# Clinicopathologic and molecular landscape of invasive mucinous adenocarcinoma of the lung

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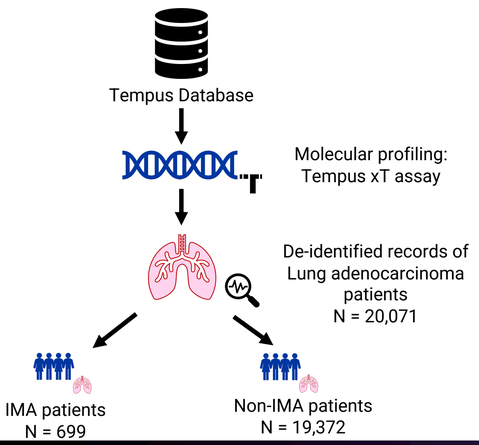
## INTRODUCTION

- Invasive mucinous adenocarcinoma (IMA), accounting for 2–10% of lung adenocarcinomas, has unique radiologic and pathologic features.
- IMA is still under-researched in terms of its comprehensive clinical and genetic characteristics in large, multicenter studies.
- Here, we assessed gene expression, tumor microenvironment as well as clinical outcomes compared to non-IMA.

## METHODS

- Primary lung cancer cases were obtained from the Tempus database, categorized into either IMA or non-IMA, and compared by patient, clinical, pathologic, and molecular characteristics.
- The normalization of RNA-seq data involved computing transcripts per million (TPM), performing log2 transformations, and adjusting for assay and batch effects.
- Significantly up- and down-regulated genes were defined as false discovery rate q-values < 0.05 and |log2(fold change)| > 0.5.




## SUMMARY

- IMA has low mutational burden (3.1 vs. 4.2 mut/Mb, p<0.001) as well as low neo-antigen level (7 vs. 9 neoantigens/Mb, p<0.001).
- IMA has lower M1 and more M2 macrophages than non-IMA indicating an immunosuppressive and tumor-promoting environment.
- High proportion of Treg and low CD8+ T cell in IMA could be related with limited benefit of immunotherapy.

## RESULTS

| Clinical variables | IMA N=699 | Non-IMA N=19,372 | p-value |
|---|---|---|---|
| Age, years | 70 (63, 77) | 68 (61, 75) | 0.002 |
| Sex | | | 0.064 |
| Female | 356 (51%) | 10,555 (54%) | |
| Male | 343 (49%) | 8,817 (46%) | |
| Smoking status | | | <0.001 |
| Current/former | 443 (63%) | 14,088 (73%) | |
| Never smoker | 167 (24%) | 3,148 (16%) | |
| Unknown | 89 (13%) | 2,136 (11%) | |
| Stages | | | <0.001 |
| Stage 1 | 207 (42%) | 3301 (21%) | |
| Stage 2 | 89 (19%) | 938 (6.6%) | |
| Stage 3 | 110 (23%) | 2,125 (15%) | |
| Stage 4 | 194 (41%) | 9,700 (68%) | |
| First-line Treatment | | | <0.001 |
| CTx | 160 (56%) | 3602 (42%) | |
| CTx + ICI | 85 (30%) | 2488 (29%) | |
| CTx + Biologic agent | 4 (1%) | 111 (1%) | |
| ICI | 18 (6%) | 808 (9%) | |
| Others | 18 (6%) | 1586 (18%) | |

**Table 1.** Cohort demographics. The IMA group were older (median age 70 vs. 68; p<0.001), had fewer smokers (63% vs. 73%; p<0.001), and more Hispanic/Latino individuals (4.3% vs. 2.7%; p=0.007). Additionally, IMA individuals were more likely to be diagnosed with early-stage cancer.

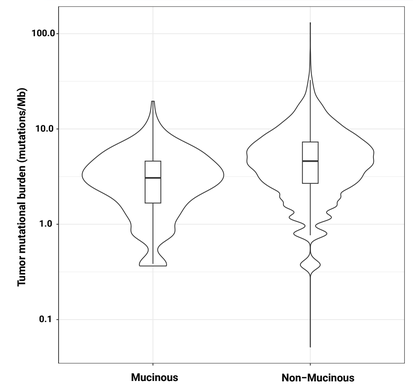



**Figure 1.** Tumor mutational burden

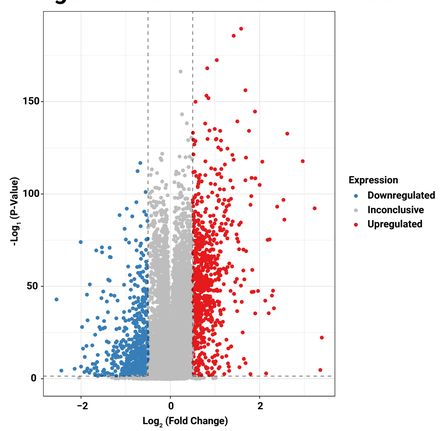



**Figure 2.** Differential Gene Expression in IMA. Gene expression analysis revealed 416 upregulated and 258 downregulated genes in the IMA group compared to non-IMA.

| Cell proportions, % | IMA N=543 | Non-IMA N=15,007 | p-value |
|---|---|---|---|
| B cells | 5.9 (4.4, 8.0) | 4.5 (3.1, 7.3) | <0.001 |
| M1 macrophages | 8 (6, 10) | 9 (6, 13) | <0.001 |
| M2 macrophages | 7.1 (5.0, 9.5) | 6.3 (3.8, 8.9) | <0.001 |
| NK cells | 2.90 (2.33, 3.63) | 2.80 (2.11, 3.62) | 0.013 |
| Neutrophils | 7.9 (6.2, 10.0) | 8.4 (6.4, 10.8) | 0.005 |
| CD4 T cells | 0.0 (0.0, 0.5) | 0.0 (0.0, 1.3) | 0.015 |
| CD8 T cells | 0.73 (0.19, 1.52) | 0.87 (0.17, 2.02) | 0.009 |
| Tregs | 5.87 (4.01, 7.77) | 4.86 (3.08, 7.28) | <0.001 |

**Table 2.** Tumor Microenvironment. IMA group displayed different immune cell infiltration patterns compared to non-IMA types.

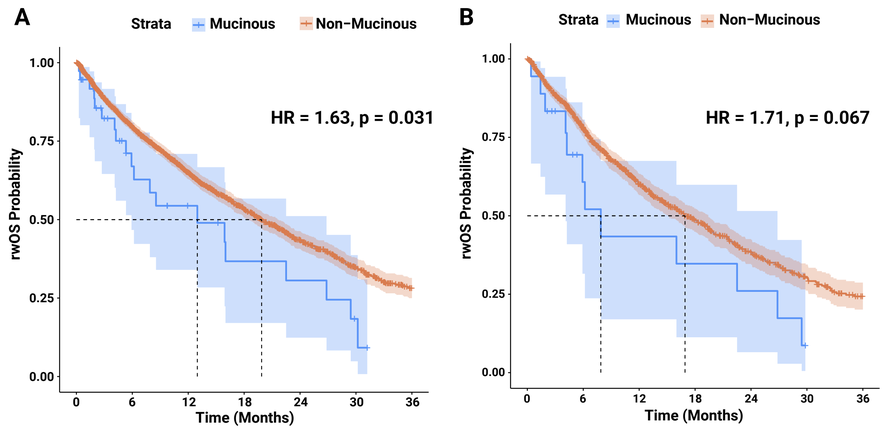



**Figure 3.** KM Survival Curves. **(A)** All treatment types, metastatic at primary diagnosis and **(B)** Chemotherapy (CTx) and immunotherapy, metastasis at primary diagnosis.

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