



Radiographic ground-glass nodules predict less aggressive features and favorable immune landscapes in early lung adenocarcinoma and its precursors

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Background: Lung adenocarcinoma (LUAD) remains the leading cause of cancer-related deaths globally, often due to late-stage diagnosis. Advancements in computed tomography (CT) have revolutionized the detection of indeterminate pulmonary nodules (IPNs), spanning benign lesions to early-stage LUAD. We aimed to understand early lung carcinogenesis and identify clinicopathological and immune features that may influence patient prognosis.

Methods: This study retrospectively integrates clinical, radiographic, pathological, and immune data from 174 patients with resected pulmonary nodules, including atypical adenomatous hyperplasia (AAH, n=19), adenocarcinoma in situ (AIS, n=50), minimally invasive adenocarcinoma (MIA, n=40), and stage I invasive adenocarcinoma (ADC, n=65).

Results: Among 174 resected nodules, ground-glass nodules (GGNs) were observed in 54.6% of all cases. Early-stage ADCs exhibited the lowest proportion of GGNs compared to AAH, AIS, and MIA, respectively (AAH: 52.6%; AIS: 86.0%; MIA: 72.5%; ADC: 20.0%; $P<0.001$). Well differentiated ADCs were significantly associated with lower rates of pleural traction (6.7%) and lymphovascular invasion (0%)

compared to poorly differentiated ADCs (pleural traction: 36.4%, lymphovascular invasion: 18.2%). Immune profiling showed a progressive decline in CD8⁺ T cells and an increased CD4/CD8 ratio from AAH to ADC. GGNs exhibited lower intratumoral CD4⁺ and CD8⁺ T cell densities than non-GGNs, consistent with their indolent histology and less invasive behavior. Radiographic appearance was strongly correlated with tumor differentiation and aggressiveness.

Conclusions: These insights deepen our understanding of early lung carcinogenesis and offer potential pathways for prognostic stratification and personalized care for patients presenting with IPNs during CT screening.

Keywords: Indeterminate pulmonary nodule (IPN); ground-glass nodule (GGN); lung adenocarcinoma (LUAD); early detection; immune profiling

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Introduction

Lung cancer remains the leading cause of cancer-related deaths globally, largely due to frequent late-stage diagnosis

when curative treatments are limited (1). In recent years, the widespread adoption of computed tomography (CT)-guided screening and high-resolution CT scans has dramatically increased the detection of indeterminate pulmonary nodules (IPNs)—radiographically identified lung lesions that lack definitive features to distinguish benign from malignant disease at the time of imaging. These nodules encompass a broad spectrum of conditions, including inflammatory or infectious processes, as well as early-stage lung adenocarcinoma (LUAD) and its precursor lesions, which often remain without histologic confirmation prior to resection (2-4).

While most IPNs are benign, a subset represents precursor lesions or early-stage LUAD, the most prevalent histological subtype of lung cancer (5). The classification of early-stage LUAD and its precursors spans a spectrum of lesions, including atypical adenomatous hyperplasia (AAH), the only recognized preneoplastic lesion leading to LUAD, through preinvasive adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), to fully invasive adenocarcinoma (ADC) (6).

IPNs are radiologically categorized into three main types: nonsolid nodules, part-solid nodules, and solid nodules. Nonsolid nodules, also known as pure ground-glass nodules (GGNs) or ground-glass opacities (GGOs), exhibit increased attenuation without obscuring bronchial or vascular structures (7,8). Part-solid nodules feature both nonsolid and solid components, while solid nodules present as homogeneously dense soft tissue (9).

Previous studies indicate that LUAD precursors exhibit simpler molecular profiles and more robust immune activity compared to invasive LUAD (5,6,10). However, the

Highlight box

Key findings

- This study clarified ground-glass nodules (GGNs) as potential biomarkers for indolent disease, underscoring their role in early detection and risk stratification in lung adenocarcinoma (LUAD). The findings provided actionable insights into the biology and progression of early-stage LUAD and its precursors, with implications for targeted surveillance and prevention strategies.

What is known and what is new?

- LUAD is the leading cause of cancer-related deaths, with indeterminate pulmonary nodules detected via computed tomography representing a spectrum from benign lesions to early-stage malignancies, where GGNs are often associated with less aggressive tumor behavior.
- This study revealed that GGNs are predominantly found in precursor LUAD lesions and exhibit a more balanced or regulated immune profile, consistent with their indolent histology and less invasive behavior. In contrast, poorly differentiated adenocarcinomas (ADCs) show increased aggressiveness and a lower prevalence of GGNs, highlighting their potential role in risk stratification.

What is the implication, and what should change now?

- Radiologic GGNs should be recognized as favorable prognostic markers to guide personalized surveillance strategies, while poorly differentiated ADCs and solid nodules require more intensive monitoring and early intervention, emphasizing the need for integrated radiologic, pathologic, and immune profiling in risk stratification.

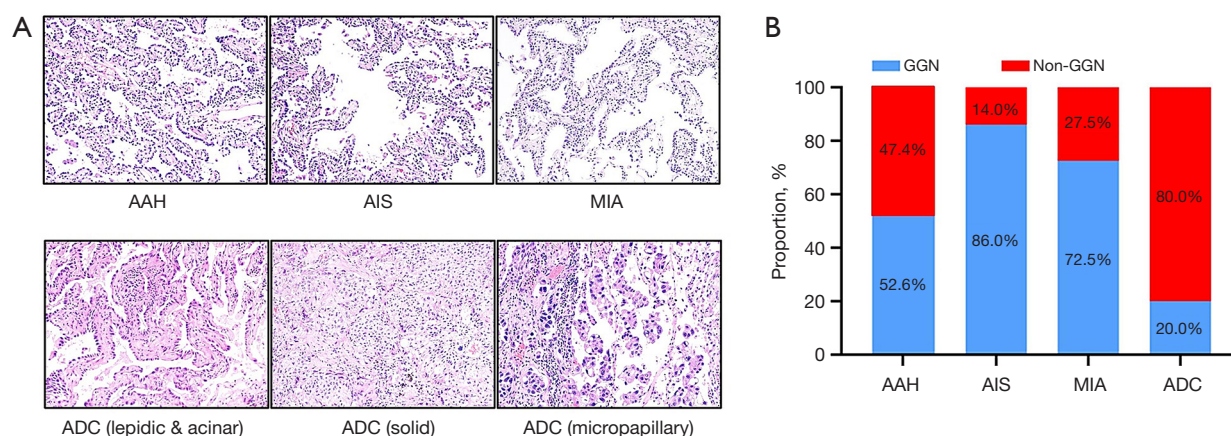


Figure 1 Early-stage LUAD and its precursor lesions: representative images and proportions of GGNs versus non-GGNs by histology. (A) Representative pathological images (H&E staining, microscopy: 200×) of AAH, preinvasive AIS, MIA, and invasive ADC included in this study. (B) Proportions of GGNs and non-GGNs observed in AAH, AIS, MIA, and ADC. AAH, atypical adenomatous hyperplasia; ADC, adenocarcinoma; AIS, adenocarcinoma in situ; GGN, ground-glass nodule; H&E, hematoxylin and eosin; LUAD, lung adenocarcinoma; MIA, minimally invasive adenocarcinoma.

correlation between pure GGNs and clinical aggressiveness in preneoplastic, preinvasive, and early-stage LUAD remains inadequately explored. Some evidence suggests that pure GGNs predict better outcomes compared to nodules with solid components, but this association is understudied due to the limited availability of clinical specimens from precursor lesions, as surgical intervention is not standard care.

In this study, we aimed to integrate clinical, radiographic, pathological, and immune data from a cohort of resected pulmonary nodules from 174 patients, including AAH (n=19), AIS (n=50), MIA (n=40), and stage I invasive ADC (n=65) (Figure 1A), with or without GGN features. Our goal is to enhance the understanding of early lung carcinogenesis and to identify clinicopathological features that may influence patient prognosis, particularly in those presenting with IPNs during CT screening. We present this article in accordance with the STROBE reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-231/rc>).

Methods

Patient cohort and sample collection

Patient specimens were retrospectively collected from 174 individuals with pulmonary nodules detected by CT scan, who underwent surgical resection at Sun Yat-

sen University Cancer Center, Guangzhou, China from January 2017 to December 2022. All included cases were initially identified as IPNs on preoperative CT imaging and subsequently confirmed by pathology as AAH, AIS, MIA, or stage I invasive ADC. None of these patients received neoadjuvant chemotherapy, radiotherapy, or immunotherapy. Pathology quality control was implemented, and all samples underwent central pathology review prior to further analyses. Hematoxylin and eosin (H&E) slides from each case were independently reviewed by two lung cancer pathologists to confirm the diagnosis (Figure 1A). All specimens were formalin-fixed paraffin-embedded (FFPE). Histological subtype was defined, and pathologic classification was performed on all samples. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Board (IRB) at Sun Yat-sen University Cancer Center (No. G2022-117-01) and individual consent for this retrospective analysis was waived.

Radiographic evaluation

All pulmonary nodules were evaluated using thin-section low-dose CT scans and categorized into GGNs, part-solid nodules, or solid nodules based on standardized radiologic criteria, including attenuation patterns and the visibility of bronchial and vascular structures. GGNs were defined as areas of increased attenuation that did not obscure

underlying bronchial or vascular markings. Part-solid nodules contained both ground-glass and solid components, with the solid portion obscuring bronchial and/or vascular structures. Solid nodules were homogeneously dense lesions that completely obscured bronchial and vascular markings (7-9). Radiographic classification was performed independently by two thoracic radiologists, with discrepancies resolved by consensus. For comparative immune analysis, lesions were further grouped as GGNs or non-GGNs, with non-GGNs comprising both part-solid and solid nodules.

LUAD tumor classification

As part of the pathologic sub-classification, growth patterns were quantified within each tumor to ensure that the combined proportions totaled 100% per tumor. LUAD tumors were classified according to the updated grading criteria established by the International Association for the Study of Lung Cancer (IASLC) (11). Based on these criteria, tumors were then categorized into three differentiation groups: well differentiated, moderately differentiated, and poorly differentiated (Figure S1). Well differentiated tumors were defined as lepidic predominant and <20% high-grade components (i.e., solid or micropapillary). Moderately differentiated tumors were acinar or papillary predominant and <20% high-grade components. Poorly differentiated tumors were defined by the presence of $\geq 20\%$ high-grade patterns of growth.

Immunohistochemistry

Tumor tissues were FFPE. Sections were cut at a thickness of 4 μm and mounted on slides for immunohistochemical staining. Slides were incubated with primary antibodies against CD4 or CD8 (Zhongshan Jinqiao Biotech Company, Beijing, China), followed by treatment with an enzyme-conjugate secondary anti-mouse antibody. A DAB substrate-chromogen solution was then applied for visualization. Stained slides were scanned using the Aperio AT2 digital whole slide scanner (Leica, Wetzlar, Germany) and analyzed using Qupath software (Figure S2). Immune cell densities were quantified separately in the lesion (defined as the region containing neoplastic epithelial cells) and in the peritumoral stroma (defined as the adjacent non-neoplastic connective tissue and immune infiltrate immediately surrounding the lesion). This comparison was performed to assess immune cell localization and distribution patterns,

which may reflect differences in immune surveillance or exclusion within and around lesions of varying histologic stage. The number of positive cells in the tumor/lesion and tumor/lesion stroma was calculated as % of CD4⁺ or CD8⁺ cells per mm² area.

Statistical analysis

Graphs were generated using GraphPad Prism version 8.0 (La Jolla, CA, USA). Pearson's correlation coefficient was used to evaluate associations between two continuous variables. The Mann-Whitney *U* test was used for comparisons between two independent groups. Kruskal-Wallis *H* test was applied to compare categorical variables with more than two independent groups. Categorical variables were compared using the Chi-squared test. All *P* values were derived from two-sided tests, and values of *P*<0.05 were considered statistically significant.

Results

GGNs are more frequently observed in earlier-stage lesions

Our analysis of 174 patients with incidentally detected IPNs, all of whom underwent curative-intent surgery, revealed distinct radiographic growth patterns classified by expert thoracic radiologists using low-dose CT. IPNs were categorized into three groups based on tissue attenuation and the degree of bronchial and vascular margin obliteration: solid nodules, nonsolid nodules (GGNs), and part-solid nodules (mixed-solid) based on radiological findings. Pathological correlations were subsequently assessed.

As shown in Table 1, among 174 lesions representing LUAD precursors and early-stage ADCs, 95 (54.6%) were GGNs, 37 (21.3%) were part-solid nodules, and 42 (24.1%) were solid nodules. Notably, early-stage ADCs exhibited the lowest proportion of GGNs compared to AAH, AIS, and MIA, respectively (AAH: 52.6%; AIS: 86.0%; MIA: 72.5%; ADC: 20.0%; *P*<0.001) (Figure 1B). Interestingly, the proportion of non-GGNs among AAH lesions appears relatively high compared to AIS and MIA. We believe this finding may be partly attributable to the small sample size of the AAH group (*n*=19), which makes the proportions more sensitive to individual variability.

Of all lesions, only 7 (4.0%) exhibited pleural traction, and 5 (2.9%) showed lymphovascular invasion—both indicative of aggressiveness—all of which were early ADCs.

Table 1 Clinical and pathologic characteristics of the included patients

Characteristics	Overall (n=174)	AAH (n=19)	AIS (n=50)	MIA (n=40)	ADC (n=65)
Age (years)	57 [29–79]	51 [42–70]	53 [31–79]	56 [29–77]	57 [36–75]
Gender					
Female	103 (59.2)	10 (52.6)	27 (54.0)	29 (72.5)	37 (56.9)
Male	71 (40.8)	9 (47.4)	23 (46.0)	11 (27.5)	28 (43.1)
Smoking status					
Never smokers	147 (84.5)	13 (68.4)	39 (78.0)	38 (95.0)	57 (87.7)
Smokers	27 (15.5)	6 (31.6)	11 (22.0)	2 (5.0)	8 (12.3)
Lesion size (mm)	9 [0.5–40]	2 [0.5–10]	7 [0.5–17]	8.5 [2–25]	15 [5–40]
Location					
Right upper lobe	63 (36.2)	5 (26.3)	20 (40.0)	15 (37.5)	23 (35.4)
Right middle lobe	12 (6.9)	2 (10.5)	5 (10.0)	4 (10.0)	1 (1.5)
Right lower lobe	31 (17.8)	6 (31.6)	5 (10.0)	5 (12.5)	15 (23.1)
Left upper lobe	47 (27.0)	6 (31.6)	13 (26.0)	11 (27.5)	17 (26.2)
Left lower lobe	21 (12.1)	0	7 (14.0)	5 (12.5)	9 (13.8)
EGFR mutation					
<i>Ex19del</i>	27 (15.5)	0	1 (2.0)	6 (15.0)	20 (30.8)
<i>L858R</i>	30 (17.2)	0	1 (2.0)	10 (25.0)	19 (29.2)
Rare (e.g., <i>Exon 20, G719X</i>)	7 (4.0)	0	2 (4.0)	2 (5.0)	3 (4.6)
Absent	52 (29.9)	1 (5.3)	6 (12.0)	22 (55.0)	23 (35.4)
Unknown	58 (33.3)	18 (94.7)	40 (80.0)	0	0
GGN					
Yes	95 (54.6)	10 (52.6)	43 (86.0)	29 (72.5)	13 (20.0)
No	79 (45.4)	9 (47.4)	7 (14.0)	11 (27.5)	52 (80.0)
Radiographic pattern					
GGN	95 (54.6)	10 (52.6)	43 (86.0)	29 (72.5)	13 (20.0)
Part-solid	37 (21.3)	1 (5.3)	4 (8.0)	9 (22.5)	23 (35.4)
Solid	42 (24.1)	8 (42.1)	3 (6.0)	2 (5.0)	29 (44.6)
Pleural traction					
Yes	7 (4.0)	0	0	0	7 (10.8)
No	167 (96.0)	19 (100.0)	50 (100.0)	40 (100.0)	58 (89.2)
Lymphovascular invasion					
Yes	5 (2.9)	0	0	0	5 (7.7)
No	169 (97.1)	19 (100.0)	50 (100.0)	40 (100.0)	60 (92.3)

Data are presented as median [range] or n (%). AAH, atypical adenomatous hyperplasia; ADC, adenocarcinoma; AIS, adenocarcinoma in situ; GGN, ground-glass nodule; MIA, minimally invasive adenocarcinoma.

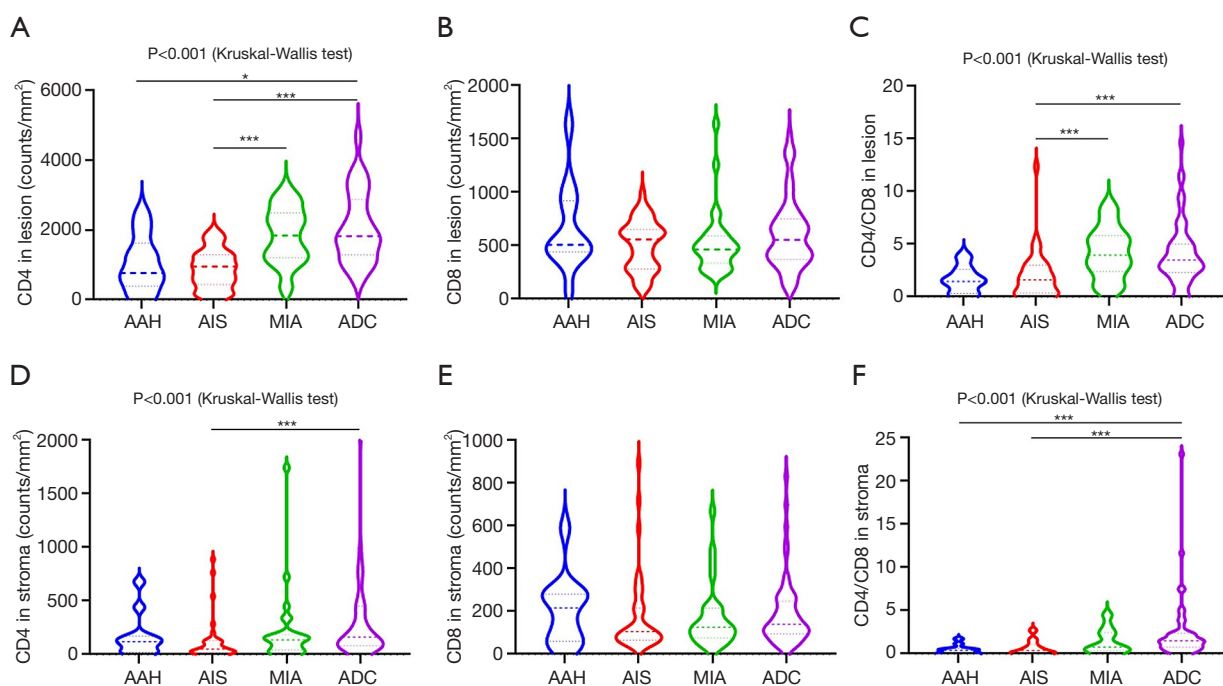


Figure 2 Immune landscape from preneoplasia to invasive LUAD. (A) CD4 density, (B) CD8 density, and (C) CD4/CD8 ratio within lesions of AAH, AIS, MIA, and invasive ADC. (D) CD4 density, (E) CD8 density, and (F) CD4/CD8 ratio within tumor/lesion stroma of AAH, AIS, MIA, and invasive ADC. The difference of T cell matrix among different stages was evaluated using two-sided Kruskal-Wallis H test. Data was used including AAH, AIS, MIA, invasive ADC. Statistical significance is indicated as: *, $P < 0.05$; ***, $P < 0.001$. AAH, atypical adenomatous hyperplasia; ADC, adenocarcinoma; AIS, adenocarcinoma in situ; LUAD, lung adenocarcinoma; MIA, minimally invasive adenocarcinoma.

Among these, six of the tumors with pleural traction and all five tumors with lymphovascular invasion were not GGNs. These findings suggest that GGNs are more common in earlier-stage lesions and are associated with less aggressive features.

Baseline characteristics, including age, gender, race, smoking status, and lesion location, did not differ significantly among groups (Table 1).

Gradually impaired immune response from pre-invasive to early invasive stages in LUAD

To evaluate the immune landscape across histologically confirmed lesions, we analyzed T cell markers using immunohistochemical staining. CD4⁺ (helper T cells) and CD8⁺ (cytotoxic T cells) densities were quantified. As lesions progressed from AAH to AIS, MIA, and ultimately early-stage ADC, we observed a gradual decline in CD8⁺ T cells, along with an increase in CD4⁺ T cells and a rising CD4/CD8 ratio (Figure 2A-2C). This trend was similarly

observed in the peritumoral stromal regions, although stromal T cell densities were consistently lower than those within the lesion (Figure 2D-2F).

When comparing GGNs to non-GGNs, CD4⁺, CD8⁺, and CD4/CD8 ratios were significantly lower in GGNs across all lesion types, both within the tumor and in the stroma (Figure 3A-3F). These findings may suggest a shift toward a cytotoxic T cell-dominant immune environment in non-GGNs, potentially reflecting an immune response to increased tumor aggressiveness. In contrast, GGNs may exhibit a more balanced or regulated immune profile, consistent with their indolent histology and less invasive behavior.

Increased aggressiveness in poorly differentiated ADC tumors

Among 65 early ADC tumors (Table 2), stratification by histologic grade—well differentiated, moderately differentiated, and poorly differentiated—revealed

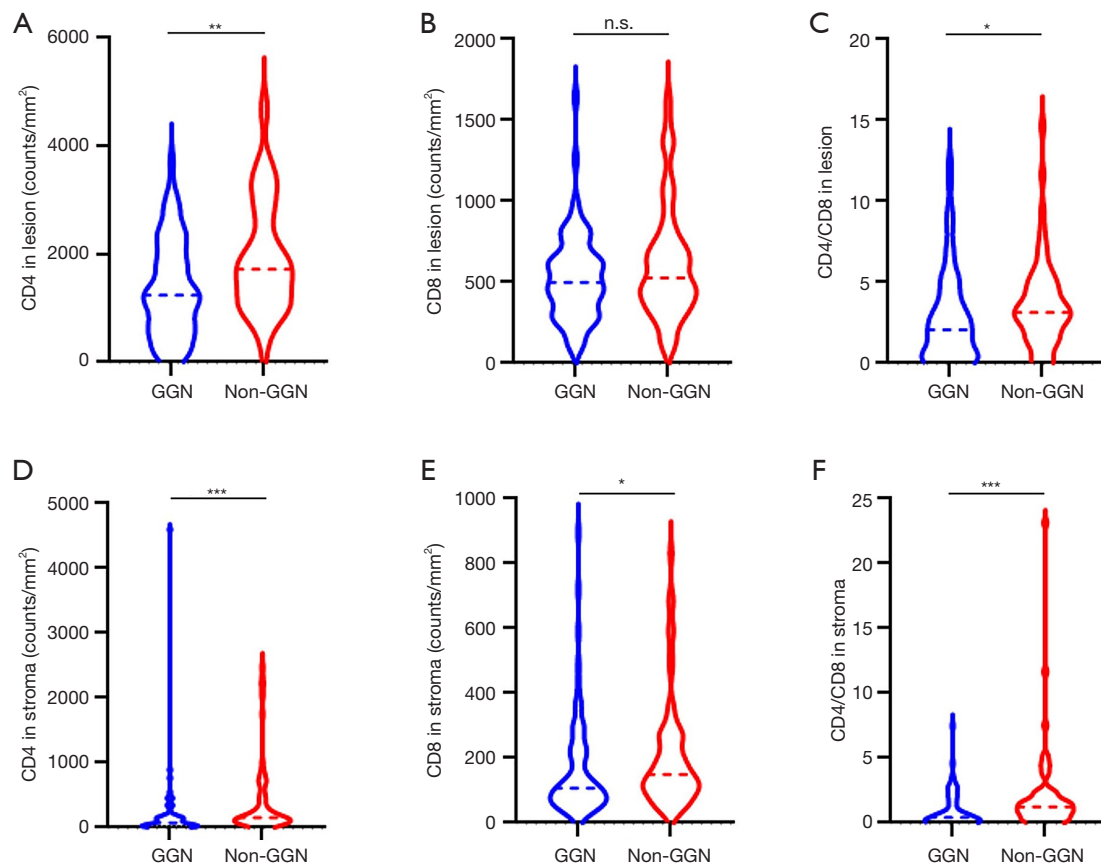


Figure 3 Immune landscape comparison in GGNs versus non-GGNs. (A) CD4 density, (B) CD8 density, and (C) CD4/CD8 ratio within lesions in GGNs versus non-GGNs. (D) CD4 density, (E) CD8 density, and (F) CD4/CD8 ratio in stroma in GGNs versus non-GGNs. Statistical significance is indicated as: *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$; n.s., not statistically significant. GGN, ground-glass nodule.

significant differences in aggressiveness. The percentage of stage Ia tumors progressively decreased from well differentiated to moderately differentiated and poorly differentiated tumors (Figure 4A). Additionally, poorly differentiated tumors exhibited higher rates of pleural traction (36.4%) and lymphovascular invasion (18.2%) compared to well differentiated (6.7% and 0%, respectively) and moderately differentiated tumors (5.1% and 7.7%, respectively) (Figure 4B,4C).

GGNs were predominantly observed in well differentiated tumors (46.7%) and were absent in poorly differentiated tumors. Conversely, solid nodules were more common in poorly differentiated ADCs (81.8%) compared to moderately (46.2%) and well differentiated tumors (13.3%) (Figure 5). These findings underscore that radiographic and histologic characteristics align with tumor aggressiveness.

GGN prevalence in well differentiated ADC tumors

To explore the relationship between the radiological features of pulmonary nodules and the histologic grade of ADC, we then categorized IPNs into GGNs, part-solid nodules, and solid nodules. As expected, the radiographic pattern of GGNs was more prevalent in well differentiated tumors, observed in 46.7% of cases. In contrast, only 15.4% of moderately differentiated tumors exhibited GGNs, and none were seen in poorly differentiated tumors (Figure 5). Conversely, the prevalence of solid nodules increased with tumor grade: 13.3% of solid nodules were well differentiated tumors, 46.2% were moderately differentiated, and 81.8% were poorly differentiated, demonstrating a clear trend of increasing solid nodule presentation with higher tumor grades (Figure 5). Interestingly, in both moderately and poorly differentiated tumors with pleural traction features,

Table 2 Baseline characteristics of the included LUAD patients

Characteristics	Well differentiated (n=15)	Moderately differentiated (n=39)	Poorly differentiated (n=11)	P value
Age (years)	53 [45–73]	58 [36–74]	59 [38–75]	0.37
Gender				0.69
Female	10 (66.7)	21 (53.8)	6 (54.5)	
Male	5 (33.3)	18 (46.2)	5 (45.5)	
Smoking status				0.94
Never smokers	13 (86.7)	34 (87.2)	10 (90.9)	
Smokers	2 (13.3)	5 (12.8)	1 (9.1)	
Lesion size (mm)	10 [6–25]	15 [5–40]	20 [7–25]	0.37
Pathological stage				0.15
Ia	8 (53.3)	13 (33.3)	2 (18.2)	
Ib	6 (40.0)	20 (51.3)	9 (81.8)	
Ic	1 (6.7)	6 (15.4)	0	
EGFR mutation				0.18
<i>Ex19del</i>	5 (33.3)	12 (30.8)	3 (27.3)	
<i>L858R</i>	4 (26.7)	14 (35.9)	1 (9.1)	
Rare (e.g., <i>Exon 20</i> , <i>G719X</i>)	1 (6.7)	0	2 (18.2)	
Absent	5 (33.3)	13 (33.3)	5 (45.5)	
GGN				0.007
Yes	7 (46.7)	6 (15.4)	0	
No	8 (53.3)	33 (84.6)	11 (100.0)	
Radiographic pattern				0.003
GGN	7 (46.7)	6 (15.4)	0	
Part-solid	6 (40.0)	15 (38.5)	2 (18.2)	
Solid	2 (13.3)	18 (46.2)	9 (81.8)	
Pleural traction				0.01
Yes	1 (6.7)	2 (5.1)	4 (36.4)	
No	14 (93.3)	37 (94.9)	7 (63.6)	
Lymphovascular invasion				0.23
Yes	0	3 (7.7)	2 (18.2)	
No	15 (100.0)	36 (92.3)	9 (81.8)	

Data are presented as median [range] or n (%). Stage was determined by AJCC 9th edition. AJCC, American Joint Committee on Cancer; GGN, ground-glass nodule; LUAD, lung adenocarcinoma.

none were GGNs. Conversely, the only well differentiated tumor with pleural traction presented as a GGN. Additionally, none of the five tumors with lymphovascular invasion were GGNs. These findings suggest that GGNs

are indicative of a less aggressive phenotype, even in ADC tumors. The observation that higher-grade tumors are less likely to present as GGNs on radiology aligns with this pattern.

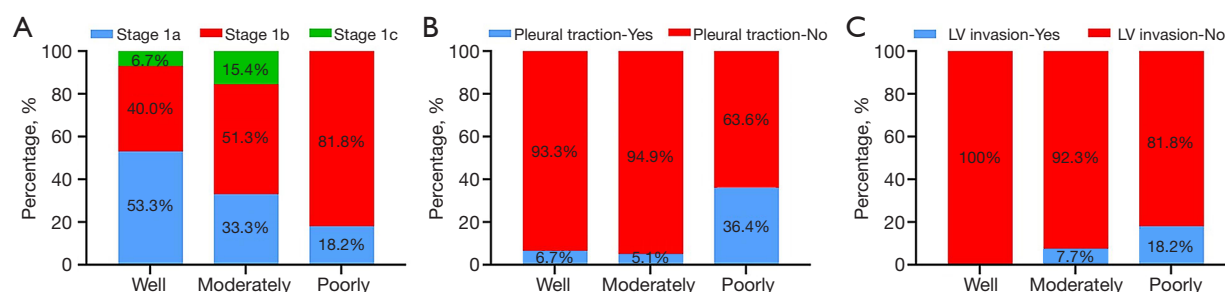


Figure 4 Aggressive features by histologic differentiation of invasive ADC. (A) Stage distribution in well differentiated, moderately differentiated, and poorly differentiated tumors. (B) Pleural traction status across well differentiated, moderately differentiated, and poorly differentiated tumors. (C) Lymphovascular invasion status in well differentiated, moderately differentiated, and poorly differentiated tumors. ADC, adenocarcinoma; LV, lymphovascular.

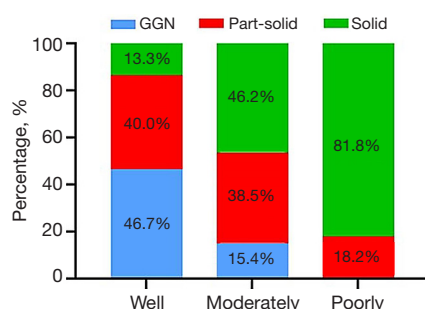


Figure 5 Solid nodule presentation in ADC tumors by histologic grade. Presentation of nodule types (non-solid nodules, part-solid nodules, and solid nodules) in well differentiated, moderately differentiated, and poorly differentiated invasive ADC tumors. ADC, adenocarcinoma; GGN, ground-glass nodule.

Discussion

This study provides a comprehensive analysis of the radiographic, pathological, and immune characteristics of resected pulmonary nodules spanning the spectrum from preneoplastic lesions to early-stage LUAD. Our findings underscore the significance of GGNs as radiographic indicators of less aggressive tumor biology and favorable immune profiles, highlighting their potential utility in early lung cancer detection and risk stratification.

GGNs were more frequently observed in precursor lesions such as AAH, AIS, and MIA, compared to invasive ADC (7). This pattern aligns with a prior study suggesting that GGNs represent a less aggressive phenotype, with lower rates of pleural traction and lymphovascular invasion compared to solid nodules (12). Notably, GGNs were more prevalent in well differentiated tumors and

absent in poorly differentiated ADCs, reinforcing their association with indolent disease. The immune landscape further corroborated the less aggressive nature of GGNs. A progressive decline in CD8⁺ cytotoxic T cells and an increase in the CD4/CD8 ratio were observed as tumors advanced from preneoplastic to invasive stages, consistent with our previous studies (10,13). The lower intratumoral CD4⁺ and CD8⁺ T cell densities observed in GGNs likely reflect their indolent nature and early developmental stage. These lesions typically exhibit preserved architecture, low immunogenicity, and limited inflammatory signaling, which may result in minimal immune cell recruitment. In contrast, non-GGNs—often representing more invasive and biologically active tumors—may provoke a stronger immune response due to increased antigenicity and tissue remodeling. In contrast, poorly differentiated ADCs, which predominantly presented as solid nodules, were associated with significantly higher rates of pleural traction and lymphovascular invasion, hallmarks of aggressive tumor behavior. These findings highlight the critical interplay between tumor grade, radiographic appearance, and immune dynamics in shaping disease progression.

From a clinical perspective, our study underscores the importance of integrating radiologic, pathologic, and immune data to inform the management of pulmonary nodules detected on imaging, particularly those suspected to represent early-stage LUAD. GGNs, with their less aggressive features and favorable immune profiles, could serve as biomarkers for identifying patients who may benefit from less intensive surveillance strategies. Conversely, solid nodules and poorly differentiated tumors may warrant more aggressive monitoring or intervention. The observed decline in immune activity as tumors progress from

precursor to invasive stages also highlights the potential of immunotherapy in early intervention. Strategies aimed at preserving or enhancing the immune response in GGN-associated lesions may help mitigate disease progression and improve outcomes.

Despite these insights, our study has several limitations. First, the retrospective nature and single-institution cohort may limit the generalizability of our findings. Second, the absence of comprehensive molecular profiling restricts our ability to explore the genetic drivers underlying the observed radiographic and immune patterns. Additionally, while our analysis of CD4⁺ and CD8⁺ T cell densities offers an initial view of immune dynamics during the progression from pre-invasive to invasive LUAD, we acknowledge that these markers capture only a fraction of the complex tumor microenvironment. A more comprehensive immune characterization—including regulatory T cells (Tregs), tumor-associated macrophages (TAMs), immune checkpoint molecules (e.g., PD-1, PD-L1, CTLA-4), and key cytokines—will be essential to fully elucidate the immunologic landscape of early LUAD. Future studies should also prioritize longitudinal designs to monitor the evolution of GGNs and their immune contexture over time, and to develop integrated biomarkers for risk stratification and personalized surveillance.

In conclusion, GGNs are radiographic markers of less aggressive tumor biology and indolent immune environments in early-stage LUAD and its precursors. These findings advance our understanding of early lung carcinogenesis and provide a foundation for improving cancer prevention, early detection, and tailored treatment strategies.

Conclusions

This study provides an integrated analysis of radiologic, pathologic, and immune characteristics of pulmonary nodules and their progression to early-stage LUAD. Our findings highlight that GGNs are predominantly observed in precursor lesions (AAH, AIS, MIA) and are associated with less aggressive tumor behavior and a more balanced or regulated immune profile, whereas poorly differentiated adenocarcinomas exhibit increased aggressiveness, immune suppression, and a lower prevalence of GGNs. The observed decline in CD8⁺ cytotoxic T cells and the increasing CD4/CD8 ratio with tumor progression suggest immune suppression as a key driver of LUAD evolution. These findings underscore the importance of

GGNs as potential prognostic markers, which could guide personalized surveillance strategies and risk stratification for patients with IPNs. Future studies integrating molecular and immune profiling are needed to further refine early detection and intervention strategies in LUAD.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://tclr.amegroups.com/article/view/10.21037/tclr-2025-231/rc>

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and its subsequent amendments. The study was approved by the Institutional Review Board (IRB) at Sun Yat-sen University Cancer Center (No. G2022-117-01) and individual consent for this retrospective analysis was waived.

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