REVIEW

Men with High Prostate Specific Antigen Have Higher Risk of Gleason Upgrading after Prostatectomy: A Systematic Review and Meta-analysis

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Purpose: To examine the correlation between prostate specific antigen (PSA) and the risk of Gleason sum upgrading (GSU) from biopsy Gleason sum (bGS) to prostatectomy Gleason sum (pGS).

Materials and Methods: Five electronic databases (Web of Science, Ovid Medline, Ovid Embase, SCOPUS and the Cochrane Library) were searched from inception until March 2020. Studies were included if they focused on the relationship between PSA and GSU analyzed in multivariable analysis. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were utilized. Quality of included studies was appraised utilizing the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control studies. The publication bias was evaluated by funnel plot and Egger's test.

Results: Our search yielded 19 studies with high quality including 42193 patients. GSU was found in 28.2% of patients. Higher PSA level was associated with a significant increased risk of GSU (pooled OR = 1.14, 95% CI: 1.10–1.18; $P < .05$; $I^2 = 92\%$). For the definition of upgrading from bGS ≤ 6 to pGS ≥ 7, the odds of upgrading with higher PSA level as opposed to lower PSA level was 1.12 (95% CI: 1.11–1.14; $P < .05$; $I^2 = 13\%$), while the odds of upgrading with other definitions were 1.11 (95% CI: 1.05–1.18; $P < .05$; $I^2 = 89\%$).

Conclusion: Patients with high level of serum PSA are at high risk of undergoing pathologic upgrading at prostatectomy. Combined with other risk factors, PSA prompts risk reclassification and improve confidence of urologists in management decisions for optimal therapy. Nevertheless, further robust studies are necessitated to confirm these results.

Keywords: gleason score; meta-analysis; needle biopsy; prostate cancer; prostate specific antigen; systematic review

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in males in the world[1]. Gleason score (GS) is a critical prognostic factor for risk stratification and disease management of PCa. Even if Gleason grading system has been modified over time[2], the accuracy of biopsy Gleason sum (bGS) for predicting prostatectomy Gleason sum (pGS) was reported to be barely satisfactory. A systematic review of 14839 patients reported that concordance rate between bGS and pGS was 63%, while overall upgrading from bGS to pGS was found in 30%[3].

Active surveillance (AS) is recommended for patients with GS 6 or 3+4 and not appropriate for ones with GS 4+3 or greater[4]. Patients with GS 8 or greater reap the benefit of undergoing RP followed by lymph node dissection and/ or other ancillary therapy against unfavorable outcomes[5]. In these scenarios, unpredictable Gleason sum upgrading (GSU) bring urologists into a dilemma that how to assess the true risk for patients with PCa and select optimal treatment modalities for them. It has been demonstrated in large-scale studies that patients with GSU were significantly associated with biochemical recurrence and other unfavourable surgical outcomes[6-8].

Prostate specific antigen (PSA) is another critical factor not only for early detection of PCa but also for risk classification. PSA has appeared in view of urologists with its predictive performance on GSU. In recent years, robust multivariable models with nomograms consisting of PSA were built for predicting GSU[9]. However, previous literatures were mostly based on single-center studies with limited population and PSA was marginally significant in a few studies. In this systematic review and meta-analysis, we aimed to investigate the correlation between PSA and the risk of GSU in the current literature.

MATERIALS AND METHODS

Our study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[10]. Methods of this analysis and inclusion criteria were specified in advance and documented in a protocol as a reference for our investigators.

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Table 1. Summary data for included studies with definitions of upgrading from bGS ≤ 6 to pGS ≥ 7 for this review.

Author (Year)	Study Region (Interval)	Study Characteristic[a] Study Size, N	No. Upgrading, N (%)	Selection Criteria of AS for Eligible Patients Who Turned to Immediate Prostatectomy	Variables Adjusted in Multiple Regression	Patient Characteristic Age, yr	PSA, ng/mL PV, mL	cT	No. Cores Obtained, N
Epstein 2012 [18]	USA (2002-2010)	5071	1841(36.3)	NA	age; PW; GPC	Mean 57.6, Range 34.0-79.0	Mean 5.4, Range 0.2-97.2	NA	T1-3	≥ 10
Fu 2012	USA (1993-2009)	1632	723(44.3)	D'Amico criteria b	age; race; PW; cT; TPC; cancer laterality; pT; ECE; SVI; PSM	Median 61.0, Range 34.0-79.0	Median 5, Range 0.2-9.9	NA	T1c-2a	NR
Gofrit 2007 [24]	USA (2003-2006)	448	91(20.3)	NA	age; PV; PSAD; cT; GPC; PPC; cancer laterality	Mean 59.1, SD 6.5	Mean 6.0	Mean 52.7	T1c-2	8-12
Gokce 2016 [29]	Turkey (2005-2015)	210	69(32.9)	PSA < 10 ng/mL; GS ≤ 6; ≤ T2a; ≤ 2 positive cores; ≤ 50% cancer involvement	Neutrophil-to-lymphocyte ratio	Mean 59.2, SD 8.1	Mean 5.4, SD 1.1	NR	T1c-2a	NR
Jalloh 2015 [21]	USA (1990-2012)	4231	1123(26.5)	D'Amico criteria b	age; race; No. cores obtained; GPC; prostatectomy approach; year of diagnosis	Mean 59.9	NA	NA	T1-2	Mean 9.15
Lee 2015 [22]	Korea (2007-2012)	339	102(30.1)	D'Amico criteria b	age; BMI; PV; cT; No. cores obtained; GPC; PPC; TPC; core length	Mean 65.4, SD 6.8	Mean 5.4, SD 2.0	Mean 38.0, SD 14.3	T1c-2a	Mean 12.4, SD 0.8
Lyon 2016 [13]	USA (1999-2015)	1256	647(51.5)	NA	age; race; BMI; PW; cT; No. cores obtained; GPC; PPC; TPC; year of surgery; statin use; Charlson comorbidity index; IBP; biopsy pathology reviewed	NR	NR	NR	T1-4	≥ 6
Pietzak 2014 [33]	USA (1998-2008)	400	86(21.5)	MSK criteria c	age; cT; No. cores obtained; No. positive cores; ASAP; HGPIN; biopsy history	NR	NR	NR	T1c-2a	≥ 10
Porcaro 2017 [14]	Italy (2013-2014)	170	111(65.3)	D'Amico criteria b	PV; PPC	Mean 73.8, SD 6.0, Median 64.0, Range 46.0-75.0	Median 5.7, Range 0.8-9.9, Mean 5.9, SD 1.9	Median 40.0, Range 15.0-120.0, Mean 41.3, SD 15.8	T1c-2a	≥ 12
Quintana 2016 [20]	USA (2003-2013)	375	76(20.3)	NA	age; race; PV; cT; No. cores obtained; No. positive cores; age; race; PSAD; PV; cT; PPC	NA	NA	NA	T1-2	12-33
Santok 2017 [15]	Korea (2005-2010)	359	145(40.4)	NA	Mean 63.0, SD 7.5	Mean 6.8, IQR 5.0–10.0	Mean 39.2, SD 20.9, IQR 10.5-164.0	T1-4	12
Sooriakumaran 2012 [16]	USA (2005-2010)	750	297(39.6)	PSA ≤ 10 ng/mL; GS ≤ 6; ≤ T2a; ≤ 2 positive cores; ≤ 50% cancer involvement	age; PV; cT; No. cores. obtained; No positive cores; GPC; HGPIN	Mean 59.0, SD 6.9	Mean 4.6, SD 1.9	Mean 54.0, SD 23.2	T1-2a	NR
Tosoian 2013	USA (1975-2013)	7486	1620(21.6)	D'Amico criteria b	age; race; BMI; No. cores obtained; GPC; risk stratification; year of surgery	Mean 57.3, SD 6.4	Mean 5.2, SD 2.2	NR	T1c-2a	Mean \ 12.2, SD 3.6

Abbreviations: AS, active surveillance cT, clinical T-stage; pT, pathologic T-stage; PSA, prostate specific antigen; PSAD, PSA density; PV, prostate volume; PW, prostate weight; BMI, body mass index; bGS, biopsy Gleason sum; pGS, prostatectomy Gleason sum; GSU, Gleason sum upgrading; PPC, percentage of positive cores; GPC, greatest percentage of cancer in any core; TPC, total percentage of cancer in all cores; ASAP, atypical small acinar proliferation; HGPIN, high-grade prostatic intraepithelial neoplasia; ECE, extra-capsular extension; SVI, seminal vesical invasion; PSM, positive surgical margin; NR, not reported; NA, not available; SD, standard deviation; IQR, interquartile range.
a all studies were case-control designs; b PSA ≤ 10 ng/mL; GS ≤ 6; ≤ T2a; c PSA ≤ 10 ng/mL; GS ≤ 6; ≤ T2a; ≤ 3 positive cores; ≤ 50% cancer involvement

Table 2. Summary data for included studies with other definitions of Gleason sum upgrading for this review.

Author (Year)	Study Characteristic [a]				Patient Characteristic					
	Study Region (Interval)	Study Size, N	No. Upgrading, N (%)	Definition of Upgrading	Variables Adjusted in Multiple Regression	Age, yr	PSA, ng/mL	PV, mL	GS	cT	No. Cores Obtained, N
Bullock 2019 [27]	UK (2011-2016)	17598	4489(25.5)	Any GSU	age; cT; bGG; year of surgery; geographical region	Mean 63.2, Median 64.0, Range 35.0-92.0	Median 7.9, Range 0-181.0, Mean 10.1	NR	> 7: 14%	T1-4	NR
Freedland 2007 [32]	USA (1996-2007)	1113	299(26.9)	Any GSU	BMI; bGS; No. cores obtained; No. positive cores; year of surgery	Mean 60.6, SD 6.5	Median 6.4, Mean 8.3, SD 7.4	NR	> 3+4: 13%	T1-3	Median 10, Range 6-40
Kassouf 2007 [19]	Canada (1997-2004)	247	80(32.4)	Any GSU	age; PV; cT; bGS	Median 61.0, Range 56.0-65.0	Median 5.5, Range 4.3-8.7	Median 37.0, Range 28.5-48.0	> 7: 10%	T1c-3	10-11
Martin 2017 [30]	USA (2005-2008)	136	19(14.0)	From bGS ≤ 7 to pGS ≥ 8	age; cT; bGS; GPC; PPC	Median 60.5, IQR 56.1-64.3	Median 5.8, IQR 4.7-8.1	NR	≤ 7	T1c-2	≥ 10
Porcaro(2) 2017 [23]	Italy (2014-2015)	135	12(8.9)	From bGS = 6/3+4 to pGS ≥ 8	total testosterone; PSAD	Median 65.0, Range 51.0-75.0	Median 6.4, Range 1.2–17.9	Median 40.0, Range 14.0-105.0	≤ 3+4	T1c-2b	≥ 12
Xu 2017	China (2011-2015)	237	62(26.2)	Any GSU	age; BMI; cT; bGS; DRE;	Mean 67.8, Median 67.0, Range 47.0-86.0	Mean 19.2, Median 13.4, Range 1.0-293.	NA	> 7: 19%	T1-3	10

Abbreviations: cT, clinical T-stage; PSA, prostate specific antigen; PSAD, PSA density; PV, prostate volume; BMI, body mass index; GS, Gleason sum; bGS, biopsy Gleason sum; pGS, prostatectomy Gleason sum; GSU, Gleason sum upgrading; bGG, biopsy grade group; PPC, percentage of positive cores; GPC, greatest percentage of cancer in any core; DRE, digital rectal examination; NR, not reported; NA, not available; SD, standard deviation; IQR, interquartile range.
a all studies were case-control designs

Search strategy

A comprehensive search for eligible records was conducted using the following databases from inception until March 10th, 2020: Web of Science, Ovid Medline, Ovid Embase, SCOPUS and the Cochrane Library. Besides, we managed to find relevant records from electronic website of grey literatures including Grey Literature Report, Open Grey and GreyNet International. No restriction of language was included in the search. The search used search terms included MeSH and Emtree terms combined with free-words. The major terms consist of 'Prostatic Neoplasms', 'Multivariate Analysis', 'Neoplasm Grading', 'Odds Ratio' and 'Upgrad*'. The full Ovid Medline search strategy was shown in Supplementary Figure 1. Additional records were identified through reviewing reference lists of relevant articles.

Eligibility criteria and study selection

Eligible studies had to meet the following inclusion criteria: (1) original studies with experimental design; (2) peer-reviewed studies; (3) studies with a sample size more than 50 patients. Exclusion criteria included as follows: (1) case reports, reviews, meta-analyses, and commentaries; (2) studies not in the field of Gleason upgrading of prostate cancer; (3) full-text was not available; (4) studies in which PSA was not included in multivariable analysis (MVA); (5) studies in which adjusted odds ratios (AORs), confidence intervals (CIs) or p value were not available for pooled analysis. Records retrieved from electronic databases and reference lists were deduplicated and the remaining were screened via title and abstract for eligibility of full-text review. If studies reported the overlapping results (same author or institution), we selected the one with the latest year of publication. The final included articles were evaluated in both qualitative synthesis and quantitative synthesis (meta-analysis). See **Figure 1** for the PRISMA flow diagram detailing the study criteria and the selection process. This whole selection process was conducted by two investigators (XW, YZ) independently and disagreement was resolved by consensus and approved by a third investigator (ZJ).

Data extraction, data synthesis, and quality evaluation

Included studies were categorized into subgroups by definition of upgrading. Subgroup A consisted of studies with the upgrading definition (from bGS ≤ 6 to pGS ≥ 7). Patients in studies of subgroup A might be eligible for active surveillance but finally turned to immediate prostatectomy. Subgroup B consisted of studies with other definitions of Gleason upgrading. Data from included studies were independently extracted by two investigators (XW, YZ) and any discrepancies were resolved by consensus and approved by a third investigator (ZJ). Procedures of extraction were performed using

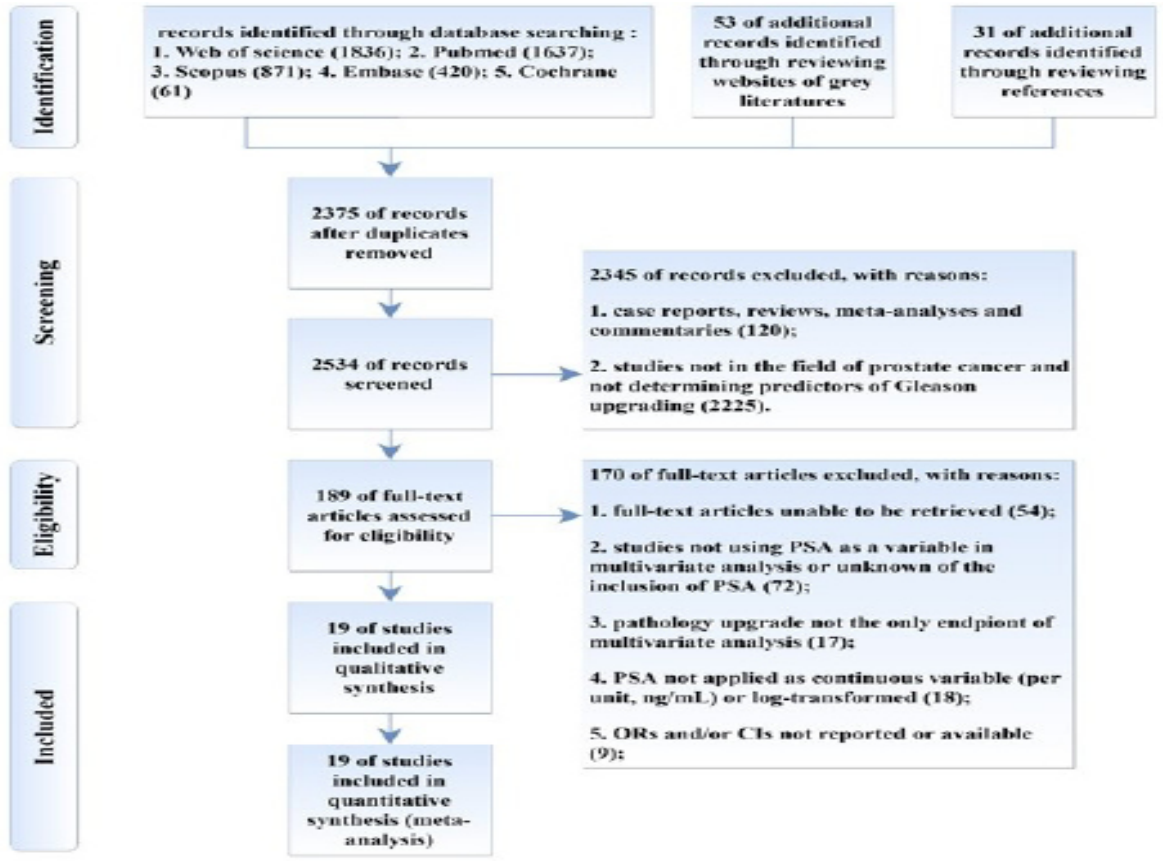

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram.

a standardized form (**Table 1 and Table 2**).

Two investigators (ZJ and QP) independently evaluated each included study utilizing the Newcastle-Ottawa Quality Assessment Scale (NOS) for case-control studies. Discrepancies in score assignment were later resolved by consensus.

Statistical analysis

The conversion to means of variables was roughly calculated using medians combined with range or in-

Study	Selection				Comparability	Exposure			Total score (Sum of stars)
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Bullock 2019	★	★	☆	★	★☆	★	★	★	7
Epstein 2012	★	★	☆	★	★☆	★	★	★	7
Freedland 2007	★	★	☆	★	★★	★	★	★	8
Fu 2012	★	★	☆	★	★★	★	★	★	8
Gofrit 2007	★	★	☆	★	★★	★	★	★	8
Gokce 2016	★	★	☆	★	★☆	★	★	★	7
Jalloh 2015	★	★	☆	★	★★	★	★	★	8
Kassouf 2007	★	★	☆	★	★★	★	★	★	8
Lee 2015	★	★	☆	★	★★	★	★	★	8
Lyon 2016	★	★	☆	★	★★	★	★	★	8
Martin 2017	★	★	☆	★	★☆	★	★	★	7
Pietzak 2014	★	★	☆	★	★☆	★	★	★	7
Porcaro 2017	★	★	☆	★	★☆	★	★	★	7
Porcaro(2) 2017	★	★	☆	★	★★	★	★	★	8
Quintana 2016	★	★	☆	★	★☆	★	★	★	7
Santok 2017	★	★	☆	★	★☆	★	★	★	7
Sooriakumaran 2012	★	★	☆	★	★☆	★	★	★	7
Tosolan 2013	★	★	☆	★	★☆	★	★	★	7
Xu 2017	★	★	☆	★	★☆	★	★	★	7

Figure 2. Newcastle-Ottawa Quality Assessment Scale (NOS) of 19 included studies.

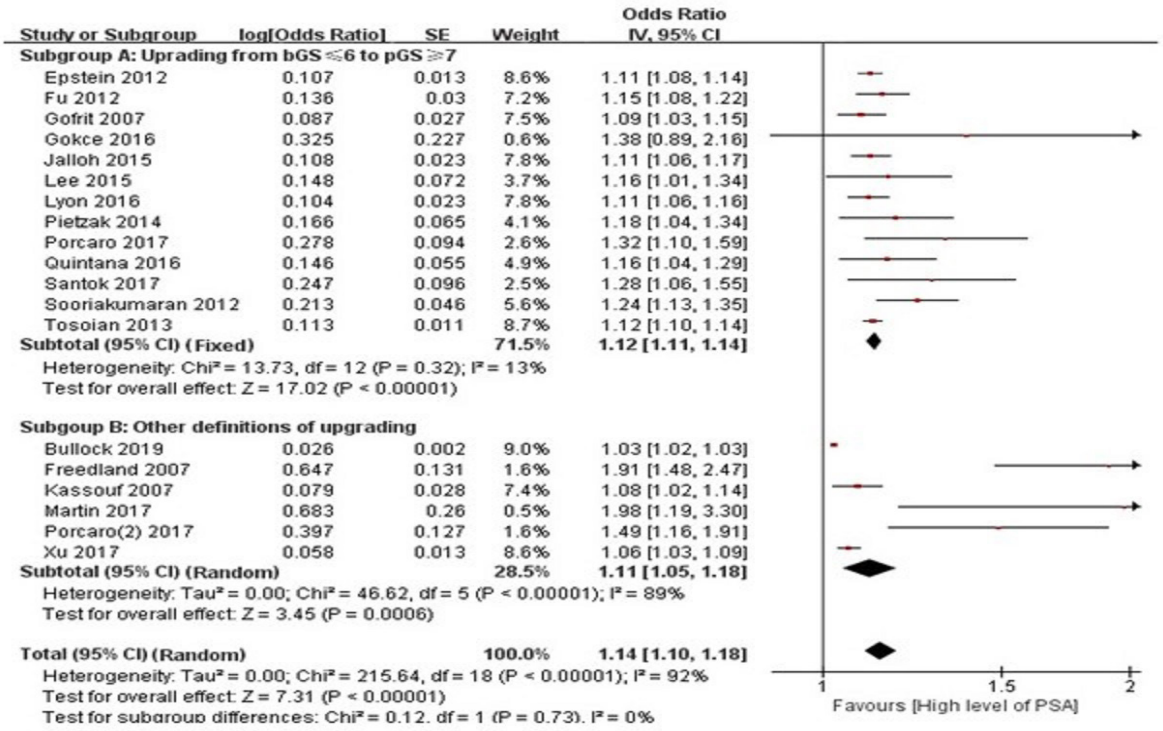

Figure 3. Forest plot of prostate specific antigen (PSA) predicting Gleason sum upgrading in total and subgroups. An odds ratio of > 1 indicates relative chance of upgrading for higher level of PSA versus lower level of PSA.

terquartile range (IQR) according to Luo's methods [11]. The meta-analysis was conducted by computing log-transformed AORs (logAORs) and their standard errors (SEs). Fixed effect model was used for analysis of subgroup A and random effect models were used for analysis of subgroup B and total group in order to assess the predictive performance of PSA on GSU. Further subgroup analysis was carried out utilizing subgroup A and B. Forest plot was performed to provide the pooled results in total and subgroups. The forest plot also provided the overall effect measure (Z) and heterogeneity among studies. Heterogeneity was appraised using I^2 statistic, which represented whether the variation was attributed to heterogeneity or chance. The publication bias was evaluated by visually inspecting the asymmetry of funnel plot and subsequently quantifying the asymmetry by Egger's test. Tests were 2 sided and $P = .05$ was the threshold for statistical significance. Me-

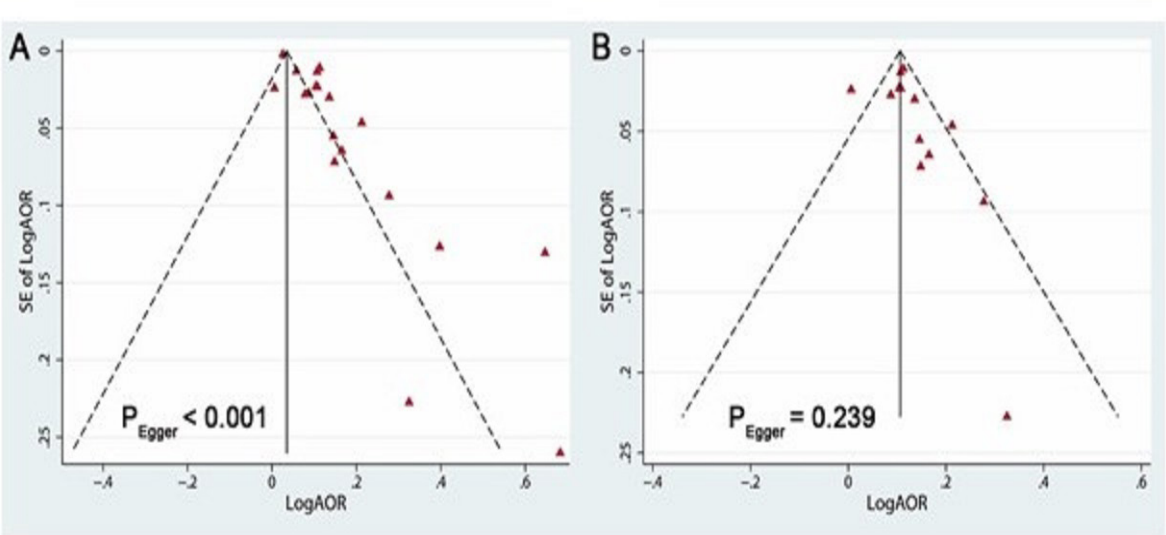

Figure 4. Funnel plot of studies focused on Gleason sum upgrading. **A:** all 19 included studies; **B:** studies defining upgrading from bGS ≤ 6 to pGS ≥ 7.

ta-analysis and statistical tests were performed using computer software of RevMan version 5.3 and Stata version 12.0.

RESULTS

4878 records were retrieved from electronic databases (53 records from electronic websites of grey literatures) and 31 were from pertinent references. Total 2375 results were deduplicated and the remaining 2534 records were screened via title and abstract for eligibility of full-text review. 189 articles were selected after screening and 19 of them published between 2007 and 2019 met the criteria for this review. All were studies of case-control series with total sample size of 42193 patients and with a study interval of 41 years (1975-2016). 7 studies were large series (sample size greater than 1000) from the USA and the UK. There were 11 articles from the USA, 2 from Korea and another 2 from Italy and the remaining 4 were from the China, UK, Canada and Turkey respectively. 13 series applied the definition of upgrading from bGS $\leq$ 6 to pGS $\geq$ 7, while 4 focused on any GSU and 2 consisted of patients upgraded from bGS $\leq$ 3+4 or 7 to pGS $\geq$ 8. (**Table 1 and Table 2**)

Of 42193 patients, the GSU was found in 11892 (28.2%) with higher-grade RP specimens. The rate of GSU in subgroup A (25.5%) was lower than that in subgroup B (30.5%). The pooled mean age of 40537 patients was 60.8 years (95%CI: 46.3-75.3) from 17 articles with extractable data. The pooled mean age of 21071 patients in subgroup A was 58.7 years (95%CI: 44.9-72.5), whilst the 19466 patients in subgroup B were older with pooled mean age of 63.1 years (95%CI: 49.1-77.0). Patients in 8 subgroup A studies were eligible for AS criteria but turned to prostatectomy instead. Even if patients in other 5 subgroup A studies were not all eligible for AS criteria, they all had opportunities to undergo surgeries for curative treatment. Patients in subgroup A were likely to have lower PSA level (mean or median 4.6-6.8 ng/mL) than ones in subgroup B (mean or median 5.5-19.2 ng/mL). Most patients (at least 77.7%) had organ confined disease ($\leq$ T2) in subgroup B. (**Table 1 and Table 2**)

All included studies had high quality according to NOS scale with attained scores greater than 6. 11 articles were rated as a total score of 7, while other studies were rated 8. (**Figure 2**)

As shown in the forest plot (**Figure 3**), PSA level was found to be an independent predictor of GSU regardless of definitions of upgrading. Higher PSA level was associated with a significant increased risk of GSU with high heterogeneity observed (pooled AOR = 1.14, 95% CI: 1.10–1.18; $P < .05$; $I^2 = 92\%$). For the definition of upgrading from bGS $\leq$ 6 to pGS $\geq$ 7 (subgroup A), the odds of upgrading with higher PSA level as opposed to lower PSA level was 1.12 (95% CI: 1.11–1.14, P < .05; $I^2 = 13\%$), while the odds of upgrading in subgroup B was 1.11 (95% CI: 1.05–1.18, $P < .05$; $I^2 = 89\%$). As shown in funnel plots (**Figure 4**), publication bias was pronounced with apparent asymmetry in the analysis of 19 included studies. Egger's test also demonstrated that the publication bias existed with PEgger < .05. After 6 studies of subgroup B removed, asymmetry of funnel plot improved significantly with PEgger = .239 which indicated that no evidence of publication bias was observed in the 13 studies for PSA predicting upgrading from bGS $\leq$ 6 to pGS $\geq$ 7.

DISCUSSION

In this systematic review and meta-analysis of 19 studies with high ranking of quality, we identified PSA as a predictor for GSU regardless of the definition of upgrading in patients eligible for curative treatment or AS. The most convincing finding was observed within the subgroup of upgrading from bGS $\leq$ 6 to pGS $\geq$ 7 in which all studies consistently verified the predictive performance of PSA on GSU with small heterogeneity (OR = 1.12; 95% CI: 1.11–1.14; $P < .05$; $I^2 = 13\%$; PEgger = .239). This review also demonstrated the inaccuracy of bGS to predict pGS with upgrading occurring in 28.2% of 42193 patients.

Gleason upgrading has always been a prolonged invariable topic over time. Even if agreement between bGS and pGS has improved over decades[12], due to the nature of diagnostic method, the phenomena of Gleason upgrading cannot be eliminated. A systematic review [3] including 14839 patients from 1982–2007 reported upgrading from bGS to pGS was found in 30% (range from 6% to 36%), which had no overlapping population with our review and was comparable with what we had found (28.9%, range from 8.9% to 65.3%). Lyon et.al [13], Porcaro et.al[14], Santok et.al[15] and Sooriakumaran et.al[16] identified 51.5%, 65.3%, 40.4% and 39.6% of patients with GSU partly due to the upgrading from the 'bottom' (bGS = 6).

Although PSA is typically elevated in high-grade disease, some patients present with the discordant scenario of high-grade disease and low PSA. For Gleason 8–10 disease, these patients with low PSA have a higher risk for PCa death and are more likely to be associated with neuroendocrine genomic features than ones with high PSA[17]. High-grade disease could be harboured in these patients which may result in upgrading. However, our pooled results showed that there is a positive linear relationship between PSA and GSU. The following two reasons might explain. The proportion of these patients in the population is small which may not influence the linearity of multivariable analysis. The diagnoses of these patients are difficult via PSA screening and these patients might be ineligible for prostatectomy when they are diagnosed. Hence, most of these patients may not be incorporated in the included studies of this review.

PSA is organ but not cancer specific and hence it may be elevated in patients with large prostate gland or other clinical scenarios such as prostatitis. Counterintuitively, small rather than large prostate volume (PV) was strongly associated with pathologic outcomes including GSU[18], which was also determined by 2 included studies[19,20] in our review. In 9 articles included[14-16, 20-25], PV was also incorporated into MVA to adjust for confounders or collinearity. However, PSA was still an independent predictor for GSU. PSA density (PSAD) is the level of PSA divided by the TRUS-determined PV, which is another predictor for risk stratification and prognosis and more likely to be associated with clinically significant PCa[26]. Due to PSAD as a better indicator adjusting for PV, it has been reported that PSAD other than PSA was an independent predictor of upgrading (27). Controversially, 3 articles[15,24,25] included in this review demonstrated that PSA was still strongly asso-

ciated with GSU even when PSAD was incorporated into MVA. However, no matter what we will find from further studies addressing this issue, PSA is a critical factor which urologists or oncologists should be fully considerate to in terms of risk reclassification.

All the articles except one[28] incorporated at least one pathologic variable into MVA. Including variables such as the number of positive cores and/or tumor extent in cores improved the predictive performance for a comprehensive risk assessment of GSU. Individual differences including racial variation[13,20-22,26], body mass index[13,14, 22-24,26] and comorbidity[13,22] which might potentially affect GSU were also adjusted. Multifarious variables being included in different articles verified PSA as the independent risk factor, but would do so at the cost of inducing the heterogeneity between studies. Heterogeneity among studies focused on upgrading from bGS ≤ 6 to pGS ≥ 7 was acceptable, whilst the variation within subgroup B was significant. The combination of different definitions in subgroup B was a major source of heterogeneity. The number of biopsy cores obtained was a vital factor influencing the accuracy of predicting pGS[29]. Most studies adjusted for it or it was an invariant part of study design, however, there were 6 studies[14,19,24,28,30,31] did not do so or report the details, which might contribute to significant variation in outcomes. Given the nature of case-control studies, the limitation of study design was also an inevitable reason of heterogeneity. Further prospective, large-scale and well-designed research is needed to determine PSA's impact on GSU. Experience in GS assignment varies across pathologists especially in different hospitals and regions. Interobserver variability was found to correlate with the accuracy between bGS and pGS[32]. In view of pooled analysis of studies, this interobserver variability cannot be eliminated but reflect the true contemporary clinical practice.

Except the heterogeneity discussed above, our review still has several limitations. First of all, the quality of the studies varied. Moreover, incomplete retrieval of all research due to inevitable reasons such as no access to full-text, non-extractable data or inappropriate data type. Last but not least, only patients who had undergone RP were selected for analysis which might not represent the reality.

According to our pooled analysis, there are several clinical implications of PSA predicting GSU in current clinical practice. Patients who are reevaluated to have high probabilities of GSU during AS could adhere to more active follow-up policies in case of delay of treatment. On the contrary, patients with low probabilities of GSU who are unwilling to or could not receive interventions are more inclined to undergo the watchful waiting or AS. These clinical recommendations might give urologists more confidence in clinical decision-making and provide more precise and comprehensive assessment of the risk and more personalized and optimal treatment options for PCa patients.

CONCLUSIONS

PSA is an independent predictor for Gleason sum upgrading regardless of the definition of upgrading. Patients with high level of serum PSA are at high risk of undergoing pathologic upgrading at prostatectomy. Combined with other risk factors, PSA prompts more accurate risk stratification and helps providers to select optimal therapies for PCa patients. Nevertheless, further robust studies are necessitated to confirm these results.

CONFLICTS OF INTEREST:

None of the authors have any conflicts of interest to declare.

APPENDIX

https://journals.sbmu.ac.ir/urolj/index.php/uj/libraryFiles/downloadPublic/30

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