

## Review Article

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## A comprehensive systematic review and meta-analysis of uterine cancer in Asian countries

### Abstract

**Background:** Uterine cancer ranks among the leading causes of mortality in women, particularly prevalent in countries with low to moderate income levels. Present treatment and healthcare success rates are assessed by the survival rate index. This study aimed to determine the uterine cancer survival rate in Asia.

**Methods:** Five international databases were analyzed to perform this systematic review: Medline/PubMed, ProQuest, Scopus, Web of Knowledge, and Google Scholar, until the end of August 2021. The Newcastle-Ottawa quality assessment form was utilized in the evaluation of quality for cohort studies.  $I^2$  statistic and Cochran test were used to check the analysis process and assess the heterogeneity among the studies. Also, the study year was used as the basis for a meta-regression analysis.

**Results:** The study covered 75 papers in total. The survival rates of uterine cancer after one, three, five, and seven years are 76.68% (95% CI, 66.76–78.61), 63.56% (95% CI, 58.60–68.37), 59.04% (95% CI, 55.62–62.43), and 57.86% (95% CI, 51.16–64.42) according to the random model. Furthermore, according to the outcomes of the meta-regression, there was no correlation found between the study year and the survival rate.

**Conclusions:** Compared to European and American countries, Asian countries have a poorer uterine cancer survival rate, which makes it crucial to improve the survival rate of patients through ensuring early diagnosis of the disease in its early stages and providing new diagnostic methods, modified surgical techniques, and targeted therapies.

**Keywords:** Uterine cancer, Asia, Survival, Systematic review, Meta-analysis

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Currently, non-communicable diseases stand as the primary global cause of mortality, and cancer is anticipated to rank among the foremost contributors to mortality and the main obstacle to increasing life expectancy in different countries in the 21st century (1). Invasive neoplasms within the pelvic organs of females constitute 15% of all cancers in women, of which uterine cancer, which refers to any type of invasive neoplasm in the uterus, is the most common (2). According to the latest published reports of Globocan 2020, there were 417,367 new cases of uterine corpus cancer in the worldwide, resulting in 97,370 deaths. Also, the crude and standardized incidence rates of this cancer were 10.8 and 8.7, respectively. Moreover, the crude and standardized mortality rates were 2.5 and 1.8 per 100,000 (3). Uterine cancer ranks among the leading causes of mortality in women, particularly prevalent in countries with low to moderate income levels (4). Also, in the US and other developed countries where women have access to quality healthcare, this cancer is the most common type of cancer among women. Endometrial cancer accounts for around 95% of all cancers in these communities (5). The prevalence of various risk factors and the screening and diagnostic techniques used can be the cause of discrepancies in the data published in different countries.



Risk factors that cause precancerous lesions of the uterus are human papillomavirus, multiple sexual partners, age of first sexual encounter (less than 16 years), race, a high number of pregnancies over 20 weeks, smoking, low socioeconomic status, sexually transmitted infections (Chlamydia, Gonorrhea, Gardnerella, Mycoplasma, Trichomonas, Herpes Simplex Virus type 2), and factors that reduce the body's immunity, such as AIDS (6).

In a study by Madlin et al., the increased risk of uterine cancer in people taking oral contraceptive pills is related to the duration of taking the pills. People who use these pills for more than 12 years have a fivefold increase in cancer risk (7). According to studies on thousands of cancer patients, women with uterine cancer have a five-year survival rate of over 82%. Also, women diagnosed with uterine cancer exhibited a 79% survival rate over a 10-year period. Furthermore, these studies showed that when cancer is diagnosed in its early stages, the five-year survival rate rises to 95%; it decreases to 68% if it is in an advanced stage. Moreover, if the tumor has metastasized to other sites, the five-year survival rate drops to 17% (8). In general, the incidence of aggressive cases of this cancer is decreasing, and since these patients are diagnosed earlier, their survival has also improved. Several surveys have revealed that the burden of this disease varies by ethnicity and social group (9). The first step to controlling the frequency of diseases and their complications in any population is to know their prevalence and gather data about their incidence, location, type, and survival.

The studies conducted regarding the different outcomes that have been observed in the survival rates of uterine cancer in Asia, and the populations examined in these studies have also been different. Knowing the survival rate of uterine cancer in Asian countries can offer valuable insights into prevention, screening, and treatment of individuals affected by the disease. Moreover, no thorough study has been done regarding the survival rate of uterine cancer in Asia. Therefore, the current investigation was undertaken to perform a systematic review and meta-analysis, aiming to assess the survival rate of uterine cancer in Asian countries.

## Methods

The present study is a systematic review and meta-analysis regarding the survival rate of uterine cancer. In 2021, the design and implementation of the study were completed. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist serves as the basis for this study reporting methodology (10).

**Search strategy:** Researchers investigated 5 international databases, including Medline/PubMed, ProQuest, Scopus, Web of Knowledge, and Google Scholar, until the end of August 2021. Google Scholar was searched for gray literature. The following keywords were chosen while conducting searches across databases: Uterine neoplasms [Mesh], Asian countries (names of countries), survival OR survival study OR survival rate. (Appendix 1). The software EndNote X7 was used to enter the gathered data, and duplicate content was automatically removed. It should be noted that the articles were independently reviewed by two researchers. Additionally, the search approach is provided in Appendix 1.

**Inclusion and exclusion criteria:** The study includes all observational studies (cross-sectional, case-control, and cohort) that were published in English up until the end of August 2021 and that indicated the observed uterine cancer survival. There was no time restriction on these experiments. We excluded review studies and meta-analyses. Moreover, it should be mentioned that studies that omitted sample size or confidence intervals for survival rates were excluded.

**Quality assessment:** The assessment of article quality was conducted using the Newcastle-Ottawa article quality evaluation scale, which consists of three segments: Part 1 covers Selection (4 questions), Part 2 addresses Comparison (1 question), and Part 3 focuses on Conclusion (3 questions). Categorized according to their final score, articles are classified into three groups, Good (achieving 3 or 4 stars in the selection section, 1 or 2 stars in the comparison section, and 2 or 3 stars in the result section); Fair (earning 2 stars in the selection part, 1 or 2 stars in the comparison part, and 2 or 3 stars in the result part); and Poor (0 or 1 star in the selection part, 0 stars in the comparable part, and 0 or 1 star in the result part) (11).

**Screening of studies:** Two individuals conducted the initial search for studies, and they independently performed the screening, results extraction, and evaluation of quality control for articles. In case of disagreements between the two, the team leader will declare the ultimate opinion regarding that specific article.

**Data extraction form:** All the final articles ultimately included in the study were retrieved using a pre-prepared checklist, including details such as the author's name, country, study period, publication year, sample size, and one-, three-, five-, and seven-year survival rates.

**Statistical analysis:** The Cochran test (with a significance level less than 0.1) and its combination with the I<sup>2</sup> statistics were used to assess the heterogeneity between studies. When heterogeneity was present, the random effects model

employing the inverse-variance method was utilized, while in the absence of heterogeneity, the fixed effects model was applied. When heterogeneity existed among studies, analytical approaches like meta-regression analysis and subgroup analysis were employed. The statistical analyses were conducted using software applications, including STATA Version 12, MedCalc Version 14, and Jamovi Version 2.3.12.

**Additional analysis:** Meta-regression analysis was also performed because of the significant heterogeneity across the studies. The variable employed in the meta-regression analysis was the study year.

**Risk of bias among studies:** The utilization of the random effects model aimed to minimize the potential for bias in studies (12, 13). Additionally, Egger's test for publication bias was employed to assess and address the risk of publication bias (14).

## Results

**Study selection:** 1889 papers in total were located after reviewing all worldwide databases; duplicate articles were eliminated, providing 1656 articles for title and abstract

examination. Following a thorough assessment of the article titles and abstracts, 278 articles progressed to the next stage, where the articles' entire texts were looked over and 75 were chosen for final analysis.

It should be emphasized that the references of the entered articles were also checked to include relevant/pertinent studies. The selection of papers for the study is illustrated in figure 1.

**Study characteristics:** The publication date of the included studies was from 1985 to 2021. 75 articles containing 288 records based on years of survival related to uterine cancer survival in Asian countries in the specified time period were eligible to be included in this study. 43 studies were from China, 5 from India, 3 from Iran, 2 from Israel, 95 from Japan, 30 from South Korea, 2 from Saudi Arabia, 34 from Singapore, 37 from Thailand, 28 from Taiwan, and 9 studies were conducted in Turkey. Descriptive information about these studies is given in Appendix 2.

**Quality appraisal:** The findings from the assessment of the articles' quality are presented in Appendix 3. According to the review conducted based on relevant checklist, 36 studies met the criteria for good quality, while 39 studies were classified moderate quality.

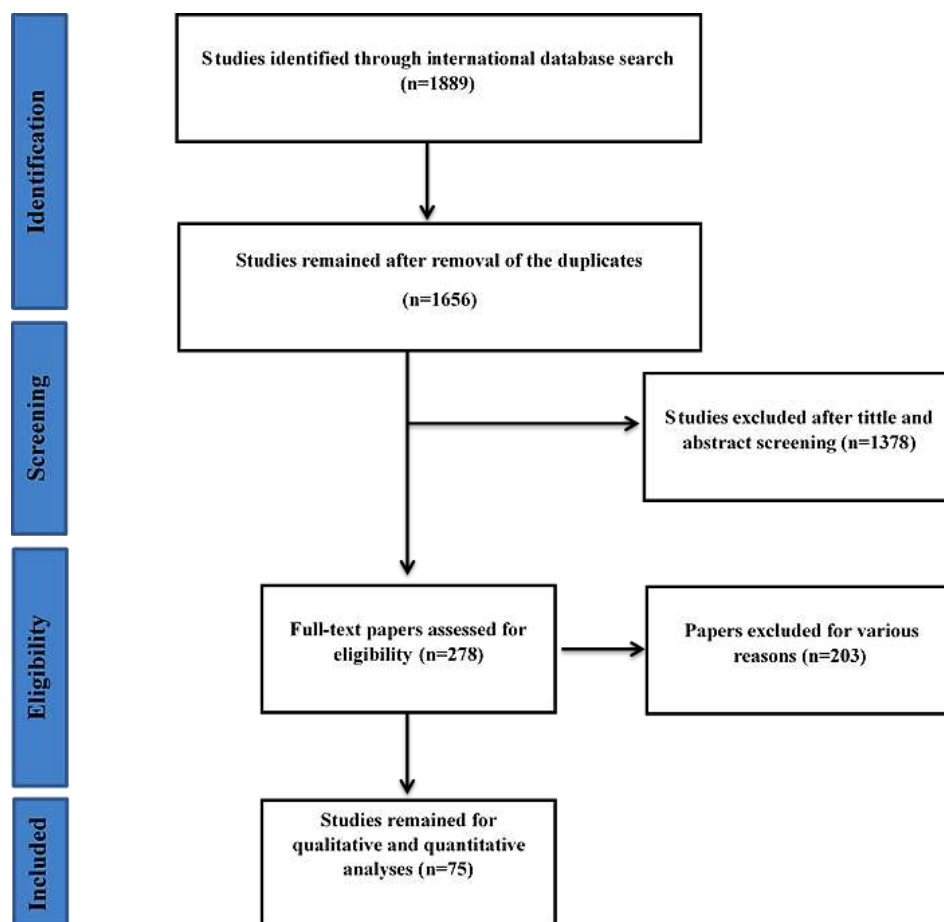


Figure 1. Diagram illustrating the selected qualifying studies in systematic review

**Heterogeneity:** The result of the chi-square test and the  $I^2$  index showed that there is significant heterogeneity between the studies of uterine cancer in Asian countries, which are for one-year survival ( $I^2 = 98.61\%$ ,  $p < 0.001$ ), three-year survival ( $I^2 = 98.3\%$ ,  $p < 0.001$ ), five-year survival ( $I^2 = 97.89\%$ ,  $p < 0.001$ ) and seven-year survival ( $I^2 = 95.6\%$ ,  $p < 0.001$ ). The outcomes of every analysis were obtained using the random effects model.

**Results of the meta-analysis:** Initially, the articles were organized based on the study's year of publication. And subsequently, the survival rate obtained was divided into the following categories: survival rates at one, three, five, and

seven years. Also, meta-regression was done based on the year of the study.

**Asian countries' one-year survival rate for uterine cancer:** Of the final papers, 51 studies provided the one-year survival rate, and the study outcomes revealed that the one-year survival rate was 76.68% (95% CI, 66.76–78.61) based on the random effects model (figure 2).

**Asian countries' three-year survival rate of uterine cancer:** Of the final papers, 82 studies provided the three-year survival rate. And the study outcomes revealed that the three-year survival rate was 63.56% (95% CI, 58.60–68.37) based on the random effects model (figure 2).

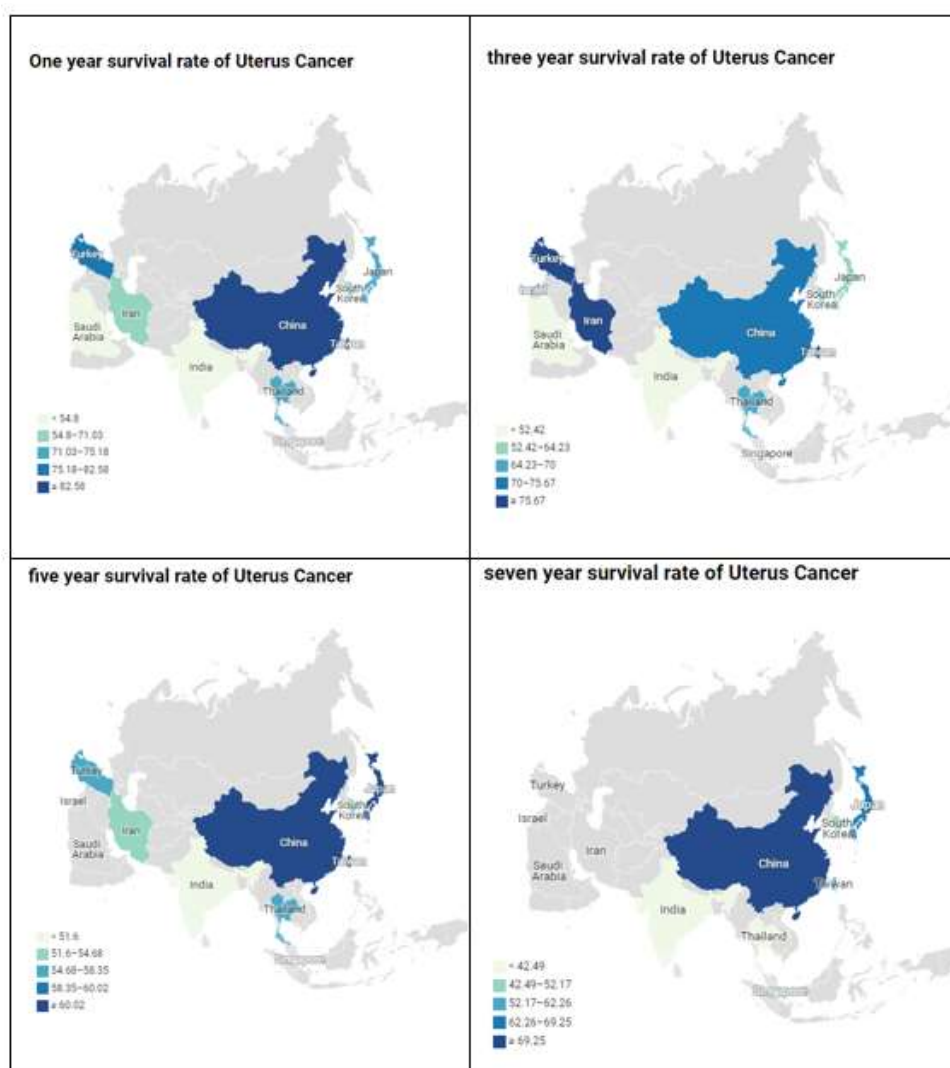


Figure 2. One, three, five and seven year survival rate of uterus cancer in Asian countries

**Asian countries' five-year survival rate of uterine cancer:** Of the final papers, 134 studies provided the five-year survival rate, and the study outcomes revealed that the five-year survival rate was 59.04% (95% CI, 55.62–62.43) based on the random effects model (figure 2).

**Asian countries' seven-year survival rate of uterine cancer:** Of the final papers, 21 studies provided the seven-year survival rate, and the study outcomes revealed that the seven-year survival rate was 57.86% (95% CI, 51.16–64.42) based on the random effects model (figures 2 and 3).

**Asian countries' survival rate of uterine cancer:** The survival outcomes for uterine cancer across 11 countries are presented in table 1. The highest one-, three-, five-, and seven-year survival rates are, respectively, in China (85.27), Taiwan (84.41), China (63.19), and China (79.00), and the lowest survival rates in these years are also in Saudi Arabia (14.00), Saudi Arabia (22.00), India (49.14), and India (36.00).

**Meta-regression of uterine cancer survival rate in Asian countries:** There was no relationship between the years of conducting the study and one-year (Regression coefficients = -0.257, P = 0.672), three-year (Regression coefficients = 0.085, P = 0.778), five-year (Regression coefficients = 0.226, P = 0.302) and seven-year (Regression coefficients =

0.0103, P = 0.991) survival of uterine cancer in Asian countries. Recent studies have shown higher three, five, and seven-year survival rates, none of the relationships were statistically significant though (figure 4).

**Publication bias:** Finally, Funnel plots were utilized to assess publication bias in the one, three, five, and seven-year survival of uterine cancer in Asian countries. Confirmation of this bias was obtained through the results of the Egger test.

Bias for one year: -4.79, 95% CI = -7.03 to -2.55; P = 0.0001. Bias for three years: -2.85, 95% CI = -5.74 to 0.03; P = 0.0528. Bias for five years: -2.65, 95% CI = -4.61 to -0.6; P = 0.0086. Bias for seven years: -4.81, 95% CI = -7.17 to -2.44; P = 0.0004 (figure 4).

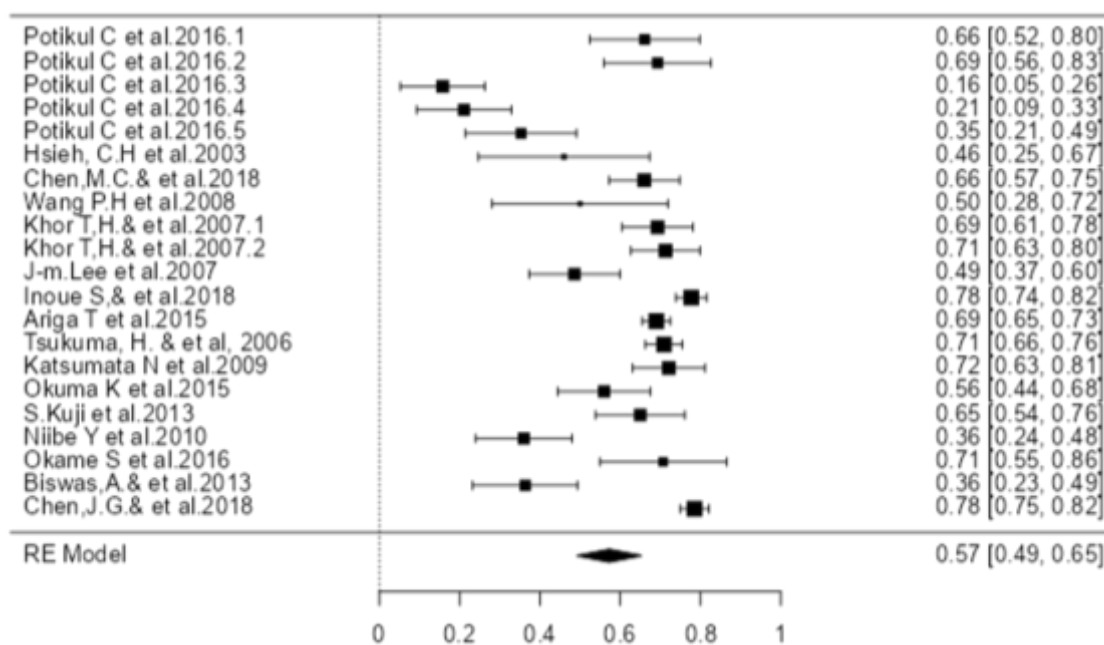


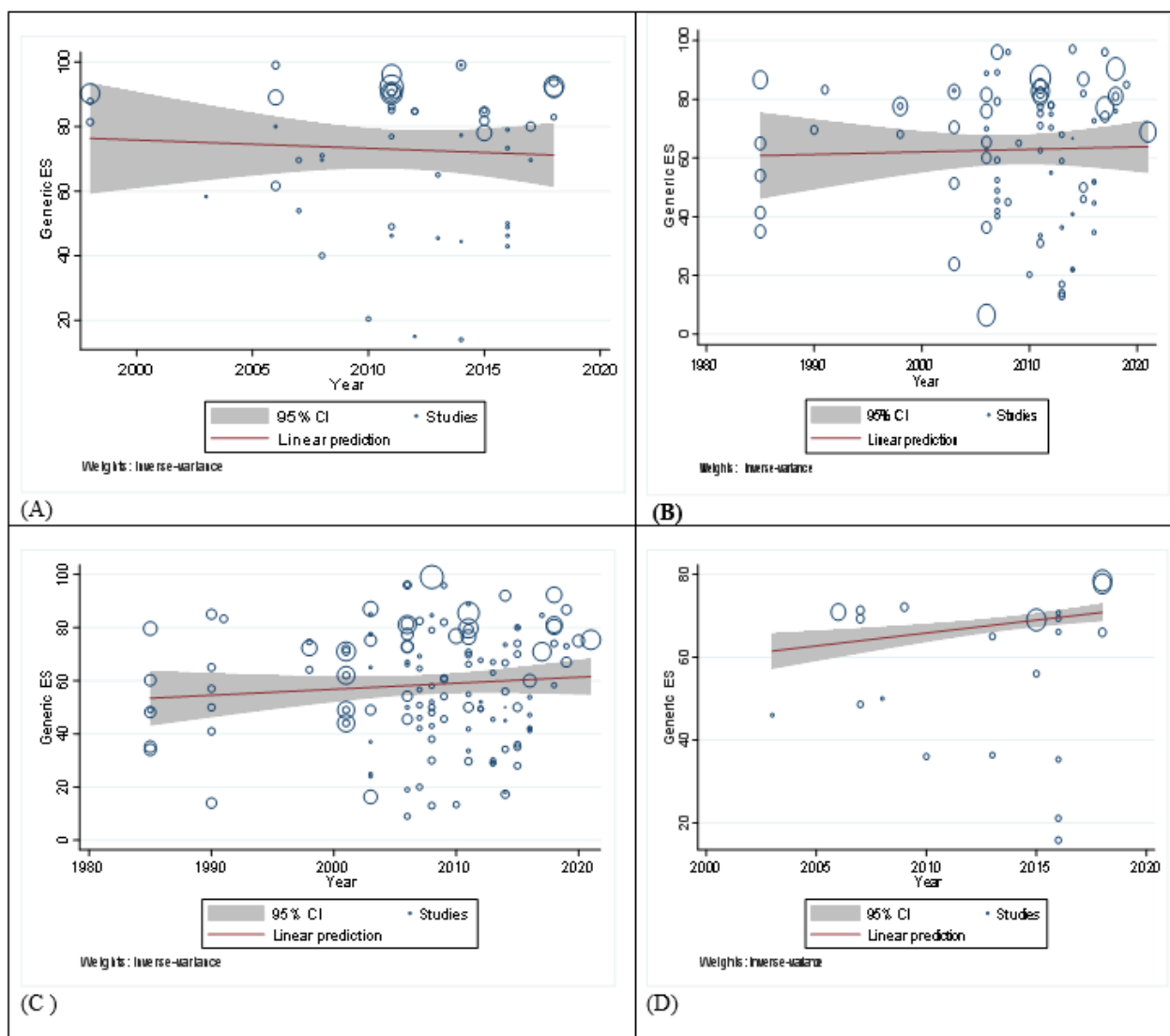
Figure 3. Seven years uterus cancer survival Forest Plot

Table 1. Meta-analysis results and heterogeneity in uterine cancer survival rate across Asian Countries: country and year-wise Analysis

Country	Total	Year of Survival												
		1			3			5			7			
	N	Effect estimate	P	N	Effect estimate	P	N	Effect estimate	P	N	Effect estimate	P		
China	43	14	85.27 (78.97, 90.61)	≤0.001	14	70.32 (61.78, 78.19)	≤0.001	14	63.19 (53.32, 72.53)	96.53	≤0.001	79	79.00 (74.64, 82.02)	NR
India	5	1	45 (28.10, 63.64)	NR	36	36 (20.39, 54.87)	NR	2	49.14 (43.29, 55.01)	0.00	0.5581	36	36 (23.47, 50.86)	NR







**Figure 4. Bubble plot illustrating the standard error by point estimate for assessment of publication bias (1, 3, 5 and 7 year uterus cancer survival rate) [A: One-year uterus cancer survival rate, B: Three uterus cancer survival rate, C: Five-year uterus cancer survival rate, D: Seven-year uterus cancer survival rate]**

### Discussion

This study aimed to investigate the survival rate of uterine cancer in Asian countries. The results of the study showed that the one-year survival rate of uterine cancer in Asian countries is 76.68%, which is lower than the reported rates in developed countries. As a result, the reported results of the study demonstrated that the three-year survival rate of uterine was reported to be 92% in Germany (15), and 87% in the United States (16). Also, the results of the study demonstrated that the three-year survival rate of uterine cancer in Asian countries is 63.56%, which is lower than the rates in developed countries. A three-year survival rate of 74% was reported in a Germany study (15) while a separate study revealed a three-year survival rate of 74% in the United States (16). The results of the study demonstrated

that the five-year survival rate of uterine cancer in Asian countries is 59.04 percent, which is lower than in developed countries. Several studies have reported the five-year survival rate of uterine cancer to be 73% in Germany (15), 82% in Denmark, 84% in Finland, Iceland, Norway, and Sweden (17), 71% in Canada (18), and 73% in America (19). The results of the study showed that the seven-year survival rate of uterine cancer in Asian countries is 57.86%, which is lower than in European countries. In a study conducted in Germany, the 7-year survival rate was reported as 71% (15). Also, in a review study, seven-year survival rate of uterine cancer among African Americans in the United States was 68.4% (20).

The greater rate uterine cancer survival in European and American than in Asian countries can be attributed to the

introduction of new diagnostic methods along with targeted therapies, new oncology treatments, and modified surgical techniques. New diagnostic tools not only lead to more accurate characterization and staging of the tumor but also leads to diagnosis of the disease in its early stages (21, 22). Another reason for the higher survival rate of uterine cancer in European and American countries when compared to Asian countries is the long waiting time for surgery in Asian countries, time for cancer surgery is an important healthcare access issue for many countries and a major barrier to accessing treatment in many countries is the time it takes for cancer surgery (23, 24). Prolonged wait times are linked to inefficiency, poor quality of care, and limited access to services, which can be indicators of issues within healthcare systems (23, 25). Patients experience stress while waiting for surgery (26-29), and research indicates that prolonged wait times may have a detrimental impact on survival rates, affect patient satisfaction, and decrease quality of life (23, 27). Another reason for the higher uterine cancer survival rate in European and American countries compared to Asian countries could be the implementation of care programs for people at risk of endometrial cancer, one of the uterine cancers. As the majority of women diagnosed with endometrial cancer exhibit early indicators such as abnormal uterine bleeding, implementing screening measures is unlikely to be cost-effective or contribute to a reduction in mortality (30, 31). Therefore, screening is not routinely recommended in the general population. However, surveillance and care for high-risk populations, including patients at high risk for uterine cancer who may benefit from routine care, is a warranted recommendation. These people include people with a family history of endometrial cancer; people with a history of hormone replacement therapy with less than 12 to 14 days of progesterone; long-term users of tamoxifen; people with the familial syndrome of hereditary non-polyposis colorectal cancer (HNPCC); people with Cowden syndrome and Peter-Jeghers syndrome; people with a history of breast cancer; and obese individuals (32, 33).

The present study is subject to limitations related to the types and quality of studies examined in this review. The outcomes of this study may be influenced by both the quantity of studies conducted in each country and the sample size of those studies. Furthermore, over half of the Asian nations had not released any research findings regarding the survival rates of individuals with uterine cancer. Thus, more research needs to be conducted to achieve a more precise estimation, especially in non-reporting countries. Also, due to the lack of review or meta-analysis articles that have reported the overall survival of

uterine cancer, in the discussion section, the results of this study were compared as much as possible with the existing articles in different countries. Among the strengths of the current study, we can mention the inclusion of observational studies with a cohort follow-up design and performing meta-regression analysis to identify sources of heterogeneity. The survival rate for some years (such as 2, 4, and 10-year survival) was not estimated because few studies had reported them and there was a need for future studies in this field.

The survival rate of uterine cancer in Asian countries are comparatively lower than those in European countries and the US. Therefore, there is a need to enhance patient survival by introducing new diagnostic methods, modified surgical techniques, and targeted therapies, as well as early diagnosis of the disease. Also, proper and coordinated planning to improve cancer care through national cancer registry programs is necessary to monitor cancer survival and evaluate the impact of changes in policies and quality of care. In addition, cancer registry data enable the quantification and comprehension of national and worldwide cancer survival, incidence, and mortality trends and differences. With better access to superior treatment options and disease-specific information, such as the histological stage and subtype, it will be possible to make more detailed comparisons and learn more about the factors that lead to different survival rates between countries.

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**Conflict of Interests:** The authors declare that there is no conflict of interest.

**Authors' contribution:** Conceived and designed the study: HA.N, M.V and Z.M. Collected the data: MA.J, M.V, S.H and M.J. Analyzed the data: HA.N, S.H and M.GG. Wrote the paper: M.J, MA.J and S.H. Supervision: M.GG, approval of the final manuscript: HA. N. The decision to submit this manuscript for publication was jointly made by all authors and the manuscript was confirmed to be accurate and approved by all authors.

**Data availability:** Not applicable.



**Consent to publication:** Not applicable.

**Availability of data and materials:** The corresponding author can provide the data supporting the findings of this study upon a reasonable request.

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