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# MUSCLE INVASIVE BLADDER CANCER: WHO SHOULD NOT UNDERGO RADICAL CYSTECTOMY? A RISK PREDICTIVE MODEL

by
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# ABSTRACT
# OF THE THESIS OF

Mohamad Ali Hassan Tfaily for Master of Science
Major: Scholars in HeAlth Research Program (SHARP)

Title: Muscle Invasive Bladder Cancer: Who Should Not Undergo Radical Cystectomy? A Risk Predictive Model

Background: The gold standard treatment of muscle invasive bladder cancer (MIBC) is radical cystectomy (RC) for eligible patients. Recently, trimodal therapy has been recommended as an alternative bladder preserving approach. We aim to identify patients to whom trimodal therapy is the optimal approach by constructing risk calculators of morbidity and mortality.

Methods: Using ACS-NSQIP database, we selected the patients having MIBC undergoing RC, making 10642 patients. Our primary outcome was mortality and secondary outcome was morbidity within 30 days of the procedure. Morbidity was assessed using prolonged length of stay (>10 days). We underwent multivariate logistic regression to obtain the best fit model for each outcome on 60% of the sample. Validation of the models was done on 40% of the sample. Model performance was assessed using discrimination and calibration abilities. Risk calculator was constructed using Excel.

Results: Of the full cohort, 199 patients (1.9%) experienced death and 2328 patients (21.9%) experienced morbidity. For the mortality model, the area under the curve was 70% with Hosmer-Lemeshow statistic of 0.64. Variables significant in the model included age, frailty, ASA status and preoperative creatinine. For the morbidity model, the area under the curve was 65% with a Hosmer-Lemeshow statistic of 0.8. Variables significant in the model included age, frailty, albumin, preoperative creatinine, robotic surgery and continent diversion.

Conclusion: We provide statistically significant and clinically relevant models to be used in the clinical setting to provide patients with individualized risks of morbidity and mortality from RC.

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# CHAPTER I

# INTRODUCTION

This thesis project aims at identifying patients who are subject to high complications and to mortality following radical cystectomy. In this introduction, we will begin by presenting bladder cancer's epidemiology, staging and risk factors. We will then cover the standard of management of muscle invasive bladder cancer, which is radical cystectomy. Finally, we will explore alternative treatment options such as trimodal therapy that might be suitable for patients who are at high risk for morbidity and mortality following radical cystectomy.

## A. Epidemiology

Bladder cancer is a substantial health burden causing significant mortality and morbidity rates globally. It is the 10$^{th}$ most common cause of cancer worldwide, with 573,278 incident cases in 2020.(Globocan, 2020a) In 2020 alone, bladder cancer was responsible for the loss of 212,536 individuals globally.(Globocan, 2020a) Disparities in the incidence rates of bladder cancer exist between the sexes, with males having higher incidence rates than females, as global incidence of bladder cancer is 9.6 per 100,000 in men versus a 2.4 per 100,000 in women.(Bray et al., 2018) According to the 2021 cancer statistics in the US, bladder cancer was found to be the fourth most common cause of cancer among males in the US, accounting for 7% of the cases. Incidence was 64,280 in males, compared to 19,450 in females.(Siegel, Miller, Fuchs, & Jemal) It was also noted to account for 4% of cancer deaths among males in the US.(Siegel et al.)

The global age standardized incidence rates (ASR) was 9.5 per 100,000 in 2020. The burden of this disease is heaviest on Mediterranean countries, Europe, and Northern America. These regions had the highest ASRs, ranging from 15.4 per 100,000 in Western Asia to 26.5 in Southern Europe.(Globocan, 2020a) Globally, incidence of bladder cancer is expected to increase by 72.8% by 2040, with an estimated 990,763 new cases by 2040.(Globocan, 2020b) Nevertheless, bladder cancer mortality has been steady globally despite the surge in incidence.(Saginala et al., 2020)

### *1. Lebanon*

Lebanon has one of the highest ASRs of bladder cancer globally. In 2012, the ASR in males was 29.1, ranking Lebanon second after Belgium.(Lakkis, Adib, Hamadeh, El-Jarrah, & Osman, 2018) According to the 2018 estimates, Lebanon had the highest ASR of bladder cancers among females worldwide.(Bray et al., 2018) Nevertheless, Globacan data in 2020 show a marked decrease in incidence of bladder cancer in Lebanon, with ASRs of 12.8 and 4.3 in males and females, respectively. We hypothesize that this data is inaccurate given the steep and unjustified low trend. Shamseddine et al. projected an incidence rate of 41.2 among Lebanese males and 13.4 among Lebanese females by the year 2018.(Shamseddine et al., 2014) No data is available on incidence of bladder cancer from other sources, as the Lebanese national cancer registry has data available until 2016.(MoPH, 2016) The change in ASR of bladder cancer in males and females is plotted and shown in Figure 1, with the 2018 projections included in figure 1.

In the most recent Globocan 2020 statistics, the incidence ASR of bladder cancer in Lebanon was 8.4 for both sexes. This was accompanied with 299 deaths and a

mortality ASR of 3.9, the highest in Asia after Syria.(Globocan, 2020a) This information is estimated as there is no official record for cancer mortality in Lebanon. The mortality rate is expected to increase by 107% in 2040, reaching 619 deaths attributed to bladder cancer in 2040.(Globocan, 2020b) This may be explained by the high prevalence of smoking among both genders in Lebanon.(Saade, Warren, Jones, Asma, & Mokdad, 2008; Shamseddine et al., 2014; Tessier, Nejjari, & Bennani-Othmani, 1999)

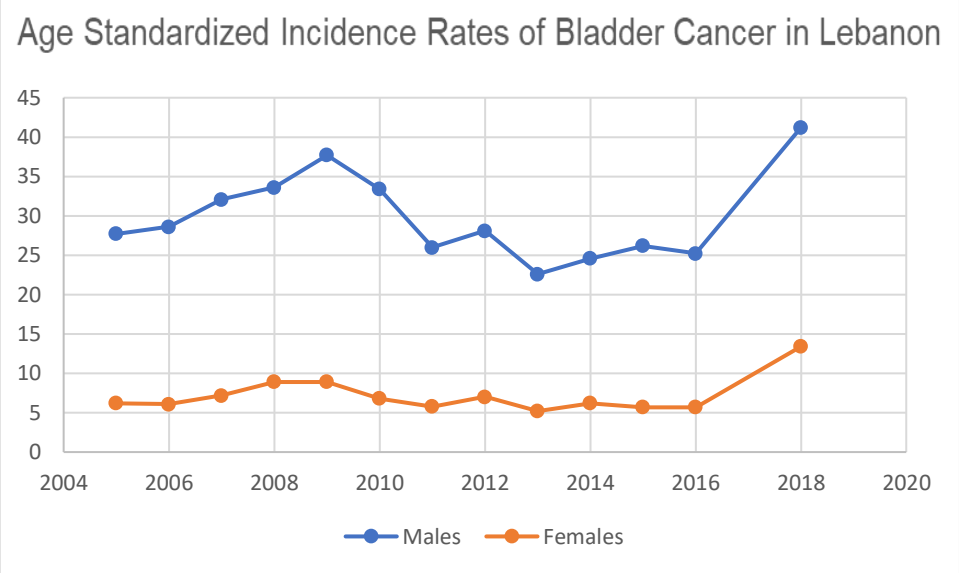


Figure 1 Age standardized incidence rates of bladder cancer in Lebanon.

## B. Risk Factors

### *1. Genetic Susceptibility*

Genetics play an important role in bladder cancer (UBC). This was demonstrated by the observation that first-degree relatives of patients with UBC had a two-fold increase in the risk of developing the disease.(Burger et al., 2013) Genetic risk factors include polymorphisms in acetylator N-acetyltransferase 2 (NAT2) and

glutathione S-transferase mu 1(GSTM1) genotypes.(Burger et al., 2013) NAT2 genotype is notorious for numerous polymorphisms in the coding region, with carriers being either slow, intermediate or rapid acetylators based on the polymorphism.(Kadlubar, 1994) A known mutation would lead to slow acetylation by NAT2, as proteins are either unstable or poorly expressed.(Lin, Han, Lin, & Hardy, 1994) In a meta-analysis of 54 case-control studies examining the relation of NAT2 to bladder cancer, patients with slow acetylator NAT2 were 1.46 times more likely to develop bladder cancer than there intermediate and rapid counterparts.(Song et al., 2016) Interestingly, the effect of the NAT2 genotype was associated with ethnicity.(Song et al., 2016) Caucasian and Asian ethnicities showed significant increase in odds of developing bladder cancer when having the slow NAT2 genotype as compared to the rapid NAT2 genotype.(Song et al., 2016) On the other hand, such association was not significant in the African population.(Song et al., 2016) Further subgroup analyses of NAT2 genotypes showed a potential interaction with the carrier's susceptibility to individual carcinogens.(Burger et al., 2013) For example, subgroup analysis by smoking status showed that the effect of slow NAT2 genotype was significant only in smokers and insignificant in nonsmokers.(Song et al., 2016) The bioactivation and detoxification of aromatic amines in tobacco products and other carcinogens involves NAT2.(Badawi, Hirvonen, Bell, Lang, & Kadlubar, 1995) As for subgroup analysis by tumor stage, the effect of NAT2 was significant only in the patients with muscle-invasive bladder cancer.(Song et al., 2016) This indicates that the slow NAT2 genotype can hasten disease progression and promote muscle invasion. Regarding the GSTM1 genotypes, which is another enzyme involved in the biotransformation of bladder carcinogens, a population based study found that females

with inactive GSTM1 were more likely to develop bladder cancer than their counterparts with the active enzyme.(Karagas et al., 2005)

### *2. Tobacco smoking*

Smoking is recognized as the most essential risk factor for bladder cancer. Smoking accounts for 50-60% of incident cases of BC annually.(Saginala et al., 2020) A study on the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study cohort showed that current smokers had 4-fold increase in the risk of bladder cancer as compared to their never-smoking counterparts.(Freedman, Silverman, Hollenbeck, Schatzkin, & Abnet, 2011) Former smokers, on the other hand, were 2.22 times more likely to develop bladder cancer as compared to never-smokers.(Freedman et al., 2011) In addition, the population attributable risk of bladder cancer was similar between males and females, being 0.5 for men and 0.52 for women.(Freedman et al., 2011) Interestingly, another study on a large population based cohort in New Hampshire showed an increase in the hazard ratio (HR) of smoking with time.(Baris et al., 2009) The HR in 1994-1998 was lower than that of 1998-2001 and 2002-2004. This was attributed to changes in cigarette smoke, with higher nitrate content of smoke. An increase in the concentrations of beta-napthylamine and tobacco-specific nitrosamines, the major carcinogens in cigarette smoke leading to bladder cancer accompanied this change.(D. Hoffmann, Hoffmann, & El-Bayoumy, 2001; D Hoffmann & Rathkamp, 1968; D. H. I. Hoffmann, 1997) Smoking is also associated with higher morbidity and mortality from bladder cancer, as these patients are often smokers with multiple comorbidities associated with smoking.(Haeuser et al.)

a. Mechanism of smoking and bladder cancer:

Although the carcinogenicity of tobacco-related products in bladder cancer is well established, the underlying mechanism has not been defined.(Besaratinia & Tommasi, 2013) A genotoxic mechanism of action was identified. Nitrosamino ketones (NNK) and nitrosonornicotine (NNN) are two nitrosamines in cigarette smoke related to oncogenesis. Alpha hydroxylation is believed to be the metabolic activation pathway of NNK, ultimately causing DNA methylation.(S. S. Hecht & Hoffmann, 1988) NNK and NNN also share a common pathway that converges at an alkylating compound that forms DNA or globin adducts.(Carmella & Hecht, 1987; S. S. Hecht & Hoffmann, 1988; S. S. Hecht, Spratt, & Trushin, 1988) During DNA replication, these adducts can lead to mutations that, when in key cancer-related genes, give rise to tumorigenesis.(Stephen S Hecht, 2003; Luch, 2005; Poirier, 2004)

Similarly, another aromatic amine, 4-aminobiphenyl appears to promote bladder cancer by a genotoxic mode of action, causing DNA adducts and mutations.(Talaska, Al-Juburi, & Kadlubar, 1991) After biotransformation and several subsequent steps that include catalyzation by cytochrome P450 1A2(McMahon, Turner, & Whitaker, 1980), an intermediate will circulate and be excreted into the urinary tract, where it will undergo hydrolysis amidst the urine's acidic medium.(Poupko, Hearn, & Radomski, 1979) The resulting electrophilic compound can bind to uroepithelial cells forming adducts involved in bladder cancer genesis.(Frederickson, Hatcher, Reznikoff, & Swaminathan, 1992; Talaska et al., 1991)

b. Smoking and type of inhalation:

There is conflicting evidence on the impact of inhalation on bladder cancer risk. Some studies reported no significant association between inhalation and risk of bladder cancer (Baris et al., 2009; Castelao et al., 2001; Howe et al., 1980; Lockwood, 1961), while others found higher risk upon inhalation past the mouth.(Burch et al., 1989; López-Abente et al., 1991) A study by Samanic et al. showed that patients who inhaled into the chest or throat had a significant increase in the risk of bladder cancer as compared to those who inhaled into the mouth only, with an increase of 50% and 70%, respectively.(Samanic et al., 2006) However, these are retrospective studies where the assessment of inhalation is subject to recall bias by the participants.

### *3. Environmental risk factors:*

A systematic review examining occupational bladder cancer identified numerous occupations associated with higher risk of bladder cancer. These occupations involved exposure to aromatic amines and include hairdressers, painters and plastic, dye and rubber workers(Cumberbatch, Cox, Teare, & Catto, 2015).

a. Arsenic:

The link between Arsenic and bladder cancer was mostly examined in Taiwan, China and Chile, where removing arsenic from drinking water was associated with a decreased incidence of bladder cancer.(Smith et al., 2017; S.-M. Tsai, 1998) While most of these studies are ecological in nature, observational studies adjusting for confounders also revealed a significant association. In a cohort study in Taiwan involving 788 subjects, after adjusting for age, sex, smoking and other covariates, the relative risks of

developing bladder cancer were 1.9, 8.2 and 15.3 corresponding to arsenic concentrations of 10-50, 50-100 and over 100 μg/L with levels <10 μg/L being the reference.(Chiou et al., 2001) Another meta-analysis examining 17 studies showed increasing risk of bladder cancer with increasing arsenic water concentration. The predicted increase in incidence risk was 2.7, 4.2 and 5.8 with arsenic water concentration of 10 μg/L, 15 μg/L and 150 μg/L respectively.(Saint-Jacques, Parker, Brown, & Dummer, 2014) This meta-analysis contained several studies that were ecological in design, hence that did not account for confounding. The association was also found in the case control and cohort studies included in the meta-analysis. (Saint-Jacques et al., 2014) Increased urinary arsenic concentration was also associated with increased production of DNA adducts, which are in turn associated with higher incidence of bladder cancer.(T.-L. Tsai et al., 2021) It was thus hypothesized that arsenic can lead to bladder cancer by oxidative DNA levels or by DNA methylation.(T.-L. Tsai et al., 2021)

b. Chlorination:

A meta-analysis of 6 case control studies and two cohort studies showed that long term exposure to chlorinated drinking water was associated with a 40% increase of the risk of bladder cancer in both males and females.(Villanueva, Fernández, Malats, Grimalt, & Kogevinas, 2003) When stratified by sex, the risk estimate for men was 1.4 and significant; however, no significant association was found for women.(Villanueva et al., 2003) Moreover, men who were exposed to trihalomethane level >50 μg/L were found to have a 47% increase in the chance of developing bladder cancer as compared to males exposed to levels <= 5 μg/L.(Costet et al., 2011)

c. Occupational exposure:

Various occupations are linked to bladder cancer, and these include painters, hairdressers, metal workers, and many others. The exposure behind each occupation is shown in Figure 2.

***4. Other risk factors:***

These include chronic cystitis as chronic inflammation can lead to dysplasia and later carcinogenesis. The inflammation can also lead to augmented production of nitrosamines, which are associated with bladder cancer in animal models.(Magee & Barnes, 1967; Matanoski & Elliott, 1981)

a. HPV infection:

A meta-analysis of 17 case control studies showed a significant increase in bladder cancer incidence in the presence of any HPV infection, with an odds ratio (OR) of 2.84.(Li et al., 2011) Interestingly, one study included the meta-analysis showed a protective effect of HPV infection with an OR of 0.25.(Li et al., 2011) Upon exclusion of this study from the analysis, the OR of bladder cancer increases to 4.11 in presence of an HPV infection.(Li et al., 2011) Moreover, patients with HPV-16 were 5.74 times more likely to develop bladder cancer, while those with high risk HPV types (-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59 and -68) were 3.48 times more likely to develop bladder cancer.(Li et al., 2011)

b. Cyclophosphamide:

Cyclophosphamide is a well-established bladder carcinogen.(Pedersen-Bjergaard et al., 1988) A study that included more than 6000 patients with hematologic malignancy treated with cyclophosphamide showed an increased risk of bladder cancer following cyclophosphamide with an OR of 4.5.(Travis et al., 1995)

### *5. Gender*

While the incidence of bladder cancer is higher among men than women,(Siegel et al.) prognosis in men with bladder cancer is better than that in women.(Ahmedin Jemal et al., 2008; Shariat et al., 2010) Nevertheless, the underlying mechanisms behind this discordance are not completely understood.(Shariat et al., 2010) Several hypotheses are posed in the literature to explain the gender disparities, ranging from gender inequalities expressed in other risk factors for bladder cancer, to genetic differences among genders.(Dobruch et al., 2016) In the below section, we will examine the interaction between gender and other risk factors of bladder cancer.

a. Gender and Smoking

The aforementioned study on NIH-AARP showed comparable PAR between men and women. It was argued that the difference in bladder cancer incidence between genders can be attributed to the higher smoking rates in men. This is similar to the case of lung cancer, where the equalizing rates of smoking between genders in the past decades led the incidence of lung cancer in both genders to converge, especially in the United States.(Control & Prevention, 2002; M. B. Cook et al., 2009; Devesa, Bray, Vizcaino, & Parkin, 2005; A. Jemal, Travis, Tarone, Travis, & Devesa, 2003)

Nevertheless, whether this is the case with bladder cancer is still debatable. In Spain, after eliminating the effect of smoking on the risk of bladder cancer, the incidence ratio in males to females dropped from 8.2 to 1.7.(Samanic et al., 2006) In a study on white population in the US, the incidence ratio of males to females was 2.7 when eliminating other risk factors.(Hartge et al., 1990) another study in Orange Country, California revealed a higher odds ratio for men compared to women even after adjusting for age, smoking and occupational exposures.(Anton-Culver, Lee-Feldstein, & Taylor, 1993) A meta-analysis by Hemelt et al. that includes 34 studies across 21 world regions implied that smoking can only partly explain the difference in bladder cancer incidence between both genders.(Hemelt, Yamamoto, Cheng, & Zeegers, 2009) It was thus posed that differences in metabolic pathways might explain the gender differences in bladder cancer incidence.

b. Gender differences in biological mechanisms

Genetic differences between genders can be a risk factor for development of bladder cancer. Gender disparities in the metabolism of bladder cancer carcinogens will be examined in each step of the pathways. Aromatic amines, found in tobacco smoke and other occupational exposures, undergo a four-step metabolism process: Hydroxylation, acetylation, glucuronidation and sulfation.

i. Hydroxylation

Hydroxylation occurs in mainly in Cytochrome P450 (CYP) 1A2 in the liver. However, it is believed that there are additional enzymes and pathways by which hydroxylation of aromatic amines occurs to form the ABP-DNA adduct. CYP4B1, for example, was shown to similarly activate aromatic amines.(Imaoka et al., 2001)

While gender differences were not explained by CYP1A2,(Tsuneoka et al., 2003) CYP4B1 was found to be expressed at higher levels in the bladders of male rats than female rats, as its expression was amplified by androgens.(Imaoka et al., 2001) This suggests that androgens might also affect similar enzymes in the liver; however, this requires further evidence on animal models.

ii. Acetylation

NAT1 and NAT2 are responsible for the acetylation of aromatic amines, the second step in their metabolic pathway after hydroxylation. Current animal models examining the effect of gender on this step of aromatic amine pathways do not demonstrate a gender difference in the acetylation levels between male and female rats.(Sugamori, Brenneman, & Grant, 2006)

iii. Glucuronidation

The third step in the biotransformation of aromatic amines involves glucuronidation. This is done with uridine 5' diphosphoglucuronosyltransferases (UGTs), which are phase II drug metabolism enzymes used in the glucuronidation of several endo- and xeno-biotics like aromatic amines.(Izumi, Zheng, Hsu, Chang, & Miyamoto, 2013) Glucuronic acid is added to give rise to O- and N-glucuronides that will be excreted in bile and urine.(Poupko et al., 1979) In the acidic urine, these compounds will become highly labile, promoting carcinogenesis in the bladder epithelium.(Babu, Lakshmi, Huang, Zenser, & Davis, 1996; Ciotti et al., 1999) UGT was shown in mouse models to protect the urinary bladder against chemical carcinogens.(Iida et al., 2010; Paonessa, Munday, Mhawech-Fauceglia, Munday, & Zhang, 2009) Alterations in UGT expression were demonstrated across genders due to the effect of sex hormones.(Janisch, Shariat, Schernhammer, Rink, & Fajkovic, 2019) Animal

models also proved androgen-mediated signals to downregulate the expression of UGTs, thereby promoting bladder carcinogenesis.(Izumi et al., 2013) Another pilot study on 19 males and 5 females with bladder cancer showed that androgen receptor activation is associated with bladder cancer progression by intracellular pathways.(Zheng, Izumi, Yao, & Miyamoto, 2011) These results warrant further studies on the role of androgen receptors and UGT in bladder cancer. Interestingly, an inverse relation was found between the expression of these enzymes and liver and bladder cancer.

iv. Sulfation

Sulfotransferases (SULTs) catalyze the sulfation of aromatic amines and their derivatives, and numerous SULTS were proven to be active on N-OH-ABP.(Yasuda et al., 2007) Studies on mice and rat models of SULT expression and liver and bladder susceptibility to carcinogenesis showed conflicting results, pointing towards a tentative species and gender related expression of SULT.(Y. Zhang, 2013) In addition, it can be concluded that SULT expression generates highly electrophilic metabolites that are consumed in the liver prior to reaching the bladder.(Y. Zhang, 2013) They thus protect the bladder from aromatic amines at the expense of liver damage.(Y. Zhang, 2013)

Abufaraj et al. while surveying the Nurse's Health Study (NHS) and NHS II also demonstrated a role of hormones. Women who reached menopause before the age of 46 were 1.41 times more likely to develop bladder cancer than women who developed cancer after the age of 50.(Abufaraj et al., 2020) Additionally, animal models have shown hormonal effects on bladder carcinogenesis as early as the 1970s, where male mice treated with bladder carcinogens developed bladder cancer

earlier than female mice, with a significantly higher incidence rate.(Bertram & Craig, 1972; Okajima, Hiramatsu, Iriya, Ijuin, & Matsushima, 1975)

### C. Staging and Physiology

Two families of tumors arise from the bladder: urothelial and nonurothelial carcinomas. Urothelial carcinomas, accounting for 75% of bladder tumors, stem from the epithelial (urothelial) layer of the inner surface of the bladder.(Sanli et al., 2017) The type of epithelium in the bladder, ureters and kidneys is unique: multilayered epithelium with longitudinal nuclear grooves that mature to form umbrella cells.(Koss, 1969) Despite its distinctiveness, some experts in the field preferred the term transitional over urothelial as they believed the term urothelial may refer to any tumor in the bladder wall including adenocarcinomas and squamous cell carcinomas. Although the majority of experts favor the term urothelial, transitional carcinoma can be used synonymously.(Epstein, Amin, Reuter, & Mostofi, 1998) In the meantime, monurothelial bladder carcinomas account for the remaining 25% of bladder tumors and include histology types as adenocarcinoma, squamous cell carcinoma and small cell carcinoma.(Willis & Kamat, 2015) We will focus on urothelial tumors, as the rest are out of the scope of this thesis project. Urothelial tumors are divided into two categories: nonmuscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Fortunately, 75% of bladder cancer cases are NMIBC while the remaining 25% are MIBC.(Burger et al., 2013) However, up to 70% of NMIBC recur, and around 20% of NMIBC will progress into MIBC.(Rübben et al., 1988) MIBC invade the epithelial layer reaching the underlying detrusor muscle.(Sanli et al., 2017) Given that they are more likely to metastasize, through blood, lymph or tissues, MIBCs are divided

into two groups, nonmetastatic (limited to the bladder muscle) and metastatic.(Sanli et al., 2017)

Several systems exist for the grading and classification of bladder neoplasms. The first differentiation of World Health Organization (WHO) dates back to 1972.(Mostofi, Sobin, Torloni, & World Health, 1973) The proposition was upgraded in 1998 in collaboration with the International Society of Urologic Pathologists (ISUP), as they published a consensus classification of urothelial (transitional cell) tumors of the bladder.(Epstein et al., 1998) This schema was validated and later adopted in 2004, and is the currently used schema as per the latest WHO report.(Humphrey, Moch, Cubilla, Ulbright, & Reuter, 2016) The grading of papillary lesions includes: urothelial papilloma (completely benign lesion), papillary urothelial neoplasm of low malignant potential (PUNLMP), low grade (LG) papillary urothelial carcinoma and high grade (HG) papillary urothelial carcinoma.(Humphrey et al., 2016) Moreover, the grading of flat lesions is as follows: urothelial proliferation of uncertain malignant potential (arcinia hyperplasia), reactive atypia (flat lesion with atypia, atypia of unknown significance, urothelial dysplasia and urothelial CIS (always HG).(Humphrey et al., 2016)

Data from the Surveillance, Epidemiology, and End Results (SEER) registry in the United States shows constant staging for urothelial carcinoma (Sanli et al., 2017). The American Joint Committee on Cancer (AJCC) developed a staging system for urothelial carcinomas with the most recent update being in 2017, demonstrated in the Table below.(Magers et al., 2019)  Ta tumors are papillary tumors that tend to recur and Tis (carcinoma in situ) are high-grade intraepithelial neoplasms without invasion into subepithelial connective tissue. Papillary tumors limited to the mucosa or invading the

lamina propria are termed Stage 1, Ta and T1, respectively. Tumors that have invaded the muscle layer superficially (T2a) or deeply (T2b) are Stage 2. Interestingly, the TNM system separates tumors that have invaded perivesical fat from those that have invaded adjacent organs. The former, that have invaded the detrusor beyond the muscularis mucosa and reached the perivisceral fat on the outer layer of the bladder are termed Stage 3, while the latter are termed Stage 4. T4a tumors enter the surrounding organs as the prostate, uterus, or bowel while T4b tumors invade the abdominal or pelvic walls.(Brierley, Gospodarowicz, & Wittekind, 2017; Sanli et al., 2017) The N and M staging are further provided in the table below, copied verbatim from the report of the American Joint Committee on Cancer (AJCC) Staging System, 8th edition, 2017.(Magers et al., 2019)

| **Primary Tumor** | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Ta | Non-invasive papillary carcinoma |
| Tis | Carcinoma in situ: flat tumor |
| T1 | Tumor invades subepithelial connective tissue |
| T2 | Tumor invades muscularis propria |
| pT2a | Tumor invades superficial muscularis propria (inner half) |
| pT2b | Tumor invades deep muscularis propria (outer half) |
| T3 | Tumor invades perivesical tissue |
| pT3a | Microscopically |
| pT3b | Macroscopically |
| T4 | Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall. Abdominal wall |
| T4a | Tumor invades prostatic stroma, uterus, vagina |
| T4b | Tumor invades pelvic wall, abdominal wall |
| **Regional Lymph Nodes** | |
| NX | Lymph nodes cannot be assessed |
| N0 | No lymph node metastasis |
| N1 | Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node) |

| | |
|---|---|
| N2 | Multiple regional lymph node metastasis in the true pelvis |
| N3 | Lymph node metasasis to the common iliac lymph nodes |
| **Distant Metastasis** | |
| M0 | No distant metastasis |
| M1 | Distant metasasis |

Table 1 Table showing the Tumor, Node, Metastasis staging of bladder cancer

The current diagnosis and management of bladder cancer is dependent on the stage and spread of the disease.(NCCN, 2019) The European Association of Urology has developed different guidelines for NMIBC and MIBC.

We will briefly cover NMIBC as it is out of the scope of this thesis.

**D. NMIBC Diagnosis and Management:**

The presentation of patients with NMIBC is most commonly hematuria. In patients presenting with lower urinary tract symptoms related to storage, CIS may be suspected. As the physical examination is futile, computed tomography (CT) urography can show filling defects or hydronephrosis, which may be suggestive of papillary tumors. Carcinoma in situ is eventually diagnosed by cystoscopy, urine cytology and histologic evaluation of bladder biopsies.(Hall et al., 2007) For NMIBC, the standard treatment is transurethral resection of the bladder tumor (TURBT). Although TURBT may be enough to cure the disease, recurrence or progression to MIBC is common. Further therapy after TURBT is recommended. TURBT followed by Bacille Calmette-Guerin (BCG) instillation was confirmed to be superior to TURBT alone or TURBT with chemotherapy and is hence part of the treatment guideline.(Babjuk et al., 2017)

## E. MIBCs Diagnosis and Management

MIBC can be either confined to the bladder or metastatic and spread to the adjacent structures. Diagnosis is ultimately made by cystoscopy and histologic evaluation of resected tissue. Local invasion may be assessed by CT and magnetic resonance imaging (MRI). After confirming the diagnosis of MIBC, CT urography for the upper urinary tract in addition to CT of the chest, abdomen and pelvis are strongly recommended for staging of the disease. In the meantime, there is insufficient evidence for the use of fluorodeoxyglucose positron emission tomography/computed tomography, hence the absence of recommendation regarding its use.(Witjes et al., 2021)

For MIBCs that are organ-confined, the treatment of choice is radical cystectomy with neoadjuvant chemotherapy (usually platinum-based) in eligible patients.

However, if the MIBC has crossed through the bladder wall and spread to surrounding organs, the treatment of choice is systemic therapy, varying between immunotherapy and platinum based chemotherapy, depending the patient's eligibility and treatment history.

## F. Radical Cystectomy

Radical cystectomy has proven its superiority over radiotherapy alone in the 1960s.(Powel-Smith & Reid, 1970; Wallace & Bloom, 1976) Today globally, radical cystectomy (RC) is the treatment of choice for patients with MIBC stage T2-T4a, N0-Nx and M0. Intuitively, the technique of RC differs between men and women, as shown in figure 3.

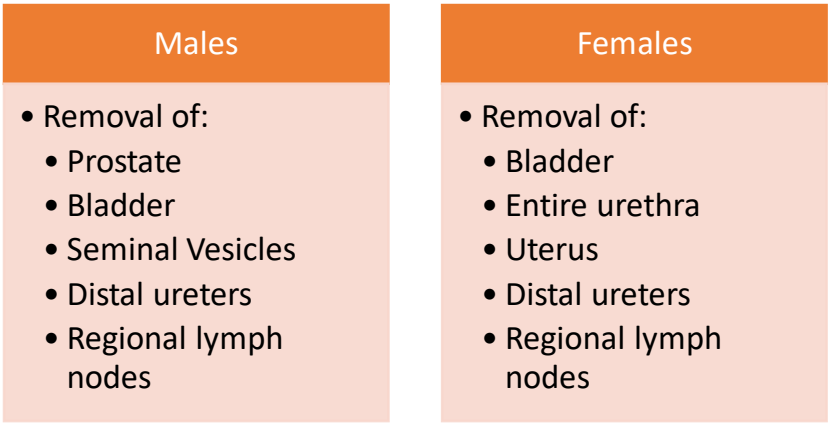


Figure 2: Radical cystectomy in males and females.

### *1. Radical Cystectomy Survival*

Survival outcomes of radical cystectomy, in the absence of neoadjuvant chemotherapy, are dependent on the extent of lymph node involvement. On average, perioperative mortality ranges between 2-3%.(Stein et al., 2001) The 5-year overall recurrence free survival in a cohort of 1054 patients was 68%.(Stein et al., 2001) When stratified by stage, patients with T2, T3a and T3b bladder cancer had 77%, 64% and 49% 5-year overall survival following radical cystectomy, respectively.(Stein et al., 2001) Despite the available treatment options for MIBC, 5-year survival remains dismal. Patients with confined MIBC have a survival rate of 62%.(Park, Citrin, Agarwal, & Apolo, 2014)

The median age of patients undergoing radical cystectomy ranged from 63-67 years old,(Clark et al., 2005) with 5% being above 80 years.(Stroumbakis, Herr, Cookson, & Fair, 1997) In addition, up to 50% have a high perioperative risk with a score of 3 or greater on the American Society of Anesthesiologists (ASA) classification.(Chang, Cookson, Baumgartner, Wells, & Smith, 2002)

*a.* Neoadjuvant chemotherapy

Neoadjuvant chemotherapy improves overall survival of patients with MIBC undergoing radical cystectomy. (Meeks et al., 2012; Vale, 2005) The typical choice of chemotherapy regimens includes the classic MVAC: Methotrexate, vinblastine, doxorubicin and cisplatin every 28 days for three cycles prior to surgery.(Grossman et al., 2003) Another regimen is GC regimen that consists of gemcitabine and cisplatin every 21 days for a maximum of four cycles.(Galsky et al., 2015) No trials conclude the effectiveness of the GC regimen; however, it was shown to be comparable to the classic MVAC in a retrospective study.(Galsky et al., 2015)

### *2. Radical Cystectomy Comorbidities*

Radical cystectomy is still associated with cumbersome complications and high post-operative mortality rate. The risk of comorbidities with radical cystectomy remains high, as up to 48% of the patients have a comorbidity within a week.(Quek et al., 2006) Factors that increased the risk of post-operative morbidity and mortality, including age, comorbid conditions and American Society of Anesthesiologist (ASA) score have been examined.(Mayr, Fritsche, Pycha, & Pycha, 2014; Mayr et al., 2012) Other factors associated with morbidity include preoperative functional status and mental health.(Jensen, Laustsen, Jensen, Borre, & Petersen, 2016; Sharma et al., 2016) A universal surgical risk calculator by NSQIP is available; however, it was shown not to be accurate enough for adaptation into clinical practice.(Miles P. Mannas et al., 2020) The area under the curve C-statistics was 80% for cardiac complications and 75% for pneumonia. However, it was poor for other complications.(Miles P. Mannas et al.,

2020) Moreover, the comorbidities and suboptimal survival rate following radical cystectomy led to the exploration of bladder preserving strategies, the most common of which is trimodal therapy.(Park et al., 2014) In this section, we will explore the post-operative complications of radical cystectomy, to later explore the bladder preserving strategies.

*a.* Sexual Dysfunction:

The conservative RC in male patients is associated with high rates of postoperative erectile dysfunction, lowering the patients' quality of life, as up to 86% of patients suffer from erectile dysfunction after RC.(Zippe et al., 2004) This led to the exploration of several sexual function-preserving cystectomy techniques, such as prostate-, capsule-, seminal- or nerve-sparing cystectomy. These have been assessed in a meta-analysis that included 12 studies from 2000 to 2015. The authors delineated better sexual outcomes for these procedures while sparing oncological outcomes. Nevertheless, the risk of bias in these studies was moderate to high, making the evidence insufficient for a strong guideline recommendation.(Witjes et al., 2021)

In females, sexual dysfunction and pelvic floor disorders can be prevented by sparing reproductive organs. Concomitant malignancy in the reproductive organs is rare;(Ali-El-Dein et al., 2013) however, there is weak evidence to promote this practice on most women.(Veskimae et al., 2017) The studies reporting the efficacy of this technique have large heterogeneity with high risk of bias.(Veskimae et al., 2017) Instead, there is a strong recommendation to preserve sexual function for select women with organ confined disease and absence of tumor in bladder neck or urethra.(Witjes et al., 2021)

*b.* Infection

This is the most common complication following Radical cystectomy. In a cohort of more than 7600 patients undergoing RC in Sweden, urinary tract infection (UTI)/septicemia occurred with an incidence of 90.4 per thousand person years.(van Hemelrijck, Thorstenson, Smith, Adolfsson, & Akre, 2013) The type of urinary diversion was associated with the risk of UTI, as continent cutaneous reservoir and orthotopic neobladder increased the hazard by an insignificant 11% and a significant 21%, respectively, when compared to ileal conduit.(van Hemelrijck et al., 2013) Age, high BMI and using an open approach were associated with a higher risk of infectious complications.(Kaczmarek, Lemiński, Bańcarz, Zakrzewska, & Słojewski, 2018)

*c.* Kidney failure and bowel obstruction

In the same Swedish cohort, the second most common post-operative morbidity for RC was hospitalization for kidney failure and bowel obstruction, with an incidence of 59 per thousand person year.(van Hemelrijck et al., 2013) In a study on urological surgeries done in Florida and California, the 5-year cumulative incidence of small bowel obstruction following RC was 12.4%.(Blackwell et al., 2017) In another cohort on 4015 patients undergoing RC with previously normal renal function, 7.2% developed end stage kidney disease (ESKD). Interestingly, there was no significant difference in the incidence of renal failure when comparing ileal conduits to continent urinary diversion.(Zabell, Adejoro, Konety, & Weight, 2015) Other factors that increased risk of postoperative ESKD were age and Charlson score. Patients whose age was between 66-69, 70-74, 75-79 and 80 or greater had hazard ratios of 1.5, 1.508 and 1.93,

respectively.(Zabell et al., 2015) Moreover, patients who had a Charlson score of 1 or higher had a 78% increase in the risk of developing ESKD when compared to patients with a score of 0.(Zabell et al., 2015) Interestingly, tumor stage and grade were not significantly associated with this comorbidity.(Zabell et al., 2015)

d. Cardiac complications

New onset arrythmia and myocardial infarctions have been reported to occur after radical cystectomy, with an indicidence of 8% and 4%, respectively. Using ileal conduit urinary diversion and Charlson Index score were associated with higher risk of post-operative cardiac complications.(Fisher et al., 2009) However, the presence of higher risk with ileal conduit might be attributed to its preference in older patients with higher comorbidities.(Fisher et al., 2009)

### *3. Trimodal Therapy*

Trimodal therapy consists of the incorporation of maximal transurethral resection of bladder tumor (TURBT), followed by chemotherapy with concurrent radiotherapy. (Chang et al., 2017) Observational studies have shown that a subset of patients can achieve long term disease control with bladder preservation.(Park et al., 2014) 5-year overall survival of patients with MIBC who underwent trimodal therapy was shown to be 57%, which is comparable to that of radical cystectomy.(N. J. Giacalone et al., 2017) In a series of 98 patients with nonmetastatic MIBC at the American University of Beirut Medical Center, there was no significant difference between patients receiving CRT, NAC with CRT or RC ($p=0.83$).(Halabi et al., 2020) In a systematic review including 83 studies, the 5 year over-all survival was between

36% and 74%.(Ploussard et al., 2014) Unfortunately, there are no randomized controlled trials comparing radical cystectomy to trimodal therapy, as the only ongoing randomized controlled trial comparing trimodal therapy to radical cystectomy was halted due to trial accrual.(Huddart, Hall, Lewis, & Birtle, 2010) Based on the recommendations of the EUA, the decision to go for radical cystectomy vs bladder preservation approaches in elderly or frail patients with MIBC should be based on tumor stage and comorbidity scoring, such as the Charlson score.(Abdollah et al., 2012) However, A movement in the genitourinary oncology community is pushing TMT further and considering it for healthy patients who wish to preserve their bladder.(Winquist & Booth, 2020)

This is based on the principle that not all patients with MIBC require immediate cystectomy. Therefore, the decision to go for cystectomy can be based on the response to trimodal therapy (organ preserving therapy). These bladder preservation approaches have been supported by numerous guidelines such as the EAU and the UK National Institute for Health and Care Excellence (NICE) and the American Urological Association. In the most recent National Comprehensive Cancer Network Guidelines (NCCN), bladder preservation with maximal TURBT followed by CRT has been recommended as a category I primary treatment option for patients with Stage II and IIIA tumors who are cystectomy candidates. Similarly, concurrent chemoradiotherapy has been recommended for patients with stage IIIB (cT1-T4a, N2,3) as category 2A recommendation.(Flaig et al., 2021) No clinically implemented tool to date, up to our knowledge, aims at identifying the patients at risk of organ system complications post cystectomy and those in whom trimodal therapy confers higher survival benefit than the current standard of care (radical cystectomy).

## G. Objectives

Given the recent interest in trimodal therapy as a noninferior treatment to radical cystectomy and given the cumbersome side effects of radical cystectomy that affect the quality of life, we aim at identifying patients who are better fit for bladder preservation approaches.

Our primary outcome is predicting the risk of death within 30 days after radical cystectomy for patients with MIBC.

Our secondary outcome is predicting morbidity for patients within 30 days of radical cystectomy. These predictions will be based on preoperative characteristics and be applied in the clinical setting to optimize the management approaches for these patients.

# CHAPTER II

# METHODS

## A. Study Design and Methods:

### *1. Data source*

The ACS-NSQIP database from years 2008 to 2017 will be used to test the research hypotheses. This externally validated database obtains patient information from more than 400 medical centers and maintains information for up to 30 days after undergoing surgical procedures (Khuri et al., 2007). This study retrospectively analyzes deidentified patient data from the registry. This study is IRB exempt as ACS-NSQIP provides deidentified data, which waives the need for informed consent.

### *2. Patient selection*

Patients who underwent radical cystectomy during the years 2008-2017 were identified using the current procedure terminology (CPT) codes:

- 51570 for total removal of bladder,
- 51575 for Complete cystectomy with bilateral pelvic lymphadenectomy
- 51585 for Cystectomy, complete, with ureterosigmoidostomy or ureterocutaneous transplantations,
- 51580 for Complete cystectomy with ureterosigmoidostomy
- 51590 and 51595 for Cystectomy, complete, with ureteroileal conduit or sigmoid bladder, including intestine anastomosis
- 51596 for Removal of bladder and lymph nodes on both sides of pelvis with transplantation of urinary ducts

- 51597 for Pelvic exenteration, complete, for vesical, prostatic or urethral malignancy, with removal of bladder and ureteral transplantations

Patients with ICD codes corresponding to nonmetastatic bladder cancer were selected. ICD 10 codes include: C66, C67, C68, C79.11, C79.19, D09.0, D30.3, D41.4, and D49.4. ICD 9 codes selected were: 188, 236.7, and 239.4. Furthermore, patients with disseminated cancer, a variable present in ACS-NSQIP, were excluded from the study. Patients with missing ICD codes (NULL) were excluded from the study. A total of 10,642 individuals will be included in the study.

### *3. Study covariates*

**Baseline demographic characteristics** will be included (age, gender, race) as well as anthropomorphic data (BMI). Other characteristics as smoking status, steroid use, more than 10% loss body weight in last 6 months, functional health status and the American Society of Anesthesiologists (ASA) physical status classification will also be studied.

**Baseline comorbidities** will be included as covariates such as diabetes mellitus, congestive heart failure, acute renal failure, use of dialysis, use of steroids for chronic conditions, and presence of disseminated cancer, ascites or sepsis prior to surgery. **Surgical factors and intraoperative characteristics** such as wound classification, total operation time, total length of hospital stay, time from OR to discharge and peri-operative bleeding will not be included as the study aims to examine pre-operative characteristics. The modified frailty index score (mFI5) will be used to assess baseline morbidity. mFI5 has been validated and used on ACS- NSQIP dataset.(Subramaniam,

Aalberg, Soriano, & Divino, 2018) mFI5 is a score that ranges from 0 to 1 calculated as follows:

*mFI5= (number of comorbidities)/5*

The comorbidities included are hypertension requiring medication, history of congestive heart failure within 30 days prior to operation, chronic obstructive pulmonary disease (COPD), Functional status and diabetes mellitus. 1 point is given for the presence of each of the following comorbidities, and the final score is divided by 5 to obtain the mFI5 value (0, 0.2, 0.4, 0.6, 0.8 and 1).

**Laboratory values** in the complete blood count, liver function tests complete metabolic panels such as sodium, creatinine, albumin; as well as hematology tests and liver function tests will be included. CPT codes for radical cystectomy surgery (varying by type) will be entered in the analysis.

Missing values for categorical variables (such as ASA status) will be imputed using the mode. For some of the continuous variables, for example, height's missing values will be imputed based on the median. The effect modification of several covariates suspected of having an interaction with our exposures of interest will be explored (such as age and smoking). Albumin is a continuous variable for whom 30% of the data is missing. Imputation by linear regression using age, BMI, gender, and preoperative laboratory values will be performed to replace missing values of albumin.

Sensitivity analysis will be performed given the high rate of missing values for albumin.

### *4. Study outcomes*

The study outcomes consist of 30-day mortality and post-operative morbidity. Post-operative morbidity will be defined using several models.

- For mortality, pre-operative predictors will be assessed. The mortality prediction model will be validated on the above morbidity scores to assess for similarity.
- For morbidity, length of post-operative stay will be used. A post-operative stay more than 10 days (>75$^{th}$ percentile) will be considered a morbidity, and less than 10 days is no morbidity.
- These study endpoints were defined as death or prolonged hospital stay occurring within 30 days after the surgical procedure. Detailed description of each variable was extracted from the Participant Data Use file (2017).

**B. Statistical analyses**

All statistical analyses will be conducted using IBM Statistical Package for Social Sciences version 26 (IBM Corp, Armonk, NY). A sample of 60% will be randomly selected from our total sample to derive the best fit model. The derived model will be validated on the remaining 40%. Descriptive analysis will be performed on the derivation sample and expressed as mean +/- standard deviation for continuous variables and count N, percent (%) for categorical variables. For bivariate analysis, categorical variables will be analyzed using the chi-square or Fischer exact test, adjusting for Bonferroni when performing pairwise analysis. Comparison of means of continuous variables will be performed using the t test. For possible cofounders, the association between the covariates and the outcome of interest will also be studied.

Clinically relevant factors and variables with P<0.2 from the bivariate analyses will be considered in the multivariable logistic regression model building. Models will be computed using the forward LR model in multivariate logistic regression. Clinically relevant variables will be inserted in the model using the Enter method. Comparison of

the variables included in each will be done to choose the most clinically relevant model. Factors significant at the $p<0.05$ level will be retained in the final model predictions.

### *1. Model Performance*

Two final models will be designed: predicting morbidity as a binary outcome (patients staying in the hospital for more than 10 days after surgery) as well as predicting risk of 30-day mortality. Each model's performance will be assessed by both its discriminatory ability and its calibration.

### *2. Model Validation*

The final models will be applied to the 40% of the residual initial sample size. Discrimination and overall validation will also be assessed in the validation cohort.

### *3. Risk Calculator*

Risk calculator will be developed on Excel for each of the best-fit models based on the multivariate logistic regression.

## C. Imputation of Albumin

Missing albumin values were imputed based on the following regression that includes age, BMI, gender and additional preoperative laboratory values.

Table 2: Linear regression results for imputation of albumin.

| | UNSTANDARDIZED B | T-VALUE | P-VALUE |
|---|---|---|---|
| **(CONSTANT)** | 1.938 | 5.933 | 0.000 |
| **AGE** | -0.007 | -9.365 | 0.000 |
| **BMI** | -0.001 | -0.941 | 0.347 |
| **GENDER** | 0.001 | 0.033 | 0.974 |
| **SODIUM** | 0.012 | 5.017 | 0.000 |
| **BUN** | 0.002 | 2.347 | 0.019 |
| **CREAT** | -0.077 | -5.699 | 0.000 |
| **WBC** | -0.022 | -10.084 | 0.000 |
| **HCT** | 0.031 | 23.022 | 0.000 |
| **PLATELETS** | 0.000 | -1.826 | 0.068 |

# CHAPTER III

# RESULTS OF MORTALITY

## A. Patient characteristics

The ACS-NSQIP dataset from 2008 till 2017 yielded 10642 patients who underwent radical cystectomy due to bladder malignancy. The average patient age was 69, and 77% of the cohort were males. 24% of the patients were current smokers and the most common ASA class was class III (70%). The most common pre-operative morbidity was hypertension requiring medication (60%) followed by diabetes mellitus (20%). The average modified frailty index (between 0 and 1) was 0.18. 31% of the patients had a pre-operative creatinine greater than 1.2 mg/dL. The means of sodium, hematocrit and white blood cell counts were 139.1 mEq/L, 37.7% and 7,750 cells/$m^3$. 13% had a serum albumin lower than 3.5, 2.7% had weight loss prior to surgery and 1.6% had BMI lower than 18.5 $kg/m^2$.

12% of the surgeries were robotic surgeries, and 18.5% employed continent diversion. The average operative time was 328 minutes.

1.9% of the patients experienced death within 30 days of the operation. Moreover, within the 30-day post-operative period, 5.6% required a return to the operation room, 2.5% experienced a cardiac complication (cardiac arrest or MI), 8.8% developed post-operative sepsis and 36.9% required a postoperative transfusion. 28% experienced a serious complication and 53.7% experienced any complication.
23% of the patients had a total length of hospital stay greater than 10 days.
The overall patient characteristics as well as the characteristics of both derivation and validation models are shown in Figures 5 and 6.

| | DERIVATION COHORT | | VALIDATION COHORT | | FULL COHORT | |
|---|---|---|---|---|---|---|
| | Count | Column N % | Count | Column N % | Count | Column N % |
| **WHITE** | 4962 | 78.5% | 3406 | 78.9% | 8368 | 78.6% |
| **FEMALE** | 1465 | 23.2% | 958 | 22.2% | 2423 | 22.8% |
| **SMOKING** | 1481 | 23.4% | 1036 | 24.0% | 2517 | 23.7% |
| **ROBOTIC** | 762 | 12.0% | 505 | 11.7% | 1267 | 11.9% |
| **CONTINENT** | 999 | 18.2% | 707 | 18.8% | 1706 | 18.5% |
| **ASA LEVEL 4** | 363 | 5.7% | 258 | 6.0% | 636 | 6.0% |
| **COPD** | 514 | 8.1% | 352 | 8.2% | 866 | 8.1% |
| **CHF** | 42 | 0.7% | 29 | 0.7% | 71 | 0.7% |
| **HTN** | 3828 | 60.5% | 2619 | 60.7% | 6447 | 60.6% |
| **CREATININE >1.2** | 1979 | 31.3% | 1341 | 31.1% | 3320 | 31.2% |

Table 3: Descriptive statistics of the population in the derivation, validation and full cohorts.

| | DERIVATION COHORT | | VALIDATION COHORT | | FULL COHORT | |
|---|---|---|---|---|---|---|
| | **Count** | **%** | **Count** | **%** | **Count** | **%** |
| **ORGAN SSI** | 411 | 6.5% | 276 | 6.4% | 687 | 6.5% |
| **PNEUMONIA** | 176 | 2.8% | 131 | 3.0% | 307 | 2.9% |
| **ARF** | 71 | 1.1% | 69 | 1.6% | 140 | 1.3% |
| **UTI** | 540 | 8.5% | 375 | 8.7% | 915 | 8.6% |
| **CARDIAC ARREST** | 69 | 1.1% | 45 | 1.0% | 114 | 1.1% |
| **MI** | 103 | 1.6% | 73 | 1.7% | 176 | 1.7% |
| **DVT** | 176 | 2.8% | 123 | 2.8% | 299 | 2.8% |
| **RETURN TO OR** | 356 | 5.6% | 245 | 5.7% | 601 | 5.6% |
| **LENGTH OF STAY>10** | 1353 | 21.4% | 975 | 22.6% | 2328 | 21.9% |
| **DEATH** | 110 | 1.7% | 89 | 2.1% | 199 | 1.9% |

Table 4: Descriptive statistics of the outcomes in the derivation, validation and full cohorts.

## B. Mortality Model

### *1. Bivariate Analysis*

Pre-operative factors associated with post-operative mortality were examined on the derivation cohort that constituted 60% of our sample. Age was significantly associated with the outcome (OR=1.05; CI: 1.02-1.07; p-value=0.000). Patients with pre-operative COPD had 2.1 times higher odds of experiencing the outcomes than patients who did not (95% CI, 1.24 - 3.56; p-value=0.01). Additionally, patients with wound infection prior to surgery were 4.81 times more likely to die within the 30-day period after radical cystectomy. Smoking, gender, race and diabetes mellitus were not associated with higher risk of death. A higher preoperative white blood cell count and creatinine levels were associated with post-operative mortality, while higher preoperative albumin levels were associated with lower odds of death. Having a higher modified frailty index and higher ASA class were also associated with higher odds of death.

| | OR | 95% C.I. | | P-VALUE |
|---|---|---|---|---|
| | | Lower | Upper | |
| **AGE** | 1.03 | 1.01 | 1.06 | 0.00 |
| **SMOKING** | 0.69 | 0.40 | 1.19 | 0.18 |
| **ASA LEVEL 2** | 0.49 | 0.22 | 1.06 | 0.07 |
| **ASA LEVEL 3** | 0.63 | 0.35 | 1.13 | 0.12 |
| **FUNCTIONAL HEALTH STATUS >3** | 2.53 | 1.09 | 5.84 | 0.03 |
| **MFI5** | 7.82 | 2.47 | 24.77 | 0.000 |
| **ASA LEVEL 1 OR 2** | | | | 0.000 |
| **ASA LEVEL 3** | 1.86 | 1.07 | 3.23 | 0.029 |
| **ASA LEVEL 4** | 4.35 | 2.11 | 8.99 | 0.000 |
| **COPD** | 1.81 | 1.05 | 3.11 | 0.03 |
| **WOUND INFECTION PRIOR TO SURGERY** | 2.95 | 0.82 | 10.63 | 0.10 |
| **COMORBIDITY SCORE** | 1.22 | 0.95 | 1.56 | 0.12 |
| **PREOPERATIVE CREATININE >1.2** | 1.53 | 1.03 | 2.26 | 0.03 |
| **PREOPERATIVE ALBUMIN LEVEL** | 0.47 | 0.32 | 0.67 | 0.000 |
| **PREOPERATIVE WBC COUNT** | 1.03 | 0.98 | 1.08 | 0.21 |
| **PREOPERATIVE BUN** | 1.02 | 1.01 | 1.04 | 0.004 |
| **PREOPERATIVE SODIUM** | 1.00 | 0.94 | 1.07 | 0.922 |

Table 5: Bivariate analysis of morrtality in the derivation cohort.

Abbreviations: OR: Odds Ratio; C.I: Confidence Interval; ASA: American Society of Anesthesiologists; WBC: White blood cells; BUN: Blood urea nitrogen.

### *2. Multivariate Analysis*

On multivariate analysis of the derivation cohort, age was significantly associated with death, with a 3.2% increase in the odds of death with every 1-year

increase in age [OR 1.03; 95% CI, 1.01-1.06; p-value=0.005]. Having an ASA level of 4 significantly increased the odds of death by 1.2 from baseline [OR 2.2; 95% CI, 1.00 - 4.83; p-value=0.049]. Finally, preoperative albumin decreased risk of death [OR 0.67; 95% CI, 0.44, 1.01; p-value=0.058). The modified frailty index score of 0.6 or 0.8 was also significantly associated with a risk of death [OR 3.69; 95% CI 01.57, 8.66; p-value=0.003] (Fig 8).

| | OR | 95% C.I.FOR OR | | P-VALUE |
|---|---|---|---|---|
| | | Lower | Upper | |
| **AGE** | 1.03 | 1.01 | 1.06 | 0.005 |
| **SMOKING** | 0.71 | 0.41 | 1.22 | 0.212 |
| **ASA** | | | | 0.140 |
| **ASA LEVEL 3** | 1.38 | 0.78 | 2.45 | 0.269 |
| **ASA LEVEL 4** | 2.20 | 1.00 | 4.83 | 0.049 |
| **MODIFIED FRAILTY INDEX=0** | | | | 0.018 |
| **MFI5=0.2** | 1.06 | 0.65 | 1.73 | 0.820 |
| **MFI5=0.4** | 1.24 | 0.70 | 2.18 | 0.459 |
| **MFI5=0.6 OR 0.8** | 3.69 | 1.57 | 8.66 | 0.003 |
| **PREOPERATIVE WOUND INFECTION** | 3.33 | 0.92 | 12.02 | 0.066 |
| **PREOPERATIVE ALBUMIN** | 0.67 | 0.44 | 1.01 | 0.058 |
| **PREOPERATIVE CREATININE** | 1.50 | 1.01 | 2.22 | 0.044 |
| **PREOPERATIVE WBC** | 1.03 | 0.98 | 1.08 | 0.191 |
| **PREOPERATIVE SODIUM** | 1.03 | 0.97 | 1.10 | 0.3835 |

Table 6: Multivariate logistic regression of mortality in the derivation cohort.

Abbreviations: OR: Odds Ratio; C.I: Confidence Interval; ASA: American Society of Anesthesiologists; WBC: White blood cells; BUN: Blood urea nitrogen.

### 3. *Risk predictor*

The final model of risk prediction included the variables listed in Fig 9. The area under the curve (ROC) of the model was 0.7, with a standard error of 0.023 [95% CI, 0.65, 0.74; alpha of 0.000] (Fig. 09 and 10) The Hosmer-Lemeshow goodness-of-fit for this model had a statistic of 0.64, slope of 0.96, intercept of 0.0007 and $R^2$ of 90%.

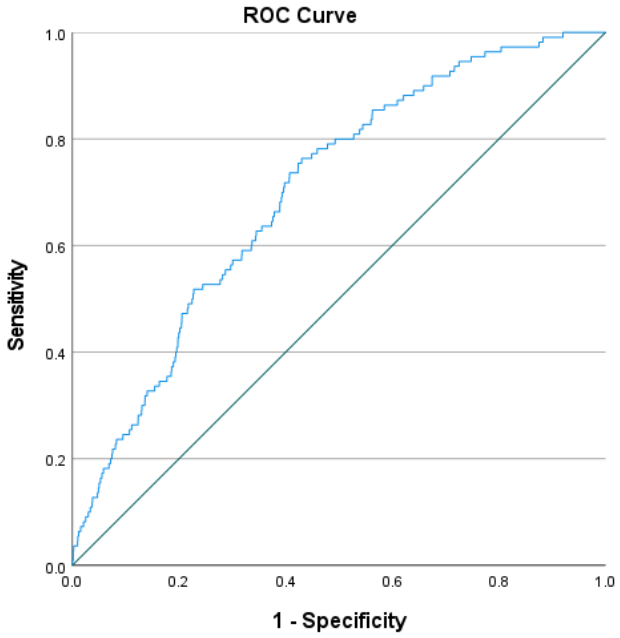


Figure 3: Receiver Operator Curve for the mortality model.

| Area Under the Curve | 95% C.I. | Significance |
|---|---|---|
| 0.70 | 0.66 - 0.75 | 0.000 |

Table 7: Receiver operator curve statistics for the mortality model.
Abbreviations: C.I.: Confidence Interval

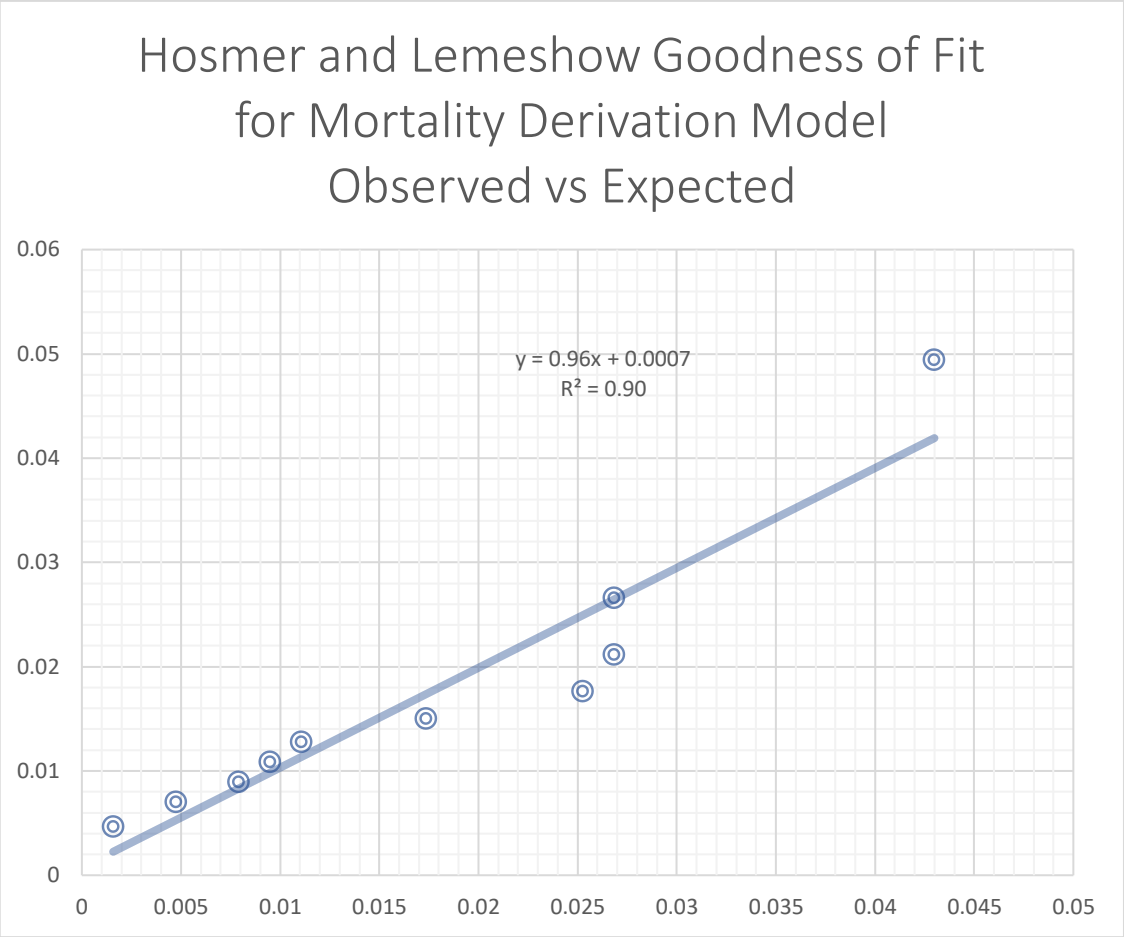


Figure 4: Hosmerr and Lemeshow Goodness of Fit test for mortality derivation model.

### *4. Validation*

The validation cohort consisted of 4317 patients of whom 2.1% (89) died. Age was significantly associated with mortality with an OR of 1.07 [95% CI, 1.04-1.10; p<0.000]. A lower serum albumin was associated with a higher chance of death with an OR of 0.47 (p=0.001). Moreover, ASA IV was associated with a 2.97-fold higher chance of death [95% CI, 1.42, 6.21; p=0.003]. (Figure 11)

| | OR | 95% C.I.FOR OR | | SIG. |
|---|---|---|---|---|
| | | Lower | Upper | |
| **AGE** | 1.07 | 1.04 | 1.10 | 0.000 |
| **SMOKING** | 1.41 | 0.81 | 2.46 | 0.215 |

| | | | | |
|---|---|---|---|---|
| **ASA** | | | | 0.000 |
| **ASA LEVEL 3** | 0.83 | 0.46 | 1.52 | 0.608 |
| **ASA LEVEL 4** | 2.97 | 1.42 | 6.21 | 0.003 |
| **MODIFIED FRAILTY INDEX** | | | | 0.349 |
| **MODIFIED FRAILTY INDEX=0.2** | 0.69 | 0.40 | 1.18 | 0.175 |
| **MFI5=0.4** | 1.07 | 0.59 | 1.94 | 0.827 |
| **MFI5=0.6 OR 0.8** | 1.00 | 0.32 | 3.17 | 1.000 |
| **PREOPERATIVE WOUND INFECTION** | 1.67 | 0.21 | 13.63 | 0.630 |
| **PREOPERATIVE ALBUMIN** | 0.47 | 0.30 | 0.72 | 0.001 |
| **PREOPERATIVE CREATININE** | 1.35 | 0.86 | 2.10 | 0.189 |
| **PREOPERATIVE WBC** | 0.99 | 0.92 | 1.06 | 0.694 |
| **PREOPERATIVE SODIUM** | 1.00 | 0.93 | 1.07 | 0.981 |

Table 8:Multivariate logistic regression results of mortality on the validation cohort. Abbreviations: OR: Odds Ratio; C.I: Confidence Interval; ASA: American Society of Anesthesiologists; WBC: White blood cells; BUN: Blood urea nitrogen.

The ROC of the validation model was 77% with a Hosmer-Lemeshow goodness-of-fit statistic of 0.55.

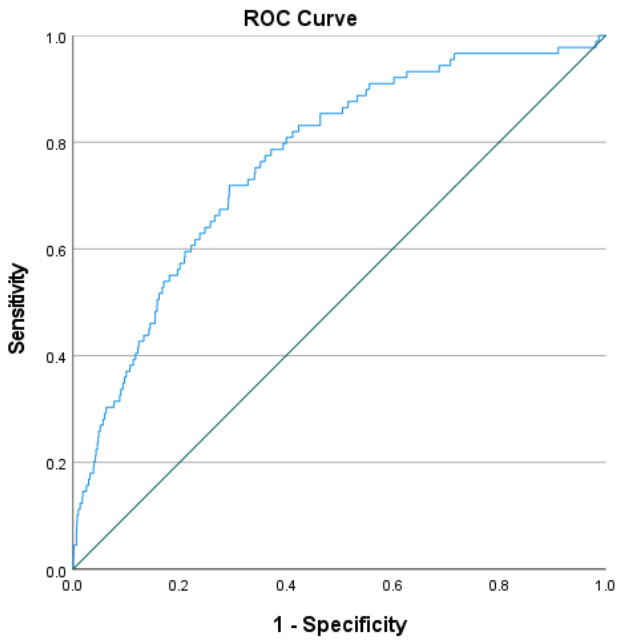


Figure 5: Receiver Operator Curve of the mortality model on the validation cohort.

| AREA UNDER THE CURVE | 95% C.I. | SIGNIFICANCE |
|---|---|---|
| **0.77** | 0.72-0.81 | 0.000 |

Table 9: Receiver Operator Curve of the mortality model on the validation cohort.

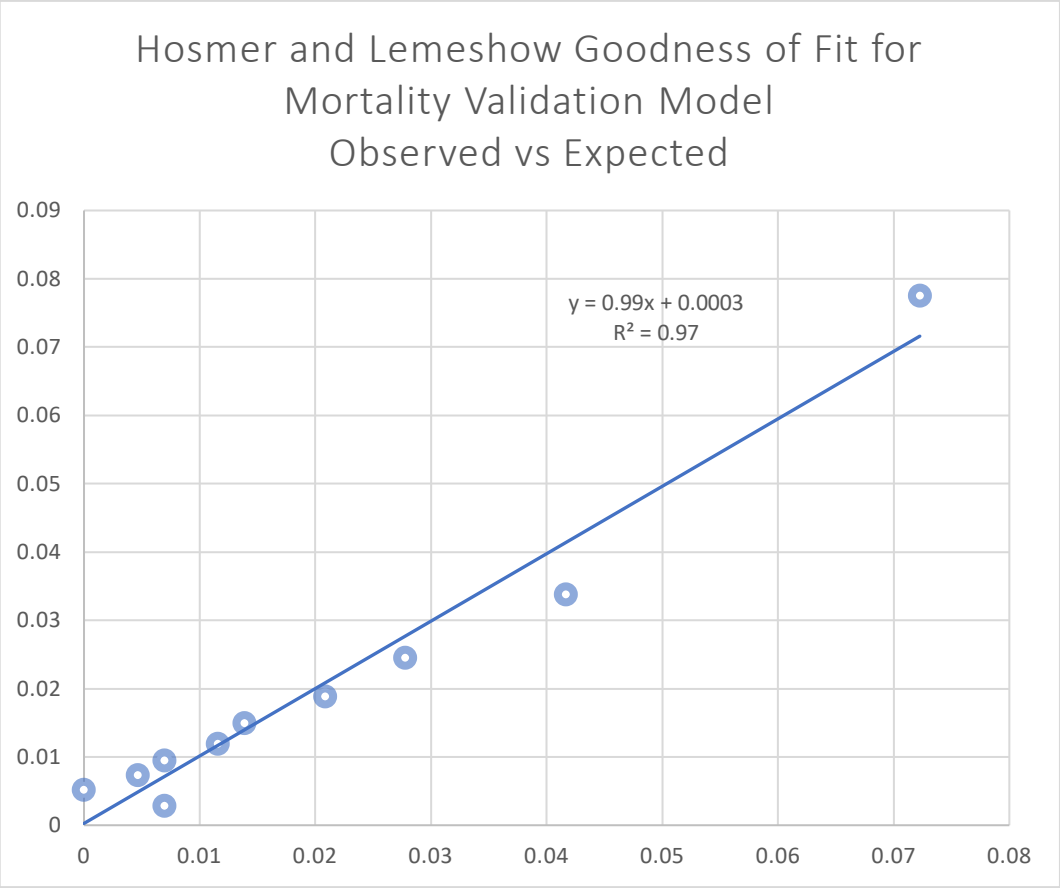


Figure 6: Hosmer and Lemeshow goodness of fit for the mortality model on the validation cohort.

### *5. NSQIP predicted mortality*

When comparing our model's predicted values with the values provided by the ACS-NSQIP mortality predictor, a significant weak correlation is found with a spearman's correlation coefficient of 0.621 ($p<0.000$).

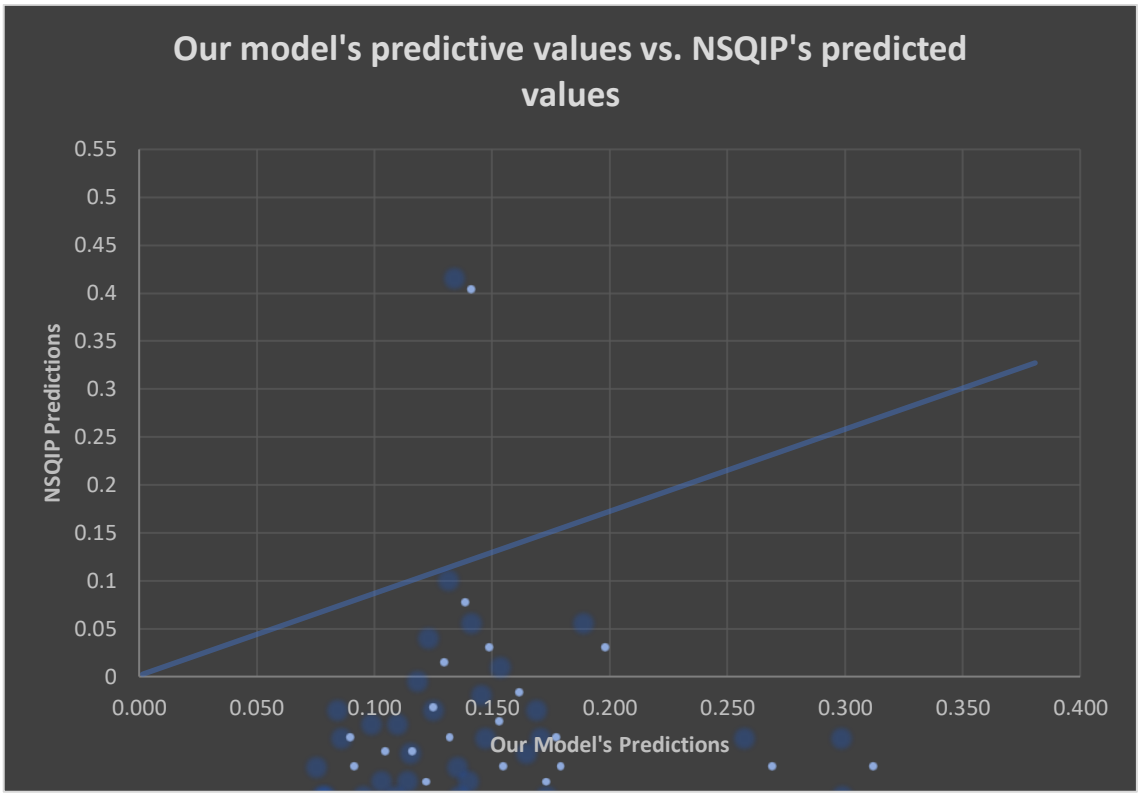


Figure 7: Our model's predictive values vs. NSQIP's predicted values.

### *6. Age-Smoking Interaction*

The interaction between age and smoking and their association with mortality was examined in the derivation cohort and is shown in the figure below. The p-value of the interaction between age and smoking was 0.016. The Pearson Chi-Square test was conducted. The effect on smoking on death in patients below the age of 70 was not significant (p-value=0.391). The effect of smoking on death in patients above the age of 70 was significant (p-value=0.009).

| **Age>70** | | **Death** | | **Total** |
|---|---|---|---|---|
| | | No | Yes | |
| **Smoking** | No | 2694 (97.8) | 61 (2.2) | 2755 |
| | Yes | 403 (97.1) | 12 (2.9) | 415 |
| Total | | 3097 | 73 | 3170 |

| **Age<70** | | **Death** | | **Total** |
|---|---|---|---|---|
| | | No | Yes | |
| **Smoking** | No | 2057 (98.5) | 32 (1.5) | 2089 |
| | Yes | 1061 (99.5) | 5 (0.5) | 1066 |
| Total | | 3118 | 37 | 3155 |

Table 10: Stratification of smoking by age.

### *7. Mortality over time*

Mortality rate in our full cohort was compared across different years in the full cohort. The Pearson Chi-Square of the model was not significant (0.139). The rate of death varied from 4.7% in 2008 to 2.3% in 2017.

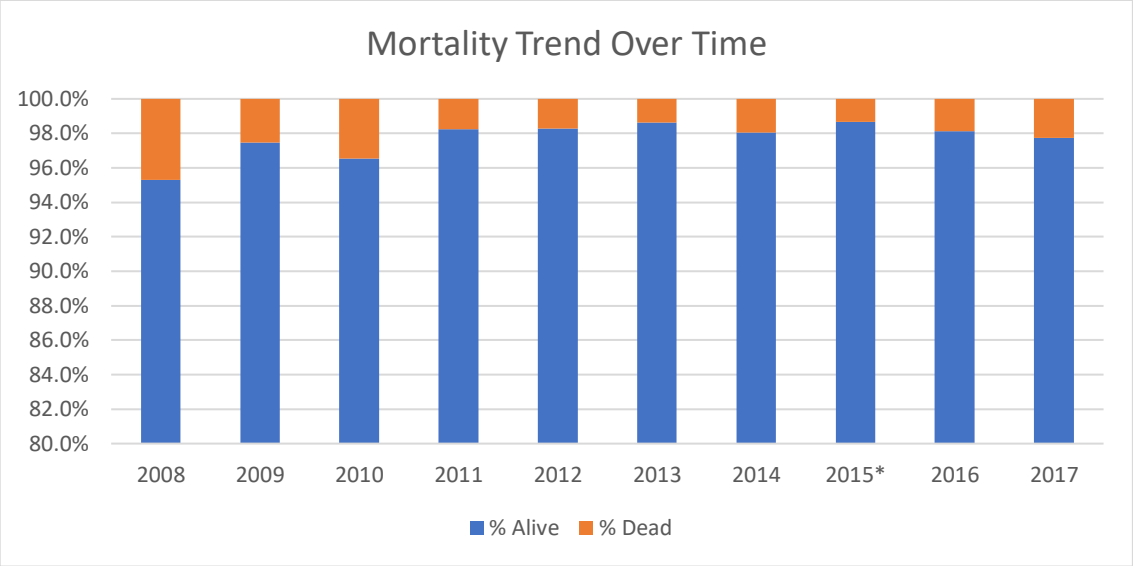


Figure 8: The trend of mortality over time.
* indicates statistically significant difference in mortality.

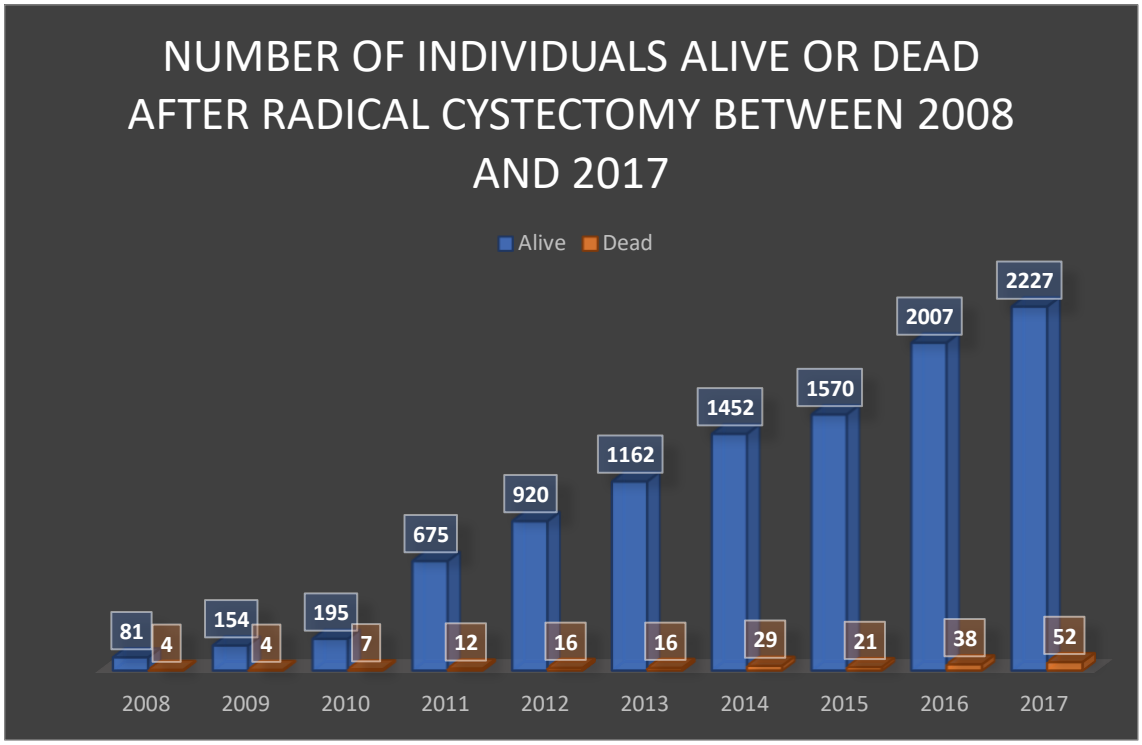

Figure 9: Number of individuals alive or dead after radical cystectomy between 2008 and 2017 in full cohort.

| | OR OF DEATH | P-VALUE |
|---|---|---|
| **2017 (REFERENCE)** | | 0.164 |
| **2008** | 2.115 | 0.158 |
| **2009** | 1.112 | 0.839 |
| **2010** | 1.537 | 0.294 |
| **2011** | 0.761 | 0.399 |
| **2012** | 0.745 | 0.307 |
| **2013** | 0.590 | 0.067 |
| **2014** | 0.855 | 0.505 |
| **2015** | 0.573 | **0.033** |
| **2016** | 0.811 | 0.331 |

Table 11: Logistic regression comparing year of operation to death.

## 8. Risk Calculator

To be able to access a link to the calculator, kindly scan the QR code below to access the online excel file. An example of the risk calculator is shown below.

| Calculator | |
|---|---|
| Age | 70 |
| Smoking | 1 |
| ASA Category 3 | 1 |
| ASA Category 4 | 0 |
| mFI5 score | 0 |
| mFI5 =0.2 | 0 |
| mFI5=0.4 | 1 |
| mFI5=0.6 or 0.8 | 0 |
| Wound Infection Prior to Surgery | 0 |
| Creatinine >1.2 | 1 |
| Albumin | 3.5 |
| Sodium | 138 |
| WBC | 9.5 |
| Probability of Death | 0.0210 |
| % Probability of Death | 2.10 |

Table 12: Risk calculator example for death.

Figure 10: QR code of the excel file

# CHAPTER IV

# RESULTS OF MORBIDITY

## A. Morbidity Model

### *1. Bivariate Analysis*

| | OR | 95% C.I. FOR OR | | P-VALUE |
|---|---|---|---|---|
| | | Lower | Upper | |
| **AGE** | 1.02 | 1.02 | 1.03 | **0.000** |
| **RACE** | 0.51 | 0.45 | 0.58 | **0.000** |
| **ROBOTIC** | 0.59 | 0.48 | 0.73 | **0.000** |
| **CONTINENT** | 1.00 | 0.85 | 1.18 | 0.974 |
| **FUNCTIONAL HEALTH STATUS** | 2.86 | 1.98 | 4.14 | **0.000** |
| **COPD** | 1.74 | 1.43 | 2.11 | **0.000** |
| **HYPERTENSION** | 1.33 | 1.18 | 1.51 | **0.000** |
| **CONGESTIVE HEART FAILURE** | 2.81 | 1.53 | 5.18 | **0.001** |
| **DIABETES** | 1.15 | 1.06 | 1.25 | **0.001** |
| **ASA LEVEL I OR II** | | | | **0.000** |
| **ASA CLASS III** | 1.17 | 1.02 | 1.36 | **0.028** |
| **ASA CLASS IV** | 2.34 | 1.83 | 3.00 | **0.000** |
| **MFI5** | 4.17 | 2.87 | 6.07 | **0.000** |
| **ALBUMIN<3.5** | 1.89 | 1.61 | 2.21 | **0.000** |
| **BMI<18.5** | 1.34 | 0.86 | 2.08 | 0.197 |
| **NUTRITIONAL DEFICIENCY** | 1.78 | 1.53 | 2.07 | **0.000** |
| **PREOP SODIUM** | 0.94 | 0.92 | 0.96 | **0.000** |
| **PREOP BUN** | 1.01 | 1.00 | 1.02 | **0.002** |
| **PREOP CREATININE** | 1.32 | 1.16 | 1.49 | **0.000** |
| **PREOP LEUKOPENIA** | 0.69 | 0.54 | 0.89 | **0.004** |
| **PREOP LEUKOCYTOSIS** | 1.81 | 1.53 | 2.15 | **0.000** |

Table 13: Bivariate analysis of the morbidity model on the derivation cohort. Abbreviations: OR: Odds Ratio; C.I: Confidence Interval; ASA: American Society of Anesthesiologists; WBC: White blood cells; BUN: Blood urea nitrogen.

### *2. Multivariate analysis*

On multivariate analysis, age was significantly correlated with prolonged hospital stay (more than ten days post-operation) [OR 1.026; 95% CI 1.018 – 1.034; p<0.000]. Being white was associated with lower length of stay with an OR of 0.51 [95% CI 0.44 – 0.59; p<0.000]. Having leukocytosis was associated with a 52% increase in the odds of staying more than 10 days in the hospital post-operatively. Robotic surgery decreased the chance of a prolonged length of stay by 29% (p<0.005). A continent diversion, nevertheless, increased the odds of prolonged LOS by 52% [OR 1.52; 95% CI 1.26 – 1.82].

Table 14:Multivariate analysis of morbidity model on the derivation cohort.

| | OR | 95% C.I.FOR OR | | P-VALUE |
|---|---|---|---|---|
| | | Lower | Upper | |
| **AGE** | 1.026 | 1.018 | 1.034 | **0.000** |
| **RACE (MINORITY)** | 0.51 | 0.44 | 0.59 | **0.000** |
| **GENDER (MALE)** | 1.12 | 0.94 | 1.34 | 0.187 |
| **SMOKING** | 1.04 | 0.88 | 1.23 | 0.616 |
| **LEUKOPENIA** | 0.65 | 0.49 | 0.88 | 0.004 |
| **LEUKOCYTOSIS** | 1.52 | 1.24 | 1.86 | 0.000 |
| **SODIUM** | 0.97 | 0.95 | 0.99 | **0.005** |
| **WOUND INFECTION** | 3.33 | 1.56 | 7.13 | 0.002 |
| **ROBOTIC** | 0.71 | 0.56 | 0.89 | 0.003 |
| **CONTINENT** | 1.52 | 1.26 | 1.82 | **0.000** |
| **MFI** | | | | 0.000 |
| **MFI=0.2** | 1.31 | 1.11 | 1.54 | 0.001 |
| **MFI=0.4** | 1.47 | 1.22 | 1.78 | 0.000 |
| **MFI=0.6 OR 0.8** | 3.06 | 1.95 | 4.79 | 0.000 |
| **PREOPERATIVE ALBUMIN** | 0.78 | 0.66 | 0.92 | 0.003 |

### *3. Risk predictor*

The developed model had an area-under-the-curve of 0.65 [95% CI 0.64 – 0.67; p<0.000]. The Hosmer-Lemeshow goodness-of-fit statistic was 0.8. The calibration of the model had an R2 of 99% with a slope of 0.97 and intercept of 0.007 when comparing observed to expected values.

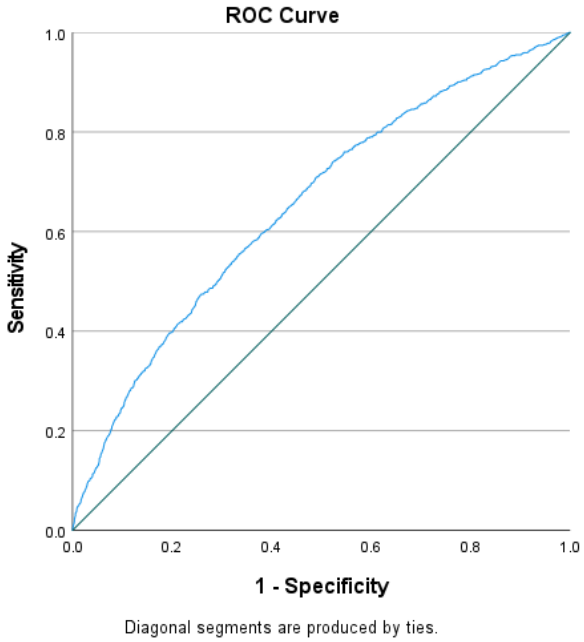


Figure 11: Receiver Operator Curve on the mobidity model, derivation cohort.

| AREA UNDER THE CURVE | 95% C.I. | SIGNIFICANCE |
|---|---|---|
| **0.65** | 0.64-0.67 | 0.000 |

Table 15: Receiver Operator Curve of the derivation model for morbidity.

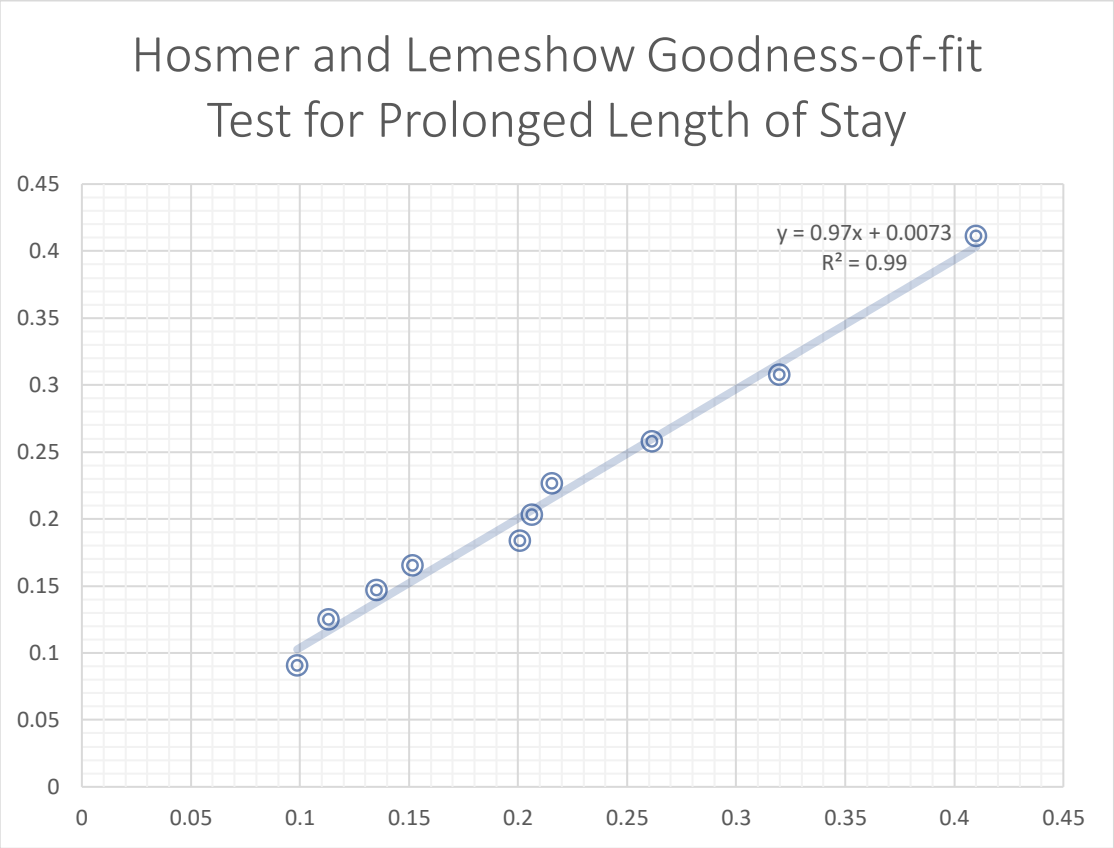

Figure 12:Hosmer and Lemeshow Goodness-of-fit Test for Prolonged Length of Stay on the Derivation Model.

### *4. Validation*

The validation cohort consisted of 4317 patients. Age, race, nutritional deficiency and having a robotic procedure were significantly associated with the outcome. Every 1-year increase in age increased the odds of prolonged LOS by 2.4 % [OR 1.024; 95% CI 1.014– 1.033; p<0.000]. The model's c statistic was 0.62 [95% CI 0.60 – 0.65; p<0.000]. Hosmer-Lemeshow goodness-of-fit statistic 0.85.

| | OR | 95% C.I.FOR OR | | P-VALUE. |
|---|---|---|---|---|
| | | Lower | Upper | |
| **AGE** | 1.024 | 1.014 | 1.033 | 0.000 |
| **RACE** | 0.62 | 0.52 | 0.74 | 0.000 |
| **GENDER** | 0.91 | 0.74 | 1.12 | 0.379 |
| **SMOKING** | 1.18 | 0.97 | 1.42 | 0.098 |
| **ROBOTIC** | 0.53 | 0.39 | 0.71 | 0.000 |
| **CONTINENT** | 1.19 | 0.96 | 1.48 | 0.103 |
| **MFI5** | | | | 0.386 |
| | 1.15 | 0.95 | 1.38 | 0.144 |
| | 1.06 | 0.84 | 1.34 | 0.605 |
| | 1.37 | 0.81 | 2.33 | 0.238 |
| **PREOPERATIVE ALBUMIN** | 0.68 | 0.56 | 0.81 | 0.000 |
| **WOUND INFECTION** | 2.28 | 0.83 | 6.21 | 0.108 |
| **PREOP SODIUM** | 0.98 | 0.96 | 1.01 | 0.220 |
| **PREOP LEUKOPENIA** | 0.75 | 0.53 | 1.05 | 0.093 |
| **PREOP LEUKOCYTOSIS** | 1.12 | 0.86 | 1.47 | 0.392 |

Table 16: Multivariate analysis of morbidity on the validation cohort. Abbreviations: OR: Odds Ratio; C.I: Confidence Interval; ASA: American Society of Anesthesiologists; WBC: White blood cells; BUN: Blood urea nitrogen.

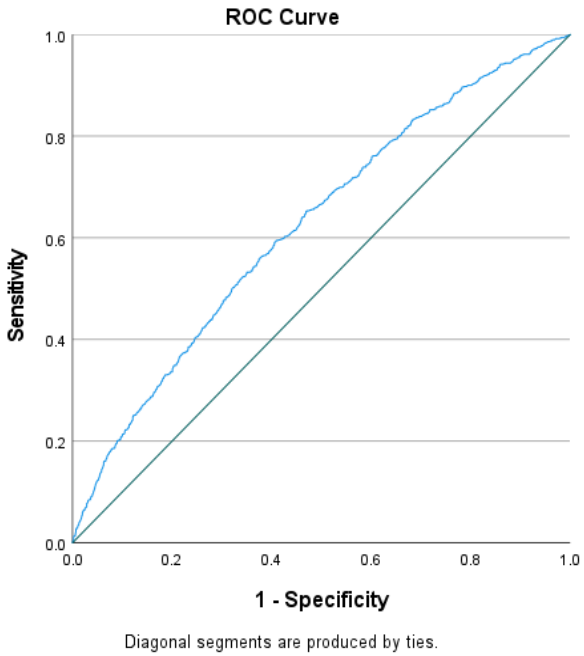


Figure 13: Receiver Operator Curve of the morbidity model in the validation cohort.

| AREA UNDER THE CURVE | 95% C.I. | SIGNIFICANCE |
|---|---|---|
| **0.62** | 0.60-0.65 | 0.000 |

Table 17: Receiver Operator Curve of the morbidity model in the validation cohort.

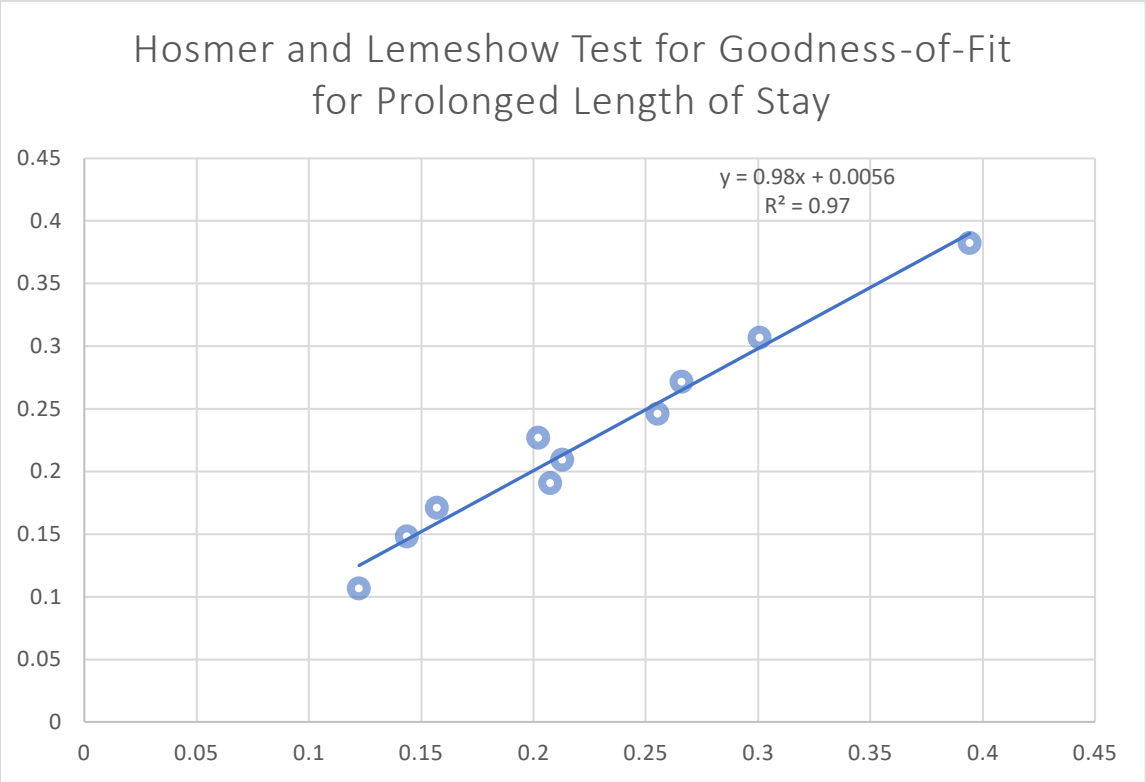


Figure 14: Hosmer and Lemeshow Test for Goodness-of-Fit for Prolonged Length of Stay on the Validation Cohort.

### *5. Sensitivity analysis of Continent Diversion*

The above model was repeated excluding the continent diversion variable. Results of the multivariate analysis are presented in Figure 27. The ROC curve is presented in Figure 28.

| | OR | 95% C.I. FOR OR | | P-VALUE |
|---|---|---|---|---|
| | | Lower | Upper | |
| **AGE** | 1.020 | 1.012 | 1.028 | 0.000 |
| **RACE** | 0.61 | 0.51 | 0.72 | 0.000 |
| **GENDER** | 0.98 | 0.82 | 1.16 | 0.793 |
| **SMOKING** | 1.09 | 0.91 | 1.31 | 0.325 |
| **ROBOTIC** | 0.56 | 0.43 | 0.73 | 0.000 |
| **WOUND INFECTION** | 1.82 | 0.75 | 4.43 | 0.187 |
| **MODIFIED FRAILTY INDEX** | | | | 0.396 |
| **MFI5=0.2** | 1.15 | 0.96 | 1.36 | 0.121 |
| **MFI5=0.4** | 1.06 | 0.86 | 1.31 | 0.582 |
| **MFI5=0.6 OR 0.8** | 1.29 | 0.78 | 2.13 | 0.322 |
| **ALBUMIN** | 0.65 | 0.54 | 0.77 | 0.000 |
| **LEUKOPENIA** | 0.77 | 0.57 | 1.05 | 0.103 |
| **LEUKOCYTOSIS** | 1.11 | 0.87 | 1.42 | 0.407 |
| **SODIUM** | 0.99 | 0.96 | 1.01 | 0.311 |

Table 18: Sensitivity analysis of the morbidity model excluding continent diversion.

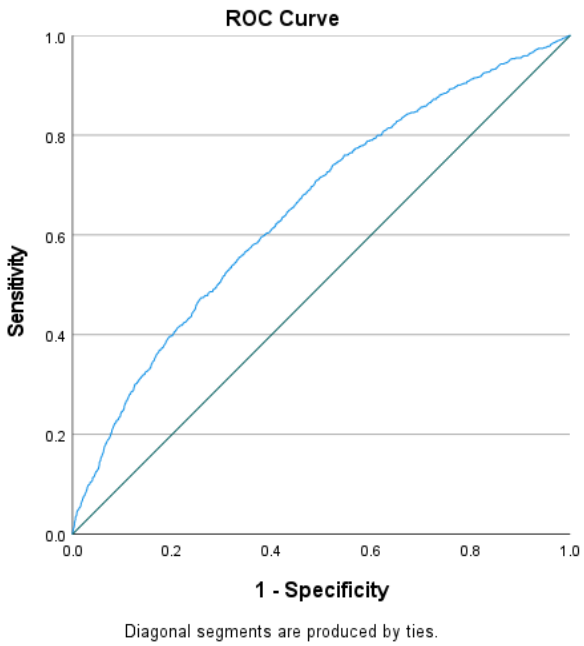


Figure 15: Receiver Operator Curve of the Morbidity Model Excluding Continent Diversion, Sensitivity Analysis.

| AREA UNDER THE CURVE | 95% C.I. | P-VALUE |
|---|---|---|
| **0.65** | 0.64-0.67 | 0.000 |

Table 19: Receiver Operator Curve of the Morbidity Model Excluding Continent Diversion, Sensitivity Analysis.

### *6. Risk calculator*

Presented below is the risk calculator of morbidity. The outcome is staying in the hospital for more than 10 days. The QR provides access to the calculator through a OneDrive Link.

| Calculator | |
|---|---|
| Age | 60 |
| Smoking | 1 |
| Continent | 0 |
| Robotic | 1 |
| Race (White) | 1 |
| Gender | 1 |
| mFI5=0 | 1 |
| mFI5 =0.2 | 0 |
| mFI5=0.4 | 0 |
| mFI5=0.6 or 0.8 | 0 |
| Wound Infection Prior to Surgery | 0 |
| Albumin | 4 |
| Sodium | 145 |
| Leukopenia | 0 |
| Leukocytosis | 0 |
| Probability of Prolonged Stay (>10 days) | 0.0777 |
| % Probability of Death | 7.77 |

| Calculator | |
|---|---|
| Age | 60 |
| Smoking | 1 |
| Continent | 0 |
| Robotic | 0 |
| Race (White) | 1 |
| Gender | 1 |
| mFI5=0 | 1 |
| mFI5 =0.2 | 0 |
| mFI5=0.4 | 0 |
| mFI5=0.6 or 0.8 | 0 |
| Wound Infection Prior to Surgery | 0 |
| Albumin | 4 |
| Sodium | 145 |
| Leukopenia | 0 |
| Leukocytosis | 0 |
| Probability of Prolonged Stay (>10 days) | 0.1066 |

| % Probability of Death | 10.66 |
|---|---|

Table 20: Example of risk calculator for morbidity after radical cystectomy.


Figure 16: QR code of the excel file containing the morbidity calculator of prolonged length of stay.

# CHAPTER IV

# DISCUSSION

## A. RC and DEATH

### *1. Mortality*

The post-operative mortality following RC is significant and varies between 0.3% and 7.9%.(Aziz et al., 2014)

The AC-NSQIP dataset from 2008-17 had 10,642 patients who had undergone radical cystectomy due to bladder malignancy. We predicted post-operative mortality and morbidity by analyzing several preoperative risk factors. For the mortality model, age, ASA class, preoperative albumin and preoperative wound infection were significantly associated with death. These variables can be easily assessed in the clinic setting prior to surgery, to provide the patient with individualized estimates of mortality and morbidity after the surgery.

Patients presenting with bladder cancer are often elderly male smokers. In an analysis of the SEER database, 75% of the patients were male, with an average age at diagnosis of 70 years old, similar to our cohort.(Wang, Chang, & Li, 2018) Tobacco use, a significant risk factor for the development of bladder cancer, was also shown to be associated with higher bladder cancer mortality. A study analyzing the World Health Organization (WHO) database found a linear association between smoking and bladder cancer mortality in men and women with a correlation coefficient of 0.38 and 0.22, respectively.(Teoh et al., 2020) While a significant amount of our cohort were smokers, smoking was not significantly associated with mortality in our model. Nevertheless, the effect of smoking on post-operative 30-day mortality was evident when adjusting for

age. Interestingly, smoking appeared to be insignificantly protective in younger patients, and significantly deleterious among septuagenarians and octogenarians. This can be explained by a survival bias (collider bias), whereby healthy, younger patients would continue smoking while those with more comorbidities would discontinue smoking. The continuation of smoking could imply the absence of red flags to discontinue, and these red flags can be associated with mortality. It is worth noting that NSQIP does not account of pack years and only assesses smoking status at the time of surgery. These findings were in accord with another study examining the relation between smoking and age in patients undergoing radical cystectomy using the NSQIP database.(Haeuser et al.)

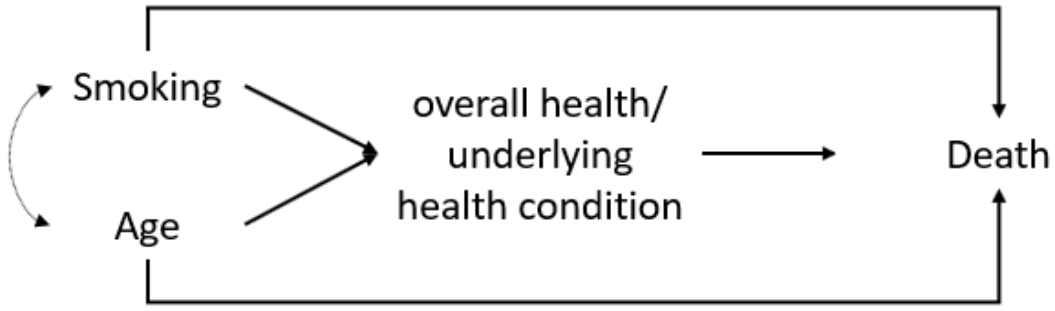


Figure 17: Directed Acyclic Graph showing the collider bias in the relationship between age, smoking and death.

In our multivariate analysis of mortality, every 10 years increase in age were associated with a 32% increase in the odds of death. This is certainly in consensus with the literature where advanced age is an established risk factor for post-operative

morbidity and mortality.(Djaladat et al., 2014; Massarweh, Legner, Symons, McCormick, & Flum, 2009)

Low serum albumin was associated with higher mortality rate in our cohort and in other studies in the literature. The detrimental effect of low serum albumin was also proven by Gibbs et al., with an increase in 30-day mortality rate from 1% in patients with a high albumin level to 28% in their counterparts albumin levels below 2.2 g/dL.(Gibbs et al., 1999) The effect of albumin on mortality was also found for up to 90 days after surgery. In a single-center retrospective study on 1,964 patients undergoing RC for UBC, low serum albumin decreases 90 day overall survival, with a hazard ratio of 1.93.(Djaladat et al., 2014). A study on 905 patients who underwent RC in Vanderbilt University Medical Center assessed the effect of pre-operative nutritional deficiency (ND) on perioperative outcomes.(Gregg et al., 2011), albumin was the lead indicator of ND among the three examined components.(Gregg et al., 2011) These components of ND included low serum albumin <3.5 mg/dL, low BMI or >5% weight loss prior to surgery. The study found that patients with ND had a 1.82-fold higher risk of mortality (HR 1.82, $p<0.01$).(Gregg et al., 2011) A meta-analysis involving ten studies on 4692 geriatric patients with cancer found that malnutrition is significantly associated with all-cause mortality with a relative risk of 1.73. It is worth noting that this study included only observational studies and had a high level of heterogeneity ($I2=73\%$; $p<0.01$).(X. Zhang et al., 2019) In our cohort, weight loss and lower albumin levels were not significantly associated with death, and this could be due to the low power of the analysis. However, it is worth noting that 35% of the cohort had missing albumin levels, as it is not routinely ordered prior to surgery. Our results add to the

body of the literature that shows the importance of this laboratory marker prior to surgery.

In our model, ASA class IV was associated with higher post-operative mortality. An ASA IV is defined by the American Society of Anesthesiologists as “a patient with severe systemic disease that is a constant threat to life.”(ASA, 2020) This is in-line with the findings in the literature, where ASA was a strong predictor of postoperative mortality and morbidity.(Davenport, Bowe, Henderson, Khuri, & Mentzer, 2006; Hackett, De Oliveira, Jain, & Kim, 2015) A study on the NSQIP database including over 2,250,000 patients found a significant association of ASA class with mortality, with odds ratios ranging from 2.05 for class II to 63.25 for class V, taking class I as a reference. Similar results were found when adjusting for the type of surgery.(Hackett et al., 2015)

Other variables associated with overall survival in the literature included adjuvant chemotherapy that had a protective effect (HR 0.41, $p<0.001$) and tumor stage ≥pT3a (HR 2.27, $p<0.001$).(Djaladat et al., 2014) ACS-NSQIP does not include information on tumor stage, lymph node status or adjuvant chemotherapy, thus we were unable to examine these effects.

In our study, we used the modified Frailty Index as an assessment of pre-operative comorbidity. mFI5 started being used after the mFI-11 was no longer applicable to NSQIP database after dropping certain variables crucial to this index. mFI5 was thus developed and it includes COPD, DM, Functional health status, hypertension, and congestive heart failure. This score was validated using NSQIP and had a Spearman’s correlation coefficient with mFI-11 greater than 90%.(Subramaniam et al., 2018) It is worth noting that this study done on NSQIP also adjusted for

urological surgeries.(Subramaniam et al., 2018) In a systematic review by Ornaghi et al., 8% of patients with UBC undergoing RC were frail while 31% were pre-frail.(Ornaghi et al., 2020) In our full cohort where 1.8% had 4 of the 5 mFI comorbidities, and around 20% had 3.

### *2. RC and Risk calculator*

Our risk calculator had fair predictive accuracy of 70%, and the Hosmer-Lemeshow goodness-of-fit statistic was 0.64. Our model was well calibrated with a slope of 0.96, intercept of 0.0007 and $R^2$ of 90% when comparing observed vs expected values. Our model's discrimination was like that in the literature, and our model is highly calibrated. Aziz et al. developed a nomogram for the prediction of 90 day mortality after RC for UBC, with an ROC of 68.8% using age, ASA class, hospital volume and presence of preoperative nodal or distant metastasis.(Aziz et al., 2014) Our model excluded patients with metastasis, as these do not fall under the category of localized MIBC, on whom our study focused. Another model incorporating age, stage, and histological subtype had a predictive accuracy of 70%.(Isbarn et al., 2009) However, this model included patients who underwent partial cystectomy and uses pre-operative and post-operative characteristics. Taylor et al. also developed a model using age and Charlson comorbidity score (CCI) with a discrimination area-under-the-curve of 70.2%.(J. M. Taylor et al., 2012) Moreover, Morgan et al. developed a nomogram using age, CCI, clinical stage and preoperative albumin to predict time to death within 90 days of radical cystectomy. The model's adjusted c-statistic after internal validation was 0.71.(Morgan et al., 2011) While we had similar predictive ability, our model was restricted to 30 days post-operation given the dataset used. Another study by Mannas et

al. developed a model with 62% accuracy in predicting death.(M. P. Mannas et al., 2020) We attribute this difference with the literature to our inclusion criteria whereby we selected patients by ICD codes indicating bladder malignancy and CPT codes referring to radical cystectomy while excluding patients with metastatic disease.

Importantly, our population of patients includes only individuals who were cleared for surgery and have passed all prior screenings by different specialties as cardiology and anesthesiology. Although our model had fair to moderate accuracy, there are no other clinically relevant tools, up to our knowledge, that aid in the clinical decision for these patients. We believe that this model can add another sheet of screening onto these patients; therefore, it can act as an additional layer of protection in the swiss cheese model of hospital quality improvement to minimize mortality and optimize patient outcomes.

**B. RC and Morbidity**

We used length of hospital stay as a marker of post-operative morbidity. The cut-off of 10 days was chosen as the median post-operative stay was 7 days and the 75$^{th}$ percentile was 10 days. In our model, several factors were significantly associated with prolonged postoperative stay. These included age, race, pre-operative WBC count and sodium levels and mFI5. Gender showed no significant association with post-operative length of stay. A study on 348 patients examining several pre-operative variables found that only age and gender were significantly associated with a prolonged LOS.(Pietzak, Hwang, Malkowicz, & Guzzo, 2014) Another retrospective population-based study from the US and Germany found that higher patient age and lower hospital caseload increased the risk of having a prolonged LOS.(Groeben et al., 2019) A study using

SEER database found that receipt of neo-adjuvant chemotherapy can increase the risk of prolonged LOS after radical cystectomy. Interestingly in this study, age, gender and race were not associated with prolonged LOS.(Ray-Zack et al., 2019) Our study found lower rates of PLOS among patients who underwent robotic assisted radical cystectomy, a finding well reported in the literature.(Guillotreau et al., 2009; Khalil et al., 2020; Musch et al., 2014) In a cohort of 142 patients undergoing robotic vs open radical cystectomy, patients undergoing robotic cystectomy lower overall rate of complications.(Musch et al., 2014) Despite having a longer operation time, these patients were at lower risk of blood loss, thus at lower need for transfusions.(Musch et al., 2014) A study by Chang et al. found that being of an ethnic minority and having an ileus diversion significantly prolong postoperative hospital stay. These findings concur with our study where being nonwhite was associated with a prolonged hospital stay. This can be justified by health inequity manifested by different socioeconomic status, educational levels, and many other factors. The relationship between race and ethnicity and health disparities is intricate and is intertwined with a rich scientific and philosophical debate.(National Academies of Sciences et al., 2017)

We considered continent diversion as a preoperative variable as it is usually preplanned in more than 90% of the patients.(Chang, Baumgartner, Wells, Cookson, & Smith, 2002) We performed a sensitivity analysis excluding continent diversion, as including continent diversion as a variable leads to the exclusion of patients with unknown diversion status. The sensitivity analysis showed no significant difference between both models. Given the clinical importance of diversion status in prolonged hospital stay, we opted to include it in our model.

Models in the literature using NSQIP for morbidity had poor predictive accuracy with AUC between 60 and 65%.(Golan et al., 2018; Meng et al., 2018; Sathianathen, Jarosek, Lawrentschuk, Bolton, & Konety, 2019) A model predicting extended length of stay had area-under-the-curve of 65%.(J. Taylor et al., 2019) However, this study focused on machine learning and is not yet applicable in the clinical setting. These literature findings are comparable to those of our model that had a poor predictive accuracy 65% yet a high calibration.

**C. Impact on clinical practice**

Heavy emphasis has been placed on risk predictive models in the literature in the past decades.(N. R. Cook, Buring, & Ridker, 2006; Lauer, Pothier, Magid, Smith, & Kattan, 2007; Parikh et al., 2008; Tice et al., 2008; van der Steeg et al., 2007) These models aim at improving the decision making process and involving the patients in their own management plan.(Janes, Pepe, & Gu, 2008) An increased risk of post-operative morbidity or mortality can aid the stakeholders involved in the patient's care in choosing the most appropriate management plan. Information from risk predictors as ours can thus aid in:

- Informing patients of their personalized risk of morbidity and mortality
- Informed decision-making
- Guide peri-operative management to reduce adverse outcomes(Meguid, Bronsert, Juarez-Colunga, Hammermeister, & Henderson, 2016)
- Most importantly, deferring radical cystectomy and opting for trimodal therapy or vice versa

As aforementioned, there are no RCTs that compare RC to TMT.(Huddart et al., 2010) Recent evidence in the literature is conflicting, as some studies and systematic reviews show noninferiority of TMT to RC, with higher costs and higher quality of life.(Fahmy et al., 2018; Royce et al., 2019; Williams et al., 2019) In addition, an analysis of 475 patients at Massachusetts General Hospital proved TMT as an alternative treatment approach to RC.(Nicholas J. Giacalone et al., 2017) However, in the absence of an RCT comparing these two treatments, causality cannot be inferred as the studies above are observational in nature. With the rise of trimodal therapy as an alternative to RC, identifying patients at high risk of morbidity and mortality from RC can aid in the clinical decision-making process.

## D. Strengths and Limitations

### *1. Limitations*

While our study provides input for future studies and for clinical practice, several limitations exist. We used the ACS National Surgical Quality Improvement Program, a large dataset that includes information from a variety of institutions in the United States. The large sample gives studies derived from the NSQIP a high statistical power, and the variety of patients captured allows to better establish external validity. Unfortunately, the dataset lacks data relevant to radical cystectomy in terms of variables specific to procedural details. Other variables which may have been of relevance to the study but which we did not have access to are chemotherapy/radiotherapy administration which was dropped from NSQIP after 2012. Moreover, antibiotic receipt prior to operation have been shown to be associated with post-operative morbidity, especially those infectious in nature. However, this variable was not available in our

dataset. Another essential yet missing variable was tumor characteristics and stage, which was shown to be associated with some of our outcomes in the literature. Finally, our analysis was limited with 30-days after surgery, which is below the standard follow-up period for radical cystectomy which is 90 days. Another limitation is that the mortality rate might decrease over time because of improved medical practices. We did not adjust for it in our model because we developed a risk calculator designed for prediction. However, we overcame this limitation by comparing mortality rates across different years; this trend was not significant in our database.

While the NSQIP dataset is large and inclusive, it depends on the data provided by each institution.(Elliott et al., 2017) The dataset has missing information for several variables, while others could be inaccurately recorded. To go about the lack of some data, we assumed that the values missing are missing at random, which may be another limitation to our study. We could not verify extreme values with the raw data. In addition, although multiple imputation methods were used, imputation of missing variables might impose an additional bias to our data. In addition, despite the high power of the study, we limited our analysis to mortality and one indicator of morbidity, prolonged hospital stays, as to avoid multiple testing and increasing the change of obtaining falsely significant associations.

### *2. Strengths*

Our study has several strengths. To our knowledge, it is the first tool for the population of patients who are cleared for surgery, and it serves as an additional criterion for optimizing patient outcomes. The tool is well calibrated with moderate accuracy. It can be used while sparing the two very important resources: cost and time.

Additionally, ACS NSQIP is a large and inclusive dataset that provided our study, especially the morbidity model, with high power. Our models were very well calibrated using the Hosmer-Lemeshow goodness-of-fit. Moreover, we anticipate that our models can be of clinical use given the variables used that can be easily assessed prior to surgery such as ASA class, age and comorbidities. As aforementioned, this risk predictor can aid in individualizing patient care and in incorporating the patient in the decision-making process of his/her own management. As it may pave the way of a nonsurgical approach, it can also encourage surgery for patients who the model can see fit. Our model of morbidity, despite its poor accuracy, sheds light on several factors that increase hospital stay. Arguably, it manifests the effect of racial and social inequity on the outcomes of this surgical procedure. Our model emphasizes the importance of nutritional status, especially preoperative albumin as pre-operative factors, especially that it is not a routinely ordered lab test prior surgery.

# CHAPTER VI

# CONCLUSION

In this thesis project we developed a clinically meaningful tool to stratify patients with nonmetastatic MIBC based on preexisting comorbidities. Recently, trimodal therapy has been recommended as a category I primary treatment plan for these patients, with the alternative option being radical cystectomy. Identifying patients who are at high risk of complications from radical cystectomy can aid in the decision between both treatments and can assist in the optimal management of these patients.

We aim to implement this project through dissemination into a peer-reviewed journal. We also aim to present these findings in urology and oncology conferences. We will begin implementation locally, at the American University of Beirut Medical Center clinics. We will then expand and invite additional centers such as cancer centers in Jordan. We will collect clinical outcome data to explore the relevance of our calculator in the real-world setting and validate our findings by constructing local observational studies with variables that are deemed essential and might be missing from the ACS-NSQIP dataset.

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