Journal of Medicinal and Chemical Sciences 6 (2023) 142-151

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Review Article

Prognostic Value of Immune Checkpoints in Prostate Cancer: A Systematic Review and Meta-Analysis of Reconstructed Time to Event Data

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ARTICLE INFO

Article history
Receive: 2022-05-27
Received in revised: 2022-06-29
Accepted: 2022-08-01
Manuscript ID: JMCS-2207-1596
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatimah Ramezani
Editor who approved publication:
Dr. Azahar Ali

DOI:10.26655/JMCHEMSCI.2023.1.17

KEYWORDS
PD-L1
immune checkpoints
prostate cancer
time to event
meta-analysis

ABSTRACT

Introduction: Various molecular pathways are proposed to predict the prognosis of prostate cancer. However, due to previous achievements in prostate cancer management by immune checkpoint (IC) inhibitors, multiple studies have addressed the ICs role in the prognosis of prostate cancer and PD-L1 is known as one of the most cited ICs in this era.
Objective: To systematically review the prognostic value of the immune checkpoints (ICs) in prostate cancer.
Methods: This was a systematic review and meta-analysis study on online databases for studies reporting hazard ratios (HRs) of different survival outcomes of prostate cancer based on the dichotomized gene expression data of immune checkpoints. Studies presenting Kaplan Meier (KM) curves were included and time to event data was extracted for the KM reconstruction and HRs calculations for meta-analysis. Newcastle-Ottawa scale for cohort studies was used to assess the quality of studies.
Results: In the qualitative review, among the relevant selected ICs, 7 studies were available for PD-L1. Six studies were included in the meta-analysis for PD-L1. Concerning the high PD-L1 status as the reference, the chance of Biochemical Recurrence Free Survival was statistically lower in cases with low PD-L1 status (HR= 0.69, 95%CI of 0.57 to 0.58), under a fixed effect model with no heterogeneity (I2= 8%). There was a low possibility of publication bias based on the funnel plot.
Conclusion: High PD-L1 expression role in the prognosis of prostate cancer was shown to be supported by good levels of high-quality cohort studies, supported by pooled quantitative results of a meta-analysis.

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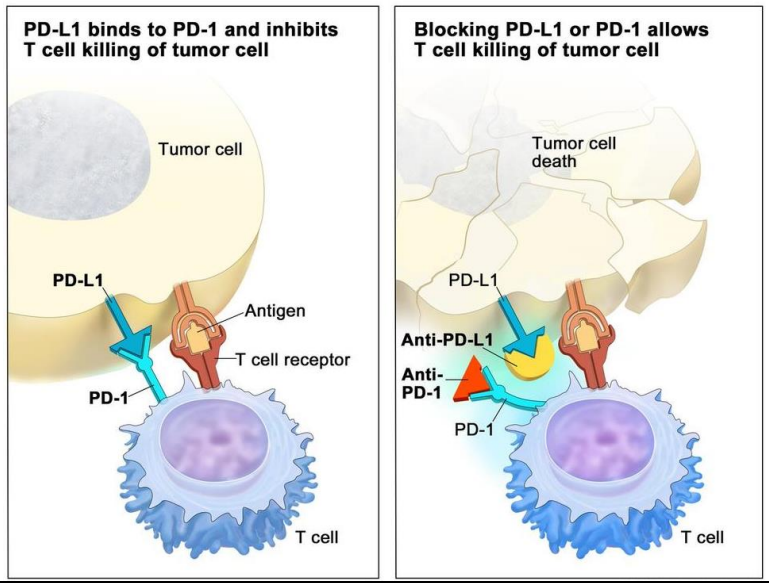
GRAPHICAL ABSTRACT



Introduction

Prostate cancer is the most common cancer in men [1], and despite the decrease in the incidence and death rate of prostate cancer in the United States and some other western countries [2], the incidence and death rate of this cancer is increasing in less developed and developing countries [3]. The rate of prostate cancer in Asian countries is much lower than the cases reported in the western population [3]. Prostate cancer is a disease related to the elderly [4] because the incidence and mortality rate of this disease is directly related to age [4]. Radical prostatectomy is a procedure in which the entire prostate gland and surrounding lymph nodes are removed to treat localized prostate cancer [5]. Prognosis and treatment options for prostate cancer depend on the cancer stage (Prostate-Specific Antigen (PSA) levels, Gleason score, tumor grade, and spread of cancer to nearby organs, and other parts of the body, age of the patient, and whether the cancer was newly diagnosed or diagnosed at advanced stages. Most men with prostate cancer do not die from prostate cancer [6]. In the context of genetic prognostic factors of prostate cancer, environmental suppressors of the tumor immune system are one of the distinct biological features that cause tumor growth and metastasis [7-8]. Currently, immunotherapy with checkpoint inhibitors has shown unprecedented clinical activity in a wide range of tumor types, like melanoma [9] and lung cancer [10]. Cells and tissues are constantly monitored by the immune system, and cancer has evolved in a way that can disrupt the immune checkpoints (ICs) and escape the host's immune system [11]. Sometimes cancer cells use immune checkpoint proteins as a shield to avoid being recognized and attacked by the immune system. Controlling molecules of the immune system including Cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), and T-cell immunoglobulin mucin-3 (TIM-3), galectins are immune checkpoints that are proposed as therapeutic goals and prognostic factors in prostate cancer [12-14]. Considering the importance of ICs molecules such as PD-1/PD-L1, along with lesser-known ICs such as TIM3 and galectins, in suppressing immune responses in prostate cancer, prompted us to investigate the relationship between the intensity of the expression of the mentioned ICs with the prognosis of prostate cancer.

Method

This was a systematic review (SR) and meta-analysis (MA) study based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. PI (E) CO model was used to design the study question. Our study patients are prostate cancer patients. Exposure in our study was the expression or presence of inhibitory immune checkpoints genes. Based on our initial search, a list of inhibitory immune checkpoints was extracted; the most

studied ICs include B7-H [15], BTLA [16], TIM-3, galectin 9, and PD-1/PD-L1. A comparison was made to examine the presence or absence of high or low expression of these genes among patients with prostate cancer, taking into account survival variables of biochemical recurrence (BCR) free survival or overall survival. There were no restrictions on the year of the publication.

The search strategy was a combination of selected ICs with keywords of "prostate cancer", "prostatic neoplasms", "prostate carcinoma", and "immune checkpoints" in databases of PubMed, Scopus, Elsevier, Web of Science, and Google Scholar Search Engine. Two independent authors carried out the searches. As there were not enough studies for other ICs than the PD-L1, we excluded other ICs from the study.

The inclusion condition in the present study was to investigate the protein expression of inhibitory ICs in a population of prostate cancer patients by separating patients with high and low expression of inhibitory ICs. Studies that presented Kaplan Meier (KM) curves were considered. RCTs reporting data of particular interventions were not included.

A piloted form was used to record the study information was filled by two independent reviewers. Newcastle-Ottawa score was used to evaluate the quality of studies. A pooled estimate of Hazard ratios (HRs) and the related 95 % confidence intervals (CIs) were estimated based on the reconstructed Kaplan Meier data. KM *data were pooled by extracting data using Engauge .Digitizer software* Modena et al. proposed a method by using their spreadsheet of HR calculation based on the time to event data [17]. In the meta-analysis, for non-heterogeneous or heterogeneous data, a fixed-effects model (Peto technique) or a random-effects model (Mantel-Haenszel method) was utilized. The z-test was used to determine the overall impact, and the statistical significance threshold would be set to $P< 0.05$. I^2 was used to address the amount of heterogeneity, where higher than 50% values were considered non-heterogenic. The possibility of publication bias was grossly assessed by a funnel plot.

Result

The process of study selection is displayed in Figure 1. As two independent authors carried out the searches for PD-L1, 734 potentially relevant study titles were queried. As two independent authors carried out the queries, duplicated records were deleted. Ninety-four studies were evaluated based on the abstract. 39 studies were full text reviewed. The reason for the exclusion of studies is reported in Table 1. Eleven studies were included in SR (Table 1). Six studies were included in MA. Data were simulated based on the recurrence rate calculations and was descriptively reported. MA of PD-L1 low versus high expression was made based on the 7 studies.

In Li *et al.* study, the KM curves were stratified by PD-1 positive or negative and HR was calculated based on the reported univariate HR of 7.295 (2.981-17.852) high PD-L1 vs. low PD-L1 status, as listed in Table S2. We were not able to perform any Interrater agreement calculation between the reconstructed data and the reported HR as only comparisons were available in 3 studies. In Ness *et al.* study HR of 1.34, 95% CI of 0.97 to 1.85 was reported that matched our calculation of 1.32, 95% CI of 0.949 to 1.837. Finally in the MA, with no heterogeneity (I2= 8%), considering the high PD-L1 status as the reference, the BCR chance was statistically lower in cases with low PD-L1 status (HR= 0.69, 95%CI of 0.57 to 0.58), as indicated in **Table** 2. There was a low possibility of publication bias, based on the funnel plot, as displayed in Figure 2.

Possibility of bias

Newcastle-Ottawa scale for cohort study's quality was used to evaluate the bias possibility in the included studies. The scales are summarized in Figure 3. A minimum score of 6 was approved to be included in the study. Most studies had an acceptable quality, while there were not adequate follow-ups performed in some studies.

Table 1: Characteristics of included studies

PD-L1	Gevensleben *et al.*, 2016 [test cohort] [18]	Sharma *et al.*, 2019 [19]	Vicier *et al.*, 2021 [20]	Mo *et al.*, 2019 [21]	Li *et al.*, 2019 [22]	Goltz *et al.*, 2016 [23]	Ness *et al.*, 2017[24]	
N	611	220	109	80	127	247 (only 86 entered MA)	535	
Patients	Aggressive Primary Prostate Cancer	Radical prostatectomy patient cohort	Radical prostatectomy patient cohort	Localized and castration-resistant prostate cancer	Received adjuvant hormonal therapy (AHT) after radical prostatectomy	Radical prostatectomy patient cohort	Radical prostatectomy patient cohort	
Design	Cohort	Cohort	Retrospective cohort	Cohort	Cohort	Cohort	Cohort	
Outcome	BCR-free survival	BCR-free survival	BCR-free survival Metastasis free survival	BCR-free survival	BCR-free survival	BCR-free survival	BCR-free survival	
Mean follow-up	49.5 months	48.2 months	8.1 years	11.9 years	40 months	61.3 months	150 months	
Age	62	60.4 vs 58.8, in low and high PD-L1	58	NA	66	64.13	357 >65 years old	
N1 Nodal status	9 (1.5)	11	NA	NA	41(32.3)	14 (5.7%)	NA	
ICS method of assessment	Cytometric analysis, Pd-L1 cut-off: median expression of PD-L1	Strong staining in at least 1% of cells.	Immunohistochemistry	Immunohistochemistry in tumor-associated nerves*	Immunohistochemical PD-L1 assessment; Pd-L1 cut-off: median expression of PD-L0	CXCL12 gene was also evaluated a cohort of low CXCL12 Immunohistochemical PD-L1 assessment; Pd-L1 cut-off: median	Immunohistochemistry, dichotomization based on the staining extent	

**There was a confounding effect of other evaluated genes*.

Table 2: Comparison of the reconstructed time to event data and main data

	Reconstructed			Reported in the main text		
	HR	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI
Gevensleben *et al.*, 2016 [test cohort] [18]	1.186	0.808	1.741	NR		
Sharma *et al.*, 2019 [19]	1.706	0.687	4.232	NR		
Vicier *et al.*, 2021 [20]	3.267	0.619	17.241	2.88	0.97	8.61
Mo *et al.*, 2019 [21]	1.294	0.52	3.223	1.012	1.002	1.022
Li *et al.*, 2019 [4]	-	-	-	7.295	2.981	17.852
Goltz *et al.*, 2016 [23]	4.362	1.314	14.483	NR		
Ness *et al.*, 2017 [24]	1.32	0.949	1.837	1.34	0.97	1.85

Table 3: MA of log(HR) for PD-L1 status effect on BCR-free survival

Study ID	Log (HR)	Standard Error	Weight (%)	HR	95% CI	
					Lower	Upper
Goltz *et al.*, 2016 [23]	-1.47	0.61	2.9	0.27	0.07	0.76
Vicier *et al.*, 2021 [20]	-1.18	0.84	1.5	0.31	0.06	1.62
Li *et al.*, 2019	-0.59	0.24	18.1	0.55	0.34	0.90
Sharma *et al.*, 2019 [19]	-0.53	0.46	5.1	0.59	0.24	1.45
Ness *et al.*, 2017 [24]	-0.27	0.16	38.6	0.76	0.54	1.05
Mo *et al.*, 2019 [21]	-0.25	0.46	5.1	0.77	0.31	1.92
Gevensleben *et al.*, 2016 [18]	-0.17	0.19	28.6	0.84	0.57	1.24
Total	-	-	-	0.69	0.57	0.85

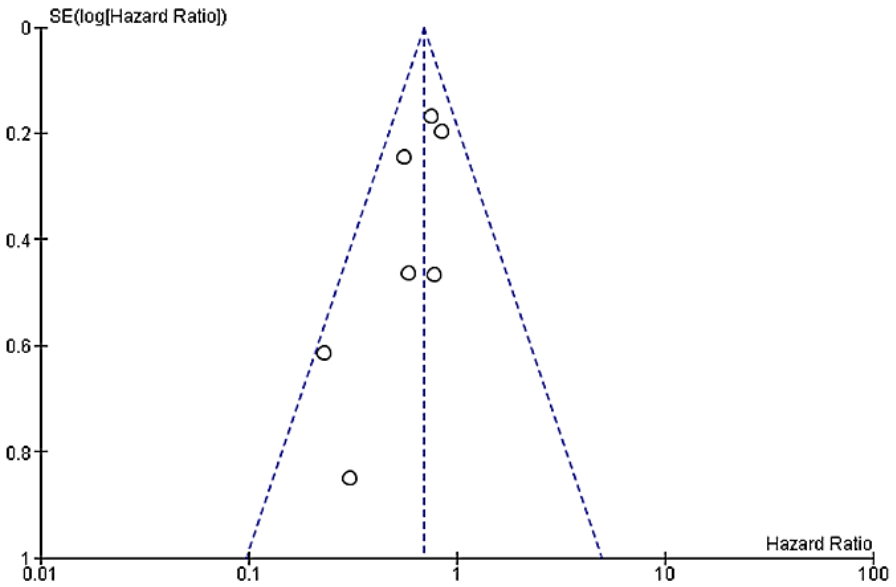


Figure 1: Funnel plot of MA for PD-L1 status effect on BCR-free survival

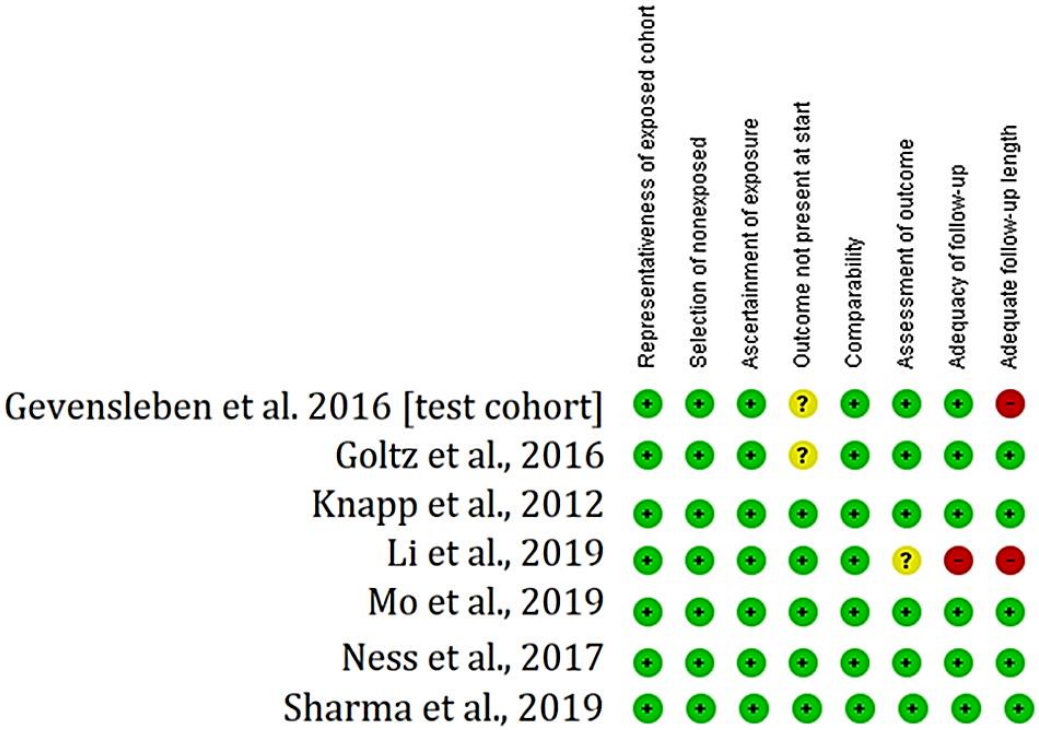


Figure 2: Newcastle-Ottawa scale of cohort study quality

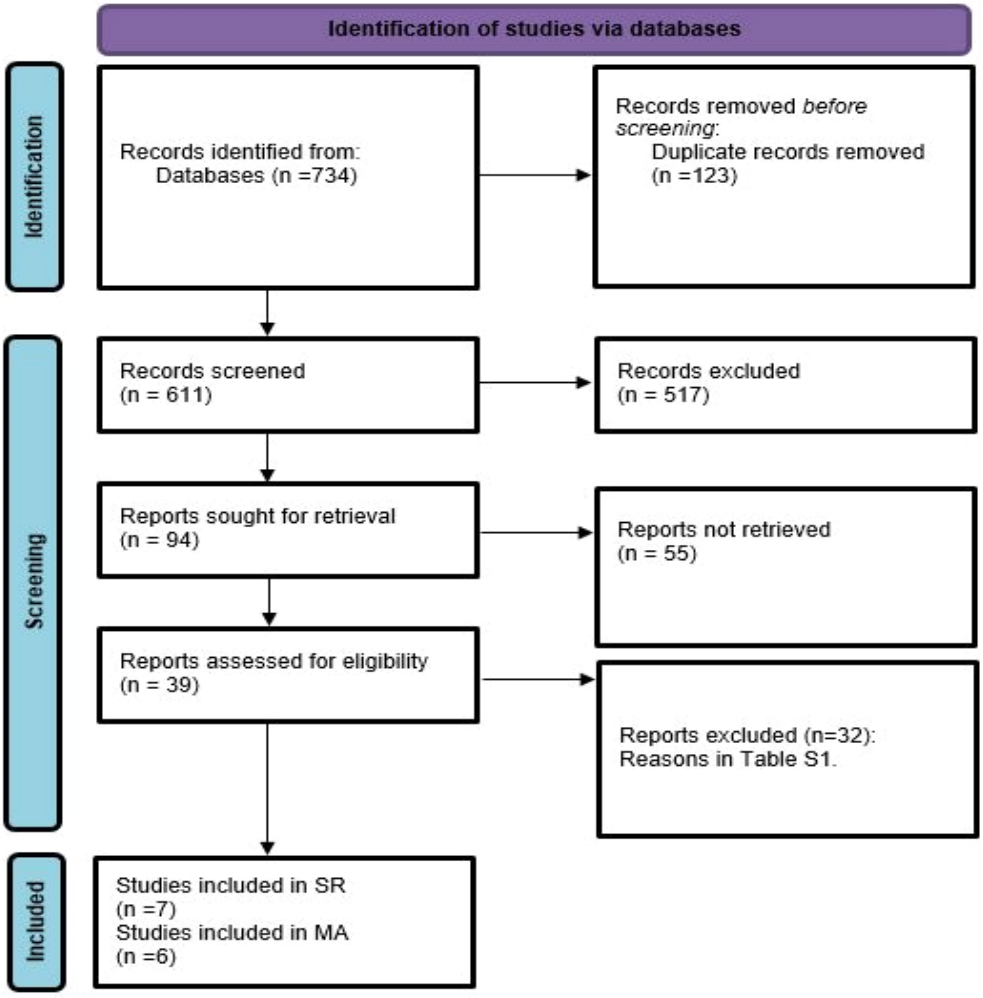


Figure 3: PRISMA flow chart of study

Discussion

Our review showed that while most studies were not individually conclusive for the prognostic role of the high PD-L1 expression in BCR-free survival of prostate cancer, pooled results revealed significant findings in line with poor prognosis of high PD-L1 status patients with a high chance of recurrence.

The previous similar MA study included only four studies [25], but the results were similar and found PD-L1 expression (HR = 1.78; 95% CI 1.39 to 2.27; $p < 0.00001$) associated with poor BCR free survival. While this statement of their MA was not true as they only had included 2 cohorts of the same study by Gevensleben et al. actually, they only represented the study results of Gevensleben *et al.*

PD-1 and its ligand PD-L1 are part of the inhibitory pathways that act to maintain environmental tolerance by limiting the lytic activity of immune cells [30]. As soon as the T cell receptor is activated, it is expressed on its surface and its connection to PD-L1 and PD-L2 ligands reduces the messages sent from the T cell receptor, and finally suppresses the immune system by inducing apoptosis in T cells [26]. It is notable that the PD-1/PD-L1 pathway is an important factor related to tumor-induced immunosuppression [27]. Several shreds of evidence point to the failure and exhaustion of T cells by the PD-1/PD-L1 pathway. Among this evidence is that PD-1 is expressed on the surface of TCD8+ cells infiltrating many solid tumors and antigen-specific CD8+ T cells in non-solid tumors [28]. Dysfunction of PD1+ T cells and high expression of PD-L1 has been observed in many cancers, which are associated with poor disease prognosis [29]. Disrupting the PD-1/PD-L1 pathway, either through a blocking antibody or through creating a gene defect in PD-1, leads to better clinical results and recovery of T cell function [30].

Our study was not conclusive for TIM-3 as we were not able to data extraction for MA. However, the results obtained from a meta-analysis study conducted by Yang Zhang *et al.* in 2016 showed that the high expression of TIM3 in patients with solid tumors decreased the overall survival of the patients is associated and the increased expression of TIM3 is also related to the advanced stages of the tumor [31].

PD-L1 roles have also been evaluated in meta-analysis studies for other cancers that we would mention for comparison of the meta-analysis methods and research methods. Li *et al.* investigated its role in colorectal cancer and showed that it is a poor prognostic marker of colorectal cancer [32]. Wang *et al.* conducted a similar analysis on solid tumors and included 61 studies in their review as distinct types of the cancers evaluated in their study. They had a similar approach to extracting HRs from the KM curves [36].

Limitations and suggestions

We were not able to generate evidence for other ICs as there were not enough studies. Likewise, in the case of PD-1, the same problem exists and still many studies are needed for any pooled analysis of HRs. Another limitation of this study was that some studies had evaluated the PD-L1 gene expression along with some other genes that we tried to use cohorts of patients with the lowest expression of secondary evaluated genes to decrease the chance of heterogeneity.

In the study of Li *et al.* [35] in addition to the pooled HR analysis, they compared the rate of PD-L1 positivity in different stages of the tumor and different pathological stratifications. In further analyses, we suggest considering this issue for PDl-L1. Furthermore, Wang et al. analyzed alternative survival indicators, the overall survival (OS), and disease-free survival (DFS) that we suggest such analysis for further meta-analysis study, while there were not enough reported OSs to be analyzed in our study.

Re-analyzing the KM data might be associated with some sources of human error as it was extracted by hand-drawn paths based on the original KM. As mentioned in supplementary Table S2, in some circumstances, the difference between re-calculated HR and published one was so significant that further studies should aid decreasing this error of calculations.

Conclusion

Our review showed that while most studies were not individually conclusive for the prognostic role of the high PD-L1 expression in BCR-free survival

of prostate cancer, pooled results revealed significant findings in line with poor prognosis of high PD-L1 status patients with a high chance of recurrence.

Acknowledgment

We would like to thank the Clinical Research Development Unit of Peymanieh Educational and Research and Therapeutic Center of Jahrom University of Medical Sciences for providing facilities to this work.

Funding

This research did not receive any specific grant from fundig agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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HOW TO CITE THIS ARTICLE

Hossein Hakimelahi, Alireza Yousefi, Marzieh Haghbeen, Mohammad Sadegh Sanie Jahromi, Hasan Zabetian, Reza Inaloo, Prognostic Value of Immune Checkpoints in Prostate Cancer: A Systematic Review and Meta-Analysis of Reconstructed Time to Event Data. *J. Med. Chem. Sci*., 2023, 6(1) 142-151

https://doi.org/10.26655/JMCHEMSCI.2023.1.17

URL: http://www.jmchemsci.com/article_154651.html