The Possibility of Developing Screening Criteria for Patients Suspected Multiple Myeloma (MM) at Thammasat University Hospital

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Background: *Patients suspected with multiple myeloma (MM) are often delayed investigation and diagnosis because of multiple factors. The objective of this study was to evaluate factors leading to diagnosis of MM would help in early diagnosis and treatments.*

Objective: *To evaluate the effectiveness of factors used for myeloma screening and to find any factors that can predict the diagnosis of multiple myeloma.*

Material and Method: *From Aug 2013 to Mar 2015, 300 patients were enrolled into this study. Every patient must have met the criteria of: 1) age above 50 years, 2) at least one of laboratory criteria (Hb <10 g/dL, serum creatinine >2 mg/dL, serum calcium >10 mg/dL), and 3) at least one skeletal criterion (bone pain, osteoporosis or history of fracture). Eligible patients' sample were sent for serum protein electrophoresis (SPEP) to screen for MM.*

Results: *From 300 patients, there were 70 patients (23.3%) diagnosed with MM. Of the 3 criteria, all patients (n = 300, 100%) had age above 50 years as inclusion criteria, mean age was 73 years, 273 cases (91%) had Hb below 10 g/dL, 83 cases (27.66%) had serum creatinine >2 mg/dL and 97 cases (32.33%) had serum calcium >10 mg/dL. However, there was no factor successfully predicted MM diagnosis.*

Conclusion: *Among many factors those are the common presentation of MM, there were no factor or combination of factors that shown statistically significant to predict the diagnosis of multiple myeloma. However, we would suggest thinking of MM in elderly patients who have bone pain or osteoporosis, hypercalcemia, and azothemia or renal failure.*

Keywords: *Multiple myeloma, MM, Screening criteria, Serum protein electrophoresis*

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Multiple myeloma (MM) is one of the common hematologic malignancies that often found in adults older than 50-year-old. Data from year 2006-2010 shows that the median age at diagnosis of myeloma patient is 69 years old (range 65-70 years)[1]. Age-adjusted incidence of MM is 5.9/100,000 persons in year 2013. In the future it was predicted that 22,350 new patients would be diagnosed and 10,710 people would die from the disease. About 70-80% of MM patients have bone related symptoms at the time of diagnosis which would lead to the diagnosis[2]. However, these bone related symptoms may progress to fracture, spinal cord compression, diffused osteoporosis or hypercalcemia and can increase morbidity and mortality in MM[3,4]. Early diagnosis will help patient to get early treatment and decrease morbidity/mortality rate.

Detection of routine blood abnormality together with clinical criteria and increase monoclonal or abnormal M-protein suggest myeloma diagnosis. Below is the criteria guide to diagnosis of MM[6-8]. For definition of active (symptomatic) myeloma[7]: all criteria must be met except as noted:

- Clonal BM plasma cells ≥10% or biopsy proven plasmacytoma.
- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically.
- Hypercalcemia: serum calcium >11.5 mg/dL or
- Renal insufficiency: serum Creatinine >173 micromoles/l (or >2 mg/dL) or estimate creatinine clearanceless than 40 ml/minute.
- Anemia: normochromic normocytic with a Hb value of >2 gm/dL below the the normal limit of normal or Hb <10 g/dL.

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- Bone lesion lytic lesion, osteopenia, or pathological fracture.

Screening of MM by using clinical syndrome such as anemia, bone pain or renal insufficiency, which known as a clinical triad, may decrease over investigation by bone marrow study.

Objective

The primary objective of this study was to evaluate the effectiveness use of factors for screening and predicting the diagnosis of multiple myeloma.

Material and Method

This is a cross sectional study which collected patients' data from Thammasat Hospital between August 2013 and March 2015 for the study.

The calculated sample size was 300; every enrolment patient (included both in and out-patient from all departments notified) must have met all inclusion criteria, which were:

1) age above 50 years

2) at least one lab criteria (Hb* <10 g/dL, serum creatinine >2 mg/dL, serum calcium* >10 mg/dL)

3) at least one skeletal criteria (bone pain, osteoporosis or history of fracture).

* Calcium was corrected total serum calcium with serum albumin of the nearest date, Hb just before screening date and serum creatinine nearest screening date. Ed note-this sentence needs rewording, not coherent.

Exclusion criteria were known case of MM or smoldering MM.

Those patients definitely diagnosed with MM had positive monoclonal antibody or very likely having CRAB (Hypercalcemia (>11 mg/dl), renal failure (CrCl <40 ml/min or sCr >2 mg/dl), anemia (Hb <10 gm/dl), and bone disease (≥1 lytic bone lesions on skeletal radiography). Criteria was confirmed by the presence of more than 10 percent of plasma cells in bone marrow evaluation and underwent standard clinical practices and further investigated. The diagnosis of MM was documented when clonal plasma cells were more than 10% and with one or more myeloma defining events. However, this study did a BM study in some patients depending on clinical judgment or other reasons; we did not persuade all patients in the study to undergo a BM aspiration or biopsy.

Data collection

After informed consent was signed, every patient who met the inclusion criteria had 3 ml of venous blood drawn and sent for serum protein electrophoresis (SPE). All data associated with the inclusion criteria, data and the results of SPE, were collected in the case record form and sent to statistical analysis.

Data analysis

Using SPSS software version 13.0 statistical analysis was performed. Basic statistics including means, standard deviations, and percentage were used to characterize patients. The association between the prevalence of disease and important factors was measured using one-way ANOVA, and Pearson's Chi-squared with a reference of p-value <0.05 was considered a statistical significance.

Results

From Aug 2013 to Mar 2015, 300 patients were enrolled into this study. Eligible patients' blood samples were sent for serum protein electrophoresis (SPEP) to screen for MM.

Demographic data of all 300 cases are shown in Table 1. Of the total 300 cases, there were 165 males and 135 females. We found 70 cases (23.3%) with confirmed diagnosis of MM, male 40 cases, female 30 cases. The mean ages were 74 years and 73 years in MM and no definite evidence MM group respectively. (Range 62-84 years and 62-83 years) (p = 0.562), the mean hemoglobin levels were 8.6 g/dL and 9.1 g/dL in MM and no-definite evidence of MM group, respectively (Range 7.4-10.37 g/dL and 7.55-10.35g/dL) (p = 0.359). The mean serum creatinine was 1.4 mg/dL and 1.9 mg/dL in MM and no-definite MM group, respectively (Range 0.45-3.42 mg/dL and 0.34-3.54 mg/dL) (p = 0.844). The mean serum calcium levels were 10.1 mg/dL and 9.6 mg/dL in MM and no definite evidence MM group, respectively (Range 8.75-10.82 mg/dL and 8.69-10.84 mg/dL) (p = 0.559). The mean age in total case was 73 years (62-84 year), mean Hb 8.96 gm/dL (7.55-10.37 gm/dL), mean serum creatinine 1.79 mg/dL (0.34-3.54 mg/dL), mean serum calcium 9.74 mg/dL (8.69-10.84 mg/dL), respectively, range in each factor as shown in Table 1.

For age variable factor, the patients were sub-grouped into age 75 year and older but younger than 80 years, and age 80 years and older (Table 2). Of 36 cases age 75-79 years, there were 8 cases (2.67%) diagnosed with MM compared with 28 cases (9.33%). Of 264 cases (88%) aged ≥80 years, 62 cases (20.67%) were diagnosed with MM compared with 202 cases (67.3%) shown in Table 2 (p = 0.86).

All 300 patients had bone pain but no

osteoporosis or fractures were confirmed by screening.

Regarding anemia and hemoglobin levels (Table 3), there were 17 cases (5.67%) from total 300 cases who had Hb <8 g/dL and diagnosed with MM. There were 38 cases (12.67%) who had Hb <8 gm/dl but no definite evidence of MM detected. From 245 cases with Hb >8 gm/dl, there were 53 cases (17.67%) was diagnosed with MM and there were 192 cases (64%) in no definite evidence of MM group ($p = 0.14$).

In terms of renal function, use of serum creatinine (sCr) and subgroup analysis are shown in Table 4. Of the total patients, there were 84 cases (28%)

Table 1. Demographic data

Total (300)	MM (70 cases) 23.3%	No definite evidence of MM (230 cases) 76.7%	*p*-value
Gender (M: F)	40:30	125:105	NA
Age (years)	62-83	62-84	0.562
Mean	74.1	73.2	
Median	73.5	74	
Hb (gm/dL)	7.4-10.37	7.55-10.35	0.359
Mean	8.6	9.1	
Median	8.7	9.25	
Serum creatinine (mg/dL)	0.45-3.42	0.34-3.54	0.844
Mean	1.4	1.9	
Median	1.14	1.4	
Serum calcium (mg/dL)	8.75-10.82	8.69-10.84	0.559
Mean	10.1	9.6	
Median	9.82	9.43	

Table 2. Age subgroups

Age (years)	Total cases (300 cases)	MM (70 cases) 23.3%	No definite evidence of MM (230 cases) 76.7%	*p*-value
Age ≥75	36 (12%)	8 (2.67%)	28 (9.33%)	0.86
Age ≥80	264 (88%)	62 (20.67%)	202 (67.33%)	

Table 3. Hemoglobin subgroups

Hb (g/dL)	Total case (300 case)	MM (70 cases) 23.3%	No definite evidence of MM (230 cases) 76.7%	*p*-value
Hb <8.0	55 (18.33%)	17 (5.67%)	38 (12.67%)	0.14
Hb ≥8.0	245 (81.67%)	53 (17.67%)	192 (64%)	

Table 4. Serum creatinine subgroup

sCr (mg/dL)	Total case (300 case)	MM (70 cases) 23.3%	No definite evidence of MM (230 cases) 76.7%	*p*-value
sCr <1	84 (28%)	23 (7.67%)	61 (20.33%)	0.02
sCr 1.0-2.0	130 (43.33%)	36 (12%)	94 (31.33%)	
sCr >2.0	86 (28.67%)	11 (3.67%)	75 (25%)	

had sCr below 1.0 mg/dL, 130 cases (43.33%) had sCr 1.0-2.0 mg/dL, and 86 cases (28.67%) had sCr > 2.0 mg/dL. In MM group, 23 cases (7.67%) had sCr <1.0 mg/dL, 36 cases (12%) had sCr 1.0-2.0 mg/dL, and 11 cases (3.67%) had sCr >2.0 mg/dL. And for non-definite evidence of MM group, 61 cases (20.33%) had sCr <1.0 mg/dL, 94 cases (31.33%) had sCr 1.0-2.0 mg/dL and 75 cases (25%) had sCr >2.0 mg/dL ($p = 0.02$).

From total 300 cases we collected, there were 200 cases (66.67%) with serum calcium lower than 10 mg/dL, 100 cases (33.33%) with serum calcium from 10.0 mg/dL. In the group of MM patients, 41 cases (10.33%) had serum calcium less than 10 mg/dL and 29 cases (9.67%) had serum calcium >10 gm/dL; however, no definite evidence of MM group of 159 cases (53%) had serum calcium less than 10 mg/dL and 71 cases (23.67%) had serum calcium >10 gm/dL.

Thirty-nine cases had serum calcium of more than 10 mg/dL but not more than 12 mg/dL. Only one had serum calcium more than 12 mg/dL. The detail about serum calcium group is shown in Table 5.

Discussion

Multiple myeloma (MM) is the second most common clonal B-cell malignancy worldwide. Diagnosis of MM as recommendations of International Myeloma Working Group (IMWG) guidelines for the management of multiple myeloma patients need more than 10% of plasma cell in BM and/or a biopsy proving plasmacytoma with positive monoclonal protein in serum or urine with myeloma-related organ damage[8].

This study tried to investigate the efficacy of an early screening of any patients who might have myeloma by using serum protein electrophoresis before knowing the definite diagnosis of myeloma or pathological results in the patients who have clinical symptoms, signs, or laboratory results similar to myeloma-related organ damage.

Using serum protein electrophoresis (SPE) as a screening in patients who have one or more of these criteria (age ≥60 years, anemia (Hb <8 g/dl), hypercalcemia (serum calcium >10 mg/dL), renal failure (serum creatinine ≥1 mg/dL) and bone pain or bone lesion to predict MM in this study, found that the increase in serum creatinine (>1 mg/dl) levels had a correlation with positive SPE with a statistical significance. All enrolled patients have bone pain but no osteoporosis or fracture confirmed at screening. This could be due to the enrollment of a small sample size. However, criteria for diagnosis of MM according to WHO classification of lymphoid and plasma cell disorder had shown factors using in this study (CRAB criteria) which might help the early diagnosis of MM (we found 23.3% of patients confirmed MM).

Another point, some patients did not go further with their investigation depending on clinical judgment. However, we know that for negative SPE patients group, some may have non-secretory myeloma or light chain multiple myeloma; therefore, we may miss some patients with non-secretory or light chain multiple myeloma.

This study confirms that using CRAB criteria to suggest likelihood of myeloma along with SPE will lead to early definite diagnosis of multiple myeloma, especially in patients with increased serum creatinine 1 mg/dL or more. However, SPE in non-secretory myeloma or light chain multiple myeloma should be of concern; other laboratory tools such as serum-free light chain or definite bone marrow study should be used to exclude plasma cell malignancy. Further screening studies should be planned to compare SPE to other lab investigation. This could be interesting.

Conclusion

At this point, from our study, age ≥50 years, anemia (Hb <8 g/dl), hypercalcemia (serum calcium >10 mg/dL), and bone pain or bone lesion age have no statistical correlation with the definite diagnosis of myeloma. Serum creatinine ≥1 mg/Dl together with age ≥50 years, anemia (Hb <8 g/dl), and hypercalcemia (serum calcium >10 mg/dL) might be correlated with positive SPE and multiple myeloma. Only the increase in serum creatinine (>1 mg/dl) level has a correlation with positive SPE with statistical significance. However, we would suggest using all these clinical data (age ≥60 years, anemia (Hb <8 g/dl), hypercalcemia (serum

Table 5. Serum calcium subgroup

sCa (mg/dL)	Total case (300 case)	MM (70 cases) 23.3%	No definite evidence of MM (230 cases) 76.7%	*p*-value
sCa <10	200 (66.67%)	41 (13.67%)	159 (53%)	0.10
sCa ≥10	100 (33.33%)	29 (9.67%)	71 (23.67%)	

calcium >10 mg/dL), renal failure (serum creatinine ≥1 mg/dL) and bone pain or bone lesion to predict MM, which we already know from the past, for not missing some elderly patient who is not older than 85 year-olds.

What is already known on this topic?

It was already known that using CRAB criteria to suggest likelihood of myeloma. However, waiting until meet all CRAB criteria, we could frequently see patieint with more end organ damage. Detection of routine blood abnormality together with some clinical criteria and increase monoclonal or abnormal M-protein will suggest the myeloma diagnosis.

What this study adds?

This study confirms that using CRAB criteria along with SPE will lead to early, definite diagnosis of multiple myeloma, especially in patients with increase serum creatinine 1 mg/dL or more. However, SPE in non-secretory myeloma or light chain multiple myeloma should be concerned, and using other laboratory tools such as serum free light chain or definite bone marrow study to exclude plasma cell malignancy. Further screening studies need to be with planned to compare SPE to other lab investigation, which could be interesting.

Potential conflicts of interest

None.

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ความเป็นไปได้ของการตรวจคัดกรองผู้ป่วยที่สงสัยโรคมัลติเพิลมัยอิโลมาที่โรงพยาบาลธรรมศาสตร์

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ภูมิหลัง: ผู้ป่วยมัลติเพิลมัยอิโลมาสามารถมาด้วยอาการหลากหลายหลายครั้ง ที่การวินิจฉัยล่าช้าการวินิจฉัยได้รวดเร็วมีโอกาสทำให้การรักษาประสบความสำเร็จหรือเกิดภาวะแทรกซ้อนมากกว่า

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพและความเป็นไปได้ของปัจจัยที่ใช้ในการวินิจฉัยเบื้องต้นสำหรับโรค ผู้ป่วยและวิธีการศึกษาผู้ป่วยทุกรายที่เข้าเกณฑ์การศึกษาในช่วงเดือนสิงหาคม พ.ศ. 2556 ถึง เดือนมีนาคม พ.ศ. 2558 (จำนวน 300 ราย) โดยมีเกณฑ์การศึกษาดังนี้ 1) อายุมากกว่า 50 ปี 2) มีความผิดปกติของการตรวจทางห้องปฏิบัติการอย่างน้อย 1 ใน 3 ข้อต่อไปนี้ (Hb <10 g/dL, serum creatinine >2 mg/dL, serum calcium >10 mg/dL) and 3) at least one skeletal criteria (bone pain, osteoporosis or history of fracture) ผู้ป่วยที่เข้าเกณฑ์ดังกล่าวจะได้รับการส่งตรวจเลือดสำหรับตรวจ serum protein electrophoresis (SPEP)

ผลการศึกษา: ผู้ป่วยจำนวน 300 รายที่เข้าเกณฑ์พบว่าอายุเฉลี่ย 73 ปี 70 ราย (ร้อยละ 23.3) ได้รับการวินิจฉัยเป็นมัลติเพิลมัยอิโลมา 273 cases (91%) 83 รายมีระดับฮีโมโกลบินต่ำกว่า 10 g/dL (ร้อยละ 27.66) 97 ราย (ร้อยละ 32.33) มีระดับ serum creatinine >2 mg/dL และ serum calcium >10 mg/dL อย่างไรก็ตามผลการศึกษาไม่พบว่าสามารถใช้ปัจจัยใดในการประเมินเบื้องต้นว่าผู้ป่วยน่าจะเป็นโรคมัลติเพิลมัยอิโลมาได้

สรุป: ปัจจัยส่วนของอาการที่พบบ่อยของผู้ป่วยโรคมัยอิโลมา เช่น ปวดกระดูกเรื้อรัง ไตวาย หรือภาวะระดับแคลเซียมในเลือดสูงจะไม่สามารถประเมินได้ถูกต้องว่าผู้ป่วยมีโอกาสเป็นโรคมัลติเพิลมัยอิโลมาได้ อย่างไรก็ตามผู้นิพนธ์ยังเห็นว่ายังมีความจำเป็นที่จะคิดถึงและตรวจเพิ่มเติมเพื่อการวินิจฉัยโรคนี้ในผู้ป่วยสูงอายุที่มีปวดกระดูกเรื้อรังไตวายหรือภาวะระดับแคลเซียมในเลือดสูงเพื่อการวินิจฉัยที่รวดเร็ว