Prognostic Value of systemic inflammatory factors (NLR, LMR, PLR) and LDH in penile cancer

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Abstract

Background: Penile squamous cell carcinoma (PSCC) represents an important public health problem for developing countries, the major prognostic factors in PSCC are Pathological subtype, perineural invasion, lymphovascular invasion, depth of invasion and grade, these factors are hard to precisely obtain before the operation. Besides, intermediate-risk patients with clinically non-palpable inguinal lymph nodes, only about 30% of them are able to detect micro-metastases after ILND. That means the rest of patients approximately 70% have no benefit from ILND and suffered from the complications of surgery, so we hope to find some biomarkers that help us to predict the outcome before surgery and reflect the inguinal lymph nodes metastatic.

Methods: A total of 349 consecutive patients of penile cancer at Yunnan cancer hospital in China between October 2002 and December 2017. 225 was succeed to follow-up. According to the (AUROC) curve, we get the cut-off point, K-M analysis and multivariate logistic regression models and Bivariate correlations were used to detect the results.

Results: Multivariate analysis reveal NLR, LMR, PLR was significant independent factors was associated with inferior OS; Only PLR was associated with inferior PFS; LDH was not associated with inferior OS and PFS. Anatomic stage and lymph node status remained significant for OS and PFS as NCCN and EAU Guidelines indicated. The tumor type and primary treatment was not significant for OS and PFS. In logistic regression analyses NLR, LMR, PLR was corresponded to N stage which divided into the Node-negative group and Node-positive groups, however the LDH was not associated with the N stage. However Kendall’s tau-b evaluated the correlations, NLR, LMR, PLR were weakly correlated to the N stage.

Conclusions: NLR and LMR was significant independent factors for OS, PLR was significant independent factors both for OS and PFS. NLR, LMR, PLR was significant corresponded to N
stage.

Background

Penile squamous cell carcinoma has a low incidence among all cancers, according to the report there are 26,000 new cases occurring worldwide annually [1]. However, in developing countries such as Africa, Asia, South America, etc., penile cancer is still a difficult problem, where its incidence varies from 3 to 8.3 cases per 100,000[2], especially in southwestern of China. The management of the regional lymph nodes is extremely important for long-term survival of the patient according to the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) clinical practice guidelines. Both guidelines subdivide penile cancer into three groups of low risk, intermediate risk and high risk. Low-risk patients with non-palpable inguinal lymph node (cN0) can be managed by surveillance, however as long as the inguinal lymph node are palpable , whether it is low-risk, moderate or high risk, surgery is recommended including inguinal lymph node dissection(ILND) or dynamic sentinel node biopsy(DSNB). The reason for this recommendation is that early surgery of ILND lead to far superior overall survival compared to do the surgery of ILND after regional nodal recurrence has occurred[3]. However intermediate-risk patients with clinically non-palpable inguinal lymph nodes, only about 30% of them are able to detect micro-metastases after ILND. That means the rest of patients approximately 70% have no benefit from ILND and suffered from the complications of surgery. So it is crucial to selected the patients who are really benefits from ILND before surgery. Because prognosis of PSCC is highly correlated with lymph nodes stage, plenty of articles have select patients through the prognostic role of biomarkers. The major prognostic factors in PSCC are perineural invasion, pathological subtype, depth of invasion,grade and lymphovascular invasion[4, 5]. These factors are hard to precisely obtain before the operation. Besides some articles used biomarkers such as p53 and squamous cell carcinoma antigen to predict inguinal lymph
node positive rate and prognosis of penile cancer, but they were not applied to clinical practice[6, 7]. So we hope to find some markers that is associated with inguinal lymph nodes metastatic or can predict the outcomes.

As we known that systemic inflammatory factors play an significant role in cancer progression [8, 9]. The tumor micro-environment regulated by inflammatory cells is clearly related to cancer progression[8]. Systemic inflammatory factors are obviously reflected by changes of peripheral leukocyte, lymphocytes, neutrophils, monocytes and platelets. These factors above mentioned can reflect the tumor micro environment indirectly[8], so we collected the data of peripheral blood parameters including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), which have been reported to be independent prognostic factors in various of cancers[8, 10, 11]. It is also reported in the articles that the platelet-to-lymphocyte ratio (PLR) which has shown a significant prognostic marker in breast cancer[12], ovarian cancer [13], colorectal cancer[14] and so on. Besides, high LDH(lactate dehydrogenase) has also shown that associated with poor OS in urologic cancer[15].

Recently it has been reported that cancer patients with high NLR is associated with worse OS[16] and worse RFS and CSS[17, 18]. However, there has been no study evaluating the PLR associated with outcomes of penile cancer. In this retrospective study, we investigated the role of NLR, LMR, PLR and LDH before surgery to predicting whether micro-metastases of inguinal lymph node exist and assessed the prognostic value in penile cancer.

Methods

We reviewed our electronic medical records system to identify men treated for penile SCC at Yunnan cancer hospital in China between October 2002 and December
Experimental procedures were approved by Yunnan Cancer Hospital Ethics Committee.

A total of 349 consecutive patients treated with ILND in PSCC225 was succeeded to follow-up, Epidemiological and clinical data, including age, preoperative full blood count results (NLR, LMR, PLR), LDH (lactate dehydrogenase), TNM clinical staging, tumour pathology, treatment history and oncological outcome (OS, PFS). Survival analysis was performed by the Kaplan–Meier method for univariate analysis and Cox regression method for multivariate analysis. The NLR was calculated by neutrophil-to-lymphocyte ratio, LMR was lymphocyte-to-monocyte ratio and PLR was platelet-to-lymphocyte ratio which were obtained through peripheral complete blood count and blood biochemistry before the surgery. We calculate the cut-off point of the NLR, LMR, PLR and LDH according to the area under receiver operator characteristic (AUROC) curve given consieration to sensitivity and specificity levels.

The primary end point were overall survival (OS) and progression free survival (PFS) which defined as the time from the dates of pathological diagnosis to death and tumor progression. Univariate analysis (K-M analysis) was performed to compare the higher and lower groups of NLR, LMR, PLR and LDH. Multivariate analysis (COX logistic regression) were used to verify the individual factors respectively. P values less than 0.05 were considered statistical significance.

we also analyse the relation between the NLR, LMR, PLR, LDH and N stage through the logistic regression, meantime we use method of Bivariate correlations to determine the correlation. Results

NLR, LMR, PLR, LDH vs OS/PFS

A total of 225 patients had collected peripheral complete blood count and blood
biochemistry before surgery. The median and mean (±SD) ages were 52.8 and 50.6±13.4. The detailed data of patients are summarized in Table 1. We performed AUROC curve to determine the NLR, LMR, PLR and LDH cut-off value which was 2.94, 4.74, 133.5 and 188.5 respectively. The median interquartile range follow-up was 30 (16.0–63.5) months.

On Kaplan-Meier analysis, NLR>2.94 was associated with inferior OS (log-rank p = 0.001), and inferior PFS (log-rank p = 0.004) in Figure 1 and 2; LMR>4.74 was associated with inferior OS (log-rank p = 0.001), but not associated with PFS (log-rank p = 0.547) in Figure 3 and 4; PLR>133.5 was associated with inferior OS (log-rank p<0.001) and inferior PFS (log-rank p = 0.001) in Figure 5 and 6. LDH<188.5 was associated with inferior OS (log-rank p = 0.004), but not associated with PFS (log-rank p = 0.155) in Figure 7 and 8.

In univariable analyses, NLR>2.94 was associated with inferior OS (HR = 2.967; 95% CI: 1.739–5.064, p < 0.001) and inferior PFS (HR = 1.944; 95% CI: 1.226–3.081, p = 0.005); LMR>4.74 was associated with inferior OS (HR = 0.394; 95% CI: 0.225–0.689, p = 0.001) and not associated with inferior PFS (HR = 0.871; 95% CI: 0.553–1.372, p = 0.551); PLR>133.5 was associated with inferior OS (HR = 3.439; 95% CI: 2.011–5.881, p < 0.001) and inferior PFS (HR = 2.194; 95% CI: 1.384–3.478, p = 0.001); LDH>188.5 was associated with inferior OS (HR = 2.252; 95% CI: 1.267–4.002, p = 0.006) and not associated with inferior PFS (HR = 1.462; 95% CI: 0.859–2.487, p = 0.162).

We performed a multivariate analysis which reveal NLR was significant independent factors for OS (p=0.045) but was not significant for PFS (p=0.275); LMR was associated with
OS (p=0.056) but not significant for PFS (p=0.676); PLR was significant independent factors for OS (p=0.000) and also for the PFS (p=0.008); LDH was not significant both for OS (P=0.317) and PFS (P=0.951).

At multivariate analysis, Anatomic stage and lymph node status (P = 0.03) remained significant for OS and PFS as NCCN or EAU Guidelines indicated. However, the tumor type and primary treatment was not significant for OS and PFS in multivariable analyses.

NLR LMR PLR LDH vs inguinal lymph node-negative/positive

In logistic regression analyses, NLR (HR = 2.212; 95% CI: 1.228–3.985, p = 0.008), LMR (HR = 0.537; 95% CI: 0.308–0.937, p = 0.029), PLR (HR = 2.478; 95% CI: 1.365–4.497, p = 0.003) was significant corresponded to N stage which divided into the Node-negative group and Node-positive groups, however the LDH (p=0.165) was not associated with the N stage.

Meantime we also use Kendall’s tau-b method to evaluated the correlations, NLR (Kendall’s tau-b = 0.131, P=0.017) LMR (Kendall’s tau-b = -0.109, P=0.046) PLR (Kendall’s tau-b = 0.161, P=0.003) were weakly correlated to the N stage.

Discussion

In recent years, the role of inflammatory factors in cancer development and progression has received more attention. The tumor micro-environment may be associated with systemic inflammation. Several types of cancer have been adopt inflammatory factors in prognostic scores for predict the outcome[19] and IMDC scores of advanced renal cell carcinoma also added those factors.

Recently, an elevated ratio of peripheral neutrophils-to-lymphocytes (NLR) has been recognized as a poor prognostic indicator in penile cancer, Patients with a high NLR had
significantly worse CSS [17, 18] and OS[16]; Patients with a low LMR had significantly worse RFS and CSS than those with a high LMR[18].

However, there is no date about the PLR and LDH in penile cancer, this paper aims to collect data from China and conduct comparative analysis of NLR, LMR, PLR and LDH, these bio-markers are critical in guiding clinical management decisions and follow-up strategies.

The incidence of penile cancer itself is very low, so it is difficult to analyze with a large sample size. The incidence of penile cancer is relatively high in China, especially in Yunnan Province, so the sample size of this paper is relatively large.

In addition, it is difficult to judge whether there is lymph node metastasis before ILND, therefore, we also hope to assist in judgment whether there is lymph node metastasis from these indicators, so that we can choose the different surgical approach.

We acknowledge the several limitations to this study including inherent biases associated with its retrospective design, insufficient time to follow-up and population heterogeneity.

We originally wanted to analyze C-reactive protein (CRP) at the same time. Since the early patients failed to perform CRP testing uniformly, the indicator failed to enter the analysis.

Conclusion

NLR and LMR was significant independent factors for OS, PLR was significant independent factors both for OS and PFS. NLR, LMR, PLR was significant corresponded to N stage.

Abbreviations

NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio; LDH: lactate dehydrogenase.
Declarations

Ethics approval and consent to participate

no consent was required due to the retrospective nature of this study

Consent for publication

Not applicable

Availability of data and materials

The data obtained in the study were available in the Yunnan Cancer Hospital Database

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

BY,HC were participate in the conception and initial design. LJ,YLB,BCW performed the clinical treatment of the penile cancer, HC,BY was a major contributor in writing the manuscript. HC,ZB,YY,LRQ were participate in articles search, review, data extract, statistical analysis. HC,WHY were participate in project development and pictures production.WQL,LYH,QY were participate in manuscript writing and revising. All authors read and approved the final manuscript.
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Table

| Variable          | NLR≤2.94 | NLR>2.94 | LMR≤4.74 | LMR>4.74 |
|-------------------|----------|----------|----------|----------|
| all               |          |          |          |          |
| A number of patients | 225      | 157      | 68       | 100      |
| Age(years)        | 50.56    | 49.94±12.96 | 51.9±14.47 | 0.296    | 51.94±13.64 | 49.45±1 |
| Tumor type        |          |          |          |          |
| benign tumor      | 44       | 35       | 9        | 0.026    | 17         |
| Well              | 96       | 69       | 27       | 39       |
| moderate          | 74       | 49       | 25       | 35       |
| poor/undifferentiated | 8         | 4        | 4        | 7        |
| others            | 3        | 0        | 3        | 2        |
| Anatomic stage | 0 | 1 | 2 | 3 |
|----------------|---|---|---|---|
|                | 44 | 67 | 39 | 62 |
|                | 33 | 51 | 28 | 41 |
|                | 9  | 16 | 11 | 21 |
|                |    |    |    |    |
| N              | 0  | 1  | 2  | 3  |
|                | 148| 28 | 36 | 13 |
|                | 112| 15 | 26 | 4 |
|                | 36 | 13 | 10 | 9  |
|                |    |    |    |    |
| M              | 0  | 1  |    |    |
|                | 222| 3  |    |    |
|                | 157| 0  |    |    |
|                | 65 | 3  |    |    |
|                |    |    |    |    |
| Primary treatment | | | | |
| surveillance  | 23 | 10 | 13 | |
| surgery       | 225| 147| 55 | |
| Recurrence | | | | |
| no            | 150| 113| 37 | |
| yes           | 75 | 44 | 31 | |
| Vital status | | | | |
| Alive         | 171| 131| 40 | |
| Dead          | 54 | 26 | 28 | |

Figures
Figure 1  
Kaplan-Meier curve of NLR for overall survival (OS)

Figure 2  
Kaplan-Meier curve of NLR for progression free survival (PFS)

Figure 3  
Kaplan-Meier curve of LMR for overall survival (OS) and 

Figure 4  
Kaplan-Meier curve of LMR for progression free survival (PFS)

Figure 5  
Kaplan-Meier curve of PLR for overall survival (OS)

Figure 6  
Kaplan-Meier curve of PLR for progression free survival (PFS)

Figure 7  
Kaplan-Meier curve of LDH for overall survival (OS)

Figure 8  
Kaplan-Meier curve of LDH for progression free survival (PFS)