Research Square

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Monocytic Resilience During Chemoradiotherapy Is Independently Associated With Survival in IDH-Wildtype Glioblastoma

Flavio Donnini
University of Siena
Pierpaolo Pastina
University of Siena
Giuseppe Battaglia
University of Siena
Salvatore Chibbaro
University of Siena
Alfonso Cerase
University of Siena
Valerio Nardone
University of Campania "Luigi Vanvitelli"
Isacco Desideri
University of Florence
Francesco Pasqualetti
University of Padova
Alessandra Pascucci
University of Siena, University Hospital of Siena
Vincenzo D'Alonzo
University of Siena, University Hospital of Siena
Maria Antonietta Mazzei
University of Siena
Giuseppe Minniti
Sapienza University
Anna Maria Giacomo
University of Siena, University Hospital of Siena
Paolo Tini
paolo.tini@unisi.it

University of Siena

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Abstract

Purpose

Routine blood counts may capture treatment-related host immune perturbation in glioblastoma, but most studies rely on static pretreatment values. We investigated whether the intra-individual preservation of circulating monocytes during chemoradiotherapy provides prognostic information beyond established clinical factors and other hematologic trajectories.

Methods

We retrospectively analyzed adults with histologically confirmed IDH-wildtype glioblastoma treated with radiotherapy and concurrent temozolomide. Absolute monocyte counts obtained before and at the end of chemoradiotherapy were used to define monocytic resilience as log2(post-treatment/pre-treatment monocyte ratio). Overall survival (OS) was the primary endpoint. Cox models adjusted for MGMT promoter methylation, gross total resection, Karnofsky Performance Status, and age. The ratio was analyzed continuously for primary inference. A post/pre ratio of 0.75 was additionally evaluated as an exploratory, clinically interpretable threshold for two-group Kaplan–Meier visualization and sensitivity analysis.

Results

Among 127 patients, 115 had complete monocyte trajectories and OS data. The continuous monocyte post/pre ratio was independently associated with OS in the primary adjusted model (HR 0.53 per doubling, 95% CI 0.37–0.76; p = 0.00051). Using the exploratory 0.75 threshold, 52 patients had low resilience (< 0.75) and 63 had preserved resilience (≥ 0.75), with median OS of 10.2 and 17.3 months, respectively (log-rank p = 0.00064). Preserved resilience was associated with lower mortality in univariable Cox analysis (HR 0.50, 95% CI 0.34–0.75; p = 0.00080). Bootstrap resampling showed that outcome-optimized cut-points clustered around this region (median 0.74; IQR 0.70–0.81), although the threshold remains exploratory and requires external validation.

Conclusions

Preservation or recovery of circulating monocytes during chemoradiotherapy identifies a favorable host-response phenotype in IDH-wildtype glioblastoma. This dynamic signal appears distinct from baseline monocyte burden, treatment-related lymphocyte change, systemic inflammatory imbalance, and measured corticosteroid exposure. External prospective validation and immune phenotyping are required before clinical use.

Introduction

Glioblastoma is characterized by marked biological heterogeneity and profound local and systemic immune dysregulation. Despite maximal safe resection followed by radiotherapy and temozolomide, survival remains poor, and established prognostic factors such as age, performance status, extent of resection, and MGMT promoter methylation explain only part of the inter-patient variability in outcome [1–4]. Peripheral blood therefore represents an attractive, inexpensive window into host–tumor interactions during treatment.

Most blood-based studies in glioblastoma have focused on static inflammatory indices, particularly neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, systemic immune-inflammation indices, or treatment-related lymphopenia [5–9]. These markers capture clinically relevant immune perturbation, but they do not fully describe the myeloid compartment. Monocytes are particularly complex in glioblastoma: circulating CD14-positive cells may acquire immunosuppressive phenotypes, contribute to myeloid-derived suppressor cell states, and provide precursors for tumor-associated macrophages [10–12]. Accordingly, a high absolute monocyte burden at a single time point cannot automatically be interpreted as favorable host immunity.

A potentially different question is whether an individual patient can preserve or restore circulating monocytes during chemoradiotherapy. This longitudinal characteristic may reflect hematopoietic and immune resilience under the combined pressure of tumor burden, radiotherapy, temozolomide, corticosteroids, and systemic inflammation. Recent studies have highlighted the prognostic value of dynamic rather than purely static hematologic changes in glioblastoma [13–16], but the specific prognostic role of an intra-individual monocyte trajectory during standard chemoradiotherapy has not been established.

We therefore tested the hypothesis that the post-treatment/pre-treatment monocyte ratio, analyzed primarily as a continuous variable, identifies a distinct host-response phenotype associated with survival in IDH-wildtype glioblastoma. We additionally examined an exploratory threshold of 0.75, corresponding to preservation of at least 75% of the pretreatment monocyte count, to provide a clinically interpretable two-group representation. We examined whether the signal could be explained by established prognostic factors, tumor volume, corticosteroid exposure, lymphocyte preservation, or post-treatment NLR.

Materials and Methods

Study design and population

This retrospective single-center cohort included patients treated at the Radiation Oncology Unit, University Hospital of Siena, between December 2015 and January 2024. Eligibility required histologically confirmed glioblastoma, documented IDH-wildtype status, treatment with radiotherapy plus concurrent temozolomide, available follow-up, and pretreatment hematologic data. The

consolidated cohort comprised 127 patients. Molecular and pathological variables were abstracted from institutional neuropathology reports.

Clinical variables included age, sex, Karnofsky Performance Status (KPS), extent of resection, multifocality, baseline corticosteroid use, radiotherapy dose and fractionation, temozolomide exposure, progression, and survival. Extent of resection was dichotomized as gross total resection (GTR) versus non-GTR for multivariable modeling. Where available, gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), mean brain dose, dexamethasone dose, and temozolomide completion were retained for sensitivity analyses.

Hematologic variables and definition of monocytic resilience

Routine complete blood counts were collected before chemoradiotherapy and at the end of chemoradiotherapy. When more than one pretreatment value was available, the value closest to radiotherapy initiation was used. Absolute neutrophil, lymphocyte, monocyte, platelet, eosinophil, and hemoglobin values were retained as observed; no laboratory values were imputed.

The primary exposure was the intra-individual monocyte post/pre ratio. Because ratios are right-skewed and proportional changes are naturally multiplicative, the ratio was transformed as log2(post-treatment monocytes / pretreatment monocytes). The corresponding hazard ratio therefore represents the change in hazard associated with a doubling of the post/pre ratio. Primary inference remained based on this continuous formulation. For clinical visualization, an exploratory threshold of 0.75 was evaluated, defining low monocytic resilience as a post/pre ratio < 0.75 and preserved monocytic resilience as a ratio ≥ 0.75. This threshold represents retention of at least 75% of the pretreatment monocyte count and was selected after exploratory inspection of the present cohort; it was not treated as a validated clinical cutoff. Absolute monocyte counts, absolute change, lymphocyte post/pre ratio, and NLR were secondary hematologic variables. This two-group phenotype is conceptually represented in Fig. 3.

Outcomes and statistical analysis

Overall survival (OS) was the primary endpoint and was measured from diagnosis to death or last follow-up. Progression-free survival (PFS) was secondary. Continuous variables are summarized as median and interquartile range and categorical variables as counts and percentages. Kaplan–Meier estimates and log-rank tests were used for the exploratory two-group representation based on the 0.75 threshold.

Cox proportional hazards regression was used for survival modeling. The primary adjusted model included MGMT promoter methylation, GTR, KPS (per 10-point increase), age (per 10-year increase), and continuous monocytic resilience. Prespecified sensitivity models additionally considered multifocality, GTV, CTV, PTV, baseline corticosteroid use, dexamethasone dose at radiotherapy initiation, lymphocyte post/pre ratio, and post-treatment NLR. The binary 0.75 classification was examined secondarily using Kaplan–Meier and Cox analyses. To assess threshold stability, 300 bootstrap resamples were used to re-

estimate the maximally separating cut-point while requiring at least 20% of patients in each group; the bootstrap distribution was summarized by its median, interquartile range, and 95% percentile interval. Because the post-treatment biomarker is measured at completion of chemoradiotherapy, a landmark analysis reset time zero to the end of radiotherapy among patients with internally consistent diagnosis and radiotherapy dates and who remained at risk at that time. Proportional hazards for the principal biomarker were examined using Schoenfeld residuals. Model discrimination was summarized with Harrell's C-index, and nested models were compared by likelihood-ratio testing. Two-sided $p < 0.05$ was considered statistically significant. Analyses used observed complete cases for the covariates required by each model. Reporting of the exploratory prognostic-marker analyses followed REMARK principles.

Results

Cohort and monocytic trajectories

Of 127 patients in the consolidated IDH-wildtype glioblastoma cohort, 115 had complete pretreatment and end-of-chemoradiotherapy monocyte counts together with OS data. The median monocyte post/pre ratio was 0.78. Using the exploratory 0.75 threshold, 52 patients (45.2%) were classified as low resilience and 63 (54.8%) as preserved resilience. Clinical and hematologic characteristics according to the exploratory threshold are summarized in Table 1.

The two groups showed distinct longitudinal trajectories. In the low-resilience group, median monocyte count decreased from 740 (IQR 580–898) to 405 (308–545) cells/μL, with a median post/pre ratio of 0.59 (0.46–0.66). In the preserved-resilience group, median counts were 630 (440–800) and 630 (520–855) cells/μL, respectively, with a median ratio of 1.04 (0.87–1.31). Thus, the favorable phenotype was characterized by preservation or recovery during treatment rather than by a high absolute post-treatment threshold.

Association with overall survival

The binary exploratory representation produced a clinically marked separation in OS. Median OS was 10.2 months in patients with a monocyte post/pre ratio < 0.75 and 17.3 months in those with a ratio ≥ 0.75 (log-rank $p = 0.00064$; Fig. 1). Estimated 12-month OS was 43.2% versus 62.7%, and 24-month OS was 13.3% versus 36.3%, respectively. Preserved resilience was associated with lower mortality in univariable Cox analysis (HR 0.50, 95% CI 0.34–0.75; $p = 0.00080$). Importantly, the continuous log2 monocyte post/pre ratio also remained strongly associated with OS (HR 0.63, 95% CI 0.46–0.86; $p = 0.0035$), supporting a graded relationship rather than a purely dichotomous phenomenon.

In the primary multivariable model, continuous monocytic resilience remained independently associated with survival after adjustment for MGMT methylation, GTR, KPS, and age (HR 0.53 per doubling of the post/pre ratio, 95% CI 0.37–0.76; $p = 0.00051$; Table 2). The binary 0.75 classification was therefore retained as a secondary, clinically interpretable representation rather than replacing the continuous biomarker. In contrast, when absolute monocyte measures were substituted into the clinical model,

pretreatment count was not independently prognostic and post-treatment count was attenuated, whereas absolute monocyte change retained a weaker association. These findings supported the relative intra-individual trajectory as the most informative representation.

Independence from corticosteroids, tumor burden, and other immune trajectories

The association was stable across extensive sensitivity analyses (Fig. 2). Adjustment for multifocality yielded HR 0.55 ($p = 0.0018$), for GTV HR 0.49 ($p < 0.001$), for PTV HR 0.52 ($p < 0.001$), for baseline corticosteroid use HR 0.47 ($p < 0.001$), and for dexamethasone dose at radiotherapy initiation HR 0.52 ($p = 0.0019$). The monocyte ratio was not correlated with age, KPS, GTV, PTV, mean brain dose, dexamethasone dose at treatment initiation or completion, or temozolomide completion (all $p > 0.4$ for the latter treatment-related parameters).

Importantly, the signal persisted when other immune trajectories were forced into the model. After adjustment for the lymphocyte post/pre ratio, the HR for monocytic resilience was 0.48 ($p < 0.001$). In a model also containing post-treatment NLR, the HR was 0.45 (95% CI 0.30–0.68; $p = 0.00015$). In the extended sensitivity model including clinical factors, PTV, baseline corticosteroids, lymphocyte trajectory, and post-treatment NLR, monocytic resilience remained associated with OS (HR 0.42, 95% CI 0.27–0.68; $p < 0.001$).

Because the biomarker incorporates an end-of-radiotherapy measurement, landmark analysis was performed from completion of radiotherapy. The continuous association was essentially unchanged (HR 0.52, 95% CI 0.36–0.76; $p = 0.00066$), reducing concern for guarantee-time bias. Schoenfeld residuals did not indicate violation of the proportional hazards assumption for monocytic resilience ($p = 0.429$).

Model discrimination and PFS

On the same complete-case population, Harrell's C-index was 0.695 for the clinical model and 0.715 after addition of continuous monocytic resilience ($\Delta C = 0.021$). The nested likelihood-ratio test favored inclusion of the monocyte trajectory ($p = 0.00062$).

The association was weaker for PFS than for OS. In the adjusted model, the HR per doubling of the monocyte post/pre ratio was 0.73 (95% CI 0.52–1.04; $p = 0.079$). This divergence suggests that the biomarker may capture host fitness or treatment tolerance more strongly than the timing of radiographic progression.

Discussion

This study identifies a dynamic peripheral blood phenotype associated with survival in IDH-wildtype glioblastoma: patients who preserve or recover circulating monocytes during chemoradiotherapy have a

substantially lower subsequent mortality risk. The principal finding is not that a high monocyte count is favorable. The strongest signal arose from the intra-individual post/pre trajectory. Each doubling of the ratio was associated with an approximately 47% lower adjusted hazard of death. For clinical visualization, retaining at least 75% of the pretreatment monocyte count separated patients with median OS of 17.3 versus 10.2 months, while the continuous analysis remained the inferential basis of the study.

This distinction between absolute burden and dynamic resilience is biologically important. Glioblastoma can induce profound systemic myeloid reprogramming. Classical monocytes, HLA-DR-low/negative monocytic populations, and myeloid-derived suppressor states may be expanded or functionally altered, and circulating monocyte states can show transcriptional continuity with tumor-associated macrophage programs [10–12, 17, 18]. Recent studies have even associated higher classical monocyte frequency or higher monocyte counts at recurrence with adverse outcome [12, 17]. Our results do not contradict those observations because absolute abundance and longitudinal preservation are different biological measurements. The exploratory 0.75 classification should therefore be interpreted as a measure of relative treatment-related preservation, not as an absolute monocyte-count threshold.

We use the term “monocytic resilience” descriptively to denote the capacity to maintain or restore circulating monocyte numbers during treatment. This may reflect preserved marrow output, reduced treatment-induced depletion, altered redistribution between blood and tissues, or a broader capacity to reconstitute innate immune compartments after chemoradiotherapy. It should not be interpreted as evidence that the preserved cells are functionally antitumoral. Detailed phenotyping is essential because circulating monocytes in glioblastoma include functionally divergent antigen-presenting, suppressive, inflammatory, and metabolic states [10, 17, 18]. The next translational step is therefore not merely to validate the ratio, but to determine which monocyte subsets are preserved in resilient patients.

The independence from lymphocyte dynamics is notable. Treatment-related lymphopenia is well established in glioblastoma and is associated with poorer survival across multiple studies [5–7]. In our dataset, however, adjusting for the lymphocyte post/pre ratio did not attenuate the monocyte signal. Similarly, adjustment for post-treatment NLR strengthened rather than removed the association. This supports the concept that monocytic resilience and lymphoid/inflammatory imbalance may represent partially distinct dimensions of host response to chemoradiotherapy.

Corticosteroids were an especially important potential confounder. Dexamethasone modifies peripheral immune composition, exacerbates lymphopenia, alters monocyte phenotypes, and has been associated with worse survival in glioblastoma [10, 19–21]. In the present cohort, monocytic resilience was not correlated with dexamethasone dose at radiotherapy initiation or completion, remained significant after adjustment for baseline steroid use and dexamethasone dose, and showed no obvious dependence on measured steroid exposure. These analyses reduce—but do not eliminate—confounding by corticosteroids. We lacked a complete cumulative, time-updated dexamethasone exposure for every patient, which remains an important limitation.

The stronger association with OS than with PFS also deserves attention. If the monocyte trajectory primarily reflected intrinsic tumor aggressiveness, a similarly strong relationship with progression might be expected. Instead, the weaker PFS signal raises the possibility that monocytic resilience reflects systemic reserve, susceptibility to treatment toxicity or infection, recovery capacity, or fitness for subsequent therapy. These mechanisms cannot be established retrospectively, but they provide a testable rationale for prospective studies integrating serial blood sampling, treatment exposure, infection, toxicity, and salvage therapy.

Our findings are consistent with an emerging methodological shift toward longitudinal hematologic biomarkers. Krupa and colleagues recently showed that peri-treatment changes in leukocyte–platelet coupling carried prognostic information beyond static measurements [13]. Other contemporary studies have characterized changes in peripheral immunity during radiochemotherapy and have shown that dynamic immune perturbations can be substantial [15, 16]. The present study extends this concept specifically to the monocyte compartment using a simple dimensionless ratio that is immediately obtainable from routine complete blood counts.

This study has limitations. It is retrospective, single-center, and modest in size, with complete-case modeling and missingness for some steroid, multifocality, and dosimetric variables. The post/pre ratio was developed and evaluated in the same cohort and requires external validation. The 0.75 threshold is particularly exploratory: it was selected after inspection of the present data to provide a simple clinical representation and therefore carries the risk of cut-point optimism. Bootstrap resampling suggested reasonable localization of the optimal threshold around this region (median 0.74; IQR 0.70–0.81; 95% percentile interval 0.69–0.86), but this is internal stability assessment rather than external validation. Routine blood counts do not distinguish monocyte subsets or functional states. Intercurrent infection, unmeasured inflammatory conditions, marrow reserve, medications, and cumulative corticosteroid exposure may contribute to the trajectory. Post-treatment sampling was linked to the end of chemoradiotherapy but may not be perfectly identical across patients. Finally, the increase in discrimination was modest, and neither the continuous biomarker nor the 0.75 threshold should currently be used for therapeutic decision-making.

The most appropriate next step is prospective multicenter validation using a prespecified calculation—log2(end-of-chemoradiotherapy monocytes / pretreatment monocytes)—while independently testing the candidate 0.75 threshold without re-estimation. Serial flow cytometry or single-cell profiling should then determine whether numerical resilience corresponds to preservation of specific classical, intermediate, non-classical, HLA-DR-high, or suppressive monocytic states. Such work could determine whether this inexpensive signal is merely prognostic or is a clinically accessible surrogate of a biologically meaningful host-response phenotype.

Conclusions

In IDH-wildtype glioblastoma, the intra-individual preservation or recovery of circulating monocytes during chemoradiotherapy was independently associated with longer overall survival. An exploratory post/pre ratio threshold of 0.75 identified two clinically distinct groups with median OS of 10.2 and 17.3 months, while continuous modeling confirmed a graded and independent association. The signal was not explained by established clinical prognostic factors, measured corticosteroid exposure, tumor volume, lymphocyte trajectory, or post-treatment NLR. Monocytic resilience is therefore a promising dynamic host-response biomarker; the candidate 0.75 threshold now requires prespecified external validation.

Declarations

Ethics approval: The study was approved by the Ethics Committee of Azienda Ospedaliero-Universitaria Senese, Area Vasta Sud-Est (protocol GLIOMARKERSOBS_2025-1; approved 6 May 2025) and was conducted in accordance with the Declaration of Helsinki.

Consent to participate: Informed consent was obtained from all participants according to institutional requirements.

Funding: No funding was received for this study.

Competing interests: The authors declare no competing interests.

Data availability: De-identified data may be made available from the corresponding author on reasonable request, subject to institutional and ethics requirements.

Author Contributions

Conceptualization: Paolo Tini and Flavio Donnini; Methodology: Paolo Tini, Flavio Donnini, Pierpaolo Pastina, and Giuseppe Minniti; Investigation and Data Curation: Flavio Donnini, Pierpaolo Pastina, Giuseppe Battaglia, Salvatore Chibbaro, Alfonso Cerase, Valerio Nardone, Isacco Desideri, Francesco Pasqualetti, Alessandra Pascucci, Vincenzo D'Alonzo, Anna Maria Di Giacomo, Giuseppe Minniti, and Maria Antonietta Mazzei; Formal Analysis: Paolo Tini and Flavio Donnini; Interpretation of Results: all authors; Writing—Original Draft Preparation: Paolo Tini and Flavio Donnini; Writing—Review and Editing: all authors; Supervision: Paolo Tini, Giuseppe Minniti, and Maria Antonietta Mazzei; Project Administration: Paolo Tini. All authors have read and agreed to the published version of the manuscript.

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Tables

Table 1
Clinical and hematologic characteristics according to the exploratory 0.75 monocytic-resilience threshold

Characteristic	Overall	Low resilience < 0.75	Preserved resilience ≥ 0.75	P
Patients	115	52	63	—
Deaths	99 (86.1%)	49 (94.2%)	50 (79.4%)	—
Monocytes pre-RT, cells/μL	670 (495–830)	740 (580–898)	630 (440–800)	0.006
Monocytes post-RT, cells/μL	550 (395–705)	405 (308–545)	630 (520–855)	< 0.001
Monocyte post/pre ratio	0.78 (0.61–1.06)	0.59 (0.46–0.66)	1.04 (0.87–1.31)	< 0.001
Lymphocyte post/pre ratio	0.59 (0.41–0.80)	0.50 (0.39–0.72)	0.67 (0.47–0.86)	0.019
Post-RT NLR	6.17 (4.64–9.49)	6.84 (4.89–10.19)	5.57 (4.17–8.14)	0.137
Median OS, months	—	10.2	17.3	0.00064*
12-month OS	—	43.2%	62.7%	—
24-month OS	—	13.3%	36.3%	—

Values are median (IQR) or n/N (%). Low resilience was defined as a monocyte post/pre ratio < 0.75 and preserved resilience as ≥ 0.75. The binary

classification is exploratory and is not proposed as a validated clinical cutoff.

Table 2
Cox models for overall survival

Panel A. Primary adjusted model	**HR**	**95% CI**	**P**
MGMT methylated	0.578	0.353–0.947	0.030
Gross total resection	0.300	0.178–0.506	< 0.001
KPS per + 10 points	0.784	0.607–1.014	0.063
Age per + 10 years	0.996	0.791–1.254	0.975
Monocyte post/pre ratio per doubling	0.529	0.370–0.758	< 0.001
Panel B. Sensitivity models for monocytic resilience	**n/events**	**HR (95% CI)**	**P**
+ Multifocality	85/72	0.548 (0.375–0.800)	0.002
+ GTV	84/72	0.485 (0.321–0.735)	< 0.001
+ CTV	84/72	0.482 (0.316–0.734)	< 0.001
+ PTV	102/86	0.523 (0.363–0.752)	< 0.001
+ Baseline corticosteroids	84/72	0.469 (0.309–0.713)	< 0.001
+ Dexamethasone start dose	78/69	0.516 (0.340–0.784)	0.002
+ Lymphocyte trajectory	102/86	0.483 (0.323–0.720)	< 0.001
+ Post-RT NLR	101/85	0.533 (0.370–0.768)	< 0.001
+ Lymphocyte trajectory + post-RT NLR	101/85	0.453 (0.301–0.682)	< 0.001
Extended model*	83/71	0.424 (0.265–0.676)	< 0.001

**Extended model: MGMT, GTR, KPS, age, PTV, baseline corticosteroids, lymphocyte post/pre ratio, post-RT NLR, and monocytic resilience. Sensitivity-model HRs refer to each doubling of the monocyte post/pre ratio.*

Figures

Figure 1.

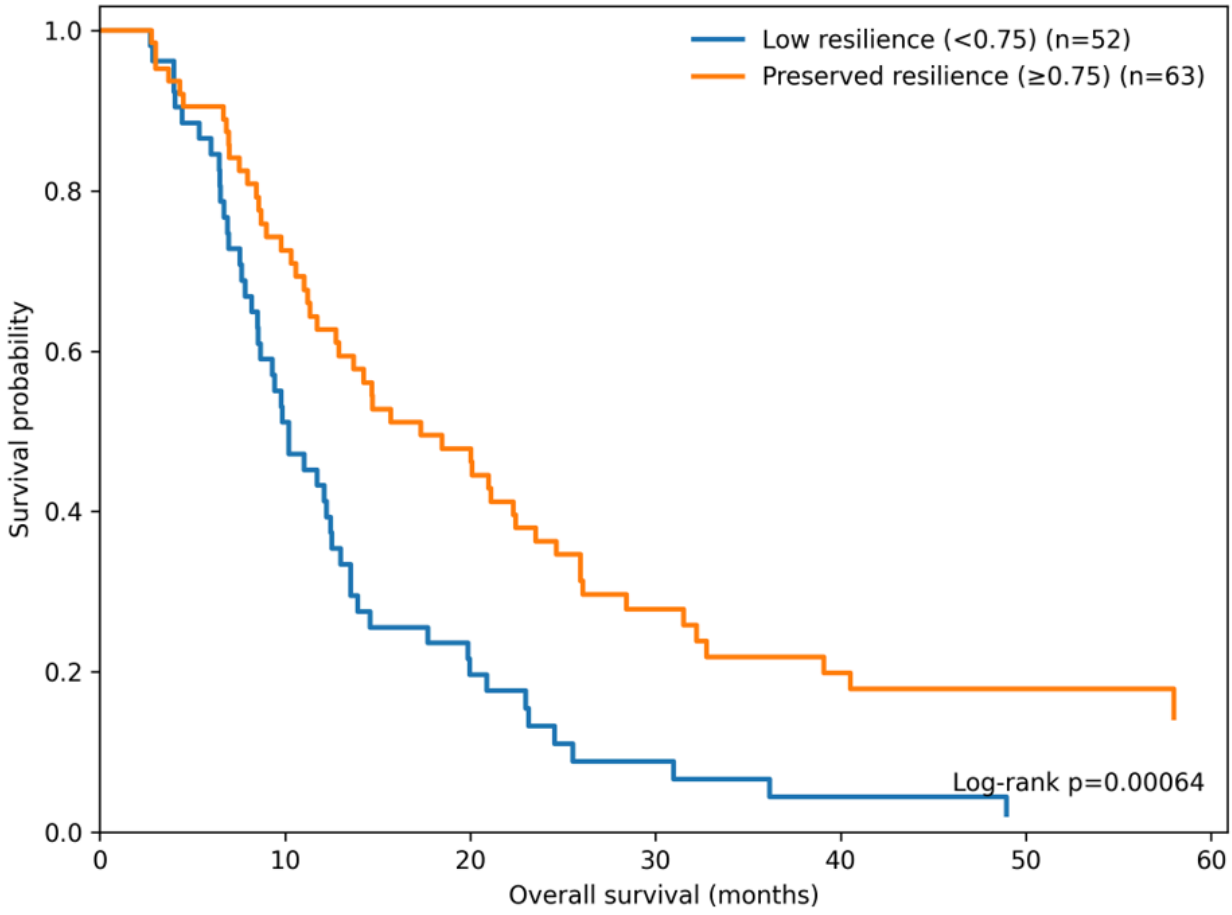


Figure 1

Overall survival according to the exploratory 0.75 monocytic-resilience threshold. Patients with a post/pre monocyte ratio <0.75 had median OS of 10.2 months versus 17.3 months for those with a ratio ≥0.75 (log-rank p=0.00064). The threshold is used for clinical visualization; primary inference is based on the continuous log2-ratio.

Figure 2.

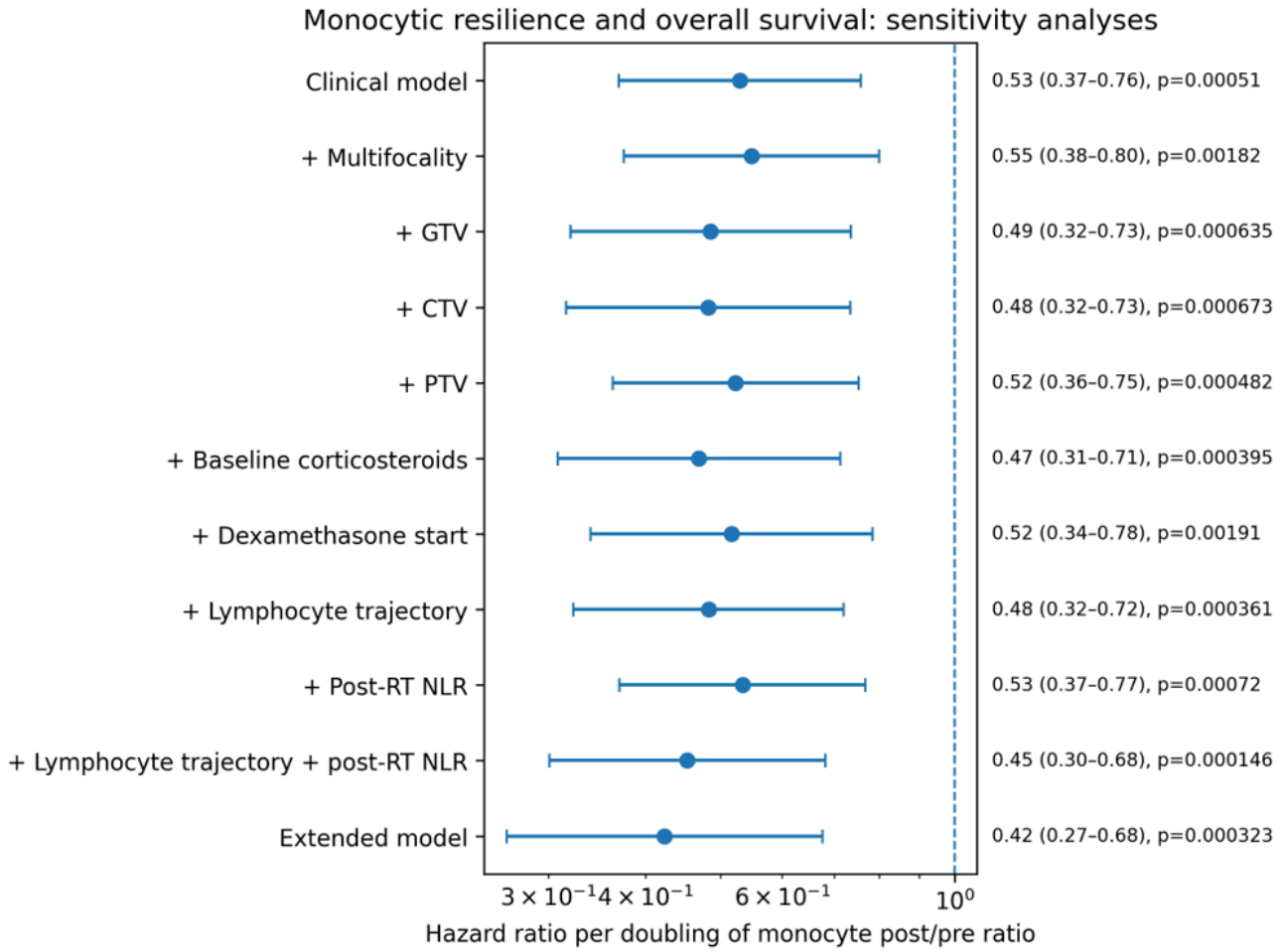


Figure 2

Sensitivity analyses for the association between monocytic resilience and overall survival. Hazard ratios are expressed per doubling of the post-treatment/pre-treatment monocyte ratio. The association remained stable after adjustment for clinical, tumor-burden, corticosteroid, lymphocyte-trajectory, and post-treatment NLR covariates.

Figure 3.

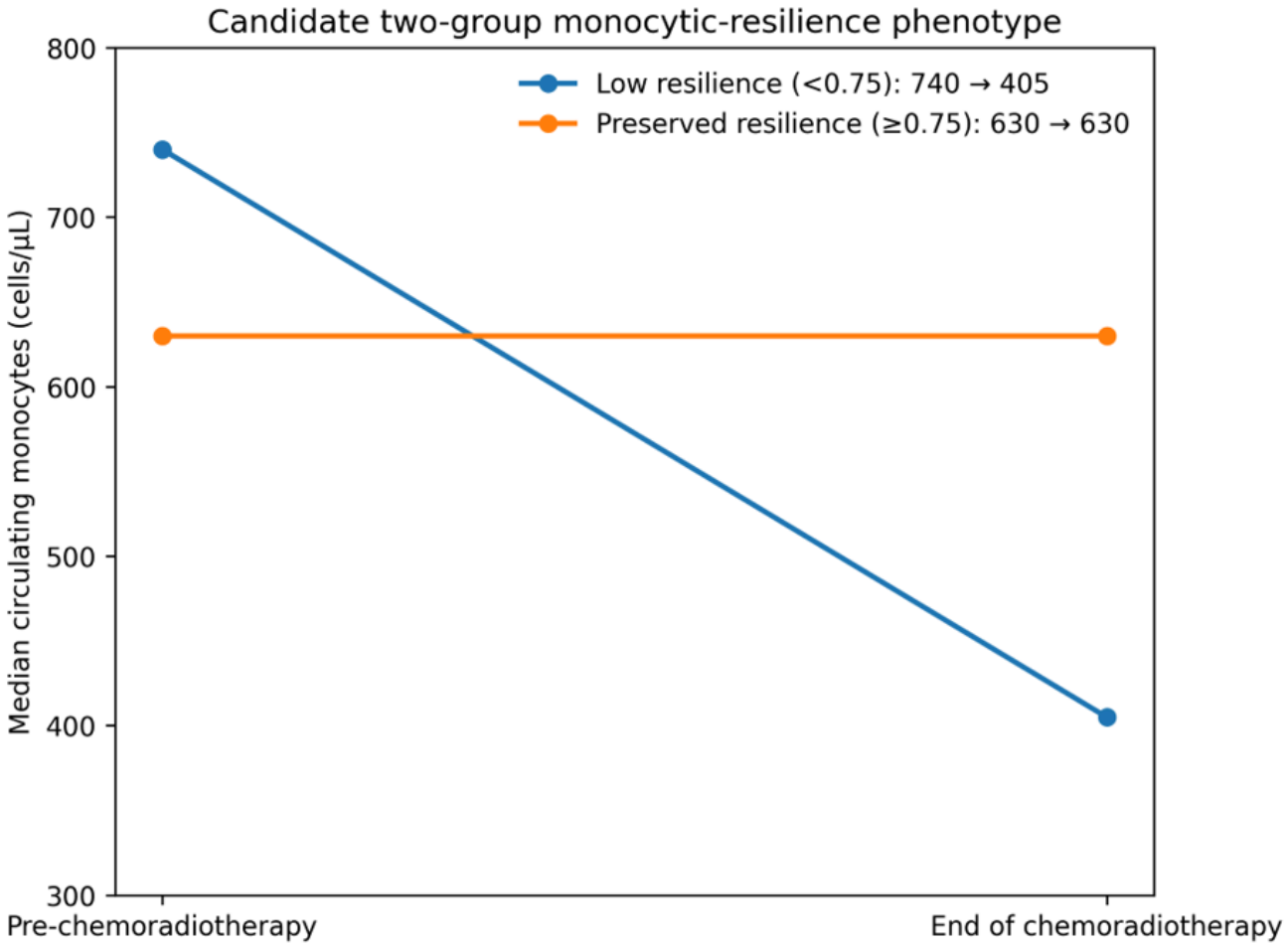


Figure 3

Conceptual representation of the candidate two-group monocytic-resilience phenotype. Low resilience denotes loss of more than 25% of the pretreatment circulating monocyte count by the end of chemoradiotherapy, whereas preserved resilience denotes retention of at least 75%. The classification is relative to each patient's own pretreatment count and does not impose an absolute monocyte-count threshold.