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Preoperative Anemia as a Simple Prognostic Factor in Patients with Urinary Bladder Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EF 1 Cheng Chen*
BDF 1 Linkun Hu*
BC 2 Xiangxiang Li
AC 1 Jianquan Hou

1 Departments of Urology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, P.R. China
2 Clinical Laboratory, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, P.R. China

* These authors contributed equally to this work

Corresponding Author: Jianquan Hou, e-mail: houjianquan@suda.edu.cn
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Background: To evaluate the incidence of preoperative anemia and its prognostic role in patients with urinary bladder cancer (BC).

Material/Methods: A total of 317 patients diagnosed with BC were enrolled in this retrospective cohort study. Univariate and multivariate analysis was used to identify independent prognostic factors and Kaplan-Meier survival analysis was applied to examine the influence of anemia on survival.

Results: 109 patients (34.4%) were anemic with a median preoperative hemoglobin of 114 g/L (interquartile range 104 to 122.5). After a median of 6 years follow-up (range: 2 to 8 years), the median recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) in anemic patients were significantly lower than non-anemic patients ($p \leq 0.001$). Multivariate Cox analysis indicated that anemia remained an independent predictor of RFS and OS ($p=0.010$, 0.007).

Conclusions: Anemic patients with BC are likely to have a shorter RFS and OS than non-anemic patients, and anemia is an independent predictor of RFS and OS.

MeSH Keywords: Anemia • Prognosis • Urinary Bladder Neoplasms

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Background

Anemia is the most persistent and common disease detected in cancer patients with cancer. European Cancer Anemia Survey reported 31% of patients with cancer were anemic preoperatively in 2004, with levels of hemoglobin (HB) <12.0 g/dL prior to treatment [1].

The causes of preoperative anemia in cancer patients are multifactorial, but main causes are the neoplastic processes (which may lead to vitamin B12 and iron deficiency) and erythropoietin (EPO) reduction (as anemia may also be a side effect of treatment modalities including surgery, radiotherapy or chemotherapy) [2].

The recommended treatments for anemia in cancer patients include oral iron supplements, erythropoietins, and erythrocyte transfusions. Unfortunately, despite the high incidence and prevalence of anemia, only 40% of anemic patients received related therapy at any time during the survey period [1]. In some centers, treatments were initiated only when the HB value less than 9.7 g/dL [1].

Several studies have indicated that anemia is associated with poor prognosis in many cancers. Socinski et al. [3] reported that baseline HB, performance status (PS), and the use of combined modality therapy, have a significant effect on outcome in stage III non-small-cell lung cancer. Henry et al. [4] also reported that throughout treatment with erythropoietic-stimulating agents, patients with cancers whose HB values were less than 120 g/L had a worse oncological outcome than those with higher HB values.

Urinary bladder cancer (BC) is the most prevalent cancer in the urological tract [5]. Older men who present with frequent hematuria (grossly visible or microscopic) are more susceptible to anemia [6]. In BC patients, preoperative anemia is often exacerbated by potential hemorrhage after transurethral resection of bladder tumor (TURBT) or radical cystectomy (RC) and myelosuppressive treatment in patients who are undergoing intensive chemotherapy and radiotherapy. Preoperative anemia was reported to be a more severe prognosis indicator in BC patients undergoing RC [7–9], metastatic transitional cell carcinoma of the urothelial tract [10], and even in patients with urothelial carcinoma of the upper urinary tract [11].

Anemia can be detected using a simple and reliable test, so physicians treating patients with BC should be aware of the HB status of patients during treatment and follow-up. Monitoring HB levels may allow prediction of recurrence-free survival (RFS) and overall survival (OS).

Material and Methods

This study was approved by Soochow University for Clinical Investigation ethics committee. A retrospective cohort analysis was conducted in patients with newly diagnosed and pathologically confirmed BC and follow-up data at the First Affiliated Hospital of Soochow University between May 2007 and March 2016. Patients with other systemic disorders or malignancies were excluded. All clinical, laboratory, and pathological data were obtained from the urology and pathology departments. Pathological stages and grades were adjusted in accordance with the 7th edition of the TNM classification system and WHO 2004 grading system [12].

The patients were followed regularly for the following five years. Cystoscopy, renal ultrasound, urinary cytology, and CT scan were reviewed. RFS, PFS, and OS were considered for the period between the first tumor diagnosis and recurrence, progression or death, with censoring at the last follow-up visit.

Patients were categorized into two groups: anemic and non-anemic, based on HB level based on the World Health Organization (WHO) classification (male and female patients with <130 and <120 g/L HB, respectively) [13]. Non-muscle-invasive bladder cancer (NMIBC) comprises stage Ta and T1 tumors, and muscle-invasive bladder cancer (MIBC) comprises stage T2, T3, and T4 tumors. Patients of both groups were undergoing standard TURBT, RC, chemotherapy or radiotherapy, according to the European Association of Urology (EAU) guidelines [12].

Statistical analyses

The Kolmogorov-Smirnov test was applied to examine whether or not the acquired data were normally distributed. Data are presented as the means ± standard deviations (SD) and medians (IQR) for normally distributed variables. The Student's two-sample *t*-test was used for normally distributed data and Mann-Whitney U test was used for uneventfully distributed data. Categorical variables were presented as percentages and analyzed by the Chi-square test and Fisher's exact test.

The Kaplan-Meier method was applied to calculate survival in BC patients, the log rank test were using to estimate the differences in RFS, PFS, and OS probabilities. The statistical significance of the relationship between survival and each variable was analyzed using the Cox model. Proportional hazards assumptions were evaluated by testing the significance of time-dependent interaction terms for all variables. Predictive accuracy calculations of Cox regression models were quantified using the Harrell's concordance index [14] and compared by the Mantel-Haenszel test. The correlation of anemia with albumin and hypersensitive C-reactive protein (Hs-CRP) was evaluated by Spearman rank correlation analysis.

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Statistical analyses were performed using SPSS version 21 (IBM, Chicago, IL, USA), R (version 3.0.0, The R Foundation for Statistical Computing, Vienna Austria) and a two-sided *p* value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 317 patients were included in this retrospective cohort study. The distribution of the baseline preoperative clinical and laboratory characteristics in the anemia group and non-anemic group at primary diagnosis are listed in Table 1. The study cohort comprised 260 male patients (82%). The median age of patients was 70 years (IQR 61–77). The median preoperative HB was 13.2 g/L (IQR 11.7, 14.3). A total of 109 patients (34.4%) had preoperative anemia, with median HB was 114 g/L (IQR 104, 122.5). All patients were pathologically diagnosed with bladder urothelial carcinoma without distant metastasis.

Univariate and multivariate aurvival analysis

Twelve potential prognostic factors were examined using Cox regression, and their association with RFS, PFS and OS were compared using univariate and multivariate survival analysis (Table 2). Univariate analysis identified four variables significantly associate with survival, which were thus included in multivariate model (Table 3). Anemia was strongly associated with RFS and OS (p=0.010, 0.007), but was not significantly associated with PFS (p=0.067). Meanwhile, Tumor T stage was significantly associated with PFS and OS (p=0.011, 0.049). The base model for predicting OS included albumin, hs-CRP, and tumor T stage, and the base model for predicting RFS included hs-CRP, and tumor T stage. The respective c-indices for RFS and OS were 0.93 and 0.79. Integration of HB levels significantly increased the predictive accuracies for RFS and OS to 0.94 and 0.87, respectively.

Survival analysis

A prognostic study of 317 patients followed up for a median of six years (range: 2 to 8 years). Seventy-four patients died within the group of 317 patients. Kaplan-Meier curves and median RFS, PFS and OS were calculated for the 317 patients.

As shown in Figure 1, the median RFS, PFS and OS of anemic patients with all stages of BC were significantly lower than those of non-anemic patients ($p \leq 0.001$), and in Figure 2, when stratified by T stage, the median RFS, PFS and OS of anemic patients with NMIBC were significantly lower than those of non-anemic patients (p<0.001). However, in patients with MIBC, the median RFS, PFS, and OS did not differ significantly between anemic and non-anemic patients (p=0.652, 0.633, 0.365, respectively).

As shown in Figure 3, when stratified by albumin and Hs-CRP, patients with all stages of BC having low albumin or high Hs-CRP values had a worse prognosis than those with normal albumin or Hs-CRP values (p<0.05). Rank correlation analysis indicated that anemia and albumin were significantly positively correlated (r=0.399; p<0.001), and anemia and Hs-CRP were significantly negatively correlated (r=–0.196; p=0.001)

Discussion

Anemia is often identified at diagnosis or after treatment of tumors [15]. Baseline anemia in patients with cancer may be triggered by lack of nutrients, such as vitamin B12 and iron; depressed levels of trophic hormones such as EPO; concurrent infection or inflammation; hematuria; immunoreaction to tumor cells; and/or overexpression of certain inflammatory cytokines which reduce survival of red blood cells, suppress erythroid progenitor cells, and impair iron utilization and erythropoietin production, ultimately disrupting normal erythropoiesis [16]. After surgery, anemia can be worsened by extensive blood loss during surgery, or adjuvant chemotherapy and/or radiotherapy

A large body of evidence suggests that anemia, one potential cause of tumor hypoxia, can affect cancer patients' quality-of-life and treatment outcomes, including survival [17]. A large-sample meta-analysis also confirmed that anemia was correlated with cancer patient survival [18]. Oxygen is an important factor influencing tumor occurrence and development. Hypoxia is often observed within solid tumors, and is an independent marker of poor prognosis. Hypoxia can induce alterations in gene expression, cellular changes and a downregulation of cell surface integrin to favor unrestricted tumor growth. These changes can produce a more clinically aggressive phenotype, and favor resistance to radiotherapy and chemotherapy [19]. Anemia can also affect tumor growth by inducing expression of cytokines involved in angiogenesis, such as vascular endothelial growth factor, which has been reported to be associated with low HB levels [20].

Preoperative anemia levels were shown to strongly related to postoperative complications and mortality in patients undergoing surgery [21]. Anemia was previously reported to be independently associated with shorter survival in cancer patients treated with chemotherapy or radiotherapy [22]. Several clinical studies have suggested that even mild anemia has a significant impact on patients' oncological outcomes [23]. Therefore, correction of anemia, to complement iron agent

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Table 1. Clinical and laboratory data between anemia group and non-anemic group.

Variables	Overall patients	Anemia group	Non-anemic group	P value
No. of patients (%)	317 (100%)	109 (34.4%)	208 (65.6%)	
Age (years)	70 (61–77)	70.71±10.68	68.24±11.35	0.062
Gender (male (%))	260 (82%)	93 (85.3%)	167 (80.3%)	0.268
Smoking (%)	46 (14.5%)	32 (15.4%)	14 (12.8%)	0.616
Hypertension (%)	132 (41.6%)	46 (41.3%)	46 (42.2%)	0.905
Diabetes mellitus (%)	30 (9.5%)	20 (9.6%)	10 (9.2%)	1
RBC (1012/L)	4.345 (3.84–4.70)	3.71 (3.44–4)	4.57 (4.30–4.81)	<0.001
HB (g/L)	134 (120–145)	114 (104–122.5)	142 (134.25–150)	<0.001
HCT (L/L)	0.4 (0.36–0.43)	0.34 (0.32–0.36)	0.42 (0.40–0.44)	<0.001
MCV (fL)	92.3 (89.1–95.4)	92.40 (87.35–95.95)	92.30 (89.70–95.20)	0.486
RDW (%)	13 (12.5–13.6)	13.20 (12.65–14.10)	12.90 (12.40–13.40)	<0.001
Albumin (g/L)	41.71±4.81	38.83±4.88	43.16±4.07	<0.001
WBC (109/L)	5.99 (4.97–7.30)	5.72 (4.79–7.19)	6.15 (5.01–7.35)	0.241
Hs-CRP (mg/L)	1.75 (0.67–5.14)	3.46 (0.94–8.29)	1.39 (0.59–3.69)	0.001
Stage at initial diagnosis (%)				0.013
Missing	63 (19.9%)	19 (17.4%)	44 (21.2%)	
Ta	61 (19.2%)	14 (12.8%)	47 (22.6%)	
T1	123 (38.8%)	46 (42.2%)	77 (37%)	
T2	53 (16.7%)	18 (16.5%)	35 (16.8%)	
T3	11 (3.5%)	8 (7.3%)	3 (1.4%)	
T4	6 (1.9%)	4 (3.7%)	2 (1.0%)	
Tumor stage (%)				0.225
Missing	63 (19.9%)	19 (17.4%)	44 (21.2%)	
Non-muscle invasive	184 (58%)	60 (55%)	124 (59.6%)	
Muscle invasive	70 (22.1%)	30 (27.5%)	40 (19.2%)	
Regional lymph node (%)				0.574
Missing	63 (19.9%)	19 (17.4%)	44 (21.2%)	
N0	246 (77.6%)	86 (78.9%)	160 (76.9%)	
N1	3 (0.9%)	2 (1.8%)	1 (0.5%)	
N2	5 (1.6%)	2 (1.8%)	3 (1.4%)	
Grade at initial diagnosis (%)				0.402
Missing	57 (18%)	24 (22.0%)	33 (15.9%)	
Low maglignant potential	6 (1.9%)	2 (1.8%)	4 (1.9%)	
Low grade	36 (11.4%)	9 (8.3%)	27 (13.0%)	
High grade	218 (68.8%)	74(67.9%)	144 (69.2%)	
Recurrence rate (%)				0.248
≤1	269 (84.9%)	96 (88.1%)	173 (83.2%)	
>1	48 (15.1%)	13 (11.9%)	35 (16.8%)	

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Table 2. Results of univariate analyses.

Variable at baseline	Recurrence-free survival			Progression-free survival			Overall survival			Reference category
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	
Age	0.998	0.977 to 1.019	0.862	1.003	0.982 to 1.023	0.802	1.003	0.983 to 1.024	0.750	Increment of 1 year
Gender	0.686	0.394 to 1.194	0.183	0.856	0.492 to 1.490	0.583	0.776	0.443 to 1.357	0.374	Female
Anemia	0.506	0.300 to 0.854	**0.011**	0.418	0.248 to 0.706	**0.001**	0.480	0.285 to 0.810	**0.006**	HB <130 g/L in men <120 g/L in women
MCV	0.793	0.288 to 2.180	0.653	0.878	0.319 to 2.419	0.801	0.678	0.247 to 1.860	0.451	<80 fL
RDW	0.803	0.291 to 2.215	0.672	0.876	0.319 to 2.402	0.797	0.990	0.361 to 2.715	0.984	<15%
Albumin	0.705	0.440 to 1.130	0.147	0.606	0.379 to 0.970	**0.037**	0.567	0.354 to 0.910	**0.019**	<30 g/L
WBC	1.127	0.354 to 3.582	0.840	1.175	0.369 to 3.736	0.785	0.889	0.280 to 2.826	0.842	$<10\times10^9$/L
Hs-CRP	1.701	1.049 to 2.759	**0.031**	1.739	1.074 to 2.815	**0.024**	1.690	1.045 to 2.735	**0.033**	<3 mg/L
T stage	1.376	1.037 to 1.824	**0.027**	1.608	1.232 to 2.100	**<0.001**	1.440	1.115 to 1.861	**0.005**	Increment of one stage
Lymph node stage	0.869	0.305 to 2.480	0.794	0.979	0.349 to 2.747	0.968	0.845	0.298 to 2.402	0.753	Increment of one stage
Grade	0.818	0.447 to 1.498	0.516	1.048	0.570 to 1.925	0.881	0.944	0.534 to 1.667	0.841	Increment of one grade
Recurrence rate	–	–	–	0.958	0.504 to 1.822	0.897	0.855	0.447 to 1.636	0.635	≤1

Table 3. Results of the multivariate Cox regression model.

Variable at baseline	Recurrence-free survival			Progression-free survival			Overall survival			Reference category
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value	
Anemia	0.474	0.268 to 0.837	**0.010**	0.551	0.291 to 1.043	0.067	0.431	0.234 to 0.792	**0.007**	HB <130 g/L in men <120 g/L in women
Albumin	–	–	–	0.911	0.488 to 1.698	0.768	0.812	0.449 to 1.470	0.493	<30 g/L
Hs-CRP	1.355	0.774 to 2.371	0.288	1.321	0.737 to 2.370	0.350	1.219	0.682 to 2.178	0.503	<3 mg/L
T stage	1.204	0.884 to 1.640	0.239	1.457	1.089 to 1.950	**0.011**	1.344	1.002 to 1.803	**0.049**	Increment of one stage

or promote red element, may have a positive impact on cancer patients' treatment outcomes [24]. These findings underscore the need to incorporate diagnosis and treatment of anemia into routine management of cancer patients. Optimal management of anemia appears to be a critical component of cancer treatment.

The main finding of this study confirms that preoperative anemia as an independent predictor of RFS and OS in BC patients. Standard clinical and pathological risk factors, such as tumor stage, were also found to be independent predictors of disease progression, and were associated with BC patient mortality. The negative association between preoperative anemia

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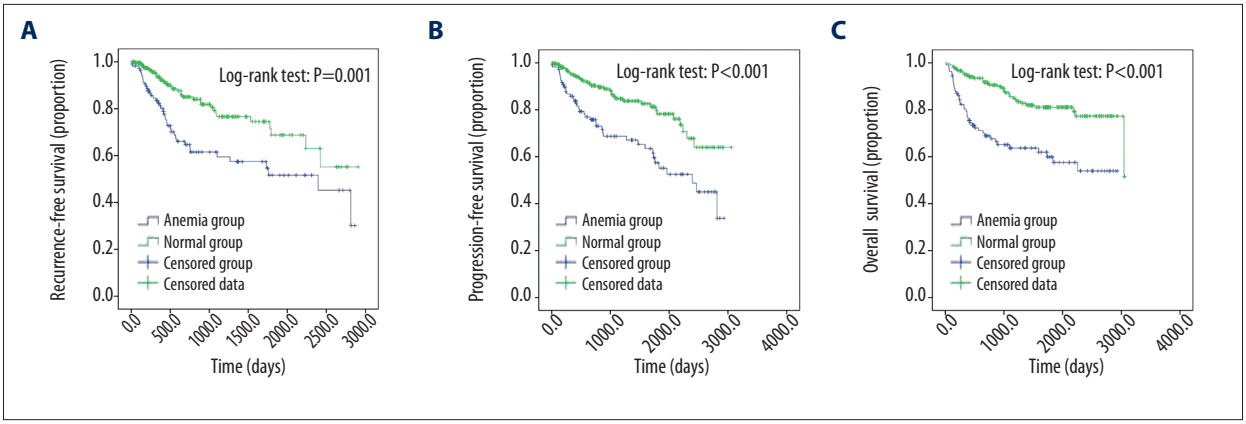

Figure 1. Kaplan-Meier plots of recurrence-free survival (**A**), progression-free survival (**B**), and overall survival (**C**) probability in patients with all stages of bladder cancer stratified by anemia.

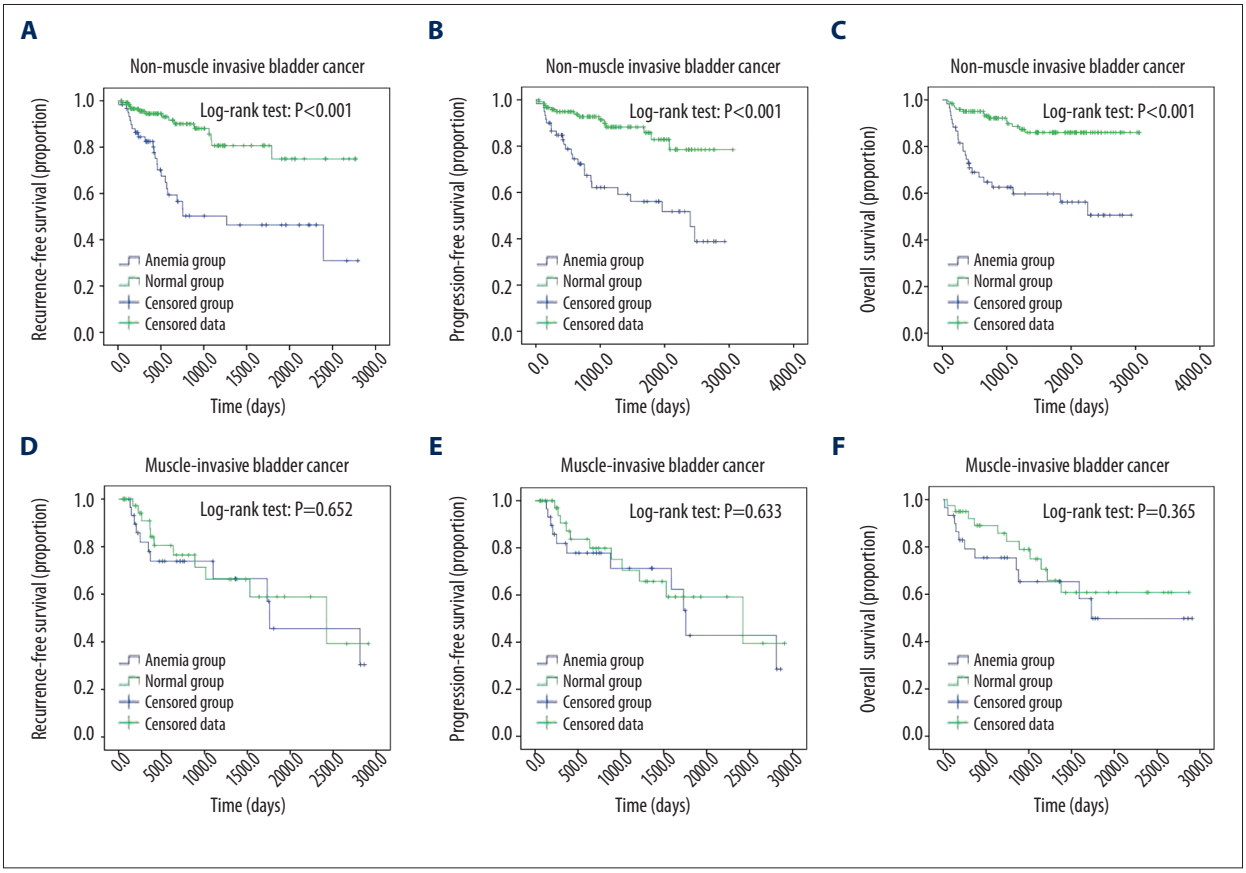

Figure 2. Kaplan-Meier plots of recurrence-free survival (**A, D**), progression-free survival (**B, E**) and overall survival (**C, F**) probability in patients with non-muscle invasive and muscle-invasive bladder cancer stratified by anemia.

and worse outcomes has been documented previously in BC patients. Our study sought to investigate this "old" topic and came to two novel conclusions.

First, the oncological outcomes of anemic NMIBC patients were significantly lower than non-anemic NMIBC patients, which did not differ significantly between anemic and non-anemic MIBC patients, so the correction of anemia may obtain the most benefits in stage Ta and T1 BC patients. We assumed that as tumor stage increased, the influence of the tumor itself, and the applied surgical procedures, would have a more significant impact on patient prognosis. Our findings were consistent with those of Shen et al. who reported that pretreatment anemia was associated with poorer survival in patients with stage I and II gastric cancer [25].

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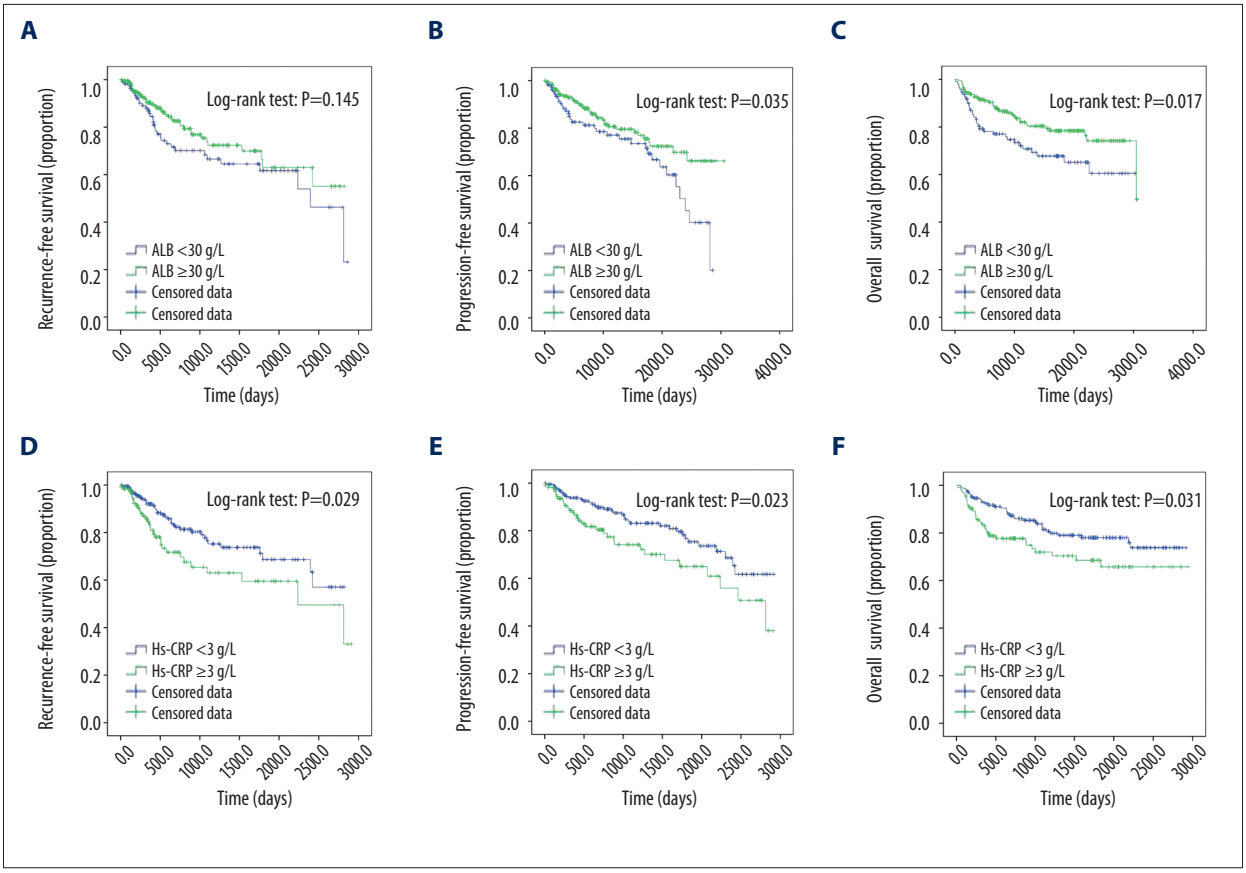

Figure 3. Kaplan-Meier plots of recurrence-free survival, progression-free survival, and overall survival probability in patients with all stages of bladder cancer, stratified by albumin (**A–C**) and Hs-CRP (**D–F**).

Second, we found that abnormal levels of baseline nutritional and inflammatory markers, such as albumin and CRP, correlated with anemia, and were also significantly associated with prognosis in BC patients. So the status of preoperative anemia can become a clue of baseline malnutrition or systematic inflammation and all of these conditions should be corrected in our clinical practice.

Our conclusions were limited by the scope of this study. First, the data of Eastern Cooperative Oncology Group (ECOG) PS and perioperative blood transfusion in BC patients were unavailable. Moreover, due to the inadequate baseline information and different grading systems applied to the included patients, the European Organization for Research and Treatment of Cancer risk scores, which were used to predict recurrence and progression in patients with stage Ta and T1 BC, could not be calculated. Thus their relationship with preoperative anemia was not assessed. Finally, an external independent validation of our data will be required to confirm our results in a prospective clinical study.

Conclusions

Preoperative anemia was a strong predictor of BC recurrence and may contribute to mortality at all stages of BC. Correction of anemia, combined with malnutrition and inflammation, before BC-directed treatment is initiated may improve outcomes of BC patients, particularly those with non-muscle-invasive bladder cancer.

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