Research Article

Huiming Gui, Yutong Song, Yongsheng Yin, Hanzhang Wang, Ronald Rodriguez, Zhiping Wang*

Prognostic value of preoperative inflammation-based predictors in patients with bladder carcinoma after radical cystectomy

https://doi.org/10.1515/med-2021-0277
received October 18, 2020; accepted March 24, 2021

Abstract

Aims – Emerging evidence has related inflammation-based biomarkers to numerous carcinomas, including bladder carcinoma (BC). However, the role of inflammatory biomarkers in the prognosis of BC remains inconclusive. This study aimed to compare preoperative plasma fibrinogen (PF) and other inflammatory biomarkers such as the platelet–lymphocyte ratio (PLR), neutrophil–lymphocyte ratio (NLR), lymphocyte–monocyte ratio (LMR), C-reactive protein (CRP) level, and serum albumin level to predict the prognosis of patients with BC.

Methods – This article focused on a retrospective analysis of 175 patients with newly diagnosed BC who were admitted to our hospital from March 2005 to March 2016. Of these BC patients, 136 had undergone radical cystectomy (RC).

Results – According to multivariate analysis, high PF level was an independent predictor of overall survival (OS) in 136 BC patients receiving RC (HR = 3.759; P = 0.011), but not for all 175 BC patients. Combining the NLR and PF values showed higher predictive accuracy for OS than NLR or PF alone (P < 0.05). Additionally, for 136 BC patients who had undergone RC, a close relationship was found between high PF levels (>3.39 g/L) and lymph node metastasis (P = 0.011).

Conclusions – The preoperative PF level may be a prognostic biomarker, and when combined with the NLR, it can improve the predictive ability of the survival of BC patients, particularly of BC patients who underwent RC.

Keywords: plasma fibrinogen, neutrophil–lymphocyte ratio, inflammatory biomarker, prognosis, bladder carcinoma

1 Introduction

Bladder carcinoma (BC) ranks 11th among all malignancies worldwide. Globally, the age-standardized incidence rates of BC (100,000 per person/year) are 9.0 for men and 2.2 for women; the age-standardized mortality rates (100,000 per person/years) are 3.2 for men versus 0.9 for women [1]. Approximately 70% of bladder tumours is confined to the mucosa (stage Ta and CIS) or submucosa (stage T1), and 30% is muscle-invasive BC ([MIBC]; T2–T4) [2]. Radical cystectomy (RC), the standard treatment of MIBC, is characterized by low mortality and an acceptable incidence of complications and is the first-choice treatment of T2–T4 BC at many institutions [3,4]. Although the survival rates of BC patients have improved in recent decades, still tumour recurrence and progression occur in many patients. The role of some prognostic factors, including the neutrophil–lymphocyte ratio (NLR), serum D-dimer, and plasma fibrinogen (PF), has been confirmed in BC [5,6]. However, thus far, most of these markers have not clinically been used because they have been ineffective in predicting the prognosis in patients. Additionally, biomarker analysis of pathologic specimens may allow for enhanced risk stratification and guide better prognostic evaluations for a more effective therapeutic strategy.
During human tumour development, inflammation plays a key role [7]. Current hypotheses suggest that the synthesis of inflammatory cytokines may be stimulated by the tumour microenvironment, resulting in increases in acute phase reactants and serum parameters involving lymphocytes and neutrophils [8]. The platelet–lymphocyte ratio (PLR), NLR, C-reactive protein (CRP) level, lymphocyte–monocyte ratio (LMR), albumin level, and PF level are emerging biomarkers of host inflammation in various malignancies [9–12]. However, few studies have simultaneously compared their prognostic value in BC patients.

Previous studies reported that many tissue- or urine-based markers can predict the prognosis of BC; most of these are based on PCR or immunohistochemical methods [13]. A promising, simple, and economical approach is ideal for future clinical assessments. The PF, NLR, LMR, PLR, CRP, and albumin values, which can easily be detected from the whole blood cell count, have been suggested as predictors and can estimate the magnitude of systemic inflammation in critically ill patients [14–17] and assess the survival outcomes of several solid malignancies [18–20].

As a marker of systemic inflammation, PF is often associated with haemostasis and plays a key role in tumour research [21,22]. The pretreatment PF level has been shown to predict oncologic outcomes for digestive system tumours, lung carcinoma, gynaecologic carcinoma, and glioblastomas, but studies of its prognostic value in BC are lacking [18,23–25]. Additionally, at this stage, the potential molecular mechanism of PF affecting tumorigenesis remains controversial. We aimed to determine the value of PF for predicting oncologic outcomes in BC patients compared with that of other inflammation-based indices (CRP and albumin) and cellular parameters (NLR, LMR, and PLR).

2 Patients and methods

2.1 Patients

The study was conducted from March 2005 to March 2016 and included 175 consecutive patients with pathologically confirmed BC and also included 136 BC patients who had undergone RC at a single academic hospital. Blood cells were counted 7 days before the surgery. The included criteria are as follows: (1) a confirmed BC histology, (2) a survival time after surgery of longer than 30 days, and (3) extensive follow-up data and medical records. Exclusion criteria included chronic inflammation, acute infection, or blood cell effects. Finally, 175 patients were included in the study. The study was approved by the Ethics Committee of the Second Hospital of Lanzhou University (Ethical Application number: 2016A-070). Each included patient was informed about the study in writing and agreed to the research agreement.

2.2 Clinicopathological features and follow-up

The clinicopathological records were reviewed to determine the tumour category and grade, clinical T stage, tumour diameter (<3 vs >3 cm), presence of comorbidities, history of adjuvant chemotherapy, lymphovascular invasion, radiotherapy focality, lymph node metastasis (LNM), and putative preoperative risk factors (preoperative PF, NLR, CRP, LMR, albumin, PLR, age at diagnosis, and gender). The tumour stage and grade were based on the 2004 TNM staging system and 1997 WHO classification, respectively. The follow-up data were obtained from telephone interviews, guardians, and patient files. The primary outcome of the study was overall survival (OS), which refers to the period from the time of surgery to the last visit or death from any cause. Patient follow-up was completed up to February 2021.

2.3 Optimal prognostic cutoff values for PF and NLR

We determined the optimal cutoff value using the minimum $p$ value method (Galon et al., 2006). Among the prognostic scores, the optimum cutoff values were 3.39 g/L for preoperative PF and 3.05 for preoperative NLR; and the areas under ROC curve (AUCs) corresponding to PF and NLR and representing the maximum values were 0.639 and 0.630, respectively (Figure S1). The patients were divided into two groups according to the ROC threshold. The higher group exhibited values greater than the optimal cutoff levels, whereas the lower group exhibited values less than the optimal cutoff levels. Among 175 patients, the corresponding median PF value and mean PF were 3.29 and 2.96 g/L, respectively. The median NLR and mean NLR values in 175 patients were 2.86 and 2.67, respectively. One hundred seventy-five patients were divided by CRP,
LMR, PLR, and albumin levels using the optimized cutoff values to predict OS, as derived from the ROC curve analysis (<3.06, >138, >5.0 mg/L, and <3.5 g/dL, respectively). The AUCs for LMR, CRP, PLR, and albumin regarding OS were 0.660 (95% CI: 0.624–0.695), 0.635 (95% CI: 0.587–0.650), 0.624 (95% CI: 0.586–0.655), and 0.652 (95% CI: 0.616–0.687), respectively.

### 2.4 Inflammatory parameters

Blood samples were collected by peripheral venous puncture between the diagnosis and initiation of treatment and were determined as follows: cell count ratios (PLR, NLR, and LMR), serum albumin levels, PF concentration, serum CRP, and individual cell counts (platelets, monocytes, neutrophils, and lymphocytes). Sample collections were usually performed 1 week before treatment initiation (median of 5 days; IQR = 2–8 days) as part of the routine pretreatment clinical assessment. The normal ranges for albumin, CRP, and fibrinogen were 0–0.5, 0–10, and 200–400 mg/dL, respectively.

### 2.5 Statistical analysis

Statistical analyses were performed using the log-rank test and Kaplan–Meier method. The association between OS and each clinicopathological variable was analysed using the multivariate Cox regression model and univariate Cox regression model. A P value less than 0.05 indicated a statistically significant level. Statistical analysis was performed using version 22.0 of the Statistical Package for the Social Sciences (SPSS Inc., New York, US).
3 Results

3.1 Patient characteristics

Among 175 BC patients, 136 patients had undergone RC. The proportion of male patients was much higher than that of female patients – 124 (70.9%) and 51 (29.1%), respectively. The average age of 175 patients at the time of treatment was 59.5 ± 6.7 years. The 5-year OS rate for 175 BC patients was 68.6%. Information on the treatment characteristics, clinical, and histopathology of these patients are provided in Table 1. The demographic characteristics of all 175 patients are shown in Table S1. Among 136 patients who had received RC, the demographic characteristics are shown in Table 3.

3.2 Univariate survival analysis of all prognostic parameters

We used univariate analysis to assess the risk of postoperative death in BC patients. During the univariate Cox analysis of OS, the following variables were statistically significant in 175 patients: clinical T stage (HR = 2.790; P < 0.001), pathological T stage (HR = 1.764; P = 0.017), LNM (HR = 3.529; P < 0.001), PF (HR = 2.372; P = 0.001), NLR (HR = 2.513; P = 0.001), PLR (HR = 2.458; P < 0.001), LMR (HR = 2.117; P = 0.002), CRP (HR = 2.639; P < 0.001), and albumin (HR = 2.153; P = 0.002; Table 1). However, in the subgroup of 135 BC patients who had undergone RC, PLR (HR = 1.400; P = 0.169) was not significant (Table 2).

Table 2: Univariate and multivariate analyses of characteristics associated with OS in 136 BC undergoing RC patients

| Characteristics | Univariate | Multivariate |
|-----------------|------------|--------------|
|                 | Hazard ratio | 95% CI     | P value | Hazard ratio | 95% CI     | P value |
| Age, years      |             |            |         |             |            |         |
| ≥60 vs <60      | 1.039       | 0.646–1.671| 0.874   |             |            |         |
| Gender          |             |            |         |             |            |         |
| Male vs Female  | 1.540       | 0.962–2.465| 0.072   |             |            |         |
| Clinical T stage|             |            |         |             |            |         |
| >T2 vs ≤T2      | 2.018       | 1.235–3.299| 0.005   | 1.825       | 1.108–3.007| 0.018   |
| Pathological grade|           |            |         |             |            |         |
| G2–G3 vs G1     | 2.518       | 1.526–4.156| <0.001  |             |            |         |
| Histological subtype|         |            |         |             |            |         |
| UBC vs Non-UBC  | 1.309       | 0.669–2.562| 0.431   |             |            |         |
| LNM             |             |            |         |             |            |         |
| Yes vs No       | 3.350       | 1.929–5.820| <0.001  | 2.409       | 1.354–4.286| 0.003   |
| PF              |             |            |         |             |            |         |
| ≥3.39 vs <3.39 g/L| 2.591     | 1.459–4.602| 0.001   | 3.759       | 1.360–10.390| 0.011  |
| LNR             |             |            |         |             |            |         |
| ≥3.05 vs <3.05  | 2.353       | 1.414–3.925| 0.001   | 4.337       | 1.426–13.191| 0.010  |
| LMR             |             |            |         |             |            |         |
| <3.06 vs ≥3.06  | 2.537       | 1.525–4.219| <0.001  |             |            |         |
| PLR             |             |            |         |             |            |         |
| ≥138 vs <138    | 1.400       | 0.867–2.262| 0.169   |             |            |         |
| CRP             |             |            |         |             |            |         |
| ≥5.0 vs <5.0 mg/L| 3.139     | 1.863–5.289| <0.001  |             |            |         |
| Serum albumin   |             |            |         |             |            |         |
| ≥3.5 vs <3.5 g/dL| 3.089     | 1.797–5.311| <0.001  |             |            |         |
| PF + NLR        |             |            |         |             |            |         |
| PF high + NLR high vs PF low + NLR low | 4.896 | 1.902–12.937| 0.001 | 0.264 | 0.077–0.906| 0.034 |

*P* values that achieved statistical significance (*P* < 0.05) are indicated in boldface. Abbreviations: CRP = C-reactive protein; LMR = lymphocyte–monocyte ratio; LNM = lymph node metastasis; NLR = neutrophil–lymphocyte ratio; PF = plasma fibrinogen; PLR = platelet–lymphocyte ratio; UBC = urothelial bladder carcinoma.
Table 3: Clinicopathological features of 136 BC undergoing RC patients stratified by PF and NLR

| Characteristic                      | Total n = 136 (%) | PF | NLR |
|-------------------------------------|-------------------|----|-----|
|                                     |                   | <3.39 g/L | ≥3.39 g/L | P value | <3.05 | ≥3.05 | P value |
| Age (years), n (%)                  |                   |     |     |        |       |       |       |
| <60                                 | 59                | 20  | 39  | 0.987  | 31    | 46    | 0.804 |
| ≥60                                 | 77                | 26  | 51  |         | 25    | 34    |       |
| Gender, n (%)                       |                   |     |     |        |       |       |       |
| Male                                | 101               | 33  | 68  | 0.630  | 45    | 56    | 0.189 |
| Female                              | 35                | 13  | 22  |         | 11    | 24    |       |
| Clinical T stage, n (%)             |                   |     |     |        |       |       |       |
| T2                                  | 63                | 28  | 35  | 0.015  | 32    | 31    | 0.034 |
| T3                                  | 43                | 12  | 31  |         | 16    | 27    |       |
| T4                                  | 30                | 6   | 24  |         | 8     | 22    |       |
| Pathological grade, n (%)           |                   |     |     |        |       |       |       |
| G1                                  | 67                | 27  | 40  | 0.116  | 33    | 34    | 0.059 |
| G2                                  | 40                | 14  | 26  |         | 15    | 25    |       |
| G3                                  | 29                | 5   | 24  |         | 8     | 21    |       |
| Histological subtype, n (%)         |                   |     |     |        |       |       |       |
| UBC                                 | 113               | 37  | 76  | 0.555  | 45    | 68    | 0.477 |
| Non-UBC                             | 23                | 9   | 14  |         | 11    | 12    |       |
| LNM, n (%)                          |                   |     |     |        |       |       |       |
| No                                  | 65                | 29  | 36  | 0.011  | 27    | 38    | <0.001|
| Yes                                 | 71                | 17  | 54  |         | 18    | 53    |       |
| NLR                                 |                   |     |     |        |       |       |       |
| ≥3.05                               | 80                | 18  | 62  | 0.001  |       |       |       |
| <3.05                               | 56                | 28  | 28  |         |       |       |       |

P values that achieved statistical significance (P < 0.05) are indicated in boldface. Abbreviations: LNM = lymph node metastasis; NLR = neutrophil–lymphocyte ratio; PF = plasma fibrinogen; UBC = urothelial bladder carcinoma.

3.3 Multivariate analysis of all prognostic parameters

Univariate values with P values less than 0.05 and prognostic factors were included in the multivariate analysis (Table 1). The NLR (HR = 4.419; P = 0.004), clinical T stage (HR = 2.320; P = 0.002), LNM (HR = 1.869; P = 0.035), and PF + NLR (HR = 0.294; P = 0.041) were independently associated with OS in all the patients. Additionally, the NLR (HR = 4.337; P = 0.010), clinical T stage (HR = 1.825; P = 0.018), PF (HR = 3.759; P = 0.011), PF + NLR (HR = 1.955; P = 0.003), and LNM (HR = 2.409; P = 0.003) were identified as independent prognostic factors of OS in those who had received RC treatment.

Kaplan–Meier analyses stratified by PF (Figure 1a and d) and NLR (Figure 1b and e) values showed that the elevation in these inflammation-based factors resulted in worse outcomes in all BC patients and those who had undergone RC. Dichotomization by the PF level demonstrated outcome differences among all the patients (5-year OS of 59.6% [PF high] vs 83.3% [PF low]), compared with dichotomization by the NLR value (5-year OS of 60.7% [NLR high] vs 82.5% [NLR low]). These results were similar to the subgroup of BC patients who had undergone RC, with estimated cumulative 5-year OS rates of 52.2% (PF high) and 78.3% (PF low) vs 50.0% (NLR high) and 76.8% (NLR low).

3.4 Associations of PF and NLR with clinicopathological factors in 136 BC patients following RC

The values of the clinicopathological variable were compared with the preoperative PF and NLR levels. LNM (P = 0.011) and an advanced clinical T stage (P = 0.015) were significantly correlated with a high PF level (≥3.39 g/L) in BC patients following RC (all Ps < 0.05; Table 3). LNM (P < 0.001) and an advanced clinical T stage (P = 0.034) were significantly correlated with a high NLR value (≥3.05) in BC patients following RC (Table 3). Additionally, a significant positive correlation was found between a high PF level and a high NLR before surgery (P = 0.001; Table 3).
3.5 Prognostic significance of the combination of PF and NLR

The results suggest a significant positive association between PF and NLR in 136 BC who had undergone RC ($P = 0.001$). The combination of NLR and PF can improve the stratification of BC patients. Therefore, we divided the BC patients into PF high and NLR high, NLR high or PF high, and NLR low and PF low, representing high-risk, intermediate-risk, and low-risk groups, respectively (Figure 1c and f). The 5-year OS rates of 175 BC patients in the high-, medium-, and low-risk groups were 59.5, 62.3, and 97.4%, respectively. Similarly, the 5-year OS rates in 136 BC patients following RC were 50.0, 54.3, and 96.4%, respectively. In the multivariate model (Tables 1 and 2), both the high- and medium-risk groups showed lower OS rates than the low-risk group.

4 Discussion

BC is a heterogeneous urological neoplasm with different recurrence and progression rates [1]. Improved understanding of the molecular biology of BC has evolved how localized and advanced diseases are diagnosed and treated. The surgical treatment transurethral resection of bladder tumor and intravesical Bacillus Calmette-Guérin are applied for intermediate- and high-risk non-MIBC; the therapeutic options for muscle-invasive and advanced disease have expanded to neoadjuvant treatment [2,26]. However, controversy persists regarding which neoadjuvant treatment should be applied to certain patients, particularly those with intermediate- to high-risk muscle-invasive and advanced disease [27]. Thus, several predictors are required to provide additional support to determine which treatment groups should be applied in a specific high-risk group [28].
Recently, several inflammation-based biomarkers (e.g., albumin, CRP, NLR and PLR) have been associated with treatment outcomes in primary operable tumours [29,30]. Most studies have demonstrated the key role of neutrophils and fibrinogen in systemic inflammation. Increased numbers of neutrophils and fibrinogen indicate the presence of high-risk solid tumours [31,32].

Our data indicated the following: (1) high NLR and PF levels predict a lower survival rate of BC patients; (2) high NLR and PF levels are associated with a more aggressive clinical stage and LNM status in BC patients; (3) PF is a superior prognostic factor compared with the LMR, PLR, CRP, and albumin values in 136 BC patients who had undergone RC; (4) combining NLR and PF levels may improve the precision of survival outcome prediction in BC patients following RC.

The biological mechanism of PF explains its prognostic significance in BC. Many in vitro studies have verified that fibrinogen promotes carcinoma cell proliferation, angiogenesis, invasion, epithelial-to-mesenchymal transition (EMT), and haematogenous dissemination; therefore, it plays an important role in tumour development [33–35]. Other studies have found that fibrinogen binds to secreted growth factors, such as inhibition of apoptosis and members of the platelet-derived growth factor family, and induces tumour cell adhesion, vascular endothelial growth factor, metastasis, and fibroblast growth factor (FGF) families [36]. Furthermore, studies using cell line models have shown that fibrinogen may promote carcinoma cell motility by inducing the EMT via the p-AKT/p-mTOR pathway [37]. Additionally, in vitro studies reported that tumour cells can produce endogenous fibrinogen and the combination of FGF-2 and fibrinogen can stimulate the proliferation of endothelial cells, leading to enhanced angiogenesis [38,39].

A high NLR level is closely correlated with aggressive clinical features and is a significant risk factor affecting survival in BC patients. Neutrophils reflect a state of host inflammation, which can contribute to carcinoma onset [40]. They are involved in different stages of the tumour process, such as tumorigenesis, growth, proliferation, or metastasis [41,42]. Interestingly, the receptor tyrosine kinase MET is induced by tumour-derived tumour necrosis factor-α or other inflammatory stimuli in human neutrophils [43]. Finally, neutrophils also promote metastasis spreading by suppressing natural killer function and enhancing the extravasation of carcinoma cells [44,45]. Therefore, the prognostic value of plasma neutrophils as an independent factor or as a part of the NLR in carcinomas is evident because they promote neutrophil responses and/or lymphocyte suppression, leading to a high NLR, a suppressed anti-tumour immune response, and enhanced metastasis [46,47].

Inflammation, as a hallmark of carcinoma, affects all stages of tumorigenesis. Inflammmasomes are a large complex of NOD-like receptors called NLRS, which have been identified as vital regulators in inflammation-related carcinogenesis, angiogenesis, metastasis, oxidative stress, cancer cell transformation, and chemoresistance [48,49]. The activity of NLRS is directly regulated by some miRNAs [50,51]. This suggests that the questing or synthesis of valuable chemotherapeutic drugs targeting these miRNAs could be a promising strategy for the treatment of BC.

Combining the PF level and NLR resulted in the lowest 5-year OS for patients in the PF high and NLR high groups. This finding further supports that high NLR and PF are related to the inflammatory response in BC patients, leading to an adverse outcome and further confirming that NLR correlates positively with PF. Additionally, this finding emphasizes that combining NLR and PF can better predict the prognosis in BC patients who have undergone RC than NLR or PF alone.

Our study has limitations. The first limitation is that our study is a retrospective analysis, and inherent choice bias cannot be eliminated. Additionally, our study evaluated a Chinese population; thus, the results cannot be generalized to other ethnic groups. More adequately designed prospective studies are required to further assess the BC patients.

In conclusion, the present study is the first to demonstrate that the PF level is an independent prognostic marker for predicting OS in BC patients who undergo RC. Additionally, the combination of PF and NLR can improve the prognostic accuracy and be used as a selection criterion for stratified treatment of risk factors in patients with BC.

Funding information: No funds.

Author contributions: H. G., Y. S., and Y. Y. designed the study and collected data. H.W., R. R., and Z. W. analyzed the data. H. G., Y. S., and Z. W. wrote the manuscript. H. G., Y. S., and Z. W. reviewed and edited the manuscript. All authors read and approved the final manuscript.

Conflict of interest: The authors declare that there are no conflicts of interest in this work.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] Babjuk M, Burger M, Comperat EM, Gontero P, Mostafid AH, Palou J, et al. European association of urology guidelines on
non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) – 2019 update. Eur Urol. 2019;76(5):639–57.
[2] Lenis AT, Lec PM, Chami K, Mshs MD. Bladder cancer: a review. JAMA. 2020;324(19):1980–91.
[3] Allfrangis C, McGovern U, Freeman A, Powles T, Linch M. Molecular and histopathology directed therapy for advanced bladder cancer. Nat Rev Urol. 2019;16(8):465–83.
[4] Cochetti G, Barillaro F, Boni A, Meanini E. Immediate radical cystectomy for massive bleeding of bladder cancer. Biomed Res Int. 2015;2015:154392.
[5] Li X, Shu K, Zhou J, Yu Q, Cui S, Liu J, et al. Preoperative plasma fibrinogen and D-dimer as prognostic biomarkers for non-muscle-invasive bladder cancer. Clin Genitourin Cancer. 2020;18(1):11–9e1.
[6] Nabavizadeh R, Bobrek K, Master VA. Risk stratification for bladder cancer: biomarkers of inflammation and immune activation. Urol Oncol. 2020;38(9):706–12.
[7] Qian BZ. Inflammation fires up cancer metastasis. Semin Cancer Biol. 2017;47:170–6.
[8] Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014;15(11):e493–503.
[9] Brkic FF, Kadletz L, Jank B, Mayer C, Heiduschka G, Brunner M. Impact of pretherapeutic neutrophil-to-lymphocyte ratio, serum albumin, body-mass index, and advanced lung cancer inflammation index on clinical outcome in sinusonal squamous cell carcinoma. J Cranio maxillofac Surg. 2020;48(1):33–7.
[10] Bruserud O, Aarstad HH, Tvedt THA. Combined C-reactive protein and novel inflammatory parameters as a predictor in cancer—what can we learn from the hematological experience? Cancers (Basel). 2020;12(7):1966.
[11] Kuzucu I, Guler I, Kum RO, Baklaci D, Ozcan M. Increased neutrophil lymphocyte ratio and platelet lymphocyte ratio in malignant parotid tumors. Braz J Otorhinolaryngol. 2020;86(1):105–10.
[12] Xu K, Li J, Hu M, Zhang H, Yang J, Gong H, et al. Prognostic significance of preoperative inflammatory biomarkers and traditional clinical parameters in patients with spinal metastasis from clear cell renal cell carcinoma: a retrospective study of 91 patients in a single center. Cancer Manag Res. 2020;12:59–70.
[13] Lucca I, de Martino M, Klatte T, Shariat SF. Novel biomarkers to predict response and prognosis in localized bladder cancer. Urol Clin North Am. 2015;42(2):225–33.
[14] Dimpfl CE, Kalsch T, Elmas F, Suvaits N, Lucke T, Munch E, et al. Impact of fibrinogen concentration in severely ill patients on mechanical properties of whole blood clots. Blood Coagul Fibrinolysis. 2008;19(8):765–70.
[15] Djordjevic D, Rondovic G, Surbatovic M, Stanojevic I, Udovicic I, Andjelic T, et al. Neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume-to-platelet count ratio as biomarkers in critically ill and injured patients: which ratio to choose to predict outcome and nature of bacteremia? Mediators Inflamm. 2018;2018:3758068.
[16] Jonsson N, Nilsen T, Gille-Johnson P, Bell M, Martling CR, Larsson A, et al. Calprotectin as an early biomarker of bacterial infections in critically ill patients: an exploratory cohort assessment. Crit Care Resusc. 2017;19(3):205–13.
[17] Ryu JA, Bang OY, Lee GH. D-dimer levels and cerebral infarction in critically ill cancer patients. BMC Cancer. 2017;17(1):591.
[18] Lin Y, Liu Z, Qiu Y, Zhang J, Wu H, Liang R, et al. Clinical significance of plasma D-dimer and fibrinogen in digestive cancer: a systematic review and meta-analysis. Eur J Surg Oncol. 2018;44(10):1494–503.
[19] Dolan RD, Lim J, McSorley ST, Horgan PG, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: Systematic review and meta-analysis. Sci Rep. 2017;7(1):16717.
[20] Dolan RD, McSorley ST, Horgan PG, Laird B, McMillan DC. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: Systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017;116:134–46.
[21] Palumbo JS, Degen JL. Mechanisms coupling the hema tostatic system to colitis-associated cancer. Thromb Res. 2010;125(Suppl 2):S39–43.
[22] Allin KH, Bojesen SE, Nordestgaard BG. Inflammatory biomarkers and risk of cancer in 84,000 individuals from the general population. Int J Cancer. 2016;139(7):1493–500.
[23] Zhang K, Xu Y, Tan S, Wang X, Du M, Liu L. The association between plasma fibrinogen levels and lung cancer: a meta-analysis. J Thorac Dis. 2019;11(11):4492–500.
[24] Wang PF, Meng Z, Song HW, Yao K, Duan ZJ, Li SW, et al. Higher plasma fibrinogen levels are associated with malignant phenotype and worse survival in patients with glioblastomas. J Cancer. 2018;9(11):2024–9.
[25] Li W, Wang YR, Song W, Chang W, Guo X, Liu Y, et al. The changes of plasma coagulation function in patients with glioma and its correlation with malignant grade of glioma. Zhonghua Yi Xue Za Zhi. 2018;98(5):336–9.
[26] Poli G, Cochetti G, Boni A, Egidio MG, Brancorsini S, Mearini E. Characterization of inflammasome-related genes in urine sediments of patients receiving intravesical BCG therapy. Urol Oncol. 2017;35(12):674e19–e24.
[27] Brausi M, Witjes JA, Lamm D, Persad R, Palou J, Colombel M, et al. A review of current guidelines and best practice recommendations for the management of nonmuscle invasive bladder cancer by the International bladder cancer group. J Urol. 2013;186(6):2158–67.
[28] Kamat AM, Vlahou A, Taylor JA, Hudson ML, Pesch B, Ingersoll MA, et al. Considerations on the use of urine markers in the management of patients with high-grade non-muscle-invasive bladder cancer. Urol Oncol. 2014;32(7):1069–77.
[29] Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6(1):149–63.
[30] Vartolomei MD, Porav-Hodade D, Ferro M, Mathieu R, Abufaraj M, Foerster B, et al. Prognostic role of pretreatment neutrophil-to-lymphocyte ratio (NLR) in patients with non-muscle-invasive bladder cancer (NMIBC): a systematic review and meta-analysis. Urol Oncol. 2018;36(9):389–99.
[31] Cao X, Zhou Y, Mao F, Lin Y, Sun Q. Combination of preoperative fibrinogen concentration and neutrophil-to-lymphocyte ratio for prediction of the prognosis of patients with resectable breast cancer. Oncol Lett. 2020;20(5):200.
[32] Yamamoto M, Kurokawa Y, Kobayashi N, Takahashi T, Miyazaki Y, Tanaka K, et al. Prognostic value of the combined
index of plasma fibrinogen and the neutrophil-lymphocyte ratio in gastric cancer. World J Surg. 2020;44(1):207–12.

[33] Staton CA, Brown NJ, Lewis CE. The role of fibrinogen and related fragments in tumour angiogenesis and metastasis. Expert Opin Biol Ther. 2003;3(7):1105–20.

[34] Steinbrecher KA, Horowitz NA, Blevins EA, Barney KA, Shaw MA, Harmel-Laws E, et al. Collis-associated cancer is dependent on the interplay between the hemostatic and inflammatory systems and supported by integrin alpha(M)/beta(2) engagement of fibrinogen. Cancer Res. 2010;70(7):2634–43.

[35] Shu YJ, Weng H, Bao RF, Wu XS, Ding Q, Cao Y, et al. Clinical and prognostic significance of preoperative plasma hyperfibrinogenemia in gallbladder cancer patients following surgical resection: a retrospective and in vitro study. BMC Cancer. 2014;14:566.

[36] Martino MM, Briqez PS, Ranga A, Lutolf MP, Hubbell JA. Heparin-binding domain of fibrinogen binds growth factors and promotes tissue repair when incorporated within a synthetic matrix. Proc Natl Acad Sci U S A. 2013;110(12):4563–8.

[37] Zhang F, Wang Y, Sun P, Wang ZQ, Wang DS, Zhang DS, et al. Fibrinogen promotes malignant biological tumor behavior involving epithelial-mesenchymal transition via the p-AGK/p-mTOR pathway in esophageal squamous cell carcinoma. J Cancer Res Clin Oncol. 2017;143(12):2413–24.

[38] Sahni A, Khorana AA, Bagg RB, Peng H, Francis CW. FGF-2 binding to fibrinogen is required for augmented angiogenesis. Blood. 2006;107(1):126–31.

[39] Sahni A, Simpson-Haidaris PJ, Sahni SK, Vadany GG, Francis CW. Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2). J Thromb Haemost. 2008;6(1):176–83.

[40] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646–74.

[41] Swierczak A, Mouchemore KA, Hamilton JA, Anderson RL. Neutrophils: important contributors to tumor progression and metastasis. Cancer Metastasis Rev. 2015;34(4):735–51.

[42] Coffelt SB, Wellenstei MD, de Visser KE. Neutrophils in cancer: neutral no more. Nat Rev Cancer. 2016;16(7):431–46.

[43] Finisguerra V, Di Conza G, Di Matteo M, Serrone J, Costa S, Thompson AA, et al. MET is required for the recruitment of anti-tumoural neutrophils. Nature. 2015;522(7556):349–53.

[44] Welch DR, Schissel DJ, Howrey RP, Aeed PA. Tumor-elicted polymorphonuclear cells, in contrast to “normal” circulating polymorphonuclear cells, stimulate invasive and metastatic potentials of rat mammary adenocarcinoma cells. Proc Natl Acad Sci U S A. 1989;86(15):5859–63.

[45] Spiegel A, Brooks MW, Houshyar S, Reinhardt F, Ardolino M, Fessler E, et al. Neutrophils suppress intraluminal NK cell-mediated tumor cell clearance and enhance extravasation of disseminated carcinoma cells. Cancer Discov. 2016;6(6):630–49.

[46] Lecot P, Sarabi M, Pereira Abrantes M, Mussard J, Koenderman L, Caux C, et al. Neutrophil heterogeneity in cancer: from biology to therapies. Front Immunol. 2019;10:2155.

[47] Ocana A, Nieto-Jimenez C, Pandiella A, Templeton AL. Neutrophils in cancer: prognostic role and therapeutic strategies. Mol Cancer. 2017;16(1):137.

[48] Liu P, Li Z, Liu L, Li R, Liang Z, Shen M, et al. NOD-like receptor signaling in inflammation-associated cancers: from functions to targeted therapies. Phytomedicine. 2019;64:052925.

[49] Poli G, Brancorsini S, Cochetti G, Barillaro F, Egidi MG, Mearini E. Expression of inflammasome-related genes in bladder cancer and their association with cytokeratin 20 messenger RNA. Urol Oncol. 2015;33(12):505e1–7.

[50] Poli G, Egidi MG, Cochetti G, Brancorsini S, Mearini E. Relationship between cellular and exosomal miRNAs targeting NOD-like receptors in bladder cancer: preliminary results. Minerva Urol Nefrol. 2020;72(2):207–13.

[51] Mearini E, Poli G, Cochetti G, Boni A, Egidi MG, Brancorsini S. Expression of urinary miRNAs targeting NLRs inflammasomes in bladder cancer. Onco Targets Ther. 2017;10:2665–73.
Appendix

Figure S1: The ROC curves of NLR (a) and PF (b) for overall survival (OS) in bladder carcinoma.

Table S1: Clinicopathological features of 175 BC patients stratified by PF and NLR

| Characteristic                  | Total n = 175 (%) | PF          | NLR          |
|--------------------------------|-------------------|-------------|--------------|
|                                | <3.39g/L | ≥3.39g/L | P-value | <3.05 | ≥3.05 | P-value |
| Age (years, n (%))             |          |          |         |       |       |         |
| <60                            | 74       | 28       | 46      | 0.875 | 28    | 46      | 0.750   |
| ≥60                            | 101      | 35       | 66      | 0.930 | 35    | 66      | 0.750   |
| Gender, n (%)                  |          |          |         |       |       |         |
| Male                           | 124      | 54       | 70      | 0.160 | 56    | 68      | 0.089   |
| Female                         | 51       | 12       | 39      | 0.160 | 7     | 44      |         |
| Clinical T stage, n (%)        |          |          |         |       |       |         |
| Ta-1                           | 35       | 13       | 22      | 0.005 | 15    | 20      | 0.082   |
| T2                             | 60       | 28       | 32      | 0.005 | 25    | 35      | 0.082   |
| T3                             | 46       | 15       | 31      | 0.005 | 14    | 32      | 0.082   |
| T4                             | 34       | 10       | 24      | 0.005 | 9     | 25      | 0.082   |
| Pathological grade, n (%)      |          |          |         |       |       |         |
| G1                             | 70       | 30       | 40      | 0.318 | 33    | 37      | 0.737   |
| G2                             | 48       | 18       | 30      | 0.318 | 15    | 33      | 0.737   |
| G3                             | 57       | 18       | 39      | 0.318 | 15    | 42      |         |
| Histological subtype, n (%)    |          |          |         |       |       |         |
| UBC                            | 147      | 55       | 92      | 0.835 | 53    | 94      | 0.973   |
| Non-UBC                        | 28       | 11       | 17      |       | 10    | 18      |         |
| LNM, n (%)                     |          |          |         |       |       |         |
| No                             | 104      | 29       | 36      | 0.011 | 51    | 53      | <0.001  |
| Yes                            | 71       | 17       | 54      | 0.011 | 12    | 59      |         |

P-values that achieved statistical significance (p < 0.05) are indicated in bold. Abbreviations: LNM = lymph node metastasis; NLR = neutrophil-lymphocyte ratio; PF = plasma fibrinogen; UBC = urothelial bladder carcinoma.