Acral Melanoma in Chinese: A Clinicopathological and Prognostic Study of 142 cases

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Acral melanoma (AM), as a peculiar subgroup of melanoma, is rare in Caucasians but has higher incidence in Asians. Large series of study on AM with clinicopathological features and prognostic factors is still limited, especially in Asian population. We retrospectively collected clinical, pathological and follow-up data of 142 AM cases. All patients were Chinese, with the age ranging from 24 to 87 years (mean 62.0; median 62.0). The Breslow thickness of primary lesions ranged from 0.6 to 16.3 mm (mean 4.9; median 3.7). 85.9% of the patients had acral lentiginous histologic subtype. Plantar was the most frequently involved site, followed by heels. Statistically, duration of the lesion before diagnosis (<2.5 years), Breslow thickness > 4.0 mm (T4), high mitotic index (>15 mm−2), presence of vascular invasion, regional lymph node metastasis at diagnosis and pathologic stage (II/III/IV) were found to be independent prognostic factors in both univariate and multivariate analyses. The prognosis of AM in Chinese is extremely poor. Our 5- and 10-year disease-specific survival (DSS) rates were 53.3% and 27.4%, respectively. Therefore, AM in Asians represents a more biologically aggressive melanoma subtype and is thought to carry a worse prognosis when compared with other races or cutaneous melanomas in other anatomic sites.

Results
Clinical features. The clinical characteristics of the patients are summarized in Table 1. All the 142 patients were Chinese. There were 84 (59.2%) male patients and 58 (40.8%) female patients, with a male to female ratio of 1.46. The age of the patients at diagnosis ranged from 24 to 87 years (mean 62.0; median 62.0). Among 9 (6.3%) patients who recalled their exact trauma history, 5 were on the plantars, 4 were on the dorsum of the feet. Most trauma was caused by a mild injury, such as tearing on a stone, pricking on a spike or glasses, or stepping on charcoal. The diameter of the lesion, in terms of major axis, ranged from 0.3 to 7.5 cm (mean 2.5; median 2.0). The duration of the lesion before diagnosis was varied from 10 days to 70 years (mean 5.1 years; median 1.8 years).
In the nonungual area, the plantar was the most common region. We did not find any case on the palms or the dorsum of the hands. In the subungual sites, the toenail is more frequently involved than the fingernail. The commonest location of subungual melanoma (SUM) was the great toe [13 lesions (56.5%)] followed by the thumb [5 lesions (21.7%)]. The lesions were distributed approximately equally between the right and the left side.

Manifestations of AM had a wide clinical spectrum. Lesions initially appeared as a pigmented macule, then progressed to a rapidly expanding plaque with irregular, notched borders, sometimes with ulceration (Fig. 1a). With the evolution of apparent vertical growth phase, an elevated papule or nodule developed within a background pigmented macule (Fig. 1b). Occasionally, multiple foci of satellites discontinuous from the main tumour were observed (Fig. 1c). In a minority of cases, it presented as achromic melanoma clinically resembling granuloma pyogenium (Fig. 1d). SUMs often began as brown to black discolouration of the nail that frequently became a well demarcated, pigmented longitudinal streak. With the time, the strip became bigger with indistinct, blurred margins (Fig. 1e). Thickening, splitting, or destruction of the nail plate may occur (Fig. 1f). The irregular macular hyperpigmentation can also spread to involve the skin of the digit, proximally, laterally and distally (Hutchinson sign, Fig. 1g). Eventually, the entire nail matrix and nail bed were occupied by a tan to black irregular plaque or mass, which involved the ungula fold and periungual skin (Fig. 1h).

**Histologic features and pathologic staging.** Histologic examination was performed on 142 AM patients by wide surgical excision. Two patients (1.4%) had a personal history of a noncutaneous cancer (one

| Characteristics | No. (%) |
|-----------------|---------|
| Sex             |         |
| Male            | 84 (59.2) |
| Female          | 58 (40.8) |
| Age, years      |         |
| <31             | 3 (2.1) |
| 31–40           | 4 (2.8) |
| 41–50           | 18 (12.7) |
| 51–60           | 37 (26.1) |
| 61–70           | 36 (25.4) |
| 71–80           | 34 (23.9) |
| >80             | 10 (7.0) |
| Trauma history  |         |
| Yes             | 9 (6.3) |
| No              | 133 (93.7) |
| Longest diameter of lesion, cm | |
| <1.0            | 8 (5.6) |
| 1.0–2.0         | 64 (45.1) |
| 2.0–3.0         | 37 (26.1) |
| 3.0–4.0         | 21 (14.8) |
| 4.0–5.0         | 6 (4.2) |
| >5.0            | 6 (4.2) |
| Duration of the lesion, years | |
| <1              | 45 (31.7) |
| 1–2.5           | 43 (30.3) |
| 2.5–5           | 24 (16.9) |
| 5–7.5           | 4 (2.8) |
| 7.5–10          | 5 (3.5) |
| >10             | 21 (14.8) |
| Site of lesion  |         |
| Nonungual location | 119 (83.8) |
| Finger          | 4 (2.8) |
| Toe             | 10 (7.0) |
| Foot            | 105 (74.0) |
| Plantar         | 59 (41.6) |
| Heel            | 38 (26.8) |
| Dorsum          | 8 (5.6) |
| Subungual location | 23 (16.2) |
| Fingernail      | 7 (4.9) |
| Toenail         | 16 (11.3) |

Table 1. Clinical characteristics of Chinese patients with acral melanoma.
liver, one pancreas). The Breslow thickness of the primary lesion ranged from 0.6 to 16.3 mm (mean 4.9; median 3.7). Of the 142 cases, the most common histologic subtype of patients were acral lentiginous melanoma (ALM) [122 cases (85.9%)] followed by nodular melanoma (NM) [17 cases (12.0%)] and superficial spreading melanoma (SSM) [3 cases (2.1%)]. Pathological characteristics, including Breslow thickness, Clark level, ulceration, mitotic rate, tumour-infiltrating lymphocytes (TILs), vascular invasion, regional lymph node metastasis at diagnosis, and pathologic stage, are shown in Table 2. Some histologic characteristics of melanoma are shown in Fig. 2.

Follow-up and survival analysis. The follow-up ranged from 5 to 151 months (mean 58.9; median 53.5). At the end of the study, 83 (58.5%) patients died of evolution of their melanoma, due to regional lymph node metastasis, in transit metastasis and/or distant metastasis (in brain, lung, liver, bone, bladder). 10 (7.0%) died of unrelated disease. 33 (23.2%) are alive without evidence of residual disease and 16 (11.3%) patients are alive after recurrence. The 5- and 10-year DSS rates were 53.3% and 27.4%, respectively. The 5-year DSS rates according to Breslow thickness are shown in Table 3.

Univariate analysis revealed that patients with one of the following poor prognostic factors (Table 4): duration of the lesion before diagnosis (≤2.5 years), Breslow thickness >4.0 mm (T4), Clark level (IV/V), presence of ulceration, high mitotic rate (>15 mm−2), presence of vascular invasion, regional lymph node metastasis at diagnosis, pathologic stage (II/III/IV) had significantly lower DSS (Table 4, Fig. 3a–h). Then, the eight significant factors in univariate analysis were introduced in a multivariate Cox model to identify independent prognostic factors. Duration of the lesion before diagnosis (≤2.5 years), Breslow thickness >4.0 mm (T4), high mitotic rate (>15 mm−2), presence of vascular invasion, regional lymph node metastasis at diagnosis and pathologic stage (II/III/IV) were found to be independent prognostic factors for DSS (Table 5).

Discussion
The present study is one of the largest single-institution series of AM with a complete review of the histologic slides and with thorough follow-up of the patients in Asia. There was no significant sex predominance in our study, which is similar to the results in most previous studies. However, a few studies of Whites reported a clear ALM predominance in females. The mean age of our cohort was 62.0 years, with a peak incidence during the sixth decade (51–60 years). The mean age is comparable with data from other studies.
years)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\), while the peak age is slightly younger than that in most studies (61–70 or ≥70 years)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\) of both Caucasians and Asians. Plantar was indicated as most frequently involved site in AM\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\). In accordance with previous reports, most AM in our series arose on the feet, most frequently on plantar sites (41.6%), followed by heels (26.8%). In our study, SUM was more frequent on toes (11.3%) than on fingers (4.9%). However, previous studies focusing on SUM indicated that it occurred more often on fingers than toes\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\). This could be due to our few cases of SUM.

Long delay with a duration ranging from 1 to 3.7 years in diagnosis of AM was described in the most representative reports\(^1\)\(^9\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\). Many factors seem to contribute to the postponement of diagnosis: elder patients, hidden site, frequent lack of pigmentation, lack of recognition and misdiagnosis by dermatologists sometimes. Clinical differential diagnoses for nonungual AM cases include wart, callus, fungal disorder, pyogenic granuloma et al. SUMs are often mistaken for chronic paronychia, subungual haematoma, keratocanthoma, nonhealing ulcer, tinea et al. Interestingly and notably, our study demonstrated that patients with duration of the lesion before diagnosis (≤2.5 years) had significantly lower DSS. We considered that the tumour of shorter disease course may progress more rapidly and tends to be more aggressive than that of longer disease duration.

### Table 2. Pathological characteristics of Chinese patients with acral melanoma.

| Characteristics                        | No. (%) |
|----------------------------------------|---------|
| Histologic subtype                     |         |
| ALM                                    | 122 (85.9) |
| NM                                     | 17 (12.0)  |
| SSM                                    | 3 (2.1)   |
| Breslow thickness, mm                  |         |
| ≤1.0                                   | 8 (5.6)  |
| 1.01–2.0                               | 21 (14.8) |
| 2.01–4.0                               | 55 (38.8) |
| >4.0                                   | 58 (40.8) |
| Clark level                            |         |
| I                                      | 1 (0.7)  |
| II                                     | 10 (7.0) |
| III                                    | 3 (2.1)  |
| IV                                     | 83 (58.5) |
| V                                      | 45 (31.7) |
| Ulceration                             |         |
| Yes                                    | 68 (47.9) |
| No                                     | 74 (52.1) |
| Mitotic rate, mm\(^{-2}\)              |         |
| ≤15                                    | 131 (92.3) |
| >15                                    | 11 (7.7)  |
| TILs                                    |         |
| Absent                                 | 46 (32.4) |
| Brisk                                  | 9 (6.3)   |
| Non-brisk                              | 87 (61.3) |
| Vascular invasion                      |         |
| Absent                                 | 139 (97.9) |
| Present                                | 3 (2.1)   |
| Regional lymph node metastasis at diagnosis |       |
| Yes                                    | 46 (32.4) |
| No                                     | 96 (67.6) |
| Pathologic stage                       |         |
| 0                                      | 1 (0.7)   |
| I                                      | 19 (13.4) |
| II                                     | 74 (52.1) |
| III                                    | 44 (31.0) |
| IV                                     | 4 (2.8)   |

While the peak age is slightly younger than that in most studies (61–70 or ≥70 years)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\) of both Caucasians and Asians. Plantar was indicated as most frequently involved site in AM\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\). In accordance with previous reports, most AM in our series arose on the feet, most frequently on plantar sites (41.6%), followed by heels (26.8%). In our study, SUM was more frequent on toes (11.3%) than on fingers (4.9%). However, previous studies focusing on SUM indicated that it occurred more often on fingers than toes\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\)\(^21\). This could be due to our few cases of SUM.

Long delay with a duration ranging from 1 to 3.7 years in diagnosis of AM was described in the most representative reports\(^1\)\(^9\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\)\(^20\). Many factors seem to contribute to the postponement of diagnosis: elder patients, hidden site, frequent lack of pigmentation, lack of recognition and misdiagnosis by dermatologists sometimes. Clinical differential diagnoses for nonungual AM cases include wart, callus, fungal disorder, pyogenic granuloma et al. SUMs are often mistaken for chronic paronychia, subungual haematoma, keratocanthoma, nonhealing ulcer, tinea et al. Interestingly and notably, our study demonstrated that patients with duration of the lesion before diagnosis (≤2.5 years) had significantly lower DSS. We considered that the tumour of shorter disease course may progress more rapidly and tends to be more aggressive than that of longer disease duration.

In the largest population-based evaluation of acral-lentiginous melanoma by Bradford et al., Asia/Pacific Islanders had the highest percentage of T4 compared to Whites and Blacks\(^3\)\(^1\). In consistent with previous data, our study indicated a high proportion of Breslow thickness of T4 (40.8%) and it is even higher than that reported in Koreans (33%)\(^1\)\(^8\). In addition, the mean Breslow thickness in our study was 4.9 mm, which is much more
thicker than that in studies of Whites (2.0–2.6 mm)\(^1\),\(^2\),\(^6\),\(^6\). Therefore, we conclude that AM had a more advanced thickness in Asians, especially in Chinese. Furthermore, Breslow thickness (>4.0 mm) was a significant prognostic factor in both univariate and multivariate DSS analyses in our study. It was also indicated as an independent adverse prognostic factor in three of the four studies evaluating disease-free survival (DFS)\(^1\),\(^2\),\(^7\),\(^6\),\(^7\) and in three of the five studies evaluating overall survival (OS) or DSS\(^1\),\(^2\),\(^6\),\(^7\),\(^8\),\(^9\).

The proportion of ulceration (47.9%) in our series was higher than that previously described in both Asians and Whites (36–42%)\(^4\),\(^1\),\(^4\),\(^6\),\(^1\). In our study, ulceration was significantly associated with a lower DSS in univariate analysis, but did not show any significant effect in multivariate analysis. Other studies indicated that it has an independent prognostic value in one of the two studies evaluating DFS\(^1\),\(^2\) and in three of the four studies evaluating OS\(^1\),\(^6\),\(^8\),\(^9\) or DSS\(^6\). In addition, another prominent finding in our study was that high mitotic rate (>15 mm\(^2\)) appeared to be a powerful independent prognostic factor. The mitotic rate reflects the proliferative activity in a neoplastic system. There was only a few reports of AM that had done some research on it\(^6\),\(^1\),\(^4\),\(^6\). Only mitotic rate >6.0 mm\(^2\) was found to be associated with a greater relative risk for short DFS and DSS in ALM study of Whites by Phan et al.\(^6\).

Table 3. Specific survival rates according to Breslow thickness.

| Thickness (mm) | 5 year survival (%) |
|---------------|---------------------|
| ≤1.0          | 100                 |
| 1.01–2.0      | 66.7                |
| 2.01–4.0      | 56.4                |
| >4.0          | 27.6                |

Figure 2. (a) ALM in situ. Lentiginous proliferation of atypical melanocytes along the basal epidermis (original magnification ×100). (b) ALM with vertical growth phase, Clark level IV (original magnification ×100). (c) Ulceration (original magnification ×100). (d) Scattered mitoses in dermal lesion of melanoma (arrows) (original magnification ×400). (e) Vascular invasion by melanoma cells in septa of adipose tissue (original magnification ×200). (f) Melanoma metastasis with prominent pigment in regional lymph node (original magnification ×40).
The prognosis of Chinese patients with AM was clearly not optimistic: The 5- and 10-year DSS rates in our patients were 53.3% and 27.4%, respectively. In the largest report of AM, Bradford et al. reported a population-based analysis, with 5- and 10-year DSS rates of 80.3% and 67.5%, respectively. They also concluded that 5- and 10-year DSS rates were highest in non-Hispanic Whites (82.6% and 69.4%), intermediate in Blacks (77.2% and 71.5%), and lowest in Hispanic Whites (72.8% and 57.3%) and Asian/Pacific Islanders (70.2% and 54.1%). Bello et al. reported a 5-year DSS rate of 70%16, comparable with the rate reported by Kuchelmeister et al. (71%)14 and Phan et al. (76%)20. Our 5-year DSS results are substantially worse than those observed in AM (70–82%)14,16 and ALM (76–80%)19,20,26 of Whites. However, our data are comparable with those observed in other

| Characteristics                        | No. Pts | No. of DOD (%) | P value* |
|----------------------------------------|---------|----------------|----------|
| All patients                           | 142     | 83 (58.5)      |          |
| Sex                                     |         |                |          |
| Male                                    | 84      | 48 (57.1)      |          |
| Female                                  | 58      | 35 (60.3)      | 0.512    |
| Age, years                              |         |                |          |
| <55                                     | 41      | 26 (63.4)      |          |
| ≥55                                     | 101     | 57 (56.4)      | 0.732    |
| Trauma history                          |         |                |          |
| Yes                                     | 8       | 5 (62.5)       |          |
| No                                      | 134     | 78 (58.2)      | 0.486    |
| Longest diameter of lesion, cm          |         |                |          |
| ≤2                                      | 72      | 42 (58.3)      |          |
| >2                                      | 70      | 41 (58.6)      | 0.492    |
| Duration of the lesion, years           |         |                |          |
| ≤2.5                                    | 88      | 61 (69.3)      |          |
| >2.5                                    | 54      | 22 (40.7)      | <0.001   |
| Site of lesion                          |         |                |          |
| Nonungual location                      | 119     | 68 (57.1)      |          |
| Subungual location                      | 23      | 15 (65.2)      | 0.895    |
| Histologic subtype                     |         |                |          |
| ALM                                     | 122     | 67 (54.9)      |          |
| Other                                   | 20      | 16 (80.0)      | 0.081    |
| Breslow thickness, mm                   |         |                |          |
| ≤4.0                                    | 83      | 35 (42.2)      |          |
| >4.0                                    | 59      | 48 (81.4)      | <0.001   |
| Clark level                             |         |                |          |
| I/II/III                                | 14      | 2 (14.3)       |          |
| IV/V                                    | 128     | 81 (63.3)      | 0.009    |
| Ulceration                              |         |                |          |
| Yes                                     | 68      | 54 (79.4)      |          |
| No                                      | 74      | 29 (39.2)      | <0.001   |
| Mitotic rate, mm-1                      |         |                |          |
| ≤15                                     | 131     | 73 (55.7)      |          |
| >15                                     | 11      | 10 (90.9)      | <0.001   |
| TILs                                    |         |                |          |
| Absent                                  | 46      | 21 (45.7)      |          |
| Present                                 | 96      | 62 (64.6)      | 0.155    |
| Vascular invasion                       |         |                |          |
| Absent                                  | 139     | 80 (57.6)      |          |
| Present                                 | 3       | 3 (100.0)      | 0.002    |
| Regional lymph node metastasis at diagnosis |      |                |          |
| Yes                                     | 46      | 39 (84.8)      |          |
| No                                      | 96      | 44 (45.8)      | <0.001   |
| Pathologic stage                        |         |                |          |
| 0/I                                     | 20      | 1 (5.0)        |          |
| II/III/IV                               | 122     | 82 (67.2)      | <0.001   |

Table 4. Univariate analysis of factors associated with disease-specific survival in the acral melanoma cohort. *Log-rank test; DOD, died of disease.
Asian studies. 5-year survival rates of AM reported from Korean and Japan ranged from 35.0% to 49.3%\(^1\). In addition, when controlling the survival rates for Breslow thickness, our 5-year DSS rates of AM were still 10–30% lower than those in previous studies\(^1\). So we concluded that the DSS rates of AM in Asians are worse than that in other races. Several factors including high ulcerative rate (47.9%), extreme proportion of Breslow thickness > 4 mm (40.8%), high mitotic rate (>15 mm\(^-2\)) may contribute to the poor survival in our patients. In addition, lack of recognition by patients and misdiagnosed as benign by clinicians sometimes can also contribute to the poor survival in our patients.

In conclusion, this study represents one of the largest single-institution series describing the clinicopathological characteristics and prognostic factors of AM in Asia. Duration of the lesion before diagnosis (≤2.5 vs >2.5), Breslow thickness (≤4.0 vs >4.0), Clark level (I/II vs III/IV V), Ulceration (Yes vs No), Mitotic rate (≤15 vs >15), Vascular invasion (Absent vs Present), Regional lymph node metastasis at diagnosis (Yes vs No), Pathologic stage (0 vs I II III IV) are prognostic indicators associated with DSS. As a particular subgroup of melanoma, the prognosis of AM in Asians is worse, compared with AM in other ethnic group and cutaneous melanomas in other sites.

### Methods

#### Clinical data.

The computerized databases in the pathology department of Fudan University Shanghai Cancer Center were used for the study. The key words ‘melanoma’ were used to identify the patients. Among them, melanomas located on acral sites were included. Data were collected between January 2004 and December 2010 to allow determination of 5-year survival statistics. Only those patients with primary tumour and treated with wide surgical excision at our institution were included in our study. After reviewing the clinical records, pathological slides and complete follow-up data of these patients, 142 patients with AM were included in the present study. Informed consent was obtained from each patient. The study has been approved by Institutional Review Board.

### Results

#### Characteristics HR (95% CI) P value

| Characteristics                                          | HR (95% CI) | P value |
|----------------------------------------------------------|-------------|---------|
| Duration of the lesion (≤2.5 vs >2.5)                    | 0.056 (0.332–0.930) | 0.025   |
| Breslow thickness (≤4.0 vs >4.0)                         | 1.749 (1.060–2.886) | 0.029   |
| Clark level (I/II vs III/IV V)                           | 1.188 (0.276–5.113) | 0.817   |
| Ulceration (Yes vs No)                                   | 0.869 (0.524–1.442) | 0.588   |
| Mitotic rate (≤15 vs >15)                                | 2.399 (1.146–5.019) | 0.020   |
| Vascular invasion (Absent vs Present)                    | 0.272 (0.082–0.901) | 0.033   |
| Regional lymph node metastasis at diagnosis (Yes vs No)  | 1.757 (1.105–2.792) | 0.017   |
| Pathologic stage (0 vs II III IV)                         | 12.891 (1.689–98.425) | 0.014   |

Table 5. Multivariate analysis of factors associated with disease-specific survival in the acral melanoma cohort.
Ethics Committee at Fudan University Shanghai Cancer Center. All procedures were conducted according to the guidelines approved by Institutional Ethics Committee at Fudan University Shanghai Cancer Center.

For each patient, the following clinical data were retrieved from medical records: sex, age at the time of diagnosis, presence or absence of a history of trauma, longest diameter of lesion, site of lesion, tumor thickness, Clark level, ulceration, mitotic rate (mitotic count per millimeters squared), TILs, presence of vascular invasion, regional lymph node metastasis at diagnosis. The pathologic stage of disease was determined based on the most recent classification of the American Joint Committee on Cancer (AJCC)31.

Histopathological study and pathologic staging. Pathological slides of surgical specimens were reviewed by two experienced dermatopathologists. The following data were recorded: histologic subtype, Breslow thickness, Clark level, ulceration, mitotic rate (mitotic count per millimeters squared), TILs, presence of vascular invasion, regional lymph node metastasis at diagnosis. The pathologic stage of disease was determined based on the most recent classification of the American Joint Committee on Cancer (AJCC)31.

Statistical analysis. The evaluation of data was performed using the statistical package SPSS, version 22.0 (SPSS, Inc). The Kaplan-Meier method was used to calculate survival curves, and significant differences were determined by the log-rank test. DSS was defined as the time from pathological diagnosis to the time of death due to melanoma or last follow-up. Univariate Cox regression model was used to examine the association of clinical and pathologic variables with DSS. Characteristics significant on univariate analysis with a p value of <0.05 were entered into a multivariate Cox proportional hazards model.

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**Acknowledgements**

This study was supported in part by Grants from Shanghai Natural Science (No. 12ZR1406600), Shanghai Hospital Development Center Emerging Advanced Technology Joint Research Project (HDC12014105) and Shanghai Key Developing Disciplines (2015ZB0201).

**Author Contributions**

J.L. did statistical analysis and drafted the paper. B.D. revised the paper. Y.K. designed the study and revised the paper. X.S. collected the data and reviewed all the slides. J.K. reviewed all the slides. All authors reviewed the manuscript, and contributed to the final manuscript.

**Additional Information**

**Competing financial interests:** The authors declare no competing financial interests.

**How to cite this article:** Lv, J. *et al.* Acral Melanoma in Chinese: A Clinicopathological and Prognostic Study of 142 cases. *Sci. Rep.* **6**, 31432; doi: 10.1038/srep31432 (2016).

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