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Low serum total testosterone level as a predictor of upgrading in low-risk prostate cancer patients after radical prostatectomy: A systematic review and meta-analysis

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Purpose: To investigated the association between serum total testosterone and Gleason score upgrading of low-risk prostate cancer after radical prostatectomy (RP).

Materials and Methods: Medline, Web of Science, Embase, and Cochrane Library databases were searched to identify eligible studies published before October 2021. Multivariate adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated using random or fixed effects models.

Results: Five studies comprising 1,203 low-risk prostate cancer patients were included. The results showed that low serum total testosterone (<300 ng/dL) is associated with a high rate of Gleason score upgrading after RP (OR, 2.3; 95% CI, 1.38–3.83; p<0.001; I^2, 92.2%). Notably, sensitivity and meta-regression analyses further strengthen the reliability of our results.

Conclusions: Our results support the idea that low serum total testosterone is associated with a high rate of Gleason score upgrading in prostate cancer patients after RP. It is beneficial for urologist to ensure close monitoring of prostate-specific antigen levels and imaging examination when choosing non-RP treatment for low-risk prostate cancer patients.

Keywords: Meta-analysis; Prostatectomy; Prostatic neoplasms; Testosterone

INTRODUCTION

Generally, 1,918,030 new cancer cases and 609,360 cancer deaths are projected to occur in the United States in 2022, and the proportion of prostate cancer diagnosed at a distant stage increased from 3.9% to 8.2% over the past decade [1]. Active surveillance, watchful waiting, radical prostatectomy (RP), and definitive radiotherapy have long been considered a treatment for low–risk prostate cancer patients [2]. Recent studies and our experience indicated that pathological Gleason score and staging are often inconsistent with biopsy, and in most cases, it was upgrading or upstaging. At present, the ability of urologists to reliably predict tumor aggressiveness before surgery is still limited. Clinical staging, tumor grade

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(biopsy Gleason score) and prostate-specific antigen (PSA) are potential preoperative prognostic indicators [3-5]. It was necessary to determine an independent predictor of upgrading to assist selecting therapy in low-risk prostate cancer patients. It is well known that the prostate is an androgen-dependent organ, and serum testosterone contributes to the growth and development of prostate cancer. Previous studies have suggested that low serum testosterone can predict high Gleason score and can be used as an indicator of prostate cancer aggressiveness [6-10]. However, they are still controversial.

Against this background, we performed the present systematic review and meta-analysis of the previous literature to explore the association between serum total testosterone and Gleason score upgrading of prostate cancer after RP. Furthermore, we also performed stratified analyses by different studying methodological characteristics to determine if these variables affect the merged results and the level of heterogeneity of the meta-analysis.

MATRIALS AND METHODS

The methods of this meta-analysis were performed in accordance with the Cochrane Collaboration criterion [11]. Furthermore, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed in reporting our study [12]. Thus, no ethical approval and patient consent are required. The trial and protocol registration number is PROSPERO CRD42022310497.

1. Literature search

We conducted a comprehensive literature search in the electronic databases of MEDLINE (via PubMed), Web of Science, Embase, and Cochrane Library for eligible studies regarding the association between serum total testosterone level and Gleason score upgrading after RP in low-risk prostate cancer from database inception to October 2021. Each database was searched without language, study size, publication type, or region restrictions by using the following combination of Medical Subject Headings (MeSH) and non-MeSH search terms: "prostatic neoplasms" OR "prostate cancer") AND ("radical prostatectomy") AND ("testosterone") AND ("upgrad*" OR "downgrad*"). Moreover, we also obtained potentially relevant articles by screening bibliographies of selected original trials and previous review articles. The main search was completed by the senior author. Any discrepancy was solved by consulting an investigator who was not involved in the initial procedure.

2. Selection criteria

Study selection was conducted by two investigators independently, assessed by title, abstract and full text. Eligible were included if they met the following eligibility criteria: (1) original studies regarding the association between serum total testosterone level and Gleason score upgrading after RP (i.e., retropubic RP, robot-assisted RP, or pure laparoscopic RP) in low-risk prostate cancer; (2) total testosterone was measured before surgery and low serum testosterone levels were defined as less than 300 ng/dL; (3) studies reporting sufficient data of risk estimates with corresponding 95% confidence intervals (CIs) or enough data to calculate them; and (4) studies that used either a case-control, cross-sectional, retrospective cohort, or prospective cohort design. If several trials pertained to overlapping patient population, we retained only the most recent or largest study (where appropriate) to avoid duplication of information. Moreover, case series, case reports, and expert opinion articles were excluded. Disagreements were resolved through discussion between the two investigators.

3. Data extraction and methodological quality assessment

The data extraction was performed using a pre-established data extraction form and the correctness of all extractions were checked by investigators independently. Any disagreement was resolved by the adjudicating senior authors. The following data were extracted into a standardized Excel (Microsoft Corp., Redmond, WA, USA) file: first author, year of publication, country, study design, participants characteristics (i.e., mean age and sample size), duration, mean PSA level, mean prostate volume, mean testosterone, and odds ratios (ORs) with corresponding 95% CIs for outcome. Moreover, if potentially eligible records did not provide sufficient information, we contacted the primary authors to acquire missing data.

Quality of the observational studies was evaluated by two independent reviewers according to the Newcastle–Ottawa scale (NOS) [13], which consists of ten items that evaluates the representativeness of the included studies. Each item was evaluated as either "yes," "no," or "unclear," which correspond to "1," "0," or "0" in accordance with the information provided by the studies. The total score ranged from 0 to 9 and categorized as follows: a score of 8 to 9 was considered high quality, a score of 6 to 7 was considered moderate quality, and a score of 5 or below was considered low quality. Disagreements were also settled by discussion among authors.

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4. Data synthesis and analysis

For this study, the total risk estimates of the extracted data were calculated using ORs with their corresponding 95% CIs with the Stata statistical software (version 15.0, StataCorp Wyb, Guangzhou, China) for postoperative outcomes of percutaneous nephrostolithotomy. The I-squared (I^2) test was conducted to evaluate the effect of study heterogeneity on the meta-analysis results, with I^2 values of 0%, 25%, 50%, and 75% representing no, low, moderate, and high heterogeneity, respectively. According to the Cochrane review guidelines [11], severe heterogeneity of $I^2 \geq 50\%$ warrants the use of random effects models. Otherwise, a fixed effects model was utilized. Statistical significance was set at $p<0.05$. To explore the influence of various methodological considerations and patient characteristics on heterogeneity, we conducted subgroup analyses with included studies stratified by country and study design. Moreover, we performed sensitivity analysis by omitting each study individually to assess the quality and consistency of the results. A meta-regression analysis was performed to investigate the possible sources of heterogeneity in several variables, and the restricted maximum likelihood method was used for analysis. Finally, the use of Egger et al. [14] and Begg and Mazumdar [15] tests could not be performed due to the limited number of including studies.

RESULTS

1. Study identification and selection

In general, a total of 168 records were identified initially based on the comprehensive search strategy described at the search stage. After removing 56 duplicates, only 112 studies remained. Then, we read the titles and abstracts of 112 articles in detail, of which 12 articles were further assessed via full-texts. Finally, 7 full-text articles were excluded for the following reasons: 1 study did not report testosterone [16]; 3 studies did not report RP [17-19]; 3 studies had no sufficient data for extraction (as shown in Fig. 1) [20-22]. Of these, 5 observational studies [6-10] that comprised a total of 1,203 patients were selected and subsequently included for review in accordance with the eligibility criteria.

2. Study characteristics

On the whole, the basic characteristics of the included studies are summarized in Table 1 [6-10]. The included studies were published between 2015 and 2017 on the basis of the sample sizes ranged from 135 patients to 354 patients. Moreover, mean age ranged from 62.2 years to 69.72 years, and the men PSA level ranged from 5.6 ng/mL to 8.6 ng/mL. Among the included studies, four were retrospective studies [6,7,9,10] and one was prospective study [8]. Additionally, three were performed in Italy [6,9,10], one in China [7], and one in France [8]. All studies were published in English. RP

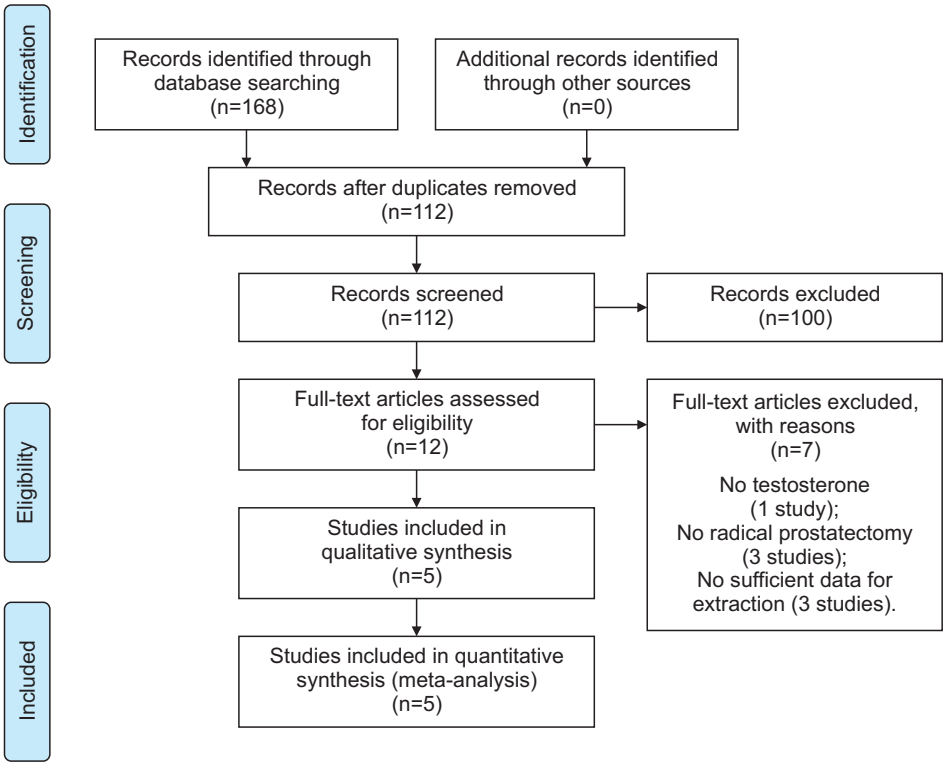

Fig. 1. Flow diagram of literature screening procedures.

Table 1. Characteristics of the included studies

Reference	Study design	Country (duration, y)	Sample size (No. upgrading, %)	Definition of Gleason score change (from bGS to pGS)	Surgical procedure	Biopsy methods	Mean testosterone, ng/dL	Mean PV, mL	Mean age, y	Mean PSA, ng/mL	Confounding factor
Ferro et al. (2017) [6]	Retrospective cohort	Italy (NA)	338 (146, 43.2%)	≤6 to ≥7	RP	TRUS biopsy	451.5	49	63.5	5.6	Age, PSA, PSA density, perineural invasion, and testosterone
Gao et al. (2016) [7]	Retrospective cohort	China (2009–2015)	167 (62, 37.1%)	≤6 to ≥7	RP	TRUS biopsy	425	49.4	69.72	6.92	Age, PSA, BMI, and PV
Léon et al. (2015) [8]	Prospective cohort	France (2010–2013)	354 (125, 35.9%)	≤6 to ≥7	Robot-assisted RP	TRUS biopsy	NA	49.8	62.2	8.6	Age, BMI, PSA, PV, PSA density, and clinical stage
Porcaro et al. (2016) [9]	Retrospective cohort	Italy (2007–2011)	209 (76, 36.3%)	≤6 to ≥7	RP	TRUS biopsy	590	56.4	64.5	7.7	Age, PSA, and testosterone
Porcaro et al. (2017) [10]	Retrospective cohort	Italy (2014–2015)	135 (12, 8.9%)	≤6 to ≥7	RP	TRUS biopsy	333	40	65	6.4	Age, BMI, PSA, testosterone, PV, and PSA density

bGS, biopsy Gleason score; pGS, prostatectomy Gleason score; PV, prostate volume; PSA, prostate-specific antigen; NA, not available; RP, radical prostatectomy; TRUS, transrectal ultrasonography; BMI, body mass index.

was performed in four studies [6,7,9,10], while robot-assisted RP was performed in one study [8].

3. Methodological quality assessment

In all, the methodological quality of the included studies is evaluated on the basis of the NOS (as shown in Supplementary Table). One study [8] acquired eight points and was considered of high quality, and the remaining four studies [6,7,9,10] acquired seven points which were considered of moderate quality.

4. Association of serum total testosterone level and Gleason score upgrading

Five studies [6-10] comprising 1,203 patients report relevant data regarding the association between serum total testosterone level and Gleason score upgrading after RP in low-risk prostate cancer. We suggest that low serum total testosterone (<300 ng/dL) is associated with a high rate of Gleason score upgrading after RP (OR, 2.3; 95% CI, 1.38–3.83; $p<0.001$; I^2, 92.2%) with significant heterogeneity. Therefore, a random effects model was applied for pooled analysis, and the results are illustrated in Fig. 2. The results of our subgroup analyses showed that preoperative low serum total testosterone levels remained a significant risk factor of Gleason score upgrading stratifying studies by different countries except for studies performed in Italy and France. Moreover, in the subgroup analyses stratified by different study designs, low serum total testosterone levels were associated with Gleason score upgrading in the retrospective study whereas not in the prospective study (as shown in Table 2). To further investigate the significant heterogeneity among studies, we conducted the meta-regression analysis, and the results demonstrated that none of the covariates (country, p=0.263; study design, p=0.248) resulted in heterogeneity among the included studies, which indicated that the regressors only slightly contributed to the explanation of the response variables. Sensitivity analysis revealed that the stability of the results exhibited no significant change by omitting each study individually (Table 3).

DISCUSSION

1. Main findings

This meta-analysis synthesized evidence about the association between the total testosterone and Gleason score upgrading in prostate cancer patients after RP. The analysis demonstrated that low serum testosterone is an independent predictor for Gleason score upgrading in prostate cancer after RP. Notably, sensitivity analysis demonstrated that the

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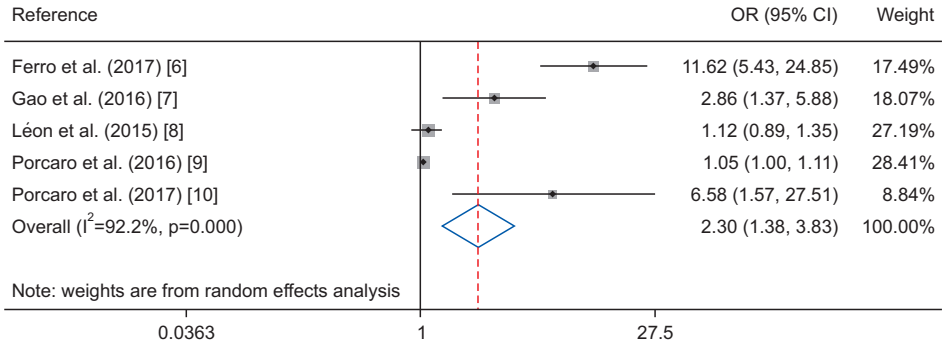

Fig. 2. Forrest plots of association of serum total testosterone level and Gleason score upgrading. OR, odds ratio; CI, confidence interval; I^2, heterogeneity among studies.

Table 2. Results of subgroup analyses

	Study	Participant	OR (95% CI)	p-value	p-value of heterogeneity	I^2 (%)
Overall result	5	1,203	2.3 (1.38–3.83)	<0.001	<0.001	92.2
Country						
Italy	3	682	4.12 (0.64–26.5)	0.136	<0.001	95.5
China	1	167	2.86 (1.38–5.93)	0.005	NA	NA
France	1	354	1.12 (0.91–1.38)	0.286	NA	NA
Study design						
Retrospective	4	849	3.68 (1.01–13.34)	0.048	<0.001	94.2
Prospective	1	354	1.12 (0.91–1.38)	0.286	NA	NA

OR, odds ratio; CI, confidence interval; NA, not applicable.

Table 3. Results of sensitivity analyses

Study omitted	Odds ratio	95% confidence interval
Ferro et al. (2017) [6]	1.33	0.97–1.83
Gao et al. (2016) [7]	2.16	1.24–3.75
Léon et al. (2015) [8]	3.68	1.01–13.34
Porcaro et al. (2016) [9]	3.73	1.09–12.79
Porcaro et al. (2017) [10]	2.04	1.22–3.42
Combined	2.3	1.38– 3.83

stability of the results had no significant change by omitting each study individually, although the meta-regression could not identify the potential factors that may affect the level of heterogeneity between studies. Through our meta-analyses, we observed that almost all of the included studies reported an significant association of preoperative serum testosterone level and Gleason score upgrading, whereas one study yielded conflicting results [8]. Léon et al. [8] conducted a prospective cohort study comprising 354 patients who underwent RP. The authors reported that serum testosterone level was not an independent predictor (OR, 1.12; 95% CI, 0.89–1.35; p=0.13) of upgrading after RP.

2. Implications for clinical practice

To the best of our knowledge, biopsy Gleason score and clinical stage have the greatest impact on prostate cancer treatment options; however, pathological upgrading after RP is common [23-25]. Previous study has shown that the upgrading rate after RP is 30% to 60%, which means that nearly half of the biopsy grades did not correctly present real malignant tumors [26]. Moreover, upgrading is related to poor pathological characteristics and the risk of biochemical progression [27,28]. The role of testosterone in predicting Gleason score upgrading, pathological staging, biochemical recurrence, unfavorable disease and even survival has been widely evaluated [17,29]. Moreover, other predictor such as increased body mass index (BMI) is also a significant predictor of pathological unfavorable disease at RP in patients with preoperative low-to intermediate-risk diseases [30]. We also found that hypogonadism can lead to pathological upstaging, which may be caused by the negative feedback control of high-grade prostate cancer that inhibits the secretion of testosterone and pituitary gonadotropin. Furthermore, growing evidence supports the idea that reduced serum testosterone concentrations associated with different metabolic disorders including obesity and metabolic syndrome may modulate prostate cancer aggressiveness [31,32]. Consistently, most large observational series have demonstrated that obesity is a risk factor for adverse pathologic features, a more advanced stage, higher risk for biochemical recurrence and death after RP [33-35]. On the other hand, metabolic syndrome has previously been shown to lead to reduced serum testosterone lev-

els, but other potential biological mechanisms have also been advocated to explain the propensity for metabolic disorders to promote the development of aggressive prostate cancer. It may be related to factors such as chronic inflammation-related cytokine release, insulin resistance-induced increase in insulin-like growth factor 1 levels, etc. [36]. Moreover, our results might be explained by the physiology of human androgens. In fact, testosterone is biologically active and the moiety linked to sex hormone-binding globulin is inactivated by high-affinity binding. Therefore, we believe that low levels of testosterone may logically lead to an active androgen-depleted environment, which represents a more severe facilitator for the development of advanced prostate cancer [8]. Importantly, we found that patients with upgrading or upstaging had lower testosterone than patients who did not through the multivariate statistical analysis after controlling for age, PSA, BMI, and prostate volume. Hence, this has great clinical practice significance for urologists. Although intraoperative observation and frozen section analysis can help eliminate nerve sparing surgery and remove neurovascular bundles, their accuracy and cost are limited. Interestingly, the risk of multiple pelvic lymph node metastasis may be increased by low endogenous testosterone levels [37]. Therefore, these findings might have obvious implications in clinical practice and the confirmatory studies are required.

3. Strength and limitations

Overall, the meta-analysis exhibited crucial strengths in several ways. First, the present meta-analysis was the first to explore the association between serum total testosterone and Gleason score upgrading of prostate cancer after RP, and subgroup stratification was performed by study methodology characteristics (i.e., study design and countries) to determine if these variables moderated such an association and level of heterogeneity of the meta-analysis according to the PRISMA guidelines. Second, multivariate-adjusted risk estimates were used to minimize the other relevant confounding factors that may influence the overall results. Finally, the results of the sensitivity analysis and meta-regression validated the rationality and reliability of this meta-analysis.

However, some limitations still exit in the meta-analysis, which needed to be addressed and merited further discussion. First, most of the included studies performed a retrospective design with disadvantages regarding potential missing data and risk of bias. Second, this study was limited by the small sample size; thus, an overfitting bias in the multivariate-adjusted analysis must be considered. Third, significant heterogeneity was observed and the risk of introducing potentially significant heterogeneity was imminent even though meta-regression was conducted. However, the subgroup and meta-regression analyses could not identify the potential factors that may affect the level of heterogeneity between studies. The reason may be that all included studies were observational design with the disadvantages of heterogeneity and variations in terms of histopathological examination. Finally, selection bias may be exit due to the limited number and quality of included literatures, although sensitivity analysis indicated that the stability of the results had no significant change by omitting each study individually. Hence, more high-quality and multi-center researches need to be carried out to verify the results of the study.

CONCLUSIONS

In conclusion, low preoperative serum total testosterone is associated with a high rate of Gleason score upgrading in prostate cancer patients after RP. It is beneficial for urologist to ensure close monitoring of PSA levels and imaging examination when choosing non-RP treatment for low-risk prostate cancer patients. These findings might have obvious implications in clinical practice; however, confirmatory studies are required.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Shusheng Wang and Shu Gan. Data acquisition: Shu Gan and Jian Liu. Statistical analysis: Songtao Xiang and Chiming Gu. Data analysis and interpretation: Zhiqiang Chen and Siyi Li. Drafting of the manuscript: Shu Gan and Jian Liu. Critical revision of the manuscript: Shusheng Wang and Zhiqiang Chen. Obtaining funding: Shu Gan. Administrative, technical, or material support: none. Supervision: Shusheng Wang. Approval of the final manuscript: all authors.

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SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20210459.

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