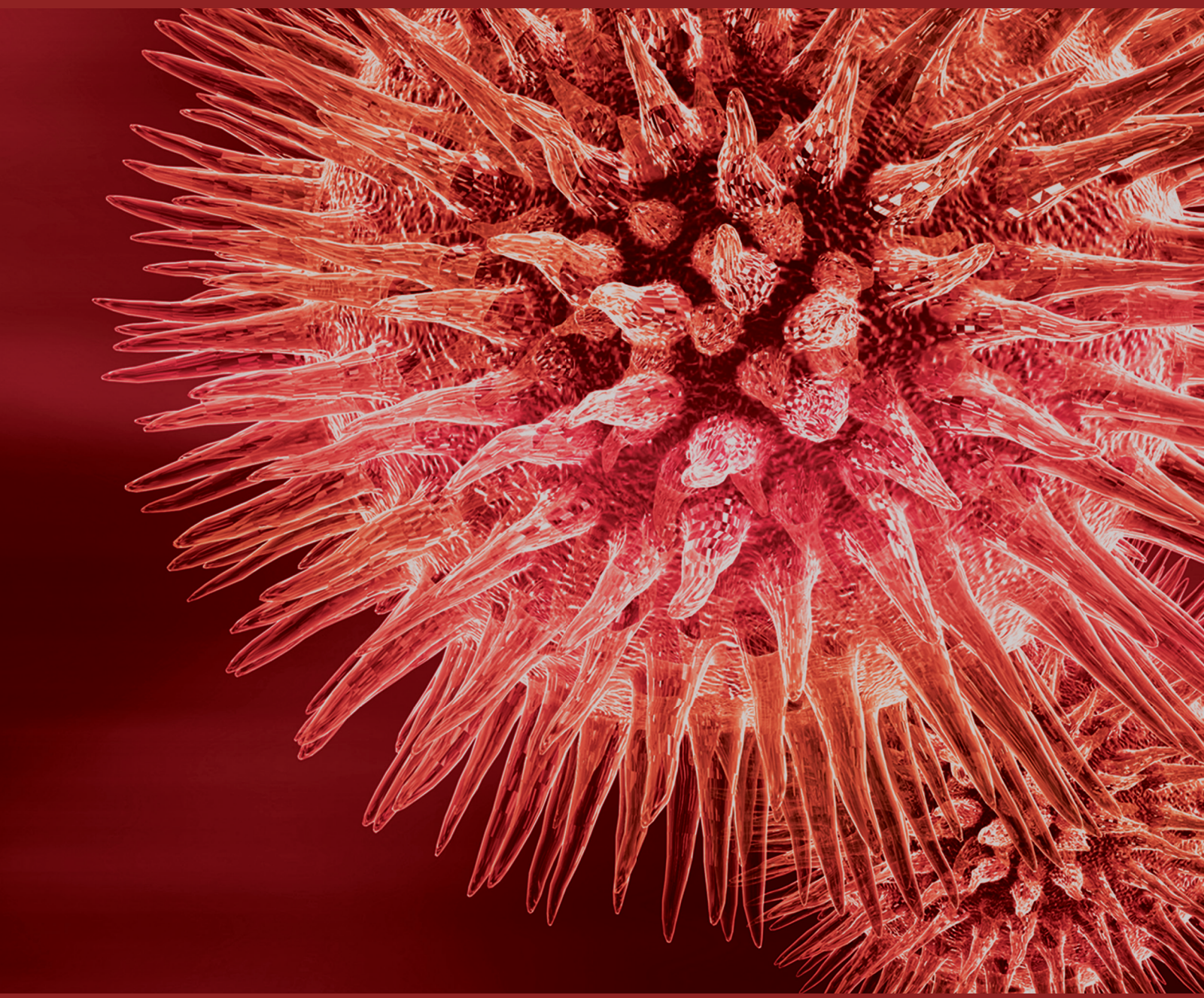
BioMed Research International

New Insights into Diagnosis and Treatment of Renal Cell Carcinoma, Bladder Cancer, and Prostate Cancer

Guest Editors: Piotr L. Chlosta, Tomasz Golabek, and Péter Nyirády



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Editorial

New Insights into Diagnosis and Treatment of Renal Cell Carcinoma, Bladder Cancer, and Prostate Cancer

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In recent years, substantial changes in urological cancer-related mortality have occurred. These have resulted from therapeutic improvements of prostatic cancer, decreased exposure to tobacco smoking, and occupational carcinogens of bladder and possibly kidney cancers. Despite improved primary prevention, detection, and treatment, the incidence of age-related cancers of the urinary tract is likely to rise as a result of global population ageing. Therefore, it is vital to identify and address the most relevant targets for further early detection, investigation, and therapy of urological malignancies.

In keeping with this spirit, this special issue brings articles that investigated clinical and prognostic significance of several factors in the three most common urological cancers: renal cell carcinoma, prostate cancer, and bladder cancer.

G. Ji et al. in their report analysed pathological features of 2,929 men diagnosed with prostate cancer within different age groups including patients older than 75 years of age. They found that both patients aged ≤55 years and >75 years are more likely to be diagnosed with more aggressive disease. These findings have certain consequences including more aggressive treatment of the disease also in elderly healthy men and bring us into opposition with supporters of nonradical management of prostate cancer in older men.

Two research articles are dedicated to the prognostic role of blood-derived factors in patients with renal cell carcinoma. Y. Tian et al. in their systematic review and meta-analysis provide an evidence for elevated plasma fibrinogen to be adversely associated with overall, cancer-specific, and disease-free survival. S.-S. Byun et al. assessed the prognostic significance of preoperative neutrophil-to-lymphocyte ratio in nonmetastatic renal cell carcinoma. Their findings showed that the investigated parameter was associated with worse clinical tumour behavior, and it was a significant prognostic factor for both recurrence-free and cancer-specific survival in that group of patients.

Predictors of short- and long-term deterioration in renal function after partial nephrectomy in patients with renal cell carcinoma or benign tumour with or without preoperative predisposition to chronic kidney disease were studied by S. H. Kim et al. Their findings confirmed our understanding that abnormal preoperative renal function is associated with long-term deterioration of renal function and also indicated the baseline state of the renal function as the predominant factor affecting the postoperative functional outcome more than other determinants including partial nephrectomy procedure or renal cell carcinoma itself.

Urothelial bladder cancer remains a lethal malignancy in a significant proportion of advanced cases; thus more useful and reliable biomarkers that provide additional prognostic information are needed. In the quest for the better prognosticator in that group of patients, for the first time S. Ohtake et al. evaluated an impact of neutrophil-to-lymphocyte ratio in patients with advanced bladder cancer who received gemcitabine and nedaplatin therapy. Their findings suggest that this simple biomarker may serve as a new biomarker to predict responses to chemotherapy in advanced bladder cancer patients.

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Research Article

Are the Pathological Characteristics of Prostate Cancer More Aggressive or More Indolent Depending upon the Patient Age?

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Purpose. To identify pathological characteristics of prostate cancer according to patient age at diagnosis. *Methods*. A retrospective review of 2,929 men diagnosed with prostate cancer was performed. Pathological characteristics were compared across age groups: ≤55, 56–75, and >75 years. *Results*. The study cohort included 133 patients (4.5%), 2,033 patients (69.5%), and 763 patients (26.0%) in the three age groups, respectively. The median pathological Gleason sums in the three age groups were 8, 7, and 8, respectively. The Gleason sum, primary Gleason score, and second primary Gleason score were significantly different among the three age groups ($Z = 12.975$, $p = 0.002$; $Z = 9.264$, $p = 0.010$; $Z = 6.692$, $p = 0.035$, resp.). The percentages of Gleason pattern 5 tumors for the three age groups were 44.4%, 32.3%, and 36.8%, respectively; they were significantly different ($\chi^2 = 11.641$, $p = 0.003$). The percentages of tumors with Gleason score grade groups 3–5 for the three age groups were 66.9%, 60.5%, and 66.3%, respectively; they were significantly different ($\chi^2 = 9.401$, $p = 0.009$). *Conclusions*. The present study indicated that men aged ≤55 years or >75 years show higher levels of clinically significant prostate cancer compared to patients between the ages of 55 and 75 years. Younger and more elderly male patients are more likely to have a more aggressive disease.

1. Introduction

Prostate cancer is considered a disease of older men and is infrequently reported in patients aged 55 years or younger [1]. However, presently over 10% of new cases of prostate cancer in the US occur in men aged 55 years or younger [2]. Compared with those in older men, the pathological characteristics of prostate cancer in patients 55 years or younger appear to be significantly different [3]. However, limited information is currently available on the pathological features of prostate cancer in younger men. Radical prostatectomy is recommended as the standard treatment modality for early stage prostate cancer in men aged 75 years or younger with a life expectancy of more than 10 years [4, 5]. However, patients over the age of 75 years with prostate cancer are more likely to receive treatment recommendations of primary hormonal therapy [6]. In addition, the pathological features of prostate cancer in elderly patients are different from those of other age cohorts.

It is widely accepted that prostate cancer comprises aggressive and indolent varieties. Indolent prostate cancer may exist for a long period without causing any symptoms or death. In contrast, aggressive prostate cancer may cause symptoms and lead to cancer-specific mortality. However, there is no consensus regarding the indolent or aggressive pathological characteristics of prostate cancer in younger or elderly patients with prostate cancer. To our knowledge, there is a lack of research reports regarding the main clinical and pathological characteristics of prostate cancer among different age groups. Thus, the aim of this retrospective study

was to ascertain the differences in prostate cancer among different age groups, improve the accuracy of clinical diagnosis, and assist in treatment decisions.

2. Materials and Methods

2.1. Study Population and Design. A retrospective review of the pathological features of patients diagnosed with prostate cancer in the Department of Urology, Peking University First Hospital (Institute of Urology, Peking University, National Urological Cancer Center of China) from January 2001 to June 2016 was performed. All patients were pathologically diagnosed with prostate cancer via prostate biopsy and have not received any form of hormonal therapy or radiotherapy before biopsy. Accordingly, all the Gleason score information of patients was obtained from biopsy specimen. The ethics committee of the Peking University First Hospital approved this study.

Patients were stratified by age at the diagnosis into the following groups: ≤55 years (Group 1, young men), 56–75 years (Group 2, middle-aged and old men), and >75 years (Group 3, very old men). Pathological characteristics (Gleason sum, primary Gleason score, second primary Gleason score, and percent of Gleason pattern 5) were compared among the three groups. A new grading system, proposed by the International Society of Urological Pathology (ISUP) in 2014, has been incorporated in the new 2016 World Health Organization (WHO) prostate cancer reporting guidelines. The pathological characteristics of prostate biopsy can be classified into five distinct grade groups on the basis of the new grading system as follows: grade group 1 = Gleason score ≤ 6; grade group 2 = Gleason score 3 + 4 = 7; grade group 3 = Gleason score 4 + 3 = 7; grade group 4 = Gleason score 4 + 4 = 8; and grade group 5 = Gleason scores 9 and 10. Clinically significant prostate cancer is defined as grade groups 3–5. Comparisons were also made in the present study among the three age groups in the proportions of grade group 1-2 and grade group 3–5 tumors according to the newest grading system.

2.2. Statistical Analysis. All analyses were codified and performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Pathological features were compared across age groups using the Kruskal-Wallis test, and statistical significance was set at a p value < 0.05. ANOVA tests were applied to analyze the difference of median age between each of the Gleason grade groups. Further comparisons (Group 1 versus Group 2; Group 2 versus Group 3) were performed using the Mann-Whitney-Wilcoxon test and the significance level was set at $p < 0.025$. Pearson's chi-square test was applied to compare the percentage of Gleason pattern 5 and the percentage of Gleason score grade groups 3–5 among the age groups. A p value < 0.05 was considered significant.

3. Results and Discussion

3.1. Results. A total of 2,929 men were pathologically diagnosed with prostate cancer in our institution between January 2001 and June 2016. Of the 2,929 men evaluated, 133 (4.5%) were in Group 1 (≤55 years, young men); 2,033 (69.5%) were in Group 2 (56–75 years, middle-aged and old men); and 763 (26.0%) were in Group 3 (>75 years, very old men). More clinical information of all patients is shown in Table 1.

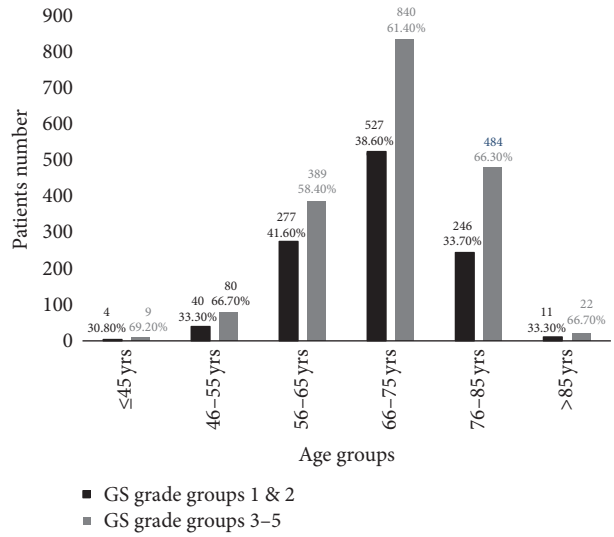

Figure 1: The distribution of Gleason score (GS) in different age groups.

The median pathological Gleason sums were 8 (range: 6–10), 7 (range: 3–10), and 8 (range: 3–10) in Groups 1, 2, and 3, respectively. There were significant differences among the three age cohorts in pathological characteristics including Gleason sum, primary Gleason score, and second primary Gleason score ($p < 0.05$). After further comparisons performed between Groups 1 and 2 and Groups 2 and 3, it was found that Gleason sum, primary Gleason score, and second primary Gleason score were significantly higher in Group 3 than in Group 2 ($p < 0.025$). All data are presented in Table 2. Meanwhile, the median age was 71 years (range: 42–87), 70 years (range: 36–87), 71 years (range: 37–89), 72 years (range: 43–91), and 71 years (range: 33–89) in Gleason grade groups (GGG) 1, 2, 3, 4, and 5, respectively ($F = 2.15$, $p = 0.072$).

The percent of Gleason pattern 5 was significant different among the three groups (44.4%, 32.3%, and 36.8%, resp., $\chi^2 = 11.641$, $p = 0.003$, Table 3). When compared to Group 2 (56–75 years), Groups 1 (≤55 years) and 3 (>75 years) showed significantly higher percentages of Gleason pattern 5 ($\chi^2 = 8.183$, $p = 0.004$; $\chi^2 = 5.065$, $p = 0.024$, resp.).

The distribution of Gleason scores in different age quartiles (≤45, 46–55, 56–65, 66–75, 76–85, and >85 years), based on the new grading system proposed by the 2016 WHO prostate cancer reporting guidelines, is given in Figure 1. When a comparison was performed across the three age groups (≤55, 56–75, and >75 years) for all study subjects (Table 4), the percentages of patients assigned to grade groups 3–5 were higher than those assigned to grade groups 1-2 in all three age groups. There were statistically significant differences in the percentages of patients from each of the age groups assigned to Gleason score grade groups 3–5, with 66.9%, 60.5%, and 66.3% of patients in Groups 1, 2, and 3 ($\chi^2 = 9.401$, $p = 0.009$). The difference between patients in

Table 1: Clinical data of all 2929 patients in different age groups.

	Total (2929)	Group 1 (133)	Group 2 (2033)	Group 3 (763)
Median Age (years)	71 (33–91)	52 (33–55)	69 (56–75)	79 (76–91)
Median tPSA (μg/dL)	19.0 (1.7–>1000)	20 (3.7–500)	18.0 (1.7–>1000)	20.7 (1.7–>1000)
Median BMI (kg/m^2)	24.2 (15.1–41.7)	25.1 (18.0–32.5)	24.1 (16.4–40.1)	23.7 (15.1–41.7)
T stage				
T1-T2	1490 (50.8%)	56 (42.1%)	1128 (55.5%)	306 (40.1%)
T3-T4	1439 (49.2%)	77 (57.9%)	905 (44.5%)	457 (59.9%)
N				
0	2021 (68.9%)	90 (67.7%)	1450 (71.3%)	481 (63.0%)
1	908 (31.1%)	43 (32.3%)	583 (28.7%)	282 (37.0%)
M				
0	1976 (67.5%)	86 (64.7%)	1423 (70.0%)	467 (61.2%)
1	953 (32.5%)	47 (35.3%)	610 (30.0%)	296 (38.8%)

Group 1: age ≤ 55 years (young men).
Group 2: age 56–75 years (middle-aged and old men).
Group 3: age > 75 years (very old men).
tPSA: total prostate-specific antigen; BMI: body mass index.

Table 2: Comparisons of pathological characteristics between different groups.

	Groups 1, 2, and 3		Group 1 versus Group 2		Group 2 versus Group 3	
	Z	p value	Z	p value	Z	p value
Gleason sum	12.975	*0.002**	2.120	0.034	3.155	*0.002**
Primary Gleason score	9.264	*0.010**	1.954	0.051	2.564	*0.010**
Second primary Gleason score	6.692	*0.035**	1.496	0.153	2.285	*0.022**

Group 1: age ≤ 55 years (young men).
Group 2: age 56–75 years (middle-aged and old men).
Group 3: age > 75 years (very old men).
*Statistically significant difference.

Table 3: The percentages of Gleason pattern 5 tumors in the three age groups.

	Group 1 (≤55 years)	Group 2 (56–75 years)	Group 3 (>75 years)
Gleason pattern < 5	74 (55.6%)	1376 (67.7%)	482 (63.2%)
Gleason pattern = 5	59 (44.4%)	657 (32.3%)	281 (36.8%)

Table 4: The percentages of Gleason grade groups (GGG) in the three age groups.

	Group 1 (≤55 years)	Group 2 (56–75 years)	Group 3 (>75 years)
GGG 1	21 (15.8%)	305 (15.0%)	95 (12.5%)
GGG 2	23 (17.3%)	499 (24.5%)	162 (21.4%)
GGG 3	16 (12.0%)	308 (15.2%)	104 (13.6%)
GGG 4	19 (14.3%)	320 (15.7%)	145 (18.9%)
GGG 5	54 (40.6%)	601 (29.6%)	257 (33.7%)
GGG 1-2	44 (33.1%)	804 (39.5%)	257 (33.6%)
GGG 3–5	89 (66.9%)	1229 (60.5%)	506 (66.3%)
SUM	133 (100%)	2033 (100%)	763 (100%)

Groups 2 and 3 was also significant ($\chi^2 = 8.103$, $p = 0.004$), whereas no statistically significant difference was observed between Group 1 and Group 2 ($\chi^2 = 2.190$, $p = 0.139$).

3.2. Discussion. Prostate cancer is the most commonly diagnosed malignant tumor in older men, but it is infrequently reported in younger men [1]. Most previous studies on prostate cancer have led many clinicians to reach a consensus that elderly men are not good candidates for radical prostatectomy and they would present better outcomes in response to hormonal therapy [4, 5]. However, till date, there is no specific criterion for defining the different age groups of prostate cancer [1]. An earlier retrospective study conducted on young patients discussed the clinicopathological features of prostate cancer in men under 50 years of age [7]; however, there have also been several reports classifying adults under 55 or 59 years, respectively, as young patients [1, 8]. A retrospective report focusing on age-related outcomes for elderly men with prostate cancer used a cutoff age of 70 years [9]. Moreover, a large body of literature on the oncological outcomes of prostate cancer has suggested that patients aged more than 75 years should not be treated with radical prostatectomy owing to their very short life expectancy [10]. In the current study, we assigned 2,929 patients with prostate cancer into three age groups: Group 1 (≤55 years, young men), Group 2 (56–75 years, middle-aged and old men), and Group 3 (>75 years, very old men). The purpose of the present study was to identify and analyze the pathological characteristics of prostate cancer in different age groups.

Several reports have indicated that older men often harbor more advanced tumors [11–13]. Our findings suggested a significant difference in Gleason sum among the three age groups (scores of 8, 7, and 8 in Groups 1, 2, and 3, resp.). There was also a significant difference when Groups 2 and 3 were compared in isolation. These results indicated that patients aged more than 75 years are more likely to be diagnosed with high-risk prostate cancer. However, a recent study focusing on Korean patients found that radical therapy might be an appropriate treatment option for selected healthy men aged 75 years or more [14]. Although the differences between the Gleason sum in Groups 1 and 2 was not statistically significant ($p = 0.034$ [>0.025]), this finding might have been observed because of the large imbalance in the patient population, in which only 133 subjects were ≤55 years of age and there were 2,033 patients between the ages of 55 to 75 years. The results indicated a trend towards the association of patients aged ≤55 years with higher biopsy Gleason scores compared to the middle-aged and old patient group.

Most researchers have concluded that young patients with prostate cancer have less aggressive clinicopathological characteristics and more favorable outcomes compared with older men [15–17]. The Cancer of the Prostate Risk Assessment (CAPRA) score, a widely used predictive model for biochemical recurrence and survival after radical prostatectomy, indicates that age under 50 years is one of the independent favorable risk factors [18]. Kinnear et al. [16] argued that Australian men aged ≤50 years diagnosed with prostate cancer have more favorable pathological features. Similarly, two other studies reported that early age at diagnosis was associated with less advanced disease characteristics and improved outcomes [9, 19]. Nevertheless, several studies showed completely different perspectives, detecting a poor prognosis in younger patients [7, 20].

A recent study conducted to analyze the prognostic significance of the percent of Gleason pattern 4 suggested that an increase in the percent of Gleason pattern 4 correlated with adverse risk and poorer outcomes [21]. Many clinicians believe that the Gleason pattern 5 might also predict an adverse prognosis in prostatic neoplasms. Our findings showed that both the young and the very old group had significantly higher percentages of Gleason pattern 5 than the middle-aged and old group, which indicated that the patients younger than 55 years or older than 75 years in this cohort appeared to have a greater likelihood of tumors with aggressive behavior. The new grading system, adopted by the new 2016 WHO prostate cancer reporting guidelines, was shown to provide a stratification instrument for tumors that is more accurate in predicting progression than the Gleason risk stratification system (≤6, 7, and 8 to 10) [22]. One large multiinstitutional study [23] revealed that the patients diagnosed with grade group 1 tumors (Gleason score ≤ 6) did not appear to experience metastasis to lymph nodes, with a more predictable and favorable prognosis. Grade group 2 (Gleason score 3 + 4 = 7) also has a relatively favorable prognosis, with rare metastases. Comparing the percentage of grade groups 3–5 between all three age groups, we found that the percentage in the very old group was statistically higher than that in the middle-aged and old group, while there was no significant difference between the percentage in the young group and the middle-aged and old group. Given the higher percent of Gleason pattern 5, there might be fewer cases of Gleason scores 4 + 3 and 4 + 4 in the young group. The results suggested that the younger and older age at the time of prostate cancer diagnosis were associated with aggressive cancer characteristics.

The results of our research were contrasting to the findings of most published reports, which concluded that younger men have better disease-free outcomes compared to older patients [24]. One reason for this finding might be the different grouping strategy [16]. It may also be due to the ethnic diversity among the studies. The incidence of prostate cancer in younger men had increased remarkably since the initiation of widespread use of serum prostate specific antigen (PSA) screening; however, the results of PSA screening would be affected by individual differences in malignant latency [3]. The slow-growing or indolent tumors would have a better opportunity to be identified, while missing the timely diagnosis of early onset prostate cancer (diagnosis at ≤55 years) because of the very short window for detection before symptoms appear. Consequently, it is no accident that younger patients diagnosed with early onset prostate cancer would tend to have more advanced disease characteristics and higher cancer-specific mortality than other subgroups. At present, there remains a lack of large studies on the clinicopathological features of prostate cancer in Chinese patients who were diagnosed with the disease at an early age. In addition, a prior report indicated that race might play a significant role in the tumor biology of prostate cancer in younger

adults [9]. In the present study, the existing data suggested that early onset prostate cancer occurred in a higher proportion in the Chinese younger population.

Many studies have demonstrated that men with a family history or genetic mutations were at increased risk of prostate cancer, particularly at a young age. Edwards et al. [25] argued that the risk of prostate cancer was almost 23-fold higher in *BRCA2* mutation carriers compared to those with no mutation. Moreover, Sigurdsson et al. [26] found that *BRCA2* mutation in the Icelandic population might be a possible biomarker for an aggressive form of prostate cancer. Two other reports also confirmed that *BRCA2* mutations were associated with more advanced disease and shorter disease-specific life expectancy [27, 28]. Furthermore, a novel gene variant named *HOXB13 G84E* was identified by several genetic studies that found a strong relationship between this mutation and susceptibility to prostate cancer. However, interestingly, patients with *HOXB13 G84E* germline mutation appeared to have a more favorable prognosis [29–31]. These observations might open up a new avenue for the screening and diagnosis of the selected germline mutations and even point to new targets for cancer therapy.

There are two reasons why our study included merely pathological grading of prostate cancer in this cohort, without involving the clinical or pathological stages. Firstly, the tumor staging could not characterize the pathological features well because the results might have been affected by the method or timing of diagnosis. Secondly, the urologists could only determine exact pathological stages of diseases in the patients who underwent prostatectomy. Thus, there were no analyses regarding the tumor stages in this study.

The present study has certain limitations and constraints, of which the most obvious is the deficiency of a retrospective approach. Another important limitation is that all the grade information of the patients was evaluated via biopsy not surgical specimens which could be more representative of prostate cancer progression compared to biopsy tissues, despite the fact that biopsy outcome may be more clinical instructive for urologist at tumor diagnosis moment.

4. Conclusions

The results of this single institution retrospective analysis indicated that in relation to differences in Gleason scores among various age groups, men aged ≤55 years or >75 years, show significantly higher percentages of Gleason pattern 5 compared to patients aged 56–75 years. Younger and elderly ages in this Chinese cohort are associated with more aggressive disease characteristics. Further studies that evaluate the clinicopathological features of prostate cancer in different age groups are warranted.

Disclosure

Guangjie Ji and Cong Huang are first authors.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Guangjie Ji and Cong Huang contributed equally to this work. Gang Song and Liqun Zhou are senior authors contribute equally.

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Review Article

Clinical and Prognostic Effect of Plasma Fibrinogen in Renal Cell Carcinoma: A Meta-Analysis

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Background. Although numerous studies have shown that plasma fibrinogen is linked to renal cell carcinoma (RCC) risk, the consistency and magnitude of the effect of plasma fibrinogen are unclear. The aim of the study was to explore the association between plasma fibrinogen and RCC prognosis. *Methods*. An electronic search of Embase, PubMed/MEDLINE, and the Cochrane databases was performed to identify relevant studies published prior to June 1, 2016. *Results*. A total of 3744 patients with RCC from 7 published studies were included in the meta-analysis. The prognostic and clinical relevance of plasma fibrinogen are evaluated in RCC patients. Statistical significance of the combined hazard ratio (HR) was detected for overall survival, cancer-specific survival, and disease-free survival. Our pooled results showed that elevated plasma fibrinogen was significantly associated with clinical stage and Fuhrman grading. The level of plasma fibrinogen was not found to be associated with tumor type and gender. *Conclusions*. Elevated plasma fibrinogen is a strong indicator of poorer prognosis of patients with RCC, whereas the plasma fibrinogen is not significantly associated with tumor type. Therefore, plasma fibrinogen could be used in patients with RCC for risk stratification and decision providing a proper therapeutic strategy.

1. Introduction

Renal cell carcinoma (RCC) is the third most frequent malignancy in the urogenital system, which represents about 2% to 3% of cancers in adults [1]. Although the diagnosis and therapeutic modalities of RCC have changed remarkably rapidly, up to one-third of patients present with locally advanced or metastatic disease at initial diagnosis, and the subsequent 5-year survival rate of metastatic RCC is only 10% [2–4]. Therefore, prognostic predictors of high-risk RCC are urgently needed.

Plasma fibrinogen, as an acute phase glycoprotein that is commonly associated with the maintenance of hemostasis, has a critical role in both inflammatory responses and cancer progression. A number of studies have shown that plasma fibrinogen level is upregulated in various cancers and may account for progression and metastasis [5–8]. However, there are conflicting findings on the role of plasma fibrinogen and survival outcomes in RCC. For example, Xiao et al. [9] found that plasma fibrinogen level is an effective tumor marker to evaluate lymph node status, clinical stage, and distant metastases. Sasaki and Onishi [10] also demonstrated that plasma fibrinogen was a prognostic factor predicting worse overall survival (OS) in RCC patients. However, Erdem et al. [11] suggested that preexisting plasma fibrinogen had no significant effect on the outcome of localized RCC.

The aim of our overarching systematic review was to provide a comprehensive and up-to-date summary for the role of fibrinogen in RCC. In addition, we completed meta-analyses

to quantify the changes in OS, cancer-specific survival (CSS), and disease-free survival (DFS).

2. Materials and Methods

2.1. Search Strategy. This meta-analysis was conducted in accordance with the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses [12]. Because the studies included in this meta-analysis have been published, thus no ethical approval is required. A literature search for published original articles was conducted in Embase, PubMed/MEDLINE, and Cochrane databases. The last updated search was carried out on June 1, 2016. The key search items consist of plasma fibrinogen ("fibrinogen" OR "plasma fibrinogen"), renal cell carcinoma ("renal cell cancer" OR "kidney cancer" OR "renal tumor" OR "renal cell carcinoma"), and "prognosis or prognostic or survival or outcome" and relevant variants of these search terms. The search was confined to articles that were published in English. In addition, references of relevant articles were manually searched for potential eligible trials.

2.2. Selection Criteria and Definition. The eligible studies were included only if they met the following criteria: (1) articles were published in English; (2) any clinical study comprising the evaluation of plasma fibrinogen on renal cell cancer prognosis was eligible; (3) the authors must offer the hazard ratios (HRs) and their p values, or the information that allowed manual calculation of 95% CI in the papers. Accordingly, studies with the following criteria were excluded: (1) reviews and nonoriginal articles; (2) studies not related to RCC; (3) studies that did not analyze the plasma fibrinogen and the clinical features and survival outcome; (4) studies lacking sufficient data to acquire HR and its standard error (SE). When duplicate articles emerged, the one with the largest data set was adopted. Two researchers (MH and SSJ) screened titles and abstracts of all the searched literatures and verified the studies that met the inclusion criteria for next analysis.

2.3. Data Extraction and Study Quality. The following information was retrieved independently by 2 reviewers (MH and SSJ) from the final set of literatures: publication year, name of the first author, number of patients enrolled, recruitment period, age of patients, gender ratio, cut-off value, follow-up time, adjusted factors, and Newcastle-Ottawa Scale (NOS) score. The data were extracted from the original articles. If a study provided the results of both multivariate outcome and univariate outcome, we chose the former. There are no standard quality assessment tools for prognostic studies in systematic reviews. Study quality was independently applied according to the "NOS score" for a cohort study that includes 3 domains with 8 items. Studies with scores of 6 or higher were graded as high quality [13].

2.4. Statistical Analysis. The pooled HR and its corresponding 95% CI were calculated to assess the association between plasma fibrinogen and patient survival. The pooled OR and its corresponding 95% CI were used to quantitatively determine the association between plasma fibrinogen and the clinical parameters of RCC. Statistical heterogeneity among studies was assessed using Cochran's Q test and Higgins I^2 statistic [14]. A fixed-effect model (Mantel–Haenszel method) was used to calculate parameters when no obvious heterogeneity existed among studies ($I^2 > 50\%$ suggested high heterogeneity). Sensitivity analysis was performed to test the reliability of the total pooled results by sequential omission of individual studies. Publication bias was assessed using funnel plots and Egger's test. All statistical manipulations in this meta-analysis were undertaken using Stata 14.0 software (Stata Corporation, College Station, TX) with 2-tailed p values. A p value of <0.05 was considered the significance level.

3. Results

3.1. Study Characteristics. The initial search identified 48 studies that were considered eligible according to the inclusion criteria. Eventually, 7 studies were included [10, 11, 15–19] (Figure 1). Two studies provided original information on the relationships between plasma fibrinogen and clinical parameters in RCC patients directly [10, 18]. The main characteristics of the 19 studies included in our meta-analysis are shown in Table 1. Our data has 3,744 patients from 6 countries (China, Austria, Turkey, Germany, Japan, and Korea).

Plasma fibrinogen levels were measured in 4 studies by a functional method based on the Clauss assay [11, 15–17]; fibrinogen tests were included in the coagulation panel among the preoperative workups in one study [19]; and, in the rest of the two studies, no comments were made on this point [10, 17]. Differences in the cut-off value for high plasma fibrinogen were observed among the studies. The high level of the plasma fibrinogen was considered to be positive, and a low level was considered to be negative.

3.2. Relationship between Plasma Fibrinogen and RCC Prognosis. The forest plots of the meta-analyses for plasma fibrinogen are shown in Figure 2 and Table 2. The pooled HRs were statistically significant for OS (HR: 2.13; 95% CI: 1.74–2.61), CSS (HR: 3.12; 95% CI: 2.19–4.44), and DFS (HR: 1.67; 95% CI: 1.30–2.15).

3.3. Association between Plasma Fibrinogen in RCC and Clinical Parameters. As shown in Figure 3(a), elevated plasma fibrinogen was significantly higher in advanced RCC (T3-T4) than in early stage RCC (T1-T2) (OR = 3.69, 95% CI: 1.81–7.54; $p = 0.0003$). The pooled OR from 3 studies including 1,430 RCC grade G1-G2 and 787 RCC grade G3-G4 patients is presented in Figure 3(b) (OR = 2.04, 95% CI: 1.68–2.48; $p < 0.00001$), which indicates that plasma fibrinogen was significantly higher in RCC patients of low Fuhrman grades than in those of high Fuhrman grades. The pooled OR from three studies, including 1834 ccRCC (clear cell renal cell carcinoma) and 383 non-ccRCC cases, is shown in Figure 3(c) (OR = 0.79, 95% CI: 0.62–1.01; $p = 0.06$), indicating that plasma fibrinogen was not strongly associated with tumor type in RCC patients. The pooled OR from four studies,

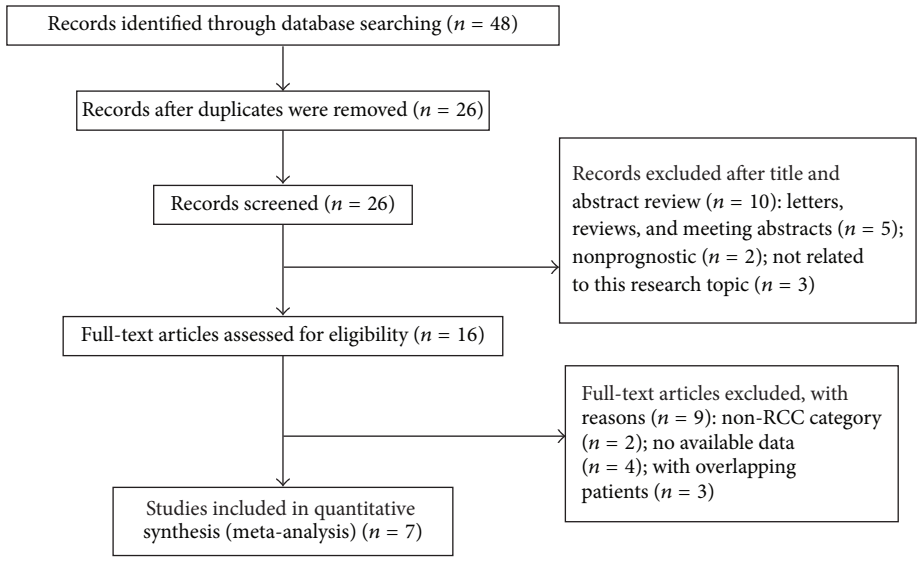


Figure 1: Flow chart of study selection.

including 1,601 males and 596 females, is shown in Figure 3(d) (OR = 0.86, 95% CI: 0.70–1.05; $p = 0.14$), indicating that plasma fibrinogen was not strongly associated with gender in RCC patients (Table 3).

3.4. Publication Bias. The Egger and Begg tests did not indicate any significant publication bias in the analysis of OS in RCC ($P_{begg} = 0.707$, $P_{egger} = 0.272$). No evidence of asymmetry was found in our funnel plot (Figure 4).

4. Discussion

Numerous researchers have reported various results relating plasma fibrinogen to RCC. However, up to now, no meta-analysis had been performed for the studies evaluating plasma fibrinogen as a prognostic marker in RCC.

In the current study, we enrolled 7 eligible studies comparing the correlations of RCC according to plasma fibrinogen. The individual data were organised according to OS, CSS, and DFS, and we identified the notion that an elevated plasma fibrinogen level predicts shorter OS, CSS, and DFS. Our results also indicate that RCC patients with elevated plasma fibrinogen level are likely to have a higher pathological T stage and a lower Fuhrman grade. The estimated pooled HRs of 7 trials for RCC were statistically significant, suggesting that plasma fibrinogen is a strong predictor of poor prognosis among patients with RCC. Our analysis helps to elucidate the results of individual studies which are related to the hypothesis that plasma fibrinogen is a prognostic factor for RCC, in addition to the identification of the high-risk subgroups of patients for whom adjuvant therapy may be useful.

The biological mechanism of plasma fibrinogen can explain its prognostic significance in RCC. It has been shown that tumor progression may set up a cascade of events which includes increased systemic inflammatory response, which in turn leads to increased plasma fibrinogen level [20–22].

Other studies show that fibrinogen can be endogenously synthesised by cancer cells [23, 24]. Fibrinogen is an extracellular matrix element and regulates the growth of cancer cells by binding to the vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), and platelet-derived growth factor (PDGF) [24–26]. The binding of growth factors promotes cellular adhesion, proliferation, and metastasis during angiogenesis and tumor cell growth. Fibrinogen promotes platelets to adhere to tumor cells, and platelets also conversely induce more fibrinogen to aggregate around tumor cells by forming thrombin. Fibrinogen and platelets are promoted mutually and protect tumor cells from natural killer cytotoxicity [27]. Furthermore, using cell line models, it has been shown that highly concentrated fibrinogen can induce epithelial-mesenchymal transition (EMT) by increasing the expression of vimentin and reducing expression of E-cadherin, which enhances cancer cell invasion and metastasis [28]. Moreover, in vitro studies have shown that one possible mechanism is the association between tissue factor (TF) and VEGF. TF, which is expressed on the surface of tumor cells, is a key inducer of the coagulation pathway in carcinogenesis [29]. VEGF stimulates TF in endothelial cells, leading to activation of the coagulation cascade, which includes fibrinogen [25, 30]. Therefore, in RCC, which is characterised as a hypervascular tumor, it may be that an elevated plasma fibrinogen level is clearly associated with more aggressive pathological features and subsequent worse survival [16, 31].

To our knowledge, this meta-analysis is the first study to systematically evaluate the clinical and prognostic value of plasma fibrinogen level in RCC. The elevated plasma fibrinogen level predicted poorer pathological outcomes and was a significant risk factor affecting survival.

However, several limitations of this study need to be acknowledged. First, the applied methods for detecting

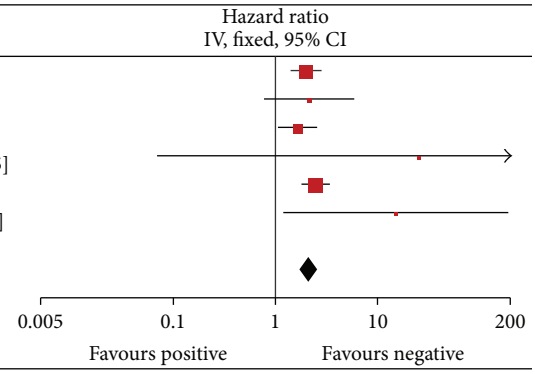
Table 1: Characteristics of individual studies included in the meta-analysis.

Study (year)	Country	Patients	Included period	Age (range) (year)	Gender (M/F)	Cut-off (mg/dL)	FU (range) (year)	Cofactors	NOS score
Du et al._2013	China	286	2000–2003	Median: 55.72 (28–77)	185/101	400	Median: 56 (34.6–94.5)	Hemoglobin, calcium, LDH, pT stage, Fuhrman grade, tumor size	7
Pichler et al._2013	Austria	994	2000–2010	Mean (63.2 ± 11.9)	599/395	466	Mean: 48.1 (0–132)	Age, gender, pT stage, Fuhrman grade, necrosis	8
Erdem et al._2014	Turkey	128	2006–2011	Mean (58.66 ± 11.31)	91/37	343	Median: 36.5	Gender, age, pT stage, Fuhrman grade, tumor size, histologic subtypes, plasma D-dimer	8
Niedworok et al._2015	Germany	98	2002–2011	Mean: 63.5 (18–82)	61/37	281	Mean: 36 (20–122)	NA	7
Sasaki and Onishi_2015	Japan	126	2003–2013	Median: 67 (37–86)	84/42	399	Median: 30.8 (2–125)	PS, pT stage, Hb, Alb, LDH	8
Obata et al._2016	Japan	601	1995–2010	Median: 58 (50–67)	467/134	420	Median: 74 (47–107)	Fuhrman grade, pT stage, histologic subtypes	8
Lee et al._2016	Korea	1511	2006–2013	Median: 58 (49–67)	1077/434	328	Median: 36 (24–57)	Age, BMI, hypertension, diabetes mellitus, ECOG score, tumor size, Fuhrman grade, pT stage, histologic subtypes, tumor necrosis, sarcomatoid differentiation	8

Alb: albumin; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; FU: follow-up; LDH: lactate dehydrogenase; Hb: hemoglobin; PS: performance status; NA: not available.

Study or subgroup	log[hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95% CI
Du et al. 2013	0.6916	0.1783	33.9%	2.00 [1.41, 2.83]
Erdem et al. 2014	0.7608	0.5194	4.0%	2.14 [0.77, 5.92]
Lee et al. 2016	0.499	0.2256	21.1%	1.65 [1.06, 2.56]
Niedworok et al. 2015	3.2351	3.0133	0.1%	25.41 [0.07, 9330.65]
Pichler et al. 2013	0.9083	0.1635	40.3%	2.48 [1.80, 3.42]
Sasaki and Onishi 2015	2.716	1.2952	0.6%	15.12 [1.19, 191.43]
Total (95% CI)			*100.0%*	*2.13 [1.74, 2.61]*

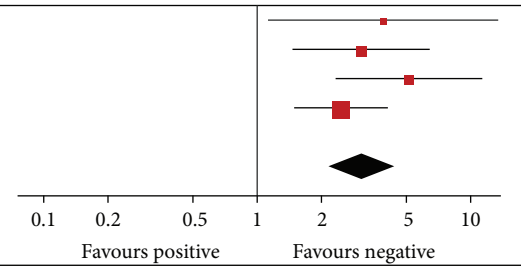
Heterogeneity: $\chi^2 = 5.26$, df = 5 ($p = 0.38$); $I^2 = 5\%$
Test for overall effect: $Z = 7.30$ ($p < 0.00001$)



(a)

Study or subgroup	log[hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95% CI
Erdem et al. 2014	1.3584	0.6335	8.1%	3.89 [1.12, 13.46]
Lee et al. 2016	1.121	0.3777	22.9%	3.07 [1.46, 6.43]
Obata et al. 2016	1.6371	0.4037	20.0%	5.14 [2.33, 11.34]
Pichler et al. 2013	0.9042	0.2579	49.0%	2.47 [1.49, 4.09]
Total (95% CI)			*100.0%*	*3.12 [2.19, 4.44]*

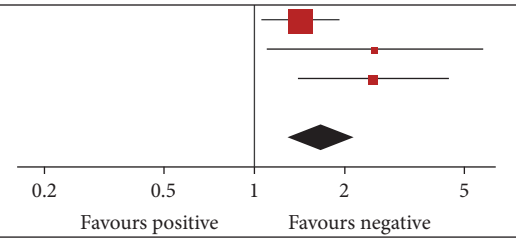
Heterogeneity: $\chi^2 = 2.47$, df = 3 ($p = 0.48$); $I^2 = 0\%$
Test for overall effect: $Z = 6.30$ ($p < 0.00001$)



(b)

Study or subgroup	log[hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95% CI
Du et al. 2013	0.3528	0.1528	71.5%	1.42 [1.05, 1.92]
Erdem et al. 2014	0.9243	0.4233	9.3%	2.52 [1.10, 5.78]
Obata et al. 2016	0.9123	0.2952	19.2%	2.49 [1.40, 4.44]
Total (95% CI)			*100.0%*	*1.67 [1.30, 2.15]*

Heterogeneity: $\chi^2 = 3.87$, df = 2 ($p = 0.14$); $I^2 = 48\%$
Test for overall effect: $Z = 3.97$ ($p < 0.0001$)



(c)

Figure 2: Results of subgroup analysis of the association between plasma fibrinogen and OS/CSS/DFS of RCC. (a) Six studies included investigating the relationship between OS and plasma fibrinogen. (b) Four studies included investigating the relationship between CSS and plasma fibrinogen. (c) Three studies included investigating the relationship between DFS and plasma fibrinogen. CI: confidence interval; CSS: cancer-specific survival; DFS: disease-free survival; OS: overall survival; RCC: renal cell carcinoma.

Table 2: HR values of the OS, CSS, and DFS of the RCC.

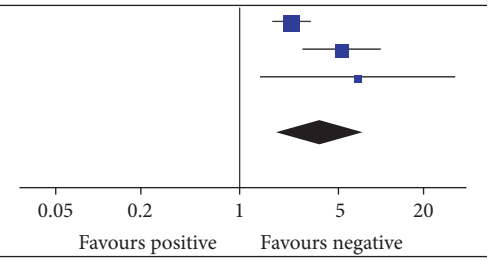
Outcome	Studies (n)	Patients	HR	95% CI	p value	Model	Chi^2, I^2, p value
OS	6	3143	2.13	1.74–2.61	0.000	Fixed	5.26, 5%, 0.38
CSS	4	3234	3.12	2.19–4.44	0.000	Fixed	2.47, 0%, 0.48
DFS	3	1015	1.67	1.30–2.15	0.000	Fixed	3.87, 48%, 0.14

CI: confidence interval; CSS: cancer-specific survival; Fixed: fixed, inverse variance model; HR: hazard ratio; I^2: I-squared; OS: overall survival; Random: random, I–V heterogeneity model; DFS: disease-free survival.

plasma fibrinogen and the cut-off values were varied in the eligible studies, which could cause heterogeneity among the studies. Second, studies in other languages were excluded except for English; the literatures were not comprehensive. Third, other clinical factors such as race, age, and gender in each study might lead to bias. Fourth, subgroup analysis and metaregression were performed by type of RCC (clear cell RCC versus non-clear cell RCC); we lumped together the non-clear cell RCC group, but in this group there are a lot of different kinds of malignancies with different biological behaviors and genetic abnormalities, which might render the results less reliable. Finally, we could not ascertain a relationship between plasma fibrinogen and tumor type of RCC patients; clear cell RCC is more aggressive than other

Study or subgroup	T3-T4 Events	T3-T4 Total	T1-T2 Events	T1-T2 Total	Weight	Odds ratio M-H, random, 95% CI
Lee et al. 2016	143	206	644	1305	48.1%	2.33 [1.70, 3.19]
Obata et al. 2016	18	63	38	538	37.3%	5.26 [2.78, 9.97]
Sasaki and Onishi 2015	4	7	16	98	14.6%	6.83 [1.39, 33.51]
Total (95% CI)		*276*		*1941*	*100.0%*	*3.69 [1.81, 7.54]*
Total events	165		698			

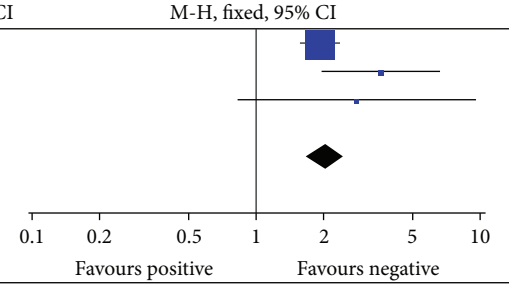
Heterogeneity: $\tau^2 = 0.25$; $\chi^2 = 6.39$, df = 2 ($p = 0.04$); $I^2 = 69\%$
Test for overall effect: $Z = 3.59$ ($p = 0.0003$)



(a)

Study or subgroup	G3-G4 Events	G3-G4 Total	G1-G2 Events	G1-G2 Total	Weight	Odds ratio M-H, fixed, 95% CI
Lee et al. 2016	418	686	369	825	92.3%	1.93 [1.57, 2.37]
Obata et al. 2016	19	87	37	514	5.9%	3.60 [1.96, 6.62]
Sasaki and Onishi 2015	5	14	15	91	1.8%	2.81 [0.83, 9.59]
Total (95% CI)		*787*		*1430*	*100.0%*	*2.04 [1.68, 2.48]*
Total events	442		421			

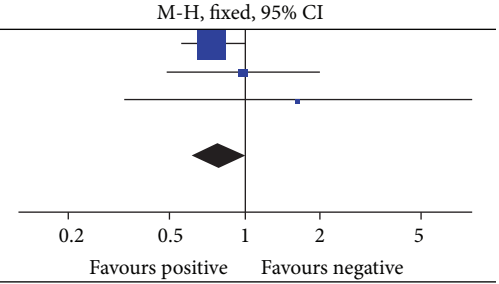
Heterogeneity: $\chi^2 = 3.91$, df = 2 ($p = 0.14$); $I^2 = 49\%$
Test for overall effect: $Z = 7.23$ ($p < 0.00001$)



(b)

Study or subgroup	CcRCC Events	CcRCC Total	Non-ccRCC Events	Non-ccRCC Total	Weight	Odds ratio M-H, fixed, 95% CI
Lee et al. 2016	641	1260	146	251	86.4%	0.74 [0.57, 0.98]
Obata et al. 2016	45	484	11	117	11.6%	0.99 [0.49, 1.97]
Sasaki and Onishi 2015	18	90	2	15	2.0%	1.63 [0.34, 7.86]
Total (95% CI)		*1834*		*383*	*100.0%*	*0.79 [0.62, 1.01]*
Total events	704		159			

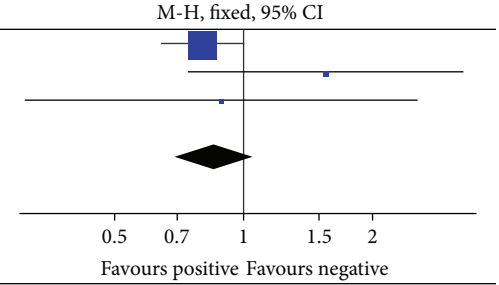
Heterogeneity: $\chi^2 = 1.38$, df = 2 ($p = 0.50$); $I^2 = 0\%$
Test for overall effect: $Z = 1.85$ ($p = 0.06$)



(c)

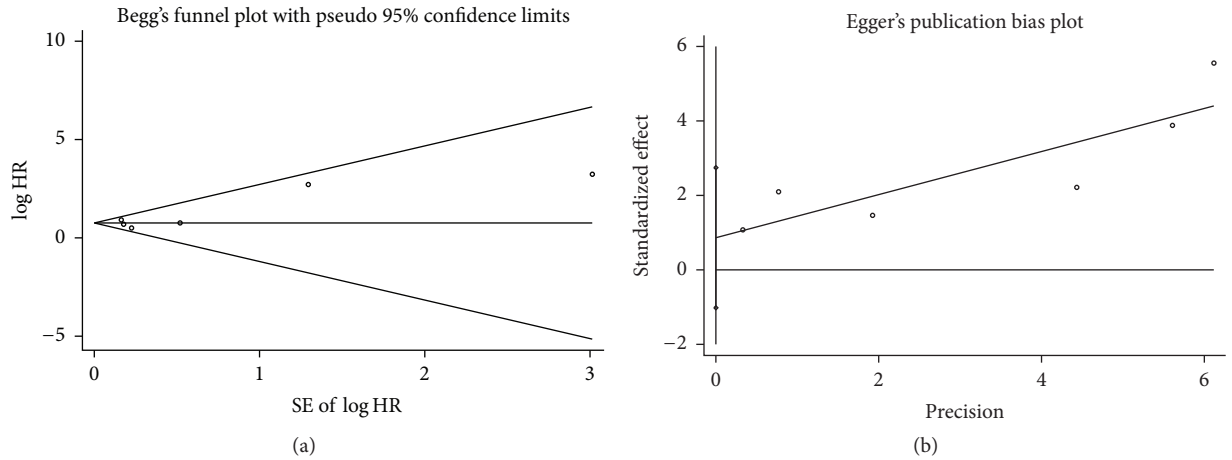
Study or subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Odds ratio M-H, fixed, 95% CI
Lee et al. 2016	544	1077	243	434	89.5%	0.80 [0.64, 1.00]
Obata et al. 2016	47	467	9	134	6.6%	1.55 [0.74, 3.26]
Sasaki and Onishi 2015	13	70	7	35	4.0%	0.91 [0.33, 2.54]
Total (95% CI)		*1614*		*603*	*100.0%*	*0.86 [0.70, 1.05]*
Total events	604		259			

Heterogeneity: $\chi^2 = 2.82$, df = 2 ($p = 0.24$); $I^2 = 29\%$
Test for overall effect: $Z = 1.48$ ($p = 0.14$)



(d)

Figure 3: Results of subgroup analysis of the association between plasma fibrinogen and clinicopathological parameters. (a) The pooled OR from three studies including 1941 stage T1 and T2 and 276 stage T3 and T4 cases. (b) The pooled OR from three studies including 1430 grade G1 and G2 and 787 grade G3 and G4 cases. (c) The pooled OR from three studies including 1834 ccRCC and 383 non-ccRCC cases. (d) A total of 2277 RCC patients were pooled from three studies to assess whether plasma fibrinogen in RCC was associated with gender. ccRCC: clear cell renal cell carcinoma; RCC: renal cell carcinoma.



(a) (b)

Figure 4: Funnel plots of Begg and Egger were used to detect publication bias on overall survival (OS). They showed no publication bias on OS in Begg's test (a) and Egger's test (b).

Table 3: Plasma fibrinogen according to clinicopathological features.

Outcome of interest	Studies (n)	Patients	OR	95% CI	p value	Model	Chi^2, I^2, p value
T3-T4 versus T1-T2	3	2217	3.69	1.81–7.54	0.0003	Random	6.39, 69%, 0.04
G3-G4 versus G1-G2	3	2217	2.04	1.68–2.48	0.000	Fixed	3.91, 49%, 0.14
CcRCC versus non-ccRCC	3	2217	0.79	0.62–1.01	0.06	Fixed	1.38, 0%, 0.06
Male versus female	3	2217	0.86	0.70–1.05	0.14	Fixed	2.83, 29%, 0.24

CcRCC: clear cell renal cell carcinoma; Fixed: fixed, inverse variance model; I^2: I-squared; OR: odds ratio; Random: random, I–V heterogeneity model; RCC: renal cell carcinoma.

subtypes; however, only one study determined the plasma fibrinogen level differences between clear cell and other types and found no statistically significant differences. In this respect, other factors might also play a role in affecting RCC prognosis, such as clinical stage and Fuhrman grade.

In conclusion, this meta-analysis indicates that high plasma fibrinogen level is closely associated with poor survival and aggressive clinical feature in patients with RCC. While these are hypothesis generating results, the excellent accessibility and low cost of plasma fibrinogen should further facilitate its wider application in patients with RCC for risk stratification and decision-making of individualized treatment. We require further validation of our study.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

Authors' Contributions

Yuejun Tian and Mei Hong contributed equally to this work.

Acknowledgments

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Research Article

Baseline Chronic Kidney Disease and Ischemic Method of Partial Nephrectomy Are Important Factors for the Short- and Long-Term Deterioration in Renal Function for Renal Cell Carcinoma Staged T1-T2: A Retrospective Single Center Study

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The renal functions of 215 patients (24 with benign renal mass, the rest with RCC staged T1-T2) who underwent partial nephrectomy (PN) between 2003 and 2014 were evaluated to identify predictors of short- and long-term deterioration in renal function after PN among renal cell carcinoma (RCC) patients with or without preoperative predisposition to chronic kidney disease (CKD) and among patients with benign renal mass. The 1- and 5-year predictive factors for de novo CKD were statistically analyzed. The incidence of de novo CKD differed significantly ($p < 0.001$) among patients with benign renal mass, those with RCC but no preoperative CKD predisposition, and those with RCC combined with preoperative CKD predisposition. Independent predictors for de novo CKD at 1 year postoperatively included intraoperative ischemic method, ECOG score, elevated albumin levels, male sex, and smoking exposure (in pack-years). Predictors for de novo CKD at 5 years postoperatively included hypertension, high preoperative albumin levels, De Ritis ratio (aspartate aminotransferase/alanine aminotransferase ratio), smoking exposure, and preoperative predisposition to CKD. Preoperative predisposition to CKD and ischemic method applied during PN, along with other preoperative parameters, were important factors affecting postoperative renal function deterioration in patients with T1-T2 RCC.

1. Introduction

With the improvement in diagnostic modalities and widespread implementation of early screening systems, the ability to detect small, early-stage, localized renal cell carcinoma (RCC) has increased, which has made it possible to initiate oncological treatment with improved safety and efficacy, resulting in prolonged survival for patients with RCC [1]. Furthermore, the standard treatment strategy for RCC staged T1-T2 has changed from radical nephrectomy to partial nephrectomy (PN), taking into account comorbidities and life expectancy [2], as a strong association was found between renal function decline and the surgical management of small renal masses [2–4]. PN should also be recommended as the first therapeutic option for other types of RCC including familial RCC, von Hippel-Lindau RCC, or bilateral RCC, as well as in patients with a history of underlying chronic renal disease.

The effect of various aggravating and protective factors was investigated during the postoperative follow-up of RCC patients who underwent PN, with the aim to identify the key aspects involved in preserving renal function and preventing or delaying the development of chronic kidney disease (CKD) [5]. It was found that the volume of resected renal tissue, which affects postoperative renal function, depends on the location and size of the tumor lesions, the presence of peritumoral structures, and renal vascular state. However, it is not easy to predict the postoperative development of CKD in RCC patients because that would require monitoring very many factors during the follow-up, whose range of action may or may not overlap in time (i.e., some should be monitored during the short-term follow-up, while others during the

long-term follow-up). Moreover, the moment and direction of aggravation of renal function in RCC patients were only evaluated in comparison to the evolution of patients who underwent PN but had normal kidneys.

Several groups have attempted to describe the functional outcomes after renal surgery in terms of serum creatinine levels as indicative of kidney function [6, 7]. However, the National Kidney Foundation guidelines assert that the assessment of renal function should be based on the estimated glomerular filtration rate (eGFR), which is a more accurate measure of kidney function because it considers serum creatinine levels in addition to the patient's age, sex, race, and body mass index. A reduced eGFR has been associated with increased risk of death, cardiovascular events, and hospitalization [8]; end-stage renal disease, characterized by low eGFR, leads to significant morbidity and mortality and represents a major burden to any healthcare system.

Therefore, in the present study, we monitored the change in renal function, assessed in terms of eGFR, in patients who underwent PN for RCC staged T1-T2. The patients were stratified into two groups based on their predisposition to CKD, and these two groups were compared against a control group (which included patients who underwent PN for benign renal mass) in terms of renal function. The development of de novo CKD and the predictive factors for renal deterioration were evaluated statistically for the first and fifth year after PN in patients with a predisposition for CKD and in those without such predisposition.

2. Patients and Methods

2.1. Ethical Statement. Following approval by the Institutional Review Board (IRB) of the Research Institute and Hospital of the National Cancer Center (IRB approval number: NCC2014-0193), every patient record was anonymized and deidentified prior to analysis. All study protocols were conducted according to the ethical guidelines of the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. The need for written consent was waived by the IRB.

2.2. Patients. The Kidney Cancer Database of the National Cancer Center in Korea was searched for records of RCC patients who underwent PN between 2003 and 2014. The medical records of 252 RCC patients who underwent PN in that period were identified in order to retrospectively evaluate the development of de novo CKD and its predictive factors. Patients with a single kidney, metastatic RCC, other metastases to the kidney, or any preoperative histories of kidney intervention or therapies were excluded, resulting in a final enrollment of 215 patients including 24 (11.2%) PN patients with benign renal mass. The cases with benign renal masses diagnosed pathologically after PN included 6 renal cysts, 1 pyelonephrosis, 1 pheochromocytomas, 3 cystic nephromas, 9 angiomyolymphomas, 1 hemangioendothelioma, 1 Castleman's disease, 1 mucinous adenoma, and 1 case with no tumor. All enrolled patients had complete follow-up data regarding renal function for at least one year postoperatively, whereas 124 (57.7%) patients had such data for five years postoperatively.

The clinicopathological parameters including intraoperative findings, smoking history, and laboratory findings were used for the analysis of predictive factors for renal functional deterioration within one year and after five years from PN. Renal function was assessed based on serum creatinine levels evaluated at the following points: preoperatively and at 1, 3, 6, 9, 12, 24, 36, 48, and 60 months postoperatively. Preexisting CKD was defined as a preoperative eGFR < 60 mL/min/1.73 m^2 (stage 3 according to the National Kidney Foundation guidelines) [9]. Postoperative CKD, acute kidney injury, and renal functional deterioration were defined either as a decline in the renal function, using the classification given in the National Kidney Foundation guidelines, from stages 1 or 2 to stage 3, or as a decline in the renal condition from stage 3A (eGFR, 45–59 mL/min/1.73 m^2) to stage 3B (eGFR, 30–44 mL/min/1.73 m^2) [9].

2.3. Definition of Groups by Preoperative Condition. Two groups of RCC patients were defined according to the preoperative state of the renal function: the preoperative non-CKD RCC group (non-CKD group) and the preoperative CKD RCC group (CKD group). A third group was defined including the patients with benign renal disease (control group).

2.4. Definition of Renal Function Aggravation for Each Group. Renal function deterioration was defined differently for each group. For the non-CKD and control groups, it was defined as having a postoperative eGFR < 60 mL/min/1.73 m^2; for the CKD group, it was defined as a decline in the renal function from CKD stage 3A to 3B or from CKD stage 3B to 4 [9].

2.5. Statistical Analyses. The differences in the occurrence of postoperative de novo CKD or renal functional deterioration at the first year and at the fifth year of follow-up were statistically evaluated for the three groups. Time to progression either to renal functional deterioration or to de novo CKD development was assessed using the Kaplan-Meier analysis with the log-rank test. The predictive risk factors for renal functional deterioration or de novo CKD development were analyzed using the Cox-regression hazard analysis with backward selection (alpha = 0.05). Statistical analyses were performed by using Stata software (Release 9.2, StataCorp, College Station, TX, USA). A p value of < 0.5 was deemed statistically significant.

3. Results

A total of 145 (67.4%) patients were included in the non-CKD group, whereas 46 (21.4%) patients were included in the CKD group (Table 1). The median follow-up time for all patients was 43 months (12–134 months). All RCC patients (88.8%) had T1 stage RCC and only 0.5% experienced tumor recurrence despite the tumor-free resection margin. A total of 84.6% of the patients underwent open PN, with a median ischemic time of 21 minutes; warm ischemia was applied in

Table 1: Patient baseline demographics ($N = 215$).

Parameter	Median (range)	Percentage or SD
Age (years)	55 (24–78)	
Gender (male/female)	154/61	71.6/28.4
BMI (kg/m^2)	24.7 (16.6–39.8)	
Underlying disease		
Diabetes	32	14.9
Hypertension	89	41.4
Hypercholesterolemia	9	4.2
Ischemic heart disease	5	2.3
Anticoagulation therapy history	8	3.7
Aspirin therapy	21	9.8
ASA score 0/1/2	112/95/8	52.1/44.2/3.7
ECOG 0/1/2	143/70/2	66.5/32.6/0.9
Smoking	121	56.3
Smoking volume (PY)	8 (0–87)	
Follow-up duration (mo)	43 (12–134)	
Preoperative laboratory findings		
Hemoglobin	14 (8.6–17.5)	
Albumin	4.6 (3.6–5.9)	
Calcium	9.4 (8.3–10.9)	
Total Cholesterol	185.5 (97–335)	
De Ritis ratio (AST/APT)	1.1 (0.3–3.1)	
Creatinine	1.0 (0.6–1.8)	
Estimated GFR	69.7 (37.3–103.4)	
Preoperative PADUA score	8.0 (5–12)	
Tumor number	2.4 (0.3–16)	
Low/intermediate/high	67/86/62	31.2/40.0/28.8
Longitudinal: Inf/interpolar/med/mid/sup	60/42/3/60/50	27.9/19.5/1.4/27.9/23.3
RENAL score	7 (3–18)	
Ant/post	107/108	49.8/50.2
Disease category		
Preoperative		
CKD RCC	46	21.4
Non-CKD RCC	145	67.4
Benign renal mass	24	11.2
Operative method		
Laparoscopy	33	15.4
Open	182	84.6
Pathologic T stage		
T1	193	89.8
T2	22	10.2
Fuhrman grade		
1	20	9.3
2	131	60.9
3	43	20.0
4	2	1.4
Unknown	19	8.8
Margin positive	30	14.0
Safety resection margin (mm)	2.0 (1.0–9.0)	
Ischemic method warm/cold/no	131/42/42	60.9/19.5/19.5
Ischemic time (min)	21 (0–70)	
Number of clamping vessels	2 (1–4)	
Tumor diameter (cm)	2.0 (0.5–2.2)	

Table 1: Continued.

Parameter	Median (range)	Percentage or SD
Postoperative 5-year follow-up		
Creatinine	1.6 (0.6–2.2)	
eGFR	78.1 (29–118.8)	
Histology		
Clear cell, pure	167	77.7
Papillary	16	7.4
Chromophobe	8	3.7
Benign renal mass	24	11.2
Recurrence	1	0.5
Time to recurrence	52.1 (4.8–48.8)	

SD, standard deviation; MSKCC, Memorial Sloane Kettering Cancer Center; LN, lymph node; F/U, follow-up; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; RECIST, Response Evaluation Criteria In Solid Tumors.

Table 2: Creatinine and estimated GFR data at baseline ($N = 215$) and postoperative first ($N = 215$) and last year ($N = 124$).

	Median (min–max, range) or N (percentage, %)
Baseline	
Baseline sCr	1.0 (0.6–1.8)
Baseline eGFR	69.7 (37.3–103.4)
First year	
Change of sCr at first year	2.0 (1–4)
Change of eGFR at first year	69.5 (25.6–129.1)
First year CKD	14 (6.5)
Time to CKD at first year (mo.)	13 (2–16)
Fifth year	
Last CKD	32 (14.9)
Time to CKD at fifth year	35.4 (0.9–133.7)
Change of sCr at fifth year	1.0 (0.6–2.2)
Change of eGFR at fifth year	78.1 (29–118.8)

most cases (60.9%). Other baseline demographics including clinicopathological characteristics and intraoperative findings are described in Table 1.

When comparing the data regarding renal function changes from the 5-year follow-up with those from the 1-year follow-up, there were higher changes in eGFR after 5-years than after 1 year (5 years, 78.1 mL/min/1.73 m^2; 1 year, 69.5 mL/min/1.73 m^2) and higher development of de novo CKD after 5 years than the after 1 year (5 years, 14.9%; 1 year, 6.5%; Table 2). The incidence of de novo CKD in the control, non-CKD, and CKD groups was, respectively, 0%, 2.8%, and 5.2% after 1 year and 0%, 3.2%, and 6.5% after 5 years (both $p < 0.001$, Figure 1). However, the difference regarding the incidence of de novo CKD between the control and the non-CKD groups was not statistically significant after 1 year ($p = 0.648$); compared to the control group, the non-CKD group had a decline in renal function after five years of follow-up (Figure 1(b)). The median time to develop CKD, as identified after 1 and 5 years after PN, was 13 (2–16) months and 35.4 (0.9–133.7) months, respectively ($p < 0.001$; Table 2, Figure 1).

The results of the multivariate analyses of predictive factors for renal functional deterioration or de novo CKD development, given in terms of hazard ratio (HR) and 95% confidence interval (95% CI), for each variable that showed significance at 1 year after PN ($p < 0.05$, Table 3) were as follows: cold ischemia, HR = 0.053, 95% CI = 0.004–0.699; no ischemia, HR = 0.077, 95% CI = 0.007–0.827; Eastern Cooperative Oncology Group (ECOG) score 1, HR = 0.0002, 95% CI = 0.0001–0.077; ECOG score 0, HR = 0.002, 95% CI = 0.0001–0.203; preoperative albumin levels, HR = 0.010, 95% CI = 0.0001–0793; male sex, HR = 31.401, 95% CI = 3.037–324.649; and smoking exposure expressed as pack-years, HR = 1.061, 95% CI = 1.021–1.1036. For each variable that showed significance at 5 years after PN ($p < 0.05$, Table 3), the results of the multivariate analyses were as follows: hypertension, HR = 16.991, 95% CI = 2.666–108.298; preoperative albumin levels, HR = 28.172, 95% CI = 2.177–364.577; De Retis ratio of aspartate aminotransferase/alanine aminotransferase (AST/ALT), HR = 13.772, 95% CI = 1.330–142.550; smoking exposure, HR = 1.081, 95% CI = 1.028–1.137; and preoperative CKD, HR = 13.158, 95% CI = 1.654–104.659.

4. Discussion

In the present study, we evaluated renal functional deterioration and its predictive factors at one and five years after PN in patients with RCC staged T1-T2. The CKD and non-CKD groups accounted for 21.4% and 67.4% of our study sample, respectively, which is in agreement with previously reported rates for CKD (20–24%) [9]. The RCC patients were stratified into CKD or non-CKD groups according to the preoperative state of their renal function, to rule out the oncologic effect of RCC itself on the change in renal function and to differentiate among the factors predisposing for CKD in RCC patients whose renal function is recovering after PN. In addition, we also considered a control group, which included patients who underwent PN for removal of benign renal masses. We examined and compared the postoperative changes in renal

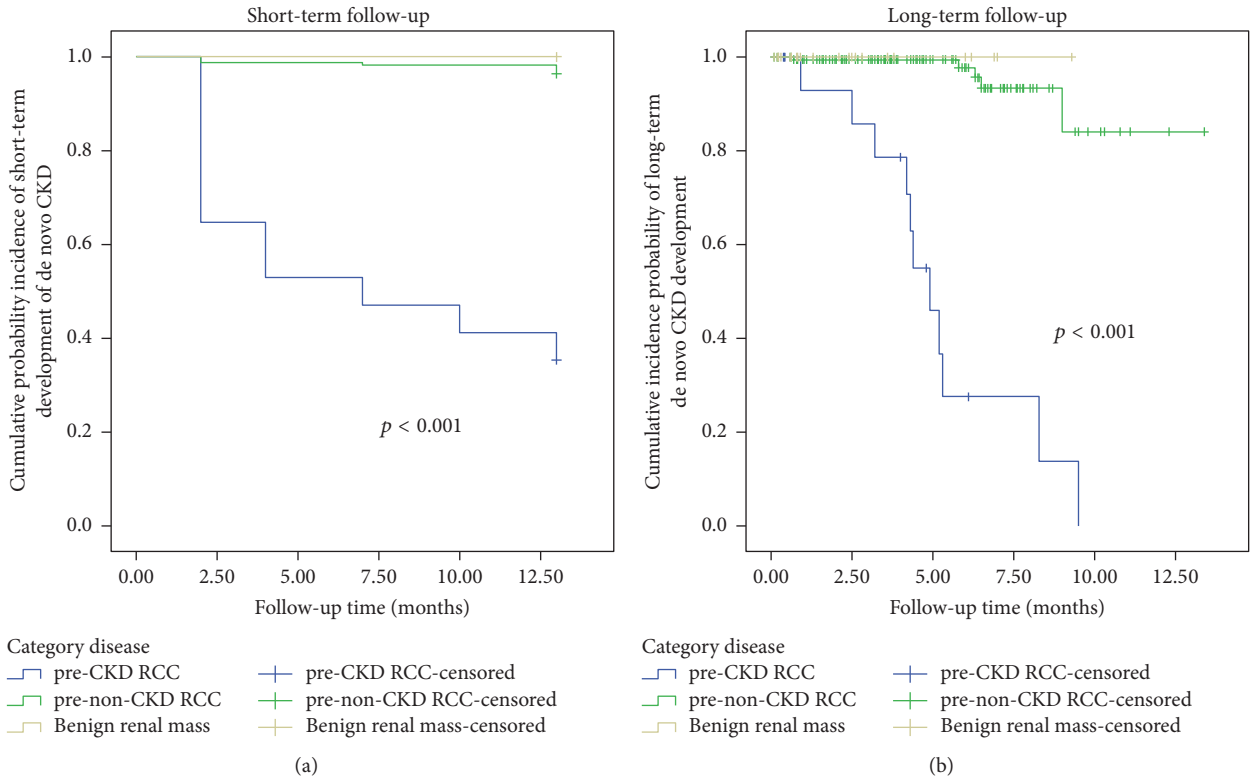

Figure 1: Incidence curve for chronic kidney disease (CKD) (a) during the short-term (first year postoperatively) and (b) during the long-term (fifth year postoperatively) follow-up in patients with renal cell carcinoma (RCC) staged T1-T2, treated with partial nephrectomy.

function for patients of the CKD, non-CKD, and control groups.

As expected, the changes in renal function indicated more deterioration and higher incidence of de novo CKD within 5 years after PN than within the first year (14.9% versus 6.5%; Table 2). The number of patients who developed de novo CKD was almost twice as high ($p < 0.001$; Figure 1) in the CKD group than in the non-CKD group, both during the first year (5.2% versus 2.8%) and during the fifth year (6.5% versus 3.2%) of follow-up, whereas none of the patients in the control group showed postoperative development of CKD. Furthermore, for the first postoperative year, there was no statistically significant difference between the control group and the non-CKD group regarding the number of patients with de novo CKD (Figure 1(b)). These results indicate that, in patients with small localized RCC staged T1-T2, the long-term deterioration of renal function is influenced mostly by the baseline state of the renal function rather than by the PN procedure or by RCC itself. Therefore, an active, close monitoring of renal function is necessary in such high-risk patients undergoing PN, especially those already predisposed to CKD in the preoperative stage. Patients with benign tumors undergoing PN are unlikely to experience deterioration of the renal function merely due to PN itself. However, the renal function in RCC patients with no preoperative CKD should be monitored for at least 5 years after PN, and further investigation should be performed to identify and monitor potential aggravating factors.

We assessed the differences between short-term- and long-term-acting risk factors for renal function deterioration and development of de novo CKD. We considered all known risk factors reported in previous studies [4, 8–13]. Only smoking exposure was found as a significant factor for both the short-term and long-term deterioration of renal function ($p < 0.05$; Table 3). Smoking is known to have detrimental effects on the state of the vessels and kidneys, and heavier smoking may have a more significant effect on renal function recovery [1, 7].

We found that the intraoperative ischemic method (cold ischemia, HR = 0.053; no ischemia, HR = 0.077) represented a significant preventive factor for development of de novo CKD in the short term, which is similar to what has been reported in previous studies [12, 14]. The ischemic method prevented ischemic changes in the nephrons. The no-clamping technique without ischemia was the best PN procedure for preservation of renal function, where possible. However, this observation might be affected by the fact that most of the renal masses included in our study were staged T1 (89.8%) and represented small-sized (2.0 cm) RCC. Under such circumstances, the removal of a small volume of kidney tissue is not expected to critically influence the degree of postoperative deterioration in renal function. In addition, our multivariate analysis did not indicate any significance of ischemic time in terms of CKD prediction ($p > 0.05$), despite the fact that univariate analysis showed that ischemic time differed significantly among the groups (29.5 ± 13.0 min for

Table 3: Multivariate analysis of predictive risk factors with backward selection ($p = 0.05$) for 1-year short-term and 5-year long-term renal functional deterioration.

	p value	Hazard ratio	95.0% confidence interval	
			Lower	Upper
Significant parameters at 1 year				
Sex	0.004	31.401	3.037	324.649
Smoking volume	0.003	1.061	1.021	1.103
Albumin	0.039	.010	.0001	.793
Hemoglobin	0.077	1.619	.949	2.765
Ischemic method				
Warm	0.076			
Cold	0.026	.053	.004	.699
None	0.034	.077	.007	.827
ECOG				
Group 2	0.012			
Group 1	0.004	.0002	.0001	.077
Group 0	0.009	.002	.0001	.203
Significant parameters at 5 years				
Hypertension	0.003	16.991	2.666	108.298
Preoperative Albumin (mg/dl)	0.011	28.172	2.177	364.577
Calcium level (mg/dl)	0.132	.135	.010	1.829
De Ritis ratio	0.028	13.772	1.330	142.550
ASA class 1	0.001			
ASA class 2	0.317	.101	.001	8.968
ASA class 3	0.212	16.464	.202	1343.216
Smoking volume (PY)	0.003	1.081	1.028	1.137
Predisposing CKD	0.015	13.158	1.654	104.659

ECOG, Eastern Cooperative Oncology Group score; De Ritis ratio, AST/APT; ASA, American Society of Anesthesiologist Score; CKD, chronic kidney disease.

the CKD RCC group, 21.9 ± 21 min for the non-CKD RCC group, and 10.7 ± 16.1 min for the control group; $p < 0.001$; data not shown). A recent systematic review showed that warm ischemia does not harm long-term renal function as long as ischemia time is kept between 20 and 25 minutes [15].

We also found that, in the short term, further significant factors influencing the postoperative evolution of renal function were male sex (HR, 31.401), albumin levels (HR, 0.010), and ECOG score (0 and 1, HR < 1.0), which were previously reported as factors affecting renal function [16–18]. Patients with good nutritional status and general performance in the preoperative stage are expected to have good baseline renal function and postoperative recovery after PN [16]. Compared to female patients, male Korean patients have a higher tendency of exposing themselves to negative social factors that may affect the recovery of renal function, likely because of their stressful occupational environment and habit of social drinking [17, 19, 20]. Another interesting finding regarding short-term risk factors was that an ECOG score of 1 was associated with less deterioration of renal function than an ECOG score of 0, probably because patients with ECOG score 1 were more likely to visit their physician for health issues and have their renal function closely monitored by clinicians, who intervened sufficiently early to prevent or delay renal function deterioration or detect newly developed, small renal masses.

As for the long-term factors, we found no protecting factors but did identify detrimental factors such as hypertension (HR = 16.991), high levels of serum albumin (HR = 28.172), high De Ritis ratio (HR = 13.772), and baseline predisposition to CKD (HR = 13.158) in addition to smoking exposure (HR = 1.081). These findings are in line with those reported by previous studies [1, 7, 9, 10, 17, 20–22]. In particular, hypertension and predisposition for CKD represent well-known aggravating factors in combination with smoking exposure, causing systemic cardiovascular changes and deterioration in renal function [10, 17, 20–22]. Interestingly, our multivariate analysis did not indicate diabetes as a significant predictor of short- or long-term CKD development, in spite of the significant differences in the incidence of diabetes among the three groups (3.7% in the CKD RCC group, 9.8% in the non-CKD RCC group, and 1.4% in the control group; $p = 0.002$; data not shown). This observation is likely related to the fact that our study sample included patients with RCC staged T1-T2, which required removing only a small volume of tissue during PN; furthermore, most patients did not exhibit severe

diabetic state, suggesting that this aspect did not significantly affect kidney function and, consequently, was not related to the development of CKD postoperatively.

Abnormalities in albumin levels and De Ritis ratio values are factors indicating chronic liver disease [23]. It is well known that patients with chronic liver disease also had poor renal function, mostly related to the development of acute kidney injury, precipitated by either an acute disturbance of hemodynamics or an acute structural damage to the kidneys [10]. The incidence of chronic renal failure has been rising, due to increasing prevalence of conditions such as diabetes or viral hepatitis, which can be associated with renal damage. In addition, AST and ALT levels, which provide the De Ritis ratio [24], have been previously reported as significant prognostic biomarkers in several malignancies including kidney diseases [25]. The mechanism underlying the relationship of AST and RCC is related to the vital role of AST in glycolysis by relocation of NADH into the mitochondria through the malate-aspartate shuttle pathway, in which clear cell RCC with VHL loss was known to induce the expression of hypoxia factors known to be connected to extensively increased glycolysis in the mitochondria, which is well-known as the Warburg effect [26, 27]. No studies have ever suggested the importance of De Ritis ratio on postoperative renal functional changes after renal surgeries for which the levels of hepatic factors and serum albumin are significant.

Our study has several limitations related to the small sample size and retrospective design. Not all the patients completed at least five years of follow-up, and thus the long-term evaluation of renal function and underlying hepatic diseases was incomplete for such patients. However, it is clinically relevant to identify significant risk factors (among which those related to hepatic disease) for renal function deterioration, and our study is the first to identify long-term-acting risk factors related to hepatic function that affect postoperative renal function in RCC patients who underwent PN. Further prospective studies with long-term follow-up are warranted to evaluate the role of hepatic function in the recovery of renal function.

5. Conclusion

The study showed the significant predisposal of CKD patients for long-term renal function deterioration, and the significant influence of intraoperative ischemic method and time for short-term renal function deterioration in patients with T1-T2 RCC who underwent PN. Further parameters including smoking exposure, hypertension, preoperative albumin levels, and De Ritis ratio values were also significant factors for postoperative renal functional deterioration. Careful patient selection for postoperative general management, as well as intraoperative planning, may help reduce this unfavorable outcome in renal function.

Competing Interests

The authors declared no competing interests.

Authors' Contributions

Sung Han Kim, Jae Young Joung, Ho Kyung Seo, Kang Hyun Lee, and Jinsoo Chung contributed to project development, data collection, and manuscript writing. Jae Young Joung, Ho Kyung Seo, Kang Hyun Lee, and Jinsoo Chung assisted in data collection. Sung Han Kim helped in manuscript writing.

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Research Article

Prognostic Significance of Preoperative Neutrophil-to-Lymphocyte Ratio in Nonmetastatic Renal Cell Carcinoma: A Large, Multicenter Cohort Analysis

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Background. The prognostic significance of the neutrophil-to-lymphocyte ratio (NLR) in nonmetastatic renal cell carcinoma (non-mRCC) is controversial, although NLR has been established as a prognostic factor in several cancers. The objective of our study was to assess the prognostic significance of preoperative NLR in non-mRCC, based on a large, multicenter cohort analysis. *Methods*. Totally, 1,284 non-mRCC patients undergoing surgery were enrolled from six institutions between 2000 and 2014. Recurrence-free survival (RFS) and cancer-specific survival (CSS) were calculated, and the prognostic significance of NLR was evaluated. *Results*. Patients with higher NLR had larger tumors ($p < 0.001$), higher T stage ($p < 0.001$), worse Eastern Cooperative Oncology Group performance status ($p < 0.001$), worse symptoms ($p = 0.003$), sarcomatoid differentiation ($p = 0.004$), and tumor necrosis ($p < 0.001$). The 5-year RFS and CSS rates were significantly lower in patients with high NLR than in those with low NLR (each $p < 0.001$). Multivariate analysis identified NLR to be an independent predictor of RFS and CSS (each $p < 0.05$). Moreover, predictive accuracy of multivariate models for RFS and CSS increased by 2.2% and 4.2%, respectively, with NLR inclusion. *Conclusions*. Higher NLR was associated with worse clinical behavior of non-mRCC. Also, NLR was a significant prognostic factor of both RFS and CSS.

1. Introduction

Renal cell carcinoma (RCC) accounts for 3-4% of all adult malignancies, and its incidence rate has been steadily increasing worldwide [1]. In the United States, the estimated numbers of new cases and deaths in 2015 were 61,560 and 14,080, respectively [1]. Therefore, it is essential to optimize decision making in treatment and prognosis of RCC and to provide better counseling for each RCC patient. Until now, many characteristics of RCC itself and patients have been suggested as possible prognostic factors. However, only a few, including pathological stage and Fuhrman grade, are undisputed prognostic factors for RCC, especially nonmetastatic RCC (non-mRCC) [2].

Inflammation has an impact on tumorigenesis and tumor progression [3]. In addition, inflammation has been recently shown to predict the prognosis of various operable cancers [4]. As inflammation is easily accessible, can be measured reliably, and can be incorporated into the tumor staging system [4], its use as a prognostic factor seems promising.

Of the many hematological and biochemical markers for systemic inflammatory response, neutrophil-to-lymphocyte

Table 1: Main characteristics of recently published studies on prognostic value of neutrophil-to-lymphocyte ratio in patients with nonmetastatic renal cell carcinoma.

Study cohort	Study cases	Histologic subtype	TNM stage	NLR				Adjustment variables
				Value	Cut-off	Prognostic significance*		
						RFS#	CSS	
Lucca et al. [15]	430	Clear cell	T1–3	Median 2.9	4.2	Yes	NA	Stage, grade, tumor size, necrosis
Pichler et al. [16]	678	Clear cell	T1–4	Mean 3.51	3.3	No	No	Age, gender, stage, grade, necrosis
Viers et al. [17]	827	Clear cell	M0	Median 3.51	4.0	No	Yes	Age, gender, ECOG PS, tumor size, Sx, stage, grade, necrosis
Huang et al. [18]	218	Papillary	T1–3Nx	Median 3.1	3.6	Yes	NA	Age, gender, Sx, DM, HTN, stage, node, TNM group, grade, necrosis, ANC, ALC
De Martino et al. [19]	281	Papillary and chromophobe	T1–3Nx	Median 2.6	3.6	Yes	NA	Age, gender, ECOG PS, stage, TNM group, grade, MVI, ANC, ALC
Wen et al. [20]	327	All	T1–4	Mean 2.72	1.7	Yes	NA	Age, gender, tumor size, stage, subtype
Forget et al. [21]	227	All	M0	Median 3.01	5.0	Yes	NA	Age, gender, stage, grade, node
Jagdev et al. [22]	228	3 major subtypes	M0	NA	NA	No	NA	NA
Present study	1,284	3 major subtypes	T1–4	Mean 2.2	3.7	Yes	Yes	Age, gender, BMI, ECOG PS, Sx, tumor size, stage, grade, subtype, sarcomatoid differentiation, necrosis

*Results from multivariate analysis.
#RFS stands for disease-free, progression-free, and metastasis-free survival as well as recurrence-free survival.
TNM, tumor-node-metastasis; NLR, neutrophil-to-lymphocyte ratio; RFS, recurrence-free survival; CSS, cancer-specific survival; necrosis, tumor necrosis; NA, not available; ECOG PS, Eastern Cooperative Oncology Group performance status; MVI, microvascular invasion; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Sx, symptoms at presentation; DM, diabetes mellitus; HTN, hypertension.

ratio (NLR) has been introduced relatively recently [5]. Neutrophils represent the inflammatory response, whereas lymphocytes reflect cell-mediated immunity [3]. Therefore, NLR may be a better indicator of inflammation compared to existing conventional markers. Furthermore, NLR is an inexpensive, easily accessible, and widely available marker. Initially, NLR was validated as a prognostic factor of major cardiac events [6, 7]. Since then, it has been established as a prognostic factor in several cancers including hepatocellular carcinoma and colorectal cancer [8–10].

Multiple studies suggested that NLR might be a prognostic factor in mRCC, irrespective of the treatment method [8, 11–13]. However, the few studies investigating the prognostic significance of NLR in non-mRCC have reported conflicting results [14–22]. Furthermore, previous studies were small-scale and lacked other possible prognostic factors as confounding variables (Table 1).

We assessed the prognostic significance of NLR in a large, multicenter cohort of non-mRCC patients. To our knowledge, this is the largest scale study conducted in the field, which also included the most widely accepted prognostic factors.

2. Patients and Methods

2.1. Patients. Approval for the study was obtained from the relevant institutional ethics committee. A total of 3,410 patients with RCC underwent curative partial or radical nephrectomy at six institutions between 2000 and 2014. We consecutively excluded 239 patients with lymph node and/or distant metastasis immediately after surgery, 574 patients who did not have any of the three major RCC subtypes (clear cell, papillary, and chromophobe variants), 351 patients with postoperative follow-up durations within 3 months, and 962

patients with unavailable data on at least one of the relevant parameters. Only patients with complete absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) data within the 2 weeks before surgery were included in the study. Finally, 1,284 non-mRCC patients (pathologically, TxN0M0) from any of the three major RCC subtypes were included in this study and retrospectively reviewed.

2.2. Variables. The characteristics of RCC and patients are detailed in Table 2.

For most patients, postoperative follow-up was scheduled every 3 months for 6 months, every 6 months for the next 3 years, and yearly thereafter. NLR was defined as the ANC divided by the ALC. The general health status was determined by the Eastern Cooperative Oncology Group performance status (ECOG PS). Tumor size was measured as the greatest diameter of the pathologic specimen. Pathologic staging was performed using the 2002 tumor-node-metastasis (TNM) classification system, and grading was performed using Fuhrman nuclear grading system. The histologic subtype was determined using the 2004 World Health Organization (WHO) international histological classification of tumors. For all specimens, urologic pathologists of each institution determined the pathologic features of the tumor. Recurrence-free survival (RFS) and cancer-specific survival (CSS) were calculated from the date of surgery to the date of recurrence and RCC-specific death, respectively, and were confirmed by imaging studies.

2.3. Statistical Analysis. The primary endpoints were RFS and CSS. The ideal cut-off level of NLR was estimated by testing all possible cut-off levels that were likely to discriminate between survival and recurrence and RCC-specific death, using the Cox proportional hazard model. The ideal cut-off level determined was then rounded to clinically relevant levels [11]. To compare the relationship between the characteristics of RCC and the patients, Student *t*-test, Pearson chi-squared test, or Fisher exact test stratified by NLR was used.

The RFS and CSS rates were calculated using the Kaplan-Meier method stratified by NLR, and the log-rank test was used to compare the groups. The prognostic significance of NLR as a continuous and categorical variable was evaluated using variables entered into the Cox proportional hazards model. The variables analyzed included patient age, gender, body mass index (BMI), ECOG PS, symptoms at presentation, tumor size, pathologic T stage, Fuhrman grade, histologic subtype, sarcomatoid differentiation, and tumor necrosis. The accuracy of NLR in predicting RFS and CSS was reflected by Harrell concordance index (c-index) calculated using the Cox proportional hazard models with and without the incorporation of NLR.

All tests were two-sided, and $p < 0.05$ was considered statistically significant. Survival, the Cox regression method in R 3.2.2 (R Development Core Team, Vienna, Austria, https://www.R-project.org/) was used to calculate the c-index, whereas IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was used for other statistical assessments.

3. Results

3.1. The Association between Clinical and Pathologic Characteristics and NLR. A cut-off NLR level of 3.7 was estimated to be the optimal cut-off level for discriminating between patients' recurrences (hazard ratio (HR) = 3.049, 95% confidence interval (CI) = 2.015–4.614, and $p < 0.001$). The same NLR cut-off level was effective for discriminating between patients' RCC-specific deaths (HR = 4.947, 95% CI = 2.766–8.849, and $p < 0.001$). Based on these results, the NLR cut-off level of 3.7 was used in all subsequent analyses (low NLR, <3.7; high NLR, ≥3.7).

The mean follow-up period was 46.8 months for all patients (median 39 months; interquartile range, 19–69 months). The mean NLRs of patients with low and high NLR were 1.8 ± 0.7 and 6.0 ± 3.2, respectively ($p < 0.001$). Table 1 shows the association of NLR with different clinical and pathological characteristics. Patients with high NLR differed significantly from those with low NLR in various parameters. Patients with high NLR were older ($p = 0.001$) and had higher ECOG PS ($p < 0.001$) and T stage ($p < 0.001$) and larger tumors ($p < 0.001$) compared to those with low NLR. Patients with high NLR also had greater symptom ratios ($p = 0.003$), sarcomatoid differentiation ratios ($p = 0.004$), and tumor necrosis ratios ($p < 0.001$).

3.2. Recurrence-Free Survival in relation to NLR. During follow-up, 142 (11.1%) patients had recurrence (Table 2). The 5-year RFS rates were 71.6% in patients with high NLR and 88.2% in those with low NLR. The 5-year RFS rate was significantly lower in patients with high NLR than in those with low NLR ($p < 0.001$; Figure 1(a)).

Multivariate analysis identified NLR to be an independent predictor of RFS (HR of NLR as a continuous variable = 1.081, $p = 0.028$; HR of NLR as a categorical variable = 1.788, $p = 0.009$; Table 3). The predictive accuracy of the multivariate model with NLR was 81.1%, whereas that of the multivariate model without NLR was 78.9%.

3.3. Cancer-Specific Survival in relation to NLR. During follow-up, 56 (4.4%) patients died of RCC-related causes (Table 2). The 5-year CSS rates were 84.2% in patients with high NLR and 96.4% in those with low NLR. The 5-year CSS rate was significantly lower in patients with high NLR than in those with low NLR ($p < 0.001$; Figure 1(b)).

Multivariate analysis identified NLR to be an independent predictor of CSS (HR of NLR as a continuous variable = 1.156, $p = 0.009$; HR of NLR as a categorical variable = 2.566, $p = 0.004$; Table 4). The predictive accuracy of the multivariate model with NLR was 87.9%, whereas that of the multivariate model without NLR was 83.7%.

4. Discussion

In this study, NLR was identified to be a significant prognostic factor of both RFS and CSS in patients with non-mRCC, even when the models were adjusted for other well-known prognostic factors. The predictive accuracy of the

Table 2: Association of different clinical and pathological characteristics with neutrophil-to-lymphocyte ratio in patients with nonmetastatic renal cell carcinoma.

Variable	All	Low NLR	High NLR	p value
Number of subjects	1,284	1,168	116	
NLR, mean ± SD	2.2 ± 1.7	1.8 ± 0.7	6.0 ± 3.2	<0.001*
Age, mean ± SD, year	55.9 ± 12.9	55.5 ± 12.8	59.8 ± 12.9	0.001*
Gender				0.236**
Male, *n* (%)	913 (71.1)	825 (70.6)	88 (75.9)	
Female, *n* (%)	371 (28.9)	343 (29.4)	28 (24.1)	
BMI, mean ± SD, kg/m^2	24.6 ± 3.3	24.7 ± 3.2	23.8 ± 3.4	0.006*
ECOG PS ≥ 1, *n* (%)	180 (14.0)	148 (12.7)	32 (27.6)	<0.001**
Symptoms at presentation				0.003**
No symptom, *n* (%)	975 (75.9)	900 (77.1)	75 (64.7)	
Symptom, *n* (%)	309 (24.1)	268 (22.9)	41 (35.3)	
Tumor size				
(1) mean ± SD, cm	4.08 ± 2.68	3.94 ± 2.54	5.50 ± 3.55	<0.001*
(2) Category				<0.001**
<4 cm, *n* (%)	748 (58.3)	701 (60.0)	47 (40.5)	
4–7 cm, *n* (%)	351 (27.3)	321 (27.5)	30 (25.9)	
≥7 cm, *n* (%)	185 (14.4)	146 (12.5)	39 (33.6)	
Side				1.000***
Unilateral, *n* (%)	1,268 (98.8)	1,153 (98.7)	115 (99.1)	
Bilateral, *n* (%)	16 (1.2)	15 (1.3)	1 (0.9)	
Type of nephrectomy				<0.001**
Radical, *n* (%)	634 (49.4)	552 (47.3)	82 (70.7)	
Partial, *n* (%)	650 (50.6)	616 (52.7)	34 (29.3)	
Method of surgery				0.042**
Open, *n* (%)	697 (54.3)	628 (53.8)	69 (59.5)	
Laparoscopic, *n* (%)	316 (24.6)	283 (24.2)	33 (28.4)	
Robot, *n* (%)	271 (21.1)	257 (22.0)	14 (12.1)	
T stage				<0.001**
T1, *n* (%)	1,016 (79.1)	945 (80.9)	71 (61.2)	
T2, *n* (%)	89 (6.9)	75 (6.4)	14 (12.1)	
T3-4, *n* (%)	179 (13.9)	148 (12.7)	31 (26.7)	
Fuhrman's grade				0.561**
G1-2, *n* (%)	664 (51.7)	607 (52.0)	57 (49.1)	
G3-4, *n* (%)	620 (48.3)	561 (48.0)	59 (50.9)	
Histologic subtype				0.042**
Clear cell, *n* (%)	1,114 (86.8)	1,017 (87.1)	97 (83.6)	
Papillary, *n* (%)	87 (6.8)	73 (6.3)	14 (12.1)	
Chromophobe, *n* (%)	83 (6.5)	78 (6.7)	5 (4.3)	
Sarcomatoid differentiation, yes, *n* (%)	29 (2.3)	22 (1.9)	7 (6.0)	0.004**
Tumor necrosis, yes, *n* (%)	208 (16.2)	174 (14.9)	34 (29.3)	<0.001**
Recurrence, *n* (%)	142 (11.1)	114 (9.8)	28 (24.1)	<0.001**
RCC-specific death, *n* (%)	56 (4.4)	40 (3.4)	16 (13.8)	<0.001**

NLR, neutrophil-to-lymphocyte ratio; low NLR, <3.7; high NLR, ≥3.7; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; RCC, renal cell carcinoma; *n*, number of subjects; SD, standard deviation.

*Student *t*-test.

**Pearson's chi-square test.

***Fisher's exact test.

Table 3: Multivariate analyses predicting probability of cancer recurrence in relation to the neutrophil-to-lymphocyte ratio in patients with nonmetastatic renal cell carcinoma.

Variables	NLR as a continuous variable			NLR as a categorical variable		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.011	0.997–1.025	0.134	1.011	0.997–1.026	0.123
Gender						
Female versus male	0.873	0.588–1.296	0.502	0.876	0.591–1.299	0.510
BMI	0.959	0.907–1.015	0.146	0.959	0.907–1.014	0.146
ECOG PS						
≥1 versus 0	1.936	1.270–2.950	0.002	1.900	1.244–2.902	0.003
Symptoms at presentation	1.185	0.811–1.731	0.380	1.208	0.830–1.758	0.325
Tumor size	1.011	1.005–1.017	0.001	1.011	1.004–1.017	0.001
T stage			0.009			0.010
T2 versus T1	1.384	0.745–2.571	0.303	1.376	0.743–2.550	0.310
T3-4 versus T1	2.068	1.281–3.340	0.003	2.050	1.267–3.314	0.003
Fuhrman's grade						
G3-4 versus G1-2	1.974	1.352–2.882	<0.001	1.958	1.340–2.863	0.001
Histologic subtype			0.012			0.019
pRCC versus cRCC	1.044	0.582–1.872	0.886	1.029	0.575–1.841	0.924
chRCC versus cRCC	0.104	0.023–0.467	0.003	0.132	0.032–0.545	0.005
Sarcomatoid differentiation	2.095	1.061–4.137	0.033	2.004	1.010–3.977	0.047
Tumor necrosis	1.255	0.817–1.927	0.300	1.265	0.825–1.939	0.282
NLR						
(1) Continuous	1.081	1.009–1.160	0.028			
(2) High versus low NLR				1.788	1.153–2.771	0.009

NLR, neutrophil-to-lymphocyte ratio; low NLR, <3.7; high NLR, ≥3.7; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; cRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; HR, hazard ratio; CI, confidence interval.

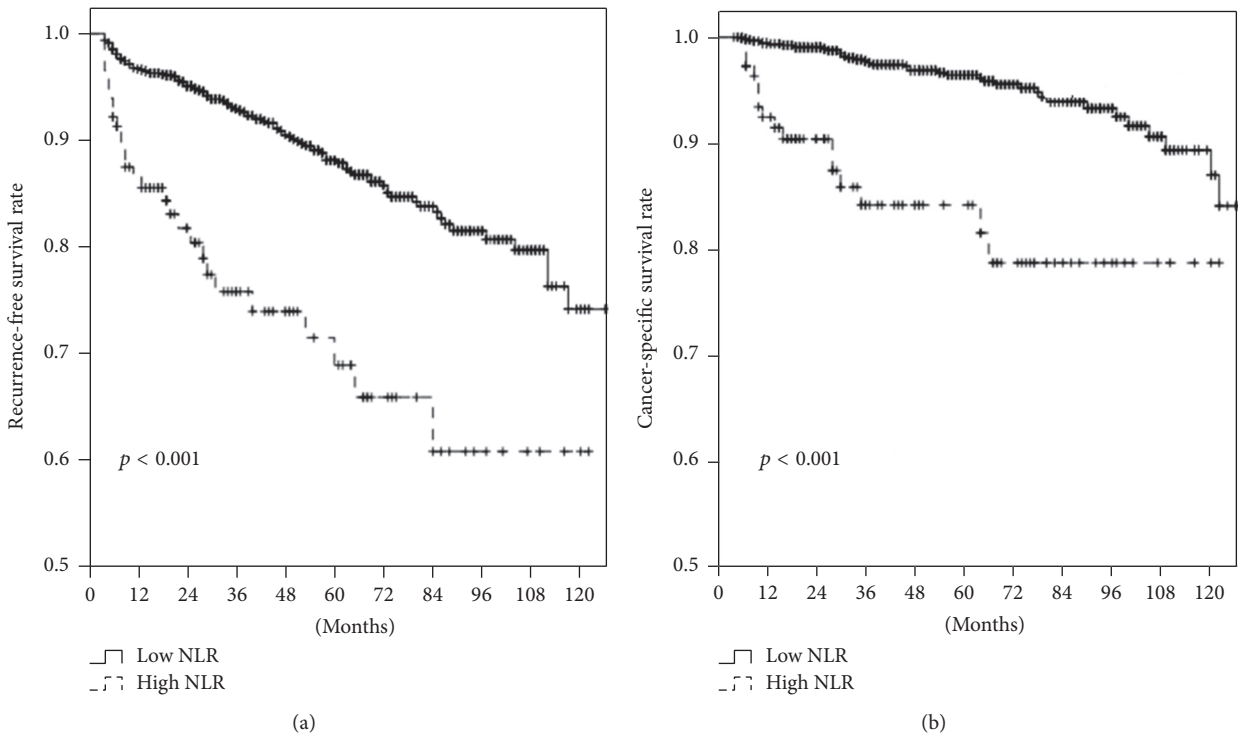

Figure 1: Kaplan-Meier curve for recurrence-free survival (a) and cancer-specific survival (b) for patients with nonmetastatic renal cell carcinoma according to neutrophil-to-lymphocyte ratio. NLR, neutrophil-to-lymphocyte ratio.

Table 4: Multivariate analyses predicting probability of cancer-specific death in relation to the neutrophil-to-lymphocyte ratio in patients with nonmetastatic renal cell carcinoma.

Variables	NLR as a continuous variable			NLR as a categorical variable		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.042	1.016–1.069	0.002	1.044	1.018–1.072	0.001
Gender						
Female versus male	0.652	0.324–1.313	0.231	0.648	0.323–1.300	0.222
BMI	0.916	0.832–1.009	0.074	0.924	0.840–1.017	0.105
ECOG PS						
≥1 versus 0	2.820	1.498–5.309	0.001	2.672	1.408–5.071	0.003
Symptoms at presentation	1.029	0.558–1.897	0.927	1.056	0.577–1.932	0.860
Tumor size	1.012	1.002–1.022	0.015	1.012	1.002–1.022	0.018
T stage			0.022			0.020
T2 versus T1	0.665	0.198–2.233	0.509	0.662	0.198–2.215	0.503
T3-4 versus T1	2.175	1.025–4.617	0.043	2.209	1.041–4.688	0.039
Fuhrman's grade						
G3-4 versus G1-2	2.155	1.141–4.072	0.018	2.101	1.110–3.977	0.023
Histologic subtype			0.854			0.860
pRCC versus cRCC	1.268	0.551–2.919	0.576	1.257	0.554–2.850	0.584
chRCC versus cRCC	0.001	<0.001–5.496	0.959	0.001	<0.001–6.687	0.962
Sarcomatoid differentiation	3.355	1.230–9.148	0.018	3.092	1.123–8.514	0.029
Tumor necrosis	1.054	0.509–2.181	0.888	1.097	0.537–2.242	0.799
NLR						
(1) Continuous	1.156	1.037–1.289	0.009			
(2) High versus low NLR				2.566	1.348–4.887	0.004

NLR, neutrophil-to-lymphocyte ratio; low NLR, <3.7; high NLR, ≥3.7; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; cRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; HR, hazard ratio; CI, confidence interval.

multivariate models for RFS and CSS increased by 2.2% and 4.2%, respectively, with NLR inclusion.

The present study had several strengths, compared to the previous studies in the field (Table 1). Firstly, this was the largest study that included the three major histologic subtypes of RCC. Secondly, while the present study evaluated both RFS and CSS, most of the previous studies did not evaluate CSS. The identification of CSS as well as RFS is a corner stone to prove the prognostic value of NLR. Finally, the present study included the most widely accepted independent prognostic factors of non-mRCC, including age, gender, and BMI; ECOG PS; symptoms at presentation; tumor size, stage, and grade; histologic subtype, sarcomatoid differentiation, and tumor necrosis.

In terms of clinical and pathologic characteristics at diagnosis, patients with high NLR differed significantly from those with low NLR in various parameters. Patients with high NLR had a larger tumor, a higher T stage, worse ECOG PS, worse symptoms, sarcomatoid differentiation, and tumor necrosis. These results are similar to those reported in previous studies [17, 18, 20], suggesting that higher NLR may be associated with worse clinical behavior of non-mRCC.

NLR was shown to be a possible prognostic factor for mRCC in multiple studies, irrespective of the treatment method [8, 11–13]. However, studies concerning the prognostic significance of NLR for non-mRCC are scarce, with conflicting results. Some studies did not show a relationship between NLR and non-mRCC prognosis [16, 22], while others did [14, 15, 18–21]. Interestingly, one study reported different results for RFS and CSS [17]. These conflicting results may partly be because previous studies were relatively small-scale and lacked other possible prognostic factors as confounding variables (Table 1).

An important point is that most of the previous studies incorporated NLR as a categorical variable in their models. The use of a continuous variable reflects an intrinsic effect, whereas that of a categorical variable seems to adjust itself and to be created [23]. In addition, it is difficult to interpret the prognostic value of NLR using different cut-off levels, although most studies including the present one showed that the cut-off levels of NLR were in the range 3-4 (Table 1). In this respect, it is remarkable that NLR was not only used as a categorical variable but also as a continuous variable in this study. We identified that NLR as a continuous variable was also an independent prognostic factor. Interestingly, NLR cut-off level of 3.7 was estimated for CSS as well as RFS in this study. Considering that CSS is in alignment with RFS in non-mRCC, these results may strengthen our conclusion.

It is well known that inflammation affects tumorigenesis and progression [3, 17]. Neutrophils represent the inflammatory response, whereas lymphocytes reflect cell-mediated immunity [3]. Therefore, a high NLR reflects both an increased inflammatory and a decreased antitumor immune response, suggesting a possible contribution to aggressive

tumor biology, tumor progression, and poor survival [17]. In various cancers including hepatocellular carcinoma and colorectal cancer, high NLR was associated with poor outcome [9, 10]. This was also supported by the results of our clinical study, which showed that higher NLR was likely to be associated with worse clinical behavior and indicated poor prognosis for RFS and CSS.

In contrast to our findings, some studies did not show a relationship between NLR and non-mRCC prognosis [16, 22]. In a study of 678 patients with cRCC, Pichler et al. [16] reported that NLR was not an independent prognostic factor for CSS or metastasis-free survival. However, NLR was only included as a categorical variable in this analysis. Certainly, a specified cut-off level may create a false or misleading association. Furthermore, they only analyzed patients with cRCC. As RCC is a heterogeneous and complex disease [24, 25], its results may not be directly applicable to patients with non-cRCC. In a study of 228 patients with non-mRCC, Jagdev et al. [22] reported that NLR was not an independent prognostic factor for disease-free survival. However, their study involved only a small number of patients. Furthermore, as their study did not focus on NLR, the data on NLR were insufficient and were logarithmically transformed for analysis.

This study also had a few limitations. Firstly, data were retrospectively collected. Secondly, preoperative conditions such as chronic infection and chronic disease, which might affect the level of NLR, were not included. However, it is impossible to identify all the conditions associated with the NLR level in the clinical setting. Therefore, this study may be a better representation of the prognostic significance of NLR in actual practice. Lastly, this study lacked a central review of pathology, although most of the previous large multicenter studies did. Instead, urologic pathologists determined all pathologic features at each institution.

Despite limitations, it is noted that this study is the largest in the field, incorporating the most widely accepted independent prognostic factors of non-mRCC and evaluating both RFS and CSS.

5. Conclusion

This study showed that patients with high NLR differed significantly from those with low NLR in various clinical and pathologic parameters, suggesting that higher NLR may indicate worse clinical behavior of non-mRCC. In addition, NLR was a significant prognostic factor of both RFS and CSS, and incorporation of NLR into conventional prognostic predictors increased the predictive accuracy by 2.2% and 4.2%, respectively. This study suggests that the use of preoperative NLR may be helpful in counseling and clinical trial design in patients with non-mRCC.

Abbreviations

Non-mRCC: Nonmetastatic renal cell carcinoma
NLR: Neutrophil-to-lymphocyte ratio
ANC: Absolute neutrophil count
ALC: Absolute lymphocyte count
ECOG PS: Eastern Cooperative Oncology Group performance status
TNM: Tumor-node-metastasis
WHO: World Health Organization
RFS: Recurrence-free survival
CSS: Cancer-specific survival
BMI: Body mass index
HR: Hazard ratio
CI: Confidence interval.

Competing Interests

The authors have nothing to disclose.

Authors' Contributions

Seok-Soo Byun participated in the study's design, coordination, treatment of patients, and data collection. Eu Chang Hwang, Seok Ho Kang, Sung-Hoo Hong, Jinsoo Chung, Tae Gyun Kwon, Hyeon Hoe Kim, Cheol Kwak, and Yong-June Kim were members of the research group and participated in the treatment of patients and data collection. Won Ki Lee conceived the study, participated in its design, performed the statistical analysis, and drafted the manuscript. All authors read and approved the final manuscript.

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Clinical Study

Pretreatment Neutrophil-to-Lymphocyte Ratio Can Predict the Prognosis in Bladder Cancer Patients Who Receive Gemcitabine and Nedaplatin Therapy

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Introduction and Objectives. Neutrophil-to-lymphocyte ratio (NLR) has been suggested to be a simple marker of the systemic inflammatory response in critical care patients. We previously assessed the utility of NLR as a biomarker to predict tumor recurrence and cancer death in bladder cancer patients who underwent radical cystectomy. In this study, we evaluated the prognostic impact of NLR in bladder cancer patients who received gemcitabine and nedaplatin (GN) chemotherapy. *Methods*. A total of 23 patients who received GN chemotherapy for advanced bladder cancer were enrolled in this study. The cut-off point of NLR according to the sensitivity and specificity levels was derived from the area under receiver operator characteristics (AUROC) curve plotted for disease progression or overall mortality. *Results*. The NLR cut-off point was determined as 4.14 for both tumor progression and overall mortality. Median progression-free survival (PFS)/overall survival (OS) in the higher NLR group (NLR $\geq$ 4.14) and lower NLR group (NLR $<$ 4.14) were 194/468 days versus 73/237 days, respectively. Kaplan-Meier analysis showed that higher NLR significantly correlated with poorer PFS ($p = 0.011$) and OS ($p = 0.045$). *Conclusions*. NLR may serve as a new biomarker to predict responses to GN-based chemotherapy in advanced bladder cancer patients and/or their prognosis.

1. Introduction

Cisplatin alone, gemcitabine and cisplatin (GC), and methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) have evolved as the standard first-line systemic therapy for recurrent or metastatic urothelial carcinoma (UC). However, its serious dose-limiting adverse effects include considerable renal toxicity, marked emesis, and neurotoxicity. Its nephrotoxic properties particularly make it unsuitable for patients with renal dysfunction. Indeed, UC is usually seen in the elderly, and due to age-associated impairment in the renal function and performance status, approximately 30–50% of patients are ineligible for cisplatin-based chemotherapy [1]. Instead, nedaplatin, a second-generation platinum complex with lower renal and gastrointestinal toxicities than cisplatin, can be used in patients with marginal renal function [2].

Neutrophil-to-lymphocyte ratio (NLR) has been suggested as a simple marker of the systemic inflammatory response in critical care patients [3]. NLR can be easily calculated from routine complete blood counts in the peripheral blood [4, 5]. It has also been reported to be an independent

prognosticator for some solid malignancies including bladder cancer [4–13].

We previously assessed the utility of NLR as a biomarker to predict tumor recurrence and cancer death in bladder cancer patients who underwent radical cystectomy [14]. In the current study, we investigated whether NLR could predict the prognosis of bladder cancer patients who received gemcitabine and nedaplatin (GN) chemotherapy.

2. Materials and Methods

2.1. Patients. A total of 23 patients (17 men and 6 women) with measurable lesions were treated with GN chemotherapy for their advanced bladder UC at our institutions from 2005 to 2014. Of these patients, 4 underwent radical cystectomy prior to GN therapy. The mean age was 63.0 years (range 46–74), the mean creatinine clearance was 80.5 mL/min (range 43–157.1), and the mean follow-up period was 11.5 months (range 2.3–29.8). Written informed consent was obtained from all patients and the institutional review board approved this study.

2.2. Drug Administration and Evaluation of Responses. Patients received gemcitabine 1,000 mg/m^2 on days 1 and 8 plus nedaplatin 80 or 100 mg/m^2 on day 1. Dose modification was allowed depending on the patient's condition, renal function, or bone marrow suppression. Twelve patients received at least 3 cycles of GN chemotherapy, whereas the remaining 10 received 1 or 2 cycles. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumor (RECIST). Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 3.0.

2.3. Clinical and Laboratory Assessments. Complete blood cell counts (CBCs) were performed, and NLR was calculated using the neutrophil and lymphocyte counts obtained on the same day or a few days before the initial chemotherapy. We determined the cut-off point of the NLR based on the sensitivity and specificity levels derived from the area under receiver operator characteristics (AUROC) curve plotted using disease progression or overall mortality.

2.4. Statistical Analysis. The patient characteristics and pretreatment factors were analyzed using the Mann-Whitney U test and chi-square test, respectively. The Kaplan-Meier curve was used to estimate the progression-free survival (PFS) and overall survival (OS). The survival duration was defined as the time between the date of installation of GN chemotherapy and the time of tumor progression or death. The log-rank test was performed for comparison of two groups. All statistical analyses were performed using the GraphPad Prism software program (GraphPad Software, La Jolla, CA, USA). $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Patients. Of 23 patients, complete response (CR) and partial response (PR) were obtained in 2 (8.7%) and 3 (13.0%) patients, respectively. The median PFS and OS were 147 days and 396 days, respectively. Grade 3 or 4 anemia, thrombocytopenia, and neutropenia were observed in 10 (43.5%), 10 (82.6%), and 21 (91.3%) patients, respectively. None of these patients died of adverse effects of GN therapy.

3.2. The NLR Cut-Off Value. Based on the AUROC curve, the NLR cut-off point was determined to be 4.14 for both PFS (AUROC: 0.618) and OS (AUROC: 0.717) [Figure 1]. Clinicopathological characteristics of the 23 patients are summarized in Table 1. There were no statistically significant differences in the baseline characteristics between high (≥4.14) and low (<4.14) NLRs.

3.3. NLR and Patient Outcomes. We compared PFS and OS in patients with high versus low NLRs. Kaplan-Meier analysis showed that higher NLR strongly correlated with the risks of disease progression ($p = 0.006$; Figure 2(a)) and mortality ($p = 0.045$; Figure 2(b)).

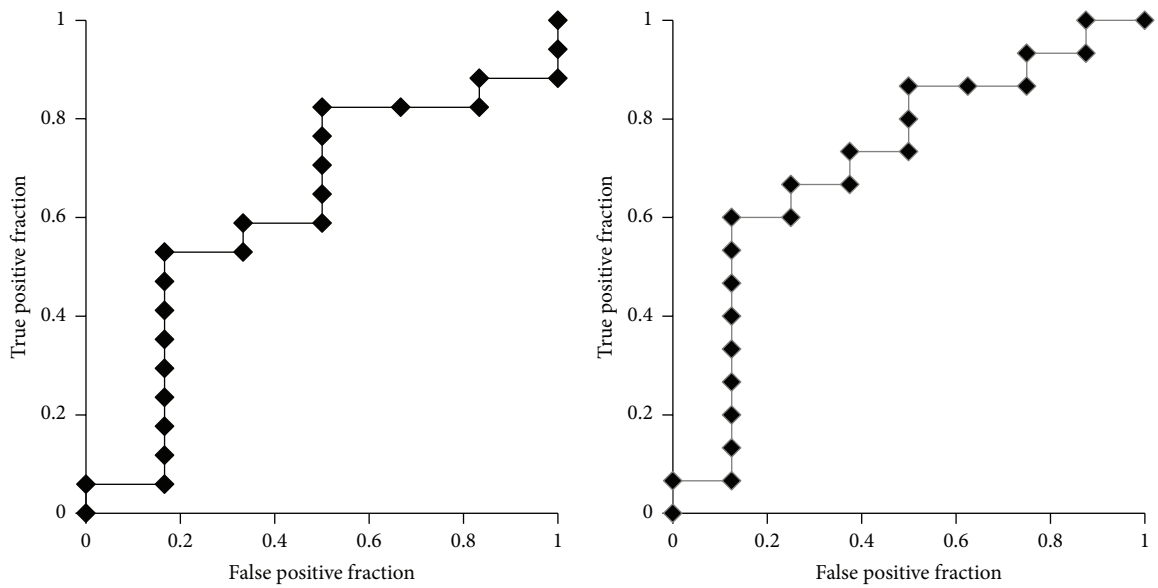
4. Discussion

Although advances in chemotherapy have improved the survival of patients with recurrent or metastatic UC, a portion of patients still die within a few months of disease progression. Therefore, more useful and reliable biomarkers that provide additional prognostic information are needed. CBCs are typically examined during the clinical check-up, and the NLR can be applied to all patients virtually either before or after surgery/medical treatment. We previously reported NLR as an independent prognosticator in men presenting with metastatic prostate cancer as well as in bladder cancer patients who received radical cystectomy [14]. Indeed, NLR has been shown to be a prognostic factor in patients with bladder cancer [12, 15–19]. On the other hand, the association between NLR and tumor progression remains controversial [12, 15–19]. Several studies have shown a higher NLR to predict a worse prognosis in bladder cancer patients [16, 18–20], whereas others have concluded that NLR is not strongly correlated with OS [12, 15–18]. In the current study, higher NLR significantly correlated with a poorer prognosis in patients who received GN chemotherapy for their advanced bladder cancer.

In addition to cisplatin, various anticancer platinum complexes have been developed. Carboplatin, a cisplatin analogue, has been shown to exhibit improved toxicity and favorable antitumor effects, resulting in response rates of 18.4% for upper urinary tract UC [20]. Additionally, nedaplatin was developed as a second-generation platinum complex with lower renal and gastrointestinal toxicities compared with cisplatin [21]. Sasaki et al. demonstrated that the pharmacokinetic behavior of nedaplatin was similar to that of carboplatin but is strikingly different from that of cisplatin. Cisplatin easily binds to serum proteins, resulting in a smaller percentage of platinum excreted into the urine after infusion compared with nedaplatin or carboplatin [22]. Matsumoto et al. showed greater activity of GN therapy against lung cancer models than the activity of a combination of gemcitabine with cisplatin or carboplatin [23]. In our institution,

Table 1: Clinicopathological characteristics of the patients.

	Total ($n = 23$)	NLR < 4.14 ($n = 9$)	NLR ≧ 4.14 ($n = 14$)	p value
Age (years)				
<65	11 (47.6%)	4 (44.4%)	7 (50.0%)	0.566
≥65	12 (52.4%)	5 (55.6%)	7 (50.0%)	
Gender				
Female	6 (26.1%)	4 (44.4%)	2 (14.3%)	0.131
Male	17 (73.9%)	5 (55.6%)	12 (85.7%)	
Creatinine clearance (mL/min)				
<60	3 (13.0%)	2 (22.2%)	1 (7.1%)	0.332
≥60	20 (87.0%)	7 (77.8%)	13 (92.9%)	
Clinical lymph node metastasis				
Yes	19 (82.6%)	8 (88.9%)	11 (78.6%)	0.483
No	4 (17.4%)	1 (11.1%)	3 (21.4%)	
Neoadjuvant chemotherapy				
Yes	4 (17.4%)	3 (33.3%)	1 (7.1%)	0.147
No	19 (82.6%)	6 (66.7%)	13 (92.9%)	
Clinical T stage				
≤2	6 (26.1%)	2 (22.2%)	4 (28.6%)	0.565
≥3	17 (73.9%)	7 (77.8%)	10 (71.4%)	



(a) Progression-free survival (b) Overall survival

Figure 1: The AUROC for NLR: (a) PFS and (b) OS.

we have used nedaplatin-based chemotherapy for high-grade UC and have demonstrated good responses, with the median PFS and OS times of 147 and 396 days, respectively [2, 24].

There are several limitations associated with this study, including selection bias and missing data for some of the variables due to its retrospective nature. However, this study may provide supportive data for other studies as well as future prospective studies. Another potential limitation is that we did not determine the mechanism of NLR for bladder cancer progression. Previous studies showed a correlation between NLR as a marker of systemic inflammation in cancer patients and patient outcomes.

In conclusion, we demonstrated that NLR might be a new biomarker to predict the prognosis of advanced bladder cancer in patients undergoing GN chemotherapy.

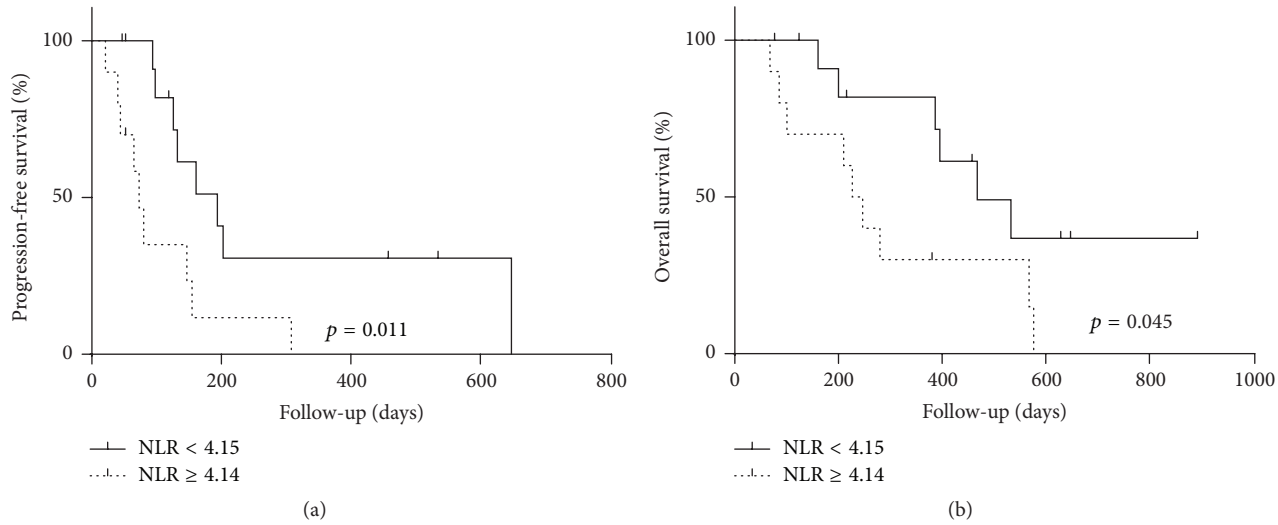


Figure 2: The association between NLR and patient outcomes: (a) PFS and (b) OS.

Competing Interests

The authors declare that they have no competing interests.

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