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SYSTEMATIC REVIEW

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Mortality prediction models after radical cystectomy for bladder tumour: A systematic review and critical appraisal

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Abstract

Introduction: To identify risk-predictive models for bladder-specific cancer mortality in patients undergoing radical cystectomy and assess their clinical utility and risk of bias.

Methods: Systematic review (CRD42021224626:PROSPERO) in Medline and EMBASE (from their creation until 31/10/2021) was screened to include articles focused on the development and internal validation of a predictive model of specific cancer mortality in patients undergoing radical cystectomy. CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) and Prediction model Risk Of Bias ASsessment Tool (PROBAST) were applied.

Results: Nineteen observational studies were included. The main predictors were sociodemographic variables, such as age (18 studies, 94.7%) and sex (17, 89.5% studies), tumour characteristics (TNM stage (18 studies, 94.7%), histological subtype/grade (15 studies, 78.9%), lymphovascular invasion (10 studies, 52.6%) and treatment with chemotherapy (13 studies, 68.4%). C-index values were presented in 14 studies. The overall risk of bias assessed using PROBAST led to 100% of studies being classified as high risk (the analysis domain was rated to be at high risk of bias in all the studies), and 52.6% showed low applicability. Only 5 studies (26.3%) included an external validation and 2 (10.5%) included a prospective study design.

Conclusions: Using clinical predictors to assess the risk of bladder-specific cancer mortality is a feasibility alternative. However, the studies showed a high risk of bias and their applicability is uncertain. Studies should improve the conducting and reporting, and subsequent external validation studies should be developed.

KEYWORDS
models, mortality, nomograms, radical cystectomy, urinary bladder neoplasms

Abbreviations: CHARMS, CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies; CSS, Cancer-specific survival; EPV, Events per variable; KI, Kappa index; LVI, Lymphovascular invasion; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROBAST, Prediction Model Risk Of Bias Assessment Tool; SIGN, The Scottish Intercollegiate Guidelines Network Grading Review Group; UBC, Urothelial bladder carcinoma.

1 | INTRODUCTION

Urothelial bladder carcinoma (UBC) is the most common type of bladder neoplasia. It is associated with smoking (causing about 50% of cases) and environmental risk factors such as occupational exposure to toxic products.[1–3] According to GLOBOCAN data, in 2020 bladder carcinoma was the fifth most common tumour in Europe.[4,5]

Urothelial bladder carcinoma is classified into superficial (non-muscle-invasive) or infiltrative (muscle-invasive) tumour based on whether or not they involve the muscular layer of the bladder. Most of the UBC (75%) are non-muscle-invasive, with a high recurrence rate but a low rate of progression and mortality.[1,3] The remainder are muscle-invasive (T2-T4) and result in higher morbidity and mortality, with 5-year cancer-specific survival ranging from 23.5% to 65% depending on the study.[3,6,7] The standard treatment for nonmetastatic muscle-invasive UBC is radical cystectomy preceded by neoadjuvant chemotherapy.[3] However, radical cystectomy is associated with high morbidity and mortality, with complication rates ranging from 25% to 35% and perioperative mortality rates ranging from 0.7% to 11%.[8]

In addition to tumour stage, there are other prognostic factors for mortality in patients with UBC, such as age, sex, positive margins, lymphovascular invasion (LVI), and neoadjuvant and adjuvant treatments.[9–15] UBC is therefore a heterogeneous disease with a variable clinical course. Prediction models can be useful tools to assess each patient's individualized risk and the treatment to be applied to achieve maximum oncologic efficacy with the least possible comorbidity.[16]

Predictive mortality models, which incorporate relevant prognostic factors, may determine a patient's individual risk of death. They are often presented in the form of intuitive graphs, mathematical formulas, or risk groups that facilitate their use.[17] However, predictive mortality models can have a high risk of bias and often lack independent external validation, limiting their applicability to clinical practice.[18] This is why in 2014 the 'CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies' (CHARMS) was developed as a guideline to develop systematic reviews of predictive models.[19] Five years later, Prediction Model Risk Of Bias Assessment Tool (PROBAST) was published to assess the clinical applicability and risk of bias of prediction models, based on the results obtained from a CHARMS review.[20,21] Both tools have been widely used in several diseases, showing limitations and difficulty of models to be applied in clinical practice when they have biases.[22–24]

As far as we know, no systematic review of prediction models of UBC mortality has been carried out with the application of CHARMS and PROBAST.[19–21] Hence, a summary of the existing models is lacking, including the description of the risk of bias in each model, to allow clinicians to better stratify the mortality risk of these patients.

Consequently, the objective of this study is to systematically review the available evidence focused on predictive models of cancer-specific mortality in patients with UBC undergoing radical cystectomy, to evaluate their main characteristics and to assess the risk of bias and clinical applicability.

2 | METHODS

2.1 | Study design and literature search

This systematic review was performed following a prespecified protocol (registered in the PROSPERO database, CRD42021224626), and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[25]

We included original studies in English, Spanish or Portuguese describing the development and internal validation of a multivariable predictive model for cancer-specific mortality in patients with UBC who underwent or were candidates for radical cystectomy. We also included studies that carried out external validation in the same study. We considered studies that predicted mortality in short, medium and long term. Review articles, studies evaluating recurrence or all-cause mortality, and those performing external validation only or using clinical markers not available in clinical practice (genetic or biomarker analysis) were excluded.

A literature search was performed in the MEDLINE (through PubMed) and EMBASE databases, including all studies published since their creation until 10/31/2021, using the following descriptors: 1) Related to cancer: bladder cancer and bladder neoplasms; 2) Related to predictive models: nomograms, predictive models, scoring system, points system, risk score and prediction model; 3) Related to the outcome: mortality, recurrence, death, prognosis and survival. The complete search equations are included in Appendix S1.

Titles and abstracts were reviewed independently by two researchers (PS-S and LM-C). To validate the inclusion of the articles, the concordance between authors was assessed (kappa index (KI)), which had to be greater than 0.60.[26]If this condition was met, possible discrepancies were resolved by consensus among all the authors of the review. Once the abstracts were selected, the same procedure was replicated for the full text of the articles selected in the previous step. In addition, to reduce the possibility of publication bias, a manual search was performed using

the bibliographic references of the models selected for the review. According to previous evidence,[27] we also search for and include grey literature through three strategies: search in grey literature databases, searches in clinical trial registers, and searches in conference proceedings.

2.2 | Data extraction

Variables were extracted according to the 11 items in the CHARMS checklist,[19] to identify potential sources of bias, organize information, and identify relevant information used to evaluate prediction modelling studies. Two of the authors (PS-S and LM-C) reviewed the studies independently according to CHARMS, and disagreements were resolved by discussion and consensus with a third author.[19] To validate the concordance between authors in the CHARMS items, the KI was used, which had to be >0.60.[26]

Aspects related to the risk of bias were analysed using the PROBAST tool,[19–21] which assesses the presence of systematic errors and the applicability of predictive models. Risk of bias is analysed in four domains (participants, predictors, outcome and analysis) and applicability in three (participants, predictors and outcome). These refer to the patients selected, how the predictors are handled and their timing in the measurement, how the outcome is measured and whether the statistical analysis has been performed correctly. Each domain has a number of items, in which the PROBAST statement itself gives guidelines for assessment,[20,21] categorizing each of them into 'yes', 'partly yes', 'no', 'partly no' and 'no information'. Based on the response to all items, the domain is categorized as 'low', 'high' or 'unclear' risk of bias and 'low', 'high' or 'unclear' concern regarding applicability. After the assessment of all domains, an overall evaluation is arrived at, which follows the principle of 'the worst score counts', whereby the worst score of all domains is obtained. The KI was also used among the authors to assess concordance.[26]

The Scottish Intercollegiate Guidelines Network Grading Review Group (SIGN) recommendations were used to assess the level of recommendation and level of evidence.[28]

The PROBAST and SIGN assessments followed the same procedure previously defined for the CHARMS application, in which two independent investigators assessed each of the studies.

2.3 | Statistical analysis

A descriptive analysis of the CHARMS and PROBAST items was carried out,[20,21,29] detailing frequencies and percentages of the characteristics of the models and of the assessment of the domains.

3 | RESULTS

3.1 | Results of literature search

Figure 1 shows the flow diagram of the systematic review. A total of 3544 citations were screened (1382 from MEDLINE, 2160 in EMBASE, and 2 via grey literature search) and 29 studies were selected for full-text analysis. Of these, 19 studies met the inclusion criteria.[6,9–13,15,30–41]

3.2 | Consistency among observers

The concordance between the evaluators for the inclusion of the selected studies (KI) was 77.02% ($p = .001\%$). The KI between authors was 73.68% ($p < .001\%$) for CHARMS and 93.98% ($p < .001\%$) for PROBAST.

3.3 | Characteristics of the studies according to CHARMS

Tables S1-S7 show the analysis of the 11 CHARMS domains in full detail.

Most of the studies were retrospective (17, 89.5%)[6,9–13,15,30,32,34–38,40,41] and only 2 (10.5%) were prospective.[31,33] The studies included mainly patients who underwent radical cystectomy for bladder tumour, M0; one study included patients with neoadjuvant chemotherapy,[15] another included T1-3N0 patients,[11] and May et al. included pT4N0–2 patients.[39]

The outcome to be predicted was cancer-specific survival (CSS) and the time of prediction was highly variable from 1,[10,32,36] to 10 years.[35,40] Only 1 of the studies included indicated that the pathologist reviewed blindly the specimens.[34]

The *Candidate Predictors* chosen included clinical, anatomopathological and analytical variables (Table 1 summarizes the most relevant variables. The full table is attached as Table S2). Of the 19 studies reviewed, most included sociodemographic variables in the model, such as age (18 studies, 94.7%) and sex (17 studies, 89.5%); tumour characteristics: TNM stage (18 studies, 94.7%), histological subtype/grade (15 studies, 78.9%), lymphovascular invasion (10 studies, 52.6%) and treatment with chemotherapy (13 studies, 68.4%).[6,12,13,31,32,36,38,40,41]

In the *Sample Size* domain, the number of events per variable (EPV) ranged from 2.33,[10] to 172,[40] being higher than 20 in three models.[6,35,40] EPV could not be calculated in

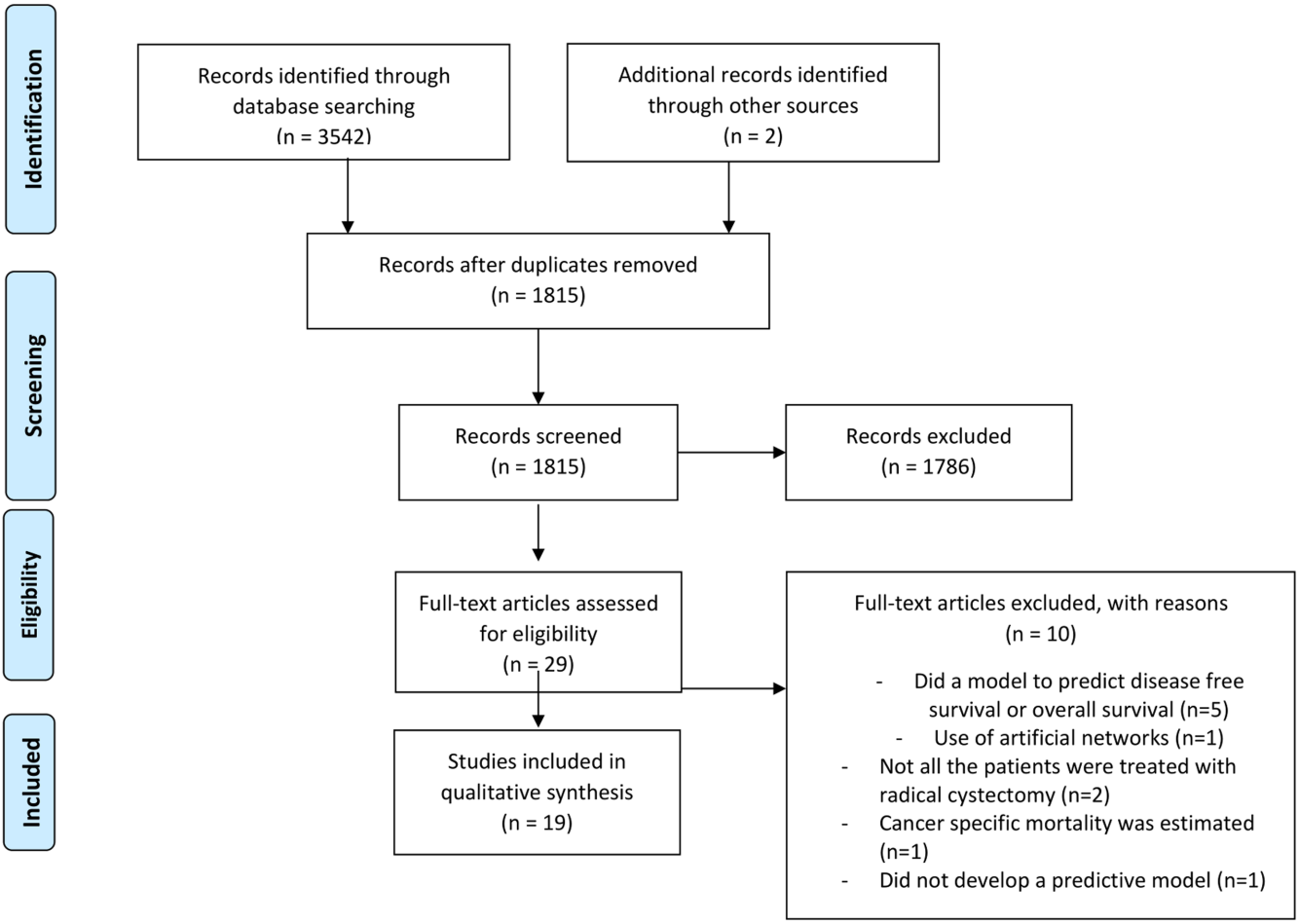

FIGURE 1 PRISMA flow chart for the systematic review of predictive models in cancer-specific mortality for bladder cancer in patients treated with radical cystectomy

5 (26.3%) studies.[9,11,37,38,41] Nine studies (47.4%) did not indicate how *Missing Data* were handled,[11–13,33–37,39] and the rest performed a complete-case analysis.[6,9,10,15,30–32,38,40,41]

The Cox regression model was used in all papers, except Xylinas et al.'s in which a competing risk model was carried out (*Model Development)*.[11] The proportional hazards assumptions were tested in 3 papers.[30,31,41] The selection of predictors included in the multivariate analysis was done by univariate analysis in 9 papers.[6,12,13,15,31,32,34,37,40] The selection during multivariable model building was not clear enough in one article,[11] was performed with the full model in 7,[6,12,31,32,34,37,40] by backward stepwise selection in 7 models,[10,13,15,30,35,36,39]based on maxima of low hazards ratios in one study,[38] least absolute shrinkage and selection operator in another[41] and unknown in the rest.[9,33]The slope index was used as a shrinkage model in only two of the papers.[39,41]

In *Model performance*, most of the studies applied the C-index,[6,9,10,12,30,31,33,35–41] for model discrimination and calibration was performed in 12 papers,[6,9–11,15,30–33,38,40,41] generally constructing calibration plots.

In *Model evaluation*, 12 papers performed bootstrapping.[6,9–11,15,30,31,35,38–41]: 8 of these studies only included one data set[9,10,15,30,31,35,39,40] and 4 divided the sample into two internal and external validation cohorts.[6,11,38,41]

As *Results*, the model was presented through nomograms in 10 investigations,[6,9–11,15,30,31,33,40,41] and through risk stratification models in 9 studies.[12,13,32,34–39] Baseline survival was not indicated in any of the manuscripts studied. Table 2 presents the different values obtained in the different studies: C-index for cancer-specific survival ranged from 0.61 to 0.85 and AUC from 0.708 to 0.77.

In the *Interpretation and Discussion* domain, the conclusions indicate that the results obtained would be further validated in an independent study,[6,9–12,15,30–32,34–41] with the exception of Simone and Solsona et al. who were conclusive in the use of the models in clinical practice.[13,33] All authors interpreted the relationship between predictors and outcome, compared their results with other studies, and discussed the strengths and limitations of their research. Discussion of generalization to other geographic areas was not addressed in two papers.[13,33]

TABLE 1 Predictors included in the final models in each paper

	Sociodemographic variables		Tumour characteristics						Treatment characteristics
	Age	Sex	Histological subtype/grade	TNM stage	Tumour size/ shape	N nodes removed	Positive surgical margins	Lymphovascular invasion	Chemotherapy
Tian et al., 2021[40]	X	X	X	X	X	X			X
Schuettfort et al., 2021[41]	X	X	X	X		X	X	X	X
Yang et al., 2020[6]	X	X	X	X	X				X
Mir et al., 2020[15]	X		X	X		X	X		X
Del Pozo et al., 2020[32]			X	X					
Hirasawa et al., 2016[10]	X	X	X	X	X	X			X
Di Trapani et al., 2015[9]	X	X		X					X
Ku et al., 2015[31]	X	X	X	X			X	X	
Simone et al., 2014[33]	X	X		X			X	X	
Eisenberg et al., 2013[34]	X	X	X	X	X			X	X
Sejima et al., 2013[35]	X	X		X			X	X	X
Xylinas et al., 2012[11]	X	X	X			X	X	X	X
Gondo et al., 2012[36]	X	X	X	X	X	X			
Gakis et al., 2011[37]	X	X	X	X	X		X		X
Welty et al., 2017[38]	X	X	X	X		X			
May et al., 2013[39]	X	X	X	X		X		X	X
Shariat et al., 2006[14]	X	X	X	X				X	X

(Continues)

TABLE 1 (Continued)

	Sociodemographic variables		Tumour characteristics					Treatment characteristics
	Age	Sex	Histological subtype/grade	TNM stage	Tumour size/shape	N nodes removed	Positive surgical margins	Lymphovascular invasion	Chemotherapy
Todenhöfer et al., 2012[12]	X	X		X	X		X	X	X
Solsona et al., 2005[13]	X	X	X	X	X	X		X	
Total	18	17	15	18	8	9	8	10	13

Note: This table summarized the most used variables, the full table is attached as Table S2. N nodes removed = number of nodes removed.

3.4 | PROBAST analysis

The PROBAST analysis is detailed in Appendix S2, and the results are summarized in Table 3 and Figure 2. In the *participants*' domain, the risk of bias or nonapplicability was high in 52.6% of the articles.[9,11–13,31,34,35,37,39,40] In the *analysis* section, the risk was high in all papers, except for Xylinas et al.[11] Generally, the reasons for the risk of bias in this domain were the low number of participants, the categorization of continuous variables, the misuse of missing data and the calibration of the models.

Finally, in the *Overall Section*, the risk of bias was high in all the studies and the applicability was low in 10 of the articles,[9,11–13,31,34,35,37,39,40] all the studies showed the high risk of bias and 52.6% showed low applicability.

3.5 | Scottish intercollegiate guidelines network grading review group (SIGN) recommendations

Based on the SIGN criteria, the review has a grade of evidence 2++: high-quality systematic reviews of case–control or cohort studies with a grade B recommendation.

4 | DISCUSSION

4.1 | Synopsis and results

More than 3000 abstracts have been reviewed for this systematic review, eventually including a total of 19 prognostic models of CSS in patients with UBC after radical cystectomy of which 100% have a high risk of bias and near 53% have low applicability.[6,9–13,15,30–41]

Several predictors were consistently selected for inclusion in the different models, such as the sociodemographic variables of age and sex, tumour characteristics such as TNM stage, histological subtype/grade and LVI, and neoadjuvant chemotherapy. Most of the models showed C-index values higher than 0.7, indicating a good model, and only one study presented C-index values higher than 0.8 (strong model).

4.2 | Strengths and limitations

The main strength of our work is that it provides a synthesis of all the predictive models published to date, indicating their main characteristics, and an assessment of their methodology and clinical applicability. Hence, this paper provides a global overview of the different predictive models of specific mortality in UBC, which could help in the

TABLE 2 Description of the main results obtained in each study

	Concordance index	Area under the curve
Tian et al., 2021[40]	0.728	
Schuettfort et al., 2021[41]	0.733	
Yang et al., 2020[6]	0.707	0.767
Hirasawa et al., 2016[10]	0.749	
Eisenberg et al., 2013[34]	0.75	
Gakis et al., 2011[37]	0.788	
Welty et al., 2017[38]	0.705	
May et al., 2013[39]	0.61	
Simone et al., 2014[33]	2, 5 and 8 years: 0.85, 0.85, 0.83 for European centres; 0.80, 0.74, 0.68 for African series; 0.79, 0.76, 0.73 for American series.	
Di Trapani et al., 2015[9]	0.79	
Xylinas et al., 2012[11]	2, 5, and 7 years: 0.693, 0.664, and 0.655, respectively.	
Todenhöfer et al., 2012[12]	0.745	
Shariat et al., 2006[30]	0.791	
Mir et al., 2020[15]		5 years: 0.754
Del Pozo et al., 2020[32]		1 year: 0.708; 3 years: 0.739, 5 years: 0.779
Solsona et al., 2005[13]		0,77

elaboration of consensus documents and clinical practice guidelines.

One possible limitation could be selection bias, relating to the possible exclusion of some articles that did meet the inclusion criteria and none of the exclusion criteria, or that may have been published in a language other than those used by the authors. However, independent peer review minimizes the risk of such bias. Scopus and Web of Science databases were not included in the search as these have been found to produce studies similar to the databases used and hence their use can produce high 'noise', as has been observed in previous reviews.[42,43] Cochrane Database was not used either, as it usually indexes systematic reviews and clinical trials, which are not the subject of this systematic review.

The process of extracting information from each article included by peers was carried out systematically and using an objective tool such as PROBAST to assess the risk of bias and applicability in order to minimize the possibility of information bias.

4.3 | Comparison with existing literature

Our systematic review shows that existing models in the literature have a high risk of bias and low clinical applicability. These findings are consistent with others, a previous systematic review by Beneyto et al.,[23] which identified and summarized, through the use of the PROBAST criteria the predictive models for predicting mortality in sepsis. The included studies showed a high risk of bias in the Participants, Predictors, Outcome and Analysis domains, with the risk of bias in the latter domain being high in 80%–100% of the studies. Furthermore, the models were not applicable in 12%–53% of the models included. Our results were in line with these studies, finding a high risk of *Analysis* bias in 94% of the papers included, while 53% of the models presented low applicability in clinical practice.

In our systematic review, only 5 of the 19 studies included an external validation.[6,11,33,38,41] Previous studies[44,45] also showed a similar percentage of studies including external validation of the developed model. External validation of the models in a new context is essential to assess the impact on health outcomes in clinical practice. However, this is not the subject of this review, and thus, we did not check whether the other studies had been externally validated in a different posterior study. In addition, to reduce the risk of bias the study design should be prospective, and we only included 2 studies with this study design in our systematic review.[31,33]

4.4 | Implications for research and clinical practice

There are other models centered in UBC that predict other types of outcomes, such as overall survival[46–49]or the risk of recurrence,[50,51] and models in the population with non-muscle-invasive bladder tumors[52] or with metastatic UBC.[53–55] We decided to focus on studies that evaluated patients after radical cystectomy, nonmetastatic and predicting CSS, since this is one of the groups of patients with the highest morbidity and mortality. Consequently, it could be worthwhile to carry out systematic reviews for other types of outcomes and patients.

TABLE 3 Risk of bias and concern regarding applicability of the included studies that evaluated cancer-specific mortality prediction models in patients with bladder cancer (PROBAST)

	ROB				Applicability			Overall	
Study	**Participants**	**Predictors**	**Outcome**	**Analysis**	**Participants**	**Predictors**	**Outcome**	**ROB**	**Applicability**
Tian et al., 2021[40]	−	+	+	−	−	+	+	−	−
Schuettfort et al., 2021[41]	+	+	+	−	+	+	+	−	+
Yang et al., 2020[6]	+	−	+	−	+	+	+	−	+
Mir et al., 2020[15]	+	+	+	−	+	+	+	−	+
Del Pozo et al., 2020[32]	+	+	+	−	+	+	+	−	+
Hirasawa et al., 2016[10]	+	+	+	−	+	+	+	−	+
Di Trapani et al., 2015[9]	−	+	+	−	−	+	+	−	−
Ku et al., 2015[31]	−	+	+	−	−	+	+	−	−
Simone et al., 2014[33]	+	+	+	−	+	+	+	−	+
Eisenberg et al., 2013[34]	−	+	+	−	−	+	+	−	−
Sejima et al., 2013[35]	−	+	+	−	−	+	+	−	−
Xylinas et al., 2012[11]	−	+	+	?	−	+	+	−	−
Gondo et al., 2012[36]	+	+	+	−	+	+	+	−	+
Gakis et al., 2011[37]	−	+	+	−	−	+	+	−	−
Shariat et al., 2006[14]	+	+	+	−	+	+	+	−	+
Todenhöfer et al., 2012[12]	−	+	+	−	−	+	+	−	−
Solsona et al., 2005[13]	−	+	+	−	−	+	+	−	−
Welty et al., 2017[38]	+	+	+	−	+	+	+	−	+
May et al., 2013[39]	−	+	+	−	−	+	+	−	−

Abbreviations: −, high ROB/high concern regarding applicability; ?, unclear ROB/unclear concern regarding applicability; +, low ROB/low concern regarding applicability; PROBAST, Prediction model Risk Of Bias ASsessment Tool; ROB, risk of bias.

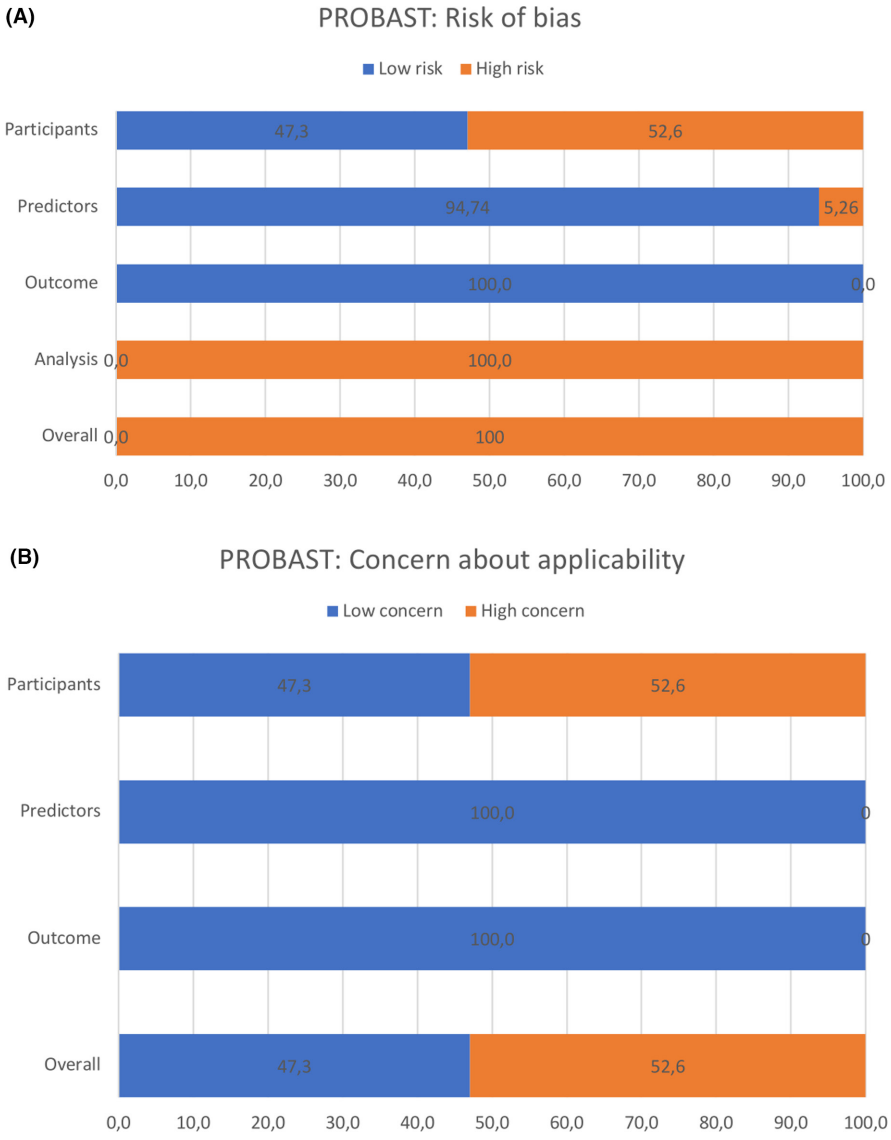

FIGURE 2 Representation of PROBAST results. (A) PROBAST risk of bias. (B) PROBAST applicability

Based on our results, further research should be also focused on the development of new prognostic models that consider the recommendations of CHARMS and PROBAST, to increase their applicability in clinical practice.

5 | CONCLUSIONS

This systematic review analyses the predictive models for specific mortality in patients with UBC after radical cystectomy, through the application of CHARMS and PROBAST. Although the C-index values were considered good, the models included have a high risk of bias and low applicability, so they should be applied with caution. There is a need for studies that enable the development of new prognostic models that meet the standards called for within international consensus frameworks, including a prospective design and an external validation of the model.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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