

Supplementary

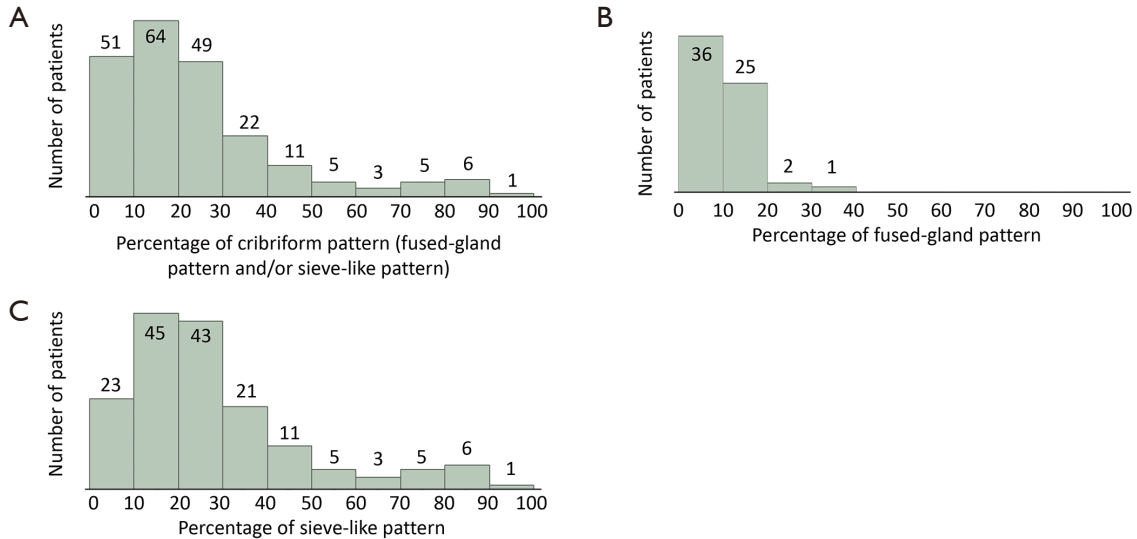


Figure S1 Histograms showing the proportions of cribriform patterns among patients with lung adenocarcinoma. (A) Percentages of cribriform patterns overall (i.e., combined fused-gland and sieve-like patterns); (B) percentages of fused-gland patterns; (C) percentages of sieve-like patterns.

Table S1 Comparison among detailed cribriform patterns

| Variable | Total number of tumors with Cribriform-p* | Cribriform pattern detail | | P value |
|-----------------|--|---------------------------|-----------|---------|
| | | FGP only | FGP + SLP | |
| N | 217 | 54 | 163 | |
| Age (years) | | | | 0.221 |
| <65 | 100 | 21 | 79 | |
| ≥65 | 117 | 33 | 84 | |
| Sex | | | | 0.72 |
| Male | 129 | 31 | 98 | |
| Female | 88 | 23 | 65 | |
| Smoking | | | | 0.24 |
| Ever | 139 | 31 | 108 | |
| Never | 78 | 23 | 55 | |
| Stage | | | | 0.58 |
| I | 130 | 37 | 93 | |
| II | 38 | 8 | 30 | |
| III | 49 | 9 | 40 | |
| Tumor size (mm) | | | | 0.314 |
| ≤30 | 80 | 23 | 57 | |
| >30 | 137 | 31 | 106 | |
| Pleural inv. | | | | 0.159 |
| Absent | 148 | 41 | 107 | |
| Present | 69 | 13 | 56 | |
| Vascular inv. | | | | 0.597 |
| Absent | 130 | 34 | 96 | |
| Present | 87 | 20 | 67 | |
| Lymphatic inv. | | | | 0.109 |
| Absent | 177 | 48 | 129 | |
| Present | 40 | 6 | 34 | |
| MP pattern | | | | 0.456 |
| Absent | 110 | 25 | 85 | |
| Present | 107 | 29 | 78 | |
| Solid pattern | | | | <0.0001 |
| Absent | 53 | 26 | 27 | |
| Present | 164 | 28 | 138 | |
| STAS | | | | 0.41 |
| Absent | 90 | 25 | 65 | |
| Present | 127 | 29 | 98 | |

*, Cribriform-p includes fused-gland pattern and/or sieve-like pattern. inv. invasion; MP p, micropapillary pattern; STAS, spread through air spaces; Cribriform-p, cribriform pattern; FGP, fused-glands pattern; SLP, sieve-like pattern.

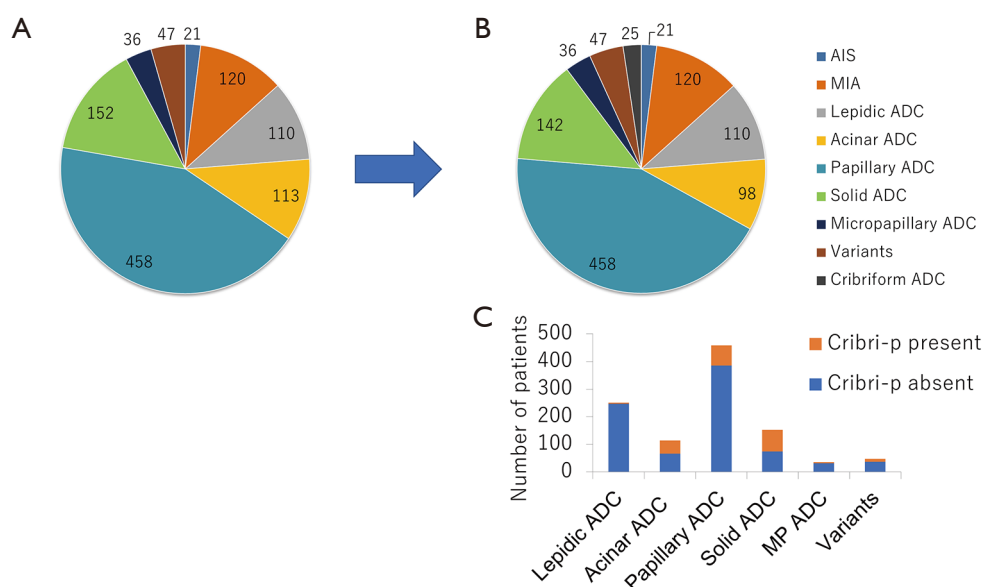


Figure S2 Association between the cribriform pattern and other histological patterns. (A) Proportion of histological subtype based on the 2015 World Health Organization classification; (B) proportion of histological subtypes when considering cribriform ADC; (C) cribriform pattern was the most frequently observed in solid ADCs (51.3%) followed by adjusted acinar ADCs (32.7%), whereas it was rare in lepidic ADCs (2.8%). ADC, adenocarcinoma; AIS, adenocarcinoma *in situ*; Cribriform pattern, cribriform pattern; MIA, minimally invasive adenocarcinoma; MP, micropapillary.

Table S2 Univariate analysis of cribriform pattern and risk of death or recurrence per subgroup

| Patient group | Cribriform pattern | | Recurrence | | | Death | | |
|---------------|--------------------|--------|------------|----------|---------|-------|----------|---------|
| | Present | Absent | RR | 95% CI | P value | RR | 95% CI | P value |
| All stage | 217 | 840 | 2.5 | 1.9–3.2 | <0.0001 | 2.3 | 1.7–3.2 | <0.0001 |
| Stage I | 130 | 699 | 2.0 | 1.3–3.0 | 0.0034 | 2.1 | 1.3–3.3 | 0.0044 |
| Stage II | 38 | 71 | 0.91 | 0.50–1.6 | 0.74 | 0.97 | 0.50–1.8 | 0.94 |
| Stage III | 49 | 49 | 1.3 | 0.81–2.1 | 0.28 | 1.2 | 0.66–2.0 | 0.61 |
| Lepidic ADC | 3 | 107 | NA | NA | NA | NA | NA | NA |
| Acinar ADC* | 32 | 66 | 1.2 | 0.52–2.8 | 0.61 | 1.1 | 0.48–2.5 | 0.78 |
| Papillary ADC | 73 | 385 | 2.1 | 1.3–3.2 | 0.0016 | 2.2 | 1.2–3.6 | 0.0096 |
| Solid ADC | 68 | 74 | 1.4 | 0.82–2.5 | 0.22 | 1.6 | 0.90–2.9 | 0.11 |
| MP ADC | 3 | 31 | 3.9 | 1.2–10 | 0.024 | 3.6 | 0.80–12 | 0.089 |

*, after extracting Cribriform pattern from 'acinar pattern' according to the 2015 World Health Organization classification. RR, relative risk; NA, not available; CI, confidence interval; ADC, adenocarcinoma; Cribriform pattern, cribriform pattern; MP, micropapillary.

Table S3 Multivariate analysis of cribriform pattern and cribriform adenocarcinoma

| Trial | Group | Disease-free survival | | | Overall survival | | |
|-----------------|-----------------------|-----------------------|----------|---------|------------------|----------|---------|
| | | RR | 95% CI | P value | RR | 95% CI | P value |
| Trial 1 | | | | | | | |
| Age (years) | >65 vs. ≤65 | 1.6 | 1.2–2.1 | 0.0007 | 2.0 | 1.5–2.9 | <0.0001 |
| Sex | Male vs. female | 0.87 | 0.79–1.6 | 0.47 | 1.2 | 0.77–1.8 | 0.47 |
| Smoking | Ever vs. never | 1.3 | 0.93–1.9 | 0.11 | 1.4 | 0.89–2.1 | 0.16 |
| Stage | II vs. I | 2.8 | 1.9–3.9 | <0.0001 | 2.7 | 1.8–4.1 | <0.0001 |
| | III vs. I | 4.3 | 3.0–6.3 | | 4.4 | 2.8–6.8 | |
| Lymphatic inv. | Present vs. absent | 1.3 | 0.95–1.9 | 0.097 | 1.5 | 1.0–2.3 | 0.046 |
| Vascular inv. | Present vs. absent | 1.5 | 1.1–2.1 | 0.0077 | 1.1 | 0.80–1.6 | 0.48 |
| Pleural inv. | Present vs. absent | 1.3 | 1.0–2.0 | 0.049 | 1.3 | 0.94–1.9 | 0.11 |
| Lepidic-pattern | Present vs. absent | 1.1 | 0.80–1.5 | 0.59 | 0.87 | 0.61–1.2 | 0.45 |
| MP pattern | Present vs. absent | 1.9 | 1.4–2.5 | <0.0001 | 1.1 | 0.74–1.4 | 0.91 |
| Solid pattern | Present vs. absent | 2.0 | 1.4–2.9 | <0.0001 | 1.5 | 0.99–2.1 | 0.054 |
| Cribri-p | Present vs. absent | 1.1 | 0.80–1.5 | 0.60 | 1.2 | 0.82–1.6 | 0.39 |
| Trial 2 | | | | | | | |
| Age (years) | >65 vs. ≤65 | 1.6 | 1.2–2.1 | 0.001 | 2.0 | 1.4–2.7 | <0.0001 |
| Sex | Male vs. female | 1.1 | 0.75–1.6 | 0.66 | 0.82 | 0.53–1.3 | 0.37 |
| Smoking | Ever vs. never | 1.3 | 0.92–1.9 | 0.14 | 1.4 | 0.90–2.2 | 0.13 |
| Stage | II vs. I | 3.4 | 2.4–4.9 | <0.0001 | 3.0 | 2.0–4.4 | <0.0001 |
| | III vs. I | 5.3 | 3.6–7.8 | | 4.8 | 3.1–7.3 | |
| Lymphatic inv. | Present vs. absent | 1.4 | 1.0–2.0 | 0.080 | 1.6 | 1.0–2.3 | 0.036 |
| Vascular inv. | Present vs. absent | 1.7 | 1.3–2.4 | 0.0002 | 1.3 | 0.87–1.8 | 0.23 |
| Pleural inv. | Present vs. absent | 1.4 | 1.0–1.9 | 0.027 | 1.4 | 1.0–2.0 | 0.054 |
| MP-ADC | MP-ADC or others | 2.2 | 1.4–3.6 | 0.0007 | 1.2 | 0.66–2.2 | 0.49 |
| Solid-ADC | Solid-ADC or others | 1.0 | 0.70–1.4 | 0.87 | 1.2 | 0.80–1.8 | 0.39 |
| Cribri-ADC | Cribri-ADC vs. others | 1.3 | 0.65–2.6 | 0.46 | 1.04 | 0.36–2.4 | 0.94 |

RR, relative risk; CI, confidence interval; Cribri-p, cribriform pattern; inv., invasion; MP, micropapillary; MP-ADC, micropapillary adenocarcinoma; Solid-ADC, solid adenocarcinoma; Cribri-ADC, cribriform adenocarcinoma.

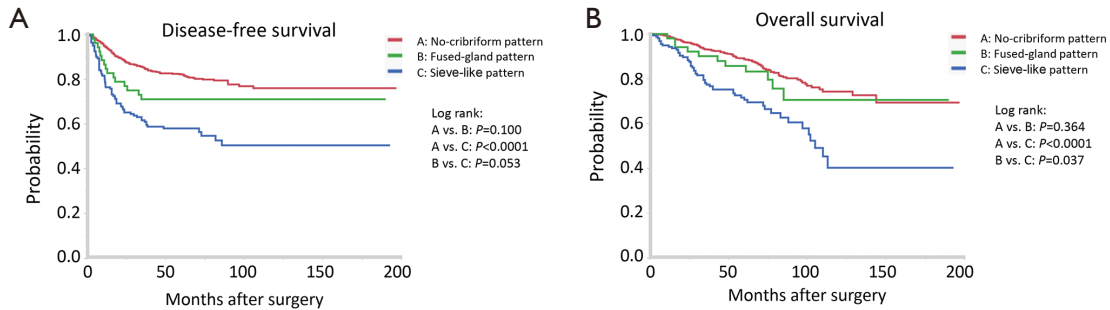


Figure S3 Comparison of the prognostic impacts of the fused-gland versus sieve-like patterns. (A) Disease-free survival of patients with fused-gland patterns tended to be better than that of patients with sieve-like patterns, although the difference was not significant; (B) overall survival of patients with only fused-gland patterns was significantly better than that of patients with sieve-like patterns.