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### Sex-Based Differences in STAS Distribution and Survival in Stage I Lung Adenocarcinoma

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*Türkiye, China, Spain, Italy*

## Introduction

- Tumor spread through air spaces (STAS) is a well-recognized adverse prognostic factor in lung adenocarcinoma.
- Although male sex is generally associated with poorer survival in non-small cell lung cancer, the underlying reasons remain unclear.
- This study aimed to investigate whether sex-based differences in survival may be related to differences in STAS distribution.

## Methods

- Multicenter, retrospective (2016-2024)
- Türkiye, China, Spain, Italy cohorts
- n=770 (female: 375 (48.7%), male: 395 (51.3%))
- Kaplan Meier, Cox regression analysis
- Female and male patients were compared in terms of clinicopathological variables, including smoking status, histologic subtype, resection type, tumor size, lymphovascular invasion, visceral pleural invasion, and grade (Table 1).

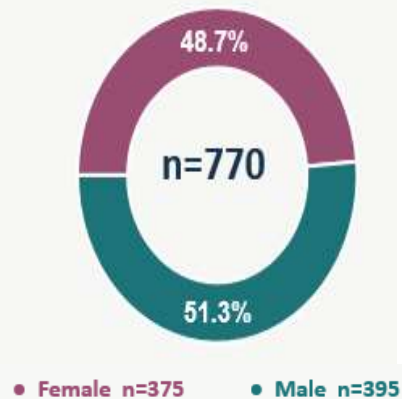
## Results-1 (Outcomes)

| Variables                | Total<br>n (%) | Female<br>n (%) | Male<br>n (%) | p-value |
|--------------------------|----------------|-----------------|---------------|---------|
| Age                      | 770 (100)      | 375 (48.7)      | 395 (51.3)    |         |
| Age                      | 64.03 ± 0.3    | 62.07 ± 0.5     | 65.9 ± 0.5    |         |
| Smoker                   |                |                 |               | <0.001  |
| Non-smoker               | 377 (49.0)     | 282 (75.2)      | 95 (24.0)     |         |
| Former smoker            | 263 (34.1)     | 66 (17.6)       | 197 (49.9)    |         |
| Active smoker            | 130 (16.9)     | 27 (7.2)        | 103 (26.1)    |         |
| Resection type           |                |                 |               | 0.982   |
| Lobar                    | 567 (73.6)     | 276 (73.6)      | 291 (73.7)    |         |
| Sublobar                 | 203 (26.4)     | 99 (26.4)       | 104 (26.3)    |         |
| Predominant Pattern      |                |                 |               | 0.012   |
| Lepidic                  | 158 (20.5)     | 86 (22.9)       | 72 (18.2)     |         |
| Papillary+ Acinar        | 470 (61.0)     | 235 (62.7)      | 235 (59.5)    |         |
| Micropapillary+ Solid    | 142 (18.5)     | 54 (14.4)       | 88 (22.3)     |         |
| Grade                    |                |                 |               | 0.002   |
| Low Grade                | 641 (100)      | 313 (83.8)      | 328 (83.2)    |         |
| High Grade               | 417 (66.7)     | 230 (73.5)      | 197 (60.1)    |         |
| Lymphovascular invasion  |                |                 |               | <0.001  |
| Absent                   | 682 (88.6)     | 350 (93.3)      | 332 (84.1)    |         |
| Present                  | 88 (11.4)      | 25 (6.7)        | 63 (15.9)     |         |
| Visceral pleura invasion |                |                 |               | 0.389   |
| Absent                   | 646 (83.9)     | 319 (85.1)      | 327 (82.8)    |         |
| Present                  | 124 (16.1)     | 56 (14.9)       | 68 (17.2)     |         |
| STAS                     |                |                 |               | <0.001  |
| Absent                   | 576 (74.8)     | 302 (80.5)      | 274 (69.4)    |         |
| Present                  | 194 (25.2)     | 73 (19.5)       | 121 (30.6)    |         |
| Study center             |                |                 |               | <0.001  |
| Türkiye                  | 297 (38.6)     | 137 (36.5)      | 160 (40.5)    |         |
| Spain                    | 121 (15.7)     | 45 (12.0)       | 76 (19.3)     |         |
| Italy                    | 62 (8.0)       | 22 (5.9)        | 40 (10.1)     |         |
| China                    | 290 (37.7)     | 171 (45.6)      | 119 (30.1)    |         |

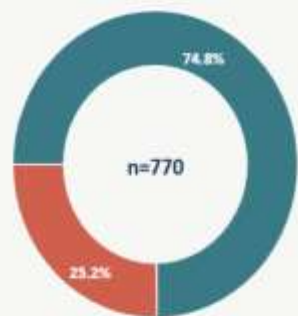
**Table 1.** Baseline clinicopathological characteristics according to sex

**STAS positivity: 30.6% in men vs 19.5% in women (p<0.001)**

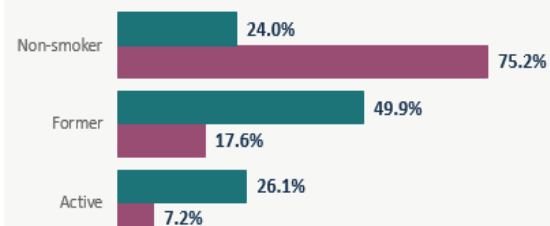
### Sex distribution



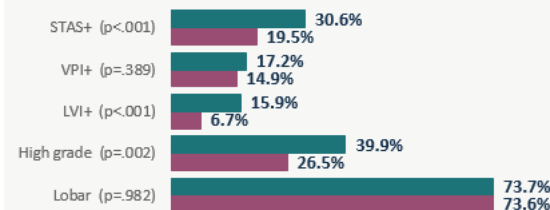
### STAS distribution



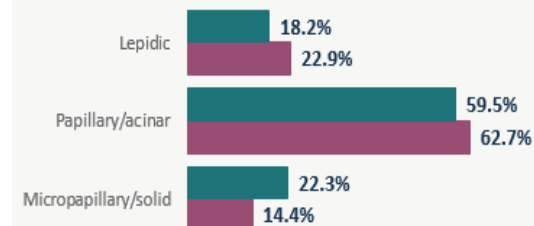
### Smoking status | p<0.001



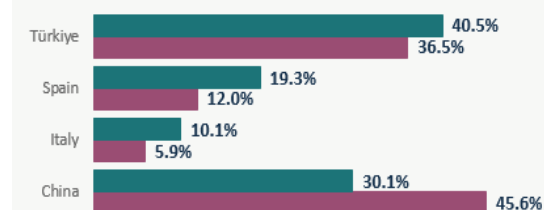
### Surgical and pathologic features



### Predominant pattern | p=0.012



### Study center | p<0.001



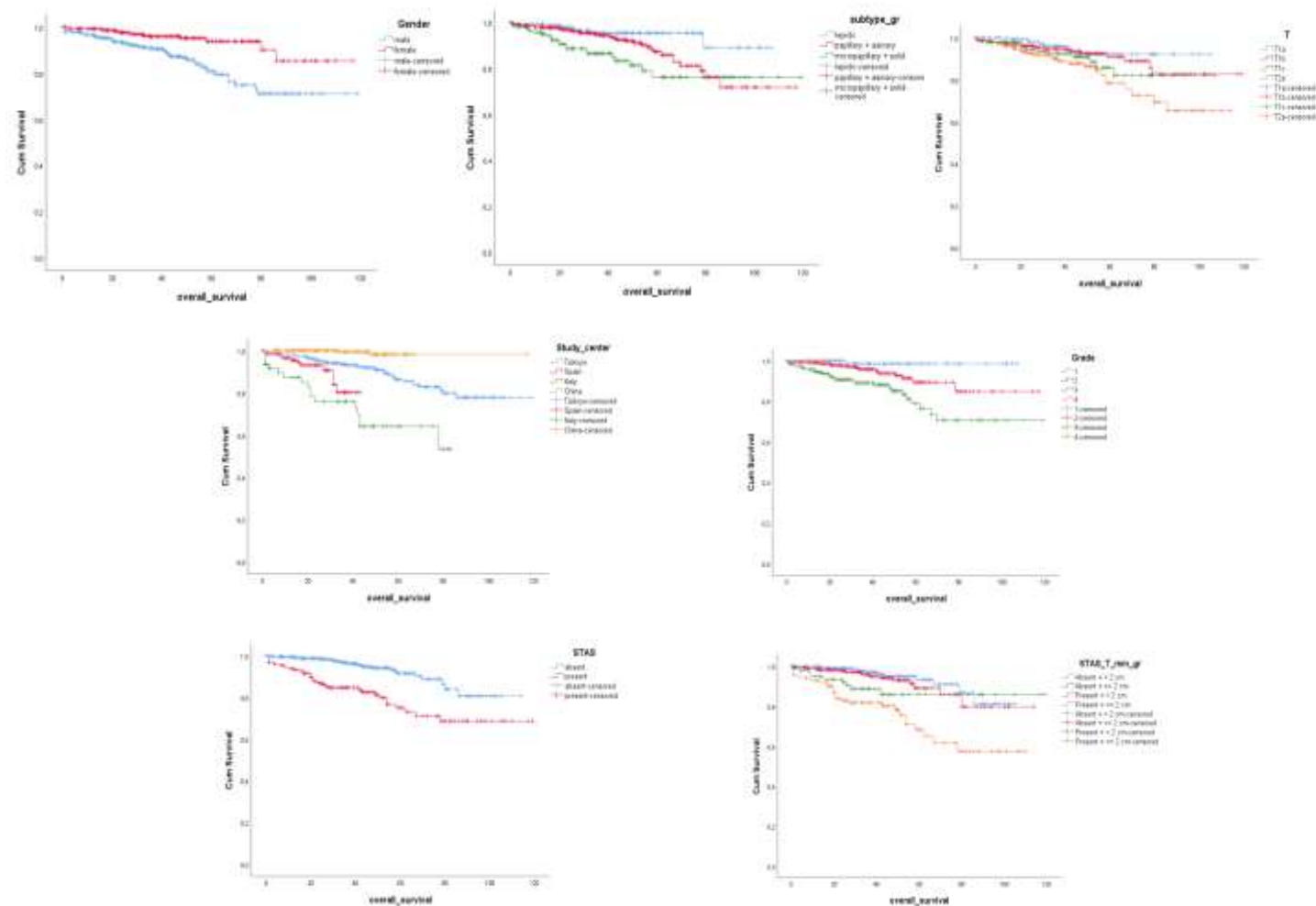
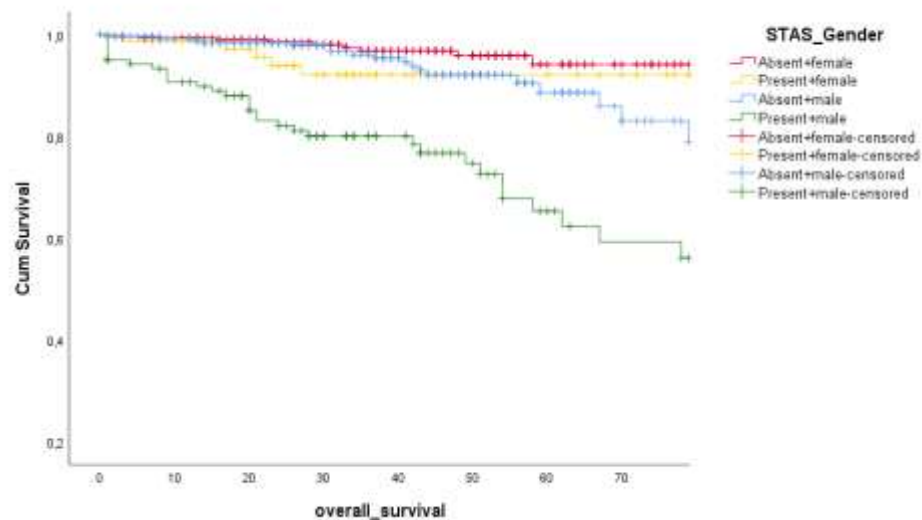
### STAS positivity was higher in men



STAS positivity: 30.6% in men vs 19.5% in women | Absolute difference: 11.1 percentage points

## Results-2 (Survival)

**Figure 1: Sex-Specific Survival Differences According to STAS Status in Stage I Lung Adenocarcinoma**



Compared with STAS-negative women, STAS-positive men had a 7.04-fold higher mortality hazard (95% CI: 3.54–13.99;  $p < 0.001$ )

## Discussion and Conclusion

- In stage I lung adenocarcinoma, male patients experience worse survival despite otherwise comparable clinicopathological characteristics. This difference may be partly related to the higher prevalence of STAS in men.
- In addition, our findings suggest that the impact of STAS on survival may differ between sexes, with a more pronounced effect observed in males.
- These findings suggest that the sex-specific impact of STAS on survival may represent one of the factors contributing to survival differences between males and females in lung cancer, and warrant further investigation.

