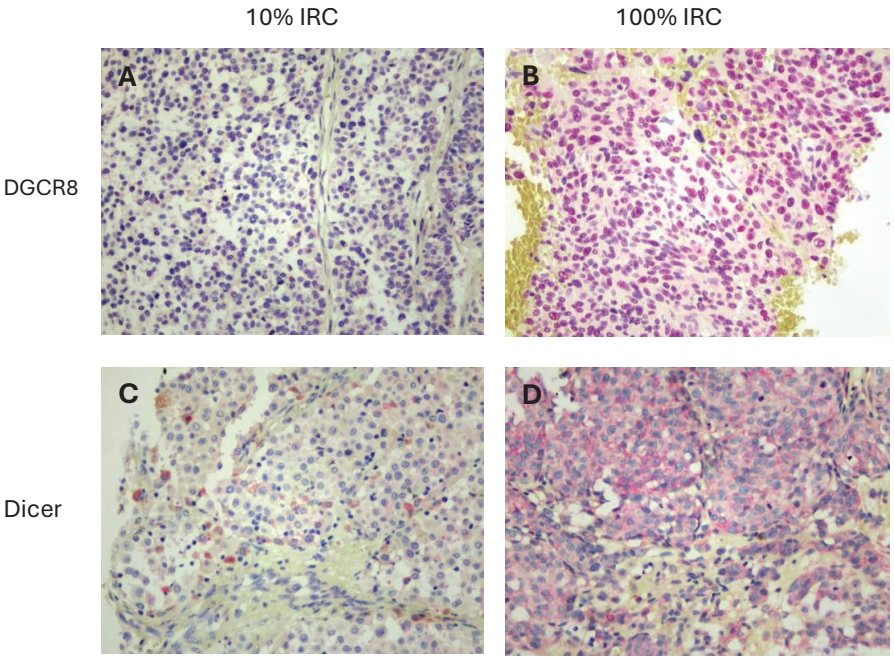

Fig. 1. IHC showing nuclear staining of DGCR8 and cytoplasmic staining of Dicer in melanoma patients, based on the %IRC. (A) and (B) Melanoma tissues showing 10% and 100% of DGCR8 IRC, respectively. (C) and (D) Melanoma tissues showing 10% and 100% of Dicer IRC, respectively. Original magnification 200x. IHC, immunohistochemistry; % IRC, percentage of immunoreactive cells.

dichotomous breakdown of a negative or positive test for DGCR8 and Dicer expression was performed using a cut-off point of 80% of immunoreactive tumour cells (IRC) (<80%, ≥80%) (10).

Statistical analysis

Descriptive statistical analysis was performed, which included percentage for the categorical variables, range, mean or median, and standard deviation or interquartile range for the continuous variables.

For the bivariate analysis, Kaplan–Meier curves were used to present observed and expected survival rates using confidence intervals (95%) according to the exposure variables. The corresponding *p*-value is also included as a global test (Cox Model) for the comparison of survival rates. Results were considered significant at $p<0.05$.

A multivariate Cox proportional hazards model was used to analyse the association between the exposure variable and the outcome while accounting for confounders. Statistical analysis was performed using Stata software, version 18 for Windows (StataCorp LLC, College Staton, TX, USA).

RESULTS

A total of 74 malignant melanomas were studied, 42 being primary cutaneous melanomas and 32 metastatic melanomas. The mean age was 55.8±18.6 years. Of the total, 52 (70.3%) patients were females and 12 (16.2%) patients were Mapuches. Patients who presented metastasis were 54 (73%) and 30 patients had distant metastasis (40.5%). According to the eighth edition of the American Joint Committee on Cancer (AJCC) melanoma staging system, 20 (27%) patients were categorized into stages 0–I–II and 54 (73%) patients into stages III–IV. In primary cutaneous melanomas, the mean values (% IRC) of Dicer and DGCR8 immunoexpression were 42.3±41.7 and 43.0±40.9, respectively. In metastatic melanomas, the mean values (% IRC) of Dicer and DGCR8 immunoexpression were 19.4±36.0 and 20.2±30.0, respectively.

The total time at risk for the 74 cases was 4,569 months with a median (IR) follow-up time of 24.5 (10.8–136.0) months and a mortality rate of 70.3%, being 61.9% for primary cutaneous melanomas and 81.3% for metastatic melanomas. The 5-year survival rate of stage 0–I–II was 89.5% [60.4%–94.9%] and stage III–IV was 9.1% [1.6%–25.1%] in primary cutaneous melanoma group and 25.0% [11.8%–40.7%] in metastatic melanoma group. The clinical and pathological characteristics of both groups are summarized in **Table I**.

In the bivariate analysis, the following variables were associated with lower survival for melanoma patients: aged more than 42 years, histologic subtypes (nodular, acral, or lentigo), Breslow thickness ≥0.8mm, ulceration, vascular invasion, metastatic melanoma, positive sentinel node, more than 1 positive node, LDH >200 IU/L, distant metastasis, and stage III–IV (**Table II**).

Comparison of the survival curve of melanoma patients, by stage, showed a statistically significant difference ($p=0.0001$); patients with stage III–IV had higher

Table I. Clinical and pathological characteristics of the study patients

Variables	Cutaneous melanomas (*n* = 42)	Metastatic melanomas (*n* = 32)	Total (*n* = 74)
Age (years), mean ± SD	58.2 ± 20.9	52.5 ± 14.8	55.8 (18.6)
Female sex (%)	28 (66.7)	24 (75.0)	52 (70.3)
Mapuche ethnicity (%)	9 (21.4)	3 (9.4)	12 (16.2)
Invasive melanoma (%)	38 (90.5)	32 (100)	70 (94.6)
Metastatic melanoma (%)	22 (52.4)	32 (100)	54 (73.0)
Positive sentinel node (%)†	7 (16.7)	18 (56.2)	25 (33.8)
More than 1 positive node (%)	4 (9.5)	11 (34.4)	15 (20.3)
LDH (IU/L), mean ± SD¶	343.6 ± 499.1	353.4 ± 317.1	348.0 ± 429.2
Distant metastasis (%)	13 (31.0)	17 (53.1)	30 (40.5)
Tumour stage 0–I–II (%)	20 (47.6)	–	20 (27.0)
Tumour stage III–IV (%)	22 (52.4)	32 (100)	54 (73.0)
Dicer (%IRC), mean ± SD*	42.3 ± 41.7	19.4 ± 36.0	32.4 ± 40.7
DGCR8 (%IRC), mean ± SD*	43.0 ± 40.9	20.2 ± 30.0	33.3 ± 38.1
Mortality (%)	26 (61.9)	26 (81.3)	52 (70.3)
Survival median (months), (RI)	42 (14.4→)	15.8 (6.8–51.2)	24.2 (10.8→)
5 years survival (%) [IC95%]			
Stage (0–I–II)	89.5 [60.4–94.9]	–	89.5 [60.4–94.9]
Stage (III–IV)	9.1[1.6–25.1]	25.0 [11.8–40.7]	18.5 [9.5–29.8]

†Sentinel node data were available for 12 and 19 patients in the primary cutaneous melanoma and metastatic group, respectively. ¶LDH was available for 16 and 13 patients in the primary cutaneous melanoma and metastatic group, respectively. *Immunohistochemical analysis of Dicer and DGCR8 expression was available for 58 and 59 patients, respectively.
SD: standard deviation.

Table II. Bivariate Cox model and hazard ratio according to variables in melanoma patients

Variables	Patients, *n*	*n* (%)	Hazard ratio	*p*-value	95% CI
Age (>42 years)	74	58 (78.4)	4.3	0.002	1.7–11.0
Sex (Female)	74	52 (70.2)	1.3	0.317	0.8–2.4
Ethnicity (Mapuche)	74	12 (16.2)	1.5	0.277	0.7–3.0
Photo-exposed area (yes)	36	11 (30.6)	0.8	0.600	0.3–1.9
Histologic subtype	42				
— Superficial		15 (35.7)	1.0	–	–
— Nodular		22 (52.3)	9.8	0.0003	2.8–33.9
— Acral		2 (4.8)	35.3	0.0003	5.2–240.1
— Lentigo		3 (7.1)	16.0	0.0012	3.0–85.3
Anatomic location	42				
— Head		10 (23.8)	2.0	0.3040	0.5–7.9
— Upper limbs		8 (19.0)	1.0	–	–
— Trunk		7 (16.7)	2.1	0.3095	0.5–8.8
— Lower limbs		17 (40.5)	2.0	0.2863	0.6–7.2
Invasive melanoma (yes)	74	70 (94.6)	2.3	0.2481	0.6–9.5
Breslow (≥0.8 mm)	38	27 (71.1)	3.3	0.0306	1.1–9.7
Ulceration (yes)	36	15 (41.7)	10.0	0.0000	3.4–29.4
Mitotic rate (≥2 cells/mm^2)	29	22 (75.9)	3.5	0.0951	0.8–15.6
Vascular invasion (yes)	23	9 (39.1)	9.1	0.0007	2.5–32.3
Tumour-infiltrating lymphocytes (yes)	11	8 (72.7)	1.1	0.9591	0.1–10.2
Metastatic melanoma (yes)	73	54 (74.0)	7.3	0.0000	2.8–18.5
Sentinel node (yes)	31	25 (80.7)	8.6	0.0370	1.1–64.9
Number of positive nodes (>1)	26	15 (57.7)	3.0	0.0306	1.1–8.2
LDH (>200 IU/L)	29	14 (48.3)	3.1	0.0154	1.2–7.6
Distant metastasis (yes)	50	30 (60.0)	2.1	0.0194	1.1–4.1
Stage (III–IV)	74	54 (73.0)	6.4	0.0001	2.7–15.2
Dicer ≥80 (positive)	58	17 (29.3)	1.4	0.3590	0.7–2.6
DGCR8 ≥80 (positive)	59	16 (27.1)	1.6	0.1428	0.9–3.1

p-values and confidence intervals were obtained from the bivariate Cox model.

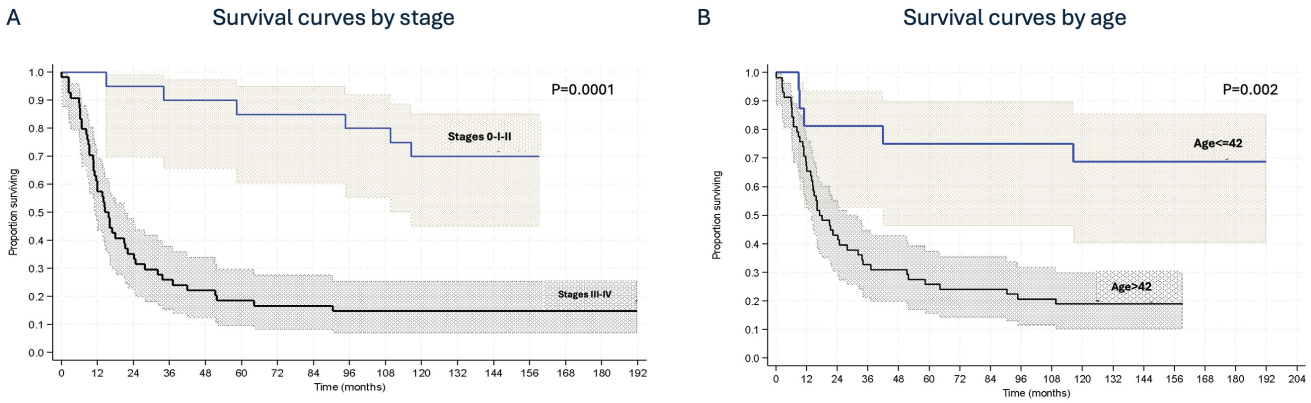

Fig. 2. Kaplan–Meier curves from the bivariate Cox model by stage and age. (A) Patients with stages III–IV presented significantly lower survival ($p = 0.0001$). (B) Patients aged >42 years presented significantly lower survival ($p = 0.002$).

mortality in a shorter time period (**Fig. 2**A). Also, the comparison of the survival curve of melanoma patients, by age, showed a statistically significant difference ($p = 0.002$); patients aged >42 presented higher mortality in a shorter period of time (Fig. 2B).

Comparison of the survival curve of melanoma patients from the multivariate Cox model in stage 0–I–II, by DGCR8 test result and age, showed differences in the survival curves; however, none of them were statistically significant compared with patients with a negative DGCR8 test and aged ≤42 years ($p > 0.05$, Wald test, **Fig. 3**A). In the analysis for stage III–IV, the comparison of the survival curve, from the multivariate Cox model, showed that there were lower survival curves with statistically significant *p*-values in patients with all combinations of test results and age compared with patients with a negative DGCR8 test and aged ≤42 ($p < 0.0152$, Wald test, Fig. 3B). The multivariate Cox proportional hazards model, applied to patients with melanoma and DGCR8 test result, controlling for stage (**Table III**), showed that a positive DGCR8 test was a predictive factor for mortality in patients aged ≤42 years (HR = 14.3, 95% CI 1.5–140, $p = 0.024$). In patients aged >42 years, the test was not a predictive factor (HR = 1.5, 95% CI 0.7–3.1, $p = 0.2698$, Table III). The predictivity of the DGCR8 test depended on the age of the patients (interaction *p*-value = 0.0594).

Clinical and pathological characteristics of young patients with melanoma

Patients aged ≤42 years and >42 years were analysed. Five-year survival rate for the group aged ≤42 years was 75% [46.3–89.8] and for the >42 years was 25.9% [15.5–37.5], $p = 0.002$. There were no statistically significant differences between the groups in terms of clinical and histopathological characteristics with the exception that more older patients had more than 1 positive lymph node than younger patients (72% vs 25%, respectively, $p = 0.038$).

On the other hand, Dicer expression was not a predictive factor for mortality in a multivariate analysis.

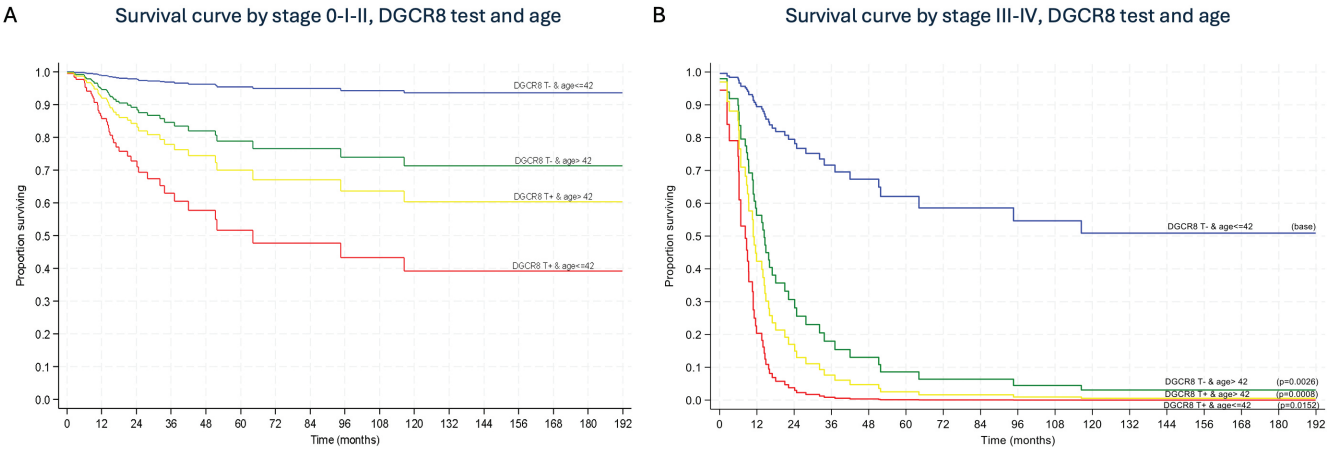

Fig. 3. Kaplan–Meier curves from the multivariate Cox model by stage. (A) For stage 0–I–II, there were differences in the survival curves; however, none of them were statistically significant compared with patients with a negative DGCR8 test and aged ≤ 42 (p-values > 0.05, Wald test). (B) For stage III–IV, there were lower survival curves with statistically significant *p*-values in patients with all combinations of test results and age compared with patients with a negative DGCR8 test and aged ≤ 42 ($p < 0.0152$, Wald test).

Table III. Multivariate Cox proportional hazards model including the following variables: positive DGCR8 test (T+), age >42 years old, and melanoma stage III and IV

Variables	Coeff	*p*-value	95% CI
Multivariate Cox proportional hazards model			
DGCR8 (≥80%)	2.7	0.0224	0.38–4.94
Age (> 42 years old)	1.6	0.0032	0.55–2.73
Melanoma stage (III–IV)	2.3	0.0002	1.09–3.57
DGCR8*Age	–2.3	0.0594	–4.6–0.09
Mortality HR of DGCR8 test by age, controlling for stage			
Age	HR	*p*-value	95% CI
≤42	14.3	0.0224	1.5–140.0
>42	1.5	0.2698	0.7–3.1

This model controlling by stage showed that a DGCR8 T+ was an important and statistically significant predictive factor for mortality in patients aged ≤42 years old.

DISCUSSION

Melanoma represents the second most common type of cancer in adolescents and young people (20). Although its incidence among young adults has been increasing over time, the disease-specific mortality is actually decreasing. This situation has been attributed, in part, to increased skin cancer screening with detection of early-stage melanomas (5). However, some authors have reported an increased burden of melanoma in all socioeconomic groups, histologic subtypes, and tumour thickness, suggesting that skin screening could not explain the increasing incidence of thicker tumours in lower socioeconomic groups with poorer access to healthcare (21). Overall, melanoma mortality rates increase with age, with the highest rates observed in older individuals; therefore, younger patients generally have better prognoses (7, 22, 23). However, a study into age-specific differences in melanoma has reported that adolescents and young adult had a higher risk of death than older adults with stage IV and melanomas with a Breslow thickness ≥4 mm (6). Also, higher mitotic rates and sentinel lymph node (SLN) biopsy positivity have been described in younger patients compared with older patients (6, 7). Nevertheless, lower non-SLN positivity and 5-year mortality rates were observed in the younger group (21%) compared with the adult group (42%) (7). In our study, we also found that younger patients (≤42 years) had a higher 5-year survival rate than older patients (75% vs 25.9%, respectively, $p=0.002$), except when a positive DGCR8 test was present in stage III–IV.

Our study provides insights into age-related differences in melanoma survival. Younger patients (≤42 years) with a positive DGCR8 test presented worse survival than patients with a negative DGCR8 test. In older patients (>42 years), there were no statistically significant differences in terms of DGCR8 test results and survival. This finding supports the idea that melanomas in younger patients may behave differently than those in older patients and it should encourage future efforts to investigate the biologic role of DGCR8 in melanoma development. According to the statistical model, a positive DGCR8 test proved to be a significant predictive factor for mortality in younger patients. DGCR8 is part of the miRNA maturing microprocessor complex, which is responsible for cleaving primary miRNA to produce miRNA precursors. DGCR8 overexpression has been associated with tumour cell proliferation and reduced tumour suppressor protein expression (24–26). Indeed, the knockdown of DGCR8 significantly decreases proliferation, migration, and invasion of cancer cells (13). Therefore, further studies are warranted to better understand melanoma biology at different ages.

On the other hand, a retrospective study in melanoma patients with T1a disease demonstrated that significant high-risk factors for positive SLN were associated with age ≤42 years (7.5%), head/neck primary tumour (9.2%), lymphovascular invasion (21.4%), and ≥2 mitoses/mm^2 (8.2%) (19). Patients who had 2 adverse features such as age < 42 years and ≥2 mitoses/mm^2 had an 18.4% positive SLN rate, so there was an additive increased risk when multiple adverse features were presented simultaneously (19). The NCCN Guidelines recommend discussing and considering biopsy of SLN for patients with a tumour thickness of ≥0.5 mm associated with these adverse features (18).

The limitations of our study were the relatively small sample size and its retrospective nature. Further studies with larger populations are warranted to validate these findings.

Our study provides insight into a potential biomarker for melanoma survival in the context of age-related differences. Therefore, it is crucial to identify high-risk patients so that additional interventions can be implemented to achieve better outcomes.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

The authors have no conflicts of interest to declare.

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