# C-Reactive Protein and Lymphocyte-to-Monocyte Ratio Predict recurrence in Stage III Melanoma Patients with Microscopic Sentinel Lymph Node Metastasis

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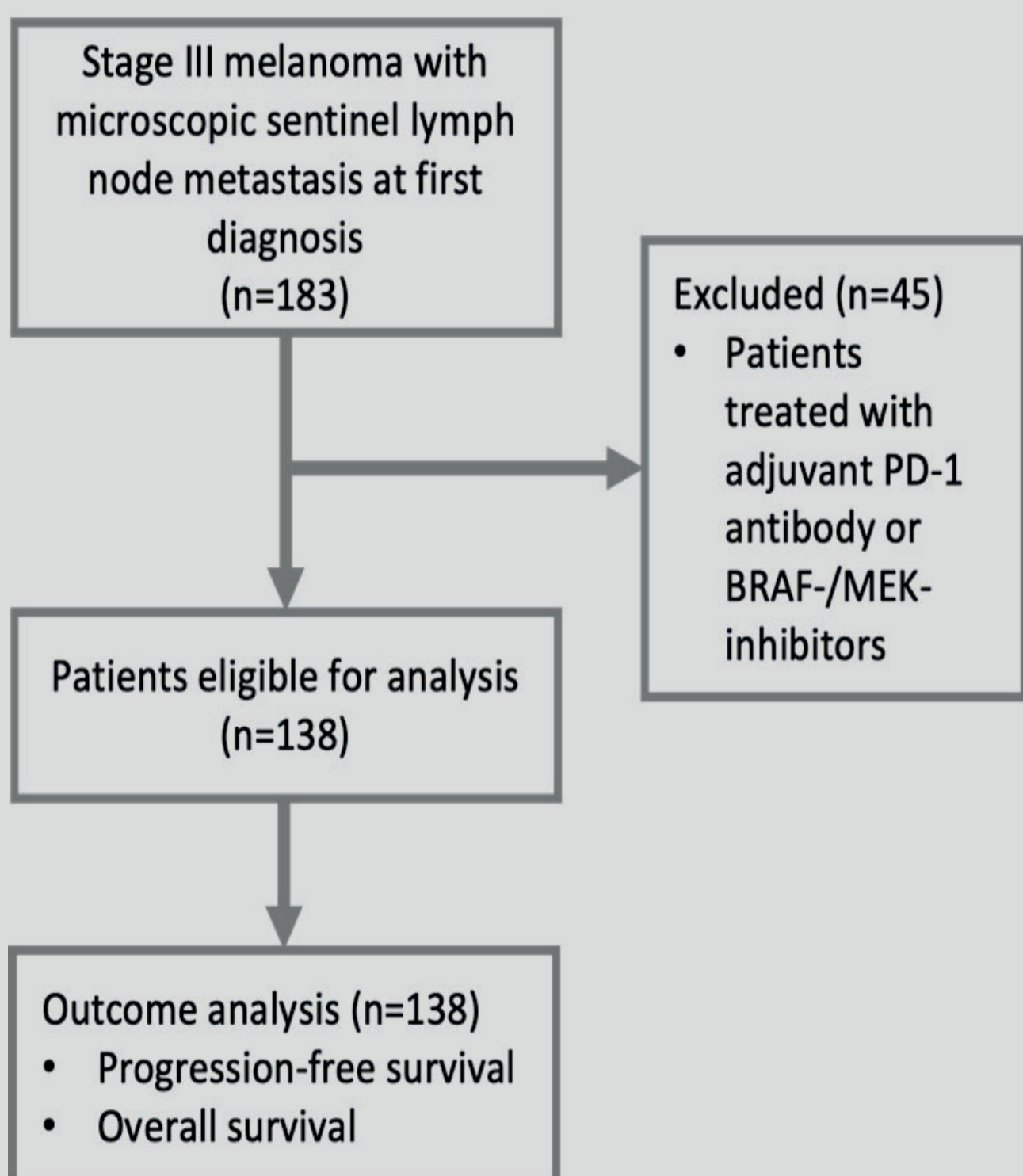
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**BACKGROUND:** Although adjuvant therapies with immune checkpoint inhibitors (ICI) and BRAF/MEK inhibitors improve recurrence-free survival (RFS) in stage III melanoma patients significantly, prognostic factors are needed to identify patients with a high risk of disease recurrence.

**AIM:** The aim of our study was to investigate the prognostic potential of routinely collected blood parameters for stage III melanoma patients with microscopic sentinel lymph node (SLN) metastasis.

**PATIENTS AND METHODS:** Altogether, we retrospectively analyzed 138 stage III melanoma patients who were diagnosed with microscopic SLN metastasis at the skin cancer center of the University Hospital Cologne between 2011 and 2020 and who did not receive prior adjuvant therapy with ICI or BRAF/MEK-inhibitors. Univariate and multivariate Cox regression analyses, Kaplan–Meier survival analyses and receiver operating characteristic (ROC) curves were performed to assess the impact of preoperatively collected blood parameters and blood ratios on recurrence-free survival (RFS; primary endpoint) and overall survival (OS).



**Figure 1. Study flow.** 183 patients with stage III melanoma with microscopic sentinel lymph node metastasis were identified at the Department of Dermatology at the University Hospital Cologne. Of these, 138 patients were eligible for analysis.

**RESULTS:** Following parameters were included into the multivariate Cox regression analysis with respective blood parameters (absolute leukocyte count, absolute neutrophil count, neutrophil-to lymphocyte ratio, NLR; derived NLR, dNLR; lymphocyte-to-monocyte ratio, LMR, platelet-to-lymphocyte ratio; PLR; C-reactive protein, CRP): age, AJCC-Stage (8th edition), presence of capsule invasion, adjuvant therapy with interferon-α and size of largest SLN metastasis. A high NLR, low LMR and high CRP value were significantly associated with shorter RFS in multivariate analysis. For LMR (cut-off 3.5) and for CRP (cut-off 3.0) this effect remained after dichotomization. CRP showed a stronger association with RFS than NLR or LMR, with the highest association being detected for the combination of low LMR and high CRP. Additionally, derived NLR≥2.0 was significantly associated with shorter OS in multivariate analysis.
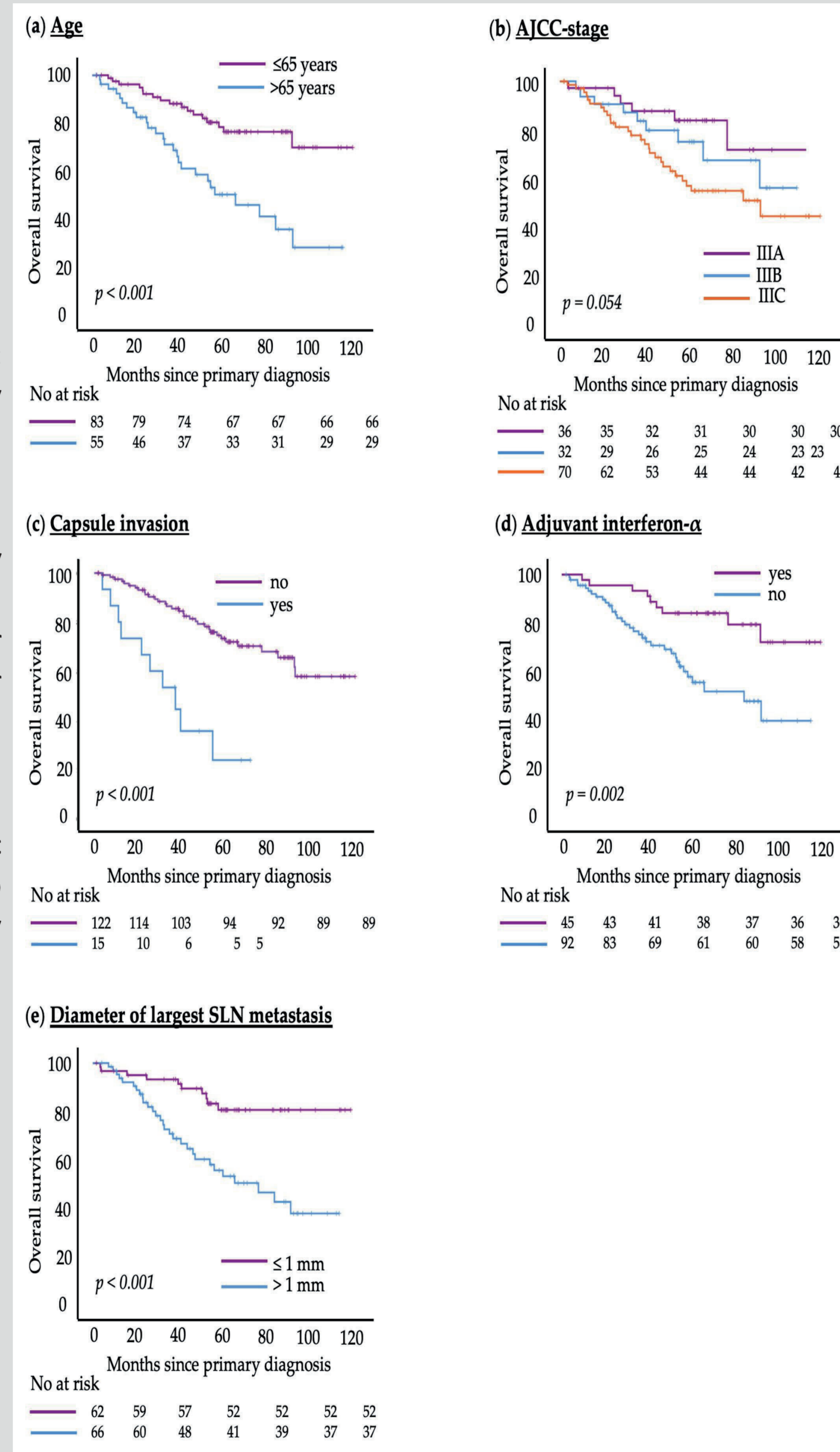


**Figure 2. Kaplan-Meier survival curves showing recurrence-free survival for covariates of the multivariate Cox regression model. A** patient age; **B** AJCC-stage; **C** capsule invasion of SLN metastasis; **D** adjuvant interferon-α therapy; **E** diameter of largest SLN metastasis. The log-rank test was used to compare between groups; p <0.05 was considered significant.
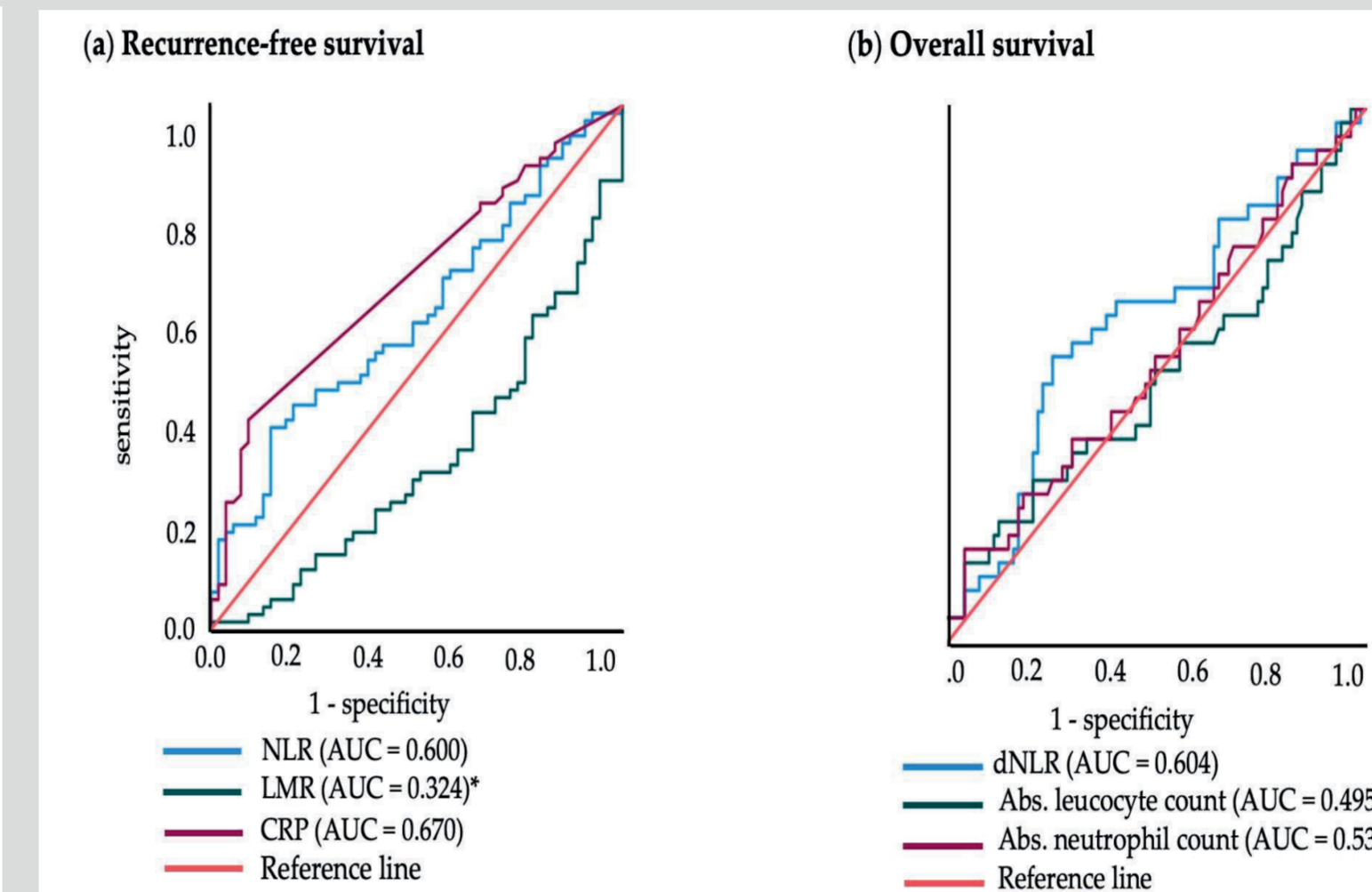


**Figure 3.** ROC curves for recurrence-free survival (RFS) and overall survival (OS) for dichotomization of blood values: (**a**) sensitivity and specificity with neutrophil-to-lymphocyte ratio (NLR); lymphocyte- to-monocyte ratio (LMR); C-reactive protein (CRP) for RFS survival; (**b**) sensitivity and specificity with derived NLR (dNLR), absolute leukocyte and neutrophil count for OS.
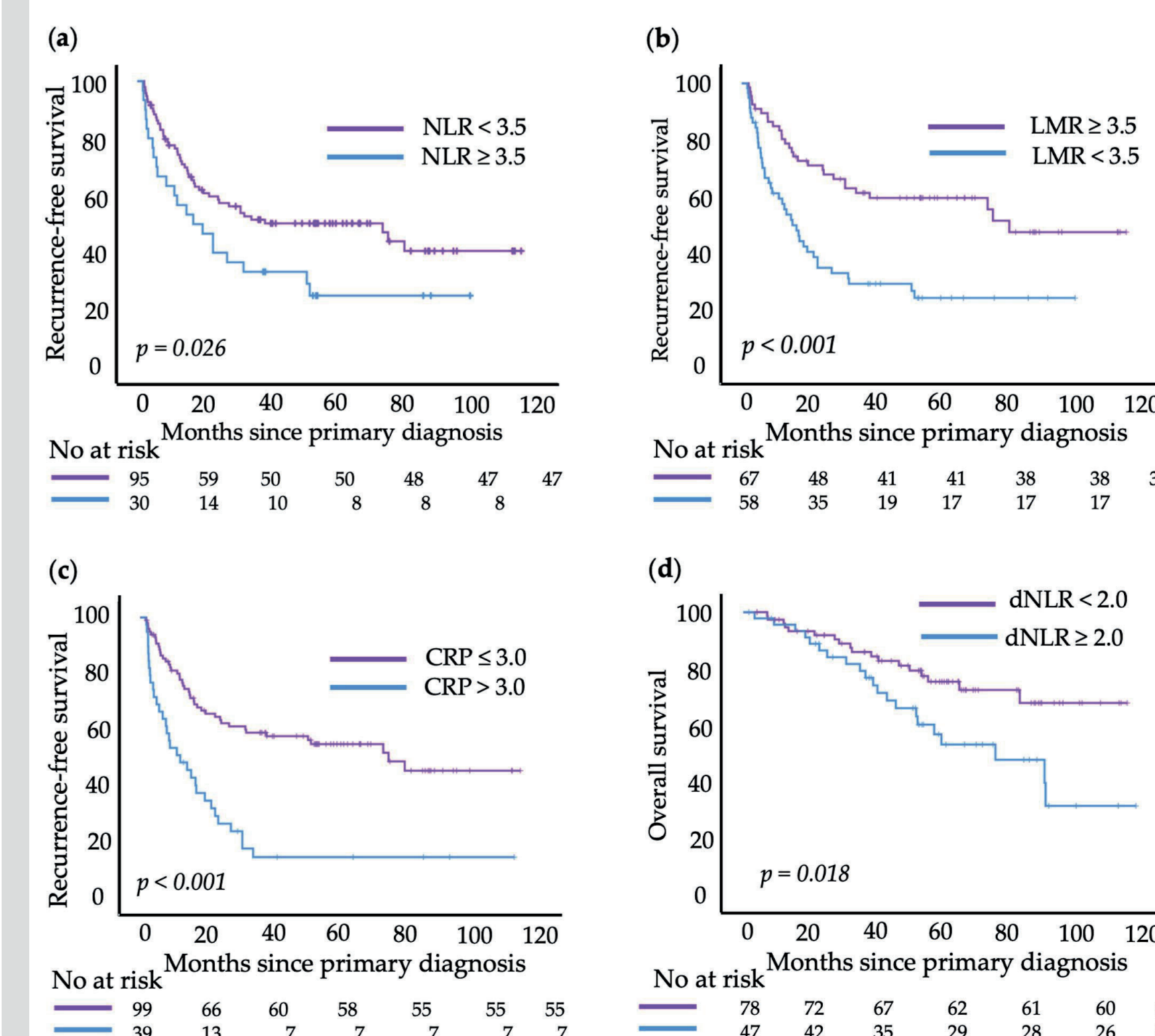


**Figure 4.** Kaplan–Meier survival curves showing recurrence-free survival (RFS) and overall survival (OS) for dichotomized blood values: (**a**) neutrophil-to-lymphocyte ratio (NLR); (**b**) lymphocyte-to-monocyte ratio (LMR); (**c**) C-reactive protein (CRP); (**d**) derived NLR (dNLR). The log-rank test was used to compare between groups; p <0.05 was considered significant.

| Blood Values | Univariate Cox Regression Analysis | | Multivariate Cox Regression Analysis [a] | |
|---|---|---|---|---|
| | n | HR (95%CI) p-Value | n | HR (95%CI) p-Value |
| **Outcome RFS** | | | | |
| **Model 1: NLR** | continuous (n = 125) | 1.236 (1.064–1.437) 0.006 | continuous (n = 114) | 1.340 (1.050–1.711) 0.019 |
| | cut-off 3.5 (n = 30; n = 95) (≥3.5 vs. <3.5) | 1.761 (1.063–2.919) 0.028 | cut-off 3.5 (n = 27; n = 87) (≥3.5 vs. <3.5) | 1.512 (0.845–2.705) 0.164 |
| **Model 2: LMR** | continuous (n = 125) | 0.689 (0.564–0.841) <0.001 | continuous (n = 114) | 0.608 (0.422–0.877) 0.008 |
| | cut-off 3.5 (n = 58; n = 67) (<3.5 vs. ≥3.5) | 2.433 (1.505–3.934) <0.001 | cut-off 3.5 (n = 51; n = 63) (<3.5 vs. ≥3.5) | 2.198 (1.301–3.715) 0.003 |
| **Model 3: CRP** | continuous (n = 138) | 1.065 (1.026–1.105) <0.001 | continuous (n = 126) | 1.457 (1.214–1.747) <0.001 |
| | cut-off 3.0 (n = 39 vs. 99) (>3.0 vs. ≤3.0) | 2.841 (1.791–4.508) <0.001 | cut-off 3.0 (n = 34 vs. 92) (>3.0 vs. ≤3.0) | 3.355 (2.017–5.582) <0.001 |
| **Outcome OS** | | | | |
| **Model 4: dNLR** | continuous (n = 124) | 1.287 (0.945–1.753) 0.109 | continuous (n = 114) | 1.410 (1.024–1.942) 0.035 |
| | cut-off 2.0 (n = 47; n = 78) (≥2.0 vs. <2.0) | 2.102 (1.119–3.948) 0.021 | cut-off 2.0 (n = 44; n = 70) (≥2.0 vs. <2.0) | 2.428 (1.186–4.968) 0.015 |

[a] Following parameters were additionally included in the multivariate Cox regression analysis: age, AJCC-stage, capsule invasion, adjuvant interferon-α, size of largest SLN metastasis. Note: values in bold indicate significant results.

**CONCLUSION:** Altogether, we detected strong associations of NLR, LMR and CRP with RFS, which were independent of other known prognostic parameters in our cohort of stage III melanoma patients with microscopic SLN metastasis. CRP was the parameter with the strongest association with RFS compared to the other parameters. Nevertheless, the combination of CRP and LMR was associated with the strongest potential to predict progression.

Therefore, we propose to consider these variables when assessing a patient's risk of disease recurrence, the necessity for closer monitoring, or for an adjuvant therapy. Nevertheless, further studies in larger, prospectively collected patient cohorts are required to validate our findings.

**LITERATURE:**

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The authors declare no conflicts of interest regarding this work. Please direct questions to: cindy.franklin@uk-koeln.de