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Impact of Routine Laboratory Parameters in Patients Undergoing Radical Cystectomy for Urothelial Carcinoma of the Bladder: A Long-Term Follow-Up

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Keywords
C-reactive protein · Hemoglobin · Muscle invasive cancer of the bladder · Prognostic factors · Radical cystectomy

Abstract
Objectives: Patients' oncological outcome after radical cystectomy (RC) due to urothelial carcinoma of the urinary bladder (UCB) is always up for debate. There is accumulating evidence on the influence of routine blood parameters. We aimed to identify reasonable and easy-to-detect biomarkers, such as preoperative C-reactive protein (CRP) and hemoglobin (Hb) levels, as predictors of overall survival (OS) and cancer-specific survival (CSS) in patients undergoing RC for UCB. ***Materials and Methods:*** This is a large single-center study in which both preoperative CRP and Hb levels were available in 1,043 patients undergoing RC for UCB from 2004 to 2018 with a median follow-up time of 22 months (mean 38, max. 170). We used the Kaplan-Meier method, log-rank test, and Cox regression models for assessment of OS and CSS. Using our data, we validated an existing outcome prediction score (TNR-C). ***Results:*** Median CRP level was 0.5 mg/dL (IQR 0.2–1.4), and median Hb level was 13.4 g/dL (IQR 11.9–14.7). We found that patients with CRP values above the median reached a significantly lower median survival than those with CRP values below the median (23 vs. 83 months, $p < 0.001$). The TNR-C score was successfully validated, and we discriminated between 3 risk groups (5-year CSS: 76, 40, and 16% for low, intermediate, and high risk, respectively). We observed a similar outcome for patients with a Hb level below the median: CSS was significantly poorer than with Hb levels above the median (median CSS 27 vs. 91 months, $p < 0.001$). Multivariant analysis showed CRP and Hb levels to be independent prognostic parameters for CSS and OS. ***Conclusions:*** We found elevated preoperative CRP levels and decreased Hb levels to be independent prognostic factors indicating an unfavorable outcome in patients undergoing RC for UCB and were able to validate the TNR-C score in a large patient cohort. We propose using these routine biomarkers for individual risk stratification and optimization of therapeutic strategies in patients undergoing RC for UCB.

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Introduction

Bladder cancer is the 6th most common cancer in the United States with 81,190 newly diagnosed cases in 2018. According to the American Cancer Society, there will be 17,240 disease-associated deaths in 2018. Bladder cancer

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is more common in men than in women with a median age at the time of primary diagnosis of 73 years [1]. Approximately 25% of patients already have muscle-invasive bladder cancer at time of primary diagnosis, which leaves the majority of patients with non-muscle invasive tumor stages [2, 3]. Based on the data from the Surveillance, Epidemiology and End Results (SSER) registry, the rates have not changed over the last 10 years, although up to 50% of patients with high-risk non-muscle invasive bladder cancer can progress to invasive disease [2, 4].

Still, TNM classification of the postoperative specimen is mainly used to predict cancer-specific survival (CSS) rates after radical cystectomy (RC) [1, 5]. Tumor stage and nodal status remain the dominant pathologic predictors for recurrence and, ultimately, survival. Other prognostic factors, such as lymphovascular invasion, presence of hydronephrosis, soft tissue margin status, or gender, can be relevant [6].

Predictive routine serum biomarkers, such as hemoglobin (Hb) and C-reactive protein (CRP), are still up for debate. The prognostic value of Hb and CRP for CSS after RC was recently proposed, and new biochemical predictors have been studied [7, 8]. The prognostic value of Hb and CRP regarding overall survival (OS) in various cancerous diseases is commonly recognized, and understanding their importance may be critical [9].

Shrotriya et al. [9] recently published a systematic literature review to determine the relationship between elevated CRP and prognosis of solid tumor patients. They later identified CRP to be a universal cost-effective independent prognostic indicator in most solid tumors, a proposition in unison with previous and current findings [8, 9].

Furthermore, studies were conducted to investigate the role of Hb as a predictive prognostic factor in malignancies [10]. It is widely accepted that anemia serves as a negative predictor of outcome and OS with a predominance in hematological malignancies [11]. Paitan et al. [11] could show that anemia in solid tumor patients with urological malignancies was limited to less than half of all patients, which may indicate a more specific prognostic value for Hb in urological solid cancer patients.

At our institution, standard pretreatment laboratory blood work always includes CRP and Hb for patients preparing for RC. We, therefore, analyzed the impact of preoperative Hb and CRP levels on OS and CSS in patients undergoing RC for urothelial carcinoma of the urinary bladder (UCB) in a long-term follow-up.

Since publishing our manuscript on that topic, we are not aware of any other group investigating the impact of preoperative Hb and CRP levels in such a large cohort (n = 1,043). We hypothesized that preoperative Hb and CRP values are strongly associated with the oncological outcome of urological solid tumor patients in our largest cohort so far.

Table 1. Patient characteristics

TNM classification	%
pTX	1.2
pT0	8.5
pTa/is	15.2
pT1	7.5
pT2	20.9
pT3	33.5
pT4	13.4
pN0	71.5
pN+	28.5
M0	90.4
M1	9.6
G1–2	10.1
G3	89.9
R0	86.2
R1	13.8

Materials and Methods

We prospectively gathered our data at 1 German academic center; solely for this purpose, a computerized database was created. Both Hb and CRP values were available in 1,043 patients undergoing RC for UCB from 2004 to 2018. RC for UCB was indicated in accordance with the EAU guidelines.

Blood samples, including CRP and Hb values, were routinely drawn immediately before RC. For randomization and considering laboratory-depending variability, we defined our threshold for CRP at 0.5 mg/dL, which represented our standard laboratory cutoff and median as well. For Hb, we also chose the median as cutoff, placing the subjects either into a cohort with levels above or below the median.

We evaluated the bladder specimens in our pathological department according to standard histopathological procedures and only included confirmed urothelial cancer histology (UCB) into our final analysis.

We followed up all patients to the present date or until deceased by current EAU guidelines [12]. We ensured a complete follow-up of all patients by contacting them twice in the first year following RC and sent validated questionnaires once a year afterwards. Therefore, complete follow-up was ensured, even in patients who were followed up outside of our institute.

Our primary endpoint was CSS with cause of death being determined by the attending physician or through death certificate. Additionally, we analyzed OS.

We correlated Hb and CRP blood levels with tumor size or spread using the Kruskal-Wallis test. Multivariate analysis was

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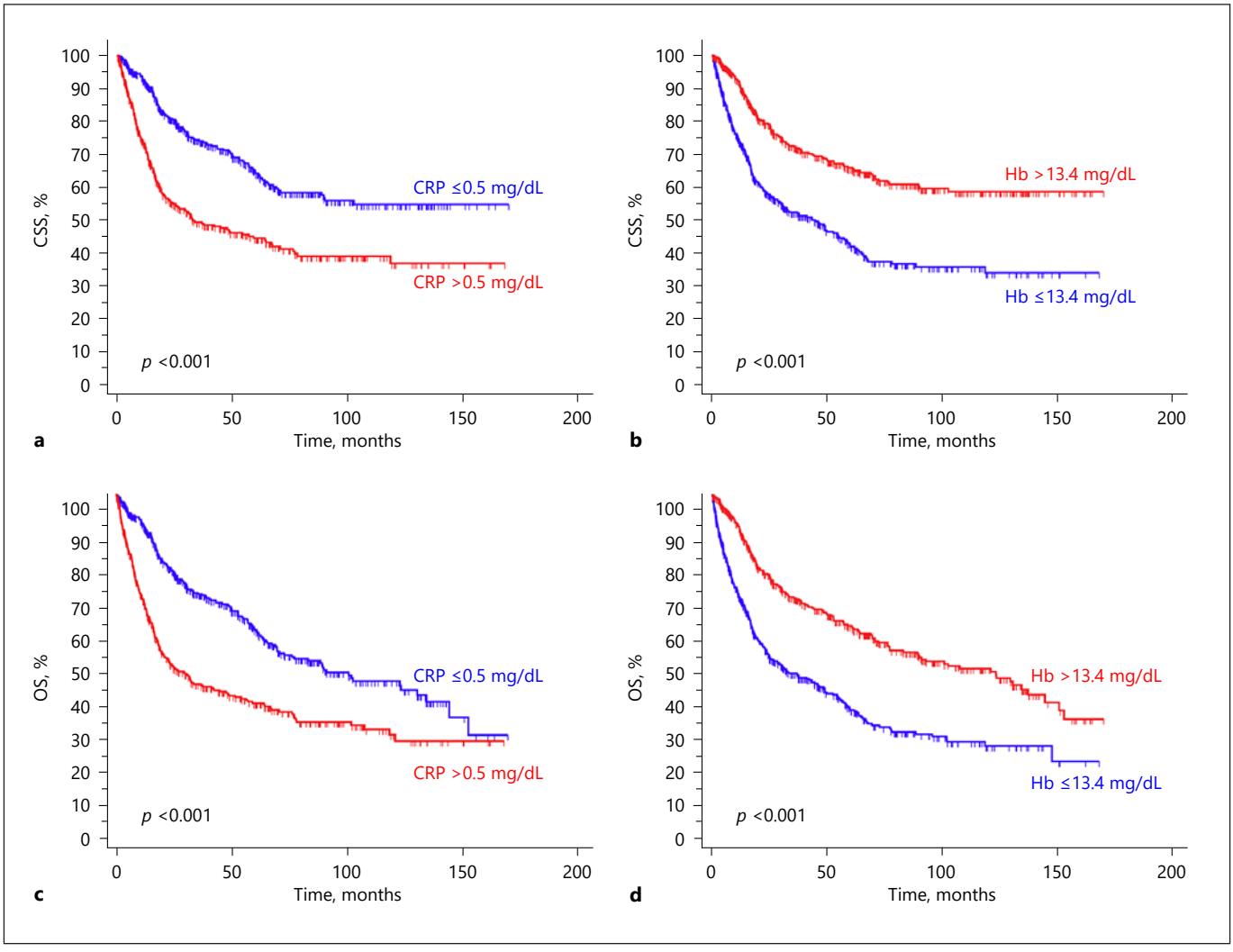

Fig. 1. Univariate analysis of CSS and OS in relation to preoperative CRP (**a**, **c**) and Hb levels (**b**, **d**).

used to fit a Cox proportional hazards model. We used the Kaplan-Meier method and log-rank test to determine median survival.

The TNR-C score developed by Gakis et al. [13] was validated using our study cohort. The score was calculated as 4 (if positive resection margins) + 3 (if ≥pT3a) + 2 (if lymph node density ≥0.09) + 1 (if CRP >0.5 mg/dL) and 0 (if otherwise). Patients were then divided into 3 groups: low risk (score 0–2), intermediate risk (score 3–6), and high risk (score 7–10).

Results

More men than women (76 vs. 24%) underwent surgery with a median age of 70 years (IQR 62–76) and a median BMI of 26.1 (IQR 23.5–29.0). Median follow-up time was 22 months (mean 38, max. 170). Metabolic disease (e.g., diabetes mellitus, hyperlipidemia) was present in 41% (422/1,033) of patients, cardiac disease in 36% (371/1,031), and pulmonary disease in 24% (248/1,033). More patient characteristics can be seen in Table 1.

Hemoglobin

Median preoperative Hb level in our patients was 13.4 g/dL with an IQR of 11.9–14.7. We observed significantly higher preoperative Hb levels in men than in women ($p < 0.001$). Gross hematuria was present in 59% (539/914) of patients; this information was not available in 129 cases. Patients with gross hematuria had a significantly lower preoperative Hb than patients without hematuria (13.3 vs. 13.7 g/dL, $p = 0.024$), without any association between CSS and OS ($p = 0.279$ and $p = 0.726$, respectively).

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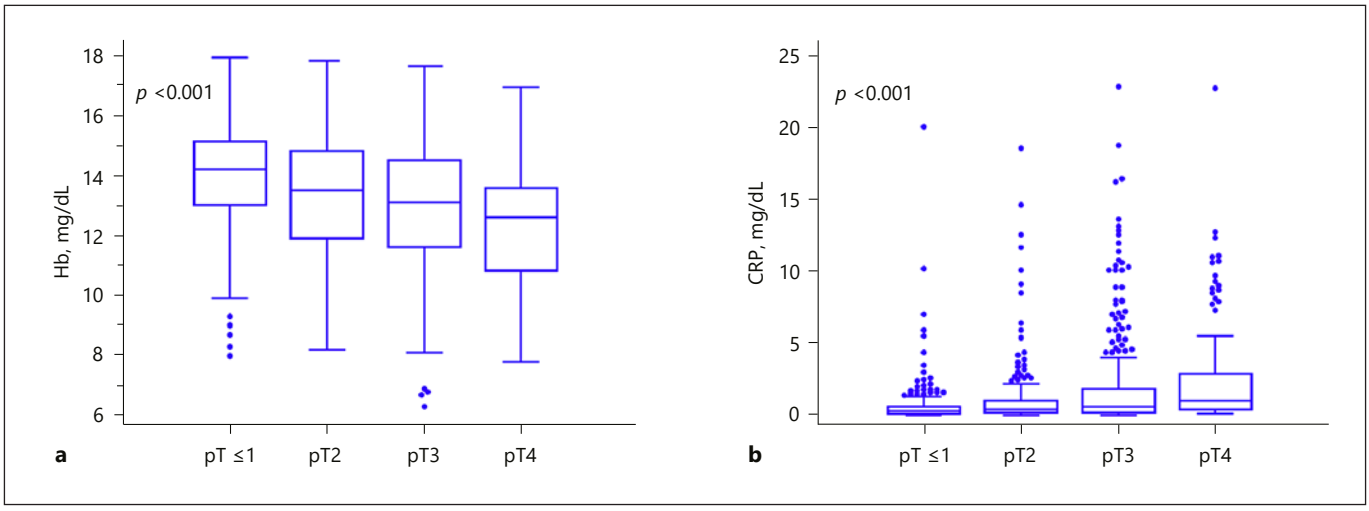

Fig. 2. Preoperative Hb (**a**) and CRP levels (**b**) in relation to T stages.

Table 2. Multivariate analysis of different parameters

	Hazard ratio	95% CI	*p* value
Multivariate analysis (Cox regression) CSS			
pT (<3/3–4)	1.94	1.41–2.66	<0.001
pN (0/1)	1.93	1.45–2.57	<0.001
M (0/1)	2.24	1.59–3.17	<0.001
G (1 + 2/3)	1.36	0.83–2.21	0.218
R (0/1)	1.61	1.14–2.28	0.007
Periop. transfusion (0/1)	1.45	1.09–1.93	0.011
Age (continuous)	1.02	1.01–1.04	0.009
Gender	0.87	0.63–1.21	0.406
Cardiac disease	1.41	1.06–1.87	0.018
Pulmonary disease	1.39	1.04–1.85	0.026
Metabolic disease	0.92	0.70–1.20	0.527
CRP (>/≤ median)	1.46	1.11–1.93	**0.008**
Hb (>/≤ median)	0.69	0.51–0.92	**0.010**
Multivariate analysis (Cox regression) OS			
pT (<3/3–4)	1.79	1.36–2.35	<0.001
pN (0/1)	1.88	1.45–2.43	<0.001
M (0/1)	2.14	1.56–2.93	<0.001
G (1 + 2/3)	1.30	0.85–1.96	0.222
R (0/1)	1.55	1.12–2.13	0.008
Periop. transfusion (0/1)	1.49	1.15–1.92	0.002
Age (continuous)	1.03	1.01–1.04	<0.001
Gender	0.87	0.65–1.17	0.355
Cardiac disease	1.55	1.20–1.98	<0.001
Pulmonary disease	1.42	1.11–1.84	0.006
Metabolic disease	0.92	0.72–1.17	0.499
CRP (>/≤ median)	1.42	1.11–1.82	**0.005**
Hb (>/≤ median)	0.73	0.57–0.95	**0.020**

Bold values indicate statistical significance. CI, confidence interval; periop., perioperative.

Univariate Analysis

Univariate analysis showed a significant correlation between a preoperative Hb level below the median and CSS, reaching a median of 27 versus 91 months for patients with Hb levels above the median ($p < 0.001$; Fig. 1). Also, OS was significantly decreased in patients with Hb levels below the median ($p < 0.001$).

The presence of regional lymph node and distant metastases as well as primary tumor stages showed a significant correlation with Hb levels below the median (pT1–pT4, $p < 0.001$, respectively; Fig. 2). Metabolic, cardiac, and pulmonary disease was significantly associated with poor CSS and OS in univariate analysis ($p = 0.037$ and $p = 0.001$, $p < 0.001$ and $p < 0.001$, $p = 0.036$ and $p < 0.001$, respectively).

Multivariate Analysis

Multivariate analysis showed Hb levels below the median to be an unfavorable independent prognostic factor regarding CSS and OS ($p = 0.01$ and $p = 0.02$, respectively; Table 1). Cardiac and pulmonary disease were independent predictors of OS and CSS in multivariate analysis, while metabolic disease was not (Table 2).

C-Reactive Protein

Considering laboratory-depending variability, we defined our threshold for CRP at 0.5 mg/dL, which was the median with an IQR of 0.2–1.4 mg/dL and at the same time corresponded to our standard laboratory cutoff. We could not detect any significant difference between men and women ($p = 0.349$).

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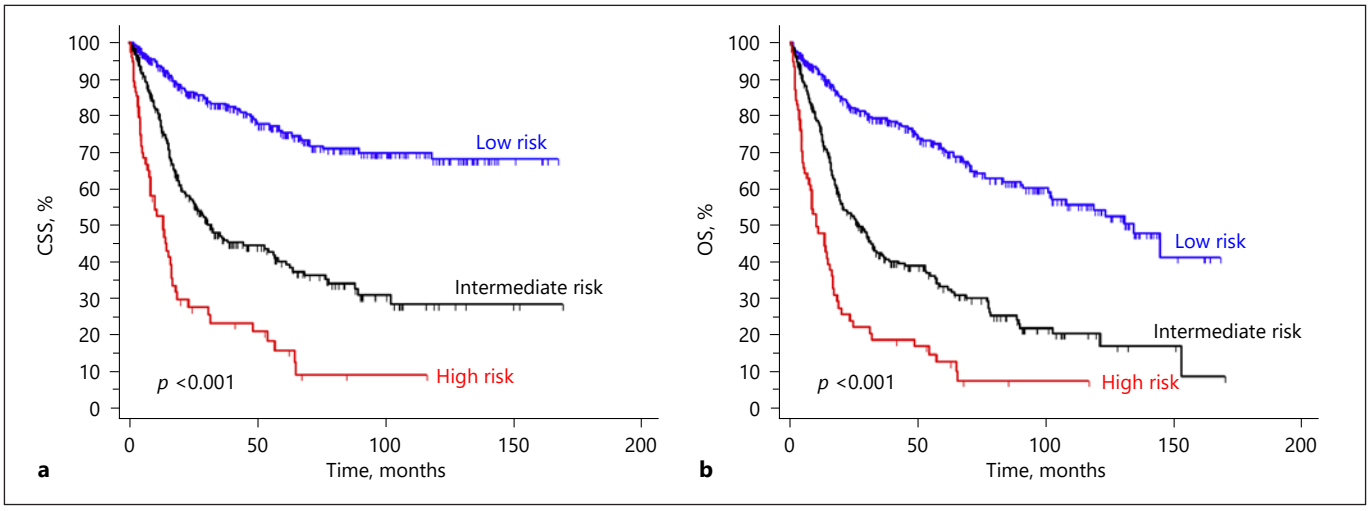

Fig. 3. CCS (**a**) and OS (**b**) in relation to TNR-C score categories.

Univariate Analysis

CSS and preoperative CRP levels were directly correlated in univariate analysis. A CRP level below the median showed a CSS of 83 months, while patients with a CRP level above the median deceased at 23 months ($p < 0.001$; Fig. 1). In the univariate analysis, we found a statistically significant correlation between preoperative CRP level and CSS. Patients with a preoperative CRP value below the median showed a disease-specific survival of 83 months, whereas those with a CRP value above the median died significantly earlier due to their disease (23 months; $p < 0.001$; Fig. 1) and showed an OS which was significantly shorter ($p < 0.001$). Primary tumor stages and the presence of regional lymph node and distant metastases also showed a significant association with CRP levels in patients (pT1–pT4, $p < 0.001$; Fig. 2).

Multivariate Analysis

Elevated CRP levels were an unfavorable independent prognostic factor for CSS and OS as shown by multivariate analysis ($p = 0.008$ and $p = 0.005$, respectively; Table 2). The TNR-C score, an outcome prediction model developed by Gakis et al. [13], was validated with our study cohort. The median score was 3 (mean 2.85, range 0–10). The 5-year CSS in patients with a score of 0–2 (low risk), 3–6 (intermediate risk), and 7–10 (high risk) was 76, 40, and 16%, respectively (Fig. 3a). The 5-year OS in patients with a score of 0–2 (low risk), 3–6 (intermediate risk), and 7–10 (high risk) was 71, 33, and 13%, respectively (Fig. 3b).

Discussion

We prospectively analyzed the influence of CRP and Hb levels on CSS and OS in patients undergoing RC for UCB, updating our previous work and increasing our study population by over 57% [8]. Preoperatively elevated CRP levels and decreased Hb levels were found to be independent prognostic factors indicating an unfavorable outcome after RC.

We already showed an association between preoperative CRP levels and outcome in patients undergoing RC for UCB in our previous study, including data of 664 patients. We now reevaluated our previous data and updated our database to include data from 1,043 patients, gathering follow-up data from more than 14 years. We now observed a strong and significant correlation between preoperative CRP levels and CSS in patients undergoing RC for UCB. We could show that CRP levels above the median were associated with significantly shorter CSS and OS ($p < 0.001$).

The importance of CRP levels in cancer prognosis has already been recognized. Kersten et al. [14] demonstrated a correlation between elevated CRP levels and poor prognosis in colon cancer patients. Most recently, others have followed in showing an association between high CRP levels and higher mortality in solid tumor patients, indicating that CRP may be an important biomarker for tumor recurrence, progression, and treatment response [9]. Concerning other urological malignancies, high serum CRP levels have been associated with an impaired OS and in certain cases even with a more aggressive tumor biol-

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ogy and worse CSS [15–17]. Most importantly, Shrotriya et al. [9] identified high CRP levels as a powerful prognostic predictor in most solid tumors, with bladder cancer patients even ranking amongst those with the highest CRP values.

In general, CRP answers inflammatory stimuli due to elevated cytokine levels. It is produced by the liver in the presence of acute or chronic inflammation [18]. When trying to explain these findings, we considered two main hypotheses: CRP elevation as a reaction to inflammation due to tumor growth or CRP elevation caused by the tumor itself.

In our study population, increased CRP levels were significantly associated with primary tumor stage (pT1–pT4) and presence of lymph node metastasis ($p < 0.001$; Fig. 2). The correlation between inflammation and cancer is nowadays widely accepted but incompletely understood [19]. Tissue inflammation in proximity to the tumor may account for CRP elevation in relation to tumor stage.

Inflammatory cells and cytokines produced by tumors, in particular interleukin 6 and 8, are mediators of inflammation which increase CRP and may even promote tumor growth itself [19, 20]. One cannot rule out the possibility that CRP elevation is part of a host tumor response, but rather than amounting to an effective host antitumor response, these cytokines have been found to contribute to tumor growth, progression, and immunosuppression [18, 19, 21]. Cytokines also play an important role in apoptosis and angiogenesis, while the latter seems to regulate and influence mechanisms of tumor and metastatic spread itself [22, 23].

Although there was a strong correlation between CRP and outcome, we cannot be sure whether the cause of the elevated CRP levels we observed in our patient cohort is carcinogenesis itself or general inflammation. Nevertheless, CRP seems to be an independent prognostic factor for CSS and OS in many solid tumor patients, but especially the ones undergoing RC for UCB.

We used our study patients as a validation cohort for the TNR-C score, a prognostic score developed by Gakis et al. [13] for patients undergoing RC. The score successfully discriminated between 3 risk groups with distinct outcomes (76, 40, and 16% for low, intermediate, and high risk, respectively). The 5-year CSS in the risk groups of our patients was very similar to the outcome in the patients used for the development of the TNR-C score. These results further support elevated CRP levels as a valid prognostic biomarker in RC patients.

In parallel to our findings regarding CRP levels, we observed an association of preoperative Hb values and CSS in our patients. Those patients with Hb values above the median had a significantly higher CSS than those with Hb values below the median ($p < 0.001$).

Hb levels are proposed as a prognostic factor regarding CSS in various cancerous diseases [24, 25]. A meta-analysis by Huang et al. [24] obtained data from over 22,000 patients and observed a significant correlation between Hb levels and survival in lung cancer patients. They concluded that a decreased pretreatment Hb value is a prognostic factor for poor CSS and OS. Regarding urological malignancies, Schubert et al. [25] have investigated the prognostic role of precystectomy Hb levels in patients with UCB. In this study, they could show that decreased preoperative Hb levels were not only associated with impaired CSS and OS, but also with adverse histopathological characteristics.

Anemia in bladder cancer patients has a high prevalence of up to 50% [26]. This may be explained by two reasons. Firstly, patients undergoing neoadjuvant treatment can suffer from bone marrow suppression and, secondly, gross hematuria may lead to decreased Hb levels. Obviously, all patients with preoperative systemic chemotherapy or radiotherapy were excluded from this study. Information about the individual blood loss volume during hematuria could not be obtained. Altogether, about 59% of patients reported gross hematuria prior to RC.

We acknowledge our median to be above what the WHO considers anemia. Nonetheless, for better comparison and disregarding gender specificities, we could show a significant association between Hb levels and CSS and OS even for Hb values above WHO borderline.

Regarding anemia, molecular mechanisms related to disease progression and dissemination are multifactorial and not completely understood. Anemia can lead to poor tumor oxygenation, which itself can lead to activation of hypoxia-induced factor 1 (HIF1) [27]. To compensate tumor hypoxia due to anemia, HIF1 induces tumor cell dissemination, which facilitates micro-metastases and may account for decreased CSS and OS. There is also evidence that anemia-related hypoxia upregulates genes, e.g., VEGF, to promote angiogenesis and inhibit apoptosis, therefore leading to an increased biological aggressiveness and, ultimately, promoting cancer cell dissemination even in early stages [28].

Also, tumor-related inflammatory cytokines, such as TNF-α, hepcidin, or IL-6, have been identified as important factors in the development of anemia. Morceau et al.

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[29] state that those cytokines affect erythroid cell differentiation either by inducing inhibition of erythropoietin or even by preventing its physiological functions on a cellular level [30].

Based on the current literature and our findings, there is accumulating evidence that preoperative anemia and elevated CRP levels may be connected to tumor growth velocity itself. As increased CRP levels may show an interaction with the patient's immune system and increased cytokine production, the Hb level could be directly affected by this interaction [30, 31]. This could form a vicious circle, in which the overexpression of inflammatory cytokines leads to inhibition of erythropoietin, increasing the severity of anemia and, ultimately, resulting in tumor progression and early dissemination, which again induces cytokine expression.

Corroborating this hypothesis, we found tendencies and significant correlations between primary tumor stage, cancer dissemination, and CRP and Hb levels, respectively. High CRP levels and low Hb levels result in higher tumor stages or advanced tumor spread, ultimately affecting CSS and OS in patients undergoing RC for UCB in our study population.

We, therefore, propose a model in which pretreatment Hb and CRP levels are regarded as independent predictors of CSS and OS in patients undergoing RC for UCB, which should be considered in determining prognosis and therapy in the future.

Although all CRP and Hb measurements were performed in the same laboratory, a certain bias during the long study period cannot be completely excluded. The surgical technique did not change significantly over time, and a small number of experienced surgeons performed most cystectomies. Nevertheless, there might be a certain bias. Another limitation is the short follow-up time (median 22 months).

In conclusion, we could show in a large representative cohort of patients undergoing RC for UCB that the patients' risk of death was clinically and statistically significantly greater with elevated CRP and decreased Hb levels. This was independent of other variables and regardless of statistical method. CRP and Hb appear to be underutilized routine laboratory parameters. Our results corroborate the TNR-C score by Gakis et al. [13] and strongly support the use of CRP and Hb as universal, routine, and cost-effective independent prognostic indicators for individual risk stratification in patients undergoing RC for UCB.

Statement of Ethics

All human subjects provided written informed consent with guarantees of confidentiality. In lieu of an ethical review board, the authors state that this article does not contain any studies with human participants performed by any of the authors. Our research was carried out in accordance with the Declaration of Helsinki of the World Medical Association, and informed consent was obtained from all patients. All data were collected and analyzed anonymously.

Disclosure Statement

The authors have not received any financial grants and have no industrial links or affiliations. They have no conflicts of interest to declare.

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Author Contributions

Alexander Tamalunas was in charge of the project, managed data collection, and wrote the manuscript. Alexander Buchner was in charge of data analysis and helped editing the manuscript. Alexander Kretschmer, Gerald Schulz, Lennert Eismann, and Friedrich Jokisch helped with data collection and edited the manuscript. Christian Stief and Tobias Grimm were in charge of project development and were responsible for the project.

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