

BMJ Open Association of resilience with health-related quality of life and depression in multiple myeloma and its precursors: results of a German cross-sectional study

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ABSTRACT

Objectives To investigate the relation between resilience, health-related quality of life (HRQOL) and depression in multiple myeloma (MM) and its premalignant stages. MM is one of the most frequent haematological disorders. It is regularly preceded by asymptomatic stages of the disease namely monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM). Survivors have to cope with mental and physical impairment in terms of HRQOL and depression. The concept of resilience refers to a person's ability to adapt to adversity.

Design Cross-sectional study.

Setting MM outpatient department at a University Hospital in Germany (tertiary care).

Participants 292 consecutive patients from our MM outpatient department.

Outcome measures HRQOL, depression and psychological resilience were assessed with validated questionnaires.

Results Regression analyses were performed to determine associations between resilience, HRQOL and depression. 98 patients (33.6%) had a new diagnosis of active MM, 106 patients (36.3%) were already treated for MM and 88 patients had the diagnosis of a precursor (MGUS or SMM; 30.1%) of MM. Multivariate linear regression analyses revealed a strong positive impact of resilience on physical (b 7.20; 95% CI 4.43 to 9.98; $p < 0.001$) and mental (b 12.12; 95% CI 9.36 to 14.87; $p < 0.001$) HRQOL. Ordered logistic regression analysis showed that the odds for higher depression severity were lowered for individuals with a high level of resilience in comparison to the individuals with a low level of resilience (OR 0.11; 95% CI 0.06 to 0.19; $p < 0.001$).

Conclusions Resilience may be a protective factor in the disease trajectory of MM and its precursors. As a next step, future research should focus on longitudinal assessments at various time points to elucidate the role of resilience in one of the most frequent haematological malignancies.

BACKGROUND

Multiple myeloma (MM) is one of the most frequent haematological malignancies with increasing incidence and prevalence due to

Strengths and limitations of this study

- Our study is the first to investigate the impact of resilience in the course of disease of multiple myeloma.
- Another strength of the study is its large sample size of 292 patients.
- Health-related quality of life (HRQOL) and other psychosocial constructs were measured with validated questionnaires.
- The main limitation of our study is related to its cross-sectional design that does not allow for either temporal or causal inferences.
- For measurement of HRQOL, we used a generic questionnaire.

demographic change and improvements in therapy. It is regularly preceded by asymptomatic stages namely monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM) with a risk of progression of approximately 1% and 10% per year, respectively.^{1,2}

As a result of improvements in therapeutic interventions such as high-dose chemotherapy with autologous stem cell transplantation (ASCT) and introduction of novel agents, survival after diagnosis of MM has been extended impressively even in elderly patients.³ Survivors of MM have to cope with numerous symptoms due to organ damage caused by the disease as well as with the psychosocial burden over years. Long-lasting effects due to the drugs toxicities may be apparent after its completion.⁴

Due to the by definition absence of symptoms in MGUS and SMM, respectively, most patients do not need treatment right away but have to be monitored in an adequate manner.

However, in all phases of the disease trajectory (including premalignant stages) patients may experience impairment of physical and mental health-related quality of life (HRQOL).^{4,5} HRQOL 'refers to the physical, psychological and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations and perceptions'.⁶ Clinical observations show that older patients more often tend to name physical symptoms/limitations than mental difficulties.

In premalignant stages of MM, the awareness of the risk of developing full-blown MM could impair the perception of one's own physical quality of life. From a clinical perspective, this is a burden for many patients. However, there is no single published study that investigated HRQOL or psychological burden in patients with MGUS and SMM.

Prior studies have shown that about 25% of patients with MM suffer from high mental strain and depressive symptoms.^{7,8} Since the psychosocial dimensions of HRQOL were found to be independent prognostic factors in patients with MM,⁹ it is important to gain more knowledge about protective factors, contributing to the patient's ability to cope with the situation. Complementary to the study of impairment, researchers postulate the study of positive constructs such as resilience that could be important to maintain HRQOL and mental health in the course of a disease.

The concept of resilience was developed concurrently in many disciplines and contexts. Initially, it was viewed as a trait limited to few individuals that succeeded in life despite adverse circumstances during their childhood. Later studies focused on a developmental perspective and an investigation of paediatric cancer survivors.¹⁰ The concept of resilience has been well studied in recent decades in the field of cancer. In a recently published comprehensive review of resilience in adult cancer care, the authors conclude to 'define resilience in adult patients with cancer and survivors as a dynamic process of facing adversity related to the cancer experience'.¹⁰ It is conceptualised as the ability to bounce back from highly adverse conditions like a serious health problem. Studies in patients with different cancer types (eg, breast, lung, gastric cancer) suggest positive associations between resilience and HRQOL¹¹⁻¹⁴ and lower emotional distress, respectively.^{15,16} However, there is a paucity of research evaluating the possible relevance of resilience in patients with MM. Myeloma is still incurable today. In the preliminary stages (without treatment), the uncertainty represents a strong burden and after the possibly achieved remission (after treatment), there is a high risk of recurrence.⁴ Furthermore, men are predominantly affected at a median age of 70 years. This group is known to have less access to psycho-oncological interventions, often evaluated in younger patients with breast cancer.¹⁷ Therefore, the nature of protective factors such as resilience in MM and its precursors has to be elucidated.

The purpose of this study was therefore to examine associations between resilience, HRQOL and depressive

symptoms in a large sample of adult patients with MM, SMM and MGUS.

The following research questions were addressed:

Is there a significant relation between resilience and mental and physical HRQOL, respectively? Is there a significant relation between resilience and depression severity?

Further, we wanted investigate possible differences in the associations between resilience and the various outcomes (HRQOL and depression, respectively) for the different stages of MM. To the best of our knowledge, this is the first study to investigate the impact of resilience in the course of disease of MM.

PATIENTS AND METHODS

Design and study population

Questionnaires to assess different levels of HRQOL are part of a screening measure at time of first presentation within the clinical routine at our outpatient department. All patients who made the first appointment from November 2014 to April 2016 received a letter before they met the doctor in the hospital. This letter included information on the survey and a psychosocial questionnaire package. During the aforementioned period, all patients who had a first presentation at the centre with a diagnosis of MM, SMM and MGUS who had sufficient skills in reading and writing German were eligible for study participation. Exclusion criteria were as follows: cognitive impairment (ie, not being able to follow the informed consent or other indications that the contents of the procedure cannot be followed) and serious psychiatric illnesses at the time of presentation. Severe psychiatric symptoms were defined as follows: requiring an immediate treatment such as acute suicidal tendencies, psychotic symptoms, dissociation or flash backs and severe addictive diseases. The questionnaires were to be completed at home and given to a staff member at the first appointment in the clinic. Participation was voluntary, and participants could withdraw at any time without any consequences.

Measurements

HRQOL was assessed with the short form health survey-12, a widely used generic questionnaire.^{18,19} HRQOL is measured by two summarised components: a Physical Component Score (PCS) and a Mental Component Score (MCS). A higher score in the respective summary scale indicates a higher quality of life.

The Patient Health Questionnaire-9 (PHQ-9) was used to assess the presence and severity of depression symptoms.^{20,21} The proven psychometric properties of the PHQ have been reported in various large-scale studies. The total score of all items of the PHQ-9 ranges between 0 and 27 points. A range from 0 to 4 points suggests no clinically significant symptoms, 5-9 points indicate mild depressive symptoms, 10-14 points refer to moderate symptoms and 15-27 points suggest the existence of

severe depressive symptoms. Resilience was measured by the short form of the Resilience scale-13 (RS-13), a well validated questionnaire derived from the original scale of Wagnild and Young.^{22 23} The total score of all items ranges between 13 and 91 points. Respective ranges were used to categorise the 'level of resilience'. A range from 13 to 66 points refers to a low level of resilience, a range from 67 to 72 points suggests a moderate level of resilience and 73–91 points indicate a high level of resilience.

Sociodemographic variables and medical history were collected from each participant's medical record. The following variables of interest were selected from the electronic medical record: age, gender, date of diagnosis, laboratory tests (haemoglobin, creatinine, calcium, serum-free light chains, monoclonal protein in serum and urine), presence of lytic bone lesions at the time of diagnosis and comorbidities. Comorbid conditions were used to calculate the Charlson Comorbidity Index.²⁴ For multivariate analyses, we had to consider different categories of MM. Therefore, classification was determined according to the guidelines of the International Myeloma Working Group²⁵ as follows: new diagnosis of MM (before treatment) or treated MM and MGUS or SMM.

Statistical analysis

Multivariate regression models were estimated to determine the impact of resilience levels (low(referent)/average/high) on the variables of interest. We performed multiple linear regression analyses for continuous variables (MCS/PCS) and ordered logistic regression for a categorical variable (depression severity). A reference model was defined, comprised a set of the following control variables: age, gender (referent: female) and stage of myeloma (referent: MGUS or SMM). All analyses were two sided; p values below 0.05 were considered statistically significant. In additional sensitivity analyses, we performed all analyses with continuous scores (of the

PHQ-9 and the RS-13, respectively) instead of categorical variables. Further, we included an interaction term (disease stage×resilience score) to investigate possible differences in the associations between resilience and the various outcomes (HRQOL and depression, respectively) for the different stages of myeloma. All statistical analyses were performed using R statistical software (V.3.3.2).

Patient and public involvement

Patients were not involved in the recruitment to and conduct of the study. Results will be disseminated to study participants through annual information events and contact with self-help groups.

RESULTS

Study sample

During the study period, 292 out of 578 eligible Patients (response rate: 50.5%) were enrolled (figure 1). Mean age of the sample was 62.5 years with a range from 30.9 to 87.5 years. The majority of the patients was male (n=173; 59.2%). Ninety-eight patients (33.6%) had a new diagnosis of active MM, 106 patients (36.3%) were already treated for MM and 88 patients had the diagnosis of a precursor (MGUS or SMM; 30.1%) of MM. High level of resilience, according to the RS-13 was present in 57.3% of the sample, 15.6% had a moderate and 27.1% reported a low level of resilience. Mean values of the SF-12 sum scores were 43.2 for MCS (range 11.5–68.9) and 37.5 for PCS (range 16.4–59.6), respectively. Moderate to severe depressive symptoms, according to the PHQ-9, were prevalent in 21% of all participants. Characteristics of the entire sample are shown in table 1.

Non-responder analyses

We analysed differences in age, sex and disease stage between study participants (n=292) and non-participants

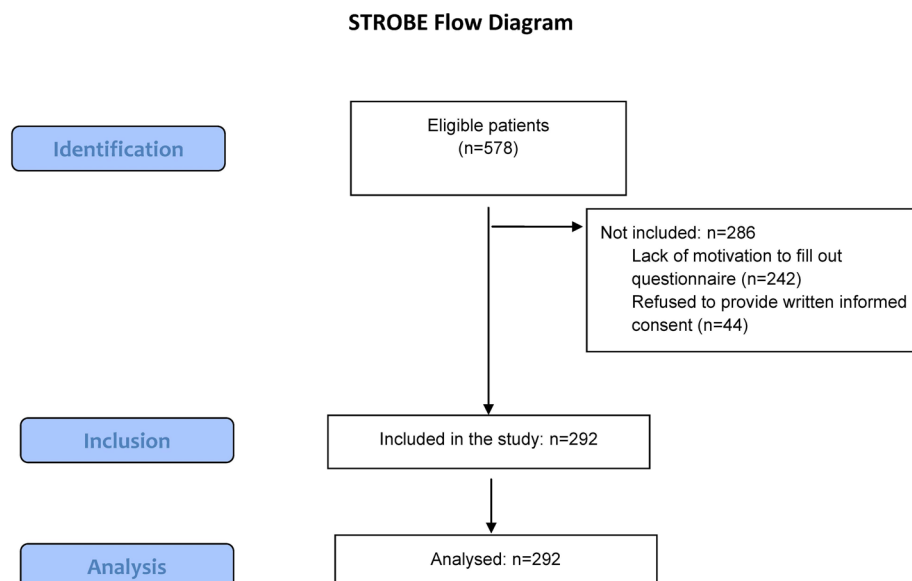


Figure 1 Study enrolment flow chart. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Table 1 Characteristics of the study sample

Variables	N	
All patients	292	(100%)
Age, median (range)	62.5 (30.9–87.5)	
Sex		
Female	119	(40.8%)
Male	173	(59.2%)
Stage of MM		
New diagnosis of MM	98	(33.6%)
Treated MM	106	(36.3%)
Premalignant stage (MGUS; SMM)	88	(30.1%)
Comorbidity		
Charlson Comorbidity Index ≤ 2	224	(76.7%)
Charlson Comorbidity Index > 2	68	(23.3%)
Health-related quality of life		
PCS, median (range)	286	37.5 (16.4–59.6)
MCS, median (range)	286	43.2 (11.5–68.9)
Depression severity (PHQ-9 sum score)		
None (0–4)	123	(45.2%)
Mild (4–9)	92	(33.8%)
Medium (10–14)	34	(12.5%)
Severe (15–27)	23	(8.5%)

MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; PCS, Physical Component Score; PHQ-9, Patient Health Questionnaire-9; SMM, smouldering multiple myeloma.

(n=286). No statistically significant differences were found with regard to age (participants: median=62.5 vs non-participants: median=62.9; $p=0.77$), sex (participants: female n=119 (40.8%) vs non-participants: female

n=114 (39.9%); $p=0.89$) and disease stage (participants: MGUS, SMM n=88 (30.1%); new diagnosis of MM n=98 (33.6%); treated MM n=106 (36.3%) vs non-participants: MGUS, SMM n=95 (33.2%); new diagnosis of MM n=73 (25.5%); treated MM n=118 (41.3%); $p=0.11$)

Results of multiple regression analyses for HRQOL

Table 2 and table 3 show the results of the multiple linear regression analyses for MCS and PCS. As mentioned above, our dependent (outcome) variables were MCS and PCS, respectively. A high level of resilience was significantly associated with elevated MCS ($p<0.001$). No significant association was found between a moderate level of resilience and MCS ($p=0.14$). Further, a high level of resilience was significantly associated with PCS ($p<0.001$). No significant association was found between a moderate level of resilience and PCS ($p=0.39$).

Results of multiple regression analysis for depression severity

Table 4 shows the results of the multiple regression analysis for depression severity as dependent outcome variable. Multivariate ordered logistic regression analysis showed that the odds for higher depression severity were significantly lowered for individuals with a high level of resilience compared with the individuals with a low level of resilience (OR 0.11; $p<0.001$). Individuals with moderate level of resilience showed a trend towards significance with lowered odds for higher depression severity (OR 0.51; $p=0.06$).

Sensitivity analyses

Linear regression analyses with the continuous resilience variable showed a significant linear association with the respective outcomes of PCS/MCS (positive association) and continuous PHQ-9 score (negative association). Graphical inspection of the data did not indicate quadratic or other non-linear relationships. The results are shown in online supplementary tables 1–3.

Table 2 Results of the multiple linear regression analyses with resilience as independent variable and HRQOL Physical Component Score as outcome variable adjusted by age, sex and stage of MM (pre-malignant stage: MGUS or SMM)

Variable	b* (95% CI)	P values
Level of resilience; reference low level		
Moderate level of resilience	1.65 (–2.12 to 5.41)	0.39
High level of resilience	7.20 (4.43 to 9.98)	<0.001†
Age; 5 years increase	–0.88 (–1.44 to –0.33)	0.002†
Sex; reference: female	0.37 (–2.06 to 2.80)	0.76
Stage of MM; reference: pre-malignant stage‡		
New diagnosis of MM	–3.56 (–6.55 to –0.57)	0.02†
Treated MM	–7.78 (–10.65 to –4.81)	<0.001†

*Regression coefficient: the usual interpretation of a regression coefficient is the average change in the outcome variable when the corresponding predictor variable is changed by one unit.

†p-value <0.05.

‡Pre-malignant stage: MGUS or SMM.

HRQOL, health-related quality of life; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; SMM, smouldering multiple myeloma.

Table 3 Results of the multiple linear regression analyses with resilience as independent variable and HRQOL (MCS) as outcome variable adjusted by age, sex and stage of MM

Variable	b* (95% CI)	P values
Level of resilience; reference low level		
Moderate level of resilience	2.81 (−0.92 to 6.54)	0.14
High level of resilience	12.12 (9.36 to 14.87)	<0.001†
Age; 5 years increase	0.29 (−0.26 to 0.84)	0.3
Sex; reference: female	4.01 (1.60 to 6.41)	0.0012†
Stage MM; reference: premalignant stage‡		
New diagnosis of MM	−0.07 (−3.03 to 2.89)	0.96
Treated MM	−0.92 (−3.81 to 1.97)	0.53

*Regression coefficient: the usual interpretation of a regression coefficient is the average change in the outcome variable when the corresponding predictor variable is changed by one unit.

†p-value <0.05.

‡Premalignant stage: monoclonal gammopathy of undetermined significance or smouldering multiple myeloma.
HRQOL, health-related quality of life; MCS, Mental Component Score; MM, multiple myeloma.

Moderator analyses

Moderator analyses revealed that stage of myeloma moderates the association between resilience and HRQOL and depression, respectively. The association between resilience and mental quality of life (MCS) was significantly stronger in patients with a new diagnosis. Further, the association between resilience and physical quality of life (PCS) was significantly weaker in patients with treated MM. With regard to PCS in the ‘treated MM’ group, the remaining effect of resilience was very small. Further, the inverse association of resilience and depression was significantly stronger in patients with a new diagnosis of MM. Results of moderator analyses are shown in online supplementary tables 1–3.

DISCUSSION

Principal findings

In this cross-sectional study of 292 patients with monoclonal gammopathies including patients with MM as well as premalignant stages (MGUS and SMM), we found

primarily that patients with a high level of resilience had a better HRQOL according to physical (PCS) and mental (MCS) sum scores of the SF-12. Furthermore, patients with a moderate or high level of resilience had significantly decreased odds of having moderate or severe depressive symptoms. Moderator analyses revealed that resilience had a stronger impact on MCS and depression in patients with a new diagnosis (before treatment). The association between resilience and physical quality of life (PCS) was significantly weaker in patients with treated MM.

Comparison to other studies in the field

Our results are in line with a smaller study of Schumacher *et al* that were the first who demonstrated a link between resilience and HRQOL in a rather small and heterogeneous sample of 75 haematological patients after stem cell transplantation (SCT).²⁶ Due to the heterogeneity of the patient cohort (including patients with leukaemia, lymphoma, myeloma and aplastic anaemia) in a specific clinical situation (of SCT), a comparison to our study appears to be rather complicated.

Table 4 Results of the ordered logistic regression analysis with resilience as independent variable and depression severity (no/low/medium/severe) as outcome variable adjusted by age, sex and stage of MM

Variable	OR (95% CI)	P values
Level of resilience; reference low level		
Moderate level of resilience	0.51 (0.24 to 0.98)	0.06
High level of resilience	0.11 (0.06 to 0.19)	<0.001*
Age; 5 years increase	1 (0.98 to 1.03)	0.88
Sex; reference female	0.63 (0.39 to 1.02)	0.06
Stage of myeloma: premalignant stage†		
New diagnosis of MM	1.39 (0.74 to 2.61)	0.31
Treated MM	2.38 (1.32 to 4.38)	0.0046*

*p-value <0.05.

†Premalignant stage: monoclonal gammopathy of undetermined significance or smouldering multiple myeloma.
MM, multiple myeloma.

We found a positive link between resilience and physical aspects of HRQOL. This corresponds to results from other studies that reported reduced symptom severity and side effects such as fatigue, pain or insomnia in patients with high levels of resilience.¹²⁻²⁷ Resilience seems to mediate the relationship between cancer symptom distress and HRQOL.¹⁴ In our sample, resilience was strongly associated to mental HRQOL and inversely related to depression symptom severity. These results are consistent with findings from studies in other cancer entities: Sharpley *et al* observed a negative association between resilience and depression in 425 patients with prostate cancer.²⁸ Further studies suggest relations between high levels of resilience and lower levels of anxiety and depression.²⁹

Significance of resilience in the course of monoclonal plasma cell disorders

The regression analyses show that the stage of the disease was significantly related to PCS but not to MCS. This appears to be plausible because physical problems increase in later phases of the disease, while mental burden seems to be high in all phases.

Moderator analyses reveal that resilience has a stronger link to MCS and depression in patients with a new diagnosis and a weaker association to PCS in patients with treated MM.

With regard to MM, one can imagine that patients at an early stage (before the start of therapy) are particularly challenged to anticipate coping with the disease and the upcoming therapy. In our sample, resilience could have a stronger protective effect on mental aspects of HRQOL and depression in early (untreated) stages, than at a later point in time, if the burden by the demanding therapy such as high-dose chemotherapy with ASCT determines the state of perceived mental health. Physical aspects of quality of life (PCS) hardly seem to be influenced by resilience in treated patients, since other factors (eg, symptoms of illness, side effects of therapy) probably play an overwhelming role. However, to confirm this conclusion, longitudinal studies must be carried out in which patients are observed over a longer period of time.

Definition of resilience and its role in cancer

In the current scientific discussion, resilience is described as a multidimensional construct that encompasses both, relatively stable personality traits and a state that is triggered by adverse events (AEs) such as undergoing a treatment for cancer.³⁰ In a recent study of Markovitz *et al*, the results suggest that resilience has a stronger relation to psychosocial factors in patients with cancer compared with non-cancer patients.³¹ The authors conclude that resilience can be seen as a trait variable and may protect against emotional burden in patients with cancer. Wagnild and Young (the authors of the scale, which was used in our current study) define resilience as a personality trait, which has a moderating effect on negative feelings and stress and a flexible adaptation to adverse situations.²³ In a recently published comprehensive review of the

literature, Deshields *et al* give an overview of the large body of resilience literature in oncology.³² Further, the authors propose an interesting model of resilience in adult patients with cancer based on the literature and extensive clinical experience. The researchers 'take the position that resilience is both an outcome and a dynamic process that can be fostered...'.³² Resilience can be seen as a common response to cancer diagnosis and treatment. According to the model by Richardson,³³ personal traits and environmental circumstances as well as experiences after diagnosis/treatment of cancer may contribute to resilience which is defined as a dynamic process. In the future, longitudinal studies should clarify whether resilience is stable or changes in the course of monoclonal plasma cell disorders and other diseases.

Clinical implications

The concept of resilience is promising for its potential application in interventional research in order to support patients with MGUS, SMM and MM to cope with the situation. In a recently conducted systematic review and meta-analysis, modest effects of resiliency training were reported.³⁴ However, only 2 of the 25 studies included focused on patients with cancer without considering haematological malignancies.³⁵⁻³⁶ In a sample of ambulatory patients with cancer, high levels of resilience were strongly associated with lower levels of unmet supportive care needs.³⁷ Therefore, within a complex intervention for supportive care in cancer the researchers tried to facilitate resilience and reduce unmet supportive care needs.³⁸ Resilience levels could only be significantly influenced in a few participants. It must be concluded that it remains unclear whether resilience can be trained in patients with MM and other cancer entities.

Strengths and limitations

The major strength of this study is the large clinical sample and that most data are based on physician-recorded information. HRQOL and other psychosocial constructs were measured with validated questionnaires. A further strength of this analysis is the consideration of all stages of monoclonal plasma cell disorders including MGUS and SMM.

The main limitation of our study is related to its cross-sectional design that does not allow for either temporal or causal inferences. Further studies with consecutive measurements are needed to gain deeper knowledge of psychosocial and physical factors that could be linked to resilience in MM.

Second, in our study, we had no healthy control group to investigate differences of resilience level and relations to our outcome measures.

Third, for measurement of HRQOL, we used a generic questionnaire. Disease-specific questionnaires, such as the Core Quality of Life Questionnaire - 30 or the Multiple Myeloma Module-20, allow to quantify several disease-specific aspects of HRQOL (such as fatigue and nausea) and symptoms of myeloma, respectively.³⁹ Previously, Jordan

et al could show that both severity and type of disease symptoms, and treatment-related AEs are all important determinants of HRQOL in patients with MM.⁴⁰ Further, disease-specific measures seem to be more sensitive for the detection of small changes in interventional or longitudinal studies.²⁹ However, clinicians report, that even (asymptomatic) precursors of MM (that are not treated yet) seem to be associated with a deterioration of HRQOL and augmented psychological burden. Therefore, we used a generic measure that offers the opportunity to compare outcomes across different populations including asymptomatic prestages of MM. Furthermore, the SF-12 is one of the most widely used generic questionnaires in HRQOL research. In future longitudinal observations, a combination of disease-specific and generic measures is recommended to detect small changes in HRQOL.⁴¹

CONCLUSION

In conclusion, resilience may be a protective factor in the disease trajectory of MM and its precursors. As a next step, future research should focus on longitudinal assessments at various time points to elucidate the role of resilience in one of the most frequent haematological malignancies.

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