Evaluation of overall survival among patients suffering from cutaneous malignant melanoma

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Background: Survival studies are needed in patients with cutaneous malignant melanoma (CMM) due to the growing incidence trend worldwide. We aimed to determine the survival trend in patients suffering from CMM, considering various demographic and tumor characteristics.

Methods: In this descriptive-analytical study, we examined 57 patients with confirmed melanoma from April 2014 to February 2019. Using the Kaplan-Meier method and log-rank test, we assessed the correlation between survival probability and factors with prognostic potential, such as gender, age, tumor thickness, mitotic rate, anatomical sites, and chemotherapy.

Results: Out of 57 patients with a mean age of 59.5 ± 22.7 years, 33 (57.9%) were females. The mean survival was 43 ± 15 months, ranging from 15 to 82 months. Regarding tumor thickness, 26 patients had 1–4 mm tumor thickness, 18 patients 5–10 mm, and five patients 11–30 mm. The tumor mitotic rate was 1–2 mitoses/mm^2 in 19 patients and ≥ 3 mitoses/mm^2 in 32 patients. Infiltrated lymphocytes were present in 36 patients (36.6%). In the case of therapeutic intervention, 55 patients received chemotherapy. According to the results of the Kaplan-Meyer test, the mean survival did not show a significant difference ($P < 0.05$) in patient subgroups. Moreover, a profound correlation was not found between survival rate and different age groups, mitotic rate, thickness, lymphocyte infiltration, and chemotherapy.

Conclusion: Irrespective of disease stage and histopathology examination, we found no significant correlation between survival rate and demographic/tumor characteristics in patients with CMM.

Keywords: melanoma, mitotic index, survival, tumor thickness

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INTRODUCTION

Cutaneous malignant melanoma (CMM) is an aggressive skin malignancy that has become more prevalent worldwide in recent decades [1]. Melanoma originates from the excessive replication of resident melanocytes (pigment cells) in the dermal-epidermal

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junction that can either locally invade or metastasize to other tissues [2]. In 2020, 100,350 new cases of melanoma were diagnosed in the United States (US), accounting for nearly 6% of all reported primary cancers [3]. Multiple subtypes of melanoma can target various organs from the skin (e.g., CMM) to the mucosal lining, including the head and neck [4,5] and respiratory, gastrointestinal [6], and genitourinary tracts [7], as well as ocular involvement (conjunctival and uveal melanomas) [8-10]. An early diagnosis through attentive assessment and careful use of prognostic and diagnostic biomarkers can improve the prognosis, decreasing morbidity and mortality [1]. In the case of CMM, the tumor mitotic rate (TMR), thickness, and ulceration, from a typically pigmented macular/proliferative lesion to a non-pigmented form, are considered potential prognostic indicators. Also, the lesion may take single/multiple and primary/metastatic forms [11].

Beyond the histopathology examination, specific immunohistochemical staining, genetic tests, dermatoscopy, and reflectance confocal microscopy are valuable tools that can recognize the critical characteristics of unusual MM subtypes and help clinicians in decision-making [12]. Disease risk factors include age, gender, genetic predisposition, environmental conditions (e.g., long-term exposure to ultraviolet (UV) radiation), light skin pigmentation, and immunodeficiency [13]. Regarding therapeutic options, conventional treatments failed to induce complete regression; however, surgical interventions such as local tumor excision, along with immunosurveillance-based therapies, including immune checkpoint inhibitors (ICIs), targeted therapy (e.g., vemurafenib, dabrafenib, trametinib), immunotherapy (such as pembrolizumab, nivolumab, ipilimumab), and T cell receptor (TCR)-engineered T cells [14] aim to improve the host immune system and can lead to a substantial breakthrough in the treatment of patients with CMM regardless of inherent or acquired resistance [15].

The main aim of this multi-center retrospective study was to evaluate the survival rate of CMM patients referred to tertiary hospitals. As the secondary endpoint, we assessed whether survival is related to demographic characteristics, tumor thickness, TMR, anatomic sites, lymphocyte infiltration, and chemotherapy.

METHODS

Study population

All patients (both inpatients and outpatients) referred to tertiary hospitals, named Imam Khomeini and Ayatollah Taleghani hospitals affiliated to the Urmia University of Medical Sciences, Urmia, Iran, were included from April 2014 to February 2019 following the early diagnosis and pathological confirmation of the primary malignant melanoma. Data collection was performed based on the electronic health records (EHR) using a standard checklist.

Data processing and statistical analysis

This study reported quantitative variables as mean ± standard deviation (SD) and qualitative variables as percentages (%). In addition, the survival rate was calculated using the Kaplan-Meier curve with a confidence interval (CI) of 95%. We used the log-rank test to determine a possible correlation between the survival rate and independent variables. Data analysis was performed using SPSS17 software, and a P-value less than 0.05 was considered significant.

Ethical considerations

The ethical approval for this research was issued from the Urmia University of Medical Sciences with Ethics Committee No. IR-UMSU.REC.1398.498. It should be noted that the information of all patients was confidential and identified by an assigned code number. Also, no costs were imposed on the patients for conducting this study.

Eligibility criteria

All patients with pathology-confirmed CMM were included in this study. We excluded patients with incomplete medical records.

Design limitations

Histopathology artifacts, potential quality pitfalls in the pathological slides, and lack of cooperation of some patients through telephone interviews were considered major study limitations.

RESULTS

Demographic characteristics

In this descriptive-analytical study, 57 patients were included. Of 57 patients, 33 (57.9%) were females, and 24 (42.1%) were males. The mean

age was 59.5 ± 22.7 years (range: 1–96). Although the number of females was higher than males, this difference was insignificant ($P > 0.05$). The median survival rate of patients with CMM was 43 ± 15 months, ranging from 15 to 82 months. The tumor thickness, reflecting the depth of invasion, was between 1–4 mm in 53.1% of patients, while 36.7% and 10.2% had a tumor thickness between 5–10 mm and 11–30 mm, respectively. Regarding the TMR, our results showed that 37.3% of patients had 1–2 mitoses in each mm^2, while this figure was ≥3 in each mm^2 (with high metastatic and invasion potential) in 62.7% of patients. Noteworthy, 15 patients (26.3%) also showed tumor-infiltrating lymphocytes (TILs). Of all patients, merely ten received chemotherapy.

Association between survival rate and demographic characteristics

As shown in Table 1, the survival rate of patients with melanoma was the same for both genders ($P > 0.05$). The Kaplan-Meier curve also confirmed this finding (Figure 1-a). Moreover, the survival rate of patients with melanoma did not show a significant difference in various age groups ($P > 0.05$, Table 1, Figure 1-b).

Association between survival rate and disease characteristics

According to the obtained results from the Kaplan-Meier analysis, there was no relation between tumor thickness and survival rate (Table 2, Figure 1-d). In addition, a significant relation was not found between tumor anatomic sites and survival rate (Supplementary Figure 1 and Supplementary Table 1, $P > 0.05$). Also, we found no correlation of prognostic significance between survival trend and TMR (Table 3, Figure 1-c, $P > 0.05$), tumor-infiltrating lymphocytes (Table 4, Figure 1-e, $P > 0.05$), and chemotherapy (Table 5, Figure 1-f, $P > 0.05$).

DISCUSSION

With an unpredictable evolution, malignant melanoma is considered one of the skin cancers with poor clinical prognosis worldwide [16]. Despite increasing evidence regarding the determination of various variables' prognostic potential, this matter has remained controversial. The current study intended to evaluate the overall survival trend in 57 patients with cutaneous malignant melanoma (CMM) admitted to multiple tertiary hospitals. Further, the association between the survival rate and critical determinants, including age, gender, tumor thickness, TMR, anatomic sites, and TIL, was assessed using Kaplan-Meier analysis. Although a previous study linked decreased survival with tumor thickness, gender, phototype, and tumor subtype [17], none of our study's variables showed significance pertinent to survival.

In line with our findings, Ardakani *et al.* found no relationship between survival and TMR, gender, age, tumor thickness, and lymphocyte infiltration.

Table 1. Association of age and gender with survival rate in patients with cutaneous malignant melanoma

Age (years)	Number	Deaths	Censored Data for Surviving Patients	
			Number	Percentage (%)
21-40	5	0	5	100
41-60	15	1	14	93.3
61-80	22	6	16	72.7
> 80	10	4	6	60
Total	52	11	41	78.8
Survival analysis				
	Degrees of freedom	**Chi-square**	***P*-value**	
Log-rank	3	5.895	0.117	
			95% confidence interval (CI)	
Gender	**Estimation**	**Mean Squared Error (MSE)**	**Min**	**Max**
Male	5.432	0.484	4.484	6.380
Female	6.381	0.327	5.740	7.022
Total	5.803	0.324	5.167	6.439
Survival analysis				
	Degrees of freedom	**Chi-square**	***P*-value**	
Log-rank	1	2.021	0.155	

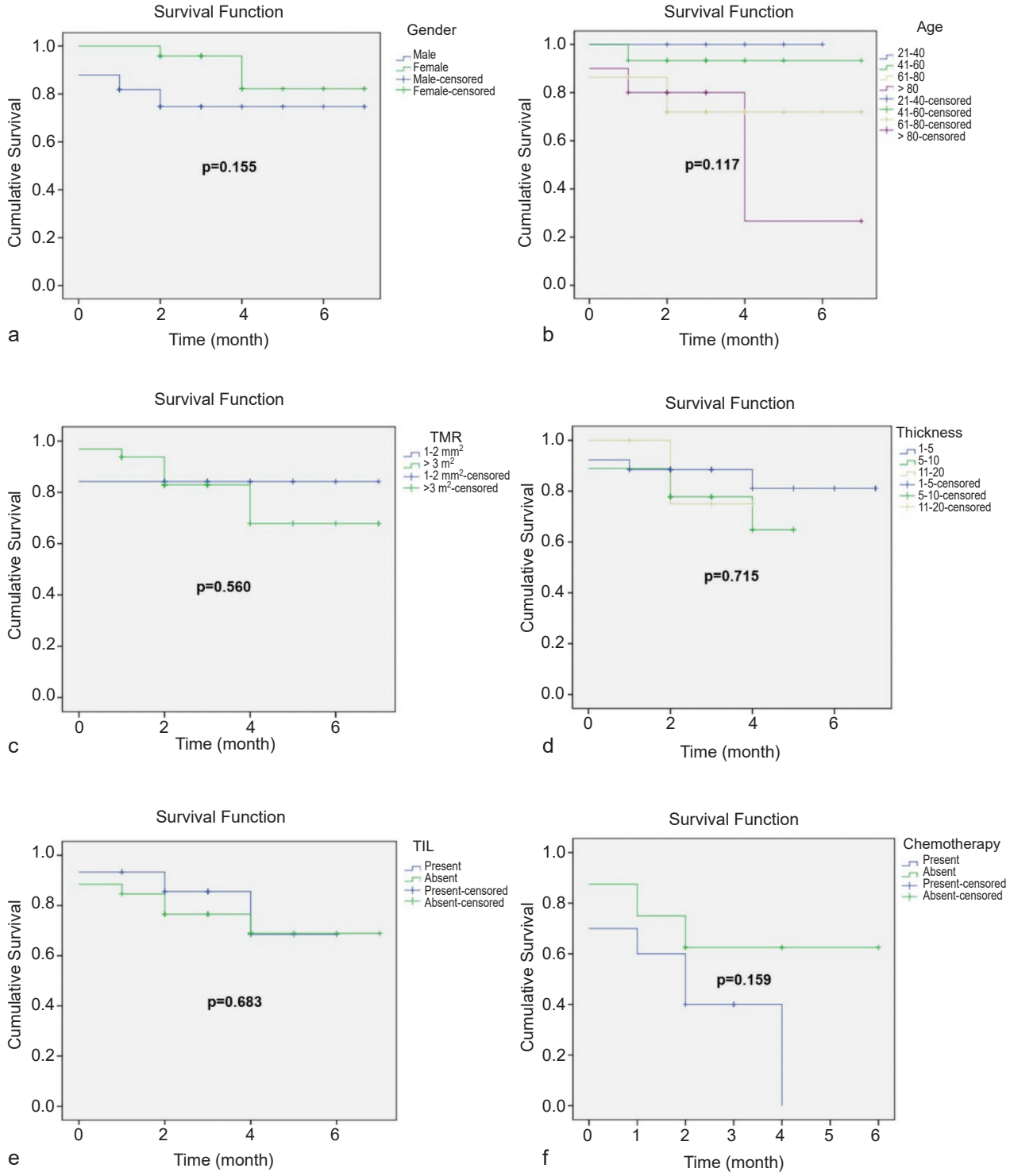
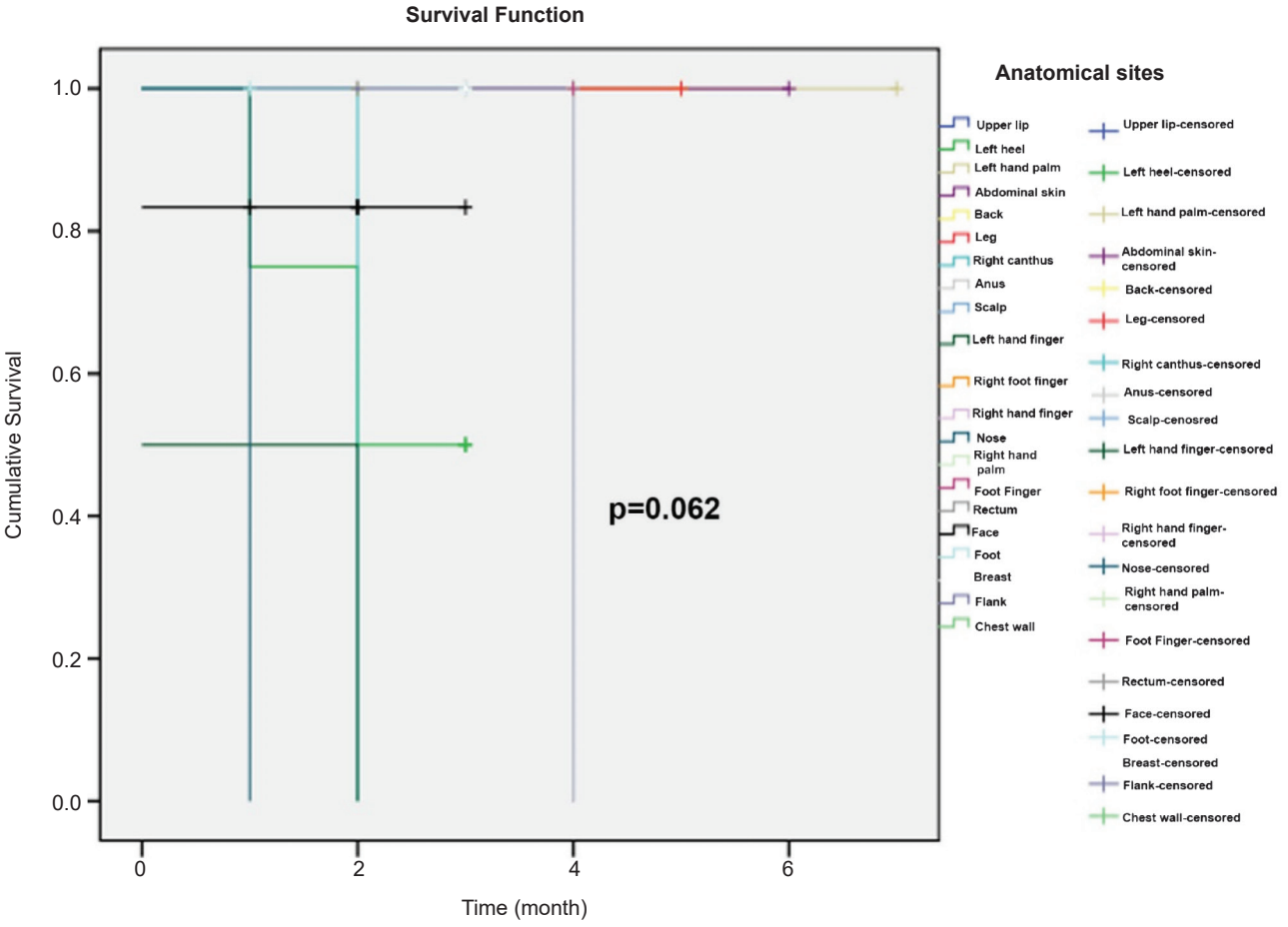


Figure 1. Overall survival curves using the Kaplan-Meier analysis in cutaneous malignant melanoma patients according to (a) gender, (b) age, (c) tumor mitotic rate (TMR), (d) tumor thickness, (e) tumor-infiltrating lymphocyte (TIL) status, and (f) chemotherapy status. No significant differences were found (P > 0.05).

However, they reported that the survival of patients with malignant melanoma had a significant relationship with tumor stage and anatomic sites [18]. Moreover, our study estimated that the survival rate was non-significantly higher among female patients. Similarly, a cohort study reported a considerable advantage of

Table 2. Association between survival rate and tumor thickness in patients with cutaneous malignant melanoma

Thickness (mm)	Number	Death rate	Censored Data for Surviving Patients	
			Number	(%)
1-4	26	4	22	84.6
5-10	18	5	13	72.2
11-20	5	1	4	80
Total	49	10	39	79.6
Survival analysis				
Log Rank	**Degrees of freedom**	**Chi-square**	***P*-value**	
Thickness	3	0.615	0.715	
Tumor Location	11	18.955	0.062	



Supplementary Figure 1. Assessment of the relationship between the anatomic site and survival of patients with cutaneous malignant melanoma. No significant relationship was found (P > 0.05).

melanoma-specific survival in females (HR 0.68; 95% CI 0.62–0.75), with a lower risk of disease progression [19]. In our study, age and gender did not emerge as predictors with clinical significance, while Tas *et al.* revealed that the elderly population in Turkey was likely to have more aggressive histological features and poorer survival [20]. In detail, they found that higher TMR, ulceration, and Clark invasion levels in older patients led to adverse outcomes [20].

Regarding the tumor thickness, a primary investigation reported a negative relationship with survival rate [21]. For each 1-mm increase in tumor thickness, the survival rate declined by nearly 3% and 9% in females and males, respectively [21]. Parallel with our findings, a large-scale retrospective study in the U.S. (1989–2009) demonstrated that [22], over time,

Supplementary Table 1. Assessment of melanoma skin manifestation in various sites and possible association with the survival rate

Side	Number	Censored Data for Surviving Patients	
		Number	(%)
Upper lip	1	1	100
Left heel	1	1	100
Abdominal skin	1	1	100
Back	1	1	100
Canthus	1	1	100
Anus	1	1	100
Left hand	1	1	100
Right hand	1	1	100
Nose	1	1	100
Right hand palm	2	2	100
Face	1	1	100
Chest wall	1	1	100
Total	23	23	67.6
	Degrees of freedom	**Chi-square**	***P*-value**
Log-rank	11	18.955	0.062

survival is generally refining independent of tumor thickness; however, improvement in survival trend has not been met in certain minorities, as well as in nodular and acral lentiginous melanoma subtypes [22].

In the case of TMR, as a strong independent prognostic value of melanoma-specific survival, similar to our findings, a previous study by the Sydney Melanoma Unit database reported no significant survival differences for the stepwise increases of TMR in melanoma patients [23]. However, Ghasemi Basir *et al.* highlighted a positive correlation between melanoma tumor thickness and mitotic rate, reflecting the depth of tumor invasion, where a one-unit increase in mitotic rate correlated with a 0.8 mm increase in tumor thickness [24]. Interestingly, it has been well-established that ulceration and significantly lower ten-year survival probability are associated with a higher mitotic rate (> 20/mm^2) [25]. We also assessed the levels of TIL among melanoma patients, but a significant correlation was not found based on the

Table 3. Association between survival rate and tumor mitotic rate per mm^2 in patients with cutaneous malignant melanoma

Tumor mitotic rate (TMR, mm^2)	Number	Death rate	Censored Data for Surviving Patients	
			Number	(%)
1-2	19 (33.3%)	3	16	84.2
≥ 3	32 (56.2%)	7	25	78.1
Unknown information	6 (10.5%)	-	-	-
Total	57	10	41	80.4
Mitotic rate (mm^2)	**Estimation**	**Mean Squared Error (MSE)**	**95% Confidence Interval (CI)**	
			Min	**Max**
1-2		0.586	4.747	7.042
≥ 3	5.601	0.455	4.709	6.492
Total	5.760	0.351	5.073	6.447
Survival analysis				
	Degrees of freedom		**Chi-square**	***P*-value**
Log Rank	1		0.340	0.560

Table 4. Association between survival rate and tumor-infiltrating lymphocytes in patients with cutaneous malignant melanoma

Tumor-Infiltrating Lymphocytes (TIL)	Number	Death rate	Censored Data for Surviving Patients	
			Number	(%)
Present	15	3	12	80
Absent	26	7	19	73.1
Total	41	10	31	75.6
Mitotic rate	**Estimation**	**Mean Squared Error (MSE)**	**95% Confidence Interval (CI)**	
			Min	**Max**
Present	4.947	0.531	3.906	5.988
Absent	5.329	0.542	4.266	6.391
Total	5.452	0.432	4.623	6.281
Survival Analysis				
	Degrees of freedom		**Chi-square**	***P*-value**
Log-rank	1		0.167	0.683

Table 5. Association between survival rates and chemotherapy in patients with cutaneous malignant melanoma

Chemotherapy	Number	Death rate	Censored Data for Surviving Patients	
			Number	(%)
Yes	10	7	3	30
No	8	3	5	62.5
Total	18	10	8	44.4
Mitotic rate	**Estimation**	**Mean Squared Error (MSE)**	**95% Confidence Interval (CI)**	
			Min	**Max**
Yes	2.100	0.581	0.962	3.238
No	4.125	0.874	2.412	5.838
Total	3.194	0.603	2.013	4.376
Survival analysis				
	Degrees of freedom		**Chi-square**	***P*- value**
Log-rank	1		1.981	0.159

Kaplan-Meier method.

Besides, Pinto-Paz *et al.* designed a study to explore the correlation between the neutrophil-to-lymphocyte ratio (NLR) and mortality in subjects with CMM [26], indicating that NLR is also considered a critical risk factor for mortality according to Cox regression analysis [HR = 2.52; 95%CI (2.03–3.14)] [26]. It has also been documented that declined TIL intensity is an adverse prognostic factor, presenting shorter overall, cancer-specific, disease-free survival and a worse prognosis in favor of lymph node metastasis [27]. A recent molecular study supported that TIL clusters are associated with improved survival and response to immune checkpoint inhibition (CPI) in BRAF V600E/K mutated malignant melanoma [28]. During survival analysis in a large cohort through natural language processing (NLP), unlike our results, diffuse TILs (brisk TILs) offered independent prognostic value in predicting improved overall survival among melanoma patients [29].

CONCLUSION

Irrespective of disease stage and histopathology examination, we found no significant correlation between survival rate and demographic and tumor characteristics in patients with CMM. However, large-scale population studies are required to unveil the details regarding prognostic factors.

Authors contributions

FA, worte the first draft; YR, concieved, desigend, and supervised the work; RA, gathered and collated the data.; AM, analyzed and interpreted the data. All authors read and approved the final manuscript.

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