EXTERNAL VALIDATION OF A PREDICTIVE MODEL OF SURVIVAL AFTER CYTOREDUCTIVE NEPHRECTOMY FOR METASTATIC RENAL CELL CARCINOMA

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Abstract

Introduction: Recent trials have emphasized the importance of a precise patient selection for cytoreductive nephrectomy(CN). In 2013, a nomogram was developed for pre- and postoperative prediction of the probability of death (PoD) after CN in patients with metastatic renal cell carcinoma (mRCC). To date, the single-institutional nomogram which included mostly patients from the cytokine era has not been externally validated. Our objective is to validate the predictive model in contemporary patients in the targeted therapy era.

Methods: Multi-institutional European and North American data from patients who underwent CN between 2006 and 2013 were used for external validation. Variables evaluated included pre-operative serum albumin and lactate dehydrogenase levels, intraoperative blood transfusions (yes/no) and postoperative pathologic stage (primary tumour and nodes). In addition, patient characteristics and MSKCC risk factors were collected. Using the original calibration indices and quantiles of the distribution of predictions, Kaplan-Meier estimates and calibration plots of observed versus predicted PoD were calculated. For the preoperative model a decision curve analysis (DCA) was performed.

Results: Of 1108 patients (median OS of 27 months [95% CI 24.6-29.4]), 536 and 469 patients had full data for the validation of the pre-and postoperative models, respectively. The AUC for the pre- and postoperative model was 0.68 [95% CI 0.62-0.74] and 0.73 [95% CI 0.68-0.78], respectively. In the DCA the preoperative model performs well within threshold survival probabilities of 20-50%. Most important limitation was the retrospective collection of this external validation dataset.

Conclusions: In this external validation, the pre- and postoperative nomograms predicting PoD following CN were well calibrated. Although performance of the preoperative nomogram was lower than in the internal validation, it retains the ability to predict early death after CN.

1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of all adult malignancies and 90-95% of all kidney neoplasms[1] [2]. Fifteen to 30% of the patients are diagnosed with metastatic renal cell cancer (mRCC) at presentation[3].

The current European Association of Urology (EAU) RCC Guidelines recommend cytoreductive nephrectomy (CN) in patients with primary mRCC with a good performance status, a large primary tumor and low metastatic volume.[4] In the cytokine era, CN was supported by two landmark randomized controlled trials (RCTs) [5, 6] A combined analysis of both studies yielded a median survival of 13.6 months for nephrectomy plus interferon vs. 7.8 months for interferon alone, representing a 31% decrease in the risk of death (p=0.002) and an absolute OS advantage of 5.8 months [7]. With the advent of targeted therapy(TT) the utility if CN in patients with mRCC has been clinically challenged although multiple arguments in favor of CN in this setting remain[8, 9]. Two RCTs to investigate the role and sequence of CN were recently presented (CARMENA Trial - NCT00930033; EORTC SURTIME NCT01099423). Results from both trials suggest that only very few indications for CN remain for patients who require systemic therapy with TT.[10, 11] Nonetheless, as the systemic therapy landscape moves quickly into second generation of RCC immunotherapy, it is unlikely that we will define the ideal role of CN in patients treated with these new therapeutic agents.[12]

Patients with mRCC are clinically and pathologically heterogeneous. The results of CARMENA confirm that they present a great variability in oncologic outcomes after CN and systemic therapy.[10] CN has a 3-4% mortality rate and some patients will not derive a clinical benefit from this potentially morbid surgical resection.[13] Indeed, up to 15% of patients never receive systemic therapy following CN due to rapid disease progression or perioperative death. [13] Validated, accurate and clinically useful models to predict survival are paramount in the selection of patients in whom CN may still be indicated.[14] Retrospective studies have identified potential clinical and laboratory risk factors that can be used to identify patients unlikely to benefit from cytoreductive surgery.[15-17] [18]. Although risk models like the Memorial Sloan Kettering Cancer Center (MSKCC) or International Metastatic Renal Cell

Carcinoma Database Consortium (IMDC) models are widely used to assess the prognosis of patients with mRCC, they are not predictive for outcome after CN.[23,24] Therefore, predictive models, based on preoperative clinical factors are needed to define the role of CN for the individual patient.

In 2013, a nomogram was developed for the pre- and postoperative prediction of the probability of death (PoD) after CN.[17] Although this nomogram discriminates between long and short-term survivors, it was generated from a single-institutional database, included patients from the cytokine era and has not been externally validated. Whereas non-validated models have limited utility in clinical practice,[19] we tested the validity of this model in a contemporary multi-institutional European and North American dataset of patients treated in the targeted therapy era.

2. Methods

2.1 Participants

We included patients who underwent CN for mRCC between 2006 and 2013, from 9 European and North American high-volume cancer centers (Netherlands Cancer Institute, Amsterdam, Netherlands; Umeå University Hospital, Umeå, Sweden; Medical University of Vienna, Vienna, Austria; Haukeland University Hospital Bergen, Norway; Addenbrooks Hospital, Cambridge, UK; Western General Hospital, Edinburgh, UK; Ludwig-Maximilians-University Hospital, Munich, Germany; Uniklinik Cologne, Cologne, Germany; Fox Chase Cancer Center, Philadelphia) as well as patients in the Canadian Kidney Cancer Information System (prospective data from 15 academic institutions across Canada). Contributing centers had appropriate institutional review board approval for data collection. For patients to be included in the pre-operative model validation cohort full data on pre-operative serum albumin and lactate dehydrogenase (LDH) and status at follow-up were required. For the postoperative model validation, full data on pre-operative albumin, pre-operative LDH, pN stage (N0/x vs. N1 vs. N2), intraoperative blood transfusion (no vs. yes); pT-stage >= pT3 (no vs. yes) and status at follow-up were required.

146 **2.2 Source of data**

147 A global database from the individual institutions' renal cancer databases was
148 constructed collecting the following variables: age, gender, number of metastatic sites,
149 presence of metastasis in specific sites (for sites see Table 1), ECOG performance status,
150 MSKCC risk group, pre-operative albumin, pre-operative LDH, intraoperative transfusions,
151 RCC histological subtype, pT-stage, pN-stage, first line systemic treatment and second line
152 systemic treatment.

153

154 **2.3 Statistical analysis**

155 The primary end-point was overall survival (OS) at 6 months (for the pre-operative
156 model validation) and at 12 months (for the post-operative model validation). OS was defined
157 as the time from CN to death or censored at date of last follow-up.

158 The predictive accuracy of the model was assessed by concordance index, which is
159 the area under the receiver operating curve (ROC) for time-to-event data. Time-dependent
160 ROC curves were calculated using the Nearest Neighbor Estimation method[20]. The 95%
161 confidence interval (CI) was obtained using the bootstrap percentile method with 2000
162 bootstrap replicates. A concordance index of 0.5 represents no predictive discrimination and
163 an index of 1 represents perfect ability to distinguish patients. Calibration was assessed by
164 grouping patients into deciles according to their predicted risk. The Kaplan-Meier estimate in
165 each decile of the observed probability of death at 6 months was plotted against the mean
166 predicted risk in a calibration plot and a locally-weighted regression line was added. Software
167 R version 3.4.4 with package survivalROC version 1.0.3.

168 To determine the clinical value of the model, decision curve analysis was used.[21]
169 We defined that only patients who survived for 6 months or more may potentially have
170 benefited from CN. To find the net benefit of the treatment strategy using the prediction from
171 the preoperative nomogram, we looked at each combination of predicted and true benefit,
172 and compared the utility values obtained with this strategy with the utility of the default
173 strategy (treating all patients). We chose a 20% threshold for risk of death at 6 months after
174 CN, meaning that patients with lower than 20% risk of death would not benefit from not
175 recommending CN. Finally, to test the clinical value of the nomogram, we assessed the

calibration (i.e., compared the predicted 6-months PoD of the preoperative nomogram to the observed 6-months rate of death after CN) in each risk group of the MSKCC prognostic model.

3. Results

Between 2006 and 2013, 1108 patients underwent CN. Median follow-up of the subjects still alive was 24 months [range 0-123 months]. Median OS was 27 months [95% CI 24.6-29.4]. Of those patients, 536 and 469 patients had complete data for the validation of the preoperative and postoperative models, respectively . (**Figure 1**) Patient characteristics are listed in **Table 1** and **Supplementary Table 1**. The majority of patients received systemic therapy.

3.1 Preoperative model

The median OS of the 536 patients included in the external validation of the preoperative model was 21.0 months [95% CI 17.7-24.3]. The AUC for the preoperative model was 0.68 [95% CI 0.62-0.74].The calibration plot indicates that the risk model is well calibrated (**Figure 2**) Decision curve analysis demonstrate that the model has a greater net benefit compared with the strategies of using CN in all or none of the patients when examined within the threshold survival probabilities of 20-50%. (**Figure 3**) If the threshold was set 20%, then 458 patients would have been considered low-risk (prediction below 20%) and 80.3% (95% CI 76.7–84.1) of them would still be alive at 5 years. With the 50% risk threshold, 515 patients would have got a predicted risk below 50% and 78.7% of them would still be aliveat 5 years.

3.2 Postoperative model

The median OS of the 469 patients included in the external validation of the postoperative model was 20.6 months [95% CI 17.5 – 23.7]. The AUC for the postoperative model was 0.73 [95% CI 0.68-0.78]. The calibration plot shows that the model is well calibrated and underestimates the PoD to a minor extent. (**Figure 4**)

3.3 Performance of the preoperative model per MSKCC prognostic risk group

A total of 450 patients had full data available to assign them to MSKCC favorable, intermediate and poor prognosis. Median OS per MSKCC risk group were as published previously [22]. When separating patients with full data available into MSKCC risk groups, the observed 6-months rate of death after CN in patients with intermediate and poor prognosis was higher than the predicted 6-months probability of death (**Supplementary Figure 1**).

4. Discussion

Here we present the largest external validation and comparison of a predictive model assessing the preoperative PoD for patients being considered for CN. The model was validated using a contemporary cohort of patients receiving targeted therapy in association with CN. This is a multi-institutional study receiving contributions from centers across Europe and North America, representing a true external validation. A previous attempt to validate this model [22] included only a smaller series with multiple imputations to overcome significant quantities of missing data. Moreover those authors did not obtain the original model and calibration indices.

Our external validation revealed that the accuracy of the preoperative model was lower (0.68) than the one reported in the MD Anderson internal validation cohort (0.76).[17] The decision curve analysis demonstrates that there is a certain range of probability thresholds (p_t) within which the prediction model is of value (20-50%). We estimated the range of p_t in a typical CN population, where the typical threshold probability of death at 6 months would allow the patient and their urologists to consider CN, as being 20-40%. Overall, this demonstrates that the model is of *clinical* value. On the other hand, if for example it were the case that clinicians offered CN only if there was less than 15% of PoD at 6 months, the model would have a lesser role. The accuracy for the post-operative model (0.73) was similar to the one found in the internal validation (0.74).[17]. However, this model has limited clinical application when compared with the pre-operative model which estimates the PoD before CN is performed.

Adequate patient selection for CN is critical in the management of mRCC. Although the results of CARMENA demonstrate non-inferiority of sunitinib versus CN followed by sunitinib[10], it has to be acknowledged that the study did not reach full accrual and included many poor surgical candidates, suggesting selection bias by physicians responsible for selecting patients into the trial. In addition, a minority of patients still required secondary CN when treated with sunitinib only. As a consequence, the results of CARMENA are not universally accepted and suggestions are made to carefully select potential candidates for CN instead of abandoning the procedure completely[23].

Multiple retrospective studies have identified factors associated with worse outcomes following CN[15]. Negative prognostic factors included systemic symptoms (e.g. weight loss, fever) at the time of CN, multiple sites of metastatic disease, Fuhrman nuclear grade of 4, sarcomatoid dedifferentiation, coagulative necrosis in the tumor, abnormally high thyroid-stimulating hormone (TSH) levels, retroperitoneal lymphadenopathy, or tumor thrombus.

Several prognostic models of OS or progression free survival (PFS) in mRCC were developed in the cytokine and targeted therapy era [24] and have been externally validated [25]. One of the most commonly used prognostic models, the MSKCC risk score, has been established in the cytokine era. Karnofsky PS <80%, high serum lactate dehydrogenase (> 1.5 times upper limit of normal), low haemoglobin (< lower limit of normal), high "corrected" serum calcium (> 10 mg/dL), and absence of prior nephrectomy were used to categorize patients as being at favourable, intermediate or poor risk. The absence of prior nephrectomy was later changed to the factor ‘time from diagnosis to systemic treatment < 1 year’ [26]. Similary, the IMDC model using components of the MSKCC model with the addition of platelet and neutrophil count but has been validated for use in clinical trials and patient care in the era of targeted therapy [27]. A retrospective study involving 1652 patients with or without CN suggests that patients with an estimated OS of < 12 months and IMDC poor risk of 4 or more factors derive no benefit from CN [28]. However, despite being used to aid in the decision to offer CN, the IMDC and MSKCC models are prognostic and not predictive for the PoD after surgery. In addition, they included both metachronous and primary mRCC in the validation sets.

Although in our study the observed 6-months death after CN is higher in MSKCC intermediate and poor risk patients compared to the predicted 6-months PoD with the nomogram, it should be kept in mind that the MSKCC and IMDC models in addition to not being predictive merely provide a categorical assessment of prognosis, expressed as median OS, for all patients within the same risk group. Therefore, the predictive pre-operative model which can estimate an individual's PoD at 6 months prior to CN retains clinical value in this setting. This value is especially apparent for patients of MSKCC intermediate risk, which generally constitute 60-70% of all mRCC patients. While their median OS is 26 months, the observed rate of death at 6 months was almost 18%. Although the pre-operative nomogram underestimates the 6 months death rate, it provides a tool to identify those with a high probability of a poor outcome in conjunction with CN among patients with intermediate risk. From the surgeon and patient's perspective identification of patients unlikely to benefit from CN prior to surgery is the ultimate goal. The model that was the subject of this external validation was developed from a previous study by Culp et al who established a risk score from 566 patients who underwent CN, which included: 1) raised LDH, 2) low albumin, 3) symptoms at presentation caused by metastatic site, 4) metastasis in the liver, 5) retroperitoneal or 6) supradiaphragmatic adenopathy and 6) >=cT3 stage. OS of 110 patients with mRCC who did not undergo CN was used as a reference group. Patients who underwent CN had a median OS of 12.2 months, 22.7months and 40.6months for ≥4, 3-1 or 0 risk factors, respectively.[14] Patients who had ≥4 risk factors did not appear to benefit from CN.

The accuracy of risk models based on clinical factors is limited, regardless of their prognostic or predictive use. The AUC obtained in our external validation of the prediction model of survival after CN compares very favorably with those obtained for prognostic models. In one of the largest external validations done thus far, the concordance index was 0.71(95% CI 0.68-0.73) for the IDMC model [24], 0.662 (95% CI 0.636–0.687) for the CCF model [29], 0.640 (0.614–0.665) for the French model[30], 0.668 (0.645–0.692) for the IKCWG model[31], and 0.657 (0.632–0.682) for the MSKCC model[26].[25]

This external validation has a number of limitations. First of all, the main weakness is the retrospective design, despite being based on prospective renal cancer databases. Complete data for validation was only present in half of the total cohort and relatively few patients had complete information on cancer specific survival (CSS) available. Secondly, It is important to note that we used OS and not CSS as reported in the original model [17]. This may in part explain the higher observed 6-months death rate compared to the predicted 6-months probability of death since patients who died of surgical complications are included in OS but would be excluded from CSS. However, in the setting of mRCC the potential difference between both outcome measures is likely to be small. It could even be argued that OS is the correct endpoint to evaluate the model, because in deciding whether to perform CN any death should be considered as a failure, regardless if that death was attributed to cancer. Thirdly, only data for comparison with the MSKCC model were available, which excludes the more contemporary IMDC model from the analysis. Despite this limitation, our study represents the largest cohort validating a predictive model developed to select patients for CN.

5. Conclusion

In this external validation, the pre- and postoperative nomograms predicting PoD following CN were well calibrated. Although performance of the preoperative nomogram was lower than in the internal validation, it retains the ability to predict early death after CN.

FIGURE AND TABLE LEGEND

Figure 1 – Flowchart of 1108 patients that underwent cytoreductive nephrectomy (CN)
LHD= Lactate dehydrogenase

Figure 2 Calibration plot – Pre operative model

Figure 3 Decision curve analysis of the Pre operative model.
The blue line represents treating all patients. The black line represents treating no patients. The red line represents treating patients based on their predicted risk of death within 6 months.

Figure 4 - Calibration plot – Post operative model

Supplementary Figure 1 - Comparison of the observed versus expected probability of death at 6 months across MSKCC Risk Groups for the 450 patients with full data for MSKCC risk assignment available. (95% confidence interval of the observed survival percentage.)

Table 1 - Patient characteristics

Supplementary table 1 Patient characteristics: Included versus excluded patients

Informed consent: Informed consent was obtained from all individual participants included in the study.

Ethical approval: For this type of study formal consent is not required.

Conflict of Interest: The authors declare that they have no conflict of interest.

Author's Contribution

Marconi: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing
Bruijn Data collection or management
van Werkhoven: Data collection or management, Data analysis, Manuscript writing/editing
Beisland Manuscript writing/editing, Data collection
Fife Manuscript writing/editing, Data collection
Heidenreich Manuscript writing/editing, Data collection
Kapoor Manuscript writing/editing, Data collection
Karam Manuscript writing/editing, Data collection
Kauffmann Manuscript writing/editing, Data collection
Klatte Manuscript writing/editing, Data collection
Ljungberg Manuscript writing/editing, Data collection
Matin Manuscript writing/editing, Data collection
Sjoberg Manuscript writing/editing, Data collection
Staehler Manuscript writing/editing, Data collection
Stewart Manuscript writing/editing, Data collection
Tanguay Manuscript writing/editing, Data collection
Uzzo Manuscript writing/editing, Data collection
Welsh Manuscript writing/editing, Data collection
L. Wood Manuscript writing/editing, Data collection
C. Wood Manuscript writing/editing, Data collection
Bex: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing

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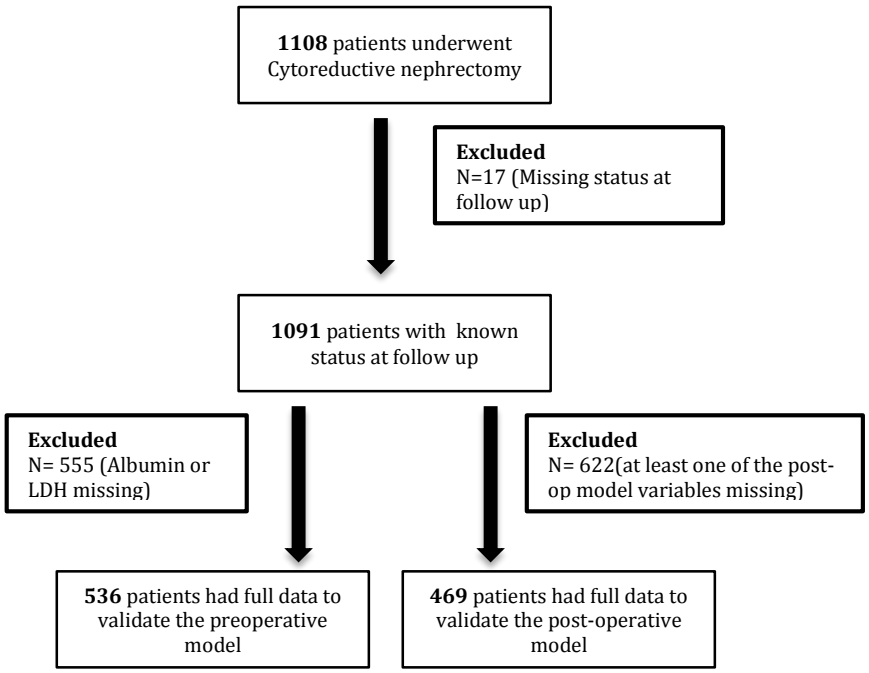
493

Figure 1 – Flowchart of 1108 patients that underwent cytoreductive nephrectomy (CN)



LHD= Lactate dehydrogenase

Figure 2

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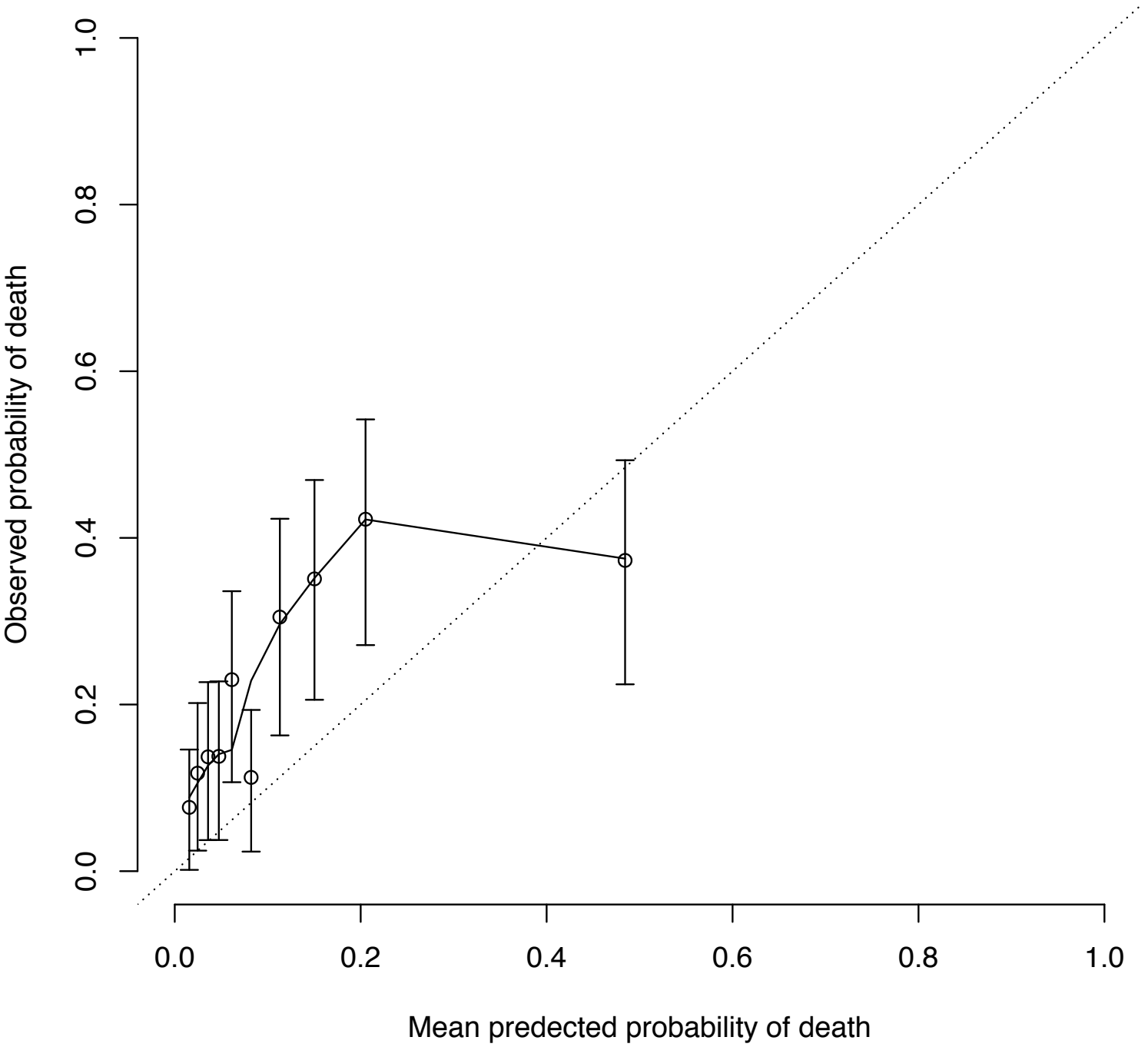

Figure 3

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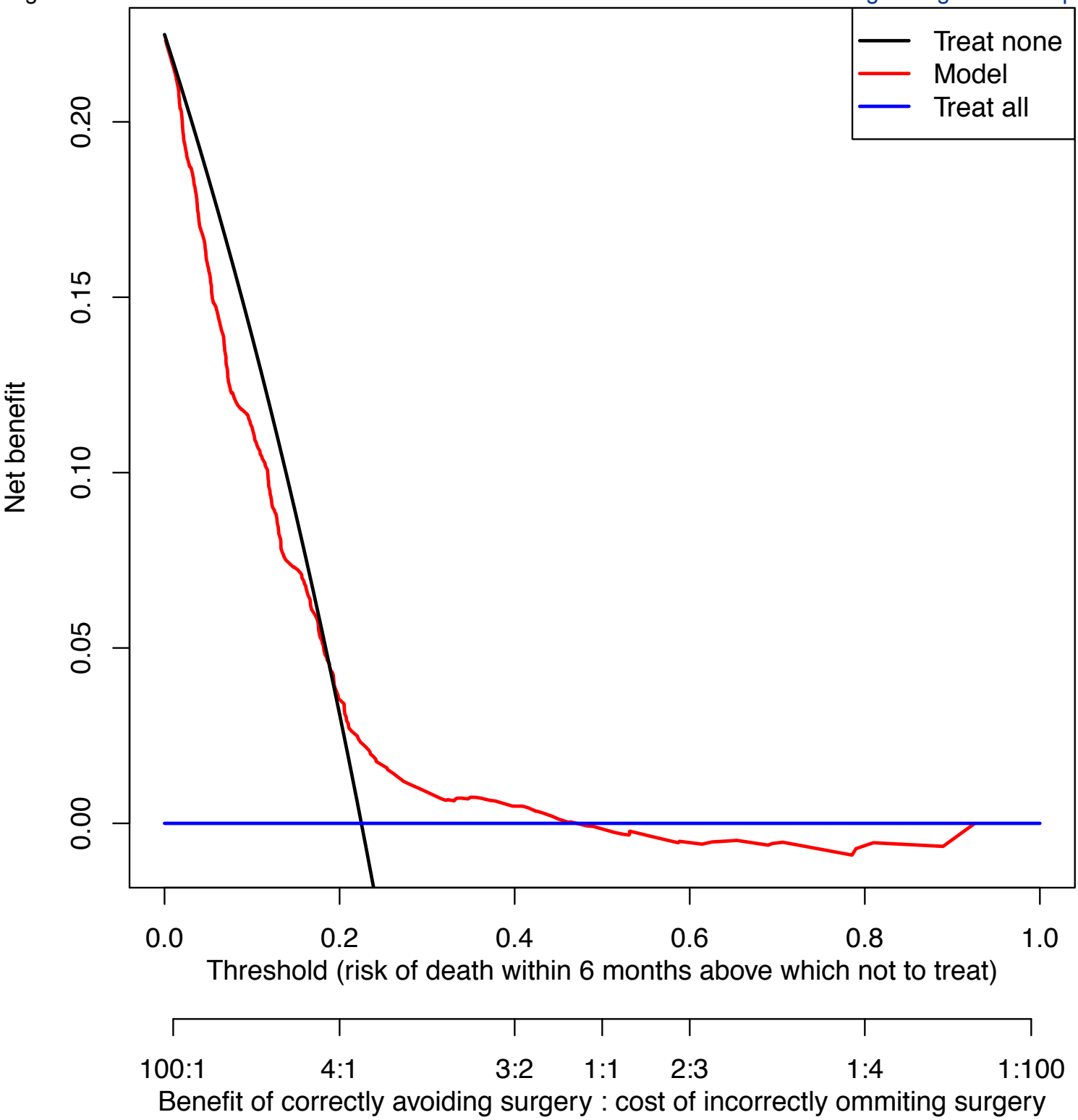

Figure 4

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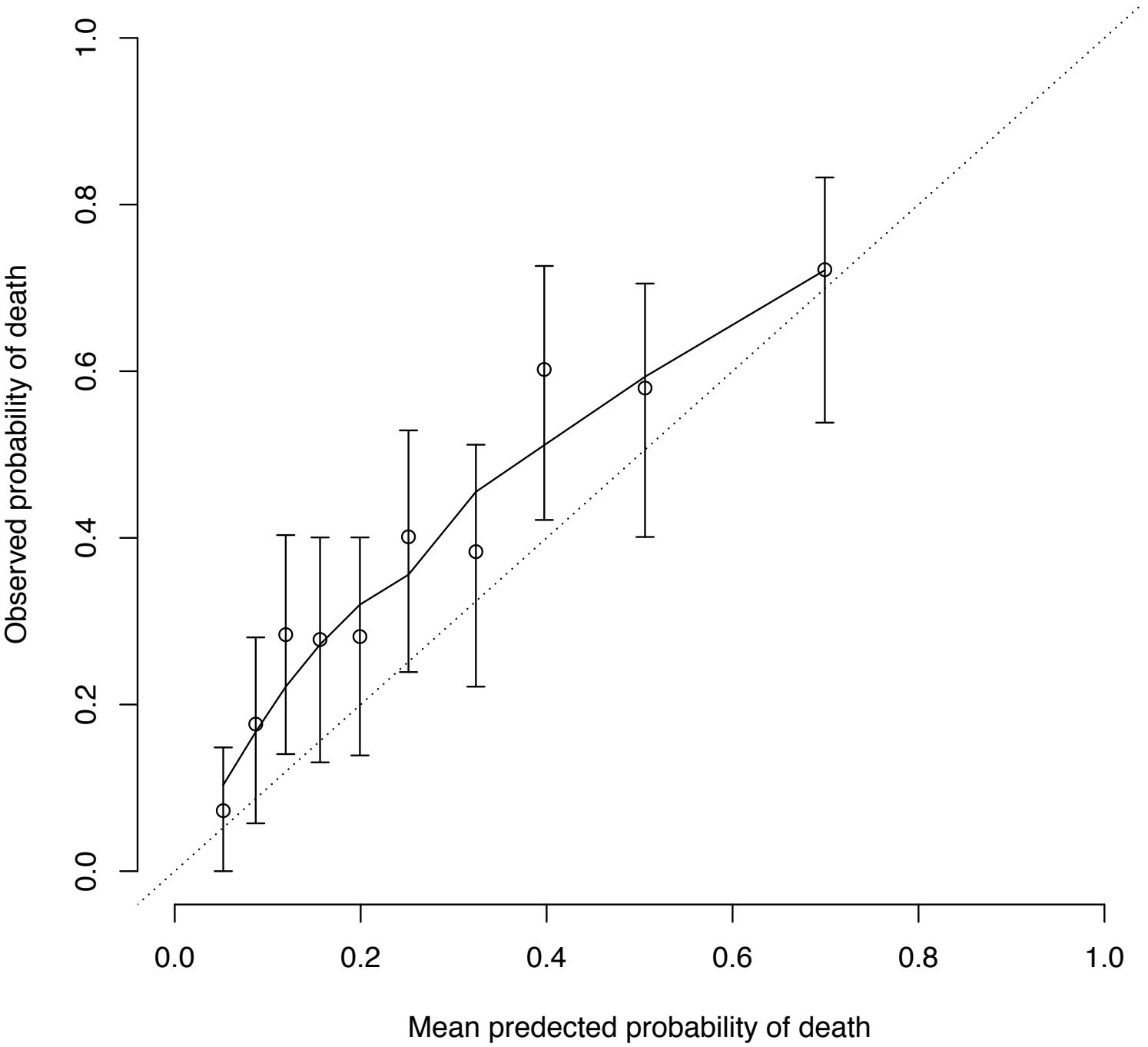

Table 1 – Patient characteristics

Patient characteristics	Pre-op model Median [IQR] or N(%)	Post-op model Median [IQR] or N(%)
Number of patients	536	469
Age (yrs)	64 [56-70]	64 [56-70]
Gender		
Female	165 (30.8%)	148(31.6%)
Male	371 (69.2%)	321(68.4%)
Albumin (g/dL)	3.9 [3.4-4.3]	3.9[3.4-4.3]
LDH (IU/L)	202.5[164.3-300]	204[165.0-311.5]
Primary tumour		
pT1	69(13.1%)	61(13%)
pT2	70(13.3%)	59(12.6%)
pT3	338(64.4%)	304(64.8%)
pT4	48(9.1%)	45(9.6%)
Number of metastatic sites		
1	249(48.3%)	227(50.7%)
2	161(31.3%%)	143(31.9%)
3	78(15.1%)	61(13.6%)
>=4	26(5.1 %)	16(3.6%)
Metastatic sites		
-lung only metastasis	124	119
- lung	245	210
-brain metastasis	56	53
-liver metastasis	87	72
-bone metastasis	194	173
-adrenal	79	74
-lymphnodes	204	167
- other sites	118	94

Subtypes		
Clear cell	420(85.7%)	373(85.9%)
papillary	45(9.2%)	39(9%)
Chromophobe	5(1.0%)	3(0.7%)
RCC other	19 (3.9%)	18(4.1%)
MSKCC score		
-Favourable	24(5.3%)	24(6.1%)
-Intermediate	276(61.3%)	233(59.4%)
-Poor	150(33.3%)	135(34.4%)
- Missing	86	77
ECOG performance status		
0	264 (55.6%)	231(54.2%)
1	124(26.1%)	113(26.5%)
2	81(17.1%)	76(17.8%)
3	5(1.05%)	5 (1.2%)
4	1(0.2%)	1(0.2%)
1st line Targeted therapy		
- sunitinib	220(58.4%)	176(55.3%)
- pazopanib	53 (14.1%)	48(15.1%)
- Sorafenib	16(4.2%)	14(4.4%)
- Everolimus	4(1%)	4(1.3%)
- Bevacizumab	3(0.8%)	3(0.9%)
- Temsirolimus	2(0.5%)	2(0.6%)
- Unknown TKI	3(0.8%)	3(0.9%)
- Other	11(2.9%)	6(1.9%)
- No systemic treat	65(17.2%)	62(19.5%)
- Missing	159	151
2nd line therapy		
- sunitinib	12(7%)	8(5.7%)
- pazopanib	8(4.7%)	4(2.8%)
- Axitinib	12(7%)	11(7.8%)
- Sorafenib	18(10.5%)	12(8.5%)
- Everolimus	21(12.2%)	18(12.8%)
- Bevacizumab	1(0.6%)	-
- Nivolumab	2(1.2%)	2(1.4%)
- Cabozantinib	1(0.6%)	1(0.7%)
- Other	3(1.7%)	3(2.1%)
- No systemic treat	94(54.7%)	82(58.2%)
- Missing	364	328

Supplementary Figure 1

Supplementary Table 1