RESEARCH ARTICLE

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Tumor Budding Significance as a Biomarker for Clinicopathology and Prognostic Evaluation in Gynecological Malignancy: A Bayesian Meta-Analysis

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Abstract

Objective: Tumor budding (TB) has been recommended as a marker for prognosis and therapeutic decision-making in various types of cancer, yet it has not been comprehensively studied in gynecological malignancies. This study aimed to evaluate the relationship between TB and clinicopathological features, as well as prognosis, in patients with gynecological malignancies, using a Bayesian meta-analysis design. **Methods:** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 protocol was followed. A systematic literature search was conducted using PubMed, ScienceDirect, and Cochrane databases. A meta-analysis was performed to assess the relationship between TB and clinicopathological parameters using odds ratios (ORs). Prognostic outcomes were analyzed using hazard ratios (HRs). Specific Bayesian priors were applied to each variable. Data analysis was conducted using R (version 4.4.0). **Results:** Eighteen cohort studies (n = 3,320) involving patients with cervical and endometrial cancer were included. Bayesian meta-analysis showed that TB was significantly associated with clinicopathological parameters, specifically cancer stage (OR=2.91; 95%CrI: 1.86–4.41; prediction interval (PI) OR=2.92; 95%CrI: 0.82–9.92; τ^2=0.53), grading (OR=5.00; 95%CrI: 2.83–8.76; PI OR=5.00; 95% CrI: 0.89–27.87; τ^2=0.77), nodal involvement (OR=3.63; 95%CrI: 2.41–5.47; PI OR=3.63; 95%CrI: 0.85–15.52; τ^2=0.66), and lymphovascular invasion (LVI) (OR=4.22; 95%CrI: 2.52–6.92; PI OR=4.22; 95%CrI: 0.63–27.80; τ^2=0.89). Overall survival (OS) showed an HR of 2.14 (95%CrI: 1.27–3.63; PI HR=2.14; 95%CrI: 0.83–5.58; τ^2=0.25) and DFS showed an HR of 1.20 (95%CrI: 0.77–1.59; PI HR=1.21; 95%CrI: 0.14–2.20; τ^2=0.42). **Conclusion:** Tumor budding is significantly associated with clinicopathological features and prognosis in patients with gynecological malignancies.

Keywords: Clinicopathology- gynecological malignancy - prognosis - tumor budding

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Introduction

Gynecological malignancy is an entity for all malignancies of the female reproductive organs, including vagina, vulvar, cervical, endometrial, and ovarian cancers. Gynecological malignancy is among the leading causes of morbidity and mortality in women globally, with more than 600,000 new cases of cervical cancer and more than 340,000 deaths recorded in 2020 globally [1]. Cervical cancer, as one of the gynecological malignancies, in Indonesia remains one of the deadliest cancers in women, with many cases diagnosed at an advanced stage due to late diagnosis and limited access to adequate therapy [2]. A study at the second largest referral hospital in Indonesia showed that the majority of cervical cancer patients presented with advanced symptoms and took more than three months from symptom onset to a definitive diagnosis. This challenge is compounded in developing

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countries by limited resources, including access to chemotherapy and advanced treatment modalities [3]. Given the biological and clinical heterogeneity of each type of gynecological malignancy, a uniform therapeutic approach is often inadequate. Therefore, a more precise and biomarker-based risk stratification system is needed to support more individualized and effective therapeutic decision-making [4, 5]. The development of data-driven systems and prognostic biomarkers is increasingly crucial for bridging the gap between early diagnosis and personalized therapy in gynecological malignancy.

Although advances in molecular understanding have yielded a variety of histopathological parameters and biomarkers to assess prognosis in gynecological malignancies, clinical decision-making still predominantly relies on conventional staging systems and basic tissue morphology [6, 7]. This reliance on conventional methods limits the ability to personalize therapy, especially in borderline or early-stage cases, where metastatic potential or aggressive tumor behavior is often not detected early [8]. Additionally, conventional classification methods are not based on molecular characteristics that can be determining factors of tumor characteristics that lead to therapeutic strategies and patient prognosis. Molecular-based approaches and clinical data in other oncology areas, such as breast, colon, and hepatocellular cancers, have been shown to improve the accuracy of risk stratification and more specific therapy selection [9–11]. Therefore, there is an urgent need to identify and integrate additional biomarkers that can more accurately reflect tumor aggressiveness, thereby supporting individualized risk-based therapy decisions. This approach, including the use of molecular classification and predictive modeling, shows significant potential in improving clinical outcomes of patients with endometrial cancer and other types of gynecological malignancy [12].

Tumor budding (TB) is a histopathological feature that describes the presence of single tumor cells or small clusters (<5 cells) separated from the main tumor mass in the invasive area, reflecting a more aggressive and migratory tumor cell phenotype. Tumor budding has been recognized as an independent prognostic biomarker for invasion, metastasis, and recurrence in colorectal cancer, and its use is recommended internationally through the International Tumor Budding Consensus Conference (ITBCC) guidelines [13]. Recent studies have begun to identify a similar role for TB in various cancer types, including breast, cervical, and endometrial [14–16]. Several previous studies have shown that higher grades of TB are associated with more aggressive tumor characteristics, LVI, and poorer prognosis in gynecological malignancy [17, 18]. However, there is no consensus or universal guideline regarding the assessment standards and their application in the clinical practice of gynecological malignancy. This makes it urgent to evaluate, considering that TB is an emerging parameter that is increasingly being investigated and is related to molecular aspects related to tumor progression, both related to the epithelial-to-mesenchymal transition (EMT) process, metastasis, and aggressiveness. Therefore, a systematic and quantitative evaluation is urgently needed to assess the consistency and strength of the association between TB and key clinicopathological parameters. Additionally, a Bayesian statistical approach will be used to obtain more realistic estimates, especially in heterogeneous or limited data due to relatively small sample sizes. The Bayesian approach uses prior information to help stabilize estimates of effects arising from small and heterogeneous data in the form of probability distributions, thus producing more robust and informative analysis results [19]. This study aims to conduct a Bayesian-based meta-analysis to synthesize current evidence on the significance of TB as a clinicopathologic and prognostic biomarker in gynecological malignancy.

Materials and Methods

Identification of Relevant Literature

Literature searching was conducted using the PRISMA guideline in online databases, including PubMed, ScienceDirect, and Cochrane Library. Relevant studies were identified by utilizing Boolean operators ("Tumor Budding") AND ("Prognosis" OR "Prognostic" OR "Recurrence" OR "Stage" OR "Grade" OR "Recurrence") AND ("Cancer"). All authors contributed to the screening process, followed by an independent evaluation of each study according to predetermined eligibility criteria. The final selection of included studies was determined through discussion among all authors, requiring unanimous agreement before inclusion. Any disagreements among reviewers were resolved by consensus.

Eligibility Criteria

Studies were considered eligible if they fulfilled the following criteria: (1) Prospective or retrospective cohort studies that involved diagnosed cancer patient, (2) studies stratified the presence of TB as low-grade TB (LGTB) and high-grade TB (HGTB) or positive and negative, (3) studies reported correlation TB stratification with prognostic parameter such as clinicopathological characteristics, OS, and DFS, (4) analysis between TB stratification and prognostic parameter was reported in OR and/or HR with 95% credible interval (95%CrI). The exclusion criteria in this study were (1) the inability to access the full text of the article, which hindered complete data extraction and analysis, and (2) studies reported that TB was classified into three levels (low, intermediate, and high). Four independent investigators were involved in this process.

Data Extraction

Four independent reviewers were involved in data extraction. The following correlational information was collected in a predefined table from the eligible articles. The following information was extracted from the included studies: general information of the studies (author, years of publication, and country), study design, number of samples, cancer type, and TB classification.

Risk of Bias Assessment

Risk of bias in non-randomized and quasi-randomized studies (cohort and case-control) is evaluated using

ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions). ROBINS-I is applied to the following seven domains with a series of signaling questions and assessment categories of low, moderate, serious, critical, or no information: domain confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Four independent reviewers were involved in this process (I.G.W.W.W., N.P.K.M., P.M.W.S.P., and K.M.K.T). All involved reviewers will assess either low, moderate, or high concerns of bias for each category. Any disagreement will be resolved through discussion.

Statistical Analysis

Statistical analysis was conducted using R version 4.4.0 with a Bayesian meta-analysis approach to assess the association between TB and clinicopathological features (stage, grade, lymph node involvement, and LVI) as well as prognostic outcomes (OS and DFS) in gynecological malignancies. Odds ratios (ORs) and HRs with 95%CrIs were calculated using a Bayesian hierarchical model with weakly informative priors. The selection of priors for effect sizes with their respective standard deviations will use the normal distribution of the analyzed data using the notation $\theta \sim N(\mu, \sigma)$, where μ is the mean, and σ is the standard deviation. where the value of $\mu = 0$, so as not to skew to any side, and $\sigma = 15u$, where u is the largest maximum likelihood estimator (MLE) value based on the observed dataset [20, 21]. Between-study heterogeneity was estimated using τ^2, and 95% prediction intervals (PIs) were reported to reflect expected effect sizes in future settings. Posterior distributions were obtained via Markov Chain Monte Carlo (MCMC) simulation, and model convergence was assessed using the Gelman–Rubin diagnostic. Sensitivity analyses were not conducted in this study because the data analysis tools in this study design did not support sensitivity analysis, so we tried to conduct subgroup and critical appraisal-based analyses to increase its validity.

Results

Literature searching

A systematic literature search was performed using predefined databases and keywords, yielding a total of 2,465 articles. After removing duplicates (n=2) and exclusion using specific automation tools (n=1805) in each database namely PubMed ("2016-2025", "free full text"), ScienceDirect ("2016-2025", "research article", "open access & open archive"), Cochrane ("2016-2025", and "PubMed"). These were further assessed based on predefined inclusion and exclusion criteria, excluding studies with incomplete data or that did not meet the eligibility requirements. A total of 18 articles met the criteria and were included in the final analysis. The detailed selection process is illustrated in the flow diagram in Figure 1.

Study Characteristics

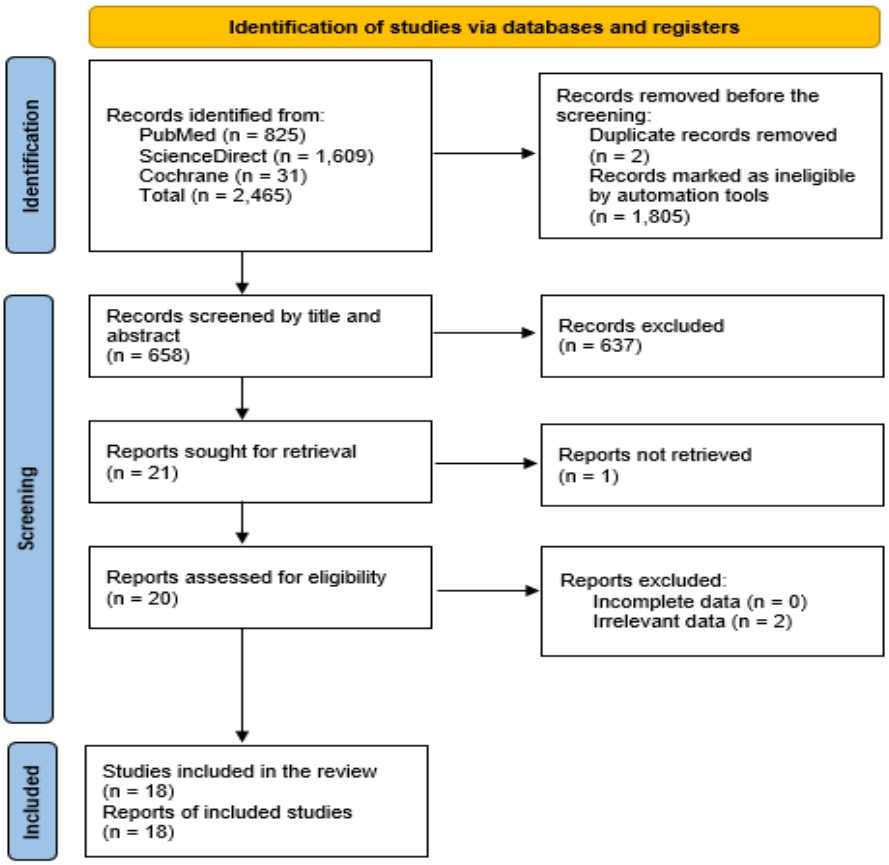

Figure 1. PRISMA Flowchart

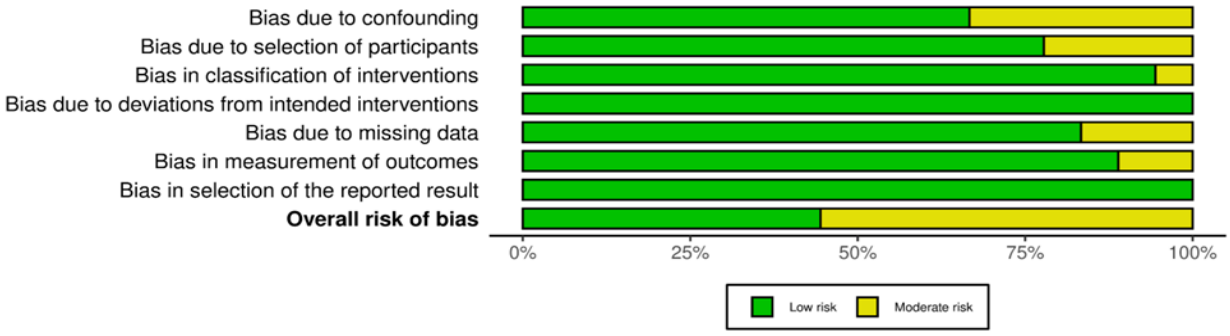

Figure 2. The Overall Risk of Bias Plot

This study included 18 cohort studies, consisting of three prospective and fifteen retrospective designs. The studies were conducted in various countries, with the majority from China, followed by three from South Korea; two each from Germany and Turkey; and one each from Thailand, Serbia, India, Poland, Switzerland, and the United States. Regarding cancer types, eight studies focused on cervical cancer, and eight on endometrial cancer. The total sample size used in each study varied, ranging from 30 to 643 participants, with a total of 3320 patients. Tumor budding (TB) was assessed using either positive/negative, in four studies, or high/low classifications (HGTB vs LGTB). A detailed summary of study characteristics is provided in Table 1.

Risk of bias assessment results

Risk of bias assessment using the ROBINS-I tool indicated that none of the included studies had a high overall risk of bias. The most frequently identified concerns were related to the domain of confounding, either due to baseline differences between groups or insufficient reporting on strategies used to control for confounding, such as adjustment or stratification. Nevertheless, no domain demonstrated a level of bias considered high enough to compromise the validity of the study outcomes. A summary of the risk of bias assessment is illustrated in Figure 2.

Outcome results

This Bayesian meta-analysis found that TB is significantly associated with aggressive clinicopathological features in gynecologic malignancies, including advanced cancer stage, poor histological differentiation (higher grade), nodal involvement, and LVI. Specifically, the presence of TB was nearly three times more likely in patients with advanced-stage disease compared to early-stage counterparts (OR=2.91; 95%CrI: 1.86-4.40). After analysis by considering the level of heterogeneity between studies ($\tau^2 = 0.53$), it was found that the predictive value of the ratio of TB presence was still equivalent, almost

Table 1. Study Characteristics

Author, years	Country	Study Design	Sample Size	Cancer Type	Tumor Budding Assessment
Jesinghaus et al., 2018[33]	Germany	Retrospective study	125	Cervical SCC	High vs low
Cao et al., 2020[61]	China	Retrospective study	122	Cervical SCC	High vs low
Chong et al., 2021a[34]	South Korea	Retrospective study	151	Cervical cancer	High vs low
Chong et al., 2021b[34]	South Korea	Retrospective study	151	Cervical cancer	High vs low
Huang et al., 2016[46]	China	Retrospective study	643	ESCC	High vs low
Park et al., 2020[35]	South Korea	Retrospective study	136	ESCC	High vs low
Satabongkoch et al., 2017[36]	Thailand	Prospective study	129	ESCC	High vs low
Stanulović et al., 2021[37]	Serbia	Retrospective study	91	Cervical cancer	High vs low
Zare et al., 2020[38]	USA	Prospective study	94	Cervical SCC	High vs low
Dubey et al., 2025[39]	India	Prospective study	30	Endometrial cancer	High vs low
Kluz et al., 2020[52]	Poland	Retrospective study	137	Endometrial cancer	Positive vs negative
Koyuncuoglu et al., 2012[41]	Turkey	Retrospective study	95	Endometrial cancer	High vs low
Ocal et al., 2022[16]	Turkey	Retrospective study	211	Endometrial cancer	Positive vs negative
Park et al., 2019[17]	South Korea	Retrospective study	96	EEC	Positive vs negative
Rau et al., 2021[47]	Switzerland	Retrospective study	255	Endometrial cancer	Positive vs negative
Shi et al., 2022[40]	China	Retrospective study	398	EAC	High vs low
Stögbauer et al., 2023a[32]	Germany	Retrospective study	228	Endometrial adenocarcinomas	Positive vs negative
Stögbauer et al., 2023b[32]	Germany	Retrospective study	228	Endometrial adenocarcinomas	Positive vs negative

SCC, Squamous Cell Carcinoma; ESCC, Early-Stage Cervical Cancer; EEC, Endometrial Endometrioid Carcinoma; EAC, Endocervical Adenocarcinoma

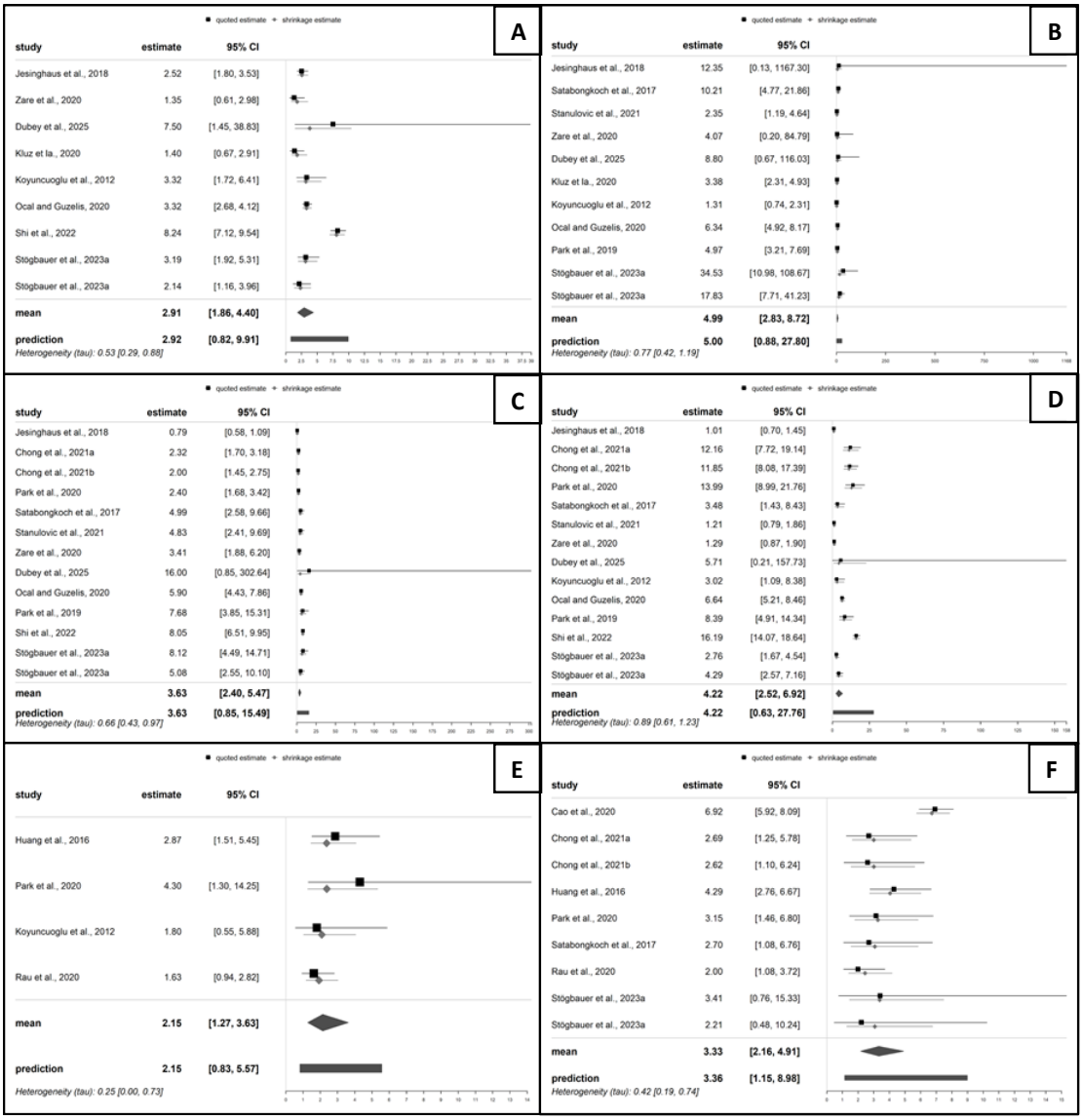

Figure 3. Forest Plot. A) Stage, B) Grade, C) Nodal involvement, D) Lymphovascular invasion (LVI), E) Overall Survival (OS), F) Disease Free Survival (DFS)

three times more likely to be found in patients with advanced cancer compared to early stages (PI OR=2.92; 95%CrI: 0.82-9.91). Furthermore, the PI shows that if similar studies are conducted in the future, the HR value can be between 1.05 and 3.10, depending on the characteristics of the population and the study method (Figure 3A). Subgroup analysis was performed in the analysis of advanced stages compared to early stages, and showed that TB was more likely to be found in the endometrial cancer population (OR=3.85; 95%CrI: 2.06-6.07) than in cervical cancer (OR=2.49; 95%CrI: 0.96-5.44) (Figure 4A). However, it should also be noted that this subgroup analysis has a high CrI range.

Tumor budding (TB) incidence was also markedly higher in poorly differentiated tumors (grade II or III), being five times more likely than in well-differentiated (grade I) tumors (OR=4.99; 95%CrI: 2.83-8.72; τ^2=0.77). Meanwhile, the results of the PI analysis show a higher OR value of 5.00 (95%CrI: 0.80-27.80) (Figure 3B). Meanwhile, subgroup analysis of high and low grades showed that the incidence of TB was still comparable in both endometrial and cervical cancer, with OR=5.62; 95%CrI: 2.60-10.48 and OR=5.83; 95%CrI: 1.91-13.83, respectively (Figure 4B). Similarly, TB was more frequently observed in the population of patients with metastases with nodal involvement (OR=3.63; 95%CrI: 2.40-5.47; τ^2=0.66) (Figure 3C) as well as the population of patients with LVI (OR=4.22; 95%CrI: 2.52-6.92; τ^2=0.89) (Figure 3D). Both showed equivalent PI results, confirming that future studies are expected to have similar values, but actual effects may vary significantly. The PI OR of nodal involvement and LVI are 3.63 (95%CrI: 0.85-15.49) and 4.22 (95%CrI: 0.63-27.76), respectively. Although for some parameters, the PI OR value has a higher value than the posterior mean effect size, it should be noted that CrI does not show any statistically significant difference, so further evaluation is needed. Furthermore, subgroup analysis based on the presence or absence of nodal involvement, the incidence of TB in endometrial cancer was significantly higher (OR=6.95; 95%CrI: 4.13-10.78) than in cervical cancer (OR=2.43; 95%CrI: 1.59-3.72) (Figure 4C). Similarly, in the LVI subgroup analysis,

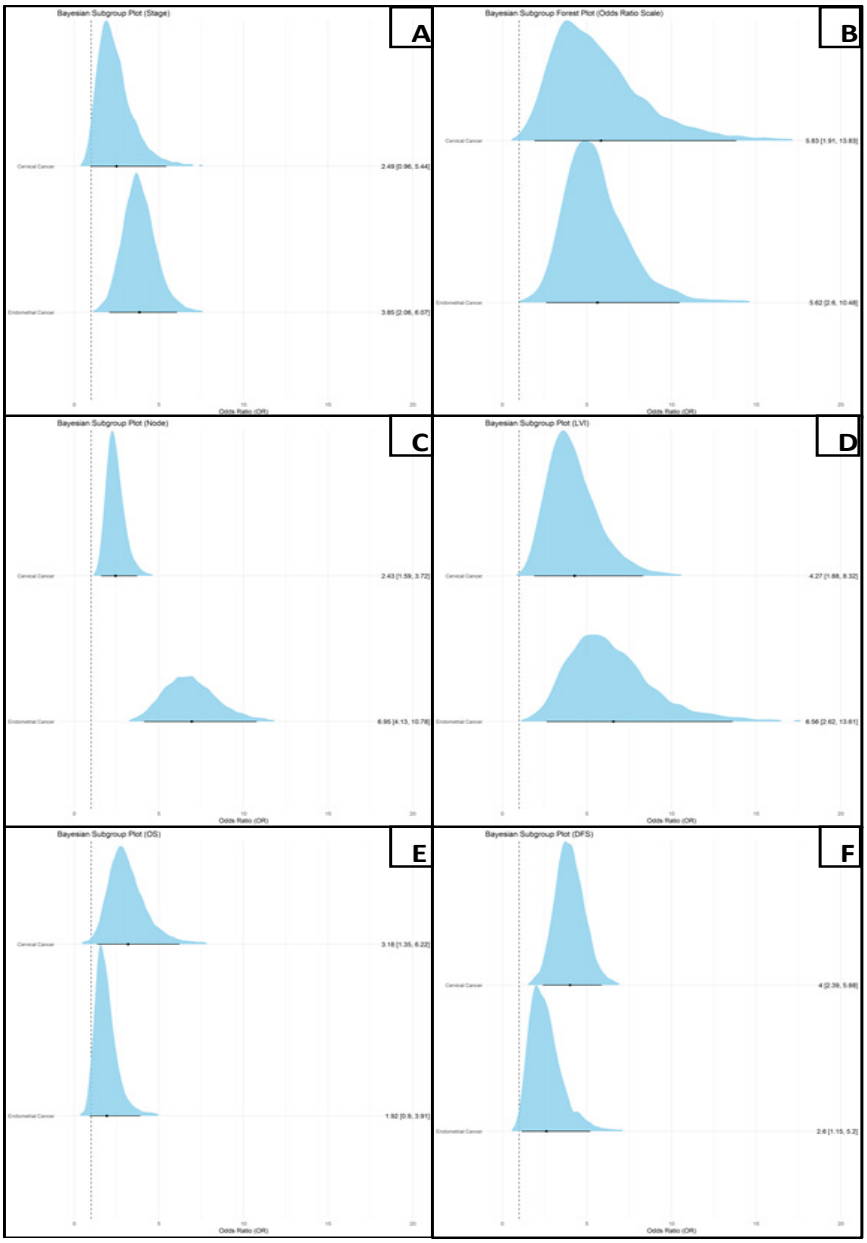

Figure 4. Subgroup Analysis. A) Stage, B) Grade, C) Nodal involvement, D) Lymphovascular invasion (LVI), E) Overall Survival (OS), F) Disease Free Survival (DFS)

endometrial cancer also showed a higher incidence of TB with OR=6.56; 95% CrI: 2.62-13.61 (Figure 4D).

In addition, TB was identified as a negative prognostic marker for OS, reinforcing its potential as a dual-purpose biomarker for both pathological stratification and long-term outcome prediction in cervical and endometrial cancers. Specifically, patients who did not achieve OS exhibited a twofold higher incidence of TB compared to those who survived (HR=2.15; 95%CrI: 1.27-3.63; τ^2=0.25) (Figure 3E). Subgroup analysis then showed that cervical cancer patients who did not achieve OS had a higher incidence of TB, HR=3.18; 95%CrI: 1.35-6.22, compared to endometrial cancer, HR=1.92; 95%CrI: 0.90-3.91 (Figure 4E).

Furthermore, the incidence of TB was 3.1 times higher among patients who experienced disease recurrence than in those who remained disease-free (HR 3.33; 95%CrI: 2.16-4.91; τ^2=0.42) (Figure 3F). Survival outcome analysis demonstrated similar PI, with HR for OS and DFS observed at 2.15 (95%CrI: 0.83-5.57) and 3.36 (95%CrI: 1.15-8.98), respectively. In this case, evaluation of DFS may also require further evaluation, considering that there is a slight difference in the PI HR value with the posterior effect size value, but CrI does not show a statistically significant difference. In cervical cancer, patients who did not achieve DFS had higher TB with HR=4.00; 95%CrI: 2.39-5.88, compared to endometrial cancer with HR=2.60; 95%CrI: 1.15-5.20 (Figure 4F).

Discussion

This Bayesian meta-analysis quantitatively affirms the significance of TB as a strong indicator of tumor aggressiveness in gynecological malignancies. The pooled effect results demonstrate a very strong correlation between TB and key histopathological parameters. The

most prominent finding is the association between TB and tumor differentiation. Tumor budding (TB) was found to be nearly five-fold more probable in poorly differentiated tumors (grade II/III) compared to grade I. This strong association is also evident in invasion parameters, where TB is significantly linked to the presence of LVI, nodal involvement, and advanced cancer stage.

Scientifically, these quantitative findings validate the biological basis of TB, histopathologically defined as small clusters of cells (<5 cells) detached from the main tumor mass [22]. This phenomenon reflects the activation of EMT, in which tumor cells lose cohesion, undergo morphological changes, and acquire migratory and invasive capabilities. Major signaling pathways, such as transforming growth factor beta (TGF-β), Wnt/β-catenin, and Notch, actively suppress cell adhesion molecules like E-cadherin while upregulating mesenchymal markers such as vimentin, thereby enhancing the invasive potential of tumor cells [23]. This mechanism explains why TB is closely linked to deeper local invasion, LVI, and regional lymph node metastasis [24].

Our findings do not stand alone; they corroborate and expand upon previous evidence. Our prognostic pooled effect (OS HR=2.15; DFS HR=3.33) closely aligns with the previous meta-analysis by Ailia et al. (n=1652 gynecological malignancies), which reported an OS HR of 2.40 and a DFS HR of 3.32 [18]. This cross-tumor consistency is validated by large-scale studies outside of gynecology. Specifically, Zlobec et al., in a major analysis of 959 colorectal cancer cases using the standardized ITBCC system, definitively demonstrated an association ($p<0.01$) between budding (BD1 vs. BD0) and nearly all parameters of aggressiveness, including tumor grade, pT, TNM stage, lymphatic, vascular, and perineural invasion [25]. Similarly, Rueda-Lara et al. (n=390 colorectal cancer patients) not only found a correlation with poor differentiation but also identified HGTB as an independent predictor of recurrence (HR 2.39), outperforming traditional factors like T4/N2 status [26]. Further support is reported by Barman et al. (n=53 head/neck carcinoma), who showed an HGTB correlation with advanced T stage [27]. This finding is part of a broader, consistent trend observed across various other solid organ malignancies, where TB is similarly validated as a marker of poor prognosis and aggressive tumor behavior. This includes consistent reports in colorectal cancer (which forms the basis for ITBCC guidelines) [28], as well as in gastric cancer [29], hepatocellular carcinoma [30], and lung adenocarcinoma [31], reinforcing TB's role as a fundamental biological marker of aggressiveness.

The subgroup analysis in our study provides crucial new insights, revealing distinct dynamics between endometrial and cervical cancer. Regarding clinicopathological features, TB demonstrated a consistently stronger association in endometrial cancer. This was particularly evident for lymph node involvement (NI OR=6.95 vs. 2.43 in cervical) and LVI (OR=6.56). These findings indicate that TB may be a more sensitive indicator of local invasion and lymphatic metastasis in endometrial cancer. However, this pattern reverses dramatically when evaluating prognosis. The presence of TB predicts a significantly worse outcome in cervical cancer. Its impact on OS was nearly twice as strong in cervical cancer (HR=3.18) compared to endometrial cancer (HR=1.92). This disparity was even more pronounced for DFS, where TB in cervical cancer (HR=4.00) carried a far heavier prognostic weight than in endometrial cancer (HR=2.60).

Despite the significant pooled effects, interpretation must be cautious given the substantial heterogeneity observed between studies, particularly for LVI ($\tau 2=0.89$) and grade ($\tau 2=0.77$). This heterogeneity is reflected in the extremely wide PI (e.g., LVI OR=4.22; 95%CrI: 0.63-27.76), indicating that the true effect in other populations may vary considerably. The primary limitations and sources of this heterogeneity stem from the methodologies of the included studies. Critically, the majority of studies did not explicitly report the use of IHC (e.g., D2-40/CD31) to confirm LVI or micro-metastasis detection techniques for nodal involvement [16, 17, 32–40]. Evaluations likely based solely on standard H&E carry a high risk of under-detection (false-negatives), contributing to the extreme variability observed in the PI. Furthermore, inconsistencies in TB assessment and clinical confounding factors, such as histological subtypes or neoadjuvant therapy, also contributed [34, 35, 37, 41]. Therefore, future research necessitates strict standardization using ITBCC criteria for TB assessment and mandating the use of IHC for LVI/nodal involvement confirmation to reduce heterogeneity.

The follow-up duration among the included studies ranged from approximately 1 to 127 months. However, these follow-up times could not be compared quantitatively due to different studies using distinct reporting measures (mean or median) and variable observation lengths. Most cohorts had intermediate follow-up durations of about 37–60 months (median or mean), meaning that the pooled survival estimates primarily reflect mid-term outcomes. Although these follow-up periods captured most early and intermediate recurrences, they do not fully represent late events, as approximately 75% of endometrial cancer relapses occur within the first three years after treatment, with a subset of patients experiencing late recurrences thereafter [42]. Therefore, there is a need for future studies with standardized and extended follow-up to clarify the sustained impact of TB in gynecological malignancy.

The analysis demonstrated that TB is significantly associated with poor OS in gynecological malignancies, with a pooled HR of 2.15 (95% CrI: 1.27–3.63). This suggested that patients with TB had more than twice the risk of mortality compared to those without TB. However, the prediction interval (PI HR = 2.15; 95% CrI: 0.83–5.57) indicated that the effect could be inconsistent in future studies, suggesting a non-significant association between TB and OS. The moderate heterogeneity ($I2 = 0.25$) supported the robustness of this finding. Thereby, clinical settings should consider this variability. Previous meta-analyses have shown promising prognostic cancers of TB in many types of malignancies. TB positivity was found to be associated with increased risk of mortality in colorectal cancer [43], breast cancer [44], esophageal carcinoma [45], and many other types of cancers. Huang et al. reported high-grade TB as a prognostic factor for

overall survival in early-stage squamous cell carcinoma of the cervix [46]. Additionally, Park et al. reported a significant independent prognostic factor even after adjusting for other clinical-pathological variables [17]. Rau et al. reported that more advanced tumor stage, high-grade tumor, and nodal involvement were associated with worse OS [47]. However, no significant association was found between OS with LVI and venous invasion. Koyuncuoglu et al. linked TB with adverse staging characteristics [41].

The analysis revealed that TB was significantly associated with DFS in gynecological malignancies. This indicates that patients with high TB were more than three times as likely to experience recurrence compared to those with low or no TB. The included studies involved patients with cervical SCC, cervical cancer, ESCC, endometrial cancer, and endometrial adenocarcinoma. Furthermore, the pooled PI HR of 3.36 (95%CrI: 1.15-8.98) indicates that although the effect size may vary across future studies, the association consistently supports tumor budding as a predictor of recurrence. However, moderate heterogeneity was observed ($\tau^2 = 0.42$) due to variability of stage tumor, cancer type, and sample size across studies. These findings are consistent with the meta-analysis by Ailia et al. demonstrated that HGTB was significantly associated with poor DFS (HR: 3.32, 95% CI: 2.46–4.48, $p<0.00001$), focusing specifically on cervical and endometrial carcinomas [18].

Subgroup analysis revealed distinct prognostic trends between cervical and endometrial cancers. In cervical cancer, TB demonstrated a stronger adverse association with survival, indicating a substantially higher risk of recurrence and mortality among TB-positive patients. This pronounced effect reflects TB's close association with histopathological aggressiveness, characterized by deeper stromal invasion, lymph node involvement, and reduced cellular cohesion at the invasive front, rather than tumor stage alone [33, 34, 46]. In endometrial carcinoma, the pooled effect was lower, suggesting that the prognostic value of TB varies with molecular and hormonal profiles. Stronger associations have been observed in microsatellite instability high and copy number low subtypes, where TB correlates with E-cadherin loss, β-catenin activation, and ER/PR negativity, whereas POLE-mutated or ER/PR-positive tumors generally show better differentiation and lower recurrence rates [17, 40, 47]. Overall, TB serves as a potent recurrence predictor in cervical cancer but a context-dependent biomarker in endometrial cancer, influenced by molecular subtype and hormonal microenvironment.

The correlation between TB and poor DFS is closely linked to EMT activity. Epithelial-to-mesenchymal transition (EMT) promotes the loss of epithelial cell adhesion and enhances tumor cell motility, facilitating early tumor dissemination [48]. In gynecologic malignancies, HGTB is frequently associated with reduced E-cadherin expression and abnormal activity of β-catenin signaling, which disrupts the cohesive epithelial structure [49, 50]. This promotes tumor cell invasion, increasing the likelihood of metastasis and ultimately contributing to poorer DFS outcomes. Another point of view that can be explained in endometrial carcinoma is that the loss of ER and PR expression contributes to a poorer prognosis. The reduction of ER and PR correlates with a decreased therapeutic response to hormonal agents, such as medroxyprogesterone acetate. Consequently, the absence of ER and PR reflects a more aggressive and treatment-resistant tumor phenotype, which negatively affects DFS [51]. In cervical cancer, the TB-related immune microenvironment can influence the aggressive behavior of cancer. One of its components is the infiltration of FOXP3-positive lymphocytes, a subset of immune cells known as regulatory T cells (Tregs). These cells suppress the host's immune response against cancer cells, rendering the body's defense mechanisms less effective. This condition provides tumor cells with an advantage to survive, extend their invasion into surrounding tissues, and potentially enhance their metastatic capacity. In addition, HGTB is also associated with increased angiogenesis, as demonstrated in endometrial cancer [51, 52]. This process supports the proliferating tumor cells and accelerates the dissemination of cancer cells, further worsening the patient's prognosis. This indicates that the TB level may serve as a predictive indicator of patient response to therapies targeting angiogenesis.

In both endometrial and cervical cancer subgroup analyses, TB consistently demonstrated its potential as a prognostic biomarker. Overall, TB was more frequently observed in aggressive endometrial cancers, regardless of stage, grade, nodal involvement, or LVI. In contrast, cervical cancer cases tended to show pooled effects crossing the reference line to the left, particularly for stage and grade variables, indicating a weaker and less consistent association between TB and these parameters. In contrast, both cancer types showed pooled effects that crossed the reference line in the OS analysis, while in the DFS analysis, this pattern appeared only in the endometrial cancer subgroup. This suggests that TB may not serve as a strong predictor of overall survival but could independently indicate a higher risk of recurrence in endometrial cancer, though not in cervical cancer. However, the smaller number of studies and patients included in the cervical cancer subgroup likely limited the statistical power of these findings. A lower pooled effect was also observed in variable analyses with fewer contributing studies. Conversely, the DFS analysis of cervical cancer involved more studies (6 studies) than that of endometrial cancer or the OS analysis, suggesting that heterogeneity and case distribution could also influence the pooled effect estimates.

Furthermore, per-variable analysis still shows that TB has a superior pooled effect as a biomarker, although the results fluctuate. This varying value may be due to differences in TB assessment methods, either positive vs negative or high vs low TB. Studies using lower TB cutoffs (e.g., ≥10 TB in Dubey et al., ≥3 TB in Stögbauer et al., and ≥5 TB in Park et al.) generally demonstrated stronger associations [34, 38, 40]. However, this pattern is not universal; for instance, the study by Kluz et al., despite using a similarly low cutoff (≥5 TB), showed a weaker effect, likely due to its inclusion of non-cancerous hyperplasia cases and a smaller case population [52].

Overall, the robustness of the TB association appeared to depend not only on sample size but also on the balance between case and control groups. Studies with more balanced designs, such as those by Shi et al. and Park et al., tended to yield more stable results [34, 39]. In contrast, small or highly imbalanced studies showed less reliable outcomes, while extremely disproportionate samples, as in Jesinghaus et al., produced strong but imprecise effects [32].

The included studies also covered various gynecologic malignancy subtypes, such as squamous cervical carcinoma, cervical adenocarcinoma, and endometrial carcinoma, which differ in tumor biology and invasion patterns that may influence TB intensity. Methodological variation also contributed to the observed heterogeneity. Some studies, like those by Jesinghaus et al. and Shi et al., combined TB with cell nest size into a composite grading system [32, 39], whereas others, such as Chong et al. [33], quantified TB per high-power field without standardized cutoffs, leading to inconsistent classification between high and low-grade TB. Additionally, most studies did not mention the use of IHC for detecting LVI or nodal metastasis, instead relying on conventional H&E staining. This was evident in studies by Jesinghaus et al. [32], Chong et al. [33], Park et al. [17], Satabongkoch et al. [35], Stanulović et al. [36], Zare et al. [37], Dubey et al. [38], Ocal & Guzelis [16], Park JY et al. [34], Shi et al. [39], and Stögbauer et al. [40], none of which reported using markers like D2-40 or CD31, or techniques such as sentinel node mapping or cytokeratin IHC. Such methodological limitations increase the risk of underdetection of LVI and microscopic nodal involvement, thereby introducing potential bias into the reported associations.

While both cervical and endometrial carcinomas demonstrate that TB is closely associated with aggressive disease, they differ fundamentally in how tumor and stroma interactions and EMT dynamics contribute to invasion and progression. In cervical carcinoma, particularly invasive squamous cell types, a pronounced desmoplastic reaction, characterized by dense collagen deposition and activation of carcinoma-associated fibroblasts (CAFs), is almost universal and correlates strongly with deep stromal invasion, LVI, nodal metastasis, and parametrial extension [53]. Tumor cells within this environment can reprogram resident fibroblasts into CAFs that secrete matrix metalloproteinases (MMPs) and pro-inflammatory cytokines, facilitating matrix remodeling, angiogenesis, and immune evasion [54]. Consequently, cervical cancers with prominent desmoplasia and TB constitute a biologically aggressive phenotype in which stromal-tumor crosstalk actively drives progression. In contrast, endometrial carcinoma, particularly endometrioid adenocarcinoma, arises in a hormonally responsive uterine microenvironment where desmoplasia is less pronounced and the tumor–stroma ratio (TSR) inversely correlates with prognosis [55]. These mechanistic distinctions align with our subgroup findings, where TB was more consistently associated with advanced stage, grade, and recurrence in endometrial carcinoma.

Another interesting aspect to discuss in comparing the progression of endometrial and cervical cancer based on the findings of this study is the involvement of variance in stromal tissue characteristics and their effect on cancer progression. Essentially, the stromal tissue of the endometrium and cervix has fundamental differences that can differentiate how the two work molecularly, potentially influencing the progression of both cancers. Endometrial cancer generally has a higher tumor-stroma ratio (TSR) than cervical cancer, or in other words, stromal-poor, and is associated with a worse prognosis and is strongly influenced by the hormonal dynamics of estrogen and progesterone [55, 56]. This finding is interesting because in most cases of solid tumors, a higher TSR value with stromal-poor is associated with a better prognosis, indicating the possibility of a unique interaction between tumor cells and stromal tissue in the uterus. On the other hand, cervical cancer with a lower TSR (stromal-rich) is associated with a worse prognosis and has a mechanism that tends to be influenced by factors other than hormones, namely related to the tendency to be involved in human papillomavirus (HPV) infection [57, 58]. This indicates a fundamental difference in how cancer cells in endometrial and cervical cancer interact with their stromal tissue to support disease progression.

Furthermore, one implication of the differences in histological status between endometrial and cervical cancers in terms of TSR is how TB testing is performed. In endometrial cancers with a tendency toward stromal-poor, this makes it difficult to evaluate TB findings using TB grade categorization. This is supported by studies included in this review, namely those by Kluz et al. [52], Ocal et al. [16], Park et al. [17], Rau et al. [47], and Stögbauer et al. [40], which used the TB-positive vs.TB-negative categorization rather than HBTG vs. LGTB as is done in studies with cervical cancer. However, several studies on endometrial cancer, including those reported by Dubey et al.[38], Koyuncuoglu et al. [41], and Shi et al. [39], have instead reported the classification of TB into HGTB and LGTB, which raises concerns about bias due to different TB evaluation and reporting methods between studies in endometrial cancer evaluation, although subgroup analysis in the endometrial cancer population shows relatively more consistent results compared to cervical cancer studies. This is an important emphasis in determining the evaluation standards of TB in endometrial cancer, considering the tumor biology is different from other solid cancers, for example, in cervical cancer.

This meta-analysis's main strengths lie in its comprehensive statistical approach using a Bayesian hierarchical model, allowing for more conservative and relevant estimates of inter-study uncertainty. It also utilizes MCMC to ensure convergence of results. Other strengths include its extensive literature coverage across countries and gynecological cancer types (cervical and endometrial), and its systematic risk of bias assessment using ROBINS-I, which revealed no studies with a high risk of bias. However, the study also has several important limitations, including significant inter-study heterogeneity in TB assessment methods, variations in cancer type and histopathology, and inconsistencies in the use of immunohistochemistry to detect LVI and microscopic metastases, potentially leading to underdetection.

Furthermore, the wide range of prediction intervals for some parameters indicates uncertainty about the true effect in the broader population, necessitating further validation using a more uniform and representative methodology. Although this study attempted to conduct a comprehensive analysis of gynecological malignancies involving cervical and endometrial cancer patients followed by subgroup analysis, differences in tumor biology and histology may lead to reporting bias and require further evaluation.

This study found that TB is a significant and consistent biomarker associated with aggressive clinicopathological characteristics and poor prognosis in gynecologic cancers, including advanced stage, poor differentiation, lymph node involvement, lymphovascular invasion, and decreased OS and DFS. Therefore, TB has potential as an additional tool in risk stratification and prognosis determination for patients with cervical and endometrial cancer. Prospective studies using standardized TB assessment methods, including IHC, are needed to improve the accuracy and consistency of results. In addition, standardization is needed to determine how to interpret TB, either by using the HGTB vs LGTB or positive vs negative categories based on the biological and histological characteristics of each tumor to avoid reporting errors. Furthermore, further research should explore the integration of TB into routine pathological assessment systems to support more targeted clinical decision-making in gynecological malignancy.

Author Contribution Statement

IGWWW and NWA: Conceptualization, methodology, investigation, writing - original draft, writing - review & editing, supervision, and project administration. CTM: formal analysis. IGKAS, NPKM, PMWSP, KMKT, AMTS, FPSW, and SK: Writing - original draft, and writing - review & editing. IGSW: writing - review & editing, supervision.

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Approval

This study has been registered in PROSPERO with the registration ID: CRD420251118223

Data Availability

The data supporting the findings of this study are available in the supplementary file and upon request from the corresponding author.

Study Registration

This study has been registered in PROSPERO with the registration ID: CRD420251118223.

Conflict of Interest

None.

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