A multicentric analysis of prognostic factors in malignant pleural mesothelioma

Análise multicêntrica dos fatores de prognóstico no mesotelioma pleural maligno

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ABSTRACT

Background: Malignant pleural mesothelioma is a rare entity with poor prognosis, linked to previous asbestos exposure. The main goal of this study was to analyse the impact of clinical factors on mesothelioma prognosis.
Methods: Retrospective cohort study of patients with malignant pleural mesothelioma in three Portuguese institutions, from 1999 to 2020. Statistical analysis was performed with Kaplan–Meier method and Cox regression using IBM SPSS® v25.
Results: 60 patients were included, with male predominance (70%) and a median age of 69 years old. At diagnosis, 61% had advanced TNM stage (TNM III-IV) and 18% had an ECOG-PS ≥ 2. Asbestos exposure was stated in 48%. Epithelioid mesothelioma was the most prevalent histological subtype (81%). The majority received first line chemotherapy, in 10% combined with surgery, and two patients received immunotherapy after progression. Median overall survival (OS) was 13 months and median progression free survival was 10 months. A lower OS was observed in patients with ECOG-PS ≥ 2, age ≥ 70 years, TNM stage III-IV, anaemia, and hypoalbuminemia. Applying the decision tree model proposed by *Brims et al.* in our population, a significant difference in median OS was observed between the risk groups. In a multivariate analysis using Cox regression, *Brims* risk group 4, older age and advanced TNM stage were identified as independent negative prognostic factors.

Conclusion: Recognition of these prognostic factors at diagnosis and use of specific prognostic models can help guide malignant pleural mesothelioma management.

Keywords: Malignant mesothelioma, pleural tumours, prognosis, survival analysis, asbestos.

RESUMO

Introdução: O mesotelioma pleural maligno é uma entidade rara com mau prognóstico, associada à exposição prévia a asbestos. O objetivo principal deste estudo foi analisar o impacto dos fatores clínicos no prognóstico do mesotelioma.
Métodos: Estudo retrospetivo de doentes com mesotelioma pleural maligno em três instituições portuguesas, de 1999 a 2020. A análise estatística foi realizada com o método de *Kaplan-Meier* e regressão de Cox com o software IBM SPSS® v25.
Resultados: Foram incluídos 60 doentes, com predomínio do sexo masculino (70%) e idade mediana de 69 anos. Ao diagnóstico, 61% apresentavam estadio TNM avançado (TNM III-IV) e 18% tinham ECOG-PS ≥ 2. 48% tinha registo de exposição a asbestos. O subtipo histológico epitelióide foi o mais prevalente (81%). A maioria recebeu quimioterapia de primeira linha, em 10% combinada com cirurgia e dois doentes receberam imunoterapia.
A sobrevida global mediana (SG) foi 13 meses e a sobrevida livre de progressão mediana foi 10 meses. A SG foi menor nos doentes com ECOG-PS ≥ 2, idade ≥ 70 anos, estadio TNM III-IV, anemia e hipoalbuminémia. Aplicando o modelo de árvore de decisão proposto por *Brims et al.* na nossa população, observou-se uma diferença significativa na SG entre os grupos de risco. Na análise multivariada, o grupo de risco 4, idade avançada e estadio TNM avançado foram identificados como fatores independentes de prognóstico negativo.
Conclusão: O reconhecimento destes de fatores prognósticos no momento do diagnóstico e o uso de modelos prognósticos específicos podem orientar a abordagem do doente com mesotelioma pleural maligno.

Palavras-chave: Mesotelioma maligno, neoplasias pleurais, prognóstico, análise de sobrevivência, asbestos.

INTRODUCTION

Mesothelioma is a rare tumour with origin in mesothelial cells, more frequently from the pleura (81%). Malignant pleural mesothelioma (MPM) affects mainly males and people older than 60 years old. It has a poor prognosis, with a median survival of 12 months and 5-year survival of 5-10%.[1] In the United States and Europe, MPM accounts for 3000 and 5000 deaths per year, respectively.[2]

There is a well-established causal relationship with asbestos exposure, with a latency period that

can reach 40 years.[2,3] These mineral fibres can be found in multiple materials, such as tiles and thermal insulators, and have numerous applications in construction and industry. Most patients were exposed to asbestos in the occupational setting.[3]

Incidence varies greatly with geographic location, depending on the pattern of asbestos use.[2,3] In Europe, asbestos use peaked between 1945 and 1990 and peak incidence was expected around 2020, but there are some hot spots.[1–3] In developing countries, where the use of asbestos is not yet regulated, a rise is expected in the coming years.[2] Use and commercialization in Portugal has been banned since 2005 (Decree-Law no. 101/2005, 23/06/2005).

MPM arises from an unregulated immune response to asbestos, in which mesothelial cells undergo malignant transformation due to a continuous inflammatory response and escape from immune surveillance.[2] Other risk factors include exposure to erionite and ionizing radiation. Genetic predisposition can also contribute, and a familial form associated with BAP1 gene mutation is well known.[3]

Pleural biopsy by thoracoscopy is the gold standard for diagnosis, allowing histological and immunohistochemical confirmation and definition of the histological subtype.[3]

The updates in the 8th edition of TNM for Mesothelioma were based on the International Association for the Study of Lung Cancer (IASLC) staging project and included reorganization of T and N categories and redefinition of stage IV as only M1.[4–6] Significant differences were observed between clinical and pathologic staging, so PET-CT and invasive node staging is recommended in patients suitable for surgery.[3]

In the recent European guidelines, chemotherapy (ChT) with pemetrexed plus platinum doublet remains the first line therapy, despite its limited effectiveness. Several studies with immunotherapy and target therapies are underway, which can bring great advances in the coming years.[3] NCCN guidelines already include nivolumab (+/- ipilimumab) and pembrolizumab as options in systemic therapy.[1] Surgical approach should be reserved for highly selected patients as part of multimodality treatment. Treatment choice must take into account multiple variables and be decided by a multidisciplinary board.[1,3]

Several prognostic factors have been described in MPM, including histological subtype and Eastern Cooperative Oncology Group Performance Status (ECOG-PS). However, there is no single prognostic factor to define treatment allocation. Prognostic scores are preferable but, to date, none has been validated for clinical practice.[3] Multiple scores have been proposed by different organizations, including the European Organisation for Research and Treatment of Cancer (EORTC) and Cancer and Leukaemia Group B (CALGB).[7,8] More recently *Brims* and colleagues proposed the decision tree model, which uses parameters routinely available at the time of diagnosis to define risk groups with different survival.[9]

The main goal of this study was to identify clinical factors with impact on MPM prognosis. Secondary objectives included applying the decision tree model in our population, demographic and clinic characterization of patients with MPM and description of diagnostic and therapeutic approach.

MATERIAL AND METHODS

Retrospective observational cohort study of patients diagnosed with MPM between 1999 and 2020 in three Portuguese hospitals – Centro Hos-

pitalar Universitário Cova da Beira (CHUCB), Centro Hospitalar Universitário São João (CHUSJ) and Instituto Português de Oncologia do Porto (IPOP). This study was conducted according to the Declaration of Helsinki and was approved by the Ethics committee of each institution (CHUCB 61/2020-14/12/2020; CHUSJ 296/20-26/11/2020; IPOP 331R/020-18/12/2020).

Patients were identified from the database of Pathology Departments. Histologic confirmation of MPM was required for inclusion in the study. Data were collected from digital clinical records and included demographic, clinical and pathological features, diagnostic and treatment approach, overall and progression free survival.

8th edition TNM staging for MPM was used. Age was divided in two groups, with a cut-off at 70 years old. Anaemia was defined as a value of haemoglobin under 12 g/dl and hypoalbuminemia as a value of albumin under 3,5 g/dl.

Statistical analysis was performed with Software IBM SPSS® v25 and p-value <0.05 was considered statistically significant. Missing data were treated by listwise deletion method.

Survival analysis was performed with Kaplan–Meier method, using log-rank test. To evaluate prognostic factors associated with MPM, a univariate and multivariate Cox regression analysis was performed.

The decision tree model for MPM prognosis proposed by *Brims* and colleagues in 2016 was applied in this study population. It includes weight loss, ECOG-PS, histological subtype, haemoglobin and albumin values.[9]

RESULTS

60 patients with MPM were included, with male predominance (70%) and a median age of 69 years old (range 39-84). 48,3% were 70 years old or more. Patient, diagnosis, and treatment data are presented in Table I.

At diagnosis, 53,1% of patients reported significant weight loss and 17,9% had an ECOG-PS of 2 or more. 60,8% had advanced stage disease, with TNM stage III or IV. 29,5% of the patients had anaemia (haemoglobin <12 g/dL) and 30% had hypoalbuminemia (albumin <3,5 g/dL).

Previous asbestos exposure was documented in 48,3% of the cases, but 41,7% had no data on this subject. 44,2% of patients had smoking habits.

The diagnosis was made mainly through percutaneous pleural biopsy (53,3%) and medical thoracoscopy (20%). Epithelioid mesothelioma was the main histological subtype (80,7%). Most MPM were right-sided (62,5%).

Most patients received first line ChT (88,7%), mainly with pemetrexed plus platinum doublet, but only 34% had second line ChT or rechallenge at disease progression. 2 patients received immunotherapy with Nivolumab after progression. Radiotherapy (RT) was performed in 26,8% of the patients, mainly prophylactic procedure-tract RT. Multimodality treatment with surgery and adjuvant ChT was performed in 6 patients (10%), 4 of whom also had RT. Surgery included pleurectomy and decortication (P/D) in 4 cases and extrapleural pneumonectomy (EPP) in 2. 11,3% of the patients got only best supportive care (BSC).

The median OS observed was 13 months (95% CI 7,4-18,6), with median progression free survival of 10 months (95% CI 7,5-12,5). We performed a survival analysis with the Kaplan-Meier method using log-rank test to evaluate differences in survival and a Cox regression analysis to assess prognostic value (Figure 1 and Table II).

Patients aged 70 years or older had shorter OS (Figure 1.a). ECOG-PS ≥ 2 and TNM stage

Table I. Characterization of patients with Malignant pleural mesothelioma included in the study

Variable	Group	n	%
Patient			
Gender	Male	42	70,0
	Female	18	30,0
Weight loss (N=32)	Yes	17	53,1
	No	15	46,9
Anaemia (N=44)	Yes - Hgb <12 g/dl	13	29,5
	No - Hgb ≥ 12 g/dl	31	70,5
Hypoalbuminemia (N=40)	Yes - Alb <3,5 g/dl	12	30,0
	No - Alb ≥ 3,5 g/dl	28	70,0
ECOG-PS (N= 39)	0	20	51,3
	1	12	30,8
	2 - 3	7	17,9
Smoking habits (N=43)	Smokers	7	16,3
	Former smokers	12	27,9
	Non-smokers	24	55,8
Asbestos exposure	Yes	29	48,3
	No	6	10,0
	Unknown	25	41,7
Diagnosis			
Pleural biopsy	Percutaneous	32	53,3
	Medical thoracoscopy	12	20,0
	CT-guided transthoracic	8	13,3
	Surgical	8	13,3
Histological subtype (N=57)	Epithelioid	46	80,7
	Biphasic/mixed	8	14,0
	Sarcomatoid	3	5,3
TNM Stage (N=51)	Stage I	17	33,3
	Stage II	3	5,9
	Stage III	14	27,5
	Stage IV	17	33,3
Decision tree risk group (N=45)	Group 2	15	33,3
	Group 3	13	28,9
	Group 4	17	37,8
Treatment			
Chemotherapy (N=53)	1st line Chemotherapy	47	88,7
	2nd line ChT	18	34,0
	Further ChT lines	6	11,3
Surgery	Pleurectomy/Decortication	4	6,7
	Extrapleural Pneumectomy	2	3,3
Radiotherapy (N=56)	Prophylactic procedure-tract RT	12	21,4
	Palliative RT	2	3,6
	Sequential ChT/ thoracic RT	1	1,8

(N=60 if not otherwise specified; Hgb – Hemoglobin; Alb – Albumin; ECOG-PS – Eastern Cooperative Oncology Group Performance Status; CT – Computed tomography; ChT – Chemotherapy; RT – Radiotherapy.)

Table II. Prognostic factors of overall survival in malignant pleural mesothelioma: Kaplan-Meier and Cox regression - univariate and multivariate analysis.

Variable	Group	Median OS (months)	Log-rank X^2	Cox regression (Hazard ratio [95% CI])	
				Univariate	Multivariate
Age	< 70	20	5,43 *p = 0,020*	2,02 [1,09-3,77] *p = 0,026*	3,91 [1,45-10,53] *p = 0,007*
	≥ 70	10			
ECOG-PS	< 2	20	29,43 *p < 0,001*	14,36 [3,93-52,44] *p < 0,001*	[a]
	≥ 2	2			
TNM stage	I - II	20	4,77 *p = 0,029*	2,10 [1,05-4,22] *p = 0,037*	2,87 [1,20-6,86] *p = 0,018*
	III - IV	11			
Chemotherapy	No	1	48,87 *p < 0,001*	*0,04* [0,01-0,16] *p < 0,001*	0,17 [0,04-0,81] *p = 0,026*
	Yes	20			
Anaemia	No	20	6,40 *p = 0,011*	2,40 [1,17-4,92] *p = 0,017*	[a]
	Yes	10			
Hypoalbuminemia	No	20	6,99 *p = 0,008*	2,59 [1,22-5,49] *p = 0,013*	[a]
	Yes	4			
Decision tree risk group	2 - 3	20	11,81 *p = 0,001*	3,11 [1,54-6,29] *p = 0,002*	4,38 [1,81-10,59] *p = 0,001*
	4	4			

[a] Factors already contained in the decision tree model were excluded from the multivariate analysis.

III-IV also showed shorter OS (Figure 1.b-c). The risk of death was more than two times higher in patients with anaemia or hypoalbuminemia (Table II).

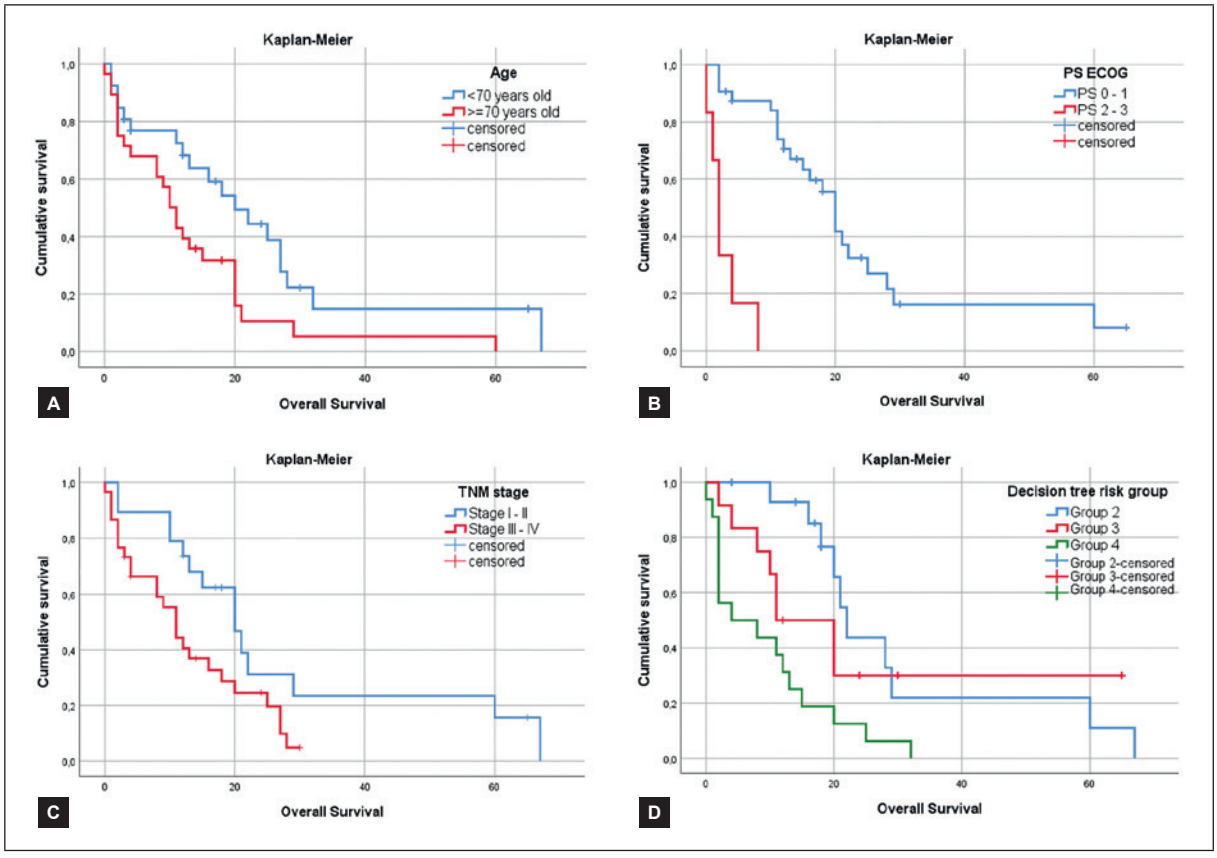
Patients that received ChT had a longer OS than those who only got supportive care (Table II). Median OS was higher in patients that performed surgery (22 *vs* 12 months, p=0,352) or RT (18 *vs* 11 months, p=0,248), but the difference was not statistically significant.

Patients with non-epithelioid histology (11 *vs* 16 months, p=0,108) and weight loss at diagnosis (10 *vs* 21 months, p=0,243) presented shorter OS but it was not statistically significant. Gender, laterality of the tumour, and asbestos exposure did not show an effect on survival.

Patients were allocated to the risk groups of the decision tree model (Table I).[9] There were no patients in Group 1. We observed that median OS was significantly different between risk groups, with group 4 showing the lower survival (4 months, [IQR 2-13]) (Figure 1.d).

We then included the significant variables in a multivariate analysis with a Cox regression model, eliminating factors that are already contained in the decision tree model (ECOG-PS, anaemia, and hypoalbuminemia). Risk group 4 (HR 4,38), age ≥ 70 years old (HR 3,91) and TNM

Figure 1. Kaplan-Meier overall survival analysis: (a) Age ≥ 70 years old, (b) ECOG performance status ≥ 2, (c) TNM stage III or IV, and (d) Decision tree risk group 4 were associated with lower overall survival.



stage III-IV (HR 2,87) were identified as independent negative prognostic factors for MPM (Table II). On the other hand, ChT was associated with a better prognosis (HR 0,17).

DISCUSSION

In our study, MPM patients were mainly male, nearly half had 70 years old or more, and older age showed an independent negative impact on prognosis. Males account for 70 to 84% of MPM cases in multiple studies.[4,10–14] The median age of MPM patients varies from 62 to 73 years old, probably due to differences in the type of cases selected.[4,11–13,15] Despite variable cut-offs, several studies corroborate the negative impact of older age on prognosis.[4,16,17]

Almost half the patients had documented asbestos exposure, but this value may be underestimated due to the large latency period and retrospective design based on clinical records. The

cases without known asbestos exposure may represent the effect of other risk factors like ionizing radiation.[3]

Advanced TNM stage (III-IV), higher ECOG--PS (≥2), anaemia and hypoalbuminemia were also identified as negative prognostic factors in our MPM patients.

TNM stage and ECOG-PS are well-defined prognostic factors. In the IASLC database, overall tumour stage, T and N categories had a statistically significant impact on survival.[4] Median OS for M1 cases was significantly lower than for cases without metastasis.[6] Percentage of patients with ECOG-PS of 2 or more varies from 8 to 47.7% in different studies.[9,12,14,18] An Italian study with a similar size also described ECOG-PS as a significant prognostic factor.[12]

Anaemia is a recognized prognostic parameter in MPM, but haemoglobin cut-offs are heterogeneous, varying from 10 to 14.6 g/dL.[12,15,19] Hypoalbuminaemia is an indicator of nutritional status and its adverse impact on prognosis has been reported in MPM, as well as in other types of cancer.[18]

Patients that received ChT presented longer survival, but this might have been influenced by selection bias since patients with poor performance status are less likely to receive oncological treatment. The percentage of patients treated with ChT was above other reports (53-64%).[15,18]

The decision tree model proposed by *Brims* was applied to this population.[9] This model was designed with data from 482 cases from an Australian institution (derivation cohort) and then tested on a cohort of 174 cases from a British institution (validation cohort). Median OS observed (13 months) was in line with the derivation cohort (12,6 months) and higher than in the validation cohort (9,7 months). OS observed for each of our study groups was within the interquartile range (IQR), with significant differences between groups. Group 4 was associated with the worst prognosis and median OS was lower than the reference article (4 *vs* 7,4 months, IQR 3,3 – 11,1).[9] A systematic review of randomized trials reported higher survival rates in the more recent calendar years, with OS up to 17 months.[20]

Non-epithelioid histology showed a tendency to lower survival, however, the small number of other histological subtypes did not allow statistical significance. Non-epithelioid mesothelioma is widely described in the literature as a negative prognostic factor.[4,10,12,13,15] In the IASLC database, epithelioid histology presented a median survival of 19 months, compared to 13 months in biphasic and 8 months in sarcomatoid subtypes.[4]

Right-side predominance was previously reported and it may be related to the anatomy of the right bronchus that allows higher deposition of asbestos on this side.[13,16] Laterality of tumour did not affect survival in our population, but left--sided tumours have been associated with a better prognosis.[13]

The small number of patients that underwent surgery, RT, and immunotherapy did not allow evaluation of its impact on survival. A multicentric retrospective study of 1365 patients demonstrated a better survival with surgical resection and adjuvant ChT compared to ChT alone. However, those with good prognostic factors, like age under 70 years or epithelioid histology, had similar survival with medical therapy only or surgery.[10] The MARS trial, a randomised controlled trial, revealed high morbidity associated with EPP and no benefit in survival, but some doubts about study design have been elicited.[21] Results from a similar trial for extended P/D (MARS-2 trial) are awaited. Despite widespread use, prophylactic radiotherapy following drainage or thoracoscopy is no longer recommended. Palliative radiotherapy can be effective for pain relief.[3]

Since MPM is a rare malignancy, gathering data from multiple institutions and over a long period of time allowed the construction of a larger dataset. However, this can also produce a heterogeneous population concerning diagnostic methods and therapeutic approach.

Analysis of some results was limited by the size of the population and the retrospective design of the study. Missing data on clinical records were handled in a manner to minimize bias. Nevertheless, description of symptoms and pleural fluid management, like pleurodesis, were not generally available and this might undervalue the impact of MPM on morbidity and quality of life.

CONCLUSION

This study describes the experience of 20 years in MPM management in three different Portuguese institutions. Age, TNM stage, and *Brims* risk group were identified as independent prognostic factors, in accordance with current literature.

Recognizing the prognostic value of these clinical factors at diagnosis can help guide the management of patients with MPM. The application of specific prognostic models for MPM allows the stratification into risk groups, which can represent an additional value for clinical decision.

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