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ORIGINAL ARTICLE

Prostate Cancer

Prognostic value of ECOG performance status and Gleason score in the survival of castration-resistant prostate cancer: a systematic review

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Eastern Cooperative Oncology Group (ECOG) performance status and Gleason score are commonly investigated factors for overall survival (OS) in men with castration-resistant prostate cancer (CRPC). However, there is a lack of consistency regarding their prognostic or predictive value for OS. Therefore, we performed this meta-analysis to assess the associations of ECOG performance status and Gleason score with OS in CRPC patients and compare the two markers in patients under different treatment regimens or with different chemotherapy histories. A systematic literature review of monotherapy studies in CRPC patients was conducted in the PubMed database until May 2019. The data from 8247 patients in 34 studies, including clinical trials and real-world data, were included in our meta-analysis. Of these, twenty studies reported multivariate results and were included in our main analysis. CRPC patients with higher ECOG performance statuses (≥2) had a significantly increased mortality risk than those with lower ECOG performance statuses (<2), hazard ratio (HR): 2.10, 95% confidence interval (CI): 1.68–2.62, and $P < 0.001$. The synthesized HR of OS stratified by Gleason score was 1.01, with a 95% CI of 0.62–1.67 (Gleason score ≥8 *vs* <8). Subgroup analysis showed that there was no significant difference in pooled HRs for patients administered taxane chemotherapy (docetaxel and cabazitaxel) and androgen-targeting therapy (abiraterone acetate and enzalutamide) or for patients with different chemotherapy histories. ECOG performance status was identified as a significant prognostic factor in CRPC patients, while Gleason score showed a weak prognostic value for OS based on the available data in our meta-analysis.

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INTRODUCTION

The incidence of prostate cancer is the highest among men in the United States,[1] and it has shown the largest increase in China in recent years.[2] In general, the disease eventually progresses to castration-resistant prostate cancer (CRPC), during which stage most deaths occur. To date, six agents have been approved by the United States Food and Drug Administration (FDA) for the treatment of CRPC, including two taxane-based chemotherapy agents (docetaxel and cabazitaxel), two novel hormone therapies (abiraterone acetate and enzalutamide), sipuleucel-T immunotherapy, and the α-emitter radium-223.[3]

Eastern Cooperative Oncology Group (ECOG) performance status and Gleason score are two commonly used markers to evaluate the disease status of patients in urological oncology. Although their use as prognostic factors for overall survival (OS) in men with CRPC has been investigated in several studies,[4–10] the results have been inconsistent, and the conclusions were mainly drawn based on observational data from a single institution. Furthermore, a few studies analyzing combined individual data from several random controlled trials (RCTs) have been reported. For example, Halabi *et al.*[11] developed a prognostic model for predicting OS in first-line chemotherapy for patients with CRPC, and a small number of prognostic models based on combined individual data from several RCTs available on Project Data Sphere[12] have been developed.[13,14] However, only studies on docetaxel or mitoxantrone regimens were included because of the limitations of the dataset in their analyses. To the best of our knowledge, the OS of patients stratified by ECOG performance status or Gleason score has not been comprehensively investigated in CRPC, and the predictive or prognostic ability of these two markers has not been compared among different treatment regimens. Therefore, in this study, we performed a comprehensive literature-based analysis, including both clinical trials and real-world data (RWD), in CRPC patients under monotherapy to summarize the available evidence on the association of ECOG performance status and Gleason score with OS in patients with CRPC. We also compared the two markers in different treatment regimens and patient groups.

MATERIALS AND METHODS

Literature search

A systematic literature search of published articles on "docetaxel," "cabazitaxel," "abiraterone acetate," "enzalutamide," "sipuleucel-T,"

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and "radium-223" was conducted in the online PubMed database. Each agent was searched separately using the following combined search terms: name of intended drug (Title/Abstract), prostate cancer (Title/Abstract), and patient. The search of the database was initially conducted in March 2018 and last updated in May 2019. In addition, references in relevant reviews were manually screened for further inclusion.

Study selection and data extraction

Studies that reported the hazard ratio (HR) and the corresponding 95% confidence intervals (CI) of OS according to ECOG performance status (≥2 *vs* <2) and Gleason score (≥8 *vs* <8) were included. Both prospective RCTs and retrospective observational studies were considered. Reviews, case reports, editorials, preclinical studies, studies on combination therapies, non-English language articles, and studies without HRs of OS according to ECOG performance (≥2 *vs* <2) or Gleason score (≥8 *vs* <8) were excluded.

For each included study, the following information was extracted: (1) publication characteristics: title, authors, and publication year; (2) trial characteristics: study design, geographic location, sample size, intended treatment, and dose regimen; (3) patient population characteristics: subject type, demographics, background therapy, ECOG performance status, Gleason score, and others; and (4) HRs of OS according to the stratified criteria above.

Study assessments and data extraction were conducted independently by two reviewers (WJC and DMK). Disagreements were resolved by discussing with a third investigator (LL) to reach a final consensus.

Data synthesis

Because multivariate analyses adjust for confounding factors and selection bias, the results are more reliable.[15] Only HRs from multivariate models were included in our main analysis. HRs from univariate analysis were analyzed for comparison. If the HR of the reverse comparison was reported, the data were transformed according to the method reported.[16]

Meta-analyses were performed using RevMan software (version 5.3, Cochrane Collaboration, Oxford, UK). HRs and their 95% CIs were synthesized with fixed-effects or random-effects models, depending on the heterogeneity. Values of $P < 0.10$ or $I^2 > 50\%$ indicated significant heterogeneity, and the random-effects model was used. Otherwise, a fixed-effects model was used. Publication bias was tested using Begg's and Egger's methods with R software (version 3.5.1, http://www.r-project.org/).

Sensitivity analysis and comparison analysis

Sensitivity analyses were performed by excluding any single publication to evaluate the robustness of the findings. In addition, studies that reported reverse comparisons (*i.e.,* HRs of OS according to ECOG performance status [<2 *vs* ≥2] and Gleason score [<8 *vs* ≥8]) were removed from the dataset to explore the results of the original studies. In addition, subgroup analyses stratified by the chemotherapy history of patients were performed. Furthermore, the HR of OS from the results of the univariate analysis was synthesized to compare with the synthesized HR based on multivariate analysis.

RESULTS

Characteristics of eligible studies

A total of 4892 studies were identified through electronic searches. The flow diagram for literature selection is shown in **Figure 1**. The 34 studies selected for analysis included 9 abiraterone acetate, 4 enzalutamide, 18 docetaxel, and 3 cabazitaxel studies. Sipuleucel-T and radium-223 were not included in our meta-analysis because there were no available studies that reported multivariate analyses. The total number of patients enrolled in the included studies was 8247, ranging from 30 to 1186 patients per study. Among the 34 studies, 15 studies (16 articles)[4–6,10,17–28] reported both univariate and multivariate analysis results, 6[29–34] reported multivariate HRs, and 13[7–9,35–44] reported univariate HRs only. Most of the studies ($n = 28$) had a retrospective design; 3[9,24,32] were clinical trials; and 3 study designs included named patient programs (NPP),[35] compassionate-use programs (CUP),[19,20] or expanded access programs.[7] Further details on the study characteristics are presented in **Table 1**.

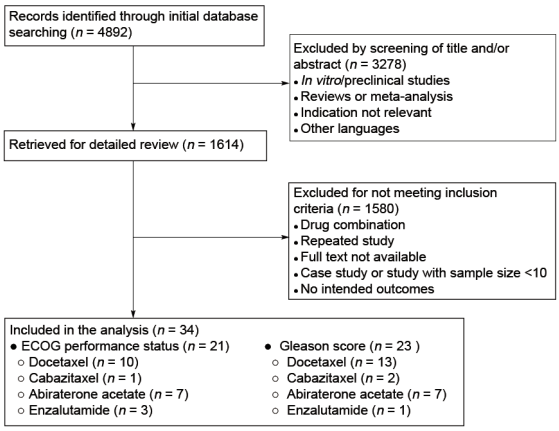

Figure 1: Flowchart of the study selection process in the meta-analysis. ECOG: Eastern Cooperative Oncology Group.

Impact of ECOG performance status on OS

Twenty-one studies[4–6,10,17–25,27,29,32,33,35–38] evaluated the association between ECOG performance status and OS, of which 16 studies reported multivariate models and 18 studies included univariate HRs. The data synthesis of multivariate HRs of OS using a random-effects model is shown in **Figure 2a**. CRPC patients with a higher ECOG performance status (ECOG ≥2) showed a statistically significantly increased mortality risk (HR: 2.10, 95% CI: 1.68–2.62, $P < 0.0001$) than those with a lower ECOG performance status (ECOG <2). Patients who received taxane chemotherapy (docetaxel and cabazitaxel) and androgen-targeting therapy (abiraterone acetate and enzalutamide) did not show a statistically significant difference in the HR results ($P = 0.57$). A sensitivity analysis was performed in which any single study was excluded one by one. The results showed that the merged HRs for OS did not significantly change, indicating the robustness of the findings (**Figure 2b**).

After removing the studies that reported reversed comparisons (ECOG <2 *vs* ECOG ≥2), the synthesized HR was 2.03, with a 95% CI of 1.78–2.31. Subgroup analysis stratified by the chemotherapy history of patients indicated that there was no significant difference between chemotherapy-naïve patients (HR: 2.08, 95% CI: 1.48–2.92) and postchemotherapy patients (HR: 2.27, 95% CI: 1.44–3.58; **Supplementary Figure 1**). The HR synthesized by the univariate results was 2.25 (95% CI: 1.67–3.03), and no significant difference was found between taxane chemotherapy (HR: 2.06, 95% CI: 1.23–3.44) and androgen-targeting therapy (HR: 2.61, 95% CI: 2.18–3.13; **Supplementary Figure 2**), while the prognostic effect of ECOG performance status on postchemotherapy patients (HR: 3.26, 95%

Table 1: Characteristics of the included studies

Study	*Published year*	*Study type*	*Patient population*	*Treatment*	*Chemotherapy history*	*Number of patients included*	*Comparison (univariate)*	*Comparison (multivariate)*
Poon *et al.*[4]	2016	RWD	Asian	Abiraterone	Chemo naïve (arm 1)	58	ECOG (≥2 *vs* <2) Gleason score (≥8 *vs* <8)	ECOG (≥2 *vs* <2)
					Post chemo (arm 2)	52	ECOG (≥2 *vs* <2) Gleason score (≥8 *vs* <8)	Gleason score (≥8 *vs* <8)
Fröbe *et al.*[35]	2016	NPP	Caucasian	Abiraterone	Post chemo	30	ECOG (≥2 *vs* <2) Gleason score (≥8 *vs* <8)	
Azad *et al.*[29]	2015	RWD	Caucasian	Abiraterone	Unknown	519		ECOG (2 *vs* <2)
Mikah *et al.*[18]	2016	RWD	Caucasian	Abiraterone	Unknown	84	ECOG (2 *vs* <2) Gleason score (≥8 *vs* <8)	ECOG (≥2 *vs* <2)
Van Praet *et al.*[5]	2017	RWD	Caucasian	Abiraterone	Post chemo	368	ECOG (≥2 *vs* <2)	ECOG (≥2 *vs* <2)
Fizazi *et al.*[9]	2016	RCT	Caucasian	Abiraterone	Chemo naïve	488	Gleason score (≥8 *vs* <8)	
					Post chemo	698	Gleason score (≥8 *vs* <8)	
Yasui *et al.*[30]	2018	RWD	Asian	Abiraterone	Unknown	972		Gleason score (≥8 *vs* <8)
Lin *et al.*[36]	2019	RWD	Asian	Abiraterone	Unknown	146	ECOG (≥2 *vs* <2) Gleason score (≥8 *vs* <8)	
Zhao *et al.*[17]	2018	RWD	Asian	Abiraterone	Chemo naïve	87	ECOG (≥2 *vs* <2) Gleason score (≥8 *vs* <8)	ECOG (≥2 *vs* <2)
Conteduca *et al.*[19,20]	2016	CUP and RWD	Caucasian	Enzalutamide	Post chemo	193	ECOG (≥2 *vs* <2)	ECOG (≥2 *vs* <2)
Choi *et al.*[10]	2018	RWD	Asian	Enzalutamide	Chemo naïve	113	ECOG (≥2 *vs* <2)	ECOG (≥2 *vs* <2)
Poon *et al.*[37]	2018	RWD	Asian	Enzalutamide	Unknown	117	ECOG (≥2 *vs* <2)	
Beardo *et al.*[38]	2019	RWD	Caucasian	Enzalutamide	Chemo naïve	70	Gleason score (<8 *vs* ≥8)	
Miyake *et al.*[21]	2018	RWD	Asian	Docetaxel	Chemo naïve	114	ECOG (<2 *vs* ≥2) Gleason score (<8 *vs* ≥8)	ECOG (<2 *vs* ≥2)
Song *et al.*[31]	2016	RWD	Asian	Docetaxel	Unknown	71		Gleason score (≥8 *vs* <8)
Kongsted *et al.*[22]	2017	RWD	Caucasian	Docetaxel	Chemo naïve	292	ECOG (<2 *vs* ≥2)	ECOG (<2 *vs* ≥2)
Shigeta *et al.*[23]	2016	RWD	Asian	Docetaxel	Chemo naïve (arm 1)	106	ECOG (≥2 *vs* <2) Gleason score (≥8 *vs* <8)	
					Chemo naïve (arm 2)	108	ECOG (≥2 *vs* <2) Gleason score (≥8 *vs* <8)	ECOG (≥2 *vs* <2)
Yao *et al.*[39]	2015	RWD	Asian	Docetaxel	Unknown	57	Gleason score (<8 *vs* ≥8)	
Narita *et al.*[40]	2016	Phase II	Asian	Docetaxel	Unknown	120	Gleason score (≥8 *vs* <8)	
Caffo *et al.*[41]	2015	RWD	Caucasian	Docetaxel	Unknown	134	Gleason score (<8 *vs* ≥8)	
Poon *et al.*[42]	2015	RWD	Asian	Docetaxel	Unknown	57	ECOG (<2 *vs* 2) Gleason score (<8 *vs* ≥8)	
Italiano *et al.*[6]	2009	RWD	Caucasian	Docetaxel	Chemo naïve	175	ECOG (≥2 *vs* <2)	ECOG (≥2 *vs* <2)
de Morrée *et al.*[24]	2017	RCT	Global	Docetaxel	Chemo naïve	1058	ECOG (≥2 *vs* <2)	ECOG (≥2 *vs* <2)
Quinn *et al.*[32]	2013	RCT	Caucasian	Docetaxel	Chemo naïve	994		ECOG (≥2 *vs* <2)
Kita *et al.*[33]	2013	RWD	Asian	Docetaxel	Unknown	57		ECOG (≥2 *vs* <2)
Nakano *et al.*[25]	2012	RWD	Asian	Docetaxel	Post chemo	61	ECOG (2 *vs* <2) Gleason score (≥8 *vs* <8)	ECOG (2 *vs* <2)
Azad *et al.*[43]	2014	RWD	Caucasian	Docetaxel	Unknown	86	ECOG (<2 *vs* ≥2) Gleason score (<8 *vs* ≥8)	
Yamashita *et al.*[8]	2016	RWD	Asian	Docetaxel	Post chemo	79	Gleason score (≥8 *vs* <8)	
Cho *et al.*[26]	2014	RWD	Asian	Docetaxel	Unknown	94	Gleason score (<8 *vs* ≥8)	Gleason score (<8 *vs* ≥8)
Templeton *et al.*[44]	2013	RWD	Caucasian	Docetaxel	Unknown	285	Gleason score (<8 *vs* ≥8)	
Howard *et al.*[34]	2008	RWD	Caucasian	Docetaxel	Unknown	113		Gleason score (<8 *vs* ≥8)
Miyake *et al.*[27]	2017	RWD	Asian	Cabazitaxel	Post chemo	63	ECOG (<2 *vs* ≥2)	ECOG (<2 *vs* ≥2)
Buonerba *et al.*[7]	2013	Expanded access program	Caucasian	Cabazitaxel	Post chemo	47	Gleason score (≥8 *vs* <8)	
Buonerba *et al.*[28]	2017	RWD	Caucasian	Cabazitaxel	Post chemo	81	Gleason score (≥8 *vs* <8)	Gleason score (≥8 *vs* <8)

RWD: real-world data; RCT: random controlled trial; NPP: named patient program; CUP: compassionate-use program; Chemo naïve: chemotherapy naïve; Post chemo: post chemotherapy; ECOG: Eastern Cooperative Oncology Group

CI: 2.45–4.34) was stronger than that on chemotherapy-naïve patients (HR: 2.13, 95% CI: 1.27–3.56; **Supplementary Figure 3**).

Impact of Gleason score on OS

OS grouped by Gleason score (≥8 or <8) was reported in 23 studies,[4,7–9,17,18,20,21,23,25,26,28,30,31,34–36,38–44] including 6 multivariate models and 20 univariate analyses. As shown in **Figure 3a**, the synthesized HR of OS based on multivariate studies was 1.01, with a 95% CI of 0.62–1.67 (Gleason ≥8 *vs* <8), indicating that Gleason score had no significant prognostic effect on OS based on the available data in our meta-analysis. In addition, when the studies

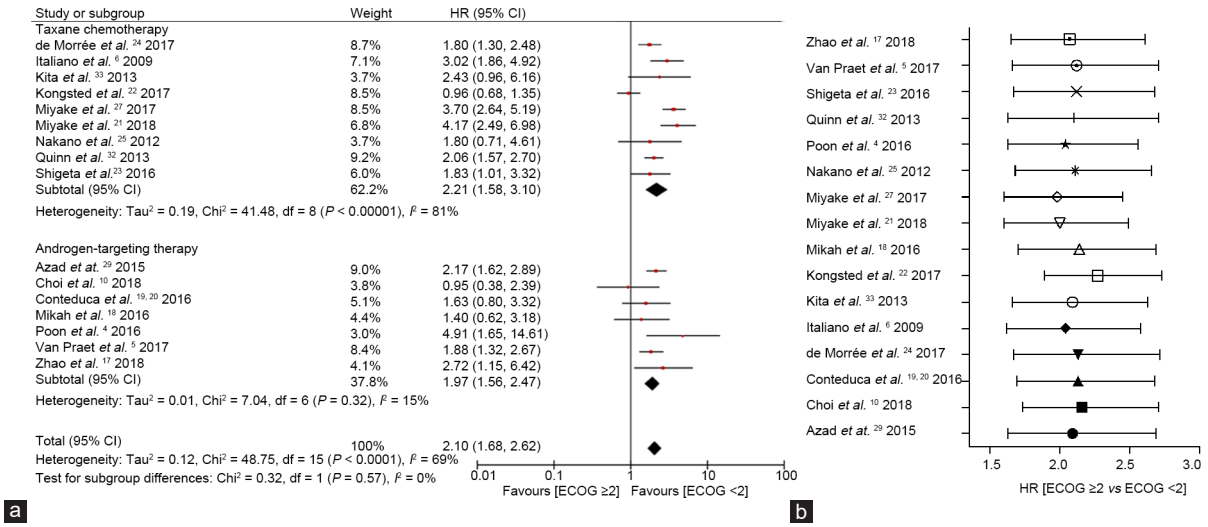

Figure 2: The synthesized hazard ratios of OS according to ECOG performance status (≥2 *vs* <2) (based on multivariate results). (**a**) Forest plots. (**b**) Results of sensitivity analysis; the study on the left Y axis was excluded by turn. OS: overall survival; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; CI: confidence interval; df: degree of freedom.

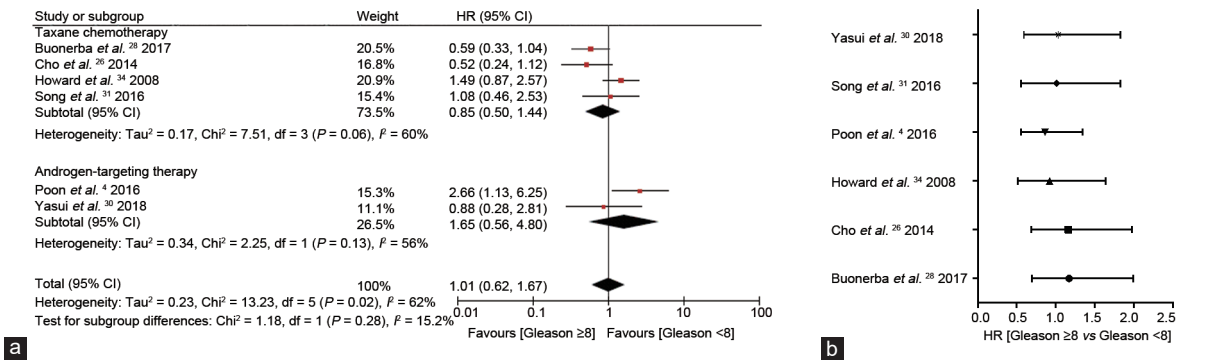

Figure 3: The synthesized hazard ratios of OS according to Gleason score (≥8 *vs* <8) (based on multivariate results). (**a**) Forest plots. (**b**) Results of sensitivity analysis; the study on the left Y axis was excluded by turn. OS: overall survival; HR: hazard ratio; CI: confidence interval; df: degree of freedom.

of reversed comparisons were removed (only four studies left), the synthesized HR was 1.07 (95% CI: 0.54–2.15). The HR of OS (Gleason ≥8 *vs* <8) in patients administered taxane chemotherapy (HR: 0.85, 95% CI: 0.50–1.44) was lower than that in patients who received androgen-targeting therapy (HR: 1.65, 95% CI: 0.56–4.80), as shown in **Figure 3a**, but this result was not statistically significant. The results of sensitivity analyses showed that the CIs of HRs all included 1 when any single study was excluded (**Figure 3b**). Subgroup analysis (multivariate studies) for chemotherapy history was not performed because there was no study conducted on chemotherapy-naïve patients.

The HRs synthesized by univariate results were 1.08 (95% CI: 0.92–1.27), 0.98 (95% CI: 0.76–1.26), and 1.19 (95% CI: 1.04–1.37) for the total patients, taxane chemotherapy group, and androgen-targeting therapy group, respectively (**Supplementary Figure 4**). For patients on androgen-targeting therapy, the mortality risk for the Gleason ≥8 group was slightly higher than that for the Gleason <8 group (HR: 1.19, 95% CI: 1.04–1.37), while the mortality risk of the two groups showed no significant difference in patients administered taxane chemotherapy. Grouped by chemotherapy history, there was no significant difference among chemotherapy-naïve patients, postchemotherapy patients, and others (part of patients' postchemotherapy or unknown; **Supplementary Figure 5**).

Publication bias

In studies that reported multivariate HRs of OS stratified by ECOG performance status, the funnel plot appeared asymmetrical (**Figure 4a**). The results of Egger's and Begg's tests indicated no presence of publication bias for the included studies (P = 0.902 for Egger's test; P = 0.964 for Begg's test). Similarly, for studies that reported the relationship between Gleason score and OS, there was no obvious publication bias indicated by the funnel plot (**Figure 4b**), Egger's test (P = 0.834), or Begg's test (P = 0.719).

DISCUSSION

ECOG performance status is a known prognostic factor in oncology, but studies evaluating its use as a predictive factor for mortality have shown inconsistent results for all cancer patients. For example, patients with an ECOG score of 0 were associated with better OS according to multivariate analyses of five clinical trials investigating 5-fluorouracil-based treatments for metastatic colorectal cancer,[45] whereas the OS difference between ECOG = 0 and ECOG = 1–2 cancer patients treated with immune checkpoint inhibitors was not significant.[46] For patients

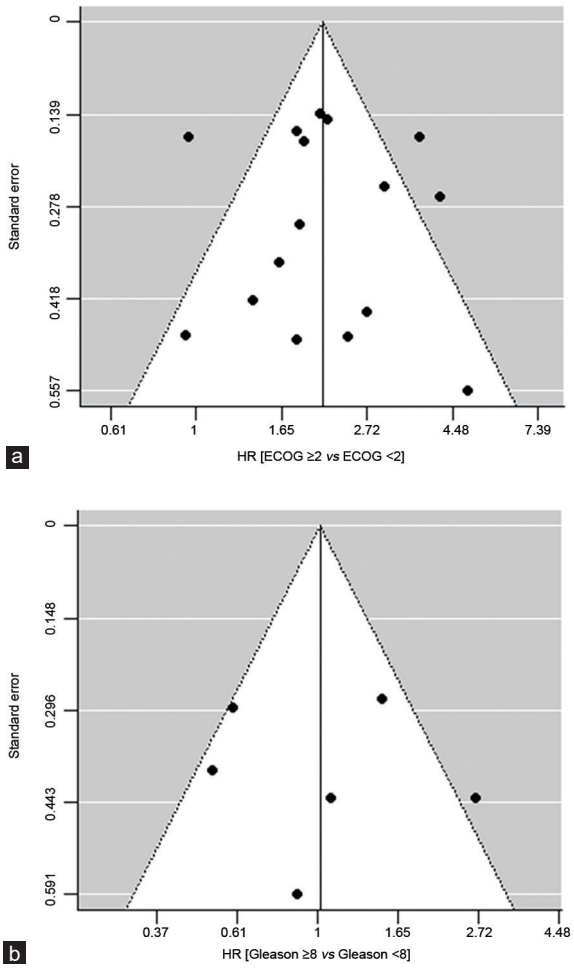

Figure 4: Funnel plots for publication bias (multivariate studies). (**a**) ECOG performance status, (**b**) Gleason score. ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio.

with CRPC, many developed prognostic models include ECOG as a significant factor.[47] In this meta-analysis, the synthesized HR from both multivariate and univariate results was significantly >1 (ECOG ≥2 *vs* <2), demonstrating the potential predictive value of ECOG for OS in patients with CRPC.

Historically, Gleason score has been used as a standardized risk assessment for biochemical recurrence, development of metastases, and OS in men with localized noncastrate prostate cancer.[48] Fizazi *et al.*[9] assessed the predictive value of Gleason score (<8 or ≥8) in two abiraterone regulatory Phase III trials (COU-AA-301 and COU-AA-302) and concluded that the Gleason scores of the original diagnostic sample may have weak prognostic value in CRPC. Consistent with the finding from individual data in large RCTs, Gleason score was not demonstrated as a significant prognostic factor for OS from the results of our meta-analysis. In addition, this was indicated by the small number of included studies. In five studies with univariate analyses of both ECOG performance status and Gleason score,[17,18,21,23,25] no study identified Gleason score as a significant prognostic factor in the further multivariate analyses, while ECOG performance status was included in all the five multivariate models. However, this does not necessarily indicate that Gleason score is of no prognostic value for OS in CRPC. The weak correlation between Gleason score and OS is probably due to limited valid information. Gleason score is frequently evaluated using initial prostatectomy biopsy specimens, and thus most studies included did not consider histologic variants at the time of CRPC. In addition, confounding correlations between Gleason score and other factors may contribute to the weak prognostic value of Gleason score for OS.

We selected multivariate HRs in our main analysis because multivariate HRs are less likely to lead to false-positive results compared with univariate HRs because they are adjusted for confounding factors and selection bias. For reference, we also performed meta-analyses using univariate HRs. To our interest, we noticed that although the exact figure of merged HRs was different between multivariate and univariate results, the values of merged HRs were close, and the conclusions drawn from the results were consistent.

In recent years, several systemic therapies for CRPC (docetaxel, abiraterone acetate, and enzalutamide) have demonstrated efficacy and tolerability in men with hormone-sensitive prostate cancer (HSPC). Several prognostic and predictive factors have been proposed in CRPC, whereas less information is available for HSPC. With respect to docetaxel chemotherapy, a secondary analysis of the CHAARTED study identified Gleason score as a significant factor in a multivariate Cox regression model with an HR of 0.654 and 95% CI of 0.457–0.936 (Gleason <8 *vs* ≥8).[49] However, in a RWD-based analysis, Gleason scores >7 showed a weak prognostic value for OS (HR: 1.13, 95% CI: 0.48–2.7, $P = 0.78$) in patients with castration-sensitive prostate cancer (CSPC).[50] We did not synthesize the HRs of OS because there were no enough studies available. In addition, a retrospective analysis of 106 *de novo* metastatic HSPC patients performed by Iacovelli *et al.*[51] demonstrated that ECOG statuses ≥1 were a prognostic variable associated with poor OS. The survival results of four recent Phase 3 RCTs for abiraterone and enzalutamide (LATITUDE,[52] STAMPEDE,[53] ARCHES,[54] and ENZAMET[55]) have been reported. The LATITUDE study classified high-risk disease based on the presence of at least two criteria in addition to visceral metastases, including the number of bone lesions ≥3 or Gleason score ≥8,[52] indicating that Gleason score ≥8 is a high-risk factor for patients with HSPC. However, no prognostic or predictive model based on the four RCTs has been reported to date. Therefore, whether ECOG performance status and Gleason score can predict OS in patients with HSPC requires further investigation.

The power of a meta-analysis comes from integrating data from different studies. Most meta-analyses only include RCTs, whereas the database in our study included both clinical trials and retrospective studies. On the one hand, the HR of OS stratified by ECOG performance status or Gleason score was only available in the study of abiraterone[9] among Phase III studies. On the other hand, there has been a growing interest in applying RWD to medical decisions and the development of new drugs,[56–58] and it is of great significance to use reliable research methods to analyze RWD and supplement the information obtained from RCTs.[59] Therefore, incorporation of RWD into our database may be more comprehensive and representative for clinical practice.

However, there were some limitations to our study. A potential bias of this study may be publication related. During the process of literature selection, studies that reported other grouped criteria of ECOG performance status and Gleason score, such as ECOG = 0 and ECOG ≥1[39,60–62] or Gleason score ≥7 and Gleason score <7,[5,63–65] were not included because of the limited number of studies. Thus, valuable information may have been excluded. In addition, because studies with positive results were potentially more likely to be published than work with negative results, studies in which ECOG performance status or Gleason score was insignificant in multivariate analyses would have

been excluded, which may lead to an overrepresentation of positive studies. This is a limitation commonly shared by meta-analyses.

CONCLUSION

The prognostic value of ECOG performance status and Gleason score in the survival of CRPC has not been comprehensively evaluated. Our meta-analysis demonstrated that patients with an ECOG performance status >1 had a significantly higher mortality risk than those with lower ECOG performance status, while Gleason score may have weak prognostic value (nonsignificant) for OS. Subgroup analyses showed that there were no significant differences in merged HRs for different treatment regimens or patients with different chemotherapy histories.

AUTHOR CONTRIBUTIONS

WJC and LL conceived the study. WJC and DMK reviewed the literature, collected the data, and performed the analysis. WJC drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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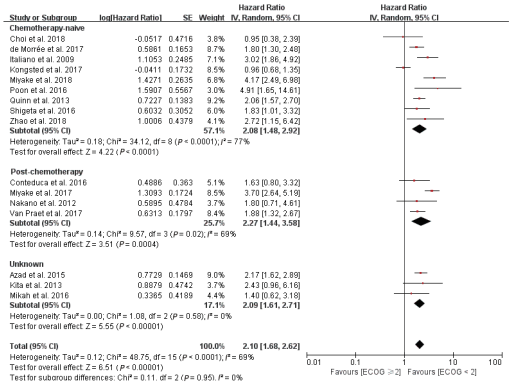
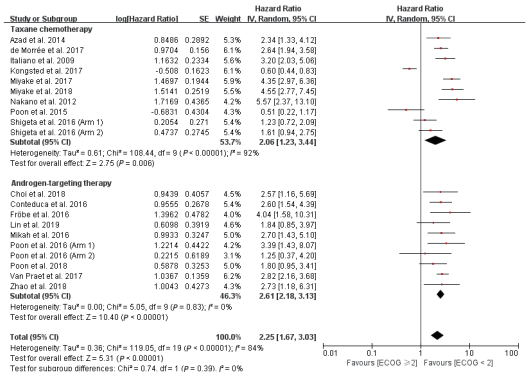
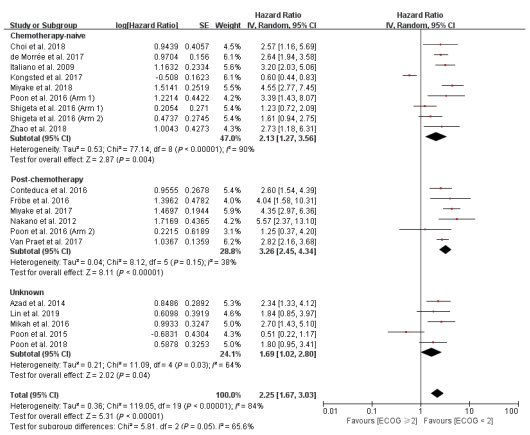


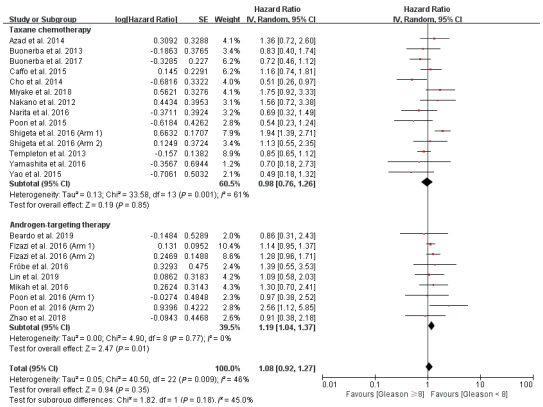
Supplementary Figure 1: Hazard ratios of OS according to ECOG performance status (≥2 *vs* <2) in patients with different chemotherapy history (based on multivariate results). OS: overall survival; ECOG: Eastern Cooperative Oncology Group; CI: confidence interval.



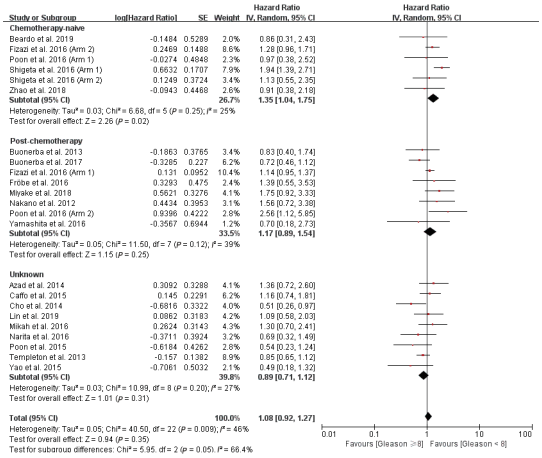
Supplementary Figure 2: Forest plots of hazard ratios of OS according to ECOG performance status (≥2 *vs* <2) (based on univariate results). OS: overall survival; ECOG: Eastern Cooperative Oncology Group; CI: confidence interval.



Supplementary Figure 3: Hazard ratios of OS according to ECOG performance status (≥2 *vs* <2) in patients with different chemotherapy history (based on univariate results). OS: overall survival; ECOG: Eastern Cooperative Oncology Group; CI: confidence interval.



Supplementary Figure 4: Forest plots of hazard ratios of OS according to Gleason score (≥8 *vs* <8) (based on univariate results). OS: overall survival; CI: confidence interval.



Supplementary Figure 5: Hazard ratios of OS according to Gleason score (≥8 *vs* <8) in patients with different chemotherapy history (based on univariate results). OS: overall survival; CI: confidence interval.