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Circulating fibrinogen is a prognostic and predictive biomarker in malignant pleural mesothelioma

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Background: To investigate the clinical utility of pretreatment plasma fibrinogen levels in malignant pleural mesothelioma (MPM) patients.

Methods: A retrospective multicenter study was performed in histologically proven MPM patients. All fibrinogen levels were measured at the time of diagnosis and clinical data were retrospectively collected after approval of the corresponding ethics committees.

Results: In total, 176 MPM patients (mean age: 63.5 years \pm 10.4 years, 38 females and 138 males) were analysed. Most patients ($n = 154$, 87.5%) had elevated (≥ 390 mg dl⁻¹) plasma fibrinogen levels. When patients were grouped by median fibrinogen, patients with low level (≤ 627 mg dl⁻¹) had significantly longer overall survival (OS) (19.1 months, confidence interval (CI) 14.5–23.7 months) when compared with those with high level (OS 8.5; CI 6.2–10.7 months). In multivariate survival analyses, fibrinogen was found to be an independent prognostic factor (hazard ratio 1.81, CI 1.23–2.65). Most interestingly, fibrinogen (cutoff 75th percentile per 750 mg dl⁻¹) proved to be a predictive biomarker indicating treatment benefit achieved by surgery within multimodality therapy (interaction term: $P = 0.034$). Accordingly, only patients below the 75th percentile benefit from surgery within multimodality therapy (31.3 vs 5.3 months OS).

Conclusions: Fibrinogen is a novel independent prognostic biomarker in MPM. Most importantly, fibrinogen predicted treatment benefit achieved by surgery within multimodality therapy.

Malignant pleural mesothelioma (MPM) is a devastating and treatment-resistant disease. The pathogenesis of MPM is closely related to chronic inflammation, induced in up to 80% of all cases by former asbestos exposure (Ostroff *et al*, 2012). Despite recent

advances in chemotherapy, the outcome of MPM treatment is still disappointing and median overall survival (OS) of patients receiving current standard chemotherapy regimens is 9–12 months only (Vogelzang *et al*, 2003). More promising results have been

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achieved in MPM patients who were able to complete trimodality treatment protocols – consisting of induction chemotherapy, followed by macroscopic radical surgery and adjuvant radiation –, resulting in median OS time of 29.1 months. Nevertheless, even in this selected prospective cohort, only around 50% of the patients completed the trimodality therapy protocol leading to the aforementioned superior survival time, whereas the median OS of the full study cohort was 16.8 months only (Krug *et al*, 2009). Accordingly, there is an urgent need for biomarkers that can stratify the MPM patients who are likely to benefit from certain treatment modalities. Recently, our group demonstrated that serum C-reactive protein levels (CRP) at the time of MPM diagnosis predict survival benefit achieved by macroscopic radical tumour surgery within multimodality treatment regimens (Ghanim *et al*, 2012). In this study we showed, that patients with normal CRP values at time of diagnosis receiving multimodality therapy including surgery had a significantly better prognosis when compared with patients with elevated serum CRP undergoing surgery within multimodality therapy (median OS: 35.9 months vs 7.9 months) (Ghanim *et al*, 2012). These data suggested that other inflammation-related markers may also be utilised as clinically useful biomarkers for MPM patients.

Fibrinogen is an acute phase response protein, produced by the liver in response to pro-inflammatory cytokines. Similar to CRP, fibrinogen belongs to the positive acute phase response proteins, characterised by its elevation during systemic inflammation (Duvoix *et al*, 2013). Furthermore, fibrinogen has a central role in the blood coagulation cascade and during wound healing (Polterauer *et al*, 2009). It has also been shown that fibrinogen can act as a biomarker in several diseases such as coronary heart disease, chronic obstructive pulmonary disease and various types of malignancies (Rosenson and Koenig, 2003; Polterauer *et al*, 2009; Seebacher *et al*, 2010; Tang *et al*, 2010; Qiu *et al*, 2012; Seebacher *et al*, 2012; Tanaka *et al*, 2012; Du *et al*, 2013; Duvoix *et al*, 2013; Son *et al*, 2013). In addition, fibrinogen also has an important role during vessel formation, and thus can promote tumour progression by inducing neoangiogenesis (Laurens *et al*, 2006).

So far only one study investigated the fibrinogen levels in MPM patients. Fibrinogen levels were found to be elevated in MPM when compared with adenocarcinomas of the lung. Furthermore, plasma fibrinogen levels correlated with interleukin-6 and CRP levels (Nakano *et al*, 1998). However, to date, the prognostic or predictive impacts of fibrinogen levels have not been reported in MPM patients. Accordingly, we analysed the pretreatment plasma fibrinogen levels of histologically verified MPM patients at the time of diagnosis and its correlation to clinicopathological variables and outcome.

PATIENTS AND METHODS

Patients. Clinical data of 176 histologically verified MPM patients were analysed. Twenty-two patients were included by the LKH Hohegg, 91 patients by the Medical University of Vienna and 63 patients by the University Hospital Center Zagreb. Finally, the data of 150 patients were used for multivariate analyses as information regarding tumour stage was missing in 26 patients.

Patients receiving curative resection were pathologically staged according to the current IMIG staging system (Rusch, 1996) and dichotomized into the groups early- vs late-stage MPM (stage I and II were defined as early and stage III and IV as late stage of disease). In patients receiving chemo- and/or radiotherapy or best supportive care (BSC) only, clinical staging including CT/PET/PET-CT was used for allocating to the late-stage and early-stage group. The data of all patients were analysed after approval of the local ethics committees.

Fifty-four patients (30.7%) received macroscopic radical surgery within multimodality treatment protocols (induction chemotherapy and surgery: $n=17$; induction chemotherapy, surgery and radiotherapy (trimodality treatment): $n=14$; surgery and adjuvant radiotherapy: $n=4$; surgery and adjuvant chemotherapy: $n=5$; surgery and adjuvant chemoradiation: $n=4$; induction chemotherapy, surgery and adjuvant chemotherapy: $n=8$; and induction chemotherapy surgery and adjuvant chemoradiation: $n=2$), whereas 78 patients (44.3%) received chemo- and/or radiotherapy alone (chemo alone: $n=58$; radiation alone: $n=4$; chemotherapy and radiation: $n=16$) and furthermore, 44 patients received BSC (25%). Macroscopic complete resection (MCR) was achieved in most cases by extrapleural pneumonectomy (EPP) (46 patients), in five cases by pleurectomy/decortications and in three cases by wide radical tumour resections. Chemotherapy consisted of platinum-based doublet therapy in most of the cases both in the multimodality therapy as well as in the chemotherapy/chemoradiation treatment groups.

Fibrinogen plasma levels. In all patients included in the study, fibrinogen was measured during routine work-up to exclude coagulation disorders or presence of acute infection before surgery or diagnostic interventions. Only pretreatment and pre-interventional fibrinogen levels were used for statistical analyses. Patients suffering from acute infectious disease were excluded from all analyses due to the acute phase response characteristics of fibrinogen. For fibrinogen routine analyses, blood samples were derived from peripheral venous punctures on the day of admission to the hospital. Fibrinogen levels were measured according to the Claus method as previously described (Claus, 1957).

Statistical analysis. Median fibrinogen level of the whole-study population (627, range 196–1200, s.e. of the mean 15.8 mg dl^{-1}) was used to dichotomise into the high- and low-fibrinogen groups. The association of fibrinogen and patients' age, sex, stage of disease, applied treatment modality and histological subtype was investigated by the two-sided χ^2 test. Overall survival was defined as time between histological MPM confirmation and date of last follow up (censored patients) or date of death. The Kaplan–Meier method was used for survival estimation and the log-rank test was performed to investigate univariate impact on OS. The Cox regression model was assessed for uni- and multivariate survival analyses. Receiver Operating Characteristic (ROC) curve analysis was performed to investigate the sensitivity and specificity of fibrinogen levels and compared with CRP for predicting short-term survival in MPM. Therefore, the median OS (13.8 months) of the entire study population was used as cutoff point to divide the study population into long ($n=47$) and short-term survivors ($n=49$). Patients still alive but not reaching median OS were excluded from these analyses ($n=17$). In 63 patients, no diagnostic CRP level was available. Accordingly, for the ROC analysis comparing CRP with fibrinogen, 96 patients were used. All reported P -values were given as two sided and were considered statistically significant below 0.05. The Youden Index was calculated as (sensitivity + specificity) – 1 for each cutoff point. All statistical analyses were performed using the PASW Statistics 18.0 package (Predictive Analytics Software, SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 176 histologically verified MPM patients (mean age: 63.5 years \pm 10.4 years, 38 females and 138 males) were included. Most patients had epithelioid histological subtype ($n=146$, 83%) followed by biphasic ($n=18$, 10.2%) and sarcomatoid MPM ($n=12$, 6.8%). For the statistical analysis, we combined the biphasic and the sarcomatoid subtype as non-epithelioid MPM

($n = 30$, 17%). One hundred and thirty-one patients (87.3%) were diagnosed as late-stage MPM (either stage III or IV), whereas only 19 patients (12.7%) were detected at the early stage (stage I and II) of disease. In 26 patients (14.8%), information about the staging was missing in the medical records. All patients were allocated to the three major treatment groups: BSC ($n = 44$), chemo- and/or radiotherapy ($n = 78$) and multimodality therapy including surgical MCR ($n = 54$) as previously defined (Ghanim *et al*, 2012).

The majority ($n = 154$, 87.5%) of all analysed patients had clinically relevant elevated (≥ 390 mg dl⁻¹) plasma fibrinogen levels at the time of MPM diagnosis. Fibrinogen levels were strongly correlating with serum CRP ($n = 113$, Pearson's correlation coefficient: 0.68, $P < 0.001$) as already previously shown (Nakano *et al*, 1998). At diagnosis, median fibrinogen level of the entire study population was 627 mg dl⁻¹ (range: 196–1200, s.e.m. 15.8). When patients were divided by median fibrinogen level, 87 patients were allocated to the high-fibrinogen group (> 627 mg dl⁻¹) and 89 patients were allocated to the low-fibrinogen group (≤ 627 mg dl⁻¹). Table 1 shows patient characteristics according to fibrinogen levels. There was no significant difference between the high vs low-fibrinogen group with regard to age, gender or histological subtype, whereas patients in the high-fibrinogen group were more frequently diagnosed at the late stage of disease and were more frequently treated by BSC or chemo- and/or radiotherapy than by multimodality therapy including macroscopic radical surgery.

Median OS of the entire study population was 13.8 months (95% CI 11–16.7 months). In univariate survival analyses, treatment ($P < 0.001$), histology ($P = 0.001$), stage ($P = 0.012$) and fibrinogen (either as metric factor ($P < 0.001$), grouped by median ($P < 0.001$) or clinical cutoff ($P = 0.001$)) had significant prognostic impact on OS, whereas age (neither as metric nor as grouped by

median) and gender showed no prognostic value (as summarised in Table 2).

Patients receiving multimodality therapy including macroscopic radical surgery survived significantly longer (OS 30.9 months, CI 12.9–48.9 months) than patients treated by chemo- and/or radiotherapy alone (OS 12.6 months, CI 8.7–16.5 months, $P = 0.001$) or those receiving BSC (OS 6.5 months, CI 3.8–9.3 months, $P < 0.001$) as shown in Figure 1A. Patients with the epithelioid histological subtype had significantly better prognosis (OS 14.6 months, CI 10.5–18.7 months) when compared with those with non-epithelioid subtype (OS 6.5 months, CI 2.9–10.1 months, $P = 0.001$, Figure 1B). Furthermore, the late stage of disease was associated with poor outcome (OS 12.8 months, CI 9.7–15.9 months) when compared with early stage (OS 18.6 months, 0–39.8 months, $P = 0.012$) in univariate survival analyses (Figure 1C).

Fibrinogen was a prognostic marker when analysed either as a metric variable ($P < 0.001$), grouped by the clinical cutoff value (hazard ratio (HR) 2.5, CI 1.4–4.2, $P = 0.001$) or by the median fibrinogen level of the entire study population (HR 2.1, CI 1.5–3.0, $P < 0.001$). Accordingly, patients in the low-fibrinogen group (≤ 627 mg dl⁻¹) survived significantly longer (OS 19.1 months, 14.5–23.7 months) than patients in the high-fibrinogen group (OS 8.5 months, 6.2–10.7 months, $P < 0.001$) (Figure 2A).

In order to clarify whether fibrinogen is an independent prognostic factor in MPM, we performed multivariate survival analyses. Therefore, Cox regression was utilised and the model was adjusted for age (grouped by median age), gender, stage (early vs late stage), histology (epithelioid vs non-epithelioid MPM), treatment (BSC vs chemo- and/or radiotherapy vs multimodality therapy including macroscopic radical surgery) and fibrinogen. Histological subtype (HR 2.5, CI 1.4–4.2, $P = 0.001$), treatment

Table 1. Patient characteristics and distribution according to median fibrinogen level

Characteristics	High fibrinogen (> 627 mg dl ⁻¹)		Low fibrinogen (≤ 627 mg dl ⁻¹)		P-value ^a	All patients	
	Numbers	(%)	Numbers	(%)		Numbers	(%)
Age, years							
≤ 64	46	52.9	39	43.8	0.23	85	48.3
> 64	41	47.1	50	56.2		91	51.7
Sex							
Female	17	19.5	21	23.6	0.51	38	21.6
Male	70	80.5	68	76.4		138	78.4
Histology							
Epithelioid	68	78.2	78	87.6	0.10	146	83.0
Non-epithelioid	19	21.8	11	12.4		30	17.0
Stage^b							
Early stage	5	6.9	14	17.9	0.04	19	12.7
Late stage	67	93.1	64	82.1		131	87.3
Treatment							
Best supportive care	26	29.9	18	20.2	0.01	44	25.0
Chemo- and/or radiotherapy	44	50.6	34	38.2		78	44.3
Multimodality treatment including radical surgery	17	19.5	37	41.6		54	30.7

^aTwo-sided χ^2 -test.
^bMissing cases: $n = 26$ (14.8%).

Table 2. Univariate survival analyses (n = 176)

Characteristics	OS (CI)	P-value ^a	HR (CI)
Age, years			
≤ 64	13.7 (10.0–17.4)	0.52	0.90 (0.64–1.25)
> 64	13.9 (10.3–17.6)		
Sex			
Female	12.0 (8.2–15.9)	0.54	0.88 (0.58–1.33)
Male	13.9 (10.7–17.2)		
Histology			
Epithelioid	14.6 (10.5–18.7)	<0.01	2.01 (1.31–3.10)
Non-epithelioid	6.5 (2.9–10.1)		
Stage^b			
Early stage	18.6 (0–39.8)	0.01	2.09 (1.17–3.76)
Late stage	12.8 (9.7–15.9)		
Treatment			
Best supportive care	6.5 (3.8–9.3)	<0.01	2.81 (1.75–4.51)
Chemo- and/or radiotherapy	12.6 (8.7–16.5)		2.03 (1.33–3.10)
Multimodality treatment including radical surgery	30.9 (12.9–48.9)		1
Fibrinogen			
High fibrinogen	8.5 (6.2–10.7)	<0.01	2.11 (1.49–2.99)
Low fibrinogen	19.1 (14.5–23.7)		

Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival.
^aTwo-sided log-rank test.
^bMissing cases: n = 26 (14.8%).

(BSC: HR 2.5, CI 1.4–4.4, P = 0.002, chemo- and/or radiotherapy: HR 1.7, CI 1.0–2.8, P = 0.036, multimodality therapy including surgery: P = 0.009) and fibrinogen (HR 1.8, CI 1.2–2.7, P = 0.003) were found to be independent prognostic factors after multivariate survival analyses, whereas age, gender and tumour stage had no independent prognostic impact on OS in our study population as shown in Table 3.

As fibrinogen showed independent prognostic power in our retrospective study, we explored the possibility that fibrinogen — similar to CRP (Ghanim *et al*, 2012) — could also predict response to various treatment modalities. We therefore utilised the above mentioned Cox regression model and calculated the interaction terms for treatment and fibrinogen. No significant interaction was found between treatment and median fibrinogen (interaction P-value for BSC: 0.901, chemo- and/or radiotherapy: 0.816 and for multimodality therapy: 0.926) excluding a predictive value of median fibrinogen in our study population. However, using the 75th percentile for grouping the study population, fibrinogen showed a significant interaction P-value (interaction term 0.034) indicating that patients with remarkably elevated fibrinogen (> 750 mg dl⁻¹) do not benefit from radical surgery within multimodality therapy when compared with patients receiving chemo- and/or radiotherapy and BSC. Accordingly, patients above the 75th percentile receiving multimodality therapy survived significantly shorter than patients under the 75th percentile also receiving macroscopic radical surgery within multimodality therapy (5.3 vs 31.3 months OS, Figure 2B). Thus, circulating fibrinogen below the cutoff level of 750 mg dl⁻¹ was found to be a predictive biomarker, indicating benefit achieved by surgery as part of the multimodality treatment regimen.

Finally, we investigated the sensitivity and specificity of plasma fibrinogen levels in predicting short-term OS and compared its prognostic power with the CRP levels. Therefore, ROC analysis

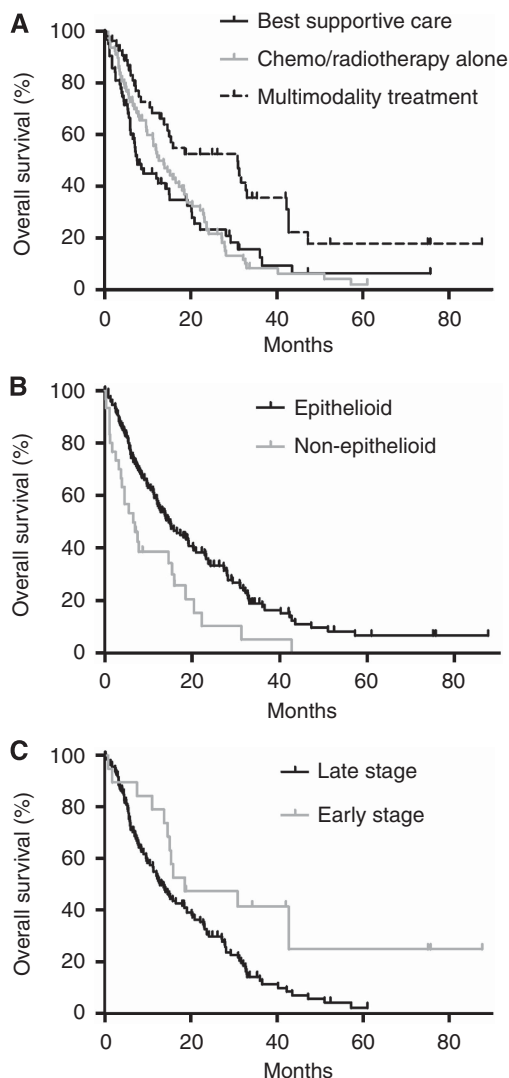


Figure 1. Overall survival of patients according to treatment regimen (A), histological subtype (B) and disease stage at the time of diagnosis (C). Multimodality treatment results in a significant increase in OS when compared with best supportive care or to chemo- and/or radiotherapy alone (P < 0.001). Epithelioid mesothelioma confers a better prognosis in terms of OS over non-epithelioid mesothelioma (P = 0.001). Mesothelioma patients diagnosed at early stage have significantly increased OS when compared with late-stage (P = 0.012).

was performed and we tested both markers for early mortality prediction (death before median OS (13.8 months) of the entire study population was reached). The area under the curve (AUC) for prognosticating early death was 0.771 and 0.734 for CRP and fibrinogen, respectively, indicating that both biomarkers had equally high accuracy for predicting poor outcome in MPM (Figure 3). We also determined the cutoff point with the highest Youden index for prognosticating early death. It was found to be very close to the median fibrinogen level (the highest Youden index was 0.335 at 623.5 mg dl⁻¹ (sensitivity 65.1%, specificity 68.4%). In turn, the prognostic value at the two different cutoff points was essentially the same (fibrinogen median (≤ 627 mg dl⁻¹) HR 2.1, CI 1.5–3.0 vs fibrinogen Youden (at 623.5 mg dl⁻¹) HR 2.2, CI 1.5–3.1). Considering sensitivity/specificity analysis, median fibrinogen level (≤ 627 mg dl⁻¹) reached a sensitivity of 63.9% and a specificity of 68.4% for early death prediction. When using the 75th percentile (750 mg dl⁻¹) as cutoff point, a lower sensitivity of 31.3% but higher specificity of even 82.9% was reached for

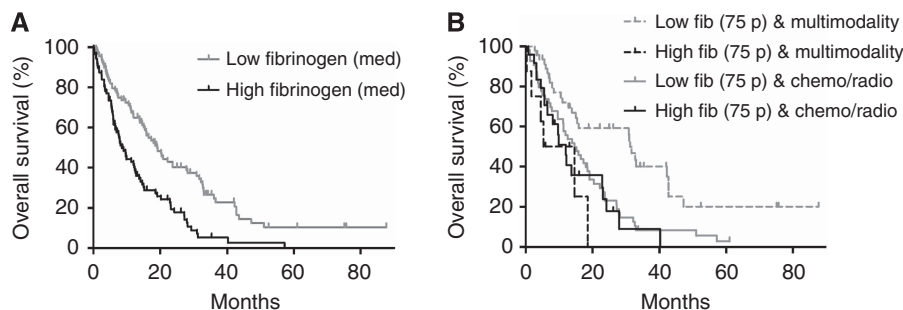


Figure 2. The prognostic and predictive impact of plasma fibrinogen levels in MPM. (A) Patients with low fibrinogen (below median, $\leq 627 \text{ mg dl}^{-1}$) demonstrate superior OS as opposed to patients with high levels ($> 627 \text{ mg dl}^{-1}$). (B) The Kaplan–Meier survival analysis demonstrated the predictive impact of fibrinogen at the cutoff of 750 mg dl^{-1} (75th percentile). Patients with higher fibrinogen levels than the 75th percentile/ 750 mg dl^{-1} do not benefit from multimodality treatment including macroscopic radical surgery when compared with chemo- and/or radiotherapy alone.

Table 3. Cox regression model adjusted for patient characteristics of all patients with available complete data for model adjustment ($n = 150$, 85.2% of the total study population)

Characteristics	Adjusted HR for death	95% CI	Adjusted P-value
Age, years			
≤ 64	0.87	0.60–1.27	0.47
> 64	1		
Sex			
Female	1.22	0.74–2.02	0.44
Male	1		
Histology			
Epithelioid	1		<0.01
Non-epithelioid	2.45	1.43–4.21	
Stage			
Early stage	1		0.25
Late stage	1.52	0.75–3.10	
Treatment			
Best supportive care	2.45	1.38–4.35	<0.01
Chemo- and/or radiotherapy	1.70	1.04–2.80	0.04
Multimodality treatment including radical surgery	1		<0.01
Fibrinogen			
High fibrinogen	1.81	1.23–2.65	<0.01
Low fibrinogen	1		

Abbreviations: CI = confidence interval; HR = hazard ratio.

predicting early death in MPM. In contrast, CRP (cutoff 1 mg dl^{-1}) reached a very high sensitivity of 93.9%, whereas the specificity was 46.8% only.

DISCUSSION

Here we report, to the best of our knowledge for the first time, that the plasma fibrinogen level at the time of diagnosis is an independent prognostic biomarker in MPM patients. More importantly, fibrinogen was found to be a predictive biomarker

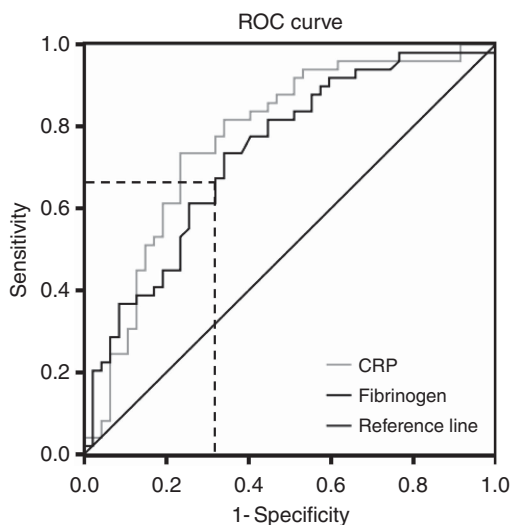


Figure 3. The accuracy of the plasma fibrinogen level and the CRP level to predict short-term OS in MPM. Receiver Operating Characteristic curve considering early death prediction (death before median overall survival of 13.8 months) showed an AUC of 0.734 and 0.771 for fibrinogen and CRP, respectively. The dotted lines mark the highest Youden index for fibrinogen (Youden index = 0.335, sensitivity = 0.651, specificity = 0.684, cutoff at 623.5 mg dl^{-1}).

in MPM, indicating survival benefit achieved by macroscopic radical surgery within multimodality treatment regimens. Patients with diagnostic fibrinogen levels above the 75th percentile did not benefit from macroscopic complete resection within multimodality treatment protocols in our retrospective multicenter study.

Recently, the survival benefit of MCR by EPP in MPM patients has been questioned (Treasure *et al*, 2011). However, in the past decades superior survival was described in retrospective studies for patients receiving MCR especially in subgroups able to complete trimodality therapy (Krug *et al*, 2009). These findings highlight the urgent need for better patient selection criteria and predictive biomarkers especially with regard to MCR within multimodality treatment regimens to offer the opportunity of life prolonging radical treatments on the one hand and protecting patients from futile and harmful therapy on the other hand (Scherpereel *et al*, 2010; Stahel *et al*, 2010; Cao *et al*, 2011). Recently we showed, that pretreatment serum CRP levels at the time of diagnosis can predict survival benefit, achieved by MCR within multimodal therapy. Patients with normal CRP receiving multimodality therapy had a superior median OS of 35.9 months (95% CI 7.7–11.7) when

compared with patients with elevated CRP receiving multimodality therapy (OS 7.9 months, 95% CI 4.9–10.8) (Ghanim *et al*, 2012). In other words: patients with normal CRP receiving radical surgery within multimodality therapy had more than two-fold longer OS time when compared with the patients included in the Mesothelioma and Radical Surgery (MARS) feasibility study receiving EPP (Treasure *et al*, 2011). Similar to our previous findings (Ghanim *et al*, 2012), we show in our present study, that patients with diagnostic fibrinogen levels above the 75th percentile receiving multimodality therapy survived significantly shorter than patients under the 75th percentile also treated by multimodality therapy (5.3 vs 31.3 months OS, Figure 2).

Similar to the study of Seebacher *et al* (2010) on endometrial cancer and to the study of Polterauer *et al* (2009 on ovarian cancer, we found an association of elevated diagnostic fibrinogen level with the advanced stage of disease. However, it is not clear yet, whether elevated fibrinogen in late-stage cancer patients is a result of enhanced immune response against the higher tumour load or due to increased autocrine growth stimulation (Polterauer *et al*, 2009; Seebacher *et al*, 2010). In accordance with other studies on thoracic malignancies, there was a strong positive correlation between fibrinogen and CRP levels (Nakano *et al*, 1998; Gulen *et al*, 2012). These findings suggest that increased fibrinogen and CRP levels in MPM patients are a consequence of similar pro-inflammatory mechanisms as it has been already proposed by Nakano *et al* (1998). Furthermore, sensitivity and specificity analysis in our study indicated that both CRP and fibrinogen are promising biomarkers in MPM. The combination of the two markers would result in increased accuracy as CRP has a higher sensitivity and fibrinogen is characterised by higher specificity in predicting early death in MPM.

To date, it is not understood whether fibrinogen and its prognostic power in cancer patients is only a bystander characteristic or fibrinogen itself has an active role during cancer progression by promoting cell adhesion, proliferation, angiogenesis and cell migration (Laurens *et al*, 2006). Furthermore, the biological background of fibrinogen's prognostic and predictive power also remains to be unveiled.

In summary, in this study we were able to show for the first time that fibrinogen is an independent prognostic biomarker in MPM patients. More importantly, we found a significant interaction between diagnostic fibrinogen levels and treatment modality, indicating, that MPM patients with remarkably elevated fibrinogen levels do not benefit from aggressive multimodality therapy including MCR. However, further independent investigations and future prospective studies are needed to fully explore the potential of these markers in MPM. In the past few years, a set of clinically already available biomarkers – including CRP and fibrinogen – has emerged that could (cost) effectively support the therapeutic decision making process in cancer patients in addition to their classical (inflammatory/coagulation system) indications.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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