# RLC-Score (R-status, Lymphovascular invasion, C-reactive protein) predicts survival following radical cystectomy for muscle-invasive bladder cancer

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# Abstract

Background:

The TNR-C score (tumor stage, lymph node density, resection margin status, and serum CRP) correlates with cancer specific survival (CSS) in patients with bladder cancer (BCa) undergoing radical cystectomy (RC). Our retrospective single center study aimed to evaluate CRP as a prognostic parameter in patients with BCa undergoing RC, to externally validate the TNR-C score, and based on the findings, to develop our own outcome score for muscle-invasive bladder cancer (MIBC) patients undergoing RC that can identify patients with a high risk of progression.

Material and methods:

In total, 254 patients who underwent RC at Hanover Medical School between 1996 and 2007 were reviewed. The clinicopathologic parameters assessed included age; co-morbidities; pre-/postoperative serum levels of CRP; leucocytes; hemoglobin; creatinine; urinary diversion; tumor grading, staging, and lymph node status; lymph node density (LND); lymphovascular invasion (LVI); metastases; and resection margin status. Regarding outcome, overall survival (OS) was assessed.

Results:

Single parameters of the TNR-C-score, such as T-stage (p=0.012) and R-status (p=0.002), were independent prognostic parameters for overall survival (OS). Univariate analysis showed a significant association of OS with the T-stage (≥pT2, p=0.001), R-status (p<0.001), LVI (p=0.011), and preoperative CRP level (p=0.02). The multivariate analysis excluding lymph node (LN) positive and metastatic patients showed a significant association of the R-status (R; p<0.001), LVI (L; p=0.021), and preoperative CRP level >5 mg/L (C; p=0.008) with OS. Based on these parameters, the RLC-score was developed. The median OS in the low, intermediate, and high-risk groups according to the RLC score was 62, 22, and 6.5 months, respectively. The score had a high predictive accuracy of 0.752.

Conclusion:

The RLC-score identifies BCa patients at a higher risk of disease progression and overall mortality after RC. Regarding the TNR-C score, only T-stage and R-status were independent prognostic factors for OS. Nevertheless, the survival curves showed a significantly lower OS for TNR-C high risk group members than low and intermediate risk group members. Overall, our study supports the role of CRP in prognostic score models for BCa.


# Background

Bladder cancer (BCa) is estimated to be among the 10 leading cancer types regarding new cases (62,380) and deaths (12,520) among males in the United States in 2018, thus representing a frequent and lethal disease[1]. Current 5-year survival rates for BCa average 70% for localized disease, 35% for regional

disease, and 5% for distant disease[1]. Approximately three-quarters of the newly diagnosed BCa patients present with non-muscle invasive BCa (NMIBC)[2]. As of now, the EORTC (European Organisation for Research and Treatment of Cancer) BCa risk calculator is the only routinely used score for outcome prediction. Within this score, parameters such as grading, tumor size, concomitant carcinoma in situ (CIS), T-stage, the number of tumors, and prior recurrence rate are used to predict the recurrence and progression of NMIBC Ta/T1 tumors[2, 3]. There are currently no clinically established score systems for outcome prediction in patients with locally advanced or metastasized BCa.

In 2011, Gakis et al. pointed out the prognostic potential of serum CRP (C-reactive protein level) for BCa patients[4]. The authors proposed the TNR-C score for the prediction of cancer-specific survival (CSS) for BCa patients undergoing radical cystectomy (RC), which was a new outcome prediction model including the variables tumour stage (T), lymph node density (N), resection margin status (R), and preoperative serum CRP level (C)[4]. Later on, our working group confirmed the predictive value of CRP for BCa patients following RC in a retrospective analysis of our RC cohort (n = 194, 1996–2005)[5]. However, we did not externally validate the TNR-C score system by Gakis et al. in that study[4, 5].

CRP represents an acute-phase protein and indicates systemic inflammation. Currently discussed hypotheses for elevated CRP levels in cancer patients are CRP secretion by the tumor itself, which makes CRP intriguing as a tumor burden marker, and physiological CRP production by hepatocytes initiated by tumor-released cytokines[6, 7].

The primary aim of this retrospective single center study was to externally validate the TNR-C score proposed by Gakis et al. for the first time on our RC cohort, thus enabling future evaluations in the course of evidence-based recommendations. The secondary aim was to develop our own prognosis score for BCa patients undergoing RC.

# Material And Methods

In the present retrospective study, 254 patients who underwent RC at the Department of Urology of Hanover Medical School (MHH) between 1996 and 2007 were reviewed. The histological assessment was performed in the pathology department of MHH and was based on the TNM classification approved by the American Joint Cancer Committee. Positive surgical margins were defined as the microscopic presence of malignant cells at the resection margins.

Twenty-five patients were excluded due to histologically confirmed malignancies other than urothelial carcinoma (UCC). Gakis et al. excluded patients who had undergone platin-based, neoadjuvant chemotherapy due to this being a potential reason for preoperative CRP elevation. For external validation and purposes of comparison with the study by Gakis et al., 70 patients were additionally excluded due to synchronous metastases or suspected other reasons for CRP elevation (e.g. urosepsis or other cancer entities). This first cohort (n = 159) was named the “validation cohort”. For further development of our own prognosis score, we additionally excluded four radiologically node-positive patients at the time of RC

because this group bears a high progression risk. This second cohort (n = 155) was named the “development cohort”. Approval of the Ethics Committee of Hanover Medical School was obtained for this study (vote nr. 2044 – 2014). The clinicopathologic parameters assessed were: age, gender, pre-/postoperative serum CRP, pre-/postoperative leucocytes and hemoglobin, pre-/postoperative serum creatinine, urinary diversion, WHO tumour grading (G1/G2/G3), tumor staging (T1-T4), LN status, lymph node density (LND), lymphovascular invasion, vascular invasion, tumor necrosis, concomitant CIS, the number of tumors, synchronous/metachronous metastases, and the resection margin status. The CRP cut-off was set at > 5 mg/L. The cut-off values for hemoglobin were set at 14–18 g/dL for men and 12–16 g/dL for women. For the creatinine levels, we defined cut-offs from 85 to 104 µmol/L [8]. All these cutoffs were defined following German standards for laboratory diagnostics. The clinical outcome was measured from the date of RC to date of death or date of last follow-up. The RLC score is based on a multivariate analysis and on previous work by Iimura et al [9]. Patients with positive resection margins received 3 points. Patients with preoperatively elevated CRP ≥ 5 mg/L received 1 point, and patients with lymphatic vessel invasion also received 1 point. The low risk group (group 1, n = 134) was defined as 0–1 points, the intermediate risk group (group 2, n = 13) as 2–3 points, and the high risk group (group 3, n = 8) as 4–5 points. Equivalent to Gakis et al., we analysed the parameters T stage, LND, R-status, and preoperative CRP-level via multivariate analyses. Instead of CSS, we chose OS as the correlation variable since in the authors opinion, CSS is a difficult parameter to assess. Since cox regression models cannot sufficiently evaluate more than four risk factors[22], we developed a risk stratified model for patients with negative LN and no sign of synchronic metastasis after RC based on the significant parameters in multivariate analysis—the RLC score.

The Chi-square test was used for univariate analyses and Cox regression for multivariate analyses. Kaplan-Meier estimates and the log-rank test were used for survival analyses. Statistical analyses were performed with IBM SPSS Statistics version 21 and 22. The significance level was set as α = 5%, thus p-values < 0.05 were considered statistically significant.

# Results

# Descriptive statistics

The majority of the validation cohort was male (79.5%). Their mean age at the time of RC was 65.9 years (CI 64.6–67.2); the women were 2.5 years older on average (CI 65.5–71.3). Adjuvant chemotherapy was administered in 17.9% of cases. A total of 62.4% of the patients received an ileum conduit, 23.6% received an orthotopic bladder substitution, 8.7% a ureterosigmoidostomy (Mainz-II-pouch), and 2.2% an ileocecal pouch (Mainz-I-pouch) as urinary diversions. The mean OS (overall survival) rate was 54.9 months (95% CI 47.58–62.2; median 28). The prevalence of tumor stages was 10.9% for pT1, 29.3% for pT2, 32.3% for pT3, and 16.6% for pT4. One quarter (26.2%) of the patients had nodal positive disease. At the time of RC, 5.7% had metastases other than LN. During follow-up, another 22.3% developed metachronous distant metastases. Tables 1 and 2 describe the patient and tumor characteristics.

Table 1
Patient characteristics

| **Parameters** | | **95% CI** |
|---|---|---|
| Age (median; in years) | | |
| Male | 65.9 | 64.6–67.2 |
| Female | 68.4 | 65.5–71.3 |
| Sex (n) | | |
| Male | 182 (79.5%) | |
| Female | 47 (20.5%) | |
| Urinary diversion | | |
| Neobladder | 54 (23.6%) | |
| Ileumconduit | 143 (62.4%) | |
| Mainz-I-pouch | 5 (2.2%) | |
| Mainz-II-pouch | 20 (8.7%) | |
| None (nephrectomy) | 7 (3.1%) | |
| Chemotherapy | | |
| none | 174 (76.0%) | |
| adjuvant | 41 (17.9%) | |
| neoadjuvant | 14 (6.1%) | |
| Overall survival (months) | 54.9 (mean)<br>28.0 (median) | 47.6–62.2 |

Table 2
Tumor characteristics

| **Parameters** | |
|---|---|
| T stage | |
| pTa | 11 (4.8%) |
| pT1 | 25 (10.9%) |
| pT2 | 67 (29.3%) |
| pT3 | 74 (32.3%) |
| pT4 | 38 (16.6%) |
| Cis | 11 (4.8%) |
| N stage | |
| N0 | 165 (72.1%) |
| N1 | 27 (11.8%) |
| N2 | 30 (13.1%) |
| N3 | 3 (1.3%) |
| Lymph node density ≥ 0.09 | |
| Negative | 180 (78.6%) |
| Positive | 49 (21.4%) |
| M Stage | |
| M0 | 197 (86.0%) |
| M1(synchronous) | 13 (5.7%) |
| M1(metachronous) | 51 (22.3%) |
| Grade | |
| G1 | 4 (1.7%) |
| G2 | 51 (22.3%) |
| G3 | 172 (75.1%) |
| R-Status | |
| R0 | 199 (86.9%) |
| R1 | 25 (10.9%) |

| Parameters | |
|---|---|
| R2 | 4 (1.7%) |
| Lymphatic vessel invasion | |
| L0 | 162 (70.7%) |
| L1 | 66 (28.8%) |
| Vessel invasion | |
| V0 | 214 (93.4%) |
| V1 | 14 (6.1%) |
| Concomittant CIS | 43 (18.7%) |
| Multifocal tumor | 54 (23.6%) |

# Laboratory parameters

Based on the previous work of other groups[4, 10], the cut-off for preoperatively evaluated CRP levels was set at 5 mg/L following German standards for laboratory diagnostics. Overall, an elevated preoperative CRP level was found in 49.8% of all cases. Leukocytosis of > 10,000/µL was found in 28.8% of all cases. Table 3 illustrates the CRP values in relation to T stage, LN status, and R-status. The association of preoperative elevated CRP levels with the overall T stage (NMIBC vs MIBC) showed no statistical significance (p = 0.582), although the subgroup analysis of MIBC alone (pT2 vs. pT3–4) showed a significant association (p = 0.002). Nodal status was significantly associated with CRP level (lymph node positive vs negative; p = 0.006), whereas no significant association could be found for the CRP level and R-status (p = 0.061). Instead, there was a significant association between the preoperative elevated CRP level and OS (86.2 months vs 61.7 months, p = 0.020).

Table 3
Elevated preoperative CRP value and T stage, LN-, and R-status

| T stage | CRP ≥ 5 mg/L |
|---|---|
| pT0 | 2 (0.9%) |
| pTa | 6 (2.8%) |
| Cis | 1 (0.5%) |
| pT1 | 13 (6.0%) |
| pT2 | 25 (11.6%) |
| pT3 | 42 (19.4%) |
| pT4 | 25 (11.6%) |
| LN status | |
| Negative | 73 (34.4%) |
| Positive | 37 (17.5%) |
| R-Status | |
| Negative | 94 (43.7%) |
| Positive | 19 (8.8%) |

# Validation of TNR-C score

The TNR-C score was retrospectively validated on the validation cohort of 159 patients. A significant association between the variables CRP, LND, and OS (see Table 4) could not be found. Only T-stage and R-status were independent prognostic factors for OS (p = 0.012 and p = 0.002, respectively).

Table 4
Multivariate analysis of TNR-C (endpoint OS)

| Parameter | Regression coefficient | p-value | Hazard ratio | 95% CI |
|---|---|---|---|---|
| T stage | 0.499 | 0.012 | 1.646 | 1.114–2.433 |
| LND | 0.367 | 0.089 | 1.443 | 0.945–2.204 |
| R-Status | 0.795 | 0.002 | 2.214 | 1.333–3.676 |
| CRP | 0.155 | 0.409 | 1.168 | 0.808–1.689 |

Similarly to Gakis et al., the patients were classified into three risk groups: 59 patients were low risk; 81 patients were intermediate risk, and 19 patients were high risk. Figure 1 illustrates the respective Kaplan-Meier-curves.

After 5 years, 53.4% of the low risk, 22.2% of the intermediate risk, and 5.3% of the high risk patients were still alive. The area under the curve (AUC) of the Receiver Operating Characteristics (ROC-) curve, which demonstrates the diagnostic ability of TNR-C-score for OS, was 0.673 with a p-value of 0.004 (95% CI 0.570–0.775).

# RLC-score

The univariate analysis revealed a significant association between OS and T-stage (pT2 vs pT3 or higher, p = 0.001), R-status (p≤0.001), LVI (p = 0.011), and preoperative CRP levels (p = 0.02). All significant parameters of the univariate analysis were then included in the multivariate analysis, which identified R-status, LVI, and preoperative CRP level as independent prognostic markers for OS in the development cohort (n = 155), as shown in Table 5.

Table 5
Multivariate analysis of RLC Score in the development cohort (endpoint OS)

| Parameter | Regression coefficient | Significance | Hazard Ratio | 95% CI |
|---|---|---|---|---|
| Lymphovascular invasion | 0.548 | 0.021 | 1.729 | 1.088–2.748 |
| R-Status | 1.639 | < 0.001 | 5.151 | 2.755–9.631 |
| CRP | 0.513 | 0.008 | 1.670 | 1.142–2.443 |

In the low risk group, 77 (49.7%) patients showed a preoperative elevated CRP level (mean 12.85 mg/L), 15 (9.7%) patients LVI, and 30 (19.4%) patients showed progressive disease during follow-up. The median OS after RC was 62 months.

The intermediate risk group contained 13 patients. The mean preoperative CRP level was 18.92 mg/L. The median OS time was 22 months. In cases of metachronous metastases, the median OS decreased to 18.2 months. All of the 8 high risk group patients showed a T stage of pT3 or higher and 6 patients (75%) showed an elevated preoperative CRP level (mean 45.11 mg/L). The median OS time was 6.5 months. Kaplan-Meier-curves for OS in RLC risk groups are shown in Fig. 2. The AUC of the ROC curve for the RLC-Score was 0.752 (p = 0.056, 95% CI 0.485–1.000).

# Discussion

BCa is an aggressive disease and is associated with high morbidity and mortality rates if not treated optimally[11]. Even though BCa is common, it is often mismanaged. Despite RC with extended lymph node dissection, there is a high risk of tumor progression[12–14]. Approximately 50% of the patients with a

T stage higher than T2 and/or LVI develop metastases within 5 years[12] and up to 15% present with local recurrent disease[15]. It is assumed that these patients already bear lymphogenous and haematogenous micro-metastases at time of surgery[16]. Several meta-analyses of adjuvant treatment trials have shown a 22 to 25% reduction in the risk of death with cisplatin-based adjuvant treatment[17, 18], however, they might have been underpowered to draw final conclusions. The selection of patients with a higher risk of disease progression after RC and a valuable tool to predict the outcome for OS and CSS in patients after RC and to identify those patients who will benefit from early adjuvant treatment are therefore needed.

The aim of this study was to evaluate CRP as a prognostic parameter in patients with BCa undergoing RC, to validate the TNR-C score, and based on the findings, to develop a new score to measure OS in patients with BCa after RC. In univariate analysis, the OS was significantly associated with T-stage (pT2 vs pT3 or higher, $p = 0.001$), R-status ($p \leq 0.001$), and LVI ($p = 0.011$). All of these pathologic parameters have been identified as being of prognostic importance in MIBC[12] and were therefore used for the multivariate analysis and score development. Furthermore, preoperative CRP levels showed a significant association ($p = 0.002$) with the later T stage (pT2 vs. pT3–4) in MIBC after RC, lymph node infiltration (lymph node positive vs negative; $p = 0.006$), and a lower OS (86.2 months vs. 61.7 months, $p = 0.02$). In the recent past, our own and several other groups identified CRP as a prognostic predictor in cancer patients[5, 6, 19–21]. High CRP levels yielded a worse survival in renal cell carcinoma, prostate cancer, BCa, and upper tract urothelial carcinoma (UTUC). The main advantages of CRP as a serum biomarker are its widespread availability due to its routine use as an inflammation marker and its inexpensive assessment. The main disadvantage is the possibility of false negative results due to true infectious inflammation[5].

In multivariate analysis, R-status, LVI, and the preoperative CRP level were independent prognostic markers for OS. The final model consisting of these three parameters, the RLC score, yielded a high predictive accuracy of 0.752. Our model used OS as an endpoint instead of CSS, in contrast to other score systems such as the TNR-C score of Gakis et al.[4] or the TNM-C score of Iimura et al.[9], since in the authors opinion, CSS is a difficult parameter to assess. Despite our intense analysis of multiple sources, such as the central German cancer registry, the given clinical chart data, and data from the patients' general practitioners, no certain CSS was evaluable. Nevertheless, there was a correlation of OS with stratification of TNR-C risk groups (Fig. 1). The survival curves showed a significantly lower OS for TNR-C high risk group members than low and intermediate risk group members. Whereas Gakis et al. included LN positive patients, our RLC-score excluded this group. This limits the direct comparison of results but might be an advantage of the RLC score since we assessed a patient group not highly suspected to develop a metastatic disease.

In the low risk group of our RLC score, more than a fifth (22.4%) showed tumour progression. In comparison to the aforementioned scores, the survival rates showed a significantly lower OS for RLC high risk group members compared to the other groups. The R-status represented the most important independent prognostic factor. It is noteworthy that CRP is, per se, a marker for inflammation processes and occurs ubiquitously in the human body. However, it has clinical relevance because it is a standard

parameter of the preoperative evaluation of patients with BCa in most urologic clinics. Overall, the RLC score can identify patients with a higher risk of progression who would benefit from a close follow-up or early adjuvant chemotherapy. The RLC score itself now needs an external validation.

Due to the retrospective nature with a small cohort, this study bears limitations. Despite of primary LN invasion absence, many patients died after a couple of months from disease progression or developed metastases. In the RLC intermediate risk group, 75% of the patients showed metachronous metastases, whereas in the high risk group, only one patient was diagnosed with metastases. This can be explained by the short OS (median 6.5 months) of the high risk group.

It is important to mention that the mean age in the RLC high risk group exceeded the other two groups by around five years (73.5 years vs 67.5 and 68.9 years). A correlation of age at the time of RC and OS has be shown[23–25], although comorbidities were found to be more important. In our study, comorbidities were not registered and therefore could not be analysed.

# Conclusion

The RLC-score identifies BCa patients undergoing RC with a higher risk of disease progression and, therefore, a reduced OS. Regarding the TNR-C score, only T-stage and R-status were independent prognostic factors for OS. Nevertheless, the survival curves showed a significantly lower OS for TNR-C high risk group members than low and intermediate risk group members. Overall, our study supports the role of CRP in prognostic score models for BCa. Furthermore, there is a need for prospective trials to confirm these findings.

# Declarations

### List of abbreviations

TNR-C - tumor stage, lymph node density, resection margin status, and serum CRP

CSS - cancer specific survival (CSS)

BCa - bladder cancer

RC – radical cystectomy

MIBC - muscle-invasive bladder cancer

OS - overall survival

LN - lymph node

NMIBC - non-muscle invasive BCa

EORTC - European Organisation for Research and Treatment of Cancer

CIS - carcinoma in situ

MHH - Hanover Medical School

UCC - urothelial carcinoma

LND - lymph node density

AUC – area under the curve

ROC - Receiver Operating Characteristics

UTUC - upper tract urothelial carcinoma

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## Authors' contributions

N/A

## Ethics approval and compliance with ethics guidelines

This article does not contain any studies with human participants or animals performed by any of the authors. Approval of the Ethics Committee of Hanover Medical School was obtained for this study (vote nr. 2044-2014).

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## Competing interests

The authors declare that there are no financial or non-financial competing interests.

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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# Figures

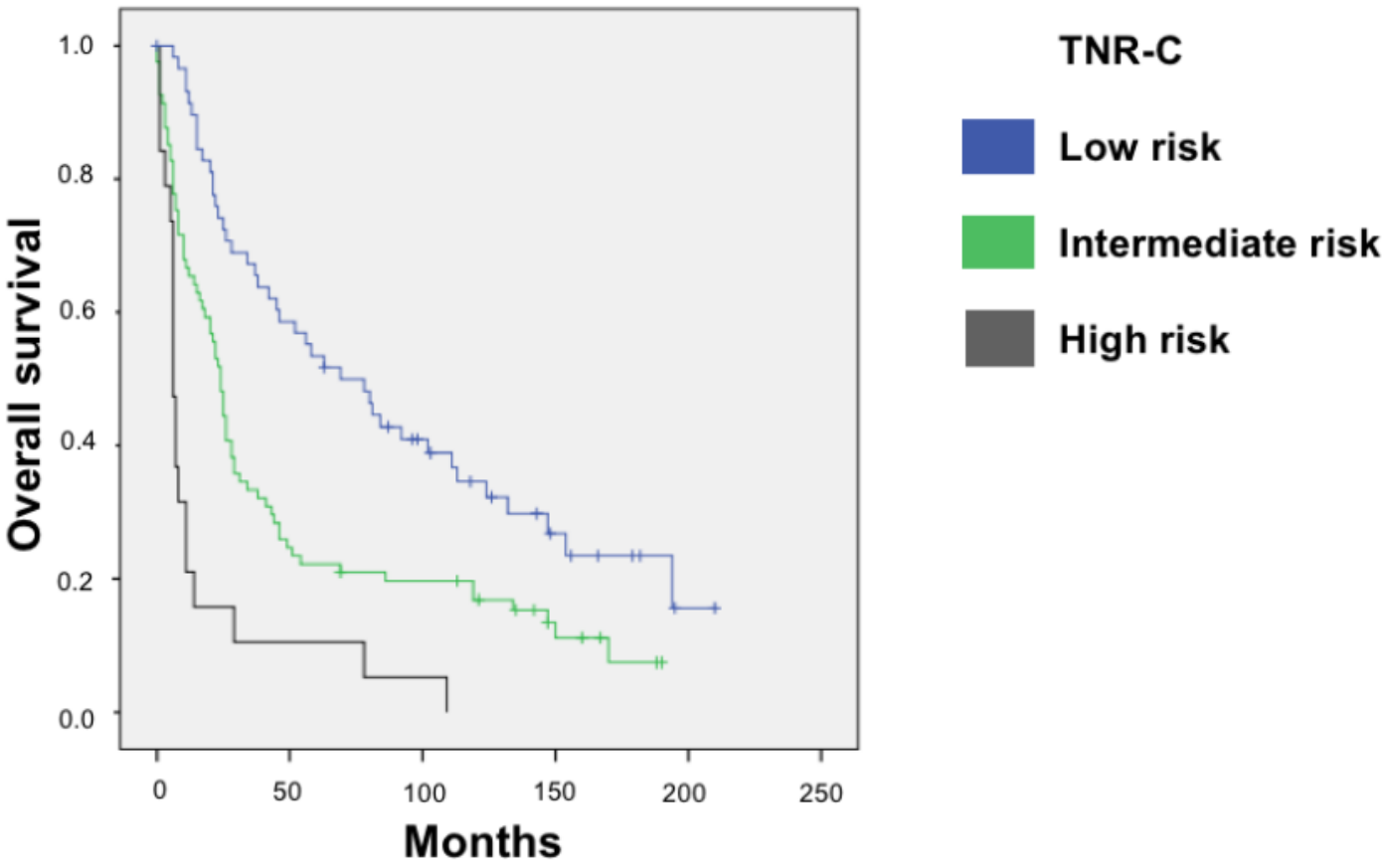


**Figure 1: Kaplan-Meier-plot for TNR-C Score regarding OS**

## Figure 1

Kaplan-Meier-plot for TNR-C Score regarding OS

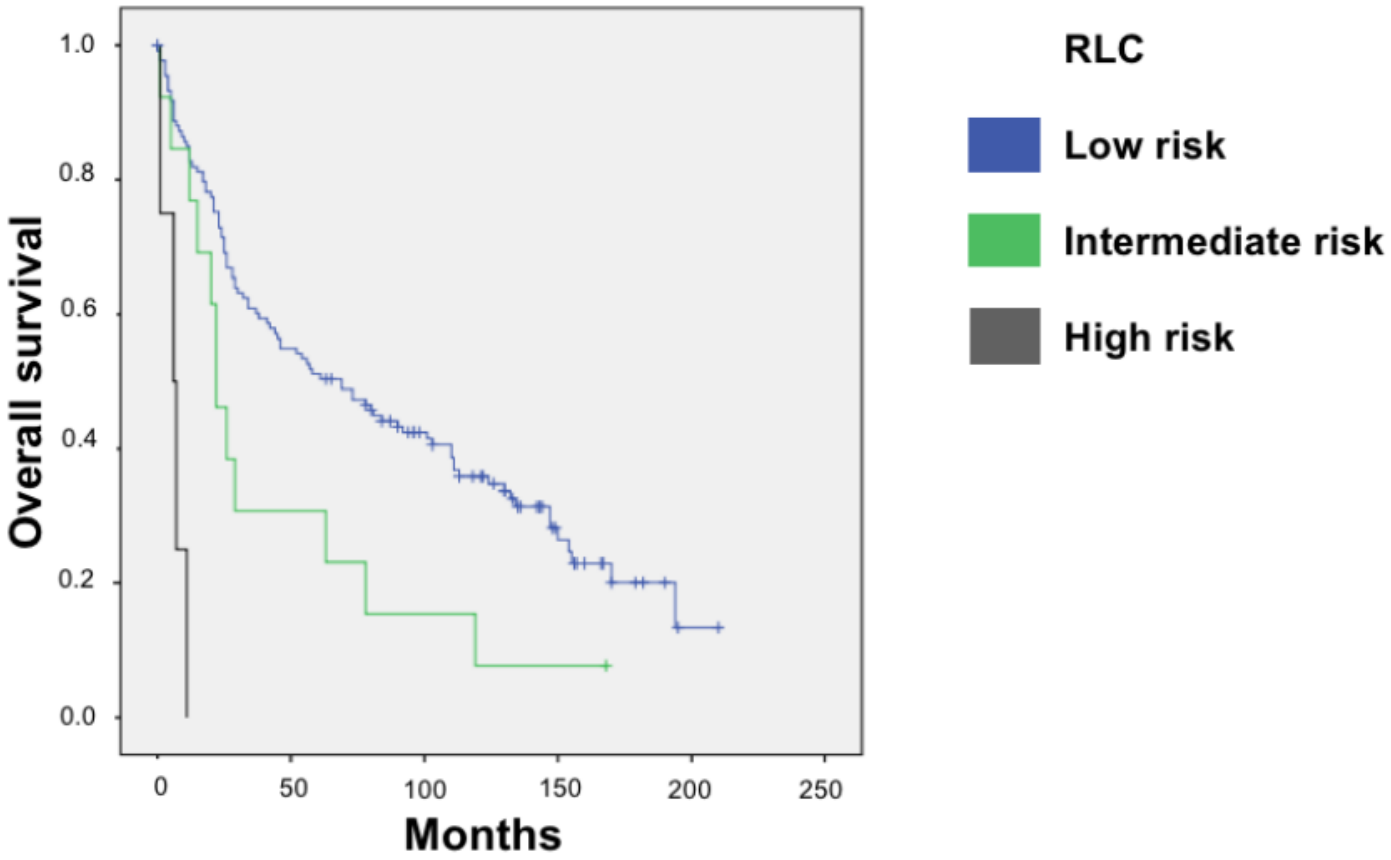


**Figure 2: Kaplan-Meier-plot for RLC score regarding OS**

## Figure 2

Kaplan-Meier-plot for RLC score regarding OS