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ORIGINAL ARTICLE

Prostate Disease

The presence of intraductal carcinoma of the prostate is closely associated with poor prognosis: a systematic review and meta-analysis

Yu-Cong Zhang[1,2,*], Guo-Liang Sun[1,*], De-Lin Ma[3], Chao Wei[1], Hao-Jie Shang[1], Zhuo Liu[1], Rui Li[1], Tao Wang[1], Shao-Gang Wang[1], Ji-Hong Liu[1], Xia-Ming Liu[1]

We aimed to confirm the predictive ability of the presence of intraductal carcinoma of the prostate (IDC-P) for prognosis and the associations between IDC-P and clinicopathological parameters. Studies were identified in PubMed, Cochrane Library, EMBASE, Web of Science, and SCOPUS up to December 1, 2019. Hazard ratios (HRs) for survival data and odds ratios for clinicopathological data with 95% confidence intervals (CIs) were extracted. Heterogeneity was evaluated by the I^2 value, and quality was assessed by the Newcastle–Ottawa Scale criteria. A total of 4179 patients from 13 studies were included. The results showed that IDC-P presence was significantly associated with poor progression-free survival (PFS; HR = 2.31; 95% CI: 1.96–2.73), cancer-specific survival (HR = 1.89; 95% CI: 1.28–2.77), and overall survival (HR = 2.14; 95% CI: 1.53–3.01). In the subgroup analysis, IDC-P presence was significantly associated with poor PFS in prostate cancer treated by radical prostatectomy (HR = 2.48; 95% CI: 2.05–3.00) and treated by radiotherapy (HR = 2.83; 95% CI: 1.65–4.85). Regarding clinicopathological characteristics, patients with IDC-P presence had significantly higher tumor clinical stages, Gleason scores, probabilities of lymph node invasion, positive surgical margins, and positive extraprostatic extension. Our meta-analysis indicates that the presence of IDC-P is closely associated with poor prognosis and adverse clinicopathological characteristics. Our data support the value and clinical utility of the routine detection of IDC-P by pathological examination. These conclusions need further validation, and prospective studies are needed to find better treatment modalities other than traditional first-line therapy for patients with IDC-P.

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Keywords: clinicopathological; intraductal carcinoma of the prostate; meta-analysis; prognostic; prostate cancer

INTRODUCTION

Due to the high heterogeneity in histology, genetics, and clinical outcomes, the management of newly diagnosed prostate cancer remains challenging. Currently, the clinical decision is usually made according to the serum prostate-specific antigen (PSA) level, clinical tumor stage, and Gleason score by biopsy. Although there are several powerful prognostic predictive factors, including TNM staging, a stronger one remains lacking so far. Intraductal carcinoma of the prostate (IDC-P) is a histological variant of prostate cancer that has been identified as a potential prognostic factor. IDC-P is a distinctive morphologic entity characterized by malignant cells expanding the lumen of prostatic ducts and acini, but a partial rim of basal cells continues to be present.[1,2] Originally, IDC-P was considered a representation of the intraductal spread of frankly invasive carcinoma, and it was also used to represent a prostate cancer precursor.[1,2] The criteria for IDC-P are as follows: (1) 2-fold expansion of prostate gland lumina; (2) neoplastic cell span in a solid or cribriform architecture of the lumen of glands in which a basal cell layer is retained; and (3) nuclear atypia.[3] IDC-P is strongly associated with high-grade and high-volume invasive prostate cancer and unfavorable clinical outcomes.[4,5] The incidence of IDC-P is approximately 20%.[6–8] Moreover, IDC-P has been recognized in the 2014 International Society of Urological Pathology (ISUP) and 2016 World Health Organization classifications[9,10] and was officially recommended to be reported by the College of American Pathologists in 2017.[11]

Until now, some clinical studies have reported the treatment prognosis of IDC-P with conflicting results.[12] To further confirm the predictive ability of IDC-P for treatment outcome, we conducted this systematic review and meta-analysis of relevant studies.

MATERIALS AND METHODS

Data sources and searches

A comprehensive literature search was performed in databases including PubMed, Cochrane Library, EMBASE, Web of Science, and SCOPUS to identify relevant studies up to December 1, 2019. The following terms and their combinations were employed: ([“prostate

[1]Department of Urology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China; [2]Department of Geriatric, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China; [3]Department of Endocrine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.
*These authors contributed equally to this work.
Correspondence: Dr. XM Liu (xmliu77@hust.edu.cn)
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cancer"] AND ["intraductal carcinoma"]) OR ("IDC-P") OR ("intraductal carcinoma of the prostate") OR ("intraductal carcinoma of prostate").

Study selection

Each study was independently examined by two reviewers (GLS and YCZ) for a comprehensive evaluation according to the following inclusion criteria: (1) patients were confirmed to have prostate cancer by pathological examination; (2) IDC-P was identified in prostate cancer by either needle biopsies or whole tumor specimen examination and was divided into present and absent categories; (3) studies investigated the associations between IDC-P and clinicopathological features or prognosis; (4) studies directly provided the hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs) or survival curves of patients to estimate them; and (5) studies were published in English. The exclusion criteria were as follows: (1) case reports, letters, reviews, editorials, notes, or meeting abstracts; (2) nonhuman studies or *in vitro* studies; (3) duplicated studies with overlapping data; or (4) studies that provided information unable to be pooled.

Data extraction

Two authors (CW and HJS) independently extracted and summarized the data of interest, and any disagreements were resolved by discussion. The following basic characteristics were collected: name of the first author, year of publication, country, tumor type, treatment, number of patients, age, Gleason score, tumor stage, nodal status, PSA, and follow-up months. For survival data, IDC-P status (present or absent) with HRs and 95% CIs for progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS) was collected. The following clinicopathological data were extracted: numbers of IDC-P present and absent patients with (1) PSA values, (2) tumor stages cT1–cT2, (3) tumor stages cT3–cT4, (4) Gleason scores ≥8, (5) Gleason scores <8, (6) lymph node metastasis N0, (7) lymph node metastasis N1, (8) positive surgical margins, (9) negative surgical margins, (10) positive extraprostatic extension, and (11) negative extraprostatic extension.

Population, interventions, comparators, outcomes, and study designs (PICOS)

The population of our study was prostate cancer patients. IDC-P status was assessed in these patients. The presence or absence of IDC-P was compared by the endpoints including PFS, CSS, and OS. The associations between IDC-P status and clinicopathological characteristics were evaluated. The study was designed to evaluate the associations between IDC-P status and prognosis and clinicopathological characteristics.

Quality assessment

Quality assessment was independently performed by two investigators (ZL and RL) according to the Newcastle–Ottawa Scale (NOS) criteria.[13] The NOS criteria consist of the following three parameters of quality: (1) selection 0–4; (2) comparability 0–2; and (3) exposure/outcome 0–3.[13] Studies scoring greater than five were considered to be of high quality.

Data synthesis and analyses

HRs with their 95% CIs were used to estimate the associations between PFS, CSS, and OS and IDC-P status. Patients were dichotomized by tumor stage (cT1–T2 *vs* cT3–T4), Gleason score (<8 *vs* ≥8), lymph node metastasis (N0 *vs* N1), surgical margins (positive *vs* negative), and extraprostatic extension (positive *vs* negative). Odds ratios (ORs) with 95% CIs were used to evaluate the associations between IDC-P status and clinicopathological features. We used Review Manager software version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) to calculate the HRs and ORs with 95% CIs. Heterogeneity was assessed by the Chi-squared test and I^2 statistic. Fixed-effects models were employed when the *P*-values of the Chi-squared test were greater than or equal to 0.05, and random-effects models were employed when the *P*-values were less than 0.05. The statistical tests were two-sided, and $P < 0.05$ was considered to be statistically significant. Publication bias was assessed by funnel plots if the number of included cohorts was ≥10.

RESULTS

Study characteristics

As shown in **Figure 1**, 906 records were initially identified, and 13 articles were included in the final qualitative and quantitative synthesis. **Supplementary Table 1** shows the characteristics of the included studies.[3,14–25] These studies were published between 2010 and 2019. A total of 4179 patients from 5 countries, including America, Canada, Japan, China, and Norway, were included. Of note, the article by van der Kwast *et al*.[23] offered two cohorts, one of which included 2 arms. In these articles, IDC-P status was detected by immunohistochemistry, with the percentage ranging from 9.4% to 76.5%. According to the NOS score, all included studies were of high quality (**Supplementary Table 2**).

Prognostic value of IDC-P status in prostate cancer

Nine studies including 11 comparisons reported the relationship between PFS and IDC-P status.[3,14,16–19,21,23,25] The HR for PFS showed that IDC-P present status was significantly associated with poor PFS in prostate cancer. IDC-P present status increased the risk of progression by 131% with fixed effects (HR = 2.31; 95% CI: 1.96–2.73; $P < 0.00001$; **Figure 2a**). There was no significant heterogeneity ($P = 0.31$; $I^2 = 14\%$). Publication bias was assessed by a funnel plot, which indicated moderate publication bias (**Supplementary Figure 1**).

Four studies reported the association between CSS and IDC-P status.[14,17,20,22] The HR showed that IDC-P present status was significantly associated with poor CSS in prostate cancer, and it increased the risk of cancer-specific death by 89% (HR = 1.89; 95% CI: 1.28–2.77; $P = 0.001$; **Figure 2b**). There was no significant heterogeneity ($P = 0.38$; $I^2 = 3\%$), so a fixed-effects model was used.

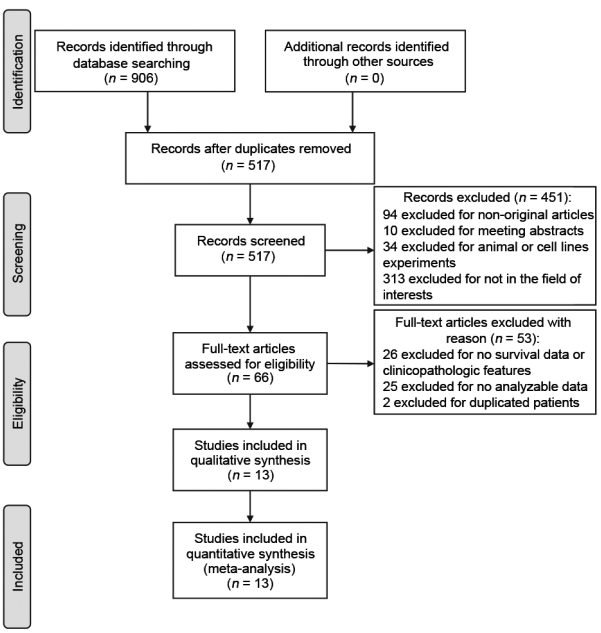

Figure 1: Study selection process.

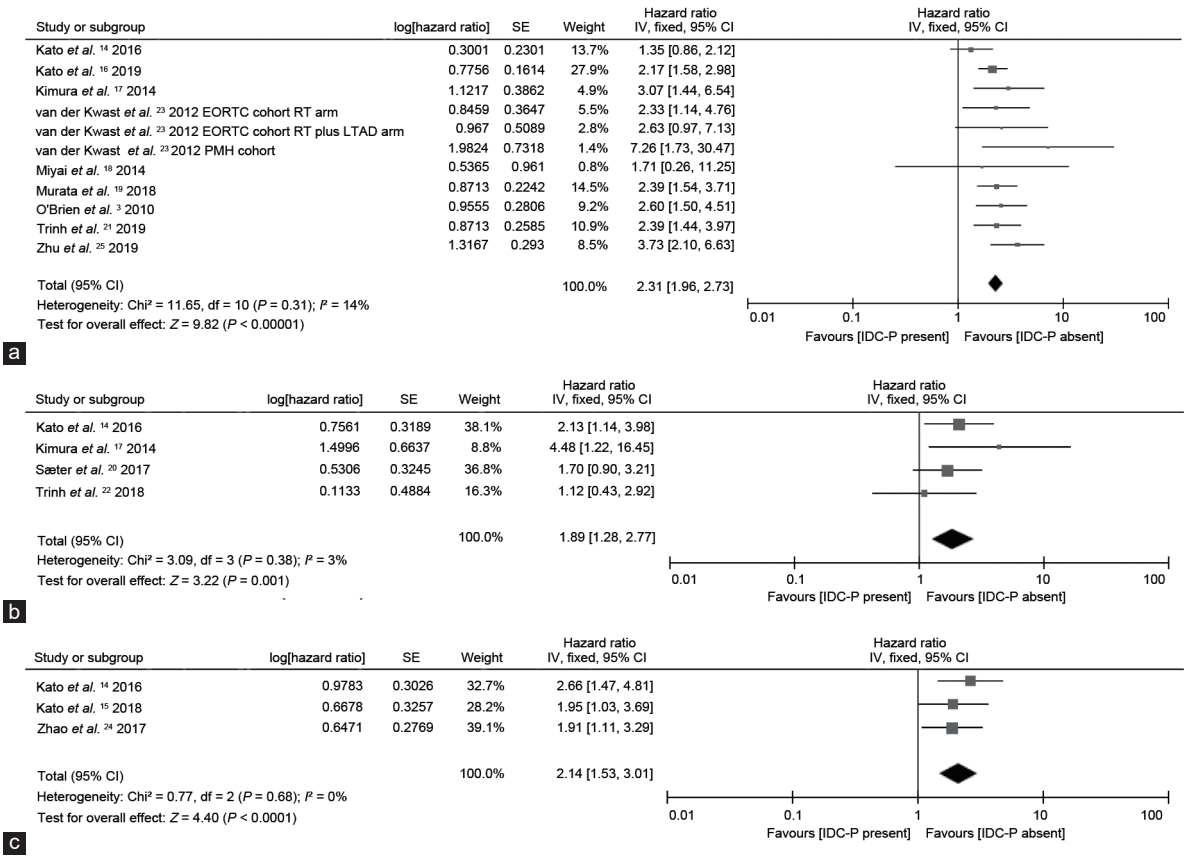

Figure 2: Forest plots assessing the association between IDC-P status and (**a**) progression-free survival, (**b**) cancer-specific survival, and (**c**) overall survival in patients with prostate cancer. SE: standard error; CI: confidence interval; df: degrees of freedom; IDC-P: intraductal carcinoma of the prostate.

Three studies discussed the relation between CSS and IDC-P status.[14,15,24] A significant association between IDC-P present status and an increased risk for death was found (fixed-effects model, HR = 2.14; 95% CI: 1.53–3.01; $P < 0.0001$; **Figure 2c**), without significant heterogeneity ($P = 0.68$; $I^2 = 0\%$).

Prognostic value of IDC-P status in prostate cancer with radical prostatectomy (RP)

Seven studies reported the relationship between PFS and the IDC-P status of prostate cancer treated by RP.[3,16–19,21,25] IDC-P present status was significantly associated with poor PFS in prostate cancer treated by RP with a fixed effect (HR = 2.48; 95% CI: 2.05–3.00; $P < 0.00001$; **Figure 3a**).

Prognostic value of IDC-P status in prostate cancer with radiotherapy (RT)

IDC-P present status was significantly related to poor PFS in prostate cancer treated by RT, and it increased the risk of progression by 183% (HR = 2.83; 95% CI: 1.65–4.85; $P = 0.0002$; **Figure 3b**). There was no significant heterogeneity ($P = 0.37$; $I^2 = 0\%$), so a fixed-effects model was used.

Associations between clinicopathological characteristics and IDC-P status in prostate cancer

We compared the clinicopathological characteristics of IDC-P present and absent patients (**Figure 4**). There was no significant difference in the PSA values between the two groups (weighted mean difference [WMD] = 1.59, 95% CI: -1.62–4.79; $P = 0.33$). Furthermore, significantly more IDC-P present patients seemed to have clinical stage T3–T4 (OR = 2.20, 95% CI: 1.14–4.22; $P = 0.02$), higher Gleason scores (OR = 4.03, 95% CI: 2.40–6.75; $P < 0.00001$), N1 lymph node status (OR = 3.79, 95% CI: 1.97–7.28; $P < 0.0001$), positive surgical margins (OR = 1.77; 95% CI: 1.26–2.48; $P = 0.0009$), and positive extraprostatic extension (OR = 3.49, 95% CI: 1.88–6.47; $P < 0.0001$) than IDC-P absent patients. Significant heterogeneity was detected in the analyses of clinical stage ($P = 0.008$), Gleason score ($P = 0.004$), and extraprostatic extension ($P = 0.02$), so random-effects models were used. In the other analyses, fixed-effects models were used.

DISCUSSION

IDC-P is defined as the growth of tumor cells within benign prostatic ducts and acini.[26] Specifically, it is defined as malignant epithelial cells filling large acini and prostatic ducts, with the preservation of basal cells forming either solid or dense cribriform patterns or loose cribriform or micropapillary patterns with marked nuclear atypia (nuclei six times the normal size or larger) or comedonecrosis.[27] IDC-P is usually juxtaposed with invasive adenocarcinoma, and both histopathologies arise from a common tumor clone.[28] Tumors with IDC-P are also enriched for copy number aberrations, which are associated with poor prognosis.[29] Several studies have reported on genetic abnormalities related to cribriform (CR)/IDC-P. Dawkins *et al.*[30] reported frequent losses of 8p22 and 16q23.1 in intraductal carcinoma. Bettendorf *et al.*[31] found that intraductal carcinoma has more frequent losses of tumor protein p53 (TP53), RB transcriptional corepressor 1 (RB1), and phosphatase and tensin homolog (PTEN). Using breakpoint regions

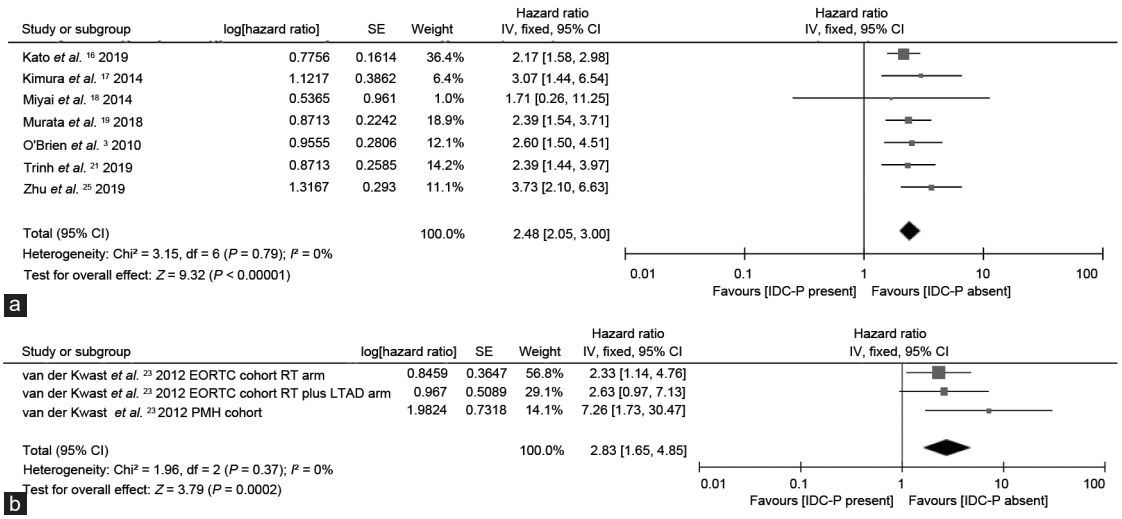

Figure 3: Forest plots assessing the association between IDC-P status and progression-free survival in patients with prostate cancer treated by (**a**) RP or (**b**) RT. SE: standard error; CI: confidence interval; df: degrees of freedom; RT: radiotherapy; RP: radical prostatectomy; IDC-P: intraductal carcinoma of the prostate.

to infer phylogenetic relationships, Lindberg *et al.*[32] showed that the clone closely related to metastases was found in intraductal carcinoma. These findings are consistent with the reporting of IDC-P in patients with adverse pathological and clinical features.[28]

The incidence of IDC-P was reported to be 36.3% in needle biopsies and 50.5% in radical prostatectomy specimens of high-risk prostate cancer patients, and the incidence rose to 67% in patients with distant metastasis at initial diagnosis.[14] Although in the TAX327 study, visceral metastasis, performance status, pain, and hemoglobin and alkaline phosphatase levels were proposed as prognostic parameters for overall survival,[33,34] they demonstrated that the presence of IDC-P on needle biopsy was the strongest prognostic parameter for cancer-specific survival and overall survival among previously reported parameters, including clinical parameters, in patients with distant metastasis at initial diagnosis.

However, two studies also discussed the relationship between the presence of IDC-P on diagnostic needle biopsy and a high risk of mortality in localized and metastatic prostate cancer patients.[20,35] Neither of these studies demonstrated that the presence of IDC-P was a prognostic factor by multivariate analysis, although they showed that it was a prognostic factor by univariate analysis. Even so, the detection of IDC-P in a needle biopsy may still be superior to prostatectomy in predicting high-risk and aggressive prostate cancer. Furthermore, the detection of IDC-P in a needle biopsy can provide useful information regarding patient outcomes prior to radical prostatectomy. Pre- and/or postsurgical therapies may be needed to improve outcomes in patients with IDC-P in needle biopsies.[15]

Although some conflicting results have been reported, our meta-analysis also demonstrates that IDC-P is related to poor prognosis and adverse pathological and clinical features. Overall, the presence of IDC-P is significantly related to shorter PFS, CSS, and OS. Whether undergoing RP or RT, patients with IDC-P show a higher risk of tumor progression. In addition, patients with IDC-P showed significantly higher PSA values, tumor stages, Gleason scores, probabilities of lymph node invasion, positive surgical margins, and positive extraprostatic extension. Therefore, beyond RP and RT, other antitumor modalities may be necessary for IDC-P patients.

The chemohormonal therapy *versus* androgen ablation randomized trial for extensive disease in prostate cancer (CHAARTED) study and the systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy (STAMPEDE) trial demonstrated that upfront chemotherapy combined with androgen deprivation therapy could improve survival in high-volume hormone-sensitive metastatic prostate cancer.[36–38] van Soest *et al.*[39] reported that docetaxel had the most pronounced survival benefit in patients with poorly differentiated tumors (Gleason scores 7–10). Therefore, patients with metastatic prostate cancer with intraductal carcinoma of the prostate detected in biopsy specimens are highly likely to obtain the greatest benefit from chemotherapy as a first-line treatment instead of androgen deprivation therapy.[14] Prospective studies are needed to verify this finding.

Porter *et al.*[12] demonstrated in their systematic review that high IDC-P prevalence was strongly associated with aggressive prostate cancer. Specifically, the IDC-P prevalence was 2.1% in low-risk patients, but increased to 23.1%, 36.7%, and 56.0% in moderate-risk, high-risk, and metastatic or recurrent disease patients, respectively.[12] In addition, IDC-P had a prevalence of 60% in patients following androgen deprivation therapy or chemotherapy.[12] In our study, a detailed meta-analysis was implemented, and new elements were reported. We compared the survival data between IDC-P present and absent patients. Stratified analysis according to treatment modalities, including RP and RT therapy, was also conducted. Moreover, pathological and clinical characteristics were compared between IDC-P present and absent patients.

Our meta-analysis has the following limitations that must be taken into consideration. The quality of the present meta-analysis was limited by several factors that might contribute to seemingly contrary results reported in the included studies. First, among the 13 included studies, most studies were retrospective studies without randomized controlled studies. Hence, confounding factors cannot be eliminated, which introduced bias to the results. Second, the small sample size of some studies may lead to completely opposite results caused by publication bias. Third, adjunctive therapy for RT or RP was not fully described in most studies, which may also introduce bias to the results. Fourth, as described above, the presence of IDC-P is often related to poor clinicopathological characteristics, which might account for some part of the poor outcome. This important confounding factor remains to be addressed, even in a randomized setting. Without multifactor analysis, IDC-P may not be considered an independent

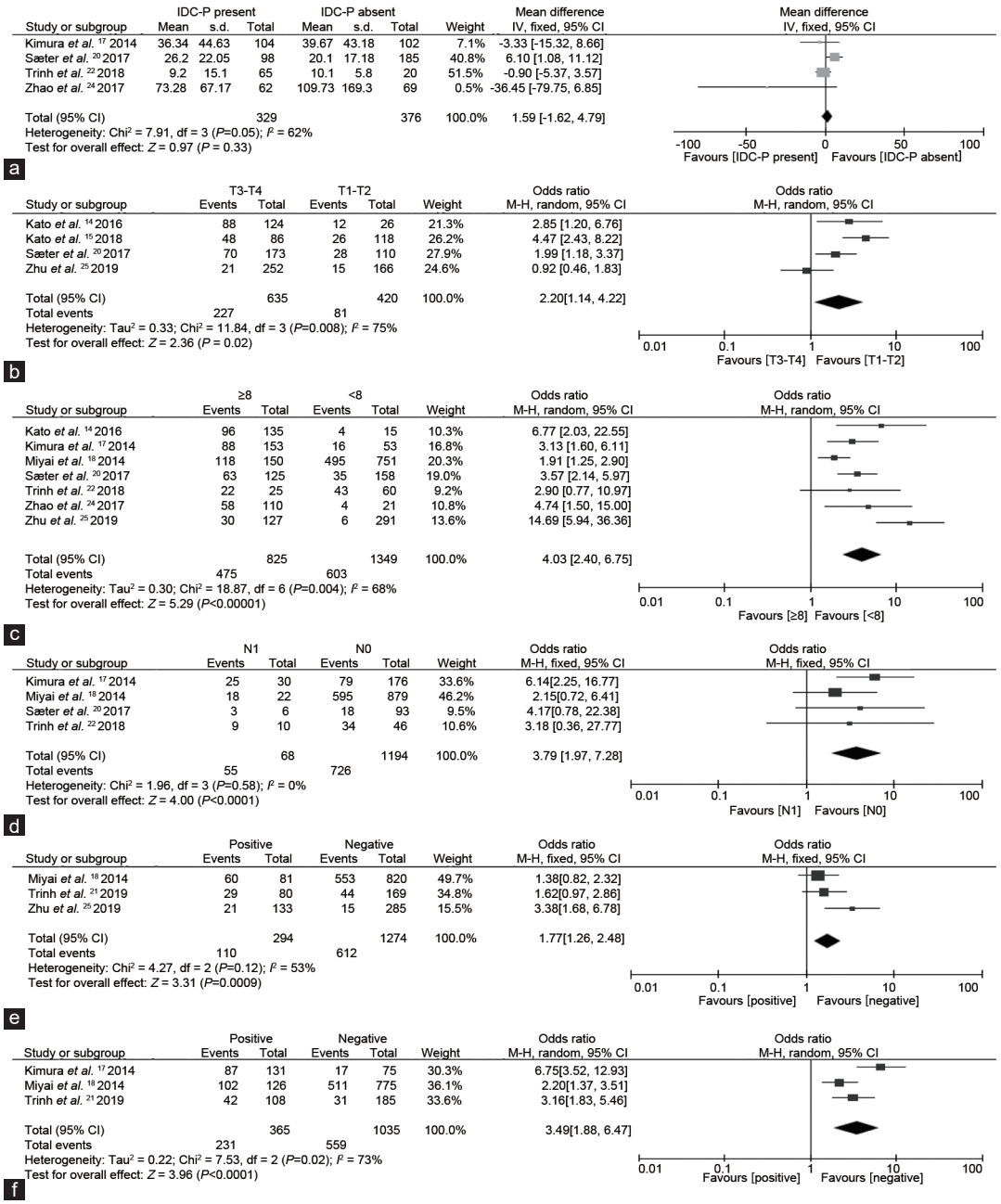

Figure 4: Forest plots assessing the association between IDC-P status and clinicopathological characteristics: (**a**) PSA, (**b**) clinical stage, (**c**) Gleason score, (**d**) lymph node status, (**e**) surgical margin, and (**f**) extraprostatic extension. s.d.: standard deviation; CI: confidence interval; df: degrees of freedom; PSA: prostate-specific antigen; IDC-P: intraductal carcinoma of the prostate.

predictive factor of prognosis. Fifth, OS and CSS were only reported in a few articles (articles without an extractable HR were excluded). Long-term prognosis has not been adequately assessed. Sixth, studies without extractable HR data were excluded, resulting in the omission of results from those studies. Several vital measures were made to reduce these limitations. First, we conducted a systematic, comprehensive search across multiple online databases. Second, we strictly stipulated the inclusion criteria, eliminating the bias caused by some potential confounding factors, and the data were independently extracted by two reviewers. Third, we conducted a subgroup analysis of different treatment modalities and clinicopathological characteristics.

CONCLUSION

Our meta-analysis indicates that the presence of IDC-P is closely associated with poor prognosis. Chemotherapy should be considered to be recommended to patients with IDC-P as a treatment option. Our data support the value and clinical utility of the routine detection of IDC-P by pathological examination.

AUTHOR CONTRIBUTIONS

SGW and JHL performed the literature search. GLS, XML and YCZ carried out the studies examination. ZL, XML and RL participated in the quality assessment. HJS, TW, YCZ, and XML performed the data

analysis. YCZ, GLS, XML, DLM, and CW drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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

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Supplementary Table 1: Characteristics of studies included in the meta-analysis

Author/year	Study design	Country	Specimen source	Tumor type	Treatment	Case, n		Positive rate (%)	Median age, year (range) (Positive vs negative)	Gleason score, n (%)	Tumor stage, n (%)	Nodal status, n (%)	Median PSA, ng ml^{-1} (range) (Positive vs negative)	Follow-up, months (range)
						Positive	Negative							
O'Brien *et al.*[3] 2010	Prospective	America	RP or needle biopsy	High-risk, localized PCa	RP (100%); neoadjuvant chemotherapy (100%)	10	40	20.0	63 (52–74)	6, 5 (10); 7, 19 (38); 8, 13 (26); 9, 12 (24); 10, 1 (2)	pT1, 0 (0); pT2, 24 (48); pT3, 24 (48); pT4, 2 (4)	NA	12.0 (1.4–58.6)	65.1
van der Kwast *et al.*[23] 2012 PMH cohort	Retrospective	Canada	Needle biopsy	Intermediate-risk PCa	RT (100%); neoadjuvant ADT (22%)	23	93	19.8	71 (55–82)	≤6, 38 (32); 7, 80 (68); 8, 0 (0); 9, 0 (0)	cT1, 51 (43); cT2, 67 (57); cT3, 0 (0); cT4, 0 (0)	NA	7.9 (1.3–19.3)	78.0 (9.6–124.8)
van der Kwast *et al.*[23] 2012 EORTC cohort	Retrospective	Canada	Needle biopsy or transurethral resection	High-risk PCa	RT arm: RT (100%); RT plus LTAD arm: RT plus LTAD (100%)	30	102	22.7	70 (51–79)	≤6, 12 (9); 7, 75 (58); 8, 30 (23); 9, 13 (10); U, 5 (4)	cT1, 0 (0); cT2, 6 (4); cT3, 116 (86); cT4, 13 (10)	NA	NA	109.2 (61.2–151.2)[#]
Kimura *et al.*[17] 2014	Retrospective	Japan	RP	High-risk, localized PCa	RP (100%); Neoadjuvant hormone therapy (39%); Adjuvant hormone therapy (11%); Neoadjuvant and adjuvant therapies (27%)	104	102	50.5	68 (46–80)	≤6, 11 (53); 7, 42 (20); ≥8, 153 (74)	cT1, 35 (17); cT2, 85 (41); cT3, 86 (42); cT4, 0 (0)	N0, 176 (85); N1, 30 (15)	25.0 (2.4–296.0)	82.8 (3.6–237.6)
Miyai *et al.*[18] 2014	Retrospective	America	RP	PCa	RP (100%)	613	288	68.0	61 (41–79) *versus* 59 (42–84)	≤7, 751 (83); ≥8, 150 (17)	≤pT2, 759 (84); ≥pT3, 142 (16)	N0, 879 (98); N1, 22 (2)	<10, 826 (92) ≥10, 75 (8)	17 (1–86)
Kato *et al.*[14] 2016	Retrospective	Japan	Needle biopsy	Metastatic PCa	ADT (100%); chemotherapy	100	50	66.7	73 (50–90)	7, 15 (10); 8, 18 (12); 9, 108 (72); 10, 9 (6)	cT2, 26 (17); cT3, 71 (48); cT4, 53 (35)	NA	328.00 (4.18–10992.00)	38.00 (0.67–141.10)
Zhao *et al.*[24] 2017	Retrospective	China	Needle biopsy	Metastatic PCa progressed to mCRPC	MAB (100%); standard first-line therapies (abiraterone or docetaxel) (73%)	62	69	47.3	72 (64–75)[#]	≤7, 21 (16); ≥8, 110 (84)	NA	NA	65.7 (23.3–172.7)[#]	59
Saeter *et al.*[20] 2017	Retrospective	Norway	Needle biopsy	M0 or Mx PCa	RP (14%); RT (12%); Endocrine treatment (34%); Watchful waiting (39%); Other (1%)	98	185	34.6	71 (66–78)[#]	≤7, 158 (56); ≥8, 125 (44)	cT1, 54 (19); cT2, 56 (20); cT3, 173 (61)	N0, 93 (33); N1, 6 (2); Nx, 184 (65)	19.0 (10.6–35.1)[#]	110 (52–172)[#]
Murata *et al.*[19] 2018	Retrospective	Japan	RP	High-risk PCa	RP (100%)	75	116	39.3	70 (41–78)	≤6, 10 (5); 7, 107 (56); 8, 26 (14); ≥9, 48 (25)	pT2, 78 (41); pT3, 113 (59)	N0, 187 (98); N1, 4 (2)	12.1 (2.5–139.0)	49 (6–164)
Kato *et al.*[15] 2018	Retrospective	Japan	Needle biopsy	High-risk, localized PCa	RP (100%)	74	130	36.3	68 (46–80)	NA	≤cT2, 118 (58); ≥cT3, 86 (42)	NA	<20, 121 (59) ≥20, 83 (41)	108 (11–257)

Contd...

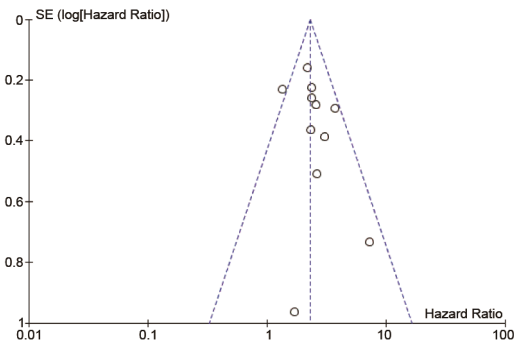
Supplementary Table 1: Contd...

Author/year	*Study design*	*Country*	*Specimen source*	*Tumor type*	*Treatment*	*Case, n*		*Positive rate (%)*	*Median age, year (range) (Positive vs negative)*	*Gleason score, n (%)*	*Tumor stage, n (%)*	*Nodal status, n (%)*	*Median PSA, ng ml^{-1} (range) (Positive vs negative)*	*Follow-up, months (range)*
						Positive	*Negative*							
Trinh *et al.*[22] 2018	Retrospective	Canada	RP	Localized PCa	RP (100%)	65	20	76.5	62.0±5.5[&]	6, 7 (8); 7, 53 (62); 8, 6 (7); ≥9, 19 (22)	NA	N0, 46 (52); N1, 10 (12); Nx, 29 (34)	NA	112.2±54.4[&]
Trinh *et al.*[21] 2019	Retrospective	Canada	RP	Localized PCa	RP (100%); adjuvant RT (16%)	73	220	24.9	62.1±6.8 *versus* 62.0±6.8[&]	NA	NA	NA	NA	99 (59–136)[#]
Kato *et al.*[16] 2019	Retrospective	Japan	RP	Localized PCa	RP (100%)	157	862	15.4	67 (45–80)	NA	pT2, 743 (73); pT3, 276 (27)	NA	6.8 (0.4–82.0)	82.0 (0.7–148.0)
Zhu *et al.*[25] 2019	Retrospective	China	RP or needle biopsy	High-risk PCa	RP (100%)	36	382	9.4	69 (64–73)[#]	6, 60 (14); 7, 231 (55); 8, 48 (12); 9–10, 79 (19)	≤cT2, 166 (40); ≥cT3, 252 (60)	NA	17.36 (10.05–35.50)[#]	42

[#]IQR; [&]Mean±s.d. PSA: prostate-specific antigen; PCa: prostate cancer; RP: radical prostatectomy; NA: not available; RT: radiotherapy; ADT: androgen deprivation therapy; LTAD: long-term androgen deprivation; U: unknown; MAB: maximal androgen blockade; mCRPC: metastatic castration-resistant prostate cancer; s.d.: standard deviation; IQR: interquartile range

Supplementary Table 2: The quality assessment of cohort studies by using the Newcastle–Ottawa Scale]

Studies Author (year)	*Selection*				*Comparability*	*Outcome*			*Total*
	Representative of exposed cohort	*Selection of nonexposed cohort*	*Ascertainment of exposure*	*Presence of outcome*		*Assessment*	*Time for follow-up*	*Adequacy of follow-up*	
O'Brien 2010	★	★	★	0	★	★	★	★	7
Kwast 2012 PMH cohort	★	★	★	0	★	★	★	★	7
Kwast 2012 EORTC cohort	★	★	★	0	★	★	★	★	7
Kimura 2014	★	★	★	0	★	★	★	★	7
Miyai 2014	★	★	★	0	★	★	0	★	6
Kato 2016	★	★	★	0	★	★	0	★	6
Zhao 2017	★	★	★	0	★	★	★	★	7
Sæter 2017	★	★	★	0	★	★	★	★	7
Murata 2018	★	★	★	0	★	★	0	★	6
Kato 2018	★	★	★	0	★	★	★	★	7
Trinh 2018	★	★	★	0	★	★	★	★	7
Trinh 2019	★	★	★	0	★	★	★	★	7
Kato 2019	★	★	★	0	★	★	★	★	7
Zhu 2019	★	★	★	0	★	★	0	★	6



Supplementary Figure 1: Funnel plot assessing the publication bias when reporting the association between IDC-P status and PFS in patients with prostate cancer. SE: standard error; IDC-P: intraductal carcinoma of the prostate; PFS: progression-free survival.