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

Yüksel Ürün (yukselurun@gmail.com)
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi https://orcid.org/0000-0002-9152-9887

Emre Yekedüz
Ankara University Faculty of Medicine: Ankara Universitesi Tip Fakultesi

Deniz Tural
Bakirkoy Dr Sadi Konuk Training and Research Hospital: Istanbul Bakirkoy Dr Sadi Konuk Egitim ve Arastirma Hastanesi

İsmail Ertürk
Gülhane Training and Research Hospital: Ankara Gulhane Egitim ve Arastirma Hastanesi

Serdar Karakaya
Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital: Ankara Dr Abdurrahman Yurtaslan Onkoloji Egitim ve Arastirma Hastanesi

Cihan Erol
Yildirim Beyazit University Faculty of Medicine: Ankara Yildirim Beyazit Universitesi Tip Fakultesi

Özlem Ercelep
Marmara University: Marmara Universitesi

Çağatay Arslan
Izmir University of Economics: Izmir Ekonomi Universitesi

Özlem Nuray Sever
Gaziantep University: Gaziantep Universitesi

Saadettin Kılıçkap
Istinye University: Istinye Universitesi

Nihan Şentürk Öztaş
Istanbul University Cerrahpasa Faculty of Medicine: Istanbul Universitesi-Cerrahpasa Cerrahpasa Tip Fakultesi

Ahmet Küçükarda

Trakya University Faculty of Medicine: Trakya Universitesi Tip Fakultesi

Orçun Can

Prof Dr Cemil Tascioglu City Hospital: Prof Dr Cemil Tascioglu Sehir Hastanesi

Berna Öksüzoğlu

Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital: Ankara Dr Abdurrahman Yurtaslan Onkoloji Egitim ve Arastirma Hastanesi

Mehmet Ali Şendur

Yildirim Beyazit University Faculty of Medicine: Ankara Yildirim Beyazit Universitesi Tip Fakultesi

Nuri Karadurmuş

Gülhane Training and Research Hospital: Ankara Gulhane Egitim ve Arastirma Hastanesi

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Abstract

Background

Pan-immune-inflammation value (PIV) is an easily accessible immune marker based on peripheral blood to estimate prognosis in patients with cancer. This study evaluates the prognostic value of PIV in patients with metastatic renal cell carcinoma (mRCC) treated with nivolumab.

Methods

In this retrospective cohort study, patients with mRCC treated with nivolumab in the second line and beyond were selected from the Turkish Oncology Group Kidney Cancer Consortium (TKCC) database. PIV was calculated by using the following formula: neutrophil (10^3/mm^3) x monocyte (10^3/mm^3) x platelet (10^3/mm^3) / lymphocyte (10^3/mm^3).

Results

A total of 152 patients with mRCC were included in this study. According to cut-off value for PIV, 77 (50.7%) and 75 (49.3%) patients fell into PIV-low ($\leq$ 372) and PIV-high (>372) groups, respectively. In multivariate analysis, PIV-high (HR:1.64, 95% CI: 1.04–2.58, p = 0.033 for overall survival (OS); HR:1.55, 95% CI: 1.02–2.38, p = 0.042 for progression-free survival (PFS)) was independent risk factor for OS and PFS after adjusting for confounding variables such as performance score, the International mRCC Database Consortium (IMDC) risk score, and liver metastasis.

Conclusion

This study established that pre-treatment PIV might be a prognostic biomarker in patients with mRCC treated with nivolumab in the second line and beyond.

Introduction

Treatment options in metastatic renal cell carcinoma (mRCC) have been expanding over the last decade. Anti-vascular endothelial growth factor (VEGF) targeted therapies (TTs), immune checkpoint inhibitors (ICIs), and combinations of TTs and ICIs are the mainstay of treatment in patients with mRCC.(Choueiri et al. 2021; Motzer et al. 2021; Motzer et al. 2015; Motzer et al. 2018; Posadas et al. 2017) Nivolumab is a human immunoglobulin G4 programmed death-1 (PD-1) ICI antibody. The CheckMate 025 trial showed the superiority of nivolumab to everolimus in patients with mRCC previously treated with anti-VEGF TTs. After this trial, the Food and Drug Administration (FDA) approved an ICI, nivolumab, for the first time in the treatment of mRCC. (Motzer et al. 2015; Xu et al. 2017)

It is well known that inflammation plays a crucial role in tumor pathogenesis and response to treatment with anti-cancer drugs .(Grivennikov et al. 2010) In fact, peripheral blood cells, such as neutrophils, platelets, lymphocytes, and monocytes, are the main indicator of tumor-associated inflammation. (Dymicka-Piekarska et al. 2021) In this context, neutrophils, monocytes, and platelets contribute to the tumor progression, while lymphocytes fight against cancer.(Grivennikov et al. 2010; Laubli et al. 2009; Mantovani et al. 2008; Wu et al. 2019) Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) are the commonly investigated immune-inflammatory biomarkers (IIBs), which are calculated by using the peripheral blood parameters such as neutrophils, lymphocytes, monocytes, and platelets. Numerous studies showed their prognostic values in solid tumors (Gao et al. 2019; Liu et al. 2019; Vicente Conesa et al. 2012; Wang and Zhu 2019) and renal cell carcinoma (RCC) (Garcia-Rojo et al. 2021; Hizal et al. 2020; Na et al. 2016; Templeton et al. 2016; Yasar et al. 2020).

Pan-immune-inflammation value (PIV) is a new composite biomarker to predict inflammation status in cancer patients. It was reported for the first time in patients with metastatic colorectal cancer (mCRC). (Fuca et al. 2020) After this study, its prognostic value was shown in patients with malign melanoma, breast cancer, Merkel cell carcinoma and mCRC treated with ICIs.(Corti et al. 2021; Fuca et al. 2021; Gambichler et al. 2022; Ligorio et al. 2021; Susok et al. 2022) Unlike the other peripheral blood IIBs, as mentioned before, it is calculated by using the four peripheral blood cells, such as neutrophil, lymphocyte, monocyte, and platelet. To date, no study assessed the prognostic value of PIV among patients with mRCC.

In this study, we aimed to evaluate the prognostic value of PIV in patients with mRCC treated with nivolumab in the second line and beyond.

Methods

Patients and Data Collection

Turkish Oncology Group Kidney Cancer Consortium (TKCC) is a multi-center registry consisting of 13 cancer centers in Turkey. In this retrospective study, we selected patients with mRCC treated with nivolumab in the second line and beyond from the TKCC database. After excluding 21 patients due to missing laboratory values for PIV, we included 152 patients in this study. The flowchart of patient selection is shown in Fig. 1.

Demographic (e.g., age, gender), clinical (e.g., Eastern Cooperative Oncology Group performance score (ECOG PS), nephrectomy status, metastasis sites, treatment line of nivolumab, laboratory values) and pathological (e.g., histological type, grade, presence of sarcomatoid feature) data were extracted from the TKCC database.

This study was approved by the local ethical committee and conducted in accordance with the "*Declaration of Helsinki*".

Statistical Analysis

Median (interquartile range (IQR)) or mean ± standard deviation (SD) for continuous variables and percentages for categorical variables were used to describe the data. PIV was calculated by using the following formula as described previous studies (Corti et al. 2021): neutrophil ($10^3/mm^3$) x monocyte ($10^3/mm^3$) x platelet ($10^3/mm^3$) / lymphocyte ($10^3/mm^3$). Laboratory values for calculating PIV were obtained from the laboratory results in the last week before the initiation of nivolumab. A cut-off value for PIV was calculated by the using the maximally selected rank statistics method for overall survival (OS). Patients were divided into two groups as PIV-low (≤ 372) and PIV-high (>372).

OS was calculated from initiation of nivolumab to death and PFS was calculated

from initiation of nivolumab to disease progression or death, whichever first occurred. Kaplan-Meier estimates were used for survival analyses. A log-rank test was performed to compare survival curves. Cox's proportional hazard regression models were used for multivariate analysis of OS and PFS. To estimate independent variables for OS and PFS, regression models were constructed using the statistically significant variables in univariate survival analyses. All statistical analyses were performed by using SPSS 27.0 for Mac (IBM Corp., Armonk, NY) and R Studio (version 1.4.1106) with *survminer, maxstat*, and *ggsurvplot* packages.

Results

Patient Characteristics

A total of 152 patients with mRCC were included in this study. The median age was 60 years (IQR:54–67 years). Most patients were male (77%), had clear cell histology (82.2%), and underwent nephrectomy (77%). The sarcomatoid feature was observed in 18 patients (11.8%). Approximately half of the patients received nivolumab in the second line, while the remaining patients received the third line and beyond. There were 13 (8.6%), 94 (61.8%), and 23 (15.1%) patients in the International mRCC Database Consortium (IMDC) favorable, intermediate, and poor-risk groups, respectively. The most common metastatic site was the lung (85.5%). About two out of three patients had an ECOG PS of ≤ 1. According to cut-off value for PIV, 77 (50.7%) and 75 (49.3%) patients fell into the PIV-low (≤ 372) and PIV-high (>372) groups, respectively. All baseline characteristics are shown in Table 1.

Table 1
Baseline Characteristics

	PIV-Low		PIV-High		All Patients	
	n = 77	(%)	n = 75	(%)	n = 152	(%)
Age - *years, median (IQR)*	61 (53–67)		60 (55–66)		60 (54–67)	
Gender						
Male	58	(75.3)	59	(78.7)	117	*(77.0)*
Female	19	(24.7)	16	(21.3)	35	*(23.0)*
Histological Type						
Clear Cell	65	(84.4)	60	(80.0)	125	*(82.2)*
Non-Clear Cell	7	(9.1)	9	(12.0)	16	*(10.6)*
Missing	5	(6.5)	6	(8.0)	11	*(7.2)*
Sarcomatoid Feature						
Yes	5	(6.5)	13	(17.3)	18	*(11.8)*
No	53	(68.8)	48	(64.0)	101	*(66.4)*
Missing	19	(24.7)	14	(18.7)	33	*(21.7)*
Fuhrman Grade						
1–2	15	(19.5)	6	(8.0)	21	*(13.8)*
3–4	36	(46.8)	37	(49.3)	73	*(48.0)*
Missing	26	(33.8)	32	(42.7)	58	*(38.2)*
Previous Nephrectomy						
Yes	63	(81.8)	54	(72.0)	117	*(77.0)*
No	14	(18.2)	21	(28.0)	35	*(23.0)*
Nivolumab Line						
Second	48	(62.3)	34	(45.3)	82	*(53.9)*
Third and beyond	29	(37.7)	41	(54.7)	70	*(46.1)*
IMDC Risk						
Favorable	9	(11.7)	4	(5.3)	13	*(8.6)*
Intermediate	51	(66.2)	43	(57.3)	94	*(61.8)*
Poor	7	(9.1)	16	(21.3)	23	*(15.1)*

	PIV-Low		PIV-High		All Patients	
	n = 77	(%)	n = 75	(%)	n = 152	(%)
Missing	10	(13.0)	12	(16.0)	22	*(14.5)*
Metastatic Sites						
Lung	62	(80.5)	68	(90.7)	130	*(85.5)*
Bone	47	(61.0)	53	(70.7)	100	*(65.8)*
Liver	19	(24.7)	23	(30.7)	42	*(27.6)*
CNS	14	(18.2)	20	(26.7)	34	*(22.4)*
Performance Status						
ECOG 0–1	52	(67.5)	45	(60.0)	97	*(63.8)*
ECOG 2-3-4	20	(26.0)	25	(33.3)	45	*(29.6)*
Missing	5	(6.5)	5	(6.7)	10	*(6.6)*

Abbreviations: *CNS = Central Nervous System, ECOG = Eastern Cooperative Oncology Group, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, IQR = Inter-quartile Range, PIV = Pan-Immune-Inflammation Value*

Survival Outcomes

At the median 29.1 months follow-up for OS, the median OS was 27.1 months (95% Confidence Interval (CI): 21.1–33.1) and 11.2 months (95% CI: 3.1–19.2) in the PIV-low and PIV-high groups, respectively. The difference between the groups was statistically significant (Hazard Ratio (HR):1.90, 95% CI:1.25–2.89, p = 0.002) **(**Fig. 2a**)**. The median PFS was 19.6 months (95% CI: 12.1–27.1) and 10.5 months (95% CI: 5.0-15.9) in the PIV-low and PIV-high groups, respectively. The difference between the groups was statistically significant (HR:1.59, 95% CI: 1.08–2.36, p = 0.018) **(**Fig. 2b**)**. ECOG PS (p < 0.001 for OS and PFS), the IMDC risk score (p = 0.002 for OS, p = 0.022 for PFS), and liver metastasis (p = 0.002 for OS, p = 0.007 for PFS) were also prognostic for OS and PFS in univariate analyses **(**Table 2 **and** Table 3**).**

Table 2
Univariate and Multivariate Analysis for Overall Survival

	Univariate		*p* value*	Multivariate		*p* value#
	HR	95% CI		HR	95% CI	
Age			0.730			
< 65	1					
≥ 65	0.92	*0.59–1.44*				
Gender			0.796			
Male	1.07	*0.65–1.76*				
Female	1					
Histological Type			0.270			
Clear Cell	1					
Non-clear Cell	1.43	*0.75–2.71*				
Sarcomatoid Feature			0.176			
Yes	1.53	*0.82–2.87*				
No	1					
Fuhrman Grade			0.304			
1–2	1					
3–4	1.45	*0.71–2.99*				
Previous Nephrectomy			0.296			
Yes	0.77	*0.47–1.26*				
No	1					
CNS Metastasis			0.910			
Yes	1.03	*0.63–1.66*				
No	1					
Bone Metastasis			0.101			
Yes	1.48	*0.92–2.35*				
No	1					
Liver Metastasis			**0.002**			**0.031**

	Univariate		*p* value*	Multivariate		*p* value#
	HR	**95% CI**		**HR**	**95% CI**	
Yes	1.95	*1.26–3.01*		1.69	*1.05–2.72*	
No	1			1		
Lung Metastasis			0.768			
Yes	1.09	*0.61–1.93*				
No	1					
Performance Status			**< 0.001**			**< 0.001**
ECOG 0–1	1			*1*		
ECOG 2-3-4	2.71	*1.75–4.22*		*2.38*	*1.50–3.76*	
IMDC Risk			**0.002**			*0.166*
Favorable	1.55	*0.76–3.17*		2.10	*0.94–4.72*	
Intermediate	1			1		
Poor	2.57	*1.49–4.42*		1.23	*0.64–2.38*	
Previous Treatment Line			0.245			
1	1					
≥ 2	1.27	*0.84–1.93*				
PIV			**0.002**			**0.033**
Low	1			1		
High	1.90	*1.25–2.89*		1.64	*1.04–2.58*	

Abbreviations: *CI = Confidence Interval, CNS = Central Nervous System, HR = Hazard Ratio, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, PIV = Pan-Immune-Inflammation Value*

**p value was calculated by using the log-rank test.*

#p value was calculated by using Cox's proportional hazard regression model.

Table 3
Univariate and Multivariate Analysis for Progression-Free Survival

	Univariate		*p* value*	Multivariate		*p* value#
	HR	95% CI		HR	95% CI	
Age			0.970			
< 65	1					
≥ 65	0.99	*0.66–1.48*				
Gender			0.805			
Male	1.06	*0.66–1.68*				
Female	1					
Histological Type			0.261			
Clear Cell	1					
Non-clear Cell	1.41	*0.77–2.59*				
Sarcomatoid Feature			0.332			
Yes	1.35	*0.73–2.52*				
No	1					
Fuhrman Grade			0.422			
1–2	1					
3–4	1.29	*0.68–2.43*				
Previous Nephrectomy			0.350			
Yes	0.81	*0.52–1.26*				
No	1					
CNS Metastasis			0.352			
Yes	1.23	*0.79–1.91*				
No	1					
Bone Metastasis			0.101			
Yes	1.43	*0.93–2.18*				
No	1					
Liver Metastasis			**0.007**			**0.025**

	Univariate		*p* value*	Multivariate		*p* value#
	HR	**95% CI**		**HR**	**95% CI**	
Yes	1.75	*1.16–2.66*		1.66	*1.07–2.61*	
No	1			1		
Lung Metastasis			0.317			
Yes	1.33	*0.75–2.34*				
No	1					
Performance Status			**< 0.001**			**< 0.001**
ECOG 0–1	1			*1*		
ECOG 2-3-4	2.46	*1.63–3.73*		*2.27*	*1.47–3.49*	
IMDC Risk			**0.022**			*0.366*
Favorable	1.36	*0.69–2.67*		1.72	*0.81–3.62*	
Intermediate	1			1		
Poor	2.07	*1.21–3.52*		1.04	*0.55–1.96*	
Previous Treatment Line			0.137			
1	1					
≥ 2	1.34	*0.91–1.97*				
PIV			**0.018**			**0.042**
Low	1			1		
High	1.59	*1.08–2.36*		1.55	*1.02–2.38*	

Abbreviations: *CI = Confidence Interval, CNS = Central Nervous System, HR = Hazard Ratio, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, PIV = Pan-Immune-Inflammation Value*

**p value was calculated by using the log-rank test.*

#p value was calculated by using Cox's proportional hazard regression model.

In multivariate analysis, PIV-high (HR:1.64, 95% CI: 1.04–2.58, p = 0.033 for OS; HR:1.55, 95% CI: 1.02–2.38, p = 0.042 for PFS), ECOG PS ≥ 2 (HR:2.38, 95% CI:1.50–3.76, p<0.001 for OS; HR:2.27, 95% CI: 1.47–3.49, p < 0.001 for PFS), and presence of liver metastasis (HR:1.69, 95% CI:1.05–2.72, p=0.031 for OS; HR:1.66, 95% CI:1.07–2.61, p = 0.025 for PFS) were independent risk factors for OS and PFS after

adjusting for confounding variables such as, ECOG PS, the IMDC risk score, and liver metastasis **(**Table 2 **and** Table 3**).**

Discussion

In this study, we established that pre-treatment PIV was an independent prognostic factor in patients with mRCC treated with nivolumab in the second line and beyond. To the best of our knowledge, this was the first study assessing the prognostic value of PIV in patients with mRCC treated with nivolumab.

In fact, the easy access to peripheral blood IIBs makes them more attractive for use as a prognostic biomarker. To date, many studies evaluated the prognostic value of NLR and SII in patients with mRCC. (Hizal et al. 2020; Rebuzzi et al. 2020; Teishima et al. 2020) However, a few studies assessed these biomarkers in patients with mRCC treated with ICIs. One of these studies showed that NLR was a prognostic factor for OS and PFS in patients with mRCC treated with nivolumab. However, a small sample size (n = 38) was an important limitation of this study.(Bilen et al. 2018) Similarly, in another study including a small number of patients (n = 42), Jeyakumar et al. showed that pre-treatment NLR was an independent prognostic factor for OS and PFS in patients with mRCC treated with ICIs.(Jeyakumar et al. 2017) On the other hand, Lalani et al. concluded that not only pre-treatment NLR but also change in NLR during the treatment period was associated with survival outcomes.(Lalani et al. 2018) In contrast to these studies, Nishiyama et al. established that baseline NLR was not associated with survival outcomes in patients with mRCC treated with nivolumab.(Nishiyama et al. 2020)

Composite biomarkers, such as NLR, PLR, and lymphocyte-to-monocyte (LMR), include only two parameters, while SII consists of three parameters (i.e., neutrophil, platelet, and lymphocyte). The conflicting results mentioned above may be associated with the parameters used to calculate peripheral blood IIBs. At that point, a question arises in terms of whether the effect of more parameters may increase the prognostic value of composite biomarkers. Interestingly, a study comparing the LMR and SII showed that SII was an independent prognostic factor, while LMR had no impact on survival outcomes after adjusting for confounding factors.(Rebuzzi et al. 2020) In another study, De Giorgi et al. showed that SII was superior to NLR in prognostic value.(De Giorgi et al. 2019) On the other hand, the pivotal study of PIV showed that PIV had a greater relative influence on OS and PFS than NLR and SII in patients with mCRC.(Fuca et al. 2020) Taken together, including four parameters (i.e., neutrophil, monocyte, platelet, and lymphocyte) of PIV might contribute to the prognostic value on patients with mRCC treated with nivolumab in the second line and beyond.

The IMDC risk score is a well-known prognostic tool in patients with mRCC. It is composed of six parameters, including two peripheral blood IIBs (i.e., neutrophil and platelet).(Heng et al. 2009) However, it was not an independent prognostic factor in multivariate analysis in our study. Similar to our results, a study of De Giorgi et al., which was evaluated the SII in patients with mRCC treated with nivolumab, established that the IMDC risk score was not an independent prognostic indicator, while SII was prognostic for survival outcomes in multivariate analysis.(De Giorgi et al. 2019) The IMDC risk score is

used to stratify patients with mRCC before the initiation of the first line treatment.(National Comprehensive Cancer Network-Kidney Cancer 2021) Furthermore, studies showed that the IMDC risk score was a prognostic indicator in patients with mRCC treated with nivolumab in the second line.(Dudani et al. 2020; Yip et al. 2018) Interestingly, our study suggested that PIV might be a better option than the IMDC risk score to guide the prognosis in patients with mRCC treated with nivolumab in the second line and beyond.

In this study, we have several limitations. One of the most important limitations of our study was based on its retrospective nature. With this regard, PFS was not appropriately assessed by cross-sectional imaging in the prespecified intervals. Furthermore, we had to exclude patients with missing data because of the retrospective feature of our study. Additionally, our study was a multi-center study, and it might have led to variations in laboratory values and imaging methods. To mitigate the impact of variations on laboratory values, we included only laboratory data collected in the last week before the initiation of nivolumab.

Conclusion

In conclusion, our study showed that PIV might be an easily accessible composite biomarker in patients with mRCC treated with nivolumab in the second line and beyond.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

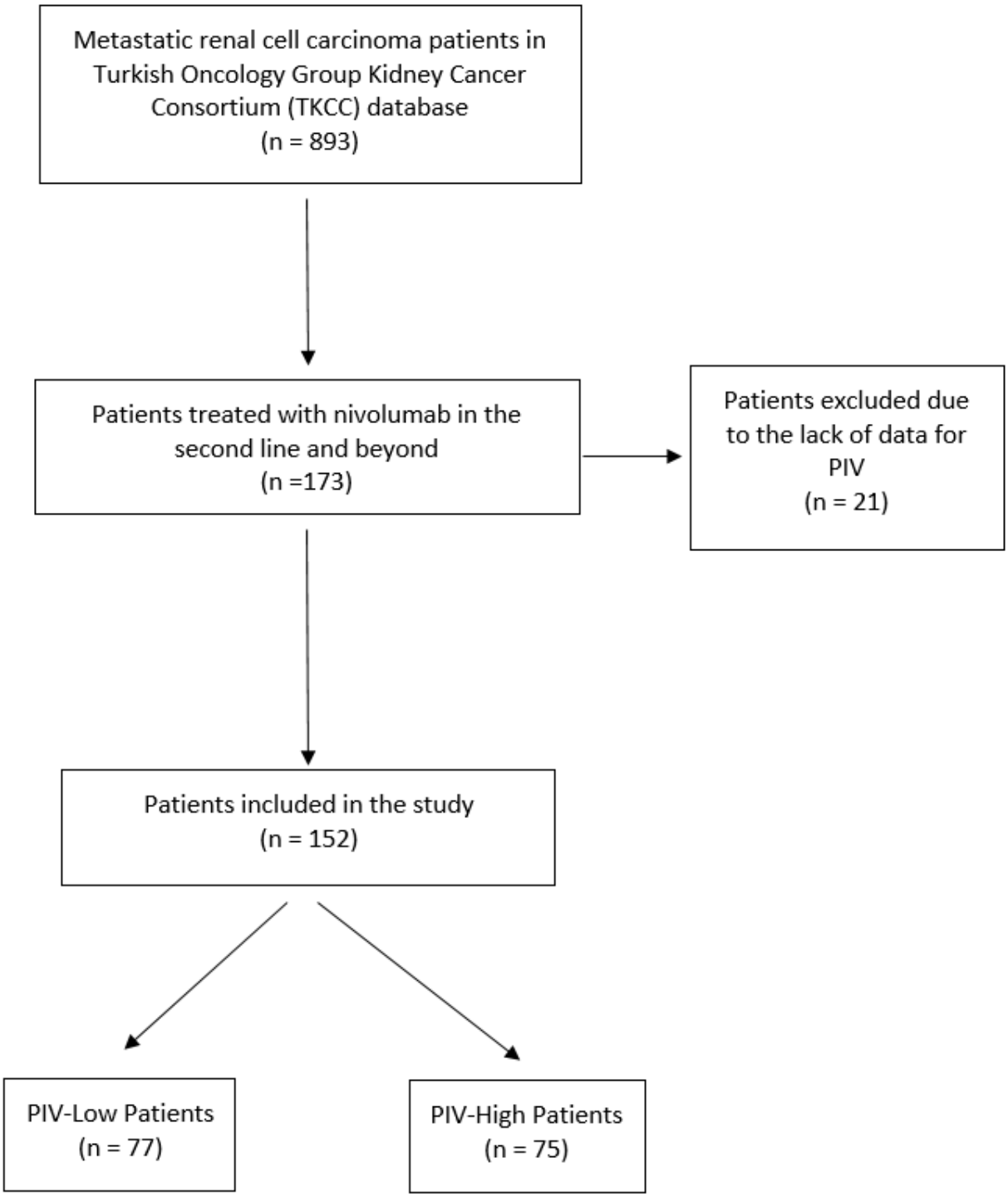

Figure 1

Figure 1. Flowchart of Patient Selection

Abbreviations: *PIV=Pan-Immune-Inflammation Value*

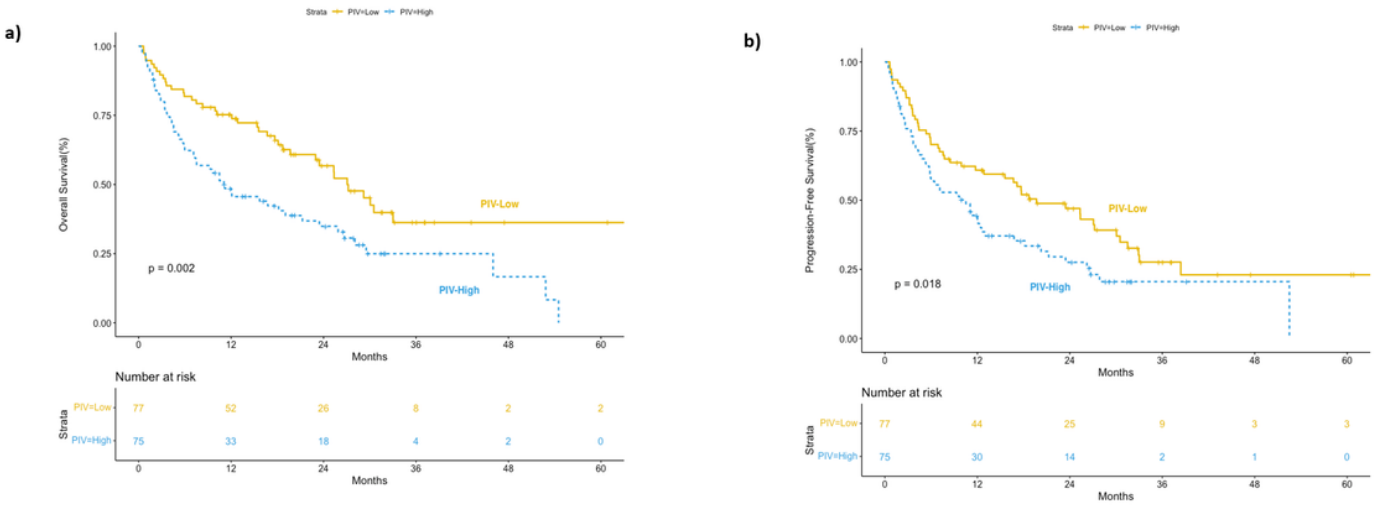

Figure 2

Kaplan-Meier estimates of overall survival (a) and progression-free Survival (b) according to pan-immune-inflammation value (PIV) category *(p value was calculated by using the log-rank test)*