High Expression of Phosphorylated Extracellular Signal-Regulated Kinase (ERK1/2) is Associated with Poor Prognosis in Newly Diagnosed Patients with Multiple Myeloma

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Background: Previous research has demonstrated that the extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway is commonly activated in multiple myeloma (MM) patients. However, the prognostic value of activation of the MEK/ERK signaling pathway in newly diagnosed patients with MM has not been reported.

Material/Methods: Expression levels of p-ERK1/2 protein in bone marrow biopsy specimens obtained from 60 newly diagnosed patients with MM were analyzed using immunohistochemistry, and classified into 3 groups: high p-ERK1/2 expression, low p-ERK1/2 expression, and negative group. Correlations between clinicopathological characteristics, including expression levels of p-ERK1/2 protein, progression-free survival (PFS), and overall survival (OS), were analyzed using univariate and multivariate analysis.

Results: Phosphorylated-ERK1/2 protein was positive in 47 bone marrow specimens, including 19 specimens with high p-ERK1/2 expression and 28 specimens with low p-ERK1/2 expression. Univariate Kaplan-Meier analysis showed that in newly diagnosed patients with MM, high p-ERK1/2 expression, high ISS staging, serum creatinine (Scr) ≥177 μmol/l, serum β2-microglobulin (β2-MG) ≥5.5 μmol/l, and serum calcium (Ca) ≥2.75 mmol/l were significantly associated with shorter OS and PFS. Additionally, high ECOG scores (score 2–4) were associated with shorter PFS in newly diagnosed patients with MM. Multivariate Cox regression analysis showed that in newly diagnosed patients with MM, high p-ERK1/2 expression was significantly associated with shorter OS and PFS. Additionally, in newly diagnosed patients with MM, serum Ca ≥2.75 mmol/l was significantly associated with shorter PFS, and serum β2-MG ≥5.5 μmol/l was significantly associated with shorter OS.

Conclusions: High p-ERK1/2 expression is an independent factor for poor prognosis in newly diagnosed patients with MM.

MeSH Keywords: Biopsy • Bone Marrow • MAP Kinase Signaling System • Multiple Myeloma • Prognosis

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Background

Multiple myeloma (MM) is a malignant plasma cell disease, characterized by the clonal proliferation of plasma cells in bone marrow, accounting for 10-15% of all hematological malignancies. Some Chinese experts predicted that there are about 200,000 cases in China [1]. Several studies revealed that clinical outcome of patients is heterogeneous, and the pathogenesis of MM is not understood clearly [2,3]. Therefore, exploration of pathogenic development of MM may help to improve MM patient outcome.

The extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling transduction pathway can be activated in response to extracellular stimuli, and has been reported to play an important role in several pathophysiological processes such as cell proliferation and cell death. After stimulation, ERK1/2 protein of the MEK/ERK signaling pathway is phosphorylated, leading to activation of downstream targets [4–6]. Recent studies found that abnormal activation of the MEK/ERK signaling pathway is involved in pathogenesis of many kinds of solid tumors and hematological malignancies, including MM [7–14]. Furthermore, the MEK/ERK signaling pathway participates in abnormal biological behavior of MM cells, induced by some intracellular or extracellular stimuli [15,16]. In MM, abnormality of the MEK/ERK signaling pathway is recurrent and is detected only on the genomic level, not on the protein level [13]. Furthermore, the correlation between ERK signaling pathway abnormality and survival time in MM patients has not been reported.

In this study, we detected the expression of phosphorylated-ERK1/2 (p-ERK1/2) protein in 60 bone marrow biopsy specimens obtained from newly diagnosed patients with MM. We analyzed the correlations among expression levels of p-ERK1/2 protein, clinicopathological characteristics, and survival data of these patients, aiming to gain insight into the potential role of the ERK1/2 signaling pathway in pathogenesis of MM and its prognosis value in newly diagnosed patients with MM.

Material and Methods

Patients and samples

A total of 60 formalin-fixed, paraffin-embedded bone marrow biopsy specimens were obtained from newly diagnosed patients with MM at Fujian Medical University Union Hospital (Fuzhou, China) from January 2012 to February 2015. Before bone marrow biopsy, no prior chemotherapy was administered in any case. This study was approved by the Ethics Committee of Fujian Medical University Union Hospital. The samples were collected with patient consent.

Immunohistochemistry and evaluation of p-ERK1/2 protein expression

The thickness of the sections was 5 μm. Antigen retrieval was carried out in 10 mmol/l sodium citrate buffer (pH 6.0) at 120°C for 5 min in a pressure cooker. Endogenous peroxidase activity was blocked with 3% H2O2 at 37°C for 10 min. Sections were incubated with p-ERK1/2 rabbit monoclonal antibody (CST-4370, dilution 1: 400) (Cell Signaling Technologies, USA) at 37°C for 60 min. Immunoreactive proteins were visualized with the MaxVision™ HRP-Polymer Anti-Rabbit IHC Kit (Maixin Bio, China) following the manufacturer’s protocol. Negative control sections were treated without p-ERK1/2 antibody under the same experimental conditions. Lastly, sections were counterstained with hematoxylin and observed by microscopy (BX41 microscope, Olympus Corporation, Tokyo, Japan) in a number of high-power microscopic fields (magnification, ×400).

Evaluation of p-ERK1/2 protein expression was performed by 2 pathologists blinded to the clinicopathological and survival information of the patients, according to the intensity of cellular staining and the percentage of positively immunoreactive cells. If disagreement emerged regarding the same slide, the pathologists discussed it until a consensus score was achieved. The p-ERK1/2 protein was immunohistochemically stained yellow-brown in the cytoplasm and/or nuclei of plasma cells. The staining intensity was scored as [17]: no staining, score 0; weak staining, score 1; moderate staining, score 2; and strong staining, score 3. The proportion of stained plasma cells was scored as: ≤5% positive cells, score 0; 6–25% positive cells, score 1; 26–50% positive cells, score 2; 51–75% positive cells, score 3; and ≥75% positive cells, score 4. The expression level of p-ERK1/2 protein was considered negative if the total score (Intensity score and positive cells score) was 0, low if it was 1 or 2, and high if it was 3 or more.

Statistical analysis

Clinical event end-points were evaluated by use of the International Myeloma Working Group criteria. Overall survival (OS) was measured from the date of diagnosis to the date of death or last follow-up. Death from all causes was included. Progression-free survival (PFS) was measured from the date of treatment start to the date of disease progression, relapse, or death, whichever came first. Survival time was measured until 31 December 2015.

The χ² test (categorical variables) and Student’s t-test (continuous variables) were used to analyze the correlation between expression levels of p-ERK1/2 protein and demographic and clinicopathological characteristics of newly diagnosed patients with MM. Kaplan-Meier method was used to plot the survival curves. The log-rank test was used to analyze the differences
**Table 1. Demographic and clinicopathological characteristics of primary MM patients.**

| Demographic and clinicopathological characteristics | Total | p-ERK1/2 expression (group) | P-value |
|-----------------------------------------------------|-------|----------------------------|---------|
|                                                     |       | High (A) | Low (B) | Negative (C) |
| Age (years)                                         |       | 63.21±2.84 | 55.96±2.16 | 56.77±3.38 | 0.11 |
| Sex                                                 |       |           |         |             |       |
| Male                                                | 36    | 14       | 13      | 9           | 0.13 |
| Female                                              | 24    | 5        | 15      | 4           |       |
| Ig isotype                                          |       | 29       | 10      | 15          | 4     |
| IgG                                                 |       | 20       | 7       | 7           | 6     |
| IgA                                                 |       | 11       | 2       | 6           | 3     |
| Light chain                                         |       | 12       | 6       | 14          | 5     |
| ISS staging                                         |       | 25       | 6       | 14          | 5     |
| I                                                   | 12    | 1        | 6       | 5           |       |
| II                                                  | 25    | 6        | 14      | 5           |       |
| III                                                 | 23    | 12       | 8       | 3           |       |
| ECOG scoring                                        |       | 48       | 13      | 24          | 11    |
| 0–1                                                 |       | 48       | 13      | 24          | 11    |
| 2–4                                                 |       | 12       | 6       | 4           | 2     |
| Plt (×10⁹/L)                                        |       | 50       | 15      | 23          | 12    |
| ≥100                                                |       | 50       | 15      | 23          | 12    |
| <100                                                |       | 10       | 4       | 5           | 1     |
| Hb (g/L)                                            |       | 19       | 4       | 10          | 5     |
| ≥100                                                |       | 19       | 4       | 10          | 5     |
| <100                                                |       | 41       | 15      | 18          | 8     |
| Scr (μmol/L)                                        |       | 7        | 4       | 1           | 2     |
| ≥177                                                |       | 7        | 4       | 1           | 2     |
| <117                                                |       | 53       | 15      | 27          | 11    |
| Serum Alb (g/L)                                     |       | 16       | 2       | 7           | 7     |
| ≥35                                                 |       | 16       | 2       | 7           | 7     |
| <35                                                 |       | 44       | 17      | 21          | 6     |
| Serum β₂-MG (μmol/L)                                |       | 19       | 11      | 5           | 3     |
| ≥5.5                                                |       | 19       | 11      | 5           | 3     |
| <5.5                                                |       | 41       | 8       | 23          | 10    |
| Serum LDH (IU/L)                                    |       | 17       | 5       | 9           | 1     |
| ≥245                                                |       | 17       | 5       | 9           | 1     |
| <245                                                |       | 48       | 14      | 22          | 12    |
| Serum Ca (mmol/L)                                   |       | 7        | 4       | 2           | 1     |
| ≥2.75                                               |       | 7        | 4       | 2           | 1     |
| <2.75                                               |       | 53       | 15      | 26          | 12    |
| Bortezomib                                          |       | 27       | 10      | 11          | 6     |
| Yes                                                 | 27    | 10       | 11      | 6           | 0.66 |
| No                                                  | 33    | 9        | 17      | 7           |       |
| Thalidomide                                         |       | 35       | 13      | 14          | 8     |
| Yes                                                 | 35    | 13       | 14      | 8           | 0.44 |
| No                                                  | 25    | 6        | 14      | 5           |       |
| Auto-HSCT                                           |       | 10       | 1       | 5           | 4     |
| Yes                                                 | 10    | 1        | 5       | 4           | 0.16 |
| No                                                  | 50    | 18       | 23      | 9           |       |

Ig – immunoglobulin; ISS – International Staging System; ECOG – Eastern Cooperative Oncology Group; Plt – platelet; Hb – hemoglobin; Scr – serum creatinine; Alb – albumin; β₂-MG – β₂-microglobulin; LDH – lactate dehydrogenase; Ca – calcium; Auto-HSCT – autologous hematopoietic stem cell transplantation.
in these survival curves. The Cox regression model was used for multivariate analysis, with adjustments for characteristics that might be significant prognostic factors according to the univariate analysis. P<0.05 was used as the criterion for statistical significance. SPSS19.0 software was used for statistical analysis.

Results

Demographic and clinicopathological characteristics of MM patients

The demographic and clinicopathological characteristics of 60 newly diagnosed patients with MM are summarized in Table 1. Ages of these patients ranged from 35 to 81. After bone marrow biopsy, all patients were treated with at least 2 courses of chemotherapy regimens containing bortezomib and/or thalidomide, and/or autologous hematopoietic stem cell transplantation. The median follow-up of all patients was 16.1 (0.3–48) months. During the follow-up period, 21 deaths occurred.

Expression of p-ERK1/2 in bone marrow biopsy specimens and its correlation with demographic and clinicopathological characteristics of MM patients

The immunohistochemistry (IHC) results showed that expression of p-ERK1/2 protein was positive in 47 of 60 bone marrow specimens. According to evaluation criterion of p-ERK1/2 protein expression, 60 newly diagnosed patients with MM were classified into 3 groups: 19 patients with high p-ERK1/2 expression (group A), 28 patients with low p-ERK1/2 expression (group B), and 13 patients without p-ERK1/2 expression (group C) (Figure 1, Table 1).

The demographic and clinicopathological characteristics according to expression levels of p-ERK1/2 protein are listed in Table 1. There were significant differences in 3 characteristics – ISS staging, serum albumin (Alb) level, and serum β2-MG level – among patients in these 3 groups. However, there were no significant differences in other characteristics such as age, sex, ECOG scoring, immunoglobulin (Ig) isotype, hemoglobin (Hb) level, platelet (Plt) counts, serum creatinine (Scr) level, serum lactate dehydrogenase (LDH) level, serum calcium (Ca) level, and therapeutic regimens containing bortezomib, thalidomide, and/or autologous hematopoietic stem cell transplantation (auto-HSCT) among patients in these 3 groups (Table 1).

Correlation between expression of p-ERK1/2 protein and survival time in newly diagnosed patients with MM

To elucidate the relationship between expression levels of p-ERK1/2 protein and survival time in newly diagnosed patients with MM, univariate Kaplan-Meier and multivariate Cox regression analysis were performed.
Table 2. Univariate analysis of the correlation between demographic and clinicopathological characteristics and survival time in primary MM patients.

| Demographic and clinicopathological characteristics | Overall survival time (mean, month) | Log-rank test | P | Progression-free survival time (mean, month) | Log-rank test | P |
|-----------------------------------------------------|------------------------------------|---------------|---|----------------------------------------------|---------------|---|
| **Age**                                             |                                    |               |   |                                              |               |   |
| ≥60                                                 | 15.712                             | 1.733         | 0.188 |                                              | 14.786        | 0.072 | 0.788 |
| <60                                                 | 19.165                             |               |     |                                              | 15.836        |       |      |
| **Sex**                                             |                                    |               |   |                                              |               |   |
| Male                                                | 16.260                             | 1.134         | 0.287 |                                              | 14.082        | 1.401 | 0.237 |
| Female                                              | 19.637                             |               |     |                                              | 17.286        |       |      |
| **Ig isotype**                                      |                                    |               |   |                                              |               |   |
| IgG                                                 | 17.347                             | 0.070         | 0.966 |                                              | 14.686        | 0.059 | 0.809 |
| IgA                                                 | 17.650                             |               |     |                                              | 14.915        |       |      |
| Light chain                                         | 18.235                             |               |     |                                              | 17.966        |       |      |
| **ISS staging**                                     |                                    |               |   |                                              |               |   |
| I                                                   | 22.182                             |               |     |                                              | 21.653        |       |      |
| II                                                  | 19.166                             | 6.094         | 0.048 |                                              | 5.085         | 0.024 |      |
| III                                                 | 13.535                             |               |     |                                              | 12.732        |       |      |
| **ECOG**                                            |                                    |               |   |                                              |               |   |
| 0–1                                                 | 18.206                             |               |     |                                              | 16.251        |       |      |
| 2–4                                                 | 15.230                             | 0.989         | 0.320 |                                              | 4.148         | 0.042 |      |
| **Plt (×10[^9]/L)**                                 |                                    |               |   |                                              |               |   |
| ≥100                                                | 17.250                             | 1.111         | 0.292 |                                              | 15.286        | 0.190 | 0.663 |
| <100                                                | 19.413                             |               |     |                                              | 15.753        |       |      |
| **Hb (g/L)**                                        |                                    |               |   |                                              |               |   |
| ≥100                                                | 21.189                             | 1.678         | 0.195 |                                              | 18.657        | 2.705 | 0.100 |
| <100                                                | 15.953                             |               |     |                                              | 13.838        |       |      |
| **Scr (µmol/L)**                                    |                                    |               |   |                                              |               |   |
| ≥177                                                | 10.110                             | 7.047         | 0.008 |                                              | 5.169         | 0.023 |      |
| <177                                                | 18.602                             |               |     |                                              | 16.152        |       |      |
| **Serum Alb (g/L)**                                 |                                    |               |   |                                              |               |   |
| ≥35                                                 | 17.855                             | 17.522        | <0.001 |                                              | 17.469        | 14.593 | 0.327 |
| <35                                                 | 18.206                             |               |     |                                              | 14.195        |       |      |
| **Serum β₂-MG (µmol/L)**                            |                                    |               |   |                                              |               |   |
| ≥5.5                                                | 11.416                             | 13.173        | <0.001 |                                              | 10.623        | 7.908 | 0.005 |
| <5.5                                                | 20.482                             |               |     |                                              | 17.516        |       |      |
| **Serum LDH (IU/L)**                                |                                    |               |   |                                              |               |   |
| ≥245                                                | 16.997                             | 0.022         | 0.883 |                                              | 14.266        | 0.140 | 0.709 |
| <245                                                | 17.764                             |               |     |                                              | 15.638        |       |      |
| **Serum Ca (mmol/L)**                               |                                    |               |   |                                              |               |   |
| ≥2.75                                               | 18.777                             | 15.119        | <0.001 |                                              | 16.419        | 22.136 | <0.001 |
| <2.75                                               | 18.777                             |               |     |                                              | 15.732        |       |      |
| **Bortezomib**                                      |                                    |               |   |                                              |               |   |
| Yes                                                 | 17.371                             | 0.020         | 0.887 |                                              | 15.159        | 15.543 | 0.979 |
| No                                                  | 17.820                             |               |     |                                              | 15.543        |       |      |
| **Thalidomide**                                     |                                    |               |   |                                              |               |   |
| Yes                                                 | 16.798                             | 1.271         | 0.260 |                                              | 14.934        | 0.383 | 0.536 |
| No                                                  | 18.749                             |               |     |                                              | 15.638        |       |      |
| **Auto-HSCT**                                       |                                    |               |   |                                              |               |   |
| Yes                                                 | 19.983                             | 0.491         | 0.483 |                                              | 17.020        | 0.171 | 0.679 |
| No                                                  | 17.136                             |               |     |                                              | 15.032        |       |      |
| **p-ERK1/2 expression**                             |                                    |               |   |                                              |               |   |
| High (A)                                            | 9.792                              | 23.674        | <0.001 |                                              | 19.028        | 8.673 | 0.003 |
| Low (B)                                             | 22.010                             |               |     |                                              | 17.352        |       |      |
| Negative (C)                                        | 19.564                             |               |     |                                              | 17.352        |       |      |

Ig – immunoglobulin; ISS – International Staging System; ECOG – Eastern Cooperative Oncology Group; Plt – platelet; Hb – hemoglobin; Scr – serum creatinine; Alb – albumin; β₂-MG – β₂-microglobulin; LDH – lactate dehydrogenase; Ca – calcium; Auto – HSCT-autologous hematopoietic stem cell transplantation.
Univariate analysis showed that in MM patients, expression level of p-ERK1/2 protein was negatively associated with OS and PFS. The OS and PFS of patients in group A were shorter than those in group B and group C. Furthermore, there were no significant differences in OS and PFS between patients in group B and those in group C (Figure 2, Table 2). In addition, the shorter OS in newly diagnosed patients with MM was significantly associated with high ISS staging, Scr ≥177 µmol/l, serum β₂-MG ≥5.5 µmol/l, and serum Ca ≥2.75 mmol/l, and the shorter PFS was significantly associated with high ISS staging, high ECOG scoring, Scr ≥177 µmol/l, serum β₂-MG ≥5.5 µmol/l, and serum Ca ≥2.75 mmol/l (Table 2).

Table 3. Multivariate analysis of the correlation between clinicopathological characteristics and survival time in primary MM patients.

| Covariates | Overall survival | Progression-free survival |
|------------|-----------------|--------------------------|
|            | Coefficient     | Standard error | HR | 95% CI for HR | P | Coefficient | Standard error | HR | 95% CI for HR | P |
| ISS staging| −0.097          | 0.257         | 0.907 | 0.548–1.502 | 0.705 | 0.044      | 0.237         | 1.045 | 0.656–1.664 | 0.853 |
| Scr (µmol/L)| 0.019          | 0.640         | 1.019 | 0.290–3.574 | 0.977 | −0.100    | 0.587         | 0.905 | 0.287–2.857 | 0.865 |
| β₂-MG (µmol/l)| 0.928         | 0.470         | 2.530 | 1.006–6.358 | 0.048 | 0.432     | 0.436         | 1.541 | 0.656–3.618 | 0.321 |
| Ca (mmol/l)| 1.010          | 0.619         | 2.745 | 0.816–9.231 | 0.103 | 1.715     | 0.605         | 5.559 | 1.697–18.212 | 0.005 |
| p-ERK1/2 expression| −0.575   | 0.234         | 0.563 | 0.355–0.891 | 0.014 | −0.546   | 0.226         | 0.579 | 0.372–0.901 | 0.015 |
| ECOG | N.A. | N.A. | N.A. | N.A. | N.A. | 0.544 | 0.348 | 1.722 | 0.870–3.407 | 0.118 |

ISS – International Staging System; ECOG – Eastern Cooperative Oncology Group; Scr – serum creatinine; Alb – albumin; β₂-MG – β₂-microglobulin; Ca – calcium; HR – hazard ratio; CI – confidence interval; N.A. – not available.

Figure 2. Kaplan-Meier survival curves of patients with newly diagnosed MM classified according to expression levels of p-ERK1/2 protein. (A) Overall survival. i. P=0.000, compared A with B; ii. P=0.007, compared A with C; iii. P=0.541, compared B with C. (B) Progression-free survival. i. P=0.000, compared A with B; ii. P=0.007, compared A with C; iii. P=0.496, compared B with C.
Multivariate analysis showed that in MM patients, high expression level of p-ERK1/2 protein was significantly associated with OS and PFS. Additionally, serum Ca ≥2.75 mmol/l was significantly associated with PFS, and serum β₂-MG ≥5.5 μmol/l was significantly associated with OS (Table 3).

**Discussion**

MM is an incurable malignant plasma cell disease. A growing number of studies show that pathogenesis and clinical outcome of MM patients are highly heterogeneous [1,18–21]. Recent studies using gene expression profiling show that the MEK/ERK signaling pathway is abnormally activated in over 50% of MM patients [13]. MEK/ERK signaling pathway inhibitor can show cytotoxicity on MM cells from newly diagnosed patients and MM cell lines in vitro [22,23]. Furthermore, MEK inhibitor used alone or in combination with conventional chemotherapy showed weak or moderate cytotoxicity to MM cells in vivo, leading to partial remission in some refractory/re lapse patients with MM in a clinical trial. Some clinical trials are ongoing to evaluate the efficacy of new MEK inhibitor on patients with MM [23]. The above evidence indicates that inhibition of the MEK/ERK signaling pathway may be a useful strategy for MM treatment. However, there has been no published research on the effect of activated molecules in the MEK/ERK signaling pathway, such as p-ERK1/2, on protein level, and the correlation between p-ERK1/2 protein expression and survival time in newly diagnosed patients with MM has not been reported.

The present study shows that the positive rate of p-ERK1/2 in bone marrow biopsy specimens of newly diagnosed patients with MM is high (78.3%), in agreement with a previous study showing that activation of the ERK signaling pathway is common in myeloma [13]. We then classified 60 patients into 3 groups according to expression levels of p-ERK1/2 protein, showing that expression levels of p-ERK1/2 were positively associated with ISS staging, serum albumin level, and serum β₂-MG level in these patients. However, there were not significant differences in the other clinicopathological characteristics mentioned above among patients in these 3 groups.

Before analysis of the correlation between expression levels of p-ERK1/2 protein and survival time in newly diagnosed patients with MM, in these 3 groups we analyzed the therapeutic regimens that have been considered to benefit MM patient survival time [24,25]. We also found that there was no significant difference in therapeutic regimens containing bortezomib and thalidomide, and auto-hematopoietic stem cell transplantation among patients in these 3 groups.

Subsequently, in univariate analysis, we found that expression levels of p-ERK1/2 protein, high ISS staging, serum Cr ≥177 μmol/l, serum β₂-MG ≥5.5 μmol/l, and serum Ca ≥2.75 mmol/l were poor prognostic factor for PFS and OS of newly diagnosed patients with MM. Otherwise, high ECOG scoring was a poor prognostic factor for PFS, but not for OS, of newly diagnosed patients with MM.

In multivariate analysis, we found that in newly diagnosed patients with MM, high expression level of p-ERK1/2 protein, but not low expression level of p-ERK1/2 protein, was an independent poor prognostic factor for OS and PFS of newly diagnosed patients with MM. In addition, in newly diagnosed patients with MM, serum Ca ≥2.75 mmol/l was also an independent poor prognostic factor for PFS, while serum β₂-MG ≥5.5 μmol/l was also an independent poor prognostic factor for OS.

Although ISS staging, consisting of serum albumin level and serum β₂-MG level, has been reported to be the most important prognostic system for MM [21], we found that it had no useful prognostic value. We found differences in ISS staging, serum albumin level, and serum β₂-MG level in newly diagnosed patients with MM with different expression levels of p-ERK1/2 protein, and these differences might have attenuated the prognostic function of ISS staging in our study.

**Conclusions**

Our data suggest that high expression of p-ERK1/2 protein is an independent factor for poor survival in newly diagnosed patients with MM, and therapeutic regimens targeting ERK1/2 may be of benefit to MM patients.

**Conflicts of interest**

None.
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