Molecular and immune landscape of invasive mucinous adenocarcinoma (IMA) of the lung and its survival outcome

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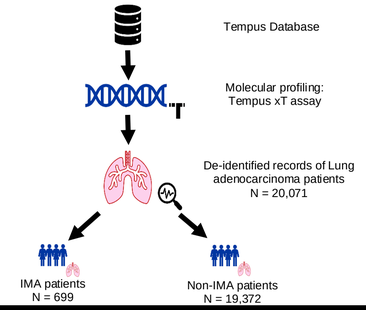
INTRODUCTION

- IMA constitutes a rare subset of lung adenocarcinomas.
- Due to its low incidence, the IMA's biology and prognosis remain poorly understood.
- In this study, we analyzed the tumor microenvironment, gene expression, and clinical outcomes of IMA patients.

METHODS

- De-identified records of patients with primary lung cancer were identified in the Tempus database and stratified into IMA or non-IMA.
- Clinical, biopsy, and molecular characteristics were assessed.
- Normalized RNA-seq data were used to test for differential gene expression (DGE).
- Real-world overall survival (OS) was compared by histological subgroup using Kaplan-Meier curves and Cox proportional hazards models using a prospective-like approach.
- Immune cell infiltration measures were estimated using the quanTIseq algorithm.



SUMMARY

- IMA patients were more likely to be **diagnosed at an earlier stage** but had **significantly worse overall survival** compared to non-IMA patients.
- IMA patients had **lower tumor mutational burden** (3.1 vs. 4.2 mut/Mb, p<0.001) with lower percentage of PD-L1 positive status (28% vs. 59%, p<0.001).
- The tumor microenvironment in IMA was characterized by high levels of M2 macrophages and Tregs, along with reduced CD8+ T cells and M1 macrophages.
- Differential gene expression analysis revealed up-regulation of immunosuppressive and mucin-related genes in IMA, potentially leading to immune evasion and reduced efficacy of immunotherapy in IMA patients.

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%)	

Table 1. Cohort demographics of IMA vs. Non-IMA patients. IMA patients had a lower percentage of smokers, and a higher proportion of Hispanic/Latino individuals. IMA patients were also more likely to be diagnosed at an earlier stage.

Number of observations	IMA N=699	Non-IMA N=19,372	p-value
Tumor mutational burden (mut/Mb)	3.1 (1.5, 4.6)	4.6 (2.5, 7.3)	<0.001
Neoantigen tumor burden	6 (3, 9)	9 (5, 15)	<0.001
PD-L1, Negative	296 (72%)	5,088 (41%)	<0.001
PD-L1, Positive	115 (28%)	7,358 (59%)	<0.001

Table 2. Molecular characteristics of IMA vs. Non-IMA. IMA had lower TMB and a lower percentage of PD-L1 positive status.

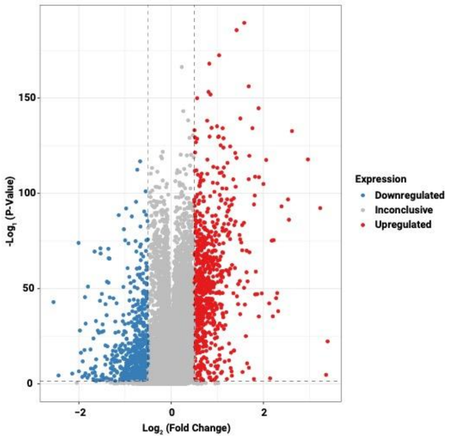


Figure 1. Differential Gene Expression (DGE) in IMA.

Gene	Log2 (fold change)	p-value
IL33	0.62753	<0.001
IL22RA1	0.8992	<0.001
CXCL5	0.73795	<0.001
ERVW-1	3.35819	<0.001
FOXA3	1.01842	<0.001
MUC5AC	1.41757	<0.001
MUC5B	0.51824	<0.001

Table 3. DGE of IMA revealed changes in immune-related gene expression and mucin-related genes.

Cell proportions, %	IMA N=699	Non-IMA N=19,372	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 4. Tumor Microenvironment. IMA group shows higher infiltration of immunosuppressive cells such as M2 macrophage, and Treg.

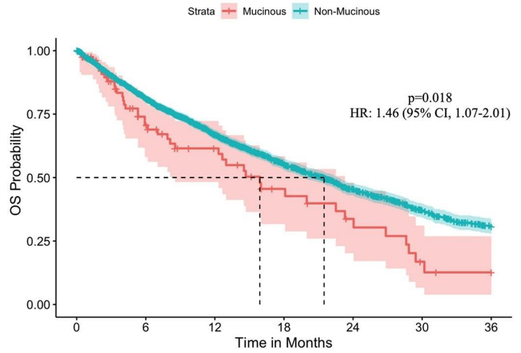


Figure 2. KM Survival analysis for IMA and non-IMA. IMA showed significantly worse overall survival compared to non-IMA

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