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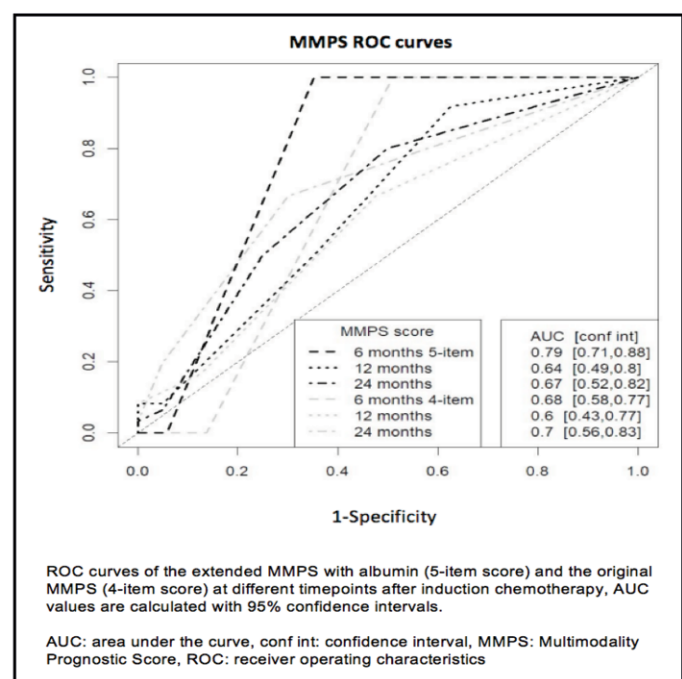
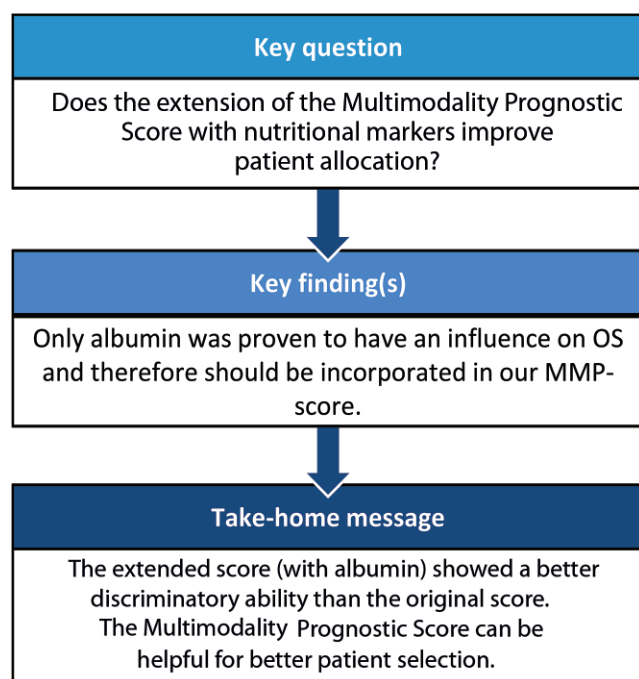
# Prospective validation and extension of the Multimodality Prognostic Score for the treatment allocation of pleural mesothelioma patients

Daria Greb, Monika Hebeisen , Alessandra Matter, Isabelle Opitz <sup>†</sup> and Olivia Lauk<sup>\*,†</sup>

Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland

\* Corresponding author. Department of Thoracic Surgery, University Hospital Zurich, Raemistrasse 100, Zurich 8091, Switzerland. Tel: +41-442558804; e-mail: olivia.lauk@usz.ch (O. Lauk).

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## Abstract

**OBJECTIVES:** Patient allocation to multimodality treatment in patients with malignant pleural mesothelioma remains a challenge. The aim of this study was to validate our previously established Multimodality Prognostic Score (MMPS) (tumour volume before chemotherapy, histological subtype, C-reactive protein before chemotherapy and tumour progression after chemotherapy) and to extend the score with additional blood parameters for better patient outcome.

**METHODS:** Patients with histologically proven malignant pleural mesothelioma and curative intended therapy with clinical stage T1–T3 N0–N2 M0 were eligible. The existing MMPS was validated and further additional blood markers (erythrocytes, neutrophils, monocytes, albumin, gamma-glutamyl transferase and alkaline phosphatase) were evaluated for potential incorporation.

**RESULTS:** For the validation of the existing MMPS, as the first part of this analysis, 117 patients treated as of September 2011 were included. A total of 88 patients were treated with macroscopic complete resection, whereas 29 patients were treated with palliative or no surgery. Patients treated with macroscopic complete resection and a high MMPS showed statistically significant lower overall

<sup>†</sup>These authors shared the last author.

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survival. In the second part, the extension of the MMPS with additional blood parameters was analysed. Albumin, the only parameter showing evidence for having influence on overall survival, was further added to the extended MMPS. When comparing the performance measures Area under the curve (AUC) and Brier score, the extended score performed better (higher AUC, lower Brier score) than the original MMPS.

**CONCLUSIONS:** The extended score with albumin showed improved performance in comparison to the original score. The extended MMPS also may help allocating patients to surgery.

**Keywords:** Malignant pleural mesothelioma • Multimodality therapy • albumin • Multimodality Prognostic Score • Extrapleural pneumonectomy • Extended pleurectomy decortication

## ABBREVIATIONS

AAPR	Albumin-to-alkaline phosphatase ratio
AUC	Area under the curve
CRP	C-reactive protein
MCR	Macroscopic complete resection
MMPS	Multimodality Prognostic Score
MPM	Malignant pleural mesothelioma
OS	Overall survival
ROC	Receiver operating characteristic

## INTRODUCTION

Patient selection, according to the latest ERS/ESTS/EACTS/ESTRO (European Respiratory Society/European Society of Thoracic Surgeons/European Association for Cardio-Thoracic Surgery/European Society for Radiotherapy and Oncology) guidelines [1], for an optimal therapy approach, remains difficult considering the limited life expectancy of malignant pleural mesothelioma (MPM) patients and the aggressive treatment. It is essential to select patients benefiting from a multimodality therapy as well as identifying and excluding patients not profiting from the surgery.

Several scores that combine independent prognostic factors have been proposed with the intention to achieve a better risk stratification, but it is difficult to choose the right one [2–6]. We developed a Multimodality Prognostic Score (MMPS) based on clinical variables available before surgery for improved patient allocation to multimodality therapy. The MMPS contains the following items: tumour volume before chemotherapy, histological subtype, C-reactive protein (CRP) before chemotherapy and tumour progression after chemotherapy [7]. The aim of the first part of this analysis was to validate the existing MMPS with new prospectively collected data.

Furthermore, blood values such as CRP, neutrophil-to-lymphocyte ratio and albumin, have been described as prognostic factors in MPM [8–11].

In a second part, the prognostic value of additional blood parameters, which have been previously proven to have good discriminative power regarding overall survival (OS) [12], has been tested with the aim to extend the existing score by the most promising factor.

## PATIENTS AND METHODS

The manuscript was written by following TRIPOD reporting guideline criteria [13].

## Patients

Patients with histologically proven MPM being treated at the Department of Thoracic Surgery of the University Hospital Zurich were eligible for inclusion (Fig. 1). The previously conducted study [7] analysed patients with multimodal treatment between May 1999 and August 2011. Further prospectively collected data, from patients with treatment until December 2019, were used in this analysis for the validation of the previous results and for the potential extension of the MMPS with additional blood markers. The eligibility criteria were the same as in the preceding article [7].

## Treatment

Whenever an item of the eligibility criteria was not known for a patient, the patient stayed in the cohort. All patients were intended to be treated within a multimodality therapy approach consisting of induction chemotherapy followed by macroscopic complete resection (MCR). All patients underwent induction chemotherapy between April 2000 and October 2019, consisting of cisplatin/pemetrexed or cisplatin/gemcitabine and others (13.5% of all cases), followed either by macroscopic complete resection with extrapleural pneumonectomy or (extended) pleurectomy/decortication (MCR group) or by palliative surgery consisting of tumour debulking or no surgery (no MCR group). For simplicity, patients treated with palliative or no surgery are summarized as no MCR group in this study.

## MMPS

The previously established MMPS, calculated with prospectively collected data, contains 4 items: tumour volume before chemotherapy >500 ml, non-epithelioid histological subtype in the diagnostic biopsy before chemotherapy, CRP >30 mg/l before chemotherapy and progressive disease after chemotherapy according to the RECIST criteria [14]. The measurement of the tumour volume is done semi-automatically on axial planes of the computed tomography scan as previously described by Frauenfelder *et al.* [15]. Each of these items count as 1 point if they apply. The highest possible score is 4, if all items are present, the lowest score is zero if none of the conditions apply.

## Treatment decision according to MMPS

According to our previous analysis by Opitz *et al.* [7] in 2015, patients with a score of >2 had a significantly shorter OS.

The cut-off at 2 was set due to the binarization that was based on a survival advantage in the  $\leq 2$  group. Therefore, this

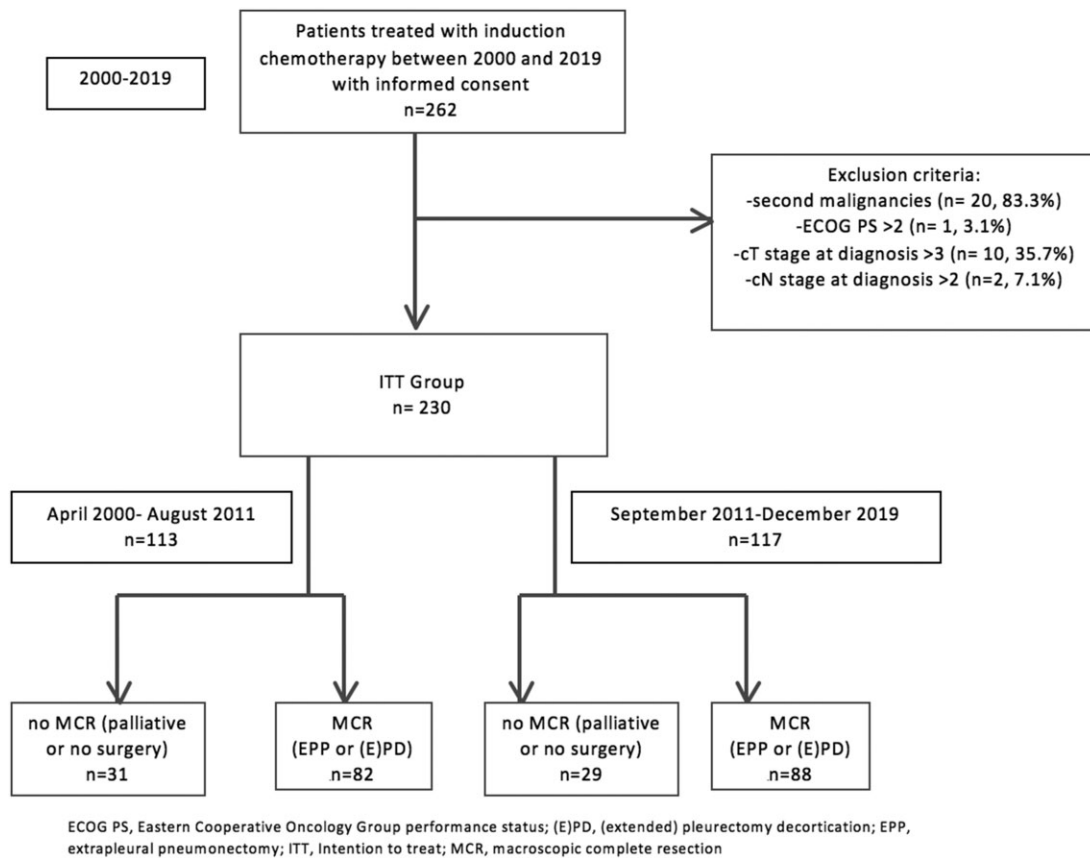


Figure 1: Flow chart of patients included in this study.

score was applied at our interdisciplinary tumour board to select patients for or against surgery: Patients with MMPS  $\leq 2$  can be allocated to surgery, whereas patients with an MMPS  $>2$  should be excluded from surgery. In addition, the score was tested with only 3 parameters (MMPS 3-item), including the 3 factors being available at initial patient evaluation (before chemotherapy), and leaving out response to chemotherapy according to the RECIST criteria. The 3-item MMPS still performed better than EORTC score regarding the cut-off  $\leq 2$  and OS.

## RESULTS

### Patient cohort for the different analyses

Demographic, surgical and clinical data for both groups (before and as of September 2011) are listed in Table 1.

### Score validation

Kaplan–Meier curves of median OS and after multimodal treatment for the MCR and no MCR patients per MMPS level are shown in Fig. 2. Supplementary Material, Fig. S1 shows receiver operating characteristic (ROC) curves and area under the curve (AUC) values for both MMPS and EORTC score of survival at 1 and 2 years after treatment.

### Score description

The median OS in the MCR group for MMPS of 0, 1 and 2 was 30 [95% confidence interval (CI) 21–45 months], 18 [95% CI 14–29] and 13 [95% CI 9 to >23] months (Fig. 3). The median OS according to the scores 0, 1 and 2 for the no MCR group was 26 [95% CI 11 to >39], 12 [95% CI 10 to >45] and 10 [95% CI 8 to >16] months, respectively (Fig. 3).

In Fig. 3, 15 patients with an MMPS of  $<2$  are represented in the no MCR group. Those patients have been originally allocated to MCR treatment. However, 4 patients showed tumour progression before MCR treatment and have been allocated to proceed with palliative systemic therapy after discussion at our interdisciplinary tumour board. The remaining 11 patients had palliative tumour debulking or the operation was aborted due to advanced tumour disease or, in 1 case, the patient decided against surgery for religious reasons.

The Cox regression analysis of the MCR group is shown in Tables 2 and 3. The MMPS items as dichotomous variables do have a similar size of effect on OS (Table 3; hazard ratios are all slightly above 2). Every item doubles the hazard of death. The MMPS as 1 linear variable (Table 2) shows similar properties (hazard ratio is slightly above 2, every item doubles the hazard of death). The hazard ratio of the dichotomized score is quite high and its confidence interval extends to a very high value (Table 3). There might be problems in estimation here, because there are only 2 patients with MMPS above 2 in the analysis.

**Table 1:** Patient characteristics of the group receiving induction chemotherapy and macroscopic complete resection consisting of extrapleural pneumonectomy or (extended) pleurectomy/ decortication

n (%)	Overall (n = 170)	Before September 2011 (n = 82)	As of September 2011 (n = 88)
Gender (male)	155 (91.2)	72 (87.8)	83 (94.3)
Age, median [IQR]	64.1 [59.10, 67.77]	61.7 [57.27, 65.43]	65.8 [62.01, 69.15]
Age ( $\leq 61$ years)	52 (30.6)	37 (45.1)	15 (17.0)
Laterality (right)	96 (56.5)	42 (51.2)	54 (61.4)
Asbestos (yes)	94 (55.6)	48 (58.5)	46 (52.9)
Smoking (yes, current or former)	89 (52.9)	46 (56.7)	43 (49.4)
weight loss (yes)	69 (43.1)	37 (45.1)	32 (41.0)
ECOG PS at diagnosis ( $\leq 1$ )	104 (96.3)	36 (94.7)	68 (97.2)
CRP before chemotherapy ( $>30$ )	47 (34.1)	26 (36.6)	21 (31.3)
tumour volume before chemotherapy ( $>500$ cm <sup>3</sup> )	17 (11.5)	5 (8.2)	12 (13.8)
RECIST			
Progressive disease (PD)	19 (12.4)	14 (20.3)	5 (5.9)
Partial regression (PR)	60 (39.2)	25 (36.2)	35 (41.7)
Stable disease (SD)	74 (48.4)	20 (43.5)	44 (52.4)
Histological subtype pre-treatment			
Epithelioid	138 (84.7)	65 (82.3)	73 (86.9)
Biphasic	22 (13.5)	13 (16.4)	9 (10.7)
Sarcomatoid	3 (1.8)	1 (1.3)	2 (2.4)
Histological subtype (non-epithelioid)	25 (15.3)	14 (17.7)	11 (13.1)
Chemotherapy			
Cis/gem	9 (5.3)	8 (9.8)	1 (1.1)
Cis/pem	138 (81.2)	68 (82.9)	70 (79.5)
Others <sup>a</sup>	23 (13.5)	6 (7.3)	17 (19.3)
IMIG stage (8th edition)			
IA	33 (22.3)	12 (14.6)	21 (31.8)
IB	65 (43.9)	33 (40.3)	32 (48.5)
II	32 (21.6)	25 (30.5)	7 (10.6)
IIIA	17 (11.5)	12 (14.6)	5 (7.6)
IIIB	1 (0.7)	0 (0.0)	1 (1.5)
Surgery type			
(E)PD	79 (46.5)	5 (6.1)	74 (84.1)
EPP	91 (53.5)	77 (93.9)	14 (15.9)
pT stage at surgery			
0	1 (0.6)	0 (0.0)	1 (1.1)
1	13 (7.7)	7 (8.5)	6 (6.9)
2	24 (14.2)	14 (17.1)	10 (11.5)
3	114 (67.5)	53 (64.6)	61 (70.1)
4	17 (10.1)	8 (9.8)	9 (10.3)
pN stage at surgery (8th edition <sup>b</sup> )			
0	110 (67.5)	54 (68.4)	56 (66.7)
1	53 (32.5)	25 (31.6)	28 (33.3)
MMPS			
0	48 (41.4)	19 (35.8)	29 (46.0)
1	49 (42.2)	22 (41.5)	27 (42.9)
2	17 (14.7)	10 (18.9)	7 (11.1)
3	1 (0.9)	1 (1.9)	0 (0.0)
4	1 (0.9)	1 (1.9)	0 (0.0)

<sup>a</sup>Chemotherapy other: carboplatin, bevacizumab, vinorelbine and etoposid.

<sup>b</sup>The former 7th edition of tumour classification was adopted into the new 8th edition according to the TNM classification.

cis: cisplatin; CRP: C-reactive protein; ECOG PS: Eastern Cooperative Oncology Group performance status; (E)PD: (extended) pleurectomy decortication; EPP: extrapleural pneumonectomy; gem: gemcitabine; IMIG: International Mesothelioma Interest Group; IQR: interquartile range; MMPS: Multimodality Prognostic Score; pem, pemetrexed; RECIST: Response Evaluation Criteria in Solid Tumors.

The predictive performance of the MMPS is determined to compare it with the performance of the extended MMPS afterwards.

### Score extension

Descriptive values of additional single blood markers are shown in Table 4, and the hazard ratios of OS of the dichotomized single

blood markers are shown in Table 5. Albumin performed best as single predictor of OS [log-rank test 0.05 (Supplementary Material, Fig. S2)]. Cox regression hazard ratio showed a *P*-value of 0.06 (Table 5) and an AUC at 6 months of 0.84 (Supplementary Material, Table S2). Therefore, it was added as an additional item to the MMPS with values below 40 g/l (the lower limit of normal) giving 1 point and higher values giving 0 points. The extended MMPS ranges from 0 to 5 points and its performance was compared to the original MMPS that ranges from 0 to 4. OS curves

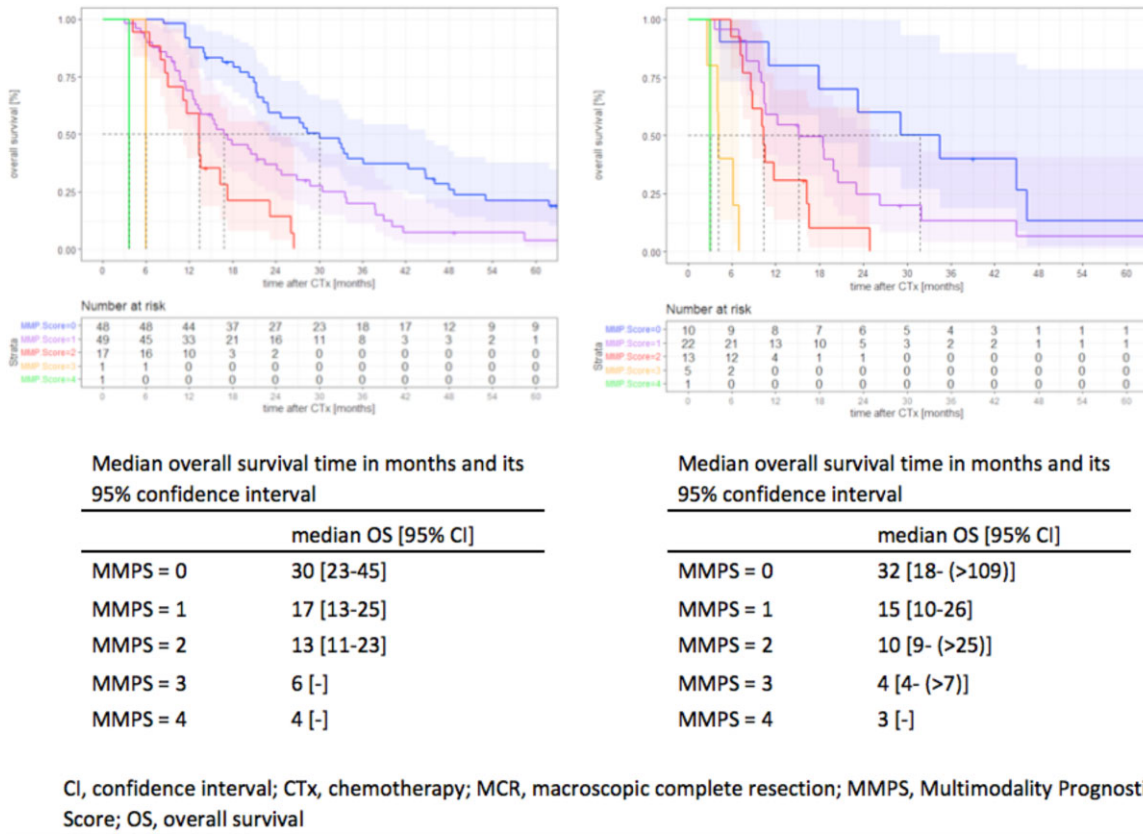


Figure 2: Kaplan-Meier curves for patients with macroscopic complete resection (left) and without macroscopic complete resection (right) per Multimodality Prognostic Score level. Patients with treatment start between May 1999 and December 2019.

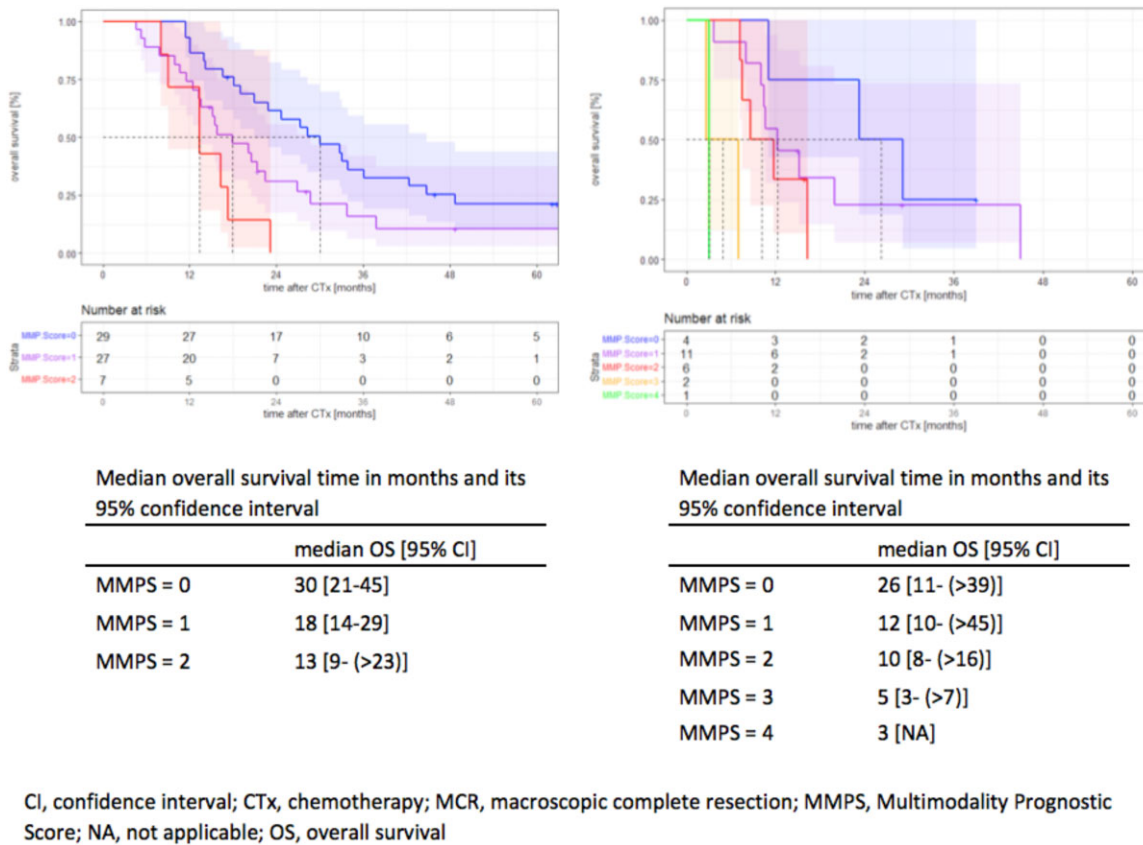


Figure 3: Kaplan-Meier curves for patients with macroscopic complete resection (left) and without macroscopic complete resection (right) per Multimodality Prognostic Score level. Patients with treatment start as of September 2011 are included.

for the original MMPS (left side) and extended MMPS (right side) are shown in Fig. 4, with the same reduced dataset, because of a high percentage of missing values in the albumin measurements. The median survival time in months and its 95% confidence interval for patients with MCR, per MMPS level for the original and extended MMPS, are shown in Fig. 4 as well.

Comparison of the original and extended MMPS gave ambiguous results. The hazard ratio of the extended score Cox model was smaller but the evidence for a difference between MMPS values was higher (Table 6) and the likelihood ratio test showed clear evidence for a difference between the Cox models ( $<0.0001$ ). When comparing the performance measures AUC and Brier score (Supplementary Material, Tables S3 and 4), the extended MMPS is better (higher AUC, lower Brier score). The models with the dichotomized MMPS resulted in high hazard

ratios (Table 6), due to very low patient numbers in the group of MMPS  $>2$ . Therefore, they cannot be interpreted well.

Further assessment of calibration resulted in the calibration slopes of 0.89 for MMPS 4 and 1.08 for MMPS 5 (Supplementary Material, Fig. S3). The 2 calibration curves are similar at lower MMPS, both slightly underestimating OS.

Due to the high absence of the predictors, especially albumin, the Cox models were fitted again with multiple imputed data. The results were similar (Supplementary Material, Table S5), but the discriminative ability of albumin and the extended MMPS was reduced, leading to less clear results.

## DISCUSSION

In 2011, our MMPS for a better treatment allocation for patients diagnosed with MPM undergoing multimodality therapy approach was developed. The usage for a better and more precise patient identification proved a better OS for patients with a score of  $\leq 2$  [7]. The aim of the present analysis was to prospectively assess the score. In a second step, the extension of the MMPS by adding the blood marker albumin was further evaluated. The good discriminatory ability of albumin with respect to survival was previously proven [12] and here again showed the best discriminative ability with the best performance and therefore was added to the MMPS.

In agreement with the original paper by Opitz *et al.* in 2015, our analysis confirmed the cut-off value of 2. Patients with

**Table 2:** Cox regression model of 4 items of Multimodality Prognostic Score, added as dichotomized variables;  $n = 114^a$ ,  $n$  events = 98

	Hazard ratio	95% CI	P-Value
CRP preCTx $>30$ mg/l	2.307	[1.470, 3.620]	0.00028
Tumour volume preCTx $>500$ ml	2.048	[1.098, 3.819]	0.02
Non-epithelioid histological subtype before treatment	2.600	[1.490, 4.537]	0.00077
RECIST progressive disease	2.012	[1.112, 3.643]	0.02

<sup>a</sup>Not all measurements were available for all 170 patients.

CI: confidence interval; CRP: C-reactive protein; preCTx: before chemotherapy; RECIST: Response Evaluation Criteria in Solid Tumors.

**Table 3:** Cox regression models of Multimodality Prognostic Score;  $n = 116^a$ ,  $n$  events = 100

	Hazard ratio	95% CI	P-Value
MMPS	2.299	[1.719, 3.074]	$<0.0001$
MMPS $>2$	35.977	[6.862, 188.632]	$<0.0001$

In the first model, the score is considered as a linear variable (0–4) and then as dichotomized variable ( $>2$  vs  $\leq 2$ ). Only patients with MCR are considered.

<sup>a</sup>Not all measurements were available for all 170 patients.

CI: confidence interval; MCR: macroscopic complete resection; MMPS: Multimodality Prognostic Score.

**Table 4:** Mean and standard deviation of blood marker levels before induction chemotherapy in patients with and without macroscopic complete resection

	Overall ( $n = 230$ )	MCR ( $n = 170$ )	No MCR ( $n = 60$ )	Missing <sup>a</sup>
Erythrocytes, mean (SD)	4.61 (0.82)	4.68 (0.91)	4.46 (0.52)	13.5
Neutrophils, mean (SD)	6.79 (2.67)	6.64 (2.63)	7.14 (2.76)	35.7
Monocytes, mean (SD)	0.73 (0.89)	0.64 (0.28)	0.99 (1.64)	38.7
Albumin, mean (SD)	38.03 (4.81)	38.70 (4.60)	36.42 (5.03)	62.6
AP, mean (SD)	96.68 (49.23)	93.40 (47.20)	105.10 (53.77)	36.5
GGT, mean (SD)	86.07 (107.18)	77.08 (95.74)	110.07 (131.86)	52.2

Erythrocytes are measured in T/l, neutrophils and monocytes are measured in G/l, albumin is measured in g/l and GGT and AP are measured in U/l.

<sup>a</sup>Percentage of missing values is shown in the last column.

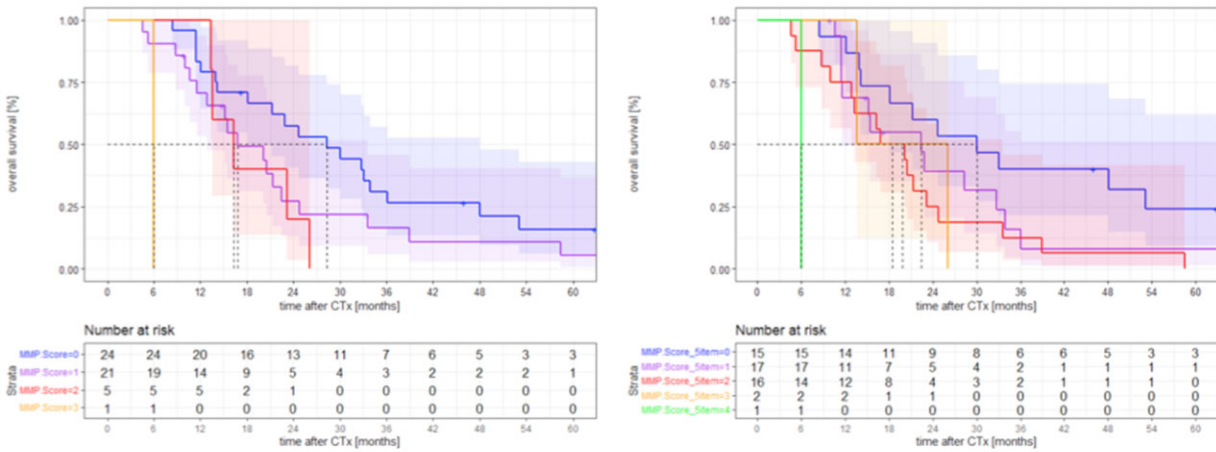
AP: alkaline phosphatase; GGT: gamma-glutamyl transferase; MCR: macroscopic complete resection; SD: standard deviation.

**Table 5:** Cox regression models of single blood markers, considered in dichotomized way

	HR = exp (coef)	95% CI	P-Value	$n$	Events
Erythrocytes preCTx	1.274	[0.800, 2.028]	0.31	142	124
Neutrophils preCTx	0.839	[0.520, 1.353]	0.47	105	96
Monocytes preCTx	1.445	[0.816, 2.560]	0.21	103	94
Albumin preCTx	1.727	[0.987, 3.020]	0.06	61	53
AP preCTx	1.571	[0.898, 2.748]	0.11	105	94
GGT preCTx	1.507	[0.908, 2.501]	0.11	80	69

Erythrocytes are measured in T/l, neutrophils and monocytes are measured in G/l, albumin is measured in g/l and GGT and AP are measured in U/l. Only patients with MCR are considered.

AP: alkaline phosphatase; CI: confidence interval; GGT: gamma-glutamyl transferase; HR: hazard ratio; MCR: macroscopic complete resection; preCTx: before chemotherapy.



Median overall survival time in months and its 95% confidence interval (n=51<sup>a</sup>, events = 44)

	median OS (95% CI)
MMPS = 0	28 (18-48)
MMPS = 1	17 (13-34)
MMPS = 2	16 (14- >26]
MMPS = 3	6 (-)

Median overall survival time in months and its 95% confidence interval (n=51<sup>a</sup>, events = 44)

	median OS (95% CI)
MMPS = 0	30 (18- >78]
MMPS = 1	22 (12- >68]
MMPS = 2	18 (13-34)
MMPS = 3	20 (14- >26]
MMPS = 4	6 (-)

<sup>a</sup> data was not available for all 170 patients

CI, confidence interval; CTx, chemotherapy; MCR, macroscopic complete resection; MMPS, Multimodality Prognostic Score; OS, overall survival

Figure 4: Kaplan-Meier curves for patients with macroscopic complete resection, per original Multimodality Prognostic Score level (left, 4 items) and extended Multimodality Prognostic Score level (right, 5 items including albumin).

Table 6: Cox regression models of original (4-item) Multimodality Prognostic Score compared to extended (5-item) Multimodality Prognostic Score

	HR = exp (coef)	95% CI	P-Value
MMPS 4-item	1.725	[1.123, 2.649]	0.01
MMPS 5-item	1.563	[1.132, 2.158]	0.0067
MMPS 4-item > 2	24.495	[2.221, 270.161]	0.009
MMPS 5-item > 2	2.168	[0.659, 7.131]	0.20
MMPS 5-item > 3	24.495	[2.221, 270.161]	0.009

In the first model, the score is considered as a linear variable and then as dichotomized variable (>2 vs ≤2) or (>3 vs ≤3). Only patients with MCR and no missing data are considered. The likelihood ratio test comparing the 2 resp. 3 models gives the P-values <0.0001, <0.0001 and 1.00.

CI: confidence interval; HR: hazard ratio; MCR: macroscopic complete resection; MMPS: Multimodality Prognostic Score.

MMPS ≤2 are eligible for MCR while patients with MMPS >2 should be excluded from surgery. Although the Kaplan-Meier curves for patients with MMPS of 0 in Fig. 2 showed a better point estimate of median OS in patients without MCR (32 months [95% CI 18 to >109]) compared to patients with MCR (30 months [95% CI 23-45]), these numbers are very close and the confidence intervals of the estimates are overlapping. Hence, we have

no evidence for a difference in median survival of the 2 groups and we cannot conclude that patients with the MMPS of 0 should be excluded from surgery.

A cut-off at MMPS 2 was used for treatment decision and patients with an MMPS of >2 were excluded from surgery. Only a few patients with an MMPS of 3 or 4 were present in our analysis, leading to very wide or non-determinable confidence intervals for estimates of MMPS 3 or 4 or >2.

Despite the fact that prognostic factors have been a major focus of research in MPM over the past few years [2-6, 8-11, 16, 17], no general consensus has been established and blood-based biomarkers are not routinely used in the management and treatment allocation of patients with MPM, yet. Thus, the aim to achieve a better patient selection for MPM therapy remains challenging.

Recently, some studies have focused on the optimization of a better patient selection in cancer patients for one or the other therapy pathway. Particular attention has been paid to a simplified method involving the determination of certain parameters in the blood. Blood can be obtained quickly, easily and, above all, without enormous costs without the patient undergoing more invasive examinations with anaesthesia. Another advantage is the fast evaluation of blood values.

Due to the rarity of the disease of pleural mesothelioma, there has been little work to date on serum markers for better patient selection. Many results come from cancer studies of primary lung carcinoma or from the digestive cancer spectrum. In the past few

years, serum biomarkers for the prediction of prognosis in cancer patients have been the subject of several studies investigating their effect on better patient selection.

A recent meta-analysis by Xie *et al.* [18], on purely Asian population, revealed the prognostic significance of albumin-to-alkaline phosphatase ratio (AAPR), available before treatment, for OS in cancer. The results in this meta-analysis indicated that low AAPR was significantly associated with poor OS, compared with high AAPR (hazard ratio = 2:12 [95% CI 1:80–2:50],  $P$ -value <0.001). Another study by Zhou *et al.* [19] also investigated the relation between AAPR and OS in patients in a purely lung cancer population (advanced non-small-cell lung cancer) and also demonstrated their ability of patient stratification. Patients with a low AAPR had a statistically significant lower median OS compared to patients with a high AAPR (9.3 vs 16.9 months, respectively) ( $P$ -value <0.0001) [18].

However, only a limited number of blood-based markers have been identified and most of them are discussed controversial. Unfortunately, their role in clinical practice is still diminutive.

Serum markers, as C-reactive protein and albumin, both inflammatory markers and potentially reflecting the equilibrium between nutritional status and cancer-related inflammation, have been proven in studies to serve as biomarkers with good discriminative ability regarding patient selection before cancer treatments [5, 10, 11, 16, 17]. The relationship between acute-phase proteins, such as albumin, and cancer survival has been demonstrated in multiple studies. Albumin not only reflects the nutritional status and liver function but also plays a crucial role in the body's inflammatory reaction and as an antioxidant in the development of cancer. Since proinflammatory cytokines have been proven to cause reduced concentration of albumin, hypoalbuminemia can serve as a marker of systemic inflammation. In addition, significant systemic inflammation can lead to reduced appetite, gastrointestinal motility and haemodynamic stability resulting in malnutrition, adding to the decreased albumin levels. Hence, decreased albumin levels are presumed to lead to impaired immune function and adverse anticancer reactions [20–24].

This is in line with our results, although to be taken with caution due to missing values despite imputation, that of the 6 markers studied (erythrocytes, neutrophils, monocytes, albumin, gamma-glutamyl transferase and alkaline phosphatase), only albumin at early timepoints reached AUC values of 0.7 and above and was therefore the most promising blood marker to discriminate OS in this performance analysis.

Looking at all investigated blood markers in our analysis influencing on OS, only albumin showed a marginal statistical significance with a  $P$ -value of 0.05 and a median OS of 22 months [95% CI 16–48]. Albumin (<40 g/dl) was then incorporated in our existing MMPS, and thus, this score was extended from 4 items to 5 items. The AUC value of the original MMPS was lower than the AUC calculated from the extended score. According to these results and model, the extended MMPS would be the preferred one. The likelihood ratio test revealed a  $P$ -value of statistical significance (<0.001). Those findings were supported by the calibration analysis that revealed better prediction of the outcome with the 5-item score.

## Limitations

The aim of this analysis was to evaluate the performance of the original and extended score applied in both MCR and no MCR patients. Due to the prospective treatment allocation and its

prospective application in our interdisciplinary tumour board, patients undergoing MCR were mostly absent in the data for MMPS >2, which lead to the smaller sample size in the cohort for MMPS >2. In both the MCR group and the no MCR group, there are a few patients above or below the cut-off of 2. This shows that there are cases where a treatment decision should not be based solely on a score, but medical experience and assessment still play a decisive role. The human judgement and the interdisciplinary discussion of each case at a tumour board should not be neglected.

In the extended score, the addition of albumin did not have a big effect ( $P$ -values of likelihood ratio tests were high) in the analysis of the Cox models with all predictors and multiple imputed data. With imputation, the effects of the predictors tended to become smaller. Possibly the 'missing at random' condition was not fulfilled, i.e. missing values are more likely to occur in certain patients (those with short or long survival). This could be the case in this present cohort and if such effects apply, it is difficult to impute. More data should be collected to gain more evidence.

Nevertheless, this analysis underlines the discriminative ability of the newly extended score, despite the high missingness of values necessary to calculate the MMPS.

## CONCLUSION

This analysis confirmed the benefit of the MMPS for patient allocation to surgery after it was prospectively incorporated into our treatment decision during interdisciplinary tumour board. The patients had a median survival of 30 months [95% CI 23–45 months] in case of MMPS = 0.

Albumin was the blood marker with the largest influence on OS and therefore incorporated in our extended MMPS with improved performance. Further analysis in a prospective manner and best randomized with a no MCR patient cohort is needed for full clarification of albumin's discriminative potential for a better patient selection.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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**Conflict of interest:** Isabelle Opitz Disclosures: Institutional Grant: Roche und Medtronic; Advisory's board: AstraZeneca und MSD; Speakers board: Astra Zeneca und Roche.

## Data Availability Statement

Data are available on request to the authors.



## Author contributions

**Daria Greb:** Data curation; Validation; Visualization; Writing—original draft; Writing—review & editing. **Monika Hebeisen:** Formal analysis; Methodology; Writing—review & editing; figures. **Alessandra Matter:** Data curation. **Isabelle Opitz:** Funding acquisition; Supervision; Writing—original draft; Writing—review & editing. **Olivia Lauk:** Data curation; Methodology; Validation; Visualization; Writing—original draft; Writing—review & editing.

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