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The Role of Monocyte Percentage in Osteoporosis in Male Rheumatic Diseases

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Abstract

Osteoporosis is easily overlooked in male patients, especially in the field of rheumatic diseases mostly prevalent with female patients, and its link to pathogenesis is still lacking. Attenuated monocyte apoptosis from a transcriptome-wide expression study illustrates the role of monocytes in osteoporosis. This study tested the hypothesis that the monocyte percentage among leukocytes could be a biomarker of osteoporosis in rheumatic diseases. Eighty-seven males with rheumatic diseases were evaluated in rheumatology outpatient clinics for bone mineral density (BMD) and surrogate markers, such as routine peripheral blood parameters and autoantibodies. From the total number of 87 patients included in this study, only 15 met the criteria for diagnosis of osteoporosis. Both age and monocyte percentage remained independently associated with the presence of osteoporosis. Steroid dose (equivalent prednisolone dose) was negatively associated with BMD of the hip area and platelet counts were negatively associated with BMD and *T* score of the spine area. Besides age, monocyte percentage meets the major requirements for osteoporosis in male rheumatic diseases. A higher monocyte percentage in male rheumatic disease patients, aged over 50 years in this study, and BMD study should be considered in order to reduce the risk of osteoporosis-related fractures.

Keywords

male, monocyte, osteoporosis, rheumatic diseases

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Osteoporosis occurs in normal subjects and in patients with any rheumatic disease, and its prevalence is especially underestimated in male patients (Willson, Nelson, Newbold, Nelson, & LaFleur, 2015). Osteoporosis is easily overlooked in males, especially in the field of rheumatic diseases mostly prevalent with female patients, and its link to pathogenesis is still lacking. Some rheumatic diseases are more vulnerable to bone loss (C. Lee & Ramsey-Goldman, 2005), but there are no available biomarkers for detecting osteoporosis, including the markers indicative of bone formation or bone resorption (Bieglmayer et al., 2012; Eastell & Hannon, 2008; Garnero, 2008), and none of them are predictive of osteoporosis.

Osteoporosis in men's health is underappreciated. A study from Wong et al. demonstrated men over 55 years old have less knowledge about osteoporosis than women (Wong, Lok, Wun, & Pang, 2014). Recommendation for osteoporosis screening in men is especially focused on men with inflammatory diseases, such as inflammatory bowel diseases (Wada et al., 2015) or rheumatic diseases (Sambrook & Geusens, 2012). Osteoporosis has significant physical, emotional, and financial consequences, and osteoporosis-related fractures may lead to decreased quality of life, disability, and even death. Several studies mentioned that the direct and indirect costs of male osteoporotic fracture are high (Borgstrom et al., 2006; Konnopka, Jerusel, & Konig, 2009; Max, Sinnot, Kao, Sung, & Rice, 2002; Rabenda et al., 2006). Mean direct hospital cost for hip fractures in men was estimated as US$32,195 in 2003 in the United States (Gehlbach, Avrunin, & Puleo, 2007), US$20,323 in 2001 in Singapore (Y. H. Lee, Lim, & Lam, 2008), and US$125,520 in 1995 in Australia (Koeck et al., 2001). The indirect cost of male osteoporotic compression fracture was even higher than female patients according to previous studies

(Borgstrom et al., 2006; Konnopka et al., 2009; Max et al., 2002; Rabenda et al., 2006). Physicians should assess male rheumatic disease patients in order to facilitate early prevention of osteoporotic fracture for saving lives and medical cost purposes. The goal in this study was to find clinical laboratory markers for early detection of osteoporosis in male rheumatic patients to promote men's health in a general aspect.

Monocytes are participants in innate immunity, which mostly act as an initiator of inflammation against pathogens (Pardali & Waltenberger, 2012; Thomas, Tacke, Hedrick, & Hanna, 2015; Torubarova, Baryshnikov, Mambetova Ch, & Ni, 1988). Monocytes act in rheumatic subjects physically and pathologically including inflammation (Gordon, 2012), atherosclerosis (Shalhoub, Falck-Hansen, Davies, & Monaco, 2011; Ter Horst et al., 2013), immunity (Leon & Ardavin, 2008; Prosch, Docke, Reinke, Volk, & Kruger, 1999), and bone physiology (Deng et al., 2011). The major difference in monocytes between rheumatic disease patients and normal subjects lies in the autoinflammatory and autoimmune characters inside the cell itself (van Kempen, Wenink, Leijten, Radstake, & Boes, 2015). These autoinflammatory and autoimmune characters of monocytes could increase their activity of secretion of inflammatory cytokines (van der Burgh et al., 2014) and amplify the damage in bone, such as osteoporosis. As mentioned above, a recommendation for osteoporosis screening in men is especially focused on men with inflammatory diseases, but the role of monocytes in male osteoporosis is not well demonstrated in previous studies.

A recent study by Daswani et al. reported that phosphorylated heat shock protein 27 (HSP27), which could be secreted by monocytes, is a stimulator of monocyte migration and is involved in the pathogenesis of osteoporosis (Daswani et al., 2015). Besides the antiapoptotic effect of HSP27 secreted from monocytes (Charette, Lavoie, Lambert, & Landry, 2000), monocytes could increase their percentage amount among leukocytes upon induction. Interestingly, another study reported attenuated monocyte apoptosis on the basis of a transcriptome-wide expression study and illustrated the role of monocytes in osteoporosis (Liu et al., 2015). Along with the above-mentioned mechanism, Deng et al. reported the ANXA2 gene from monocytes is involved in osteoporosis in humans (Deng et al., 2011). Combined, the role of monocytes in osteoporosis is evident in scientific basis rather than in clinical basis. Osteoporosis is a multifactorial disease and is easily influenced by estrogen level in female patients, but osteoporosis in men is more straightforward and is mostly secondary to underlying diseases (Reid & Harvie, 1997; Treves et al., 1998). This research focused on the role of monocytes in male osteoporosis to support the concept.

The hypothesis in this research is that the monocyte percentage of leukocytes could be a biomarker of osteoporosis in male rheumatic diseases. Little information is available in the research literature concerning osteoporosis in male rheumatic diseases. Furthermore, this study tries to link clinical and basic research, concerning the role of monocytes in male osteoporosis (Charette et al., 2000; Daswani et al., 2015; Liu et al., 2015). This study aims to find new answers on the path of decreasing osteoporosis-related fracture risks and increasing the quality of life for men.

Material and Methods

Participants

This was a retrospective medical chart review study. This study included male patients over 50 years old who have ever been investigated for monocyte percentage, with at least one ICD-9-CM diagnostic code from 710.0 to 710.9, and who visited the outpatient clinics between July 1, 2014 and July 31, 2015 in Chang-Gung Memorial

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Hospital, Kaohsiung (CGMH-KS) Medical Center. Patients diagnosed with the following diseases have been included: systemic lupus erythematosus, systemic sclerosis (scleroderma), sicca syndrome (either primary or secondary Sjogren's syndrome), dermatomyositis, polymyositis, eosinophilia myalgia syndrome, other specified diffuse diseases of connective tissue, and unspecified diffuse connective tissue disease. The CGMH-KS hospital is a tertiary care referral center located in Kaohsiung County in southern Taiwan, serving a population of about two million people. The study was conducted according to the protocol approved by the Ethics Committee of Chang Gung Memorial Hospital (IRB No: 102-4669B).

In this study, patients were assigned to a osteoporosis group or a nonosteoporosis group, according to the 2008 guidelines from the National Osteoporosis Foundation (Dawson-Hughes, 2008; Watts, Lewiecki, Miller, & Baim, 2008) and the 2014 consensus of the International Osteoporosis Foundation/International Society for Clinical Densitometry (Wu et al., 2014). Although there were 134 male patients over 50 years old enrolled in this study between July 1, 2014 and July 31, 2015, only 87 patients presented available data for monocyte percentage.

Data Collection

The demographic and clinical characteristics of the study subjects were recorded. These data were age, leukocyte differential counts, hemoglobulin, hematocrit, platelet count, C-reactive protein, erythrocyte sediment rate, rheumatoid factor, lipid profiles, antinuclear autoantibodies, anti-extractable nuclear antigen autoantibodies (including anti-Ro, anti-La, anti-U1 RNP, anti-Sm, anti-Scl 70, anti-Jo 1), anti-phospholipid autoantibodies (anti-beta 2 glycoprotein 1, anti-cardiolipin IgG or IgM), anti-neutrophil cytoplasma autoantibodies, baseline dual energy X-ray absorptiometry of the whole body, history of osteoporotic fractures, anti-osteoporosis medication, and steroid dose used.

The hip bone mineral density (BMD) and the hip *T* score were defined as "neck" BMD and *T* score. The spine BMD and spine *T* score present the lowest values in the lumbar area. The wrist BMD and wrist *T* score were defined as BMD and *T* score from the most distal third area of the radial bone in the nondominant hand.

Statistical Methods

Patient characteristics were reported as simple descriptive statistics (the mean ± standard deviation for normal distribution, median and 25% to 75% interquartile range for not normalized distribution variation). Descriptive statistics was used to summarize data for continuous variables and percentages with a non-normal distribution. In univariate analysis, categorical variables were compared using the Fisher's exact test. Continuous variables were compared using the Mann–Whitney *U* test for nonparametric method for non-normal distribution and Student *t*-test for normal distribution. Significant variables ($p < .05$) found to be associated with poor outcome were entered into a forward stepwise logistic-regression analysis model, which allows for simultaneous control of multiple factors. Variables with a strong association with fatality rate ($p < .05$) were included in the final model. All analyses were performed using the SPSS program, version 15.5 (SPSS, Chicago, IL).

Results

Baseline Characteristics of the Study Patients

There were 87 (100%) patients in this cross-sectional retrospective study and the average age was 68.26 ± 9.61 years. The hematological values were within normal ranges, including the leukocyte count, the hemoglobulin, and the platelet count. The lipid profile is presented in Table 1. The normalized distributed data are listed on the left side of Table 1, and the non-normalized distributed data on the right side of Table 1. In the right side of the table, the inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) and the screening tests of autoimmunity (antinuclear antibody and rheumatoid factor) are listed. The BMD results, the steroid doses, and the disease duration are also included in the right side of Table 1.

Comparison Between Osteoporotic and Nonosteoporotic Patients

Among these 87 (100%) patients, 15 (17.24%) patients met the criteria for the diagnosis of osteoporosis and they presented either osteoporotic compression fracture or the *T* score of any part of the whole body BMD examination lower than -2.5. As presented in Table 2, the total leukocyte count, platelet, hemoglobulin, hematocrit, lipoprotein profiles, inflammation markers (C-reactive protein, erythrocyte sediment rate), titers of antinuclear antibodies, and rheumatoid factor were similar between the two subgroups. After multivariate analysis, age and monocyte percentage were identified to be independent risk factors for osteoporosis patients (p value < .05; the relative risk, 1.08; 95% CI [1.01, 1.16] for age; the relative risk, 1.39; 95% CI [1.04, 1.84] for monocyte percentage). The steroid dose, equivalent daily prednisolone dose, and cumulative doses were similar between these two subgroups ($p = .08$ and .07, respectively).

Table 1. The Demographic Data of Study Subjects.

	All patients (n = 87, 100%)		All patients (n = 87, 100%)
Age (year)	68.26 ± 9.61	C-reactive protein (mg/dL)	6.91 (1.68, 37.98)
Leukocyte (10^9/L)	7.12 ± 2.81	Erythrocyte sediment rate (mm/hr)	14.00 (6.00, 36.00)
Neutrophil (%)	69.14 ± 13.23	ANA (titer)	60.00 (0, 640.00)
Lymphocyte (%)	22.36 ± 11.68	Rheumatoid factor (IU/mL)	11.50 (10.70, 12.00)
Monocyte (%)	6.16 ± 2.14	BMD_HIP (g/cm^2)	0.69 (0.53, 0.75)
Platelet (10^9/L)	179.27 ± 57.21	T score_HIP	−1.60 (−2.53, −1.10)
Hemoglobulin (g/dL)	13.14 ± 2.01	BMD_SPINE (g/cm^2)	0.92 (0.79, 1.02)
Hematocrit (%)	38.74 ± 5.57	T score_SPINE	−1.00 (−2.60, −0.70)
Neutrophil count (10^9/L)	5.06 ± 2.63	BMD_WRIST (g/cm^2)	0.77 (0.64, 0.81)
Lymphocyte count (10^9/L)	1.49 ± 1.00	T score_WRIST	−1.30 (−3.35, −0.40)
Monocyte count (10^9/L)	0.42 ± 0.20	Steroid daily dose (mg/day)	0 (0,0)
High density lipoprotein (mg/dL)	58.55 ± 15.57	Disease duration (year)	2.00 (2.00, 3.00)
Low density lipoprotein (mg/dL)	106.31 ± 43.82	Cumulative steroid dose (mg)	0 (0,0)

Note. BMD = bone mineral density; ANA = antinuclear antibody titer. *p < .05.

Table 2. Comparison Between Osteoporotic and Nonosteoporotic Patients.

	Osteoporosis (n = 15)	Nonosteoporosis (n = 72)	p value univariate	p value multivariate	95% CI
Age (year)	74.53 ± 8.23	69.34 ± 9.64	.02*	.02*	[1.01, 1.16]
Leukocyte (10^9/L)	6.55 ± 1.86	7.02 ± 2.67	.46		
Neutrophil (%)	64.91 ± 9.59	68.41 ± 12.73	.24		
Lymphocyte (%)	22.85 ± 8.19	22.45 ± 11.12	.88		
Monocyte (%)	7.54 ± 2.39	6.40 ± 2.24	.03*	.03*	[1.04, 1.84]
Platelet (10^9/L)	200.27 ± 57.40	182.93 ± 57.46	.20		
Hemoglobulin (g/dL)	12.97 ± 1.03	13.11 ± 1.87	.75		
Hematocrit (%)	38.34 ± 3.12	38.67 ± 5.21	.79		
Neutrophil count (10^9/L)	4.29 ± 1.55	4.92 ± 2.49	.28		
Lymphocyte count (10^9/L)	1.41 ± 0.40	1.47 ± 0.93	.77		
Monocyte count (10^9/L)	0.50 ± 0.22	0.44 ± 0.21	.22		
High density lipoprotein (mg/dL)	35.00 ± 12.73	54.92 ± 17.13	.07		
Low density lipoprotein (mg/dL)	70.50 ± 41.72	101.53 ± 43.92	.30		
C-reactive protein (mg/dL)	6.03 (4.60, 32.40)	7.79 (1.20, 402.40)	.67		
Erythrocyte sediment rate (mm/hr)	38.00 (13.50, 56.00)	11.00 (6.00, 25.25)	.13		
Rheumatoid factor (IU/mL)	11.50 (11.50, 11.50)	11.10 (10.70, 12.25)	.71		
Disease duration (year)	2.00 (2.00, 2.00)	2.00 (2.00, 3.00)	.82		
Steroid daily dose (mg/day)	0 (0, 5.00)	0 (0, 0)	.08		
Cumulative steroid dose (mg)	0 (0, 3650.00)	0 (0, 0)	.07		

The Correlations Between BMD and Clinical Markers

The association between the BMD and clinical markers is reported in Table 3. Steroid dose (equivalent daily prednisolone dose) was negatively associated with BMD of the hip area (femoral neck part). Platelet counts were negatively associated with BMD and T score of the spine area, as well as with the T score of the wrist (lower third of the radial bone of nondominant hand) (Table 3, T score data were not reported).

Monocyte Percentage in Different Rheumatic Diseases

The monocyte percentages in different rheumatic diseases are presented in Table 4 and Figure 1. The statistical analysis between osteoporosis and nonosteoporosis groups in each rheumatic disease were as follows: systemic lupus erythematosus (n = 14, 16.09%, p = .38), sicca syndrome (n = 56, 64.37%, p = .03), rheumatoid arthritis (n = 5, 5.75%, p =.27), and dermatomyositis (n = 10, 11.49%, p = .95).

Table 3. The Correlations Between BMD and Clinical Markers.

BMD/clinical markers		CRP	ESR	ANA	Steroid	WBC	Seg	Lym	Mono	Plt	Hb	Hct
BMD_HIP	*r*	–.15	–.19	.87	–.49	–.19	–.19	.45	–.05	–.37	.16	.23
(g/cm^2)	*p*	.66	.62	.33	**.02***	.39	.40	.30	.82	.09	.48	.30
BMD_SPINE	*r*	–.50	–.29	.87	–.35	–.11	–.10	.42	–.19	–.59	.26	.24
(g/cm^2)	*p*	.14	.49	.33	.14	.66	.69	.07	.45	**.01***	.29	.33
BMD_WRIST	*r*	–.14	.07	.87	–.42	.21	–.05	.14	–.05	–.35	.06	.09
(g/cm^2)	*p*	.69	.87	.33	.06	.37	.83	.54	.83	.12	.78	.68

Note. BMD = bone mineral density; CRP = C-reactive protein; ESR = erythrocyte sediment rate; ANA = antinuclear antibody; WBC = leukocyte count; Seg = neutrophil (%); Lym = lymphocyte (%); Mono = monocyte (%); Plt = platelet; Hb = hemoglobulin; Hct = hemotocrit; *r* = correlation coefficient; *p* = *p* value.
*$p < .05$.

Table 4. Monocyte Percentage Between Osteoporotic and Nonosteoporotic Patients in Different Rheumatic Diseases.

	Monocyte percentage (Mean% ± SD %)		
	Osteoporosis (*n* = 15)	No osteoporosis (*n* = 72)	*p* value[a]
Systemic lupus erythematosus (*n* = 14)	8.12 ± 1.89 (*n* = 5)	6.77 ± 2.95 (*n* = 9)	.38
Sicca syndrome (*n* = 56)[b]	7.75 ± 2.73 (*n* = 8)	6.04 ± 1.93 (*n* = 48)	.03*
Scleroderma (*n* = 6)	(*n* = 0)	6.87 ± 1.88 (*n* = 6)	—
Rheumatoid arthritis (*n* = 5)	9.10 ± 2.26 (*n* = 4)	5.70 (*n* = 1)	.27
Polymyositis (*n* = 4)	(*n* = 0)	6.43±1.28 (*n* = 4)	—
Dermatomyositis (*n*=10)	6.00 (*n* = 1)	5.81±2.69 (*n* = 9)	.95
Ankylosing spondylitis (*n*=1)	(*n* = 0)	9.20 (*n* = 1)	—

Note. SD = standard deviation.
*$p < .05$.
[a]Sicca syndrome including primary Sjogren's syndrome and secondary Sjogren's syndrome due to other autoimmune diseases.
[b]Monocyte percentage between osteoporosis and nonosteoporosis group in different rheumatic diseases were compared by mean of independent *t*- test.

Discussion

There is no early, simple marker for osteoporosis, especially in men; even the mild compression fracture itself reflects no clinical symptoms. The present study examined the clinical aspects and blood parameters in males with rheumatic diseases and identified two major findings. First, both age and monocyte percentage remained independently associated with the presence of osteoporosis. Second, steroid dose (equivalent prednisolone dose) was negatively associated with BMD of the hip area and platelet counts were negatively associated with BMD. There are several biomarkers indicative of bone formation or bone resorption (e.g., osteocalcin, C-terminal telopeptide of Type I collagen, procollagen Type I N-terminal propeptide, bone alkaline phosphatase, and urinary excretion of deoxypyridinoline), and a long-term imbalance of bone metabolism may lead to increased fragility. However, several clinical factors such as age, medication, immobilization, and the fracture itself can influence bone metabolism and therefore need to be considered in the interpretation of biochemical data and their use in individual patients [23, 24]. To the authors' knowledge, none of the biochemical markers of bone turnover has proven useful as a single diagnostic index of osteoporosis.

Monocytes and macrophages are central cells of the complex innate immune system that control innate immunity and antigen presentation to the adaptive immune system. Several lines of evidence identified that monocytes are also involved in bone changes associated with different clinical pictures, such as thyrotoxic osteodystrophy (Bisbocci et al., 1996), post-menopause osteoporosis (Chen et al., 2010; Liu et al., 2005), surgical menopause (Pacifici & Avioli, 1993), pre-menopause osteoporosis (Deng et al., 2008), hyperimmunoglobulin E syndrome (Leung et al., 1988), metastatic cancer (Park, Li, & Platt, 2012), and ankylosing spondylitis (Toussirot & Wendling, 2007). Research with genes and molecular pathways underlying the role of monocytes in osteoclast formation (Chen et al., 2010; Deng et al., 2011; Tajima et al., 2000) and differentiation (Manabe et al., 2001; Maziere et al., 2009; Winrow et al., 2008) have been published. There is not yet published clinical research on the role of monocytes in osteoporosis in male patients with rheumatic disease. This current study

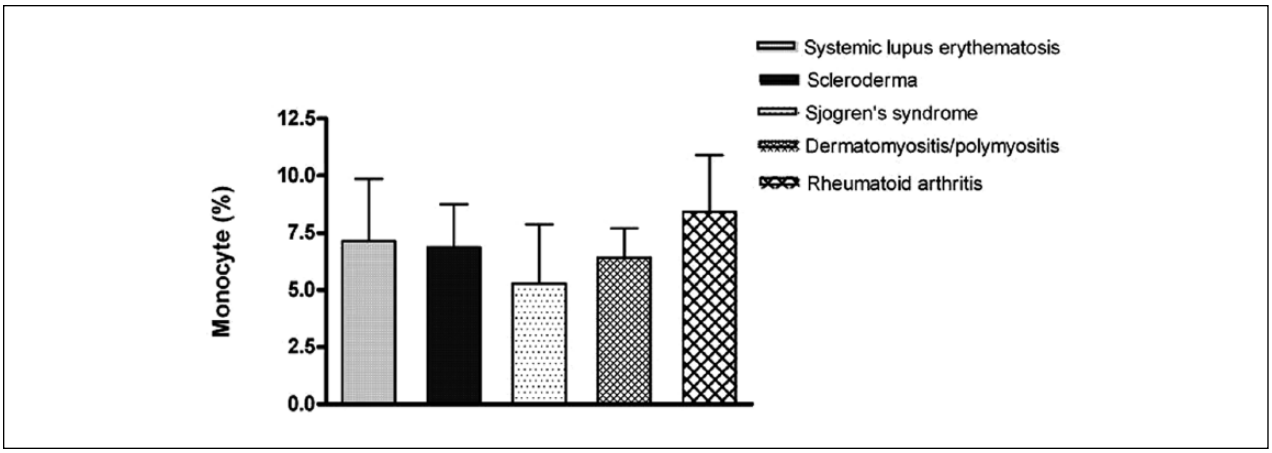

Figure 1. Monocyte percentage distribution in each specific rheumatic disease.

aims to bring new information and demonstrate that the role of monocytes in osteoporosis is not gender dependent, but is more significant in male patients.

After multivariate analysis, age (the relative risk, 1.08; 95% CI [1.01, 1.16]) and monocyte percentage (the relative risk, 1.39; 95% CI [1.04, 1.84]) are both independent risk factors for male osteoporosis (Table 2). Steroid-induced osteoporosis might be an important risk factor (Reid et al., 2000), but it is not demonstrated in the current study which identified that short-term treatment with steroids (duration of steroid usage less than 2 years) did not affect BMD much (Jacobs, Bijlsma, & van Laar, 2015) in this cohort.

Platelet counts are negatively associated with BMD and *T* score of the spine and with the *T* score of the wrist (lower third of the radial bone for the nondominant hand) (Table 3, *T* score data are not reported). Previous studies reported the platelet activity might be positively associated with bone density and in patients using platelet inhibitor medications is associated with increased fracture risk (D'Amelio et al., 2012; Vestergaard, Steinberg, Schwarz, & Jorgensen, 2012), vitamin D receptor levels are positively correlated with BMD (D'Amelio et al., 2012). Moreover, platelet-derived growth factor has proliferation and osteogenic differentiation effects on mesenchymal stem cells derived from patients with osteoporotic bone (Pountos et al., 2010). This study identified lower platelet counts, higher BMD and *T* scores, which might be due to either rheumatic disease pathogenesis itself (Tchebiner et al., 2011; Valentini, Chianese, Tirri, & Giordano, 1978), inflammation character, medication effects (Cantarini, Tinazzi, Biasi, Fioravanti, & Galeazzi, 2007), or an unknown pathway were related to bone formation/depletion.

Monocyte percentages might fluctuate in different diseases due to different pathogenetic mechanisms and the monocyte percentage according to different rheumatic diseases are presented in Figure 1. It is well known that rheumatoid arthritis is a major component of the risk factor in osteoporosis in the Fracture Risk Assessment tool (Dawson-Hughes, 2008; Watts et al., 2008). One recent report from the 2017 European League Against Rheumatism mentioned that osteoporosis should be managed in men over 50 years old in rheumatoid arthritis, which emphasizes that osteoporosis is an important issue in men's health in rheumatic diseases. Singh et al. noted that ankylosing spondylitis is also a rheumatic disease with prevalent osteoporosis, even in the young subjects (Singh et al., 2013). These were the only two reports that could be found in the field of osteoporosis in male rheumatic diseases that related to the current study. Osteoporosis is definitely a disease should not be overlooked in men's health.

This research as a retrospective cohort study presents several limitations. First, the case numbers in this study was not large, but similar (Snacken, Crenier, Fery, Praet, & Pepersack, 2015) or smaller (Amendola et al., 2011; Cortet et al., 2000; Heath, Bullivant, Boiven, & Balena, 2000) case number cohort studies within the field of osteoporosis could be found. Although the sample size of our study was not large, the number of variables considered for the multiple logistic regression analysis is small. Furthermore, based on the stepwise procedures, only two variables were selected as the important variables predicting the osteoporosis. The maximum likelihood estimates of the coefficients are valid in the analysis. Second, there could be a bias in the rheumatic disease selection, since the diagnosis by ICD-9 code is established by physicians. Third, steroid dose could be fluctuating and usually accompanies an activation in the disease activity of each patient and this cross-section study could be biased. Fourth, several details of the personal and medical histories associated with osteoporosis were not recorded in this current study, such as smoking (Jaramillo et al., 2015), inflammatory bowel disease (Wada

et al., 2015), or vasculitis (Petri, Nevitt, Sarsour, Napalkov, & Collinson, 2015).

Besides age, monocyte percentage of leukocytes meets the major criteria required for osteoporosis prediction in the treatment of male rheumatic diseases. BMD study should be part of the routine screening in patients who have higher monocyte percentages in order to reduce the risk of osteoporosis-related fracture. Appropriate primary or secondary prophylactic treatment could be beneficial not only in reducing the risks of osteoporosis-related fractures in men, but also in improving the quality of life for these male patients. It might be too early to have any conclusion based on this study, but it is worthwhile to pay more attention to aged male rheumatic disease patients with high monocyte percentages to prevent osteoporotic fracture by surveying BMD according to previous social-economic studies mentioned above.

Authors' Contributions

All authors included on the paper fulfill the criteria of authorship, and there was no other one who fulfils the criteria.
YJS contributed to recruitment, data collection, analysis, and drafting the manuscript. CTC contributed to recruitment, data collection, analysis, interpretation, and revising the manuscript. NWT contributed to study design, interpretation, and revising the manuscript. CCH contributed to analysis and revising the manuscript. HWC, CMS contributed to interpretation, and drafting the manuscript. YTC, SYH contributed to study design, interpretation, and revising the manuscript. CTK contributed to study design and revising the manuscript. WCL contributed to interpretation, and revising the manuscript. BCC, CHL contributed to study design, analysis, interpretation, and revising the manuscript. All authors approved the final version of the manuscript and all authors are guarantors.

Authors' Note

The underlying research materials related to this paper could be accessed on demand by mail requests.

Ethical Approval

The study was approved by Chang Gung Memorial Hospital's Institutional Review Committee on Human Research.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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