Association of Myometrial Invasion With Lymphovascular Space Invasion, Lymph Node Metastasis, Recurrence, and Overall Survival in Endometrial Cancer: A Meta-Analysis of 79 Studies With 68,870 Patients

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Background: Myometrial invasion has been demonstrated to correlate to clinicopathological characteristics and prognosis in endometrial cancer. However, not all the studies have the consistent results and no meta-analysis has investigated the association of myometrial invasion with lymphovascular space invasion (LVSI), lymph node metastasis (LNM), recurrence, and overall survival (OS). Therefore, a meta-analysis was performed to evaluate the relationship between myometrial invasion and clinicopathological characteristics or overall survival in endometrial cancer.

Materials and Methods: A search of Pubmed, Embase, and Web of Science was carried out to collect relevant studies from their inception until June 30, 2021. The quality of each included study was evaluated using Newcastle–Ottawa scale (NOS) scale. Review Manager version 5.4 was employed to conduct the meta-analysis.

Results: A total of 79 articles with 68,870 endometrial cancer patients were eligible including 9 articles for LVSI, 29 articles for LNM, 8 for recurrence, and 37 for OS in this meta-analysis. Myometrial invasion was associated with LVSI (RR 3.07; 95% CI 2.17–4.35; p < 0.00001), lymph node metastasis (LNM) (RR 4.45; 95% CI 3.29–6.01; p < 0.00001), and recurrence (RR 2.06; 95% CI 1.58–2.69; p < 0.00001). Deep myometrial invasion was also significantly related with poor OS via meta-synthesis of HRs in both univariate survival (HR 3.36, 95% CI 2.35–4.79, p < 0.00001) and multivariate survival (HR 2.00, 95% CI 1.59–2.53, p < 0.00001). Funnel plot suggested that there was no significant publication bias in this study.

Conclusion: Deep myometrial invasion correlated to positive LVSI, positive LNM, cancer recurrence, and poor OS for endometrial cancer patients, indicating that myometrial invasion was a useful evaluation criterion to associate with clinical outcomes and prognosis of endometrial cancer since depth of myometrial invasion can be assessed.
INTRODUCTION

Endometrial cancer is the most prevalent gynecological malignancy in developed countries (1) and the sixth most common cancer in women with continuously increasing incidence and associated mortality (2). Myometrial invasion, lymphovascular space invasion (LVSI), lymph node metastasis (LNM), and recurrence are the important molecular events and clinical behaviors for endometrial cancer. Among them, myometrial invasion is the quietly early action of cancer cells. In addition, three-dimensional ultrasound and magnetic resonance imaging are applied for preoperative assessment of the depth of myometrial invasion (3), and frozen sections are used for intraoperative estimation (4). It is meaningful to classify patients with initial stages as low-risk or high-risk patients for surgical planning when the above diagnostic methods are becoming more accurate with a better specificity and sensitivity. Therefore, it deserves more attention on myometrial invasion in endometrial cancer.

Myometrial invasion is defined as the invasion of endometrial cancer cells into myometrium. The depth of invasion is critical to the evaluation of surgical-pathological staging. According to the International Federation of Gynecology and Obstetrics (FIGO) staging system, stage IA includes those tumors with myometrial invasion of less than 50% or without myometrial invasion, and stage IB refers to more than 50% of invasion into myometrium. Although the underlying mechanism of myometrial invasion is still unclear, it is one of critical considerations for the surgery types and therapeutic methods. This is because accumulated evidences show that myometrial invasion is related to LVSI, LNM, recurrence, and OS of endometrial cancer in different reports. However, there are some different sounds, and not all the studies share the similar results. Specifically, there were more patients with positive LVSI in superficial myometrial invasion group when compared to deep myometrial invasion group (5); there was no statistically significant difference for positive LNM between superficial and deep myometrial invasion groups (6). In addition, there was no statistically significant difference for recurrence between superficial and deep myometrial invasion groups (7, 8). Therefore, a further study is valuable.

Currently, it is still a mystery whether the above non-uniform results change our previous conclusions and consensus. Until now, there is no aggregated estimate about the relationship between myometrial invasion and LVSI, LNM, recurrence, and OS. This meta-analysis is aiming to further elucidate whether myometrial invasion correlates to LVSI, LNM, recurrence, and OS based on the data available so far. The meta-analysis of multiple clinical studies will provide comprehensive descriptions about myometrial invasion not only from the past to the present but also from clinicopathological characteristics to prognostic value. We hope that the study also could provide us more certainty and confidence in mention and further investigation of myometrial invasion of endometrial cancer.

MATERIALS AND METHODS

Literature Search Strategy

Literature was searched from Pubmed, Embase, and Web of Science from their inception until June 2021. The study published only in English was further considered. The main search terms were formulated as follows: “endometrial cancer”, “endometrial carcinoma”, “endometrial tumor”, “uterine carcinoma”, “uterine cancer”, “endometrial neoplasms”, “myometrial invasion”, “myometrial infiltration”, “clinicopathological factors”, “lymphovascular space invasion”, “lymph node metastasis”, “prognostic marker”, “prognosis”, “overall survival”, “recurrence”, and “relapse”.

Inclusion and Exclusion Criteria

The study had to meet the following inclusion criteria: (1) the patients only had endometrial cancer; (2) enough data about clinicopathological factors (myometrial invasion, LVSI, LNM, or recurrence) and/or related information to extract hazard ratio (HR) and standard error (SE) of lnHR for OS; (3) article was published in English. The exclusion criteria included the following terms: (1) reviews, meta-analysis, animal experiments, and case reports; (2) republished articles; (3) incomplete and unpublished studies; (4) the study did not meet the design. Two reviewers independently reviewed the literatures according to the predefined strategy and criteria. The articles were screened with two researchers independently (JW and PX). The disagreements were further settled through discussion and resolved by a third investigator when necessary.

Data Extraction and Quality Assessment

Two investigators (JW and PX) were assigned to assess the eligibility of all studies. Moreover, a third investigator (XZ) resolved the disagreements when necessary. The following information from each study was extracted: first author, publication year, the region of the study population, the number of participants, design type. For LVSI, LNM and recurrence, and the numbers in case and control groups were extracted respectively. For OS, HR estimate with 95% confidence interval (CI) for OS was extracted. The quality of included studies was assessed using Newcastle–Ottawa scale (NOS) scale, and the score of the quality ranged from 0 to 9.
Data Analysis
Version 5.4 software of Review Manager was applied for this meta-analysis. Risk ratio (RR) with 95% CI was pooled to investigate the association between myometrial invasion and clinicopathological features (LVSI, LNM, and recurrence). HR with 95% CI was combined to study the effect of myometrial invasion on OS. The HR was extracted directly when the HR with 95% CI was reported. SE was calculated using the equation: \( SE_{lnHR} = (lnUpperCI - lnLowerCI)/3.92 \) (9). If the article did not provide direct HR while Kaplan–Meier survival curve was shown, Engauge Digitizer software was performed to acquire HR with SE (10). A random-effects model was conducted if significant heterogeneity (\( p \leq 0.1, I^2 > 50\% \)) was shown. Publication bias was evaluated by the shape of funnel plot. Statistically significant difference was pointed out when a \( p \) value was less than 0.05.

RESULTS
Study Search Results
The predefined search strategy identified 1,385 records. After screening of titles and abstracts, 1,058 records were excluded including 35 non-English papers, 18 duplicated records, 208 review/meta/letter/abstract, 19 animal studies, and 778 irrelevant literature. Full text of 327 articles was assessed, and 248 records were excluded including 8 studies with the same included literature. Full text of 327 articles was assessed, and 248 records were excluded including 8 studies with the same included literature. Eight studies including 1,649 patients were included. During the analysis, we found that there was no significant between-study heterogeneity (\( I^2 = 16\%; \ p = 0.30 \)), and fixed-effects model was used. Myometrial invasion was significantly associated with the recurrence of endometrial cancer since the risk ratio was 2.06 (CI 95% 1.58–2.69, \( p < 0.00001 \)) (Figure 3). Therefore, deep myometrial invasion is associated with higher risk of endometrial cancer recurrence.

Myometrial Invasion Is Associated With OS in Endometrial Cancer
Thirty-seven studies including 9,416 patients examined the association between myometrial invasion and OS in endometrial cancer. The pooled HRs of all-cause mortality with >1/2 myometrial invasion compared to <1/2 myometrial invasion were evaluated using random-effects model, and the results are presented in Figure 4. Pooled HRs of OS for univariate and multivariate analyses (HR 3.36, 95% CI 2.35–4.79, \( p < 0.00001 \), and HR 2.00, 95% CI 1.59–2.53, \( p < 0.00001 \), respectively) showed that the group with deep myometrial invasion was related with a higher risk of OS than the group with less than 1/2 myometrial invasion. Therefore, deep myometrial invasion is associated with poor survival in endometrial cancer.

Publication Bias of Included Studies
Funnel plot was applied for the assessment of publication bias in the literature, and tests for funnel plot asymmetry were applied only when there were at least 10 studies included in a meta-analysis. The shape of the funnel plot for the included 29 studies on the association between myometrial invasion and LNM was not significantly asymmetrical, indicating that there was no significant publication bias (Figure 5A). The results also show that no obvious publication bias was indicated in all included studies investigating myometrial invasion on OS in both univariate and multivariate analyses (Figures 5B, C).

DISCUSSION
Although there are many studies showing that myometrial invasion is definitely correlated to LVSI, LNM, recurrence, and OS, and we have reached an agreement that myometrial invasion is absolutely critical in the development of endometrial cancer, there are some inequable results, which makes us more or less feel lack confidence about that. Therefore, we searched all the studies about the relationship between myometrial invasion and clinicopathological characteristics (LVSI, LNM, and recurrence) or OS and conducted this meta-analysis.
| Author             | Year | Study period | Country | N  | Design          | Outcomes          | Quality |
|--------------------|------|--------------|---------|----|-----------------|-------------------|---------|
| Wang et al.        | 2014 | 2013-2000    | China   | 263| R Univar-HR, Multi-HR | LNM, Multi-HR      | 7       |
| Fejfi et al.       | 2019 | 2009-2019    | Turkey  | 92 | R Univar-HR     |                   | 6       |
| Cheng et al.       | 2019 | 2011-2012    | China   | 113| R Multi-HR      |                   | 7       |
| Cuyan et al.       | 2019 | 2001-2016    | Turkey  | 172| R Multi-HR      |                   | 7       |
| Erkaya et al.      | 2017 | 2007-2015    | Turkey  | 500| R Multi-HR      |                   | 6       |
| Ghezzi et al.      | 2010 | 2000-2009    | Turkey  | 336| R Univar-HR, Multi-HR | LNM, Multi-HR      | 7       |
| Güneş et al.       | 2019 | 2007-2017    | Turkey  | 762| R LNM           |                   | 6       |
| Hasenbohl et al.   | 2005 | 1997-2002    | Japan   | 109| R Multi-HR      |                   | 7       |
| Hiura et al.       | 2010 | 1987-2002    | Japan   | 284| R Multi-HR      |                   | 6       |
| Ino et al.         | 2006 | 1992-2001    | Japan   | 90 | R Multi-HR      |                   | 6       |
| Jorge et al.       | 2016 | 2010-2012    | USA     | 25,907| R LVSi       |                   | 8       |
| Kang et al.        | 2014 | 2000-2006    | South Korea | 967| R LNM           |                   | 7       |
| Koskas et al.      | 2013 | 2002-2010    | France  | 305| R LVSi           |                   | 6       |
| Kwon et al.        | 2009 | 1996-2000    | Canada  | 314| R LNM           |                   | 7       |
| Kyo et al.         | 2006 | 1995-2002    | Japan   | 70 | R Multi-HR      |                   | 6       |
| Larson et al.      | 1996 | 1987-1995    | USA     | 125| R LNM           |                   | 6       |
| Lee et al.         | 2009 | 2002-2008    | South Korea | 834| R LNM           |                   | 8       |
| Lee et al.         | 2016 | 2000-2013    | South Korea | 172| R LNM           |                   | 7       |
| Li et al.          | 2018 | 2010-2013    | China   | 143| R Multi-HR      |                   | 7       |
| Li et al.          | 2019 | 2010-2016    | China   | 874| R LNM, Multi-HR     |                   | 6       |
| Li et al.          | 2019 | 2014-2019    | China   | 388| R LNM           |                   | 7       |
| Lin et al.         | 2019 | 2006-2013    | Taiwan  | 337| R Univar-HR, Multi-HR |                   | 6       |
| Lindahl et al.     | 1994 | 1980-1987    | Sweden  | 251| R Multi-HR      |                   | 6       |
| Machida et al.     | 2018 | 2008-2015    | USA     | 611| R LVSi           |                   | 6       |
| Mahdi et al.       | 2015 | 2005-2012    | USA     | 140| R LNM           |                   | 6       |
| Matsuo et al.      | 2015 | 2000-2013    | USA     | 703| R LVSi           |                   | 6       |
| Mhawech-Faucegilla et al. | 2012 | 2000-2010 | USA | 279| R Multi-HR |                    | 8       |
| Miyamoto et al.    | 2013 | 1996-2005    | Japan   | 84 | R Univar-HR, Multi-HR |                   | 6       |
| Nakamura et al.    | 2011 | 2007-2011    | Japan   | 106| P Multi-HR      |                   | 7       |
| Neal et al.        | 2016 | 2005-2012    | USA     | 205| R Univar-HR     |                   | 7       |
| Njelstad et al.    | 2015 | 2001-2011    | Norway  | 539| R LNM           |                   | 8       |
| Nomura et al.      | 2006 | 1975-2004    | Japan   | 841| R LNM           |                   | 7       |
| Ohno et al.        | 2005 | 1995-2002    | Japan   | 70 | P Multi-HR      |                   | 8       |
| Panggdl et al.     | 2010 | 1999-2007    | Thailand | 136| R LVSi, Rec     |                   | 7       |
| Patel et al.       | 2007 | 1989-2003    | Canada  | 107| R Univar-HR     |                   | 7       |
| Pifer et al.       | 2020 | 2017-2019    | USA     | 438| R LVSi           |                   | 8       |
| Sahin et al.       | 2019 | 2007-2016    | Turkey  | 185| R Rec           |                   | 8       |
| Sal et al.         | 2016 | 2000-2008    | Turkey  | 59 | R Multi-HR      |                   | 6       |
| San et al.         | 2018 | 2007-2016    | Turkey  | 280| R LNM           |                   | 7       |
| Schink et al.      | 1991 | 1979-1988    | USA     | 142| R Multi-HR      |                   | 7       |
| Scott et al.       | 2017 | 2003-2009    | Canada  | 849| R Multi-HR      |                   | 8       |
| Shen et al.        | 2020 | 2006-2013    | China   | 263| R Univar-HR, Multi-HR |                   | 7       |
| Siesto et al.      | 2020 | 2009-2015    | Italy   | 363| R Univar-HR, Multi-HR |                   | 6       |
| Sigurdsson et al.  | 1998 | 1964-1985    | Iceland | 203| R Multi-HR      |                   | 6       |
| Solmany et al.     | 2015 | 1995-2012    | Turkey  | 827| R LNM           |                   | 7       |
| Ståberg et al.     | 2019 | 2010-2017    | Sweden  | 969| P LNM, Multi-HR |                   | 8       |
| Steikema et al.    | 2017 | 1994-2014    | Netherlands | 88 | P Univar-HR |                   | 8       |

(Continued)
The presence of LVSI is significantly associated with pelvic and paraaortic lymph node metastasis, recurrence, and poor prognosis (86, 87). As for lymph node metastasis, it is one of the evaluation criteria for the surgical-pathological staging and therapeutic schedule and is an extremely important determinant of the outcome. We paid extra attention to recurrence because it is uniformly associated with poor survival. Compared to LVSI, LNM, and recurrence, myometrial invasion is a much earlier molecular event and could be the initial driving force for the further progress of cancer cells. In addition, the depth of myometrial invasion before surgery can be accessed. Therefore, we should not only dig deeper into the underlying molecular mechanism but also pay more attention to the relevant clinical study. Since there are many studies about the relationship between myometrial invasion and clinicopathological characteristics (LVSI, LNM, and recurrence) or OS while not all the reports are consistent, we thereby pooled all the eligible studies and performed this meta-analysis.

Seventy-nine studies with a total of 68,870 endometrial cancer patients were finally included for this meta-analysis. Among them, nine studies with a total of 28,904 endometrial cancer patients were for LVSI. The pooled result showed patients with deeper myometrial invasion of endometrial cancer into myometrium (>1/2) were more prone to LVSI. As for LNM, 29 studies including 31,262 endometrial cancer patients were eligible for analysis, and the results demonstrated that deeper myometrial invasion is associated with the tendency of LNM in endometrial cancer. Furthermore, myometrial invasion was significantly associated with the recurrence of endometrial cancer according to the meta-analysis of eight studies including 1,649 patients. Since LVSI, LNM, and recurrence are

**TABLE 1** | Continued

| Author Year | Study period | Country | N | Design | Outcomes | Quality* |
|-------------|--------------|---------|---|--------|----------|---------|
| Tanaka et al. (70) | 2013 | NR Japan | 354 | R | Multi-HR | 6 |
| Tang et al. (71) | 1998 | 1979–1996 Japan | 310 | R | LNM | 6 |
| Tasjkin et al. (72) | 2017 | 2011–2014 Turkey | 279 | R | LNM | 7 |
| Taskiran et al. (73) | 2006 | 1982–2002 Turkey | 461 | R | LNM | 8 |
| Todo et al. (74) | 2013 | 2000–2008 Korea | 261 | R | LNM | 6 |
| Tuomi et al. (75) | 2017 | 2007–2013 Finland | 929 | R | Rec | 7 |
| Urabe et al. (76) | 2014 | 1990–2010 Japan | 366 | R | Univar-HR, Multi-HR | 6 |
| Vargas et al. (77) | 2014 | 1988–2010 USA | 19329 | R | LNM | 8 |
| Wakayama et al. (78) | 2018 | 2006–2013 Japan | 189 | R | Multi-HR | 6 |
| Yabushita et al. (79) | 2001 | 1986–1995 Japan | 36 | R | Rec | 6 |
| Yamada et al. (80) | 2021 | 2014–2015 Japan | 67 | P | Univar-HR | 7 |
| Yokoyama et al. (81) | 1997 | 1988–1996 Japan | 60 | R | LNM | 6 |
| Zanfagnin et al. (82) | 2019 | 1999–2008 USA | 85 | R | LNM | 7 |
| Zhang et al. (83) | 2012 | 1989–2006 China | 621 | R | LNM | 7 |
| Zhao et al. (84) | 2015 | 2007–2008 China | 188 | R | Multi-HR | 7 |
| Zhao et al. (85) | 2019 | NR China | 89 | R | Univar-HR, Multi-HR | 6 |

R, Retrospectively study; P, prospectively study; LVSI, lymphovascular space invasion; LNM, lymph node metastasis; Univar-HR, HR in univariate analysis; Multi-HR, HR in multivariate analysis. *The quality was assessed using Newcastle–Ottawa scale (NOS) scale.
### FIGURE 2

Meta-analysis of the association between myometrial invasion and LNM in endometrial cancer.

| Study or Subgroup | Events | Total | M-H. Random. 95% CI | M-H. Fixed. 95% CI |
|-------------------|--------|-------|----------------------|---------------------|
| > 1/2             | < 1/2  |       |                      |                     |
| Akbayir 2012      | 149    | 317   | 3.8%                 | 3.43 [1.97, 5.97]   |
| Alltunpulluk 2014 | 52     | 9     | 1.5%                 | 17.25 [2.33, 127.70]|
| Aoyama 2019       | 64     | 133   | 3.3%                 | 5.34 [2.35, 12.14]  |
| Bendifallah 2015  | 124    | 76    | 4.0%                 | 2.79 [1.83, 4.26]   |
| Celinkaya 2014    | 97     | 150   | 2.6%                 | 9.79 [2.98, 32.21]  |
| Gunakan 2019      | 290    | 473   | 3.8%                 | 9.46 [5.58, 16.04]  |
| Kang 2014         | 304    | 653   | 4.3%                 | 1.31 [1.12, 1.53]   |
| Kwon 2009         | 99     | 215   | 3.7%                 | 4.18 [2.23, 7.81]   |
| Larson 1996       | 48     | 77    | 2.9%                 | 6.42 [2.28, 18.06]  |
| Lee 2009          | 241    | 593   | 4.0%                 | 6.32 [4.26, 9.37]   |
| Lee 2016          | 33     | 139   | 3.2%                 | 5.27 [2.25, 12.30]  |
| Li 2019           | 288    | 586   | 4.0%                 | 2.36 [1.56, 3.55]   |
| Li 2019 (2)       | 112    | 276   | 3.6%                 | 8.63 [4.42, 16.81]  |
| Mahdi 2015        | 65     | 149   | 3.3%                 | 3.27 [1.46, 7.32]   |
| Njalstad 2015     | 197    | 342   | 3.4%                 | 8.68 [4.15, 18.17]  |
| Nomura 2006       | 245    | 596   | 2.6%                 | 15.20 [5.35, 43.23] |
| Rychlik 2020      | 393    | 84    | 3.3%                 | 0.82 [0.37, 1.83]   |
| San 2018          | 191    | 49    | 4.0%                 | 1.49 [0.98, 2.26]   |
| Schink 1991       | 40     | 102   | 3.2%                 | 4.37 [1.65, 10.30]  |
| Solmaj 2015       | 325    | 502   | 3.8%                 | 5.41 [3.16, 9.26]   |
| Stalberg 2019     | 417    | 542   | 4.1%                 | 2.87 [2.00, 4.12]   |
| Tang 1998         | 119    | 191   | 2.9%                 | 14.45 [5.28, 39.55] |
| Taskiran 2006     | 179    | 282   | 4.0%                 | 7.23 [4.75, 11.02]  |
| Tagk 2017         | 27     | 150   | 2.9%                 | 7.91 [2.84, 22.01]  |
| Todo 2013         | 78     | 203   | 3.8%                 | 2.88 [1.64, 5.05]   |
| Vargas 2014       | 4967   | 14362 | 4.3%                 | 4.68 [4.15, 5.29]   |
| Yokoyama 1997     | 24     | 36    | 2.2%                 | 7.50 [1.80, 31.27]  |
| Zannagin 2019     | 53     | 32    | 4.1%                 | 1.07 [0.74, 1.56]   |
| Zhang 2012        | 103    | 518   | 3.2%                 | 12.21 [5.20, 28.70] |
| Total (95% CI)    | 9425   | 21837 | 100.0%               | 4.45 [3.29, 6.01]   |
| Total events      | 1823   | 984   |                      |                     |

Heterogeneity: Tau² = 0.54; Chi² = 346.17, df = 28 (P < 0.00001); I² = 92%
Test for overall effect: Z = 9.72 (P < 0.00001)

### FIGURE 3

Meta-analysis of the association between myometrial invasion and recurrence in patients with endometrial cancer.

| Study or Subgroup | Events | Total | M-H. Fixed. 95% CI | M-H. Fixed. 95% CI |
|-------------------|--------|-------|---------------------|---------------------|
| > 1/2             | < 1/2  |       |                      |                     |
| Ayhan 1994        | 85     | 9     | 10.4%               | 3.13 [1.38, 7.08]   |
| Chen 2001         | 16     | 37    | 1.9%                | 4.63 [0.94, 22.74]  |
| Panggidi 2010     | 66     | 60    | 8.4%                | 1.82 [0.66, 5.02]   |
| Pradhan 2012      | 12     | 44    | 7.6%                | 1.00 [0.33, 3.02]   |
| Sahin 2019        | 118    | 67    | 12.3%               | 1.23 [0.49, 3.09]   |
| Tuomi 2017        | 255    | 674   | 45.0%               | 2.44 [1.68, 3.52]   |
| Van der Putten 2015 | 59    | 22    | 11.7%               | 0.97 [0.39, 2.40]   |
| Yabushita 2001    | 15     | 21    | 2.7%                | 2.10 [0.40, 11.07]  |
| Total (95% CI)    | 626    | 1023  | 100.0%              | 2.06 [1.58, 2.69]   |
| Total events      | 112    | 89    |                      |                     |

Heterogeneity: Chi² = 8.34, df = 7 (P = 0.30); I² = 16%
Test for overall effect: Z = 5.34 (P < 0.00001)
### Univariate analysis

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio        | Hazard Ratio          |
|-------------------|------------------|-----|--------|---------------------|-----------------------|
| Abbink 2018       | 0.9439           | 0.3487 | 7.4%   | 2.57 [1.30, 5.09]   |                       |
| Akiyama-Abe 2013  | 2.2513           | 0.4916 | 5.8%   | 9.50 [3.62, 24.90]  |                       |
| Chen 2020         | -0.2231          | 0.4359 | 6.4%   | 0.80 [0.34, 1.88]   |                       |
| Ghezzi 2010       | 1.6487           | 0.3823 | 7.0%   | 5.20 [2.46, 11.00]  |                       |
| Ino 2006          | 1.4085           | 0.7076 | 4.0%   | 4.09 [1.02, 16.37]  |                       |
| Lin 2019          | 1.6312           | 0.4343 | 6.4%   | 5.11 [2.18, 11.97]  |                       |
| Miyamoto 2013     | 2.4738           | 0.7914 | 3.5%   | 11.87 [2.52, 55.98] |                       |
| Neal 2016         | 0.3646           | 0.4911 | 5.8%   | 1.44 [0.55, 3.77]   |                       |
| Patel 2007        | 0.4866           | 0.4793 | 6.0%   | 1.63 [0.64, 4.17]   |                       |
| Rychlik 2020      | -0.0513          | 0.412 | 6.7%   | 0.95 [0.42, 2.13]   |                       |
| Shen 2020         | 1.997            | 0.3648 | 7.0%   | 7.37 [3.47, 15.68]  |                       |
| Siest 2020        | 1.4351           | 0.3774 | 7.1%   | 4.20 [2.00, 8.80]   |                       |
| Stekema 2017      | 0.6313           | 0.3788 | 7.1%   | 1.83 [0.89, 3.95]   |                       |
| Urabe 2014        | 2.596            | 0.4196 | 6.6%   | 13.41 [5.89, 30.52] |                       |
| Yamada 2021       | 1.6586           | 0.8671 | 3.1%   | 5.25 [0.96, 28.73]  |                       |
| Zhao 2019         | 1.0519           | 0.0824 | 10.0%  | 2.86 [2.44, 3.36]   |                       |

**Total (95% CI):** 100.0% 3.36 [2.35, 4.79]

Heterogeneity: Tau² = 0.32; Chi² = 54.55, df = 15 (P < 0.00001); I² = 73%

Test for overall effect: Z = 6.69 (P < 0.00001)

### Multivariate analysis

| Study or Subgroup | log(Hazard Ratio) | SE  | Weight | Hazard Ratio        | Hazard Ratio          |
|-------------------|------------------|-----|--------|---------------------|-----------------------|
| Abbink 2018       | 0.01             | 0.3537 | 4.7%   | 1.01 [0.50, 2.02]   |                       |
| Abu-Zaed 2018     | -0.4797          | 0.5421 | 3.0%   | 0.62 [0.21, 1.79]   |                       |
| Akiyama-Abe 2013  | 0.8065           | 0.5515 | 3.0%   | 2.24 [0.76, 6.60]   |                       |
| Bonatz 1999       | 0.8196           | 0.4786 | 3.5%   | 2.27 [0.89, 5.80]   |                       |
| Cheng 2019        | 0.7174           | 0.4888 | 1.6%   | 2.05 [0.39, 10.82]  |                       |
| Cuylen 2018       | 1.3863           | 0.6278 | 2.5%   | 4.00 [1.17, 13.69]  |                       |
| Erkaya 2017       | 1.1694           | 0.4169 | 4.1%   | 3.22 [1.42, 7.29]   |                       |
| Ghezzi 2010       | 0.5306           | 0.4237 | 4.0%   | 1.70 [0.74, 3.90]   |                       |
| Hasengaowa 2005   | 2.3437           | 0.914  | 1.4%   | 10.42 [1.74, 62.50] |                       |
| Hiura 2010        | 0.6387           | 0.6629 | 2.3%   | 1.89 [0.52, 6.94]   |                       |
| Kyu 2006          | 0.157            | 0.6929 | 2.2%   | 1.17 [0.30, 4.55]   |                       |
| Li 2018           | -0.137           | 0.6692 | 2.3%   | 0.87 [0.23, 3.24]   |                       |
| Li 2019           | 0.9933           | 0.4403 | 3.8%   | 2.70 [1.14, 6.40]   |                       |
| Lin 2019          | 1.2149           | 0.6191 | 2.5%   | 3.37 [1.00, 11.34]  |                       |
| Lindah 1994       | 1.0647           | 0.3357 | 4.9%   | 2.90 [1.50, 5.60]   |                       |
| Mhawech-Faucelliga 2012 | 0.7227 | 0.3953 | 4.3% | 2.06 [0.95, 4.47] |                       |
| Miyamoto 2013     | 3.1482           | 1.5949 | 0.5%   | 23.29 [1.02, 530.67] |                       |
| Nakamura 2011     | -0.3813          | 0.4873 | 3.4%   | 0.68 [0.26, 1.77]   |                       |
| Ohno 2005         | 0.7174           | 0.9149 | 1.4%   | 2.05 [0.34, 12.31]  |                       |
| Sai 2016          | -0.8326          | 0.5979 | 1.2%   | 0.18 [0.02, 1.09]   |                       |
| Scott 2017        | -0.1744          | 0.2944 | 4.9%   | 0.84 [0.43, 1.64]   |                       |
| Shen 2020         | 0.6813           | 0.5095 | 3.3%   | 2.01 [0.74, 5.46]   |                       |
| Siest 2020        | 0.2624           | 0.4434 | 3.8%   | 1.30 [0.55, 3.10]   |                       |
| Sigurdsson 1998   | 1.7561           | 0.4164 | 4.1%   | 5.79 [2.56, 13.09]  |                       |
| Stalberg 2019     | 0.4447           | 0.2447 | 6.1%   | 1.56 [0.97, 2.52]   |                       |
| Tanaka 2013       | 1.3029           | 0.3726 | 4.5%   | 3.68 [1.77, 7.64]   |                       |
| Urabe 2014        | 1.1464           | 0.5005 | 3.3%   | 3.15 [1.18, 8.39]   |                       |
| Wakyamaya 2018    | 0.0206           | 0.7155 | 2.1%   | 1.02 [0.25, 4.15]   |                       |
| Zhao 2015         | 1.6569           | 0.4596 | 3.7%   | 5.24 [2.13, 12.91]  |                       |
| Zhao 2019         | 0.9062           | 0.1057 | 7.7%   | 2.47 [2.01, 3.04]   |                       |

**Total (95% CI):** 100.0% 2.00 [1.59, 2.53]

Heterogeneity: Tau² = 0.17; Chi² = 59.64, df = 29 (P = 0.0007); I² = 51%

Test for overall effect: Z = 5.86 (P < 0.00001)

**FIGURE 4** | Meta-analysis of the association between myometrial invasion and overall survival in endometrial cancer patients according to HR from univariate or multivariate survival analyses.
independent prognostic factors for endometrial cancer patients, myometrial invasion would also be a prognostic factor. As it turned out, the group with deep myometrial invasion was related with a greater risk of OS than the group with less than 1/2 myometrial invasion based on not only univariate survival analysis but also multivariate survival analysis. Therefore, the results indicate that myometrial invasion is associated with LVSI, LNM, recurrence, and OS with much more confidence. Combined with preoperative assessment of the depth of myometrial invasion, now we know more information in regard to LVSI, LNM, recurrence, and OS of these patients before surgery, which suggests that we should especially pay more attention to myometrial invasion in clinical practice, and its underlying mechanism also deserves further investigation.

Potential limitations exist in this study, and meta-analysis without the classification of endometrial cancer is the obvious one. In the past, dualistic classification is the leading theory for the classification, which divides endometrial cancer into type I and type II tumors (88). According to histology, WHO classified endometrial cancer into the following subtypes: endometrioid, serous, mucinous, clear-cell, mixed, squamous-cell, transitional-cell, small-cell, and undifferentiated carcinomas (89). Among them, endometrioid carcinoma and serous carcinoma account for the majority. In this study, we check all the included 79 articles and found that histologic type was not only confined to endometrioid subtype although endometrioid carcinoma is the most common one. And 53 articles of the included 79 studies did not exclude other histologic types, so we did not further conduct the analysis based on histological classification. Recently, endometrial cancer is categorized into four genomic types: DNA polymerase epsilon (POLE) (ultramutated), microsatellite-instable (MSI) (hypermutated), copy-number low (endometrioid), and copy-number high (serous-like) tumors as the quick development of next-generation sequencing (90). The above genomic classification can facilitate the treatment tailored to specific subgroups and potentially enable the delivery of precision medicine to endometrial cancer patients.

Apart from classification, other potential limitations still exist in this study: (1) The data from the included studies were from the published articles instead of the original information of individual patient; (2) most included articles are the retrospective studies, and the evidence level is lower than that of prospective randomized clinical trial; (3) one of inclusion criteria is that article was published in English and negative results not being reported, which increase the risk of publication bias; (4) the number of included studies is relatively small, especially for LVSI and recurrence, which may cause biased results; (5) the heterogeneity of aggregated results was significant, and the random-effects model was applied.

CONCLUSION

In summary, a large scale and comprehensive meta-analysis of the association between myometrial invasion and other clinicopathological characteristics and prognosis is provided in the present study. Our results show that myometrial invasion is associated with LVSI, LNM, recurrence, and OS, indicating that deep myometrial invasion is a useful evaluation criterion to associate with poor clinical outcomes and prognosis in endometrial cancer patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article-supplementary material. Further inquiries can be directed to the corresponding author.
AUTHOR CONTRIBUTIONS
JW, PX, and XZ: conceptualization. JW, PX, and XY: data curation and original draft writing. QY, XX, and GZ: statistical analysis. JW and XZ: manuscript review and editing. All authors contributed to the article and approved the submitted version.

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