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# Comparative Analysis of Acral Melanoma in Chinese and Caucasian Patients

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# Abstract

Background

Acral melanoma is the most common subtype of melanoma in Chinese patients and one of the least common in Caucasian patients. It has been unclear if outcomes differ between Chinese and Caucasian patients diagnosed with Acral Melanoma. This study investigated patient characteristics and survival differences between Chinese and Caucasian Acral Melanoma patients.

Methods

Two large institutional melanoma databases from Fudan University Shanghai Cancer Center (FUSCC) and Mayo Clinic enterprise, were retrospectively reviewed from 2009 to 2015. Clinicopathologic and survival data were collected and analyzed between the two groups. The primary outcome was disease-specific survival (DSS) and was calculated using the Kaplan Meier (KM) method.

Results

The Chinese group presented with more advanced disease compared with Caucasians: thicker Breslow depth (median 3.0 mm vs. 1.2 mm, p=0.003), more ulcerated disease (66.1% vs 29%; p<0.001), and advanced stages (stage II/III 84.3% vs. 37.1%; p<0.001). No significant difference was identified in terms of age at diagnosis, location, histologic subtypes, or node positive rate. The 5-year DSS rate was 68.4% and 73% (p=0.56) for Chinese and Caucasians, respectively. Male gender, Breslow thickness, ulceration, and positive sentinel lymph nodes predicted worse DSS on multivariate Cox regression analysis.

Conclusions

There appears to be no difference in stage-stratified survival between Chinese and Caucasians, supporting the implementation of clinical trials of AM that could include both Chinese and Caucasian patients.


# Background

Malignant melanoma is a relatively common malignancy in Western countries, especially among population with lighter skin color.[1] Its incidence is higher in Australia and the United States, typically related to ultraviolet (UV) radiation damage to the skin, and most commonly originates in sun-exposed areas. Although a high density of melanin in people of color may provide better protection from UV radiation, the prognosis seems to be more severe in certain subtypes.[2] Melanoma is classified into four subtypes based on the anatomic location of the tumor and the degree of UV exposure: (1) melanomas that occur on skin without chronic sun-induced damage (non-CSD); (2) melanomas on skin with chronic sun-induced damage (CSD); (3) mucosal melanomas; and (4) acral melanomas.[16] Acral melanoma (AM) is the least common subtype of cutaneous melanoma in Caucasians (1–7%), but it is the most common

type of melanoma diagnosed in non-white populations (Asians, Hispanics, Black American, etc),[4–6] accounting for 58% of all cutaneous melanomas in Asians. It can occur in areas with little to no sun exposure (such as palms, soles, or nail apparatus).

The pathogenesis of AM remains unclear. Some studies have found penetrating injury, physical pressure, and trauma to be risk factors of AM in Asian populations, while others have found UV light exposure and chemical exposure as risk factors in Caucasian populations.[7–9] AM is thought to carry a worse prognosis than other subtypes of melanoma, possibly because of its lower awareness, delay in diagnosis, and aggressive biological behavior.[3] Due to the low incidence of melanoma in China, sentinel lymph node biopsy (SLNB) and documentation of Breslow thickness have not been widely implemented in melanoma centers in China. Only a few case series of Asian AM have been published. The clinical and pathological characters, treatment, and prognosis of Chinese AM patients have never been compared with Caucasian patients. Data are presented from two cohorts of AM patients following curative resection and SLNB in two large referring centers in China and the US.

## Patients And Methods

# Patient selection

Retrospective review identified AM patients treated at FUSCC and Mayo Clinic Enterprise between December 1, 2009 and December 1, 2015. A total of 280 primary AM patients were identified at FUSCC, and a total of 68, of whom 62 were Caucasian (3 American Indian, 3 Black Americans were excluded), were identified at Mayo Clinic. Clinical and pathological data were retrospectively analyzed from the databases after Institutional Review Board (IRB) approval at both centers. AM was defined by anatomic location, including melanoma on palmar, plantar, and subungual sites. Only patients with primary tumors, clinical node negative, treated with surgical excision were included in the study. Patients with one or more invasive melanomas located in non-acral locations, clinically positive regional lymph node, stage IV disease, or recurring disease were excluded. The primary and sentinel lymph node specimens were reviewed and confirmed by experienced dermatopathologists at each institution. Five-year disease-specific survival (DSS) statistic was analyzed using KM method.

Patients were staged according to the American Joint Committee on Cancer (AJCC) 7th Edition Staging System. The following clinical and pathological data were retrieved from medical records: age at the time of diagnosis, gender, location of lesion, greatest dimension of lesion, histological type, tumor stage at admission, Breslow depth, Clark level, ulceration, Sentinel Lymph node (SLN) status, type of surgery, and adjuvant treatment. Disease status at the latest contact was categorized as NED (alive with no evidence of disease), AWD (alive with disease), DFD (death from disease), DFO (death from other causes), and DUK (death and disease status unknown). Disease-specific survival (DSS) was defined as the time from pathologic diagnosis to the time of death due to melanoma or last follow-up. Patient current disease status at the end of follow-up and their first recurrence were listed as well, which are classified as node-only(regional), local only, in-transit disease, or distant organ metastasis (liver, lung, brain, bone, etc.).

# Surgical procedures, SLNB

Wide local excision of Acral tumor was performed with an adequate margin according to National Comprehensive Cancer Network (NCCN) guidelines. Amputation was applied for subungual lesion if adjacent joint involved in the adequate resection margin. Reconstruction of primary defect was performed by either skin graft, or second intention healing at non-weight bearing area, or rotational flap on weight bearing area at the discretion of primary surgeon or plastic surgeon. Lymphatic mapping technique, including radioisotope, methylene blue or both, were used when performing SLNB.

SLNB was performed for all patients with non-palpable lymph nodes, and SLN status was evaluated by frozen section intra-operatively at FUSCC. For those with node positive disease intraoperatively, complete lymph node dissection was performed subsequently, as well as those with node positive disease on final pathology. At Mayo, SLNB was performed for patients with Breslow thickness > 1 mm, and SLN status was evaluated only on final pathology. Some of the patients with sentinel lymph node positive disease underwent close observation with ultrasound at the discretion of primary surgeons.

# Adjuvant therapy

At FUSCC, adjuvant therapies included immunotherapy alone, or immunotherapy combined with chemotherapy. Immunotherapy include Interleukin-2 (IL-2) or Interferon (IFN)-alpha. Chemotherapy regimen included Dacabazine plus Cisplatin, or Temozolomide alone. At Mayo, adjuvant therapy included immunotherapy with IL-2 alone.

# Statistical analysis

Statistical analysis was performed using statistical package SPSS, version 23.0 (SPSS, Inc). Descriptive statistics were utilized using Chi Square method and $P < 0.05$ was consider significant. DSS was calculated using the Kaplan Meier (KM) method. Age, gender, Pathologic stage, location, histology, ulceration, LN status, surgical procedure and adjuvant therapy were analyzed as categorical variables. Breslow thickness was analyzed as continuous variable. The univariate Cox regression model was used to examine the association of clinical and pathologic variables with DSS. Characteristics significant in the univariate analysis at $\alpha<0.05$ were included in a multivariate Cox proportional hazards model.

## Results

# Patient demographics and characteristics

The clinical and pathological features of the two groups of patients are summarized in Table 1. The median age at diagnosis was 60.5 years (51–70) for Chinese and 64.5 years (49.5–75.3) for Caucasians. Older age was associated with lower DSS (HR 1.02, CI 1.001–1.035). AM was more common in males in both groups, with a male to female ratio of 1.22:1 in Chinese patients compared to 1.14:1 in Caucasians. Tumors were larger in Chinese than Caucasians (median 2.50 cm vs. 1.0 cm). Chinese patients had more advanced disease than Caucasians, in terms of thickness, ulceration, and pathologic stage, all of which

were significant between groups. The mean Breslow thickness was 4.19 mm (median 3.0 mm) in Chinese compared to 1.3 mm (median 1.0 mm) in Caucasians. The percentage of ulceration was 66.1% in Chinese vs. 29% in Caucasians, and the percentage of stage II-III disease was 84.3% in Chinese vs. 37.1% in Caucasians. Volar sites (lower limb) were more frequently involved than subungual melanoma in both groups (Chinese 68.6% vs. 31.4%, Caucasian 61.3% vs. 38.7%). Acral lentiginous melanoma was the predominant subtype of AM in both groups (92.8% Chinese vs. 96.8% Caucasian).

Table 1
– Clinical and pathological parameters of AM patients in Chinese (n = 280) and Caucasian (n = 62)

| Parameter | Chinese (n = 280) | Caucasian (n = 62) | P value |
|---|---|---|---|
| Age at diagnosis (years) | | | 0.25 |
| Median (IQR) | 60.5 (51–70) | 64.5 (49.5–75.3) | |
| Gender (%) | | | 0.80 |
| Male | 154 (55) | 33 (53.2) | |
| Female | 126 (46) | 29 (46.8) | |
| Male to Female ratio | 1.22: 1 | 1.13:1 | |
| Pathologic stage (%) | | | < 0.001 |
| 0/I | 43(15.3) | 38 (61.2) | |
| II | 160 (57.1) | 11 (17.7) | |
| III | 76 (27.2) | 12 (19.4) | |
| Unknown | 1 (0.4) | 1 (1.6) | |
| Largest Diameter (cm) | (0.4–10.0) | (0.2–4.5) | < 0.001 |
| Median (IQR) | 2.5 (1.7–3.5) | 1.0 (0.43-2.0) | |
| Unknown (%) | 90 (32.0) | 18 (29.0) | |
| Location (%) | | | 0.27 |
| Volar<br>foot<br>hand | 192 (68.6)<br>191 (68.2)<br>1 (0.4) | 38 (61.3)<br>37 (59.6)<br>1 (0.7) | |
| Subungual | 88 (31.4) | 24 (38.7) | |
| Histology | | | 0.21 |
| Acral lentiginous | 260 (92.8) | 60 (96.8) | |
| Nodular | 8 (2.9) | 1 (1.6) | |
| Superficial spreading | 12 (4.3) | 1 (1.6) | |
| Breslow thickness (mm) | | | 0.003 |
| Median (IQR) | 3.0 (1.7-5.0) | 1.2 (0.65–2.8) | |
| Unknown (%) | 54 (19.3) | 11 (17.7) | |
| Clark Level (%) | | | < 0.001 |

| Parameter | Chinese (n = 280) | Caucasian (n = 62) | P value |
|---|---|---|---|
| I | 10 (3.6) | 8 (12.9) | |
| II/III | 28 (10.0) | 22 (35.5) | |
| IV/V | 164 (58.6) | 18 (29.0) | |
| Unreported/unknown | 78 (27.8) | 14 (22.6) | |
| Ulceration (%) | | | < 0.001 |
| Yes | 185 (66.1) | 18 (29.0) | |
| No | 87 (31.1) | 44 (71.0) | |
| Unreported/unknown | 8 (2.8) | - | |
| SLN biopsy (%) | | | N/A |
| Yes | 280 (100) | 34 (54.8) | |
| No | - | 28 (45.2) | |
| SLN biopsy positive (%) | | | 0.56 |
| Yes | 85 (30.4) | 12 (35.3) | |
| No | 195 (69.6) | 22 (64.7) | |
| Number of SLN resected Mean (SD) | 3.1 (2.05) | 2.0 (1.39) | |
| CLND after SLNB+ (%) | 74/85 (87) | 8/12 (66.7) | |
| Number of Total LNs resected, Mean (SD) | 8.7 (4.35) | 23.4 (12.1) | |
| CLND positive (%) | 27/77 (35.1) | 2/8 (25) | 0.44 |
| Surgery (%) | | | N/A |
| WLE | 173 (61.8) | 30 (48.4) | |
| Amputation | 88 (31.4) | 27 (43.5) | |
| Mohs surgery | - | 3 (4.8) | |
| Unknown | 19 (6.8) | 2 (3.2) | |
| Adjuvant therapy (%) | | | N/A |
| Yes | 238 (84.7) | 4 (6.5) | |
| No | 32 (12.4) | 58 (93.5) | |
| Unreported/unknown | 10 (3.9) | – | |

# Treatments

# SLNB and CLND

All patients in the Chinese group had SLNB, 30.4% of whom had positive SLN. Fifty-four percent of patients in the Caucasian group received SLNB, 35.3% of whom had positive SLN. The mean number of SLN was 3.07 in Chinese patients compared to 2.0 in Caucasian patients. Among SLN positive patients, 74/85 (87%) of patients underwent complete lymph node dissection (CLND) in the Chinese group, with a mean of 8.7 (1–22) LNs removed and 27/77(35.1%) of patients had positive nodes. In the Caucasian group, 8/12 (66.7%) underwent CLND, 23.1 (11–48) LNs were removed, and 2/8(25%) of patients had positive nodes.

# Surgery and adjuvant therapy

The majority of patients with volar tumors (Chinese 88.5% vs. Caucasian 73.7%) underwent wide local excision (WLE), whereas amputation was performed more often for subungual tumors (Chinese 93.2% vs. Caucasian 79.2%). The majority of Chinese patients (84.7%) received adjuvant therapy, among which 97.5% received immunotherapy (IL-2 or IFN-alpha alone or combined) and 2.5% received immunotherapy combined with chemotherapy. In Caucasian group, only 6.5% of patients received immunotherapy(IL-2).

# Prognostic factors and Survival analysis

The median follow-up time was 43 months (range 3-101 months) in the Chinese group and 24.5 months (range 2–75 months) in the Caucasian group. During follow up, 25.7% (72/280) Chinese patients died from melanoma, whereas 11.3% of (7/62) Caucasian patients died of the disease, due to in-transit metastasis or distant metastasis. About 115/280 (41.1%) recurrences occurred in the Chinese group, with regional node being the most common site (33%), followed by distant organ metastasis (32.2%), and in-transit and local recurrence. The Caucasian group had 27.4% (17/62) recurrences, with in-transit metastasis being the most common (35.2%), followed by local recurrence (29.4%), distant organ (23.5%), and nodal recurrence (11.4%) [Table 2].

Table 2
– Patient disease status and recurrence of AM patients in Chinese and Caucasian.

| Parameter | Acral Melanoma in Chinese | Acral Melanoma in Caucasian |
|---|---|---|
| Patient disease status (%) | | |
| NED | 174 (62.1) | 48 (77.4) |
| DFD | 67 (23.9) | 5 (8.1) |
| AWD | 30 (10.7) | 8 (12.9) |
| DFO/DUK | 9 (3.3) | 1 (1.6) |
| First Recurrence (%) | N = 115 (41.7) | N = 17 (27.5) |
| Local | 7 (6.1) | 5 (29.4) |
| Regional LN | 38 (33.0) | 2 (11.8) |
| In transit | 18 (15.7) | 6 (35.2) |
| Distant organ Mets (lung, liver, brain, bone, etc) | 37 (32.2) | 4 (23.5) |
| Unknown | 15 (13.0) | - |
| Disease status at the latest contact: NED (alive with no evidence of disease), AWD (alive with disease), | | |
| DFD (death from disease), DFO (death from other causes), and DUK (death and disease status unknown). | | |

Among prognostic factors, gender ($p = 0.001$), pathological stage ($p < 0.001$), Breslow thickness ($p < 0.001$), Clark level ($p < 0.001$), the presence of ulceration ($p < 0.001$), and positive SLN ($p < 0.001$) were all associated with decreased DSS on univariate analysis. Age, Location of tumor, histology, type of surgery, and adjuvant therapy were not significantly associated with DSS. Using multivariate analysis, gender ($p = 0.011$), Breslow thickness ($p = 0.018$), presence of ulceration ($p = 0.026$), and positive SLN ($p = 0.003$) were independently associated with DSS [Table 3].

Table 3
– Prognostic factors associated with DSS in AM patients from Chinese and Caucasians.

| Parameter | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) | P value |
| Age (years)<br>≤ 60 (N = 166)<br>> 60 (N = 176) | 0.68 (0.43–1.05)<br>1.0 | 0.08 | | |
| Gender<br>Male (N = 187)<br>Female (N = 155) | 2.21 (1.38–3.55)<br>1.0 | 0.001 | 1.99 (1.17–3.38)<br>1.0 | 0.011 |
| Chinese vs. Caucasian<br>Chinese (n = 280)<br>Caucasian (n = 62) | 1.26 (0.58–2.76)<br>1.0 | 0.56 | | |
| Pathologic stage | | < 0.001 | | |
| 0/I (n = 81) | 0.08 (0.03–0.27) | | | |
| II (n = 171)<br>III (n = 89) | 0.42 (0.27–0.66)<br>1.0 | | | |
| Location<br>Volar (n = 230)<br>Subungual(n = 112) | 0.91 (0.57–1.46)<br>1.0 | 0.69 | | |
| Breslow thickness (mm) | 1.06 (1.03–1.09) | < 0.001 | 1.05 (1.01–1.09) | 0.018 |
| Clark Level (%) | | < 0.001 | | |
| Unknown (n = 91)<br>I /II/III (n = 68)<br>IV/V (n = 183) | 0.42 (0.23–0.77)<br>0.26 (0.11–0.60)<br>1.0 | | | |
| Histology | | 0.93 | | |
| Nodular (n = 9)<br>Superficial spreading (n = 12)<br>Acral lentiginous (n = 321) | 1.01 (0.25–4.12)<br>0.81 (0.25–2.57)<br>1.0 | | | |
| Ulceration<br>Yes (n = 203)<br>No (n = 130) | 4.06 (2.20–6.57)<br>1.0 | < 0.001 | 3.39 (1.20–8.23)<br>1.0 | 0.026 |
| SLN biopsy status<br>Positive (n = 97)<br>Negative (n = 217) | 3.45 (2.19–5.45)<br>1.0 | < 0.001 | 4.10 (1.54–10.92)<br>1.0 | 0.003 |
| Surgery<br>Amputation (n = 115)<br>WLE (n = 203) | 1.04 (0.64–1.68)<br>1.0 | 0.88 | | |

| Parameter | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) | P value |
| Adjuvant therapy<br>Yes (n = 242)<br>No (n = 90) | 0.87 (0.51–1.47)<br>1.0 | 0.60 | | |

SLN status was an independent prognostic factor associated with lower DSS in the multivariate analysis. In the subgroup analysis of patients who underwent SLNB (n = 315), AM patients who underwent an SLN biopsy and had a positive SLN had a 44.0% (95% CI: 25.9% – 55.3%) 5-year DSS compared with a 76.2% (95% CI: 67.4% – 85.0%) 5-year DSS for patients with a negative SLN.

Comparing Chinese and Caucasians, the overall 5-year DSS rate was 68.4% vs. 73% (p = 0.56), respectively. No significant difference in stage-stratified DSS between Chinese and Caucasian patients was found. The 5-year DSS rate in Stage III disease was 43.9% for Chinese vs. 49.4% for Caucasian patients, 73.3% vs. 64.3% for Stage II disease, and 95.0% vs. 94.4% for Stage I disease. There was no significance in DSS between Chinese and Caucasian patients when controlled for Breslow thickness as well (data not shown).

# Discussion

AM is a distinct subgroup of cutaneous melanoma occurring on the palmoplantar and subungual sites with specific histological and clinicopathological features, regardless of histologic type (if acral lentiginous or not). It is the most commonly occurring subtype of melanoma in Asian populations and is known to have a worse prognosis than non-acral melanoma,[3,10] likely due to its late presentation and diagnosis or its intrinsic high aggressiveness.[17] Acral lentiginous melanoma (ALM) is a histological subtype of melanoma, mostly occurring in palmoplantar and nail apparatus and occasionally in non-acral sites. Racial differences have been investigated in a few case series[10,31] and a population-based analysis on cutaneous melanoma[3].However, it is still in dispute. Black Americans was reported to have lower MSS compared to whites and other races[31]. Due to its rarity, no study has compared characteristics and outcomes in AM between Chinese and Caucasian patients. Our study represents the first direct comparative study of a large series of Chinese and Caucasian patients from two tertiary referral institutions focusing on acral melanoma. To capture the disease process for newly diagnosed AM treated in a standard fashion, patients were selected from a consecutive time period, with surgery being the initial treatment. Patients presenting with recurrent disease or metastatic disease were excluded.

Considering epidemiological pathological characteristics, Chinese and Caucasian patients were very similar in terms of mean age of diagnosis (early 60 s), no significant gender predominance, volar (lower limb) predilection, and acral lentiginous type predominance, which were consistent with prior studies.[19] This study also found that Chinese patients presented with advanced disease compared to Caucasian

patients. This is consistent with other studies that have reported a higher percentage of T4 disease in Asia/Pacific Islanders compared with white skin and black skin patients,[3] as well as a high proportion of Breslow T4 disease in Chinese and Koreans (40.8% and 33%, respectively). Lv et al also reported a mean Breslow Thickness of 4.9 mm and 47.9% of ulceration in their series.[8,13] Delay in diagnosis of AM with a duration ranging from 1 to 3.7 years was described in the literature[13,32], due to hidden site, frequent lack of pigmentation, lack of recognition and misdiagnosis by dermatologists was an explanation of the advanced stage disease in Chinese.[13]

Decreased melanoma-specific survival was associated with male gender, thick Breslow depth, high Clark level, presence of ulceration, advanced pathological stage, and positive SLN. Gender has been reported to be an independent prognostic factor.[11,20,22,23] We also found that male sex was associated with a worse prognosis, even after controlling for other factors. In the Chinese group, male patients had a 5-year DSS of 59.4% compared with 77.9% in female patients; whereas, DSS was 55.1% in males versus 93.8% in females in the Caucasian group. Breslow thickness and presence of ulceration have been shown to be important prognostic factors for cutaneous melanoma and AM.[3,10,15] Breslow thickness was the most significant prognostic factor in previous studies, before the prevalence of SLNB.[20] SLN status has proven to be an important prognostic factor for cutaneous melanoma[24 – 28] and has been reported to be an important prognostic factor for AM as well, in a few recent series. A recent study of AM patients by Bello et al found that, out of 157 patients who underwent SLN biopsy, 63 (40%) were positive.[15] Our study has the largest series of Chinese AM patients undergoing SLN biopsy to-date. We found 30.4% of patients were SLN positive in the Chinese group, who all underwent SLN for staging purposes, and 35% of patients were SLN positive in the Caucasian group, of whom 54.8% (34/62) underwent biopsy. In our study, we found that SLN status (HR 4.10, 95% CI 1.54–10.92) was the strongest prognostic factor in AM patients who underwent SLN biopsy. The SLN positive rate was 2.9% in T1, 20.9% in T2, 39.2% in T3, and 48.7% in T4 disease. Five-year DSS was 44.0% in patients with positive SLN compared with 76.2% in patients with a negative SLN, which is consistent with prior literature.[15]

The prognostic value of racial difference has been investigated in the literature, but its implication on outcomes remains unclear. Some studies have identified race as an independent prognostic factor, whereas others have shown similar survival rates among different racial groups after controlling for stage.[2,6,18] Bradford et al reported on a large population of ALM patients and found the 5-year DSS rates were highest in Non-Hispanic whites (82.6%), intermediate in black Americans(77.2%), and lowest in Asian/Pacific Islanders (70.2%).[3] However, no survival difference was found between Caucasians and Asian/Pacific Islanders, after adjusting for stage and thickness. Lv et al reported on a large series of Chinese AM patients and found the 5-year DSS to be 53.5%,[13] which is worse than reported in Caucasians (e.g., the 5-year DSS of 70% reported by Bello et al,[15] 71% by Kuchelmeister et al,[21] and 76% by Phan et al[20]). In our study, race was not a prognostic factor (HR 1.26, 95% CI 0.59–2.76; P = 0.56). Also in our study, Chinese patients had more advanced disease as compared to Caucasian patients. However, there was no significant difference in the 5-year DSS survival between the two groups (68.4% vs. 73%, P =

0.56), after adjusting for stage and thickness, which was consistent with literature. In our cohort, a much higher percentage of Chinese patients received adjuvant therapy (84.7% vs. 6.5%), which may impact DSS of Chinese patients. One hypothesis is that tumor biology or genetic alterations in AM between the two groups has a similarity that plays a role. High focal amplifications, including CCND1, CDK4, and GAB2, and low mutation rates on BRAF, NRAS, and KIT have been reported in Caucasians.[16,30] A recent study of genetic alterations of Chinese showed CDK4 gain (39.5%), CCND1 gain (26.7%), and $P16^{INK4a}$ loss (60.3%).[29] Also, positive SLN was higher in the Caucasian group (35.3% vs. 30.4% in Chinese), though not statistically significant. Positive SLN was the most important detrimental prognostic factor in our study, which may be an explanation for the survival difference between the two groups.

The major strength of this study is that it includes the largest number of primary AM patients. All of our Chinese patients had sentinel lymph node biopsy, allowing more accurate pathological staging. Limitations of this study were that margin status and mitotic rates of the primary tumor were not analyzed, both of which could be potential prognostic factors. Also, the median follow-up period was nearly four years in the Chinese group versus two years in the Caucasian group. A shorter follow-up interval and limited patients included in the Caucasian group could lead to statistical limitations in identifying survival differences between two cohorts.

# Conclusions

This study represents the first (and one of the largest) contemporary series investigating AM in Chinese and Caucasians, from two large referral centers. Our results reinforce the prognostic importance of positive sentinel lymph nodes, Breslow depth, and presence of ulceration in AM disease-specific survival. There appears to be no difference in survival between Chinese and Caucasians, after controlling for stage and thickness, even though the Chinese patients presented with more advanced disease. Our results imply that the biological course of AM is likely similar between Chinese and Caucasian patients. Future studies are warranted to clarify and expand on the biological differences of AM between different racial groups. As Asian countries have a high incidence of AM, our data support the implementation of clinical trials of AM that could include both Chinese and Caucasian cohorts.

# Declarations

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the authors and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

*Ethics approval and consent to participate:* This study was approved by Institutional Review Board (IRB) by Mayo Clinic Florida and Fudan University Shanghai Cancer center.

*Consent for publication:* all the authors are consent for publication.

*Authors' contributions:* S.Bagaria, Y Chen, and S.Misra contributed to the study conceptualization and design. K Huang, Y Xu. contributed to data acquisition. K Huang. analyzed and interpreted the data. K Huang, drafted the manuscript. All authors critically reviewed and contributed to the draft submitted for publication.

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# Figures

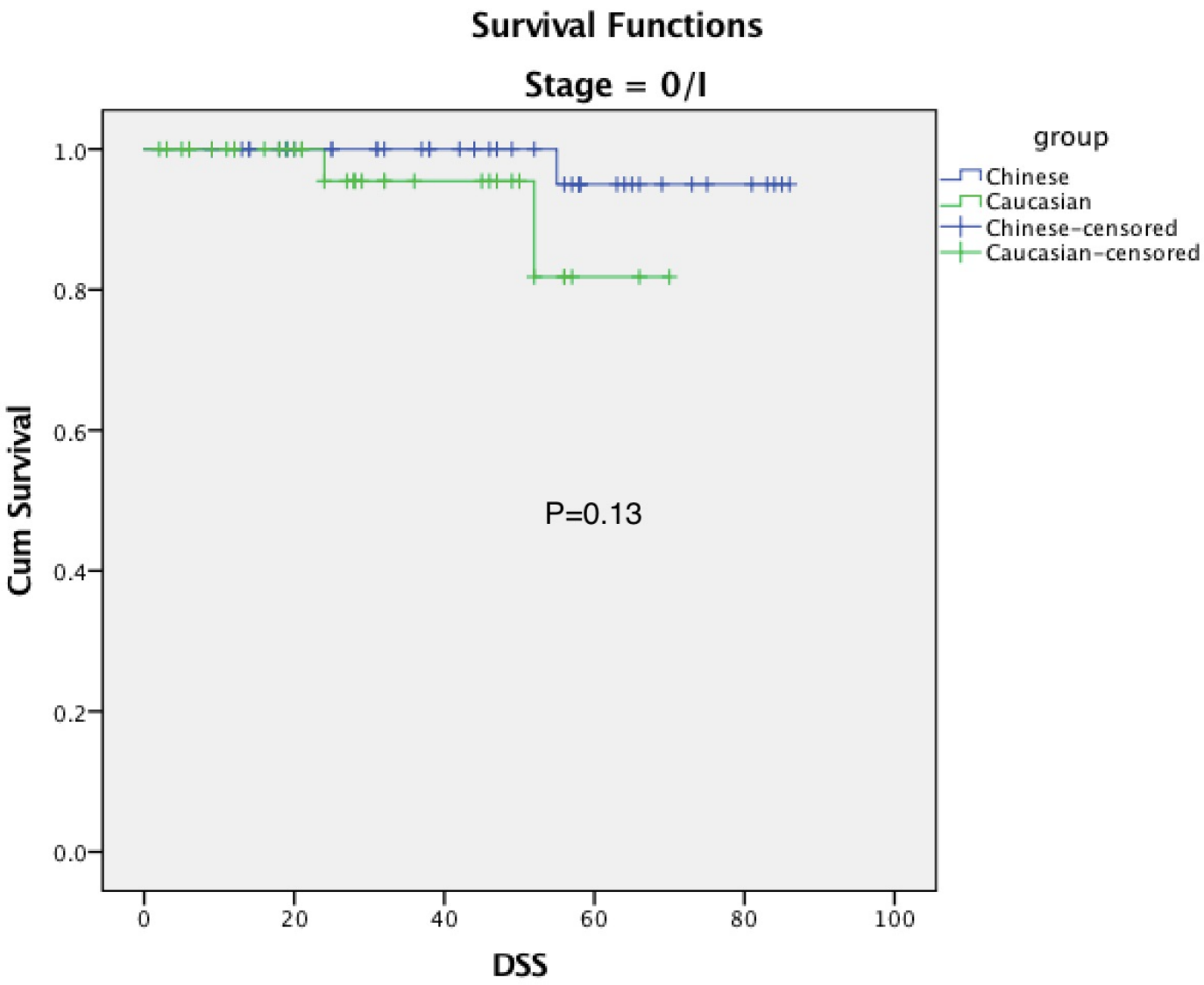


**Figure 1**

Stage stratified 5-yr DSS in Chinese and Caucasian group. Stage 0/I, p=0.13.

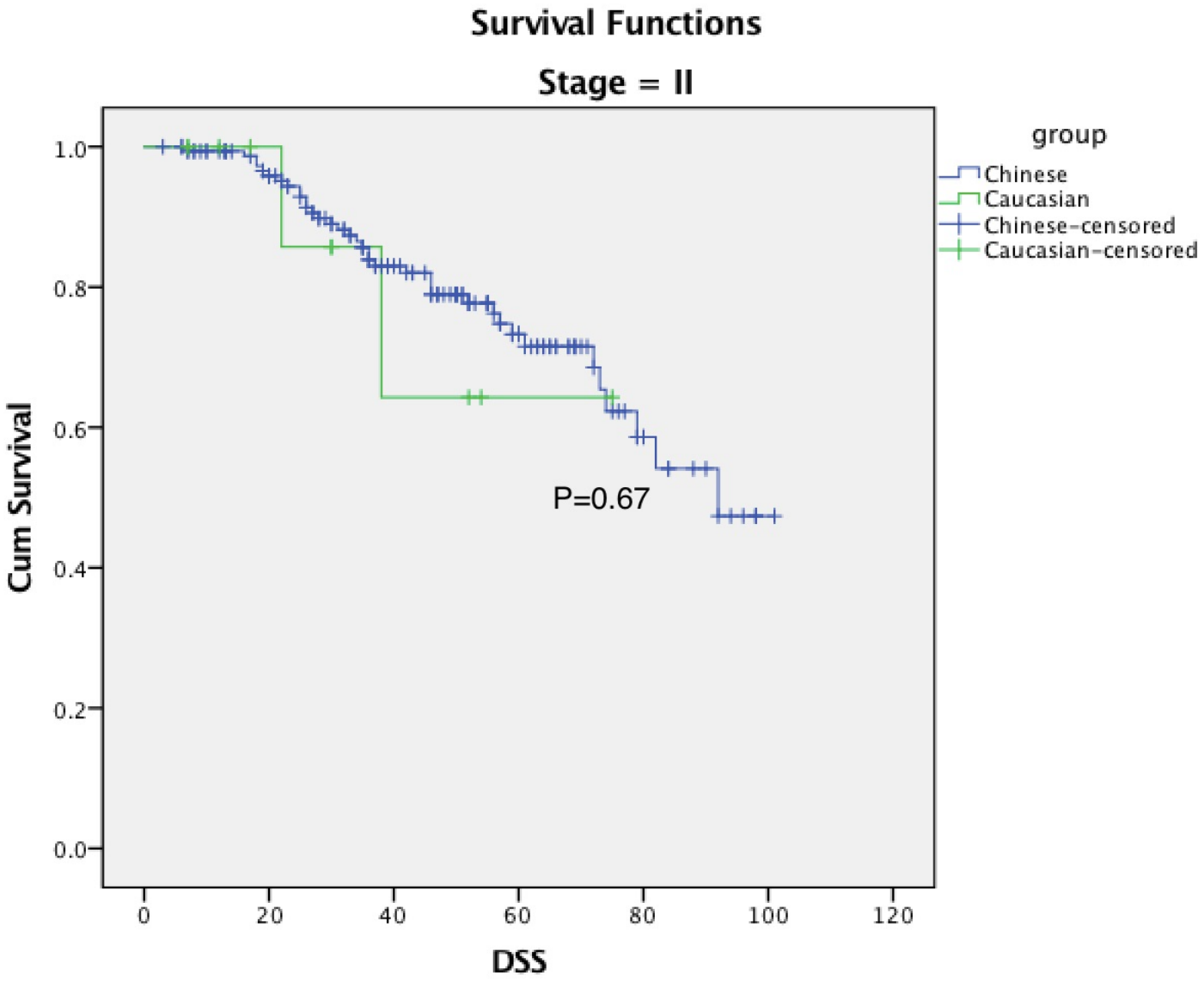


**Figure 2**

Stage stratified 5-yr DSS in Chinese and Caucasian group. Stage II, p=0.67

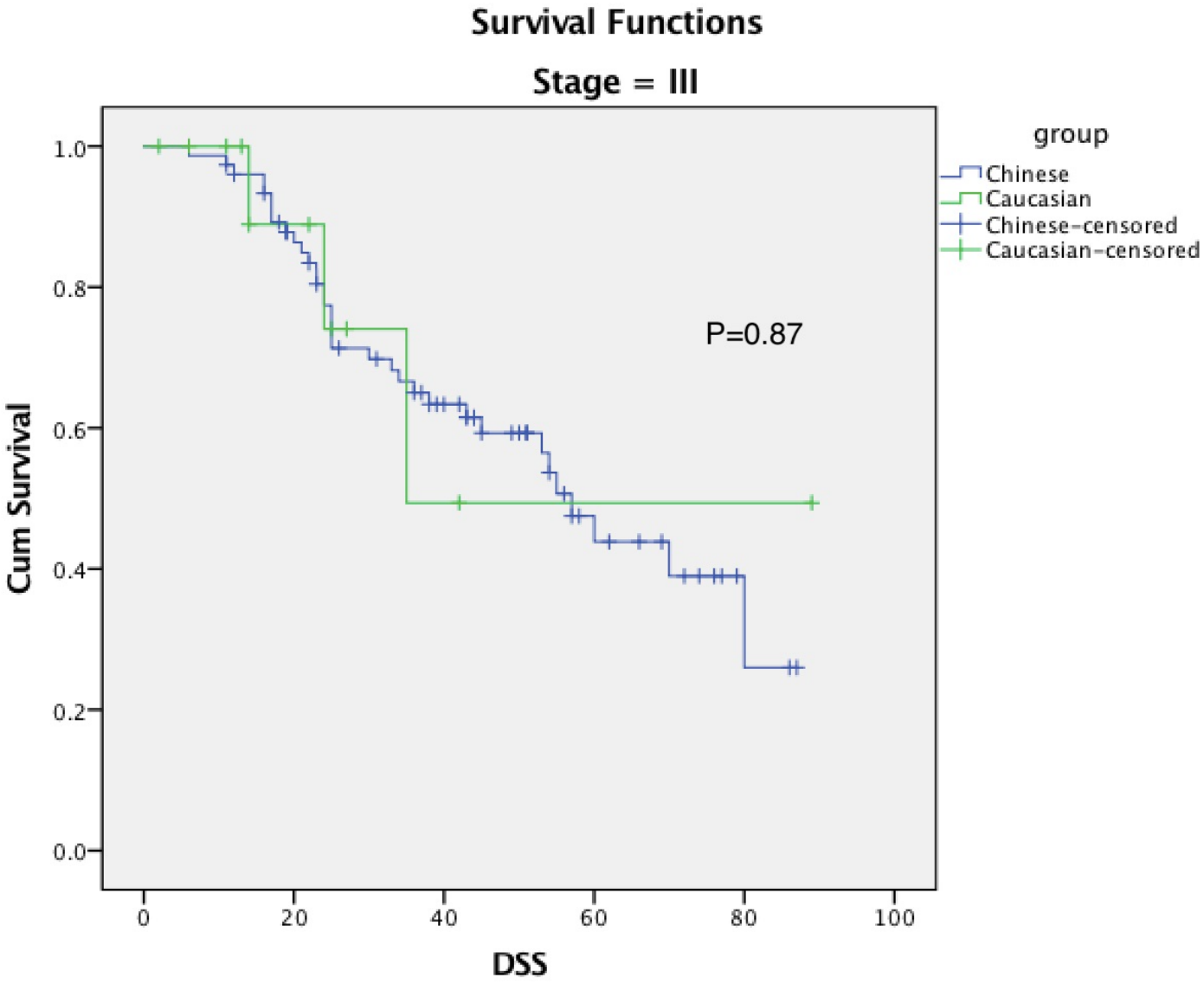


**Figure 3**

Stage stratified 5-yr DSS in Chinese and Caucasian group. Stage III, p=0.87