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MAGNETIC RESONANCE

Prognostic significance of focal lesions and diffuse infiltration on MRI for multiple myeloma: a meta-analysis

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Abstract

Objectives MRI of bone marrow of the axial skeleton is recommended for evaluation of multiple myeloma. The impact of bone marrow involvement pattern on MRI for determining progression-free survival (PFS) and overall survival (OS) is not yet clear.

Methods We performed a meta-analysis of research on the prognostic significance of MRI patterns for OS and PFS using a random effects model. Databases searched without language restriction were MEDLINE, EMBASE, and the Cochrane Library (January 1976 to April 2014). Manual searches were also conducted.

Results Of 10,953 citations identified in the original search, 10 cohort studies for a total of 2015 patients met the inclusion criteria. Nine of the 10 included studies are from three research groups. Pooled hazard ratios were 1.80 (95 % confidence interval [CI] 1.32–2.46; $P < 0.001$) for OS and 2.30 (95 % CI 1.65–3.20; $P < 0.001$) for PFS for focal lesions on MRI; and 1.70 (95 % CI 1.30–2.21; $P < 0.001$) for OS and 1.74 (95 % CI 1.07–2.85; $P = 0.03$) for PFS for diffuse infiltration on MRI. No significant heterogeneity was observed among studies.

Conclusions This meta-analysis demonstrated an association between focal lesions and diffuse infiltration and poor prognosis in this population.

Key Points

- *MRI findings of multiple myeloma include normal, focal, variegated and diffuse infiltration*
- *Focal lesions and diffuse infiltration on MRI were poor prognostic factors*
- *Bone marrow involvement pattern on MRI can help physicians assess prognosis*

Keywords Multiple myeloma · MRI · Prognosis · Bone marrow · Meta-analysis

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Abbreviations

CRAB	Hypercalcemia, renal failure, anemia and bone lesions
CT	Computed tomography
HR	Hazard ratio
IMWG	International Myeloma Working Group
ISS	International staging system
MGUS	Monoclonal gammopathy of undetermined significance
MRI	Magnetic resonance imaging
OS	Overall survival
PFS	Progression-free survival
QUIPS	Quality in prognosis studies

Introduction

Multiple myeloma is a cytogenetically heterogeneous clonal plasma cell proliferative disorder. Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic premalignant stage of this disease and is classified by the absence of hypercalcemia, renal failure, anemia and bone lesions (which are referred to as CRAB features). Smoldering multiple myeloma is the intermediate clinical stage between MGUS and multiple myeloma. Diagnosis of smoldering multiple myeloma requires the absence of CRAB features, as in MGUS, but the thresholds for monoclonal protein level and bone marrow plasma cell percentage vary from those of MGUS. Unlike MGUS and smoldering multiple myeloma, CRAB features are present in symptomatic multiple myeloma [1]. The rate of smoldering multiple myeloma progression to multiple myeloma is higher than that of MGUS.

Patients with asymptomatic multiple myeloma do not require drug treatment unless the disease progresses to symptomatic multiple myeloma. The cumulative probability of progression of asymptomatic multiple myeloma to symptomatic multiple myeloma is 73 % at 15 years [2]. The overall risk of progression is 10 % per year for the first 5 years, then 3 % per year for the next 5 years and 1 % per year over the next 10 years, but there is wide individual variance [2]. Therefore, such patients should undergo active surveillance for disease progression. The most widely accepted risk factors of progression are type and concentration of serum M protein, pattern and percentage of bone marrow plasma cells, reduction of uninvolved immunoglobulins, and amount of Bence Jones protein excreted in urine [3, 4]. In recent years, focal lesions and diffused infiltrations on MRI have been suggested as predictors of poor prognosis in patients with asymptomatic multiple myeloma [5–8].

Patients diagnosed with symptomatic multiple myeloma should be treated with various combinations of systemic chemotherapy, autologous stem cell transplantation, surgical removal, and radiation therapy, according to the patient's disease status [1]. It is necessary to recognize patients with high-risk myeloma who might benefit from more aggressive treatment. To date, the most widely accepted risk assessment method is based on staging and cytogenetic abnormalities. The international staging system (ISS) is widely used and is based on serum beta 2 microglobulin and serum albumin levels [9]. Several recent studies have suggested that an MRI pattern of bone marrow involvement is related to poor prognosis in patients with symptomatic multiple myeloma [10–15]. According to the latest International Myeloma Working Group (IMWG) guidelines [1, 16], MRI is recommended as part of the initial evaluation and prognostic assessment of patients with multiple myeloma. In the CRAB criteria, bone lesions have been defined as the presence of osteolytic bone lesions or the presence of osteoporotic compression fractures attributable to an underlying clonal plasma cell disorder [1]. MRI and CT can be used to determine the presence of bone lesions with greater sensitivity that radiographic bone survey [16]. According to the recent studies regarding diffusion-weighted imaging and dynamic contrast-enhanced imaging, MRI is also useful for differentiating symptomatic multiple myeloma from asymptomatic multiple myeloma and predicting overall survival (OS) and vertebral complications in patients with multiple myeloma [17, 18]. Abnormal MRI findings in multiple myeloma include focal lesions, variegated and diffuse infiltration [5–8, 10–15, 19]. Several studies show that poor outcomes correlate with presence of abnormal findings on MRI.

Because MRI is not included in routine protocols at many institutions for assessing multiple myeloma at diagnosis, particularly in the past, a single study might be inadequate for determining the effect of a bone marrow involvement pattern on MRI in prognosis. Prognostic assessments are essential for managing multiple myeloma because they provide physicians with a better understanding of patient survival probability. For this reason, we performed a meta-analysis of published studies to investigate the prognostic significance of MRI patterns for previously untreated multiple myeloma.

Materials and methods

Data and literature sources

We searched databases to find studies that evaluated the prognostic value of focal lesions and diffuse infiltration on MRI for patients with multiple myeloma. This study was based on the Cochrane review methods [20]. We searched MEDLINE (January 1, 1976 to April 30, 2014), EMBASE (January 1, 1985 to April 30, 2014), and the Cochrane Library (January 1, 1987 to April 30, 2014) with no restrictions on language or year. Search strategies were developed for each database (Appendix 1) using the main keywords multiple myeloma, spine and MRI. An electronic search was complemented with manual searches of the bibliographies of identified studies and pertinent reviews.

Study selection

Studies were selected based on predefined selection criteria. We first screened titles and abstracts of identified studies and obtained full texts to confirm eligibility. Two independent reviewers (S.Y.L. and Y.S.) evaluated each study. Studies were included if they: (1) contained information about pre-treatment MRI findings; (2) included OS or progression-free survival (PFS)

according to MRI pattern; (3) classified MRI findings as focal, diffuse and normal; and (4) were original research.

Data extraction

Study-specific information extracted from the studies was: (1) hazard ratios (HRs) and number of patients for each MRI pattern; (2) demographic, clinical, and treatment characteristics of patients (3) MRI protocol type; and (4) method of assessment. Data extraction was independently conducted by two reviewers (S.Y.L. and Y.S.), and discrepancies were judged by a third review author (H.J.K.). If the above variables were insufficient, we contacted the authors of primary studies by mail.

Assessment of methodological quality

Two reviewers (S.Y.L. and Y.S.) independently assessed the methodological qualities of each study using the Quality In Prognosis Studies (QUIPS) tool [21] to assess risk of bias in studies of prognostic factors. The QUIPS tool includes six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting. Disagreements between reviewers were resolved through discussion.

Statistical analysis

The main outcome of our review was HRs for OS and PFS. In the meta-analyses, a statistical expert (H.J.K.) calculated pooled effect estimates for combinations of single studies using the Cochrane Collaboration Review Manager 5.3 program. The inverse-variance random-effects method was used to allow for heterogeneity between studies.

Meta-analyses were conducted using a log HR scale with a random effects model. If provided in a study, the HR was used directly in meta-analysis. If studies did not report the necessary statistics, we estimated from the reported data [22]. Not all studies reported multivariate and univariate analysis values. We performed meta-analysis of all studies using a single value per each study, prioritizing multivariate values. We then separated multivariate and univariate values and analyzed each. In addition, we assessed heterogeneity between studies using a χ^2 test and I^2 statistic, with values of 25 %, 50 %, and 75 % considered low, moderate, and high, respectively. We conducted planned subgroup analyses for number of focal lesions and disease stage and sensitivity analyses for methodological quality.

Tests for funnel plot asymmetry are generally performed only when at least 10 studies are included in a meta-analysis [20]. Although 10 studies were included in this analysis, when sorted by intervention groups, each group contained fewer than 6. Thus, we did not assess publication bias. The funnel plots are attached as Appendix 2.

Results

Study identification

Database searches resulted in 10,953 articles (Fig. 1) and 125 studies were manually searched. Of all articles, 120 were excluded because of duplication and 10,577 were excluded because the title and abstract indicated that they did not fulfill the selection criteria. For the remaining 381 articles, we obtained full manuscripts and 371 publications were excluded for not including MRI findings ($n = 30$), classifying MRI findings by different methods ($n = 20$), not including prognosis ($n = 7$), or not being original articles ($n = 4$). Therefore, 10 studies were included [5–8, 10–15]. Six studies [5–8, 11, 13] reported HRs between focal lesions and seven studies [6–8, 10, 12–14] included HRs between diffuse infiltration and other lesions. The Hillengass et al. [15] study was not included in this meta-analysis because HRs between focal lesions and other findings were not reported [15].

Study characteristics and patient populations

Study characteristics are in Table 1. Baseline patient and tumour characteristics were balanced among normal MRI findings, diffuse patterns and focal lesions. Three studies [5, 11, 13] were prospective and seven were retrospective [6–8, 10, 12, 14, 15]; six [10–15] included symptomatic myeloma or myeloma requiring treatment; four [5–8] included asymptomatic myeloma, MGUS, or smoldering multiple myeloma. Four studies [6–8, 15] were from a single institution in Germany and two possibly included overlapping patients [6, 8]; two [10, 14] were from a single institution in Greece and possibly had overlapping patients. The patients of three studies [5, 11, 13] from a single institution in the USA did not overlap. Follow-up periods were mostly more than 24 months.

Quality of included studies

Most studies did not present clear inclusion and exclusion criteria for patient selection [6–8, 12, 14], MRI indication [5, 6, 8, 12, 14, 15] or proportion of follow-up loss [6–8, 10, 12, 14, 15]. Whether MRI reviewers were blinded to clinical information was unclear except for one study from Germany [6]. Clear definitions of MRI interpretation [6–8, 10–15] and outcome measurement [5–7, 11–15] were provided in most articles. MRI was performed before treatment in most studies except for two [5, 8] that lacked information about when MRI was performed. Quality assessments are in Table 2. Primary endpoints were clear and uniform among studies and several studies presented HRs from univariate analysis without multivariate analysis results [5, 7, 14].

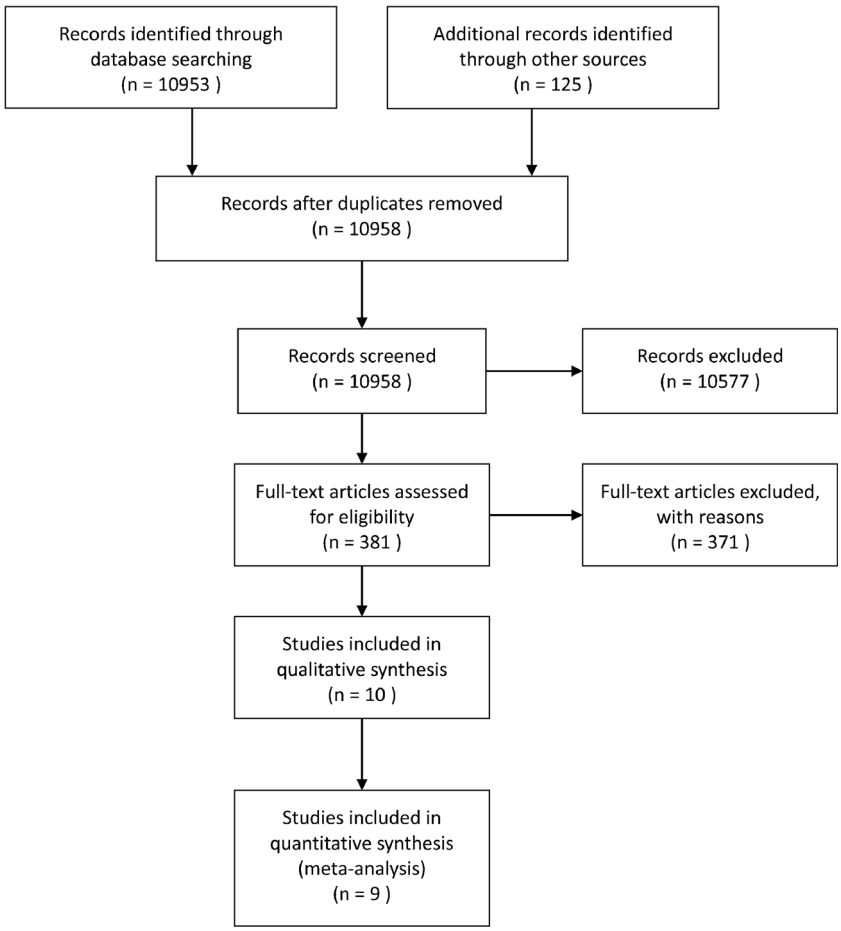

Fig. 1 Study flow diagram

Qualitative analysis

Most studies classified MRI findings as normal, focal or diffuse infiltration [6–8, 12, 13, 15]. Two [10, 14] studies classified MRI findings as normal, focal, variegated, and diffuse infiltration, and two assessed MRI as normal or focal lesions without considering diffuse patterns [5, 11]. Most studies followed uniform diagnostic criteria for focal lesions and diffuse infiltration on MRI. The cutoff number for evaluation of survival rate varied, with a range of 1 to 20 for focal lesions. One study [8] had fewer patients than 10 with focal lesions. The OS of patients with multiple myeloma was included in two studies [10, 14] and was 48 months to 60 months in patients with focal lesions, 24 months to 40 months in patients with diffuse infiltration, and 48 months to 102 months in patients with normal MRI. In Hillengass et al. [15] which was not included in the meta-analysis, focal lesions were not prognostically significant, regardless of cutoff value ($P = 0.45$).

Quantitative analysis for focal lesions on MRI

Meta-analysis of six studies demonstrated that focal lesions on MRI were poor prognostic factors for OS (HR 1.80; 95 % confidence interval [CI] 1.32–2.46; $P < 0.001$) and PFS (HR 2.30; 95 % CI 1.65–3.20; $P < 0.001$; Fig. 2a). Heterogeneity among the studies was not significant for OS ($I^2 = 0$ %; $P = 0.64$) or PFS ($I^2 = 0$ %; $P = 0.54$). No significant differences were observed for OS in results from multivariate (HR 1.80; 95 % CI 1.32–2.46; $P < 0.001$) and univariate analysis (HR 1.83; 95 % CI 1.32–2.54; $P < 0.001$). However, differences were significant for PFS in results from multivariate analysis (HR 2.09; 95 % CI 1.44–3.04; $P < 0.001$) and univariate analysis (HR 4.04; 95 % CI 2.49–6.53; $P < 0.001$).

Quantitative analysis of diffuse infiltration on MRI

Meta-analysis of seven studies demonstrated that diffuse infiltration on MRI was a poor prognostic factor for both OS (HR 1.70; 95 % CI 1.30–2.21; $P < 0.001$) and PFS (HR 1.74; 95 % CI 1.07–2.85; $P = 0.03$; Fig. 2b). Heterogeneity among the studies was not significant for OS ($I^2 = 0$ %; $P = 0.67$) or PFS ($I^2 = 31$ %; $P = 0.23$). No significant differences were observed in results from multivariate and univariate analysis for OS (HR 2.60, 95 % CI 1.00–6.76, $P = 0.05$, vs. HR 1.64, 95 % CI 1.25–2.16, $P < 0.001$) or PFS (HR 2.03, 95 % CI 1.35–3.06, $P < 0.001$ vs. HR 1.95, 95 % CI 1.10–3.44, $P = 0.02$).

Table 1 Baseline characteristics of included original researches

Study	Nation	Study esign	No. of patients	Median age (years)	Disease stage	MRI protocol	MRI finding classification (case number)	Included cases in Meta-analysis (case number)	Median follow-up (months)
Moulopoulos 2005 [14]	Greece	R	142	N/P	MM indicated for treatment	Thoracolumbar spine	Normal (11) Focal (71) Diffuse (40) Variegated (20)	Diffuse (40)	>36
Walker 2007 [13]	USA	P	611	N/P	Symptomatic or progressive MM	Axial skeleton	Normal (191) Focal (451) Diffuse (114)	Focal† (218) Diffuse (114)	55
Bartel 2009 [11]	USA	P	303	N/P	Symptomatic MM	Axial skeleton	Focal > 7 (68) Others (171)	Focal† (68)	43
Hillengass 2010 [6]	Germany	R	149	58	Asymptomatic MM	Whole body	Normal (69) Focal (20) Diffuse (60)	Focal* (10) Diffuse (60)	24
Hillengass 2012 [15]	Germany	R	100	58	Symptomatic MM	Whole body	Normal (23) Focal (77) Diffuse (100)	Not included	N/P
Moulopoulos 2012 [10]	Greece	R	228	67	Symptomatic MM	Thoracolumbar spine and pelvis	Normal (35) Focal (94) Diffuse (95) Variegated (4)	Diffuse/Variegated (99)	N/P
Dhodapkar 2014 [5]	USA	P	156	N/P	Asymptomatic MM,	Whole spine	Normal (131) Focal (25)	Focal‡ (25)	43
Hillengass 2014 [7]	Germany	R	137	58	MGUS	Whole body	Normal (105) Focal (32) Diffuse (52)	Focal‡ (32) Diffuse (52)	5
Merz 2014 [8]	Germany	R	63	55	Smoldering MM	Whole body	Normal (23) Focal (21) Diffuse (19)	Focal* (9) Diffuse (19)	65
Song 2014 [12]	South Korea	R	126	54	MM indicated for autologous stem cell transplantation	Thoracolumbar spine	Normal (27) Focal (47) Diffuse (52)	Diffuse (52)	N/P

R = retrospective, P = prospective, N/P = not presented, MM = multiple myeloma, MGUS = monoclonal gammopathy of undetermined significance

* 2 or more focal lesions

† More than 7 focal lesions

‡ 1 or more focal lesions

Subgroup and sensitivity analysis

We could not perform subgroup analyses of the number of focal lesions because the included studies used various cutoff values for the definition of focal lesions: 1 or more than 1 [5, 7], 2 or more than 2 [6, 8], and more than 7 [11, 13]. Pooled HRs for PFS in patients with asymptomatic multiple myeloma were 2.91 (95 % CI 1.87–4.54; $P < 0.001$) for focal lesions and 1.53 (95 % CI 0.65–3.65; $P = 0.33$) for diffuse infiltration (Figs. 3 and 4). Pooled HRs for OS in patients with symptomatic multiple myeloma were 1.80 (95 % CI 1.32–2.46; $P < 0.001$) for focal lesions and 1.70 (95 % CI 1.30–2.21; $P < 0.001$) for diffuse infiltration (Figs. 3 and 4). Heterogeneity among the studies was moderate in the subgroup for diffuse infiltration on MRI in patients with asymptomatic myeloma ($I^2 = 53$ %, $P = 0.12$). Heterogeneity among the studies was not significant in the other subgroups including diffuse infiltration in patients with symptomatic multiple myeloma, focal lesions in asymptomatic myeloma and focal lesions in symptomatic myeloma. Sensitivity analysis by study quality is in Table 3. As for focal lesions on MRI, researches with low risk of bias had lower pooled HRs (1.80–2.07) than those with moderate and high risk of bias (2.55–2.95). As for diffuse infiltration on MRI, there was no significant difference between researches with low risk of bias (1.52–1.73) and researches with moderate and high risk of bias (1.26–1.88).

Discussion

Our meta-analysis demonstrated that diffuse infiltration and focal lesions on MRI of patients with multiple myeloma were significantly associated with poor prognosis. Therefore, radiologists should be aware of the prognostic significance of these findings and should report the bone marrow involvement pattern on MRI for prognostic assessment. We found that most

Table 2 Risk of bias assessment

Reference	Study participation and attrition	Measurement of prognostic factor and outcome	Study confounding and statistical analysis
Moulopoulos 2005 [14]	High	Low	High
Walker 2007 [13]	Low	Low	Low
Bartel 2009 [11]	Low	Low	Low
Hillengass 2010 [6]	High	Low	Moderate
Hillengass 2012 [15]	High	Low	Moderate
Moulopoulos 2012 [10]	Moderate	Moderate	Low
Dhodapkar 2014 [5]	Low	High	High
Hillengass 2014 [7]	Moderate	Low	High
Merz 2014 [8]	High	High	Moderate
Song 2014 [12]	High	Low	Low

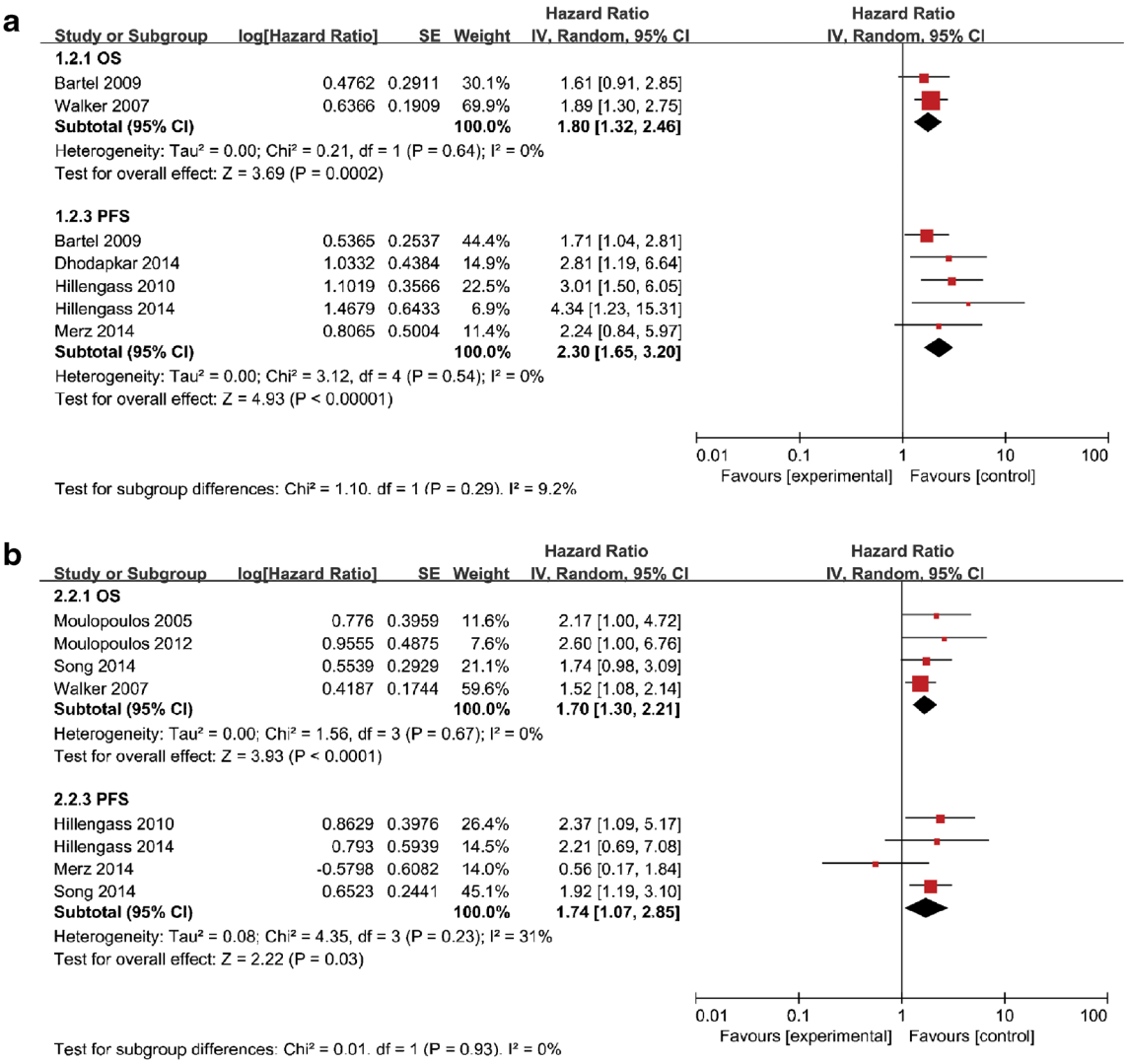

Fig. 2 Meta-analysis of studies presenting OS or PFS results for focal lesion (**a**) and diffuse infiltration (**b**) on MRI in patients with multiple myeloma

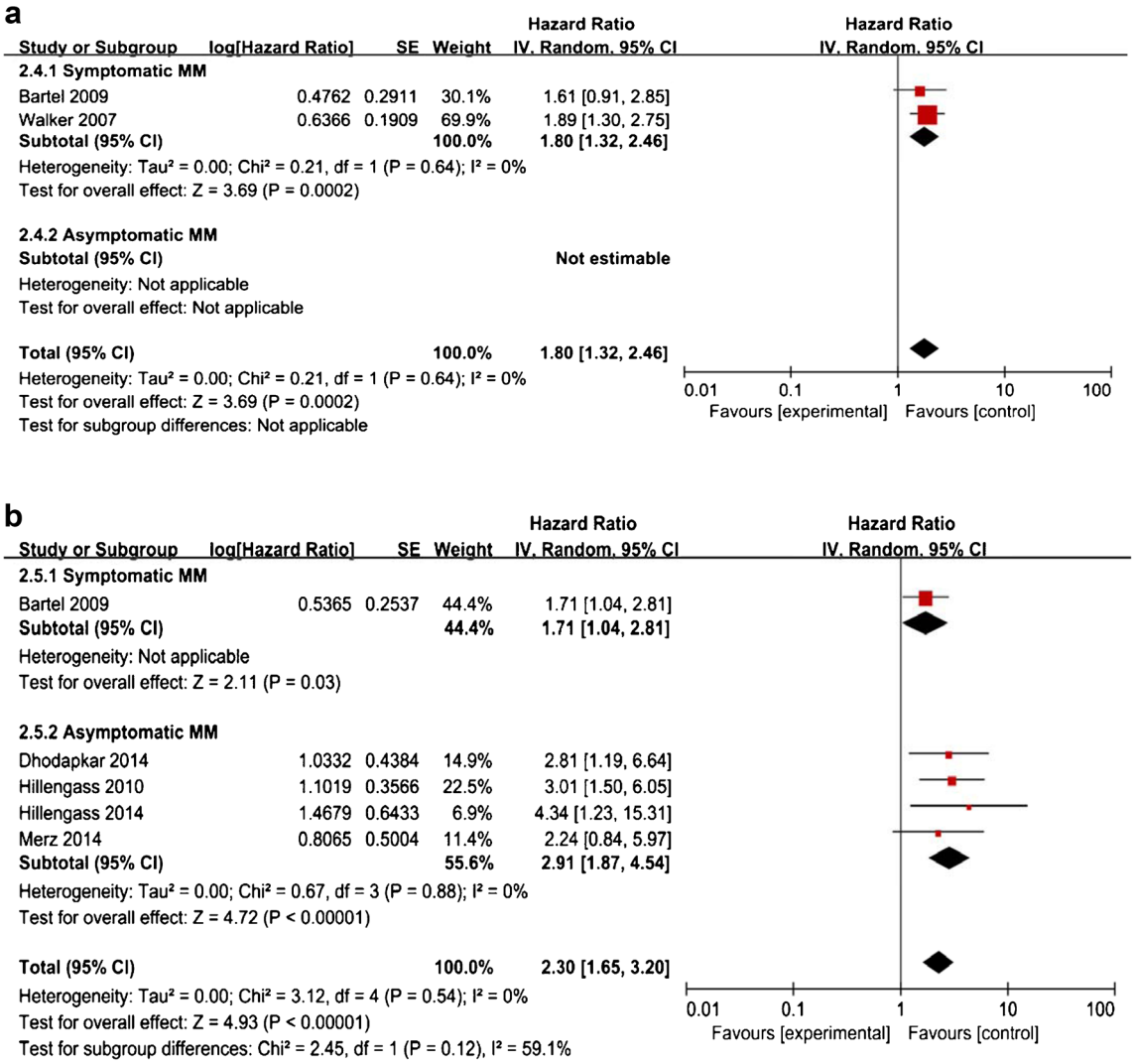

Fig. 3 Subgroup analysis of pooled studies with OS (**a**) or PFS (**b**) results related to focal lesion on MRI in patients with multiple myeloma

articles addressing the prognostic significance of MRI pattern with respect to PFS and OS are limited. In addition, 9 of the 10 studies are from three research groups [5–8, 10, 11, 13–15]. All articles [5–8] regarding patients with asymptomatic myeloma assessed only PFS without OS, because the clinically important issue in this disease status is not mortality but progression to symptomatic multiple myeloma. All studies [10–15] regarding patients with symptomatic myeloma assessed OS, and two studies also assessed PFS [11, 12].

The previous studies found that the number and presence of focal lesions on MRI was related to poor prognosis [11, 13, 23] similar to osteolytic lesions on radiography in patients with multiple myeloma. We could not perform subgroup analysis according to the number of focal lesions because of varying cutoff values in the number of the focal lesions. However, we found no bias according to the cutoff value for focal lesions. Three studies [5–7] have revealed that presence of focal lesions on MRI is a poor prognostic factor in patients with asymptomatic multiple myeloma, whereas one recent study [8] showed no significant difference in prognosis between patients with <2 focal lesions on MRI and patients without ≥2 focal lesions on MRI. Our meta-analysis concluded that focal lesions on MRI are significantly associated with poor prognosis in patients with asymptomatic multiple myeloma, with an HR of 2.91 (1.87–4.54). Treatment-related changes might have affected these results because Merz et al. [8] included patients after treatment ($n = 10$), unlike the other studies [5–7]. Focal lesions on MRI in the absence of osteolytic lesions on radiography have not been previously included as CRAB features [24]. The literature included in this meta-analysis followed those criteria. However, according to the 2015 IMWG guidelines [16], all patients with smoldering or asymptomatic myeloma should undergo whole-body MRI, and more than one focal lesion >5 mm in diameter should be considered evidence of symptomatic disease that requires therapy. Our results support these new diagnostic criteria for symptomatic multiple myeloma. Two studies [11, 13] regarding focal lesions on MRI in patients with symptomatic myeloma multiple showed contradictory conclusions. The different results in these studies

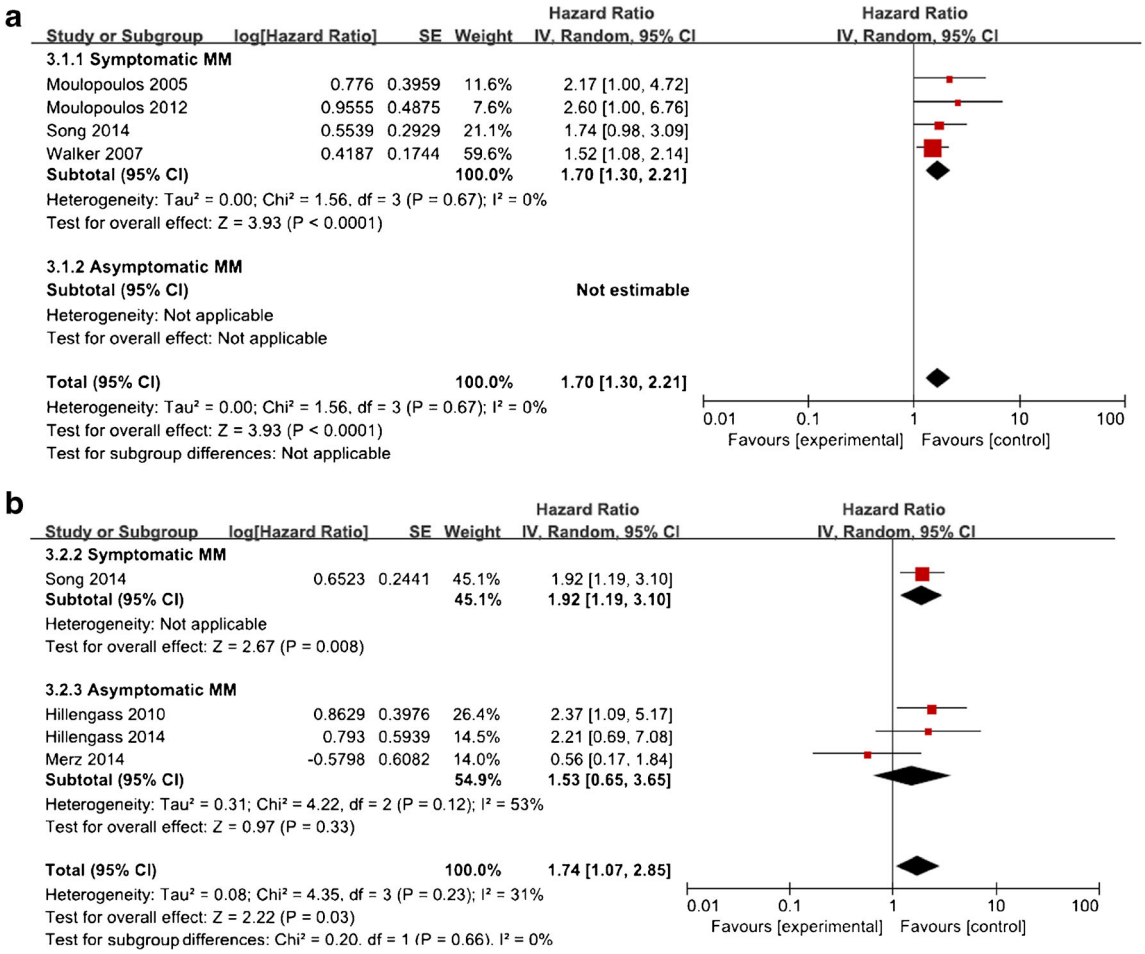

Fig. 4 Subgroup analysis of pooled studies with OS (**a**) or PFS (**b**) results related to diffuse infiltration on MRI in patients with multiple myeloma

might have resulted from the small number of cases in Bartel's study [11]. In Bartel's study ($n = 239$), the OS of patients with >7 focal lesions on MRI was lower than that of those with ≤7 focal lesions, with an HR of 1.61 (0.91–2.85); however, the difference was not significant ($P = 0.104$). In Walker's study ($n = 430$), the OS of patients with >7 focal lesions on MRI was lower than that of those with ≤7 focal lesions, with an HR of 1.89 (1.30–2.75); this difference was significant ($P < 0.001$). Our meta-analysis of pooled data concluded that focal lesions on MRI are a significant poor prognostic factor, with an HR of 1.80 (1.32–2.46). Recently, diffuse infiltration of bone marrow on MRI has been suggested to be an independent prognostic factor for multiple myeloma [6, 8, 10, 12–14]. Moulopoulos et al. found that a diffuse MRI pattern of marrow involvement was correlated with increased angiogenesis and adverse disease features [25]. Three [10, 13, 14] of four studies regarding patients with symptomatic

Table 3 Sensitivity analysis according to evidence level

Bias domain	Risk level	Focal lesion			Diffuse infiltration		
		Hazard ratio	Confidence interval	I^2 (%)	Hazard ratio	Confidence interval	I^2 (%)
Study participation and attrition	Low [5, 11, 13]	1.90	1.41, 2.55	0	1.52	1.08, 2.14	N/A
	Moderate and high [6–8, 10, 12, 14]	2.95	1.75, 4.95	0	1.88	1.34, 2.23	0
Measurement of prognostic factor and outcome	Low [6, 7, 11–14]	2.07	1.52, 2.82	11	1.73	1.34, 2.23	0
	Moderate and high [5, 8, 10]	2.55	1.33, 4.86	0	1.26	0.28, 5.66	74
Study confounding and statistical analysis	Low [6, 8, 10–13]	1.80	1.32, 2.46	0	1.64	1.24, 2.18	0
	Moderate and high [5, 7, 14]	2.91	1.87, 4.54	0	1.76	0.99, 3.13	33

multiple myeloma found a significant difference in OS between patients with diffuse bone marrow infiltration on MRI and patients without that finding on MRI. Two [10, 14] of these studies from the same research group showed a relatively wide 95 % confidence interval (1.00–6.76). Song et al.'s study [12] showed no significant relationship between poor prognosis and diffuse infiltration on MRI; HR 1.739 (0.980–3.084), $P = 0.058$. We conclusively found diffuse bone marrow filtration on MRI to be associated with poor prognosis in symptomatic multiple myeloma based on a meta-analysis. The HR of our pooled data was 1.70, with a relatively narrow confidence interval (1.30–2.21).

The HR for diffuse infiltration on MRI from pooled data was comparable to the HR for focal lesions on MRI from high-quality studies. Quality assessment showed greater heterogeneity among studies on diffuse infiltration patterns than studies on focal lesions. Subgroup analysis also revealed significant heterogeneity in diffuse infiltration pattern in patients with asymptomatic myeloma among studies. Two studies [7, 8] found that diffuse infiltration on MRI was not an independent prognostic factor, whereas, one study reported conflicting results [6] in patients with asymptomatic myeloma using PFS (Fig. 4b). Because of the study's heterogeneity, our meta-analysis is not sufficient to conclude whether diffuse infiltration is associated with poor prognosis or not in this subgroup. This heterogeneity might be the result of the inclusion criteria for patients with diffuse infiltration patterns. Patients with multiple myeloma frequently show both diffuse infiltration and focal lesions in the bone marrow on MRI [19]. However, most of the included studies were not clear about whether patients with both diffuse infiltration and focal lesions were classified in a diffuse infiltration group. Furthermore, most of the studies did not mention variegated patterns, which have a salt-and-pepper appearance on MRI. In addition, interpretation error may be existed.

Our study has some limitations. First, the number of articles addressing the prognostic significance of MRI pattern with respect to PFS and OS is limited. In addition, 9 of the 10 articles are derived from 3 research groups, suggesting possible patient overlap. Second, we did not include studies researching the prognostic significance of MRI patterns without reported parameters of PFS or OS. Third, studies regarding the prognostic significance of MRI patterns using different classifications of MRI pattern (e.g., percentage involvement area) were not included. Fourth, our conclusions were based on studies with a high risk of selection bias because most were retrospective or uncontrolled cohort studies. Most studies did not mention the criteria for performing MRI on patients with multiple myeloma. Some studies did not report summary estimates from multivariate analysis. Notably, summary estimates from multivariate models and univariate models were not significantly different, indicating that adjustment for compounding factors was not an important limitation of the studies. Fifth, because of publication bias, pooled HRs might be overestimated. Sixth, although the criteria for diagnosing focal lesions and diffuse infiltration were published, the criteria used to make diagnoses varied by study, particularly in the cutoff value for focal lesions and the combined patterns of focal and diffuse infiltration. Seventh, our systematic review included multiple analyses. Adequate multiple comparison procedures for use in systematic reviews have not yet been developed [26]. According to the Cochrane review methods, we did not adjust the type-one error [20]. We cautiously interpreted findings from multiple analyses. Finally, we have included studies with patients with all stages of monoclonal plasma cell disease. However, to control for bias related to this, we performed subgroup analysis based on disease stage.

Our study provides the first systematic review of prognosis according to MRI pattern in patients with multiple myeloma using data from cohort studies. We demonstrated an association between poor prognosis and focal lesions and diffuse infiltration on MRI in patients with symptomatic multiple myeloma. The presence of focal lesions on MRI was significantly associated with poor prognosis in patient with asymptomatic myeloma.

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Appendix 1 Search strategy for each database

1.1. MEDLINE

1. ("Multiple Myeloma"[Mesh:NoExp]) OR "Bone Marrow Neoplasms"[Mesh]
2. "Bone Marrow Neoplasms/secondary"[Mesh]
3. 1 NOT 2
4. ("Monoclonal Gammopathy of Undetermined Significance"[Mesh]) OR "Plasmacytoma"[Mesh]
5. "Bone Marrow Neoplasms"[tiab] OR "Bone Marrow Neoplasm"[tiab] OR "Myeloma"[tiab] OR "Myelomas"[tiab] OR "Monoclonal Gammopathy"[tiab] OR "Monoclonal Gammapathies"[tiab] OR "plasmacytoma"[tiab] OR "Plasmocytomas"[tiab]
6. 3 OR 4 OR 5
7. ((((("Magnetic Resonance Imaging"[Mesh:NoExp]) OR "Bone Marrow"[Mesh]) OR "Bone and Bones"[Mesh:NoExp]) OR "Spine"[Mesh]) OR "Bone Density"[Mesh]
8. marrow[tiab] OR Spine[tiab] OR Spinal[tiab] OR Vertebra*[tiab] OR "Magnetic Resonance"[tiab] OR

"MRI"[tiab] OR "MR"[tiab] OR "MRIs"[tiab] OR "Bones"[tiab] OR "Bone"[tiab]
9. 7 OR 8
10. 6 AND 9
11. Prognosis[tiab] OR Predictive Value[tiab] OR Progression[tiab] OR Progressions[tiab] OR Risk[tiab] OR Risks[tiab] OR Survival[tiab] OR Survivals[tiab]
12. ((((("Prognosis"[Mesh:NoExp]) OR "Survival Analysis"[Mesh]) OR "Risk"[Mesh]) OR "Predictive Value of Tests"[Mesh]) OR "Disease Progression"[Mesh]
13. 11 or 12
14. mortality[MeSH Terms] OR follow up studies[MeSH:noexp] OR prognos*[tiab] OR predict*[tiab] OR course*[tiab]
15. 13 OR 14
16. 15 AND 10
17. 16/humans

1.2 EMBASE

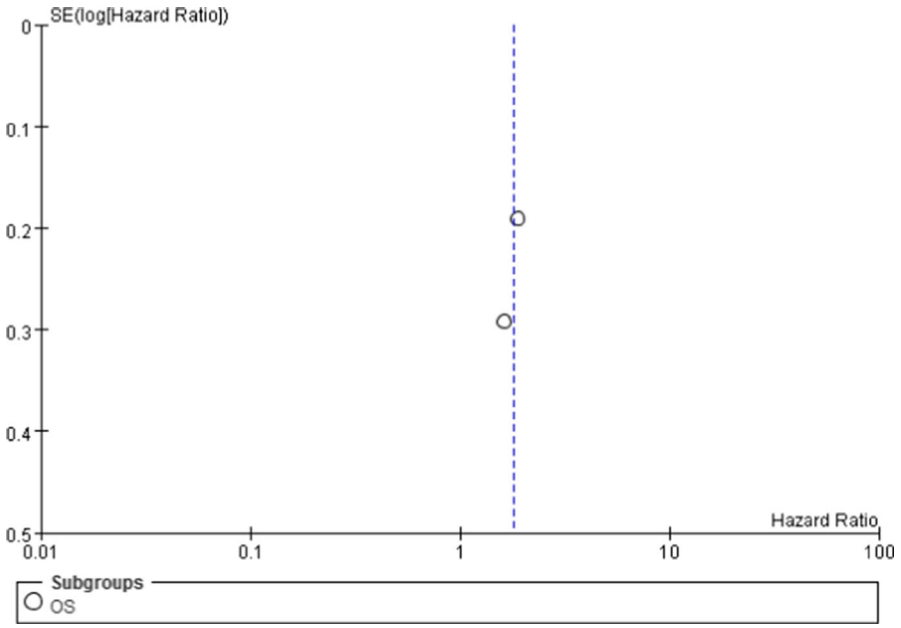
1. 'multiple myeloma'/exp OR 'bone marrow cancer'/exp
2. 'monoclonal immunoglobulinemia'/exp OR 'plasmacytoma'/exp
3. 'Bone Marrow Neoplasms':ab,ti OR 'Bone Marrow Neoplasm':ab,ti OR 'Myeloma':ab,ti OR 'Myelomas':ab,ti OR 'Monoclonal Gammopathy':ab,ti OR 'Monoclonal Gammapathies':ab,ti OR 'plasmacytoma':ab,ti OR 'Plasmocytomas':ab,ti
4. 1 OR 2 OR 3
5. 'nuclear magnetic resonance imaging'/de OR 'bone marrow'/exp OR 'bone'/de OR 'spine'/exp OR 'bone density'/exp
6. marrow:ab,ti OR Spine:ab,ti OR Spinal:ab,ti OR Vertebra*:ab,ti OR 'Magnetic Resonance':ab,ti OR 'MRI':ab,ti OR 'MR':ab,ti OR 'MRIs':ab,ti OR 'Bones':ab,ti OR 'Bone':ab,ti
7. 5 OR 6
8. 7 AND 8
9. Prognosis:ab,ti OR Predictive Value:ab,ti OR Progression:ab,ti OR Progressions:ab,ti OR Risk:ab,ti OR Risks:ab,ti OR Survival:ab,ti OR Survivals:ab,ti
10. 'cancer prognosis'/exp OR 'survival'/exp OR 'risk'/de OR 'risk assessment'/exp OR 'risk factor'/exp OR 'predictive value'/exp OR 'disease course'/exp OR 'cancer mortality'/exp
11. prognos*:ab,ti OR predict*:ab,ti OR course*:ab,ti
12. 9 OR 10 OR 11
13. 12 AND 8
14. 13/humans

1.3 Cochrane library

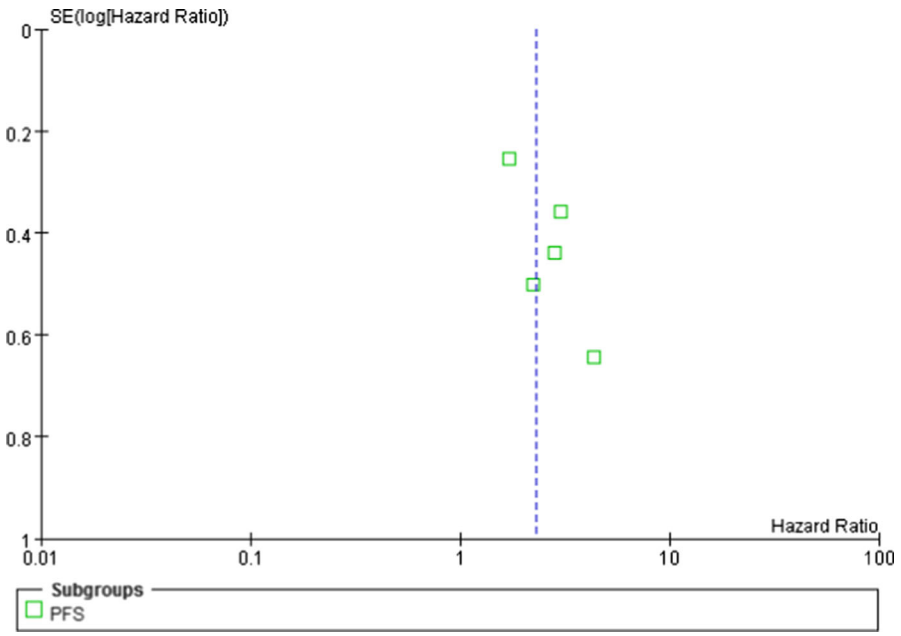
1. MeSH descriptor: [Multiple Myeloma] this term only
2. MeSH descriptor: [Bone Marrow Neoplasms] explode all trees
3. #1 or #2
4. MeSH descriptor: [Bone Marrow Neoplasms] explode all trees and with qualifier(s): [Secondary]
5. #3 not #4
6. MeSH descriptor: [Monoclonal Gammopathy of Undetermined Significance] explode all trees
7. MeSH descriptor: [Plasmacytoma] explode all trees
8. #6 or #7
9. "Bone Marrow Neoplasms" or "Bone Marrow Neoplasm" or "Myeloma" or "Myelomas" or "Monoclonal Gammopathy" or "Monoclonal Gammapathies" or "plasmacytoma" or "Plasmocytomas":ti,ab,kw (Word variations have been searched)
10. #5 or #8 or #9
11. MeSH descriptor: [Magnetic Resonance Imaging] this term only
12. MeSH descriptor: [Bone Marrow] explode all trees
13. MeSH descriptor: [Bone and Bones] this term only
14. MeSH descriptor: [Spine] explode all trees
15. MeSH descriptor: [Bone Density] explode all trees
16. #11 or #12 or #13 or #14 or #15
17. "marrow" or "Spine" or "Spinal" or "Vertebra*" or "Magnetic Resonance" or "MRI" or "MR" or "MRIs" or "Bones" or "Bone":ti,ab,kw (Word variations have been searched)
18. #16 or #17
19. #10 and #18
20. "Prognosis" or "Predictive Value" or "Progression" or "Progressions" or "Risk" or "Risks" or "Survival" or "Survivals":ti,ab,kw (Word variations have been searched)
21. MeSH descriptor: [Prognosis] this term only
22. MeSH descriptor: [Survival Analysis] explode all trees
23. MeSH descriptor: [Risk] explode all trees
24. MeSH descriptor: [Predictive Value of Tests] explode all trees
25. MeSH descriptor: [Disease Progression] explode all trees
26. #21 or #22 or #23 or #24 or #25
27. MeSH descriptor: [Mortality] explode all trees
28. MeSH descriptor: [Follow-Up Studies] this term only
29. "prognos*" or "predict*" or "course*":ti,ab,kw (Word variations have been searched)
30. #27 or #28 or #29
31. #26 or #30
32. #19 and #31
33. #32/trials

Appendix 2 Funnel Plots

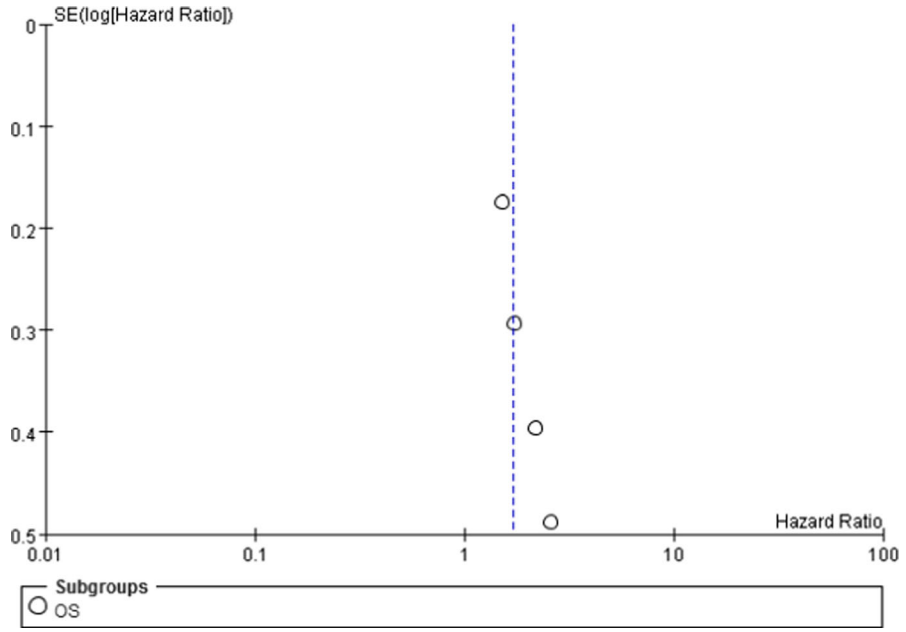
2.1. Funnel plot of pooled studies with OS related to focal lesion on MRI in patients with multiple myeloma.



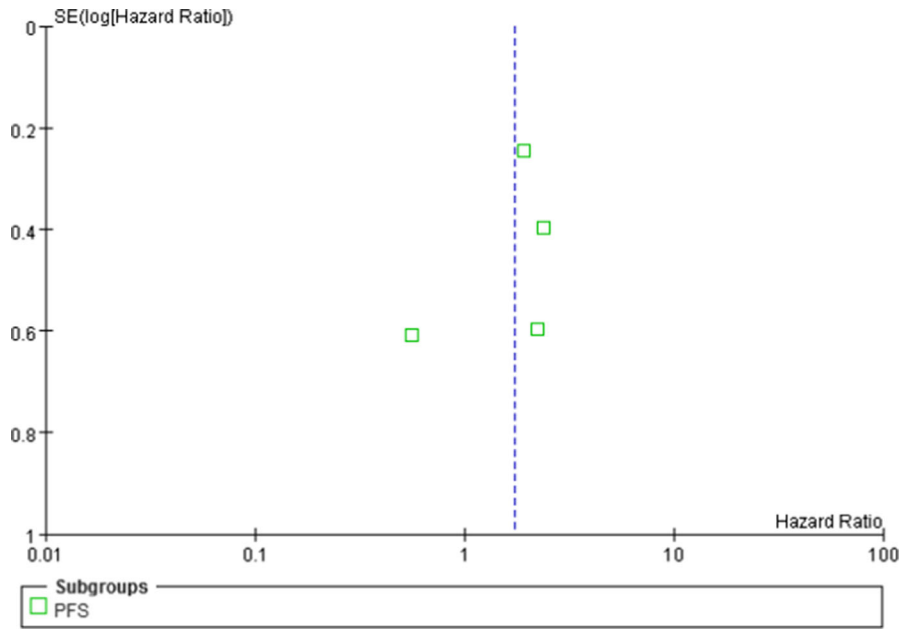
2.2. Funnel plot of pooled studies with PFS related to focal lesion on MRI in patients with multiple myeloma.



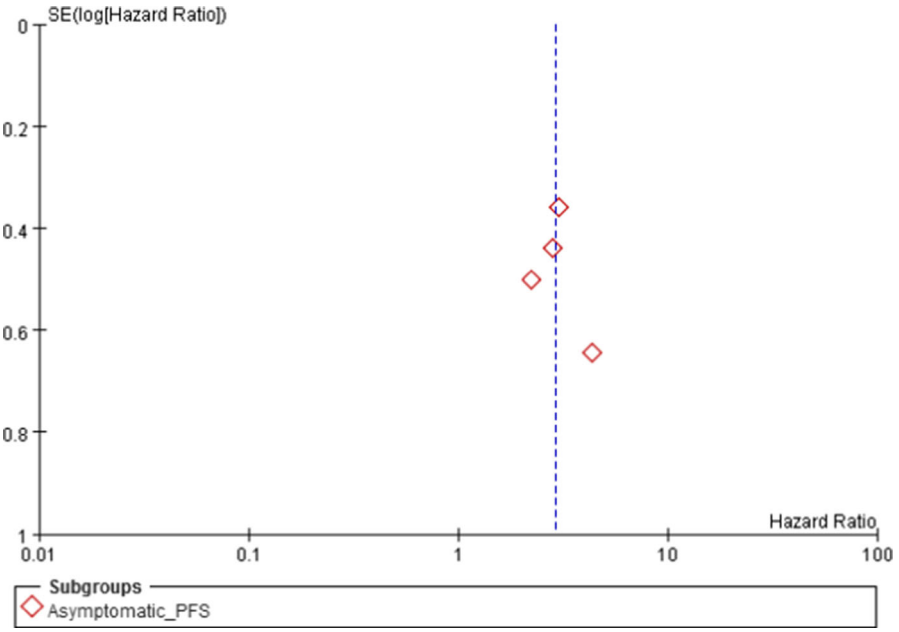
2.3. Funnel plot of pooled studies with OS related to diffuse infiltration on MRI in patients with multiple myeloma.



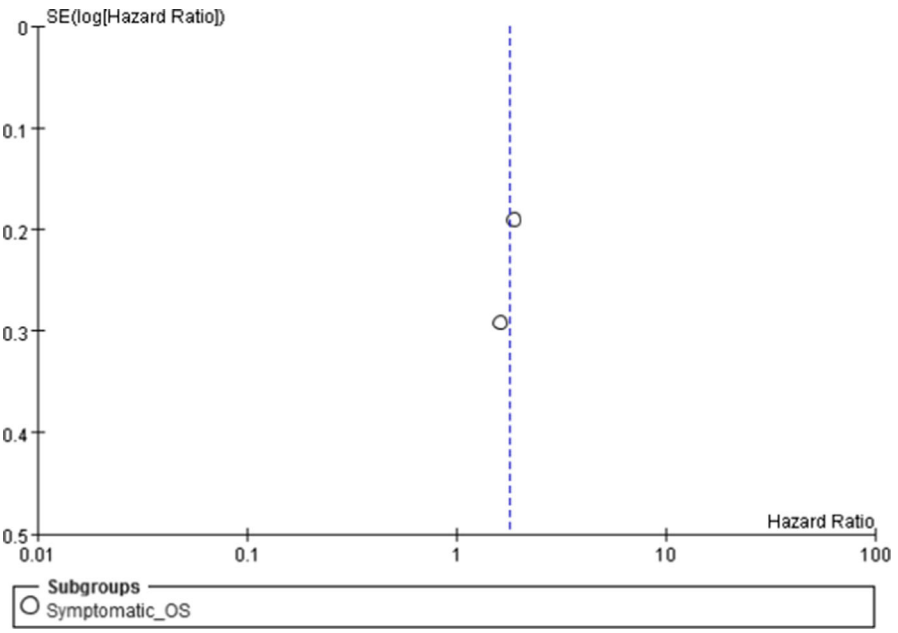
2.4. Funnel plot of pooled studies with PFS related to diffuse infiltration on MRI in patients with multiple myeloma.



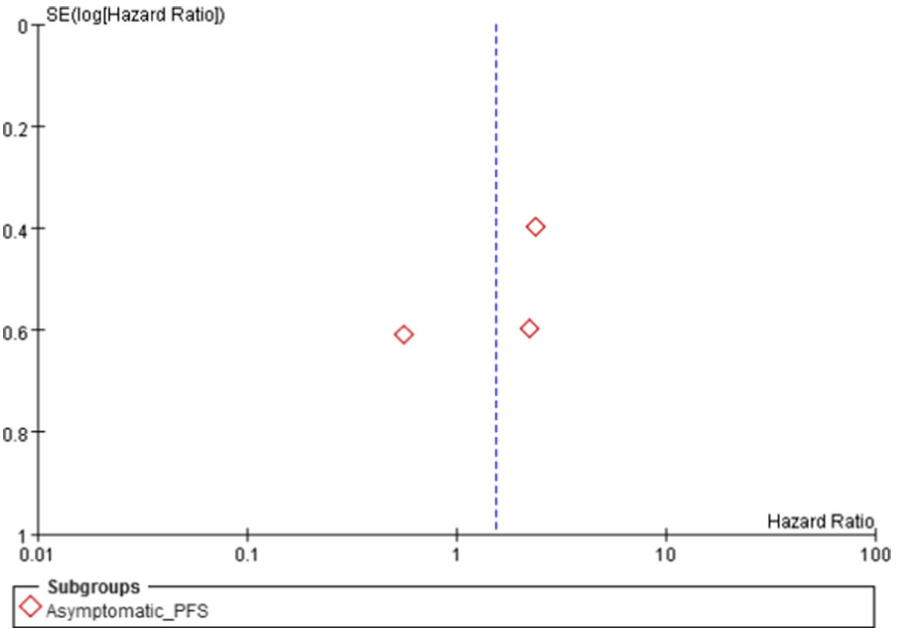
2.5. Funnel plot of pooled studies with PFS related to focal lesion on MRI in patients with asymptomatic multiple myeloma.



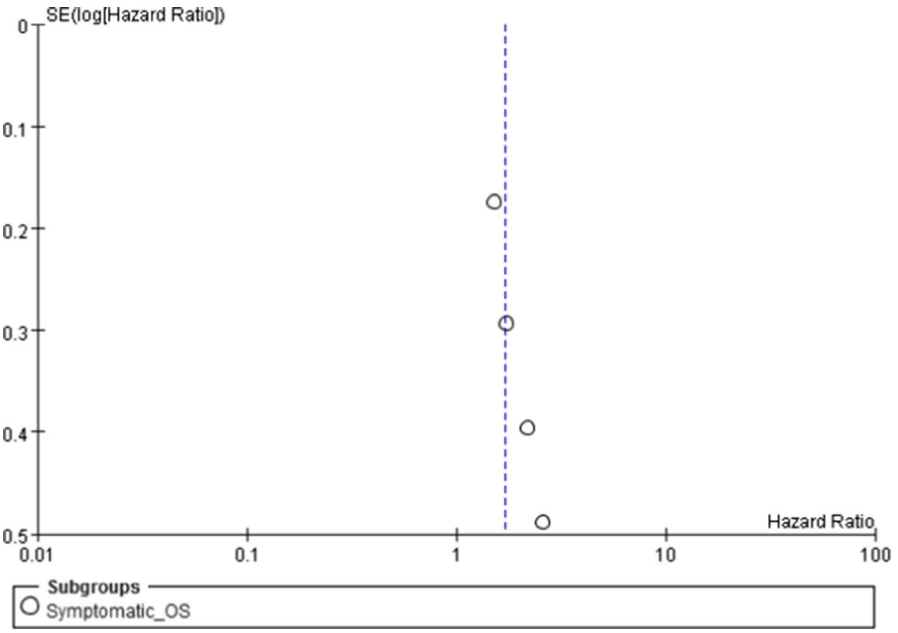
2.6. Funnel plot of pooled studies with OS related to focal lesion on MRI in patients with symptomatic multiple myeloma.



2.7. Funnel plot of pooled studies with PFS related to diffuse infiltration on MRI in patients with asymptomatic multiple myeloma.



2.8. Funnel plot of pooled studies with OS related to diffuse infiltration on MRI in patients with symptomatic multiple myeloma.



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