Prognostic Value of Circulating H3K27Me3-Nucleosomes In Newly Diagnosed Lung Cancer Patients

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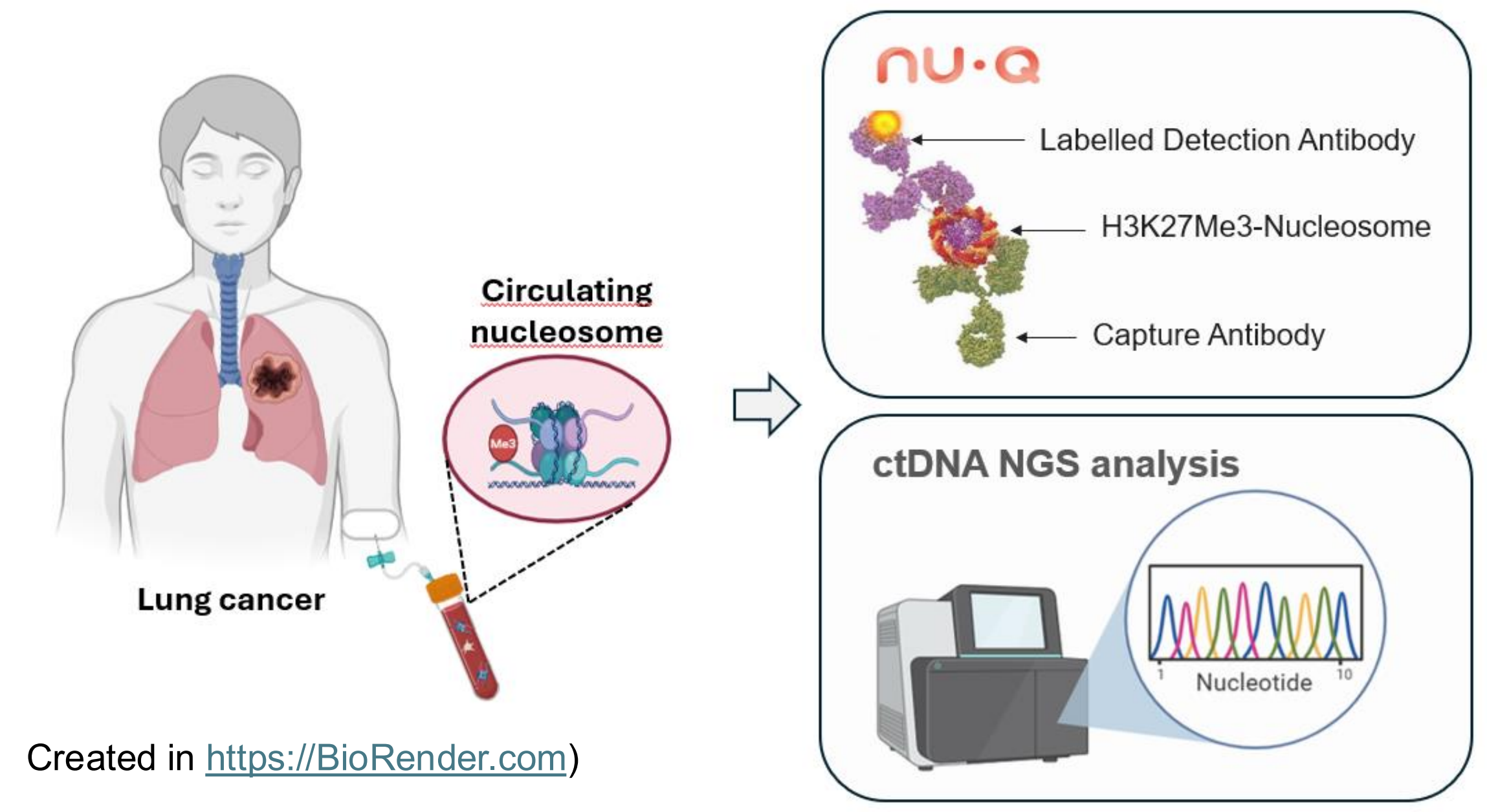
Background

Although the overall prognosis of advanced lung cancer remains poor, clinical outcomes increasingly appear to vary depending on histological subtype and the presence of targetable molecular alterations. In this context, circulating tumor DNA (ctDNA) analysis has emerged as a promising tool to detect actionable mutations and guide treatment decisions, even in non-surgical patients. However, a substantial proportion of patients present without detectable actionable mutations (ctDNA-negative group), representing a major clinical challenge. The objective of the present study was to evaluate the potential of circulating H3K27Me3-nucleosomes as a prognostic marker and risk stratification marker in advanced lung cancer, and to investigate its potential utility to provide additional epigenetic information for cancer detection and treatment guidance.

Methods

Plasma samples were retrospectively collected from treatment-naive lung cancer patients at initial diagnosis (n_{total}=617; suspicious imaging (n=34, 6%), locally-advanced cancer (stage I–III; n=130, 21%), metastatic cancer (stage IV; n= 331, 54%), and cancer with undetermined stage (n=122, 20%)). Paired plasma samples underwent targeted next-generation sequencing (NGS) and circulating H3K27Me3-nucleosome quantification using chemiluminescent Nu.Q® immunoassays (Belgian Volition SRL, Belgium). Sample with a VAF above 0.5% was considered as ctDNA positive (ctDNA(+)). A minimum follow-up of 8 months was determined for the survival analyses performed, yielding 514 evaluable patients.



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Results

- *Figure 1 & 2*: **Plasma H3K27Me3-nuclesome** levels were **stage dependent** and **highly elevated levels** in patients with a **poor outcome**.
- *Figure 3* A: **Overall survival analysis** revealed that patients with a **H3K27Me3-nucleosome levels below** 56ng/ml *(green)* had a significantly **better mean survival** compared to those with higher concentrations *(red)* (mean survival: 26 months vs 11.8 months, p<0.0001). Unstratified group represented in *grey* showed a mean survival time of 21.8 months;
- *Figure 3 B & C*: Survival by ctDNA status.

B) **Among ctDNA- patients**, those with a circulating H3K27Me3-nucleosome concentrations below 57 ng/mL (*light blue*) have a significant **better survival compared to those with higher levels** *(dark blue)* (mean survival: 28.9 months vs 11.8 months, p<0.0001).

C) In ctDNA+ patients, an optimal threshold of 123 ng/mL effectively separated "low-risk" (*light purple*, 18.1 months) and "high-risk" (*dark purple*, 7.4months) subgroups.

Circulating H3K27Me3-nuclesome levels is associated with cancer stages and mortality

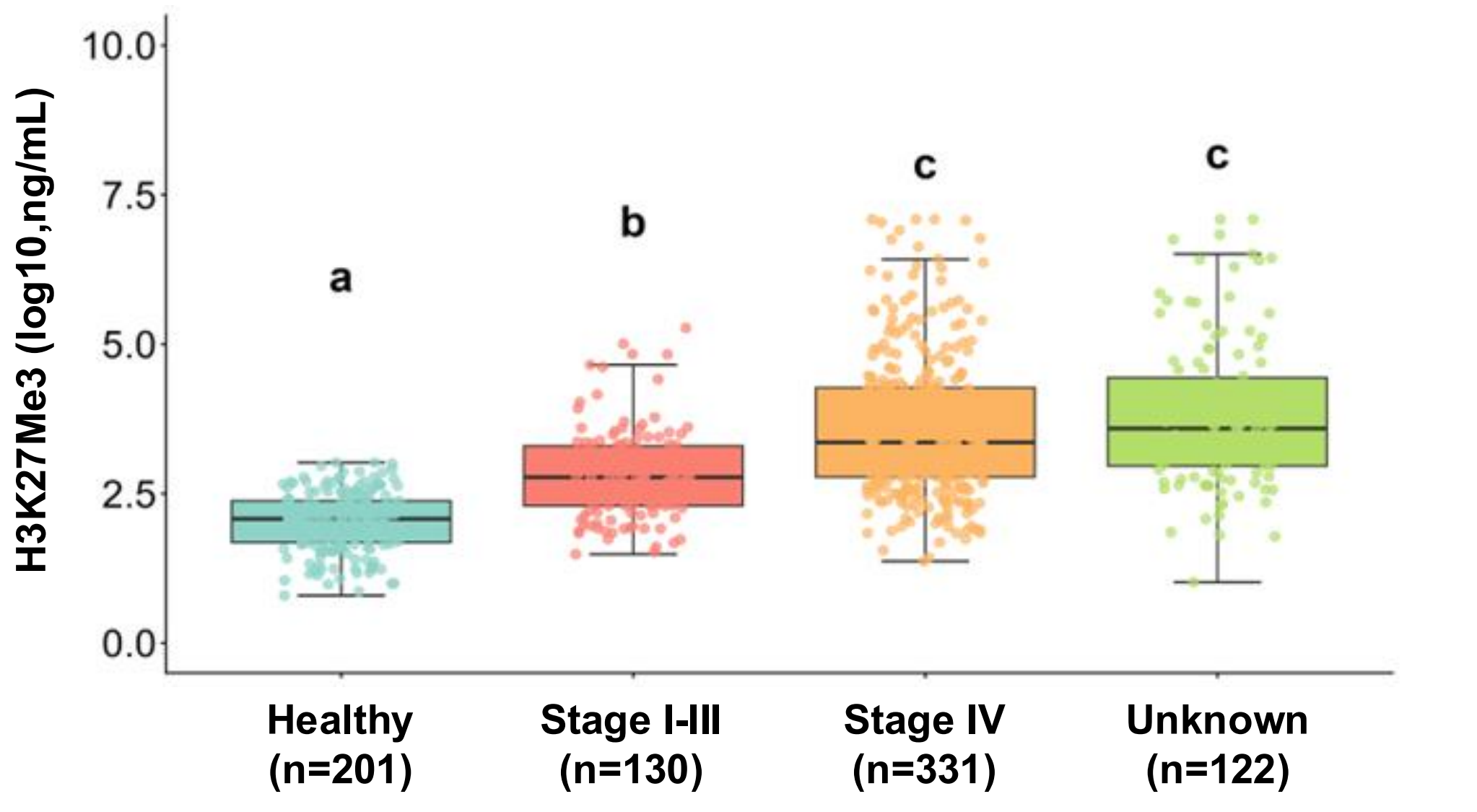


Figure 1: H3K27Me3-nucleosome levels across cancer stages. Lung cancer patients show significantly elevated nucleosome levels compared to healthy; Stage IV exceeds I–III; different letters indicate p-value<0.05.

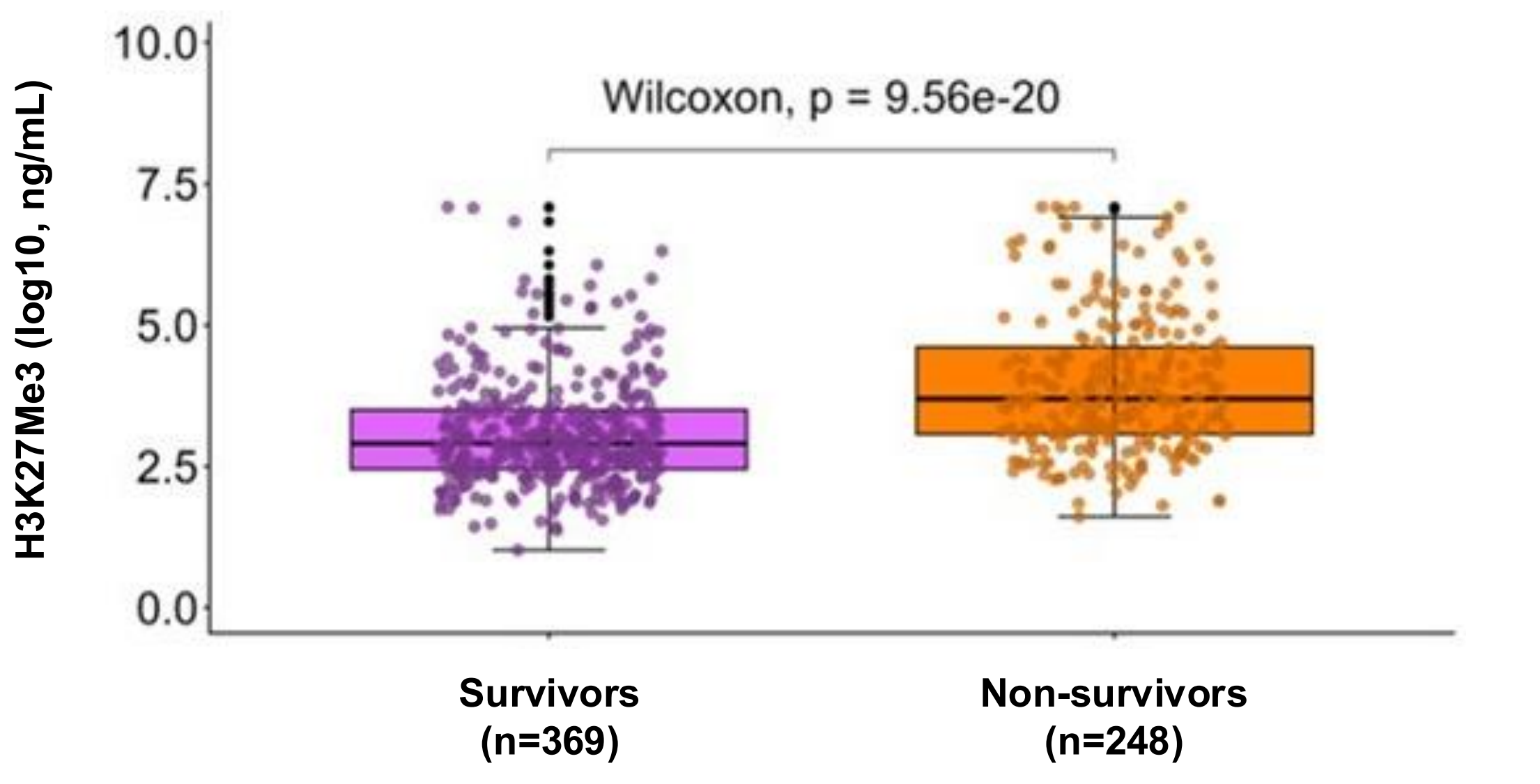
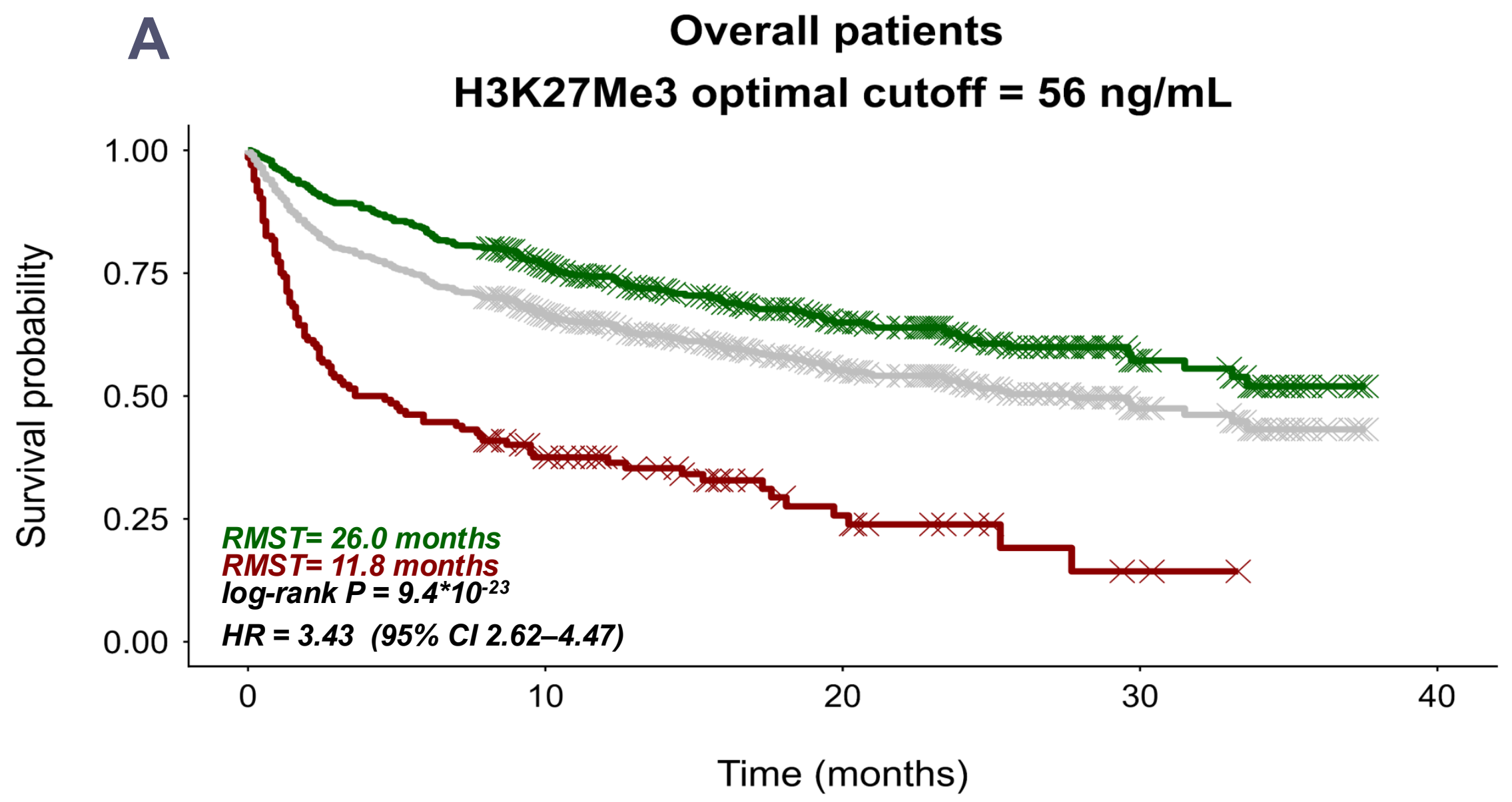


Figure 2: H3K27Me3-nucleosome levels between survivors and non-survivors. Patients who died exhibit significantly higher H3K27Me3-nucleosome levels.

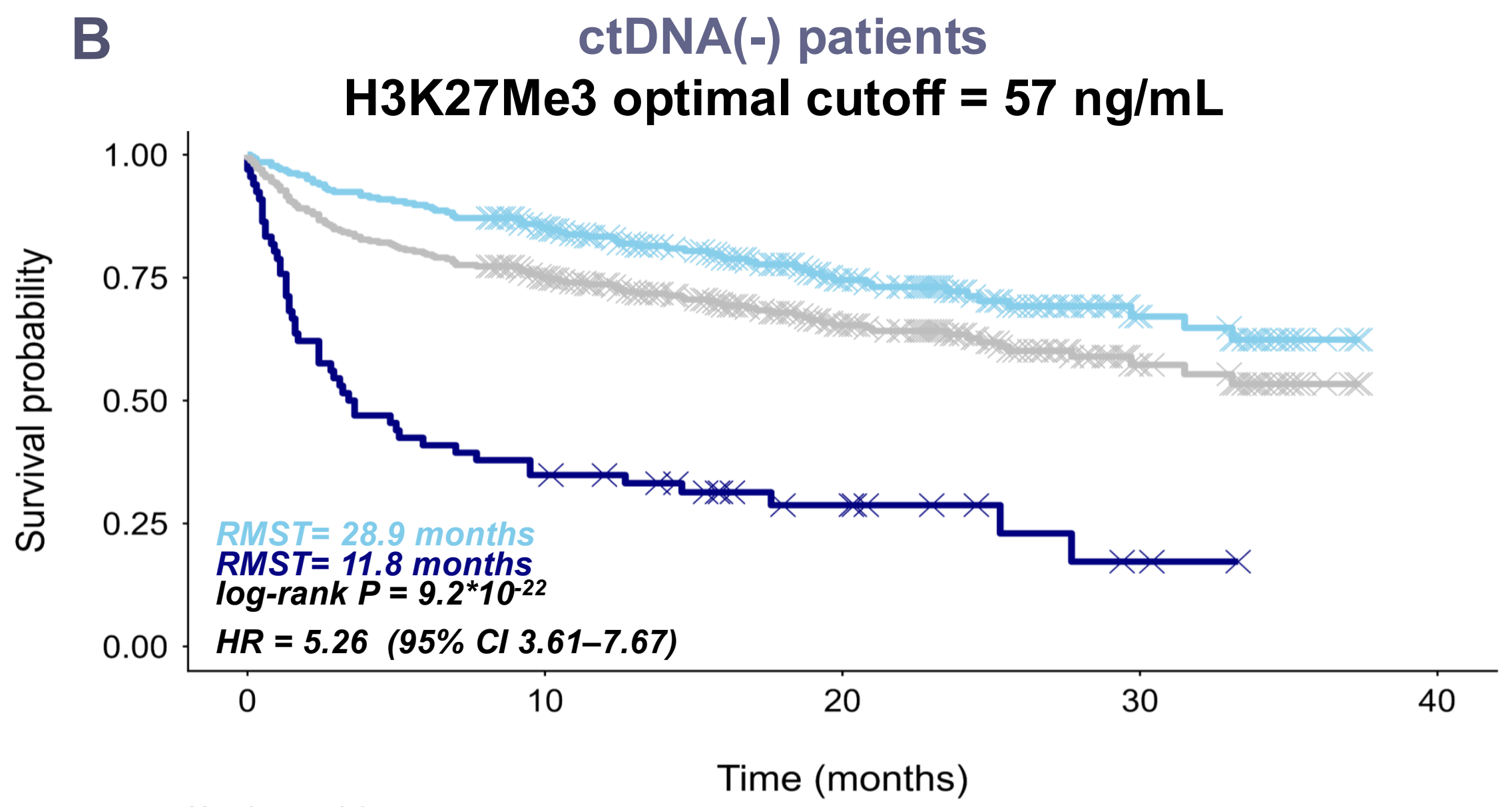
Circulating H3K27Me3-nucleosomes: a Potential Prognostic Biomarker to Identify High-Risk Lung Cancer Patients



Number at risk

Low Risk	*382*	*261*	*135*	*37*	*0*
High Risk	*132*	*44*	*14*	*2*	*0*
All	*514*	*305*	*149*	*39*	*0*

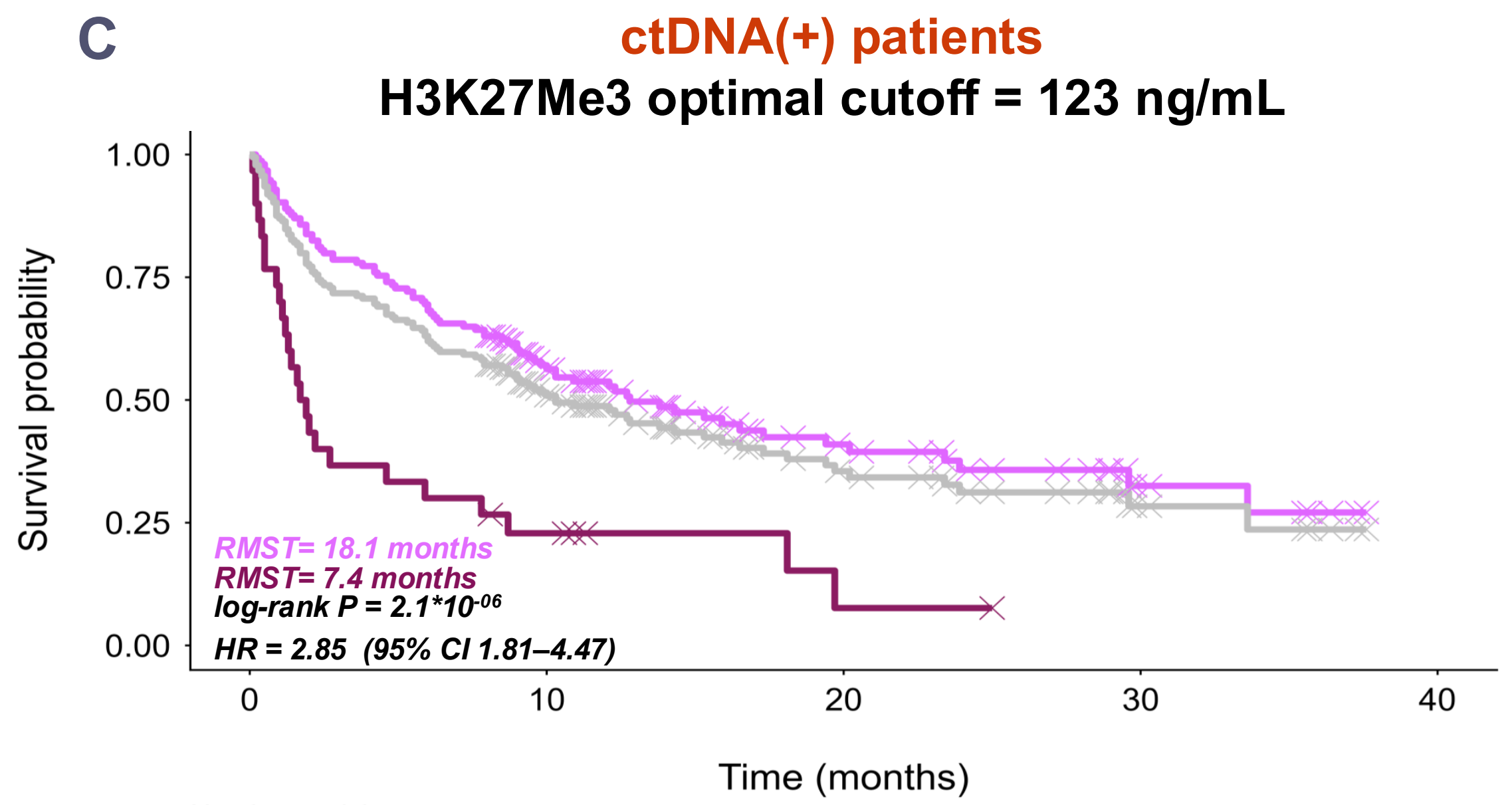
Figure 3A: Kaplan-Meier (K-M) plot by H3K27Me3-nucleosomes optimal cutoff (56 ng/mL). Low (green) and High (red) Risk groups present significantly different survival probabilities.



Number at risk

Low Risk	*264*	*204*	*111*	*30*	*0*
High Risk	*66*	*23*	*10*	*2*	*0*
	330	*227*	*121*	*32*	*0*

Figure 3B: K-M plot by H3K27Me3-nucleosomes optimal cutoff (57 ng/mL). Low (light blue) and High (dark blue) Risk groups present significantly different survival probabilities.



Number at risk

Low Risk	*154*	*72*	*27*	*7*	*0*
High Risk	*30*	*6*	*1*	*0*	*0*
All ctDNA(+)	*184*	*78*	*28*	*7*	*0*

Figure 3C: K-M plot by H3K27Me3-nucleosomes optimal cutoff (123 ng/mL). Low (light pink) and High (dark pink) Risk groups present significantly different survival probabilities.

Study sponsored by:

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Conclusions

- Circulating H3K27Me3-nuclesomes levels increase with **cancer disease stages** and is associated to **survival outcome**
- H3K27Me3-nucleosome is a **non-invasive biomarker,** that **complements ctDNA**
- Circulating H3K27Me3-nucleosome at diagnosis emerges as an **independent prognostic biomarker for overall survival**, offering a practical **approach to refine risk assessment -** particularly within the ctDNA-negative subgroup and to inform clinical decision-making in the context of personalized therapeutic strategies