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Original Article

Serum Biomarkers as Prognostic Factors for Metastatic Sarcoma

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Abstract

Aims: To investigate the prognostic value of combining inflammatory biomarkers in a prognostic index (Aarhus composite biomarker score: ACBS), adjusted for known confounders, including comorbidity, in patients with metastatic sarcoma.

Materials and methods: All patients diagnosed with metastatic sarcoma from 1993 until 2008 were extracted from the Aarhus sarcoma database. The levels of serum albumin, C-reactive protein, serum sodium, haemoglobin, neutrophils and lymphocytes were collected. ACBS as well as the neutrophil to lymphocyte ratio (NLR), Glasgow prognostic score (GPS) and a combined score of GPS and NLR known as CNG were calculated. The prognostic importance of the biomarkers on disease-specific mortality was analysed. Adjustments were made for age, comorbidity, histological type and site of metastasis using the Cox proportional hazard model. Harrell's concordance index (C-index) was used to evaluate whether the ACBS adds prognostic information to already known prognostic factors. The data were validated using the bootstrapping method.

Results: In total, 265 patients with metastatic sarcoma were included. The 2-year disease-specific mortality was 74% (95% confidence interval 68–80) and 79% (95% confidence interval 68–88) for soft-tissue sarcoma and bone sarcoma, respectively. Comorbidity was present in 21% of soft-tissue sarcoma patients and 13% of the bone sarcoma patients. All six biomarkers were independent prognostic factors. The various scoring systems (NLR, GPS, CNG and ACBS) combining more than one biomarker were also prognostic for disease-specific mortality.

Conclusion: The biomarker scoring systems are independent prognostic factors for adult patients with metastatic sarcoma. However, a modified ACBS was superior to all the other scoring systems in predicting outcome.

Keywords: Inflammation; Sarcoma; Serum biomarkers

Introduction

Metastatic disease is the primary cause of death for sarcoma patients and 12% will already have metastatic disease at the time of diagnosis [1]. Despite new advances and the introduction of new drugs, the overall survival of metastatic sarcoma patients has, for decades, been disappointingly low, with a median survival of less than 2 years and only 5–8% of patients are alive after 5 years. A large randomised phase III European Organization for Research and Treatment of Cancer (EORTC) study showed that, despite a higher response rate, a combination of ifosfamide and doxorubicin did not improve overall survival of metastatic soft-tissue sarcoma (STS) patients compared with doxorubicin alone [2]. This may suggest that an indiscriminate use of aggressive chemotherapy to all patients with metastatic sarcoma is not an optimal way to improve outcome. Therefore, there is a clear need for a way to stratify patients with metastatic sarcoma into various prognostic groups for a more tailored treatment strategy.

The systemic inflammatory response to malignancy is believed to play an important role in the development and progression of cancer [3] and, hence, treatment outcome. Testing the prognostic value of serum biomarkers involved in this inflammatory response has become the focus of recent research, particularly as it may shed some light on the biological interaction between tumour progression and the immune system.

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Certain individual serum biomarkers, such as C-reactive protein (CRP), haemoglobin, serum albumin and neutrophil count, have been reported to have a prognostic value in metastatic sarcomas [4–6]. Another serum biomarker, serum sodium, is also known to be a prognostic factor for various cancers and inflammatory conditions. We have previously shown that sodium is prognostic in a small cohort of metastatic Gastrointestinal stromal tumor (GIST) [7], as well as in metastatic sarcomas receiving trabectedin chemotherapy [8].

Combining multiple biomarkers in one scoring system may have a better ability to categorise patients in various prognostic groups. An example is the CNG system, which includes both the neutrophil to lymphocyte ratio (NLR) and the Glasgow prognostic score (GPS) and can divide the patient cohort into four groups [9–11]. Another example is our previously reported Aarhus composite biomarker score (ACBS), which includes CRP, neutrophil and lymphocyte counts, serum albumin and haemoglobin, and was shown to be an independent prognostic index superior to GPS and NLR for localised bone sarcoma and STS [12,13].

To avoid bias in estimating the prognostic value of a given biomarker, one has to correct for possible confounders, such as age and comorbidities, that can influence the serum biomarker value and the survival outcome independent of the cancer diagnosis.

Unfortunately, few literature studies have taken comorbidity into account when reporting their results and no study has compared the various prognostic scores in metastatic sarcomas.

The aim of this study was to investigate the prognostic value of a battery of serum biomarkers either alone or combined and to evaluate various scoring biomarker-based systems to clarify which is the best survival outcome predictor for patients with metastatic sarcomas. This is carried out while taking into account that comorbidity and age are confounding factors.

Materials and Methods

Study Cohort

All patients diagnosed with metastatic sarcoma treated between January 1994 and December 2008 at Aarhus Sarcoma Centre, Denmark were included in the present study. The inclusion date was the date of diagnosis of metastatic disease. Patients with unclassifiable tumours or who had no available blood samples were excluded from the analysis. This resulted in a cohort of 265 patients.

Data Sources

The clinical data were acquired from the validated population-based Aarhus Sarcoma Registry [14]. Patients with metastatic disease were diagnosed and treated according to national guidelines.

Serum biomarker data were collected from the clinical laboratory information system (LABKA) research database [15]. This database registers test results according to the international nomenclature, properties and units coding system [16]. Serum albumin, CRP, haemoglobin, neutrophils, lymphocytes and sodium were analysed. The biomarkers were divided into normal or high/low. Normal albumin was defined as levels >36 g/l or >542 μmol/l. Normal CRP was defined as values <8 mmol/l or <75 nmol/l. Normal haemoglobin was defined as levels >7.3 mmol/l in women and >8.3 mmol/l in men. Normal neutrophils were defined as values $<7 \times 10^9$/l. Normal lymphocytes was defined as values $>1.3 \times 10^9$/l. Normal sodium was defined as values >137 mmol/l.

The GPS [10,17] was determined as: normal if albumin and CRP were normal, 1 if either albumin was low or CRP was high and 2 if both albumin was low and CRP was high.

A high NLR was defined as values >5.3.

CNG (the combination of NLR and GPS) was also evaluated. A CNG of 0 was defined as normal albumin, normal CRP and NLR > 2; patients with one, two or three abnormal values were assigned a score of 1, 2 or 3, respectively.

Our own biomarker score, the ACBS, as previously described [12,13], included five biomarkers: CRP, albumin, neutrophil, lymphocytes and haemoglobin. The ACBS scoring was previously defined as: normal if albumin, CRP, neutrophils, lymphocytes and haemoglobin were normal, 1 if one of the abovementioned biomarkers was abnormal and 2 if more than one abnormal biomarker was present. In this study we tested the value of adding serum sodium to the ACBS and divided the score into four groups. We called it the modified ACBS (ACBSm).

The National Patient Registry [18] was used to obtain data on comorbidities before the sarcoma diagnosis. The comorbidities were reported as the Charlson comorbidity index [19].

Data Analysis and Statistics

Data from the Aarhus Sarcoma Registry, LABKA and LPR were linked on an individual level using the 10-digit civil personal registration number, which since 1968 has been assigned to all citizens in Denmark.

The vital status and cause of death were registered through linkage to the Central Population Registry and Cause of Death Registry [20]. The primary end points were overall and disease-specific mortality.

Crude and adjusted analyses were carried out by using the Cox proportional hazard model. The following variables were included in the adjusted analysis: age at the time of metastatic disease (continuous variable), comorbidity (yes versus no), histological type (bone sarcoma versus STS) and site of metastasis (pulmonary only, extrapulmonary metastasis existed). This adjustment is based on the direct acyclic graph shown in Figure 1. The Fine and Gray competing risk model [21] was used to illustrate the cumulative disease-specific mortality for each scoring system, with death from other causes as a competing event. In this model, adjustments were made for age at the time of metastatic disease and comorbidity.

To evaluate if the ACBS added additional information to the Cox proportional model compared with already known

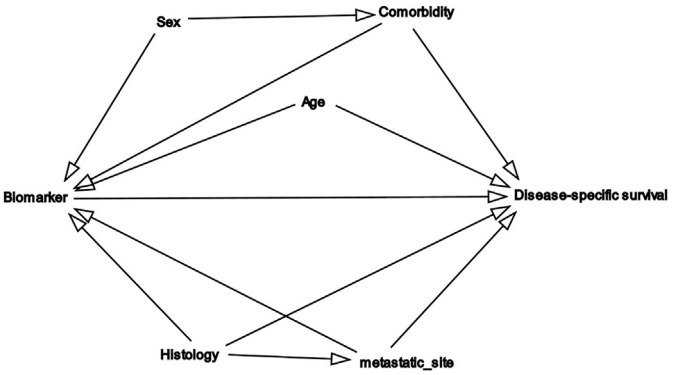

Fig 1. Direct acyclic graph model showing the confounders for the association between the biomarkers and the outcome.

prognostic factors, different methods were used. The five different scores (GPS, NLR, CNG, ACBS and ACBSm) were individually compared by Akaike Information Criterion (AIC) and the Harrell's concordance index (C-index). Validation of the ACBS was carried out using the bootstrapping method with 1000 iterations. All statistical tests were carried out by Stata version 14. A two-sided *P* value less than 0.05 was regarded as significant. If there was multiple testing over 10 tests for the same biomarker or biomarker profile, Bonferroni-corrected *P* values were used.

Ethics

The Ethics Committee of Denmark (1-10-72-233-12) and the Danish Agency of Data Protection (1-16-02-169-12) approved the study.

Results

Patient Characteristic

The median age at diagnosis of metastatic disease was 56 years (range 15–90) but there was a clear difference in the median age of metastatic disease between STS (59 years) and bone sarcoma (49 years) patients. Less than half the patients (118 patients, 34%) had metastasis only to the lungs. About 10% of patients with only lung metastasis (29 patients) had between one and three lung metastases. Comorbidity was present in 21% of the patients. Table 1 summarises the patients' tumour and treatment characteristics.

The most frequent histological types for STS were undifferentiated polymorphic sarcoma ($n = 41$), leiomyosarcoma ($n = 31$), liposarcoma ($n = 27$), synovial sarcoma ($n = 27$), malignant peripheral nerve sheath tumour ($n = 15$) and others ($n = 63$). The most frequent histological types for bone sarcoma were osteosarcoma ($n = 28$), Ewing ($n = 8$), chondrosarcoma ($n = 19$) and other bone sarcoma ($n = 8$).

Most patients in this metastatic cohort (161 patients, 61%) had metachronous metastasis, whereas 104 patients (39%) already had their metastasis at the time of primary tumour diagnosis. Thirty-two patients did not receive any treatment for metastatic disease and the median time from the metastatic diagnosis until death for these patients was 55 days. Eight patients were treated with radiation alone and 52 patients with surgery alone. The remaining patients received various types of chemotherapy according to the national standards at the time. The median follow-up time for the whole cohort was 0.9 year; for patients still alive at

Table 1
Patient, tumour and treatment characteristics of patients treated for metastatic sarcoma ($n = 265$)

	Total	Soft tissue	Bone	*P* value*
Age at diagnosis (years)				
Median (range)	56 (15–90)	59 (17–90)	49 (15–82)	<0.00
Sex				
Female	110 (42)	85 (42)	25 (40)	
Male	155 (58)	117 (58)	38 (60)	0.74
Comorbidity				
No	209 (79)	159 (79)	50 (79)	
Yes	56 (21)	43 (21)	13 (21)	0.91
Time of metastatic disease				
At the time of primary diagnosis	104 (39)	77 (38)	27 (43)	
Later developed metastatic disease	161 (61)	125 (62)	37 (57)	0.51
Metastatic site				
Only lung				
1–3 metastases	29 (11)	21 (10)	8 (12)	
>3 metastases	89 (33)	72 (35)	17 (27)	
Extrapulmonary	147 (56)	109 (54)	38 (61)	0.38
Treatment modality†				
No treatment	32 (12)	22 (11)	10 (16)	
Chemotherapy‡	153 (58)	120 (59)	33 (52)	0.32

* Fisher's exact test or chi-squared test and Wilcoxon rank-sum test.
† Surgery, chemotherapy or radiation therapy.
‡ Patients treated with chemotherapy compared with patients not treated with chemotherapy.

Table 2
Patient, tumour and treatment characteristic for each biomarker score ($n = 265$)

	Total	GPS				NLR			CNG					ACBS			
		0	1	2	P^*	0	1	P^*	0	1	2	3	P^*	0	1	2	P^*
Total number		101	121	43		198	67		26	94	104	41		49	74	142	
Age at diagnosis (years)																	
15–40	64 (24)	26 (26)	30 (25)	8 (18)		45 (23)	19 (28)		4 (15)	30 (32)	22 (21)	8 (20)		15 (31)	13 (18)	36 (25)	
>40	201 (76)	75 (74)	91 (75)	35 (80)	0.64	153 (77)	48 (72)	0.35	22 (85)	64 (68)	82 (79)	33 (80)	0.16	34 (69)	61 (82)	106 (75)	0.23
Sex																	
Female	110 (42)	44 (44)	59 (41)	16 (37)		85 (43)	25 (37)		11 (42)	45 (48)	39 (38)	15 (37)		20 (41)	36 (49)	54 (38)	
Male	155 (58)	57 (56)	71 (59)	27 (63)	0.78	113 (57)	42 (63)	0.42	15 (58)	49 (52)	65 (63)	26 (63)	0.45	29 (59)	38 (51)	88 (62)	0.32
Comorbidity																	
No	209 (79)	83 (82)	98 (81)	28 (65)		157 (79)	52 (78)		21 (81)	78 (83)	84 (81)	26 (63)		42 (86)	58 (78)	109 (77)	
Yes	56 (21)	18 (18)	23 (19)	15 (35)	0.05	41 (21)	15 (22)	0.77	5 (19)	16 (17)	20 (19)	15 (37)	0.07	7 (14)	16 (22)	33 (23)	0.41
Time of metastatic disease																	
At the time of primary diagnosis	104 (39)	31 (31)	47 (39)	36 (60)		79 (40)	25 (37)		7 (27)	31 (33)	40 (38)	26 (63)		15 (31)	30 (41)	59 (42)	
Later developed metastatic disease	161 (61)	79 (69)	74 (61)	17 (40)	0.004	119 (60)	42 (62)	0.71	19 (73)	63 (67)	64 (62)	15 (37)	0.004	34 (69)	44 (59)	83 (58)	0.39
Histology																	
Soft-tissue sarcoma	202 (77)	81 (80)	87 (72)	34 (79)		157 (79)	45 (67)		20 (77)	75 (80)	75 (72)	32 (78)		39 (80)	62 (84)	101 (71)	
Bone sarcoma	63 (23)	20 (20)	34 (28)	9 (21)	0.33	41 (21)	22 (33)	0.04	6 (23)	19 (20)	29 (28)	9 (22)	0.64	10 (20)	62 (84)	41 (29)	0.10
Metastatic site																	
Only lung																	
1–3 metastases	29 (11)	14 (14)	13 (11)	2 (5)		20 (10)	9 (13)		6 (23)	10 (11)	12 (12)	1 (2)		9 (18)	8 (11)	12 (8)	
>3 metastases	89 (33)	33 (33)	42 (35)	14 (33)		67 (34)	22 (32)		5 (19)	35 (37)	35 (34)	14 (34)		15 (31)	29 (39)	45 (32)	
Extrapulmonary	147 (56)	54 (54)	66 (55)	27 (63)	0.57	111 (56)	36 (54)	0.74	15 (58)	49 (52)	57 (55)	26 (63)	0.67	25 (51)	37 (50)	85 (60)	0.30

GPS, Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; CNG, a combined score of GPS and NLR; ACBS, Aarhus composite biomarker score.
* Fisher's exact test or chi-squared test and Wilcoxon rank-sum test.

the end of the analysis, the median follow-up time was 12 years.

Biomarkers

Each biomarker was investigated separately. Low albumin was present in 54 (20%) of the patients, high CRP in 153 (58%), low haemoglobin in 97 (37%), high neutrophil counts in 91 (34%), low lymphocytes in 88 (33%) and low sodium in 42 (16%) of the patients. The patient, tumour and treatment characteristics for each biomarker can be found in Supplementary Table S1**.** As seen in Supplementary Table S1, age, sex, comorbidity, histology and number/site of metastasis were equally distributed between the cohorts of normal and abnormal biomarkers.

The scoring systems GPS, NLR, CNG and ACBS were likewise investigated. Table 2 shows the allocations of patients into the different prognostic groups for each score. In general, no difference was seen between patient, tumour and treatment characteristics for each scoring system, except for CNG and GPS, where patients with a high score did seem to have a higher value if their metastatic disease was shown at the time of primary diagnose compared with patients who developed metastatic disease later.

Disease-specific Mortality

Two hundred and forty-six patients died during follow-up. The overall 5-year overall mortality was 92% (95% confidence interval 88–95%).

The crude and adjusted analysis for each individual biomarker is seen in Table 3. All biomarkers, except for lymphocytes, were prognostic for disease-specific survival (DSS), also after adjusting for age (at the time of metastatic disease), comorbidity, histology and site of metastasis.

The crude and adjusted analysis for the GPS, NLR, CNG and ACBS are shown in Table 4. For all scoring systems, a higher score was associated with a statistically significant worse prognosis. Adjusting for confounders did not change the association between each scoring system and outcome (DSS) and all scores were independent prognostic factors.

The cumulative incidence function of disease-specific mortality for the GCP, NLR, CNG and ACBS are illustrated in Figure 2. The graphs are adjusted for age at the time of metastasis and comorbidity.

Model Selection

As all the scoring systems were independent prognostic factors they were compared to determine which one could best predict DSS according to AIC. No difference in the ability to predict outcome was observed between GCP, NLR CNG or ACBS. However, adding serum sodium to the ACBS and dividing the cohort into four risk groups made this modified ACBS (ACBSm) superior to the other scoring systems. The ACBSm had the lowest AIC and highest C-index (see Supplementary Table S2 for AIC values and C-index).

The adjusted hazard ratio for patients with ACBSm 3 was 9.7 (95% confidence interval 6–15.7), for ACBSm 2 was 3.8 (95% confidence interval 2.4–5.9) and for ACBSm 1 was 2.4 (95% confidence interval 1.6–3.4) compared with ACBSm 0.

Bootstrapping

The robustness of ACBSm was tested using bootstrapping. The adjusted bias-corrected hazard ratio for ACBSm 1 was 2.4 (95% confidence interval 1.6–3.6), for ACBSm 2 was 3.8 (95% confidence interval 2.4–6.2) and for ACBSm 3 was 9.7 (95% confidence interval 5.3–16.8).

Table 3
Uni- and multivariate analysis using disease-specific survival ($n = 265$)

	No.	Events	Crude		Adjusted*	*P* value
			Hazard ratio	*P* value	Hazard ratio	
Albumin						
Normal	211 (80)	197	1		1	
Low	54 (20)	49	2.0 (1.5–2.7)	<0.001	2.3 (1.7–3.2)	<0.001
C-reactive protein						
Normal	112 (42)	98	1		1	
High	153 (58)	148	2.5 (1.9–3.2)	<0.001	2.4 (1.9–3.2)	<0.001
Haemoglobin						
Normal	168 (63)	152	1		1	
Low	97 (37)	94	2.4 (1.8–3.1)	<0.001	2.6 (2.0–3.4)	<0.001
Neutrophils						
Normal	174 (66)	160	1		1	
High	91 (34)	86	1.8 (1.4–2.4)	<0.001	1.9 (1.5–2.5)	<0.001
Lymphocytes						
Normal	177 (67)	163	1		1	
Low	88 (33)	83	1.3 (1.0–1.7)	0.07	1.3 (1.0–1.8)	0.035
Sodium						
Normal	223 (84)	205	1		1	
Low	42 (16)	41	2.8 (1.9–3.9)	<0.001	2.7 (1.9–3.9)	<0.001

* Adjustment was made for comorbidity, age, histology (bone versus soft tissue) and site of metastasis.

Table 4
Uni- and multivariate analysis using disease-specific survival ($n = 265$)

	No.	Events	Crude	*P* value	Adjusted*	*P* value
			Hazard ratio		Hazard ratio	
Age at diagnosis (years)						
15–40	64 (24)	58	1		1	
>40	201 (76)	188	1.2 (0.91–1.65)	0.71	1.9 (0.9–1.6)	0.28
Sex						
Female	110 (42)	104	1		1	
Male	155 (58)	142	0.9 (0.7–1.1)	0.25	0.9 (0.7–1.2)	0.48
Comorbidity						
No	209 (79)	194	1		1	
Yes	56 (21)	52	1.6 (1.2–2.1)	0.004	1.34 (1.0–1.9)	0.09
Histology						
Soft-tissue sarcoma	202 (76)	188	1		1	
Bone sarcoma	63 (24)	58	0.9 (0.7–1.2)	0.5	0.7 (0.5–1.0)	0.03
Metastatic site						
Only lung						
1–3 metastases	29 (11)	25	1		1	
>3 metastases	89 (34)	86	2.2 (1.4–3.4)	0.001	2.4 (1.5–3.8)	<0.001
Bone metastasis	19 (7)	18	1.5 (0.8–2.8)	0.19	1.6 (0.9–3.0)	0.12
Solitary metastasis elsewhere	24 (9)	20	1.1 (0.6–1.9)	0.85	1.2 (0.7–2.2)	0.5
Metastasis at more than one site	104 (39)	97	1.9 (1.2–3.0)	0.003	2.1 (1.3–3.4)	0.001
NLR						
Normal	198 (75)	184	1		1	
High	67 (25)	62	1.7 (1.3–2.3)	<0.001	1.7 (1.3–2.3)	<0.001
GPS						
0	101 (38)	89	1		1	
1	121 (46)	117	1.9 (1.4–2.5)	<0.001	2.0 (1.5–2.7)	<0.001
2	43 (16)	40	5.4 (3.6–8.0)	<0.001	5.2 (3.5–7.7)	<0.001
CNG						
0	26 (10)	21	1		1	
1	94 (35)	86	2.0 (1.2–3.2)	0.007	2.3 (1.4–3.9)	0.001
2	104 (39)	101	3.2 (2.0–5.3)	<0.001	3.8 (2.3–6.35)	<0.001
3	41 (15)	38	10.5 (6.0–18.6)	<0.001	11.4 (6.3–20.5)	<0.001
ACBS						
0	49 (18)	41	1		1	
1	74 (28)	69	2.0 (1.3–2.9)	0.001	2.1 (1.4–3.1)	<0.001
2	142 (54)	136	3.2 (2.2–4.6)	<0.001	3.7 (2.6–5.5)	<0.001

GPS, Glasgow prognostic score; NLR, neutrophil to lymphocyte ratio; CNG, a combined score for GPS and NLR; ACBS, Aarhus composite biomarker score.

* Adjustment was made for comorbidity, age, histology and site of metastasis. For age adjustment was made only for comorbidity and for comorbidity adjustment was made for only age.

Discussion

In this study of 281 metastatic sarcoma patients we found all six investigated serum biomarkers to be independent prognostic factors for DSS. The various scoring systems including two or more of these biomarkers were also independently prognostic for DSS. However, the ACBSm was statistically superior to the other scoring systems and could stratify the cohort into four groups where the best group had a 5-year DSS of 30% and the worst group had a 100% mortality within 2 years.

Even though the median overall survival for patients with metastatic STS is about 13 months [2], very little is known about prognostic factors in this group of patients. Yet, it is crucial for future clinical trials and to develop more specific treatment for subgroups of patients to identify various risk groups based on prognostic factors. Studying serum biomarkers involved in the inflammatory response to cancer is an area of research that has gained increased attention in recent years [3]. Yet, only a few studies have been published investigating inflammatory serum biomarkers in metastatic sarcoma.

For metastatic sarcoma, only albumin, haemoglobin, CRP and GPS have been investigated and the results from these papers are consistent with our findings [5,6,22–24]. However, these studies do not take comorbidity into account when analysing serum biomarkers, which might affect the results, as comorbidity can influence different inflammatory biomarkers as well as the DSS.

In our previous studies of serum biomarkers in localised bone sarcoma [13] and STS [12], most of the currently studied serum biomarkers were independent prognostic

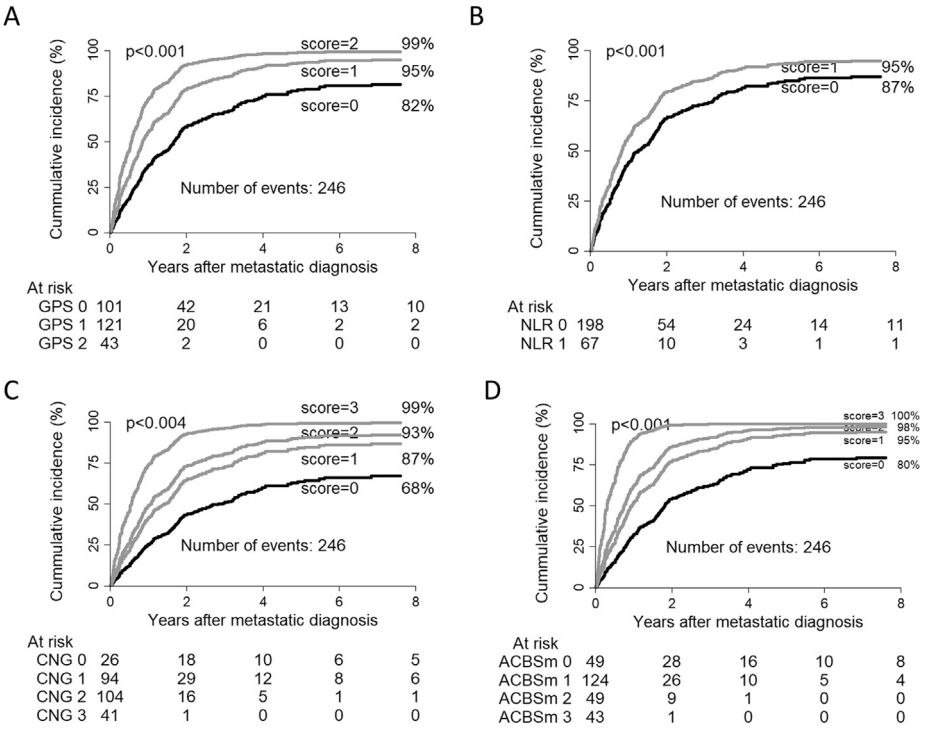

Fig 2. The disease-specific mortality for the different scoring systems. The curves are cumulative incidences estimated by using the Fine and Gray model. The resulting cumulative incidence curves are adjusted for patient age at the time of metastatic disease and comorbidity. (A) Glasgow prognostic score (GPS), (B) neutrophil to lymphocyte ratio (NLR), (C) CNG and (D) the modified ABCS.

factors for confounder-adjusted DSS, which points to the same biological mechanisms whether the sarcoma is localised or metastatic. However, contrary to patients with localised sarcomas [12,13], in this study we found serum sodium to be prognostic for DSS. Serum sodium is a good marker for stress and a known prognostic marker in cancer [7,25,26] and other life-threatening medical conditions [27] and it cannot be excluded that it may be shown to have a prognostic role in certain localised bone sarcoma or STS if tested in larger patient cohorts.

A minority of patients with oligometastasis (one to three) received radically intended local therapy (mainly surgical excision). However, there was no statistical difference between the percentage of patients with abnormal biomarkers in the oligometastasis and the systemic metastasis cohorts. Better survival in the patients with lower biomarker score cannot therefore be attributed to them receiving surgery for their metastasis.

The weakness of this study is the retrospective nature and the small number of patients in each sarcoma subgroup. Another limitation of this study is its inability to clarify whether these prognostic parameters are also predictive of response to therapy and to describe the biological mechanisms behind the phenomenon. Therefore, further studies in the role for inflammatory biomarkers in metastatic as well as localised sarcoma are needed.

Comorbidity is, in this study, regarded as a confounder as it affects both the survival and the levels of the biomarkers. However, in this study the adjustment for comorbidity was limited to only whether comorbidity was present or not. Furthermore, neither the severity of the comorbidity nor the type of comorbidity was considered. This is a limitation of this study and in future studies including more patients would be of great importance to make a more thorough adjustment.

The strengths of this study are that all patients were treated at a single-specialised institution in a free-of-charge health system. Patient, tumour and treatment details were registered prospectively in a controlled and validated database and follow-up data were complete for all patients. Moreover, data on comorbidity could be retrieved from the national registry and used to correct for possible confounder bias. Another point of strength is the validation of data using the bootstrapping method.

To our knowledge, this is the largest and first study to investigate serum inflammatory biomarkers for metastatic STS and bone sarcoma adjusted for comorbidity. Furthermore, this study is the first to compare all the different scoring systems.

Conclusion

This study clearly showed the value of inflammation serum biomarkers as a risk-stratifying tool and method to predict the outcome of metastatic sarcoma patients.

Conflict of Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2019.01.011.

References

[1] Maretty-Nielsen K, Aggerholm-Pedersen N, Safwat A, Jorgensen PH, Hansen BH, Baerentzen S, *et al*. Prognostic factors for local recurrence and mortality in adult soft tissue sarcoma of the extremities and trunk wall. *Acta Orthop* 2014;85:323–332.

[2] Judson I, Verweij J, Gelderblom H, Hartmann JT, Schoffski P, Blay JY, *et al*. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol* 2014;15:415–423.

[3] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–674.

[4] Jiang L, Jiang S, Situ D, Lin Y, Yang H, Li Y, *et al*. Prognostic value of monocyte and neutrophils to lymphocytes ratio in patients with metastatic soft tissue sarcoma. *Oncotarget* 2015;6:9542–9550.

[5] Nakamura T, Katagiri H, Shido Y, Hamada S, Yamada K, Nagano A, *et al*. Analysis of factors for predicting survival in soft-tissue sarcoma with metastatic disease at initial presentation. *Anticancer Res* 2017;37:3137–3141.

[6] Nakamura T, Matsumine A, Asanuma K, Matsubara T, Sudo A. The role of C-reactive protein in predicting post-metastatic survival of patients with metastatic bone and soft tissue sarcoma. *Tumour Biol* 2015;36:7515–7520.

[7] Aggerholm-Pedersen N, Rasmussen P, Dybdahl H, Rossen P, Nielsen OS, Safwat A. Serum natrium determines outcome of treatment of advanced GIST with imatinib: a retrospective study of 80 patients from a single institution. *ISRN Oncol* 2011;2011. Article ID 523915, 7 pages.

[8] Schack LH, Mouritsen LS, Elowsson C, Krarup-Hansen A, Safwat A. The Danish experience with trabectedin treatment for metastatic sarcoma: importance of hyponatremia. *Acta Oncol* 2015;54:34–40.

[9] Templeton AJ, McNamara MG, Seruga B, Vera-Badillo FE, Aneja P, Ocana A, *et al*. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014;106. dju124.

[10] Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 2003;89:1028–1030.

[11] Liu X, Chen S, Liu J, Xu D, Li W, Zhan Y, *et al*. Impact of systemic inflammation on gastric cancer outcomes. *PLoS One* 2017;12:e0174085.

[12] Maretty-Kongstad K, Aggerholm-Pedersen N, Keller J, Safwat A. A validated prognostic biomarker score for adult patients with nonmetastatic soft tissue sarcomas of the trunk and extremities. *Transl Oncol* 2017;10:942–948.

[13] Aggerholm-Pedersen N, Maretty-Kongstad K, Keller J, Baerentzen S, Safwat A. The prognostic value of serum biomarkers in localized bone sarcoma. *Transl Oncol* 2016;9:322–328.

[14] Maretty-Nielsen K, Aggerholm-Pedersen N, Keller J, Safwat A, Baerentzen S, Pedersen AB. Population-based Aarhus Sarcoma Registry: validity, completeness of registration, and incidence of bone and soft tissue sarcomas in western Denmark. *Clin Epidemiol* 2013;5:45–56.

[15] Grann AF, Erichsen R, Nielsen AG, Froslev T, Thomsen RW. Existing data sources for clinical epidemiology: the clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin Epidemiol* 2011;3:133–138.

[16] Joint Committee on Nomenclature, Properties and Units (C-SC-NPU) of the IFCC and IUPAC, Pontet F, Magdal Petersen U, Fuentes-Arderiu X, Nordin G, Bruunshuus I, *et al*. Clinical laboratory sciences data transmission: the NPU coding system. *Stud Health Technol Inform* 2009;150:265–269.

[17] Al Murri AM, Bartlett JM, Canney PA, Doughty JC, Wilson C, McMillan DC. Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer. *Br J Cancer* 2006;94:227–230.

[18] Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health* 2011;39:30–33.

[19] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.

[20] Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health* 2011;39:26–29.

[21] Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.

[22] Jiang SS, Jiang L, Weng DS, Li YF, Pan QZ, Zhao JJ, *et al*. Immunization-based scores as independent prognostic predictors in soft tissue sarcoma patients. *J Cancer* 2017;8:606–616.

[23] Iqbal N, Shukla NK, Deo SV, Agarwala S, Sharma DN, Sharma MC, *et al*. Prognostic factors affecting survival in metastatic soft tissue sarcoma: an analysis of 110 patients. *Clin Transl Oncol* 2016;18:310–316.

[24] Biswas B, Rastogi S, Khan SA, Mohanti BK, Sharma DN, Sharma MC, *et al*. Outcomes and prognostic factors for Ewing-family tumors of the extremities. *J Bone Joint Surg Am* 2014;96:841–849.

[25] Hansen O, Sorensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. *Lung Cancer* 2010;68:111–114.

[26] Jeppesen AN, Jensen HK, Donskov F, Marcussen N, von der Maase H. Hyponatremia as a prognostic and predictive factor in metastatic renal cell carcinoma. *Br J Cancer* 2010;102:867–872.

[27] Asadollahi K, Hastings IM, Beeching NJ, Gill GV. Laboratory risk factors for hospital mortality in acutely admitted patients. *QJM* 2007;100:501–507.