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Systematic Review of Comorbidity and Competing-risks Assessments for Bladder Cancer Patients

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Comorbidity risk assessment tools for bladder cancer are increasingly being explored. While retrospective evidence supports the use of comorbidity risk assessment tools for bladder cancer, further comparative studies evaluating the effectiveness of these tools and identifying patients most likely to benefit from a treatment according to competing-risks assessment are needed.

Abstract

Context—Radical cystectomy continues to be associated with a significant risk of morbidity and all-cause mortality (ACM). Practice pattern data demonstrating underuse of surgery for patients with muscle-invasive and high-risk non–muscle invasive bladder cancer (BC) have been linked to the advanced age and higher comorbidity status of such patients, which suggests that rates of ACM as well as cancer-specific mortality should be incorporated into patient counseling and guideline recommendations.

Objective—To review the literature on risk assessment tools for preoperative comorbidity in BC that may aid in treatment decision-making.

Evidence acquisition—A systematic search was conducted using Ovid and Medline according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines to identify studies between 1970 and 2017 reporting on comorbidity risk assessment (CRA) tools for BC. Prospective and retrospective studies were included.

Evidence synthesis—There are no published randomized control trials comparing CRA tools for BC. Patients undergoing radical cystectomy with combined high-risk comorbidity and performance scores may face up to a sevenfold greater risk of other-cause mortality compared to those with low scores. The Charlson Comorbidity Index is one of the most widely studied indices for 90-d perioperative mortality and overall and cancer-specific survival, with an area under the receiver operating characteristic curve of up to 0.810. Prospective studies of CRA tools for BC have consistently shown that patients with higher comorbidity have worse outcomes. While not specific for BC, comorbidity indices provide useful assessment of competing risks. Competing-risks assessment tools are lacking, with limited studies assessing the impact of these tools on treatment decision-making by patients and providers. We provide the impetus for incorporation of comorbidity risks into practice guidelines when discussing treatment options with patients.

Conclusions—CRA tools should be incorporated into preoperative treatment counseling and the assessment of postoperative outcomes. While retrospective evidence supports the use of CRA tools for BC, further comparative studies evaluating the effectiveness of these tools and identifying the patients most likely to benefit from a treatment according to competing-risks assessment are needed.

Patient summary—In this review we explored the clinical evidence for comorbidity risk assessment tools in bladder cancer. We found evidence to support incorporation of comorbidity risks into practice guidelines when discussing treatment options with patients.

Keywords

Comorbidity; Competing risks; Bladder cancer; Models; Indices; Survival; Mortality; Review

1. Introduction

There will be an estimated 79 000 new cases and 17 000 deaths from bladder cancer in the USA in 2017 [1]. Neoadjuvant chemotherapy followed by radical cystectomy with extended pelvic lymphadenectomy is the guideline-recommended treatment for patients with muscle-invasive bladder cancer [2–4]. The European Association of Urology and the National

Comprehensive Cancer Network recommend radical cystectomy for recurrent non–muscle-invasive and muscle-invasive bladder cancer, with trimodal therapy reserved for select patients [3,5,6]. Despite these longstanding guidelines, radical cystectomy is markedly underused [7], due at least in part to the advanced age and high rate of comorbidities in bladder cancer patients. Even with the apparent selection of only a minority of patients for treatment with radical cystectomy, this surgery is associated with a perioperative mortality rate between 2% and 13% [8,9].

The concern about performing this complex surgery in patients at high risk of complications and mortality has driven providers and patients to seek alternative treatments [10,11]. These patterns of practice suggest that both cancer-specific and all-cause mortality rates should be incorporated into patient counseling and guideline recommendations [7,10]. The literature suggests that risk assessment and prediction tools may enhance clinical decision-making and counseling of patients with bladder cancer [12]. Incorporation of comorbidity into preoperative assessments may improve preoperative prediction models and lead to implementation of preoperative interventions to improve outcomes [13]. The purpose of the present study was to perform a systematic review of the literature on preoperative comorbidity assessment tools for bladder cancer that may aid in treatment decision-making. Moreover, we wanted to identify which competing-risks assessment tool would be most suitable to aid in treatment counseling.

2. Evidence acquisition

A systematic literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement to identify studies reporting on comorbidity risk assessment and bladder cancer between 1970 and 2017 [14]. A systematic review was conducted to identify studies of relevance for the predefined research questions. (1) Does comorbidity risk assessment improve outcomes in bladder cancer patients? (2) Does competing-risks assessment improve outcomes in bladder cancer patients? (3) Do bladder cancer patients with higher comorbidity and competing risks have greater complication rates and/or mortality compared to patients with lower comorbidity and competing risks? The Ovid interface of Medline was searched along with a free-text manual search using one or several combinations of the following items: (“bladder”) AND (“cancer” OR “carcinoma” OR “tumour” OR “tumor” OR “neoplasm” OR “malignancy” OR “mass”) AND (“localized” OR “metastatic” OR “metastasis”) AND (“comorbidity” OR “coexisting disease” OR “concomitant disease”). All selected articles were further searched to identify additional relevant articles. A total of 856 studies were initially identified. The selection process was conducted in three stages. The first stage involved initial screening of the title to identify eligible publications, including a search of publications in journals not listed in Medline to avoid missing any eligible study. In the second stage, publications were screened for eligibility according to the abstracts. The third stage comprised full-text reading of the articles. For this systematic review, we excluded: (1) non-English articles, (2) review articles (without systematic review or meta-analysis), (3) editorial reports and case reports, and (4) repeated publications to avoid publication bias. We decided to exclude review articles as the interpretation of published results without systematic assessment or meta-analysis of data

does not offer significant novel insights into comorbidity risk assessment in relation to bladder cancer.

A total of 36 papers were finally considered for evidence synthesis (Table 1). Notably, these studies are retrospective and therefore inevitably inherit the risk of selection bias for which this review cannot control. A Consolidated Standards of Reporting Trials diagram is provided in Figure 1.

3. Evidence synthesis

3.1. Comorbidity and bladder cancer

3.1.1. Measures of comorbidity—Cancer patients often have comorbidities that may impact treatment decision-making, prognosis, and survival outcomes [15]. The comorbidity severity strongly influences survival in a dose-dependent fashion independent of cancer stage [15]. Bladder cancer patients present with significant competing risks, as patients are often elderly and/or have coexisting diseases that impact morbidity and mortality [7,10,16]. Radical cystectomy is associated with a significant risk of morbidity and mortality, with 5-yr overall and cancer-specific survival rates reported as approximately 50–60% and 60–70%, respectively [10,17–19]. Therefore, comorbidity and competing risks must be balanced with the benefits of treatment and inherent risks of surgery.

Individual comorbidities and combined comorbidity indices have been assessed for their ability to predict survival in bladder cancer patients undergoing radical cystectomy. Importantly, however, none of these comorbidity indices are exclusive to bladder cancer. These indices include the American Society of Anesthesiology (ASA) score, Adult Comorbidity Evaluation 27 (ACE-27) score, Charlson Comorbidity Index (CCI), Eastern Cooperative Oncology Group performance score (ECOG PS), Karnofsky Performance Status (KPS) scale, and the Elixhauser Index (EI).

The ASA score, which ranges from 1 (healthy) to 6 (brain dead), is the oldest evaluation score that assesses perioperative risk at the time of surgery. It was developed to predict mortality following general anesthesia and has been used as a method of estimating comorbidity in patients undergoing cancer surgery [19]. The ACE-27 is a 27-item comorbidity instrument validated for adult oncology patients enrolled in a hospital-based cancer registry [15]. The ACE-27 comprises 27 conditions classified into three grades according to severity, and has been extensively studied in numerous cancer types. The CCI was initially described in 1987 for general medical patients and has been converted into an age-adjusted index and the Klabunde modification using administrative claims data [20,21]. Indeed, the CCI is the most cited and most applied comorbidity index in the literature, including use in bladder cancer.

The ECOG PS is a classification of the performance status of cancer patients and runs from 0 to 5, with ECOG PS 0 describing full activity and ECOG PS 5 being equal to death [22]. Interestingly, the ECOG PS does not take any comorbidity into account, but rather only physical activity. The KPS, originally developed in 1948, was designed to measure the level of patient activity and medical care requirements among cancer patients and is a general

measure of patient independence [23]. As with ECOG PS, KPS (measured on a scale from 0 = dead to 100 = normal, no complaints, no evidence of disease) does not measure comorbidity, but rather performance activity. The EI, similar to the Klabunde modification of the CCI, is a comprehensive set of 30 comorbidity measures for use with administrative data [24]. Unlike the CCI, the EI includes mental disorders, drug and alcohol abuse, obesity, coagulopathy, weight loss, and fluid and electrolyte disorders.

3.1.2 Comorbidity indices used to predict complications—It has been reported that up to 80% of patients experience a complication following radical cystectomy (open and robotic). Higher comorbidity rates have been associated with higher frequency and severity of perioperative complications [25,26]. While standardized reporting of complications using the five-grade and ten-domain modification of the Clavien-Dindo classification system is now commonplace when reporting complications, use of comorbidity indices remains heterogeneous when reporting associations and predicting which patients may be at greatest risk [26].

In one the earliest reports comparing the ASA score to complication risk, Malavaud et al [27] reported that an ASA score ≥3 was independently associated with a higher risk of major complications (odds ratio [OR] 5.7; $p < 0.01$; Table 1). Novotny et al [28] also found that patients with an ASA score of ≥3 versus ≤2 were significantly more likely to experience a postoperative complication following radical cystectomy (37% vs 25%; $p < 0.05$). Bostrom et al [29] studied 258 patients who underwent radical cystectomy and similarly identified ASA score ≥3 as an independent risk factor for major complications (OR 3.25, 95% confidence interval [CI] 1.08–9.74). Further, in a study comparing the associations of ASA score and CCI with the risk of complications, Roghmann et al [30] found that CCI ≥3 (OR 1.93) was associated with overall complications, while CCI ≥3 (OR 1.86) and ASA score ≥3 (OR 1.92) were associated with high-grade complications. In another study assessing the correlation between ACE-27 and perioperative complications, Fairey et al [9] noted that moderate and severe comorbidity were associated with any early postoperative complications (moderate: OR 5.2; $p < 0.001$; severe: OR 7.0; $p < 0.001$), major early postoperative complications (moderate: OR 11.4; $p < 0.001$; severe: OR 15.2; $p < 0.001$), and minor early postoperative complications (moderate: OR 2.1; $p = 0.019$; severe: OR 2.2; $p = 0.038$). Higher-severity comorbidity as assessed via the ACE-27 was independently associated with a higher risk of early postoperative complications after radical cystectomy.

The American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) developed a generalizable surgical risk estimation tool (http://riskcalculator.facs.org) to provide risk estimates [31]. Variables used in the ACS NSQIP include age, sex, ASA score, functional status, and individual comorbidities. The tool exhibited excellent performance for mortality (*c*-statistic 0.944), morbidity (*c*-statistic 0.816), and complications (*c*-statistics >0.8) [31]. Golan et al [32] evaluated the ACS NSQIP tool in patients undergoing radical cystectomy. The universal ACS NSQIP calculator poorly predicted most postoperative complications by 10–81%, regardless of the urinary diversion type, suggesting the need for a procedure-specific risk calculator to better counsel cystectomy patients in the preoperative setting [32].

3.1.3. Comorbidity indices used to predict perioperative mortality—In one of the first studies to assess the impact of comorbidity on perioperative mortality, Fairey et al [9] evaluated the associations between age, comorbidity status according to ACE-27, and survival outcomes following radical cystectomy (Table 2). In multivariable logistic regression analysis, age was not associated with 90-d mortality. However, multivariable analysis adjusted for age and surgeon procedure volume demonstrated that severe comorbidity status (ACE-27 severe) compared to no or mild comorbidity was associated with a significantly higher risk of 90-d mortality (odds ratio [OR] 6.4, 95% CI 1.1–66.4; $p = 0.03$).

Mayr et al [33] compared the associations of ACE-27, CCI, ECOG PS, and ASA score with the risk of 90-d perioperative mortality among 555 patients who underwent radical cystectomy. All four indices were significantly associated with perioperative mortality, with ACE-27 (OR 1.72; $p = 0.004$; area under the receiver operating characteristic curve [AUC] 0.761) and ASA score (OR 2.19; $p = 0.004$; AUC 0.761) having the strongest correlation. The authors concluded that the ASA score is the preferred method for assessing perioperative mortality risk because of its ease of use and incorporation at the time of surgery. Eisenberg et al [10] similarly assessed the ability of the ASA score, CCI, EI, and ECOG PS to predict 90-d perioperative mortality following radical cystectomy and noted that ASA score (OR 3.17; $p = 0.001$), ECOG PS (OR 2.4; $p < 0.0001$), and EI (OR 1.48; $p = 0.002$) were significantly associated with mortality.

Dell'Oglio et al [34] recently determined the feasibility of creating a short-form CCI to assess 90-d mortality following radical cystectomy. Within the development cohort, the most parsimonious and informative model resulted in inclusion of three of the 17 (17.6%) original comorbid condition groupings: congestive heart failure, cerebrovascular disease, and chronic pulmonary disease. Within the validation cohort, the accuracy was 68.4% for CCI versus 69.7% for the short-form CCI (Table 2).

3.1.4. Comorbidity indices used to predict overall and bladder cancer–specific survival—Overall and cancer-specific survival outcomes following radical cystectomy have remained unaltered over the last three decades, with 5-yr overall survival between 50% and 60% [17,19,35]. Numerous studies have confirmed the association between comorbidity status and survival outcomes following radical cystectomy [9,10,17,19,36–46]. However, no comorbidity index has demonstrated superiority in predicting survival outcomes.

Megwalu et al [47] used the ACE-27 in one of the first studies to assess the impact of comorbidity on survival outcomes (Table 3). On multivariable analysis for 675 patients with newly diagnosed bladder cancer, comorbidity ($p = 0.0001$), tumor stage ($p = 0.0001$), age ($p = 0.0001$), and race ($p = 0.0045$) were significantly associated with overall survival. On analysis of the subset of patients who underwent cystectomy, comorbidity ($p = 0.0053$), stage ($p = 0.0001$), and race ($p = 0.0449$) significantly predicted overall survival. Several studies have confirmed that CCI, age-adjusted CCI, and ACE-27 are independently associated with survival outcomes, suggesting that comorbidity should be considered when comparing outcomes after radical cystectomy [17,41].

Comorbidity indices have also been compared against one another to assess their relative association with survival outcomes. For example, Mayr et al [19] evaluated the correlation of ACE-27, CCI, age-adjusted CCI, ECOG PS, and ASA score with survival. All the indices were independently associated with cancer-independent but not with cancer-specific mortality. The ASA score was the only index that significantly increased the predictive accuracy of the predefined cancer independent model (+2.3%; $p = 0.045$), and was thereby suggested as the instrument of choice.

A separate study by Eisenberg et al [10] investigated the comparative prognostic ability of CCI, ECOG PS, EI, and ASA score with regard to 5-yr all-cause mortality following radical cystectomy. CCI (hazard ratio [HR] 1.23; $p < 0.0001$), EI (HR 1.28; $p < 0.0001$), ASA score (HR 1.44; $p = 0.007$), and ECOG PS (HR 1.97; $p < 0.0001$) were independent predictors of 5-yr all-cause mortality. Moreover, CCI (AUC 0.798; $p < 0.0001$), EI (AUC 0.770; $p = 0.03$), and ECOG PS (AUC 0.769; $p = 0.03$) significantly enhanced the performance of a base model that did not include comorbidity status (AUC 0.757) in predicting 5-yr all-cause mortality.

Miller et al [45] assessed the impact of concurrent medical disease on tumor control and survival following radical cystectomy. As expected, CCI was significantly associated with lower disease-specific ($p = 0.049$) and overall ($p = 0.016$) survival. Interestingly, in their multivariate model, CCI was independently associated with lower cancer-specific survival ($p = 0.049$) and a higher risk of extravesical disease ($p = 0.033$), suggesting that comorbid illness may be associated with adverse pathologic outcomes.

Froehner et al [46] identified age, angina pectoris, chronic lung disease, diabetes mellitus, current smoking, ASA score 3–4, and male sex as independent predictors of competing mortality in 932 consecutive patients who underwent radical cystectomy at a single institution. Similar to other single-institution series, bladder cancer was the cause of death when uncontrolled disease progression was present at the time of death. Deaths in the absence of uncontrolled bladder cancer were considered deaths from competing causes. The combined mortality index was superior to the age-adjusted CCI and Lee Mortality Index (LMI), which stratifies patients into risk groups, with 0% 10-yr competing mortality in the lowest and approximately 50% in the highest-risk classes [46].

3.2. Comorbidity risk assessment tools for bladder cancer

Comorbidity indices have been examined to discern associations with complications and survival outcomes. Based on this understanding, prognostic models using these indices have been developed into nomograms and calculators for predicting outcomes. While several prognostic models have been developed, these tools have largely relied on pathological characteristics [13,48,49]. The association between comorbidity and outcomes after radical cystectomy using patient, tumor, and treatment factors has been evaluated using a variety of predictive models. As highlighted by Taylor et al [50], models incorporating only age and CCI have yielded similar discrepancy in predicting survival outcomes following radical cystectomy to that of models developed from pathologic characteristics alone (Isbarn nomogram). Thus, the exclusion of important preoperative comorbidity variables probably limits the performance characteristics of nomograms designed to predict outcome after

radical cystectomy. Furthermore, some nomograms have limited utility in the preoperative setting because of their dependence on postoperative pathological stage [50].

In the only study to incorporate the ACE-27, Fairey et al [17] found that severe comorbidity (ACE-27 severe) compared to no or mild comorbidity was independently associated with overall survival (moderate: HR 1.59, 95% CI 1.16–2.18; $p = 0.004$; severe: HR 1.83, 95% CI 1.22–2.72; $p = 0.003$) and bladder cancer–specific survival (moderate: HR 1.50, 95% CI 1.04–2.15; $p = 0.028$; severe: HR 1.65, 95% CI 1.04–2.62; $p = 0.034$; Table 4) [17]. Of note, the authors found higher 90-d postoperative mortality from the same center [9] which could contribute to the worse overall survival observed in this study [17]. While these results were not converted into a graphical aid, this study was one of the first to show that incorporation of a comorbidity index aids in prediction of overall and cancer-specific mortality.

A majority of predictive tools have used the CCI as a proxy for assessing comorbidity using either large single-center or nationwide cancer registry data sets. Eisenberg et al [10] used clinicopathological variables, including the CCI and ECOG PS, associated with radical cystectomy outcomes to develop the SPARC (Survival Prediction After Radical Cystectomy) score to predict bladder cancer–specific mortality. On multivariate analysis, CCI (HR 1.8; $p < 0.0001$) and ECOG PS (HR 1.9; $p < 0.0001$) were significantly associated with bladder cancer–specific mortality. The cumulative scores for these variables in stratifying patients into risk groups had estimated 5-yr cancer-specific survival of 95%, 80%, 60%, 38%, and 23% for groups with the lowest to highest risk, respectively ($p < 0.001$). Bootstrap internal validation of the model had a concordance index of 0.75. Froehner et al [37] used the LMI [51] developed in the Health and Retirement Study to assess comorbidity for older adults undergoing radical cystectomy. The LMI applies risk points for age, male sex, current tobacco use, body mass index <25 kg/m^2, diabetes mellitus, non-skin cancers, chronic lung disease, congestive heart failure, and four functional categories [51]. Beside the age-adjusted CCI, the LMI was an independent predictor of overall mortality (HR per unit increase 1.06; $p = 0.042$) and replaced the age-adjusted CCI as a predictor of competing mortality (HR per unit increase 1.27; $p < 0.001$). The authors concluded that the LMI was at least comparable to the age-adjusted CCI as a predictor of mortality after radical cystectomy. Morgan et al [52] developed a nomogram using the CCI and serum albumin to predict 90-d mortality among 220 patients following radical cystectomy ($n = 28$ died) at the University of Michigan. The model *c*-index was 0.75, and after 200 bootstrap resamples for internal validation the adjusted *c*-index was 0.71. This model used albumin and highlights the potential importance of using such nutritional/laboratory parameters in comorbidity assessments and risk stratification.

Comorbidity assessment tools have been developed using large population-based cancer registries. Abdollah et al [53] divided radical cystectomy patients in Nationwide Inpatient Sample (NIS) into discovery and validation cohorts to develop a model for predicting in-hospital postoperative mortality. Mortality increased with age (≤59 yr 0.6%, 60–69 yr 1.6%, 70–79 yr 3.1%, ≥80 yr 4.6%; $p < 0.001$) and CCI (CCI 0 1.7%, CCI 1 3.0%, CCI 2 4.2%, CCI 3 4.3%, CCI ≥4 12.1%; $p < 0.001$). A reference table was developed and validated using the NIS validation cohort and had an AUC of 70%. Most recently, Williams et al [54] developed and validated a nomogram predicting 3-yr and 5-yr overall and all-cause mortality

following radical cystectomy using Surveillance, Epidemiology and End Results-Medicare (n = 5325) and Texas Cancer Registry-Medicare (n = 1257) linked data. Comorbidity was assessed using the Klabunde modification of the CCI [21]. The nomogram predicted 3-yr and 5-yr overall and cancer-specific survival rates with concordance indices of 0.65 and 0.66, respectively, in the validation Texas Cancer Registry-Medicare cohort. This generalizable instrument has been converted into an online instrument called the Radical Cystectomy Survival Calculator available at www.utmb.edu.libux.utmb.edu/surgery/urology/RCSC.asp (Table 1).

3.3. Is there a need for a bladder cancer–specific comorbidity index?

It has been shown that cancer-specific comorbidity indices impact the prediction of outcomes in patients with other cancers [55]. All of the current indices reported for bladder cancer patients as described above are either not specific for cancer or do not incorporate comorbidities, which may limit their impact in the bladder cancer population. Clinicians must strive to gain a more precise understanding of the comorbidity risk profile among bladder cancer patients and its corresponding impact on outcomes. Moreover, given that the majority of patients are elderly with higher comorbidity compounded by the significant risk of morbidity and mortality of treatments, a bladder cancer–specific comorbidity index may have a more profound impact when compared to other cancer-specific indices.

3.4. Other measures of comorbidity to consider

While advanced age has been associated with adverse postoperative outcomes following surgery, studies have identified sarcopenia and patient frailty as potentially more accurate predictors of adverse postoperative outcomes [56,57]. Sarcopenia is defined as severe muscle-wasting according to sex-specific skeletal muscle index definitions based on 2 × standard deviations below the norm that is reproducible on axial computed tomography imaging [58]. The presence of sarcopenia among radical cystectomy patients was independently associated with worse cancer-specific and all-cause mortality [57]. Frailty can be defined as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss (10 lbs in the previous year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity [59]. Frailty incorporates functional status and medical comorbidities [60]. It has been demonstrated that patients who are frail are more likely to experience major in-hospital complications and worse survival [56,61,62]. Chappidi et al [56] found that higher frailty as measured with the modified frailty index was an independent predictor of high-grade (Clavien grade 4 or 5) complications (OR 2.58, 95% CI 1.47–4.55) among patients undergoing radical cystectomy.

It has been found that nutritional status, including preoperative serum albumin, enhances the performance of comorbidity indices in predicting survival [52]. Immunonutrition, which includes arginine-enriched supplements administered perioperatively to ameliorate complications and improve outcomes, is being extensively studied [63]. Arginine deficiency induced by surgery impairs lymphocyte proliferation and T-cell receptor integrity, which lower resistance to infection [63]. Thus, improving immune function via immunonutrition may modulate the immune response to surgery. A recent study among patients who received immunonutrition revealed reductions of 33% in postoperative complication rates (95% CI 1–

64%; $p = 0.060$) and 39% in infection rates (95% CI 8–70%; $p = 0.027$) [63]. Other potential markers of comorbidity and malnutrition may include preoperative serum arginine, asymmetric dimethylarginine, and L-citrulline, which have been associated with adverse outcomes following surgery [64]. Myeloid-derived suppressor cells (MDSCs) in blood, which suppress T cells and lower resistance to infection, may serve as a marker for patients at greater risk of adverse outcomes [63]. MDSC numbers decrease following immunonutrition.

3.5. Is there a role for incorporation of comorbidity assessment into practice guidelines for bladder cancer?

There is greater awareness of comorbidity and competing-risks assessments for bladder cancer patients and their impact on prognosis and treatment decision-making. For patients with prostate cancer and many other cancers, competing-risks assessment has been incorporated into guideline recommendations [65,66], thereby increasing awareness of the important relationship between comorbidity and cancer treatment and outcomes. Bladder cancer has markedly higher mortality once it invades the muscle and some would argue that treatment regardless of comorbidity should be the mainstay. However, the delivery of different treatment modalities in a risk-adapted fashion may be a more appropriate approach when counseling patients. Thorough patient counseling that includes the risks and benefits of treatment in the context of disease characteristics and patient factors including comorbidities may aid in treatment decision-making. While prior generalizable and bladder cancer–specific tools have been developed for the postoperative setting [10,17,31,37,50,52,53], clinical applicability in the preoperative setting remains to be determined. As demonstrated with the universal ACS NSQIP tool, we need to develop bladder cancer–specific tools for better risk-adapted strategies for our patients. Moreover, as we move towards precision-based care at the molecular level, we must also recognize the potential of comorbidity indices and decision aids in improving treatment decision-making and outcomes.

4. Conclusions

To improve outcomes for our patients, we believe that comorbidity risk assessment tools should be incorporated into both preoperative treatment counseling and assessment of postoperative outcomes. Currently there are two tools: the ASA score, which is the preferred method for assessing the risk of complications and perioperative mortality because of its ease of use and incorporation at the time of surgery; and the CCI, which is the most widely studied index used to predict overall and cancer-specific survival. The CCI has been incorporated into comorbidity risk assessment tools including nomograms and calculators to aid in treatment counseling. While retrospective evidence supports the use of comorbidity risk assessment tools for bladder cancer, prospective comparative studies evaluating the effectiveness of these tools are needed and are being developed by our group.

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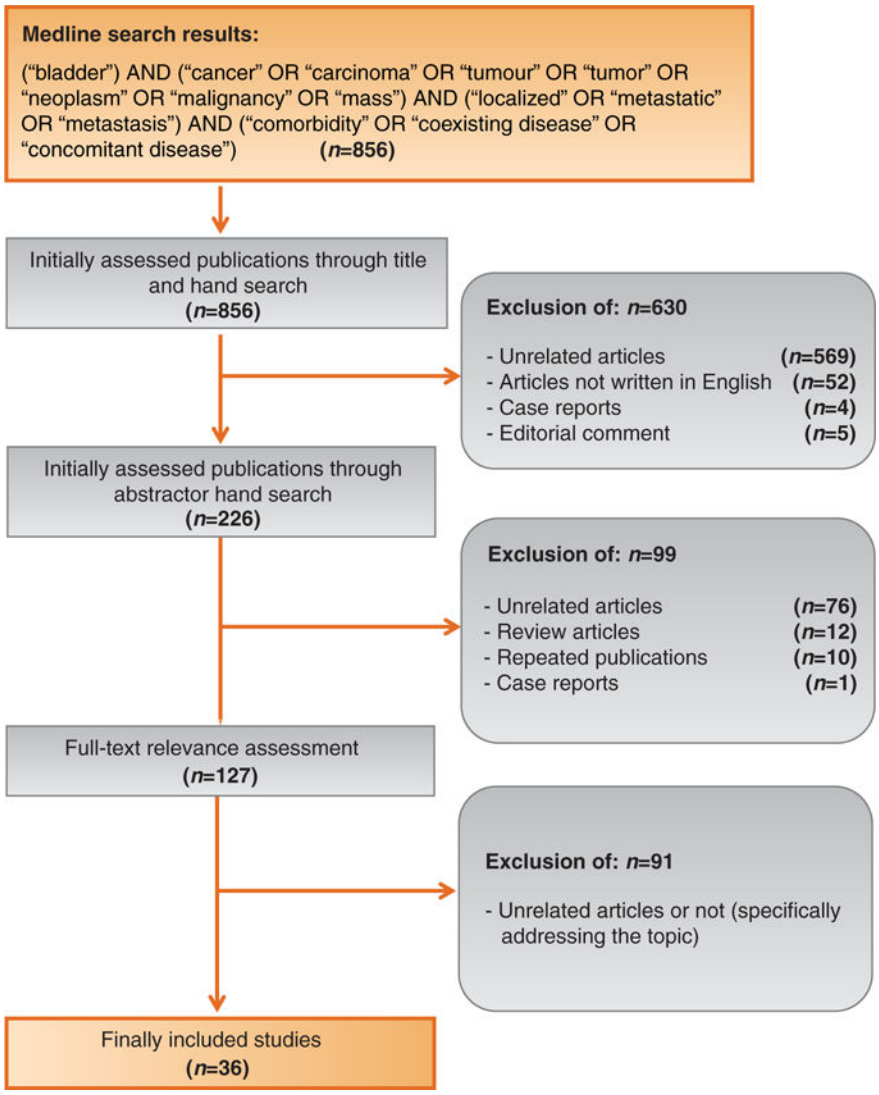

Figure 1.

This Consolidated Standards of Reporting Trials diagram outlines the selection process of the included studies.

Table 1

Overview of comorbidity indices used to predict complications

Study	Sample size		Median	CI	Hazard ratio			Odds ratio for complications	AUC
	Total	RC	FU		90-d mortality	OCM	CSM		
Malavaud 2001 [27]	161	161	NR	ASA	NR	NR	NR	5.7	NR
Novotny 2012 [28]	830	830	NR	ASA	NR	NR	NR	NR	0.609
Bostrom 2009 [29]	258	258	NR	ASA	NR	NR	NR	3.25 [1.08–9.74]	NR
Roghmann 2014 [30]	535	535	NR	CCI ASA	NR	NR	NR	Overall complications: CCI 1.93 High grade complications: CCI 1.86; ASA 1.92	NR
Fairey, 2008 [9]	314	314	NR	ACE-27	ACE-27 severe: 6.4	NR	NR	Overall complications: 5.2–7.0 High-grade complications: 11.4–15.2	NR

ACE-27 = Adult Comorbidity Evaluation 27 score; ASA = American Society of Anesthesiology score; AUC = area under the receiver operating characteristic curve; CI = comorbidity index; CCI = Charlson CI; CSM = cancer-specific mortality; FU = follow-up; NR = not recorded; OCM = other-cause mortality; RC = radical cystectomy.

Table 2

Overview of comorbidity indices used to predict perioperative mortality

Study	Sample size		Median FU (yr)	CI	Hazard ratio			Odds ratio for complications	AUC
	Total	RC			90-d mortality	OCM	CSM		
Fairey 2008 [9]	314	314	NR	ACE-27	ACE-27 (severe): 6.4	NR	`NR	Overall: 5.2–7.0 HG: 11.4–15.2	
Mayr 2012 [19]	555	555	NR	ACE-27, CCI, ACCI, ECOG, ASA	ACE-27: 1.72 ASA: 2.19	ASA 3–4: 1.59 ECOG 2–3: 2.02 ACE-27 2–3: 2.1 ACE-27 3: 1.55 CCI >2: 1.29 ACCI >5: 1.61	ASA 3–4: 2.70 ECOG 2–3: 3.07 ACE-27 2–3: 2.83 ACE-27 3: 2.65 CCI >2: 2.15 ACCI >5: 3.52	NR	ACE-27: 0.761 ASA: 0.761
Boorjian 2013 [35]	891	891	10.1	ASA, CCI, EI, ECOG	ASA: 3.17 ECOG: 2.4 EI: 1.48	ASA: 1.44 ECOG: 1.97	NR	NR	CCI: 0.798 EI: 0.770 ECOG: 0.769
Dell'Oglio 2017 [34]	7076	7076	NR	CCI, SF-CCI	NR	NR	NR	NR	CCI: 0.684 SF-CCI: 0.697

ACE-27 = Adult Comorbidity Evaluation 27 score; ACCI = age-adjusted CCI; ASA = American Society of Anesthesiology score; AUC = area under the receiver operating characteristic curve; CCI = Charlson CI; CI = comorbidity index; CSM = cancer-specific mortality; ECOG = Eastern Cooperative Oncology Group performance score; EI = Elixhauser Index; FU = follow-up; HG = high grade; NR = not recorded; OCM = other-cause mortality; RC = radical cystectomy; SF-CCI = short-form CCI.

Table 3

Overview of comorbidity indices used to predict overall and bladder cancer–specific survival

Study	Sample size		Median FU	CI	Hazard ratio			ORC	AUC
	Total	RC			90-d mortality	OCM	CSM		
Megwalu 2008 [47]	675	210	45 mo	ACE-27	NR	Overall: 1.39 RC: 1.36	NR	NR	Bootstrap: 0.636 (overall)
Mayr 2012 [19]	555	555	28 mo	ACE-27, CCI, ACCI, ECOG, ASA	NR	>75 yr or ASA 3–4 and ACE-27 >1: 3.34 >75 yr and ASA 3–4 and ACE-27 >1: 6.89	No significant predictors	NR	0.810
Boorjian 2013 [35]	891	891	10.1 yr	ASA, CCI, EI, ECOG	ASA: 3.17 ECOG: 2.4 EI: 1.48	ASA: 1.44 ECOG: 1.97	NR	NR	CCI: 0.798 EI: 0.770 ECOG: 0.769
Miller 2003 [45]	106	106	3.2 yr	CCI	NR	1.26	1.26	NR	NR
Froehner 2017 [46]	932	932	7.0 yr	ASA	NR	ASA 3–4: 1.74	NR	NR	NR

ACE-27 = Adult Comorbidity Evaluation 27 score; ACCI = age-adjusted CCI; ASA: American Society of Anesthesiology score; AUC = area under the receiver operating characteristic curve; CCI = Charlson CI; CI = comorbidity index; CSM = cancer-specific mortality; ECOG = Eastern Cooperative Oncology Group performance score; EI = Elixhauser Index; FU = follow-up; NR = not recorded; OCM = other-cause mortality; ORC = odds ratio for complications; RC = radical cystectomy.

Table 4

Overview of comorbidity risk assessment tools for bladder cancer

Study	Sample size		Median FU	CI	Hazard ratio			ORC	AUC
	Total	RC			90-d mortality	OCM	CSM		
Taylor 2012 [11]	1141	1141	NR	CCI	NR	NR	NR	NR	Bootstrap: 0.702
Fairey 2009 [17]	523	523	31 mo	ACE-27	NR	ACE-27 moderate: 1.59; severe: 1.83	ACE-27 moderate: 1.50; severe: 1.65	NR	NR
Eisenberg 2013 [10]	2403	2403	10.5 yr	CCI, ECOG	NR	CCI: 1.73 ECOG: 1.51	CCI: 1.16 ECOG: 1.34	NR	Bootstrap: 0.75
Froehner 2015 [37]	735	735	7.8 yr	LMI	NR	1.06	NR	NR	NR
Morgan 2011 [52]	220	220	NR	CCI	1.30 (NS)	NR	NR	NR	Model: 0.75 Bootstrap: 0.71
Abdollah 2012 [53]	12 274	12 274	NR	CCI	CCI 3 vs 1: 2.86	NR	NR	NR	0.70
Williams 2017 [54]	6582	6582	NR	CCI	NR	OS CCI 3 vs 1: 2.71	CSS, CCI 3 v 1: 1.17	NR	OS: 0.65 CSS: 0.66

ACE-27 = Adult Comorbidity Evaluation 27 score; AUC = area under the receiver operating characteristic curve; CCI = Charlson CI; CI = comorbidity index; CSM = cancer-specific mortality; CSS = cancer-specific survival; ECOG = Eastern Cooperative Oncology Group performance score; FU = follow-up; LMI = Lee Mortality Index; NR = not recorded; NS = not significant; OCM = other-cause mortality; ORC = odds ratio for complications; OS = overall survival; RC = radical cystectomy.