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# Understanding East-West differences in subsolid nodules: prevalence and overdiagnosis implications in lung cancer screening

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**ABSTRACT**

**Background:** Owing to the widespread opportunistic LDCT screening leading to increased overdiagnosis in Asian countries, such as South Korea, mainland China, and Taiwan, this study seeks to analyze the divergence in SSN prevalence between Eastern and Western nations, focusing on the influence of SSN on the growing overdiagnosis trend, notably among females.

**Methods:** This retrospective study collected data from 4166 participants who underwent baseline LDCT in a hospital-based cohort between January 2014 and August 2021. Clinical parameters, including age, sex, lung imaging reporting and data system (Lung-RADS) categories, smoking history, pack-year dose, and SSN characteristics, were extracted from electronic medical records. Additionally, a narrative review and pooled analysis integrated relevant published studies on the prevalence of subsolid nodules and sex disparities.

**Results:** The study encompassed 4166 participants, with females accounting for 49.3% and males for 50.7%, with a mean age of 53.38 ± 10.89. The prevalence of SSNs was significantly higher in females (20.1%) than in males (12.6%). Pooled analysis across seven studies revealed a significantly higher prevalence of SSN in Eastern countries (12.6%) compared to the prevalence in Western countries (3.6%) (test for subgroup differences: $p < 0.01$; $I^2 = 100\%$). Additionally, a notable sex difference was observed in the prevalence of SSNs (risk ratio = 0.489, 95% CI: 0.301–0.796, $p < 0.01$; reference group: male group).

**Conclusions:** Apart from differences in clinical management and health literacy regarding SSNs between Eastern and Western countries, the high prevalence of SSNs in Asian nations, particularly among females, significantly contributes to the issue of overdiagnosis in opportunistic lung cancer screening in Asian countries. Tailored sex-specific strategies and risk prediction models are essential for effective screening optimization.

**Abbreviations:** LDCT: Low-Dose computed tomography; Lung-RADS: Lung Imaging Reporting and Data System; GGNs: Ground-glass nodules; SSN: Subsolid nodule; CIs: Confidence intervals; IPD: Individual participant data

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## Introduction

With the widespread global application of low-dose computed tomography (LDCT) for lung cancer screening, numerous studies in Western countries have demonstrated reduced lung cancer mortality among high-risk smokers [1,2]. In recent years, several Eastern countries, including mainland China, South Korea, and Taiwan, have adopted similar LDCT lung cancer screening policies as those in Western countries of employing LDCT for lung cancer screening, primarily targeting high-risk smokers [3–5]. However, owing to the high prevalence of non-smoking-related lung cancer in Asia and the often-advanced stage at which the cancer is usually detected, Taiwan implemented the first national lung cancer screening policy in 2022, simultaneously targeting both high-risk smokers and

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familial lung cancer patients [6]. Moreover, due to the fear of lung cancer mortality among Asian populations, many individuals are willing to undergo LDCT lung cancer screening at their own expense [7]. Interestingly, the aforementioned countries have observed apparent instances of overdiagnosis, particularly in the female group [3–5]. However, a limited level of overdiagnosis is observed based on real-world data from the United States [8]. Due to the predominant source of overdiagnosis in Asian countries stemming from the non-smoking-related lung adenocarcinoma spectrum, particularly at stages IA and 0, the primary rationale of this study was to assume varying levels of overdiagnosis due to differences in the prevalence of Subsolid Nodules (SSNs) between Eastern and Western screening populations. Previous literature suggests that Western countries typically recommend an active surveillance approach, especially for pure ground-glass nodules, when managing subsolid nodules [9]. However, in Asian countries, there is a collective concern regarding lung cancer among nonsmokers [10]. According to relevant literature in Asia, among patients undergoing lung cancer screening, the proportion of those with ground-glass nodules undergoing surgery is 6%, while for some part-solid nodules, the rate of undergoing surgery is as high as 26% [11]. These findings highlight substantial disparities in clinical decision-making regarding subsolid nodules between Eastern and Western medical practices. The reason for potential overdiagnosis in Asian population comes from over-management. The reasons for over-management in lung cancer screening in Asia are quite complex. The complexity of overdiagnosis in lung cancer screening in Asia arises from a variety of factors, including distinctions in ethnic biological traits, diverse medical decision-making processes, and influences from health literacy and cultural aspects. This study specifically seeks to shed light on unique biological differences that might be driving overdiagnosis. Persistent SSNs in Asian populations often belong to the adenocarcinoma spectrum, especially those with ground-glass opacities, indicating indolent *in situ* or early-stage lung cancer lesions [12,13]. Therefore, if the prevalence of SSNs is higher in Asian countries than in Western countries, and a widespread concern is present about non-smoking-related lung cancer mortality in this area, excessive management of ground-glass nodules may lead to increased overdiagnosis.

Previous studies have not directly examined differences in the prevalence rates of SSNs between Eastern and Western populations, leading to scattered data across low-dose computed tomography LDCT lung cancer screening studies worldwide [14–18]. The hypothesis of this study is that if Asian populations indeed have a higher prevalence of subsolid nodules (SSNs), it would result in more frequent surgical interventions, further amplifying the likelihood of overdiagnosis. This study aims to fill this gap by investigating SSN prevalence in an Asian lung cancer screening population and comparing it with Western countries. Additionally, it seeks to explore any sex disparities in SSN prevalence within the Asian population, potentially shedding light on biological differences contributing to SSN prevalence between Eastern and Western nations and informing the understanding of potential overdiagnosis in Asian lung cancer screening programs. Thus, our study is designed to conduct a comprehensive pooled analysis of the literature to assess SSN prevalence in the baseline LDCT screening and compare rates between Eastern and Western populations. Moreover, we plan to integrate findings from a hospital-based cohort to validate the heightened prevalence of SSNs among Asian populations, particularly focusing on female cohorts.

## Methods

### *Study population cohort*

We collected data from the imaging database of our hospital, encompassing 4166 participants who underwent baseline LDCT between January 2014 and August 2021 shown in Table 1. This study was approved by the Ethics Committee of Kaohsiung Veterans General Hospital (IRB number: KSVGH23-CT12-11). Given the retrospective nature of this study, the requirement for written informed consent was waived by the Ethics Committee. The specific eligibility criteria for LDCT lung cancer screening in this study include: individuals with high-risk smoking histories, or heightened self-awareness of lung cancer risk due to the prevalence of non-smoking-related lung cancer in the Asian population. We documented the clinical profiles to categorize the LDCT screening participants into different risk-type groups. Using the electronic medical record system of the hospital, we documented various clinical characteristics such as age, sex, lung imaging reporting and data system (Lung-RADS 1.1 version) categories, smoking habits, pack-year dose, prevalence of SSNs, prevalence of pure ground-glass nodules, and the percentage of pure ground-glass nodules (GGNs) exceeding 3 cm at the individual level at the baseline LDCT. The "Smoking" definition, reflects smoking status, defined as ever-smokers with <15 years since quitting or current smokers. The "Smoking" definition indicates smoking status, classifying individuals as

**Table 1.** Clinical and demographic characteristics of the study population by gender.

| | All cohort (*N* = 4166) | Male group (*N* = 2111) | Female group (*N* = 2055) | P-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 53.38 ± 10.89 | 53.27 ± 17.54 | 53.74 ± 10.74 | 0.016 |
| Sex | | | | |
| Male | 2111 (50.7%) | – | – | – |
| Female | 2055 (49.3%) | – | – | |
| Lung-RADS | | | | 0.139 |
| 0 | 1 (0.02%) | 1 (0.05%) | 0 (0%) | |
| 1 | 2756 (66.2%) | 1466 (69.4%) | 1290 (62.8%) | |
| 2 | 1230 (29.5%) | 557 (26.4%) | 673 (32.7%) | |
| 3 | 68 (1.6%) | 37 (1.8%) | 31 (1.5%) | |
| 4 | 95 (2.3%) | 41 (1.9%) | 54 (2.6%) | |
| GGN (%) | 562 (13.5%) | 205 (9.7%) | 357 (17.4%) | <0.001 |
| SSN (%) | 679 (16.3%) | 265 (12.6%) | 414 (20.1%) | <0.001 |
| GGN >= 3 cm (%) | 2 (0.05%) | 1 (0.1%) | 1 (0.1%) | 0.926 |
| Smoking | 1134 (27.2%) | 1004 (47.6%) | 130 (6.3%) | <0.001 |
| Pack-years (dose) | 19.18 ± 14.33 | 20.03 ± 14.52 | 12.74 ± 10.90 | <0.001 |

Abbreviations: Lung-RADS: Lung imaging reporting and data system; GGN: Ground-glass nodule; SSN: Subsolid nodule.

current smokers or those who quit smoking within the past 15 years. If the SSN remains unchanged or does not show significant resolution within this timeframe, it is classified as a persistent SSN. Conversely, if the SSN resolves or disappears within three months, it is considered a transient SSN, indicating that the nodule did not persist and likely does not pose a long-term risk. During the heightened international pandemic period from 2020 to 2021, stringent isolation measures required all patients undergoing LDCT scans to undergo a COVID nucleic acid test, ensuring a negative result before entering our hospital. We also confirmed through the hospital's electronic medical record system that all cases had no diagnosis of COVID pneumonia three months before receiving LDCT examination. Therefore, covid-related GGN infiltration or nodular-like opacities could be ignored in this study.

### *Narrative evidence reviews and pooled data analysis*

Regarding the literature review, we first searched for previously published studies that aimed to report SSN prevalence in the baseline lung cancer screening study cohorts from Western or Eastern countries. This meta-analysis adhered to the PRISMA guidelines (2009). A comprehensive literature search was conducted to identify studies published in English, British English, French, or Latin available in PubMed and the Cochrane Library. Duplicate entries were removed, and the remaining articles, along with their cited references, were thoroughly reviewed. Two independent authors (F.Z.W and Y.J.W.) carried out the search using the terms: "lung cancer screening," "subsolid nodules," and "LDCT.". Ultimately, seven studies were included in the analysis shown in supplement Figure 1. Additionally, reviews addressing the SSN percentage between female and male cohorts were also included in the analysis. Finally, we included the aforementioned data in our study and relevant data derived from narrative reviews for pooled analysis. The following information was extracted from each study according to a pre-specified protocol addressing SSN prevalence: first author, publication year, research country, study population size, mean age distribution, number of SSNs (prevalence), and transient SSN number at the individual level (transient SSN prevalence). All data were independently extracted from the eligible studies by the authors (FZW). Regarding SSN prevalence between the female and male groups, the following information was extracted from each study according to a pre-specified protocol: first author, publication year, research country, study population size, male/female group number, and number of SSNs in each group. In this pooled analysis, we assessed the pooled prevalence of SSNs in six selected studies [15–19]. A random-effects model was used to calculate the pooled prevalence estimates of the SSNs in each study. Pooled prevalence estimates are expressed as mean estimates and 95% confidence intervals (CIs). We used an $I^2$ statistic estimate of ≥50% as an indicator of large statistical heterogeneity. To explore the potential sources of heterogeneity, a subgroup analysis was conducted based on Western or Eastern countries. To analyze the proportion of SSNs between female and male cohorts, we examined the incidence of SSNs in the selected studies, stratified by male and female groups, to compare the prevalence of SSNs across genders[15,19]. The study's flowchart, including the existing cohort population and the pooled analysis derived from a narrative review are represented in Figure 1.

### *Statistical analysis*

SPSS for Windows (version 22.0; SPSS Inc., Armonk, NY, USA) was used for the comprehensive statistical

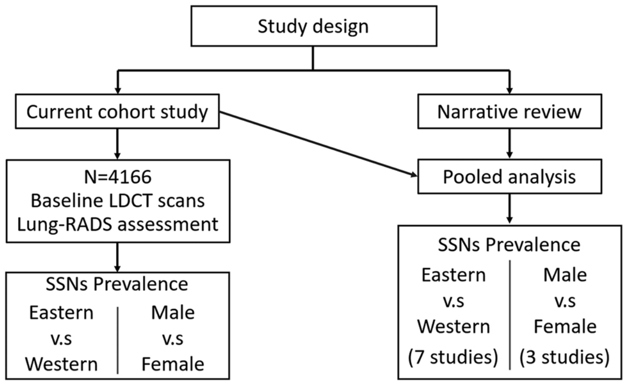


**Figure 1.** Flowchart depicting cohort study design and narrative review for pooled analysis on the prevalence of SSNs.

analysis. The chi-square test was used for categorical variables, whereas Fisher's exact test was used when the expected count reached below five. Furthermore, independent Student's t-tests were used to evaluate continuous variables. For the for-pooled analysis, we used Onlinemeta v1.0, to determine the overall pooled prevalence of SSNs according to Eastern/Western country groups [20]. In addition, sex differences were observed in SSN prevalence in Asian populations. Moreover, the differences were also investigated through pooled analysis. GLMM stands for Generalized Linear Mixed Models, a statistical framework that extends generalized linear models by incorporating both fixed and random effects.

## Results

### *Study population*

The study enrolled 4166 participants who underwent the baseline LDCT. The cohort consisted of 2111 males (50.7%) and 2055 females (49.3%), with a mean age of 53.38 ± 10.89. Of these, 1134 participants (27.2%) had a history of smoking, with an average dose of 19.18 ± 14.33 pack-years.

The Lung-RADS classification across the entire study cohort was distributed as follows: one individual was classified as Lung-RADS 0 (0.02%), 2756 individuals were categorized as Lung-RADS 1 (66.2%), 1230 individuals were classification as Lung-RADS 2 (29.5%), 68 individuals were classified as Lung-RADS 3 (1.6%), and 95 individuals were categorized as Lung-RADS 4 (2.3%). Of these, 562 (13.5%) had GGNs, meanwhile, a total of 679 patients (16.3%) had SSN lesions. For GGN ≥ 3 cm, only two participants were identified with the lesions. A comparison of the clinical characteristics of the male and female groups is displayed in Table 1. Lung-RADS distribution and the percentage of GGN ≥ 3 cm were not statistically different between the two groups. However, significant differences were identified in age, GGN prevalence, SSN prevalence, smoking habits, and pack-year dose. In contrast to 12.6% of males with SSNs, the percentage of females with SSNs was notably higher (20.1%). We further stratified the 4,166 participants in this study by smoking status, revealing a subsolid nodule prevalence of 11.2% in the smoking group and 18.2% in the non-smoking group. These rates appear higher compared to the prevalence in Western smoking populations, as shown in Supplementary Table 1. In our study cohort ($N = 4166$), SSN prevalence was 18.2% in non-smokers and significantly lower at 11.2% in smokers ($p < 0.001$). Supplementary Table 2 presents the SSN prevalence according to smoking status. The general trend shows that the prevalence rate is slightly higher among non-smokers compared to smokers. However, as only two studies are available, the data are primarily displayed in tables without further meta-analysis.

The demographics of the studies included in the investigation of the prevalence of SSNs are summarized in Table 2. The results of the forest plot based on the pooled analysis, including the seven studies, are presented in Figure 2. The overall pooled prevalence of SSN in the screened cohort population was 7.4% (95% CI = 4.1–12.8%) in a random-effect pooled analysis of these studies. Cochran's Q was significant ($Q = 1979.04$, df = 6, $I^2 = 100$), suggesting heterogeneity across the prevalence estimates, and the $I^2$ statistic was 100%, indicating very high heterogeneity. Furthermore, we conducted a subgroup analysis by country, dividing them into Eastern and Western countries. Prevalence estimates from three studies performed in Western countries (3.6%, 95% CI: 3.0–4.2%) were lower than those performed in Eastern countries shown in Figure 3 (12.6%, 95% CI: 7.5–20.5%).

In the subgroup analysis, SSN prevalence was significantly higher in the Eastern country group than in the Western country group (test for subgroup difference: $p < 0.01$; $I^2 = 100\%$).

The effect of sex on SSN prevalence in Asians was divided into male and female groups to analyze the pooled prevalence of SSN between the two groups. The results of the pooled analysis, including three studies (summarized in Table 3), are presented in Figure 4. A significant difference was observed in the prevalence of SSNs between the male and female groups (risk ratio = 0.489, 95% CI: 0.301–0.796, $p < 0.01$; reference group: male) in a random-effects pooled analysis of the three studies. Statistically different heterogeneity was observed in the study results ($p < 0.01$; $I^2$ = 93%).

**Table 2.** Demographics of included studies in investigation of the prevalence of subsolid nodules in seven studies.

| No | First Author | Year | No of patients | Age (year) | Nationality | SSN number (prevalence) | Transient SSN number (percentage) |
|---|---|---|---|---|---|---|---|
| 1 | Silva Mario[11] | 2012 | 1866 | 57.6 ± 4.8 | Italy | 56 (3.00%) | 18 (32.14%) |
| 2 | Ernst T. Scholten[12] | 2014 | 7135 | 62 | Netherlands | 234 (3.27%) | 126 (53.84%) |
| 3 | David F. Yankelevitz[13] | 2015 | 57496 | 59 | USA | 2392 (4.16%) | 628 (26.25%) |
| 4 | Fu Zong, Wu[14] | 2017 | 1975 | 56.56 ± 9.01 | Taiwan | 159 (8.05%) | 19 (11.95%) |
| 5 | Bihan Ouyang[15] | 2021 | 1582 | Adult | China | 392 (24.78%) | N.A |
| 6 | Yeon Wook Kim | 2021 | 3608 | 49.5 ± 11.3 | South Korea | 259 (7.18%) | N.A |
| 7 | Current study | 2023 | 4166 | 53.38 ± 10.89 | Taiwan | 679 (16.30%) | N.A |

Abbreviations: SSN: Subsolid nodule.
N.A = not available.

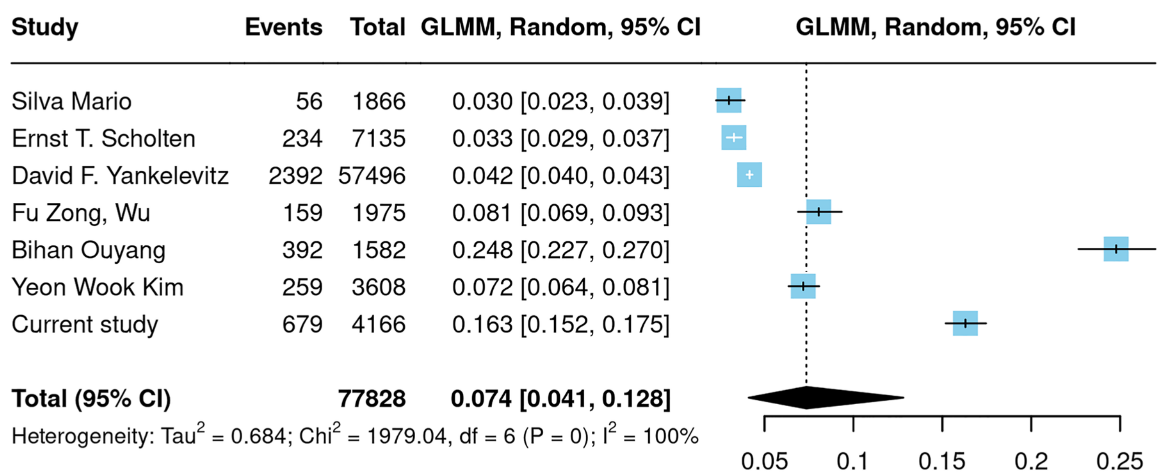


**Figure 2.** Forest plot demonstrating pooled prevalence of SSNs in seven studies.

## Discussion

Recent studies have elucidated a significant increase in apparent overdiagnosis in Asian countries such as South Korea, Taiwan, and mainland China, where LDCT lung cancer screening has been implemented in the real world, particularly through opportunistic self-paid means [3–6]. Overdiagnosis is an inevitable consequence of real-world lung cancer screening [21]. Literature comparing the extent of overdiagnosis in lung cancer screening between Western and Eastern countries suggests a more significant issue in Eastern countries compared to their Western counterparts [3–5,8]. In Western countries, lung cancer screening primarily targets high-risk populations of heavy smokers [22–24]. However, in several Asian countries such as mainland China, South Korea, and Taiwan, due to the high prevalence of lung cancer among non-smokers, particularly females, healthcare institutions generally offer self-paid LDCT for opportunistic lung cancer screening [3,14].

Moreover, in Taiwan, the first national lung cancer screening policy has been implemented since July 2022, targeting heavy smokers at risk and individuals with a family history of lung cancer, with screenings scheduled every 2 years [6]. Therefore, we assumed a high prevalence of SSNs in Asian populations, particularly in females. Given the high probability of persistent SSNs being associated with lung adenocarcinoma spectrum lesions, the promotion of lung cancer screening in Asian countries will uncover a substantial population of asymptomatic individuals with indolent growth trends. This particular population of individuals may harbor early-stage or pre-invasive lesions of lung adenocarcinoma or its precursors, lurking beneath the tip of the iceberg that has not been previously explored through opportunistic screening [12].

In essence, prior research has not specifically investigated variations in the occurrence of SSNs between Eastern and Western populations. This lack of focus has resulted in fragmented information dispersed throughout LDCT lung cancer screening studies conducted worldwide [14–18]. Therefore, this study focused on assessing the prevalence of SSNs and sex-based discrepancies in a hospital-based cohort of 4,166 participants. Furthermore, the study undertakes a combined pooled analysis of existing narratives to explore the discrepancies in SSN prevalence across Eastern and Western countries, as well as among different sexes. This study has two major findings. First, based on the results of the pooled analysis, the

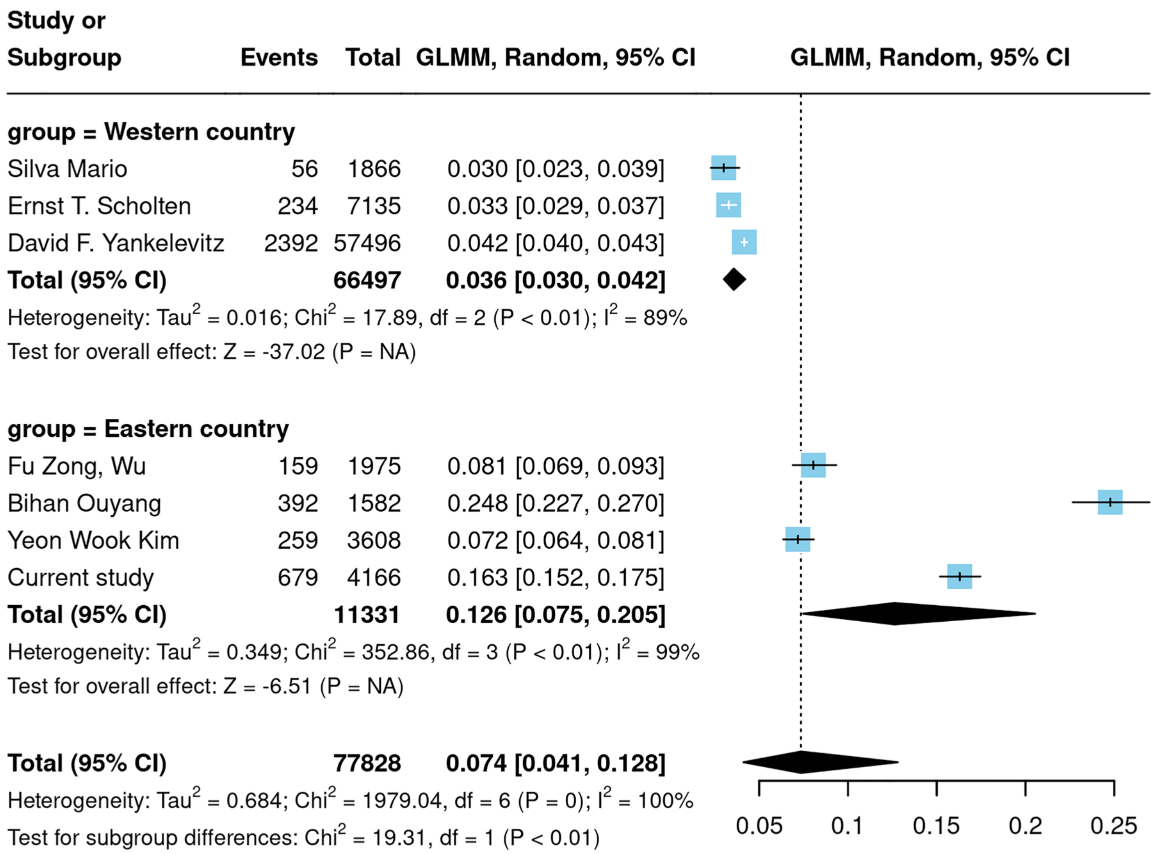


**Figure 3.** Forest plot demonstrating pooled prevalence of SSNs stratified by Western and Eastern countries.

**Table 3.** Demographics of included studies in investigation of SSN prevalence according to male and female groups.

| No | First Author | Year | No of patients | Male | Female | Age (year) | Nationality | Total SSN number | SSN number, Male (prevalence) | SSN number, Female (prevalence) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Bihan Ouyang[15] | 2021 | 1582 | 512 | 1070 | Adult | China | 392 | 102 (19.92%) | 290 (27.10%) |
| 2 | Fu Zong, Wu[14] | 2017 | 1975 | 1083 | 891 | 56.56 ± 9.01 | Taiwan | 159 | 35 (3.23%) | 124 (13.92%) |
| 3 | Current study | 2023 | 4166 | 2111 | 2055 | 53.38 ± 10.89 | Taiwan | 679 | 265 (12.55%) | 414 (20.15%) |

Abbreviations: SSN: Subsolid nodule.

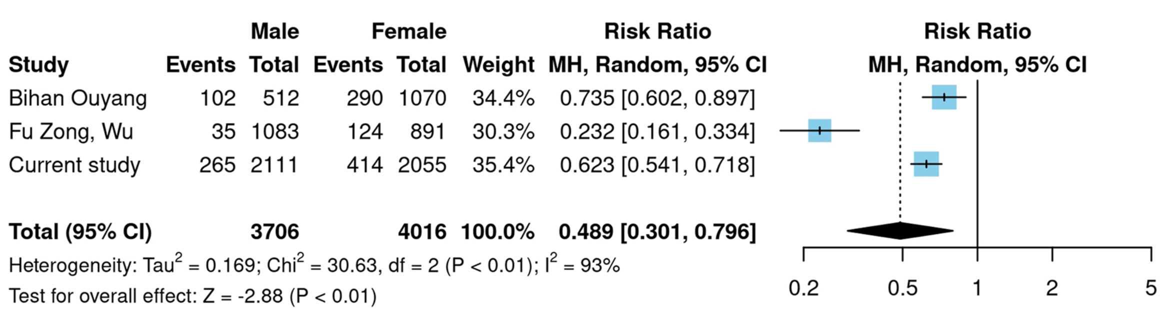


**Figure 4.** Forest plot demonstrating the impact of gender effect on pooled prevalence of SSNs in three studies.

prevalence of SSNs in Eastern countries was notably higher than that in Western countries, with figures of 12.6% and 3.6%, respectively. Second, the risk ratio for the prevalence of SSNs in the female group relative to the male group (reference) was 0.489 (CI = 0.301–0.796), highlighting a significant distinction in the Asian population. This study is the first to use primary cohort data and narrative reviews to explore the differences in SSN prevalence between Eastern and Western countries. According to a pooled analysis of seven studies, the prevalence of SSNs was 12.6% in Eastern countries, markedly surpassing the rate of 3.6% observed in Western countries. However, the pooled results demonstrated significant heterogeneity among studies. Our findings were consistent with the hypotheses of this study. Simultaneously, a pooled analysis confirmed that the prevalence of SSNs in Asian populations is higher in females than in males. In line with this, it is noteworthy that Asian populations generally harbor concerns about collective lung cancer mortality, leading them to prioritize non-smoking lung cancer screening [3,7]. However, current evidence regarding lung cancer screening for non-smokers remains unclear, and the development and validation of lung cancer risk prediction models for the non-smoking population are still ongoing [25,26]. Therefore, we infer that lung cancer screening in Asia is likely to result in a more pronounced overdiagnosis, primarily stemming from a high proportion of SSNs among Asian populations, particularly among females. This is further compounded by the prevalent culture of security-oriented practices in Asian communities and the collective lung cancer anxiety that arises from instances where family members, despite not smoking, succumb to the disease [27]. The aforementioned factors make it more likely that individuals opt for lung-sparing surgical treatments and are less inclined to adhere to the active surveillance strategies outlined in Western guidelines [17,28–30]. Although overdiagnosis is an inevitable byproduct of screening implementation, we observed a progressively evident overdiagnosis phenomenon from the pragmatic execution of opportunistic lung cancer screening in Asian countries. From an individual perspective, discerning whether one has been overdiagnosed is challenging; most people believe they have been fortunate to have their cancer detected early and successfully treated [31–33]. From the viewpoint of healthcare institutions and professionals, in the current era of volume-based reimbursement healthcare policies, the early diagnosis of lung cancer and timely surgical intervention often serve as crucial performance metrics for performance-based systems [34]. However, from the standpoint of public health epidemiology, the original intent of screening was to detect late-stage lung cancer early and alter the prognosis of the disease. Nevertheless, the high sensitivity of screening tools and the indolent growth characteristics of non-smoking-related lung cancer in Asia can lead to significant overdiagnosis and overtreatment, thereby affecting the quality and benefits of lung cancer screening [35]. However, adequate healthcare policies and strategies can help mitigate the adverse effects of LDCT screening such as overdiagnosis and over-management [7,12,36,37]. First, due to sociocultural practices in Asian countries that often involve self-payment or opportunistic screening, establishing an optimized lung cancer screening and prediction model segregating smokers and non-smokers to enhance screening efficiency and reduce overdiagnosis is crucial [3]. The current binary screening threshold system is inadequate for the identification of high-risk populations [38]. Recent studies have indicated the use of lung cancer risk prediction models for screening, which can further balance the pros and cons of screening [39]. Second, sex-specific strategies have been implemented to enhance the quality of lung cancer screening. Previous qualitative studies have revealed that compared to females certain male heavy smokers might have a lower socioeconomic status, leading to reduced willingness or probability of participating in screenings [7,40]. Consequently, it is important to develop policies that encourage smokers to undergo screening and improve the accessibility of screening, thereby increasing the screening rate and effectiveness among heavy smokers.

Concerning the non-smoking high-risk population, especially females, it has been observed that Asian females have a higher prevalence of SSNs or GGNs compared to males. Such lesions often exhibit an indolent growth trend, leading to concerns regarding overdiagnosis from premature interventions [41]. Hence, a multidisciplinary team suggests the adoption of an active surveillance strategy for SSNs and a shared decision-making health education policy to reduce public anxiety and avoid unnecessary surgeries without urgency [12]. This study provides the first direct evidence of variances in the prevalence of subsolid nodules between Eastern and Western populations. It marks the initial demonstration of a head-to-head comparison, confirming distinct prevalence rates in these two demographic regions, offering a direct comparison rather than relying on scattered data from various individual papers. Future research could investigate 2nd or 3rd generation immigrants either to or from Asia to explore the interactive effects of genetics and environment on the prevalence changes of subsolid nodules between Eastern and Western countries. Additionally, the construction of a prediction model by integrating delta-radiomic features with clinical risk factors has been proposed to identify high-risk SSNs/GGNs that may grow rapidly and affect prognosis [7,42]. This is a crucial direction for future research.

This study has four main limitations. First, the study primarily focused on a single hospital-based cohort and conducted a pooled analysis through narrative reviews. However, the current literature review reveals a lack of relevant studies on the prevalence of SSNs in different populations. Additionally, we recognize that while most Western research primarily focuses on

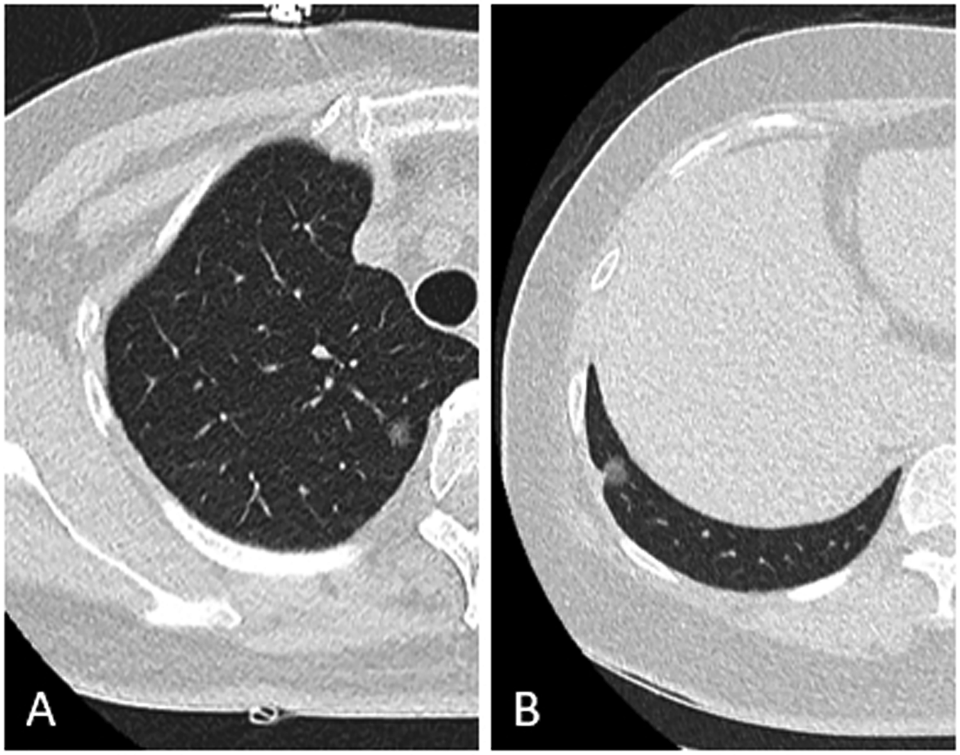


**Figure 5.** (A) A 42-year-old female presented with a 0.6 cm ground-glass opacity in the right upper lung, confirmed to be adenocarcinoma *in situ* upon thoracoscopic surgery. (B) Similarly, a 48-year-old female had a 0.65 cm nodule in the right lower lung, also confirmed to be adenocarcinoma *in situ via* thoracoscopic surgery. These cases suggest a high likelihood of overdiagnosis with nodules exhibiting ground-glass appearance.

smokers, Eastern research includes both smokers and non-smokers, which presents challenges for conducting subgroup analyses. To effectively examine subgroup factors, it would be necessary to utilize an individual population meta-analysis approach or design future studies to explore the relationship between smoking behaviors and the prevalence of subsolid nodules (SSNs). Gathering and consolidating inconsistent research data from various countries or conducting individual participant data meta-analyses for a comprehensive analysis, which poses considerable challenges is essential [43]. Therefore, future multinational studies investigating the prevalence of SSNs in different countries are critical. Second, the pooled analysis in this study demonstrated substantial heterogeneity in the prevalence rates of SSNs between Eastern and Western countries, as well as between sexes. This heterogeneity may arise from variations in study design, different screening reporting interpretation methods (centralized or local interpretation) due to interobserver variability, and differences in the criteria for case inclusion [44]. There is a need for further discussion regarding the definition of subsolid nodules (SSNs) and the variability among radiologists in identifying and classifying these nodules. Consequently, future multicenter studies are necessary to gain a more precise understanding of the prevalence rates of SSNs/GGNs in the general populations of different countries. Third, this study specifically investigates the baseline examination prevalence of SSNs in lung cancer screening in Eastern and Western countries. Due to the study design, there may be potential influence from transient GGN associated with inflammation or COVID-19-related GGN opacities. However, since this study's design rigorously excludes individuals with possible positive COVID-19 cases from screening during the pandemic, and past research indicates that the proportion of transient GGNs in Asian lung cancer screening baseline examinations is approximately 11.95%, this could mitigate the impact of potential study errors caused by these factors. Furthermore, medical record reviews confirmed no diagnoses of COVID pneumonia during the study period. The presence of GGNs alone, especially in the context of a single baseline examination, does not inherently lead to overdiagnosis. Comparing overdiagnosis rates between Eastern and Western countries is essential. However, the selected five studies lack specific data for direct comparison, revealing a significant research gap. This study did not explore the frequency of lung cancer adenocarcinoma spectrum or the proportion of overdiagnosis. Future studies should systematically assess overdiagnosis across diverse populations and healthcare systems to better understand regional variations and their underlying contributing factors. Overdiagnosis primarily stems from overtreatment. Overdiagnosis typically occurs when there is an excessively sensitive diagnostic approach that identifies indolent or non-progressing conditions, subsequently prompting unnecessary interventions (shown in Figure 5). The disparity in the prevalence of SSNs between Western and Eastern populations may heighten concerns among Eastern populations about the familial predisposition to lung adenocarcinoma spectrum lesions, particularly given the higher prevalence in female population. The fundamental principle is that in regions with a higher SSN prevalence, the association of persistent SSNs with familial predisposition to lung adenocarcinoma and the heightened anxiety about non-smoking-related lung cancer in Asian populations may lead to unnecessary treatments due to the unpredictability of the condition. Therefore, understanding the East-West differences in SSN prevalence is crucial for future adjustments in health policies to mitigate the risk of overdiagnosis. Fourth, the study's limitation lies in its inability to directly measure the impact of SSNs on lung cancer overdiagnosis or to establish a clear link between SSN prevalence and overdiagnosis rates. This indirect effect, where the higher prevalence of SSNs may influence the likelihood of detecting early-stage cancers that would not have progressed, remains unaddressed. A key limitation is that the study does not examine how these SSNs contribute to overdiagnosis or the impact of such diagnoses on long-term outcomes. While the results of this study do not directly analyze differences in overdiagnosis rates between Eastern and Western regions, the significant variation in overdiagnosis rates observed in lung cancer screening studies from these regions indirectly supports the hypothesis. One potential explanation proposed is the biological differences in the prevalence of subsolid nodules between Asian and Western populations. In addition, three studies failed to provide results on transient SSNs, highlighting a notable limitation. Future research should focus on exploring these indirect effects more robustly, considering factors like the malignancy rate, stage 0 lung cancer prevalence, and the potential for overdiagnosis, to better understand the clinical implications of SSNs in different populations.

## Conclusion

In summary, besides the differences in clinical management and health literacy regarding SSNs between Eastern and Western countries, the significant high prevalence of SSNs in Asian nations, particularly among females, could contribute to overdiagnosis through opportunistic lung cancer screening practices. It is essential to enhance screening quality and mitigate overdiagnosis by refining differential lung cancer risk prediction models and customizing sex-specific screening strategies.

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## Author contributions

YCC, YCH, and FZW contributed to the conceptualization; YCC, YCH, and FZW contributed to the methodology; YJW, and FZW contributed to the software; YJW, and FZW were involved in the validation; YJW, and FZW assisted in the formal analysis; YJW, EKT, and FZW were involved in the investigation; YCH, YJW, EKT, and FZW contributed to the resources; YJW, and FZW assisted in the data curation; YCH, and FZW contributed to the writing—original draft preparation; YCH, YJW, and FZW were involved in the writing—review and editing; YJW, and FZW contributed to the visualization; FZW assisted in the supervision. All authors have read and agreed to the published version of the manuscript.

## Compliance with ethical standards

### *Disclosure of potential conflicts of interest*

All authors completed the ICMJE uniform disclosure form. No potential conflict of interest was reported by the author(s).

## Human ethics and consent to participate declarations

All methods or experimental protocols were approved by the local institutional review board and were carried out in accordance with relevant guidelines and were conducted according to the guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants and/or their legal guardians.

## Informed consent

Given the retrospective nature of this study, the requirement for written informed consent was waived.

## Internal review board (IRB) ethics approval declaration

This study was approved by the Ethics Committee of Kaohsiung Veterans General Hospital (IRB number: KSVGH23-CT12-11).

## Research involving human participants

Human subjects.

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## Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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