Review

Renal cell carcinoma: a systematic review and meta-analysis on expression of androgen receptor

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ABSTRACT

Background: Chromosome Xq11-12 is the place that the androgen receptor (AR) sequence appears. Herein, the prevalence of this biomarker and its relation with pT stage and tumor grade was reported. **Methods:** Four online sites (PubMed, Scopus, Web of Science, and Cochrane Library) have been searched up to Sep 2018 systematically. Meta-Analysis software version 2.0 (CMA 2.0) and STATA 14.0 statistical software were utilized. Publication bias did not exist. **Results:** From the initial 1141 articles identified from the systematically searches. At last, nine of them remained for analysis. The meta-analysis included 1447 patients that 345 of them had AR expression. AR expression significantly correlated with low tumor grade and low tumor pT stage. **Conclusion:** AR expression was 28.2%, and it had the relationship with tumor low grade and low pT stage. Additional studies required to figure out the role of it on RCC patients.

Key words: AR, Grade, pT stage, RCC

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INTRODUCTION

Renal cell carcinoma (RCC) is the foremost different urological malignancy among adults[1]. The most prevalent form of malignancy RCC is clear cell RCC (ccRCC) and represents over 90% of malignant kidney tumors[2]. The androgen receptor (AR) sequence is found at chromosome Xq11-12 and includes of eight exons[3]. Prevalence of the AR is appeared in several parts of the body, principally in sexual parts of men. Also, it was reported in breast, bladder, liver, gastrointestinal[4]. High AR expression is potential prognosis factor in bladder cancer[5], and it created longer life in patients with serous carcinoma of the ovary[6], an agent for progressive the squamous cell carcinoma of head and neck[7,8]. We tend to are responsive to only rare studies evaluating AR immunohistochemical staining in RCC[9–11]. Though the targeted therapy creates an effective route for advanced RCC patients[12], the relationship between AR expression and RCC progression stay uncertain until now[13]. This meta-analysis reports the expression of AR and its relation with some pathological factors in RCC.

METHODS

Search Strategy

PubMed, Scopus, Web of science, and Cochran library included in this study. Search terms included systematically up to September 2018 were "androgen receptor", "AR", "kidney", "renal cell carcinoma", "cancer", "carcinoma", and "tumor. The studies were searched for the assessment of expression of the AR in RCC patients in English abstract.

Inclusion and Exclusion Criteria

Inclusion criteria:

1) Cohort studies

2) Human studies

Exclusion criteria:

1) Case-control, case report, and review studies; conference paper and letter to editor

2) The study with incomplete data

Data extraction

First author, year of publication, nation, RCC samples, expression, grade, pT stage, number of males, and the mean age were extracted. We could not have analysis on types of survival as a result of the studies didn't have the same data.

Statistical analysis

Comprehensive Meta-Analysis software version 2.0 (CMA 2.0) and STATA 14.0 statistical software (StataCorp LP, College Station, TX, USA) were used for random-effect analysis. P-value (2-sided) <0.05 is significant.

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CMA 2.0

The event rate (ER) with 95% confidence interval (95% CI) was calculated for estimation of the expression of AR mutations in RCC patients. Begg's and Egger's tests were calculated for bias.

STATA 14.0

P<0.1 is significant for heterogeneity. Heterogeneity is assessed by the Q
and I 2 statistics.

RESULTS

After primary searches, 1141 articles identified. Twenty one studies remained after we excluded the non-relevant studies. Then, twelve studies were removed based on reasons (five conference papers, three reviews, two articles without full text, one letter to editor, and one database). At last, nine of them remained for analysis (**Figure 1**).

From nine studies[9–11,14–19], two studies[14,17] were Germany, two studies[15,19] were USA and others were from Austria[9], Korea[10], China[11], Italy[16] and Japan[18]. From 1447 patients[9–11,14–19], 345 AR expression exist. One hundred seventy-one cases in four studies[9–11,18] of meta-analysis study were male, and 59 cases were female (sum=202). Mean age (min-max) in two studies was 60.06 (29-82). Three studies[9,11,14,18] on pT stage in 132 patients with expression AR showed 51 cases pT stage 1, 20 cases pT stage 2, 41 cases pT stage 3. And also, 160 low grade versus 42 high-grade cases exist in four studies[9–11,18] (**Table 1**).

AR Expression

The prevalence of AR expression in RCC patients has been reported in **Figure 2** by the ER. The pooled ER of the studies was 28.2% (95% CI=16.3%-44.3%; P=0.009). The Begg's and Egger's tests didn't show publication bias (P=0.53 and P=0.75, respectively)(**Figure 3**).

AR expression and tumor grade

Among three studies (502 cases), heterogeneity was existed (I^2= 85.80%, p =0.0) in a fixed-effects model. Correlation between AR expression and low grade was positive (OR, 1.98; 95% CI, 1.44-2.71; P<0.01) (**Figure 4**).

AR and pT stage

Among three studies (848 cases), heterogeneity was not existed (I^2= 4.3%, p = 0.353). Correlation between AR expression and low pT-stage was positive (OR, 4.04; 95% CI, (3.10-5.26); P< 0.01) (**Figure 5**).

DISCUSSION

Radiotherapy, chemotherapy, and immunotherapy used for treat metastatic RCC patients[12]. But, a lot of controversial for treatment of this malignancy are existed until now[13,17]. Moreover, AR expression has been related to chemo-responsiveness[20]. Exaggerated AR expression was related to attenuate responsiveness and exaggerated migration of tumor cells[21]. The clear cell RCC resists chemotherapy and radiation with a restricted therapeutic period of the anti-angiogenesis targeted therapy (6–15 months)[22]. Clinical researchers have disclosed that some patients reply to endocrine therapy objectively or subjectively[23,24]. AR can help to the pathobiology of breast malignancy[25], and maybe inhibition of androgen sign had a therapeutic role in it[26]. Firstly, AR was observed in cancerous renal tissues and then appears in other urinary organs like prostate and then breast cancer[27]. Nakano *et al*., who noted that patients with RCC showing immunoreactivity for one or a lot of hormone receptors (ER, PR and/or AR) had a considerably higher survival rate[18]. A cohort found that AR expression in clear cell RCC was prognostic which high expression[28]. Cut off for express AR reported from 12.9% to 100%[29–31]. AR expression found in non-invasive urothelial malignancies as compared to invasive urothelial malignance[32,33].

Consequently, AR immunoreactivity was related to renowned favorable prognostic factors, like tiny tumor size, low pT stage (more than 30% in pT1a tumors) in addition as low histological grade[34]. The AR-positive rate ranged from 16.3%-44.3% in RCC tissues in this study. Noh *et al*.,[10] and Concolino *et al*.,[16] showed the level of AR-positive is higher than our meta-analysis. In other hands Langne *et al*.,[9] and Klotzl *et al*.,[17] demonstrated that the AR-positive is lower than in this study among RCC patients. Nine studies (1,447 cases) surveyed for AR expression in RCC patients in the meta-analysis and also expressed relationship tumor grades and pT stages with it. Zhu *et al*.,[11] incontestable that AR expression rate was negatively accompanied pT stage and Fuhrman's grade in RCC patients. Also, this relationship was indicated by Foersch *et al*.,[14] and Langner *et al*.[9], Zhu *et al*.,[11] reported prevalence of AR had a negative relationship with pT stage and grade in RCC patients. Foersch *et al*.,[14] and Langner *et al*.,[9] reported the results opposite of him. Noh *et al*.,[10] said AR expression related with the histological nuclear grade (p<0.027) and TNM stage (p<0.002). The meta-analysis showed AR expression correlated with low grade and pT stage positively.

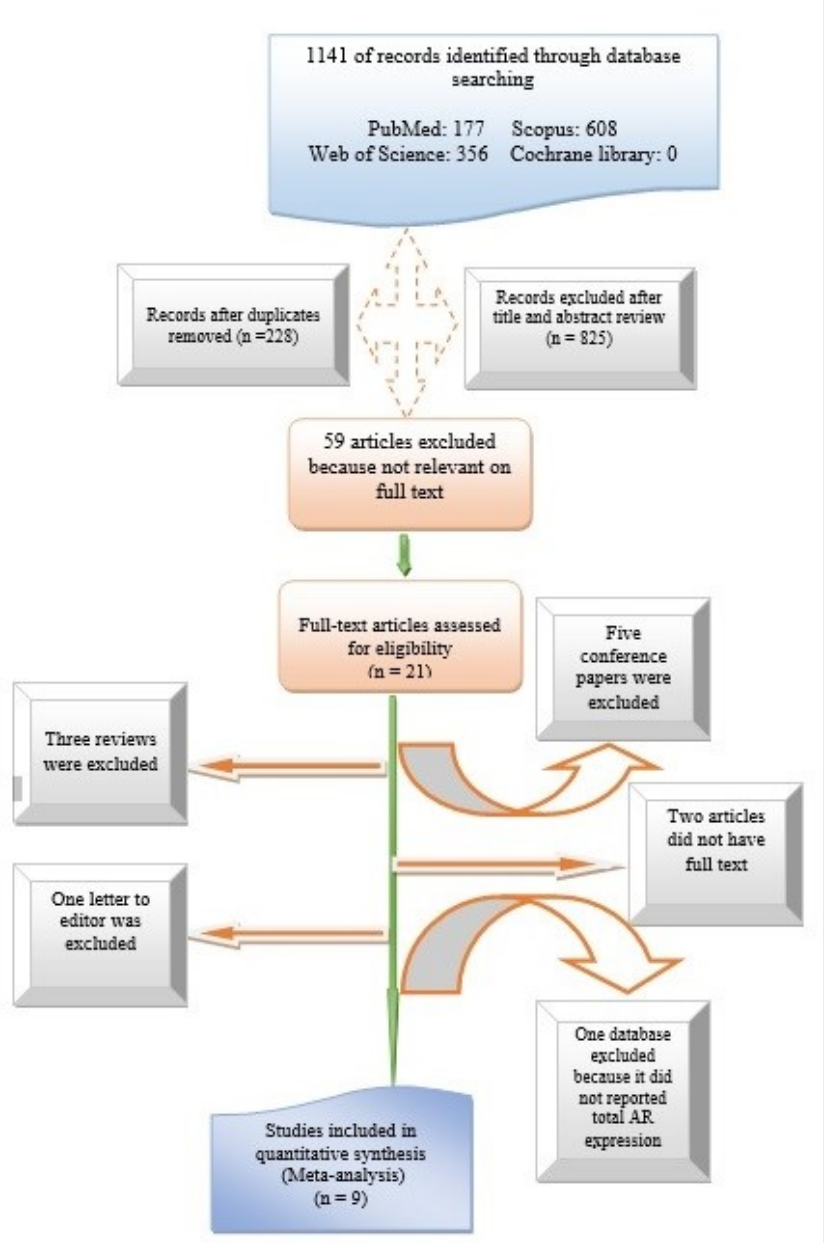

Figure 1: **Flow chart of studies reviewed and included in the present meta-analysis.**

CONCLUSION

As our knowledge, this study is first meta-analysis to research the impact of AR expression on RCC patients. The current study showed the level of expression of AR and its relative with tumor grade and pT stage in RCC patients. Additional studies are needed to the role of AR expression in these patients.

COMPETING INTERESTS

The author(s) declared no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Conceptualization: ES MP
Formal analysis: ES
Methodology: ES HA
Project administration: ES MP HA HM
Software: ES
Validation: HM HA
Writing — original draft: ES
Writing — review & editing: ES MP HA HM

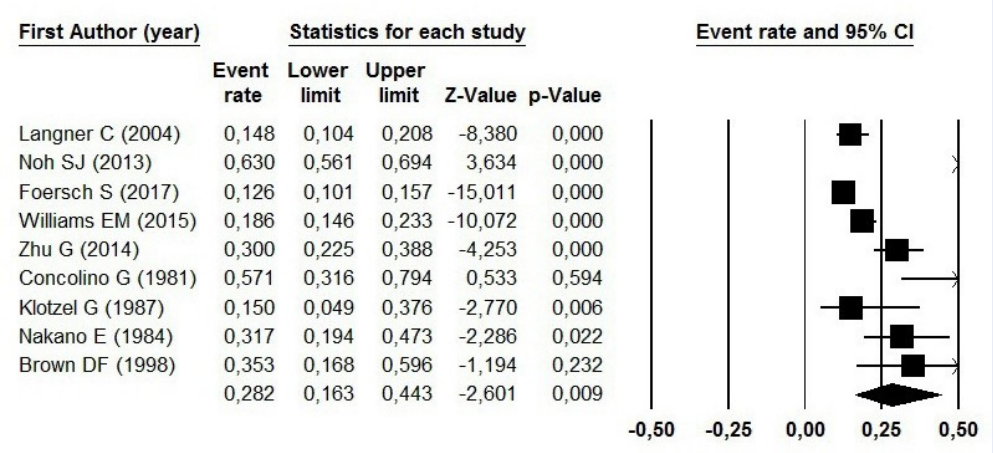

Figure 2: **Forest plot of OR for expression in RCC patients**. Horizontal line represents 95% CI of each study. The diamond indicates the pooled OR value. **OR:** odds ratio; **CI:** confidence interval.

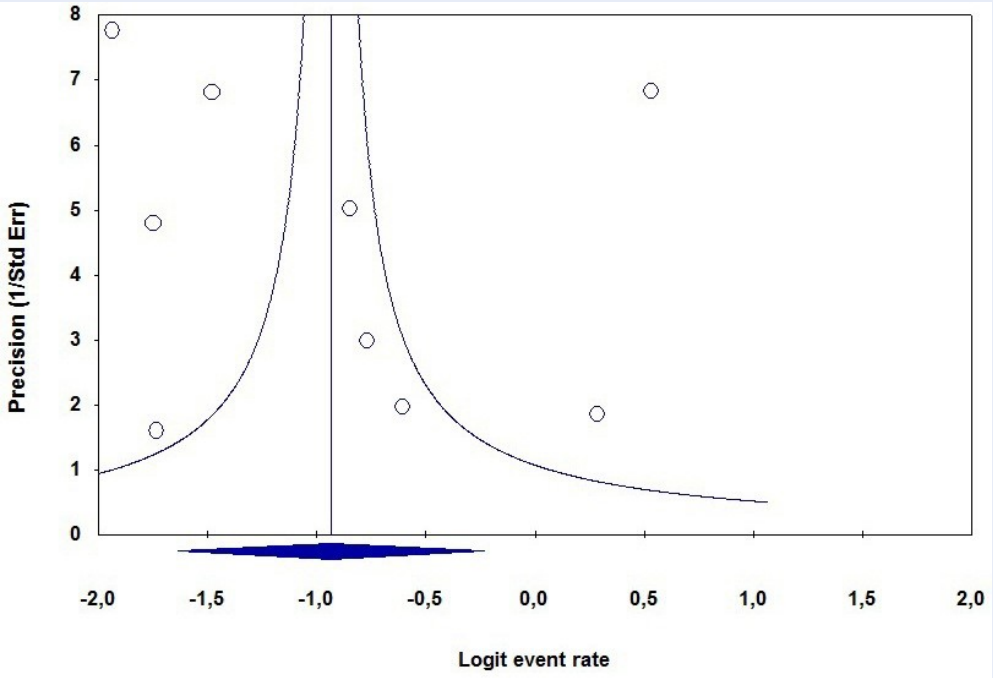

Figure 3: **Funnel plot for potential publication bias of expression of RCC.**

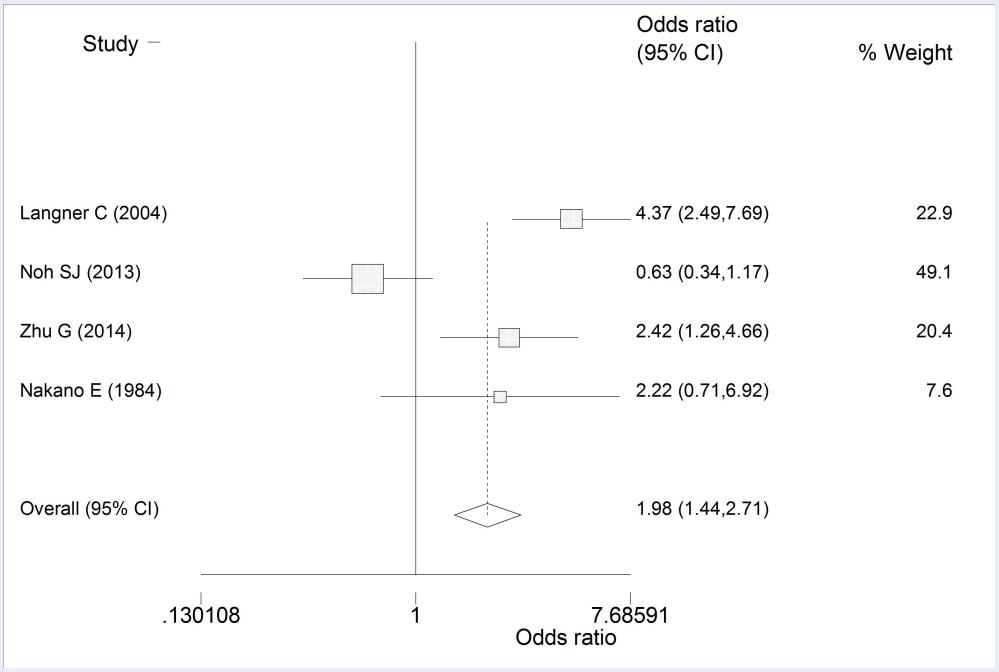

Figure 4: **Forest plot of OR for tumor grade.** Horizontal line represents 95% CI of each study. The diamond indicates the pooled OR value. **OR**: odds ratio; **CI**: confidence interval.

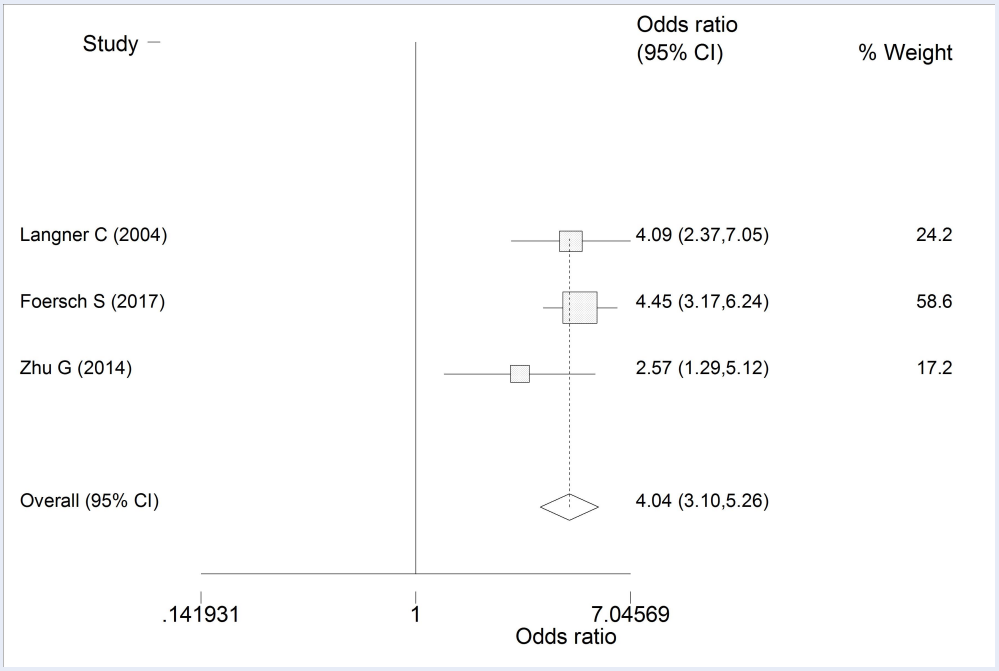

Figure 5: **Forest plot of OR for pT stage**. Horizontal line represents 95% CI of each study. The diamond indicates the pooled OR value. **OR:** odds ratio; **CI:** confidence interval.

Table 1: The information about studies of the meta-analysis

First Author (year)	Nation	Patient	Total androgen expression	Sex		pT Stage		Grade		Age Mean
				Male	Female	Low	High	Low	High	(Min-Max)
Langner C, 2004 [9]	Austria	182	27	24	3	102(24)	80(3)	99(21)	83(6)	-
Noh SJ, 2013 [10]	Korea	200	126	93	33	-	-	158(101)	42(25)	58.13(29–82)
Foersch S, 2017 [14]	Germany	546	69	-	-	348(64)	198(36)	463(NA)	83(NA)	–
Williams EM, 2015 [15]	USA	307	57	-	-	-	-	-	-	–
Zhu G, 2014 [11]	China	120	36	24	12	95(34)	25(2)	89(32)	31(4)	63(35-82)
Concolino G, 1981 [16]	Italy	14	8	-	-	-	-	-	-	–
Klotzl G, 1987 [17]	Germany	20	3	-	-	-	-	-	-	–
Nakano E, 1984 [18]	Japan	41	13	30	11	-	-	20(6)	21(7)	- (46-76)
Brown DF, 1998 [19]	USA	17	6	-	-	-	-	-	-	–

ABBREVIATIONS

AR: Androgen Receptor
ccRCC: Clear Cell Renal Cell Carcinoma
CI: Confidence Interval
ER: Estrogen Receptor
pT Stage: Pathologic Tumor Stage
PR: Progesterone Receptor
RCC: Renal Cell Carcinoma

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