PROGNOSTIC AND PREDICTIVE BIOMARKERS IN UROTHELIAL CANCER

Ph.D. Thesis

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1. INTRODUCTION

1.1. Overview of the topic

1.1.1. What is the topic?

Our research focus is on assessing different prognostic and predictive soluble biomarkers in the context of UC and ICI therapy.

1.1.2. What is the problem to solve?

ICIs have revolutionized the systemic treatment of UC; however, the majority of patients receiving this therapy do not respond. The main unmet need is to identify those patients who will benefit from ICI therapy.

1.1.3. What is the importance of the topic?

UCs are amongst the most prevalent cancers with devastating survival rates, when diagnosed in muscle-invasive disease stage. Prognostication and therapy prediction is crucial for personalized cancer therapy. As ICIs have reshaped the treatment landscape of UC, identifying which patients are most likely to benefit remains an unmet clinical need. Identifing predictive biomarkers would help to predict treatment response, improve patient stratification, and avoid unnecessary therapy.

1.1.4. What would be the impact of our research results?

The impact of our research project lies in the evaluation of the efficacy of novel immunotherapeutic approaches and the identification of reliable predictive biomarkers. Our research aims to guide the selection of patients most likely to benefit from these treatments. This precision approach can lead to improved response rates and mitigate overtreatment**.** Furthermore, the application of soluble blood-based biomarkers could enable disease by tracking therapeutic response, allowing clinicians to make individualized treatment decisions.

2. OBJECTIVES

2.1. Study I. – In this study, we conducted a systematic review and meta-analysis of published literature data to assess the prognostic significance of circulating sPD-L1 and sPD-1 levels in pre-treatment and on-treatment samples of tumor patients who underwent ICI therapy.

2.2. Study II. – In this study, we aimed to systematically investigate the prognostic relevance of NLR, CRP, PLR, and LDH in ICI-treated locally advanced and mUC patients.

2.3. Study III. – In this study, we aimed to assess the prognostic value of sPD-L1 and its changes in different treatment settings of UTUC. Therefore, in a *post hoc* pilot study, we determined sPD-L1 levels in prospectively collected pre-treatment and on-treatment serum samples of UTUC patients, who underwent either surgical or systemic (platinum or ICI) treatment.

3. METHODS

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 recommendations, and followed the Cochrane Handbook (Page, McKenzie *et al.* 2021) (Cumpston, Li *et al*. 2019). The study protocols was registered on PROSPERO (Study I: CRD42021283222, Study II: CRD42022291449).

3.1. Literature search and eligibility criteria

The electronic databases PubMed, EMBASE, and Cochrane Library were screened for study I. and we also included Scopus for study II. The dates of literature search and the searchkeys are includied in the original articles. Two independent authors performed the systematic selection process. Disagreements were resolved by a third author. References were screened using Endnote X^9 (Clarivate Analytics, Philadelphia, PA, USA) and assessed by title, abstract, and full text.

3.2. Study selection, data collection and patient cohort

3.2.1. Study selection and data collection for study I. and study II.

We used the PECO framework to formulate our research question and included original English-language studies. For Study I, we examined (P) ICI-treated patients with various tumors, and (E and C) compared the hazard of high and low serum or plasma sPD-L1 and/or sPD-1 levels in regard to (O) overall survival (OS) or progression-free survival (PFS). If available, on-treatment sPD-L1 and sPD-1 concentrations (median or mean level, range, or interquartile range) were also considered as additionally assessed parameters. For Study II, we invastigated (P) patients with ICI-treated UC and (E and C) compared the hazard of high and low serum or plasma NLR, CRP, LDH, and PLR levels for (O) OS or PFS and objective response rate (ORR). For the assessed biomarkers, we used cut-off values based on the definitions in the original articles. The following exclusion criteria were used: reviews, comments, letters, meta-analyses, systematic reviews, animal experiments, and conference abstracts were excluded.

Data were obtained by reading full-text articles by two independent authors. For Study I, we extracted the following data: the first name of the author, year of publication, cancer type, ICI therapy type, country of sample collection, study type, cohort size, patient age, sex, cut-off values for sPD1/ sPD-L1, cut-off definition method (e.g., median, receiver operating characteristic [ROC] curve), assay method, follow-up time, OS and PFS.

For Study II, parameters extracted were first name of author, publication year, tumor location (upper *vs.* lower urinary tract), type of ICI therapy, country of sample/data collection, type of study, cohort size, patient age, sex, ECOG performance status, cut-off values for NLR, CRP, LDH and PLR, follow-up time, OS, PFS, and ORR.

For eligible studies, the article provided calculated hazard ratios (HR) with 95% confidence intervals (CI). In addition, when available, ORR, data on sPD-L1 and sPD-1 level changes during ICI treatment were extracted.

3.2.2. Patient cohort for study III

Pre-treatment serum samples were collected from an overall number of 61 UTUC patients (44 males, 17 females), who underwent surgical (RNU cohort; n=37), postoperative platinum (CTX cohort; n=25), or second-line ICI therapy (ICI cohort; n=6) at the Department of Urology, Semmelweis University between 08/2014 and 07/2020. In

addition to pre-treatment samples, we collected samples following therapy start at predefined time points. For 14 patients of the RNU cohort, serum samples from the first postoperative day were available. For the CTX cohort, 18 samples from the first day of the second chemotherapy cycle, while for the ICI cohort four samples after three months of therapy were available for analysis.

Blood samples were collected in 9 ml tubes (Vacuette®) and left at room temperature for 30 – 90 minutes, then centrifuged with an Eppendorf 5702R centrifuge at 1500 x g for 10 minutes, and finally aliquoted and kept at -80°C until further analysis. The primary endpoint of this study was OS, which was calculated as the period between initiation of therapy (RNU, CTX, or ICI) and the last follow-up (01/2022) or death. The secondary endpoint was PFS. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee (TUKEB 256/2014). All patients provided a written informed consent to participate in this study.

3.3. Quality assessment and soluble PD-L1 analysis

3.3.1. Qualaty assasment for study I. and study II.

Risk of bias was assessed by two independent authors using the Quality in Prognostic Studies (QUIPS) tool (Grooten, Tseli et al. 2019). The study attrition domain was assessed only for prospective studies. The RobVisR tool was used to summarize the results of the evaluations (McGuinness and Higgins 2020). GRADEpro^{TM} program was used to evaluate the evidence (Guyatt, Oxman et al. 2011).

3.3.2. Soluble PD-L1 analysis for study III.

Quantitative sPD-L1 analyses were performed by using the sandwich ELISA method (PD-L1/B7-H1 Quantikine ELISA kit, DB7H10, R&D Systems, Wiesbaden, Germany), according to the manufacturer's instructions. To exclude possible interference between the therapeutic anti-PD-L1 antibody and the used ELISA assay, we also analyzed atezolizumab (anti-PD-L1) and pembrolizumab (anti-PD-1) on our ELISA plates.

3.4. Data synthesis and analysis

3.4.1. Statistical analysis for study I and study II

1. All statistical analyses were performed with R (R Core Team 2023, v4.3.2), using the meta (Schwarzer 2022) package for basic meta-analysis calculations and plots, and dmeta (Harrer 2022) package for additional influental analysis calculations and plots.

2. For time-to-event data, hazard ratio (HR) was used for the effect size measure with 95% confidence interval (CI). To calculate the pooled HR, we calculated the logarithm of HR and its SE from the available data following the methodology of Tierney *et al.*(Tierney, Stewart et al. 2007).

3. We extracted or calculated the total number of patients and events ("raw data") from available studies. Using these data, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) as the effect size measure. Results are reported as the odds of the event in the experimental group compared to the control group.

4. Pooled OR based on raw data was calculated using the Mantel-Haenszel method (Mantel and Haenszel 1959, Robins 1986). The pooled HR was calculated using the inverse variance weighting method (on a logarithmic scale).

5. We used a Hartung-Knapp adjustment (Knapp and Hartung 2003) for CIs (IntHout, Ioannidis et al. 2014). To estimate the heterogeneity variance measure ($\tau 2$), for raw data OR calculation, we used the Paule-Mandel method (Paule 1982) (recommended by Veroniki *et al.*(Veroniki, Jackson et al. 2016) with the Q-profile method for the confidence interval. For HRs, the restricted maximum-likelihood estimator was used with the Q profile method for the confidence interval (Veroniki, Jackson et al. 2016, Harrer 2021).

6. Results were considered statistically significant if the pooled CI did not contain the null value. We summarized the findings in forest plots. Where applicable, and where the number of studies was sufficiently large and not too heterogeneous, we also reported the prediction intervals (i.e., the expected range of effects of future studies) of results. In addition, between-study heterogeneity was described by the Higgins & Thompson's statistics (Higgins and Thompson 2002).

7. For Study I, subgroup analysis was conducted based on the used ELISA assays and cancer types. For Study II, we conducted subgroup analyses by line of therapy (first-line, second-line *vs.* mixed), drug (atezolizumab, pembrolizumab and mixed), study design (prospective *vs.* retrospective), and study site (singlecenter *vs.*multicenter). For subgroup analysis, we used a fixed-effects "plural" model (aka. mixed-effects model). We assumed that all subgroups had a common $\tau 2$ value as we did not anticipate differences in the between-study heterogeneity between the subgroups, and the number of studies was relatively small in some subgroups (recommended by Borenstein *et al.* (Borenstein 2009)., The "Cochrane Q" test (an omnibus test) was used to assess differences between subgroups (Harrer 2021). The null hypothesis was rejected at the 5% significance level. Biomarker level changes were expressed as fold-changes, and a median fold-change was calculated separately for PD-1 and PD-L1 inhibitors (Table 2.).

3.4.2. Statistical analysis for study III.

The non-parametric two-sided Wilcoxon rank-sum test (Mann-Whitney test) was used for group comparisons. Univariate OS and PFS analyses were performed using the Kaplan-Meier log-rank test and univariate Cox analysis. Low event numbers in each cohort did not allow the performance of multivariate analyses. Receiver operating characteristics (ROC) curves were applied for RNU and CTX treatment groups to determine PD-L1 cut-off values with the highest sensitivity and specificity for the dichotomized endpoint of death during the follow-up period. Spearman´s rank correlation analysis was used to test for correlation between formerly determined serum MMP-7 and PD-L1 levels (Kovacs, Mayer et al. 2022). P-value of <0.05 was considered as significant. All statistical analyses were performed with IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, N.Y., USA).

4. RESULTS

4.1. Study I. – Investigating the prognostic role of sPD-L1 and sPD-1 in human malignancies treated with immune checkpoint inhibitor

4.1.1 Elevated pre-treatment sPD-L1 predicts OS in NSCLC and melanoma

Thirteen articles reported univariate OS as a primary outcome. The pooled overall estimate showed that patients with high sPD-L1 levels had worse OS (HR:1.67; CI:1.26-2.23, I^2=79%, p<0.001; Figure 3). As for publication bias, the funnel plot seems asymmetric; however, Egger's test shows no publication bias (p=0.177).

Four of the included articles reported a multivariate Cox proportional hazard model. The pooled multivariate analysis confirmed that patients with high sPD-L1 levels had shorter OS (HR:1.62; CI:1.00-2.62, I^2=84%, p=0.05.

A subgroup analysis was performed according to cancer type. Based on six studies with NSCLC patients, high sPD-L1 levels were consequently associated with poor OS (HR:2.93; CI:2.52-3.40, I^2=0%, p<0.001). According to three publications, poor OS were found for malignant melanoma patients with high sPD-L1 (HR:1.73; CI:1.01-2.97, I^2=19% p=0.047). No difference was found between high and low sPD-L1 levels in OS in the subgroup of mixed tumor types (HR:1.22; CI:0.86-1.72, I^2=0%, p=0.263), but in this case various studies showed rather heterogeneous results (Figure 3).

4.1.2. Elevated pre-treatment sPD-L1 predicts poor PFS in NSCLC

Eleven articles reported univariate PFS as the primary outcome. The pooled overall estimate found no PFS difference between high and low sPD-L1 groups (HR:1.20; CI:0.85-1.70, I^2=78%, p=0.305; Figure 4). The visual presentation of the Funnel plot and Egger's test suggested publication bias (p=0.007)

Four of the included articles reported a multivariate Cox proportional hazard model. The pooled multivariate analysis showed that patients with high sPD-L1 levels tended to have inferior PFS (HR:1.71; CI:1.00-2.94, I^2=82%, p=0.051).

The subgroup analysis of cancer types revealed high pre-treatment sPD-L1 as a strong risk-factor in the NSCLC subgroup (HR:2.08; CI:1.81-2.38, I^2=0% p<0.001), whereas rather heterogeneous results were observed in RCC (HR:0.67; CI:0.12-3.86, I^2=88% p=0.653), melanoma (HR:1.18; CI: 0.56-2.50, I^2=74%, p=0.668) and mixed cohorts (HR:0.96; CI:0.47-1.96, I^2=74%, p=0.903) (Figure 4).

4.1.3. Pre-treatment sPD-1 and PFS and OS

Three articles reported PFS for sPD-1 (HR:1.16; CI:0.23-5.75, I^2=89%, p=0.858) (Figure 5) with heterogenous results. Meyo *et al*. in NSCLC and Ugurel *et al*. found in melanoma that higher sPD-1 level patients had shorter PFS, whereas Incorvaia *et al*. found the opposite result in metastatic RCC. Meyo *et al.* (HR:2.28; CI:1.11-4.68; p=0.025) and Ugurel *et al.* (HR:2.70; CI:1.10-6.25; p=0.055) reported sPD-1 and OS.

4.1.4. sPD-L1 levels strongly increase during anti-PD-L1 therapy

Ten articles reported both pre-treatment and on-treatment sPD-L1 levels in 12 tumor entities. Serum sPD-L1 levels remained unchanged under anti-PD-1 therapy, whereas anti-PD-L1 therapy caused a remarkable (27.67-fold) elevation of sPD-L1 levels (Table 4). Two articles reported both pre-treatment and on-treatment sPD-1 levels during anti-PD-1 (nivolumab) therapy (Table 4).

4.1.5. The assay method does not influence the correlations between sPD-L1 and OS

Our subgroup analysis according to the used assay methods suggested that the sPD-L1 assay method had no major influence on the OS (R&D: HR:2.11; CI:1.44-3.08, I^2=84%, p=0.003 vs. "others": HR:1.35; CI:0.79-2.30, I^2=54%, p=0.224; Figure 6). The same subgroup analysis was further evaluated based on PFS. Our subgroup analysis suggested that the sPD-L1 assay method might influence PFS. (R&D: HR:1.87; CI:1.52-2.32, I^2=2%, p=0.025 vs. "others": HR:0.96; CI:0.55-1.66, I^2=76%, p=0.873; Figure 5). Because of the low number of studies with sPD-1, no comparison was possible between various assay methods.

4.2. Study II. – Investigating the prognostic role of blood-based inflammatory biomarkers in urothelial cancer treated with immune checkpoint inhibitor

4.2.1. High pre-treatment NLR is associated with inferior OS and PFS.

Twenty articles provided information on NLR and OS. Pre-treatment high NLR was associated with worse OS both in univariate (HR: 2.19; 95%CI: 1.80-2.68) (Figure 7)and multivariate analyses (HR: 1.77; 95%CI: 1.61-1.94).

High pre-treatment NLR was associated with poor PFS both in univariate (HR:1.90; 95%CI: 1.57-2.31) (Figure 2) and multivariate analysis (HR: 1.77; 95%CI:1.16-2.71).

Subgroup analysis of therapy lines revealed that high pre-treatment NLR was associated with worse OS rates in the second-line (12 articles) (HR:2.21 95%CI:1.75-2.80) and the mixed-line (5 articles) (HR:3.03 95%CI:1.67-5.52) ICI settings but no significant association was found in the first-line setting (3 articles) (HR:1.32 95%CI:0.58-3.00);. Furthermore, subgroup analysis by ICI drug type revealed that NLR was associated with worse OS rates both in the pembrolizumab (12 articles) (HR:2.09; 95%CI:1.69-2.60) (Figure 7) and in the atezolizumab (4 articles) (HR:2.90; 95%CI:1.30-6.49) (Figure 2) treatment groups. In an additional subgroup analysis, OS rate remained consistently associated with NLR regardless of study design, with an HR of 2.24 (95%CI:1.67-3.01) (Figure 7) for prospective studies (3 articles) and an HR of 2.15 (95%CI: 1.67-2.78) (Figure 7) for retrospective studies (17 articles). In addition, singlecenter studies had results similar to those of multicenter studies, with singlecenter studies (8 articles) giving an HR of 2.16 (95%CI: 1.50-3.10) (Figure 7) and multicenter studies (12 articles) an HR of 2.23 (95%CI: 1.64-3.02) (Figure 7). Three articles provided information on NLR and ORR, with a pooled ORR of 1.66 (95%CI: 0.47-5.89).

4.2.3. High pre-treatment CRP levels are associated with inferior OS and PFS

Eleven articles provided information on pre-treatment serum CRP levels. High pre-treatment CRP levels were associated with lower OS rates in both the univariate (HR:1.75; 95%CI:1.37-2.24) (Figure 8) and multivariate (HR:1.66; 95%CI:1.18-2.33)

analyses. Similarly, poor PFS was associated with elevated pre-treatment CRP levels (HR:1.58; 95%CI:1.26-1.99) (Figure 8).

Our subgroup analysis revealed that in the second-line ICI setting (7 articles), high pre-treatment CRP was associated with worse OS rates (HR:1.85; 95% CI:1.19-2.88) (Figure 8). Furthermore, CRP was also associated with worse OS rates in the pembrolizumab (9 articles) (HR:1.69; 95%CI:1.20-2.38) (Figure 8) treatment group, whereas for atezolizumab, the two available studies did not allow a statistical evaluation. In addition, CRP levels were associated with poor OS in singlecenter (7 articles) (HR:1.87; 95%CI:1.23-2.86) (Figure 8), but not in multicenter studies (4 articles).

4.2.4. High pre-treatment PLR is associated with inferior OS and PFS

Three articles provided data on PLR and survival endpoints (OS, PFS). In univariate analysis, high pre-treatment PLR was associated with shorter OS (HR:2.74; 95%CI:1.74-4.31) (Figure 9) and PFS (HR:2.25; 95%CI:1.46-3.47) (Figure 9). Subgroup analyses were not possible due to the low number of available articles.

4.3. Study III. – Investigating the prognostic role of sPD-L1 in upper tract urothelial carcinoma

4.3.1. Correlation of sPD-L1 concentrations with clinicopathological parameters

For the RNU cohort, age, sex and ECOG performance status showed no significant association with preoperative sPD-L1 levels. Higher sPD-L1 levels were found in muscle-invasive, high grade (G3) as well as in lymph node and/or distant metastatic cases ($p<0.001$, $p=0.019$ and $p=0.002$ respectively) (Table 3, Figure 10).

4.3.2. Correlation of pre-treatment sPD-L1 levels with patients' prognosis

For the RNU cohort, three patients with pT0 histopathological findings were excluded from survival analyses. Muscle-invasive disease (≥pT2) and the presence of lymphatic or distant metastases at RNU were associated with shorter OS (HR:7.12; 95%CI:1.50–33.66; $p=0.013$ and HR:4.89; 95%CI:1.38 – 17.36; $p=0.014$, respectively). Similarly, shorter PFS was significantly associated with the same factors: ≥pT stage (HR:10.84; 95%CI:2.87–40.98; $p<0.001$), lymph node or distant metastasis (HR:6.19; 95%CI:2.20–17.40; $p=0.001$) (Table 5).

4.3.3. Changes of sPD-L1 levels during and after therapy

In the RNU cohort, the median preoperative sPD-L1 concentration was 84.0 ng/ml. In 14 cases, postoperative (first day after RNU) sPD-L1 levels were available with a median of 114.5 ng/ml, which was significantly higher than the pre-treatment serum concentrations ($p=0.011$) (Figure 12 A,D).

In the CTX cohort, the baseline median of sPD-L1 level was 96.1 ng/ml, which remained unchanged (99.4 ng/ml, n=18) after the first treatment cycle (Figure 12 B,D).

Interestingly, we observed a remarkable, 25-fold increase of sPD-L1 levels after 3 months of ICI treatment from 78.3 ng/ml to 1955.5 ng/ml ($p<0.001$) (Figure 12 C,D, which was in accordance with our former observation in ICI-treated UBC patients. In addition, we measured atezolizumab and pembrolizumab directly on our assay plates. These, substances did not result positive signals, excluding an assay incompatibility with the therapeutic antibodies.

5. CONCLUSION

We assessed sPD-L1 levels in UTUC for the first time, demonstrating significantly elevated levels in advanced tumor stages. High pre-treatment concentrations shown to be associated with shorter survival in both radical nephroureterectomy (RNU) and chemotherapy-treated patients. These findings, if validated in larger prospective cohorts, may enhance patient stratification and inform therapeutic decision-making in UTUC. In addition, we found that high baseline sPD-L1 levels were associated with significantly worse OS in ICI-treated cancer patients; however, this prognostic association appears to be tumor type-dependent. Thus, sPD-L1 may serve as a valuable pre-treatment prognostic biomarker, but its interpretation should be tailored to the specific tumor context. We also observed a markedly strong increase in sPD-L1 levels during anti-PD-L1 therapy, a phenomenon that appears therapy-specific; its biological basis and clinical implications require further investigation. Notably, elevated pre-treatment inflammatory biomarkers such as NLR, CRP, and PLR hold promise as reliable prognostic indicators in ICI therapy. Therefore, these markers are strong candidates for inclusion in future risk stratification models for mUC.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

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