Research Square

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The Pan Systemic Inflammation Index is a Predictive Factor for Renal Cell Carcinoma Survival

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Abstract

Background

Systemic inflammation and anemia are increasingly recognized as clinically relevant prognostic factors in renal cell carcinoma (RCC). This study aimed to define and evaluate the Pan-Systemic Inflammation Index (PanSII), a composite prognostic index integrating the Pan-Immune-Inflammation Value (PIV) with anemia, for predicting overall survival (OS) in RCC.

Methods

This retrospective cohort study included 255 patients with pathologically confirmed ≥pT2a RCC who underwent radical nephrectomy between April 2008 and December 2022. PIV was dichotomized using a predefined cut-off value of 328, and anemia was recorded as a preoperative binary variable. PanSII was categorized as follows: PanSII = 0, low PIV without anemia; PanSII = 1, either high PIV or anemia; and PanSII = 2, high PIV with anemia. OS was assessed using Kaplan–Meier analysis, log-rank testing, and Cox regression models. Incremental discriminatory performance was evaluated using Harrell's C-index.

Results

The median age was 59 years, and the median follow-up was 37 months. Preoperative anemia was present in 52.9% of patients, while 58.8% had high PIV. During follow-up, 117 patients died. Survival showed a clear stepwise decline across increasing PanSII categories: the 5-year OS rate was highest in PanSII = 0, intermediate in PanSII = 1, and lowest in PanSII = 2, at 82.6%, 63.5%, and 45.3%, respectively (log-rank $p < 0.0001$). This gradient was also reflected in multivariable analysis, where PanSII = 2 remained independently associated with worse OS compared with PanSII = 0 (HR = 4.49, 95% CI 2.26–8.91, $p < 0.0001$). Moreover, when added to the base clinicopathological model, PanSII increased the C-index from 0.749 to 0.780, indicating a modest but measurable improvement in discriminatory performance.

Conclusions

PanSII was independently associated with OS and provided additional prognostic information beyond conventional clinicopathological variables in patients with RCC undergoing radical nephrectomy. As a simple index derived from routine preoperative blood parameters, PanSII may help refine postoperative risk stratification and individualized surveillance planning, although external validation is required before incorporation into standard prognostic models.

Clinical Trial Registration

Clinical trial number: not applicable.

Introduction

Renal cell carcinoma (RCC) accounts for approximately 2–3% of adult malignancies, and its incidence has been increasing in Western countries. Despite advances in imaging techniques and an increase in incidental RCC diagnoses, 20–30% of patients present with metastatic disease at the time of diagnosis. (1) Therefore, early prognostic risk assessment and appropriate treatment planning in RCC patients are important for improving clinical decision-making and patient outcomes.

Systemic inflammation has been increasingly recognized as a contributor to tumor formation, progression, and metastasis. (2) Systemic inflammation markers, which can be easily derived from peripheral blood markers, are known to be associated with survival outcomes in various tumor types, including RCC. (3) Although many inflammatory markers have been used in the literature to predict the prognosis of RCC, many have limited prognostic value when used alone. For these indices to be used in clinical practice, they need to be easy to calculate, understandable, and reliable.

Among these markers, the Pan-Immune-Inflammation Value (PIV) is a combination of platelet count, monocyte count, and neutrophil/lymphocyte ratio (NLR), prognostic biomarkers associated with systemic inflammation, and was first described in 2020 by Fucà et al. in metastatic colorectal cancer. In that study, the cut-off value for PIV was set at 328, and patients with a PIV above this value were considered high risk. (4) Yekedüz et al. investigated the prognostic value of PIV in patients diagnosed with metastatic RCC and reported that PIV was an independent predictor of survival in patients treated with nivolumab. (5) On the other hand, Baykal et al. investigated the prognostic significance of PIV in patients with localized ≥pT2a non-metastatic RCC and reported that this parameter was an independent prognostic factor for overall survival. (6)

Anemia, seen in approximately 30–40% of RCC patients, is not only an accompanying finding but may also reflect the disease's biological aggressiveness and systemic inflammatory response. According to current guidelines, anemia is an independent poor prognostic factor in the International Metastatic RCC Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) criteria, which are widely used for risk stratification in metastatic RCC. (7, 8) Studies in the literature show that the presence of anemia in patients diagnosed with RCC is associated with poorer treatment response and shorter overall survival. (9, 10) Previous evidence suggests that combining specific RCC biomarkers with routine clinicopathological parameters may improve the prediction of oncological outcomes. (11) In light of these data, we aimed to define a new composite prognostic index called the Pan-Systemic Inflammation Index (PanSII), based on PIV and the presence of anemia, and to examine the prognostic value of this index for overall survival in patients diagnosed with RCC.

Methods

Data from 292 consecutive patients who underwent radical nephrectomy for clinically suspected RCC at the Urology Clinic of Kocaeli University Faculty of Medicine between April 2008 and December 2022 were retrospectively collected. Patients with pathologically confirmed RCC and at least pathological T2a (pT2a) tumor stage were eligible for inclusion. Cases with non-RCC malignancy or benign pathology detected on final pathological examination [urothelial carcinoma (n = 14), oncocytoma (n = 4), cystic nephroma (n = 3), angiomyolipoma (n = 3), liposarcoma (n = 2), polycystic kidney disease (n = 1), multiple myeloma (n = 1), and cystic hydatid disease (n = 1)]; patients with perioperative mortality (n = 4); and patients with incomplete data or unavailable follow-up information (n = 4) were excluded from the study. After applying these exclusion criteria, 255 patients were included in the final analysis (Fig. 1).

Insert Fig. 1

Demographic information of patients, including age, gender, body mass index (BMI), and age-adjusted Charlson Comorbidity Index (ACCI) scores, was obtained from the hospital's electronic medical records. Preoperatively, complete blood count parameters (hemoglobin, platelet, neutrophil, monocyte, and lymphocyte counts) and serum creatinine values as an indicator of renal function were recorded. Pathological data of patients who underwent radical nephrectomy were classified according to the TNM staging system and included pT and pN stages, tumor size, histological RCC subtype, and Fuhrman/ISUP grade (Grade 1–2 and 3–4). In addition, tumor necrosis, perinephric and renal sinus fat invasion, pelvicalyceal system involvement, sarcomatoid differentiation, lymphovascular invasion (LVI), and positive surgical margin status were recorded.

Oncological follow-up data (distant metastasis at diagnosis, metastasis development during follow-up, and mortality) were recorded and compiled into a dataset for statistical analysis of the associations between clinical and pathological variables and survival. Oncological follow-up was performed in accordance with institutional protocols and contemporary guidelines. Follow-up visits consisted of physical examinations and necessary investigations. Patients were initially seen 1 month after surgery, then every 3 months in the first year, every 6 months in the second year, and annually thereafter. In most patients, radiological cross-sectional imaging was performed every 6 months for the first 2 years, and then annually until the fifth year. The follow-up period was defined as the time from surgery to the date of death or the last clinical visit. No patient received neoadjuvant or adjuvant systemic treatment. Metastatic cases were treated with systemic treatment regimens including tyrosine kinase inhibitors (TKIs) and/or immunotherapy, in accordance with standard protocols. Overall survival (OS) was defined as the time from radical nephrectomy to death from any cause or, for surviving patients, to the date of the last follow-up.

Radical nephrectomy included the removal of the kidney and perirenal tissues within Gerota's fascia. Systematic retroperitoneal lymph node dissection was not routinely performed. Nodal status was

defined based on histopathologically confirmed pathological lymph node involvement when lymph node dissection was performed because of preoperative or intraoperative clinical or radiological suspicion. Surgical procedures were performed using either an open or laparoscopic approach.

Laboratory tests were performed within 1 week before nephrectomy, and when multiple sets of laboratory data were available, the most recent set before surgery was included. Based on preoperative peripheral blood laboratory test data, PIV was calculated using the following formula: PIV = monocyte count × platelet count × neutrophil count/ lymphocyte count. (4) The PIV value was used as a binary variable, indicating whether it was above or below the predefined cut-off value of 328, as used in our previous study. (6) Anemia was defined as a hemoglobin value below 12.0 g/dL in women and below 13.0 g/dL in men and was used as a binary variable.

To provide a more comprehensive prognostic assessment, we defined a composite prognostic index, the Pan-Systemic Inflammation Index (PanSII), by integrating the preoperative PIV status with anemia status.

Based on PanSII categories, patients were divided into three groups:

PanSII = 0: PIV < 328 and no anemia.

PanSII = 1: PIV ≥ 328 and no anemia, or PIV < 328 and anemia present.

PanSII = 2: PIV ≥ 328 and anemia present.

This study was conducted in accordance with the project approval number GOKAEK 2024/98, issued by the Kocaeli University Non-Interventional Clinical Research Ethics Committee at its meeting on February 15, 2024.

Overall survival analysis was performed using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. Univariable and multivariable Cox regression analyses were performed to identify factors associated with survival. The predictive accuracy of the Cox regression models was assessed using Harrell's concordance index (C-index, an approximation of the AUC in censored data). The C-index was calculated using R software (Version 1.3.959, Vienna, Austria). In these models, PanSII was used as an independent variable, and its prognostic performance was compared with that of clinicopathological factors. Because PanSII incorporates both PIV and anemia, anemia, PIV, and PanSII were added to the base multivariable model separately. Statistical significance was accepted at $p < 0.05$.

Results

A total of 255 patients were included in the study, with a median age of 59 years (IQR 51–67). Of these, 176 patients (69.0%) were male, and the median ACCI value was 6 (IQR 4–7). Preoperative anemia was detected in 52.9% of patients (n = 135) in the preoperative period. 41.2% (n = 105) of patients were in the

low PIV group (< 328), and 58.8% (n = 150) were in the high PIV group (≥ 328). According to PanSII scores, 27.5% (n = 70) of the patients were classified as PanSII = 0, 33.3% (n = 85) as PanSII = 1, and 39.2% (n = 100) as PanSII = 2. The distribution of demographic and clinical data is detailed in Table 1.

Table 1
Baseline Characteristics of the Study Cohort

Variable	**Total Cohort (n = 255)**
Age (yrs), med (IQR)	59 (51–67)
Gender, n (%)	
Male	176 (69)
Female	79 (31)
ACCI, med (IQR)	6 (4–7)
BMI (kg/m²), med (IQR)	26.95 (24.91–29.41)
Serum creatinine (mg/dL), med (IQR)	0.88 (0.72–1.07)
Hemoglobin (g/dL), med (IQR)	12.4 (10.8–13.9)
Neutrophil count (×10⁹/L), med (IQR)	5.10 (4.10–6.69)
Monocyte count (×10⁹/L), med (IQR)	0.60 (0.42–0.70)
Lymphocyte count (×10⁹/L), med (IQR)	1.83 (1.35–2.32)
Anemia, n (%)	
Present	135 (52.9)
Absent	120 (47.1)
Inflammatory Indices, n (%)	
PIV status, high (≥ 328)	150 (58.8)
PIV status; low (< 328)	105 (41.2)
PanSII score = 0	70 (27.5)
PanSII score = 1	85 (33.3)
PanSII score = 2	100 (39.2)
ACCI, age-adjusted Charlson comorbidity index; IQR, interquartile range; BMI, body mass index.; PIV, pan-immune-inflammation value; PanSII, pan-systemic inflammatory index.	

Insert Table 1

Histopathological examination after nephrectomy revealed a median tumor size of 9.7 cm (IQR 8.5–12.0). The most common histopathological subtype was clear cell RCC (71%), and 59.6% of tumors were high grade (ISUP grade 3–4). Positive surgical margins were detected in 16 cases (6.3%).

The median follow-up period was 37 months (IQR 13–82). At the final follow-up, metastasis developed during follow-up in 63 patients (31%), and 117 patients (45.9%) died. Overall survival (OS) analysis for the entire cohort showed 2- and 5-year OS rates of 73.8% and 57.7%, respectively. The median OS was 57 months (IQR 17–108.5) and 29.5 months (IQR 12–64) in the low PIV (< 328) and high PIV (≥ 328) groups, respectively. According to PanSII scores, the median OS durations were 55 months (IQR 19–115.2) in the PanSII = 0 group, 42 months (IQR 16-86.5) in the PanSII = 1 group, and 25.5 months (IQR 11–62.2) in the PanSII = 2 group (Table 2).

Table 2
Pathological Characteristics and Oncological Outcomes of the Study Cohort

Variables	Total Cohort (n = 255)
Tumor size (cm), med (IQR)	9.7 (8.5–12.0)
Positive surgical margin, n (%)	16 (6.3)
Histological subtype, n (%)	
Clear Cell	181 (71.0)
Papillary	37 (14.5)
Chromophobe	23 (9.0)
Other subtype	14 (5.5)
Fuhrman/ ISUP Grade, n (%)	
Low FG (1–2)	103 (40.3)
High FG (3–4)	152 (59.6)
Pathological UICC-TNM stage, n (%)	
T stage	
pT2	118 (46.2)
pT3	128 (50.2)
pT4	9 (3.5)
N stage	
pN0	217 (85.1)
pN1	38 (14.9)
Tumor necrosis, n (%)	160 (62.7)
Perirenal fat invasion, n (%)	84 (32.9)
Renal sinus fat invasion, n (%)	93 (36.5)
Pelvicalyceal system invasion, n (%)	40 (15.7)
Sarcomatoid differentiation, n (%)	42 (16.5)
Lymphovascular invasion, n (%)	80 (31.4)
Oncological Follow-up Data	

FG, Fuhrman grade; IQR, interquartile range; ISUP, International Society of Urological Pathology; pN, pathological nodal stage; pT, pathological tumor stage; TNM, tumor–node–metastasis; UICC, Union for International Cancer Control.

Variables	Total Cohort (n = 255)
Follow-up times, mo., med (IQR)	37 (13–82)
Metastasis during follow-up, n (%)	63 (31)
Death, n (%)	117 (45.9)
Metastasis at diagnosis, n (%)	58 (22.7)

FG, Fuhrman grade; IQR, interquartile range; ISUP, International Society of Urological Pathology; pN, pathological nodal stage; pT, pathological tumor stage; TNM, tumor–node–metastasis; UICC, Union for International Cancer Control.

Insert Table 2

Kaplan-Meier survival curves according to PanSII categories are shown in Fig. 2.

Insert Fig. 2

The 5-year OS rate was 45.3% in the PanSII = 2 group, whereas it was 63.5% and 82.6% in the PanSII = 1 and PanSII = 0 groups, respectively. Log-rank analysis showed a statistically significant difference in OS among PanSII categories ($p < 0.0001$).

In univariable Cox regression analysis, age, BMI, ACCI, anemia, ISUP grade, sarcomatoid differentiation, tumor necrosis, lymphovascular invasion, T stage, lymph node positivity, presence of distant metastasis, PIV, and PanSII were associated with OS (Table 3).

Table 3
Univariate Cox Regression Analyses for Overall Survival

Variable	HR (95% CI)	*P* value
Age	1.04 (1.02–1.06)	**< 0.0001**
Gender (male vs female)	1.41 (0.94–2.11)	0.097
BMI	0.93 (0.89–0.98)	**0.002**
ACCI	1.23 (1.13–1.35)	**< 0.0001**
Anemia	2.41 (1.63–3.56)	**< 0.0001**
Tumor size	1.02 (0.97–1.09)	0.374
Histological subtype (clear cell vs others)	0.89 (0.60–1.34)	0.595
ISUP grade (3–4 vs 1–2)	1.76 (1.19–2.61)	**0.004**
Sarcomatoid differentiation	2.26 (1.42–3.61)	**0.001**
Tumor necrosis	1.70 (1.15–2.50)	**0.007**
Lymphovascular invasion	1.69 (1.60–2.47)	**0.007**
Surgical positive margin	1.74 (0.88–3.45)	0.109
T stage (pT3–4 vs pT2)	1.72 (1.19–2.50)	**0.004**
Lymph node positivity (pN1 vs pN0)	3.74 (2.43–5.75)	**< 0.0001**
Presence of distant metastasis	4.12 (2.80–6.06)	**< 0.0001**
PIV	2.66 (1.76–4.03)	**< 0.0001**
PanSII		**< 0.0001**
PanSII = 1 (reference: PanSII = 0)	3.32 (1.79–6.17)	**< 0.0001**
PanSII = 2 (reference: PanSII = 0)	5.27 (2.87–9.67)	**< 0.0001**

ACCI, age-adjusted Charlson comorbidity index; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ISUP, International Society of Urological Pathology; PanSII, pan-systemic inflammatory index; PIV, pan-immune-inflammation value; RCC, renal cell carcinoma.

Insert Table 3

In the base multivariable Cox model, age, lymph node positivity, and presence of distant metastasis remained independently associated with OS. When inflammatory markers were added separately to the

base model, anemia, high PIV, and PanSII were each independently associated with OS (Table 4).

Table 4
Multivariable Cox Regression Models and Incremental Predictive Performance for Overall Survival

Variables	**HR (95% CI)**	***P value***
Age	1.03 (1.00-1.05)	**0.042**
BMI	0.96 (0.92-1.00)	0.087
ACCI	1.05 (0.93–1.18)	0.432
ISUP grade (3–4 vs 1–2)	1.28 (0.81–2.03)	0.292
Sarcomatoid differentiation	1.13 (0.67–1.92)	0.648
Tumor necrosis	1.30 (0.80–2.12)	0.294
Lymphovascular invasion	0.77 (0.47–1.25)	0.288
T stage (pT3–4 vs pT2)	0.99 (0.60–1.65)	0.983
Lymph node positivity (pN1 vs pN0)	2.08 (1.23–3.55)	**0.007**
Presence of distant metastasis	2.81 (1.72–4.61)	**< 0.0001**
Model performance	c-index 0.749	
Model with Anemia	1.82 (1.94–2.78)	**0.005**
Model performance with anemia (ΔC-index (%))	C-index 0.758 (+ 0.9%)	
Model with PIV	2.80 (1.53–4.52)	**< 0.0001**
Model performance with PIV ≥ 328 (%Difference)	C-index 0.777 (+ 2.8%)	
Model with PanSII		**< 0.0001**
PanSII = 1 (reference: PanSII = 0)	3.91 (1.98–7.71)	**< 0.0001**
PanSII = 2 (reference: PanSII = 0)	4.49 (2.26–8.91)	**< 0.0001**
Model performance with PanSII (%Difference)	C-index 0.780 (+ 3.0%)	

ACCI, age-adjusted Charlson comorbidity index; BMI, body mass index; CI, confidence interval; HR, hazard ratio; ISUP, International Society of Urological Pathology; PanSII, pan-systemic inflammatory index; PIV, pan-immune-inflammation value.

Stepped models were created to evaluate the incremental prognostic contribution of systemic inflammatory markers on overall survival. The discriminatory performance (C-index) of the base model, which included conventional clinicopathological variables, was 0.749. Adding preoperative anemia to the base model increased the discriminatory power to 0.758 (+ 0.9%), while adding PIV increased it to 0.777 (+ 2.8%). The highest C-index was observed after adding PanSII into the model; at this stage, the C-index increased to 0.780 (+ 3.0%) increase over the base model. In this extended multivariable model, PanSII =

2 was associated with the highest hazard of death compared with PanSII = 0 (HR = 4.49, 95% CI 2.26–8.91, p < 0.0001) (Table 4).

Insert Table 4

Discussion

Although both nomogram systems and systemic inflammatory indices have been developed to integrate components in the prognostic modeling of RCC, there is still no consensus on the optimal approach. Therefore, predicting oncological outcomes after nephrectomy in patients diagnosed with RCC remains important for determining postoperative follow-up strategies and individualizing treatment decisions. Understanding the complex interaction between the tumor microenvironment and the systemic immune response has contributed to the development of systemic inflammatory indices. Although the literature reports that factors such as advanced T stage, lymph node positivity, anemia, and ACCI negatively affect overall survival (12, 13), in recent years, increasing evidence regarding the role of systemic inflammation in tumor progression has led research to focus on blood-based biomarkers. (14)

Many studies have reported the prognostic value of various systemic inflammation indices in RCC. Martino et al. reported a significant association between the neutrophil-lymphocyte ratio (NLR) and disease-free survival (DFS) in 281 patients with non-clear cell RCC who underwent nephrectomy. (15) Wang et al., in a meta-analysis encompassing a total of 1528 RCC patients, found that high PLR levels were significant prognostic markers for both OS and progression-free survival (PFS) (HR = 3.45). (16) In their study of a large RCC cohort of 646 cases who underwent nephrectomy, Hu et al. found that high preoperative SII values were independent prognostic factors in predicting both OS (HR = 1.78) and CSS (HR = 1.8). (17) Chen et al. reported that SIRI was an independent prognostic factor for both OS (HR = 4.853) and CSS (HR = 5.913) in a series of 414 ccRCC cases. (18)

While the initial focus was on dual-parameter indices such as NLR and PLR, later studies reported that triple models, such as SII, which combine neutrophils, lymphocytes, and platelets, exhibit superior prognostic value. (19–21) De Giorgi et al. demonstrated that models that account for more variables yield purer prognostic data by eliminating confounding factors. (21) Pan-Immune Inflammation Value (PIV), one of the most comprehensive links in this evolutionary process, is considered the model that represents the broadest spectrum of inflammatory load because it includes neutrophils, lymphocytes, monocytes, and platelets. (4, 22) The prognostic value of PIV was first described by Fucà et al. in patients with metastatic colorectal cancer; in that study, it was reported that PIV showed better prognostic performance than markers such as NLR and SII. (4) Yekedüz et al. evaluated PIV in metastatic RCC cases and determined that this biomarker is a prognostic factor predicting overall

survival. In that study, patients in the high PIV (≥ 328) group had shorter overall survival (OS) and PFS than those in the low PIV (< 328) group. (5)

Although numerous studies have shown the prognostic significance of systemic inflammation indices in kidney cancer, the presence of anemia has not been routinely integrated into RCC-specific inflammatory indices. However, anemia in RCC may reflect not only reduced hemoglobin levels but also a systemic biological burden related to tumor-associated inflammation. The inclusion of anemia as an independent prognostic factor in the IMDC and MSKCC risk classifications supports this clinical relevance.

PanSII evaluates both cellular inflammatory load (PIV) and the patient's systemic physiological response (anemia) together. In our study, the overall survival time was significantly shorter in the PanSII = 2 group, which included both high PIV values (≥ 328) and anemia; this is consistent with the current literature, which highlights the prognostic significance of systemic inflammation and anemia.

According to our multivariable analysis results, PanSII = 2 was associated with a 4.49-fold higher hazard of death compared with PanSII = 0. Importantly, this association remained evident after adjustment for conventional clinicopathological variables, including distant metastasis. Furthermore, adding PanSII to the base clinicopathological model increased the C-index from 0.749 to 0.780, corresponding to an absolute increase of 0.031. Although this improvement was modest, it suggests that PanSII may provide incremental discriminatory information when added to conventional prognostic factors. Based on these findings, a high preoperative PanSII score may be considered an independent prognostic factor for overall survival in patients with RCC undergoing radical nephrectomy.

PanSII, which integrates anemia with the four cellular parameters that comprise PIV, neutrophils, monocytes, platelets, and lymphocytes, may provide a more comprehensive assessment of systemic inflammation and host status than inflammatory indices based solely on blood cell counts. While previous studies have demonstrated the potential of systemic inflammation indices in RCC, our findings suggest that combining inflammatory burden with anemia may further refine prognostic assessment. However, the clinical utility of PanSII should be confirmed in independent cohorts before routine use.

Our study has several important limitations. First, the study was conducted at a single center, which may limit the generalizability of our findings to other populations. Second, because cause-specific mortality data were not available for all patients, oncological outcomes were evaluated using OS rather than cancer-specific survival. Third, as this was a retrospective study, selection bias, information bias, residual confounding, and unmeasured variables may have affected the results. In addition, systematic retroperitoneal lymph node dissection was not routinely performed, and nodal status should therefore be interpreted with caution. Finally, the reported C-index values reflect apparent model performance and may overestimate discriminatory ability in the absence of external validation. Therefore, large-scale multicenter studies with internal and external validation are needed to confirm the predictive accuracy and clinical generalizability of PanSII. Despite these limitations, multivariable Cox regression models adjusted for relevant clinicopathological variables were used in our study to partially account for

potential confounding factors. In this context, our findings provide preliminary evidence that PanSII may offer additional prognostic information in patients with RCC undergoing radical nephrectomy.

Conclusions

In conclusion, to our knowledge, this is the first study to define and evaluate PanSII, a composite prognostic index integrating PIV-derived systemic inflammatory burden with anemia, in patients with RCC undergoing radical nephrectomy. PanSII was independently associated with overall survival and provided a modest incremental improvement in discriminatory performance when added to conventional clinicopathological variables. Because PanSII is derived from routine preoperative blood parameters and requires no additional specialized testing, it may help identify high-risk patients and support individualized postoperative surveillance strategies after nephrectomy. Further large-scale, prospective, multicenter studies with internal and external validation are warranted before PanSII can be considered for incorporation into standard prognostic models.

Declarations

Data availability

The datasets generated and/or analyzed during the current study are not publicly available because of institutional and ethical restrictions regarding patient-level clinical data, but are available from the corresponding author on reasonable request and with permission from the relevant institutional authorities.

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Conflicts of Interest

The authors declare that no conflict of interest.

Author contributions

Conception and design of this study were contributed by E.B., H.Y.; data collection was by S.B. M.U.; statistics and analysis of data were carried out by H.Y., I.E.A.; interpretation of data was by E.B.,H.Y., I.E.A.; prepared figures and tables by E.B., H.Y, I.E.A.,I.U.; supervision was done by H.Y. and I.E.A. All authors approved the final version to be published.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Kocaeli University Non-Interventional Clinical Research Ethics Committee (Project approval number:

GOKAEK 2024/98) on February 15, 2024. Written informed consent was obtained from all individual participants included in the study.

Consent to Publish

Consent to publish: not applicable.

References

1. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356–87.
2. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related Inflamm Nat. 2008;454(7203):436–44.
3. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6(1):149–63.
4. Fucà G, Guarini V, Antoniotti C, Morano F, Moretto R, Corallo S, et al. The Pan-Immune-Inflammation Value is a new prognostic biomarker in metastatic colorectal cancer: results from a pooled-analysis of the Valentino and TRIBE first-line trials. Br J Cancer. 2020;123(3):403–9.
5. Yekedüz E, Tural D, Ertürk İ, Karakaya S, Erol C, Ercelep Ö, et al. The relationship between pan-immune-inflammation value and survival outcomes in patients with metastatic renal cell carcinoma treated with nivolumab in the second line and beyond: a Turkish oncology group kidney cancer consortium (TKCC) study. J Cancer Res Clin Oncol. 2022;148(12):3537–46.
6. Baykal S, Yilmaz H, Cinar NB, Akdas EM, Baynal EA, Teke K, et al. editors. The pan-immune-inflammation value: A novel independent predictive factor for overall survival in≥ pT2a nonmetastatic renal cell carcinoma. Urologic Oncology: Seminars and Original Investigations; 2025.
7. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27(34):5794–9.
8. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002;20(1):289–96.
9. Choi Y, Park B, Kim K, Jeong B, Seo S, Jeon S, et al. Erythrocyte sedimentation rate and anaemia are independent predictors of survival in patients with clear cell renal cell carcinoma. Br J Cancer. 2013;108(2):387–94.
10. Srigley JR, Hutter RV, Gelb AB, Henson DE, Kenney G, King BF et al. Current prognostic factors-renal cell carcinoma: Workgroup No. 4. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1997;80(5):994-6.
11. Gu L, Ma X, Wang L, Li H, Chen L, Li X, et al. Prognostic value of a systemic inflammatory response index in metastatic renal cell carcinoma and construction of a predictive model. Oncotarget.

2016;8(32):52094.
12. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol. 1999;17(8):2530.
13. Capitanio U, Suardi N, Matloob R, Roscigno M, Abdollah F, Di Trapani E et al. Extent of lymph node dissection at nephrectomy affects cancer-specific survival and metastatic progression in specific sub-categories of patients with renal cell carcinoma (RCC). BJU Int. 2014;114(2).
14. Xu J, Chen P, Cao S, Hu X, Li X. Prognostic value of systemic immune-inflammation index in patients with metastatic renal cell carcinoma treated with systemic therapy: a meta-analysis. Front Oncol. 2024;14:1404753.
15. de Martino M, Pantuck AJ, Hofbauer S, Waldert M, Shariat SF, Belldegrun AS, et al. Prognostic impact of preoperative neutrophil-to-lymphocyte ratio in localized nonclear cell renal cell carcinoma. J Urol. 2013;190(6):1999–2004.
16. Wang Z, Peng S, Wang A, Xie H, Guo L, Jiang N, et al. Platelet-lymphocyte ratio acts as an independent predictor of prognosis in patients with renal cell carcinoma. Clin Chim Acta. 2018;480:166–72.
17. Hu X, Shao Y-X, Yang Z-Q, Dou W-C, Xiong S-C, Li X. Preoperative systemic immune-inflammation index predicts prognosis of patients with non-metastatic renal cell carcinoma: a propensity score-matched analysis. Cancer Cell Int. 2020;20(1):222.
18. Chen Z, Wang K, Lu H, Xue D, Fan M, Zhuang Q et al. Systemic inflammation response index predicts prognosis in patients with clear cell renal cell carcinoma: a propensity score-matched analysis. Cancer Manage Res. 2019:909–19.
19. Chrom P, Zolnierek J, Bodnar L, Stec R, Szczylik C. External validation of the systemic immune-inflammation index as a prognostic factor in metastatic renal cell carcinoma and its implementation within the international metastatic renal cell carcinoma database consortium model. Int J Clin Oncol. 2019;24(5):526–32.
20. Chen D, Zhang Z, Dong L, Feng Z, Yang J. Prognostic significance of systemic immunoinflammatory biomarkers in patients with clear cell renal cell carcinoma: a retrospective multicenter analysis. Front Immunol. 2025;16:1575497.
21. De Giorgi U, Procopio G, Giannarelli D, Sabbatini R, Bearz A, Buti S, et al. Association of systemic inflammation index and body mass index with survival in patients with renal cell cancer treated with nivolumab. Clin Cancer Res. 2019;25(13):3839–46.
22. Zeng R, Liu F, Fang C, Yang J, Luo L, Yue P, et al. PIV and PILE score at baseline predict clinical outcome of anti-PD-1/PD-L1 inhibitor combined with chemotherapy in extensive-stage small cell lung cancer patients. Front Immunol. 2021;12:724443.

Figures

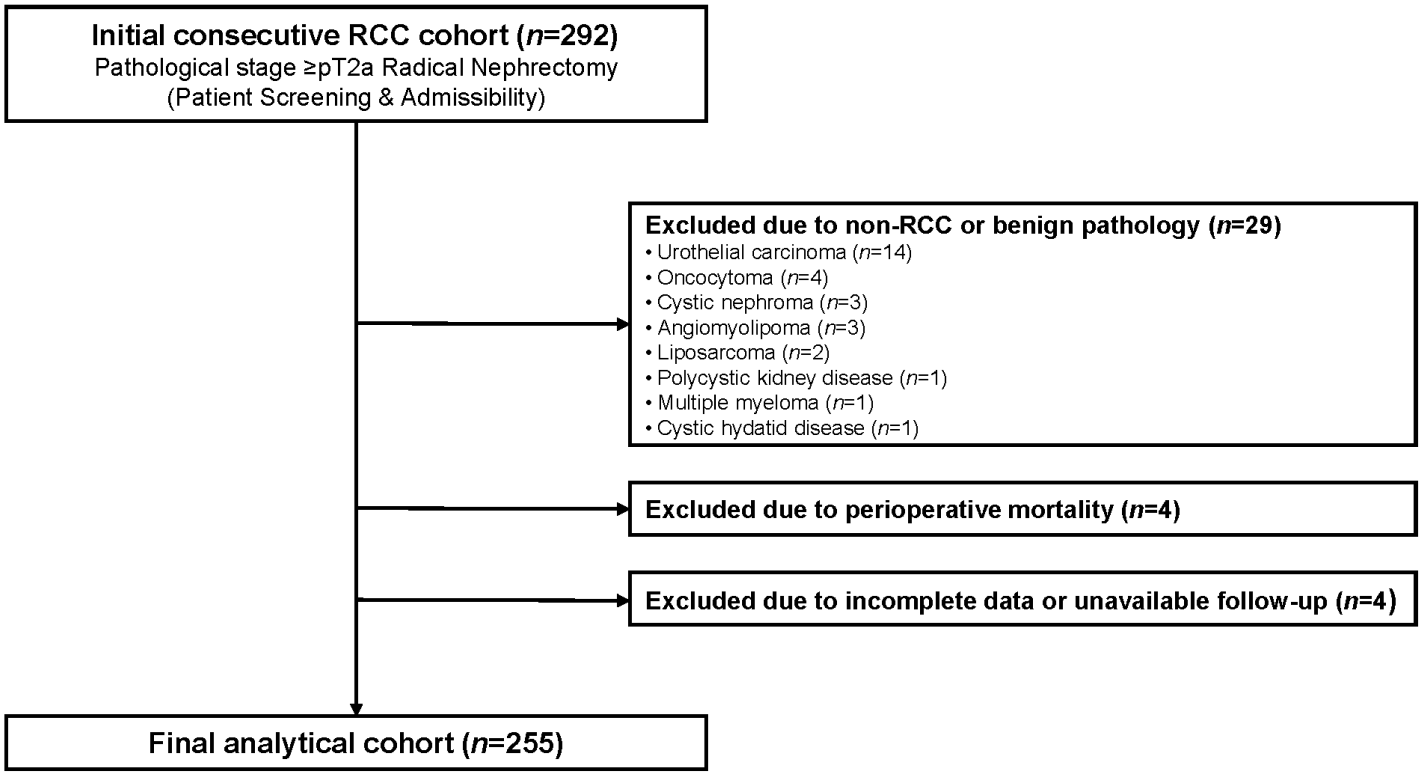


Figure 1

Patient selection flowchart for the final analytical cohort.

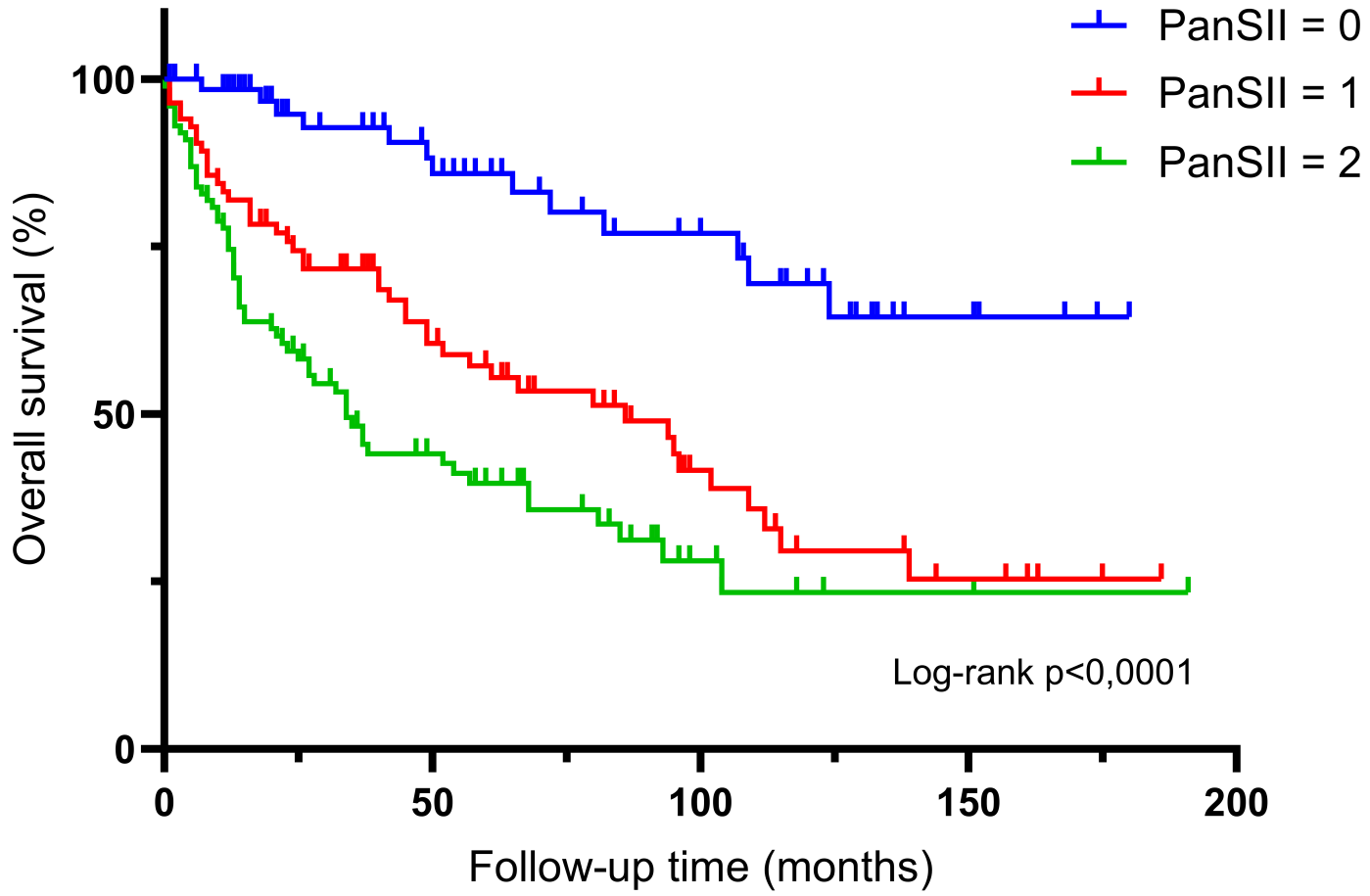


Figure 2

Kaplan–Meier overall survival curves according to PanSII categories.

Overall survival differed significantly across Pan-Systemic Inflammation Index (PanSII) categories. PanSII=0 was defined as low PIV (<328) without anemia; PanSII=1 as either high PIV (≥328) without anemia or low PIV with anemia; and PanSII=2 as high PIV with anemia. Survival decreased stepwise with increasing PanSII category, with the lowest overall survival observed in the PanSII=2 group. Differences between groups were assessed using the log-rank test. Tick marks indicate censored observations.