Low-level NLRP1 is associated with increased metastasis and risk of recurrence of non-melanoma skin cancer

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

Background. Cutaneous squamous cell carcinoma (cSCC) and cutaneous basal cell carcinoma (cBCC) are the most common types of non-melanoma skin cancer (NMSC). The NACHT, LRR and PYD domains-containing protein 1 (NLRP1) protein is considered to be inhibited in NMSC, although clinical evidence is still lacking.

Objectives. To investigate the clinical significance of NLRP1 in cSCC and cBCC patients.

Materials and methods. This prospective observational study enrolled 199 cases of cBCC and cSCC patients who reported to our hospital from January 2018 to January 2019. Additionally, 199 blood samples from healthy individuals were collected as the control. Serum NLRP1 and cancer biomarkers of CEA and CYFRA21-1 were then measured using enzyme-linked immunosorbent assay (ELISA). Clinical characteristics collected from patients included age, sex, BMI, TNM stage, cancer type, lymph node metastasis, and myometrial infiltration conditions. All patients were followed up for 1–3 years.

Results. Of all patients, 23 died during the follow-up period, with a mortality rate of 11.56%. Serum NLRP1 showed markedly lower levels in cancer patients compared with healthy controls. Furthermore, the expression of NLRP1 was significantly higher in cBCC patients compared with cSCC patients. The deceased patients, together with those with lymph node metastasis and myometrial infiltration, also showed significantly lower NLRP1 levels. Moreover, lower NLRP1 levels were associated with higher frequencies of tumor–nodule–metastasis (TNM) III–IV stage, lymph node metastasis and myometrial infiltration, as well as higher mortality and recurrence rates. The curvilinear regression showed the relationship between NLRP1 and CEA/or CYFRA21-1 was most appropriate for the reciprocal. Receiver operating characteristic (ROC) curves showed NLRP1 was a potential biomarker for lymph node metastasis, myometrial infiltration and prognosis in NMSC patients, and the Kaplan–Meier analysis found NLRP1 was associated with 1–3-year mortality and recurrence of NMSC.

Conclusions. Lower NLRP1 level is associated with worse clinical outcomes and poorer prognosis in cSCC and cBCC patients.

Key words: diagnosis, prognosis, NLRP1, cutaneous squamous cell carcinoma, cutaneous basal cell carcinoma

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Background

Non-melanoma skin cancer (NMSC) accounts for 6.2% of new cancer cases worldwide, with 1,198,073 cases per year and 63,731 cases of cancer-related deaths in 2020.[1,2] Cutaneous squamous cell carcinoma (cSCC) and cutaneous basal cell carcinoma (cBCC) are the most common NMSC types, being approx. 25% and 70% of NMSC cases, respectively.[3,4] In a recent study that included 12,692 skin cancer cases from Chinese, Malays and Indians in Singapore from 1968–2016, it was found that 65.9% of patients were diagnosed with cBCC, 28.3% had cSCC and 5.80% had melanoma.[5] Generally, cSCC has the characteristics of atypical proliferation of invasive squamous cells, the ability to invade and migrate, as well as a high potential of recurrence.[6,7] Patients with cBCC, although it shows low invasive ability, are considered to have a higher risk of developing other skin cancers, including cSCC and melanoma.[8–10] In recent years, the prevalence of cBCC and cSCC increased between 35% and 133% worldwide.[11]

Generally, early diagnosis is of great significance for cancer patients, including those with skin cancer. Thus, new cancer biomarkers are always needed in clinical research. NACHT, LRR and PYD domains-containing protein 1 (NLRP1) belongs to the NLRP family and plays an important role in many bioprocesses, including inflammation, cell function and cancer proliferation.[12–14] NLRP1 was found to be associated with different cancers through several signaling pathways. It was found that NLRP1 polymorphisms were associated with an increased incidence of mesothelioma, specifically with the NLRP1 rs12150220 allele T.[15] Another study demonstrated that NLRP1 could influence cell pyroptosis in breast cancer cells, which was associated with the regulation of caspase-4.[16] Recently, it was reported that both levels of NLRP1 and NLRP1 inflammasome were inhibited in cSCC.[17] Furthermore, NLRP3, another member of the NLRP family which shows biofunctions similar to NLRP1, was also found to be suppressed in cSCC.[18] These data led us to speculate that the expression of NLRP1 in cSCC patients may also be decreased. However, studies of NLRP1 in NMSC patients are still lacking.

Objectives

We conducted an observational study to investigate the clinical significance of NLRP1 in cSCC and cBCC patients. This study may provide a potential novel biomarker for the diagnosis and prognosis of NMSC.

Materials and methods

Patients

This prospective observational study enrolled 199 cases of cBCC and cSCC patients who reported to our hospital from January 2018 to January 2019. The sample size was calculated by the formula $(Z_{1-\alpha/2 \times \sigma}/\delta)^2$ proposed by Shalhout et al.[2] The estimated standard deviation (SD) was 36, and the allowable error was 5 (α = 0.05) thus, n = $((1.96 \times 36)/0.05)^2$ = 199. The inclusion criteria were as follows: 1) patients with cBCC or cSCC confirmed with histological analysis; 2) patients who were diagnosed for the first time with primary NMSC; 3) patients over the age of 18. The following patients were excluded: 1) patients who underwent anti-cancer treatments before participation; 2) patients with metastatic skin carcinoma but not primary skin cancer; 3) patients with severe infections such as severe pneumonia, or other systematic organ dysfunctions. Additionally, blood samples from 199 healthy individuals who reported for medical examination were enrolled as a control group.

All patients signed the informed consent, and the study protocol conformed to the Declaration of Helsinki. Ethical approval was obtained by the Ethical Committee of Meizhou People's Hospital (approval No. 2018-11).

Measurement of serum NLRP1, CEA and CYFRA21-1

Serum NLRP1, as well as cancer biomarkers carcino embryonic antigen (CEA) and CYFRA21-1 were measured using enzyme-linked immunosorbent assay (ELISA). Briefly, fasting elbow vein peripheral blood (5 mL) was collected within 48 h after admission. After obtaining the serum by centrifugation, the serum levels of NLRP1 (range 18.75–1200 pg/mL, sensitivity 4.67 pg/mL; cat. No. EL015864HU; Cusabio, Houston, USA), CEA (range: 312–20000 pg/mL, sensitivity <10 pg/mL, cat. No. EK0904 BOSTER Bio, Pleasanton, CA) and CYFRA21-1 (range: 31.25–2000 pg/mL, sensitivity 18.75 pg/mL; cat. No. EH0364; Wuhan Fine Biotech, Wuhan, China) were tested using commercially available ELISA kits according to the manufacturer's instruction.

Data collection of clinical outcomes and follow-up

All patients were followed up for 1–3 years. The patients' clinical characteristics collected included age, sex, body mass index (BMI), tumor–nodule–metastasis (TNM) stage, cancer type, lymph node metastasis, and myometrial infiltration conditions. Patients' cancer-related death and recurrence conditions were recorded. For survival analysis, overall survival (OS) or disease-free survival (DFS) duration was calculated from the time of admission to death or recurrence, or the last follow-up.

Statistical analyses

Data were expressed as median (Me) (interquartile range (IQR) and range) for non-normally distributed data (all continuous data are non-normally distributed in this study).

Data distribution was analyzed using the Kolmogorov–Smirnov method. Comparisons between 2 groups were made using the Mann–Whitney U test, and Kruskal–Wallis analysis was used for comparisons between 3 groups for age, BMI and NLRP1 level. The χ^2 test was used for analyzing the rates, and curvilinear regression was used for analyzing the correlation between NLRP1 and CEA/or CYFRA21-1. The receiver operating characteristic (ROC) curve was used for the diagnostic value of NLRP1. The Kaplan–Meier curve was applied to the survival analysis. Logistic regression was used for the analysis of risk factors of mortality, and the Hosmer–Lemeshow test was used to show the goodness-of-fit. We used Box–Tidwell method to test the linearity of independent variables and log odds. The variance inflation factor (VIF) value was used to show multicollinearity, with a value above 1.5 indicating multicollinearity. Finally, the Casewise List (Studentized residual) was used to show the influential outliers. A $p < 0.05$ indicated a significant difference between groups, and all calculations were performed using Statistical Package for Social Sciences (SPSS) v. 18.0 (SPSS Inc., Chicago, USA) and GraphPad Prism v. 6.0 (GraphPad Software, San Diego, USA).

Results

Clinical characteristics of patients and the expression of NLRP1

The clinical characteristics of all patients are listed in Table 1. All patients were followed up for 1–3 years, with a median follow-up time of 24 months. From the entire cohort, 23 patients died during the follow-up period, with a mortality rate of 11.56%. Compared with the surviving patients, the deceased ones showed a higher frequency of TNM stage III–IV, lymph node metastasis, myometrial infiltration, and recurrence (all $p < 0.05$). Furthermore, cSCC patients had a higher mortality rate than cBCC patients. No other significant differences were found between the surviving and deceased patients, including their demographics, with no significant difference found for age, sex and BMI between the surviving and deceased patients and healthy controls.

Then, we analyzed the expression of NLRP1 in different patients. It was found that NLRP1 showed markedly lower levels in serum from both cSCC and cBCC patients compared with healthy controls ($p < 0.001$; Fig. 1A). Moreover, the expression of NLRP1 was significantly higher in cBCC patients compared with cSCC patients ($p = 0.048$). Meanwhile, deceased patients, together with those with TNM III–IV, lymph node metastasis and myometrial infiltration, also showed significantly decreased NLRP1 levels compared with surviving patients, the patients with TNM I–II or those without lymph node metastasis or myometrial infiltration, respectively (all $p < 0.05$) (Fig. 1B–E).

Expression of NLRP1 was correlated with CEA and CYFRA21-1 in NMSC patients

Next, the serum levels of cancer biomarkers CEA and CYFRA21-1 were analyzed. It was found that both CEA and CYFRA21-1 levels were significantly higher in deceased patients, as well as in the patients with TNM stage III–IV, lymph node metastasis or myometrial infiltration, compared with surviving patients, patients with TNM I–II or patients without metastasis or infiltration (Table 2).

Table 1. Clinical characteristics of all non-melanoma skin cancer (NMSC) patients on admission

Variables		All patients (n = 199)	Surviving (n = 176)	Deceased (n = 23)	Healthy controls (n = 199)	p_1*	p_2#
Age [years]		56 (23, 34–75)	56 (23, 34–75)	58 (26, 36–75)	53 (21, 34–75)	0.583	0.568
Female sex, n (%)		106 (53.27)	94 (53.41)	12 (52.17)	106 (53.27)	0.861	0.982
BMI [kg/m²]		24.90 (7.30, 17.04–31.95)	25.09 (7.20, 17.05–31.92)	23.52 (8.66, 17.04–31.95)	23.91 (8.13, 17.12–31.93)	0.363	0.306
TNM stage, n (%)	I–II	153 (76.88)	151 (85.80)	2 (8.70)	–	<0.001	–
	III–IV	46 (23.12)	25 (14.20)	21 (91.30)	–		–
Pathological type, n (%)	cSCC	74 (37.19)	56 (31.82)	18 (78.26)	–	<0.001	–
	cBCC	125 (62.81)	120 (68.18)	5 (21.74)	–		–
Lymph node metastasis, n (%)		49 (24.62)	28 (15.91)	21 (91.30)	–	<0.001	–
Myometrial infiltration, n (%)		54 (27.14)	32 (18.18)	22 (95.65)	–	<0.001	–
Follow-up [months]		24 (12, 12–36)	24 (13, 12–36)	20 (12, 12–35)	–	0.299	–
Recurrence, n (%)		30 (15.08)	11 (6.25)	19 (82.61)	–	<0.001	–

*p_1 value was obtained by comparison between surviving and deceased patients, while rates were analyzed using χ^2 test. For #p_2 values, age and BMI were compared using Kruskal–Wallis analysis, while the sex rates were compared with χ^2 test among the 3 groups: surviving patients, deceased patients and healthy controls. Continuous data were expressed as median (IQR, range). BMI – body mass index; TNM – tumor–nodule–metastasis; IQR – interquartile range; cSCC – cutaneous squamous cell carcinoma; cBCC – cutaneous basal cell carcinoma.
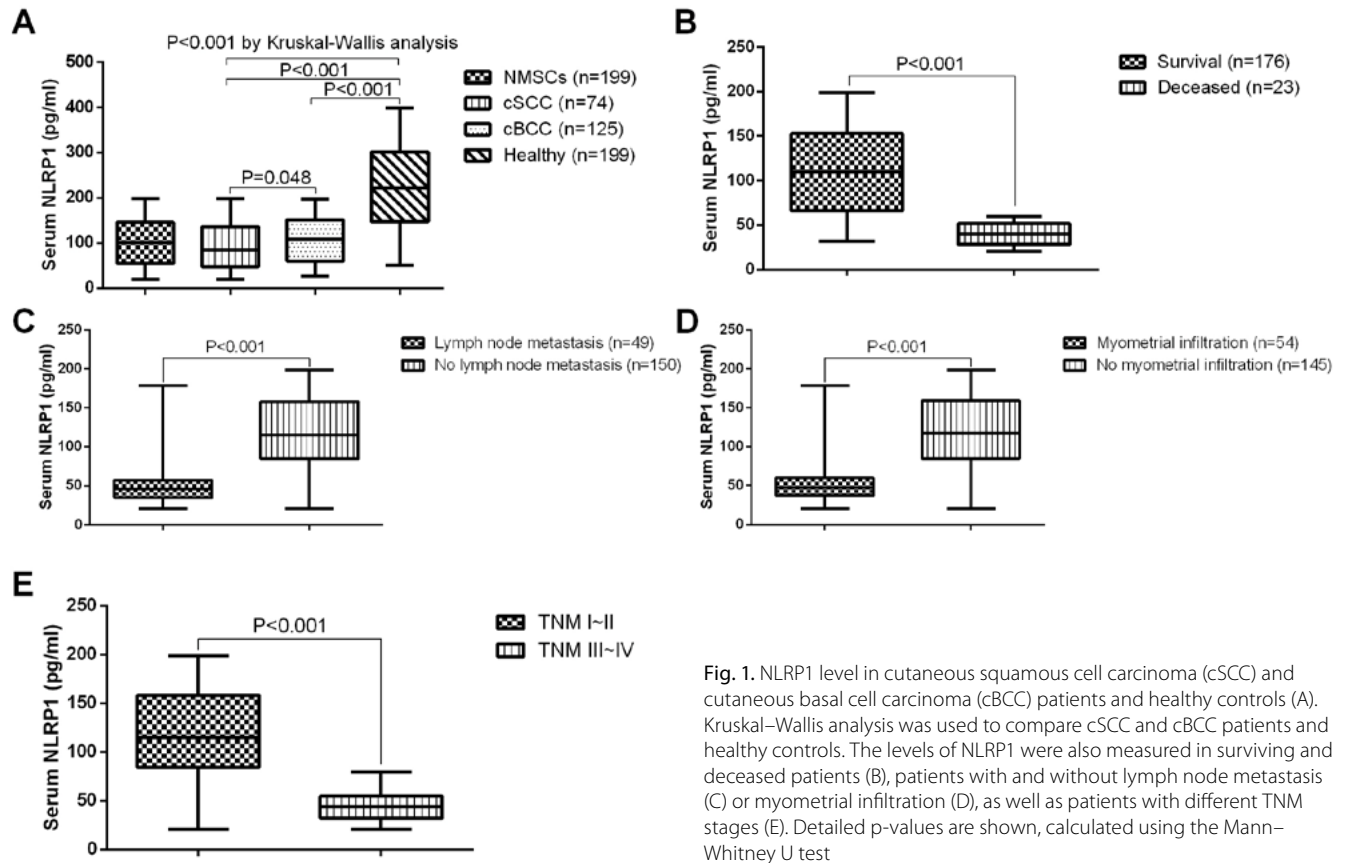
Fig. 1. NLRP1 level in cutaneous squamous cell carcinoma (cSCC) and cutaneous basal cell carcinoma (cBCC) patients and healthy controls (A). Kruskal–Wallis analysis was used to compare cSCC and cBCC patients and healthy controls. The levels of NLRP1 were also measured in surviving and deceased patients (B), patients with and without lymph node metastasis (C) or myometrial infiltration (D), as well as patients with different TNM stages (E). Detailed p-values are shown, calculated using the Mann–Whitney U test

Table 2. Serum expression of CEA and CYFRA21-1 in different groups of patients

Variables	CEA [pg/mL]	CYFRA21-1 [pg/mL]
Surviving (n = 176)	498.41 (198.90, 304.73–941.88)	67.89 (31.73, 31.20–148.99)
Deceased (n = 23)	968.04 (612.37, 548.13–1476.55)	170.69 (67.99, 95.74–241.42)
p[a]	<0.001	<0.001
TNM I–II (n = 153)	488.35 (194.29, 304.73–1313.59)	65.15 (28.58, 31.20–241.42)
TNM III–IV (n = 46)	787.95 (392.61, 405.23–1476.55)	122.24 (70.13, 51.87–222.13)
p[b]	<0.001	<0.001
With lymph node metastasis (n = 49)	783.56 (388.03, 309.54–1476.55)	121.48 (70.89, 51.87–222.13)
Without lymph node metastasis (n = 150)	489.76 (187.83, 304.73–1313.59)	65.37 (28.73, 31.20–241.42)
p[c]	<0.001	<0.001
With myometrial infiltration (n = 54)	704.09 (382.46, 309.54–1476.55)	119.10 (75.19, 36.58–222.13)
Without myometrial infiltration (n = 145)	488.35 (186.91, 304.73–1313.59)	65.15 (28.58, 31.20–241.42)
p[d]	<0.001	<0.001

All p-values were compared using Mann–Whitney U test; [a]p-value was calculated as comparison between surviving and deceased patients; [b]p-value was calculated as comparison between TNM I–II and III–IV patients; [c]p-value was calculated as comparison between patients with and without lymph node metastasis; [d]p-value was calculated as comparison between patients with and without myometrial infiltration. TNM – tumor–nodule–metastasis.

Additionally, the curvilinear regression showed the relationship between NLRP1 and CEA was mostly appropriate for reciprocal (R^2 = 0.282), and similar to the relationship between NLRP1 and CYFRA21-1 (R^2 = 0.392) (Fig. 2). The detailed data for curvilinear regression are shown in the Supplementary data.
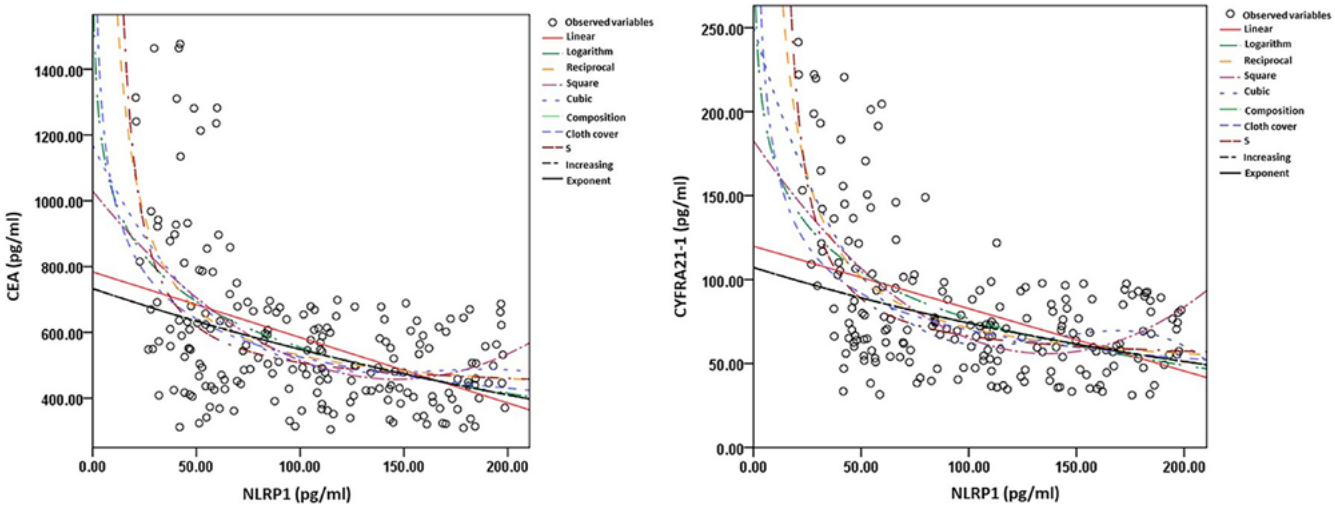
Fig. 2. Curvilinear regression shows the relationship between NLRP1 and CEA levels (A) and between NLRP1 and CYFRA21-1 levels (B)

Low expression of NLRP1 was associated with worse clinical outcomes in NMSC patients

The median value of NLRP1 level (101.65 pg/mL) was used to divide the patients into high (>101.65 pg/mL) or low NLRP1 (≤101.65 pg/mL) level groups (Table 3). Patients with low expression of NLRP1 showed significantly higher incidence of TNM III–IV, lymph node metastasis and myometrial infiltration (all p < 0.05). Unexpectedly, BMI in the low NLRP1 group was also markedly lower than in the patients with high NLRP1 level. Moreover, the mortality and recurrence rates were also markedly higher in patients with lower expression of NLRP1. These results suggested that low expression of NLRP1 may be associated with worse clinical outcomes in NMSC patients.

NLRP1 as a potential biomarker for lymph node metastasis, myometrial infiltration and prognosis in skin cancer patients

Next, ROC curves were used to investigate the diagnostic value of NLRP1. It was found that NLRP1 showed good diagnostic value for the diagnosis of lymph node metastasis (area under curve (AUC) 0.913, cutoff <60.94 pg/mL, sensitivity 87.33% (95% confidence interval (95% CI): 80.93–92.20%), specificity 83.67% (95% CI: 70.34–92.68%)), myometrial infiltration (AUC 0.891, cutoff <60.94 pg/mL, sensitivity 87.59% (95% CI: 81.09–92.47%), specificity 77.78% (95% CI: 64.40–87.96%)), recurrence (AUC 0.921, cutoff <52.40 pg/mL, sensitivity 87.57% (95% CI: 81.63–92.14%), specificity 80.00% (95% CI: 61.43–92.29%)), and mortality (AUC 0.933, cutoff <53.65 pg/mL, sensitivity

Table 3. Comparison between patients with high and low NLRP1 expression

Variables		High NLRP1 (n = 99)	Low NLRP1 (n = 100)	p-value
Age [years]		55 (25, 34–75)	57 (20.75, 35–75)	0.948
Female sex, n (%)		54 (54.55)	52 (52.00)	0.718
BMI [kg/m²]		25.26 (7.52, 17.10–31.92)	24.26 (7.15, 17.04–31.95)	0.018
TNM stage, n (%)	I–II	99 (100.00)	54 (54.00)	<0.001
	III–IV	0 (0.00)	46 (46.00)	
Pathological type, n (%)	cSCC	33 (33.33)	41 (41.00)	–
	cBCC	66 (66.67)	59 (59.00)	
Lymph node metastasis, n (%)		2 (2.02)	47 (47.00)	<0.001
Myometrial infiltration, n (%)		5 (5.05)	49 (49.00)	<0.001
Follow-up [months]		24.00 (12.00, 12–36)	23.50 (12.75, 12–36)	0.569
Mortality, n (%)		0 (0.00)	23 (23.00)	<0.001
Recurrence, n (%)		0 (0.00)	30 (30.00)	<0.001

The p-value was obtained as comparison between surviving and deceased patients using Mann–Whitney U test for continuous data. Rates were analyzed using χ² test. Continuous data were expressed as median (IQR, range). BMI – body mass index; TNM – tumor–nodule–metastasis; IQR – interquartile range; cSCC – cutaneous squamous cell carcinoma; cBCC – cutaneous basal cell carcinoma.
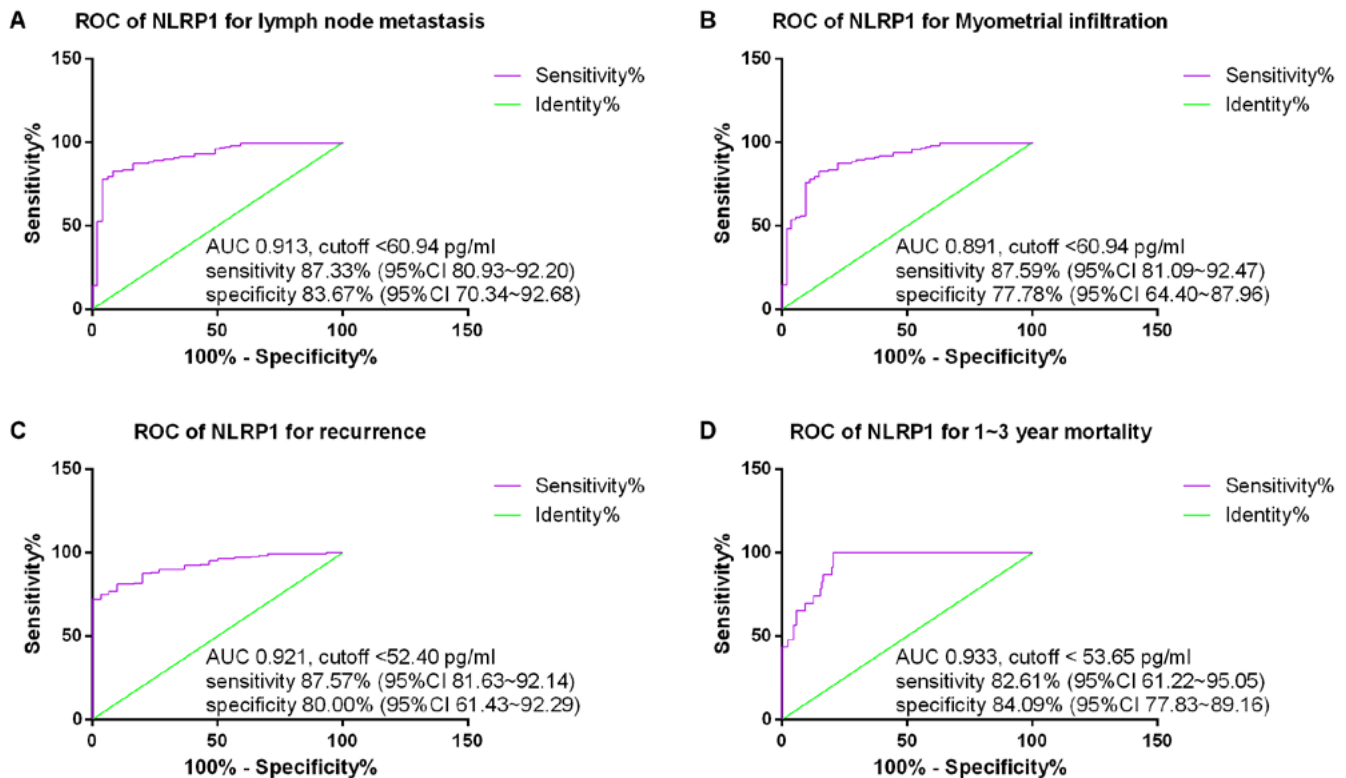
Fig. 3. ROC curves for NLRP1 levels as a tool for the detection of lymph node metastasis (A), myometrial infiltration (B) and recurrence (C) and estimating mortality (D) in non-melanoma skin cancer (NMSC) patients

82.61% (95% CI: 61.22–95.05%), specificity 84.09% (95% CI: 77.83–89.16%)) (Fig. 3).

NLRP1 was associated with 1–3-year mortality and recurrence in NMSC patients

We then used a Kaplan–Meier curve to analyze the effects of NLRP1 on patients' prognoses. It was found that patients with lower expression of NLRP1 showed significantly shorter overall 1–3-year OS and DFS (both $p < 0.001$ using log-rank test; Fig. 4). The logistic regression was performed using 3 models, with model 1 including continuous data (age, BMI, NLRP1, CEA, and CYFRA21-1), model 2 including count data on sex, TNM stage and pathological type, and model 3 including data on lymph node metastasis and myometrial infiltration incidence (Table 4). The p-values of the Hosmer–Lemeshow test were as follows: 0.999, 0.557 and 1.000, while the value of Nagelkerke R^2 were 0.894, 0.598 and 0.499, respectively, indicating the acceptable goodness-of-fit. The detailed original data of our logistic regression and the data on the linearity of independent variables, log odds and multicollinearity, as well as influential outliers are all shown in the Supplementary materials. Interestingly, logistic regression demonstrated that high expression CEA and CYFRA21-1, as well as TNM stage, pathological type and myometrial infiltration, were risk factors for 1–3-year mortality in NMSC.

Discussion

The cSCC and cBCC are the most common types of NMSC, although there is currently a lack of specific cancer biomarkers for both cBCC and cSCC. In recent years, NLRP1 has shown its potential as a novel research target in skin carcinogenesis. However, clinical studies on NLRP1 in NMSC are rare. In the present study, we demonstrated for the first time that lower NLRP1 expression was associated with worse clinical outcomes and poorer prognosis of cSCC and cBCC patients.

The NLRP1 can act as both a cancer promotor or suppressor in different cancer types. In our study, we found NLRP1 had low expression in both cBCC and cSCC, and this was associated with the patient's poor prognosis. It was found that NLRP1 was downregulated in lung adenocarcinoma patients, and decreased NLRP1 expression predicted their poor prognosis, showing its potential as an anti-cancer agent.[19] In colorectal cancer, NLRP1 was also reported to suppress colitis-associated tumorigenesis through activation of the NLRP1 inflammasome.[20] In these studies, NLRP1 was downregulated and acted as a tumor suppressor, which was consistent with our findings in NMSC. However, in breast cancer, NLRP1 was found to be a cancer promotor, its overexpression facilitating tumorigenesis and cell proliferation.[21] The molecular mechanisms of these differences are not fully understood, partly due to the different effects of NLRP1 on cancer-related immunity.

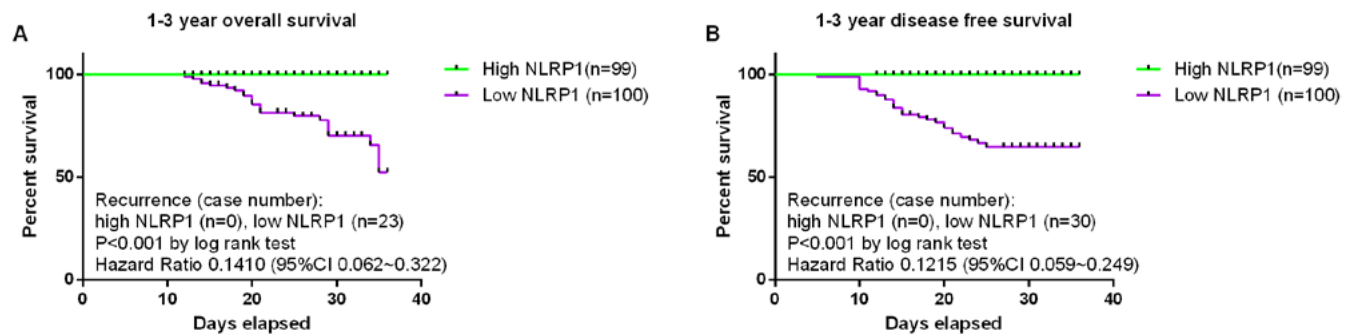**Fig. 4.** Kaplan–Meier curve for overall survival (OS) (A) and disease-free survival (DFS) (B)

Table 4. Logistic regression for 1–3-year mortality in non-melanoma skin cancer (NMSC)

Variables	Walds	OR	95% CI	p-value
Age	0.572	1.039	0.941–1.148	0.450
Sex	0.120	0.805	0.236–2.747	0.729
BMI	0.220	0.937	0.714–1.230	0.639
TNM stage	27.916	74.082	15.001–365.841	<0.001
Pathological type	12.238	0.101	0.028–0.365	<0.001
Lymph node metastasis	0.905	3.000	0.312–28.841	0.341
Myometrial infiltration	5.690	36.000	1.895–684.028	0.017
NLRP1	2.315	0.913	0.812–1.027	0.128
CEA	5.206	1.007	1.001–1.013	0.023
CYFRA21-1	6.485	1.082	1.018–1.150	0.011

BMI – body mass index; TNM – tumor–nodule–metastasis; OR – odds ratio; 95% CI – 95% confidence interval.

In skin cancers, NLRP1 also plays different roles in NMSC and melanoma. It was reported that NLRP1 was highly expressed in melanoma, along with activation of the NLRP1 inflammasome, and high NLRP1 expression, in turn, induced resistance to the drug temozolomide.[22] In another study, it was found NLRP1 could facilitate cell proliferation and suppress cell apoptosis through activating the NLRP1 inflammasome in melanoma.[23] In the present research, we mainly focused on the clinical significance of NLRP1 in cBCC and cSCC patients, finding that NLRP1 expression was decreased in both cBCC and cSCC patients, and its low expression was correlated with poorer clinical outcomes and prognosis. However, we failed to show that NLRP1 was an independent risk factor for 1–3-year mortality, indicating more studies should be conducted to confirm our results. Previous research has demonstrated NLRP1 level was decreased in cSCC, along with inhibition of ASC, caspase-1 and IL-1β, the inflammasome-related factors.[17] Furthermore, another study reported that germline NLRP1 mutations were associated with the incidence of multiple self-healing palmoplantar carcinomas (MSPC) and familial chronic lichen keratosis (FKLC), which are risk factors for various types of skin cancers.[24] All these results are consistent with our findings, although up to now, few have reported clinical expression of NLRP1 in NMSC. Interestingly, the expression of another NLRP family member, NLRP3, was also decreased in cSCC,[18] and a study found ultraviolet radiation could activate the expression of NLRP3

in cBCC.[25] Since the pathology and molecular mechanisms between NMSC and melanoma differ a lot, the difference in NLRP1 in these cancers may be caused by other signaling pathways and key genes or other proteins.

Limitations of the study

The study has some limitations. We failed to prove NLRP1 is an independent risk factor for mortality in NMSC. Moreover, we only included a small number of patients.

Conclusions

We found that NLRP1 could be used as a potential biomarker of clinical outcomes and prognosis of NMSC. Lower NLRP1 levels were associated with higher incidence of lymph node metastasis and myometrial infiltration, and higher risk of recurrence and mortality. This study may provide a potential novel biomarker as well as a research target for future NMSC investigations.

Supplementary data

The Supplementary materials are available at https://doi.org/10.5281/zenodo.7871796. The package contains the following files:

Supplementary Table 1. The test of linearity of independent variables and log-odds, multicollinearity and influential outliers. Supplementary Table 2. The original output data of logistic regression from SPSS. Supplementary Table 3. The original output data of curvilinear regression from SPSS.

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