



Prognostic nutritional index as a prognostic marker in glioblastoma: Data from a cohort of 282 Italian patients



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ABSTRACT

Preoperative prognostic nutritional index (PNI) is linked to the clinical outcome of patients with malignant tumours, however few studies have investigated its utility in predicting outcome in glioblastoma multiforme (GBM).

We performed a retrospective study on adult patients with GBM in order to evaluate the impact of PNI on overall survival (OS), after adjusting for known prognostic factor (age, extent of surgery, Karnofsky performance status, radiochemotherapy).

This is an Italian, multicentre, retrospective, cohort study. The patient's cohort includes 282 individuals with a newly diagnosed GBM followed in 3 Lombardia Hospitals. In all cases the diagnosis was supported by histological data.

Patient's information including sex, age at onset, Karnofsky performance status (KPS), extension of surgical resection (EOR), adjuvant treatment, antiepileptic treatment, serum variables and survival data were collected.

Univariate and multivariate analysis did not reveal an association between PNI and overall survival in our series of GBM patients.

PNI is a controversial marker for prognosis in GBM patients and further prospective studies are necessary to elucidate its role.

1. Introduction

Glioblastoma multiforme (GBM), the most common malignant primary brain tumor, has a dismal prognosis even with the best available treatment. The standard of care, consisting of maximum tumor resection followed by radio-chemotherapy with temozolomide (TMZ), leads to a median survival of 14.6 months [1,2]. However survival varies significantly, even among patients who receive the same treatment, suggesting that potential prognostic factors may influence overall survival (OS). Identification of potential prognostic serum biomarkers easy to perform could help in patients stratification and designing treatment strategies.

The importance of preoperative nutritional status as a prognostic marker has been investigated in various malignant tumours [3,4], however only few studies evaluated the association between nutritional

status and OS in GBM patients. A relationship between serum albumin and survival has been reported in some series of GBM patients [5–7]. More recently the prognostic nutritional index (PNI), an index that reflects the nutritional and immune status of patients with cancer, was reported as an independent predictor of survival and efficacy of adjuvant treatment in a retrospective study of 84 GBM patients [8]. Similar data were reported in a retrospective study of 188 patients with high-grade glioma including 97 GBM patients [9] and in another analysis involving 166 GBM patients [10]. All of these studies were performed in Asian patients.

In the present study we retrospectively analyzed 282 adult patients with GBM followed in 3 Lombardia Hospitals in order to evaluate the association between PNI and OS.

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2. Materials and methods

This is an Italian, multicentre, retrospective, cohort study. The patient's cohort includes 282 individuals with a newly diagnosed GBM followed in 3 Lombardia Hospitals (Lecco, Niguarda, C. Besta); patients in Lecco were enrolled between 2004 and 2014, while patients from the other hospitals were enrolled from 2007 to 2014.

In all cases the diagnosis was supported by histological data. Patient's information including sex, age at onset, Karnofsky performance status (KPS), extension of surgical resection (EOR), adjuvant treatment, antiepileptic treatment, serum variables and survival data were collected.

Major presenting symptoms were categorized as seizure, focal deficits, cognitive-behavioral symptoms, intracranial hypertension. EOR was categorized in macroscopically total resection (MTR), partial resection (PR), stereotactic biopsy (SB) as declared by the neurosurgeon and evaluated by neuroimaging 72 h post surgery.

Regarding adjuvant treatment strategies we recorded if the patient received no further treatment other than surgery, radiotherapy only, chemotherapy only, radiochemotherapy.

Biochemistry data included serum albumin, total protein levels and total lymphocyte count. PNI was calculated with the following formula: $10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$ using haematological values detected preoperatively.

Patients with infectious or chronic disease or receiving steroid treatment that influenced the status of albumin and lymphocyte counts or OS were excluded. Survival data were obtained from the death record registry of Lecco and Milan Province.

3. Statistical methods

The study endpoint was Overall Survival (OS) defined as the time from the date of surgery to the date of death. Patients alive at the last contact were right-censored. Survival functions were non-parametrically estimated using the Kaplan–Meier estimator and statistically compared using the log-rank test. Median and interquartile (IQR) range follow-up was estimated using the reverse Kaplan–Meier estimator. Cox model was used to detect and estimate statistical association between PNI and OS. In multivariable regression models predictor variables were identified a priori (age, Karnofsky PS and extent of surgery). A random-effects meta-analysis model was used to estimate an average effect size. The DerSimonian and Laird method was used to estimate the between-subgroups variance. Q and I² statistics were used respectively to detect and estimate heterogeneity. A model free approach called classification and regression trees (CART) was used to identify the best PNI threshold. CART algorithm is a non parametric statistical method. The decision tree built by CART algorithm is always a binary decision tree (i.e. each node will have only two child nodes). The best split chosen by the CART algorithm maximizes the Gini index, a statistical index whose maximum value is reached when prognosis of splitted groups is highly heterogeneous. The regression tree was generated through the R rpart package (Terry Therneau, Beth Atkinson and Brian Ripley (2015). rpart: Recursive Partitioning and Regression Trees. R package version 4.1–10. <https://CRAN.R-project.org/package=rpart>). Patients and treatment characteristics were summarized using non-parametric descriptive statistics (median and range for continuous variables, and absolute and percentage frequencies for categorical variables). Statistical analysis was generated using SAS/STAT software, version 9.4 of the SAS System for Windows. (SAS Institute, Cary NC). Copyright (c) 2002–2012 by SAS Institute Inc., Cary, NC, USA.

4. Results

4.1. Patients characteristic

A total of 282 patients (178 males and 104 females) were included

in this study. At the time of analysis (median follow-up of 3.3 years, IQR: 1.57–6.18 months) 54 patients were still alive and the remaining 228 had died. Median age at onset was 66.4 years (range 28–83). Duration of symptoms before glioblastoma diagnosis ranged from a few days to a maximum of 3 months. Median KPS value was 80 (range 30–100). 56% of patients had a KPS score higher than or equal to 70, indicating satisfactory performance in the activities of daily living. The extent of surgical resection was macroscopically total in 197/282 (70.2%) of cases and partial in 52/282 (18.5%). A biopsy was performed in 11.4% (32/282) of patients. Two hundred and two patients (71.6%) received radiochemotherapy according to the Stupp-protocol, 31 patients (11%) received radiotherapy only, 49 patients (17.4%) received no further treatment other than surgery. Major presenting symptoms, isolated or in combination, included focal deficits (136/282 = 48%), cognitive-behavioral symptoms (89/282 = 31.5%), symptoms related to intracranial hypertension (86/282 = 30%) and seizure (65/282 = 23%). At the time of diagnosis 45 tumours were plurilobar, 7 multifocal, 6 centrally located (basal ganglia and corpus callosum) and the remaining 224 were lobar-located tumours. A total of 233 patients received a prophylactic antiepileptic treatment at the moment of diagnosis. The most common drug used was levetiracetam (120/233 = 51.5%), followed by oxcarbazepine/carbamazepine (44/233 = 18.9%), valproate (20/233 = 8.6%), phenobarbital (39/233 = 16.7%) and phenytoin (10/233 = 4.3%). In total 140 patients (49.6%) received a NEIAED (i.e. either levetiracetam or valproate), whereas 93 patients (33.0%) received a EIAED (phenobarbital, phenytoin, oxcarbazepine/carbamazepine) and 49 patients (17.4%) did not receive AED. No information was collected about marital status and socioeconomic status.

4.2. Overall and subgroup analysis

Considering serum albumin and lymphocyte count as continuous variables, we did not find statistical association neither between albumin levels and OS (HR (95%CI): 0.89 (0.65–1.20) $p = .44$), nor between lymphocyte count and OS (HR (95%CI): 0.99 (0.84–1.15) $p = .85$). The median PNI was 46.9 (range 26.2–72.5). PNI was not statistically associated to OS (HR 0.90 (0.73–1.11) for each 10 units, $p = .32$). In order to describe in absolute terms patients prognosis, PNI was dichotomized. There were 166 patients (58.8%) with a PNI > 45.9 (PNI-high) and 116 patients (41.1%) with a PNI < 45.9 (PNI-low). Baseline clinical features were similar in patients with PNI-high as compared with those with PNI-low, except for a trend of older age at onset and a lower proportion of patients undergoing MTR in the subgroup with PNI-low (Table 1). Median OS was 13 months (95% CI: 6.24–22.97) in patients with PNI-high versus 11.3 (95%CI: 5.1–19.81) in patients with PNI-low (HR (95%CI): 0.79 (0.61–1.03)) (Fig. 1). Based on post-surgical treatment, no association between PNI and OS was confirmed (Fig. 2).

In order to assess whether PNI values were differently distributed in our cohort according to sex, KPS score and age we also performed a statistical analysis by Fisher's exact test; there were no significant differences in PNI values above or below the cut-off in male versus female ($p = .39$), nor in patients with KPS < 70 versus KPS > 70 ($p = .63$); a non significant trend was observed for a slightly higher frequency of patients with PNI values above the cut-off in those younger than sixty versus those older than 60 ($p = .14$).

5. Discussion

Identification of prognostic factors is clinically relevant in the management of GBM patients. Several factors including age, Karnofsky performance status, extent of surgery and molecular biomarkers have a well-documented prognostic impact, however most of them are physical or defined post-operatively. Thus, it would be of great value to define pre-treatment prognostic factors able to help in predicting

Table 1
Patients characteristic.

	Overall	PNI ^a -high (≥ 45.9)	PNI ^a -low (< 45.9)
Total number	282	166/282	116/282
Female, N(%)	104(36.9)	65 (39.2)	39 (33.6)
Male, N(%)	178(63.1)	101 (60.8)	77 (66.4)
Age (at diagnosis)			
N	282	166	116
Median	66.4	63.7	70.2
Min	28.5	28.5	31.1
Max	83.3	83.3	82.5
Karnofski performance status			
N	282	166	116
Median	80	80	80
Min	30	30	30
Max	100	100	100
Extent of surgery			
Biopsy, N(%)	32(11.4)	25 (15.1)	7 (6.0)
MTR, N(%)	198 (70.2)	123 (74.1)	75 (64.7)
Partial, N(%)	27 (9.6)	10 (6.0)	17 (14.7)
Subtotal, N(%)	25 (8.9)	8 (4.8)	17 (14.7)
Adjuvant treatment			
Stupp protocol, N(%)	202(71.6)	123(74.1)	79(68.1)
Radiotherapy, N(%)	31 (11.0)	19(11.4)	12(10.3)
No other treatment, N(%)	49 (17.4)	24(14.5)	25(21.6)
Antiepileptic therapy			
EIAED ^b , N(%)	93(33.0)	63(38.0)	30(25.9)
NEIAED ^c , N(%)	140(49.6)	77(46.4)	63(54.3)
NO, N(%)	49(17.4)	26(15.7)	23(19.8)

^a PNI prognostic nutritional index.

^b EIAED enzyme inducing antiepileptic drug.

^c NEIAED non-enzyme inducing antiepileptic drug.

survival and guiding optimal therapeutic choice. In this context, potential serum prognostic factors are important because of their accessibility, low cost and convenience.

A number of prognostic indexes combining different parameters relevant in nutritional status and efficient immune response have been proposed, both in the healthy population and in elderly/frail patients or patients suffering from cancer; among these the PINI index, initially

devised to assess elderly hospitalized patients [11] and then also applied to patients with malignancy (multiple myeloma) [12] includes quantitation of four serum proteins (CRP, orosomucoid, albumin and transthyretin) and is widely adopted in intensive care units. In our work we could not analyze this index due to lack of quantitation of orosomucoid and transthyretin in our patients.

The prognostic nutritional index (PNI) was originally used to assess the nutritional and immunological status of patients undergoing gastrointestinal surgery [13]. The PNI can be easily calculated based on total lymphocyte count and serum albumin levels. Lymphocytes are involved in the host's cellular adaptive immunity, with antitumor effects secondary to the inhibition of cancer cell proliferation, invasion and migration [14]. Lymphocyte count is a measure of cell-mediated immunity, which is critical in host defense against cancer. The other parameter of PNI is albumin that is an indicator of the host's inflammatory response and nutritional status [15]. Therefore a lower PNI reflects a decrease of lymphocytes and/or albumin and is suggestive for impaired immunological response and/or poor nutritional status with a pro-inflammatory metabolic shift in the individuals impairing anti-tumor response and treatment compliance. Several studies have demonstrated that PNI may be a powerful predictor of outcomes in different malignancies, including breast, hepatocellular and lung cancer [16–20]. More recently the role of PNI has been investigated in some retrospective series of GBM patients. Zhou et al. [8] in a series of 84 GBM patients reported that a PNI > 44.4 was an independent prognostic factor for favorable outcome (HR:0.479, 95% CI:0.235–0.975, *p* = .042), moreover patients with PNI > 44.4 had better response to adjuvant treatment than patients with PNI < 44.4 (HR: 0.259, 95 CI: 0.096–0.700).

Another study on 188 patients with high grade gliomas, including 97 GBM patients [9], showed that PNI was an independent predictor for progression free survival (PFS) (HR = 0.62, 95% CI 0.43–0.87, *p* = .007) and OS (HR = 0.56, 95% CI 0.38–0.80, *p* = .002). On the subgroup analysis by tumor grade and treatment modalities, both PFS and OS were better for patients with high PNI (> 52.5).

Finally Xu et al. [10] reported PNI as an independent predictor of OS (HR 0.757, 95% CI 0.378–0.985, *p* = .039) in a series of 166 GBM patients, in particular for patients receiving adjuvant therapy low PNI value was significantly associated with shorter OS, so these patients

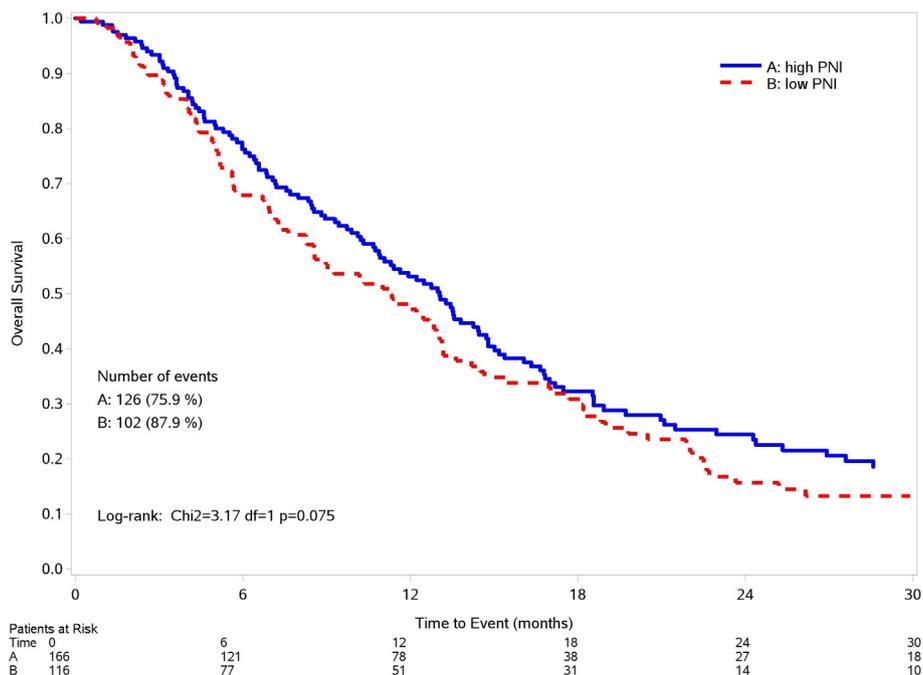


Fig. 1. Kaplan–Meier curves of OS in patients with PNI-high (A) vs patients with PNI-low (B).

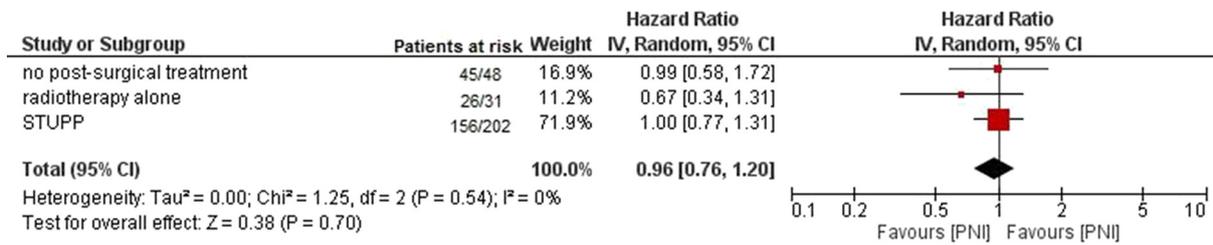


Fig. 2. Forest plot of the effect of PNI on OS according to the different adjuvant strategies.

Table 2
 Patient data in glioblastoma cohorts studied for PNI prognostic impact.

Author (ref)	Total number of GBM patients	PNI (cut off)	Sex	Age	Karnofski performance status (KPS)
Zhou et al. [8]	84	44.4	Male 59% Female 41%	> 60 years 36.9% < 60 years 63.1%	Not reported
He et al. [9]	98	52.55	Male ^a 61.7% Female ^a 38.3%	> 60 years 19% < 60 years 81%	91% KPS > 70 9% KPS < 70
Xu et al. [10]	166	48	Male 50.6% Female 49.4%	Median 50 years	55% KPS > 80 45% KPS < 70
Zheng et al. [25]	292	48.45	Male ^b 55.5% Female ^b 44.5%	Median 43 years	Not reported
Present study	282	45.9	Male 63.1% Female 36.9%	> 60 years 69.8% < 60 years 30.2%	56.7% KPS > 70 43.3% KPS < 70

^a On a total number of 188 high-grade-glioma.

^b On a total number of 750 glioma.

acquired less benefit from adjuvant therapy.

In our study we failed to confirm a statistically significant prognostic value of PNI in a large cohort of Italian GBM patients, although indeed we did observe a trend to more prolonged survival in those patients with higher PNI levels. The relationship between parameters related to nutritional status (especially BMI) and the occurrence/prognosis of various types of cancer is multi-faceted: concerning gliomas, a trend to increased occurrence has been reported by meta-analyses [21–24] for patients with increased BMI. It has to be noted that Asiatic populations contributed little, if at all, to meta-analysis studies on BMI and tumours. Also, the diagnostic value of PNI has recently been investigated in 750 patients with glioma as compared with other tumours (acoustic neuroma and meningioma) and healthy controls by Zheng and colleagues [25]; in this paper the authors detected statistically significantly lower PNI levels in glioma patients than healthy controls, while platelet/lymphocyte ratio was higher in glioma patients.

Conversely, a number of studies have shown that, once a diagnosis of high grade glioma occurs, a lower value of PNI is associated with a shorter survival; all these studies however have dealt with asiatic patients and no studies so far have investigated italian patients. The lack of a statistically significant impact of low PNI on survival in italian GBM patients may derive from a number of factors, among which obviously genetic differences may play a role; on the other hand, lack of statistical significance in our study is not likely to be due solely to relevant differences in the distribution of PNI values in our patients as compared to asiatic patients.

As a matter of fact, the investigated GBM cohorts in the literature do differ in some features, as reported in Table 2.

Overall, patients in our cohort were older and less fit than most of those included in the previous studies; we may speculate that in older patients the negative prognostic impact of a low PNI might be overshadowed by the relevance of other factors with a negative prognostic value.

Finally in our study duration of symptoms prior to GBM diagnosis was very short, precluding a meaningful statistical analysis aimed at assessing a putative relationship between nutritional status and symptoms duration; nor were we able to correlate PNI levels with marital status and socioeconomic status; analysis of impact of performance

status and age excluded a major role for KPS and only showed a trend in older patients to have lower PNI levels, which did not reach statistical significance.

6. Conclusion

Our study presents some limits. First of all, the data derive from an unplanned retrospective analysis, secondly the sample size is small, finally we do not have adequate information regarding molecular biomarkers to control for these factors in multivariate analysis. Despite these limitations, our study is the second one with the most numerous sample of patients that investigated the prognostic role of the PNI for GBM. Theoretically the assessment of PNI could assist the identification of patients with poor prognosis and stratification of patients entering clinical trials. Moreover PNI could be easily monitored in cases of interventions aimed at correcting the nutritional and immune condition of patients in order to improve survival.

In conclusion PNI is a controversial marker for the survival of GBM patients deserving further investigation.

Declarations of interest

None.

References

- [1] R. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J. Taphoorn, K. Belanger, A.A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R.C. Janzer, S.K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J.G. Cairncross, E. Eisenhauer, R.O. Mirimanoff, Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, *N. Engl. J. Med.* 352 (10) (2005) 987–996.
- [2] R. Stupp, M.E. Hegi, W.P. Mason, M.J. van den Bent, M.J. Taphoorn, R.C. Janzer, S.K. Ludwin, A. Allgeier, B. Fisher, K. Belanger, P. Hau, A.A. Brandes, J. Gijtenbeek, C. Marosi, C.J. Vecht, K. Mokhtari, P. Wesseling, S. Villa, E. Eisenhauer, T. Gorlia, M. Weller, D. Lacombe, J.G. Cairncross, R.O. Mirimanoff, Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial, *Lancet Oncol.* 10 (5) (2009) 459–466.
- [3] I. Schwegler, A. von Holzen, J.P. Gutzwiller, et al., Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer, *Br. J. Surg.* 97 (2010) 92–97.
- [4] I. Ray-Coquard, C. Cropet, M. Van Glabbeke, C. Sebban, A. Le Cesne, I. Judson,

- O. Tredan, J. Verweij, P. Biron, I. Labidi, J.P. Guastalla, T. Bachelot, D. Perol, S. Chabaud, P.C. Hogendoorn, P. Cassier, A. Dufresne, J.Y. Blay, European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas, *Cancer Res.* 69 (13) (2009) 5383–5391.
- [5] J.A. Schwartzbaum, P. Lal, W. Evanoff, S. Mamrak, A. Yates, G.H. Barnett, J. Goodman, J.L. Fisher, Presurgical serum albumin levels predict survival time from glioblastoma multiforme, *J. Neuro-Oncol.* 43 (1) (1999) 35–41.
- [6] N. Borg, M.R. Guilfoyle, D.C. Greenberg, C. Watts, S. Thomson, Serum albumin and survival in glioblastoma multiforme, *J. Neuro-Oncol.* 105 (1) (2011) 77–81.
- [7] S. Han, Y. Huang, Z. Li, H. Hou, A. Wu, The prognostic role of preoperative serum albumin in glioblastoma patients, *BMC Cancer* 8 (15) (2015) 108.
- [8] X.W. Zhou, H. Dong, Y. Yang, J.W. Luo, X. Wang, Y.H. Liu, Q. Mao, Significance of the prognostic nutritional index in patients with glioblastoma: a retrospective study, *Clin. Neurol. Neurosurg.* 151 (2016) 86–91.
- [9] Z.Q. He, C. Ke, F. Al-Nahari, H. Duan, C.C. Guo, Y. Wang, X.H. Zhang, Y.S. Chen, Z.G. Liu, J. Wang, Z.P. Chen, X.B. Jiang, Y.G. Mou, Low preoperative prognostic nutritional index predicts poor survival in patients with newly diagnosed high-grade gliomas, *J. Neuro-Oncol.* 132 (2) (2017) 239–247.
- [10] W.Z. Xu, F. Li, Z.K. Xu, X. Chen, B. Sun, J.W. Cao, Y.G. Liu, Preoperative albumin-to-globulin ratio and prognostic nutrition index predict prognosis for glioblastoma, *Onco Targets Ther.* 10 (2017) 725–733.
- [11] M. Bonnefoy, L. Ayzac, Y. Ingenbleek, T. Kostka, R.C. Boisson, J. Bienvenu, Usefulness of the prognostic inflammatory and nutritional index (PINI) in hospitalized elderly patients, *Int. J. Vitam. Nutr. Res.* 68 (3) (1998) 189–195.
- [12] S. Dupire, M. Wemeau, H. Debarri, L. Pascal, B. Hivert, C. Willekens, E. Boyle, S. Manier, T. Béatrice, B. Onraed, J.L. Faucompré, B. Hennache, C. Dumontet, T. Facon, X. Leleu, Prognostic value of PINI index in patients with multiple myeloma, *Eur. J. Haematol.* 88 (4) (2012) 306–313.
- [13] T. Onodera, N. Goseki, G. Kosaki, Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients, *Nihon Geka Gakkai Zasshi* 85 (9) (1984) 1001–1005.
- [14] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, *Nature* 454 (7203) (2008) 436–444.
- [15] K. Sánchez-Lara, J.G. Turcott, E. Juárez, P. Guevara, C. Núñez-Valencia, L.F. Oñate-Ocaña, D. Flores, O. Arrieta, Association of nutrition parameters including bioelectrical impedance and systemic inflammatory response with quality of life and prognosis in patients with advanced non-small-cell lung cancer: a prospective study, *Nutr. Cancer* 64 (4) (2012) 526–534.
- [16] S. Hong, T. Zhou, W. Fang, C. Xue, Z. Hu, T. Qin, Y. Tang, Y. Chen, Y. Ma, Y. Yang, X. Hou, Y. Huang, H. Zhao, Y. Zhao, L. Zhang, The prognostic nutritional index (PNI) predicts overall survival of small-cell lung cancer patients, *Tumour Biol.* 36 (5) (2015) 3389–3397.
- [17] D.J. Pinato, B.V. North, R. Sharma, A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI), *Br. J. Cancer* 106 (8) (2012) 1439–1445.
- [18] Z. Yang, B. Zhang, L. Hou, Y. Xie, X. Cao, Pre-operative prognostic nutritional index predicts the outcomes for triple-negative breast cancer, *Tumour Biol.* 35 (12) (2014) 12165–12171.
- [19] J. Sheng, Y.P. Yang, Y.X. Ma, T. Qin, Z.H. Hu, S.D. Hong, T. Zhou, Y. Huang, H.Y. Zhao, L. Zhang, Low prognostic nutritional index correlates with worse survival in patients with advanced NSCLC following EGFR-TKIs, *PLoS One* 11 (1) (2016) e0147226.
- [20] Z.H. Yao, G.Y. Tian, Y.Y. Wan, Y.M. Kang, H.S. Guo, Q.H. Liu, D.J. Lin, Prognostic nutritional index predicts outcomes of malignant pleural mesothelioma, *J. Cancer Res. Clin. Oncol.* 139 (2013) 2117–2123.
- [21] D. Zhang, J. Chen, J. Wang, S. Gong, H. Jin, P. Sheng, X. Qi, L. Lv, Y. Dong, L. Hou, Body mass index and risk of brain tumors: a systematic review and dose-response meta-analysis, *Eur. J. Clin. Nutr.* 70 (7) (2016) 757–765.
- [22] T.N. Sergentanis, G. Tsivgoulis, C. Perlepe, I. Ntanasis-Stathopoulos, I.G. Tzanninis, I.N. Sergentanis, T. Psaltopoulou, Obesity and risk for brain/CNS tumors, gliomas and meningiomas: a meta-analysis, *PLoS One* 10 (9) (2015) e0136974.
- [23] M.K.H. Wiedmann, C. Brunborg, A. Di Ieva, K. Lindemann, T.B. Johannesen, L. Vatten, E. Helseth, J.A. Zwart, The impact of body mass index and height on the risk for glioblastoma and other glioma subgroups: a large prospective cohort study, *Neuro-Oncology* 19 (7) (2017) 976–985.
- [24] E.K. Choi, H.B. Park, K.H. Lee, J.H. Park, M. Eisenhut, H.J. van der Vliet, G. Kim, J.I. Shin, Body mass index and 20 specific cancers: re-analyses of dose-response meta-analyses of observational studies, *Ann. Oncol.* 29 (3) (2018) 749–775.
- [25] S.H. Zheng, J.L. Huang, M. Chen, B.L. Wang, Q.S. Ou, S.Y. Huang, Diagnostic value of preoperative inflammatory markers in patients with glioma: a multicenter cohort study, *J. Neurosurg.* 129 (3) (2018) 583–592.