Annals of Hematology (2019) 98:1427–1434
https://doi.org/10.1007/s00277-019-03641-x

ORIGINAL ARTICLE

Pulmonary function abnormalities are common in patients with multiple myeloma and are independently associated with worse outcome

Georgia Trakada[1] · Efstathios Kastritis[1] · Maria Gavriatopoulou[1] · Lemonia Velentza[1] · Despina Fotiou[1] · Dimitrios C. Ziogas[1] · Ioannis Panagiotidis[1] · Evangelos Eleutherakis-Papaiakovou[1] · Maria Roussou[1] · Magdalini Migkou[1] · Nikolaos Kanellias[1] · Ioannis Ntanasis-Stathopoulos[1] · Anastasios Kallianos[1] · Evangelos Terpos[1] · Meletios A. Dimopoulos[1]

Received: 12 April 2018 / Accepted: 19 February 2019 / Published online: 5 March 2019

Abstract

Pre-existing pulmonary disease may affect treatment choices, toxicity, and survival of patients with multiple myeloma (MM). However, data on the prognostic value of pulmonary function tests (PFTs) in myeloma patients' outcome, at the time of initial assessment of newly diagnosed patients, are scarce. Here, we prospectively performed PFTs in 121 newly diagnosed MM patients, before initiation of treatment, and we evaluated possible associations of lung function with their outcomes. Fifty-four patients (44.63%) had either obstructive or restrictive pulmonary function defects, even among those not reporting a history of lung disease. The survival was significantly worse in those with obstructive pulmonary defect (median OS 32.8 months) vs. those with restrictive (median OS 52.5 months) or normal lung function (median not reached, 3-year survival 76%) ($p = 0.013$), independently of other myeloma-related factors. Forced vital capacity (FVC) (lt) ($p = 0.012$), forced expiratory volume in 1 s (FEV1) (lt) ($p = 0.018$), peak expiratory flow (PEF) (lt/min) ($p = 0.008$), carbon monoxide diffusion capacity (DLCO) ($p = 0.012$), and expiratory/inspiratory pressures (Pe) (kPa) ($p = 0.032$)/(Pi) (kPa) ($p = 0.023$) were significantly associated with OS. Myeloma-related factors associated with survival included ISS stage ($p = 0.008$), hypercalcemia ($p = 0.064$), and high-risk cytogenetics ($p = 0.004$). In the multivariate analysis, only the presence of high-risk cytogenetics and presence of either or both PEF and DLCO < 65% of predicted were independent prognostic factors. We conclude that PEF and DLCO could be useful in the initial assessment of newly diagnosed MM patients as significant predictors of survival. Further research is needed to evaluate if respiratory screening should be included in the routine initial evaluation of myeloma patients, despite the presence or absence of respiratory symptoms or abnormal clinical respiratory examination.

Keywords Pulmonary function tests (PFTs) · Multiple myeloma (MM) · Overall survival (OS)

Introduction

Multiple myeloma (MM) is a plasma cell malignancy characterized by the presence of anemia, lytic bone disease, renal insufficiency, hypercalcemia, and immunodeficiency [1, 2]. The use of novel therapeutic approaches, like immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and autologous hematopoietic stem cell transplantation in eligible patients, has significantly improved the life expectancy of myeloma patients during the last decades; however, MM remains an incurable disease [3, 4]. The prognosis of MM patients is affected by the significant heterogeneity of the disease as reflected not only by various surrogate markers such as ISS stage, elevated serum lactate dehydrogenase (LDH), and high risk cytogenetics, evaluated by FISH [5–8], but also by the characteristics of the patients such as age and the presence of comorbidities. Pre-existing comorbidities and organ dysfunction such as renal impairment may be important for treatment

✉ Meletios A. Dimopoulos
mdimop@med.uoa.gr

[1] Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, 80 Vasilissis Sofias, 11258 Athens, Greece

choice and are implicated in myeloma outcome and are associated with increased risk of treatment-related and myeloma-related complications leading to higher early mortality rates in these patients' subsets. However, particularly regarding the importance of pre-existing lung disease, its importance in the outcome of patients with MM has not been thoroughly and prospectively evaluated.

Lung function is a criterion for eligibility for high-dose therapy and hematopoietic stem cell transplantation, and patients with a pre-transplant carbon monoxide diffusion capacity (DL_{CO}) ≤ 60% have a significant 1.5-fold higher risk for mortality after transplant [9]. However, evaluation of lung function is not considered among major initial assessments before starting therapy for myeloma. While in retrospective studies, the presence of lung disease was associated with worse outcome and was also included in the Freiburg comorbidity index [10, 11], there are no prospective data with detailed evaluation of pulmonary function tests (PFTs).

Therefore, we conducted a prospective and detailed evaluation PFTs in newly diagnosed patients with symptomatic multiple myeloma in order to identify the incidence and patterns of lung disease and evaluate indices of PFTs as potential prognostic factors, especially focusing on applicability in everyday clinical practice.

Methods

This was a non-interventional prospective study that included 121 consecutive patients with symptomatic MM. These patients were non-invasively evaluated for their lung function by performing PFTs. No selection criteria were applied for performing PFTs. All patients were diagnosed and treated in the Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, at Alexandra Hospital, in Greece from September 2014 to March 2016. The Ethics Committee/Scientific Council of "Alexandra" hospital approved the study protocol; all patients have provided written informed consent for data collection, analysis, and publication.

Pulmonary function assessment

At the time of diagnosis and before institution of any anti-myeloma therapy, patients underwent PFTs in a Master screen Body (Jaeger, Germany), according to manufacturer's instructions and standard European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines [12, 13]. Calibration and leak tests were performed daily. The same technician tested all subjects. Patients were seated, and nose clips were worn. We performed spirometry, lung volumes measurement, single-breath determination of carbon monoxide uptake in the lung corrected for hemoglobin (carbon monoxide diffusion capacity, DL_{CO}), and maximal expiratory (Pe) and inspiratory (Pi) pressure measurements, in a sitting position [14–18]. The patient's age, height, and weight were recorded for use in the calculation of reference values. Because carbon monoxide–Hb binding is an important factor in carbon monoxide transfer and anemia is a hallmark of MM, we adjusted DL_{CO} for Hb prior to the interpretation of the maneuver, in the predicted values, according to the following equation: DL_{CO} (predicted for Hb) = DL_{CO} (predicted) · (1.7Hb/(0.7Hb_{ref} + Hb)) [13, 19]. Body mass index (BMI) was calculated as kilograms per square meters. Smoking habits were also recorded (smoker or no, pack/years, years of smoking cessation).

Statistical analysis

Descriptive statistics and non-parametric tests of significance (Spearman's rank correlation coefficient and Mann–Whitney *U* test) were used. Survival curves were estimated using the Kaplan–Meier method. Cox regression likelihood ratio univariate and multivariate analyses were used to determine possible independent predictive factors of survival for the whole MM group. Cutoffs for PFTs were identified by means of ROC analysis for survival at 1 year and selection of the point of the maximum product of sensitivity and specificity. A *p* value lower than 0.05, was considered as significant. All analyses were performed by using software SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY).

Results

The median age of our MM patient cohort was 67 years (range 37–90), of which 59% were > 65 years of age and 52% were males. The median follow-up for all patients was 32 months, the 3-year PFS was 47%, the median estimated PFS was 29 months, while the 3 years OS was 64% and the projected OS was 53 months.

The median hemoglobin of the patients was 10.4 g/dl and 42% had hemoglobin < 10 g/dl, 16% had hypercalcemia (corrected serum Calcium ≥ 11 mg/dl), and 79% had lytic bone disease. ISS disposition was 30%, 30%, and 40% for stages − 1, − 2, and − 3 respectively. High-risk cytogenetics were present in 20%, and LDH was elevated above upper limit of normal in 12%. Median BMI was 26 kg/m^2 and 5% had BMI < 20 kg/m^2 (cachexia), while 15% had BMI ≥ 30 kg/m^2 (morbid obesity). Regarding smoking status, 29% were active smokers with a median of 35 pack/years, 25% were ex-smokers, and 46% were never smokers; 12% of the patients reported a history of known pulmonary disease (mostly COPD). Primary treatment was bortezomib-based in 69% and lenalidomide based in 31%; 35% of the patients received

HDM with ASCT at first remission. The characteristics of the patients are summarized in Table 1.

Table 2 depicts the values of PFTs in all patients. Based on ERS/ATS guidelines, 60 (49.6%) patients had normal PFTs, whereas 29 (23.9%) demonstrated a restrictive breathing pattern, 22 (18.2%) an obstructive, and 3 (2.5%) mixed findings on PFT results (Fig. 1). There was no significant difference in the frequency of abnormal breathing patterns among current or ex-smokers vs. never smokers (54% vs. 51%). There was a trend towards higher incidence of obstructive breathing pattern for those with a history of ≥ 30 pack/years (18% vs. 30%) while a restrictive pattern was more common in those with a < 30 pack/years history (30% vs. 18%) ($p = 0.084$). Thus, even among MM patients without a history of smoking, the presence of abnormal breathing pattern was common. Except one patient who reported a history of bronchial asthma, all patients with a known history of pulmonary disease had abnormal breathing patterns; 77% of them had obstructive breathing pattern.

Table 1 Characteristics of the patients in the study

	$N = 121$
Male/female	52%/48%
Age (median/range)/age > 65 years	67 (37–90)/59%
BMI (median/range) (kg/m^2)	26 (17–44)
ECOG PS 0–1/2–3	56%/44%
Osteolytic disease	78.5%
Serum creatinine (median/range)	0.96 (0.43–14.8)
Serum creatinine > 2 mg/dl	16%
Serum calcium	9.7 (8.3–20)
Serum calcium > 11 mg/dl	16%
Hemoglobin < 10 g/dL	42%
Platelets < 130 × 10^9/l	5%
ISS stage 1/2/3	30%/30%/40%
LDH > ULN	12%
Del13q (FISH)	28%
T(4;14)	8%
Del17p	10%
T(11;14)	14%
T(14;16)	3.5%
Amp/gain1q21	25%
High-risk cytogenetics	20%
Revised ISS 1/2/3	22%/62%/16%
Primary therapy	
Bortezomib-based	69%
Lenalidomide-based	31%
HDM with ASCT in 1st remission	35%
Prior history of pulmonary disease	12%
Current smokers	29%
Quit smoking/ex smokers	25%
Never smokers	46%

The pulmonary function indices (FVC (lt), FVC (%), FEV1 (lt), PEF (lt/min), PEF (%), DL_{CO}, Pi, Pi (%), Pe, Pe (%)) were associated with age, the presence of anemia, hypercalcemia (FVC (lt), FVC (%), FEV1 (lt), PEF (lt/min), PEF (%), DL_{CO}), ISS stage (FVC (lt), FVC (%), FEV1 (lt), PEF (lt/min), PEF (%), DL_{CO}), and gender, but not with the presence of lytic bone disease, elevated serum LDH, or high risk cytogenetics (except for PEF (lt/min) and DL_{CO}).

The presence of an abnormal breathing pattern (normal, restrictive, or obstructive) was associated with prognosis: overall survival was significantly worse in those with obstructive pattern (median OS 32.8 months) vs. restrictive (median OS 52.5 months) vs. normal (median not reached, 76% survival rate at 3 years) ($p = 0.013$) (Fig. 2). History of prior lung disease was also associated with shorter overall survival (40 months vs. not reached for the rest, $p = 0.033$). In the univariate analysis, indices of respiratory function that were assessed with PFTs and were associated with overall survival included FVC (lt) ($p = 0.012$), FVC (%) ($p = 0.006$), FEV1 (lt) ($p = 0.018$), FEV1 (%) ($p = 0.013$), PEF (lt/min) ($p = 0.008$), PEF (%) ($p = 0.005$), DLCO ($p = 0.012$), Pi ($p = 0.023$), Pi (%) ($p = 0.027$), Pe ($p = 0.032$), and Pe (%) ($p = 0.024$).

In the univariate analysis, several myeloma-related factors were associated with survival including ISS stage ($p = 0.008$),

Table 2 Baseline PFTs in patients with symptomatic MM ($N = 121$)

	Median	Minimum	Maximum
FVC (lt)	2.6300	0.73	5.93
FVC (%)	86.4500	43.46	127.20
FEV1 (lt)	2.1300	0.54	4.94
FEV1 (%)	86.5900	34.86	131.10
FEV1/FVC	80.2700	46.79	97.69
PEF (lt/min)	4.7100	1.05	81.27
PEF (%)	72.5200	23.52	136.20
DLCO	78.805	20.5	121.0
R tot	0.300	0.1	2.2
R tot %	100.200	19.9	298.4
FRC (lt)	4.3200	2.07	9.91
FRC (%)	139.700	85.4	358.6
RV (lt)	3.3200	1.39	7.34
RV %	146.300	65.9	259.3
TLC (lt)	6.1000	2.74	12.31
TLC %	104.100	67.2	241.5
Pi (kPa)	4.4500	0.49	10.95
Pi %	42.1100	4.84	101.22
Pe (kPa)	6.1300	0.05	15.09
Pe %	69.3700	0.38	4755.00

FVC forced vital capacity, *FEV1* forced expiratory volume in 1 sec, *PEF* peak expiratory flow, *DLCO* carbon monoxide diffusion capacity, *FRC* functional residual capacity, *R* resistance, *TLC* total lung capacity, *RV* residual volume, *Pe/Pi* maximal expiratory I inspiratory pressures

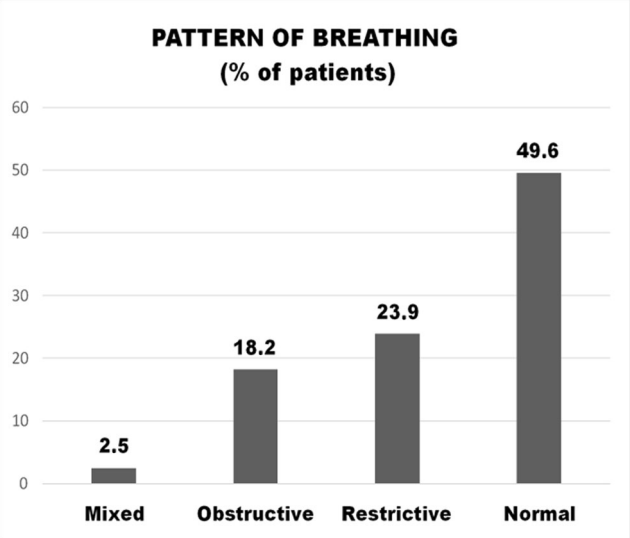

Fig. 1 Pulmonary function defects in MM patients

the presence of high-risk cytogenetics ($p = 0.004$), elevated serum LDH ($p = 0.03$), and the resulting revised ISS stage ($p = 0.004$). The presence of hypercalcemia was also of borderline statistical significance ($p = 0.064$).

Early mortality, within the 1st year from the initiation of therapy, was 16% ($N = 19$) and abnormal PFTs were associated with early mortality. Among patients that died within the 1st year since initiation of therapy, two died of pulmonary infection, two of sepsis of undefined source, and the rest of other myeloma-related complications. Among indices of lung function tested in univariate analysis, reduced PEF was the one with the strongest association with early death ($p < 0.001$); other indices included FVC ($p = 0.001$), FEV1 ($p = 0.001$), and DL_{CO} ($p = 0.005$). Abnormal breathing pattern was also associated with death within the 1st year from start of therapy, especially obstructive pattern (HR 8, 95%CI 2.1–30, $p < 0.001$); this

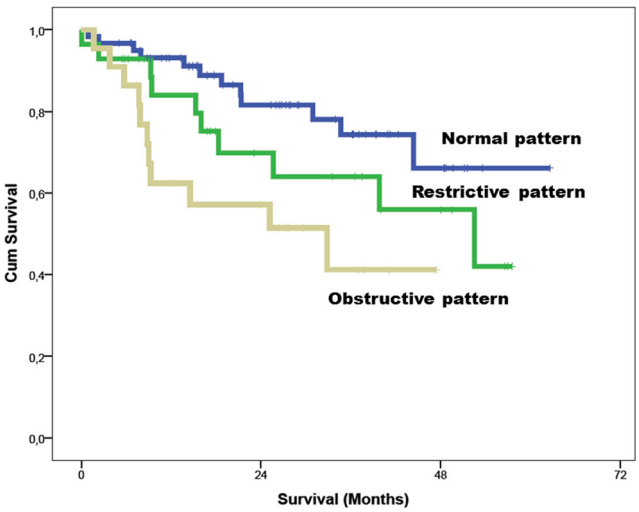

Fig. 2 Survival according to breathing pattern—normal, restrictive, and obstructive

association was less strong for restrictive pattern (HR 2.2, 95%CI 0.9–9.7, $p = 0.068$), compared to normal pattern of breathing. Other factors associated with early mortality included eGFR< 30 ml/min/1.73 m^2 at the time of diagnosis and age > 65 years; however, in multivariate analysis, reduced PEF was the strongest risk factor for early death (HR 8.8. 95% CI 3.3–33, $p = 0.001$), followed by eGFR < 30 ml/min/1.73m^2 (HR 3.3, 95% CI 1.13–14.5, $p = 0.031$).

In order to identify clinically useful cutoffs, we identified that a cutoff for PEF < 65% could discriminate groups with very different survival (33 months vs. not reached at 3 years, HR 2.8, 95%CI 1.47–5.5, $p = 0.001$). Moreover, a DL_{CO} < 65% was also associated with a median OS of 33 months vs. not reached (HR 2.54, 95%CI 1.3–5.1, $p = 0.005$). Among the PFTs, these two binary transformed indices showed the strongest association with survival and were further used in the analysis, in order to provide a clinically relevant tool (Fig. 3a, b). There was a strong association of the two indices ($p < 0.001$) with 21% of patients having both 19% only PEF < 65%, 6% only DL_{CO} < 65%, and 53% none of the two.

We then evaluated whether the inclusion of PFT indices could add prognostic information along with known myeloma-related factors. Revised ISS (R-ISS) is now considered the standard prognostic tool for patients with myeloma, as it encompasses ISS stage, increased LDH, and cytogenetics [6, 7]. Thus, we performed a multivariate analysis that included R-ISS and the presence of either or both PEF (%) < 50% and DL_{CO} < 65% of predicted (Table 3). As shown in Table 2, either or both PEF (%) < 65% and DL_{CO} < 65% of predicted was an independent prognostic factor for OS (Table 2; Fig. 4). Thus, we could formulate a prognostic score that encompasses both myeloma-related and myeloma-independent factors which could discriminate three groups with very significant difference in survival: median survival was not reached (85% and 59% at 3 years for those with none or either of the risk factors) and was 7 months (18% 3-year survival) if they had both ($p < 0.001$). Importantly, the prognostic significance of this score was independent of the age of the patients, which was of no prognostic significance when put in a single model.

Discussion

To our knowledge, this is the first study that prospectively focused on the prognostic value of a comprehensive assessment of pulmonary function in MM outcomes and shows that PFTs can provide prognostic information which is independent of any myeloma-related factors and also independent of the patients' age. It is also very interesting and of clinical significance that almost 50% of our patients that were found with abnormal PFTs did not have an established diagnosis of a previous pulmonary disease and were not receiving any lung directed therapy; however, the presence of even undiagnosed

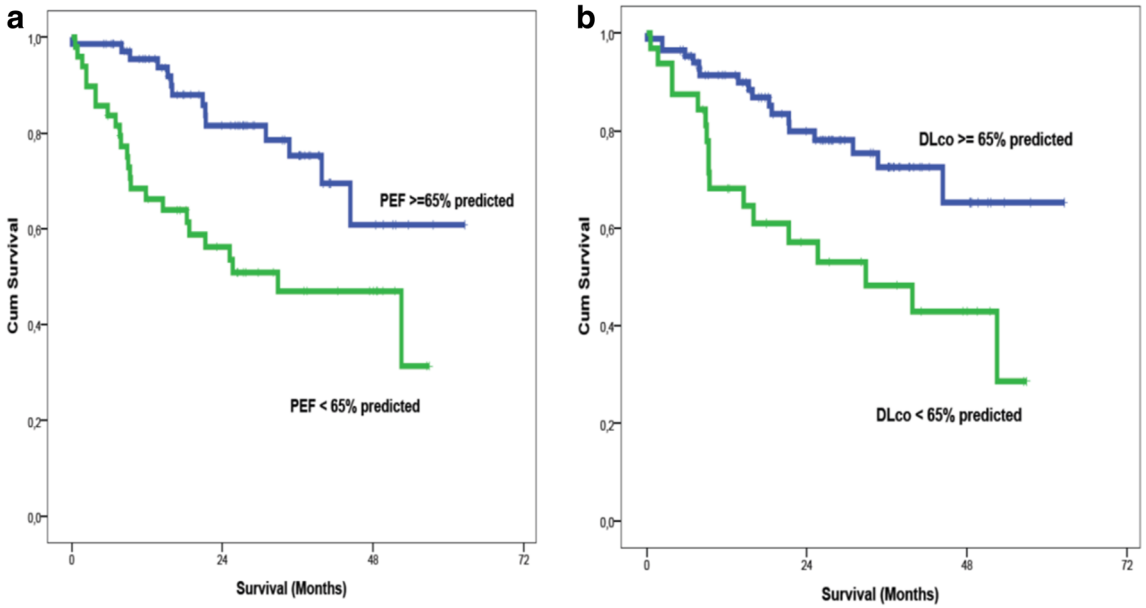

Fig. 3 Survival according to: **a** PEF ≥ 65% predicted vs. < 65% predicted and **b** DLCO ≥ 65% predicted vs. < 65% predicted

lung disease had significant impact on their outcomes. This finding also underscores the limitations of retrospective assessment of lung comorbidities without a detailed PFT assessment. Although the presence of lung disease is considered as standard high-risk co-morbidity, it is often unrecognized and its impact may go undetectable.

Previous studies have demonstrated that pre-existing pulmonary disease is a negative predictor of OS in MM patients [10, 11]. Kleber et al. [11] determined moderate or severe pulmonary disease, renal impairment, decreased Karnofsky Performance Status (KPS), and age as the most important variables for inferior OS in MM, in a univariate analysis. Mohammadi et al. [10] further demonstrated that previous cardiovascular, cerebrovascular, chronic pulmonary or renal disease, or dementia was associated with a higher all-cause as well as myeloma-specific mortality, independently of age. However, as revealed by our prospective evaluation, there are many MM patients with abnormal lung function but who do not report a previous history of lung disease; thus, the impact of an abnormal pulmonary function may be relatively underestimated. In our analysis, we also found that those with a history of pre-existing lung disease had poorer survival; however, patients without a reported history of lung disease but abnormal lung function had a poorer outcome also, similar to that of patients with known lung disease. This is not surprising, since it is well established that a significant proportion of patients with severe lung disease does not report a history of pre-existing lung disease and is only found during spirometry testing [20, 21]. This highlights the importance of a prospective evaluation of lung function in patients with MM, like in our study, in order to provide information regarding the clinical implications of under-diagnosed lung disease.

In transplant patients, an assessment of PFTs is a standard practice, and low pre-transplant $DL_{CO} \leq 60\%$ could identify patients at higher risk for poorer stem cell transplant outcomes

Table 3 Multivariate analysis including revised ISS and the presence of either a PEF < 65% or DLCO < 65% predicted

	p value	HR	95% CI for HR	
			Lower	Upper
PEF or DLCO < 65% predicted	0.002	3.253	1.551	6.823
Revised—ISS-1		1	1	
Revised—ISS-2	0.760	0.856	0.316	2.320
Revised—ISS-3	0.006	2.789	1.172	8.004

HR hazard ratio, *PEF* peak expiratory flow, *DLCO* carbon monoxide diffusion capacity, *ISS* International Staging System

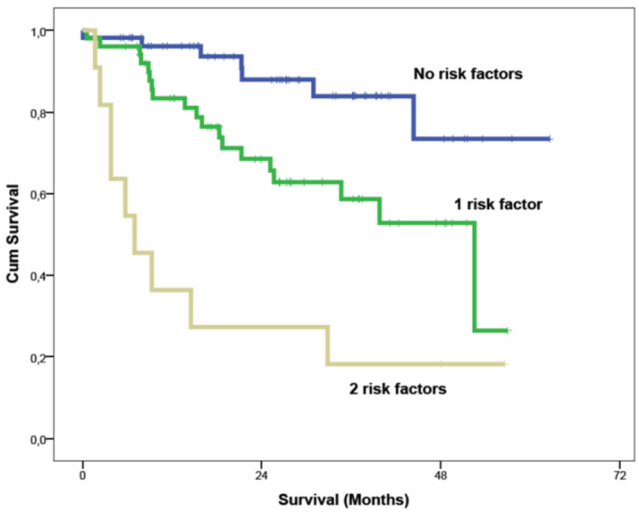

Fig. 4 Survival according to the number of risk factors

and severe complications [9, 22]. However, in MM patients, at least not in the peri-transplant period or those who are not candidates for transplant, a detailed assessment of lung function is not a standard practice [23]. Our data, however, show that all patients should have a lung function assessment, as this is commonly associated with the identification of undiagnosed lung disease that has significant impact on their survival.

The impact of abnormal PFTs in patients' outcome should not be surprising. The lung is a vital internal organ, responsible for gas exchange via respiration, and simultaneously a most vulnerable organ, as it is constantly exposed to the external environment. Respiratory diseases are very common worldwide. On behalf of the Forum of International Respiratory Societies, lung diseases cause an immense worldwide health burden and each year, about 4 million people die prematurely from chronic respiratory disease [24]. However, undiagnosed obstructive lung disease is still common among American adults and remained unchanged over two decades and, although undiagnosed subjects appeared healthier than those with a diagnosis, their risk of death was increased, compared with subjects without obstruction [25]. Moreover, by screening lung specimens from autopsy cases, the estimated prevalence of preclinical or undiagnosed interstitial lung diseases among all deaths was 1.8%, suggesting that these disorders may also frequently be unrecognized during lifetime [26, 27]. Respiratory symptoms are usually ignored by the general population and overlooked by physicians, and it is not unexpected that many of our patients had abnormal lung function although they reported no history of lung disease.

The mechanisms by which abnormal lung function affects the prognosis of myeloma may be many either direct or indirect. Patients with abnormal lung function may be more susceptible to infections, which may have detrimental effects by delaying therapy or leading to death: pulmonary complications such as pneumonia are among the leading causes of death in myeloma patients [28]. In our patients, some of the early death were directly associated with lung infection or sepsis of undefined source; however, it has been well recognized that lung disease is associated with increased mortality although not through a clear direct causal relationship [20, 21]. Patients with abnormal lung function may also be more susceptible to other drug-related toxicities, such as drug-related pneumonitis [29]. In addition, lung dysfunction may reflect a poor general condition, since many other parameters may be involved in the lung disease (for example smoking) that are also related to other comorbidities (such as vascular disease).

Spirometry is the most significant PFT to record ventilatory capacity and lung volumes; it is easy to perform and is highly reproducible [14]. A significant decrease in major spirometric parameters, such as FEV1, VC, FEV1/VC, and TLC, is consistent with a pulmonary defect (obstructive, restrictive, mixed) and is a useful and simple approach in clinical practice. In our study, we found that PEF and DLCO were the two indices that were more strongly associated with survival. PEF expresses the size of the airways, the strength of the expiratory muscles, and the compliance of lung tissue [14]. PEF recording is also easy to perform in an office visit with a peak flow meter, a small, hand-held device used to monitor a person's ability to breathe out air [14]. Diffusion capacity (DL_{CO}) reflects alveolar membrane thickness, hematocrit level, cardiac output, and heterogeneity in the regional distribution of ventilation vs. perfusion, as it measures the patient's ability to absorb alveolar gases into the capillary blood flow [30]. Any compromise in one or more of these variables can lead to a reduction of DLCO. Other variables that were evaluated during the comprehensive PFT testing were also associated with survival in univariate analysis. In several other studies, FEV1 and FEV1/FVC have also been prognostic of all-cause or respiratory disease-related mortality, even in non-smokers [26, 31, 32], and in myeloma patients, impaired lung function as expressed by the presence of dyspnea or FEV1/FVC, FEV1, TLC, and respiratory insufficiency was associated with a poor prognosis [11, 30]. In the Framingham study, lung function was a major independent predictor of cardiovascular morbidity and mortality [33]. However, in our study, PEF and DL_{CO} were the stronger prognostic indices and outperformed the other PFT indices.

Our study included a relatively small number of patients, and some patients in very poor condition were not able to perform PFTs. However, this is a prospective study, following a standardized protocol that included consecutive patients treated with contemporary regimens. Thus, despite the relatively small number, it is representative of the general myeloma patients' population, supported also by the characteristics of these patients as shown in Table 1. Whether a specific intervention is needed in myeloma patients found with abnormal PFTs, outside the standard pulmonary care, we cannot answer in this study: this was a non-interventional study, treatment for myeloma was not guided by PFTs, and furthermore, we do not have any data about the clinical significance of such interventions in patients with myeloma. Based on recently reported data on the use of antibiotic prophylaxis, we can only speculate that, for example, the use of prophylaxis could be more beneficial in myeloma patients with abnormal lung function. Our data provide only the proof of principle for further evaluation of PFTs in larger cohorts, which would establish routine pulmonary consultation in the standard initial assessment of all myeloma patients.

In conclusion, lung dysfunction affects the prognosis and the survival of MM patients independently of other prognostic factors, including established myeloma-related factors and age. Importantly, many patients have undiagnosed lung disease at the time of myeloma diagnosis, which detrimentally affects their outcomes. Thus, inclusion of PFTs as an additional test to assess a common and important comorbidity and appropriate pulmonary consultation in selected patients may further improve life expectancy and reduce treatment related complications in myeloma.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A, Ludwig H, Joshua D, Mehta J, Gertz M, Avet-Loiseau H, Beksac M, Anderson KC, Moreau P, Singhal S, Goldschmidt H, Boccadoro M, Kumar S, Giralt S, Munshi NC, Jagannath S, on behalf of the International Myeloma Workshop Consensus Panel 3 (2011) Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood 117:4701–4705
2. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65:5–29
3. Kumar S (2012) Risk of early death in multiple myeloma. Clin Adv Hematol Oncol 10:172–174
4. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, Kapoor P, Dingli D, Hayman SR, Leung N, Lust J, McCurdy A, Russell SJ, Zeldenrust SR, Kyle RA, Rajkumar SV (2014) Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 28: 1122–1128
5. Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, Chng WJ, Moreau P, Attal M, Kyle RA, Caers J, Hillengass J, San Miguel J, van de Donk NWCJ, Einsele H, Blade J, Durie BGM, Goldschmidt H, Mateos MV, Palumbo A, Orlowski R (2016) Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood 127:2955–2962
6. Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, Richardson P, Caltagirone S, Lahuerta JJ, Facon T, Bringhen S, Gay F, Attal M, Passera R, Spencer A, Offidani M, Kumar S, Musto P, Lonial S, Petrucci MT, Orlowski RZ, Zamagni E, Morgan G, Dimopoulos MA, Durie BGM, Anderson KC, Sonneveld P, San Miguel J, Cavo M, Rajkumar SV, Moreau P (2015) Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 33:2863–2869
7. Kastritis E, Terpos E, Roussou M, Gavriatopoulou M, Migkou M, Eleutherakis-Papaiakovou E, Fotiou D, Ziogas D, Panagiotidis I, Kafantari E, Giannouli S, Zomas A, Konstantopoulos K, Dimopoulos MA (2017) Evaluation of the Revised International Staging System in an independent cohort of unselected patients with multiple myeloma. Haematologica 102:593–599
8. Greipp PR, San Miguel J, Durie BG et al (2005) International staging system for multiple myeloma. J Clin Oncol 23:3412–3420
9. Crawford SW, Fisher L (1992) Predictive value of pulmonary function tests before marrow transplantation. Chest 101:1257–1264
10. Mohammadi M, Cao Y, Glimelius I, Bottai M, Eloranta S, Smedby KE (2015) The impact of comorbid disease history on all-cause and cancer-specific mortality in myeloid leukemia and myeloma—a Swedish population-based study. BMC Cancer 15:850
11. Kleber M, Ihorst G, Gross B et al (2013) Validation of the Freiburg Comorbidity Index in 466 multiple myeloma patients and combination with the international staging system are highly predictive for outcome. Clin Lymphoma Myeloma Leuk 13:541–551
12. Miller MR, Crapo R, Hankinson J et al (2005) General considerations for lung function testing. Eur Respir J 26:153–161
13. Graham BL, Brusasco V, Burgos F et al (2017) ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J 2017:49
14. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten C, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force (2005) Standardisation of spirometry. Eur Respir J 26:319–338
15. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Hankinson J, Jensen R, Johnson D, MacIntyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G (2005) Standardisation of the measurement of lung volumes. Eur Respir J 26:511–522
16. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten C, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J (2005) Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26:720–735
17. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten C, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J (2005) Interpretative strategies for lung function tests. Eur Respir J 26:948–968
18. Crapo RO, Forster RE 2nd (1989) Carbon monoxide diffusing capacity. Clin Chest Med 10:187–198
19. Cooper BG (2011) Republished review: an update on contraindications for lung function testing. Postgrad Med J 87:724–733
20. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DMG, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agusti A (2017) Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. Respirology 22:575–601
21. Mathers CD, Loncar D (2006) Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 3:e442
22. Keller CCK (2008) Evaluating adult patients prior to hematopoietic cell transplant. Available from: http://www.marrow.org
23. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, Hajek R, Dimopoulos MA, Ludwig H, Einsele H, Zweegman S, Facon T, Cavo M, Terpos E, Goldschmidt H, Attal M, Buske C, on behalf of the ESMO Guidelines Committee (2017) Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 28:iv52–iv61
24. Forum of International Respiratory Societies (2017) The global impact of respiratory disease – second edition. Sheffield, European Respiratory Society. Available from: https://www.firsnet.org
25. Martinez CH, Mannino DM, Jaimes FA, Curtis JL, Han MLK, Hansel NN, Diaz AA (2015) Undiagnosed obstructive lung disease in the United States. Associated factors and long-term mortality. Ann Am Thorac Soc 12:1788–1795
26. Kannel WB, Lew EA, Hubert HB, Castelli WP (1980) The value of measuring vital capacity for prognostic purposes. Trans Assoc Life Insur Med Dir Am 64:66–83
27. Coultas DB, Zumwalt RE, Black WC, Sobonya RE (1994) The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med 150:967–972
28. Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G, Behrens J, Smith A, Child JA, Drayson MT (2005) Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials

between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. J Clin Oncol 23:9219–9226

29. Zagouri F, Roussou M, Kastritis E, Koureas A, Tsokou E, Migkou M, Gavriatopoulou M, Nikitas N, Gkotzamanidou M, Terpos E, Dimopoulos MA (2011) Lenalidomide-associated pneumonitis in patients with plasma cell dyscrasias. Am J Hematol 86:882–884
30. Engelhardt M, Domm AS, Dold SM, Ihorst G, Reinhardt H, Zober A, Hieke S, Baayen C, Müller SJ, Einsele H, Sonneveld P, Landgren O, Schumacher M, Wäsch R (2017) A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients. Haematologica 102: 910–921
31. Tockman MS, Comstock GW (1989) Respiratory risk factors and mortality: longitudinal studies in Washington County, Maryland. Am Rev Respir Dis 140:S56–S63
32. Neas LM, Schwartz J (1998) Pulmonary function levels as predictors of mortality in a national sample of US adults. Am J Epidemiol 147:1011–1018
33. Kannel WB, Hubert H, Lew EA (1983) Vital capacity as a predictor of cardiovascular disease: the Framingham study. Am Heart J 105: 311–315