Predictive Value of Different Parameters for Estimating the First 90-days and Long-term Survival Following Radical Cystectomy

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Abstract

Objective: We aimed to define the prognostic risk factors which may have an impact on the survival by assessing the effects of the different clinical parameters and several comorbidity classifications on the oncologic outcomes within the first 90 days and long-term follow-up after radical cystectomy.

Materials and Methods: Fifty-two patients who underwent radical cystectomy between June 2013-and June 2017 due to bladder tumors and whose data were fully accessible, have been assessed retrospectively. The demographical, clinical and pathologic data of the patients were recorded along with the progression and mortality rates within the first 90 days follow up period and the subsequent long-term follow-up. Age-adjusted Charlson Comorbidity index (ACCI), Eastern Cooperative Oncology Group (ECOG) score, American Society of Anesthesiologists (ASA) score, Framingham risk score, Preoperative Score to Predict Postoperative Mortality, Rockwood frailty index, preoperative serum hemogram parameters and estimated glomerular filtration rate (eGFR) were all calculated and recorded.

Results: Out of the 52 patients the average age was 68.21±6.47, distant metastasis was observed in 17 (32.7%) patients during monthly follow ups at an average of 37.52±26.15 [minimum (min)=1, maximum (max)= 96], while morbidity was observed in 23 patients (44.2%). According to receiver operativing characteristic analysis, the two parameters as the most reliable tool in the prediction of the mortality during long term follow up were eGFR [area under the curve (AUC)=0.754, p<0.001] and Framingham score (AUC=0.782, p=0.001). It has also been observed in multivariate analysis that Framingham score and Clavien-Dindo classification was the most meaningful predictive factor in the estimation of the mortality in the first 90 days period, progression free survival (PFS) and overall survival (OS); eGFR for PFS and OS; ECOG score for PFS; ASA score for OS; monazite/lymphocyte rate for the estimation of the mortality in the first 90 days period. In addition, pT3-4 stage has been observed to be much more meaningful in the prediction of PFS, non-transitional cell carcinoma pathology for PFS and OS, and, lymph node positivity for OS.

Conclusion: Radical cystectomy is a surgical procedure with high morbidity and mortality due to perioperative complications both in the first 90-days of the postoperative period and long-term follow-up.We found that Framingham score and eGFR were superior and easily applicable parameters in prediction of PFS and OS, whereas Framingham score and MLR were better in prediction of the first 90-days mortality. In this way, we think that we can identify patients who are more suitable for cystectomy, so we can provide more successful postoperative follow-up and treatment management.

Keywords: eGFR, Framingham risk score, monocyte/lymphocyte ratio, oncologic outcomes, radical cystectomy

Introduction

Out of the cancers, the bladder cancer is the sixth malignity which is encountered widely while it is ranked to be the second frequency out of the urologic tumors (1). It is the fifth cancer type which gives way to death in all around the world (2). By the time of diagnosis, 70% of the bladder cancer is supposed to be at the non-invasive stage while the remaining 30% is at the invasive and metastatic stage (3). The diagnosis for muscle invasive cancer could be made through the transurethral

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resection (TUR) and the proposed treatment for stage T2-T4a N0-Nx M0 is the radical cystectomy subsequent to clinical evaluation (3). In addition, as far as the non-muscle invasive bladder cancers (NMIBC) are concerned, radical cystectomy is one of the options for the treatment of the cases with resistance against intravesical treatments or the presence of low-grade diffusive tumors which cannot be resected completely (3).

Since the median age of the patients during diagnosis is 70, the rate of postoperative complications reaches to 60% due to the high morbidity rates of the surgical operation with the effects of the elder age and the accompanying diseases (4). The mortality rates observed within the first 90 days of the postoperative period vary between 2.6% to 7.9%. (4). The preoperative assessment of the short and long-term mortality for the geriatric population (>70 age) is of particular importance in this respect (5). Hence, the patients and their families will be informed of the potential risks and the approaches to protect the bladder will perhaps be brought forward for the patients with higher morbidity. However, we come to an understanding that there exists no consensus for the nomogram or scoring system which may be the best for comorbidity of such patients, if we have a look at the literature (6).

In this study, we aimed to define the prognostic risk factors which may have an impact on the survivals taking into account the effects of the various clinical parameters and different comorbidity classifications on the oncologic assessments to be made within the first 90 days follow period subsequent to cystectomy and the long term follow period as well.

Materials and Methods

The data of 65 elder people who underwent radical cystectomy was applied by a primary surgeon due to a bladder tumor between June 2013 and June 2017 at our clinic were assessed retrospectively. Nine of the patients on whom no extended lymph node dissection application was performed and four patients data of whom were inaccessible were excluded from the study. Radical cystectomy for curative purposes, bilateral lymph node dissection and ileal conduit as urinary diversion were applied on 52 patients included in this study.

The demographic data of the patients involved, body mass index (BMI), preoperative hydronephrosis status, TUR pathology, cystectomy pathology, atypical variant histology were all recorded. Prior to cystectomy, the estimated glomerular filtration rate (eGFR) was calculated and kept under the records. For this particular calculation, Modification of Diet in Renal Disease formula which includes the parameters e.g preoperative creatinin, age, gender, and race, was used. Based on the patients' data obtained during the preoperative period, Age - adjusted Charlson comorbidity index (ACCI), Eastern Cooperative Oncology Group (ECOG) performance score, ECOG score, Framingham risk score, Preoperative Score to Predict Postoperative Mortality (POSPOM) and Rockwood frailty index (RFI) were calculated. The serum hemogram parameters [(neutrophile/lymphocyte rate (NLR), platelet/lymphocyte rate (PLR), monocyte/lymphocyte rate (MLR), average platelet volume (MPV), red cell distribution width (RDW)] taken one week before the cystectomy were calculated individually and recorded.

The follow-up period of the patients subsequent to cystectomy, postoperative complications according to Clavien-Dindo classification, progression and mortality rates were all recorded.

Age-adjusted Charlson Comorbidity Index

This scoring is used to predict the 30 days mortality in traumatic cases or the diseases which require emergency radical surgery (7). Scoring is based on the severity of the comorbidity (lmild, moderate or severe) in the case of cardiovascular, pulmonary, gastrointestinal, urologic, neurologic and hematologic diseases. Out of 19 parameters as a total, for each parameter score between 1 to 6 is assigned to attain to the total score. For each case above 50 years of age, one more point is added against 10 years increase.

Eastern Cooperative Oncology Group Performance Score

Eastern Cooperative Oncology Group performance score is scaled between 0 and 5 to assess the general performance status of the oncology patients where zero point shows good performance and five points shows death (8).

American Society of Anesthesiologists Score

American Society of Anesthesiologists (ASA) score is the primordial scoring system between 1 and 4 based on the perioperative risks based on the physical conditions of the patients during preoperative period as defined by the ASA in 1940 (9).

Framingham Risk Score

It is a nomogram that calculates the ten-year risk of cardiovascular disease development and associated mortality. The parameters used in this scoring systems are age, gender, blood pressure value, total cholesterol, high density lipoprotein (HDL) level smoking and diabetes. Scores are assigned against each of such parameters and the total score is thus calculated. The probability of the occurrence of any cardiovascular disease for the ten years period can be found out for each of the gender in pursuance with the percentile corresponding to the scores obtained. Accordingly, <10% shows low-risk, 10-19% intermediate risk, and ≥20% high risk (10).

Preoperative Score to Predict Postoperative Mortality

It is the risk score which not only predicts the potentiality of the mortality at the hospital for the patents who are to undergo surgical operation but also makes risk assessment in order to reach to a clinical solution. In this scoring system, a total of seventeen predictive factors which include age, cardiovascular, cerebra-vascular, renal, urologic, endocrine, and oncologic pathologies are defined. In case the total score assigned for each of such factors is more than 28, it then shows the poor prognosis (7).

Rockwood Frailty Index

Frailty can be characterized through external factors which may lead to physical stress. By the time the fragile individuals within the geriatric population are followed up at the hospital,

the risks for drops, delirium and disability increase. RFI is the nomogram used to predict the duration of hospitalization and the development of the major complications for the postoperative patients (11). Scores between 1 and 4 mean to be "no fragility", 5 and 6 "mild to moderate degree", and 7 and 9 "severe fragility "

Statistical Analysis

After evaluating the normality status with the Kolmogorov-Smirnov and Shapiro-Wilk tests, while identifying the characteristics of all patients, the continuous variables with normal distribution were shown as mean ± standard deviation, the non-normally distributed variables were shown as median (25th percentile-75th percentile), and categorical variables were shown as number (percent). To define the estimated value used to predict the mortality during long-term follow-up period subsequent to radical cystectomy, receiver operating characteristic curve analysis were made. Kaplan-Meier method was used for the survival analysis and the differences amongst the patient sub groups were defined through log rank test. Cox Regression analysis was used to define the variables which may have an impact on the mortality, progression free survival (PFS) and overall survival (OS) in the first 90 days. The analyses were made through IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. $p < 0.05$ value is considered statistically significant.

Results

The average age of the patients included in our study is 68.21±6.47 (min=50, max=78) while 48 patients (92.3%) were male and four patients (7.7%) were female. During the 37.52±26.15 (min=1, max=96) months follow-up period, distant metastasis was observed on 17 patients (2.7%) with the death of 23 (44.2%) patients. Distant metastasis has been defined in the lymph nodes of four patients, the lungs of eight patients, bones of two patients and the liver of three patients. The demographical, clinical, pathological, and oncologic outcomes for the patients are shown in Table 1.

Table 2 shows the estimated values of the parameters to be used in the prediction of the mortality in the long-term subsequent to cystectomy. Out of such values, the eGFR [area under the curve (AUC)= 0.754, p<0.001] and Framingham score (AUC=0.782, p=0.001) have been observed to be the most reliable two parameters. According to the Framingham score which makes an assessment on the risk of development of cardiovascular disease over the ten years if we classify the patients in the manner that (<10%) is low risk, (10-19%) is medium risk, and (≥20%) is high risk, the group observed with mortality, includes high risk patients more than the other group (53.8% vs 23.5%) and the patients under high risk have been observed to be assigned higher mortality (61.9%) while we have found out that much more reliable results could be attained in the prediction of the mortality if the estimated value for Framingham score is set to be 14.5. (Table 2, Figure 1-2).

Age, gender, BMI, smoking history, cystectomy pathology, atypical variant histology in cystectomy specimen, presence of carcinoma in situ, lymphovascular invasion, presence of upstaging / downstaging, surgical margin positivity, pathological

Table 1. Patients' demographical, clinical and pathological data and oncologic results	
Parameters	**Total (n=52)**
Age	68.21±6.47
Body mass index	25.78±3.72
Gender (n, %)	
Male	48 (92.3)
Female	4 (7.7)
Smoking history (n, %)	
Yes	30 (57.7)
No	22 (42.3)
TUR-BT pathology (n, %)	
-T2G3	47 (90.4)
- Non-TCC	5 (9.6)
Cystectomy pathology (n, %)	
-T0	6 (11.5)
-Ta	1 (1.9)
-T2	21 (40.4)
-T3	12 (23.1)
-T4	7 (13.5)
- Non-TCC	5 (9.6)
Atypical variant histology (n, %)	
-Micro papillary	4 (7.7)
-Sarcomatoid	10 (19.2)
- No atypical variant histology	38 (73.1)
Upstaging after cystectomy (n, %)	
Yes	23 (44.2)
No	29 (55.8)
Downstaging after cystectomy (n, %)	
Yes	7 (13.5)
No	45 (86.5)
Accompanying CIS (N, %)	
Yes	13 (25.0)
No	39 (75.0)
Positive surgical margin (n, %)	
Yes	10 (19.2)
No	42 (80.8)
Lymph vascular invasion (n, %)	
Yes	7 (13.4)
No	45 (86.6)
Positive lymph node (pN+) (n, %)	
Yes	20 (38.5)
No	32 (61.5)
Preoperative hydronephrosis (n, %)	
Yes	27 (51.9)
No	25 (48.1)
eGFR (mL/dk/1.73 m²)	74.84±9.92

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ACCI	5.25±2.37
Neo-adjuvant chemotherapy (n, %)	
Yes	9 (17.3)
No	43 (82.7)
Adjuvant chemotherapy (n, %)	
Yes	12 (23.1)
No	40 (76.9)
ECOG score	2 (2-3)
POSPOM score	27.17±9.92
Framingham score	17.02±8.10
Framingham risk classification	
Low risk	12 (23.1)
Intermediate risk	19 (36.5)
High risk	21 (40.4)
ASA score	2 (2-3)
RFI	5.83±1.86
NLR	2.23±0.72
PLR	113.18±28.37
MLR	0.27±0.09
MPV	3.61±0.99
RDW	13.61±0.99
Clavien-Dindo classification (n, %)	
-1	22 (42.3)
-2	17 (32.7)
-3a	6 (11.5)
-3b	6 (11.5)
-4b	1 (1.9)
Follow up period (month)	37.52±26.15
Rate of metastasis during follow up (n, %)	17 (32.7)
Rate of mortality in the first 90 days (n, %)	6 (11.5)
General mortality rate (%)	23 (44.2)

BMI Body/Mass index, TUR-BT: Transurethral resection of the bladder tumor, TCC: Transitional cell carcinoma, CIS: Carcinoma in situ, eGFR: Estimated glomerular filtration rate, ACCI: Age Adjusted Charlson Comorbidity Index, ECOG: Eastern Cooperative Oncology Group, POSPOM: Preoperative Score to Predict Postoperative Mortality, ASA: American society of anesthesiologists, RFI: Rockwood frailty index, NLR: Neutrophile/lymphocyte rate, PLR: Platelet/lymphocyte rate, MLR: Monocyte/lymphocyte rate, MPV: Average platelet volume, RDW: Erythrocyte distribution width

lymph node positivity, preoperative hydronephrosis status, neoadjuvant/adjuvant chemotherapy, status POSPOM, Framingham score, RFI, NLR, PLR, MLR and Clavien-Dindo classification were used, univariate and multivariate survival analyzes were performed to include these data as independent variables. Since no meaningful estimated value has been defined for MPV (AUC=0.601, p=0.214) and RDW (AUC=0.645, p=0.074) in receiver operating characteristic analysis, these two parameters have not been included in the univariate and multivariate analysis.

The predictive factors for PFS and OS within the follow-up period in the long-term, and the first 90 days mortality subsequent to radical cystectomy according to the univariate and multivariate analyses are shown in Table 3A-C. Kaplan-Meier curve for the parameters used in the prediction of the OS in accordance with the multivariate analysis is shown in Figure 1-7.

Discussion

Radical cystectomy is the surgical procedure with high morbidity and mortality both in the course of the first 90 days of the postoperative period and the follow-ups in the long-term due to the perioperative complications (7). Different publications
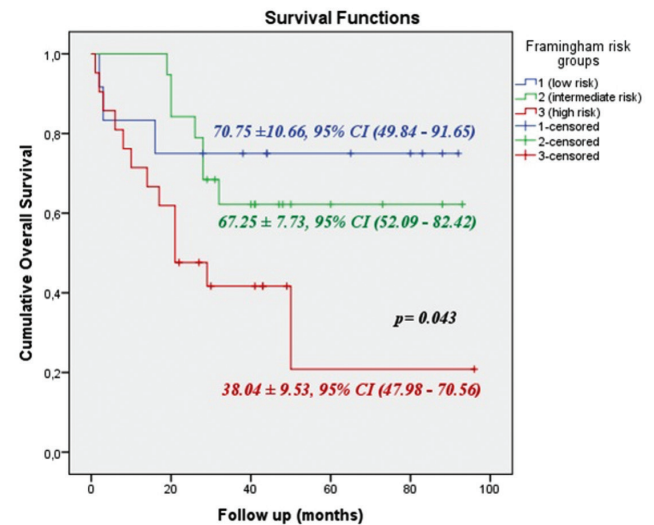
Figure 1. Kaplan-Meier plot of overall survival times predicted for Framingham risk groups

CI: Confidence interval
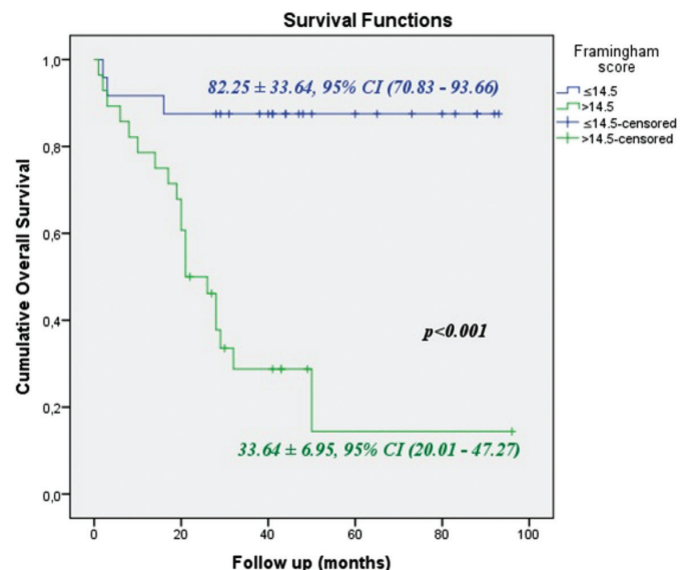
Figure 2. Kaplan-Meier plot of overall survival times predicted by Framingham risk score

CI: Confidence interval

Table 2. Cut-off values for the parameters used to predict the mortality in the long-term follow-up subsequent to radical cystectomy

	ACCI	POSPOM	Framingham score	RFI	NLR	MLR	PLR	eGFR
Cut-off value	5.5	25.5	14.5	5.5	2.13	0.26	110.36	74.10
Sensitivity (%)	60.9	65.2	87.0	73.9	60.9	73.9	73.9	82.6
Specificity (%)	69.0	65.5	72.4	51.7	55.2	65.5	65.5	69.0
PPV (%)	66.2	67.2	75.9	60.4	57.6	68.1	68.1	72.7
NPV (%)	63.8	65.3	84.7	66.4	58.8	71.5	71.5	79.8
AUC	0.705	0.713	0.782	0.697	0.666	0.726	0.669	0.754
p	0.012*	0.009*	0.001*	0.015*	0.042*	0.022*	0.037*	<0.001*

ACCI: Age-adjusted Charlson Comorbidity index, RFI: Rockwood frailty index, , POSPOM: Preoperative Score to Predict Postoperative Mortality, NLR: Neutrophile/lymphocyte rate, MLR: Monocyte/lymphocyte rate, PLR: Platelet/lymphocyte rate, eGFR: Estimated glomerular filtration rate, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve *p<0.05 (There is a significant difference between the groups)

have specified that the perioperative mortality ratio is 2-13% and general survival percentage for five years is 50-60% (12). We have observed that the said ratios are respectively 11.5% and 44.2% in accordance with the literature. Multimodal treatments for the protection of the bladders or radiotherapy for palliative purposes may be an option for the patients with high morbidity especially the elder patients, to get rid of the surgical risks despite the fact that such treatments are not deemed to be the alternatives to the cystectomy in view of curative treatment. Therefore, it is of particular concern to define the patients with high mortality ratio and morbidity associated with cystectomy (13).

There exists surplus of studies which pertain to the comorbidity index to be used in the prediction of the OS in the follow up in the long term and the perioperative mortality of 90 days for the patients on which radical cystectomy is planned due to bladder tumors (4,12,13,14). Different studies have shown that the elder age, angina pectoris, smoking history, chronic lung diseases and Diabetes Mellitus were used as independent prognostic factors to predict the 10-year mortality subsequent to cystectomy (13,15). However, instead of evaluating the comorbid conditions individually, it is thought to be more valuable to use nomograms that examine the total morbidity burden (2).

According to the updated guidelines of the European Association of Urology (EAU), it is suggested to make an evaluation for the morbidity of the potential patients who are to undergo radical cystectomy preoperatively (3). For this purpose, the widely used scoring systems are ACCI and ASA and it has been observed that they are much more beneficial for the prediction of the complications which may develop in the elder patients during the first 30 days after the operation and the cancer free mortality in the first 90 days (13,14). It has been reported that the prognostic value of ACCI may be higher in the estimation of five-year mortality due to all causes (12).

It is obvious that the predicted values of the survival analyses of the scoring systems vary in every study (4,12,16). As a matter of fact elder age (≥75), it has been reported that progressive cancer stages (T3-4) and high ASA score (≥3), increase the perioperative mortality within the 90 days period (4); make a negative impact of the five-years OS ratios through ACCI (17) and ECOG score has no additional contribution for the prediction of the 90 days mortality (4). According to Boorjian

et. al (12), ASA and ECOG scores make an impact on both the 90-days perioperative mortality and the five years OS, on the other hand ACCI predicts the OS in a much more meaningful manner. Froehner et al. (16) have specified that ACCI and ASA scores fail to predict the short and long-term mortality for the patients aged 80 and more, after cystectomy. According to the multivariate analysis in our study, we observed that advanced tumor stage (T3-4) and ECOG score affect PFS more significantly, and ASA score affects OS more significantly, while we could not determine the effect of patient age on oncological results. In addition, we have found out that non-transitional cell crcinoma pathology is much more deterministic in the prediction of the PFS and OS while positive lymph node is a determinant for the prediction of the OS. Being distinct from the publications listed in the literature we have also observed that Framingham score and Clavien-Dindo classification are the predictive factors which are much more meaningful in the determination of the first 90 days mortality, PFS and OS and eGFR is for the PFS and OS.

RFI has been in use for the estimation of the duration of hospitalization and development of major complications during postoperative period especially within the geriatric population. There exists no study showing the use of the same for the old population who underwent cystectomy (18). In our study in which we have found out that high RFI (>5.5) values decreases the OS at a rate of 2.32 in the case univariate analysis and that RFI has no meaningful impact on OS in the multi variate analysis..

Froehner et al. (5) reported that systemic disease load is effective on the survival in the long-term subsequent to cystectomy. POSPOM is one of the disease-counting classifications that can be used to predict this. In our study, although high POSPOM (> 25.5) scores decreased PFS at a rate of 2.94 times and OS at a rate of 2.37 times in univariate analysis, it did not have a significant effect in multivariate analysis.

While 28 (53.8%) of 52 patients who underwent cystectomy in our study were 70 years old and under, 24 (46.2%) were over 70 years old. Although we found that the patient's age did not affect oncological results, the rate of patients who underwent cystectomy over 75 years of age was 11.5% in accordance with the literature. Even for the cases with low ASA score (≤2), it is observed that radical cystectomy was applicable on the patients older than 75 years old, at a lesser rate (21% vs 49%) (19).

Nevertheless, Boorjian et al. (12), has stated that the elder age of the patients has no impact on the perioperative mortality and that the age is not the sole determinant for the decision to apply cystectomy In our study, 28 patients (53.8%) aged 70 or younger, out of 52 patients received cystectomy while 24 patients (46.2) were older than 70. Although we have found out that the age of the patients had no impact on the oncologic results, the percentile of the patients who under cystectomy and aged 75 and older is 11.5 % in compatible with the literature.

The updated EAU guidelines suggest the use of the Cumulative Illness Score Rating-Geriatrics (CISR-G) in the assessment of the general medical condition of the patients and when defining the most appropriate treatment alternative for the geriatric group in the case of prostate cancer (20). We consider that this scoring system may not only be used for the patients diagnosed with prostate cancer in daily practice but also for defining the geriatric patients who are to undergo cystectomy. However, the fact that this scale includes many detailed queries concerning the systemic diseases, it is neither practical nor it is possible to apply the same within the scope of the retrospective studies. Therefore, it seems much more convenient to use it in the prospective studies concerning the follow ups on the patients on whom cystectomy was applied. Froehner et al. (15) has reported that ACCI, when compared to CISR-G, is much easier to apply and is at acceptable levels to predict the postoperative mortality.

Since the use of angina pectoris classification of the New York Heart Association (NYHA) and Canadian Cardiovascular Society (CCS) for the prediction of pre-cystectomy cardiac mortality

Table 3A. Predictive factors for the first 90 days mortality in the long term follow up subsequent to radical cystectomy								
	Uni variate model				Multi variate model			
First 90 days mortality	HR	95% CI		p	HR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.010	0.941	1.084	0.770	-	-	-	-
Gender (male)	1.333	0.176	10.101	0.780	-	-	-	-
BMI	1.087	0.971	1.217	0.146	-	-	-	-
Smoking history	1.373	0.604	3.115	0.449	-	-	-	-
Atypical variant histology	1.372	0.561	3.355	0.488	-	-	-	-
Cystectomy pathology (T3-4)	1.158	0.501	2.676	0.732	-	-	-	-
Cystectomy pathology (TCC/nonTCC)	2.890	0.943	8.849	0.063	-	-	-	-
Upstaging	1.852	0.809	4.242	0.145	-	-	-	-
Downstaging	1.262	0.429	3.715	0.672	-	-	-	-
CIS presence	1.813	0.765	4.295	0.176	-	-	-	-
Positive surgical margin	1.549	0.610	3.931	0.357	-	-	-	-
Positive lymph node	1.579	0.676	3.685	0.291	-	-	-	-
Lymph vascular invasion	1.667	0.618	4.494	0.313	-	-	-	-
Preoperative hydronephrosis	1.497	0.631	3.553	0.361	-	-	-	-
Neo-adjuvant chemotherapy	2.027	0.517	3.097	0.235	-	-	-	-
Adjuvant chemotherapy	2.333	0.888	6.130	0.086	-	-	-	-
eGFR <74.10	2.702	0.981	7.462	0.044*	-	-	-	-
ACCI >5.5	1.576	0.673	3.695	0.295	-	-	-	-
ECOG >2	2.068	0.884	4.840	0.094	-	-	-	-
ASA >2	2.279	1.332	3.311	0.034*	-	-	-	-
POSPOM >25.5	2.401	1.010	5.708	0.055	-	-	-	-
Framingham score >14.5	5.064	1.500	17.095	0.009*	5.064	1.500	17.095	0.009*
RFI >5.5	1.781	0.701	4.523	0.225	-	-	-	-
NLR >2.13	1.470	0.636	3.396	0.038*	-	-	-	-
PLR >110.36	1.965	0.755	5.110	0.046*	-	-	-	-
MLR >0.26	2.541	0.628	4.590	0.042*	2.357	1.226	4.156	0.039*
Clavien-Dindo (>2)	1.444	1.045	1.994	0.026*	1.093	0.882	2.857	0.041*
BMI: Body mass index, TCC: Transitional cell carcinoma, CIS: Carcinoma *in situ*, eGFR: Estimated glomerular filtration rate, ACCI: Age-adjusted Charlson Comorbidity index, ECOG: Eastern Cooperative Oncology Group, POSPOM: Preoperative Score to Predict Postoperative Mortality, RFI: Rockwood frailty index, NLR: Neutrophile/lymphocyte rate, PLR: Platelet/lymphocyte rate, MLR: Monocyte/lymphocyte rate, MPV: Average platelet volume, HR: Hazard ratio, CI: Confidence interval *p<0.05 shows the statistically significant difference, Cox regression analysis								

Table 3B. Predictive factors for progression free survival in the long-term follow-up subsequent to radical cystectomy

Survival without progression	Uni variate model				Multi variate model				
	HR	95% CI Lower	95% CI Upper	p	HR	95% CI Lower	95% CI Upper	p	
Age	1.002	0.915	1.096	0.972	-	-	-	-	
Gender (male)	1.440	0.329	6.308	0.629	-	-	-	-	
BMI	1.035	0.913	1.173	0.590	-	-	-	-	
Smoking history	1.308	0.503	3.401	0.581	-	-	-	-	
Atypical variant histology	1.925	0.709	5.232	0.199	-	-	-	-	
Cystectomy pathology (T3-4)	1.569	0.605	4.070	0.034*	1.354	0.917	3.332	0.034*	
Cystectomy pathology (TCC/nonTCC)	4.756	2.044	12.232	0.002*	3.756	1.044	13.222	0.002*	
Upstaging	2.878	1.060	7.813	0.038*	-	-	-	-	
Down staging	2.724	0.761	7.408	0.331	-	-	-	-	
CIS presence	2.553	0.967	6.739	0.059	-	-	-	-	
Positive surgical margin	1.827	0.642	5.195	0.259	-	-	-	-	
Positive lymph node	1.924	0.739	5.015	0.180	-	-	-	-	
Lymph vascular invasion	2.649	0.858	8.176	0.090	-	-	-	-	
Preoperative hydronephrosis	2.116	0.781	5.734	0.141	-	-	-	-	
Neo-adjuvant chemotherapy	3.303	0.837	6.835	0.168	-	-	-	-	
Adjuvant chemotherapy	1.688	0.589	4.837	0.329	-	-	-	-	
eGFR<74.10	4.739	1.540	14.705	0.007*	4.504	1.443	14.084	0.002*	
ACCI >5.5	5.672	1.840	17.481	0.003*	-	-	-	-	
ECOG >2	2.993	1.102	8.128	0.031*	3.036	1.003	9.190	0.049*	
ASA >2	3.419	1.259	9.283	0.016*	-	-	-	-	-
POSPOM >25.5	2.941	1.032	8.385	0.044*	-	-	-	-	-
Framingham score >14.5	5.845	1.661	20.573	0.006*	4.466	1.128	107.684	0.033*	-
RFİ>5.5	1.523	0.562	4.132	0.408	-	-	-	-	-
NLR>2.13	1.825	0.675	4.936	0.036*	-	-	-	-	-
PLR>110.36	2.534	1.172	8.842	<0.001*	-	-	-	-	-
MLR > 0.26	2.452	1.843	6.591	0.004*	-	-	-	-	-
Clavien-Dindo (>2)	3.409	1.230	9.451	0.018*	-	2.442	1.346	6.773	0.024*

BMI: Body mass index, TCC: Transitional cell carcinoma, CIS: Carcinoma *in situ*, eGFR: Estimated glomerular filtration rate, ACCI: Age-adjusted Charlson Comorbidity index, ECOG: Eastern Cooperative Oncology Group, POSPOM: Preoperative Score to Predict Postoperative Mortality, RFI: Rockwood frailty index, NLR: Neutrophile/lymphocyte rate, PLR: Platelet/lymphocyte rate, MLR: Monocyte/lymphocyte rate, MPV: Average platelet volume, HR: Hazard ratio, CI: Confidence interval
*p<0.05 shows the statistically significant difference, Cox regression analysis

may vary both due to the requirement for clinical familiarity and the estimation of the mortality risk of any given patient, it seems much appropriate to make use of ASA score and ACCI in lieu of these (21). We have observed in our study that the Framingham risk scores which predict the cardiovascular mortality over a period of 10 years is much more successful in the prediction of the first 90 days mortality, PFS and OS when compared with ASA, ECOG, ACCI, RFI and POSPOM. Hence, we consider that Framingham risk score which is much more practical method of calculation in comparison with the ACCI, NYHA and CCS angina pectoris classification, is much easier to use in the analysis to be made to predict the survival after cystectomy.

Out of the other mortality indices for survival after cystectomy in the literature are the Elixhauser index, Lee mortality index and Adult Comorbidity Evaluation-27 which all are more popular. (4,12,15). However, none of such indices has superiority over ACCI, ECOG and ASA in view of easiness in the application and high prediction rates (4). Although we have found out that ACCI, ECOG and ASA predicted the first 90 days mortality, PFS and OS in the univariate analysis in a meaningful manner, the ECOG score has predicted the PFS and ASA score has predicted the OS in a meaningful manner in the multi variate analysis.

In the literature, it has been reported that decreased preoperative eGFR values negatively affect GS in renal cell carcinoma by increasing cancer-specific survival (CSS), recurrence-free survival and cardiovascular risk (22,23). Matsumoto et al. (24) has reported that there observed a distinct decrease in eGFR levels subsequent to radical cystectomy, in case the eGFR value is <45 mL/min/1.73 m² the PFS and CSS decreases significantly. In the multivariate analysis, we observed that preoperatively decreased eGFR levels (<74.10 mL /min/1.73 m²) decreased PFS by 4.73 times and OS by 4.10 times after cystectomy. In

Table 3C. Predictive factors for general survival in the long-term follow-up subsequent to radical cystectomy								
	Uni variate model				Multi variate model			
General survival	HR	95% CI		p	HR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.064	0.973	1.164	0.171	-	-	-	-
Gender (male)	2.074	0.278	15.384	0.477	-	-	-	-
BMI	1.048	0.942	1.166	0.389	-	-	-	-
Smoking history	1.655	0.729	13.759	0.227	-	-	-	-
Atypical variance	1.408	0.576	3.440	0.453	-	-	-	-
Cystectomy pathology (T3-4)	1.079	0.466	2.498	0.039*	-	-	-	-
Cystectomy pathology (TCC/nonTCC)	3.802	1.226	11.764	0.021*	4.901	1.345	17.857	0.016*
Upstaging	1.862	0.813	4.267	0.042*	-	-	-	-
Down staging	1.463	0.495	4.328	0.491	-	-	-	-
CIS presence	1.754	0.742	4.148	0.201	-	-	-	-
Positive surgical margin	1.494	0.587	3.803	0.403	-	-	-	-
Positive lymph node	2.787	1.212	6.407	0.016*	2.671	1.147	6.220	0.001*
Lymph vascular invasion	2.727	1.067	6.971	0.036*	-	-	-	-
Preoperative hydronephrosis	2.109	0.889	5.006	0.031*	-	-	-	-
Neo-adjuvant chemotherapy	2.258	0.511	3.002	0.123	-	-	-	-
Adjuvant chemotherapy	1.500	0.614	3.664	0.374	-	-	-	-
eGFR <74.10	4.102	1.865	13.888	0.001*	3.264	1.445	9.603	0.017*
ACCI >5.5	2.630	1.131	6.116	0.025*	-	-	-	-
ECOG >2	2.555	1.685	3.531	0.029*	-	-	-	-
ASA >2	2.810	0.796	4.118	0.007*	2.789	1.572	4.512	0.024*
POSPOM >25.5	2.370	0.998	5.627	0.041*	-	-	-	-
Framingham score >14.5	5.973	2.612	16.825	<0.001*	5.973	2.612	16.825	<0.001*
RFI >5.5	2.329	0.915	5.928	0.007*	-	-	-	-
NLR >2.13	2.407	0.609	3.252	0.004*	-	-	-	-
PLR >110.36	2.631	1.425	9.253	0.007*	-	-	-	-
MLR >0.26	4.287	1.666	11.029	0.003*	-	-	-	-
Clavien-Dindo (>2)	4.592	2.005	10.516	<0.001*	5.005	1.547	16.192	0.007*

BMI: Body mass index, TCC: Transitional cell carcinoma, CIS: Carcinoma *in situ*, eGFR: Estimated glomerular filtration rate, ACCI: Age-adjusted Charlson Comorbidity index, ECOG: Eastern Cooperative Oncology Group, POSPOM: Preoperative Score to Predict Postoperative Mortality, RFI: Rockwood frailty index, NLR: Neutrophile/lymphocyte rate, PLR: Platelet/lymphocyte rate, MLR: Monocyte/lymphocyte rate, MPV: Average platelet volume, HR: Hazard ratio, CI: Confidence interval
*p<0.05 shows the statistically significant difference, Cox regression analysis

univariate analysis, preoperative eGFR <74.10 values reduce the first 90-day mortality by 2.70 times. We are in the thought that the decrease to be observed in the basal eGFR values within any longer term will have a negative impact both in view of the renal function and the cardiovascular risks as supported by such findings.

Recently, there observed an increase in the number of studies examining the effects of the serum hemogram parameters and inflammatory determinants on the oncologic results as far as the cancers of genitourinary system are concerned (25). During tumor proliferation, it is considered that there observed an increase in the rate of neutrophile due to the effects of the inflammatory cytokines primarily the interleukin -6 and the granulocyte colony stimulating factors (26). Decrease in the lymphocytes as a consequence of the reactions against the inflammatory cases and increase in the tumor related

macrophages derived from the monocyte in circulation have been envisaged. The tumor related macrophages expedite the tumor progression (26). As per these assumptions, we may conclude that NLR and MLR may increase for the individuals with surplus of tumor progression.

The high NLR (≥2.7) levels measured prior to the radical cystectomy are found to be in the relation with both the progressed pathological tumor stages and the decreased CSS and OS (27). Another study showed that the high NLR (>4.33), preoperative hydronephrosis and preoperative tumor stages are in relation with upstaging of T3 stage of the disease after the cystectomy (28). In different studies, low lymphocyte/monocyte ratio (<2.44) and high PLR (> 111) values have been reported to predict decreased CSS and OS after cystectomy (29). Despite all these facts, according to Schulz et al. (30), the low PLR (≤28) values are in relation with the progressed
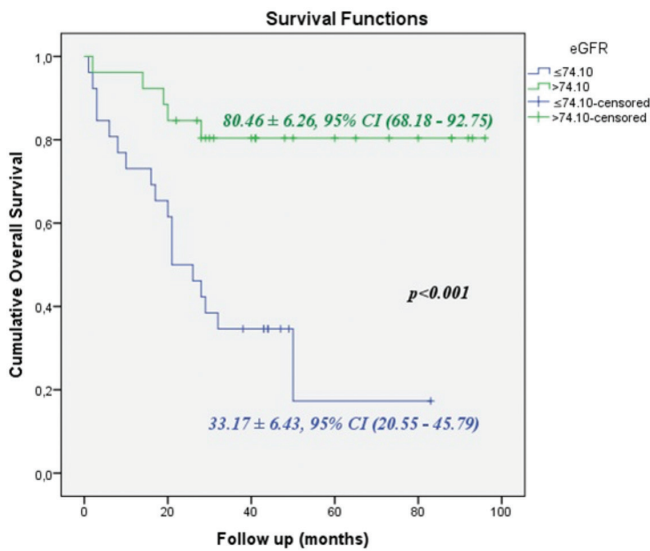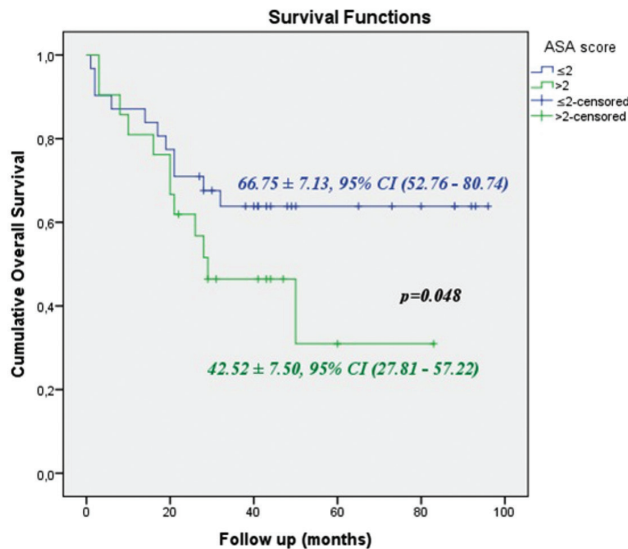
Figure 3. Graphics for Kaplan-Meier analysis showing the estimated durations of overall survival based on the eGFR values

CI: Confidence interval, eGFR: predictive glomerular filtration rate
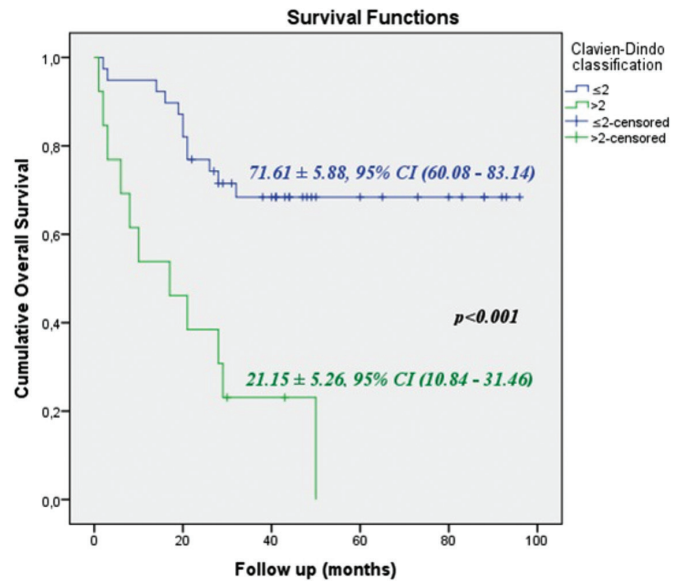
Figure 5. Graphics for Kaplan-Meier analysis showing the estimated durations of overall survival based on the Clavien-Dindo classification
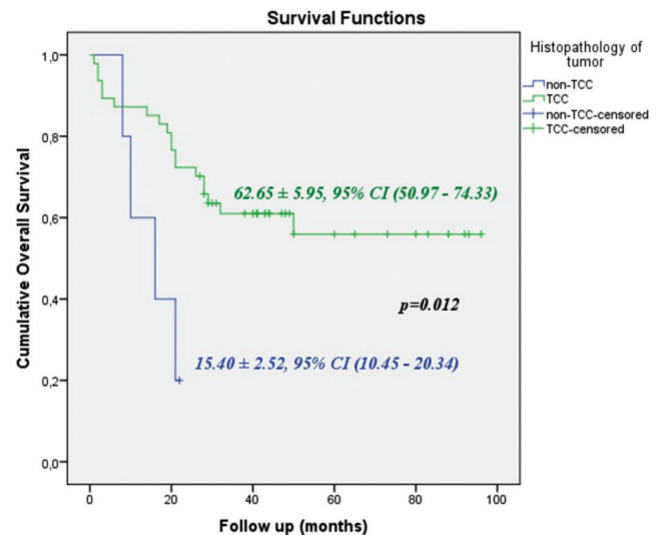
CI: Confidence interval

Figure 4. Graphics for Kaplan-Meier analysis showing the estimated durations of overall survival based on the ASA scores

CI: Confidence interval, ASA: American Society of Anesthesiologists

Figure 6. Graphics for Kaplan - Meier analysis showing the estimated durations of overall survival based on the tumor histology

CI: Confidence interval, TCC: Transitional cell carcinoma

tumor stages and decreased survival. Yoshida et al. (26) associated low perioperative LMR with shorter CSS and OS, suggesting that predictive power is better than NLR. Based on our findings, although the high NLR (>2.13), PLR (>110.36) and MLR (>0.26) levels predict the first 90 days mortality , PFS and OS significantly according to univariate analysis, high MLR increases the first 90-day mortality by 2.35 times according to multivariate analysis.

Study Limitations

The patients whose data were accessible were included in the study without a statistically significant sample size and

randomization due to the restricted number of the patients. Therefore, the major restrictive elements of our study are the retrorespective design of the study limited number of patients involved, short follow-up period and follow-up results belong to a single center without non-randomization. The patents underwent operation by the same surgeon and the same techniques to reduce the effects of the distinctive surgical experience on the outcomes attained. However, over the 4-years period of the study, the same primary surgeon executed cystectomy operation at an annual average rate of 16.25. If we consider that an annual number of 20-25 operations are executed at the high-volume centers, the low volume of cases in
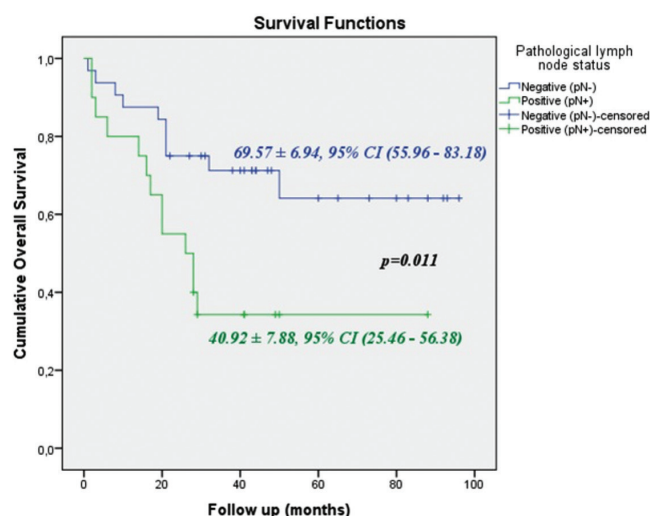
Figure 7. Graphics for Kaplan-Meier analysis showing the estimated durations of overall survival based on the status of the pathologic lymph node

our study may be deemed to be another restrictive factor which may have an impact on the results. In addition, since neoadjuvant or adjuvant chemotherapy was not applied in all cases of muscle invasion bladder cancer, we are in the thought that the heterogeneous tumor characteristics observed on the patients involved in our study might have caused a restrictive effect on the results of the survival. Nevertheless, the patients on whom no extended lymph node dissection was carried out, we have made every effort to make an assessment about the standardized group of patients as part of the surgical method applied.

Conclusions

Many of the studies evaluating the survival after cystectomy in the literature, suggest that ASA and ECOG scores predict the 90 days perioperative mortality in a substantive manner while ACCI predicts five-year OS more significantly. We have found out that the age of the patients has no sole effect on the oncologic results and that Framingham score and eGFR are much more precious and easily applicable parameters for the prediction of the PFS and OS and the Framingham score and MLR are for the prediction of the first 90 days mortality. Although Clavien-Dindo classification which categorizes the complications within the preoperative period, is one of the parameters that can not be applicable preoperatively, we are in the thought that it is particular importance in view of the postoperative follow up and treatment management due to the fact that is substantially predicts the first 90 days mortality, PFS and OS.

Nevertheless, in order to generalize our findings, we believe that long-term, prospective, multicentre, validated clinical studies are required, which include different risk classifications that predict perioperative - postoperative morbidity and mortality.

Acknowledgements

Ethics

Authorship Contributions

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