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ORIGINAL ARTICLE

Health-related quality of life and inflammatory markers in malignant pleural mesothelioma

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Abstract
Purpose Malignant pleural mesothelioma (MPM) is a highly aggressive and symptomatic disease. We examined the relationship between health-related quality of life (HRQoL) and inflammatory markers, and the prognostic role of HRQoL in MPM patients.
Methods MPM patients from two parallel phase II studies (thalidomide alone or thalidomide with chemotherapy) were included. HRQoL was assessed at baseline using the modified Lung Cancer Symptom Scale (LCSS). Baseline inflammatory markers and cytokines were measured. Spearman correlation was used to examine the relationship between inflammatory markers and HRQoL measures. The prognostic value of the HRQoL domains was examined using Cox proportional hazard model.
Results Sixty-three patients were included: median age 61 years (range 44–79); 82 % male; 77 % Eastern Cooperative Oncology Group (ECOG) performance status 0–1; 44 % epithelial histology subtype. Baseline systemic symptoms of anorexia and fatigue, the summation symptoms of overall symptomatic distress, interference with normal activity and global QoL and the aggregate score of total LCSS score were all associated with elevated neutrophil-to-lymphocyte ratio, C-reactive protein and vascular endothelial growth factor levels at baseline (rho≥0.25; $p<0.05$). Baseline anorexia, fatigue, cough, dyspnoea, pain, overall symptomatic distress, interference with normal activity, global QoL and total LCSS score were all significantly related to survival ($p<0.05$) after adjusting for established prognostic factors (age, gender, histological subtype and performance status) and treatment effect.
Conclusions In conclusion, HRQoL seems to relate to a patient's systemic inflammatory status and is associated with survival in MPM patients.

Keywords Cancer · Health-related quality of life · Lung cancer symptom scale · Malignant mesothelioma · Sickness behaviour · Systemic inflammation

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive neoplasm that arises from the mesothelial surfaces of the pleural cavity. Patients with MPM have an almost invariably fatal course. The largest randomised trial of MPM to date, demonstrated a median survival of 12 months in patients treated with combination chemotherapy of cisplatin and pemetrexed [1]. Chemotherapy has also been found to improve the quality of life of patients with MPM [2], however most patients present with locally advanced disease and relentlessly progressive symptoms and the symptom burden in MPM patients is high [3]. There is a need for palliative treatments which can decrease the tumour burden and improve symptoms, such as pain and dyspnoea.

The prognostic significance of health-related quality of life (HRQoL) has been widely reported in cancer clinical trials [4, 5]. Two HRQoL instruments have been validated in MPM patients. Two studies have demonstrated that HRQoL measured by the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and Lung Cancer Module (QLQ-LC13) predicted for survival, with improvement in HRQoL with chemotherapy [3, 6]. Similarly, a modified version of the Lung Cancer Symptom Scale (LCSS), where haemoptysis was omitted from the scale, showed predictive validity [2].

It is recognised that "sickness behaviour", used to describe a constellation of non-specific symptoms of fatigue, anorexia, fever, depression, cognitive impairment and exaggerated response to pain, evident in patients with systemic infection, is due to increased pro-inflammatory cytokines and an exaggerated inflammatory response [7, 8]. There is increasing evidence that the same underlying mechanism may also account for some of the tumour and treatment-related symptoms in cancer patients [9, 10].

Inflammation appears to play a critical role in the pathogenesis of MPM as asbestos fibres lodged in the pleura produce chronic local inflammation caused by 'frustrated phagocytosis'. As the development of MPM progresses, the systemic inflammatory response appears to be exaggerated with fatigue and weight loss being common non-specific symptoms [11]. Recently, we demonstrated that blood neutrophil-to-lymphocyte ratio (NLR), a simple marker of systemic inflammation, appears to be an independent predictor of survival in MPM patients, suggesting the importance of systemic inflammation in determining the prognosis of MPM patients [12, 13]. NLR has been extensively investigated as an inflammatory marker in critically ill patients [14], cardiovascular patients undergoing intervention [15] and a variety of cancers [16–19].

We postulated that symptoms due to the exaggerated systemic inflammatory response would impair patient's HRQoL and that peripheral inflammatory markers such as NLR, C-reactive proteins (CRP) and plasma cytokines would be positively associated with patient's HRQoL. In this current study, we have two aims: (1) to assess the relationship between HRQoL and inflammatory markers and (2) to examine the prognostic value of HRQoL in survival of MPM patients using the validated LCSS instrument.

Materials and methods

Patients

MPM patients from two parallel phase II studies (thalidomide as a single agent or thalidomide combined with cisplatin and gemcitabine) were included in this study [20]. Eligible patients had to have histologically confirmed advanced (inoperable) MPM with measurable disease and adequate renal function; adequate hepatic function; adequate bone marrow reserve; life expectancy greater than 8 weeks. Patients in these studies were recruited between April 2001 and August 2003.

All enrolled patients had baseline HRQoL assessment using the LCSS and blood samples including full blood count (haemoglobin, white cell count [WCC] and its differential counts) and inflammatory markers measured at the time of patient consent to the study. Patients had to commence the treatment within 1 week of the consent.

The study protocol was approved by the Human Research Ethics Committee at the Royal North Shore Hospital, St Leonards, Sydney, and all patients have provided informed consent to participate in the study.

Baseline assessment

Patient characteristics (including patient performance status [PS], as assessed by Eastern Cooperative Oncology Group [ECOG] score), tumour-related details, HRQoL and laboratory parameters, were recorded at baseline prior to the commencement of therapy.

The HRQoL was assessed using the LCSS [21]. This is a self-reported visual analogue scale with a range from 0 to 100 for each domain. The modified LCSS consists of five symptom items of anorexia, fatigue, cough, dyspnoea, pain, as well as three summation items of overall symptomatic distress, interference with normal activities and global QoL. A total LCSS score was derived from the mean of the eight items. The nine HRQoL items (i.e. five symptom scores, three summation items and total LCSS) were examined for their prognostic role in survival.

Blood in serum tubes was collected at baseline for biomarker analysis but was not controlled for diurnal rhythm. Collected blood was spun at 2,500×*g* for 10 min, and separated serum was stored into 250 μl aliquots at −80 °C. Baseline inflammatory markers such as CRP, interleukin 6 (IL6), IL6 soluble receptors (IL6-SR) and vascular endothelial growth factor (VEGF) were measured in duplicate at the end of the trial and therefore the serum samples were only thawed once. All biomarkers were measured by ELISA using commercially available kits and in accordance with the manufacturer's instructions. Serum VEGF was measured by the Quantikine kit (R&D Systems, Minneapolis, MN USA) and serum CRP by the Alpha Diagnostic International kit (San Antonio, TX USA). Serum IL-6 and serum IL6-SR were measured by the duo kit (R&D Systems) using Nunc C96 Maxisorp plates (Nunc, Denmark) and TMB Blue Substrate Chromagen (Dako, Sydney, Australia). The relevant absorbance was measured using a Synergy HT spectrophotometric multiwell plate reader (Bio Tek, Winooski,

VT). Analyte concentrations were calculated from a polynomial regression curve of the assay standards fitted using KC4 software (Bio Tek, Winooski, VT).

The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

Survival was calculated from the date of commencement of systemic treatment administered per protocol and the date of death or last follow-up. Patients were censored at last follow-up if still alive or lost to follow-up. These vital status data were obtained prospectively from the clinic visits.

Statistical analysis

To assess the relationship between HRQoL measures, PS and inflammatory markers (aim 1), Spearman correlation was used. For the second aim (to examine the prognostic value of HRQoL), the LCSS domains (as continuous covariates) were entered into the Cox proportional hazard model. The individual domains were entered into separate multivariate models. Each model included established prognostic factors: age (continuous variable), gender (male vs. female), ECOG PS (0 vs. ≥1) and histological subtype (epithelial vs. non-epithelial); and was controlled for the treatment effect (base model). The summation items and total LCSS score were not included together or with the individual symptom domains in the same model due to multicollinearity [22]. We have previously demonstrated the independent prognostic importance of NLR and histological subtype, while other inflammatory markers such as CRP, IL6, IL6-SR, and VEGF were not independently associated with survival in this cohort [12]. As such, we further included NLR (a continuous co-variate) in the multivariate model with two aims: (1) to determine if any HRQoL domains added further prognostic information in addition to NLR and histological subtype; (2) to assess mediation of HRQoL on the relationship between inflammation (as assessed by NLR) and survival. Patients from both arms of the study were combined for Cox proportional hazard model and Spearman's correlation analysis in this study. All analyses were performed using SPSS for Windows version 17.0.

Results

Baseline patient characteristics

Sixty-three patients were enrolled in the two parallel phase II studies: 34 had thalidomide with chemotherapy (cisplatin+ gemcitabine; arm A) and 29 had thalidomide alone (arm B). All 63 patients completed HRQoL questionnaires and had baseline bloods taken. The median age for the study participants was 61 years with a range of 44 to 78 years. There was a predominance of male participants (83 %) and the majority had good PS (78 % with ECOG 0-1). Under half of the patients (44 %) had the epithelial histological subtype. Nine patients in arm B received chemotherapy previously; however, the interval between the previous chemotherapy and commencement of thalidomide was unknown as this information was not recorded in the initial study. The baseline HRQoL measures and the PS of those who received chemotherapy previously were not significantly different to those patients who were chemotherapy-naïve ($p \geq 0.05$). The baseline HRQoL measures were not significantly different according to the treatment received ($p \geq 0.05$). The median survival for the entire cohort was 9.5 months (95 % CI: 3.7–15.3 months). Table 1 summarises the baseline patient characteristics according to the study arm.

Table 2 summarises the distribution of the baseline inflammatory markers and scores from the LCSS domains. There were no statistically significant difference in the LCSS domains or inflammatory markers by study arm, except for CRP (mean 73.6 ng/mL [standard deviation 88.8 ng/mL] vs. 34.0 ng/mL [standard deviation 51.4 ng/mL] for arm A and B respectively, $p=0.04$).

Relationship between HRQoL, PS and inflammatory markers

Table 3 summarises the association between the nine LCSS domains, patients' PS and the inflammatory markers.

Systemic symptoms such as anorexia and fatigue, the summation of overall symptomatic distress, interference with normal activity and global QoL, and the total LCSS score all showed a correlation with NLR, CRP and VEGF levels (Spearman correlation >0.25, $p<0.05$).

Local symptoms such as cough, dyspnoea and pain were not consistently associated with increased levels of the inflammatory markers and cytokines examined.

IL6 levels were associated with fatigue, interference with normal activity, global QoL and total LCSS score only (Spearman correlation >0.25, $p<0.05$), but IL6-SR levels were not associated with any of the HRQoL domains.

Patients' PS was associated with most HRQoL domains—with deteriorating PS relating to worsening HRQoL domains, with the exception of cough. Elevated PS levels were also associated with increasing CRP, IL6 and VEGF levels.

Prognostic significance of health-related quality of life

Baseline anorexia ($p=0.007$), cough ($p=0.01$), pain ($p=0.006$), overall symptomatic distress ($p=0.031$), interference with normal activity ($p=0.05$), global QoL ($p=0.001$), and total LCSS score ($p=0.004$) were found to be significantly related to survival in the univariate analysis.

Table 4 summarises the base multivariate model including the established factors (age, gender, histological subtype

Table 1 Patient characteristics

Characteristic		Arm A thalidomide+chemotherapy (n=34)	Arm B thalidomide alone (n=29)
Gender			
Male		27	25
Female		7	4
Age (years)			
Median (range)		61 (44–76)	67 (50–78)
Histology			
Epithelial		14	14
Sarcomatoid		3	1
Mixed/undifferentiated		17	14
Performance Status			
ECOG 0		4	2
ECOG 1		23	20
ECOG 2		7	6
ECOG 3		0	1
Prior Treatments			
Chemotherapy	Cisplatin±Gemcitabine	0	6
	Cisplatin/Pemetrexed	0	3
Surgery	Pleurectomy/decortication	2	2
Radiotherapy		6	3
Time from diagnosis (weeks)			
Median (range)		11 (4–402)	15 (4–126)
Time on study (weeks)			
Median (range)		17 (4–402)	15 (4–126)
Overall survival (months)			
Median		14.3	5.2
95 % confidence interval		3.3–25.3	0–10.5

Table 2 Distribution of the baseline inflammatory markers and the LCSS domains in the entire cohort

	Mean	Standard deviation	Minimum	Maximun
Inflammatory markers				
CRP (ng/ml)	55.1	75.9	0.7	324.1
IL6 (pg/ml)	16.0	20.6	0.4	93.4
IL6-SR (ng/ml)	29.6	15.5	1.3	83.8
VEGF (pg/ml)	756.3	570.8	78.5	2580.5
NLR	5.2	3.7	1.6	20.6
LCSS Domains				
Anorexia	26.0	23.3	0	77
Fatigue	38.7	23.7	2	95
Cough	24.0	23.3	0	85
Dyspnoea	40.6	24.3	1	96
Pain	28.6	27.0	0	94
Overall symptomatic distress	38.1	29.0	0	100
Interference with normal activity	42.9	29.0	0	100
Global QoL	41.9	28.6	0	98
Total LCSS Score	31.6	18.8	3.7	69.7

CRP C-reactive protein, *IL6* interleukin 6, *IL6-SR* interleukin 6 soluble receptor, *VEGF* vascular endothelial growth factor, *NLR* neutrophil-to-lymphocyte ratio, *LCSS* Lung Cancer Symptom Scale, *QoL* quality of life

Table 3 Spearman's correlation between inflammatory markers and LCSS domains

	CRP	NLR	IL6	IL6-SR	VEGF	ECOG PS
Anorexia	0.30*	0.46*	0.23	-0.01	0.32*	0.46*
Fatigue	0.38*	0.37*	0.29*	0.08	0.41*	0.44*
Cough	0.15	0.15	0.20	-0.26	0.28*	0.15
Dyspnoea	0.31*	0.23	0.24	-0.04	0.37*	0.41*
Pain	0.16	0.25*	0.09	0.03	0.16	0.3*
Overall Symptomatic Distress	0.38*	0.34*	0.24	-0.06	0.39*	0.48*
Interference with Normal Activity	0.49*	0.36*	0.33*	-0.11	0.51*	0.44*
Global QoL	0.46*	0.44*	0.33*	0.03	0.44*	0.38*
Total LCSS Score	0.43*	0.42*	0.32*	-0.04	0.47*	0.47*
ECOG PS	0.45*	0.21	0.42*	-0.07	0.46*	1

*Correlation >0.25 with $p<0.05$

Shaded box denotes correlation with a p value≤0.001

CRP C-reactive protein, *NLR* neutrophil-to-lymphocyte ratio, *IL6* interleukin 6, *IL6-SR* interleukin 6 soluble receptor, *VEGF* vascular endothelial growth factor, *QoL* quality of life, *LCSS* Lung Cancer Symptom Scale, *ECOG PS* Eastern Cooperative Oncology Group performance status

and PS) and controlling for treatment effect. Table 5 summarises the univariate and multivariate analyses for the prognostic significance of all LCSS domains. After entering the individual LCSS domains in the base multivariate model one at a time, baseline anorexia (p=0.003), fatigue (p=0.008), cough (p=0.01), dyspnoea (p=0.05), pain (p=0.007), overall symptomatic distress (p=0.003), interference with normal activity (p=0.007), global QoL (p=0.001) and total LCSS score (p=0.001) remained significant.

As NLR was previously demonstrated to have prognostic implications in this cohort of patients, we included NLR in the base multivariate model (model consisting of age, gender, histological subtype, performance status, treatment and NLR) and entered the individual LCSS domains in the new base multivariate model one at a time (Table 6). NLR remained a statistically significant factor in all analyses ($p<$ 0.05), but the effect of NLR on survival was reduced when a HRQoL domain was included as a mediator. The direct effect was *partially* mediated—it was smaller by 20 % at most. Only cough (p=0.04), overall symptomatic distress (p=0.04), interference with normal activity (p=0.04), global QoL (p= 0.02), and total LCSS score (p=0.01) remained as independent predictors for survival when NLR was included in the multivariate model. Table 6 summarises the results of the LCSS domains and NLR in the new multivariate models.

Discussion

The results in this study confirm the prognostic significance of HRQoL measured by LCSS in MPM patients. In our series of MPM patients who participated in the two parallel phase II studies, treated either with thalidomide alone or thalidomide combined with chemotherapy, numerous domains measured

Table 4 Multivariate model with established prognostic factors and treatment effect (base multivariate model)

	HR	95 % CI	*p* value
Age*	0.81	0.54–1.22	0.32
Gender (male vs. female)	1.73	0.71–4.21	0.23
Histological subtype (non-epithelial vs. epithelial)	2.19	1.16–4.12	0.02
Performance status (≥1 vs. 0)	1.98	0.66–6.00	0.23
Treatment (thalidomide alone vs. in combination with chemotherapy)	1.43	0.72–2.85	0.31

*Increase in 10 years

HR hazard ratio, *CI* confidence interval

in the LCSS proved to have prognostic significance after adjusting for well established factors (age, gender, histological subtype and ECOG performance status) and treatment effect; these included anorexia, fatigue, cough, dyspnoea, pain, overall symptomatic distress, interference with normal activity and global QoL. The total LCSS score derived from the LCSS scale also demonstrated its prognostic role in the survival of MPM patients. This means that HRQoL provides independent prognostic information in addition to the established prognostic factors listed above. Although performance status is considered an important prognostic factor for MPM, this study only revealed a trend for the association between PS and survival. After adjusting for NLR, an independent prognostic factor in these patients [12], the association of HRQoL domains and survival was weaker, with only cough, overall symptomatic distress, interference with normal activity, global QoL and total LCSS score singularly providing additional prognostic information. These HRQoL domains did appear to mediate the effect of inflammation on survival, but not to a great extent.

These results are in keeping with the previous MPM literature where HRQoL was found to predict survival using the EORTC QLQ-C30/QLQ-LC13 and LCSS instruments [2, 3, 6]. Hollen et al. [2] determined that anorexia, pain, all three summation items and the total LCSS score were statistically significant factors in patients enrolled in two international MPM trials. Using the EORTC QLQ-C30 and QLQ-LC13 instruments, Nowak et al. [23] found physical function, role function, fatigue and pain to be significant factors associated with survival in a multivariate model. Similarly, in the phase III study of cisplatin with or without raltitrexed in patients with MPM, the HRQoL domains of pain and appetite, and the EORTC prognostic index (composed of stage of disease, histological subtype, time since diagnosis, white cell count and 10 selected key symptoms and HRQoL scales) were found to be independent prognostic indicators of survival in the final multivariate model [6].

The phenomenon of "sickness behaviour" refers to a cluster of symptoms experienced by unwell patients with systemic infection. It is mediated by pro-inflammatory cytokines in both the periphery and the central nervous system. There is a clear similarity between the symptoms in patients with infection and the systemic symptoms that are associated with a number of different types of cancer and/or their treatments. There is increasing clinical evidence that the underlying mechanism in many of the disease and treatment-related

Table 5 Univariate and multivariate analyses for the quality of life domains of Lung Cancer Symptom Scale (LCSS) as predictors for survival

	Univariate Analyses			Multivariate Analyses[a]		
	HR[b]	95 % CI	*p* value	**HR[b]**	95 % CI	*p* value
Anorexia	**1.18**	**1.04–1.32**	**0.007**	**1.21**	**1.07–1.39**	**0.003**
Fatigue	1.11	0.99–1.23	0.06	**1.18**	**1.05–1.34**	**0.008**
Cough	**1.15**	**1.04–1.29**	**0.01**	**1.17**	**1.03–1.32**	**0.01**
Dyspnoea	1.07	0.98–1.17	0.16	**1.12**	**1.00–1.26**	**0.05**
Pain	**1.16**	**1.04–1.29**	**0.006**	**1.18**	**1.05–1.33**	**0.007**
Overall Symptomatic Distress	**1.1**	**1.01–1.2**	**0.031**	**1.18**	**1.06–1.32**	**0.003**
Interference with Normal Activity	**1.1**	**1–1.2**	**0.05**	**1.17**	**1.04–1.31**	**0.007**
Global QoL	**1.19**	**1.07–1.32**	**0.001**	**1.23**	**1.09–1.40**	**0.001**
Total LCSS score	**1.25**	**1.07–1.45**	**0.004**	**1.34**	**1.13–1.59**	**0.001**

[a] Factors known to have prognostic implications (from the base multivariate model as displayed in Table 4) were taken into account in the separate multivariate models for each domain

[b] HR relates to a 10-point increase in the scores

Statistically significant results were shown in bold font.

HR hazard ratio, *CI* confidence interval, *QoL* quality of life, *LCSS* Lung Cancer Symptom Scale

Table 6 Multivariate analyses with factors from Table 4, neutrophil-to-lymphocyte ratio (NLR) and the quality of life domains of Lung Cancer Symptom Scale (LCSS) as predictors for survival

	HR	95 % CI	*p* value
Anorexia	1.14	0.99–0.31	0.06
NLR	**1.16**	**1.05–1.28**	**0.04**
Fatigue	1.12	0.99–1.28	0.08
NLR	**1.16**	**1.06–1.28**	**0.002**
Cough	**1.14**	**1.01–1.28**	**0.04**
NLR	**1.18**	**1.08–1.30**	**<0.001**
Dyspnoea	1.10	0.98–1.23	0.13
NLR	**1.18**	**1.07–1.29**	**0.001**
Pain	1.13	0.99–1.28	0.07
NLR	**1.17**	**1.06–1.29**	**0.002**
Overall symptomatic distress	**1.13**	**1.00–1.27**	**0.04**
NLR	**1.16**	**1.05–1.28**	**0.003**
Interference with normal activity	**1.13**	**1.00–1.27**	**0.004**
NLR	**1.17**	**1.07–1.29**	**0.001**
Global QoL	**1.17**	**1.03–1.34**	**0.02**
NLR	**1.16**	**1.05–1.28**	**0.04**
Total LCSS score	**1.25**	**1.05–1.50**	**0.01**
NLR	**1.15**	**1.05–1.27**	**0.005**

Statistically significant results were shown in bold font

HR hazard ratio, *CI* confidence ratio, *NLR* neutrophil-to-lymphocyte ratio, *QoL* quality of life, *LCSS* Lung Cancer Symptom Scale

cancer symptoms is related to pro-inflammatory cytokines and the systemic inflammatory status [9, 10].

Our study found a positive relationship between the inflammatory markers, in particular NLR, CRP and VEGF, and patient's systemic symptoms of anorexia and fatigue and the summation items. This confirms our hypothesis that patients with elevated inflammatory markers, indicative of an exaggerated systemic inflammatory response, have increased symptom burden and poorer HRQoL. Furthermore, this translates to a poorer PS as assessed by the physicians. The HRQoL assessment was performed prior to the commencement of therapy in this study and therefore, the symptoms that the patients experienced were related to cancer itself rather than the anti-cancer treatment. Although these findings are not surprising, to the best of our knowledge, this is the first study to demonstrate this association in MPM patients. We hypothesise that the positive association between inflammatory markers and the HRQoL domains accounted for the slightly attenuated independent prognostic effects of HRQoL after adjusting for NLR.

Our findings add to the growing body of literature that suggest a positive relationship between inflammatory markers and systemic symptoms as well as HRQoL and patient-reported outcomes in cancer patients. One quantitative review found a significant correlation between fatigue and circulating levels of IL6 and IL1 receptor antagonist (IL1 ra) in patients with a variety of solid tumours and haematological malignancies [24]. In a non-small cell lung cancer (NSCLC) study, elevated pro-inflammatory cytokines such as serum soluble receptor 1 for tumour necrosis factor (sTNF-R1) were found to be associated with a significant worsening of symptoms, while IL6 and IL10 increased significantly by week 8 of the therapy, suggesting concurrent chemoradiotherapy induced peripheral cytokine release [25]. Pusztai et al. [26] found that paclitaxel chemotherapy in breast cancer patients induced a transient increase in plasma IL10, IL8 and IL6 levels and these increases in cytokine levels correlated with the paclitaxel side effects of joint pain and flu-like symptoms. Several reports have also found a positive relationship between CRP and patient-reported fatigue regardless of the questionnaires used in NSCLC [27–29].

There are limitations in this study. Firstly, the number of participants was relatively small but despite this, significant findings were demonstrated that were unlikely to be due to chance alone. Secondly, the number of cytokines (IL6, IL6-SR and VEGF) measured in this study was limited. It would be interesting to evaluate a larger panel of cytokines in a MPM population. Finally, there were only a small number of patients with serial measurements of inflammatory markers and HRQoL available and as such, no meaningful results could be presented regarding the longitudinal change of those measures or the effects of treatment on those variables. This also needs to be explored in future studies as the dynamic change in the inflammatory markers over time and its relationship with aggravating symptoms would be critical.

Conclusion

In keeping with previously reported studies, we found that HRQoL may have additional prognostic value in MPM patients. This study also confirms the 'sickness behaviour' phenomenon in MPM patients where systemic symptoms such as fatigue and anorexia are related to exaggerated systemic inflammatory response, evident with elevated NLR and CRP. Furthermore, the global HRQoL measures in LCSS show a positive relationship with systemic inflammation.

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Conflict of interest statement N Pavlakis is on an advisory board with E Lilly and has received a travel grant and speaking honoraria from E Lilly. N. van Zandwijk declares the following: advisory board for E Lilly, Merk Serono and Pfizer; speaker at Lilly Symposia.

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