Original Article

# Prognostic implication of consolidation-to-tumor ratio in early lung adenocarcinoma: a retrospective cross-sectional study

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**Background:** The threshold value of consolidation-to-tumor ratio (CTR) for distinguishing between ground-glass opacity (GGO)-predominant and solid-predominant ground-glass nodules (GGNs) needs to be clarified, as the lack of clarity has caused the prognostic implications to remain ambiguous. This study aimed to determine the threshold value of CTR for distinguishing between GGO-predominant GGNs and solid-predominant GGNs and elucidate the prognostic implications of the solid-predominant GGNs categorized by CTR on c-stage IA lung adenocarcinoma.

**Methods:** Between January 2016 and October 2018, 764 c-stage IA lung adenocarcinoma cases were assembled from the First Affiliated Hospital of Chongqing Medical University. Of the 764 lesions, 515 (67.4%) were nodules with a GGO component, and 249 (32.6%) were solid nodules (SNs) on thin-section computed tomography (CT). We evaluated the correlation of the 3-dimensional (3D) consolidation component volume ratio with CTR based on the coefficient of determination, r. After receiver operating characteristic (ROC) analysis of 515 GGNs, we defined the nodule with CTR >0.750 as solid-predominant GGN and the nodule with CTR ≤0.750 as GGO-predominant GGN. Subsequently, the prognosis of 439 patients who had follow-up registration was evaluated. Survival curves were calculated using the Kaplan-Meier method, and the log-rank test was employed to compare survival rates among different groups. Cox proportional hazard regression models were applied to evaluate the independent risk factors for recurrence-free survival (RFS).

**Results:** Among 764 patients, 515 (67.4%) were nodules with a GGO component, and 249 (32.6%) were SNs on thin-section CT. For 515 GGNs, the 3D consolidation component volume ratio correlated well with CTR (r=0.888). CTR tended to be slightly larger than the 3D consolidation component volume ratio. A 3D consolidation component volume ratio >50% was best predicted by CTR >0.750, followed by CTR >0.549. CTR >0.750 and CTR >0.549 predicted 3D consolidation component volume ratio >50% with 85% and 99.2% sensitivity and 91.6% and 57.2% specificity, respectively. The 5-year RFS and overall survival (OS) of patients with 0.750< CTR <1 were worse than those of patients with 0≤ CTR ≤0.750 (P<0.001 and P<0.001, respectively) but better than those of patients with CTR =1 (P=0.002 and P=0.03, respectively). Carcinoembryonic antigen (CEA) >2.1 [hazard ratio (HR) =12.516, 95% confidence interval (CI): 1.729–90.598], CTR >0.750 (HR =13.934, 95% CI: 3.341–58.123), larger consolidation component size with diameter more than 20 mm (HR =1.855, 95% CI: 1.242–2.770), poorly differentiated (HR =1.622, 95% CI: 1.056–2.491), lymph node metastasis (HR =2.473, 95% CI: 1.601–3.821), and sublobar resection (HR

=2.596, 95% CI: 1.701–3.962) could predict the poor prognosis. Patients with 0≤ CTR ≤0.750 receiving sublobar resection had prognoses comparable to those receiving lobar resection, whether the tumor size ≤2 cm or consolidation component size ≤3 cm. Lobar resection was superior to sublobar resection for non-small cell lung cancer (NSCLC) ≤2 cm with CTR >0.750.

**Conclusions:** Compared to CTR =0.5, the 2-dimensional (2D) CTR =0.750 found using the 3D consolidation component volume ratio as the gold standard better differentiated between solid-predominant GGNs and GGO-predominant GGNs. CTR >0.750 was an independent risk factor associated with the poor prognosis of patients with c-stage IA lung adenocarcinoma. Sublobar resection should be cautiously adopted in GGNs with 0.750< CTR ≤1.

**Keywords:** Lung adenocarcinoma; ground-glass nodule (GGN); consolidation-to-tumor ratio (CTR); prognosis

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## Introduction

The International Association for the Study of Lung Cancer (IASLC) staging committee, in 2016, suggested that the clinical T-stage should be based on the size of the consolidation component within ground-glass nodules (GGNs) (1). However, the current clinical T stage ignores the influence of the ground-glass opacity (GGO) component on prognosis. The 5-year overall survival (OS) rate of GGNs varies between 91.2% and 99.4%, whereas the 5-year OS rate of solid nodules (SNs) ranges from 68.9% to 88% (2-9). GGNs have a better prognosis than SNs without a GGO component. In this context, the new clinical staging cannot distinguish radiological GGNs from SNs, which may result in staging migration when the consolidation component of both tumors has the same diameter. Therefore, it is necessary to reclassify the T stage to differentiate radiological GGNs from SNs.

Currently, certain studies (10,11) suggest that it is appropriate to categorize all GGNs as a single type, irrespective of their overall size, the dimensions of their consolidation components, or the consolidation-to-tumor ratio (CTR). However, the clinicopathological characteristics and prognostic factors of GGNs remain unknown and warrant further investigation. The prognostic factor for early-stage lung adenocarcinoma presenting as GGNs has been indicated by several studies (4,12,13) to be the CTR. Aoki *et al.* (14) found patients with GGO components of more than 50% showed a significantly better prognosis than those with GGO components of less than 50%. Zhai *et al.* (6) analyzed 1,070 GGNs and noted that patients with CTR >0.75 had similar outcomes to those with pure-SNs. However, Hattori *et al.* (3) found that the 5-year OS was equivalent in the GGO-predominant (0.5≤ CTR <0.75) and solid-predominant (0.75≤ CTR ≤1.0) arms. Thus, the CTR range employed to differentiate GGO-predominant GGNs from solid-predominant GGNs spans from 0.5 to 0.75 (13,15,16), yet substantial discord persists, and various CTRs yield diverse research outcomes. Consequently, it becomes imperative to ascertain a precise CTR threshold capable of effectively discerning between these 2 types of nodules before we understand the impact of solid-predominant GGNs on the prognosis of c-stage IA non-small cell lung cancer (NSCLC).

Therefore, the objective of this study was to elucidate the prognostic implications of CTR in GGNs and determine the threshold value of CTR for distinguishing between GGO-predominant GGNs and solid-predominant GGNs. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1438/rc).

## Methods

### *Study design and patients*

This study retrospectively reviewed 3,387 cases of c-stage IA lung adenocarcinoma that underwent surgery at the First Affiliated Hospital of Chongqing Medical University between January 2016 and October 2018. The tumor clinical staging was determined according to the 8th edition of the IASLC guidelines. Patients' demographics (gender and age) and clinical factors, smoking index (product of the number of smoking years and the number of cigarettes

 

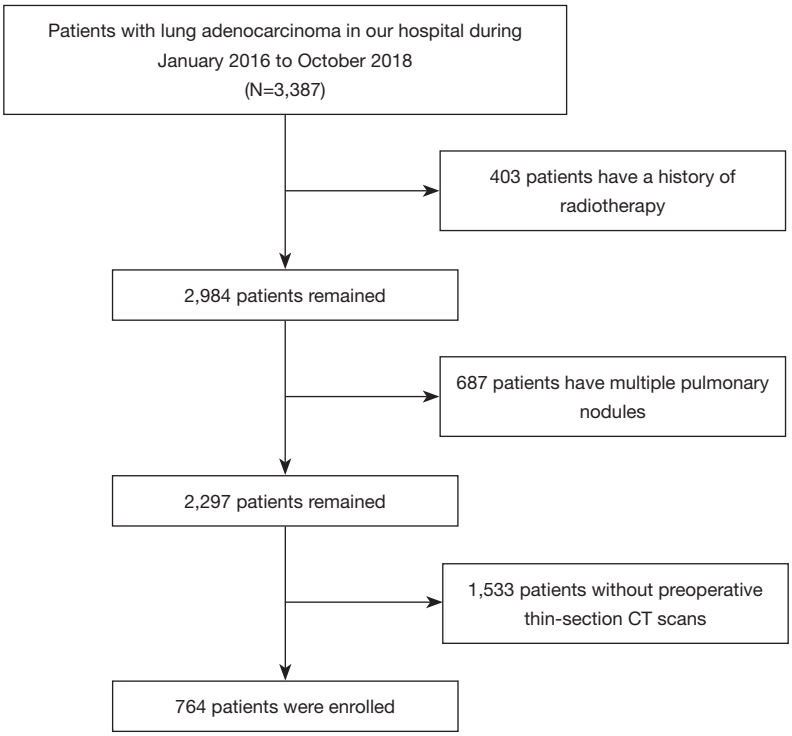


**Figure 1** Flow diagram shows the enrollment of patients. CT, computed tomography.

smoked per day), and surgical procedure (lobectomy, segmentectomy, or wedge resection) were collected. Those nodules with a history of radiotherapy (403 cases), multiple pulmonary nodules (687 cases), and cases without preoperative thin-section computed tomography (CT) scans (1,533 cases) were excluded. Ultimately, 764 patients with available data were enrolled. The enrollment of patients is shown in *Figure 1*. Of the 764 lesions, 515 (67.4%) were nodules with a GGO component, and 249 (32.6%) were SNs on thin-section CT. After receiver operating characteristic (ROC) analysis of 515 GGNs, we defined the nodule with CTR >0.750 as solid-predominant GGN and the nodule with CTR ≤0.750 as GGO-predominant GGN. Subsequently, the prognosis of 439 patients who had follow-up registration was evaluated. Approval was obtained from the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University (IRB No. K2023-223) and the requirement for written informed consent for this retrospective study was waived. The study was conducted in accordance with the ethical standards of the responsible institution regarding human subjects, as well as in compliance with the Declaration of Helsinki (as revised in 2013).

### *Radiologic evaluation*

Thin-section CT images were reconstructed with collimation of 1 mm. On preoperative thin-section CT scans, the CT images were analyzed using a lung setting, with a window level of −600 Hounsfield units (HU) and a window width of 1,800 HU. A lung nodule exhibiting both GGO and consolidation components was classified as a GGN, whereas an SN was defined as a lesion lacking any GGO component. Each nodule was assessed by 2 independent observers in the Picture Archiving and Communication Systems program. On the basis of the regions of interest of nodules drawn by radiologists for the whole boundary of nodules and their consolidation component, the program automatically calculated the volume of nodules and volume of the consolidation component. The 2 radiologists, who had over 20 and 5 years of experience, respectively, manually measured the longest diameter of each nodule and the maximum diameter of the consolidation component of each nodule using electronic calipers. The CTR was determined by calculating the proportion of the maximum diameter of the consolidation component to the longest diameter of the nodule, as observed in the maximum section of the axial

 

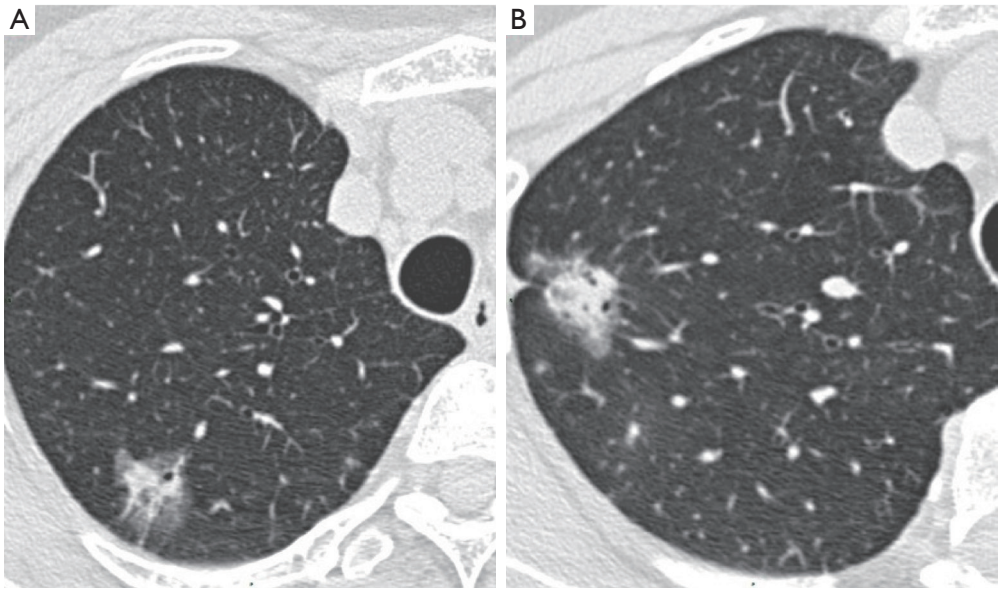


**Figure 2** Typical images of radiologically invasive NSCLC for (A) GGO-predominant and (B) solid-predominant ground-glass lung cancer. GGO, ground-glass opacity; GGNs, ground-glass nodules; NSCLC, non-small cell lung cancer.

thin-section CT. The 3-dimensional (3D) consolidation component volume ratio was determined by calculating the proportion of the volume of the consolidation component to the volume of the nodule. Actually, the nodule of 3D consolidation component volume ratio >50% was solid-predominant GGN, the nodule of 3D consolidation component volume ratio ≤50% was GGO-predominant GGN (*Figure 2*). Since the CTR >0.750 can well predict the 3D consolidation component volume ratio >50%, we defined the nodule with CTR >0.750 as solid-predominant GGN and the nodule with CTR ≤0.750 as GGO-predominant GGN.

### *Pathologic evaluation*

Formalin-fixed paraffin-embedded tissues were sectioned and subsequently subjected to staining with hematoxylin and eosin, as well as the Alcian blue-periodic acid-Schiff method, to assess cytoplasmic mucin production. A pathologist who had over 20 years of experience utilized the 5th edition of the World Health Organization classification of tumors in the lung, pleura, thymus, and heart to determine histologic typing and pathologic grade (17).

### *Follow-up protocol*

Postoperative follow-up appointments were scheduled at intervals of 3 months during the first 2 years following resection, every 6 months from the third to fifth year, and annually thereafter. These follow-up procedures consisted of regular chest and upper-abdominal CT scans, as well as head CT scans. The primary objectives of this study were to determine the OS and recurrence-free survival (RFS). OS was calculated from the date of the operation until the date of death resulting from any cause or the last follow-up. RFS was calculated from the initial operation until the occurrence of the first recurrence or the last clinical visit.

### *Statistical analysis*

Continuous data were presented as the mean ± standard deviation (SD) or median (Q1, Q3) and were subjected to comparison using either the Student's *t*-test or the Mann-Whitney *U* test. Categorical data were compared using Pearson's chi-square test or the Kruskal-Wallis H test. The optimal cutoff value for the smoking index [280] and carcinoembryonic antigen (CEA) (2.1) was analyzed by

 

X-title software (Yale School of Medicine, New Haven, CT, USA). At first, the correlation of 3D consolidation component volume ratio with CTR was evaluated by the coefficient of determination, r. Furthermore, GGNs were categorized into 2 distinct groups: consolidation component volume ratio ≤50% and consolidation component volume ratio >50%. Subsequently, ROC analysis with Youden's index was employed to determine the cutoff value of the CTR that resulted in the greatest disparity between GGNs with a consolidation component volume ratio ≤50% and that consolidation component volume ratio >50%. Delong's test was used to determine whether there is a statistical difference in 3D consolidation component volume ratio >50% prediction between CTR >0.549 and CTR >0.750. Survival curves were calculated using the Kaplan-Meier method, and the log-rank test was employed to compare survival rates among different groups. Variables with a significant impact on survival in univariable analysis were included in a multivariable Cox proportional hazard model. Cox proportional hazard regression models were applied to evaluate the independent risk factors for RFS. The variables with P values less than 0.1 in univariate analysis were entered into a multivariate model. The statistical analyses were conducted using the software SPSS 26.0 (IBM Corp., Armonk, NY, USA) and MedCalc 20.1 (MedCalc, Ostend, Belgium). A statistical significance was attributed to a P value of less than 0.05, and all reported significance levels were considered to be 2-sided.

## Results

### *Patient characteristics*

A total of 764 c-stage IA lung nodules were reviewed. Among them, 509 were diagnosed as IA, 135 as minimally invasive adenocarcinoma (MIA), and 20 as adenocarcinoma *in situ* (AIS). Of the 509 patients with IA, 439 patients were revised. Therefore, the 439 patients were finally included in the prognosis factor analysis.

Of the 764 lesions, 515 (67.4%) were nodules with a GGO component, and 249 (32.6%) were SNs on thin-section CT. We compared the clinicopathologic characteristics between the 2 groups: GGNs and SNs with and without GGO (*Table 1*). Statistically significant differences were observed between the 2 groups regarding various clinicopathological features.

### *Predictive probability of CTR for 3D consolidation component volume ratio >50%*

3D consolidation component volume ratio correlated well with CTR (r=0.888) (*Figure 3A*). As indicated in *Figure 3A*, CTR tended to be slightly larger than the 3D consolidation component volume ratio. Based upon ROC analysis, 515 cases of GGNs were classified into 2 groups: nodule with 3D consolidation component volume ratio ≤50% (n=395) and >50% (n=120) (*Figure 3B*). The CTR of more than 0.750 on 2-dimensional (2D) axial thin-section CT was the significant indicator of nodule with 3D consolidation component volume ratio >50%: sensitivity, 85%; specificity, 91.6%. However, solid-predominant GGN was always defined in other papers as a CTR of more than 0.5 on thin-section CT (13,16), so we examined the other cutoff value, 0.5, for the CTR in GGNs. As a result, the area under the curve (AUC) of the CTR >0.750 [AUC: 0.883, 95% confidence interval (CI): 0.852–0.910, P<0.001] was significantly larger than the CTR >0.549 (AUC: 0.782, 95% CI: 0.744–0.817, P<0.001), which means that the CTR >0.750 can well predict the 3D consolidation component volume ratio >50%. Hence, we defined the nodule with CTR >0.750 as solid-predominant GGN and the nodule with CTR ≤0.750 as GGO-predominant GGN.

### *Survival outcomes among 0≤ CTR ≤0.750, 0.750< CTR <1 and CTR =1 groups*

In total, 439 patients had follow-up registration. When the 439 patients with follow-up registration were classified into 3 groups, namely GGO-predominant GGNs (0≤ CTR ≤0.750), solid-predominant GGNs (0.750< CTR <1), and SNs (CTR =1), the SNs and solid-predominant GGNs showed a more oncologic invasive behavior compared with the GGO-predominant GGNs (*Table 2*). The 5-year OS and 5-year RFS of the clinical stage IA NSCLC in this study were 82.8% and 73.2%, respectively, with a median follow-up time of 66 months, which was significantly different among GGO-predominant GGNs, solid-predominant GGNs, and SNs (*Figure 4A*, 5-year RFS: GGO-predominant GGNs =98.5%, solid-predominant GGNs =81.4%, SNs =58%, P<0.001; *Figure 4B*, 5-year OS: GGO-predominant GGNs =100%, solid-predominant GGNs =86.4%, SNs =72.9%, P<0.001).

Based on a Cox proportional hazards models analysis for 5

 

**Table 1** Patient characteristics

| Variables | Clinical stage IA NSCLC | | P value |
|---|---|---|---|
| | With GGO (n=515) | Solid (n=249) | |
| Gender | | | <0.001** |
| Male | 190 (36.9) | 140 (56.2) | |
| Female | 325 (63.1) | 109 (43.8) | |
| Age (years) | 60 [52, 66] | 62 [53, 69] | 0.009* |
| Smoking index | | | <0.001** |
| ≤280 | 427 (82.9) | 150 (60.2) | |
| >280 | 88 (17.1) | 99 (39.8) | |
| CEA (ng/mL) | | | <0.001** |
| ≤2.1 | 152 (29.5) | 15 (6) | |
| >2.1 | 363 (70.5) | 234 (94) | |
| Group by consolidation component size (mm) | | | <0.001** |
| 0–10 | 285 (55.3) | 21 (8.4) | |
| 11–20 | 172 (33.4) | 87 (34.9) | |
| 21–30 | 58 (11.3) | 141 (56.6) | <0.001** |
| Pathology sub-type | | | |
| AIS | 20 (3.9) | 0 | |
| MIA | 135 (26.2) | 0 | |
| IAC | 360 (69.9) | 249 (100) | |
| Pathology grade | | | <0.001** |
| AIS/MIA | 155 (30.1) | 0 | |
| Well differentiated | 68 (13.2) | 1 (0.4) | |
| Moderately differentiated | 266 (51.7) | 176 (70.7) | |
| Poorly differentiated | 26 (5) | 72 (28.9) | |
| Pathological lymph node | | | <0.001** |
| N0 | 504 (97.9) | 197 (79.1) | |
| N1 | 2 (0.4) | 16 (6.4) | |
| N2 | 8 (1.6) | 35 (14.1) | |
| N3 | 1 (0.2) | 1 (0.4) | |
| Maximum tumor size (mm) | 17.3 [12.8, 23.6] | 21 [17, 26] | <0.001** |
| CTR | 0.581 [0.43, 0.76] | 1 [1, 1] | <0.001** |
| Surgery approach | | | <0.001** |
| Lobar resection | 294 (57.1) | 191 (76.7) | |
| Segmentectomy | 126 (24.5) | 16 (6.4) | |
| Wedge resection | 95 (18.4) | 42 (16.9) | |

Values are presented as number (%) or median [Q1, Q3]. *, P<0.01; **, P<0.001. NSCLC, non-small cell lung cancer; GGO, ground-glass opacity; CEA, carcinoembryonic antigen; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; IAC, invasive adenocarcinoma; CTR, consolidation-to-tumor ratio.

 

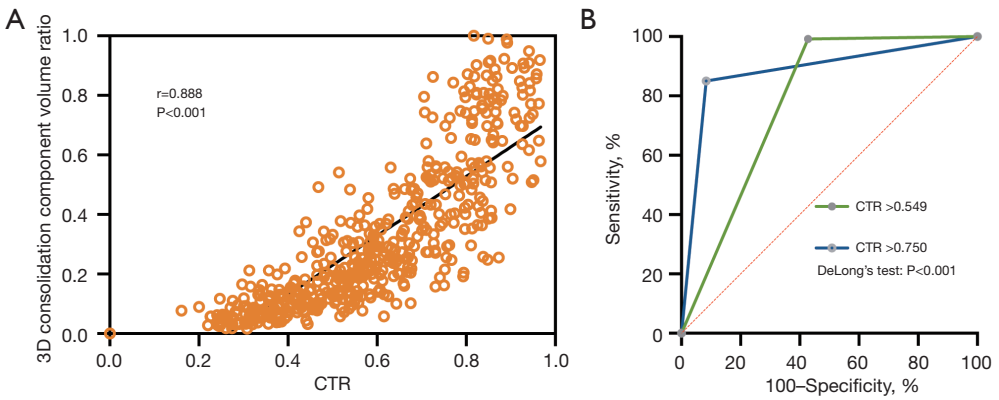


**Figure 3** Predictive probability of CTR for 3D consolidation component volume ratio >50%. (A) Correlation of 3D consolidation component volume ratio (y) and CTR (x). 3D consolidation component volume ratio correlated well with CTR (r=0.888). (B) Receiver operating characteristic analysis for 2 groups: nodule with 3D consolidation component volume ratio ≤50% (n=395) and >50% (n=120). The CTR of more than 0.750 on 2D axial thin-section CT was the significant indicator of nodule with 3D consolidation component volume ratio >50%: sensitivity, 85%; specificity, 91.6%. The AUC of the CTR >0.750 was significantly larger than the CTR >0.549 (AUC =0.883 *vs.* 0.782, P<0.001). 3D, 3-dimensional; CTR, consolidation-to-tumor ratio; r, coefficient of determination; 2D, 2-dimensional; CT, computed tomography; AUC, area under the curve.

year RFS in the 439 patients, CEA >2.1 ng/mL [hazard ratio (HR) =12.516, P=0.01, 95% CI: 1.729–90.598], CTR >0.750 (HR =13.934, P<0.001, 95% CI: 3.341–58.123), larger consolidation component size with diameter more than 20 mm (HR =1.855, P=0.003, 95% CI: 1.242–2.770), poorly differentiated (HR =1.622, P=0.03, 95% CI: 1.056–2.491), lymph node metastasis (HR =2.473, P<0.001, 95% CI: 1.601–3.821), and sublobar resection (HR =2.596, P<0.001, 95% CI: 1.701–3.962) were independent risk factors associated with the poor prognosis of patients with c-stage IA lung adenocarcinoma (*Table 3*).

### *Survival outcomes between lobar-resection and sublobar-resection groups in each CTR classification*

When we evaluated the survival outcomes based on the surgical approach, it was excellent in the GGO-predominant GGNs. In particular, the 5-year RFS of the GGO-predominant GGNs was 97.8% or more regardless of surgical approach (5-year RFS: lobar-resection GGO-predominant GGNs =97.8%, sublobar-resection GGO-predominant GGNs =100%, P=0.36, 5-year OS: lobar-resection GGO-predominant GGNs =100%, sublobar-resection GGO-predominant GGNs =100%). The difference in RFS between lobar-resection and sublobar-resection was not significant in the GGO-predominant GGNs (lobar-resection *vs.* sub lobar-resection: P=0.36).

Meanwhile, the prognostic impact of the surgical approach was definitive in the solid-predominant GGNs and SNs. In terms of solid-predominant GGNs, both the 5-year RFS and 5-year OS split almost fairly between lobar-resection and sublobar-resection groups (lobar-resection *vs* sublobar-resection: 5-year RFS, P=0.003, HR =0.167, 95% CI: 0.046–0.601; 5-year OS, P=0.008, HR =0.152, 95% CI: 0.034–0.678) (*Figure 5A*, 5-year RFS: lobar-resection =92.3%, sublobar-resection =60%; *Figure 5B*, 5-year OS: lobar-resection =94.9%, sublobar-resection =70%). As for SNs, both the 5-year OS and 5-year RFS split almost fairly between lobar-resection and sublobar-resection (lobar-resection *vs.* sublobar-resection:5-year RFS, P=0.005, HR =0.558, 95% CI: 0.345–0.903; 5-year OS, P=0.02, HR =0.551, 95% CI: 0.307–0.990) (*Figure 5C*, 5-year RFS: lobar-resection =61.9%, sublobar-resection =44.8%; *Figure 5D*, 5-year OS: lobar-resection =76.3%, sublobar-resection =61.9%).

### *Survival outcomes between lobar-resection and sublobar-resection groups with tumor size ≤2 cm in each CTR classification*

The 5-year OS revealed significant differences between lobar-resection and sublobar-resection groups of tumor

 

**Table 2** Clinicopathologic characteristics of 439 patients with resected clinical stage IA NSCLC

| Variables | Clinical stage IA NSCLC | | | P value |
|---|---|---|---|---|
| | GGO-predominant (n=131, 0≤ CTR ≤0.750) | Solid-predominant (n=59, 0.750< CTR <1) | Solid nodule (n=249, CTR =1) | |
| Gender | | | | <0.001* |
| Male | 46 (35.1) | 23 (39) | 140 (56.2) | |
| Female | 85 (64.9) | 36 (61) | 109 (43.8) | |
| Age (years) | 60 [52, 67] | 61 [55, 66] | 62 [53, 69.5] | 0.32 |
| Smoking index | | | | <0.001* |
| ≤280 | 110 (84) | 48 (81.4) | 150 (60.2) | |
| >280 | 21 (16) | 11 (18.6) | 99 (39.8) | |
| CEA (ng/mL) | | | | <0.001* |
| ≤2.1 | 36 (27.5) | 15 (25.4) | 15 (6) | |
| >2.1 | 95 (72.5) | 44 (74.6) | 234 (94) | |
| Pathology grade | | | | <0.001* |
| Well differentiated | 31 (23.7) | 1 (1.7) | 1 (0.4) | |
| Moderately differentiated | 97 (74) | 54 (91.5) | 176 (70.7) | |
| Poorly differentiated | 3 (2.3) | 4 (6.8) | 72 (28.9) | |
| Pathological lymph node metastasis | | | | |
| Negative | 129 (98.5) | 56 (94.9) | 197 (79.1) | <0.001* |
| Positive | 2 (1.5) | 3 (5.1) | 52 (20.9) | |
| Consolidation component size (mm) | | | | <0.001* |
| ≤20 | 128 (97.7) | 35 (59.3) | 108 (43.4) | |
| >20 | 3 (2.3) | 24 (40.7) | 141 (56.6) | |
| Maximum tumor size (mm) | | | | <0.001* |
| ≤30 | 125 (95.4) | 54 (91.5) | 248 (99.6) | |
| >30 | 6 (4.6) | 5 (8.5) | 1 (0.4) | |
| Surgery approach | | | | 0.16 |
| Lobar resection | 92 (70.2) | 39 (66.1) | 191 (76.7) | |
| Sublobar resection | 39 (29.8) | 20 (33.9) | 58 (23.3) | |

Values are presented as number (%) or median [Q1, Q3]. *, P<0.001. NSCLC, non-small cell lung cancer; GGO, ground-glass opacity; CTR, consolidation-to-tumor ratio; CEA, carcinoembryonic antigen.

size no more than 2 cm (*Figure 6A*, 5-year RFS: 83.3% *vs.* 74.6%, P=0.11, HR =0.589, 95% CI: 0.293–1.182; *Figure 6B*, 5-year OS: 91.1% *vs.* 80.6%, P=0.03, HR =0.421, 95% CI: 0.175–1.015). When we evaluated the outcomes based on CTR classification, both the 5-year RFS and OS were significantly different between the lobar-resection and sublobar-resection groups in NSCLC ≤2 cm with CTR >0.750 (*Figure 6C*, 5-year RFS: 77% *vs.* 60%, P=0.02, HR =0.474, 95% CI: 0.228–0.983; *Figure 6D*, 5-year OS: 87.8% *vs.* 69.6%, P=0.008, HR =0.348, 95% CI: 0.139–0.869). However, for NSCLC ≤2 cm with CTR ≤0.750, no difference in both RFS and OS was found between the lobar-resection and sublobar-resection groups (5-year RFS: 100% *vs.* 100%, 5-year OS:

 

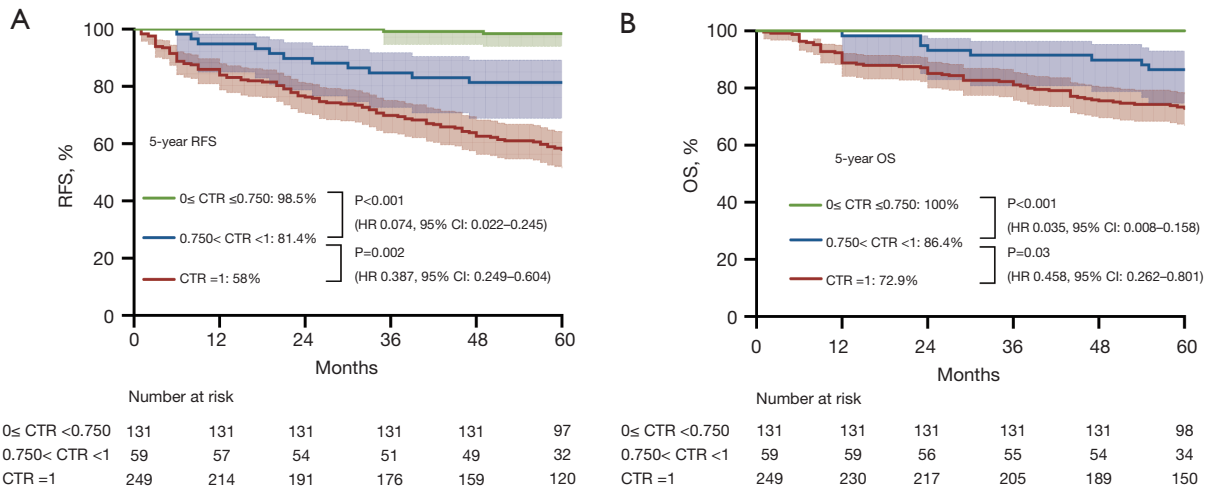


**Figure 4** Survival outcomes among 0≤ CTR ≤0.750, 0.750< CTR <1 and CTR =1 groups in c-stage IA NSCLC [(A) RFS; (B) OS]. The 5-year RFS and OS were significantly among 0≤ CTR ≤0.750, 0.750< CTR <1, and CTR =1 groups. RFS, recurrence-free survival; CTR, consolidation-to-tumor ratio; HR, hazard ratio; CI, confidence interval; OS, overall survival; NSCLC, non-small cell lung cancer.

**Table 3** Cox proportional hazard model for the 5-year recurrence-free survival in 439 patients

| Variate | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value[†] |
| Gender (female) | 0.506 (0.348–0.734) | <0.001*** | 0.855 (0.468–1.562) | 0.610 |
| Age | 1.024 (1.005–1.043) | 0.01* | 1.006 (0.987–1.026) | 0.537 |
| Smoking index (>280) | 2.669 (1.857–3.838) | <0.001*** | 1.297 (0.724–2.324) | 0.38 |
| CEA (>2.1 ng/mL) | 24.26 (3.388–173.698) | 0.001** | 12.516 (1.729–90.598) | 0.01* |
| CTR (CTR >0.750) | 30.301 (7.486–122.643) | <0.001*** | 13.934 (3.341–58.123) | <0.001*** |
| Maximum tumor size | 0.569 (0.141–2.303) | 0.43 | – | – |
| Consolidation component size (D >2 cm) | 4.073 (2.771–5.988) | <0.001*** | 1.855 (1.242–2.770) | 0.003** |
| Pathology grade (poorly differentiated) | 3.416 (2.344–4.980) | <0.001*** | 1.622 (1.056–2.491) | 0.03* |
| Lymph node metastasis (positive) | 4.108 (2.768–6.098) | <0.001*** | 2.473 (1.601–3.821) | <0.001*** |
| Surgical approach (sublobar resection) | 1.574 (1.074–2.307) | 0.02* | 2.596 (1.701–3.962) | <0.001*** |

*, P<0.05; **, P<0.01; ***, P<0.001. [†], P value determined by Cox proportional hazard model. HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; CTR, consolidation tumor ratio; D, diameter.

100% *vs.* 100%).

## Discussion

On the basis of a series of prospective studies concerning the prognostic value of CTR and its effect on decision-making of surgical approach (18), this study aimed to determine the threshold value of CTR for distinguishing between GGO-predominant GGNs and solid-predominant GGNs and elucidate the prognostic implications of the solid-predominant GGNs categorized by CTR on c-stage IA lung adenocarcinoma. The strong point of this study is that this investigation is the first to experimentally identify CTR values that differentiate between solid-predominant GGNs and GGO-predominant GGNs. As a result, this study reliably defined the solid-predominant GGNs based on CTR and found that their presence could predict poor outcomes. Thus, our study has practical implications for the

 

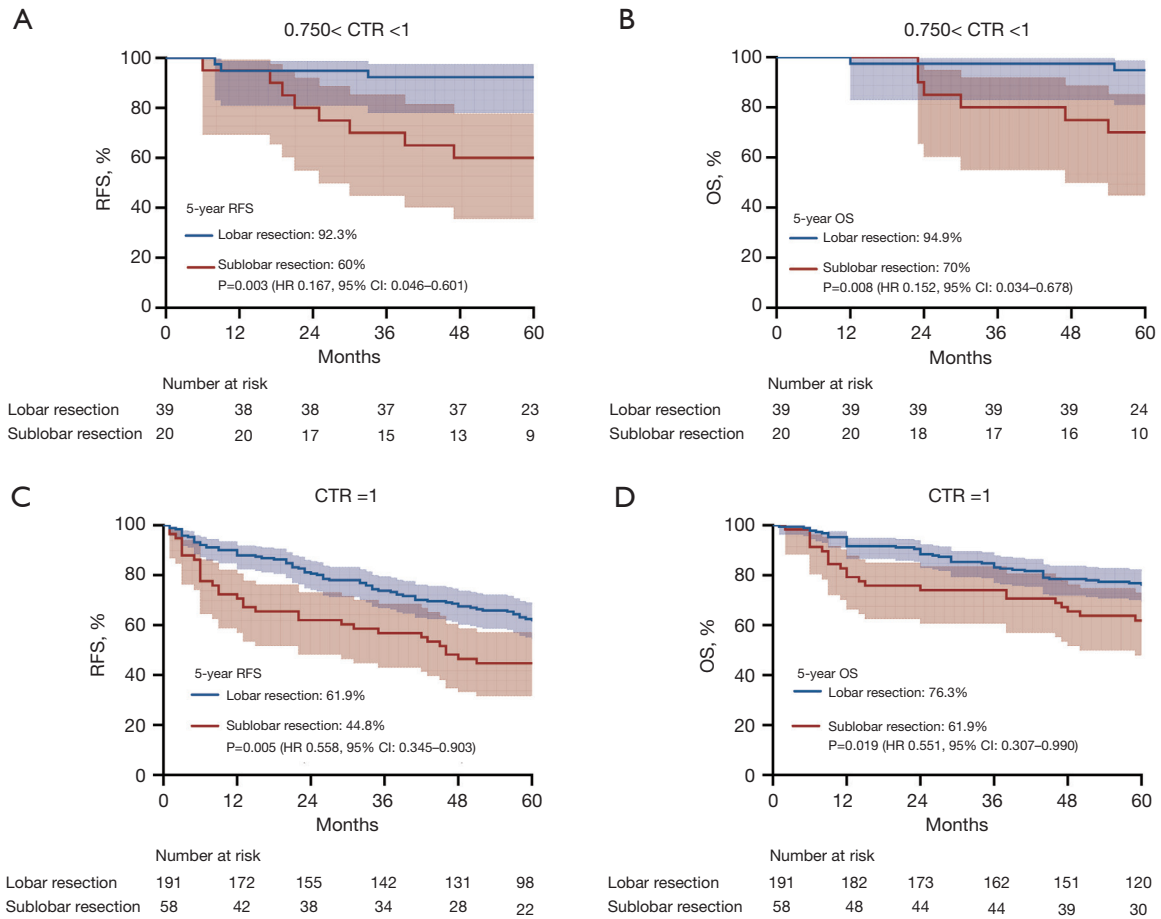


**Figure 5** Comparison of survival outcomes between lobar-resection and sublobar-resection groups in 0.750< CTR <1 [(A) RFS; (B) OS] and CTR =1 [(C) RFS; (D) OS]. Both the 5-year OS and 5-year RFS split almost fairly between lobar-resection and sublobar-resection groups, whether the 0.750< CTR <1 or CTR =1. RFS, recurrence-free survival; CTR, consolidation-to-tumor ratio; HR, hazard ratio; CI, confidence interval; OS, overall survival.

management of c-stage IA NSCLC.

The controversy surrounding the differentiation of GGO-predominant GGNs from solid-predominant GGNs based on CTR has been a subject of academic debate. So far, 2 methods have been mainly reported: Nakao *et al.* (13) have classified GGNs into 3 distinct categories: GGO-predominant (CTR ≤0.5), solid-predominant (CTR >0.5), and SNs (CTR =1); whereas Hattori *et al.* (3) established the classification of GGO types, with 0.5≤ CTR <0.75 representing GGO-predominant, and 0.75≤ CTR <1 indicating solid-predominant. This study is the first to experimentally identify CTR values that differentiate between solid-predominant GGNs and GGO-predominant GGNs. The volume ratio of consolidation components was employed as the reference standard, and it was determined that a CTR cutoff value of 0.750 effectively distinguishes consolidation components with a volume ratio of at least 50%. When the cutoff value was set as 0.5, the specificity was lower. Thus, we prefer to define GGNs with CTR >0.750 as solid-predominant GGNs.

For GGNs, one debate is whether CTR is the indicator of prognosis. The clinical trial conducted by the Japan Clinical Oncology Group (JCOG) 0201 (19) has demonstrated that a maximum consolidation diameter/maximum tumor diameter (c/t) ratio of ≤0.25 in GGNs can effectively forecast the presence of non-invasive lung adenocarcinoma, thereby establishing it as a defined entity known as imaging non-invasive adenocarcinoma. The survival outcomes of JCOG0201 (20) showed that GGNs with CTR <0.5 have a better prognosis. Following this,

 

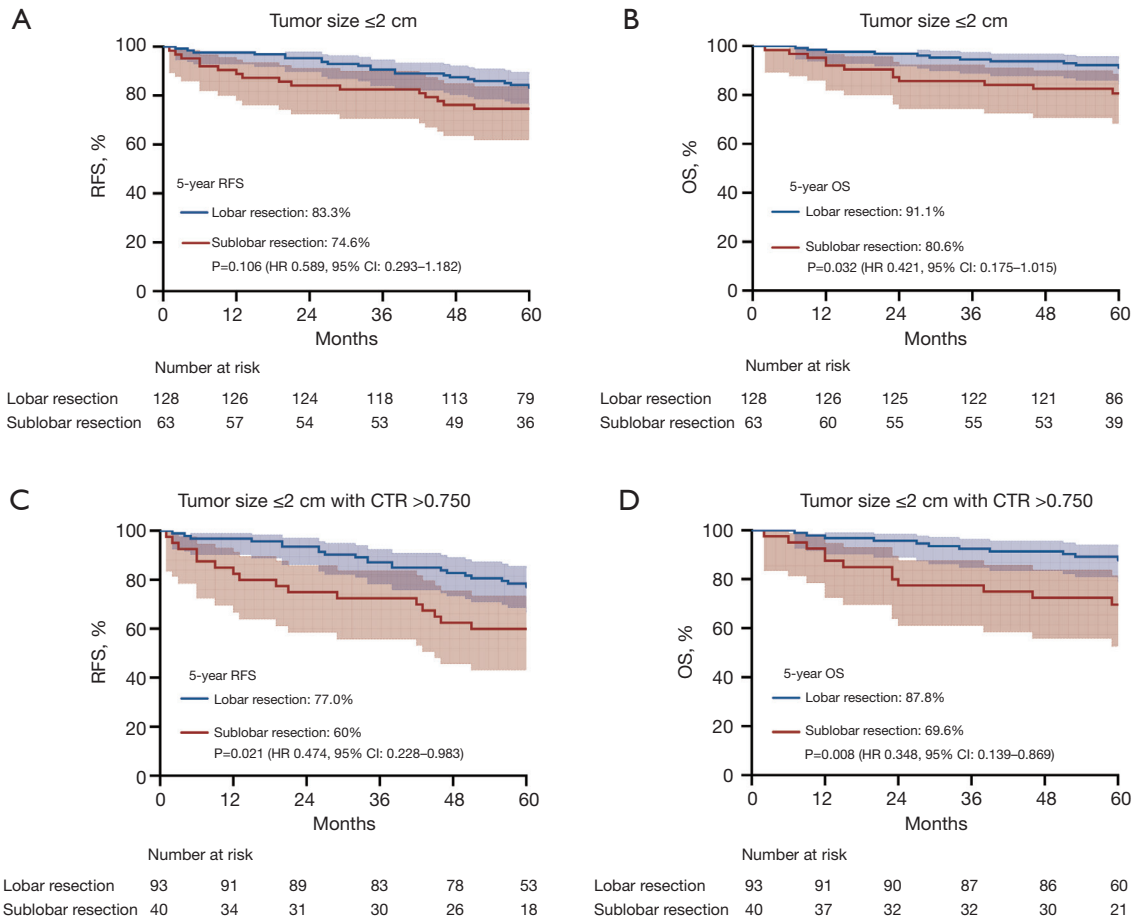


**Figure 6** Comparison of survival outcomes between lobar-resection and sublobar-resection groups with tumor size ≤2 cm in 0≤ CTR ≤1 [(A) RFS; (B) OS] and 0.750< CTR [(C) RFS; (D) OS]. The 5-year OS significantly differed between the lobar-resection and sublobar-resection groups, whether the 0≤ CTR ≤1 or CTR >0.750. RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; CTR, consolidation-to-tumor ratio.

JCOG sequentially developed JCOG0804, JCOG0802, and JCOG1211 in order to investigate the potential of image features in informing clinical decision-making for early lung adenocarcinoma based on the CTR. In this study, we found CTR >0.750 (HR =13.934, P<0.001, 95% CI: 3.341–58.123) was an independent risk factor associated with the poor prognosis of patients with c-stage IA lung adenocarcinoma. The range of 95% CI of HR in CTR as an independent risk factor associated with poor prognosis was too wide. The reason for this phenomenon may be due to a small sample size. However, Hattori *et al.* (10) reported that the CTR was not a prognostic factor for GGNs. Subsequently, the same team (3) found no statistical difference (P=0.70) in 5-year OS between GGO-predominant GGNs and solid-predominant GGNs. This discrepancy may be attributed to Hattori *et al.*'s comparable clinicopathological characteristics between GGO-predominant GGNs and solid-predominant GGNs, with no discernible variation in the distribution of pathological grade. The GGO-predominant GGNs are found to have a pathologic grading of well-differentiated in 60% of cases, whereas a solid-predominant GGNs is in 56% of cases. However, in our study, there were significant differences in pathological grade distribution and lymph node involvement between the cases with GGO-predominant GGNs and those with solid-predominant GGNs. In the case group with GGO-predominant GGNs, well-differentiated accounted for 23.7%, moderately differentiated accounted for 74%, and

 

poorly differentiated accounted for 2.3%. In the case group with solid-predominant, well-differentiated accounted for 1.7%, moderately differentiated accounted for 91.5%, and poorly differentiated accounted for 6.8% (*Table 3*). In alignment with previous studies, GGO-predominant GGNs (CTR ≤0.750) were related to better survival in c-Stage IA NSCLC. Therefore, a clear distinction based on the CTR >0.750 or not is essential when considering the clinicopathologic and oncologic outcomes of patients with c-Stage IA NSCLC.

Despite lobar resection being the established surgical approach for early lung cancer, emerging evidence suggests that sublobar resection is gaining recognition in the clinical management of early lung adenocarcinoma. The survival outcomes of JCOG0201 (20) and JCOG1211 (21) have substantiated that sublobar resection can be employed as a standardized approach for nodules measuring less than 3 cm with a CTR <0.5. A multicenter retrospective study's results supported patients with GGO-predominant clinical stage IA adenocarcinoma can be successfully treated with sublobar resection (22). The results of our study also showed that sublobar resection could achieve superior perioperative outcomes in comparison with lobar resection in GGNs with CTR ≤0.750, which is defined as GGO-predominant GGNs. However, in solid-predominant GGNs, which surgery approach should be preferred is in debate. Recently published results of CALGB140503 (23) and JCOG0802 (24) have demonstrated favorable survival time of sublobar resection, compared to lobar resection, for peripheral IA1 NSCLC. Data from Germany (25) showed that locoregional and distant recurrences were not significantly different for patients undergoing either sublobar resection or lobar resection for stage IA NSCLC. In contrast, an early study from the USA reported that lung adenocarcinoma of 2 cm or smaller with a micropapillary component of 5% or greater treated with lobar resection were at a higher risk of recurrence than similar patients treated with sublobar resection (26). Moreover, Baig *et al.* (26) reported that lobar resection was associated with better long-term survival outcomes as compared to sublobar resection for small peripheral NSCLC ≤2 cm with high grades of tumor differentiation. Ma *et al.* (27) recently published a study that showed that angioinvasive adenocarcinoma ≤2 cm treated with sublobar resection exhibits poor outcomes. In our research, lobar resection was superior to sublobar resection for NSCLC ≤2 cm with CTR >0.750. Thus, sublobar resection should be cautiously adopted in GGNs with 0.750< CTR ≤1.

### *Study limitation*

Firstly, it is imperative to acknowledge that the current study is limited due to its small sample size and reliance on data solely obtained from a single-center database. Expanding the sample size and conducting experiments across multiple centers is recommended to enhance the robustness and generalizability of future findings. Secondly, it is crucial to note that there is currently a lack of consensus regarding a universally accepted measurement method for assessing the content of ground-glass in pulmonary nodules. Although Japan has pioneered the use of the CTR as a means of evaluating ground-glass content, it is important to highlight that CTR's efficacy in distinguishing GGO-predominant GGNs from solid-predominant GGNs has exhibited considerable variability, ranging from 0.5 to 0.75. This paper presents the calculation of the CTR cutoff value, determined to be 0.750, for distinguishing between the 2 entities by utilizing the volume ratio of consolidation components as the gold standard. However, further investigation is required to validate the feasibility of this research finding. Additionally, it is important to note that this study is retrospective, and its conclusions necessitate confirmation through additional prospective trials. Moreover, the findings of this study indicate that lung nodules containing ground-glass components exhibit distinct clinicopathological characteristics and genetic alterations. Consequently, a comprehensive analysis of the biological and molecular changes associated with these 2 nodule types is imperative.

## Conclusions

It is noteworthy that this study affirms that the solid-predominant GGNs consist of nodules with a CTR greater than 0.750 rather than greater than 0.5. CTR >0.750 was an independent risk factor associated with the poor prognosis of patients with c-stage IA lung adenocarcinoma. Sublobar resection should be cautiously adopted in GGNs with 0.750< CTR ≤1.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1438/rc

*Conflicts of interest:* All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1438/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of The First Affiliated Hospital of Chongqing Medical University (No. K2023-223. Date: 2023/06/27) and the requirement for individual consent for this retrospective analysis was waived.



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