Original Article

Histopathologic fate of resected pulmonary pure ground glass nodule: a systematic review and meta-analysis

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Background: Pure ground glass nodules (GGNs) have been increasingly detected through lung cancer screening programs. However, there were limited reports about pathologic characteristics of pure GGN. Here we presented a meta-analysis of the histologic outcome and proportion analysis of pure GGN.

Methods: This study included previous pathological reports of pure GGN published until June 14, 2022 following a systematic search. A meta-analysis estimated the summary effects and between-study heterogeneity for pathologic diagnosis of invasive adenocarcinoma (IA), minimally invasive adenocarcinoma (MIA), adenocarcinoma in situ (AIS), and atypical adenomatous hyperplasia (AAH).

Results: This study incorporated 24 studies with 3,845 cases of pure GGN that underwent surgery. Among them, sublobar resection was undertaken in 60% of the patients [95% confidence interval (CI): 38–78%, I^2=95%]. The proportion of IA in cases of resected pure GGN was 27% (95% CI: 18–37%, I^2=95%), and 50% of IA had non-lepidic predominant patterns (95% CI: 35–65%, I^2=91%). The pooled proportions of MIA, AIS, and AAH were 24%, 36%, and 11%, respectively. Among nine studies with available clinical outcomes, no recurrences or metastases was observed other than one study.

Conclusions: The portion of IA in cases of pure GGN is significantly larger that expected. More than half of them owned invasiveness components if MIA and IA were combined. Furthermore, there were quite number of lesions with aggressive histologic patterns other than the lepidic subtype. Therefore, further attempts are necessary to differentiate advanced histologic subtype among radiologically favorable pure GGN.

Keywords: Lung cancer; pure ground glass opacity; ground glass nodule (GGN); early-stage lung cancer; lung pathology

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Introduction

Screening programs with high-resolution computed tomography have been introduced to lower the global burden of lung cancer-related mortality, demonstrating promising results (1-3). The advancement of screening programs has led to assessing lung cancer prognoses according to their radiological characteristics. Specifically, ground glass nodules (GGNs), which are non-specific findings with pulmonary lesions without obscuring vascular marking, represent an important issue among clinicians regarding diagnosis and management. As most GGNs are related to inflammation, respiratory infection, or other benign causes, the differentiation of malignant lesions among GGN is crucial. Several screening trials, including NELSON, revealed that a significant portion of GGN disappeared during follow-up (2). However, in many studies, a persistent pure GGN has been found to be malignant (4-6).

The 8th TNM classification categorizes GGN as indolent or lepidic predominant adenocarcinoma (7). However, there have been contradictory reports about the histopathologic diagnosis of pure GGN. Notably, subtypes other than the lepidic predominant type are frequently observed (5,8,9). As there are no comprehensive pathological reports relating to resected pure GGN, the optimal surgical candidate for pure GGN remains uncertain. If there are significant portion of invasive adenocarcinoma (IA) among pure GGN, it would be difficult to monitor those lesions without treatment. Additionally, minimally invasive surgical technique has also evolved and it has become more feasible to resect relatively early-stage lung cancer preserving lung parenchyme. Therefore, this study aimed to systematically review the pathological features of pure GGN to suggest proper surgical treatment indications. This study would give a generalized review of pathologic results so that clinicians to understand pathologic variability in pure GGN. We present this article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1089/rc).

Highlight box

Key findings

- The proportion of invasive adenocarcinoma (IA) among pure ground glass nodules (GGNs) is quite significant (27%) and half of them are non-lepidic predominant adenocarcinoma.

What is known and what is new?

- Pure GGN has been regarded as pre-invasive or lepidic-predominant adenocarcinoma.
- This study suggests different histologic outcomes even among pure GGN.

What is the implication, and what should change now?

- As there are significant portion of IA among pure GGN, the role of surgery for pure GGN still exists and further study aiming to find invasive lesions is necessary.

Methods

This study was registered with PROSPERO (CRD42021273975).

Search strategy and study selection

We searched MEDLINE, PubMed, EMBASE, and Scopus databases until June 14, 2022. The search terms are listed in Table S1. Two authors (W.W. and V.K.) independently reviewed the titles and abstracts, and disagreements were resolved by discussion with a third author (S.L.). The full literature search strategy and selection process are shown in *Figure 1*. We included studies wherein pathological diagnoses of pure GGN were reported. The exclusion criteria were as follows: (I) studies on mixed GGN and (II) studies without pathologic reports of pure GGN. All studies were limited to those published in the English language and involving humans. Abstracts, case reports, conference presentations, editorials, and reviews were also excluded.

Data extraction

The primary outcomes of interest were the proportion of IA, minimally invasive adenocarcinoma (MIA), atypical adenomatous hyperplasia (AAH), and adenocarcinoma in situ (AIS). The secondary outcomes included histologic patterns among patients with IA and long-term clinical outcomes, such as overall survival and recurrence-free survival. Other extracted data included patient demographics, radiologic characteristics and protocol, number of participants, and extent of surgery.

Statistical analysis

To estimate the proportion of each pathologic stage, we performed a meta-analysis to estimate the summary effects with a proportion of each variable and 95% confidence interval (CI), using random-effect models since there was significant heterogeneity among the included studies, with

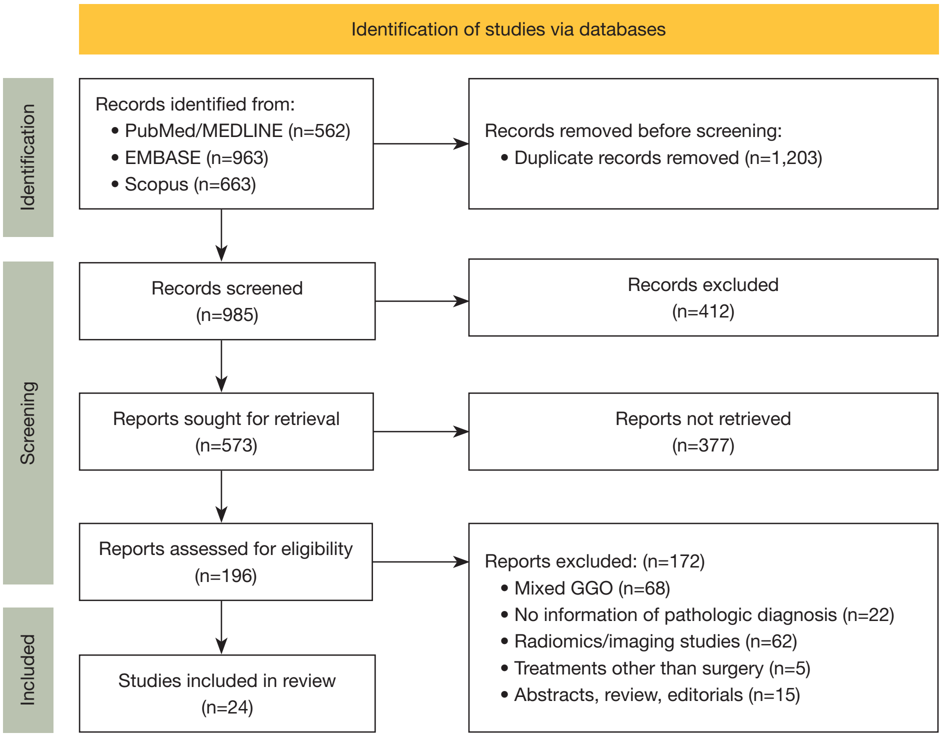

Figure 1 PRISMA flow chart showing the study selection process. GGO, ground glass opacity.

I^2>50%. Publication bias was not assessed because the proportion of meta-analyses was not comparable owing to the lack of a control arm. Statistical significance was defined as a two-sided P value <0.05. Statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager (RevMan) software version 5.2.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Following a systematic search, 24 studies were included in this analysis. The selection process is described in *Figure 1* (4-6,8-28). The study design and eligibility criteria of each article are demonstrated in Table S2. Fifteen articles applied the size criteria (4-6,11-13,18-25,27), while four studies (11,18,21,25) mentioned the persistence of pure GGN. Patient characteristics, including radiologic findings, surgical strategies, and clinical outcomes, are shown in *Table 1*. Male patients accounted for 27.5–63% of the patients, and 10 studies with clinical outcomes reported nearly no recurrence or death during the follow-up other than one study.

The histopathological outcomes of the included studies are shown in *Table 2*. Among these, 18 studies specifically described the proportion of IA among resected cases of pure GGN. The pooled proportion of IA was 29% in the overall estimation and 27% (95% CI: 18–37%, I^2=95%) in the meta-analysis (*Figure 2*). The pooled proportion of non-lepidic predominant IA was 37% by overall estimation and 50% (95% CI: 35–65%, I^2=91%) in the meta-analysis (*Figure 3*). The proportions of other types (MIA, 24%; AIS, 36%; AAH, 11%) are described in *Table 3* (Figures S1-S3).

In terms of the surgical strategy, 12 studies described the extent of surgery, such as lobectomy or sublobar resection (*Table 1*). The proportion of sublobar resection was 58% by overall estimation and 60% (95% CI: 38–78%, I^2=95%) by meta-analysis (*Figure 4*). Regarding lymph node dissection, only two studies reported the absence of lymph node metastasis (4,26).

Table 4 summarizes the predictive factors related to IA among resected cases of pure GGN. Among nine studies, five suggested the size of pure GGN as a predictive factor for IA (4,11,12,26,27). Hounsfield unit (HU) was found to be significant in two studies (13,15) and other radiologic characteristics (25), including maximal standard uptake

Table 1 Clinical characteristics of participants in included studies

Author	Year	Age, years	Demographics		Radiologic variables		Surgical extent		Prognosis	
			Male	Never smoker	Size, mm	Hounsfield unit	Lobectomy	Sublobar resection	Follow up periods, months	Clinical outcome
Zhu (20)	2022	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sun (13)	2022	Mean 61.2 (SD 6.9)	35/69	55/69	Mean 34 (SD 4)	Mean −550.6 (SD 77.0)	66/69	3/69	Median 70.3 (range, 60.1–137.4)	No recurrence or metastasis
Fu (26)	2021	N/A	119/432	364/432	N/A	N/A	120/432	312/432	Median 51.6	5-year RFS 100%, 5-year 99.5%
Wang (28)	2021	Median 59 (IQR, 52–64)	103/273	229/273	Median 19 (IQR, 15–24)	Mean −511 (SD 104.5)	185/273	88/273	Median 68 (IQR, 60–84)	5-year RFS 100%
Sun (10)	2020	Mean 56.38 (SD 10.69)	28/102	95/102	N/A	N/A	N/A	N/A	Median 30.8	No recurrence or metastasis
Li (15)	2020	Mean 55 (SD 9.99; range, 26–83)	35/90	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Chen (27)	2019	Median 49 (range, 28–72)	21/59	N/A	Mean 7.8 (range, 4–18)	N/A	3/59	56/59	N/A	N/A
Lee (4)	2019	Median 59.5 (range, 34–77)	11/36	32/36	8.5 (range, 4–19)	Median −614 (range, −770 to 442)	7/44	37/44	N/A	N/A
Mao (9)	2019	Median 58 (range, 39–78)	46/109	N/A	N/A	N/A	109/109	N/A	N/A	N/A
Wang (17)	2019	Mean 36.52 (SD 5.07)	30/91	64/91	Mean 8.65 (SD 2.34)	N/A	3/91	72/91	N/A	N/A
Ye (24)	2018	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Moon (16)	2018	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Li (14)	2018	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sawada (19)	2009	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Median 45.0 (range 1.6–95)	No recurrence or death
Yamaguchi (22)	2015	N/A	N/A	N/A	N/A	N/A	17/33	16/33	Median 30.4 (range 4.9-102.5)	No recurrence or metastasis
Ichinose (6)	2014	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lim (11)	2013	Median 59 (range, 43–71)	20/46	32/46	Mean 16.6 (SD 5.5; range, 10.1–30)	N/A	27/46	19/46	Median 51.5 (range 36-98)	No recurrence or metastasis

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Age, years	Demographics		Radiologic variables		Surgical extent		Prognosis	
			Male	Never smoker	Size, mm	Hounsfield unit	Lobectomy	Sublobar resection	Follow up periods, months	Clinical outcome
Cho (23)	2013	Mean 57.9 (range, 31–80)	29/46	22/46	Mean 9.0 (range, 6–18)	N/A	23/46	23/46	N/A	N/A
Eguchi (8)	2014	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No recurrence or metastasis
Liang (25)	2015	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kakinuma (18)	2016	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fournel (12)	2017	N/A	N/A	N/A	N/A	N/A	6/27	21/27	N/A	N/A
Zha (5)	2016	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No recurrence
Kitami (21)	2016	Median 64 (range, 39–83)	32/72	N/A	Mean 12.9 (SD 6.1)	Mean −569 (SD 126)	31/78	47/78	Median 46	Three cases with solid predominant had recurrence

Sublobar resection includes wedge resection and segmentectomy. N/A, not available; SD, standard deviation; RFS, recurrence-free survival; IQR, interquartile range.

value (SUVmax) (6), were also suggested.

Discussion

With the increasing number of GGNs in patients with lung cancer, persistent pure GGN has also received attention from thoracic surgeons. However, management strategies, such as surgery and close monitoring, vary among institutions. Clinicians has regarded pure GGN as indolent lesions, and their pathologic diagnosis has been empirically considered as lepidic predominant lesions (29). However, this study integrated histopathologic outcomes of resected pure GGN and suggested more evidence-based results of pure GGN. Notably, the proportion of IA was relatively high at 27%, and half of the IA in cases of pure GGN was not lepidic predominant. This analysis could guide surgeons to have a more comprehensive understanding and identify a suitable surgical candidate among pure GGN.

The current guidelines classify pure GGN as a lepidic predominant lesion, and the clinical stage of lesions with pure GGN is classified as clinical stage 0 (29). However, based on the analysis in this article, this approach should be reconsidered. From a histopathological perspective, there was a significant proportion of IA in cases of pure GGN, and even acinar- or papillary-dominant lesions were found at a higher frequency than expected. Since lung cancers that presented as pure GGN demonstrated excellent prognosis, it may be appropriate to have other classifications for this relatively indolent radiologic type of lung cancer.

The surgical strategy for pure GGN is not standardized, although an increasing number of studies have been favoring sublobar resection in this group (30,31). The JCOG 0804 trial demonstrated excellent outcomes of sublobar resection among tumors with a maximum diameter of ≤20 mm and consolidation-to-tumor ratio (CTR) ≤0.25 (32). Moreover, the clinical benefit of sublobar resection was achieved in radiologically invasive pulmonary lesions with a CTR >0.5 in the JCOG 0802 trial (33). Therefore, the standard extent of surgery in cases of pure GGN should be sublobar resection. In this study, the proportion of sublobar resection was approximately 60%. Further, since most of the articles included in this meta-analysis were published between 2009 and 2022, our findings represent the current preference for sublobar resection over lobectomy.

In terms of proper lymphadenectomy, there is insufficient evidence for comparing different types of mediastinal lymph node dissection (MLND) procedures. Zhang *et al.* reported lymph node metastasis among

Table 2 Pathologic outcomes of resected pure ground glass nodules in included studies

Author	Year	Pathologic criteria	AAH	AIS	MIA	IA	Lepidic predominant IA	Acinar predominant IA	Papillary predominant IA	Micropapillary or solid predominant IA
Zhu (20)	2022	WHO 2021	AAH or AIS 116/653		MIA or IA 537/653		N/A	N/A	N/A	N/A
Sun (13)	2022	IASLC/ATS/ERS 2011	N/A	8/69	5/69	56/69	35/56	10/56	11/56	N/A
Fu (26)	2021	IASLC/ATS/ERS 2011	N/A	118/432	213/432	101/432	64/101	31/101	0/101	6/101
Wang (28)	2021	IASLC/ATS/ERS 2011	N/A	N/A	N/A	273/273	239/273	13/273	21/273	0/273
Sun (10)	2020	IASLC/ATS/ERS 2011	N/A	N/A	N/A	102/102	28/102	Acinar or papillary 74/102		0/102
Li (15)	2020	IASLC/ATS/ERS 2011	N/A	20/90	22/90	48/90	N/A	N/A	N/A	N/A
Chen (27)	2019	WHO 2015	25/59	32/59	2/59	0/59	N/A	N/A	N/A	N/A
Lee (4)	2019	WHO 2015	1/44	18/44	15/44	10/44	2.0/10	7.0/10	1.0/10	0/10
Mao (9)	2019	IASLC/ATS/ERS 2011	N/A	N/A	N/A	109	63/109	28/109	18/109	0/109
Wang (17)	2019	IASLC/ATS/ERS 2011	8/91	16/91	42/91	13/91	N/A	N/A	N/A	N/A
Ye (24)	2018	IASLC/ATS/ERS 2011	N/A	AIS or MIA 475/534		59/534	N/A	N/A	N/A	N/A
Moon (16)	2018	WHO 2015	N/A	37/106	60/106	36/106	N/A	N/A	N/A	N/A
Li (14)	2018	IASLC/ATS/ERS 2011	N/A	AIS or MIA 90/167		77/167	N/A	N/A	N/A	N/A
Sawada (19)	2009	WHO 2004	N/A	AIS or MIA 53/63		10/63	0/10	1.0/10	9.0/10	N/A
Yamaguchi (22)	2015	IASLC/ATS/ERS 2011	3/47	29/47	4/47	8/47	N/A	N/A	N/A	N/A
Ichinose (6)	2014	IASLC/ATS/ERS 2011	6/114	70/114	16/114	13/114	1.0/13	2.0/13	10.0/13	N/A
Lim (11)	2013	IASLC/ATS/ERS 2011	N/A	19/46	9/46	18/46	8.0/18	8.0/18	2.0/18	N/A
Cho (23)	2013	IASLC/ATS/ERS 2011	3/46	23/46	2/46	3/46	N/A	N/A	N/A	N/A
Eguchi (8)	2014	IASLC/ATS/ERS 2011	N/A	5/33	15/33	12/33	5.0/12	4.0/12	3.0/12	N/A
Liang (25)	2015	IASLC/ATS/ERS 2011	26/74	30/74	MIA or IA 18/74		N/A	N/A	N/A	N/A
Kakinuma (18)	2016	IASLC/ATS/ERS 2011	5/35	21/35	9/35	N/A	N/A	N/A	N/A	N/A
Fournel (12)	2017	IASLC/ATS/ERS 2011	0/27	8.0/27	8.0/27	10/27	3.0/10	2.0/10	4.0/10	N/A
Zha (5)	2016	IASLC/ATS/ERS 2011	N/A	137/553	146/553	270/553	156/270	41/270	48/270	15/270
Kitami (21)	2016	IASLC/ATS/ERS 2011	10/78	30/78	19/78	18/78	14/18	N/A	N/A	N/A

AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; WHO, World Health Organization; N/A, not available; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society.

151 tumors with CTR ≤0.5, and no lymph node involvement was observed regardless of tumor size (34). Moreover, a study comparing hilar lymph node dissection and MLND among part-solid adenocarcinoma described no significant difference in clinical outcomes after propensity score matching (35). Although surgeons should consider patient risk factors and tumor characteristics to choose the appropriate MLND, extensive dissection may be inappropriate for pure GGN. Recently, several ablative treatments that only control the main tumor lesions have exhibited superior clinical outcomes among ground glass opacity-dominant lesions. Indeed, Mikami *et al.* reported no local or regional recurrence in 126 patients after SBRT (36), and radiofrequency ablation also showed promising results, with a 5-year cancer-specific survival rate of 100% (37). A multidisciplinary discussion would be appropriate to determine the optimal lymphadenectomy or treatment modality for pure GGN.

Overdiagnosis and treatment are important issues in the management of pure GGN (3). Although most cases of pure GGN are considered slow- or non-growing lesions, specific indications for surgery should be discussed based

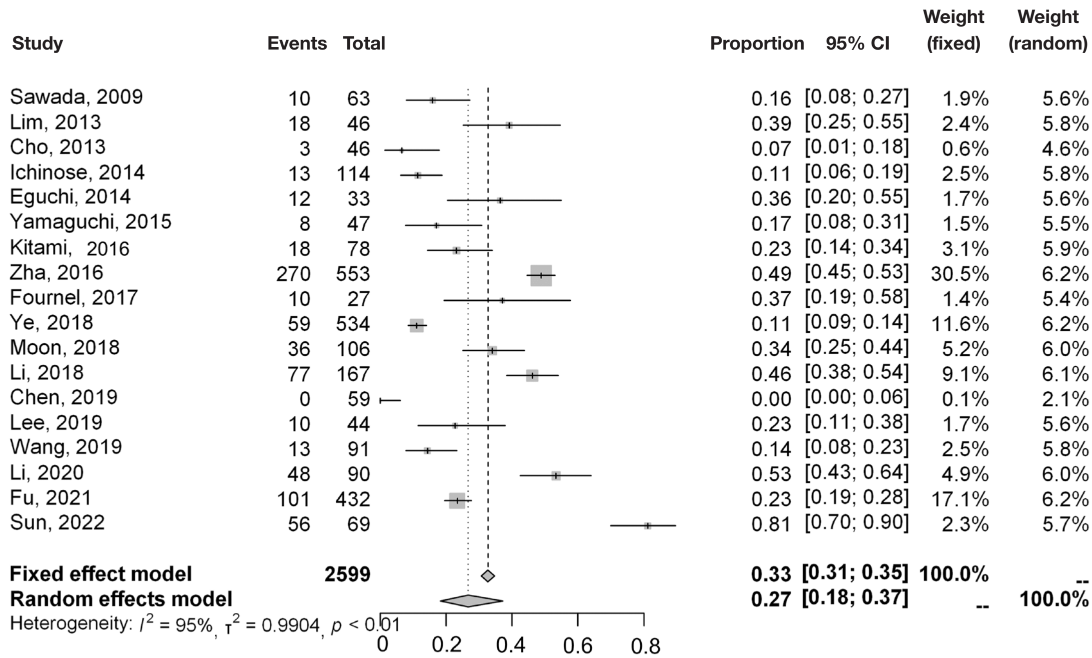

Figure 2 Forest plot of the meta-analysis to estimate the proportion of invasive adenocarcinoma among resected pure ground glass pulmonary lesions. CI, confidence interval.

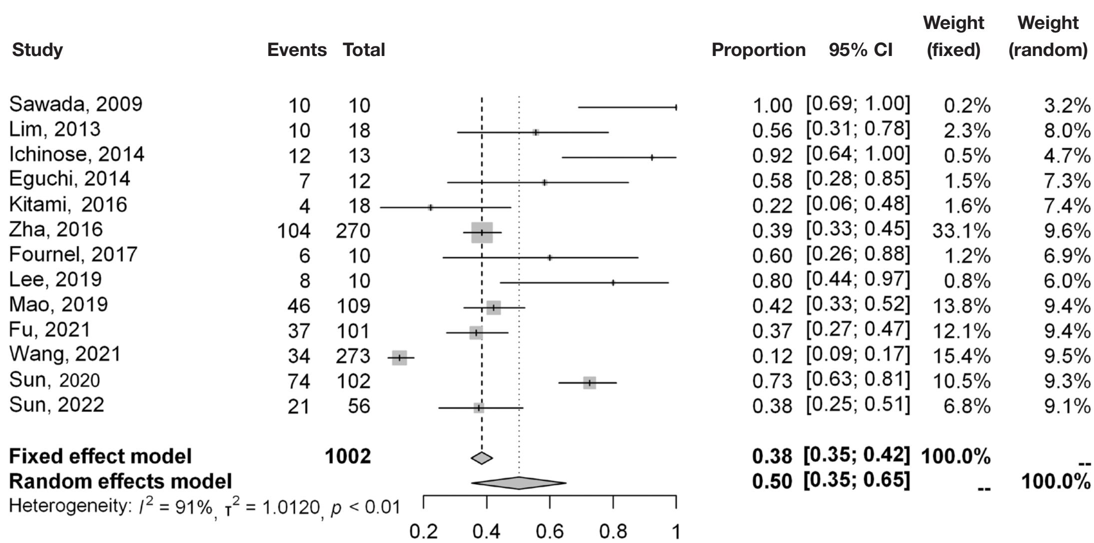

Figure 3 Forest plot of the meta-analysis to estimate the proportion of non-lepidic predominant subtypes among invasive adenocarcinoma presented as pure ground glass pulmonary lesions. CI, confidence interval.

on the pathologic diagnosis. As properly resected AIS/MIA has a favorable prognosis after a 10-year follow-up (38), detecting IA among pure GGN would be a suitable strategy to identify surgical candidates. For this purpose, radiologic characteristics and size were considered relevant factors. Although the optimum size cut-off value was not determined, it is reportedly in the range of 10 to 15 mm (4,12,26). Several radiologic characteristics, such

Table 3 Meta-analyses on the clinical characteristics and pathologic outcomes of resected pure ground glass nodules

Pathology variables	Number of studies	Total number of patients	Number of events	Proportion (overall), %	Proportion by meta-analysis [95% CI], %		I^2 (P value)	τ^2
					Random effect	Fixed effect		
IA	18	2,599	762	29	27 [18–37]	33 [31–35]	95% (<0.01)	0.990
Non-lepidic predominant IA	13	1,002	373	37	50 [35–65]	38 [35–42]	91% (<0.01)	1.012
MIA	16	1,870	587	31	24 [16–34]	34 [32–37]	91% (<0.01)	0.837
AIS	17	1,944	621	32	36 [28–44]	33 [31–35]	89% (<0.01)	0.473
AAH	10	615	87	14	11 [6–21]	19 [16–23]	87% (<0.01)	0.981
Sublobar resection	11	1,198	694	58	60 [38–78]	58 [55–62]	95% (<0.01)	1.969

CI, confidence interval; IA, invasive adenocarcinoma; MIA, minimally invasive adenocarcinoma; AIS, adenocarcinoma in situ; AAH, atypical adenomatous hyperplasia.

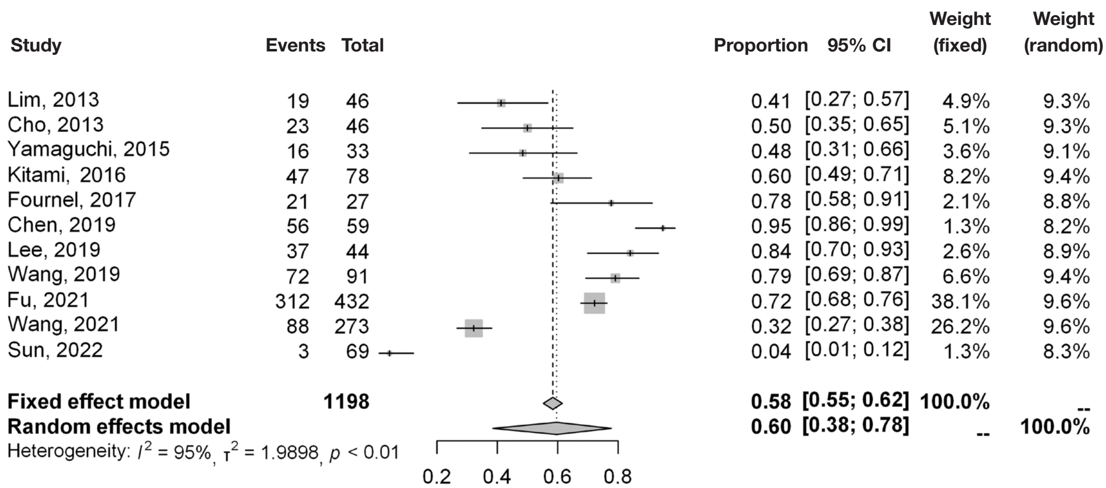

Figure 4 Forest plot of the meta-analysis to estimate the proportion of sublobar resection among resected pure ground glass pulmonary lesions. CI, confidence interval.

as irregular margin, bubble lucency, air bronchogram (27), and proportion of blood vessels (25) have been suggested; however, their standardization would be necessary to obtain reproducible results in other institutions. With the development of radiomics studies in this field, we expect a further detailed analysis of radiological variables to provide more reliable criteria for IA among pure GGN.

This study had several limitations. First, there has been a shift in determining pathologic diagnosis of early-stage lung cancer. Bronchoalveolar carcinoma, which was defined in the WHO 2004 classification, was later further differentiated into AIS, MIA, and IA based on the 2011 International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) guideline. Though most studies other than one introduced the concepts of new classification, there could be some variations. Another factor is interobserver variability in the pathologic diagnosis of GGN. Depending on patients' population and the number of experienced pathologists, final diagnosis could vary from institutions (39-41). Though several studies evaluated good correlation between pulmonary pathologists, the discrepancy exists due to complicated lung pathology such as emphysema, fibrosis, or inflammatory tissue. Third, there was a significant bias in patient selection. As the persistence of pure GGN is important to

Table 4 Predictive factors for invasive adenocarcinoma among resected pure ground glass nodules

Author	Year	Factors	P value	Size effect
Sun (13)	2022	Mean HU attenuation	0.0087	
Fu (26)	2021	Radiologic size	<0.001	OR 47.165 (95% CI: 19.279–115.390)
Li (15)	2020	Mean HU attenuation	0.019	N/A
Chen (27)	2019	Radiologic characteristics: irrelevant margin; bubble lucency; air bronchogram; size	N/A	N/A
Lee (4)	2019	Radiologic size (10 mm cut off)	0.005	OR 24.05 (95% CI: 2.607–221.908)
Ichinose (6)	2014	Positive on PET (SUV_{max} >0.8)	<0.001	OR 16.0
Lim (11)	2013	Radiologic size	0.010	OR 1.236
Liang (25)	2015	Amount of blood vessels	0.050	OR 3.13
Fournel (12)	2017	Radiologic size (13 mm cut off)	N/A	N/A

HU, Hounsfield unit; OR, odds ratio; CI, confidence interval; N/A, not available; PET, positron emission tomography; SUV_{max}, maximal standard uptake value.

predict its malignancy potential, a period of observation was necessary; however, only four studies mentioned the persistence of lesions. If some studies performed surgical resection without a sufficient observation period, benign or less-invasive malignant lesions would have also been more included. Additionally, different size criteria for inclusion could significantly impact pathological outcomes. Fourth, patient demographics and other surgical variables may be confounding factors. Owing to limited accessibility to patient data, we could not describe the impact of age, sex, smoking history, and surgical strategies. Especially, the smoking status was found as a contributing factor for the growth of GGN (42). These factors should be matched to interpret the fate of pure GGNs. Lastly, there was substantial heterogeneity among the outcomes, which may be related to the study design, number of participants, surgical strategies, or other unidentifiable factors. Therefore, result interpretation should be applied cautiously and further prospective studies with the collaboration from multiple institutions are necessary.

Conclusions

This is the first systematic review and meta-analysis of the histopathological outcomes of pure GGN. The proportion of IA was higher than expected, with different subtypes of IA observed rather than the lepidic predominant type alone. Considering the possible radiologic factors that predict IA among pure GGN, the criteria for resection or follow-up of patients with pure GGN should be investigated.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1089/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1089/coif). The authors have no conflicts of interest to declare.

Ethical Statements: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Detailed search strategy according to database (14 June 2022)

PubMed search strategy (562 hits)
Years/issue searched: inception to 2022
Search date: 14 June 2022
(ground glass opaci*) AND (adenocarcinoma) AND (patholog* OR histopathog*) Filters: English
Embase search strategy (963 hits)
#1. ‘ground glass opacity’ OR ‘ground glass’ OR ‘ground glass opacities’
#2. ‘adenocarcinoma’ OR ‘pulmonary adenocarcinoma’
#3. ‘pathology’ OR ‘pathologic’ OR ‘histopathology’ OR ‘histologic’ OR ‘histopathologic’
#4. #1 AND #2 AND #3 AND [english]/lim
Scopus search strategy (663 hits)
Years/issue searched: inception to 2021
Search date: 14 June 2022
((ground glass opaci*) AND (adenocarcinoma) AND (patholog* OR histopathog*) AND (LIMIT-TO (LANGUAGE, “English”))

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Table S2 Eligibility criteria of included studies

Author	Year	Country/ region	Study period	Study design	Number of Participants	Eligibility Criteria					
						Size	CT slice thickness	Synchronous lesions	Demographic factor	Pathologic criteria	Period of persistency
Zhu	2022	China	2018–2019	Retrospective	653	pGGN <30 mm	Less than 1.5 mm				
Sun	2022	China	2007–2015	Retrospective	69	pGGN ≥30 mm			At least 5 years of follow-up		
Fu	2021	China	2011–2015	Retrospective	432			Solitary	No history of malignancy		
Wang	2021	China	2013–2015	Retrospective	273				At least 5 years of follow-up	IA only included	
Sun	2020	China	2012–2015	Retrospective	102		1 mm			IA only included	
Li	2020	China	2015–2019	Retrospective	90		1 mm			AAH excluded	
Chen	2019	Taiwan	2015–2019	Retrospective	59	pGGN ≤20 mm		Solitary	No history of malignancy		
Lee	2019	Korea	2012–2016	Retrospective	44	pGGN <20 mm					
Mao	2019	China	2010–2012	Retrospective	109				No history of malignancy	IA only included	
Wang	2019	China	2016–2017	Retrospective	91				Age between 18 to 44 years, no history of malignancy		
Ye	2018	China	2008–2014	Retrospective	534	pGGN ≤30 mm	1 mm			AAH excluded	
Moon	2018	Korea	2010–2017	Retrospective	106						
Li	2018	China	2013–2016	Retrospective	167			Solitary			
Sawada	2009	Japan	2000–2005	Retrospective	63	pGGN ≤30 mm	1 mm from 2001 and 2 mm before				
Yamaguchi	2015	Japan	2006–2012	Retrospective	47	pGGN ≤20 mm	1 mm				
Ichinose	2014	Japan	2008–2010	Retrospective	114	pGGN ≤20 mm	1 mm slice thickness				
Lim	2013	Korea	2003–2008	Retrospective	46	pGGN >10 mm			At least 3 years of follow-up		persistent
Cho	2013	Korea	2004–2009	Retrospective	46	pGGN ≤30 mm			At least 2 years of follow-up		
Eguchi	2014	Japan	1998–2013	Retrospective	33		1.25 mm		At least 2 years of follow-up		
Liang	2015	China	2010–2014	Retrospective	74	5 mm ≤ pGGN ≤30 mm					Persistent
Kakinuma	2016	Japan	2009–2011	Multicenter prospective	35	pGGN ≤30 mm	Less than 1.25 mm				At least 3 months of persistency
Fournel	2017	France	2008–2014	Retrospective	27	pGGN ≤30 mm		Less than five			
Zha	2016	China	2008–2014	Retrospective	553	pGGN ≤30 mm			No history of malignancy		
Kitami	2016	Japan	2001–2014	Retrospective	78	pGGN ≤30 mm					At least 3 months of persistency

AAH, Atypical adenomatous hyperplasia; CT, computed tomography; IA, invasive adenocarcinoma; pGGN, pure ground glass nodule.

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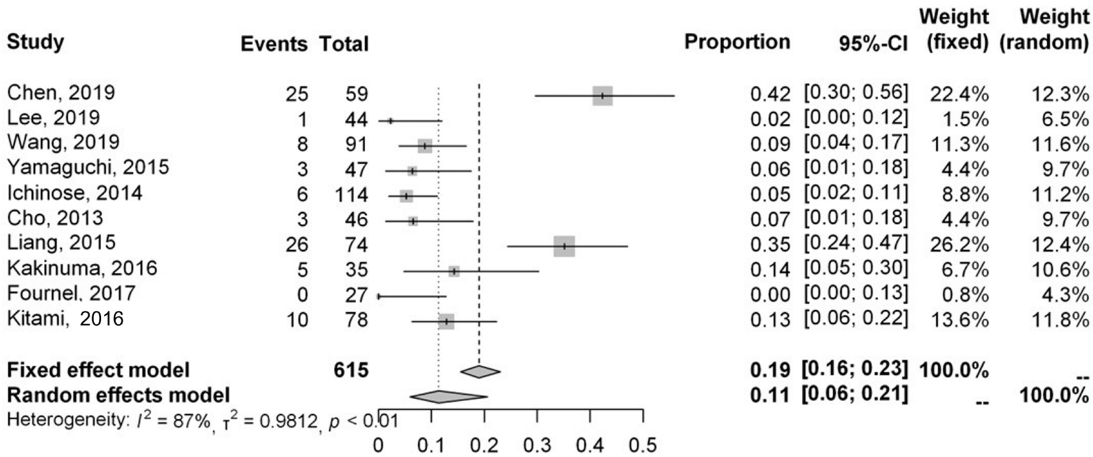

Figure S1 Forest plot of meta-analysis to estimate the proportion of atypical adenomatous hyperplasia among resected pure ground glass pulmonary lesions.

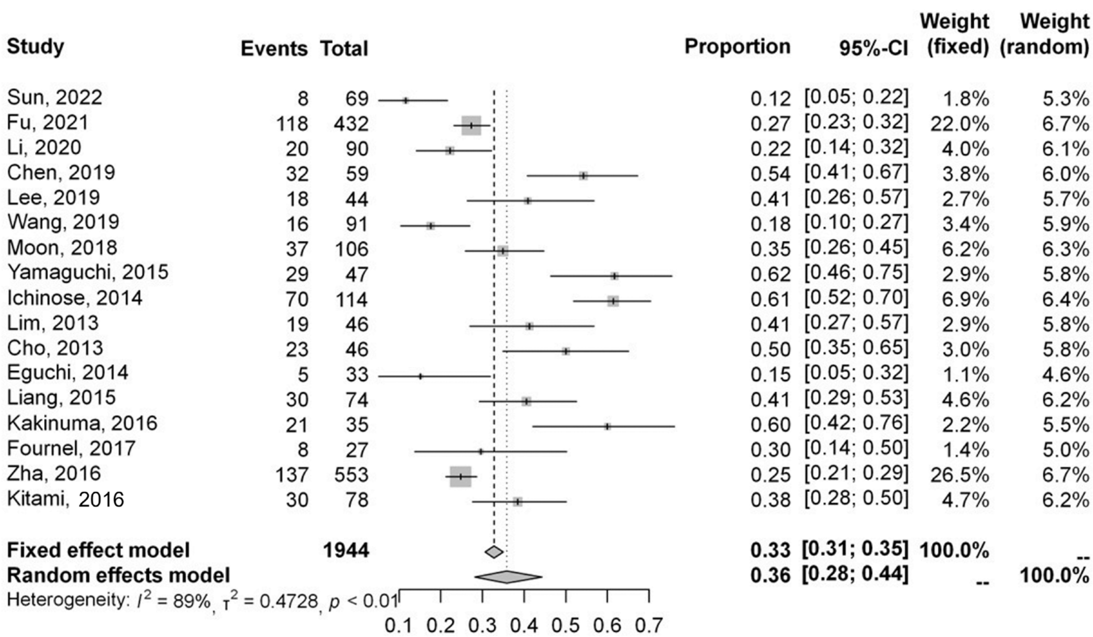

Figure S2 Forest plot of meta-analysis to estimate the proportion of adenocarcinoma in situ among resected pure ground glass pulmonary lesions.

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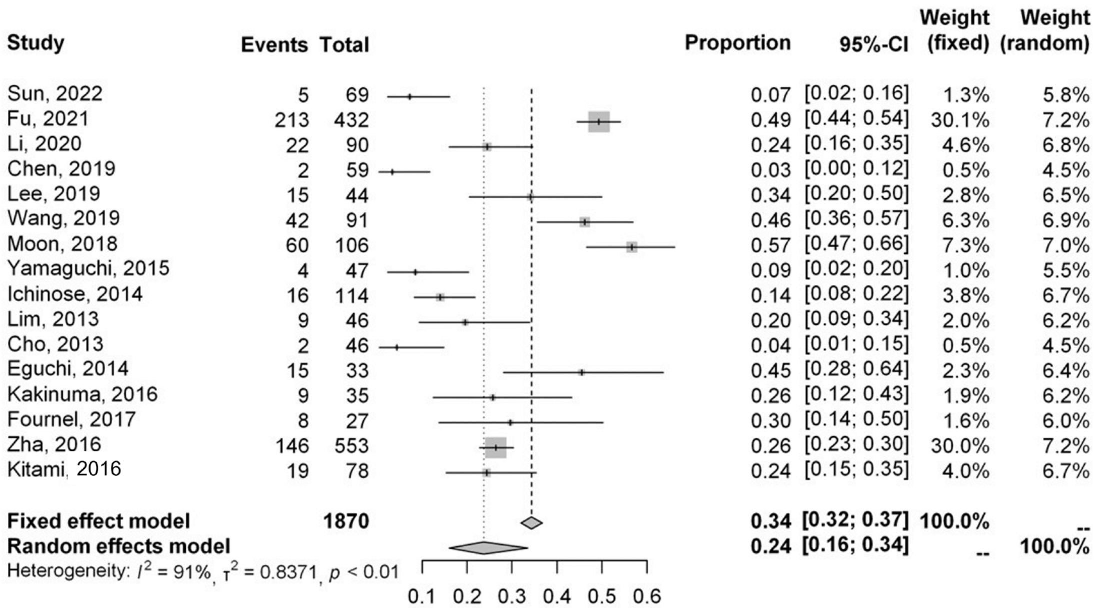

Figure S3 Forest plot of meta-analysis to estimate the proportion of minimally invasive adenocarcinoma among resected pure ground glass pulmonary lesions.

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