Article

Not peer-reviewed version

C-reactive Protein Pretreatment-Level Evaluation with Histopathological Correlation for Chondrosarcoma Prognosis Assessment—a 15-Year Retrospective Single-Centre Study

Sarah Consalvo *, Florian Hinterwimmer, Maximilian Stephan, Sebastian Breden, Ulrich Lenze, Jan Peeken, Rüdinger von Einsenhart-Rothe, Carolin Knebel

Posted Date: 28 May 2024

doi: 10.20944/preprints202405.1840.v1

Keywords: chondrosarcoma; CRP; prognosis; microenvironment

Article

C-Reactive Protein Pretreatment-Level Evaluation with histopathological Correlation for Chondrosarcoma Prognosis Assessment—A 15-Year Retrospective Single-Centre Study

Sarah Consalvo [1,*], Florian Hinterwimmer [2], Max Stephan [1], Sebastian Breden [1], Ulrich Lenze [1], Jan Peeken [3], Rüdiger von Eisenhart-Rothe [1] and Carolin Knebel [1]

[1] Department of Orthopaedics and Sport Orthopaedics, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
[2] Institute for AI and Informatics in Medicine, Technical University of Munich, Munich, Germany
[3] Department of Radiooncology and Radiotherapy, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
* Correspondence: sarah.consalvo@mri.tum.de; Tel.: +49-89-4140-8012

Abstract: *Background*: An aberrant cellular microenvironment characterized by pathological cells or inflammation represents an added risk factor across various cancer types. While the significance of chronic inflammation in the development of most diffuse tumors has been extensively studied, an exception to this analysis exists in the context of Chondrosarcomas. Chondrosarcomas represent 20–30% of all skeletal sarcomas and have an estimated incidence of 1 in 100,000 worldwide. The mean age of presentation is 50, with over 70% of patients over the age of 40 at the time of diagnosis. The aim of this retrospective study was to analyze the role of C-reactive protein (CRP) as a prognostic factor in relation to the histopathological findings for Chondrosarcoma. *Methods*: This retrospective study included 73 patients with confirmed Chondrosarcoma diagnosis treated between 2004 and 2019. Preoperative CRP determination was assessed in mg/dL with a non-pathological value below 0.5 mg/dL. Disease-free survival time was calculated as the time between the initial diagnosis and an event like local recurrence or metastasis. Follow-up status was described in death of disease, no evidence of disease and alive with disease. The exclusion criteria of this study included insufficient laboratory values, lack of information regarding the follow-up status and incomplete histopathological report. *Results:* The calculate risk estimation of a reduced follow-up time was 2,25 time higher in the patients with an CRP level >0.5 mg/dL (HR 2,25 and 95% CI 1,13-4,45) and 3 times higher in patients with a tumour size >pT2 (HR 3 and 95% CI 1,59-5,92). We can easily confirm that the most elevated risk for a reduce follow-up time relies in chondrosarcomas high grading, preoperative pathological CRP- level and a size >8 cm. *Conclusions:* In Chondrosarcoma cases, we can consider CRP pretreatment value >0.5 mg/dL a sensitive prognostic and sensitive risk factor for distant metastasis.

Keywords: chondrosarcoma; CRP; prognosis; microenvironment

1. Introduction

Chondrosarcomas, ranking as the second most prevalent bone sarcoma after osteosarcoma, contribute to 20–30% of all skeletal sarcomas, with an estimated annual incidence of 1 in 200,000 in the United States [1, 2]. Emerging literature indicates an increasing trend in chondrosarcoma rates, establishing it as the most common primary bone malignancy in certain countries, primarily due to incidental diagnoses of chondrosarcoma-associated lesions [3, 4]. Typically diagnosed at the age of 51, chondrosarcoma predominantly affects individuals over 40, constituting more than 70% of cases. However, a noteworthy exception is the mesenchymal chondrosarcoma subtype, which manifests at a significantly younger age, peaking in incidence during the second and third decades of life. Gender distribution in chondrosarcoma displays a mild male predilection, although variations exist among

 doi:10.20944/preprints202405.1840.v1

different subtypes. The incidence of Condrosarcoma cases among females although has been observed to increase by over 50%. This trend is theorized to be linked to the rising usage of oral contraceptives and menopausal hormonal therapy. A study suggest that an estrogen signaling pathway may contribute to the proliferation of malignant chondrocytes [1].The conventional primary chondrosarcoma, encompassing 85% of all cases, represents the most prevalent variant. Other less common subtypes encompass secondary chondrosarcomas originating from benign precursors, as well as dedifferentiated, periosteal, mesenchymal, and clear cell variants [2, 5].

C-reactive protein (CRP) serves as a widely utilized systemic biomarker for detecting both acute and chronic inflammation. Over the last decade, there has been a renewed emphasis on the clinical utility of serum CRP, extending beyond inflammation to encompass the prediction and diagnosis of various conditions, notably cardiovascular diseases and malignancies. Elevated serum CRP levels have been observed in patients with numerous malignancies, highlighting a close association between inflammation and cancer [6-10]. The term "tumor CRP" is commonly used but actually until now unexplained.

Preoperative CRP levels correlate with the progression and pathological stages of malignancies. Elevated CRP emerges as a significant predictor of lower survival rates across various cancers, such as esophageal, colorectal, hepatocellular, pancreatic, urinary bladder, renal, ovarian, and cervical cancer, following surgical resection [7, 11, 12]. The acute phase reaction serves the dual purpose of inducing local tissue damage through a localized response while concurrently preventing the spread of damage beyond a certain threshold. These reactions act as pertinent diagnostic markers, reflecting the magnitude of the body's response. Acute phase proteins are generated within a 24-hour timeframe, resulting in an approximately 25% elevation in their blood concentration during this period. Consequently, protein concentrations can surge up to 1000-fold [10, 13]. Given the established connection between inflammation and cancer, it becomes imperative to scrutinize the prognostic relevance of various inflammatory factors. Taking into account the recent insight into the existence of multiple isoforms of CRP, each with unique biological functions, a comprehensive model is proposed. This model elucidates how CRP serves as a mediator of host defense responses in cancer [13].The simplicity, affordability, and widespread availability of serum CRP measurements make it a valuable tool in daily clinical practice. It can function as an additional prognostic indicator for survival and post-treatment monitoring in cancer patients.

The prognostic significance of C-reactive protein (CRP) however remains in Chondrosarcomas unexplored. The objective of this retrospective study is to assess the potential utility of CRP in gauging a patient's risk of diminished life expectancy at the time of diagnosis and correlation with histopathological grading.

2. Materials and Methods

This retrospective study included 73 patients who were treated at Klinikum rechts der Isar between 2004 and 2019 and had a confirmed diagnosis of Chondrosarcoma.

For all patients, diagnoses were validated through a histopathological examination as reference standard. The local institutional review and ethics board (Klinikum rechts der Isar, Technical University of Munich) approved this retrospective study (N°48/20S). Exclusion criteria included insufficient laboratory values, lack of information regarding follow-up or histopathology and Rx or R1/R2 resection status. Also all atypical cartilaginous tumors (ACT) on the base of the benign nature of this lesions were excluded. In total, 3 patients were excluded.

We analyzed the medical records of all patients enrolled in this study. Histology was obtained via incision or CT scan-guided biopsy performed in our institution and confirmed at an interdisciplinary sarcoma board following the WHO guidelines.

Laboratory data were collected pretreatment 1 to a maximum of 7 days before biopsy or first surgical treatment. CRP levels were reported in milligrams per decilitre (mg/dL) with a non-pathological value below 0.5 mg/dL. The measurement was performed using the Cobas® 8000 modular analyser C702 (Fa. Roche).

 doi:10.20944/preprints202405.1840.v1

All patients were followed up in our department every 3 months for the first 2 years, every 6 months from the third to the fifth year and at 12-month intervals thereafter in accordance with guidelines. Disease-free survival (DFS) time was calculated as the time between the initial diagnosis and an event like local recurrence or distant metastasis. All metastasis locations were included. The follow-up time was defined as the time between the initial diagnosis and the last follow-up or the last (unscheduled) presentation of the patient for a check-up in our clinic. The follow-up status of patients were classified as death of disease (DOD), no evidence of disease (NED) and if for patients who are currently alive, but had a diagnostically confirmed distant metastasis or a proven local recurrence in alive with disease (AWD).

2.1. Statistical Analysis

Data were processed and analysed using StatPlus:mac Pro 2020 (Fa. AnalsytSoft). **T**he reporting of statistics is carried out according to STROBE guidelines. The national standard of 0.5 mg/dL was used to distinguish between 'increased' and 'decreased' CRP. The correlation between CRP value and overall survival (OS) is discussed through a Pearson correlation model. The following were selected as guide values: CC = 0,3 no linear correlation, CC = 0,3-0,5 weak positive linear correlation and CC > 0.5 positive linear correlation for the interpretation of the correlation coefficient.

Statistically significant values were calculated as $p < 0.01$. Sensibility and specificity based on the optimal identified cut point were calculated along the 95% interval.

The survival curves were generated using Kaplan–Meier analysis and evaluated using log-rank test. Cox regression test was performed to estimate the association between CRP levels and prognosis status, T status and grading.

3. Results

We treated 73 patients at Klinikum rechts der Isar between 2004 and 2019 with a confirmed diagnosis of Chondrosarcoma. From this cohort we excluded 3 patients due to the lack of precise information in the histopathology report. The clinical characteristics of the patients are summarised in Table 1. Patient mean age was 56 years with a minimum age of 26 years and a maximum age of 87 years. Majority of the cohort was male (43 patients vs. 27 female patients). The mean female age was 56,5 years (26-82 years), whereas that of males was 56 years (29-87); 50% had lower extremity localisation (40% femur,5,7 % tibia and 4,2% foot), 24,2% pelvis localisation, 20% upper extremity localization and 5,7 % a thorax cage localization.

The follow-up status was defined as DOD in 37 (52,8%), NED in 32 (45,7%) and AWD in 1 (1,4%) patients. In all patients a surgical R0 therapy was performed. R0 resection was confirmed by the pathology department (n = 70).

Table 1. Characteristics of included patients with pre-operative CRP-Levels.

	n	**Percentage**	**Mean**	**Min**	**Max**
Age	70	-	56 years	26 years	87 years
Sex					
Male	43	61,40%	-	-	-
Female	27	38,80%	-	-	-
Site					
Femur	28	40%	-	-	-
Tibia	4	5,70%	-	-	-
Hip	17	24,20%	-	-	-
Scapula	8	11,40%	-	-	-
Clavicula	1	1,40%	-	-	-
Humerus	5	7,10%	-	-	-
Thorax	4	5,70%	-	-	-

 doi:10.20944/preprints202405.1840.v1

Foot	3	4,20%	-	-	-
Follow-up					
DOD	37	52,80%	-	-	-
NED	32	45,70%	-	-	-
AWD	1	1,40%	-	-	-
Metastasis at diagnosis	28	40%	-	-	-
pulmonary	19	27%	-	-	-
Lymphnodes	4	5,70%	-	-	-
multifokal	3	4,20%	-	-	-
other	2	2,80%	-	-	-
Grading					
G1	7	10%	-	-	-
G2	38	54,20%	-	-	-
G3	22	31,40%	-	-	-
G4	2	2,80%	-	-	-
no grading	1	1,40%	-	-	-
T Status			-	-	-
pT1	21	30%	-	-	-
pT1b	2	2,80%	-	-	-
pT2	34	48,50%	-	-	-
pT2a	2	2,80%	-	-	-
pT2b	10	14,20%	-	-	-
pT3	1	1,40%	-	-	-
Follow-up					
DFS	70	-	1,3 years	0 years	12 years
Follow-up time	70	-	2,3 years	0 years	13 years
CRP					
< 0.5 mg/dL	43	61.4%	0,3 mg/dL	0,1 mg/dL	0,5 mg/dL
> 0.5 mg/dL	27	38,50%	1,7 mg/dL	0,7 mg/dL	13,2 mg/dL

The median CRP value of the entire cohort was 0.5 mg/dL (0.1–13.2 mg/dL).

In the deceased patients, the median CRP level was 0.7 mg/dL (0.1–13.2 mg/dL). Only one patient remained alive with distant metastasis and local recurrence, his pre-operative CRP level was 0.5 mg/dL. The median CRP value of the NED group was 0.3 mg/dL (0.1–6 mg/dL) (Figure 1). It can be shown that those patients in our cohort who ultimately died as a result of Chondorsarcoma had higher preoperative CRP values on average.

 doi:10.20944/preprints202405.1840.v1

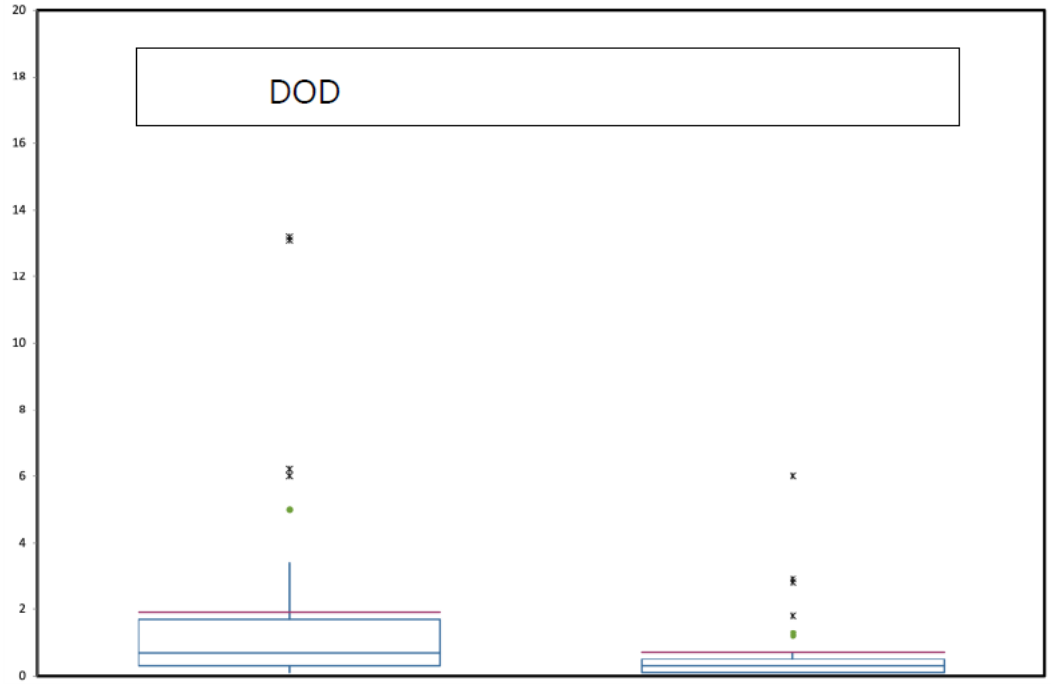

Figure 1. Box plot of the median CRP values (red line) depending on the follow-up status of the patients: no evidence of disease (NED) and death of disease (DOD). For the alive with disease (AWD) status, no diagram was created because only one patient was involved.

In the group with an elevated CRP (>0.5 mg/dL) value, 28,5% of the patients had already died and 10% was alive without any disease manifestation. In the low-CRP-value group (<0.5 mg/dL), 24% had already died, 1,4% were alive but with metastases or a local recurrence and 35,7% were alive without any manifestation of the disease (Table 2).. In evaluating the tumor size in the group with an elevated CRP the majority had a tumor size > 8cm (pT2, according to the 5th Edition 2020 WHO [14]) while the group with low CRP levels was mostly represented in by chondrosarcomas with < 8 cm size (pT1) (Table 2 and Figure 2).

Table 2. Characteristics of included patients with a pre-operative CRP level below or under 0.5 mg/dL. T Status was calculated with the WHO guidelines 2020.

	CRP < 0.5 mg/dL	**CRP > 0.5 mg/dL**
Follow-up		
DOD	17 (24,2%)	20 (28,5%)
NED	25 (35,7%)	7 (10%)
AWD	1 (1,4%)	-
T Status		
pT1	16 (22,8%)	5 (7,1%)
pT1b	2 (2,8%)	-
pT2	18 (25,7%)	6 (22,8%)
pT2a	-	2 (2,8%)
pT2b	7 (10%)	3 (4,2%)
pT3	-	1 (1,4%)

 doi:10.20944/preprints202405.1840.v1

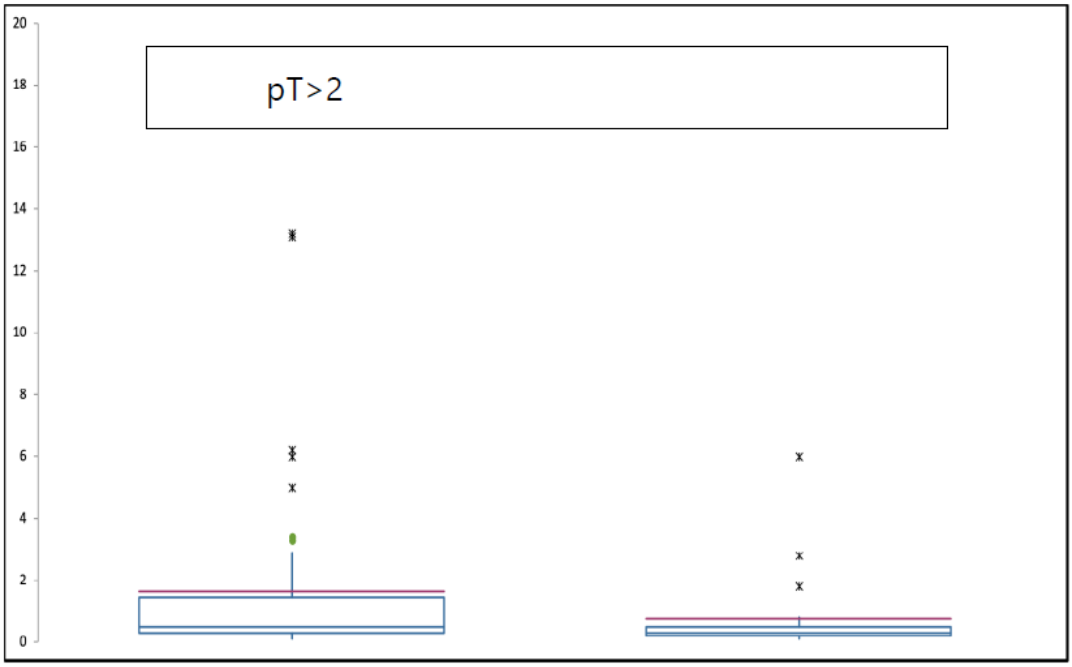

Figure 2. Box plot of the median CRP values (red line) depending on the pT status (Tumor size) of the patients, divided in 2 groups: tumor size under pT2 (<8cm) and over pT2 (<8cm) .

Patients with G1 Chondrosarcoma hat a median CRP level of 1.5 mg/dL (0.1–6 mg/dL). Two patients with G4 Grading were excluded in the mentioned below Box Plot table due to the non-statistical value. The median CRP value of the G2 group was 0.5 mg/dL (0.1–2.3 mg/dL) and in the G3 group the median CRP was 2,7 mg/dL (0.1–13.2 mg/dL) (Figure 3). It can be noticed that the CRP levels between G1 and G2 showed not much difference but the G3 group had higher preoperative CRP values on average.

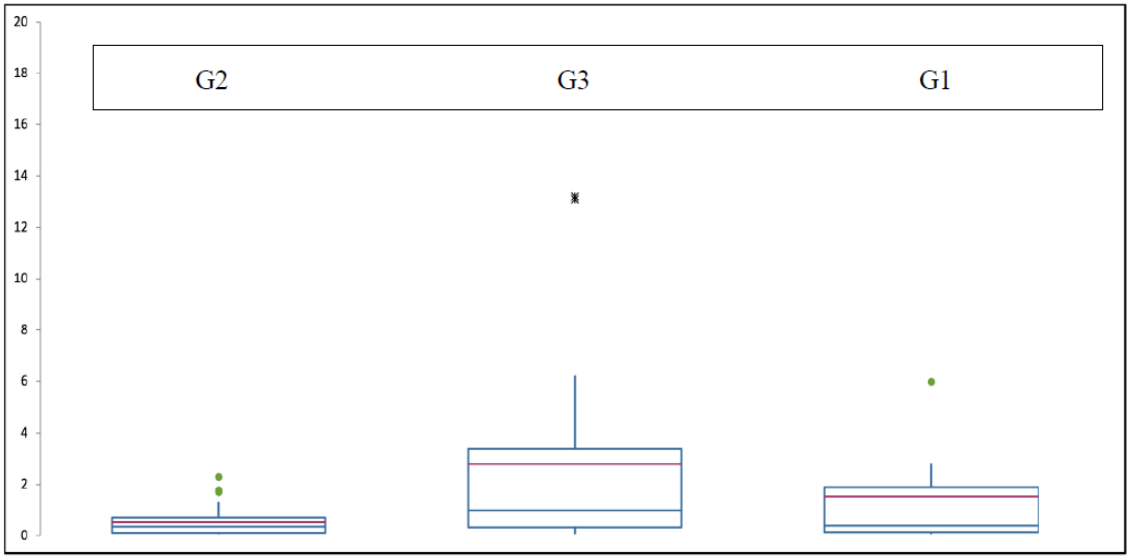

Figure 3. Box plot of the median CRP values (red line) depending on the Grading .

If we summarize the data of our cohort until this point we can statistically say that patients who had an elevated pre-operative CRP-level had a bigger tumor (>pT2), a higher Grading (>G3) and a poorer prognosis.

We calculated therefore the statistical correlation between the CRP level and the T status, the follow up and Grading.

 doi:10.20944/preprints202405.1840.v1

The Correlation Coefficient between CRP and Follow-up was 0.33 (p-value 0,004), between CRP and T status 0.24 (p-value 0,04) and between CRP and Grading 0.15 (p-value 0.20).

There is so a statistically significant direct proportion between CRP and follow-up.

We could confirm the data with a Cox regression. Here we found a significant correlation with all of the tree factors (Table 3).

Table 3. Cox regression equations with follow-up and CRP levels, T status and grading .

	Beta	Wald	p-Value	Exp(B)	*Lower*	*Upper*
CRP	0,6749	4,06006	0,04391	1,96296	1,01858	3,78677
T	1,2246	7,29320	0,00692	3,40297	1,39911	8,27679
Grading	0,6713	7,62120	0,00577	1,95686	1,21495	3,15180

3.1. Survival Curves

The median follow-up time of the cohort was 2.5 years (0–12.9 years). In contrast, the median DFS time was 1.3 years (0–11.8 years). Different survival curves could be established on the basis of the predefined cutoff value of 0.5 mg/dL depending on the CRP value. Patients with a preoperative CRP value of >0.5 mg/dL had a median follow-up time of 1.2 years (0–9.9 years). In contrast, patients with a CRP value below the cutoff value of 0.5 mg/dL showed a median follow-up time of 4.3 years (0–13 years) (Figure 4).

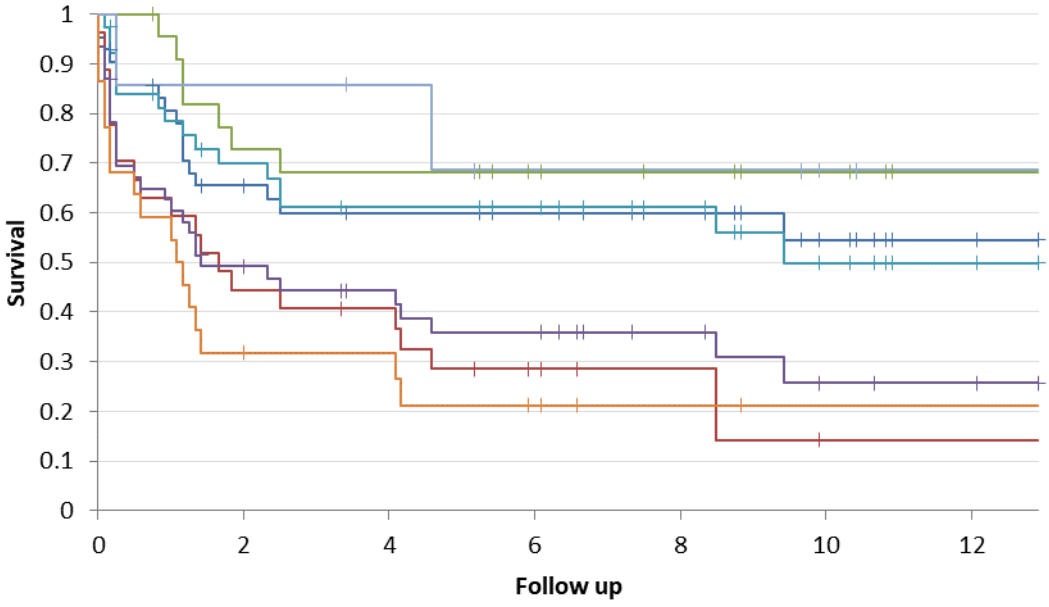

Figure 4. Kaplan-Meier curve of survival rate (Follow-up) depending on CRP levels, size of the tumour and grading: CRP < 0.5 mg/dL (blue curve), CRP > 0,5 mg/dL (red curve), size < pT2 (green curve), size > pT2 (purple curve), G1 (grey curve), G2 (light blue) and G3 (orange curve). The follow-up time is evaluated in years (*p*-value 0,00008).

A 5-year survival rate of 94% and 85% was calculated in the CRP <0.5 mg /dL and > 0.5 mg/dL groups, respectively.

The calculate risk estimation of a reduced overall survival rate time was 2,25 time higher in the patients with an CRP level >0.5 mg/dL (HR 2,25 and 95% CI 1,13-4,45) and 3 times higher in patients with a tumour size >pT2 (HR 3 and 95% CI 1,59-5,92). The risk of recurrence of an event in terms of local recurrence or distant metastasis (disease free survival) was quite the same as below for elevated CRP levels (HR 2,28 and 95% CI 1.15-5,53) and tumour size >pT2 (HR 3,1 and 95% CI 1,63-6) (Figure 5).

 doi:10.20944/preprints202405.1840.v1

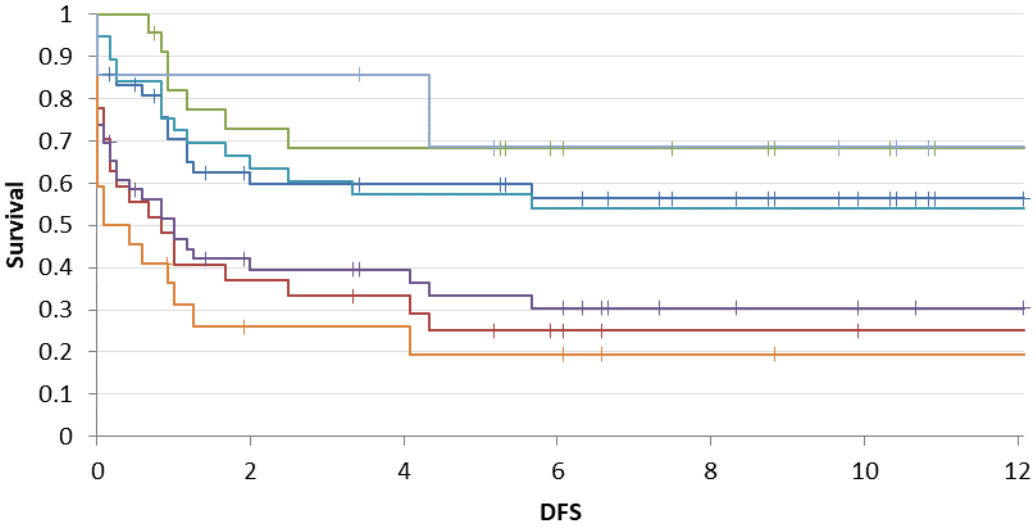

Figure 5. Kaplan-Meier survival curve for disease free survival depending on CRP levels, size of the tumour and grading: CRP < 0.5 mg/dL (blue curve), CRP > 0,5 mg/dL (red curve), size < pT2 (green curve), size > pT2 (purple curve), G1 (grey curve), G2 (light blue) and G3 (orange curve). The follow-up time is evaluated in years (*p*-value 0,00002).

By observing the curve above we can easily confirm that the most elevated risk for a reduce follow-up time relies in chondrosarcomas with high grading, a preoperative pathological CRP- level and a size >8 cm.

4. Discussion

As tumors develop and metastasize, they disrupt normal tissue function and provoke the body's acute phase inflammatory response. C-reactive protein (CRP) is a key component of this response and is commonly used as a minimally invasive marker for detecting inflammation. However, its specific role in assessing cancer progression or remission remains unclear [9, 13, 15]. In 2011 in a Copenhagen General Population Study the CRP levels of a cohort of 63500 healthy patient were analyzed. Patients with solid tumours (breast, lung or prostate cancer) and elevated CRP levels at time of diagnosis were associated with poor prognosis. On the other hand healthy patients with elevated CRP levels were associated with increased future risk of cancer. Patient with cancer and elevated CRP levels hat 80% greater risk of early death [6]. In this study the cut off limit of "elevated" CRP was > 10 mg/dL. In our study we put the cut-off at 0.5 mg/dL in line with the national guidelines.

Our research aims to assess the predictive significance of pretreatment serum CRP analysis concerning prognosis in Chondorsarcoma patients. By scrutinizing the statistical relevance of CRP values in correlation with prognosis,grading and size we cautiously discern its involvement in fostering a cancer-friendly microenvironment, indicated by local recurrence and distant metastasis.

Due to poor data due to the rarity of this tumours entities bone and soft tissue sarcomas remain a big question mark on this theme.

The relevance of CRP levels in Ewing Sarcoma patients were already demonstrate in our 2022 study [8]. CRP level >0.5 mg/dL revealed an 8.3 HR (95% CI 3–22.7). Optimal breakpoint analysis of CRP as a prognostic factor of OS revealed an AUC of 0.812. This data were also confirmed by the study of Funovics et al. with significantly correlated disease specific survival [16]. The study involved 79 patients (37 females, 42 males; average age 18 years) undergoing osteosarcoma resection, with an average follow-up of 46 months. Higher pre-operative CRP levels were significantly associated with lower survival rates. Patients who died had an average CRP level of 1.09 mg/dl, compared to 0.32 mg/dl in survivors. A significant negative correlation was found between CRP levels and both survival (correlation coefficient = -0.25) and histological subtype (correlation coefficient = -0.42), but

 doi:10.20944/preprints202405.1840.v1

not with sex, age, histological response, tumor size, or metastatic disease. Age, response to chemotherapy, and serum CRP were significant predictors of disease-specific survival. Patients with CRP levels over 1 mg/dl had a five-year survival rate of 36.7%, compared to 73.8% in those with normal CRP levels. Post-operative infection did not correlate with survival, and pre-operative CRP levels did not predict post-operative or deep prosthetic infections. In conclusion, pre-operative serum CRP showed to be an independent predictor of survival in high-grade osteosarcoma patients.

In a meta-analysis of 5 studies with a total of 816 patients with bone neoplasm higher levels of pre-operative CRP levels were associated with reduced OS [17]. This study investigated the prognostic role of the C-reactive protein to albumin ratio (CRP/Alb ratio) in osteosarcoma patients, enrolling a total of 216 participants. Survival analyses and Kaplan-Meier survival curves were conducted, along with receiver operating characteristic (ROC) curves to compare the CRP/Alb ratio's effectiveness against other inflammation-based indicators such as the Glasgow prognostic score (GPS), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). The optimal cutoff value for the CRP/Alb ratio was determined to be 0.210, with a Youden index of 0.319. Higher CRP/Alb ratio values were significantly associated with poorer overall survival in both univariate (HR = 2.62, 95% CI = 1.70-4.03; P < 0.001) and multivariate (HR = 2.21, 95% CI = 1.40-3.49; P = 0.001) analyses.The CRP/Alb ratio had significantly higher AUC values compared to GPS (P = 0.003), NLR (P < 0.001), and PLR (P < 0.001), indicating superior discriminatory ability.The study concludes that the CRP/Alb ratio is an effective and superior inflammation-based prognostic indicator in osteosarcoma compared to GPS, NLR, and PLR.

In alignment with our investigation, Aggerholm-Pendersen 8/ 1 et al. examined 172 patients with bone sarcoma, comprising 63 chondrosarcomas and 109 cases of either Ewing’s sarcomas and osteosarcomas. They found that elevated CRP levels were linked to higher overall mortality in both cohorts. However they grouped osteosarcomas and Ewing's sarcomas without distinguishing between them [18]. Elevated levels of pre-treatment CRP and an elevated score in the Glasgow prognostic score (GPS) as well as low pre-treatment Hemoglobin and Sodium concentrations were associated with increased overall mortality and disease specific mortality. The GPS in in fact an objective scoring tool that is based on the serum concentrations of C-reactive protein (CRP) and albumin and thus reflects the systemic inflammatory and nutritional status [19].

Similarly, a study in 2013 revealed a statistically poorer Disease-Free Survival (DFS) in patients with elevated CRP values, encompassing Ewing's sarcoma and chondrosarcoma, without specifying cutoff values or entity distinctions [20]. Additionally, patients with metastatic spread at diagnosis were excluded from that study. The calculated 5-year survival rates for elevated and reduced CRP levels were 57% and 79%, respectively. In contrast, in our study, we observed 5-year survival rates of 85% and 94% for elevated and reduced CRP levels, respectively [20]. Nonetheless, direct comparison is limited due to the inclusion of Ewing Sarcoma in the study by Nakamura et al.

Nemecek E. at all. were the only other study group we found in our literature research that analyzed the CRP levels in only Chondrosarcoma patients. They analyzed overall 33 patients in a time range of 38 years (from 1977 to 2015) and could demonstrate a decreased overall survival in patients with elevated CRP levels (HR 1.31; 95%CI 1.02-1.57; p = 0.031) [21].

Further investigations into the inflammatory system's role in carcinogenesis have utilized ratios. Recent studies examined the CRP–albumin ratio (CAR) [22], showing that higher CAR levels were associated with poor prognosis in Ewing's sarcoma. Additionally, Biswas et al. found that a high white blood cell (WBC) count predicted inferior Event-Free Survival (EFS) and local control rates in extraosseous Ewing's sarcomas [23].

In light of our findings, we affirm the role of pretreatment CRP values in predicting prognosis, local recurrence, and distant metastasis in Chondrosarcoma patients. Nonetheless, this study has limitations, primarily stemming from the rarity of the cancer subtype and the small size of the analyzed cohort. Though a confirmed R0 resection may mitigate bias in recurrence and metastasis, the loss of numerous patients during the 15-year follow-up period precluded a complete analysis of outcomes. If we summarize the data of our cohort until this point we can statistically say that patients

 doi:10.20944/preprints202405.1840.v1

who had an elevated pre-operative CRP-level had a bigger tumor (>pT2), a higher Grading (>G3) and a reduce live prognosis.

5. Conclusions

It is evident that assessing preoperative CRP levels in patients with Chondrosarcoma holds significant prognostic value. Consequently, adjusting the follow-up protocol for patients with preoperative CRP levels exceeding 0.5 mg/dL may be warranted for this high-risk cohort. However, further research, along with centralized data collection and analysis, is essential to establish the most accurate cutoff values for pretreatment CRP levels in predicting poor survival or distant metastasis.

Author Contributions: S. Consalvo: data curation, writing, original draft preparation and editing; H. Hinterwimmer: formal analysis, review and editing; M. Stephan: data curation; S. Breden: data curation; U.Lenze: review and editing; R.von Einsenhart-Rothe: supervision,review; C. Knebel:supervision,review, visualization.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Klinikum rechts der Isar,Technical University of Munich (N°48/20S) .

Informed Consent Statement: Not applicable.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author (S. Consalvo).The data are not publicly available due to restriction e.g., their containing information that could compromise the privacy of reseach participants.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

DOD: death of disease; AWD: alive with disease; NED: no evidence of disease; CRP: C-reactive protein; DFS: disease free survival; GPS : Glasgow Prognostic Score

References

1. Anfinsen, K. P., S. S. Devesa, F. Bray, R. Troisi, T. J. Jonasdottir, O. S. Bruland, and T. Grotmol. "Age-Period-Cohort Analysis of Primary Bone Cancer Incidence Rates in the United States (1976-2005)." *Cancer Epidemiol Biomarkers Prev* 20, no. 8 (2011): 1770-7.
2. Giuffrida, A. Y., J. E. Burgueno, L. G. Koniaris, J. C. Gutierrez, R. Duncan, and S. P. Scully. "Chondrosarcoma in the United States (1973 to 2003): An Analysis of 2890 Cases from the Seer Database." *J Bone Joint Surg Am* 91, no. 5 (2009): 1063-72.
3. Thorkildsen, J., I. Taksdal, B. Bjerkehagen, H. K. Haugland, T. Borge Johannesen, T. Viset, O. J. Norum, O. Bruland, and O. Zaikova. "Chondrosarcoma in Norway 1990-2013; an Epidemiological and Prognostic Observational Study of a Complete National Cohort." *Acta Oncol* 58, no. 3 (2019): 273-82.
4. van Praag Veroniek, V. M., A. J. Rueten-Budde, V. Ho, P. D. S. Dijkstra, Bone Study group, tumours Soft tissue, M. Fiocco, and M. A. J. van de Sande. "Incidence, Outcomes and Prognostic Factors during 25 Years of Treatment of Chondrosarcomas." *Surg Oncol* 27, no. 3 (2018): 402-08.
5. Damron, T. A., W. G. Ward, and A. Stewart. "Osteosarcoma, Chondrosarcoma, and Ewing's Sarcoma: National Cancer Data Base Report." *Clin Orthop Relat Res* 459 (2007): 40-7.
6. Allin, K. H., B. G. Nordestgaard, H. Flyger, and S. E. Bojesen. "Elevated Pre-Treatment Levels of Plasma C-Reactive Protein Are Associated with Poor Prognosis after Breast Cancer: A Cohort Study." *Breast Cancer Res* 13, no. 3 (2011): R55.
7. O'Brian, D., M. Prunty, A. Hill, and J. Shoag. "The Role of C-Reactive Protein in Kidney, Bladder, and Prostate Cancers." *Front Immunol* 12 (2021): 721989.
8. Consalvo, S., F. Hinterwimmer, N. Harrasser, U. Lenze, G. Matziolis, R. von Eisenhart-Rothe, and C. Knebel. "C-Reactive Protein Pretreatment-Level Evaluation for Ewing's Sarcoma Prognosis Assessment-a 15-Year Retrospective Single-Centre Study." *Cancers (Basel)* 14, no. 23 (2022).
9. Zhu, M., Z. Ma, X. Zhang, D. Hang, R. Yin, J. Feng, L. Xu, and H. Shen. "C-Reactive Protein and Cancer Risk: A Pan-Cancer Study of Prospective Cohort and Mendelian Randomization Analysis." *BMC Med* 20, no. 1 (2022): 301.

 doi:10.20944/preprints202405.1840.v1

10. Lapic, I., A. Padoan, D. Bozzato, and M. Plebani. "Erythrocyte Sedimentation Rate and C-Reactive Protein in Acute Inflammation." *Am J Clin Pathol* 153, no. 1 (2020): 14-29.
11. Oh, B. S., J. W. Jang, J. H. Kwon, C. R. You, K. W. Chung, C. S. Kay, H. S. Jung, and S. Lee. "Prognostic Value of C-Reactive Protein and Neutrophil-to-Lymphocyte Ratio in Patients with Hepatocellular Carcinoma." *BMC Cancer* 13 (2013): 78.
12. Park, D. S., D. Kim, K. E. Hwang, Y. R. Hwang, C. Park, C. H. Seol, K. H. Cho, B. R. Kim, S. H. Park, E. T. Jeong, and H. R. Kim. "Diagnostic Value and Prognostic Significance of Pleural C-Reactive Protein in Lung Cancer Patients with Malignant Pleural Effusions." *Yonsei Med J* 54, no. 2 (2013): 396-402.
13. Levinson, T., and A. Wasserman. "C-Reactive Protein Velocity (Crpv) as a New Biomarker for the Early Detection of Acute Infection/Inflammation." *Int J Mol Sci* 23, no. 15 (2022).
14. Schaefer, I. M., and A. Gronchi. "Who Pathology: Highlights of the 2020 Sarcoma Update." *Surg Oncol Clin N Am* 31, no. 3 (2022): 321-40.
15. Hart, P. C., I. M. Rajab, M. Alebraheem, and L. A. Potempa. "C-Reactive Protein and Cancer-Diagnostic and Therapeutic Insights." *Front Immunol* 11 (2020): 595835.
16. Funovics, P. T., G. Edelhauser, M. A. Funovics, C. Laux, D. Berzaczy, B. Kubista, R. I. Kotz, and M. Dominkus. "Pre-Operative Serum C-Reactive Protein as Independent Prognostic Factor for Survival but Not Infection in Patients with High-Grade Osteosarcoma." *Int Orthop* 35, no. 10 (2011): 1529-36.
17. Li, W., X. Luo, Z. Liu, Y. Chen, and Z. Li. "Prognostic Value of C-Reactive Protein Levels in Patients with Bone Neoplasms: A Meta-Analysis." *PLoS One* 13, no. 4 (2018): e0195769.
18. Aggerholm-Pedersen, N., K. Maretty-Kongstad, J. Keller, S. Baerentzen, and A. Safwat. "The Prognostic Value of Serum Biomarkers in Localized Bone Sarcoma." *Transl Oncol* 9, no. 4 (2016): 322-8.
19. McMillan, D. C. "The Systemic Inflammation-Based Glasgow Prognostic Score: A Decade of Experience in Patients with Cancer." *Cancer Treat Rev* 39, no. 5 (2013): 534-40.
20. Nakamura, T., R. J. Grimer, C. L. Gaston, M. Watanuki, A. Sudo, and L. Jeys. "The Prognostic Value of the Serum Level of C-Reactive Protein for the Survival of Patients with a Primary Sarcoma of Bone." *Bone Joint J* 95-B, no. 3 (2013): 411-8.
21. Nemecek, E., P. T. Funovics, G. M. Hobusch, S. Lang, M. Willegger, F. Sevelda, T. Brodowicz, C. Stihsen, R. Windhager, and J. Panotopoulos. "C-Reactive Protein: An Independent Predictor for Dedifferentiated Chondrosarcoma." *J Orthop Res* 36, no. 10 (2018): 2797-801.
22. Li, Y. J., X. Yang, W. B. Zhang, C. Yi, F. Wang, and P. Li. "Clinical Implications of Six Inflammatory Biomarkers as Prognostic Indicators in Ewing Sarcoma." *Cancer Manag Res* 9 (2017): 443-51.
23. Biswas, B., S. Rastogi, S. A. Khan, B. K. Mohanti, D. N. Sharma, M. C. Sharma, A. R. Mridha, and S. Bakhshi. "Outcomes and Prognostic Factors for Ewing-Family Tumors of the Extremities." *J Bone Joint Surg Am* 96, no. 10 (2014): 841-9.