Comprehensive Analysis of Blood Test Results Predicting Prognosis in Patients Undergoing Whole-brain Radiotherapy for Brain Metastases

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Abstract. Background/Aim: Blood tests, such as those included in the validated LabBM score (laboratory parameters in patients with brain metastases) predict survival after treatment of brain metastases. The model incorporates five test results [serum lactate dehydrogenase (LDH), C-reactive protein (CRP), albumin, platelets and hemoglobin]. However, many other abnormalities, albeit less well-studied, may be present in patients with metastatic cancer. Therefore, this study aimed to examine a broader range of blood tests. Materials and Methods: This retrospective analysis inluced 132 patients managed with primary whole-brain radiotherapy. Additional tests, such as liver enzymes, lymphopenia, hyponatremia, and others, were also conducted. Extracranial disease extent was also analyzed. Results: According to forward conditional Cox regression analyses, blood tests (albumin, hemoglobin, lymphopenia, hyponatremia) in conjunction with the number of organs affected by extracranial metastases (at least two, such as liver and bones) provided the best prognostic model. Based on these parameters, at least four prognostic strata can be assigned (median survival between 4.6 and <1 months, p=0.0001). Conclusion: This initial pilot study in a limited number of patients suggests that numerous blood test results may contribute to further refinement of existing prognostic models, and provides justification for additional large-scale studies.

Due to advancements in imaging surveillance, local therapy of brain metastases, and systemic therapy of extracranial metastases (possibly supplemented by extracranial radiotherapy in patients with limited disease extent), better survival outcomes have been achieved with multimodal treatment of brain metastases (1-4). As survival may range from few weeks to several years, and considering the numerous treatment options available, aligning patients with an appropriate management strategy is not always a trivial task (5-8). Patients with excellent prognosis can only survive for several years if their treatment provides effective overall disease control. Unfortunately, effective intracranial disease control is of limited value in patients with uncontrollable extracranial disease, untreated primary tumors, and/or other adverse prognostic features limiting survival, such as reduced Karnofsky performance status (KPS) (9, 10). The recent literature suggests that uncontrolled extracranial disease is the prevailing cause of death (1-4).

The field has recently witnessed massive efforts towards improved survival prediction, including but not limited to models that evaluate blood test results (11-15). Well-established parameters, such as elevated lactate dehydrogenase (LDH), C-reactive protein (CRP), decreased albumin, platelet count, and anemia have been included in models such as the LabBM score (13). Assessment of other types of parameters, *e.g.*, extra- or intracranial disease extent, is not necessary to predict survival with this score. We have already suggested that historically selected dichotomized test results (normal/abnormal blood tests) can be converted into 3-tiered or more granular strata, thus providing more detailed prognostic information (16). Furthermore, tumor markers such as carcinoembryonic antigen (CEA) may contribute additional information (17). Given that many more abnormalities, such as hypercalcemia or hyponatremia, among

others, may reflect disease extent and prognosis, we embarked on an additional study to evaluate expanded blood tests. The aim was to identify statistical signals as a first step towards subsequent multicentric large-scale analyses.

Materials and Methods

***Study population and data collection*.** The present pilot study included a limited, but homogeneously treated patient population to minimize confounding factors, and facilitate the process of signal detection. An already described retrospective quality-of-care database (14-16) with dichotomized blood test results extracted from electronic health records was expanded to include a larger panel of blood tests (n=15 tests). All study patients had received palliative whole-brain radiotherapy (WBRT, 10 fractions of 3 Gy, without preceding surgical resection or other brain metastases therapy) for multiple brain metastases at Nordland Hospital Trust (time period 2007-2021, consecutive patients). Sequential state-of-the-art systemic treatment and salvage for progressive brain metastases, *e.g*., radiosurgery, were offered as indicated. The blood tests were part of routine oncological assessment, *e.g*., in the context of chemotherapy or follow-up after systemic therapy, approximately 1-2 weeks before WBRT. Selected normal values are as follows: hemoglobin 11.7-15.3 g/dl (females) and 13.4-17.0 g/dl (males); platelets 130-400 $\times 10^9$; lymphocytes 0.8-5.0 $\times 10^9$; albumin 34-45 g/l; LDH <205 U/l; CRP <5 mg/l; natrium 136-146 mmol/l; calcium 2.15-2.51 mmol/l. Inclusion required that the complete panel of 15 tests in the specified timeframe before WBRT was available in the patient record. The latter was also utilized to extract extracranial disease status based on radiological reports. Even if such data are not strictly necessary to predict survival, it might improve the performance of predictive models.

***Statistical analysis*.** The prognostic impact of dichotomized blood test results (normal/abnormal; for certain tests, such as creatinine, normal *versus* low AND normal *versus* high) was analyzed in univariate log-rank tests for actuarial overall survival curves. Actuarial overall survival was calculated (Kaplan–Meier method) from the first day of WBRT. Patients who discontinued WBRT were included (n=5, 4%). Only one patient was still alive at the time of analysis in 2023. Date of death was known for all others. After these univariate analyses, the optimally stratified blood test variables were entered into a multivariate forward stepwise Cox regression analysis. The same was performed with parameters of extracranial disease extent. Test results and disease extent parameters with significant impact on survival were then employed to create a prognostic model, based on the number of adverse prognostic factors (0, 1, 2 *etc*.). *p*-Values ≤0.05 were considered statistically significant. Analyses were performed using SPSS 28, (IBM Corp., Armonk, NY, USA).

Results

The study included 132 patients with a median KPS of 70. As shown in Table I, non-small cell lung cancer (NSCLC) was the most common diagnosis (39%). Many patients had extracranial metastases (79%). Elevated LDH and WBC (white blood cell count) were the most commonly observed abnormalities (44 and 45%, respectively). Table II and Table III display an overview of common blood test abnormalities. Despite the small subgroups, certain patterns emerged. For example, hyponatremia, a rare abnormality (5%), was mainly found in patients with NSCLC. Patients with liver metastases often had elevated ALP (45%) or GGT (48%), but less often ALAT (19%) or AST (26%). Together with the fact that bilirubin was always normal, these results point towards a referral bias, meaning that patients with severely compromised liver

function did not undergo brain radiotherapy. Those with extracranial metastases from colorectal cancer often had low hemoglobin or high LDH. In those with extracranial metastases from breast cancer, low albumin was quite common. In contrast, patients with melanoma and extracranial metastases often had high WBC or high LDH. For kidney cancer with extracranial metastases, low hemoglobin and elevated CRP was commonly observed. Finally, small cell lung cancer with extracranial metastases was characterized by high LDH.

A median overall survival of 3.1 months was observed (1-year rate 14%, 2-year rate 3%). As shown in Table IV, several established (CRP, LDH, albumin, hemoglobin) and less-well studied blood tests (hyponatremia, lymphopenia, elevated liver tests) were significantly associated with survival in univariate tests. Entering these in a forward conditional Cox regression analysis showed that anemia was of high impact (selected in step 1, p=0.0001, followed by lymphopenia (step 2, p=0.0001), hyponatremia (step 3, p=0.001) and low albumin (step 4, p=0.002). An additional forward conditional Cox regression analysis with four parameters related to extracranial disease extent (primary tumor control, presence of any extracranial metastasis, number of extracranial organs involved, presence of liver metastases) showed that only one parameter remained significant: a 3-tiered extracranial metastases variable (none, one organ, at least two organs) with p=0.0001. Combining this 3-tiered extracranial metastases variable with the four blood tests (anemia, lymphopenia, hyponatremia, low albumin) in a further forward conditional Cox regression analysis showed that all variables were significantly associated with survival (p=0.001 or better). Establishing a sum score (no adverse factor, one adverse factor, two adverse factors, *etc*.) stratified the study patients into different prognostic groups, as shown in Figure 1.

Discussion

The purpose of the present proof-of-principle study was to test the impact of a broader blood test panel and the added value of extracranial disease status in a homogeneously treated patient population with few censored survival events, *i.e.*, mature outcome data. The cohort was characterized by the presence of poor prognostic features including but not limited to multiple brain metastases, which resulted in administration of WBRT as a primary treatment modality, while our institution preferred radiosurgery for patients with better prognosis. Given that oncology is not split into medical and radiation oncology in Norway, and that our department provides all types of treatment, we had access to comprehensive blood tests obtained approximately 1-2 weeks before WBRT in 132 patients. Staging and monitoring of extracranial disease extent varied with tumor type and was often based on computed tomography (CT) scans alone, with positron emission tomography, ultrasound or magnetic resonance imaging added as needed in a particular setting. While this clinical practice might introduce variation in classification of extracranial disease (small metastases visible on other scans might not be detected on CT), it is common in other institutions as well and therefore, a limitation not only in our study but also in previous studies. Regarding other limitations, small subgroups, limited statistical power and the risk of overfitting statistical models in the absence of validation strategies have to be mentioned. Nevertheless, we still believe that a moderately sized study might represent a useful first step before one allocates lots of resources to a large analysis with more sophisticated statistical methods, without knowing that positive signals support such efforts.

We identified blood test abnormalities in a large number of patients, but some findings, such as hypercalcemia and low platelet count, were too uncommon to allow for further analyses. It also appears that patients with severely compromised liver function did not undergo brain irradiation. The latter is understandable from a prognostic perspective. Despite the small subgroups, certain patterns of test abnormality related to primary tumor type emerged. Therefore, it appears possible to develop diagnosis-specific models in future large-scale studies. The well-known DS-GPA scores (12) already include hemoglobin in renal cell carcinoma, but according to our data, there is room for expansion of present scores. In multivariate analysis, anemia, lymphopenia, hyponatremia, and low albumin emerged as important parameters. They actually replaced some of the previous prognosticators that form the basis of the validated LabBM score (13), such as LDH and CRP, while anemia and low albumin persisted. Berghoff *et al.* who developed the LabBM score reported that WBC and low creatinine were significant in uni- but not multivariate analysis. Their study did not include lymphopenia and hyponatremia. Presence and burden of extracranial metastases were not included either. A relevant difference between the studies relates to initial brain-directed approach (WBRT here, whereas different modalities, such as radiosurgery or surgery, were often used in the LabBM study). Even if the blood tests to a certain degree reflect overall disease burden and its consequences on organ function, inflammation, and cachexia, our results suggest that a disease-related parameter (3-tiered extracranial metastases variable: none, one organ, at least two organs) adds important information to the final prognostic model. The latter has also been reported by Rades *et al.* who did not examine blood test results (18). Previous research has already suggested that lymphopenia may predict worse survival in patients with brain metastases (19-21).

In clinical practice, monitoring of blood test results has one main aim: intervening with therapeutic measures (correcting hypercalcemia, treating active infections, providing red blood cell transfusions *etc*.) or sometimes deferring the next cycle of systemic therapy. However, not all abnormal values are easy to correct. High LDH or liver enzymes are not amenable to specific interventions; however, systemic anticancer drugs might impact on the underlying causes, *i.e.,* extent of metastases. Correction of an abnormal blood test result, *e.g.,* red blood cell transfusion for anemia, does not necessarily eliminate its prognostic impact.

The present study is not the final step on the way towards improved survival prediction, where several challenges remain. We have recently shown that analyses of abnormal blood tests as continuous variables, *i.e*., the truly observed distribution, are feasible, but not uniformly associated with a gain in prognostic information (16). For albumin and CRP, dichotomized values continued to represent the preferred strategy in that study. Furthermore, we have demonstrated that KPS can be added to a blood test-based prediction model (LabPS) (15). KPS has long been recognized as a prognostic factor in patients with brain metastases (11, 22, 23). Simultaneous analysis of all potential predictors from the present study together with continuous blood test results, primary tumor type, and KPS requires a very large database. Nevertheless, such efforts appear warranted and should also account for shifts in preferred management strategies, that is, increasing numbers of patients receiving radiosurgery (longer survival compared to WBRT cohorts) (24-26). From a health economic perspective, improved survival prediction might result in less overtreatment and related costs close to the end of life. It is however necessary to account for additional costs if survival

prediction should rely on otherwise not indicated imaging. Ideally, all predictive information should be obtained in the framework of routine care.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figure 1. Extracranial disease and blood test-based survival prediction (Kaplan–Meier analysis; n=34 (<2 extracranial organs and normal tests, *i.e.*, no adverse factors, median 4.6 months); n=48 (one adverse factor, median 3.4 months); n=38 (two adverse factors, median 2.2 months); n=9 (three adverse factors, median 0.7 months); n=1 (more than three adverse factors, survival 0.4 months); *p*=0.0001 over all strata).

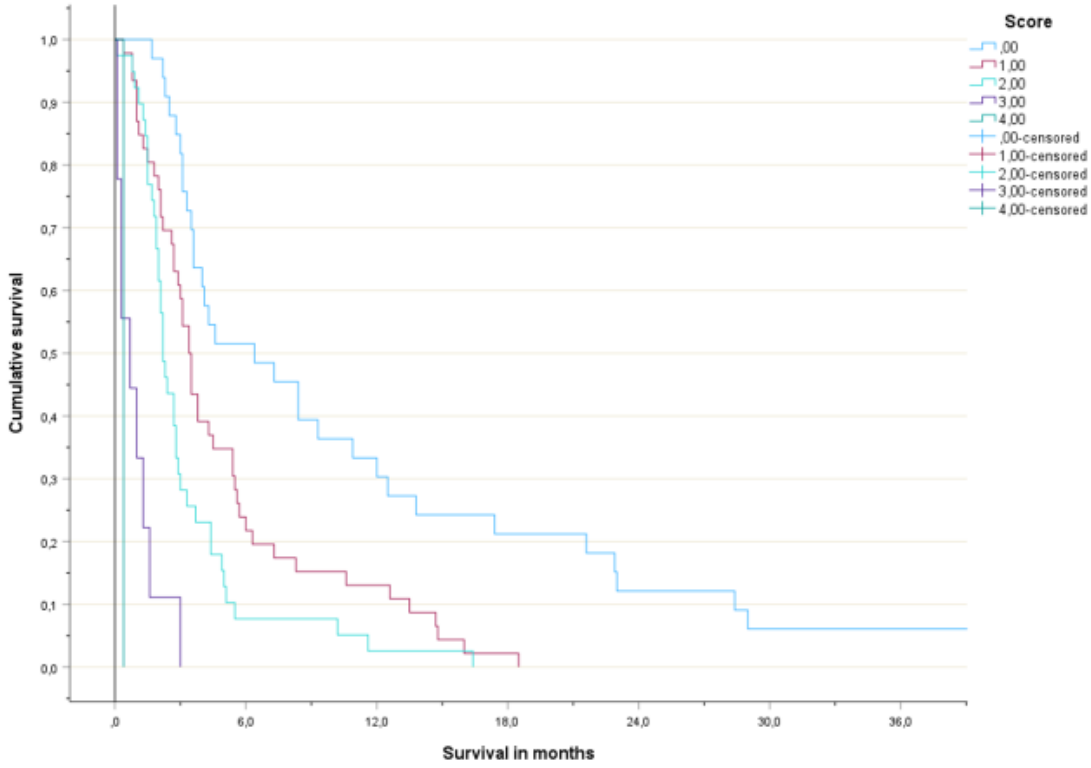

Table I. Patient characteristics (n=132).

Baseline parameter	Number	Percent
Non-small cell lung cancer	52	39
Small cell lung cancer	10	8
Breast cancer	23	17
Malignant melanoma	19	14
Renal cell cancer	11	8
Colorectal cancer	8	6
Other or unknown primary tumors	9	7
Extracranial metastases	104	79
No extracranial metastases	28	21
Liver metastases	35	27
Extracranial metastases in at least two organ sites	71	54
Controlled primary tumor	85	64
Uncontrolled primary tumor	47	36
Female gender	64	48
Male gender	68	52
Systemic therapy after whole-brain radiotherapy	68	52
Low albumin	11	8
Low hemoglobin	51	39
Low platelets	1	1
High platelets	20	15
Low lymphocytes	16	12
Low WBC	3	2
High WBC	59	45

High C-reactive protein	44	33
High lactate dehydrogenase	58	44
Low creatinine	15	11
High creatinine	5	4
Low natrium	7	5
High calcium	2	2
High alkaline phosphatase	31	23
High bilirubin	0	0
High ALAT	13	10
High AST	8	6
High GGT	24	18
Any liver test high*	28	21
At least two high liver tests	11	8

WBC: White blood cell count; ALAT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase.

*bilirubin or ALAT or AST or GGT (alkaline phosphatase which often is caused by bone metastases was excluded).

Table II.

Overview of abnormal blood test results stratified by diagnosis and metastases (no extracranial metastases, any extracranial metastases but not liver, liver with or without other extracranial metastases).

Cancer diagnosis	Number	Albumin	Anemia	WBC	Lymph.	CRP	LDH	Calcium	Na	Crea low	Crea high
Colorectal, no extracranial met.	1						1				
Colorectal, any extracranial met.	6	1	6	3	1	3	4			1	
Colorectal, liver met. (±others)	1	1		1		1	1				
Breast, no extracranial met.	1										
Breast, any extracranial met.	11	5	3	4	1	3	4				
Breast, liver met. (±others)	11	1	4	2	2	2	6		1		
Melanoma, no extracranial met.	2			1			1				
Melanoma, any extracranial met	11		2	6		4	5		1	1	1
Melanoma, liver met. (±others)	6	1	1	1	1	1	4			1	
Kidney, no extracranial met.	0										
Kidney, any extracranial met.	10		6	3	3	8	3				1
Kidney, liver met. (±others)	1		1			1					1
NSCLC, no extracranial met.	20	3	8	12	2	6	5		1	3	

NSCLC, any extracranial met.	21	4	4	12	2	8	8	1	1	3	
NSCLC, liver met. (±others)	11		8	7	1	4	6	1	2	3	1
SCLC, no extracranial met.	4		1	2			1			1	
SCLC, any extracranial met.	4		1	2		1	4				
SCLC, liver met. (±others)	2		2			1				1	

WBC: High white blood cell count; Lymph.: lymphopenia; CRP: C-reactive protein; LDH: lactate dehydrogenase; Calcium: hypercalcemia; Na: hyponatremia; Crea low.: low creatinine; Crea high: high creatinine; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

Table III.

Overview of abnormal blood test results stratified by diagnosis and metastases (no extracranial metastases, any extracranial metastases but not liver, liver with or without other extracranial metastases).

Cancer diagnosis	Number	ALAT	AST	ALP	GGT	Trc high	Trc low
Colorectal, no extracranial met.	1						
Colorectal, any extracranial met.	6				1		
Colorectal, liver met. (±others)	1	1	1	1	1		
Breast, no extracranial met.	1						
Breast, any extracranial met.	11	1		2	1	1	
Breast, liver met. (±others)	11	2	3	5	5		
Melanoma, no extracranial met.	2						
Melanoma, any extracranial met	11	1		1		3	
Melanoma, liver met. (±others)	6	1	1	2	2	1	
Kidney, no extracranial met.	0						
Kidney, any extracranial met.	10	1		2	4	3	
Kidney, liver met. (±others)	1					1	
NSCLC, no extracranial met.	20	1		1		5	1
NSCLC, any extracranial met.	21	1		5	1	5	
NSCLC, liver met. (±others)	11	2	2	6	7		
SCLC, no extracranial met.	4	1			1		
SCLC, any extracranial met.	4			1			

SCLC, liver met. (±others)	2		2				

ALAT: Alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase;Trc high: high platelet count; Trc low: low platelet count; NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer.

Table IV. Univariate predictors of survival with *p*-value <0.1.

Blood test	Median survival if absent, months	Median survival if present, months	*p*-Value
High lactate dehydrogenase	3.7	2.8	0.03
Low hemoglobin	3.5	2.3	0.001
Low lymphocytes	3.4	1.5	0.001
High C-reactive protein	3.5	2.2	0.004
Low natrium	3.1	1.3	0.001
Low albumin	3.3	1.5	0.01
Any abnormal liver test	3.4	2.1	0.02
At least two abnormal liver tests	3.1	1.9	0.06
Extracranial metastases	3.6	2.9	0.02
At least two extracranial organs*	3.7	2.7	0.001

*For example the bone, lung, liver, and adrenal gland(s).