# Correlation and prognostic value of surrogate endpoints and overall survival in multiple myeloma: a systematic literature review

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## Introduction

- Multiple myeloma (MM) is the second most common hematologic malignancy worldwide with an estimated 176,000 new cases and 117,000 deaths in 2020[1]
- Improvements in overall survival (OS) have been observed with novel, potent therapeutic advances in MM
  - Longer OS outcomes are extending the time to realization of mature OS data and subsequent health technology assessment (HTA) evaluations
- There is a need to explore the feasibility of adopting surrogate endpoints for interim HTA evaluations while extended OS outcomes remain ongoing

## Objective

- To conduct a systematic literature review (SLR) of studies evaluating the predictive value of surrogate endpoints for OS in MM

## Methods

### Study identification

- The SLR was carried out according to guidelines published by the Centre for Reviews and Dissemination[2] with searches in MEDLINE and EMBASE to identify full-text publications
- Screening of the title, abstract, and full text was conducted by 2 reviewers
  - Discrepancies were resolved by a third reviewer
- A hand search of reports from HTA organizations, including NICE, CADTH, G-BA, IQWiG, ICER, and TLV was performed to assess how surrogate endpoints were interpreted for OS in MM
- Study inclusion and exclusion criteria are shown in **Table 1**

**Table 1. Study inclusion and exclusion criteria**

| PICOS concept | Inclusion criteria | Exclusion criteria |
|---|---|---|
| Population | • Patients with MM regardless of treatment line | • Healthy patients<br>• In vitro studies<br>• Patients with MM with comorbid conditions<br>• When MM is not the focus of the research |
| Interventions/ comparators | • No specific interventions/comparators are of interest | • Not applicable |
| Outcomes | • OS prediction methodology concepts that discuss surrogate outcomes in the absence of mature OS<br>• Correlation between or extrapolation/ prediction of surrogate endpoints of survival by statistical test (eg, Spearman correlation, Pearson correlation, bivariate analysis, multivariate analysis, regression) of which one parameter should always be OS<br>• Surrogate endpoints for OS: any type of response, such as: CR, PR, VGPR, duration of CR, MRD, PFS, TTP, failure-free survival, EFS, DFS, TTNT, DOR, HRQoL, and clinical relapse/paraprotein relapse | • Studies investigating OS for specific subgroup cohorts (eg, specific biomarker subgroup has higher, or lower median OS compared to overall population)<br>• Correlation between or extrapolation/prediction of survival not investigated in relation to OS<br>• Prognostic factors (without the statistical scrutiny as defined under the inclusion criteria)<br>• Reporting only outcomes not included in the inclusion criteria |
| Study design | • Clinical trials<br>• Real-world evidence/observational studies/ registry data (with ≥ 100 enrolled patients)<br>• Review and meta-analysis<br>• Studies investigating independent patient-level data | • Phase 1 trials<br>• Trials investigating survival outcomes without specifying the appropriate techniques as listed under outcomes |
| Publication type | • Reviews<br>• Original research<br>• HTA documentation | • Conference abstracts<br>• Letters to the editor<br>• Errata<br>• Commentary<br>• Expert opinion excluded except if informing HTA decision making<br>• Case study |
| Language | • English, except for HTA documentation | • Other languages |
| Time horizon | • Full text: January 1, 2010 – April 21, 2021<br>• Reviews and HTA documentation: no time restriction | • Full text: before January 1, 2010<br>• Reviews and HTA documentation: no time restriction |

CR, complete response; DFS, disease-free survival; DOR, duration of response; EFS, event-free survival; HRQoL, health-related quality of life; MRD, minimal residual disease; PFS, progression-free survival; PICOS, patient/population, intervention, comparison, outcome, study design; PR, partial response; TTNT, time to next treatment; TTP, time to progression; VGPR, very good partial response.

### Study assessment

- Two criteria were used to evaluate if a study had established an endpoint as a surrogate for OS in MM:
  - The endpoint was shown to be correlated with OS
  - The full effect of treatment on OS was shown to be captured by the endpoint
- Selected studies were assessed to determine if they had established an association between the candidate surrogate endpoint and OS at:
  - The individual patient level, using a Pearson correlation coefficient or jointly modeling the endpoints regardless of treatment arm
  - The trial level, using the determination coefficient $R^2$ of a linear regression or a multivariate regression model weighted by study sample size

## Results

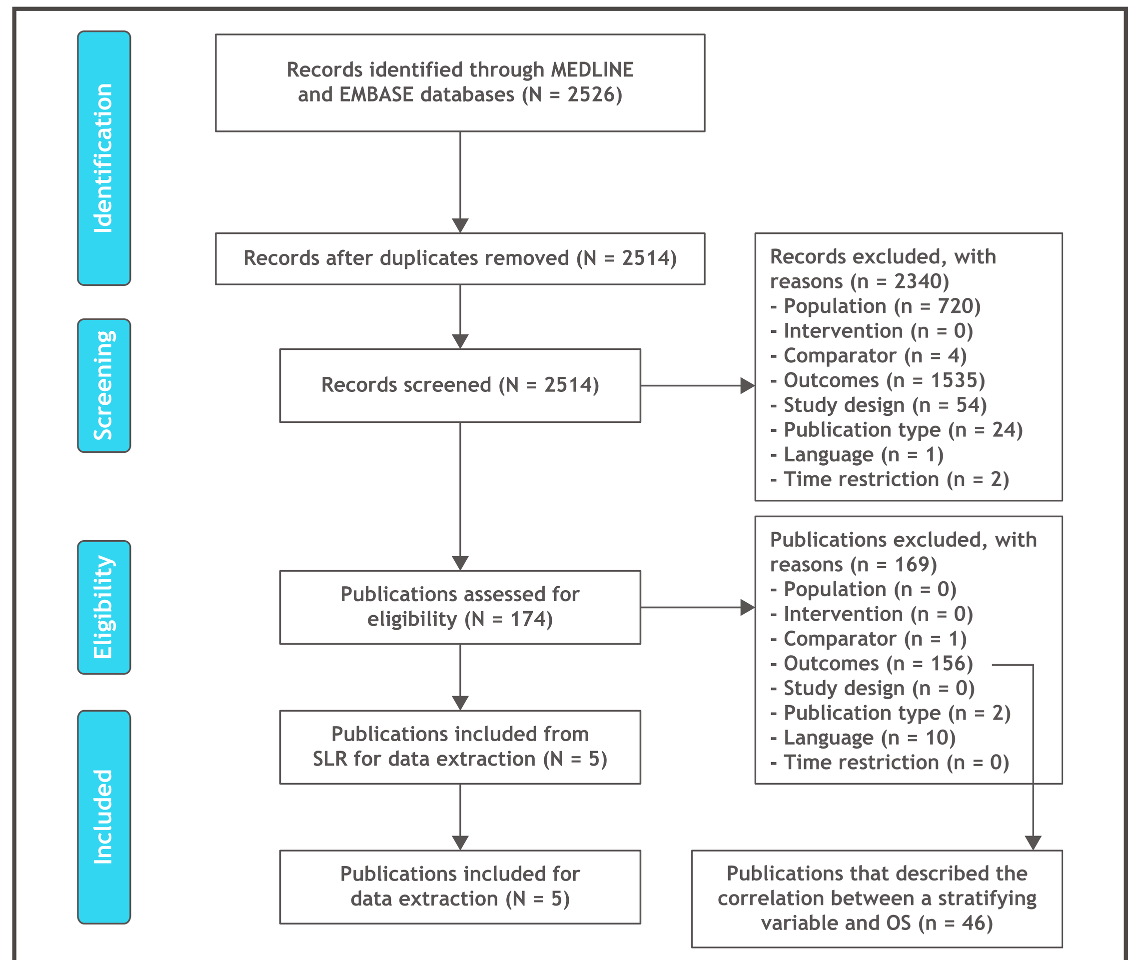
### Study characteristics

- A total of 2526 records were identified; 2514 were screened, of which 174 (6.9%) were assessed for full-text eligibility (**Figure 1**)
- Five studies (2.9%) analyzed the correlation and predictive relationship between surrogate endpoints and OS, referred to here as surrogate endpoint studies (**Table 2**)
- Forty-six studies evaluated OS in the context of certain endpoints (eg, treatment responses, MRD), referred to here as stratification studies
- Twenty-four appraisals from HTA bodies were identified discussing surrogate endpoints for OS in MM
  - Most considered PFS as a valid surrogate endpoint for OS
  - Less frequently, MRD-negative status was suggested as a surrogate endpoint for OS

### Surrogate endpoint studies

- Of the 5 surrogate endpoint studies identified, 3 used aggregated SLR data and 2 used individual patient-level data (**Table 2**)

**Figure 1. PRISMA flow chart of included studies**



Identification
Screening
Eligibility
Included
Records identified through MEDLINE and EMBASE databases (N = 2526)
Records after duplicates removed (N = 2514)
Records screened (N = 2514)
Records excluded, with reasons (n = 2340)
- Population (n = 720)
- Intervention (n = 0)
- Comparator (n = 4)
- Outcomes (n = 1535)
- Study design (n = 54)
- Publication type (n = 24)
- Language (n = 1)
- Time restriction (n = 2)
Publications assessed for eligibility (N = 174)
Publications excluded, with reasons (n = 169)
- Population (n = 0)
- Intervention (n = 0)
- Comparator (n = 1)
- Outcomes (n = 156)
- Study design (n = 0)
- Publication type (n = 2)
- Language (n = 10)
- Time restriction (n = 0)
Publications included from SLR for data extraction (N = 5)
Publications included for data extraction (N = 5)
Publications that described the correlation between a stratifying variable and OS (n = 46)


PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 2. Key findings from surrogate endpoint studies**

| Publication (author, year) | MM population | Studies/ patients (N) | Data type | Method to establish surrogacy | Surrogate endpoint used for OS | Parameter used for OS and surrogate relationship | Results | Authors' conclusion |
|---|---|---|---|---|---|---|---|---|
| Félix et al., 2013[3] | Newly diagnosed, R/R, and advanced patients | 152/22,696 | Aggregated | Spearman rank correlation, multivariate censored normal regression model | TDEs: TTP, PFS, EFS | Correlation between median OS and median TDE | *P* = 0.51; TTP<br>*P* = 0.75; PFS<br>*P* = 0.84; EFS<br>Each additional month in the observed median TDE correlated to an increase of 2.45 months (95% CI, 1.71-3.20) in median OS | TTP, PFS, and EFS are valid surrogate endpoints of OS |
| Hari et al., 2018[4] | R/R | 1/628 | Individual patient | Logistic marginal structural model | DSLT | OR, representing the odds of 1-year mortality for each additional month of contin-ued therapy | OR = 0.78 (95% CI, 0.77-0.83)<br>Each additional month of 2L therapy was associated with a reduced risk of death at 12 months | There is a strong correlation between DSLT and OS |
| Cartier et al., 2015[5] | Adults: newly diagnosed, maintenance, or R/R | 21/12,048 | Aggregated | Pearson correlation, $R^2$ from a linear regression | PFS | HRs for PFS and OS, log (HRs) for PFS and OS | Pearson r = 0.82<br>Pearson r (log transformed) = 0.80<br>There is a strong statistically significant (*P* < 0.0001) positive correlation between PFS and OS | PFS is a valid surrogate for OS |
| Mainou et al., 2017[6] | Newly diagnosed or previously treated with corticosteroids alone | 72/24,094 | Aggregated | Random effects meta-regression models | CR, VGPR | Regression coefficient between log-transformed relative risk of response (CR or VGPR) and the log-transformed HR of OS or PFS | Patients without ASCT (regression coefficient, 0.02; 95% CI, −0.06 to 0.10)<br>Patients undergoing ASCT (−0.11; 95% CI, −0.44-0.22)<br>Patients with ASCT vs non-ASCT patients (0.04; 95% CI, −0.29-0.38) | No association between response outcomes (CR and VGPR) and OS |
| Rawstron et al., 2015[7] | Newly diagnosed adults | 1/397 | Individual patient | Cox proportional model | MRD | Association between log-transformed MRD and OS | MRD ≥ 10%: 1 year<br>MRD 1% to < 10%: 4 years<br>MRD 0.1% to < 1%: 5.9 years<br>MRD 0.01% to < 0.1%: 6.8 years<br>MRD < 0.01%: 7.5 years<br>It was concluded that MRD level predicted OS and PFS with approximately 1-year median OS benefit per log depletion | MRD level is a strong predictor for OS |

CI, confidence interval; OR, odds ratio; R/R, relapsed/refractory.

- Correlation was established using Spearman rank or Pearson correlation tests, and predictive value was assessed using meta-regression models
- Key findings from each of the surrogate endpoint studies are summarized below:
  - Félix et al. 2013[3] established a positive monotonic relationship between median time-dependent endpoints (TDEs) and median OS, using Spearman rank correlation and a multivariate censored normal regression
  - Hari et al. 2018[4] reported a strong correlation of OS with duration of second-line (2L) therapy (DSLT), with a reduced risk of death for each additional month of 2L treatment
  - Cartier et al. 2015,[5] used the Pearson coefficient to establish a positive linear relationship between hazard ratios (HRs) for PFS and OS (and between the log-transformed HRs), demonstrating PFS as a valid surrogate of OS
  - Mainou et al. 2017[6] reported a meta-regression coefficient that indicated no association between treatment response outcomes (CR and VGPR) and OS for patients without autologous stem cell transplantation (ASCT), those undergoing ASCT, and those with ASCT
  - Rawstron et al. 2015[7] showed a significant benefit in median OS per log depletion in MRD percentage, although HRs from the multivariate Cox model where log (MRD) was shown to be a statistically significant predictor of OS were not reported

### Stratification studies[8-53]

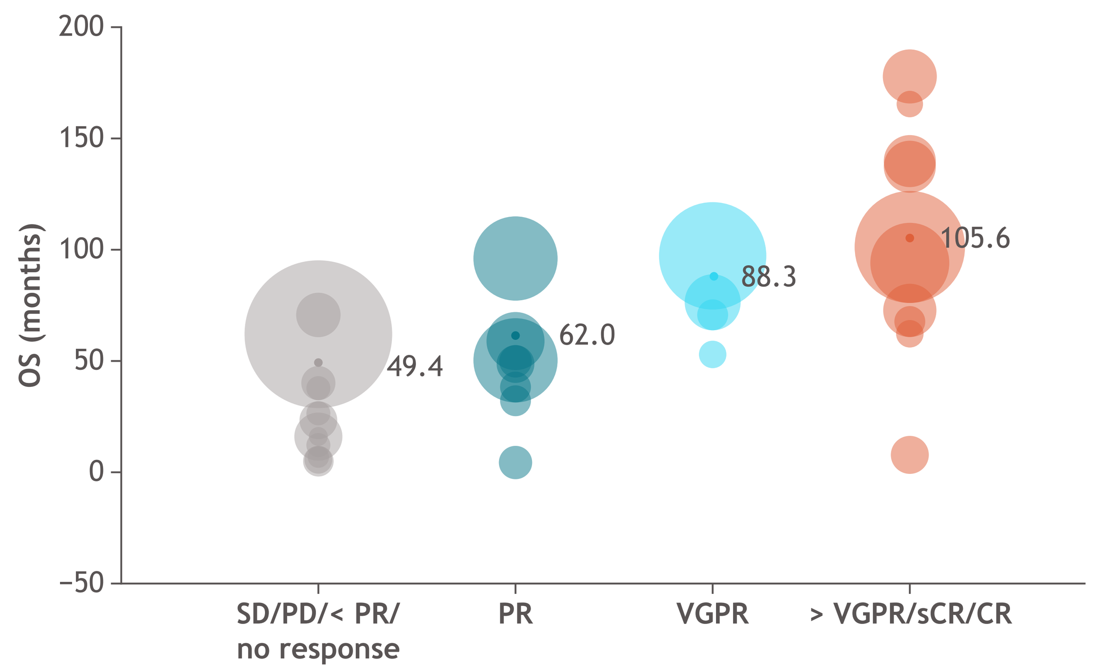
- To measure the association with OS, multiple endpoints were assessed across stratification studies: CR, VGPR, PR, progressive disease (PD), stable disease (SD), positive or negative MRD status
- Type of response was a significant factor prolonging survival, where increasingly better response indicated longer OS (**Figure 2**)
- MRD-negative (MRD-) status was a strong indicator for better survival outcomes compared with MRD-positive (MRD+) status (**Figure 3**)
- Using a Cox proportional hazards model, the effect on OS was stratified by different categories of treatment response or PD
  - The risk of dying was substantially higher for patients with ≤ PR versus patients with CR or VGPR (**Figure 4**)

### Surrogacy in HTAs

- Many HTAs acknowledged that increased PFS may be associated with better OS[54-57], and that PFS can serve as a surrogate endpoint for OS, especially in Canada and in the US for regulatory approval by the FDA[58-65]
- MRD-status was associated with improved OS, but to a lesser extent than PFS[54,55,60,65]
- Several HTA bodies (NICE,[66] CADTH,[67] IQWiG[68]) have published multiple guidance documents that provide methods for validation of surrogate endpoints
- Although many of these assessments hint toward a positive association between PFS and OS, and less frequently MRD-status, any supportive statistical analysis or predictive models applied to trial results are lacking
  - Often these claims are made by referring to the earlier published meta-analyses by Félix et al. in 2013[3] and Dimopoulos et al. in 2017,[69] which state a positive association between MRD, treatment response, or PFS, versus OS, shown by stratification or based on clinical experts

- Analyses in other types of cancers show a positive association between PFS and OS, such as metastatic melanoma, metastatic colorectal cancer, and advanced breast cancer[3,4]

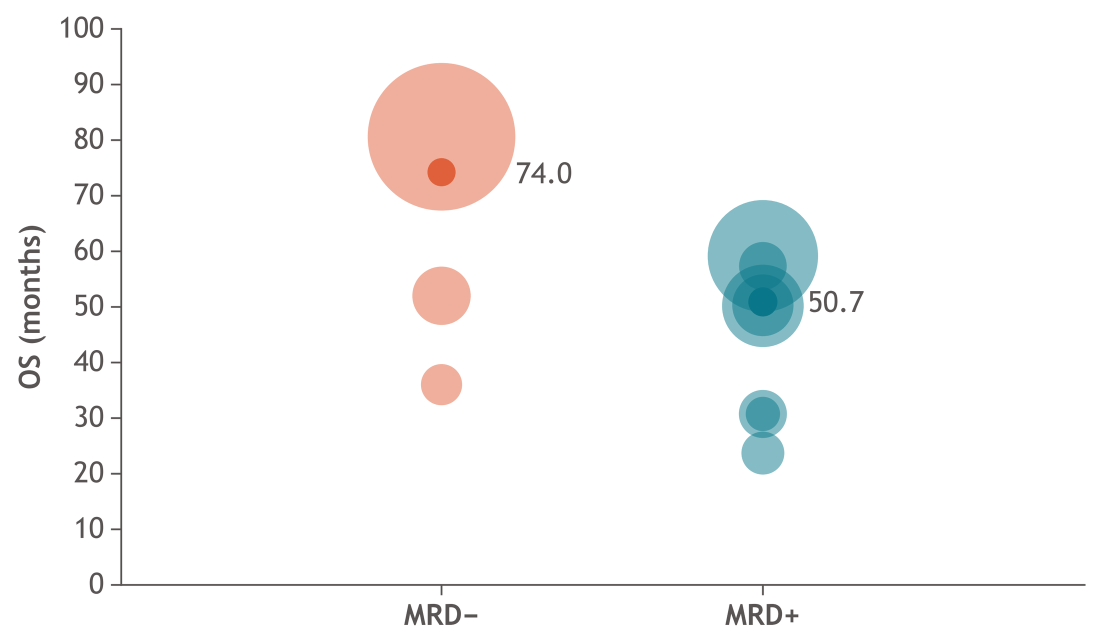
**Figure 2. Association between OS and clinical response**



OS (months)
200
150
100
50
0
−50
49.4
62.0
88.3
105.6
SD/PD/< PR/ no response
PR
VGPR
> VGPR/sCR/CR


Dark colored circles indicate mean OS.
These results do not consider disease stage or treatment approach in the MM populations, but are weighted to account for the sample size, where a larger circle indicates a larger patient population.
Additionally, these results reflect treatment response data collected from 16 publications where multiple data points for a single publications may have been provided.[8,14,22,24,27,28,30,32-35,42,46,48,51,52]
sCR, stringent complete response.

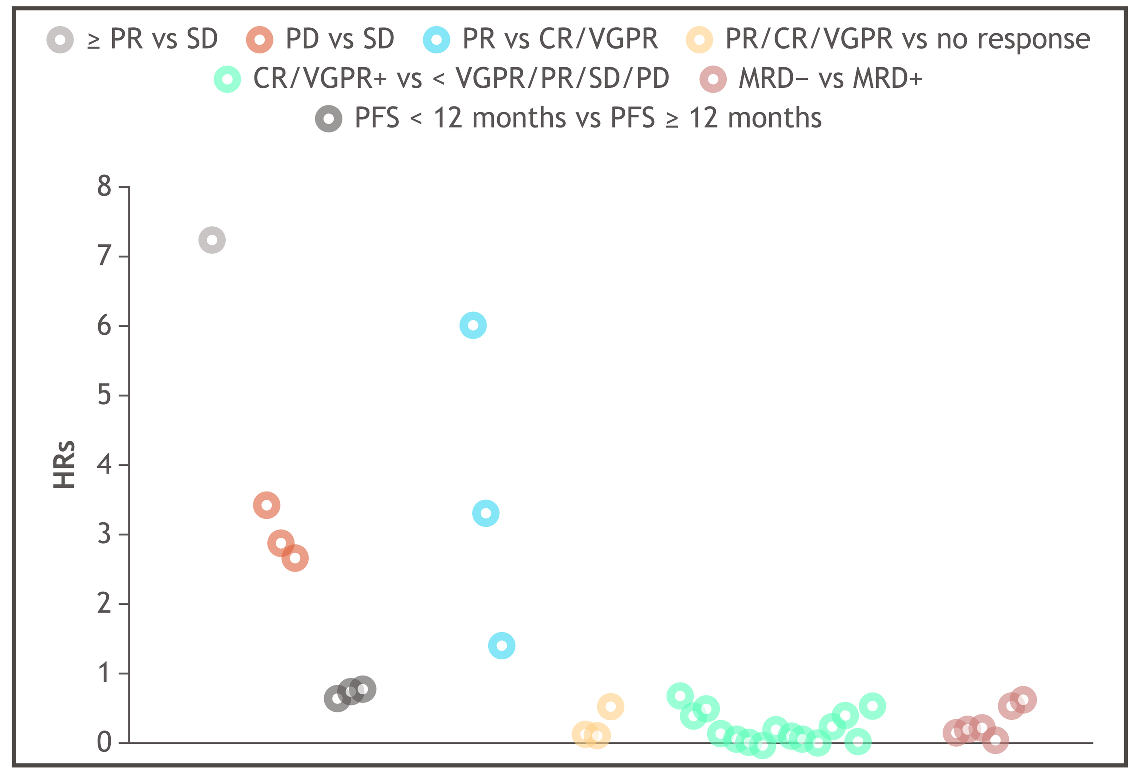
**Figure 3. Association between OS and MRD status**



OS (months)
100
90
80
70
60
50
40
30
20
10
0
74.0
50.7
MRD−
MRD+


Dark colored circles indicate mean OS.
These results do not consider disease stage or treatment approach in the MM populations, but are weighted to account for the sample size, where a larger circle indicates a larger patient population.
Additionally, these results reflect MRD data collected from 3 publications where multiple data points for a single publications may have been provided.[12,25,44]

**Figure 4. HRs for OS stratified by comparison with clinical response, MRD status, or PD**



≥ PR vs SD
PD vs SD
PR vs CR/VGPR
PR/CR/VGPR vs no response
CR/VGPR+ vs < VGPR/PR/SD/PD
MRD− vs MRD+
PFS < 12 months vs PFS ≥ 12 months
HRs
8
7
6
5
4
3
2
1
0


## Conclusions

- Evidence from the publications identified in this SLR demonstrates the prognostic value of certain endpoints such as CR, VGPR, and MRD on OS; however, only a few publications established PFS, EFS, and TTP as validated surrogate endpoints for OS in MM
- Additional studies are required to validate surrogate endpoints for OS in MM, which will help strengthen the current body of evidence surrounding surrogate endpoints for OS, potentially supporting HTA

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