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Stage-Associated Airway Microbiota Alterations and Lactate Metabolic Functional Remodeling in Non-Small Cell Lung Cancer

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INTRODUCTION

- Increasing evidence suggests that microorganisms may contribute to carcinogenesis.
- However, most studies have focused on the gut microbiota, and the role of the airway microbiota in non-small cell lung cancer (NSCLC) progression remains unclear. This study investigated the association between airway microbiota profiles and disease stage in NSCLC.

METHODS

- This retrospective study included 131 patients with NSCLC, comprising 62 with early-stage disease (stage I–IIIA) and 69 with late-stage disease (stage IIIB–IV), who underwent lesion resection or biopsy at Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, between February 2015 and March 2018.
- Surgical pathological specimens or biopsy samples were analyzed by bacterial 16S rRNA gene sequencing to evaluate associations between airway microbial characteristics and NSCLC stage.

RESULTS

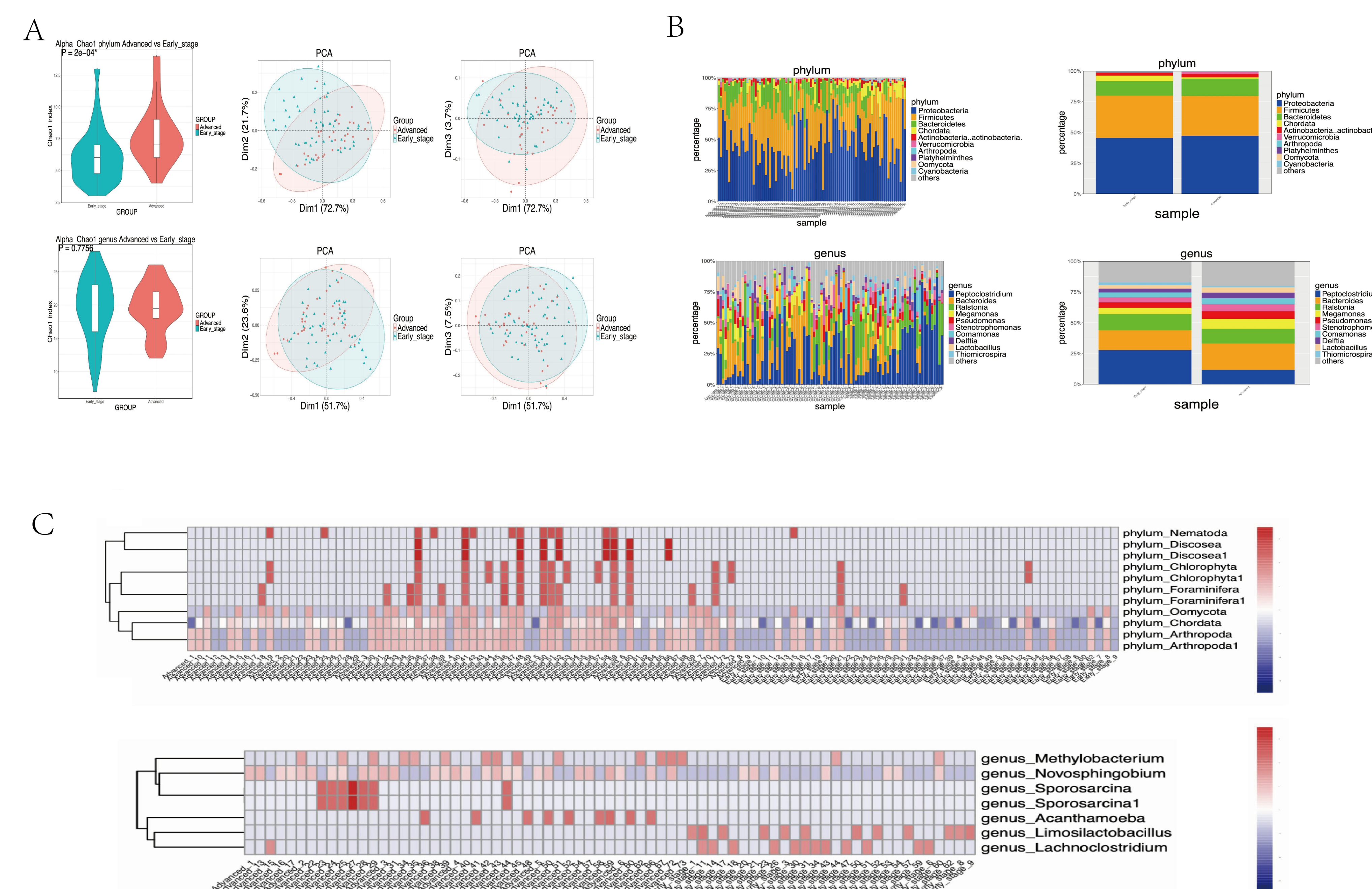


Figure 1: (A) Alpha diversity and PCA of airway microbiota. Late-stage patients showed higher phylum-level Chao1 diversity ($P = 0.0002$), whereas no significant genus-level difference was observed ($P = 0.7756$). (B) Relative microbial composition at the phylum and genus levels, showing substantial inter-individual heterogeneity. Proteobacteria, Firmicutes, and Bacteroidetes were the dominant phyla. (C) Heatmaps of differential taxa between disease stages. At the phylum level, alpha-diversity analysis showed a significantly higher Chao1 index in the late-stage group than in the early-stage group (7.81 vs. 6.14, $P = 0.0002$), indicating increased microbial richness in advanced disease. No significant differences were observed in Shannon or inverse Simpson indices at the phylum level, or in Shannon, inverse Simpson, and Chao1 indices at the genus level (all $P > 0.05$). Beta-diversity analysis revealed only modest clustering trends with substantial overlap between groups, suggesting limited overall separation of microbial community structure. Proteobacteria, Firmicutes, and Bacteroidetes predominated at the phylum level in both groups, whereas Peptoclostridium, Bacteroides, and Ralstonia were among the dominant genera, with marked inter-individual heterogeneity.

Differential abundance analysis identified several taxa enriched in late-stage disease, whereas Faecalibacterium and Bifidobacterium were relatively enriched in early-stage disease. Functional prediction using PICRUSt2 showed that, after excluding taxa present in fewer than 5% of individuals, **Lactate 2-monooxygenase was significantly upregulated in the late-stage group** ($\log_2$ fold change = 26.13, $P = 0.0076$), suggesting enhanced bacterial lactate catabolic potential in advanced NSCLC.

DISCUSSION AND CONCLUSION

Airway bacterial communities differ between early- and late-stage NSCLC in both taxonomic composition and predicted functional potential. Notably, late-stage disease was characterized by enrichment of lactate metabolism-related microbial functions, including significant upregulation of Lactate 2-monooxygenase. These findings suggest that microbiota-associated lactate metabolic reprogramming may contribute to lung cancer progression.