Systemic inflammation scores correlate with survival prognosis in patients with newly diagnosed brain metastases

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BACKGROUND: Systemic inflammation measured by the neutrophil-to-lymphocyte ratio (NLR), leucocyte-to-lymphocyte ratio (LLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR) and CRP/albumin ratio (CRP/Alb) was shown to impact the survival prognosis in patients with extracranial solid cancer.

METHODS: One thousand two hundred and fifty patients with newly diagnosed brain metastases (BM) were identified from the Vienna Brain Metastasis Registry.

RESULTS: PLR and CRP/Alb were higher in patients with progressive extracranial disease and lower in patients with no evidence of extracranial disease. Lower NLR (cut-off = 5.07; 9.3 vs. 5.0 months), LLR (cut-off = 5.76; 10.0 vs. 5.3 months), PLR (cut-off = 335; 8.0 vs. 3.8 months), MLR (cut-off = 0.53; 6.0 vs. 3.5 months) and CRP/Alb (cut-off = 2.93; 8.5 vs. 3.7 months; \( p_{\text{adj}} < 0.05 \)) were associated with longer overall survival (OS). In multivariate analysis with graded prognostic assessment (hazard ratio (HR) 1.45; 95% confidence interval (CI): 1.32–1.59; \( p_{\text{adj}} = 1.92e-11 \)), LLR (HR 1.57; 95% CI: 1.39–1.77; \( p_{\text{adj}} = 1.96e-11 \)), PLR (HR 1.60; 95% CI: 1.39–1.85; \( p_{\text{adj}} = 2.87955e-9 \)), MLR (HR 1.41; 95% CI: 1.14–1.75; \( p_{\text{adj}} = 0.027 \)) and CRP/Alb (HR 1.83; 95% CI: 1.54–2.18; \( p_{\text{adj}} = 2.73e-10 \)) remained independent factors associated with OS at BM diagnosis.

CONCLUSIONS: Systemic inflammation, measured by NLR, LLR, PLR, MLR and CRP/Alb, was associated with OS in patients with BM. Further exploration of immune modulating therapies is warranted in the setting of BM.

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extracranial disease, as previously described. The ACCI was calculated as previously published. For each included comorbidity a score was given. A total score was calculated by the sum of scores for each comorbidity and for each decade starting with 50 years 1 point was added (e.g. addition of 1 point for age group 50–59 years). The studied patient cohort was treated independently by multidisciplinary teams according to good clinical practice guidelines. This project was approved by the ethics committee of the Medical University of Vienna (078/2004).

Statistical analysis
Cancer entities occurring <10 times in the entire cohort were summarised under the primary cancer entity “others”. The Kolmogorov–Smirnov test was used to test for data normality. Differences between groups were assessed using the Kruskal–Wallis test. Correlations of metric variables were determined using the Spearman’s rho, while a correlation coefficient of $\rho > 0.7$ was interpreted as strong correlation, $0.7 > \rho > 0.5$ as medium correlation, $0.5 > \rho > 0.3$ as weak correlation and $<0.3$ as no correlation. OS from diagnosis of BM was defined as time from radiological diagnosis of BM until death or last follow-up. Patient stratification cut-offs for survival analyses were calculated according to the maximally selected rank statistics using the R package maxstat that iteratively tests all possible cut-points to identify the value with the maximum rank statistics for optimal group stratification for survival analyses. The Kaplan–Meier product limit method was used to illustrate survival times and log-rank tests were calculated to estimate survival differences between groups. Survival analyses were calculated using the R packages survival and survminer. A multivariate analysis using the Cox proportional hazard model was applied to adjust for the GPA score as an established prognostic assessment. $P$ values were Bonferroni adjusted for 27 applied statistical tests resulting in adjusted $p$ values ($p_{\text{adj}}$) for each statistical test. A two-tailed $p_{\text{adj}} < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS®) 23.0 software (SPSS Inc., Chicago, IL, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
Patients characteristics
One thousand and two hundred and fifty patients (662/1250, 53% males; 588/1250, 47% females) with a median age of 62 years (range 23–91) at diagnosis of BM were included in the analysis. Five hundred and seventy-one (45.7%) patients were diagnosed with BM simultaneously with diagnosis of the primary tumour. One hundred and eight of 1250 (8.6%) patients showed no evidence of extracranial disease at BM diagnosis, while stable extracranial disease at BM diagnosis was evident in 233/1250 (18.6%) patients. Three hundred and eighty-three of 1250 (30.6%) patients presented with synchronous progressive extracranial disease. One thousand one hundred and sixty-nine of 1250 (18.6%) patients received systemic therapy as first-line treatment of BM (radiotherapy 34/1250, 2.7% of patients), followed by a combinational therapy of surgery plus radiotherapy (14 months), surgery only (7 months), radiotherapy only (6 months) and best supportive care (1 month; log-rank test; $p_{\text{adj}} = 1.66e – 20$). Median survival in the entire cohort was 6 months (range 0–178 months; Table 1). GPA class showed a significant association with survival prognosis from diagnosis of BM in univariate analysis (hazard ratio (HR) 1.47; 95% confidence interval (CI): 1.35–1.62; $p_{\text{adj}} = 2.10e – 15$; Cox regression model; Supplementary Fig. 1).

| Table 1. Patients characteristics. |
|-----------------------------------|
| Characteristics                  | n = 1250 | 100% |
| Age at diagnosis of BM, years     |          |      |
| Median (range)                    | 62 (23–91)|      |
| Sex                               |          |      |
| Male                              | 662      | 53%  |
| Female                            | 588      | 47%  |
| Cancer entity                     |          |      |
| Lung cancer                       | 994      | 79.5 |
| Breast cancer                     | 86       | 6.9  |
| Melanoma                          | 106      | 8.5  |
| Renal cell carcinoma              | 7        | 0.6  |
| Colorectal cancer                 | 11       | 0.9  |
| CUP                               | 10       | 0.8  |
| Others                            | 36       | 2.9  |
| Surgery of the primary tumour     |          |      |
| Yes                               | 359      | 28.7 |
| No                                | 891      | 71.3 |
| Radiotherapy to the primary tumour site |       |      |
| Yes                               | 221      | 17.7 |
| No                                | 1029     | 82.3 |
| Adjuvant chemotherapy             |          |      |
| Yes                               | 346      | 27.7 |
| No                                | 904      | 72.3 |
| KPS                               |          |      |
| Median (range)                    | 80 (0–100)|    |
| GPA class                          |          |      |
| Class I                           | 41       | 3.3  |
| Class II                          | 121      | 9.7  |
| Class III                         | 761      | 60.9 |
| Class IV                          | 327      | 26.2 |
| Status of extracranial disease    |          |      |
| Synchronous diagnosis of BM at cancer diagnosis | 571 | 45.7 |
| No evidence of extracranial disease | 108  | 8.6  |
| Stable disease                    | 233      | 18.6 |
| Progressive disease               | 338      | 27.0 |
| Chemotherapy before diagnosis of BM |        |      |
| Yes                               | 581      | 46.5 |
| No                                | 669      | 53.5 |
| Steroid treatment at BM diagnosis |          |      |
| Yes                               | 479      | 38.3 |
| No                                | 728      | 58.2 |
| NA                                | 43       | 3.4  |
| First-line treatment of BM        |          |      |
| Surgery                           | 87       | 7.0  |
| Radiotherapy total                | 973      | 77.8 |
| (GK/WBRT/GK + WBRT)               | (597/280/96) | (47.8/22.4/47.6) |
| (Radiotherapy within 14 days of BM diagnosis, n = 973*) | (432) | (44.4* |
| Combinational local therapy (surgery + radiotherapy) | 109 | 8.7  |
| Systemic therapy                  | 34       | 2.7  |
| BSC                               | 47       | 3.8  |
| Overall survival, months          |          |      |
| Median (range)                    | 6 (0–178)|     |
| Alive                             | 151      | 12.1 |
| Deceased                          | 1099     | 87.9 |

BM brain metastasis, CUP cancer of unknown primary, KPS Karnofsky performance status, GPA graded prognostic assessment, NA not available, GK gamma knife, WBRT whole-brain radiotherapy, BSC best supportive care. *Total number of patients having had radiotherapy.

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Systemic inflammation in patients with newly diagnosed brain metastases

NLR, LLR and PLR were available in all included patients, while MLR was available in 379/1250 (30.3%) and CRP/Alb in 601/1250 (48.1%) patients (Table 2). No differences in NLR, LLR, PLR, MLR or CRP/Alb according to primary tumour type was observed (p_adj > 0.05; Kruskal–Wallis test; Supplementary Fig. 2).

There were no correlations of systemic inflammation scores with age nor with KPS nor with age-adjusted Charlson-comorbidity index at BM diagnosis (Spearman correlation coefficient <0.3).

Twenty-one of 1250 (1.7%) patients in this cohort showed a history of autoimmune disease. There was no correlation of investigated inflammation markers at BM diagnosis and history of autoimmune disease (Mann–Whitney U test, p_adj > 0.05).

PLR and CRP/Alb showed significant differences according to the status of the extracranial disease. PLR was highest in patients with progressive extracranial disease (median PLR = 225.0), followed by patients with stable disease (median PLR = 220.0) and patients with synchronous diagnosis of BM with the primary cancer (median PLR = 196.1) and lowest in patients with no evidence of extracranial disease at BM diagnosis (median PLR = 189.1); p_adj = 0.002; Kruskal–Wallis test; Fig. 1a). CRP/Alb was highest in patients with progressive extracranial disease (median CRP/Alb = 2.85), followed by patients with synchronous diagnosis of BM with the primary cancer (median CRP/Alb = 2.73), followed by patients with stable disease (median CRP/Alb = 2.06) and lowest in patients with no evidence of extracranial disease (median CRP/Alb = 1.07; p_adj = 0.009; Kruskal–Wallis test; Fig. 1b). NLR, LLR and MLR did not significantly differ depending on the status of the extracranial disease (p_adj > 0.05; Kruskal–Wallis test).

Patients with prior application of chemotherapy presented with a higher median PLR (median PLR 220.0) compared to chemotherapy-naive patients (median PLR 198.52; p_adj = 0.004; Mann–Whitney U test; Fig. 2). No differences in patients with or without prior chemotherapy were observed concerning the NLR, LLR, MLR and CRP/Alb (p > 0.05; Mann–Whitney U test).

Four hundred and seventy-nine of 1250 (38.3%) BM patients received steroid treatment at BM diagnosis. No significant differences in investigated inflammation scores were observed in patients treated with steroids compared to patients without steroid therapy (p_adj > 0.05; Mann–Whitney U test).

Twenty-two of 1250 patients (1.8%) in this cohort were treated with immune checkpoint inhibitors before the diagnosis of BM. No significant difference of inflammation markers at BM diagnosis according to therapy with immune checkpoint inhibitors prior to diagnosis of BM was observed (p_adj > 0.05; Mann–Whitney U test).

Correlation of systemic inflammation markers with survival prognosis

Lower NLR (cut-off = 5.07) was associated with a significantly longer OS with 9.3 months compared to 5.0 months in patients with a higher NLR (p_adj = 4.98e−14; log-rank test; Fig. 3a). Further, patients with lower LLR (cut-off = 5.76; 10.0 vs. 5.3 months, p_adj = 2.25e−14; log-rank test; Fig. 3b), lower PLR (cut-off = 335; 8.0 vs. 3.8 months; p_adj = 2.69e−11; log-rank test; Fig. 3c), lower MLR (cut-off = 0.53; 6.0 vs. 3.5 months; p_adj = 0.009; log-rank test; Fig. 3d) and lower CRP/Alb (cut-off = 2.93; 8.5 vs. 3.7 months; p_adj = 1.13e−12; log-rank test; Fig. 3e) presented with a more favourable survival prognosis.

In a multivariate model adjusting for GPA (in 1225/1250 patients), NLR (HR 1.55; 95% CI: 1.38–1.75; p_adj = 1.92e−11; Cox regression model), LLR (HR 1.57; 95% CI: 1.13–1.97; p_adj = 1.96e–11; Cox regression model), PLR (HR 1.60; 95% CI: 1.39–1.85; p_adj = 2.88e−9; Cox regression model), MLR (HR 1.41; 95% CI: 1.14–1.75; p_adj = 0.027; Cox regression model) and CRP/Alb (HR 1.83; 95% CI: 1.54–2.18; p_adj = 2.73e–10; Cox regression model) remained independent factors associated with OS after diagnosis of BM (Table 3). In adjusting for the DS-GPA (in 1239/1250 patients with the DS-GPA available), the NLR (HR 1.45; 95% CI: 1.28–1.64; p_adj = 1.30e–7; Cox regression model), LLR (HR 1.43; 95% CI: 1.26–1.63; p_adj = 5.46e–7; Cox regression model), PLR (HR 1.54; 95% CI: 1.33–1.79; p_adj = 2.32e–7; Cox regression model), MLR (HR 1.40; 95% CI: 1.13–1.74; p_adj = 0.05; Cox regression model) and CRP/Alb (HR 1.71; 95% CI: 1.42–2.05; p_adj = 2.45e–7; Cox regression model) remained independent factors associated with OS after diagnosis of BM.

**DISCUSSION**

Systemic inflammation scores correlated with survival prognosis in our cohort of advanced cancer patients with BM. The routinely and easily accessible NLR, LLR, PLR, MLR and CRP/Alb had independent prognostic impact in addition to the established GPA, suggesting that also in the advanced event of BM, flourishing systemic inflammatory processes are negatively associated with the course of cancer disease.

PLR and CRP/Alb were significantly higher in patients with simultaneous progressive extracranial disease at BM diagnosis compared to patients with a stable extracranial disease and patients with synchronous diagnosis of BM. In contrast, NLR, LLR and MLR did not correlate with the status of the extracranial disease. In consequence, PLR and CRP/Alb might be more determined by the status of the systemic disease than NLR, LLR and MLR. The acute-phase protein CRP increases during systemic inflammatory processes while the albumin production is reduced as an amino acid sparing mechanism. The Glasgow Prognostic Score includes the CRP/Alb as a prognostic marker for survival independent of cancer entity or disease stage. Previously, activated platelets were shown to stimulate inflammatory processes by the release of vascular endothelial growth factor and platelet-derived growth factor, which mediate the extravasation and migration of leucocytes. Further, platelets are postulated to contribute to cancer dissemination by depleting natural killer cells and impairing their cytotoxic activity. The cell-based scores NLR, LLR and MLR might reflect a more immediate impact of inflammation as neutrophils are the first effector immune cells recruited in case of acute inflammation followed by monocytes. Indeed, normalisation of NLR after one cycle of chemotherapy was described to result in improved PFS in colorectal cancer and mesothelioma patients.
previous treatment, but NLR, LLR, MLR and CRP/Alb were not impacted by previous treatments. Therefore, the investigated systemic inflammatory scores give a prognostic relevant insight into the systemic inflammatory status also in pretreated BM patients.

The investigated systemic inflammation scores NLR, LLR, PLR, MLR and CRP/Alb presented with sustained prognostic impact independent from the GPA. The variable set included in the GPA does only include clinical variables like age, number of BM, Karnofsky performance score and status of the extracranial disease. 

Previously, we reported that the addition of laboratory parameters, included in the LabBM score, provide a more precise prognostic prediction than the GPA alone. A precise survival prediction is of particular importance in BM patients as treatment decisions have to be taken in the careful balance between efficacy and short/long-term side effects in a palliative setting. The CRP value was the only inflammatory marker included in the LabBM score. However, systemic inflammation is of growing importance in extracranial malignancies as, besides the prognostic impact, pre-treatment NLR, MLR, PLR and CRP were recently shown to be associated with PFS and OS in melanoma, non-small cell lung cancer, renal cell carcinoma, breast and head and neck cancer patients treated with immune checkpoint inhibitor therapy.

Immune checkpoint inhibitors have increasing clinical importance in BM patients as first clinical trials strongly support the application in selected patient populations with asymptomatic newly diagnosed BM. None of the patients in the present series were treated with immune checkpoint inhibitors after diagnosis of BM and, therefore, future trials should investigate whether systemic inflammatory scores could have predictive potential for the response to immune checkpoint inhibitors in the BM population.

Although we investigated a particularly large, real-life cohort, the retrospective study argues for careful interpretation of the obtained data. The comprehensive set of clinical data allowed us to statistically investigate the impact of the primary tumour type, the status of the extracranial disease as well as the previous
Fig. 2  **Levels of platelet-to-lymphocyte ratio according to prior chemotherapy before diagnosis of BM.** Median platelet-to-lymphocyte ratio (PLR) according to prior application of chemotherapy before diagnosis of BM (median PLR 220.0) compared to patients without prior chemotherapy (median PLR 198.33; \( p = 0.004 \); Mann–Whitney U test). Bar graphs + CIs are shown.

Fig. 3  **Overall survival from diagnosis of BM according to markers of systemic inflammation.** a Neutrophil-to-lymphocyte ratio (NLR) \( (p_{\text{adj}} = 4.98 \times 10^{-14}; \text{log-rank test}) \), b Leucocyte-to-lymphocyte ratio (LLR) \( (p_{\text{adj}} = 2.25 \times 10^{-14}; \text{log-rank test}) \), c Platelet-to-lymphocyte ratio (PLR) \( (p_{\text{adj}} = 2.69 \times 10^{-11}; \text{log-rank test}) \), d Monocyte-to-lymphocyte ratio (MLR) \( (p_{\text{adj}} = 0.009; \text{log-rank test}) \), e C-reactive protein/albumin ratio (CRP/Alb) \( (p_{\text{adj}} = 1.13 \times 10^{-12}; \text{log-rank test}) \).
treatments on the investigated systemic inflammatory scores. The obtained data further reflects everyday practice as values ±14 days from diagnosis of BM were included and fluctuation in the blood values could occur in this time frame. Nevertheless, the independent association in addition to GPA supports the prognostic impact. Prospective studies would be warranted to validate the observed prognostic impact of systemic inflammation in newly diagnosed BM patients.

CONCLUSIONS
In conclusion, we show that systemic inflammation scores correlate with survival prognosis in a large real-life cohort of patients with advanced cancer and brain metastases. Further, our data suggest that activated systemic inflammation possibly impacts cancer progression also in the setting of BM. Future trials investigating immune modulating therapies should therefore also consider monitoring systemic inflammation scores and their predictive value to outcome to immunotherapy, eventually finding new predictive markers for a personalised immunotherapy approach in BM patients.

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AUTHOR CONTRIBUTIONS
Writing of manuscript draft: A.M.S., A.S.B. Statistical analysis: A.M.S., M.J.M., G.H., A.S.B. Data collection: A.M.S., A.S., A.S., C.D., G.W., B.G., K.D., M.P., A.S.B. Critical revision of important intellectual interdisciplinary content and correction of manuscript: A.M.S., A.S., M.J.M., A.S., C.D., G.W., B.G., K.D., G.H., M.P., A.S.B.

ADDITIONAL INFORMATION
Ethics approval and consent to participate This study was approved by the ethics committee of the Medical University of Vienna (Vote EK 078/2004). Due to the retrospective design of the study the ethics board waived the informed consent of individual patients. This study was performed in accordance with the Declaration of Helsinki.

Data availability The data supporting the results in this manuscript is saved at a server of the Medical University of Vienna.

Competing interests A.M.S. has received travel support from PharmaMar. A.S.B. has research support from Daichi Sankyo and Roche, honoraria for lectures, consultation or advisory board participation from Roche, Bristol-Meyers Squibb, Merck, Daichi Sankyo as well as travel support from Roche, Amgen, Daichi Sankyo and AbbVie. M.P. has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daichi Sankyo, Sanofi, Merck Sharp & Dome, Tokagen. The following for-profit companies have supported clinical trials and contracted research conducted by M.P. with payments made to his institution: Böhringer-Ingehelm, Bristol-Myers Squibb, Roche, Daichi Sankyo, Merck Sharp & Dome, Novocure, GlaxoSmithKline, AbbVie. G.H. has received research support from Bristol-Meyers Squibb and Merck. All other authors report no conflicts of interest concerning this specific publication.

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REFERENCES
1. Achrol, A. S., Rennert, R. C., Anders, C., Soffiatti, R., Ahluwlia, M. S., Nayak, L. et al. Brain metastases. Nat. Rev. Dis. Prim. 5, https://doi.org/10.1038/s41572-018-0055-y (2019).
2. Moravan, M. J., Fecci, P. E., Anders, C. K., Clarke, J. M., Salama, A. K. S., Adamson, J. D. et al. Current multidisciplinary management of brain metastases. Cancer https://doi.org/10.1002/cncr.32714 (2020).
3. Long, G. V., Atkinson, V., Lo, S., Sandhu, S., Guminski, A. D., Brown, M. P. et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 19, 672–681 (2018).
4. Tawbi, H. A., Forsyth, P. A., Algazi, A., Hamid, O., Hodi, F. S., Moschos, S. J. et al. Combined Nivolumab and Ipilimumab in melanoma metastatic to the brain. N. Engl. J. Med. 379, 722–730 (2018).
5. Galea, I., Bechmann, I. & Perry, V. H. What is immune privilege (not)? Trends Immunol. 28, 12–18 (2007).
6. Berghoff, A. S., Fuchs, E., Ricken, G., Mlecnik, B., Bindea, G., Spanberger, T. et al. Density of tumor-infiltrating lymphocytes correlates with extent of brain edema and overall survival in patients with brain metastases. Oncoimmunology 5, e1057388 (2016).
7. Diakos, C. I., Charles, K. A., McMillan, D. C. & Clarke, S. J. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 15, e493–e503 (2014).
8. Käsmann, L., Bolm, L., Schild, S. E., Janssen, S. & Rades, D. Neutrophil-to-lymphocyte ratio predicts outcome in limited disease small-cell lung cancer. Lung Oncol. 19, 217–224 (2017).
9. Fukuda, H., Takagi, T., Kondo, T., Shimizu, S. & Tanabe, K. Predictive value of inflammation-based prognostic scores in patients with metastatic renal cell carcinoma treated with cytoreductive nephrectomy. Oncotarget 9, 14296–14305 (2018).
10. Riedl, J. M., Posch, F., Moik, F., Bezan, A., Szkandera, J., Smolle, M. A. et al. High-density of tumor-infiltrating lymphocytes correlates with extent of brain edema and overall survival in patients with brain metastases. Neurosurgery 80, 217–225 (2017).
11. Bumma, N., Jeyakumar, G., Kim, S., Galasso, C., Thakur, M. K., Gadgil, S. M. et al. Neutrophil lymphocyte ratio (NLR) as a predictive biomarker for PD-1/PD-L1 targeted therapy in metastatic non-small cell lung cancer (NSCLC). J. Clin. Oncol. 35, e2063–e2106 (2017).
12. He, X., Li, J.-P., Liu, X.-H., Zhang, J.-P., Zeng, Q.-Y., Chen, H. et al. Prognostic value of C-reactive protein/albumin ratio in predicting overall survival of Chinese cervical cancer patients overall survival: comparison among various inflammation based factors. J. Cancer 9, 1877–1884 (2018).
13. Heppt, M. V., Heinzinger, L., Kahler, K. C., Forcunher, A., Kirchberger, M. C., Loqui, C. et al. Prognostic factors and outcomes in metastatic uveal melanoma treated...
Systemic inflammation scores correlate with survival prognosis in... AM Starzer et al.

with programmed cell death-1 or combined PD-1/cytotoxic T-lymphocyte anti-
gen-4 inhibition. Eur. J. Cancer 82, 56–65 (2017).

14. Ishihara, H., Tachibana, H., Takagi, T., Kondo, T., Fukuda, H., Yoshiida, K. et al. Predictive impact of peripheral blood markers and C-reactive protein in nivolumab therapy for metastatic renal cell carcinoma. Target Oncol. 14, 453–463 (2019).

15. Shoji, F., Takeoka, H., Kozuma, Y., Toyokawa, G., Yamazaki, K., Ichiki, M. et al. Pretreatment prognostic nutritional index as a novel biomarker in non-small cell lung cancer patients treated with immune checkpoint inhibitors. Lung Cancer 136, 45–51 (2019).

16. Sperruto, P. W., Chao, S. T., Sneed, P. K., Luo, X., Suh, J., Roberge, D. et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int. J. Radiat. Oncol. Biol. Phys. 77, 655–661 (2010).

17. Charlson, M. E., Pompei, P., Ales, K. L. & Mackenize, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J. Chronic Dis. 40, 373–383 (1987).

18. CRAN. Package maxstat. https://cran.r-project.org/web/packages/maxstat/index.html (2020).

19. Chen, Y., Huang, J., He, X., Gao, Y., Maharaj, G., Lin, Z. et al. A novel approach to determine two optimal cut-points of a continuous predictor with a U-shaped relationship to hazard ratio in survival data: Simulation and application. BMC Med. Res. Methodol. 19, 96 (2019).

20. Therneau, T. M. Survival analysis [R package survival version 3.1-8]. https://cran.r-project.org/web/packages/survival/index.html (2020).

21. CRAN. Package survminer. https://cran.r-project.org/web/packages/survminer/index.html (2020).

22. Ohsumi, Y. Recent advances in immunopathophysiology of interleukin-6: an innovative therapeutic drug, tocilizumab (recombinant humanized anti-human interleukin-6 receptor antibody), unveils the mysterious etiology of immune-mediated inflammatory diseases. Biol. Pharm. Bull. 30, 2001–2006 (2007).

23. McMillan, D. C. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat. Rev. 39, 534–540 (2013).

24. Klinger, M. H. F. & Jelkmann, W. Role of blood platelets in infection and inflammation adaptation of thrombopoiesis. J. Inter. Cytokine Res. 22, 913–922 (2002).

25. Palumbo, J. S., Talman, C. E., Massari, J. V., La Jeunesse, C. M., Flick, M. J., Kombirnck, K. W. et al. Platelets and fibrinogen increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 105, 178–185 (2005).

26. Coussens, L. M. & Werb, Z. Inflammation and cancer. Nature 420, 860–867 (2002).

27. Chua, W., Charles, K. A., Baracos, V. E. & Clarke, S. J. Neutrophil–lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br. J. Cancer 104, 1288–1295 (2011).

28. Kao, S. C. H., Pavlakis, N., Harvie, R., Vardy, J. L., Boyer, M. J., Van Zandwijk, N. et al. High blood neutrophil-to-lymphocyte ratio is an indicator of poor prognosis in malignant mesothelioma patients undergoing systemic therapy. Clin. Cancer Res. 16, 5805–5813 (2010).

29. Berghoff, A. S., Wolpert, F., Holland-Letz, T., Koller, R., Widhalm, G., Gatterbauer, B. et al. Combining standard clinical blood values for improving survival prediction in patients with newly diagnosed brain metastases—development and validation of the LabBM score. Neuro Oncol. 19, now290 (2017).

30. Berghoff, A. S. & Preusser, M. New developments in brain metastases. Ther. Adv. Neurol. Disord. 11, 175628641878550 (2018).

31. Capone, M., Giannarelli, D., Mallardo, D., Madonna, G., Festino, L., Grimaldi, A. M. et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. J. Immunother. Cancer 6, 74 (2018).

32. Bilen, M. A., Martini, D. J., Liu, Y., Lewis, C., Collins, H. H., Shabto, J. M. et al. The prognostic and predictive impact of inflammatory biomarkers in patients who have advanced-stage cancer treated with immunotherapy. Cancer 125, 127–134 (2019).

33. Tavbi, H. A.-H., Forsyth, P. A. J., Algazi, A. P., Hamid, O., Hodi, F. S., Moschos, S. J. et al. Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: results of the phase II study CheckMate 204. J. Clin. Oncol. 35, 9507–9507 (2017).

34. Caponnetto, S., Draghi, A., Borch, T. H., Nuti, M., Cortesi, E., Svane, I. M. et al. Cancer immunotherapy in patients with brain metastases. Cancer Immunol. Immunother. 67, 703–711 (2018).