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INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers and remains the leading cause of cancer-related death worldwide¹. Survival outcomes have been widely reported using conventional methods, although these approaches do not account for excess mortality relative to the general population or for competing causes of death. Standardized mortality ratios (SMRs) quantify excess mortality, while competing-risk methods provide more accurate estimates of cause-specific mortality.² However, the relative contribution of lung cancer and competing causes of death after complete (R0) resection of stage I–IIIA NSCLC remains poorly characterized. We therefore assessed long-term overall, excess, and cause-specific mortality after R0 resection in this cohort.

METHODS

This is a retrospective study using patients from the prospective Thoracic Tumor Registry (TTR, NCT02941458). This cohort study included adults with stage I–IIIA NSCLC who underwent R0 resection without neoadjuvant treatment (Figure 1). Overall survival (OS) was estimated using Kaplan–Meier methods. Standardized mortality ratios (SMRs) were calculated against the general Spanish population adjusted by age, sex, and calendar year. Cause-specific mortality was analyzed using competing-risks methods. To identify variables associated with lung cancer and non-lung cancer mortality, cause-specific uni- and multivariable subdistribution hazard models were fitted.

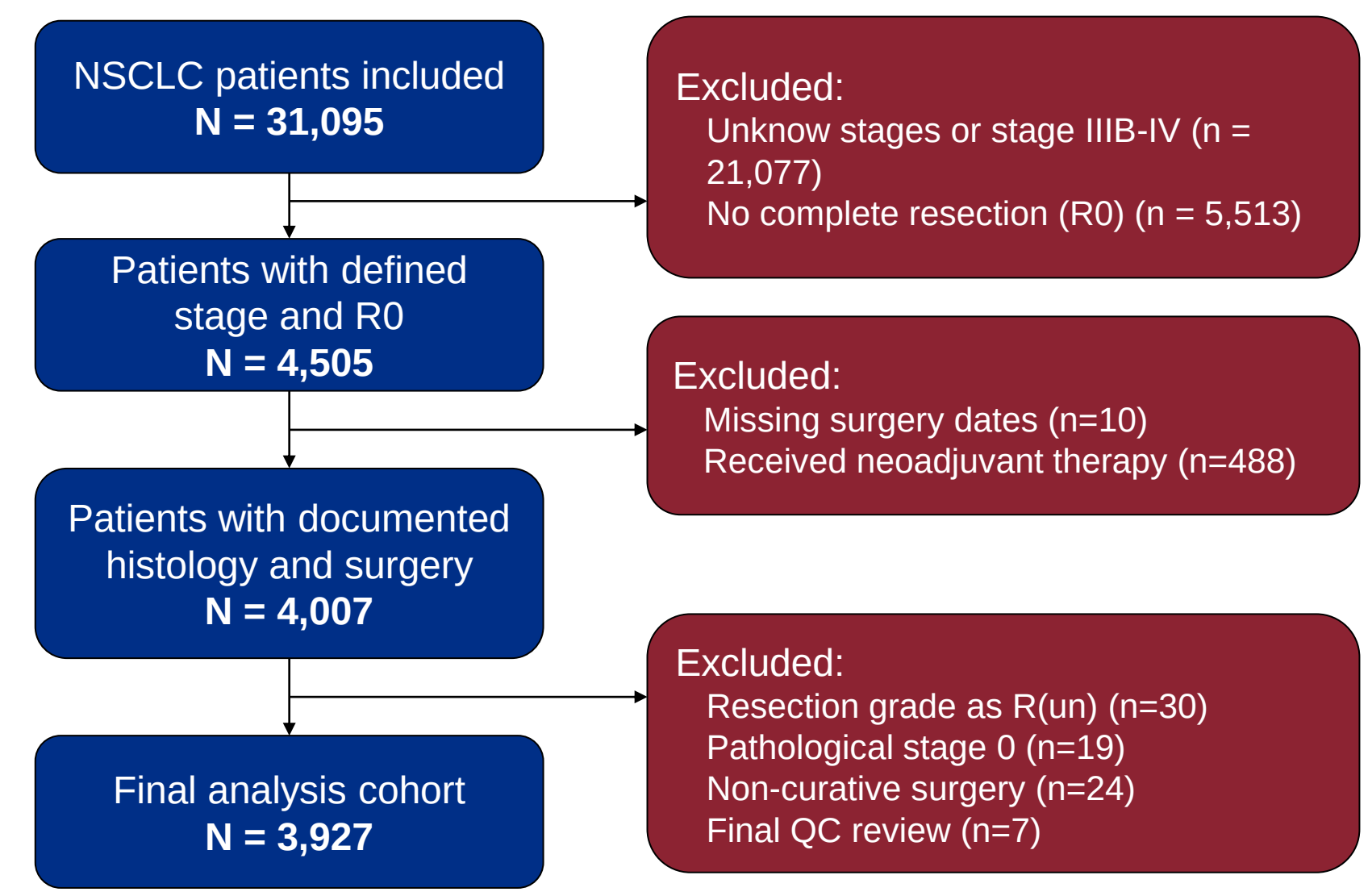


Figure 1. Flow diagram of patient selection process. Abbreviations: NSCLC: non-small cell lung cancer, QC: quality control, R0: complete resection, R(un): uncertain resection.

RESULTS

A total of 3,927 patients were included, with a median follow-up of 54.2 months. Lung cancer accounted for 63.8% of deaths. Median OS was 93.1 months (95% CI: 87.1–99.7), higher in females ($p<0.001$) and decreasing with age ($p<0.001$) (Figure 2).

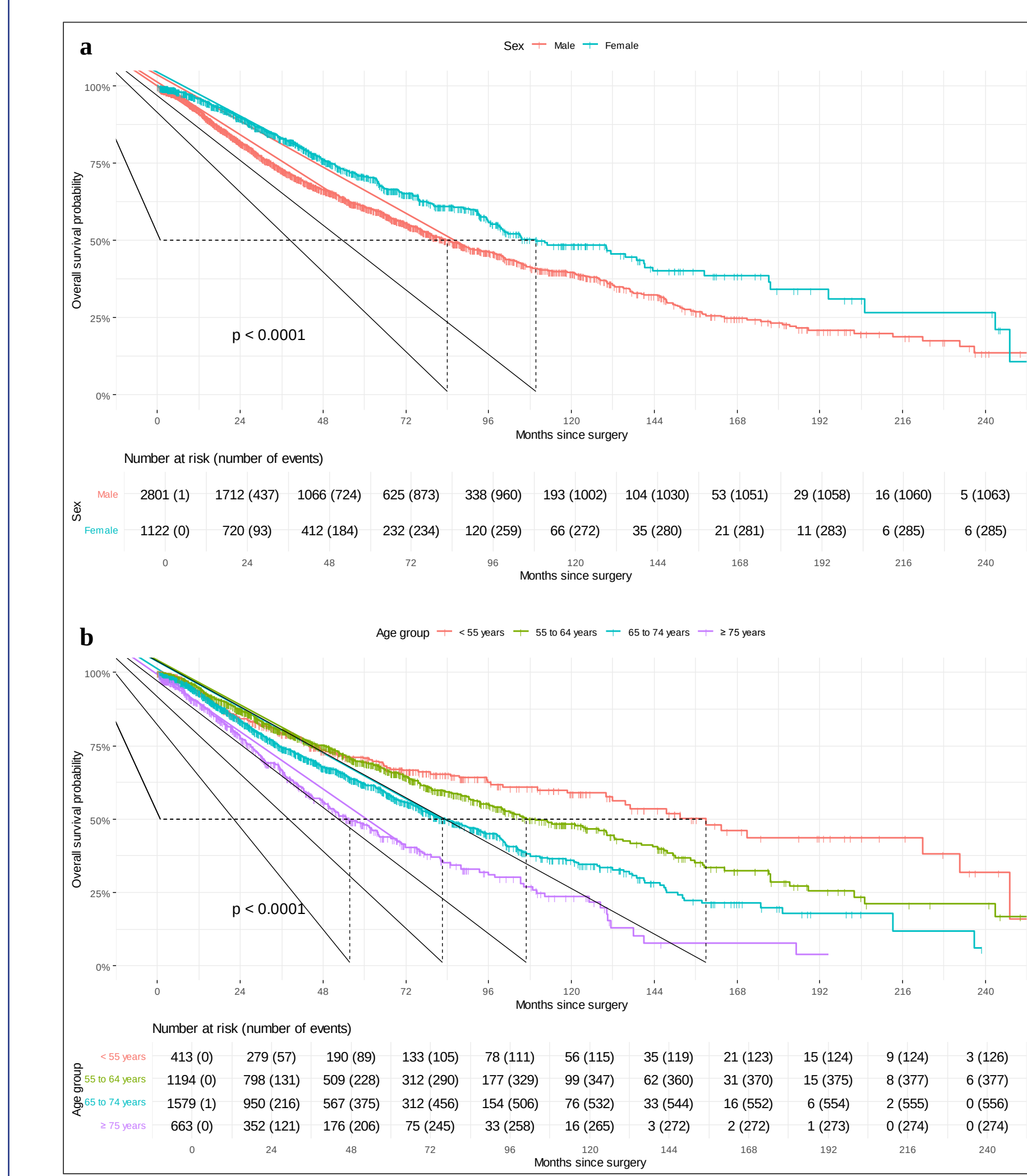


Figure 2. Kaplan–Meier curves for Overall Survival (OS) according to sex (a) and age subgroups (b) in the study cohort.

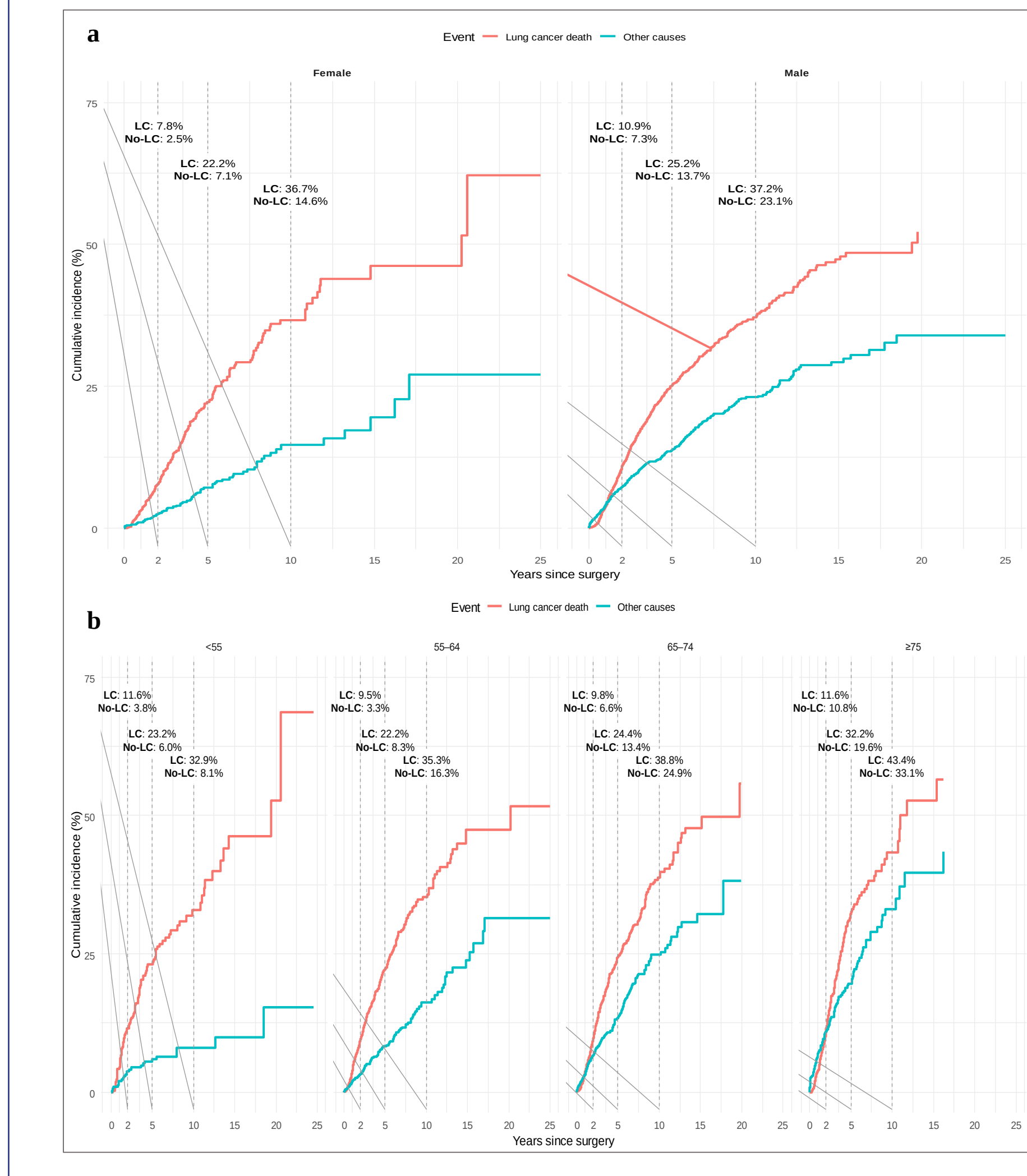


Figure 4. Cumulative incidence functions (CIFs) of lung cancer–specific (red) and non–lung cancer–specific (blue) mortality according to sex (a), and age subgroups (b) in the study cohort.

The all-cause SMR was 3.1 (95% CI, 2.9–3.2), decreasing to 1.1 (95% CI, 1.1–1.2) after excluding lung cancer deaths. All-cause SMR decreased with age, from 47.8 (95% CI: 39.9–56.3) in patients <55 years to 0.9 (95% CI 0.8–1.0) in patients ≥75, with similar results excluding lung cancer deaths (Figure 3).

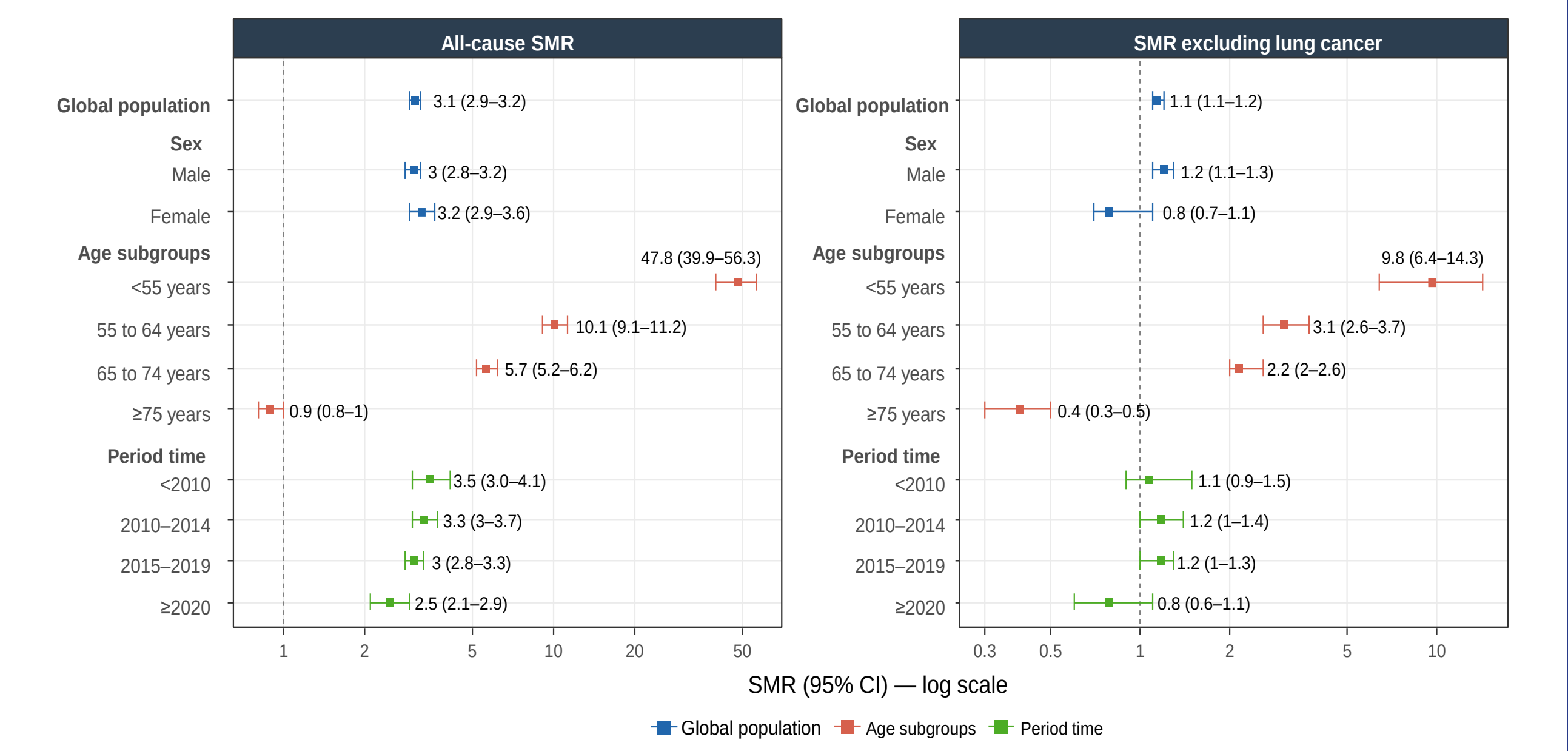


Figure 3. Standardized mortality ratio (SMR) with and without lung cancer as cause of death.

Competing-risks analysis confirmed lung cancer as the predominant cause of death, with no significant differences in lung cancer-specific mortality by sex or age. However, men and patients ≥75 years were associated with higher non-lung cancer mortality ($p<0.001$) (Figure 4).

When stratified by age, active smoking, respiratory comorbidities and squamous histology were associated with an increased non-lung cancer mortality among patients aged 65–74 years (Supplementary Table 1).

In the multivariate analysis, the presence of active tumor was the strongest predictor of lung cancer mortality. Stage II and III disease were independently associated with a higher risk of death from lung cancer. Non-lung cancer mortality was strongly associated with older age, with comorbidities losing significance in the multivariate model (Supplementary Table 2).

DISCUSSION AND CONCLUSION

To our knowledge, this is the largest study from a Spanish multicenter registry evaluating mortality in 3,927 patients with resectable stage I–III NSCLC. By incorporating SMRs and competing risks analysis, we provide a thorough assessment of both excess and cause-specific mortality in this cohort.

Our findings highlight the **importance of incorporating competing risks and excess mortality analyses** for long-term outcome assessment in resected stage I–IIIA NSCLC. Although lung cancer remained the leading cause of death and the main driver of excess mortality, competing **non–lung cancer mortality became increasingly relevant in older patients and men**, supporting the need for prolonged survivorship care, including management of comorbidities and long-term monitoring beyond traditional oncologic follow-up.

REFERENCES & ACKNOWLEDGEMENTS

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Supplementary data