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

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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 using the following formula: neutrophil (10³/mm³) x monocyte (10³/mm³) x platelet (10³/mm³)/lymphocyte (10³/mm³).

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 (≤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.

Keywords Immunotherapy · Renal cell carcinoma · Biomarker

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. 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 indicators 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 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 malignant 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 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 metastatic renal cell carcinoma (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 was used to describe the data. Chi-square and Mann–Whitney U tests were used to compare categorical and continuous variables, respectively. PIV was calculated 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. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed 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. Baseline characteristics were similar in the PIV-low and PIV-high groups, except for the number of systemic treatment lines before nivolumab. The rate of patients receiving nivolumab in the second line was higher in the PIV-low group than in the PIV-high group (62.3 vs. 45.3%). All baseline characteristics are shown in Table 1.

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 3.1–19.2) 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 (Tables 2, 3).

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 (Tables 2, 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) Similar to a 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 mRCC. (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.

| Table 1 Baseline Characteristics | All patients | PIV-low | PIV-high | p value |
|---------------------------------|-------------|---------|----------|---------|
|                                 | n = 152 (%) | n = 77 (%) | n = 75 (%) |         |
| Age-years, median (IQR)         | 60 (54–67)  | 61 (53–67) | 60 (55–66) | 0.612   |
| Gender                          |             |          |          |         |
| Male                            | 117 (77.0)  | 58 (75.3) | 59 (78.7) | 0.625   |
| Female                          | 35 (23.0)   | 19 (24.7) | 16 (21.3) |         |
| Histological type               |             |          |          | 0.534   |
| Clear cell                      | 125 (82.2)  | 65 (84.4) | 60 (80.0) |         |
| Non-clear cell                  | 16 (10.6)   | 7 (9.1)   | 9 (12.0)  |         |
| Missing                         | 11 (7.2)    | 5 (6.5)   | 6 (8.0)   |         |
| Sarcomatoid feature             |             |          |          | 0.053   |
| Yes                             | 18 (11.8)   | 5 (6.5)   | 13 (17.3) |         |
| No                              | 101 (66.4)  | 53 (68.8) | 48 (64.0) |         |
| Missing                         | 33 (21.7)   | 19 (24.7) | 14 (18.7) |         |
| Fuhrman grade                   |             |          |          | 0.073   |
| 1–2                             | 21 (13.8)   | 15 (19.5) | 6 (8.0)   |         |
| 3–4                             | 73 (48.0)   | 36 (46.8) | 37 (49.3) |         |
| Missing                         | 58 (38.2)   | 26 (33.8) | 32 (42.7) |         |
| Previous nephrectomy            |             |          |          | 0.151   |
| Yes                             | 117 (77.0)  | 63 (81.8) | 54 (72.0) |         |
| No                              | 35 (23.0)   | 14 (18.2) | 21 (28.0) |         |
| Nivolumab line                  |             |          |          | 0.035   |
| Second                          | 82 (53.9)   | 48 (62.3) | 34 (45.3) |         |
| Third and beyond                | 70 (46.1)   | 29 (37.7) | 41 (54.7) |         |
| IMDC risk                       |             |          |          | 0.050   |
| Favorable                       | 13 (8.6)    | 9 (11.7)  | 4 (5.3)   |         |
| Intermediate                    | 94 (61.8)   | 51 (66.2) | 43 (57.3) |         |
| Poor                            | 23 (15.1)   | 7 (9.1)   | 16 (21.3) |         |
| Missing                         | 22 (14.5)   | 10 (13.0) | 12 (16.0) |         |
| Metastatic sites                |             |          |          |         |
| Lung                            | 130 (85.5)  | 62 (80.5) | 68 (90.7) | 0.075   |
| Bone                            | 100 (65.8)  | 47 (61.0) | 53 (70.7) | 0.211   |
| Liver                           | 42 (27.6)   | 19 (24.7) | 23 (30.7) | 0.409   |
| CNS                             | 34 (22.4)   | 14 (18.2) | 20 (26.7) | 0.209   |
| Performance status              |             |          |          | 0.310   |
| ECOG 0–1                        | 97 (63.8)   | 52 (67.5) | 45 (60.0) |         |
| ECOG 2–3–4                      | 45 (29.6)   | 20 (26.0) | 25 (33.3) |         |
| Missing                         | 10 (6.6)    | 5 (6.5)   | 5 (6.7)   |         |

Bold values indicate statistically significant results

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
Fig. 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 using the log-rank test)
**Table 2** Univariate and Multivariate Analysis for Overall Survival

|                          | Univariate |          |          |          |          |          |          |          |
|--------------------------|------------|----------|----------|----------|----------|----------|----------|----------|
|                          | HR         | 95% CI   | p value  | HR       | 95% CI   | p value  |
| Age                      |            |          |          |          |          |          |          |          |
| < 65                     | 1          |          | 0.730    |          |          |          |          |          |
| ≥ 65                     | 0.92       | 0.59–1.44|          | 0.796    |          |          |          |          |
| Gender                   |            |          |          |          |          |          |          |          |
| 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    |          |          |
| 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          |          |          |          |          |          |          |          |
| High                     | 1.90       | 1.25–2.89|          | 1.64     | 1.04–2.58|          |          |          |

Bold values indicate statistically significant results

CI confidence interval, CNS central nervous system, HR hazard ratio, IMDC international metastatic renal cell carcinoma database consortium, PIV pan-immune-inflammation value

*a* p value was calculated using the log-rank test

*b* p value was calculated using Cox’s proportional hazard regression model
Table 3 Univariate and Multivariate Analysis for Progression-Free Survival

|                        | Univariate HR (95% CI) | p value<sup>a</sup> | Multivariate HR (95% CI) | p value<sup>b</sup> |
|------------------------|------------------------|----------------------|--------------------------|----------------------|
| Age                    |                        |                      |                          |                      |
| < 65                   | 1                      | 0.970                |                          |                      |
| ≥ 65                   | 0.99 (0.66–1.48)       |                      |                          |                      |
| Gender                 |                        |                      |                          |                      |
| Male                   | 1.06 (0.66–1.68)       | 0.805                |                          |                      |
| Female                 | 1                      |                      |                          |                      |
| Histological type      |                        |                      |                          |                      |
| Clear cell             | 1                      |                      |                          |                      |
| Non-clear cell         | 1.41 (0.77–2.59)       | 0.261                |                          |                      |
| Sarcomatoid Feature    |                        |                      |                          |                      |
| Yes                    | 1.35 (0.73–2.52)       | 0.332                |                          |                      |
| No                     | 1                      |                      |                          |                      |
| Fuhrman grade          |                        |                      |                          |                      |
| 1–2                    | 1                      | 0.422                |                          |                      |
| 3–4                    | 1.29(0.68–2.43)        |                      |                          |                      |
| Previous nephrectomy   |                        |                      |                          |                      |
| Yes                    | 0.81 (0.52–1.26)       | 0.350                |                          |                      |
| No                     | 1                      |                      |                          |                      |
| CNS metastasis         |                        |                      |                          |                      |
| Yes                    | 1.23 (0.79–1.91)       | 0.352                |                          |                      |
| No                     | 1                      |                      |                          |                      |
| Bone metastasis        |                        |                      |                          |                      |
| Yes                    | 1.43 (0.93–2.18)       | 0.101                |                          |                      |
| No                     | 1                      |                      |                          |                      |
| Liver metastasis       | 1.75 (1.16–2.66)       | 0.007                | 1.66 (1.07–2.61)         | 0.025                |
| Lung metastasis        |                        |                      |                          |                      |
| Yes                    | 1.33 (0.75–2.34)       | 0.317                |                          |                      |
| No                     | 1                      |                      |                          |                      |
| Performance status     | < 0.001                | < 0.001              |                          |                      |
| ECOG 0–1               | 1                      | 1                    |                          |                      |
| ECOG 2–3–4             | 2.46 (1.63–3.73)       | 0.022                | 2.27 (1.47–3.49)         | 0.366                |
| IMDC risk              |                        |                      |                          |                      |
| Favorable              | 1.36 (0.69–2.67)       | 0.022                | 1.72 (0.81–3.62)         | 0.366                |
| Intermediate           | 1                      | 1                    |                          |                      |
| Poor                   | 2.07 (1.21–3.52)       | 0.022                | 1.04 (0.55–1.96)         | 0.366                |
| Previous treatment line|                        |                      |                          |                      |
| 1                      | 1                      | 0.137                |                          |                      |
| ≥ 2                    | 1.34 (0.91–1.97)       |                      |                          |                      |
| PIV                    |                        |                      |                          |                      |
| Low                    | 1                      | 0.018                |                          | 0.042                |
| High                   | 1.59 (1.08–2.36)       |                      |                          |                      |

Bold values indicate statistically significant results

CI confidence interval, CNS central nervous system, HR hazard ratio, IMDC international metastatic renal cell carcinoma database consortium, PIV pan-immune-inflammation value

<sup>a</sup>p value was calculated using the log-rank test

<sup>b</sup>p value was calculated using Cox’s proportional hazard regression model
The rate of patients treated with nivolumab in the second line was higher in the PIV-low group than in the PIV-high group. However, no statistically significant was observed in survival outcomes between the patients receiving nivolumab in the second line and those receiving it in the third 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. Laboratory values that were used to calculate PIV might have been affected by any other conditions, such as infections, steroid use, smoking, etc. It was not possible to retrospectively evaluate the existence of these factors.

**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.

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

**Declarations**

**Conflict of interest** The authors have no relevant financial or non-financial interests to disclose.

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