Section: Pathology

Systematic Review

A SYSTEMATIC REVIEW ON THE GLEASON GRADING SYSTEM AND ITS REVISIONS IN PREDICTING OUTCOMES FOR PROSTATE CANCER PATIENTS

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Abstract

Background: Since its establishment in the 1960s, the Gleason grading system has served as a fundamental tool for assessing prostate cancer, providing important information on the aggressiveness of the tumour. The prognostic value of the Gleason system and its modifications is examined in this systematic review. **Materials and Methods:** A qualitative synthesis approach was used to conduct a systematic review. PubMed, Scopus, Web of Science, and Embase were searched for articles from 2014 to 2024 that evaluated the Gleason grading system, its updates. Using the PRISMA framework, inclusion and exclusion criteria were used to choose 17 relevant papers. **Result:** Despite its shortcomings in categorising specific histological subtypes, the Gleason grading system is still considered the gold standard because of its therapeutic value and versatility. The ISUP revisions in 2005 and 2014, for example, improved prognosis accuracy by establishing Grade Groups and improving scoring techniques. **Conclusion:** The Gleason system continues to play a crucial role in the assessment of prostate cancer because of its ease of use, dependability, and clinical value, even in the face of new grading schemes. Changes have strengthened its use in contemporary oncology.

INTRODUCTION

The Gleason grading system, which provides a strong framework for forecasting patient outcomes across different treatment modalities, has long been acknowledged as the foundation of prostate cancer (PCa) management and prognostication.[1] The Gleason method, which was first suggested by the American Cancer Society in 1978 due to its ease of use, repeatability, and clinical significance, has since grown to be the widely recognised norm for PCa grading. It places a distinct emphasis on architectural aspects rather than cytological details.[2] This could sometimes result in "down-grading" cases due to minor components of less aggressive types. However, the system has undergone several changes over time, including the ISUP 2005 and 2014 upgrades, to increase its predictive accuracy.[3] The more complex reporting requirements have caused misunderstandings even among specialists, and practicing pathologists have occasionally been perplexed as a result.[4] Furthermore, there is uncertainty regarding the prognostic benefits attributed to the ISUP revisions because few studies have fully compared the new Gleason scores to pre-2005 criteria in predicting significant outcomes like biochemical recurrence (BCR) or PCa-specific mortality. It is important to note that there remains a lack of supporting evidence for the efficacy of Gleason scores (GS) in forecasting prostate cancer (PCa) mortality, which is a more clinically significant outcome. This is particularly concerning because most research efforts have focused on categorizing GS instead of conducting a centralized review of diagnostic samples in accordance with the latest ISUP 2014/WHO 2016 guidelines.[5,6] However, the predictive capacity of the Gleason grading system might be enhanced through the integration of additional histopathological factors, such as cribriform patterns, intraductal carcinoma, the proportion of Gleason pattern 4, tumor area measurements and perineural invasion.

This systematic review aims to critically assess the Gleason grading system and its revisions in predicting PCa outcomes, and exploring opportunities to enhance its prognostic capabilities by incorporating additional histopathological markers.

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MATERIALS AND METHODS

Study Design: This systematic literature review was conducted to evaluate the predictive utility of the Gleason grading system and its revisions for prostate cancer outcomes. A qualitative approach was employed to synthesize findings from diverse studies, providing an in-depth understanding of their prognostic implications.

Data Collection: A comprehensive search strategy was designed to identify relevant studies published in peer-reviewed journals. The search was performed in electronic databases, including PubMed, Scopus, Web of Science, and Embase, covering articles published between 2014 -2024. The following search terms and Boolean operators were used: Keywords: "Gleason grading system," "prostate cancer," "prognostic outcomes," "ISUP revisions,".

Inclusion Criteria:

- Studies evaluating the Gleason grading system or its revisions in the context of prostate cancer.
- Articles reporting qualitative or mixed-method findings on grading systems' prognostic accuracy.
- Peer-reviewed studies published in English.

Exclusion Criteria:

- Studies focusing solely on grading systems without clinical correlations.
- Editorials, commentaries, and opinion pieces without primary data.
- Articles with incomplete or inaccessible data.
- Duplicate publications or studies unrelated to prostate cancer grading.

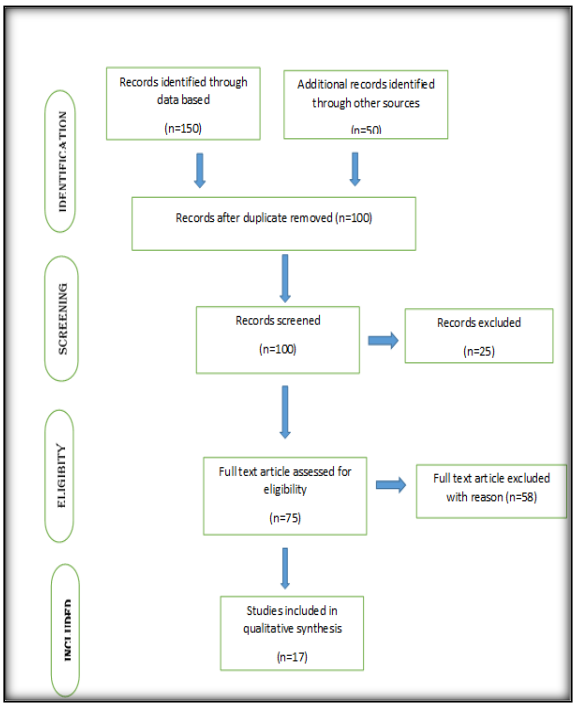

Figure 1: PRISMA Flow Diagram illustrating the systematic selection process, including the stages of identification, screening, eligibility, and inclusion of studies for the review.

Selection Process: The selection procedure followed the PRISMA framework, which included multiple steps to guarantee a methodical and exacting approach. 150 possible studies were found through database searches at the beginning of the identification stage; 50 duplicates were eliminated after titles and abstracts were screened for relevancy. The remaining 100 papers were evaluated in the screening phase based on predetermined inclusion and exclusion criteria. Following the exclusion of 58 publications during the eligibility phase, 17 papers that were judged pertinent were assessed to ensure that they aligned with the review's goals. Studies that satisfied every inclusion criterion were then added to the final synthesis during the inclusion stage. The entire selection procedure was carried out by two separate reviewers, who discussed or spoke with a third reviewer to settle any discrepancies. The identification, screening, exclusion, and inclusion of the records in the study are visually summarised in a PRISMA flow diagram [Figure 1].

Data Synthesis: The study evaluated results on the Gleason system using a qualitative synthesis approach. Important procedures included thorough data familiarisation, open coding to find recurrent factors such as clinical utility and prognosis accuracy, and data abstraction to compile advantages and disadvantages.

RESULTS

In a study by the United States Veterans Administration in the 1960s, Drs. Donald Gleason developed the Gleason grading system, which revolutionised prostate cancer diagnosis by correlating histological patterns to clinical outcomes with scores attributed to the sum of primary and secondary growth patterns (e.g., 3+4=7),7which explained that Since it was formally approved by the WHO in 2004, prostate cancer has continued to play an important role in staging and treatment decisions, based on a five-score differential diagnosis of tumors—simple but reliable, which includes PSA levels and tumour stage and provides a prognosis8. The Gleason approach for determining the advancement of prostate cancer has improved throughout time, owing to its clinical usefulness and reliability. It's the gold standard. Although relevant to most histological types, it excludes some subtypes, such as squamous cell carcinoma and small cell carcinoma, which are outside its scope. The Gleason framework's adaptability in modern oncology is illustrated by the diverse classification of newly found forms. As shown in Table 1 which summarises the Gleason grades attributed to various histological and growth/cytological types of prostate cancer. Variants such as ductal carcinoma (grade 3-5) and mucinous carcinoma (grade 4) are rated based on histological traits, although others, such as small cell and squamous cell carcinoma, cannot be classified. Growth patterns such as hypernephroid and

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pseudohyperplastic carcinoma have varied grades, which commonly range from 2 to 4. This table demonstrates the variation in grading based on histological and cytological parameters.[9]

Table 1: The table below summarizes the Gleason grades assigned to various histological variants of prostatic carcinoma.

Variants	Gleason Pattern (Grade)
Histological Variants	
Ductal (endometrioid) carcinoma	3–4 (without necrosis), 5 (with necrosis)
Signet-ring cell carcinoma	5
Mucinous (colloid) carcinoma	4
Lymphoepithelioma-like carcinoma	5
Sarcomatoid carcinoma (carcinosarcoma)	5 (glands graded separately)
Small cell carcinoma	Not applicable
Squamous cell carcinoma	Not applicable
Transitional cell carcinoma	Not applicable
Basaloid/adenoid cystic carcinoma	Not applicable
Growth/Cytological Variants	
Hypernephroid (hypernephromatoid)	4
Atrophic pattern	Variable (most 3)
Pseudohyperplastic pattern	Most 2–3
Foamy gland carcinoma	Variable (most 3–4)
Carcinoma with Paneth-like cells	Variable
Carcinoma with oncocytic cells	Variable

Revisions to the Gleason Grading System

Significant advancements in prostate cancer diagnostics and treatment have emerged since the first introduction of the Gleason grading system, necessitating updates to the grading criteria. The Gleason grading system underwent significant revisions, primarily through the 2005 ISUP consensus, eliminating Gleason scores 2–5 due to limited prognostic value. The International Society of Urological Pathology (ISUP) made some changes to the Gleason grading system that have had a big effect on how prostate cancer is graded and treated, especially in needle biopsy samples. These changes encompass three key recommendations. Firstly, definitional adjustments included the classification of poorly formed glands under pattern 4 10. Secondly, the inclusion of any minor higher-grade component (<5%) in the Gleason score (GS) was mandated. For instance, the classical system now scores a biopsy with 97% pattern 3 and 3% pattern 4 as 3 + 4 = 7, instead of 3 + 3 = 6. Finally, the ISUP recommended separately scoring each biopsy core or grouping cores within a container, and guided patient management by the highest Gleason score (HGS) observed. Some studies noted that these changes led to an upscoring in 35% of prostate cancer cases, with most instances attributed to the use of the HGS in needle biopsy series. The revisions also improved reproducibility, with interobserver agreement rising to approximately 80%. This modified system better aligns needle biopsy grading with radical prostatectomy findings, ensuring consistent reporting across sample types.

These modifications have important clinical ramifications because the previous standards relied on the traditional grading system. In order to improve prognostic correlation, the 2014 ISUP consensus implemented a grading system that allocates Gleason scores to Grade Groups (1–5). With GS ≤6 now clearly defined as Grade Group 1, indicating little risk, this system streamlines communication. Although grading is still a continuum, it might be difficult to interpret borderline grades (such as "bad GS 6" versus "good GS 7") 11. Determining the proportion of Pattern 4 in GS 7 tumours aids in distinguishing tumour aggressiveness and guiding therapeutic choices. Because a big percentage of Pattern 4 in a tiny focus is different from that of a larger tumour, tumour size and extent are also important considerations. Because of this complex methodology, Gleason grading remains applicable in forecasting results and adjusting to therapeutic requirements.[12]

Updates in Gleason score reporting enhance grading accuracy by refining criteria for core biopsies, tertiary patterns, and post-therapy evaluations. In needle biopsies, Gleason scores should be reported individually for each core, with an optional global score if needed. The highest score is prioritized in cases of tissue fragmentation.[13] Gleason scores of 3 or 4 are generally discouraged due to low repeatability and their tendency to reveal higher grades post-surgery. For tertiary patterns, they influence the final score on biopsies if they are the highest grade, whereas in radical prostatectomies, tertiary patterns are noted separately.[14] High-grade patterns must be included in the score even if they comprise less than 5% of the tumor. Cribriform carcinoma and glomeruloid patterns are now linked to Gleason Pattern 4, reflecting their association with aggressive disease, though the latter remains debated. Post-therapy grading applies only when therapy-related changes are minimal. These refinements aim to enhance grading accuracy and consistency, improving patient care and outcomes.

Prognostic Value of Grading Systems

The Gleason grading system is still a mainstay for assessing the aggressiveness and prognosis of prostate cancer, offering a strong foundation for clinical judgement. Prostate tumour histological architecture is evaluated using this approach, which

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assigns grades ranging from 1 to 5 according to structural patterns and cellular differentiation. The Gleason score, which ranges from 2 to 10, is calculated by adding the grades for the two most noticeable patterns. Higher scores indicate poorly differentiated, high-risk malignancies, while lower values indicate well-differentiated, less aggressive tumours.[15]

The Gleason score plays a pivotal role in determining prognosis. Tumors exhibiting slower growth, a reduced likelihood of metastasis and remarkable survival rates are often associated with scores of ≤6. Such scores frequently allow for conservative treatment options, including active surveillance. However, intermediate scores—particularly a 7 (where 3+4 suggests a slightly better prognosis compared to 4+3)—signal a significant risk of progression, necessitating specialized interventions such as radiation or surgery. For aggressive diseases, intense treatment methods become essential due to high recurrence rates and poorer survival outcomes, which correlate with elevated scores (8–10). The introduction of the Grade Group format has transformed the Gleason grading system, offering a more nuanced stratification. Specifically, Grade Group 1 (Gleason score ≤6) signifies the least aggressive cancers, while Grade Groups 2 and 3 (3+4=7 and 4+3=7) reflect an increasing risk. In contrast, Grade Groups 4-5 (scores of 8–10) identify high-risk tumors associated with unfavorable prognostic outcomes. This enhanced classification underscores its therapeutic value, as it closely aligns with treatment responses and patient survival statistics.[16]

The Gleason grade histological examination includes prostate biopsy analysis. Higher grades have disorganised, invasive cells, while lower grades have well-formed glandular structures. When combined, these patterns show tumour aggressiveness and can guide treatment. PSA tests and digital rectal exams are used to find clinically relevant tumours with scores of 5–7. However, benign prostate procedures often uncover incidental tumours that score 2–4. Gleason grading combines smoothly with other staging tools, notably the TNM system, to provide a complete picture of tumour behaviour. The CAPRA score, D'Amico classification, and emerging genomic assays provide additional insights, but they are not as widely used or validated as the Gleason system. However, the Gleason grading system—especially its revised Grade Group format—is critical for prostate cancer management. It properly represents tumour biology and prognosis, influencing treatment options and improving patient outcomes.

However, biomarker research and molecular profiling may improve prognosis and modify the Gleason system. Although these developments have potential, they may be complicated and require cautious execution.

DISCUSSION

This review finding suggests that the Gleason grading system has experienced significant alterations, yet it continues to function as the cornerstone for assessing prostate cancer. Its WHO classification integration into clinical guidelines—such as those established by the AJCC and NCCN highlights the importance of this system in guiding prognosis, diagnosis and treatment. Over time, the precision and consistency of the system have improved; its ability to link histological patterns to therapeutic outcomes has proven to be invaluable. The aim of the 2005 and 2014 ISUP amendments was to enhance prognostic accuracy and inter-pathologist agreement by refining the definitions of Gleason patterns, particularly patterns 3 and 4. Following the endorsement of Grade Groups (GGs) in 2014, numerous research studies examined their predictive capabilities regarding prostate cancer (PCa) mortality and biochemical recurrence (BCR). Most of these studies, however, were deficient in centrally reviewed biopsies that complied with ISUP 2014 standards. Using PCa mortality as the primary outcome, this study stands out as the first to centrally re-evaluate diagnostic biopsies in accordance with ISUP 2014/WHO 2016 criteria. In another study by Zelic et al. (2022) demonstrated that the ISUP 2014 grading method is superior at distinguishing between PCa deaths compared to the pre-2005 system.[17] This is achieved by replicating the pre-2005 Gleason patterns, incorporating cribriform patterns and poorly formed glands. However, this highlights the critical necessity of implementing these changes to the grading system, because the implications for patient outcomes are significant. Although the previous system served its purpose, it is evident that advancements are essential for better accuracy. The noteworthy improvement that resulted from classifying all cribriform patterns as Gleason pattern 4 highlighted the significance of these changes in enhancing prognostic accuracy. Mathieu et al.,(2017) provided empirical support for these modifications, observing a 35% increase in prostate cancer diagnoses upon applying the highest Gleason score from needle biopsy specimens.[18] More alignment between the outcomes of the radical prostatectomy and the biopsy findings led to increased prognostic accuracy and diagnostic consistency. In 2014, the addition of Grade Groups (1–5) further established the clinical value of the Gleason grading system by streamlining communication and coordinating scores with predictive outcomes. By specifically classifying Gleason score 6 as Grade Group 1, which denotes low-risk illness, this change successfully addressed patient misconceptions regarding the score. Research has demonstrated that these modifications have enhanced therapy stratification, as evidenced by more accurate survival forecasts and customized treatment strategies (Montironi et al.,2016).[15]

According to Pudasaini et al.,(2019) when it comes to determining the severity of prostate cancer, the

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Gleason grading system is still clinically superior.[19] Gleason scores ≤6 often suggest indolent tumours, while scores 8–10 indicate aggressive disease with adverse prognoses. These gradations are essential for prognostic assessment and treatment planning, especially when paired with TNM staging. Furthermore, improving prognostic accuracy through the incorporation of tertiary patterns and the quantification of high-grade components supports individualized patient management. The study assessed tumour extent measurements, such as the proportion of malignant cores or the overall cancer length in millimetres, as prognostic variables. Although the percentage of malignant cores has produced consistent results, it makes up a tiny portion of the total prognostic discrimination. While these metrics form part of risk systems like CAPRA and NCCN, their significance often diminishes when considering Grade Groups (GGs) and other variables.[17]

Our results show that the prognostic value lost is almost nothing, which supports the important role of the Gleason grading system in developing diagnostic methods. Therefore combining simplicity, reproducibility, and extensive validation, the Gleason system remains the gold standard for prostate cancer grading, with its integration into other frameworks providing a holistic approach to patient care Thus, prior work consistently underscores the Gleason grading system's robustness, adaptability, and indispensable role in prostate cancer assessment, forming a critical benchmark against which current study findings can be contextualized.[18-20]

CONCLUSION

In conclusion, the Gleason grading system remains a cornerstone in prostate cancer diagnosis, prognosis, and treatment, with significant improvements like the Grade Group classification enhancing its accuracy and predictive value. Combining histological findings with clinical factors such as PSA and TNM staging provides a strong foundation for personalized treatment planning. Despite the emergence of new grading methods, the Gleason system's simplicity, broad validation, and practical utility maintain its gold standard status. Further advancements, such as tertiary pattern analysis and molecular profiling, promise to enhance its prognostic accuracy and treatment outcomes, ensuring its continued relevance in precision oncology.

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