Is it possible to reduce the complications and mortality of patients undergoing radical cystectomy? Effectiveness of pre-operative parameters. A prospective study

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Summary

Objective: To evaluate the relationship between serum albumin, hematocrit (HTC), age-dependent Charlson comorbidity index, body mass index (BMI), and deleted operation time in predicting mortality and complications associated with radical cystectomy.

Materials and methods: All patients planned for radical cystectomy owing to bladder cancer were investigated prospectively between 2015 and 2016 in our clinic. A total of 55 cases were included in the study. Patients' characteristics, preoperative serum albumin values, hematocrit level, age-dependent Charlson comorbidity index (CCI), body mass index and deleted operation time, drainage catheter time, gas-stool expulsion time were recorded. The patients were followed up for 90 days.

Results: Age of cases, Charlson comorbidity index scores, and HTC were not different in patients with or without complications (overall) or severe complications nor in patients who died or survived after the procedure. The albumin value of the cases with observed mortality and complications was significantly lower than that of the cases with no mortality and complications. In multivariate and univariate analysis, low albumin level was established to be meaningful in predicting mortality and serious complications. The cut-off point for albumin, according to mortality, was found to be 4.1. Mortality within 90 days was 16.3% (n = 9).

Conclusions: We have evaluated albumin as a marker that could indicate both mortality and the presence of severe complications after radical cystectomy and urinary diversion.

Key Words: Albumin; Bladder cancer; Complications; Cystectomy; Mortality.

Submitted Submitted 28 July 2021; Accepted 9 September 2021

Introduction

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in males, while it degrades to 11th when both genders are taken into account (1); 75% of patients with BC present with disease non-muscle invasive bladder cancer at the first consult. Patients with muscle-invasive bladder tumors often present with progressed disease and approximately 20% of them are patients who progress from lower stages (2). The cancer-specific mortality rate of muscle-invasive bladder cancer (MIBC) can be predicted to increase up to 85% if left untreated (2).

Radical cystectomy (RC) and pelvic lymph node dissection (PLND) is the standard treatment for localized MIBC owing to provides the best cancer-specific survival in muscle-invasive patients (3, 4). RC provides excellent local control with a local recurrence rate of 4% in patients with lymph node-negative (5).

RC is associated with significant complications, including death, with wide variability in reported postoperative morbidity and mortality rates. In a study of 1142 patients managed by Shabsigh et al., the serious complication rate was 13% and the mortality rate within 30 days was 1.5% (6). Although the mortality rate has decreased over the past decade, early morbidity rates have remained at ranging from 11 to 68% (3, 7, 8).

Whether the disease is organ-confined to the not and the patient's comorbidity status (age-adjusted Charlson comorbidity index - ACCI) are defined indicators of mortality and complications after radical cystectomy (9). Putting forth a marker that can predict complications can be a prominent attempt to reduce mortality and morbidity. In line with this goal, and hence that there is no prospective study on this subject in the literature, we aimed to examine the usability of serum albumin. Simultaneously, we also examined hematocrit values, age-dependent Charlson comorbidity index (ACCI), BMI, and operation time.

Materials and methods

All patients scheduled to view radical cystectomy for BC between 2015 and 2016 in the urology clinic of Kartal Lutfi Kırdar City Hospital were examined prospectively. A total of 60 patients underwent radical cystectomy operation, and since five patients were out of follow-up, 55 cases, six females and 49 males were included in the study. Ethics Committee Approval was obtained from our hospital's ethics committee for our study, and all subjects signed an informed consent form (IRB number 514/65/4).

Patient's age, BMI, ACCI score, preoperative serum albumin, hematocrit (HCT), urea-creatinine values, operation time, pre-and post-cystectomy pathological stages, diversion type, amount of blood transfusion, type of complications, intestinal functions (gas-stool output time), the transition time to oral nutrition, total parenteral nutrition (TPN) time, the length of hospital stay, the duration of drainage catheter and reoperations, patients' mortality...
and morbidity until the postoperative 90th day and their application for any reason to the hospital, were recorded for each patient. Also, they routinely were called for follow-up visits in the postoperative first and third months. We preferred a well-described method, as Clavien Dindo classification system (CCS), for evaluation of postoperative complications (10, 11). Statistical analysis was conducted using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA). The quantitative and qualitative variables were analyzed with Student’s t-test, Mann Whitney U test, Pearson chi-square test, Fisher’s Exact Test, and Fisher Freeman Halton test. A p value < 0.05 was considered to indicate statistical significance.

**RESULTS**

The mean age of the patients was 65.27 ± 9.38, BMI 26.21 ± 4.17 kg/m², HCT 37.90 ± 5.37, albumin values ranged from 2.2 to 4.9, with an average of 4.03 ± 0.55. Operation times averaged 273.15 ± 74.30 minutes and ranged from 2.2 to 4.9, with an average of 4.03 ± 0.55. The majority of postoperative complications are related to gastrointestinal system (GIS) with a 47.3% rate (n = 26). Second most frequent complications with a 36.4% rate (n = 20) were infectious complications; wound/skin-related complications followed with 14.5% rate (n = 8).

In the relationship between the variety of complications and albumin value, the rate of wound/skin and neurological complications in patients with albumin below 3.5 was significantly higher than in those with a value over 3.5 (p = 0.019, p = 0.002) (Table 2). According to Clavien complication status and severity, age, Charlson comorbidity index, operation times, HCT values, gas-stool output times did not show a statistically significant difference (p > 0.05). Likewise, when the albumin values were examined according to the complication status and severity, no albumin value of 3.5 or less was observed in any of the cases without complications and with mild complication severity. Besides, the albumin value of the patients with complications was found to be significantly lower than the cases without complications (p = 0.013; p < 0.05) (Table 3).

While there is no statistically significant difference between age, Charlson comorbidity index, BMI, operation time, HCT value, gas-stool output time and mortality, the same is not current for albumin. In fact, 55.6% of the cases with mortality had an albumin value of 3.5 and below, and 8.7% of the cases with no mortality had an albumin value below 3.5 (Table 4).

The cut-off point for albumin considering mortality was found to be 4. Accordingly, it is significant that the albumin value of the cases with mortality is 4.1 and below. This cut-off value's sensitivity is 100%, the specificity is 52.17%, the positive predictive value is 29 and the negative predictive value is 100. The area under the ROC curve was 82% for the standard error of the area 6.7% (Figure 1).

**Table 1.**

**Patients characteristics findings.**

| Pre-operative parameters | Min-max (median) | Mean ± 5s |
|--------------------------|-----------------|-----------|
| **Age (years)**          | 38-85 (65)      | 65.27 ± 9.38 |
| **BMI (kg/m²)**          | Normal 45.50    | 34.50     |
|                          | Overweight 20.00 | 10.9      |
| **Gender**               | Female 6        | 49        |
|                          | Male 10.9       | 99.1      |
| **Hematocrit**           | 9.2-16 (12.1)   | 12.45 ± 1.80 |
| **Hemoglobin**           | 27.7-48.8 (37.6)| 37.90 ± 5.37 |
| **Albumin**              | 3.3-6.0 (4.1)   | 4.03 ± 0.55 |
| **Unica**                | 13.35 (39)      | 44.65 ± 20.77 |
| **Creatinine**           | 0.84 (1.1)      | 1.33 ± 0.08 |
| **Neoadjuvant chemotherapy radiotherapy/chemotherapy 6.8-11 (9.0) 0.4-0 (0)  72.7 27.3** |
| **Abdominal surgery**    | No 40           | 15        |
|                          | Yes 72.7        | 27.3      |
| **Charlson score**       | ≤ 2 9           | 16.4      |
|                          | 3-4 28          | 50.9      |
|                          | ≥ 5 18          | 32.7      |
| **Clavien Dindo (n=39)** | 2 15            | 38.5      |
|                          | 3 11            | 28.2      |
|                          | 4 4             | 10.3      |
|                          | 5 9             | 23.1      |
| **Peri-operative parameters** | No 41           | 75.9      |
|                          | Yes 14          | 24.1      |
| **Operation time (min)** | 160-540 (257.5) | 273.15 ± 74.30 |

**Preoperative parameters**

| **Re-operation**         | No 44           | 80.0      |
|                         | Yes 11          | 20.0      |
| **Intensive care unit time (d)** | 0-35 (1) 2.42 ± 5.42 |
| **Gas output time (h)**  | 18-8 (6) 2.88 ± 1.45 |
| **Stool output time (h)**  | 24-1 (4) 3.82 ± 1.60 |
| **Transition time to oral nutrition (h)** | 11-1 4.00 ± 1.79 |
| **TPN time (d)**         | 0-10 (4) 4.10 ± 2.38 |
| **Drainage catheter staying time (d)** | 4-19 (6.5) 9.74 ± 3.53 |
| **Length of Hospital stay (d)** | 2-46 (10) 12.78 ± 9.65 |

**Table 2.**

The type of complications and comparing with albumin.

| Pre-operative parameters | Albumin | Test value |
|--------------------------|---------|------------|
|                          | > 3.5   | ≤ 3.5      | P       |
| **Gastrointestinal system** | No 26 (56.5) 3 (63.3) | 6.124 | 0.283 |
|                          | Yes 20 (43.5) 6 (66.7) | 6.305 |
| **Infection**            | No 32 (66.6) 3 (63.3) | 6.270 |
|                          | Yes 14 (30.8) 6 (63.7) | 0.059  |
| **Genitourinary system** | No 43 (91.3) 8 (88.9) | 6.258  |
|                          | Yes 3 (6.5) 1 (11.1) | 6.552  |
| **Hematological/vascular** | No 42 (91.3) 8 (88.9) | 6.053 | 1.000  |
|                          | Yes 4 (8.7) 1 (11.1) | 6.412  |
| **Cardiac**              | No 44 (95.7) 8 (88.9) | 6.668 | 0.421  |
|                          | Yes 2 (4.3) 1 (11.1) | 6.193  |
| **Wound/skin**           | No 42 (91.3) 5 (55.6) | 7.738 | 0.019  |
|                          | Yes 4 (8.3) 4 (44.4) | 7.046  |
| **Pulmonary**            | No 41 (88.1) 7 (77.8) | 8.735 | 0.321  |
|                          | Yes 5 (10.9) 2 (22.2) | 8.073  |
| **Neurological**         | No 43 (93.5) 5 (55.6) | 9.746 | 0.002  |
|                          | Yes 3 (6.5) 4 (44.4) | 9.040  |
| **Metabolic**            | No 47 (99.1) 8 (88.9) | 0.000  |
|                          | Yes 1 (2.2) 0 (0.0) | 1.000  |

* Fisher’s Exact Test; ** p < 0.01; *** p < 0.05.
Complications of radical cystectomy

To examine factors that affect the severity of complications and mortality, two separate logistic regression models derived from age, BMI, albumin value, preoperative HCT value and Charlson index variables were established. The sensitivity of these models (model 1, 2) for the cases with mortality was 44.4% and 79.2% and the specificity rate was 66.7% and 93.5%, overall accuracy was 85% and 74.4%, respectively. Additionally, albumin's one-

Table 3.
Comparison of operation time, BMI and albumin values according to the presence of complications and their severity.

| Measure                  | Overall complications | Complication severity |
|--------------------------|-----------------------|-----------------------|
|                         | No (n = 16)            | Yes (n = 39)           |                         | Mild (n = 15) | Severe (n = 24) |
| Age (years)              | Mean ± Sd              | 51.77 ± 7.83          | 38.75 ± 6.73            | 38.81 ± 3.75  | 53.85 ± 6.65         |
| BMI (kg/m²)              | Mean ± Sd              | 24.6 ± 4.32           | 21.6 ± 3.54             | 17.6 ± 4.02   | 23.3 ± 5.81          |
| Charlson score           | Mean ± Sd              | 2.6 ± 1.2             | 6.8 ± 4.6               | 6.8 ± 4.6     | 6.8 ± 4.6            |
| Operative time           | Mean ± Sd              | 264.69 ± 60.84        | 276.71 ± 76.72          | 284.0 ± 97.43 | 271.96 ± 61.52 |
| Hemoglobin               | Mean ± Sd              | 33.46 ± 4.32          | 37.19 ± 5.64            | 31.67 ± 4.99  | 36.53 ± 6.03         |
| BMI (n%)                 | Normal                 | 7 (43.8)              | 4 (26.3)                | 9 (60.0)      | 9 (73.1)            |
|                         | Overweight             | 5 (31.3)              | 14 (35.9)               | 5 (36.5)      | 9 (37.5)            |
|                         | Obese                  | 4 (25.0)              | 7 (17.9)                | 1 (6.3)       | 6 (25.0)            |
| Charlson score ≤ 2      |                       | 3 (18.8)              | 6 (15.4)                | 3 (20.0)      | 3 (22.5)            |
|                         | ≥ 3                    | 2 (12.5)              | 4 (10.5)                | 4 (26.7)      | 10 (41.7)           |
| Albumin > 3.5           | Mean ± Sd              | 3.74 ± 4.03           | 21.42 ± 4.4             | 3.49 ± 4.3    | 2.22 ± 4.3           |
|                         | ≤ 3.5                  | 16 (100.0)            | 30 (78.9)               | 15 (100.0)    | 15 (62.5)           |
|                         | 0 (0.0)                | 16 (100.0)            | 30 (78.9)               | 15 (100.0)    | 15 (62.5)           |

Figure 1.
Diagnostic screening tests and ROC curve outcomes of albumin by mortality.

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Table 4. Charlson comorbidity index, BMI, HCT, and albumin values by mortality.

| Age (years) | Charlson Score | HCT (min-max (median)) | BMI (kg/m²) | Albumin (n %) |
|-------------|----------------|------------------------|-------------|--------------|
| Yes (n = 46) | No (n = 9) | Z | Yes (n = 46) | No (n = 9) | P |
| 1-7 | 0.014 | 1/71 | 0.057 | 0.014 | 1/71 |
| 8-10 | 0.457 | 37.94 ± 5.27 | 37.71 ± 6.20 | 0.794 |
| 11-13 | 0.192 | 0.376 | 0.020 | 34.123 |
| >13 | 1.140 | 0.569 | 0.062 | 158.545 |

Table 5. Logistic regression models for factors affecting mortality and complication severity.

| β | P | Odds ratio (OR) | Confidence interval for OR |
|---|---|-----------------|---------------------------|
| Age | -0.079 | 0.412 | 0.924 | 0.766 | 1.116 |
| BMI | -0.039 | 0.479 | 0.961 | 0.717 | 1.389 |
| Albumin | -4.294 | 0.005 | 0.014 | 0.001 | 0.272 |
| HCT | 0.242 | 0.036 | 1.273 | 1.016 | 1.595 |
| Charlson score | 0.457 |
| Charlson (2-5) | -0.192 | 0.919 | 0.825 | 0.020 | 34.123 |
| Charlson (> 5) | 1.140 | 0.569 | 3.128 | 0.062 | 158.545 |
| Constant | 11.709 | 0.230 | 121625.915 |

Model 2. Complication severity

| β | P | Odds ratio (OR) | Confidence interval for OR |
|---|---|-----------------|---------------------------|
| Age | 0.021 | 0.736 | 1.022 | 0.902 | 1.158 |
| BMI | 0.337 | 0.027 | 1.400 | 1.039 | 1.887 |
| Albumin | -2.057 | 0.067 | 0.006 | 0.704 |
| HCT | -0.010 | 0.917 | 0.991 | 0.828 | 1.194 |
| Charlson score | 0.822 |
| Charlson (2-5) | -0.978 | 0.531 | 0.376 | 0.018 | 8.040 |
| Charlson (> 5) | -0.956 | 0.603 | 0.384 | 0.011 | 14.063 |
| Constant | 3.135 | 0.661 | 22.993 |

p < 0.05.

Discussion

Radical cystectomy (RC) is the primary treatment modality for patients with muscle-invasive urothelial cancer of the bladder (1). Increasing patient age, female gender, more than two comorbidities, having undergone previous pelvic surgery, stage of the disease (extravesical disease) and obesity are factors that will increase complications and mortality (6, 7, 12-14). Also, the experience of the surgeon, perioperative blood loss and operation time are important items.

Assessment of comorbidities of patients is of great significance in predicting mortality and morbidity. The American Society of Anesthesiologists (ASA) score is frequently used for this goal. However, we used the Charlson comorbidity index (CCI) in our study (15). Considering their comorbidity index, we divided the patients into three groups: 2 mild, 3-4 moderate, and ≥ 5 severe.

We observed that patients with 5 and above have serious complications. In the study by Koppie et al., overall survival was demonstrated decreasing in patients with high comorbidity considering the comorbidity index, but recurrence-free survival was not affected.

Again Maffeizini et al. in his study, a CCI of more than 3 was found to be associated with survival (16). It is also noteworthy that patients with high comorbidity had been performed less lymph node dissection and less postoperative chemotherapy (9).

The complication percentage of our study is 70.9%. This value is higher than the literature obviously. (6, 15, 18-20). Whereas these literature values included 30-day morbidity and mortality, we analyzed 90-day. Although most of the complications come into being were complaints that would not be classified as serious complications, we found the serious complication rate (Clavien-Dindo: 3-5) 43.6% (n: 24), severe complication Clavien Dindo 4-5 23.6%. The mortality rate within 90 days postoperatively is 16.3% (n = 9).

We did not find a significant relationship between mortality and complication rates with BMI, Charlson comorbidity index, preoperative hematocrit values and operation time in univariate analysis. As for the multivariate analysis, we observed that the hematocrit value is strongly related to predicting mortality and BMI is also significant in the presence of severe complications. However, it would not be wrong to say that we found the most significant results in our study when we analyzed the albumin values. Albumin is an important marker to predict mortality and severe complication in both univariate and multivariate analyses. In addition, Our results showed us that wound/skin and neurological complications were significantly higher if albumin values are low.

Undernutrition is a well-known risk factor for complications (21-23). Serum albumin has been shown that is a determinant of nutritional status and is a prominent marker of prognosis and progression in many types of cancer in previous studies (24, 25). In the study by Gregg et al., they have categorized patients with preoperative albumin value of 3.5 and below, those with BMI < 18.5 and patients with pre-operative weight loss of more than 5% were as patients with malnutrition (23). In another study that had been done with similar logic, the preoperative albumin value was found to be significant in predicting complica-
tions and mortality after radical cystectomy. It was predicted that better postoperative outcomes could be achieved with preoperative nutritional support (26). The study by Djalanadat et al. investigated the relationship between ASA score and albumin with survival; they established that a high ASA score was associated with increased complication rates and low serum albumin with recurrence-free overall survival. As a result of albumin being so vital, the idea of albumin supplementation to patients had come into question, but studies have shown that it does not cause better results and may cause undesirable effects (26, 27). Similarly, when the patients who were given TPN (total parenteral nutrition) and not given were investigated, no difference was obtained in the complication rates and infectious complications (such as intraabdominal abscess and peritonitis) increased in patients who received TPN (28). We can indicate the study’s limitations as follows; it is a single-center study, the number of patients is insufficient, a single surgeon did not perform operations, complications, mortality and was not calculated according to the pathological stages of the patients, our follow-up period is short. We thought that it would cause us to have difficulty in distinguishing cancer-specific survival from postoperative mortality in a more extended follow-up period. Therefore, we considered that the 3-month period is optimal duration. The fact that our results are similar to the literature may bring a criticism that the study does not contribute to literature at first. Although accepting this as a self-criticism, our research was designed prospectively, point that it is different from existing studies. Another subject of criticism is that the patients’ postoperative albumin values were not compared with the preoperative values. Frankly, we believe that this may be the subject of a different study. It is valuable that albumin gives such significant statistical results with a small patient population. However, it would not explain the high mortality and complications with only preoperative data besides, the lack of patient outcomes who underwent laparoscopic and robotic surgery acceptable an issue of criticism. Our results are generally concordant with the literature. We believe that the fact that these supportive data were obtained prospectively will make our study privileged.

**CONCLUSIONS**

Finding a marker that predict the mortality and complications that may occur after radical cystectomy may be help to prepare the patient before surgery and manage the patient after surgery. As a result, albumin was found to be meaningful in predicting both mortality and the presence of serious complications. We believe that our results will give an opinion for future randomized controlled multicenter studies. Thus, it may be possible to minimize complications and mortality.

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