Sarcopenia does not predict outcome in patients with CNS lymphoma undergoing systemic therapy

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Abstract. Low skeletal muscle mass as a proxy parameter for sarcopenia acts as a non-invasive imaging marker that is associated with poor prognosis in numerous types of cancer. The present study aimed to assess the influence of body composition parameters on overall survival (OS) and progression free survival (PFS) in patients diagnosed with primary central nervous system lymphoma (PCNSL). A total of 98 patients with PCNSL treated at University Hospital Magdeburg (Magdeburg, Germany) from 2013-2019 were retrospectively studied. Patients with a pre-treatment staging computed tomography (CT) scan that included the third lumbar vertebra were reviewed for analysis. Skeletal muscle area (SMA), skeletal muscle index (SMI), mean muscle density and skeletal muscle gauge (SMG) were measured on the CT scan prior to treatment. Parameters were associated with OS and PFS. Overall, 72 patients were included in the present study. Results of the present study demonstrated that the median OS was 10 months (range, 1-181 months), and 37 patients (51.4%) presented with sarcopenia. Moreover, the median OS was 7 months in the sarcopenic group and 32 months in the non-sarcopenic group. Results of the present study further illustrated that SMI, SMA, density and SMG did not exert a significant effect on OS. Notably, the median PFS was 2.5 months in the low SMI group and 10 months in the normal SMI group. Body composition parameters did not exert a significant effect on PFS. Overall, the results of the present study demonstrated that sarcopenia was not a risk factor for decreased OS or PFS in patients with PCNSL undergoing systemic treatment.

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Abbreviations: CR, complete response; LSMM, low skeletal muscle mass; OS, overall survival; PCNSL, primary central nervous system lymphoma; PFS, progression free survival; PMI, psoas muscle index; SMG, skeletal muscle gauge; SMI, low skeletal muscle index; TMT, temporal muscle thickness

Key words: primary central nervous system lymphoma, sarcopenia, overall survival, skeletal muscle index

Introduction

Primary central nervous system lymphoma (PCNSL) are highly aggressive extranodal non-Hodgkin's lymphoma affecting the brain, eyes, leptomeninges or spinal cord (1-3). PCNSL account for ~3% of diagnosed brain tumors (1). High incidence rates are exhibited in immunocompromised patients, particularly among those infected with human immunodeficiency virus (4,5). PCNSL often exhibits a high chemosensitivity and radiosensitivity; however, only ~50% of patients demonstrate long-term control (1,2). Despite recent advances in treatment options, 5-year survival rates remain low and treatment-associated neurotoxicity is common (2,6). Notably, prognosis, age and performance status have been identified as treatment-independent factors, and have been introduced into applied clinical scoring systems (7,8).

Low skeletal muscle mass (LSMM) as a proxy parameter for sarcopenia acts as a non-invasive imaging tool for the prediction of prognosis in numerous cancers, including gastric, pancreatic and colorectal cancer (9-12). By contrast with other tools used to measure sarcopenia, LSMM is assessed using routine imaging. Frequently applied methods include detection of the skeletal muscle index (SMI) and the psoas muscle index (PMI). In addition, muscle density on computed tomography (CT) scans indicates lipid content, which is indicative of muscle quality (13). The skeletal muscle gauge (SMG) integrates both the muscle index and muscle density, and is associated with outcomes in patients with cancer (14,15).

Sarcopenia is an independent predictor of survival in hematologic diseases (9). In Non-Hodgkin's lymphoma, cachectic patients exhibited a shorter progression free survival (PFS) and overall survival (OS) than non-cachectic patients (16). Camus *et al* (17) demonstrated that a cachexia score, including adipopenia and sarcopenia, predicted OS in patients with diffuse large B-cell lymphoma (17).

The relevance of sarcopenia in PCNSL remains unknown. Low temporal muscle thickness (TMT) measured using T1w-magnetic resonance imaging (MRI) was associated with a shorter OS (18). In another cohort, both low TMT or SMI predicted reduced PFS and OS scores (19).

The present study aimed to evaluate whether baseline body composition parameters, such as SMI, muscle density and muscle gauge [measured using third lumbar vertebra (L3) cross-sectional CT images] were associated with OS and PFS in patients diagnosed with PCNSL.

Materials and methods

Study population. A total of 98 patients with PCNSL treated at a primary care center in Germany from 2013-2019 were retrospectively studied. Patients with a pre-treatment staging CT scan that included the L3 region were reviewed for analysis. The inclusion criteria were as follows: Histologically proven diagnosis of PCNSL (1), available CT scan, including the psoas muscle on the L3 level prior to treatment, and available clinical data regarding PFS and OS. The exclusion criteria were as follows: Missing pretreatment CT images, strong motion artifacts in CT scans and missing clinical data.

Patient characteristics, such as age, height and weight were collected from the internal hospital files. Patients were followed-up for at least two years or until death. The present retrospective study was approved by the institutional review board. Informed patient consent was waived given the retrospective nature of the study (ethics approval no. 145/21; Ethics Committee, University of Magdeburg, Magdeburg, Germany).

Overall, 72 patients were included in the present study. A total of 37 patients were male and 35 were female. The median age was 68 years (range, 23-81 years), and median OS was 10 months (range, 1-181 months). Notably, 37 patients (51.4%) presented with sarcopenia. All patients were treated with high dose-methotrexate (MTX; 8 g/m). In 7 patients, additional whole brain radiotherapy was performed. OS was defined as survival within the observation period, and PFS was defined as the time frame until PCNSL growth occurred, determined using MRI.

Image analysis. All CT scans were obtained on a multidetector CT scanner (Siemens Somatom Definition AS+, Siemens Healthineers, Germany; Canon Aquilion Prime, Canon Medical Systems Corporation, Japan). Patients were placed in the supine position. The CT protocol was as follows: Acquisition slice thickness, 1 mm with 5 mm reconstructions; tube voltage, 120 kV; automatic tube current modulation; pitch factor, 1.2; collimation, 0.6 mm and 90 ml i.v. administration of contrast medium (300 ml/mg; Accupaque).

Staging CT scans were used prior to therapy initiation. All images were assessed in consensus by two experienced radiologists who were blinded to the clinical course of the patients. Measurements of cross-sectional muscle were obtained semi-automatically on axial images at the L3 level in the soft tissue window (window, 45-250 HU) using ImageJ software (Fig. 1; version, 1.48v; National Institutes of Health). The mean muscle density was calculated using this software. SMI was calculated by dividing the SMA by the height of the patient. Sarcopenia was defined as an SMI <52.4 cm^2/m^2 for males and <38.5 cm^2/m^2 for females (20). SMG was calculated by multiplying the muscle index and mean muscle density, as reported previously (18). SMG units are cm^2 x HU/m^2 but are reported as arbitrary units (AU) for simplicity.

Statistical analysis. SPSS (version, 25; IBM Corp.) was used for statistical analysis. Mean, standard deviation (SD), median and interquartile range (IQR) were calculated for continuous variables. Influence of LSMM on OS was assessed using the log-rank test and a Cox proportional hazards regression. Odds ratios are presented together with 95% confidence intervals (CI). Multivariate regression analysis was adjusted for age and sex. $P<0.05$ was considered to indicate a statistically significant difference.

Results

OS. Results of the present study demonstrated that median OS was 7 months for the sarcopenic group and 32 months for the non-sarcopenic group (Fig. 2, Table I). Median SMI was 45.39 cm^2/m^2 (SD, 7.54 cm^2/m^2) for survivors and 46.46 cm^2/m^2 (SD, 9.91 cm^2/m^2) for non-survivors. There was no significant influence of sarcopenia on the values for survivors and non-survivors (Table II). Results of the present study also demonstrated no major difference in survival using the log-rank test (P=0.15; Fig. 1), and no influence of sarcopenia was demonstrated in the univariate analysis (HR, 0.61; 95% CI, 0.31-1.21; P=0.16). There was no influence of SMA (HR, 0.999; 95% CI, 0.99-1.01; P=0.89) or SMG (HR, 1.00; 95% CI, 0.999-1.00; P=0.07). The univariate analysis of muscle density demonstrated an influence on OS (HR, 0.97; 95% CI, 0.94-0.997; P=0.03). However, when adjusted for age and sex, there was no effect on OS in the multivariate analysis. (HR, 0.98; 95% CI, 0.94-1.02; P=0.23). Moreover, there was no significant effect of SMI on OS (Table III).

PFS. Results of the present study also demonstrated that the median PFS was 2.5 months for the low SMI group, and 10 months for the normal SMI group (Fig. 2, Table I). There were no significant differences between survivors and non-survivors (Table II), and there was no significant difference in PFS between the sarcopenic and non-sarcopenic groups, demonstrated using a log-rank test (P=0.18). Results of the present study also demonstrated that sarcopenia did not exert a significant effect on PFS, demonstrated using the univariate analysis (HR, 0.65; 95% CI, 0.33-1.27; P=0.20). Notably, there was no significant effect of SMI on PFS (Table III).

Discussion

The present study investigated whether muscle-based body composition parameters measured using cross-sectional CT images act as prognostic factors for PFS or OS in patients diagnosed with PCNSL. The present study investigated numerous body composition parameters, such as SMI, muscle density and SMG. To the best of our knowledge, the present study is the largest study employing measurements of sarcopenia in PCNSL to date. However, results of the present study did not demonstrate a significant association between body composition measurement with PFS or OS.

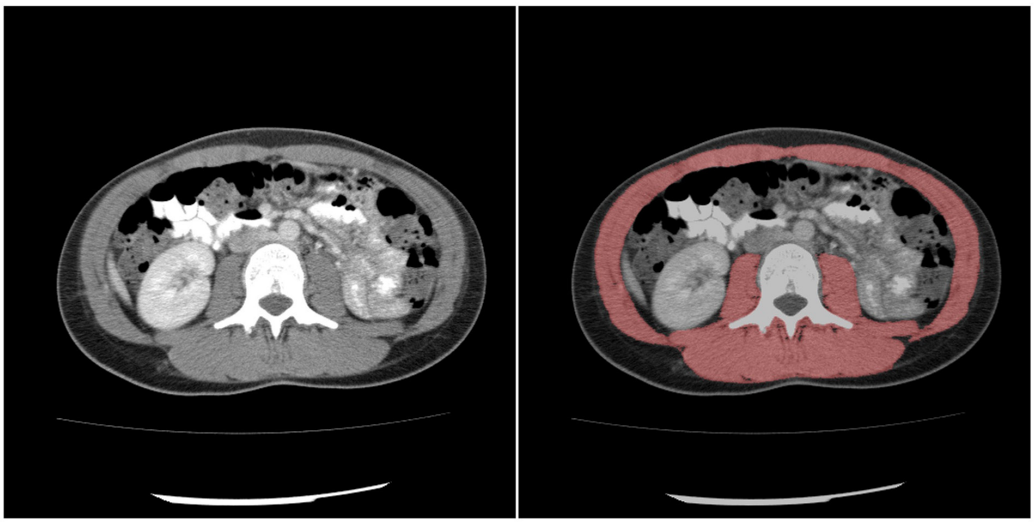

Figure 1. Example of cross-sectional muscle measurement at the L3 level. Area of skeletal muscle includes the psoas, paraspinal muscles (erector spinae, multifidus and quadratus lumborum) and abdominal wall muscles. Measured muscle areas are highlighted in red. L3, third lumbar vertebra. The patient had a skeletal muscle area of 112.1 cm^2, a skeletal muscle index of 35.8 cm^2/m^2, an average muscle density of 32 HU and an skeletal muscle gauge of 1,164.6 AU.

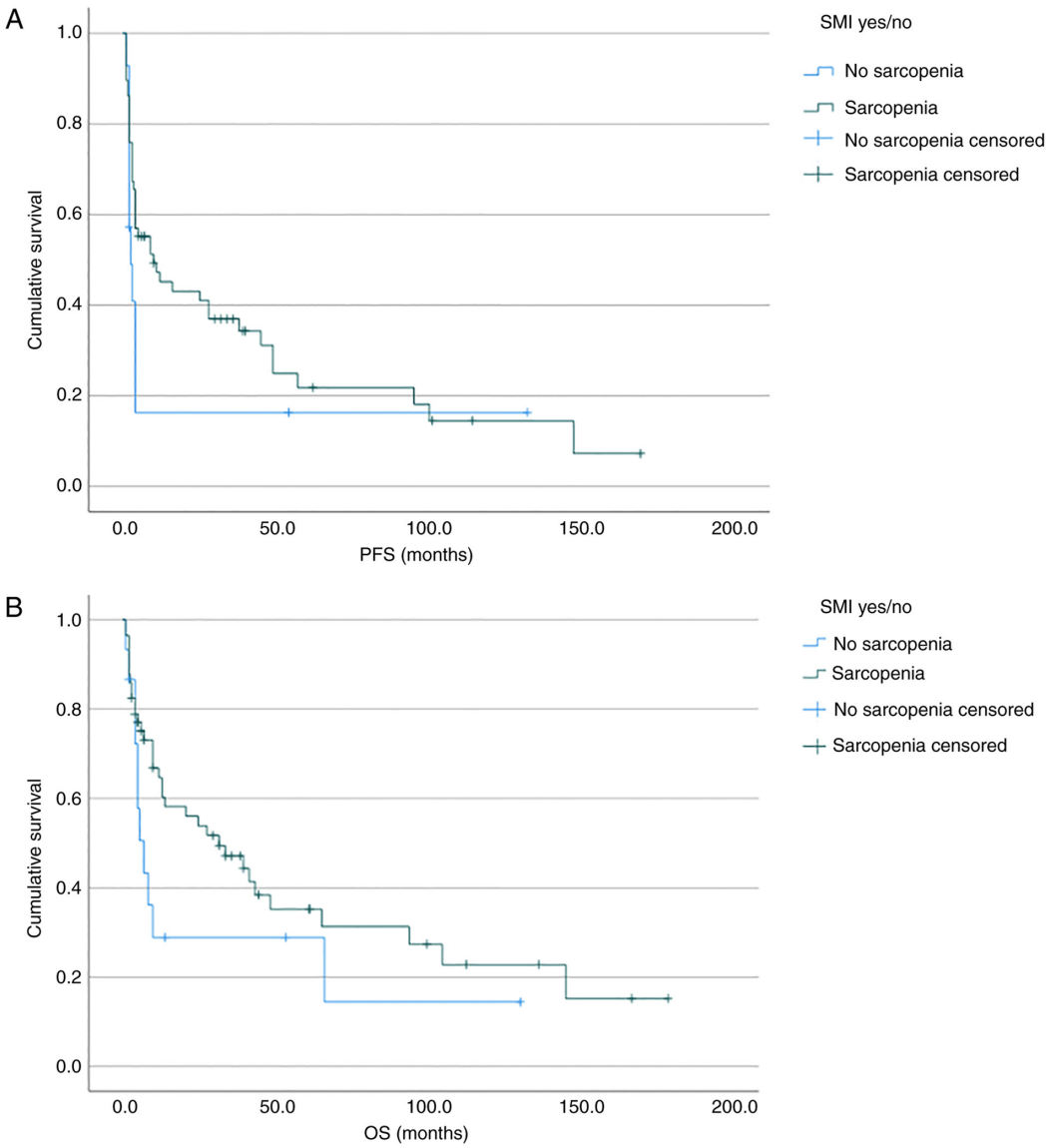

Figure 2. Kaplan-Meier curves for (A) PFS and (B) OS for patients with and without sarcopenia as measured by the SMI. There were no significant differences between groups (P=0.18 and P=0.15, respectively). PFS, progression free survival; OS, overall survival; SMI, skeletal muscle index.

Table I. PFS and OS for sarcopenic vs. non-sarcopenic patients.

Parameter	Low SMI	Normal SMI	P-value
PFS (months)	2.5	10	0.18
OS (months)	7	32	0.15

PFS, Progression free survival; OS, overall survival.

Table II. Measured values of body composition parameters for survivors and non-survivors.

A, Overall survival

Values	Survivors, M ± SD	Non-survivors, M ± SD	P-value
SMA (cm^2)	133.67±31.00	137.21±33.66	0.69
SMI (cm^2/m^2)	45.21±6.35	46.62±9.64	0.48
Muscle density (HU)	33.20±8.65	31.61±10.05	0.54
Muscle gauge (AU)	1,514.97±511.02	1,496.56±598.91	0.91

B, Progression free survival

Values	Survivors, M ± SD	Non-survivors, M ± SD	P-value
SMA (cm^2)	133.08±26.64	135.03±34.87	0.79
SMI (cm^2/m^2)	45.39±7.54	46.46±9.91	0.60
Muscle density (HU)	33.01±10.92	31.23±9.15	0.46
Muscle gauge (AU)	1,535.99±611.31	1,471.13±565.11	0.65

M ± SD, mean ± standard deviation; SMA, skeletal muscle area; SMI, skeletal muscle index.

While clinical parameters alone may not suffice to stratify patients according to prognosis and treatment-associated risks, non-invasive objective imaging markers may be an important additive tool. Notably, the results of previous studies are contradictory in detailing sarcopenia and clinical outcomes in hematologic diseases. Results of a previous meta-analysis demonstrated that sarcopenia is an independent predictor of OS in patients with diffuse large b-cell lymphoma (DLBCL) after chemotherapy (9). Clinical outcomes, such as complications and hospital stay, were negatively affected by sarcopenia in patients with lymphoma after autologous transplant (21). Chu *et al* (22) indicated that skeletal muscle density was associated with complete response and improved OS in elderly patients (22).

However, Takeoka *et al* (23) did not find an association between sarcopenia, measured using SMI, and OS in patients with multiple myeloma (23). Moreover, results of the aforementioned meta-analysis demonstrated that sarcopenia was not associated with OS in the leukemia subgroup (9). Neto *et al* (24) did not highlight any effects of sarcopenia on mortality and toxicity in patients with lymphoma undergoing autologous hematopoietic stem cell transplantation (24). Results of a multicenter study by Zilioli *et al* (25) suggested that there was no significant association between sarcopenia and either PFS or OS in patients with Hodgkin's lymphoma (25). Sarcopenia was also not associated with mortality in patients with hematopoetic malignancies in a subgroup analysis carried out by Au *et al* (26). In addition, Besutti *et al* (27) demonstrated that decreased levels of muscle density at the L3 level, but not SMI, were associated with OS in patients with diffuse large B-cell lymphoma (27).

Limited research into the potential influence of body composition parameters on PCNSL in clinical practice is available at present. Furtner *et al* (18) assessed the relevance of TMT as a proxy of sarcopenia for OS, and the results demonstrated that low levels of TMT were associated with shorter OS (HR 2.504; 95% CI, 1.608-3.911; P<0.001) (18). Leone *et al* (19) defined sarcopenia as either low L3-SMI or low TMT, demonstrating an association with both lower PFS (HR, 4.40; 95% CI, 1.66-11.61; P=0.003 and HR, 4.40; 95% CI, 1.68-11.49; P=0.003, respectively) and shorter OS (HR, 3.16; 95% CI, 1.09-9.11; P=0.034 and HR, 4.93; 95% CI, 1.78-13.65; P=0.002, respectively) (19). By contrast, results of the present study did not demonstrate a significant association with either OS or PFS in the present cohort. Compared with other datasets, differences in patient characteristics in the present cohort may account for the disparate results. Patients included in the present study exhibited an increased age. For example, the median age in the present study was 67.5 years, compared with 61 years in the study carried out by Leone *et al* and 62.7 years in the study carried out by Furtner *et al* (18,19). Moreover, 35/73 (48.0%) of the patients involved in the present study were sarcopenic (determined by SMI), while only 30.2% patients in the cohort presented by Leone *et al* (19) demonstrated an SMI below the threshold. In the cohort presented by Furtner *et al*, only 39.3% patients were sarcopenic as defined by TMT (18). In the present study, the OS time of 10 months was lower than the OS time of 31.9 months discussed by Furtner *et al* (18). In addition, 63.9% patients in the present study died during the observation period, compared with a 57% survival rate in the study carried out by Leone *et al* (19).

Notably, OS time in the present cohort may be too short to account for influences of sarcopenia on either clinical outcome. Hacker *et al* studied patients with gastric and gastroesophageal junction cancer, and reported that in cohorts with aggressive tumor characteristics and short survival times, the effect of sarcopenia may not lead to relevant differences in OS (28). In tumor entities or cohorts with an improved overall prognosis, differences in body composition may translate into relevant differences in outcome. The present cohort therefore does not prove that there is no influence of sarcopenia in PCNSL on either clinical parameter. However, within tumor entities, there will be patient groups that will not significantly profit from physical exercise in terms of prolonged survival time. Beyond survival parameters, sarcopenia may exert an influence on variables not measured in the present study, such as quality of life or other functional parameters (29).

The present study exhibits numerous limitations. This was a single center analysis with a retrospective design and a relatively small sample size. Further prospective studies on the relationship between sarcopenia and post-operative survival

Table III. Regression results for progression free survival and overall survival.

	Univariate			Multivariate		
Parameters	HR	CI 95%	P-value	HR	CI 95%	P-value
Low vs. high SMI	0.61	(0.31, 1.21)	0.16			
SMA	0.999	(0.99, 1.01)	0.89			
SMI	0.997	(0.96, 1.03)	0.85			
Muscle density	0.97	(0.94, 0.997)	0.03	0.98	(0.94, 1.02)	0.23
Muscle gauge	1.00	(0.999, 1.00)	0.07			

HR, hazard ratio; CI, confidence intervals.

are required to verify the results obtained. Moreover, the association between LSMM and patient survival remained the key focus, and further clinical parameters were not considered. For example, well-established clinical parameters that influence survival, such as involvement of deep brain structures, were not analyzed (30,31). Moreover, parameters for age and sex were adjusted for in the multivariate analysis, as age has previously been shown to exert an effect. Patients were excluded from the present study due to missing staging CT scans or missing clinical data, potentially leading to selection bias. Notably, muscle indices were not associated with comorbidities.

In this work SMI was used as a measure of LSMM and only the cut-off values determined by Prado *et al* were used (20). The effects of other measurements of LSMM, such as PMI, or other cut-off values, were not evaluated. In our view, the cut-off values presented by Prado *et al* (20). are more practicable when compared to those by Martin *et al* (32). The definitions by Prado have been adopted in the international definition of sarcopenia (33). We preferred not to use Martin's definitions because the cut-off values are discontinuous, leading to diagnostic inaccuracies (34). As the SMI has already been normalized by body height, we do not deem an additional BMI cut-off necessary. Other cut-off values, for example those based on the psoas muscle area or psoas muscle index, are not as well validated in oncologic patients (35). We therefore chose not to apply them. Similarly, muscle measurements on other levels are not well substantiated. A combination of imaging and clinical tests might provide a more accurate measurement of low skeletal muscle mass. However, every clinical test carries with it the downside of subjectivity, in that they are dependent on patients' answers or the examiner. The advantage of imaging tests are their reproducibility and reliability in a routine clinical setting.

SMI does not measure sarcopenia, but low skeletal muscle mass. It is regarded as a proxy parameter for sarcopenia. Yet sarcopenia is a complex syndrome, including low muscle strength, low muscle quality and quantity and low muscle performance. Imaging parameters can account for muscle quantity and to a lesser extent for quality. These do not capture the entire syndrome. Further studies are warranted to see whether a combination of parameters might be better suited to identify patients at risk. However, we deem LSMM as measured on routine imaging a rapid and useful marker to screen for sarcopenia and potentially initiate adequate treatment.

In conclusion, results of the present study did not demonstrate a significant association between sarcopenia and clinical outcomes in patients with PCNSL. However, further studies are required to determine whether sarcopenia exerts an influence in other patient subgroups, after receiving certain treatments or when other measurements of body composition are applied.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

VF, MT, JO, ASu performed the study conception and design, data acquisition, data interpretation, drafting and revision of manuscript. MP performed data interpretation and analysis and revision. AW and ASt performed data acquisition, data interpretation, data analysis and revision. MH, DW, DM and VZ performed data acquisition and revision. ASu and DW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present retrospective study was approved by the institutional review board. Informed patient consent was waived given the retrospective nature of the study (approval no. 145/21; Ethics Committee, University of Magdeburg, Magdeburg, Germany).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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