

Systemic inflammation in malignant pleural mesothelioma: Is neutrophil-to-lymphocyte ratio a prognostic index?

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Abstract

Malignant Pleural Mesothelioma (MPM) is an aggressive, asbestos-related tumor that arises from the mesothelium. It is a neoplasm with an increasing incidence with a poor and a dismal prognosis. Inflammation plays a crucial role in the initiation and tumor progression. In addition, the history of MPM is characterized by symptoms referred to increased inflammatory responses such as fever, sweating and loss of weight. Recent studies have identified the neutrophil-to-lymphocyte ratio (NLR) as a feasible and simple marker of systemic inflammation. The Authors report a retrospective study in 54 patients with malignant pleural mesothelioma (MPM). MPM patients were more likely to be male (75.9% versus 24.1%) with a median age of 67 years. The epithelial histotype was predominant (77.8%) compared to the biphasic (11.1%), sarcomatous (9.5%) and desmoplastic (1.9%) ones. Neutrophil-to-Lymphocyte ratio (NLR) was assessed at diagnosis with a mean value of 4.31. The aim of the study was to test bivariate correlations between independent factors (age, sex, histology, NLR, lymphocyte count, lymph node involvement) and the overall survival of the population under investigation. The median overall survival (OS) in the general population included in the study was 13 months. Median Disease Free Interval (DFI) was 3 months. Patients with the epithelial histotype survived significantly longer than those presenting with sarcomatoid, biphasic or desmoplastic subtypes (15 months versus 2, 8 and 10 months respectively; $p < 0.001$). Patients with $NLR < 3$ showed a median overall survival of 22 months, while $3 < NLR < 5$ and $NLR > 5$ ones had a poorer survival rate (12 and 8 months respectively). There was evidenced of a strong correlation between patients with inflammation index less than three and overall survival ($p < 0.001$). The Neutrophil-to-Lymphocyte Ratio (NLR) can be an independent, easily reproducible and comparable prognostic index in patients with malignant pleural mesothelioma.

Abbreviations: MPM: Malignant Pleural Mesothelioma, NLR: Neutrophil to Lymphocyte Ratio, OS: Overall Survival, DFI: Disease Free Interval

Introduction

Malignant Pleural Mesothelioma (MPM) is an aggressive, asbestos-related tumor that arises from the mesothelium [1]. It is a neoplasm with an increasing incidence [2]. Although numerous therapeutic options in patients with malignant pleural mesothelioma have been taken, the disease presents a poor and dismal prognosis [3] with a survival rates average 9-12 months [4-8].

Numerous studies report evidences about factors associated with prolonged survival and their impact on the disease's evolution. These factors include demographic characteristics (eg. sex, age), analytes (absolute value of leukocytes, lymphocytes) and tumor characteristics (histology). In this regard, the European Organisation for Research and Treatment of Cancer (EORTC) and the Cancer and Leukemia Group B have drafted two prognostic indexes for patients with MPM [9-12]. Inflammation plays a crucial role in the initiation and tumor progression [13]. In addition, the history of MPM is characterized by symptoms referred to an increased inflammatory response such as fever, sweating and loss of weight [14-17]. As mentioned, the indices of inflammation may play a prognostic role in patients with malignant pleural mesothelioma. Recent studies have identified the neutrophil-to-lymphocyte ratio (NLR) as a feasible and simple marker of systemic inflammation [18-22]. However, available data are conflicting [23,24].

Patients and methods

Study and analysis

We report a retrospective study in patients with malignant pleural mesothelioma (MPM) conducted over the last decade (2004-2015). We proceeded to a descriptive and observational demographic study. In the second part of the analysis, survival rates were tested in the general population and in selected cohorts (NLR value, histology, lymph node involvement, therapeutic strategy). Finally, a bivariate analysis was carried out to identify positive independent prognostic factors in the population.

The analysis of survival and related ratios was performed by Kaplan and Meier's method, while in the bivariate analysis values of $p < 0.005$ were considered significant.

Patient characteristics

Data on 54 patients with MPM, admitted consecutively to our Institution from 2004 to 2015, were collected. MPM patients were

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more likely to be male (75.9% versus 24.1%) with a median age of 67 years [min. 46 – max. 85 (95% CI 62.6 – 68.12) (Table 1).

The epithelial histotype was predominant (77.8%) compared to the biphasic (11.1%), sarcomatous (9.5%) and desmoplastic (1.9%) ones (Figure 1).

Of 54 patients, 53.7% were current or ex smokers, whereas 46.3% had no history of smoking. In 31.5% cases, a direct asbestos exposure (e.g. work or home) was assessed, in 16.7% an indirect one and in 51.9% patients no risk factors were recognized.

In total, 35.2% of patients received neoadjuvant chemotherapy. On immunohistochemistry, calretinin expression was showed in 87% of patients (92.8% in epithelial, 66.6% in biphasic and 60% in sarcomatoid). All patients at diagnosis were staged according to the AJCC's staging system [25], with 59.3% having an early stage (I-II stage) and 40.7% an advanced stage disease (III-IV stage).

Neutrophil-to-Lymphocyte ratio (NLR) was assessed at diagnosis with a mean value of 4.31 [min. 0.9 - max. 16.5 (95% CI 3.46-5.16)]. Clustering this series, 44.4% of patients had a $NLR < 3$, 25.9% a $3 < NLR < 5$ and 29.6% a $NLR > 5$.

Epithelial
Biphasic
Sarcomatous
Desmoplastic

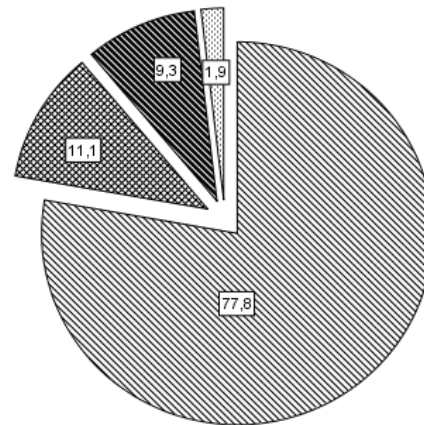


Figure 1. Malignant pleural mesothelioma histotypes.

Table 1. Patient characteristics with malignant pleural mesothelioma, 2004 -2015 (n=54).

	Number (value)	%
Demographic characteristics		
Sex		
Male	41	75.9
Female	13	24.1
Median age	67 (min. 46- max. 85)	
Smoking		
Current/ex smokers	29	53.7
No	25	46.3
Asbestos exposure		
Direct	17	31.5
Indirect	9	16.7
No	28	51.9
Clinical and pathological characteristics		
Calretinin expression		87
Epithelial	47	92.7
Biphasic		66.6
Sarcomatoid		60.0
NLR		
$NLR < 3$	24	44.4
$3 < NLR < 5$	14	25.9
$NLR > 5$	16	29.6
Histotype		
Epithelial	42	77.8
Biphasic	6	11.1
Sarcomatoid	5	9.5
Desmoplastic	1	1.9
Stage disease		
Early stage (IA-II)	32	59.3
Advanced stage (III-IV)	22	40.7
Treatment characteristics		
Neoadjuvant chemotherapy	19	35.2
Radical Surgery		
P/D	4	7.4
EPP	25	46.3
EPP+HITOC	5	7.4
Palliative surgery		
Pulmonary wedge resection/ lobectomy	2	3.8
Partial P/D	5	9.3
Pleural biopsies	18	33.3

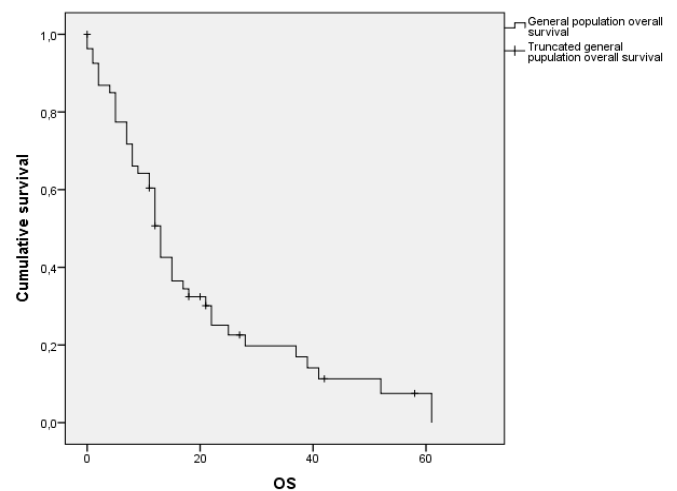


Figure 2. General population overall survival.

Radical surgery, in the form of extrapleural pneumonectomy, was undergone by 46.3% of the study population and, in 9.3% of them, a hyperthermic intrathoracic chemotherapy (HITOC) was offered. In 7.4%, a Waller's extended pleurectomy and decortication was conducted. Remanents were referred to palliative surgery such as pulmonary wedge resections, partial pleurectomy/decortication and pleural biopsies. 30-day mortality was 5.6%.

Results

The median overall survival (OS) in the general population included in the study was 13 months (95% CI 11.48-14.51) (Figure 2 and Table 2). Median Disease Free Interval (DFI) was 3 months. Clustering this data according to the AJCC's Pleural Mesothelioma staging system, stage IA patients showed a median OS of 49 months, whereas stage IV ones was only of 5 months (Table 3).

Patients with the epithelial histotype survived significantly longer than those presenting with sarcomatoid, biphasic or desmoplastic

Table 2. Malignant pleural mesothelioma: Overall survival and disease free survival.

Population median overall survival (OS)	13 months (95% CI 11.48-14.51)
Population median Disease Free Interval (DFI)	3 months (95% CI 0-9.64)

Table 3. Malignant Pleural Mesothelioma: bivariate analysis and correlations.

	Median (OS)	95% Confidence Interval	P
Disease Characteristics			
Stage			
IA	49.00	21.84-76.16	
IB	28.00	8.43-47.57	
II	13.00	11.89-14.11	
III	7.00	4.48-9.52	
IV	5.00	0.00-13.58	
Histotype			
Epithelial	15.00	12.05-17.95	0.001
Sarcomatoid	2.00	1.12-2.81	
Biphasic	8.00	0.00-16.47	
Desmoplastic	10.00		
Lymph Node			
N+	12.00	8.25-15.74	
N0	21.00	14.83-28.94	0,005
Clinical Characteristics			
Neutrophil-to-Lymphocite Ratio (NLR)			
NLR < 3	22.00	16.54-27.45	0.001
NLR < 5	16.00	12.42-19.44	0.005
NLR > 5	8.00	6.35-9.52	
Treatment strategy			
Radical surgery			
Extrapleural pneumonectomy, total pleurectomy/decortication	22.50	15.55-29.53	
Palliative surgery			
Partial pleurectomy/decortication, pulmonary wedge resections/lobectomy, Pleural biopsy	11.00	11.48-14.51	
EPP vs. P/D			
EPP	13.00	9.77-16.22	0.090
P/D	11.00	8.00-13.27	
EPP vs. EPP+HITOC			
EPP	13.00	9.77-16.22	
EPP+HITOC	19.60	11.51-27.69	

same result, although with lesser statistical significance, among patients with NLR<5 and survival (p<0.005). Therefore, it can be argued the absolute ratio between neutrophil and lymphocytes may be considered an independent prognostic index in patients with malignant pleural mesothelioma. By dividing the population according to the surgical therapeutic strategy (e.g. radical and palliative surgery), in the first group (extrapleural pneumonectomy, total pleurectomy/decortication) it was noted a median survival of 22.5 months (95% CI 15.55-29.53), as opposed to the group that underwent palliative surgery, due to the extension of the disease and/or poor performance status, where a median survival of 11 months (95% CI 11.48-14.51) was assessed.

Patients who undergone to extrapleural pneumonectomy (EPP) had a median overall survival of 13 months compared to that of pleurectomy/decortication alone (11 months). No statistical differences were noted between this two procedures (p=0.09), although EPP present higher perioperative morbidity rates than pleurectomy (21.8% vs. 9.3%). Finally, we evaluated the role of the intraoperative intrathoracic chemotherapy (HITOC) in patients amenable to radical surgery. Median survival rates in patients undergoing EPP and

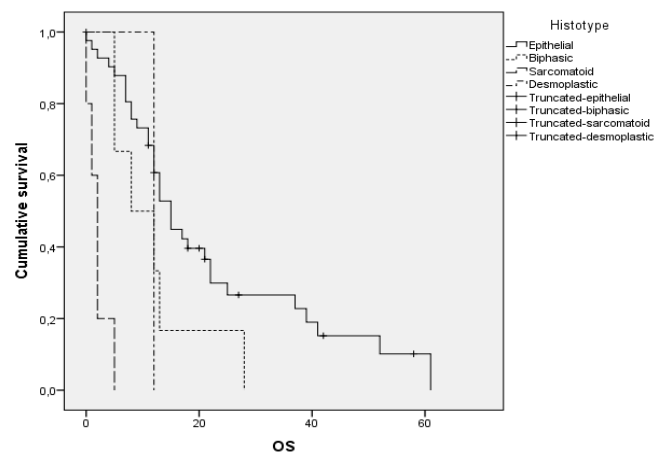


Figure 3. Overall survival according to histological pattern.

subtypes (15 months versus 2, 8 and 10 months respectively; p<0.001) (Figure 3). The presence of an intrathoracic lymph node involvement (hilar or mediastinal) is a decisive staging parameter. Infact, N+ disease (N1, N2 or N3) correlated with a median survival of 12 months (95% CI 8.25 to 15.74), while N0 one with a median of 21 months (95% CI 14.83 to 28.94). Neutrophil-to-Lymphocyte Ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Although recent reports [26-28] in the Literature indicate that a NLR more than 5 can be considered high, Authors decided to review this cut-off bringing it to a nominal value of 3 in order to understaging them and to evaluate any difference from NLR<3 patients and NLR<5 patients in terms of survival. According to this procedure, general population was clustered.

Patients with NLR<3 showed a median overall survival of 22 months (95% CI 16.54-27.45), while 3<NLR<5 and NLR>5 ones had a poorer survival rate (12 and 8 months respectively) (Figure 4). In a bivariate analysis between these groups according to survival rates, a strong correlation between patients with inflammation index less than three and overall survival was evidenced (p<0.001). It was noted the

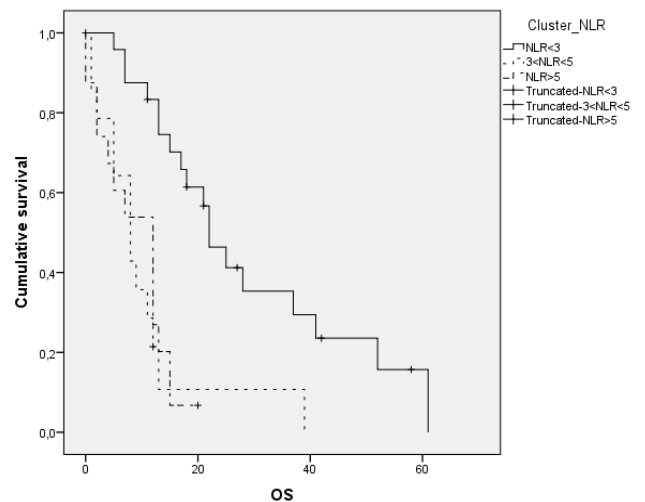


Figure 4. Overall survival according to Neutrophil-to- Lymphocyte Ratio clusters.

EPP+HITOC were 13 months (95% CI 9.77–16.22) and 19.6 (95% CI 11.51–27.69), respectively ($p < 0.005$). Therefore, it can be argued that, although burdened by higher morbidity rates (25.2% vs. 17.6%), HITOC is a valid complimentary surgical strategy for patients with malignant pleural mesothelioma and amenable for major surgery.

Discussion

Cancer is the leading cause of disease worldwide with 14.1 million of new cancer cases diagnosed in 2012 and it remains the leading cause of death with 8.2 million cancer deaths recorded in the same year [29]. Malignant pleural mesothelioma (MPM) is an aggressive cancer arising from mesothelial surfaces such as pleura (65%-70%), peritoneum (30%), tunica vaginalis testis, and pericardium (1%-2%) [30].

MPM is a rare cancer, difficult to treat and commonly associated with environmental or occupational exposure to asbestos [31]. It is subtyped into three main forms according to the histological pattern (epithelial, sarcomatoid and biphasic), thought other patterns, such as desmoplastic, are known [16]. Prognosis is poor and dismal [32].

In Europe the incidence is 20 cases per million, but this value presents a high variability between different nations [33]. It recognizes a high latency and tumor initiation time; in fact, as reported by the Italian Registry of Mesothelioma (ReNaM Study Group), the latency period between exposure to asbestos and the onset of the disease is about 44 years [34]. In Literature latency periods of less than 10 years are very rare. Some Authors report that a prolonged latency can be attributed to a less heavy exposure, recognizing a direct correlation between the amount of asbestos exposure and the onset of pleural mesothelioma [35]. Data still remain controversial [36].

MPM is considered an asbestos-related disease (ARD); in fact, pathophysiological processes are common to professional pneumoconiosis such as chronic inflammation resulting in pleural plaque formation due to asbestos fiber retention [37], promoting pro-inflammatory effects [38–40] and genotoxicity [41–43].

It is now widely recognized the outcome of cancer patients is not only determined by tumor, but also by interactions between the tumor and patient-related factors (age, sex, health status, comorbidities, microenvironment, genetic) [44]. In this regard, the role of inflammation and cytokine interaction between tumor and naive cells was investigated. These studies have demonstrated the critical role of inflammation [45,46]. In particular host response has been recognized as an independent prognostic factor in many tumors. Although the mechanisms seem still unclear, many inflammatory processes influencing important patient-related factors such as nutritional status, functional, performance status and immunological decline have been demonstrated [47,48]. Moreover, protracted inflammation alters the

balance [49] and activation of proliferative cellular pathways [23,50] perpetuating oncogenic stimuli. The neutrophil-to-lymphocyte ratio (NLR) is recognized as an independent prognostic factor in many cancers [51–53], although in Literature, opinions are conflicting (heterogeneity of populations, heterogeneity of cancer, chemotherapy).

A prognostic role for NLR in patients with Malignant Pleural Mesothelioma has been reported in a number of series, which are summarized in Table 4.

In 2010, Kao SC *et al.* [18] in a retrospective series of 173 MPM patients, showed NLR was an independent predictor for poor overall survival in such patients and that this index could stratify patients groups with survival difference. In our study, we confirm this trend clustering the population according to NLR. As reported by Guthrie *et al.* [54], in a meta-analysis conducted on 37,000 patients and more than 60 studies, a prognostic value of NLR was noted in 42 of them (non-randomized cohorts, operable patients, patients receiving neoadjuvant, adjuvant and inoperable patients).

Five studies [18,55–58], comprising 1113 patients, reported the prognostic value of the NLR in patients with primary thoracic tumors. In these patients, NLR had a prognostic value for both disease-free interval for and overall survival. The analysis also showed how the index tendency during the medical therapy presented a prognostic value. In fact, the normalization of the NLR, as expressed in the studies by Cedres, was predictive of improved survival.

For malignant pleural mesothelioma, data in the literature are conflicting. Meniawy TM *et al.* [12] reported that in 321 patients with malignant pleural mesothelioma, CALGB and EORTC models but not NLR had prognostic value.

In our study, although it is a limited 54 patients non randomized cohort one, we noted an independent prognostic value of NLR. Our retrospective study included a mixed cohort of patients clustered by age, histology, exposure to asbestos and therapeutic strategy. Tumor staging was performed according to the AJCC's staging system. The descriptive analysis of the clinical and therapeutic characteristics recorded has highlighted significant correlations between epithelial subtype, absence of nodal involvement (N0 disease) and overall survival.

We have adopted an absolute threshold of NLR lower than that reported in Literature ($NLR < 3$) in order to highlight significant differences by understaging these patients. In our experience, there is a survival advantage in patients with suboptimal index values rather than those with high values. We believe that a low ratio is an expression of a lower host immune response and therefore it prevents the onset of clinical features of chronic inflammation (fever, dysproteinaemia,

Table 4. Prognostic value of NLR in MPM patients.

Study	Centre	Tumor	N	p-value	NLR threshold
Linton A. (2014) [59]	Sydney (AUS)	MPM	919	< 0.001	5
Clive AO (2014) [60]	Bristol (UK)	MPM	67/83 (UK Cohort 2)	< 0.001	5
Abakay O (2014) [61]	Diyarbakir (TUR)	MPM	155	< 0.001	3
Anevlavis S (2014) [62]	Alexandroupolis (GR)	MPM	90	0.002	continuous
Kao SC (2013) [19]	Sydney (AUS)	MPM	148	0.01	3
Pinato DL (2012) [21]	London (UK)	MPM	171	0.0008	continuous
Kao SC (2011) [22]	Sydney (AUS)	MPM	85	< 0.01	3
Kao SC (2010) [18]	Sydney (AUS)	MPM	173	< 0.001	5

MPM: Malignant Pleural Mesothelioma

weight loss), factors definitely recognized as prognostically negative. At the same time, we do not think that NLR is a direct expression of the stage of the disease, as we have noted also in patients with advanced stage disease (stage III-IV), low values of the index were noted. In this case, we believe that in a metastatic patient, a low NLR could be an expression of the exhaustion of proinflammatory processes and of clinical manifestations related characteristics of the terminal disease.

Conclusions

In conclusion, we believe that the Neutrophil-to-Lymphocyte Ratio can be an independent, easily reproducible and comparable prognostic index in patients with malignant pleural mesothelioma. We hope future prospective studies about it in order to validate a universally shared decision.

Compliance with ethical standards

The authors have no conflict of interest to be disclosed. The article is in accordance with ethical standards. The article does not contain any studies with human participants performed by the authors. For this type of study, no formal consent is not required. It is an anonymous study referring only to clinical data.

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