Risk prediction models for recurrence after curative treatment of localised kidney cancer: a systematic review

Supplementary material

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Supplementary Methods 1. Details of risk of bias assessment

For this systematic review we carried out a risk of bias (RoB) assessment for each included validation. Validations of different models and outcomes (CSS, OS, RFS) carried out in the same study were assessed separately. The RoB assessments were carried out by one reviewer (HH), and 10% of the assessments (for each outcome) were checked by a second reviewer (LL, LR). Reviewers were in complete agreement for >80% of studies and all discrepancies were resolved through discussion. Any issues found were checked in the remaining 90% of assessments. The overall assessment was changed for five validations (out of 228) following second review.

The assessments were carried out using the PROBAST tool, which was specifically designed to assess the applicability and RoB of studies that develop and validated clinical prediction models. The PROBAST RoB assessment tool looks at four domains of interest to clinical prediction models: population, risk factors, outcomes and analysis. Each of the four domains can receive a low, unclear or high risk of bias rating. Within each domain a series of signalling questions are used to determine if the risk of bias was minimised during the model validation (or development) and the subsequent reporting.

Signalling questions can be answered Y (Yes), PY (Probably Yes), PN (Probably No), N (No) and NI (No Information). All the signalling questions are phrased in such a way that an answer of "Y" indicates low RoB. In general, a validation is assessed as having low RoB for a domain if all the signalling questions within that domain can be answered Y or PY. However, answering a signalling question "N" does not automatically mean that the validation will receive a high RoB rating for that domain.

The reviewer is required to determine, on a case-by-case basis, if the issue highlighted by the signalling question introduces RoB. This assessment may differ between systematic reviews, depending on the type of models and their intended application.

Within a review it is important to ensure consistency across all the assessments. In the section below, we have drawn attention to common issues identified in each domain for the validations included in this systematic review. Detail of how the corresponding RoB assessment was resolved are also given. An unclear rating was given if there is not sufficient information reported in the study to conclude on the level of bias, this is typically indicated by answering "NI" to the signalling questions.

The overall RoB assessment for each validation was considered low if each of the four domains receives a low RoB score. If at least one domain receives a high risk of bias rating, the overall score was considered high. If at least one domain receives an unclear RoB rating (and no domains receive a high RoB rating), then the overall validation was rated unclear.

We did not carry out applicability assessments using the PROBAST tool. We considered all of the included studies to be highly applicable to the research question, as determined by the inclusion criteria during the screening process. In order to investigate the applicability of individual models we looked at the availability of the risk factors used, in the context of existing clinical practice. The risk factors for each model were classified as available, possibly available and not available.

<u>Domain 1: Participants</u>

1.1 Were appropriate data sources used?

In this systematic review, all the included validations used retrospective cohorts for their analysis. This is considered a study design with a low risk of bias; all validations were given a "Y" response for this question.

1.2 Were all inclusions and exclusions appropriate?

In this review, most of the exclusions related to the type or severity of the kidney cancer. For example, many validations excluded individuals with metastases from their analysis. Additionally, rarer or unusual forms of kidney cancer (i.e. bilateral kidney cancer) were commonly excluded. We considered these exclusions appropriate.

The exclusion criteria often also defined the minimum amount of follow-up required for an individual to be included in the study. In a small number of validations, the minimum required follow-up was different for cases and controls. For example,

"[participants were excluded for the following reasons] …and a follow-up of less than 12 months without an event." May2009

Different inclusion and exclusion criteria for cases and controls was considered to introduce a RoB into the study. For the example above, the signalling question was answered "N" and domain 1 was assessed to have a high RoB.

Domain 2: Risk Factors

1.1 Were predictors defined and assessed in a similar way for all participants?

The risk factors were defined and assessed (for almost all validations) based on electronic health records or similar databases. These are considered suitable sources of data on risk factors, and are assumed reasonably consistent over the whole cohort. In some cases a "NI" rating is given for this signalling question if the source of risk factor data is not given for some or all of the cohort. An "NI" response for this signalling question would be sufficient to receive an unclear rating for this domain.

1.2 Were predictor assessments made without knowledge of outcome data?

As all the validations use retrospective cohorts, this is assumed to be "Y" for all. Note an "NI" rating was given if no information was given about data sources. An "NI" response for this signalling question would be sufficient to receive an unclear rating for this domain.

1.3 Are all predictors available at the time the model is intended to be used?

We assumed that this would be true in all cases (signalling question ignored). All the models validated in the study use risk factors that could be available post-operatively – but availability may vary depending on details of setting/usage.

Domain 3: Outcome

3.1 Was the outcome determined appropriately?

We expect that validation studies describe follow-up appointments, in which appropriate imaging and medical tests will be used to test for recurrence. In some studies this was explicit ("Y"), and in others implicit ("PY"). Where no information is reported a "NI" rating is given. An "NI" response for this signalling question would be sufficient to receive an unclear rating for this domain.

3.2 Was a pre-specified or standard outcome definition used?

This was answered "Y" for all, as the placement of the validation on the data extraction spreadsheets for CSS/RFS/OS makes it clear a standard and well understood outcome definition was used.

3.3 Were predictors excluded from outcome definition?

This was assumed true in all cases (signalling question ignored). All the models validated in this study satisfy this requirement.

3.4 Was the outcome determined in the same way for all participants?

To minimise the RoB in the validation, we expect that the follow-up procedure is the same for all included individuals. Some key problems highlighted included: centres pursuing different or ad hoc follow-up strategies and different follow-up for individuals classified as low risk and high risk (in some cases this classification was carried out by the model being validated). For example,

"Information on follow-up was updated in each center by direct phone call and, alternatively, by contacting general practitioners or relatives." Cindolo 2005

"Patients who survived to discharge were prospectively followed up according to Leibovich risk stratification protocol; patients classified as low risk underwent annual ultrasound scan and chest X-ray, intermediate risk underwent 6 monthly computed tomography scan for 2 years then annually until 5 years, and those classified as high risk underwent 6 monthly computed tomography scan for 3 years and then annually until 5 years." Lamb 2012

3.5 Was the outcome determined without knowledge of predictor information?

We felt this was an unreasonable expectation for this type of study (signalling question ignored). Typically, clinicians making a diagnosis of recurrent kidney cancer will have access to all medical records.

3.6 Was the interval between predictor assessment and outcome determination appropriate?

We would generally expect models of this type to be validated over a follow-up period of a number of years (e.g. 5/10 years). Most of the cohorts used in this validation have a range of follow-up periods, with a small number of individuals having a very short follow-up (<12 months). Note that other studies exclude individuals with <12 months of follow-up. On the condition that variable follow-up times are appropriately handled in analysis and the median follow-up times are reasonable, this does not present an issue. All validations were given a "Y" response for this question.

<u>Domain 4: Analysis</u>

4.1 Were there a reasonable number of participants with the outcome?

PROBAST guidance states that at least 100 events should be included in a validation to avoid high RoB. While many of the studies did not satisfy this criterion, we decided this (in the absence of other issues in this domain) was not sufficient to merit a high RoB rating. Validations with less than 50 events automatically received a high RoB rating for this domain. Validations that did not provide event numbers ("NI") automatically received an unclear rating for this domain (if no other issues were identified).

4.2 Were continuous and categorical predictors handled appropriately?

We assumed that all of the validations used the predictors as described by the model development studies (signalling question ignored).

4.3 Were all enrolled participants included in the analysis?

To answer this question we looked at the information provided by the studies on the handling of participants lost to follow-up. To minimise RoB we would expect to see the studies employing a suitable technique, such as censoring. Many of the studies simply excluded participants lost to follow-up, however - as these participants are likely to be different to those successfully

followed up - this approach introduces a RoB. Validations assessed as “N” for this signalling question automatically received a “high” RoB score for this domain.

4.4 Were participants with missing data handled appropriately?

According to PROBAST guidance, missing data should be handled using an appropriate method – such as multiple imputation. Complete-case analysis (excluding those with missing data) is explicitly stated as an approach that introduces RoB – and this signalling question has been answered accordingly. However, validations using complete-case analysis for a small amount of missing data (from medical records) were not automatically classified as “high” RoB for this domain, and could receive a “low” rating if no other issues were seen, as this was seen as an acceptable approach within the context of these types of validation. Note, that studies receiving a “NI” rating for this question did automatically receive an “unclear” rating for this domain (assuming no other issues).

4.5. Was selection of predictors using univariate analysis avoided (model development studies only)?

Not applicable (signalling question ignored).

4.6 Were complexities in the data accounted for?

Given general lack of information about this in the studies included in the review, this area was not considered (signalling question ignored).

4.7 Were relevant model performance measures evaluated appropriately?

The PROBAST guidance instructs that reporting for both discrimination and calibration should be taken into account. Within this systematic review, we have focussed on the reporting of discrimination measures (c-statistic). In order to include the results from each validation in the meta-analysis, the c-statistic and its confidence intervals must be available. Where the confidence intervals are not directly reported they can be calculated if the number of events is reported. This signalling question was answered “N” if the c-statistic was reported but neither the confidence intervals nor the number of events was given. Validations assessed as “N” for this signally question automatically received a “high” RoB score for this domain.

4.8 Were model overfitting, underfitting and optimism accounted for (dev only)?

Not applicable (signalling question ignored).

4.9 Do predictors and assigned weights in final model correspond to multivariate?

Assumed to be true for all model validations included in this review (signalling question ignored).

Supplementary Table 1. Medline search strategy

	Search Line	Results
1.	exp Kidney Neoplasms/	72712
2.	exp Carcinoma, Renal Cell/ or renal cell carcinoma.mp.	42888
3.	((renal or kidney* or nephric) adj6 (cancer* or neoplas* or tumo?r* or carcinom*)).mp.	103746
4.	(((clear adj3 cell*) or papilla* or chromophob*) adj6 ((renal adj3 (carcinom* or cancer*)) or RCC)).mp.	9140
5.	1 or 2 or 3 or 4	106113
6.	incidence.sh. OR exp mortality/ OR follow-up studies.sh. OR prognos*.tw. OR predict*.tw. OR course*.tw.	3336655
7.	exp Neoplasm Recurrence, Local/ or recur*.mp.	693493
8.	remission.mp.	147393
9.	metastas*.mp.	439138
10.	exp Survival Rate/ or surviv*.mp. or exp Survival/ or exp Survival Analysis/	1414099
11.	exp Disease-Free Survival/	71330
12.	mortality.mp.	1098741
13.	exp Follow-Up Studies/ or follow-up.mp.	1276463
14.	(follow* adj3 up).mp.	1330627
15	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	5607745
16.	(Validat$ OR Predict$.ti. OR Rule$) OR (Predict$ AND (Outcome$ OR Risk$ OR Model$)) OR ((History OR Variable$ OR Criteria OR Scor$ OR Characteristic$ OR Finding$ OR Factor$) AND (Predict$ OR Model$ OR Decision$ OR Identif$ OR Prognos$)) OR (Decision$ AND (Model$ OR Clinical$ OR Logistic Models/)) OR (Prognostic AND (History OR Variable$ OR Criteria OR Scor$ OR Characteristic$ OR Finding$ OR Factor$ OR Model$)) OR stratification.mp. OR exp ROC Curve/ OR discrimin*.mp. OR c statistic.mp. OR Area under the curve.mp. OR AUC.mp. OR Calibration.mp. OR Indices.mp. OR Algorithm.mp. OR Multivariable.mp.	5110496
17.	ablat*.af. or exp Ablation Techniques/	182881
18.	excis*.af.	202771
19.	remov*.af.	630063
20.	surgery.af. or surgical*.af. or exp General Surgery/	3908953
21.	Pre?operative.af. or post?operative.af.	913965
22.	Nephrectomy.af.	47604
23.	17 or 18 or 19 or 20 or 21 or 22	4603014
24.	letter.pt.	1052638
25.	editorial.pt.	510362
26.	24 or 25	1562824
27.	5 and 15 and 16 and 23	8929
28.	27 not 26	8848
29.	limit 28 to yr="2000 -Current"	7709

Supplementary Table 2. Embase search strategy

	Search Line	Results
1.	((renal or kidney* or nephric) adj6 (cancer* or neoplas* or tumo?r* or carcinom*)).ti,ab.	91924
2.	(((clear adj3 cell*) or papilla* or chromophob*) adj6 ((renal adj3 (carcinom* or cancer*)) or RCC)).ti,ab.	13872
3.	renal cell carcinoma.ti,ab. or exp *kidney carcinoma/ or exp *renal cell carcinoma/ or exp *kidney tumor/	67335
4.	exp *kidney cancer/	46685
5.	1 or 2 or 3 or 4	100443
6.	exp *tumor recurrence/ or recur*.ti,ab.	707680
7.	remission.ti,ab.	156623
8.	metastas*.ti,ab.	424834
9.	exp *survival/ or exp *survival prediction/ or exp *survival analysis/ or exp *cancer specific survival/ or exp *survival rate/ or exp *overall survival/ or exp *post treatment survival/ or exp *disease free survival/ or exp *cancer survival/ or exp *recurrence free survival/ or exp *survival time/ or exp *local recurrence free survival/ or exp *metastasis free survival/ or exp *progression free survival/ or surviv*.ti,ab.	1405358
10.	exp *cancer mortality/ or exp *mortality risk/ or mortality.ti,ab. or exp *mortality/	951986
11.	follow-up.ti,ab. or exp *follow up/	1317440
12.	(follow* adj3 up).ti,ab.	1404039
13	6 or 7 or 8 or 9 or 10 or 11 or 12	3838949
14.	(Validat$ OR Predict$.ti. OR Rule$) OR (Predict$ AND (Outcome$ OR Risk$ OR Model$)) OR ((History OR Variable$ OR Criteria OR Scor$ OR Characteristic$ OR Finding$ OR Factor$) AND (Predict$ OR Model$ OR Decision$ OR Identif$ OR Prognos$)) OR (Decision$ AND (Model$ OR Clinical$ OR *Logistic Models/)) OR (Prognostic AND (History OR Variable$ OR Criteria OR Scor$ OR Characteristic$ OR Finding$ OR Factor$ OR Model$)) OR stratification.ti,ab. OR exp *ROC Curve/ OR discrimin*.ti,ab. OR c statistic.ti,ab. OR Area under the curve.ti,ab. OR AUC.ti,ab. OR Calibration.ti,ab. OR Indices.ti,ab. OR Algorithm.ti,ab. OR Multivariable.ti,ab.	6158460
15.	ablat*.af. or exp *radiofrequency ablation/ or exp *tumor ablation/	169184
16.	excis*.ti,ab. or exp *excision/ or exp *local excision/	179157
17.	remov*.af.	623812
18.	surgery.af. or surgical*.af. or exp *kidney surgery/ or *abdominal surgery/ or exp *elective surgery/ or exp *surgery/ or exp *cancer surgery/	4400256
19.	Pre?operative.af. or post?operative.af.	1014495
20.	nephrectomy.af. or exp *nephrectomy/ or exp *"patient history of nephrectomy"/	54967
21.	15 or 16 or 17 or 18 or 19 or 20	4984632
22.	letter.pt.	794696
23.	editorial.pt.	545429
24.	22 or 23	1340125
25.	5 and 13 and 14 and 21	11856
26.	25 not 24	11856
27.	limit 26 to yr="2000 -Current"	11461

Supplementary Table 3. Characteristics of included studies

Author year	Country	Recruitment period	Selection of cohort	N	Follow-up	Exclusions
An 2015	China	2003-2008	Single centre	191	Physical examinations, laboratory studies, chest imaging and abdominal US or CT scans biannually for the first 5 years and annually thereafter.	Prior anti-cancer therapy, history of other malignant tumours, metastatic disease (N1 or M1).
Bai 2015	China	2005-2007	Single centre	271	Every 6 months for first 2 years and every 12 months thereafter.	Prior anti-cancer therapy, history of malignancy, >80% necrosis, mixed RCC histology.
Beisland 2015	Norway	1997-2013	Consecutive patients from single centre	383	Clinical examination, blood tests and chest XR every 6 months for 5 years. Nephrectomy patients with intermediate- and high-risk tumours had routine abdominal CT for follow-up. Chest CT was used based on individual evaluation.	Non-ccRCC, distant metastases before or at the time of surgery.
Bezan 2015*	Austria	2005-2013	Single centre	698	Clinical and laboratory examination every 3 months in the first 3 years, every 6 months in years 4 and 5, and every 12 months in years 6 and 9. Imaging included chest XR and abdominal US in patients at low risk for relapse (pT1 and G1-2) every 6 months. CT or MRI of the abdomen and chest was done every 6 months in the first 3 years in all other patients and every 12 months between years 4 and 5 postoperatively.	Non-ccRCC, metastatic disease, hereditary RCC, metachronous secondary RCC, competitive invasive cancer originating from other sites.
Brookman-Amissah 2009	Germany	1992-2006	Consecutive patients from single centre	771	Physical examination and US every 3 months with CT abdomen and thorax every 6 months for first 2 years. Then physical examination and US every 6 months and CT abdomen and thorax annually, with further investigation according to symptoms and disease progression.	Metastatic disease, bilateral synchronous tumours, Von Hippel-Lindau syndrome, Ductus-Bellini carcinoma, death from surgical complications (within a month of surgery), follow-up of <1 year without event.
Brooks 2014	USA	TCGA: not specified; UNC cohort: 1992-2010	Multicentre data from TCGA, single centre data from University of North Carolina	266	No details.	Non-ccRCC, metastasis.
Buti 2019	USA	2001-2015	SEER database	73217	No details.	Metastatic disease, death certificate only, autopsy cases, bilateral tumours, unknown tumour grade, lymph node status, T classification, age and follow-up data.
Capogrosso 2018	Italy	1995-2016	Single centre	Early recurrence cohort (≤15 months): 1,429; Late recurrence sub-cohort (>60	Clinical evaluation and total-body CT scans at 3–6 months and at 12 months after surgery over the first year, then annually thereafter. Additional evaluations were performed if the patient's symptoms raised clinical suspicion of relapse.	No details.

				months): 669		
Capogrosso 2019	Italy	1987-2016	Single centre	730	Clinical evaluation and chest-abdomen CT scans performed at 3–6 months and at 12 months after surgery over the first year, and annually thereafter. Additional imaging were performed if the patient's symptoms raised clinical suspicion of relapse.	No details.
Chang 2015*	China	2003-2004	Consecutive patients from single centre	194	Physical examination, laboratory studies, chest imaging and abdominal US or CT scans semi-annually for the first 2 years and annually thereafter.	Mixed types of primary RCC, N1 or M1 disease, prior history of other malignancies, death within the first month after surgery from surgical complications.
Chang 2016*	China	2008-2009	Consecutive patients from single centre	430	Physical examination, laboratory studies, chest XR, and abdominal US or CT every 6 months for the first 2 years and annually thereafter.	Non-ccRCC confirmed histopathologically, metastatic disease at diagnosis, history of previous anti-cancer therapies and other malignancies, bilateral renal cancer, perioperative mortality, preoperative routine blood parameters unavailable.
Chen 2017	China	2012-2013	Single centre	176	For locally advanced ccRCC patients, every 6 months for the first 3 years and annually thereafter. For localized ccRCC patients, imaging was performed twice in the first year and annually thereafter.	Anti-tumour therapy, other concurrent tumours, other acute or chronic concurrent non-cancer diseases (including liver disease, inflammation, and infection), concurrent distant metastasis, lost to follow-up.
Cindolo 2005	Italy, France and Austria	1984-2002	Institutional databases	2404 (815 for RFS)	In accordance with the protocols of the centres. Information on follow-up was updated in each centre by direct phone call and, alternatively, by contacting general practitioners or relatives.	Distant metastases, lymph node metastases, pT4 tumours, benign lesions, bilateral disease and Bellini ducts carcinoma, death after surgical complications, death within 1 month, missing data.
Cindolo 2008	Italy, France and Austria	1984-2002	Institutional databases	2471	In accordance with the protocols of the centres. Information on follow-up was updated in each centre by direct phone call and, alternatively, by contacting general practitioners or relatives.	Distant metastases, lymph node metastases, benign lesions, bilateral disease and Bellini ducts carcinoma, death after surgical complications or within 1 month, missing data.
Ficarra 2008	Italy	1986-2000	Single centre	351	Abdominal imaging twice yearly with alternating US and CT, and chest XR annually for the first 5 years. Abdominal imaging and chest XR annually thereafter.	Non-ccRCC.
Fu 2014*	China	2001 and 2003-2004	Single centre	259	No details.	No FFPE tumour sample, non-ccRCC, missing follow-up information, death within 1 month of surgery, sections that easily fell off during standard ISH procedure, N1 or M1 status.
Fu 2015	China	2001-2004	Single centre	180	Physical examination every 5–6 months during the first 5 years and annually thereafter.	Deficient follow-up, unreached clinical records, poor tumour sample preservation for TMA, unqualified HE section, suspicious death (died within 1 months after surgery), extensive necrosis (> 50% or with massive haemorrhage), inadequate control staining or ambiguous marker staining, previously treated with cytokine.
Fu 2015	China	2003-2004	Consecutive patients from single centre	188	Physical examination, laboratory studies, chest imaging, and abdominal US or CT scan every 6 months for the first 2 years and annually for 5 years.	Non-ccRCC, incomplete follow-up data, bilateral disease, familial RCC, preoperative neoadjuvant and/or

						postoperative adjuvant therapy, death within 1 month after surgery.
Haddad 2017	USA	1997-2010	Single centre	Training set: 183; Validation set: 184	Physical examination, serum chemistry, liver function tests, chest radiography and abdominal US or CT every 3 months for the first year and semi-annually thereafter.	Non-ccRCC, metastasis, incomplete immunostaining.
Han 2003	Netherlands and US	NN: 1990-2001; MDA: 1987-2000; UCLA: 1989-2001	Three centres	NN: 177; MDA: 399; UCLA: 484	No details.	Metastatic disease.
Hupertan 2006	France	1985-2000	Single centre	565	Annual abdominal US and CT abdomen.	Performance status >3 and/or metastatic disease at diagnosis, pT4, bilateral synchronous disease, preoperative lymph node invasion, benign disease, collecting duct carcinoma, tumour with unclassified histology, chronic renal insufficiency, solitary kidney, lost to follow-up.
Hutterer 2014	Austria	2000-2010	Single centre	678	Clinical and laboratory examination with chest XR and abdominal US predominantly and CT or MRI in higher risk patients every 6 months for the first 5 years and annually thereafter.	Non-ccRCC.
Jensen 2009	Denmark	1992-2001	Consecutive patients from single centre	121	No details.	Non-ccRCC, metastatic disease, recurrence of previous RCC, previous IL-2 treatment, synchronic cancers, perioperative mortality, renal transplantation, lack of tumour tissue.
Jeong 2017	South Korea	2005-2011	Consecutive patients from one centre and randomly selected patients from second centre	399	No details.	Non-ccRCC, no gross photographs available, metastatic ccRCC, multiple or bilateral masses, received preoperative chemoembolisation or targeted therapy.
Klatte 2009	USA	1989-2000	Randomly selected patients from single centre	170	No details.	Not N0M0, non-ccRCC.
Lamb 2012	UK	1997-2007	Single centre	169	Prospectively followed up according to Leibovich risk stratification protocol; low risk patients underwent annual US and chest XR, intermediate risk underwent 6 monthly CT scan for 2 years then annually until 5 years, and high risk underwent 6 monthly CT scan for 3 years and then annually until 5 years. Thereafter, annual US and chest XR.	Nodal or distant disease on preoperative CT scanning, non-ccRCC.
Lee 2018	USA	1990-2009	Single centre	1642	Chest radiograph and renal/retroperitoneal US or cross-sectional imaging every 3–6 months, depending on pathologic stage and grade. Pathologic T2 or Fuhrman grade 3–4 had more intense follow-up. For patients who chose not to obtain follow-up studies	Bilateral renal masses, familial RCC syndromes, T3c or T4 tumours, sarcomatoid elements.

					at the study centre, outside imaging was reviewed when available.	
Liu 2009	China	1993-2004	Single centre	653	Annual abdominal US and CT.	Distant metastases, lymph node invasion, pT4, bilateral disease, unclassified histology or Fuhrman grade, chronic renal insufficiency, lost to follow up.
Liu 2014	China	2004	Single centre	104	No details.	Samples were necrotic and haemorrhagic in large areas, missing follow-up data, neoadjuvant or adjuvant therapy.
Liu 2014*	China	2004	Single centre	104	No details.	Metastatic disease, incomplete data, severe medical problems, adjuvant anticancer therapy.
Liu 2015*	China	Training cohort: 2003-2004; Validation cohort: 2001	Single centre	Training cohort: 189; Validation cohort: 63	No details.	Missing follow-up data, coexisting severe medical problems and familial RCC, neoadjuvant or adjuvant therapy, death within 1 month after surgery, tumour metastasis (N1 or M1).
Liu 2015*	China	Group A: 2003-2004; Group B: 2001	Single centre	Group A: 188; Group B: 67	No details.	Missing follow-up data, large area of necrotic and haemorrhagic tissue in samples, neoadjuvant or adjuvant therapy.
Liu 2016	China	2001-2004	Single centre	263	No details.	Larger necrotic and haemorrhagic area hampering the obtaining of representative area in sample, preoperative neoadjuvant therapy.
Lucca 2015	Austria	2002-2014	Single centre database	430	According to guidelines.	Non-ccRCC, co-morbidities affecting systematic inflammatory response markers, missing data, bilateral disease, metastatic disease.
May 2009	Germany	1992-2006	Single centre	771	Physical examination and US every 3 months and CT abdomen and thorax every 6 months in the first 2 years. Then physical and US examination every 6 months, and CT abdomen and thorax annually. Further investigation (i.e. MRI, cranial CT, radioisotope bone scan) was carried out individually in response to existing symptoms of the patient or tumour progress.	Advanced disease, bilateral synchronous tumours, Von Hippel-Lindau syndrome, Bellini duct carcinoma, death within 1 month of surgery from surgical complications, follow-up <12 months without any defined event.
Morgan 2018	USA	2000-2009	Two centres	565	No details.	Neoadjuvant therapy, bilateral, sarcomatoid, collecting duct, node-positive tumours, any clinical evidence of metastatic disease, <37 days follow-up, insufficient tumour content or extracted RNA.
Morshaeuser 2018	Germany	1999-2004	Consecutive patients from single centre	343	No details.	Metastatic or lymph node positive disease, failed immunochemical staining.
Na 2016	China	2003-2004	Two centres	162	No details.	Preoperative radiotherapy or chemotherapy, metastatic disease, died of postoperative complications.
Niu 2016*	China	2008-2009	Single centre	384	Physical examination, laboratory tests, MRI and CT scans semi-annually for the first 2 years and annually thereafter.	Non-ccRCC , T4, N1 or M1 disease, history of other malignancies, neoadjuvant therapy, perioperative mortality, bilateral disease, familial RCC.

Pan 2015*	China	2003-2004	Single centre	184	Every 3–4 months for the first year, every 6 months from year 2–5, and annually thereafter. Abdominal and chest CT were alternated with abdominal US and chest radiographs. Bone and brain scans were requested only in the case of overt symptoms.	Preoperative neoadjuvant therapy, metastasis (N1 or M1 tumours) at the time of surgery.
Pichler 2011	Austria	1984-2006	Consecutive patients from single centre	1,754	Evaluation was done every 6 months for 5 years and annually thereafter for locally advanced tumour stages.	Non-ccRCC , metastatic disease at diagnosis, synchronous bilateral tumours, younger than 18 years at diagnosis.
Pichler 2012	Austria	1984-2006	Consecutive patients from single centre	1,754	Evaluation was done every 6 months for 5 years and annually thereafter for locally advanced tumour stages.	Non-ccRCC, metastatic disease at diagnosis, synchronous bilateral tumours, younger than 18 years at diagnosis.
Pichler 2013	Austria	1984-2010	Consecutive patients from single centre	2127	Routine clinical, laboratory examinations and radiological examinations.	Synchronous bilateral tumours, von Hippel-Lindau disease, lacking follow-up data. Only the first tumour was chosen for analysis in bilateral metachronous RCCs for whole cohort calculations.
Qu 2016*	China	2005-2007	Single centre	258	Physical examination, laboratory studies, chest imaging and abdominal US or CT scan every 3 months for the first 5 years and annually thereafter.	Neoadjuvant or adjuvant therapy, perioperative mortalities, mixed RCC.
Rini 2015	France	1995-2007	Two centres	626	No details.	Neoadjuvant or adjuvant therapy, synchronous or metachronous bilateral RCC, Von Hippel-Lindau disease very little tumour (<5% of the area occupied by invasive cancer cells), insufficient RNA (<167 ng for the validation study) for RT-PCR analysis, inadequate RNA quality measured by standard methods, recurrence within 6 months of surgery in the absence of adequate imaging at the time of surgery or during the 6 months following surgery.
Sekar 2017	USA	2007-2014	Single centre	314	Physical examination, laboratory studies, and imaging.	Benign tumours or mucinous tubular and spindle cell carcinoma, unavailable preoperative laboratory results, age <18 years.
Seles 2017	Austria	2005-2013	Single centre	652	No details.	No details.
Sim 2012	UK	1999-2006	Single centre	164	No details.	Non-ccRCC, Von Hippel-Lindau disease, polycystic kidney disease, T4 disease
Song 2019	China	2010-2012	Single centre	325	Routine blood tests and imaging, examination every 3 months within the first 3 years, every 6 months for the next 2 years and then annually until death.	Distant metastasis at surgery, other tumours, immune system disease, insufficient data from medical record, missing follow-up.
Sorbellini 2005	USA	Not explicit for validation cohort (recruitment period for development cohort 1989-2002)	Single centre	200	No details.	Von Hippel-Lindau disease, hereditary papillary RCC, bilateral renal masses, distant metastases or metastatic regional lymph nodes before or at the time of operation, stage pT4 and pT3c, data lost in audit.

Suzuki 2011	Japan	1991-2004	Single centre	211	Clinical examination, laboratory tests, chest–abdominal CT every 6 months during the first 5 years, and yearly thereafter.	Non-ccRCC.
Tan 2010	Singapore	1990-2006	Single centre	355	No details.	Regional or nonregional lymph nodes, distant metastases.
Tan 2011	Singapore	1990-2006	Single centre	Kattan and Karovicz: 390; Sorbellini: 322; Liebovich: 322	No details.	Non-ccRCC, pT4, ECOG performance status >1.
Tsujino 2017	Japan	2002-2015	Single centre	268	Followed NCCN Clinical Practice Guidelines. CT and chest XR to detect disease progression every 3 months in the first year and every 6 months thereafter.	Metastatic disease at the time of nephrectomy, missing clinicopathological information.
Tsujino 2018	Japan	2005-2015	Single centre	195	CT and chest XR to detect disease progression every 3 months in the first year and every 6 months thereafter.	Did not undergo nephrectomy or had missing clinicopathological information.
Tsujino 2019	Japan	1990-2015	RCC databases from two centres	627	CT and chest XR to detect disease progression every 3 months in the first 2 years and every 6 months thereafter.	Did not undergo nephrectomy or had missing clinicopathological information.
Utsumi 2011	Japan	1990-2005	Two centres: CUH and CCC	217 (CUH: 152; CCC: 65)	Clinical and laboratory examinations every 3 months. Radiological tests were carried out in accordance with the protocols of each institution.	Large tumour (T4), bilateral disease, tumour with unclassified histology, chronic renal insufficiency or lost to follow up.
Vasudev 2019	UK	Contemporary cohort: 2011-2014; Historical cohort: 1998-2006	Contemporary: multicentre (11 UK centres); Historic: single centre	Contemporary cohort: 384; Historical cohort: 191	No details.	Known familial RCC (e.g., Von Hippel-Lindau syndrome), renal cancer acquired following and/or during renal replacement therapy, high risk or with known HIV, Hepatitis B/C or other blood-borne infectious disease, not localised ccRCC.
Verine 2018	France	1998-2014	Consecutive patients from two centres	448	No details.	<18 month follow-up without an early metastatic evolution (< 12 month), non-ccRCC.
Viers 2014	USA	1995-2008	Single centre	827	Quarterly for the first 2 years, semi-annually for the next 2 years, and annually thereafter for patients without evidence of recurrent disease.	Non-ccRCC, metastatic disease, no pre-treatment NLR collected within 90 days before radical nephrectomy.
Wang 2016	China	2001-2004	Single centre	268	Physical examination, laboratory diagnosis, chest imaging, abdominal CT scans or US twice a year for the first 2 years and annually thereafter.	Non-ccRCC, history of previous anti-cancer therapy.
Wang 2016*	China	2008-2009	Consecutive patients from single centre	416	No details.	Non ccRCC, radiotherapy/chemotherapy prior to surgery, nodal, metastatic or T4 disease.
Wei 2019	China and USA	China: 2004-2012; USA: 1998-2010	China: three centres; TCGA set: 13 medical centres in the USA	China set: 410; USA/TCGA set: 441	No details.	Synchronous or metachronous bilateral RCC, inherited Von Hippel-Lindau disease, neoadjuvant therapy or adjuvant therapy

Wu 2015*	China	2001 and 2003-2004	Consecutive patients from single centre	255	No details.	Non-cRCC, tumours with necrosis >80 %, death within 1 month after surgery due to surgical complications.
Xia 2016	China	2005-2007	Consecutive patients from single centre	265	Every 3 months during the first 5 years and annually thereafter.	Other former malignant tumour, perioperative mortalities, adjuvant or neoadjuvant therapy, mixed RCC, bilateral renal cancer, FFPE samples necrosis area >80%.
Xia 2017*	China	2005-2007	Single centre	268	Every 3 months.	Other malignant tumours, targeted therapy prior to or following surgery, mixed RCC, bilateral renal cancer, tumour necrosis area >80%, perioperative morbidity.
Xiong 2016	China	2005-2007	Consecutive patients from single centre	254	Every 3 months during the first 5 years and annually thereafter.	Other malignant tumour before, adjuvant or neo-adjuvant therapies including targeted therapies, samples with over 80% necrotic or haemorrhagic area, bilateral tumours
Xu 2015*	China	2001-2004	Consecutive patients from single centre	267	Physical examination, laboratory studies, chest imaging, and abdominal US or CT scans every 6 months for the first 2 years and annually thereafter.	N1- or M1-stage tumours.
Xu 2017*	China	2008-2009	Single centre	410	No details.	Incomplete follow-up data, bilateral disease and familial RCC, neoadjuvant or adjuvant therapy, death within 1 month after surgery.
Yang 2015*	China	Validation cohort: 2001; Training cohort: 2003-2004	Single centre	Training cohort: 186; Validation cohort: 64	Physical examination, laboratory studies, chest imaging, and abdominal US or CT scans every six months for the first 2 years and annually thereafter.	Neoadjuvant treatment, death within 30 days of surgery or before discharge.
Yang 2016*	China	2001-2004	Consecutive patients from single centre	268	Physical examination, laboratory studies, chest imaging, and abdominal US or CT scans every 6 months for the first 2 years and annually thereafter.	Non-ccRCC, neoadjuvant or adjuvant treatments.
Zhang 2017	China	2008-2009	Single centre	585	No details.	Mixed RCC, tumours with necrosis >80%, death within 1 month after surgery due to surgical complications, N1 or M1 tumours.
Zhu 2015*	China	No details	Single centre	67	No details.	Pre-op neoadjuvant and/or post-op adjuvant therapy
Zhu 2017	China	2003-2008	Single centre	446	No details.	N1/M1 disease, history of anticancer therapy, history of other malignant tumours, non-ccRCC.
Zhu 2019	China	2006-2013	Consecutive patients from single centre	942	Clinical and radiological assessments every 3 months for first 2 years post-surgery, then every 6 months until 4 years, then every year thereafter.	Non-ccRCC, distant metastases, bilateral renal masses before or at the time of surgery, hereditary RCC or Von Hippel–Lindau disease, lost to follow up.

*studies included only for assessment of improvement in performance of previously published risk models with the addition of one or more additional prognostic markers

CCC: Chiba Cancer Center; ccRCC: clear cell renal cell carcinoma; CT: computerised tomography; CUH: Chiba University Hospital; ECOG: Eastern Cooperative Oncology Group; FFPE: formalin-fixed paraffin-embedded; HE: haematoxylin and eosin; ISH: in situ hybridisation; MDA: MD Anderson; MRI: magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; NN: University Medical Center Nijmegen, Netherlands; RCC: renal cell carcinoma; NLR: neutrophil-lymphocyte ratio; RFS: recurrence free survival; RT-PCR: reverse transcription polymerase chain reaction; SEER: Surveillance, Epidemiology, and End Results; TCGA: The Cancer Genome Atlas; TMA: tissue microarray; UNC: University of North Carolina; UCLA: University of California, Los Angeles; US: ultrasound; XR: x-ray

Supplementary Table 4. Key study characteristics and risk of bias assessment for external validations of models predicting recurrence free survival

Risk model	Author, year	Country	Recruitment period	Median follow-up (months)	Time period (years)	N	Event rate (%)	ccRCC (%)	Risk of bias assessment				
									Domain 1	Domain 2	Domain 3	Domain 4	Overall
Cindolo	Brookman-Am 09	Germany	1992-2006	67	7	771	22.4	100	High	Low	Low	Unclear	High
	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	815	18.7	86.9	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	23.9	81	Low	Low	Low	High	High
	Utsumi 2011	Japan (CUH)	1990-2005	.	5	152	25	94.1	Low	Low	Unclear	High	High
	Utsumi 2011	Japan (CCC)	1990-2005	.	5	65	20	89.2	Low	Low	Unclear	High	High
GPS	Tsujino 2019*	Japan	1990-2015	73	5	627	.	89.6	Low	Low	Low	High	High
Jeong 2017	Jeong 2017	South Korea	2005-2011	.	5	399	23.3	100	Low	Low	Unclear	Unclear	Unclear
Karakiewicz	Liu 2009	China	1993-2004	65	16	653	23.9	81	Low	Low	Low	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	390	25.1	86	Low	Low	Unclear	Unclear	Unclear
Kattan	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	815	18.7	86.9	Low	Low	High	High	High
	Hupertan 2006	France	1985-2000	60	5	565	17.9	83.2	Low	Low	Low	High	High
	Liu 2009	China	1993-2004	65	16	653	23.9	81	Low	Low	Low	High	High
	Suzuki 2011	Japan	1991-2004	81	5	211	27.0	100	Low	Low	Low	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	390	25.1	86	Low	Low	Unclear	Unclear	Unclear
	Utsumi 2011	Japan (CUH)	1990-2005	.	5	152	25	94.1	Low	Low	Unclear	High	High
	Utsumi 2011	Japan (CCC)	1990-2005	.	5	65	20	89.2	Low	Low	Unclear	High	High
Klatte 2009	Morshaeuser 18	Germany	1999-2004	100	10	343	.	72.3	Low	Low	Unclear	High	High
Leibovich	An 2015	China	2003-2008	67	5	191	19.9	100	Low	Low	Low	High	High
	Beisland 2015	Norway	1997-2013	38.3	10	383	17.0	100	Low	Low	High	Unclear	High
	Jensen 2009	Denmark	1992-2001	124	16	121	50.4	100	Low	Low	Unclear	Unclear	Unclear
	Pichler 2011	Austria	1984-2006	82	10	1754	21.4	100	Low	Low	Unclear	Unclear	Unclear
	Rini 2015	France	1995-2007	66	5	626	16	100	Low	Low	Unclear	Unclear	Unclear
	Seles 2017	Austria	2005-2013	73	10	652	10.3	81.4	Unclear	Low	Unclear	High	High
	Tan 2010	Singapore	1990-2006	56	5	355	22	100	Low	Low	Unclear	Unclear	Unclear
	Tan 2011*	Singapore	1990 - 2006	65	5	322	25.2	86	Low	Low	Unclear	Unclear	Unclear
	Vasudev 2019	UK	2011-2014	52.8	5	384	.	100	Low	Low	Unclear	High	High
	Vasudev 2019	UK	1998-2006	128.4	5	191	.	100	Low	Low	Unclear	High	High
	Verine 2018*	France	1998-2014	50	5	448	16.5	100	High	Low	Unclear	Low	High
	Wang 2016	China	2001-2004	89	10	268	23.5	100	Low	Low	Low	Unclear	Unclear
	Wei 2019	China	2004-2012	76	5	410	23.9	100	Low	Low	Unclear	Unclear	Unclear
	Xia 2016	China	2005-2007	99	8	265	27.2	100	Low	Low	Low	Low	Low
	Zhang 2017	China	2008-2009	67	6	585	19.32	100	Low	Low	Unclear	Unclear	Unclear
	Zhu 2019	China	2006-2013	72	10	942	20.7	100	Low	Low	Low	High	High
mGPS	Tsujino 2019*	Japan	1990-2015	73	5	627	.	89.6	Low	Low	Low	High	High
Recurrence	Rini 2015	France	1995-2007	66	5	626	16	100	Low	Low	Unclear	Unclear	Unclear
Sao Paulo	May-09	Germany	1992-2006	67	5	771	22.4	78.5	High	Low	Low	Unclear	High
Sorbellini	Lee 2018	USA	1990-2009	39	5	1642	3.0	100	Low	Low	High	Unclear	High

	Liu 2009	China	1993-2004	65	16	653	23.9	81	Low	Low	Low	High	High
	Sorbellini 2005	USA	No details	33	5	200	13	100	High	Low	Unclear	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	322	24.8	86	Low	Low	Unclear	Unclear	Unclear
SSIGN	Haddad 2017 (t)	USA	1997 - 2010	63.5	15	183	13.4	100	Low	Low	Low	High	High
	Haddad 2017 (v)	USA	1997 - 2010	63.5	15	184	13.4	100	Low	Low	Low	High	High
	Liu 2016	China	2001-2004	98	10	263	23.2	100	Low	Low	Unclear	Unclear	Unclear
	Liu 2009	China	1993-2004	65	16	653	23.9	81	Low	Low	Low	High	High
	Lucca 2015	Austria	2002-2014	40	4	430	10.7	100	Low	Low	Unclear	High	High
	Zhang 2017	China	2008-2009	67	6	585	19.32	100	Low	Low	Unclear	Unclear	Unclear
	Zhu 2017	China	2003-2008	.	10	446	.	100	Low	Low	Unclear	Unclear	Unclear
	Xiong 2016	China	2005-2007	99	8	254	26.8	100	Low	Low	Low	Low	Low
S-TRAC trial	Capogrosso 2019	Italy	1987-2016	49	1	730	.	100	Unclear	Low	Low	High	High
TNM 2002	Pichler 2013	Austria	1984-2010	75	25	2127	20.8	100	Low	Low	Low	High	High
TNM 2010	Fu 2015	China	2003-2004	106	10	188	32.4	100	Low	Low	Low	Unclear	Unclear
	Pichler 2013	Austria	1984-2010	75	25	2127	20.8	100	Low	Low	Low	High	High
	Xia 2016	China	2005-2007	99	8	265	27.2	100	Low	Low	Low	Low	Low
TNM 2016	Wei 2019	China	2004-2012	76	5	410	23.9	100	Low	Low	Unclear	Unclear	Unclear
UISS	Capogrosso 2018	Italy	1995-2016	.	15	1429	.	78*	Unclear	Low	Unclear	High	High
	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	815	18.7	86.9	Low	Low	High	High	High
	Klatte 2009	USA	1989-2000	85	5	170	19.4	100	Low	Low	Unclear	High	High
	Liu 2009	China	1993-2004	65	16	653	23.9	81	Low	Low	Low	High	High
	Tan 2010	Singapore	1990-2006	56	5	355	22	100	Low	Low	Unclear	Unclear	Unclear
	Tsujino 2019*	Japan	1990-2015	73	5	627	.	89.6	Low	Low	Low	High	High
	Wang 2016	China	2001-2004	89	10	268	23.5	100	Low	Low	Low	Unclear	Unclear
	Xia 2016	China	2005-2007	99	8	265	27.2	100	Low	Low	Low	Low	Low
	Zhang 2017	China	2008-2009	67	6	585	19.32	100	Low	Low	Unclear	Unclear	Unclear
	Zhu 2017	China	2003-2008	.	10	446	.	100	Low	Low	Unclear	Unclear	Unclear
Wei 2009	Wei 2019	China	2004-2012	76	5	410	23.9	100	Low	Low	Unclear	Unclear	Unclear
Yaycioglu	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	815	18.7	86.9	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	23.9	81	Low	Low	Low	High	High
	Utsumi 2011	Japan (CUH)	1990-2005	.	5	152	25	94.1	Low	Low	Unclear	High	High
	Utsumi 2011	Japan (CCC)	1990-2005	.	5	65	20	89.2	Low	Low	Unclear	High	High

*Details for number of participants, event rate and percentage with clear cell renal cell carcinoma (ccRCC) include participants with metastases. t – test cohort; v – validation cohort

Supplementary Table 5. Results of meta-regression for recurrence-free survival

	Univariable			Multivariable			
	Number of studies	**Coefficient***	**p value**	**Number of studies**	**Coefficient***	**Unadjusted p value**	**Adjusted p value****
Leibovich							
Baseline year of recruitment	15	0.000040 (-0.018-0.018)	0.996	13	-0.0042 (-0.028-0.019)	0.692	0.987
Duration of prediction	16	0.010 (-0.034-0.055)	0.627		0.023 (-0.049-0.095)	0.476	0.889
Event rate	14	-0.010 (-0.029-0.0082)	0.249		-0.012 (-0.041-0.016)	0.341	0.736
Proportion of ccRCC	16	-0.016 (-0.035-0.0039)	0.107		-0.010 (-0.041-0.020)	0.454	0.861
UISS							
Baseline year of recruitment	10	-0.0064 (-0.040-0.030)	0.669	7	0.0045 (-0.089-0.099)	0.856	0.996
Duration of prediction	10	-0.039 (-0.091-0.013)	0.124		-0.046 (-0.53-0.44)	0.722	0.948
Event rate	7	-0.061 (-0.13-0.0085)	0.074		-0.042 (-0.31-0.23)	0.571	0.800
Proportion of ccRCC	10	-0.012 (-0.041-0.017)	0.367		-0.019 (-0.26-0.22)	0.765	0.971
SSIGN							
Baseline year of recruitment	8	0.0018 (-0.066-0.069)	0.951	7	0.047 (-0.23-0.32)	0.534	0.826
Duration of prediction	8	-0.014 (-0.09-0.059)	0.664		-0.016 (-0.25-0.22)	0.801	0.984
Event rate	7	0.010 (-0.049-0.069)	0.684		-0.021 (-0.14-0.094)	0.509	0.796
Proportion of ccRCC	8	-0.024 (-0.062-0.015)	0.181		-0.058 (-0.18-0.059)	0.168	0.309

*Coefficients are on the logit scale

**Adjusted for multiple testing (5000 permutations)

ccRCC – clear cell renal cell carcinoma

Supplementary Table 6. Key study characteristics and risk of bias assessment for external validations of models predicting cancer specific survival

Risk model	Author, year	Country	Recruitment period	Median follow-up (months)	Time period (years)	N	Event rate (%)	ccRCC (%)	Risk of bias assessment				
									Domain 1	Domain 2	Domain 3	Domain 4	Overall
Cindolo	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	2404	15	86.9	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
Karakiewicz	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Morgan 2018	USA	2000-2009	90.8	5	565	5.7	81	Low	Low	Unclear	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	390	16.2	86	Low	Low	Unclear	Unclear	Unclear
Kattan	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	2404	15	86.9	Low	Low	High	High	High
	Lamb 2012	UK	1997-2007	98	4	169	20.7	100	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	390	16.2	86	Low	Low	Unclear	Unclear	Unclear
Klatte	Morshaeuser 2018	Germany	1999-2004	100	10	343	.	72.3	Low	Low	Unclear	High	High
Leibovich	Hutterer 2014	Austria	2000-2010	.	10	678	7.2	100	Low	Low	High	High	High
	Lamb 2012	UK	1997-2007	98	4	169	20.7	100	Low	Low	High	High	High
	Tan 2010	Singapore	1990-2006	56	5	355	13	100	Low	Low	Unclear	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	322	15.8	86	Low	Low	Unclear	Unclear	Unclear
mGPS	Lamb 2012	UK	1997-2007	98	4	169	20.7	100	Low	Low	High	High	High
Sao Paulo	May 2009	Germany	1992-2006	67	5	771	15.8	78.5	High	Low	Low	Unclear	High
Sorbellini	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	322	15	86	Low	Low	Unclear	Unclear	Unclear
SSIGN	Brooks 2014	USA	1992-2010**	.	16	266	.	100	Low	Unclear	Unclear	High	High
	Ficarra 2008	Italy	1986-2000	56	10	351	22.2	100	Low	Low	Low	Unclear	Unclear
	Fu 2015*	China	2001-2004	111	5	180	20.3	100	Low	Low	Low	Low	Low
	Lamb 2012	UK	1997-2007	.	4	169	20.7	100	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Sim 2012	USA	1999 - 2006	85	10	164	.	100	Low	Unclear	Unclear	High	High
	Verine 2018*	France	1998-2014	50	5	448	11.5	100	High	Low	Unclear	Low	High
	Viers 2014	USA	1995-2008	111.6	10	827	28.2	100	Low	Low	Low	Unclear	Unclear
UISS	Brooks 2014	USA	1992-2010**	.	16	266	.	100	Low	Unclear	Unclear	High	High
	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	2404	15	86.9	Low	Low	High	High	High
	Fu 2015*	China	2001-2004	111	5	180	20.3	100	Low	Low	Low	Low	Low
	Lamb 2012	UK	1997-2007	98	4	169	20.7	100	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Tan 2010	Singapore	1990-2006	56	5	355	13	100	Low	Low	Unclear	High	High
	Verine 2018*	France	1998-2014	50	5	448	11.5	100	High	Low	Unclear	Low	High
Yaycioglu	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	2404	15	86.9	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
Zisman	Han 2003 (MDA)	USA	1987-2000	32	5	399	27	.	Low	Low	Unclear	Unclear	Unclear
	Han 2003 (NN)	Netherlands	1990-2001	63	5	177	35	.	Low	Low	Unclear	Unclear	Unclear

	Han 2003 (UCLA)	USA	1989-2001	33	5	484	22	.	Low	Low	Unclear	Unclear	Unclear

*Details for number of participants, event rate and percentage with clear cell renal cell carcinoma (ccRCC) include participants with metastases. **Also includes data from The Cancer Genoma Atlas (TCGA) with no date of recruitment specified.

Supplementary Table 7. Key study characteristics and risk of bias assessment for external validations of models predicting overall survival

Risk model	Author, year	Country	Recruitment period	Median follow-up (months)	Time period (years)	N	Event rate (%)	ccRCC (%)	Risk of bias assessment				
									Domain 1	Domain 2	Domain 3	Domain 4	Overall
Chen 2017	Chen 2017	China	2012-2013	42.3	12	176	13.1	100	Low	Low	High	High	High
Cindolo	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	2404	22.5	86.9	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
CONUT	Song 2019	China	2010-2012	64	5	325	12	89.8	Low	Low	Low	High	High
GRANT	Buti 2019	USA	2001-2015	.	5	73217	13.74	83.2	Low	Low	Unclear	High	High
Karakiewicz	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	390	22	86	Low	Low	Unclear	Unclear	Unclear
Kattan	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	2404	22.5	86.9	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	390	22	86	Low	Low	Unclear	Unclear	Unclear
Leibovich	An 2015	China	2003-2008	67	5	191	15.2	100	Low	Low	Low	High	High
	Chen 2017	China	2012-2013	42.3	12	176	13.1	100	Low	Low	High	High	High
	Sekar 2017	USA	2007-2014	.	5	216	.	100	Low	Low	Unclear	High	High
	Tan 2010	Singapore	1990-2006	56	5	355	20.3	100	Low	Low	Unclear	Unclear	Unclear
	Tan 2011*	Singapore	1990 - 2006	65	5	322	21.9	86	Low	Low	Unclear	Unclear	Unclear
	Wang 2016	China	2001-2004	89	10	268	35.82	100	Low	Low	Low	Unclear	Unclear
	Zhang 2017	China	2008-2009	67	6	585	17.44	100	Low	Low	Unclear	Unclear	Unclear
mGPS	Tsujino 2017	Japan	2002-2015	60	5	268	18.6	89.9	Low	Low	Low	High	High
PNI	Song 2019	China	2010-2012	64	5	325	12	89.8	Low	Low	Low	High	High
Sorbellini	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Tan 2011*	Singapore	1990 - 2006	65	5	322	21.7	86	Low	Low	Unclear	Unclear	Unclear
SSIGN	Chen 2017	China	2012-2013	42.3	12	176	13.1	100	Low	Low	High	High	High
	Liu 2016	China	2001-2004	98	10	263	35.36	100	Low	Low	Unclear	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Na 2016	China	2003-2004	.	10	162	37.65	100	Low	Low	Unclear	Unclear	Unclear
	Sim 2012	UK	1999 - 2006	85	10	164	.	100	Low	Unclear	Unclear	High	High
	Tsujino 2018*	Japan	2005-2015	57	3	195	14.1	91.8	Low	Low	Low	High	High
	Zhang 2017	China	2008-2009	67	6	585	17.44	100	Low	Low	Unclear	Unclear	Unclear
	Zhu 2017	China	2003-2008	.	10	446	.	100	Low	Low	Unclear	Unclear	Unclear
TNM 2010	Chen 2017	China	2012-2013	42.3	12	176	13.1	100	Low	Low	High	High	High
	Liu 2014	China	2004	.	10	104	32.69	100	Low	Low	Unclear	High	High
	Na 2016	China	2003-2004	.	10	162	37.65	100	Low	Low	Unclear	Unclear	Unclear
UISS	Bai 2015	China	2005-2007	99	8	271	.	100	Low	Low	Low	Unclear	Unclear
	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	2404	22.5	86.9	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High
	Na 2016	China	2003-2004	.	10	162	37.65	100	Low	Low	Unclear	Unclear	Unclear
	Tan 2010	Singapore	1990-2006	56	5	355	20.3	100	Low	Low	Unclear	Unclear	Unclear

	Tsujino 2018*	Japan	2005-2015	57	3	195	14.1	91.8	Low	Low	Low	High	High
	Wang 2016	China	2001-2004	89	10	268	35.82	100	Low	Low	Low	Unclear	Unclear
	Zhang 2017	China	2008-2009	67	6	585	17.44	100	Low	Low	Unclear	Unclear	Unclear
	Zhu 2017	China	2003-2008	.	10	446	.	100	Low	Low	Unclear	Unclear	Unclear
Yaycioglu	Cindolo 2005	Italy, France & Austria	1984-2002	60	10	2404	22.5	86.9	Low	Low	High	High	High
	Liu 2009	China	1993-2004	65	16	653	18.8	81	Low	Low	Low	High	High

*Details for number of participants, event rate and percentage with clear cell renal cell carcinoma (ccRCC) include participants with metastases.

Supplementary Table 8. Multivariate meta-analysis of discrimination of risk models in Europe/US populations

Risk model	Number of external validations	Summary risk of bias	Number of patients	Events	Borrowing of strength	Mean rank	SUCRA
Recurrence free survival							
Recurrence score	1	1U	626	99	21.3	3.4	0.8
Sorbellini	2	2H	1842	76	0	3.1	0.8
Klatte 2009	1	1H	343	---	0	5.1	0.7
Leibovich	8	5H, 3U	4559	741**	0	4.8	0.7
UISS	3	3H	2414	185***	7.7	4.7	0.7
Sao Paulo	1	1H	771	173	0	7.4	0.5
Kattan	2	2H	1380	253	12.3	7.2	0.5
TNM 2002	1	1H	2127	443	0	7.5	0.5
S-TRAC trial	1	1H	730	---	0	7.7	0.4
TNM 2010	1	1H	2127	443	0	8.3	0.4
SSIGN	3	3H	797	144	0	10.2	0.2
Cindolo	2	2H	1586	325	13.3	10.3	0.2
Yaycioglu	1	1H	815	152	26.9	11.3	0.1
Cancer specific survival							
SSIGN	4	2H, 2U	1795	404	8.0	3.1	0.8
Karakiewicz	1	1H	565	32	0	3.3	0.8
Zisman	3	3U	1060	276	0	3.4	0.8
Leibovich	2	2H	847	84	14.7	4.6	0.6
mGPS	1	1H	169	35	33.4	4.6	0.6
Klatte 2009	1	1H	343	---	0	4.6	0.6
Kattan	2	2H	2573	395	17.4	6.9	0.4
Sao Paulo	1	1H	771	122	0	7.5	0.3
UISS	3	3H	3021	453	11.6	8.3	0.3
Cindolo	1	1H	2404	360	19.8	9.8	0.1
Yaycioglu	1	1H	2404	360	19.8	10.0	0.1

*H – High risk of bias, U – Unclear risk of bias, L – Low risk of bias

**One study did not give number of events; ***Two studies did not give number of events

Supplementary Table 9. Multivariate meta-analysis of discrimination of risk models in Asian populations

Risk model	Number of external validations	Summary risk of bias	Number of patients	Events	Borrowing of strength	Mean rank	SUCRA
Recurrence free survival							
Jeong 2017	1	1U	399	93	0	2.6	0.9
Wei 2009	1	1U	410	98	22.0	3.8	0.8
Karakiewicz	2	1H, 1U	1043	254	29.6	3.7	0.8
Sorbellini	2	1H, 1U	975	236	29.6	3.1	0.8
Kattan	5	4H, 1U	1471	362	13.3	4.4	0.7
Leibovich	8	3H, 4U, 1L	3338	740	10.7	5.7	0.6
SSIGN	4	1H, 2U, 1L	1755	398	18.9	7.2	0.5
Cindolo	3	3H	870	207	26.6	8.5	0.4
UISS	6	2H, 3U, 1L	2753	482**	16.9	9.5	0.3
TNM 2016	1	1U	410	98	22.0	10.4	0.3
TNM 2010	2	1U, 1L	453	133	19.0	11.4	0.2
mGPS	1	1H	627	---	21.4	11.7	0.2
GPS	1	1H	627	---	21.4	11.7	0.2
Yaycioglu	3	3H	870	207	26.6	11.4	0.2
Overall survival							
Chen 2017	1	1H	176	23	34.5	1.2	1.0
Leibovich	6	1H, 5U	1897	394	12.3	5.1	0.7
Karakiewicz	2	1H, 1U	1043	209	22.7	4.9	0.7
Sorbellini	2	1H, 1U	975	193	22.7	4.9	0.7
SSIGN	6	4H, 2U	2034	429	14.5	5.8	0.6
CONUT	1	1H	39	325	0	7.1	0.5
Kattan	2	1H, 1U	1043	209	22.6	7.0	0.5
PNI	1	1H	325	39	0	8.4	0.4
mGPS	1	1H	268	50	0	8.7	0.4
Cindolo	1	1H	653	123	31.8	7.6	0.4
TNM (2010)	3	2H, 1U	442	118	20.2	8.9	0.3
UISS	6	2H, 4U	2218	481	12.5	9.5	0.3
Yaycioglu	1	1H	653	123	31.8	11.8	0.1

*H – High risk of bias, U – Unclear risk of bias, L – Low risk of bias

**One study did not give number of events

Supplementary Table 10. Discrimination of externally validated risk models without and with the addition of one or more additional prognostic markers

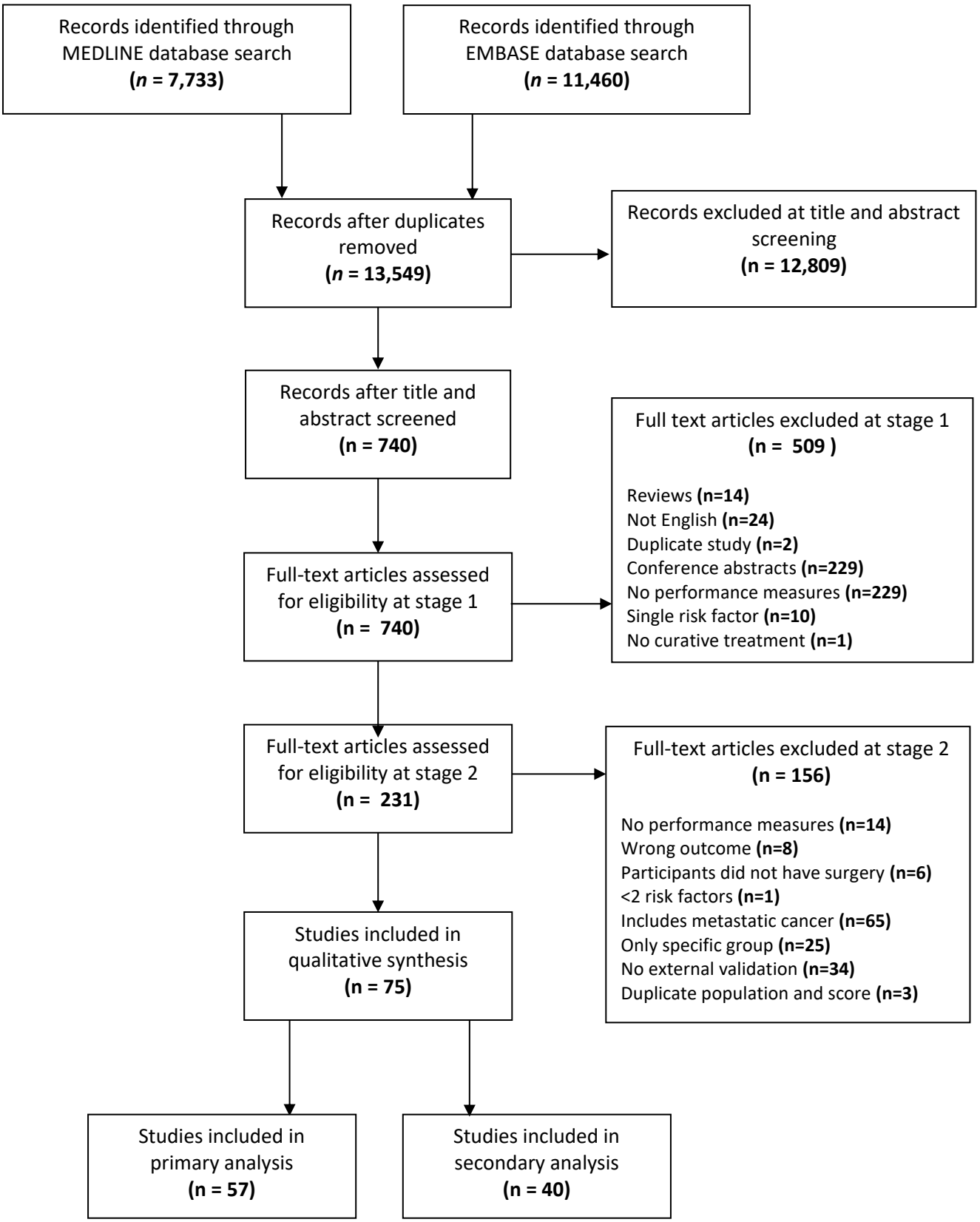
Additional predictor(s)	TRIPOD level*	C-statistic for model without and with (+) the additional predictor(s)										Study
		Leibovich	Leibovich +	UISS	UISS +	SSIGN	SSIGN +	TNM	TNM +	Other	Other +	
Recurrence free survival												
Blood biomarker												
AST/ALT ratio	1a	0.77	0.81									Bezan 2015
GPS (Glasgow prognostic score) with **MLR** (monocyte to lymphocyte ratio)	1a					0.729	0.791					Lucca 2015
LMR (Lymphocyte to monocyte ratio)	1a	0.72	0.738	0.66	0.701	0.707	0.729					Chang 2016
MPV (mean platelet volume) - 3 types	1b	0.80 (0.75-0.84)	0.83 (0.78-0.87)									Seles 2017
Immunohistochemistry												
CCL2 (Chemokine C-C motif ligand 2)	1a	0.71	0.76									Yang 2016
CCR2/CCL2 signature	1a	0.742	0.762	0.676	0.724							Wang 2016
CLEC-2 (c-type lectin-like receptor 2)	1b			0.638	0.682	0.631	0.672	0.608	0.664			Xiong 2016
CSF-1 (Colony stimulating factor-1)	Not clear			0.638	0.678	0.71	0.718					Yang 2015
CTR1 (Copper transporter 1)	1a	0.725		0.713	0.75		0.763	0.653	0.722			Xia 2017
CXCR2 (CXC Chemochine receptor 2)	Not clear	0.669	0.717									An 2015
Dectin-1	1b	0.718 (0.67–0.77)	0.762 (0.71–0.82)	0.713 (0.66–0.76)	0.760 (0.71–0.81)			0.658 (0.60–0.72)	0.708 (0.65–0.77)			Xia 2016
Dot1l (Disruptor of telomeric silencing 1-like)	1b			0.721	0.761	0.707	0.735	0.677	0.720			Qu 2016
Epithelial CXCR1(CXC Chemochine receptor 1)	1a			0.696	0.723	0.709	0.725					Zhu 2017
Five-marker risk score (N-cadherin, E-cadherin, Ki67, cyclin D1 and p-4EBP1)	2a					0.626	0.797					Haddad 2017
Gal-9 (Galectin-9)	1a			0.622	0.66	0.692	0.708	0.621	0.665			Fu 2015
GALNT10 (N-acetylgalactosaminyl-transferase 10)	1a			0.624	0.671	0.695	0.724	0.645	0.695			Wu 2015
GALNT4 (N-acetylgalactosaminyl-transferase 4)	1a							0.701 (0.60-0.79)	0.761 (0.67-0.84)			Liu 2014

ICL score (IFN-inducible CXCR3 ligands score)	1a					0.712	0.765					Liu 2016
IL-11	1a			0.62	0.678	0.662	0.686					Pan 2015
IL-1β/IL-18 signature	1a	0.701	0.771	0.689	0.741							Xu 2015
IL-4/IL-13 signature	1a			0.66	0.712							Chang 2015
MGAT5 (β1,6-N-acetylglucosaminyl-transferase V)	3			0.73	0.821	0.73	0.798	0.661	0.74			Liu 2015
MUC13 (mucin13)	1a					0.7336	0.7836					Xu 2017
MUC3A (Mucin 3A)	1a	0.815	0.847	0.724	0.779	0.756	0.812					Niu 2016
Nuclear Snail (zinc-finger transcription factor)	1a			A: 0.695 B: 0.764	A: 0.749 B: 0.81	A: 0.704 B: 0.758	A: 0.730 B: 0.809					Liu 2015
PAK1 (p21-activated kinase 1)	2b			0.763	0.818	0.758	0.815					Zhu 2015
PAK6 (p21-activated Kinase 6)	1a					0.75		0.713 (0.62 -0.80)	0.769 (0.68- 0.85)			Liu 2014
ST3GAL-1 (β-galactoside α-2,3-sialyltransferase 1)	1a			0.63	0.68							Bai 2015
Pathology												
Intratumoural neutrophils	1a	0.74	0.8									Jensen 2009
Pathologic lymph node status	1b									S-TRAC trial 0.72 (0.68-0.76)	S-TRAC trial+ 0.75 (0.71-0.79)	Capogrosso 2019
Tumour size	1a									Sao Paulo Score - 0.73	Sao Paulo Score - 0.78	May 2009
Vascular invasion	1a		0.792									Pichler 2012
Genetic												
Recurrence score	3	0.74	0.81									Rini 2015
six-SNP- based classifier	3	China 0·738; USA/TCGA 0·752	China 0·791; USA/TCGA 0·816									Wei 2019
In-situ hybridisation												
miR-125b (Tumour microRNA-125b)	1b			0.653 (0.61–0.70)	0.705 (0.65–0.76)	0.711 (0.66–0.77)	0.723 (0.67–0.78)	0.626 (0.57–0.68)	0.697 (0.64–0.75)			Fu 2014
Cancer specific survival												
Blood biomarker												
LMR (Lymphocyte to monocyte ratio)	1a	0.83	0.86									Hutterer 2014
NLR (neutrophil to lymphocyte ratio)	1a					0.81	0.82					Viers 2014
Quantitative RT-PCR												
CCP score (Cell cycle proliferation score)	1b							0.84	0.87 (0.82-0.92)	Karakiewicz 0.84	Karakiewicz 0.87	Morgan 2018

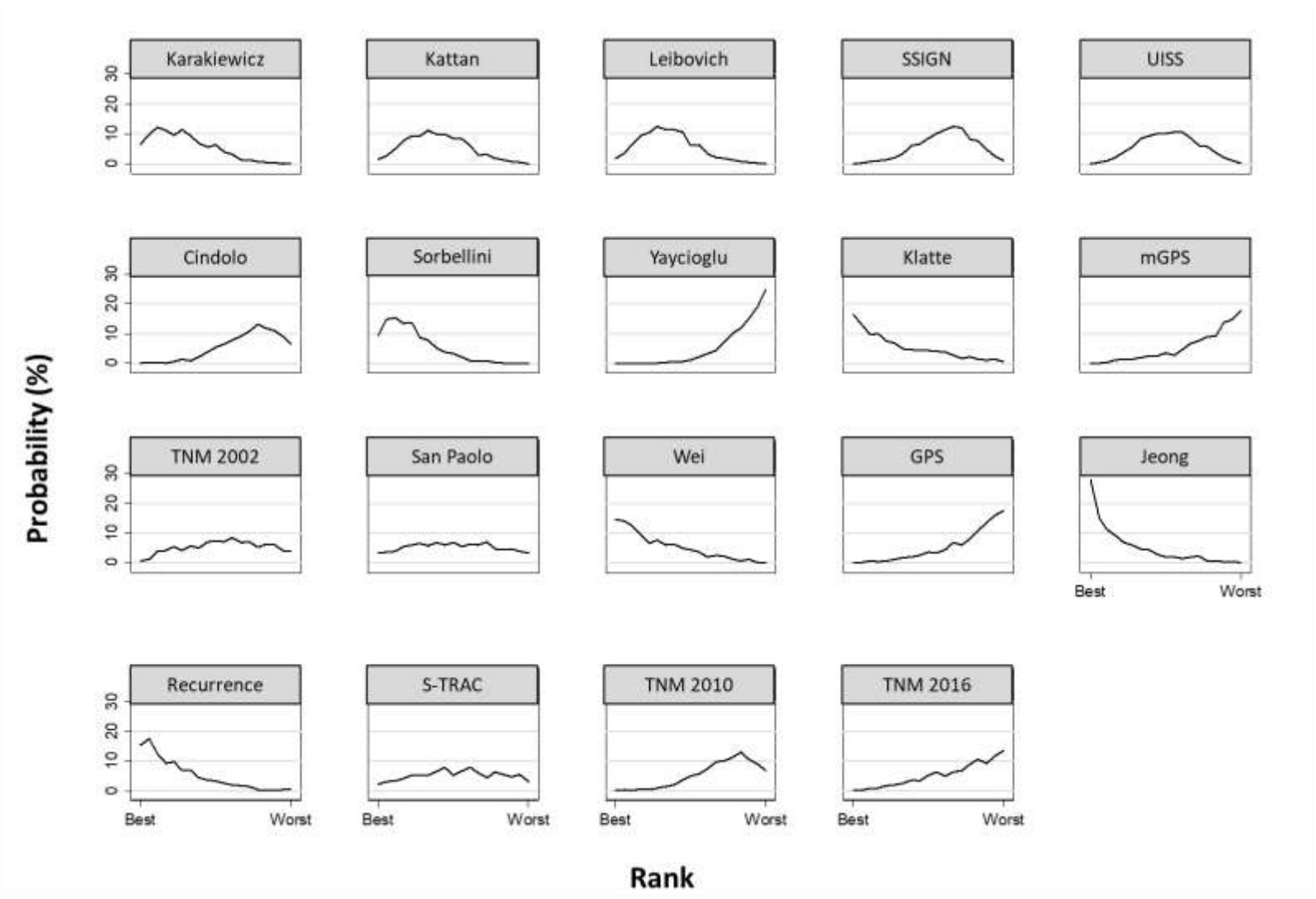
											(0.82-0.92)	
Overall Survival												
Blood biomarker												
LMR (Lymphocyte to monocyte ratio)	1a	0.721	0.754	0.673	0.72	0.71	0.75					Chang 2016
Immunohistochemistry												
CCR2/CCL2 signature	1a	0.724	0.75	0.658	0.714							Wang 2016
CXCR2 (CXC Chemochine receptor 2)	2b	0.671	0.724									An 2015
Epithelial CXCR1(CXC Chemochine receptor 1)	1a			0.683	0.718	0.673	0.704					Zhu 2017
Galectin-7	1a	0.816	0.829	0.743	0.779	0.805	0.822					Wang 2016
HMGA2 (High-mobility group AT-hook 2)	1a			0.711	0.723	0.726	0.736	0.671	0.719			Na 2016
ICL score (IFN-inducible CXCR3 ligands score)	1a					0.705	0.746					Liu 2016
IL-1β/IL-18 signature	1a	0.684	0.722	0.696	0.753							Xu 2015
IL-4/IL-13 signature	1a			0.665	0.715							Chang 2015
MUC13 (Mucin 13)	1a					0.744	0.7933					Xu 2017
MUC3A (Mucin 3A)	1a	0.82	0.859	0.723	0.781	0.768	0.83					Niu 2016
Nuclear Snail (zinc-finger transcription factor)	1a			A: 0.706 B: 0.744	A: 0.762 B: 0.801	A: 0.709 B: 0.756	A: 0.746 B: 0.819					Liu 2015
PAK1 (p21-activated kinase1)	2b			0.744	0.8408	0.756	0.8613					Zhu 2015
PAK6 (p21-activated Kinase 6)	1a					0.76		0.724 (0.63-0.81)	0.790 (0.70-0.86)			Liu 2014
ST3GAL-1 (β-galactoside α-2,3-sialyltransferase 1)	1a			0.65	0.69							Bai 2015

* 1a – Development only; 1b – Development and validation using resampling; 2a – Random split-sample development and validation; 2b – Non-random split-sample development and validation; 3 – Development and validation using separate data; 4 – Validation study

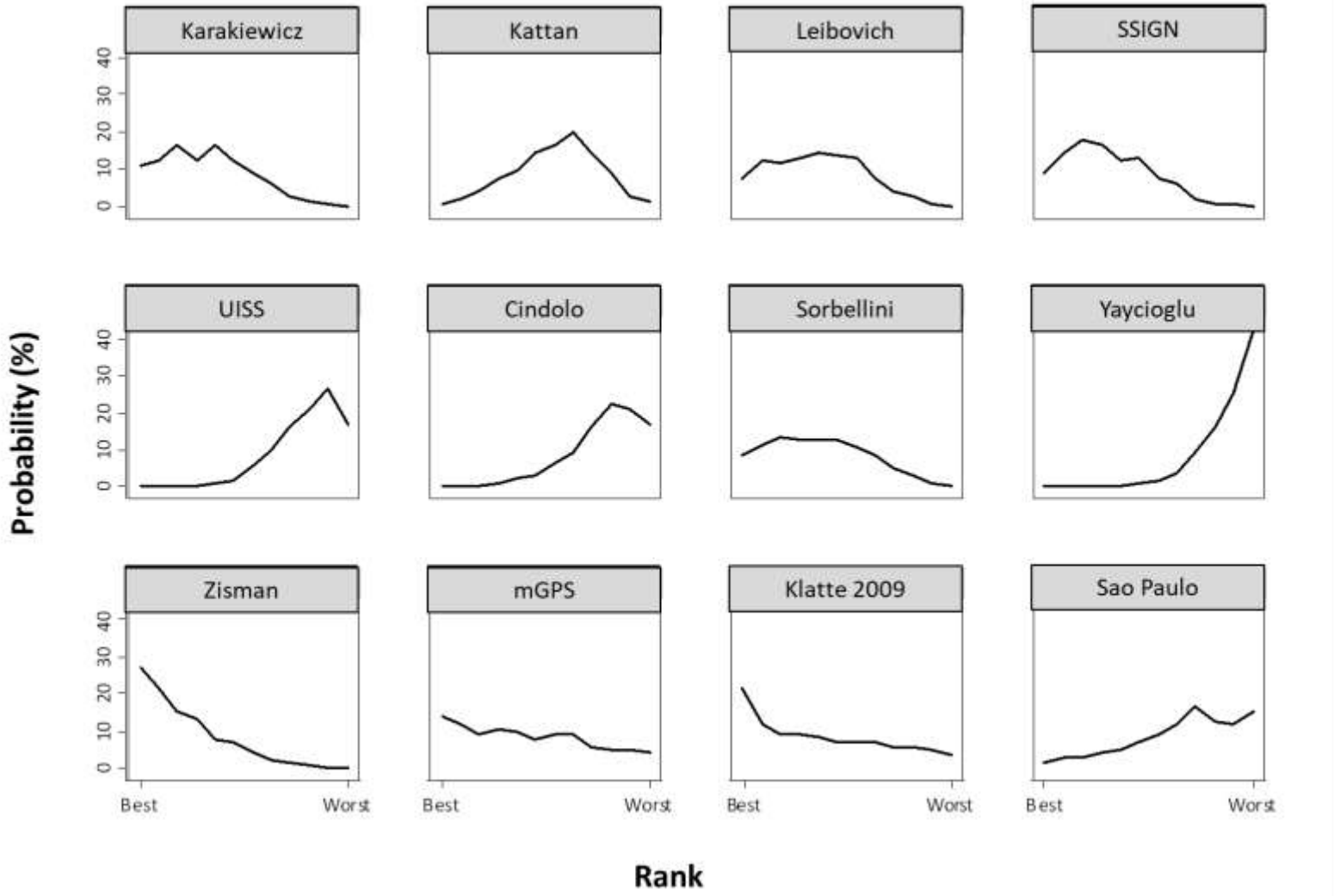
Supplementary Figure 1. PRISMA flow diagram



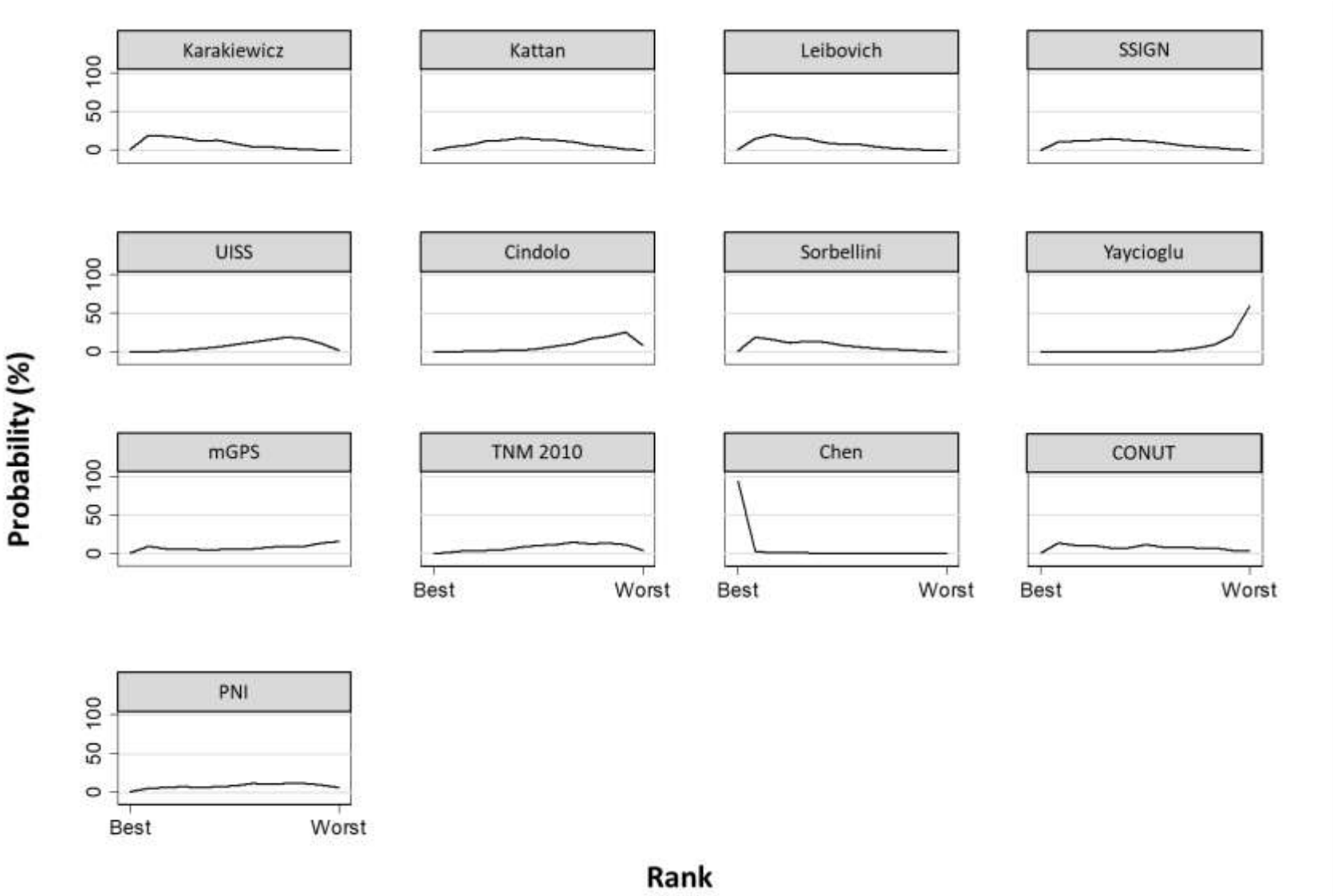
Supplementary Figure 2. Plots of the ranking for each risk score considered in the multivariate meta-analysis for recurrence free survival



Supplementary Figure 3. Plots of the ranking for each risk score considered in the multivariate meta-analysis for cancer specific survival



Supplementary Figure 4. Plots of the ranking for each risk score considered in the multivariate meta-analysis for overall survival



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