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Review Article

Socioeconomic Status is Globally a Prognostic Factor for Overall Survival of Multiple Myeloma Patients: Synthesis of Studies and Review of the Literature

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Abstract. ***Background:*** **Socioeconomic status (SES) is reflecting differences in sociodemographic factors affecting cancer survivorship. Deprived, low SES populations have a higher prevalence of multiple myeloma and worst survival, a condition which widens over time.**
Methods: **We performed a meta-analysis of 16 studies (registries and cohorts) reporting myeloma patients' survival data according to SES. Ten studies reported Hazzard Ratio (H.R.) (95 % CI), and 16 studies reported p values. We combined the H.R. from 10 studies, and by using the Mosteller-Bush formula, we performed a synthesis of p values according to the area of the globe.**
Results: **Combination of H.R. from 10 studies including 85198 myeloma patients weighted to sample size of each study and adopting the hypothesis of random effect returned a combined H.R.: 1,26 (1,13-1,31) in favor of high SES patients.**
USA: Synthesis of p values coming from 6 studies (n=89807 pts) by using the Mosteller and Bush formula extracted a p-value of <0.0001 favoring high SES patients.
Oceania: Synthesis of p values in two cohorts from Australia and New Zealand (n= 10196 pts) returned a p-value of 0,022 favoring high SES patients.
Europe: The synthesis of p values from the U.K. and Greece studies (n=18533 pts) returned a p-value of <0,0001 favoring high SES patients.
Asia: Synthesis of 2 studies from Asia (n=915 pts) returned a p-value of <0,0001 favoring high SES patients.
Conclusions: **Across the globe and widening over decades, the socioeconomic status remains a gap for equality in myeloma care.**

Keywords: Myeloma; Socioeconomic status.

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Introduction. Overall Survival (O.S.) of multiple myeloma (MM) patients has improved over the last decades, with 50% of patients surviving beyond five years after diagnosis.[1] Autologous transplantation (ASCT) is still the most effective anti-myeloma therapy.[2] However, the introduction of proteasome inhibitors (bortezomib, carfilzomib, ixazomib), new IMiDs (lenalidomide, pomalidomide), and anti-CD38 and anti-SLAM monoclonal antibodies improved survival for both newly diagnosed myeloma (NDMM) and refractory/relapsed myeloma (RRMM) patients.[3]

Despite all this progress, disparities in myeloma care

are globally noted, with not all myeloma patients finally achieving the expected survival benefit. A primary reason for inequalities in myeloma care is differences in social resources. The socioeconomic status (SES) is an index calculated based on education, social support, and income but, actually, is a surrogate marker reflecting differences in factors like ethnicity or race, availability of new treatment options, access to health system facilities, disparities in insurance status/ refurbishment of anti-myeloma drugs, occupation and place of living (rural or urban vs. metropolitan).[4] Racial or ethnic differences in myeloma reflect differences in factors that interfere with the SES status and disease biology during all stages of myeloma evolution (from monoclonal gammopathy to symptomatic myeloma).[5]

Ethnicity/Racial Disparities in Myeloma Care. The incidence of myeloma in California is higher for African-Americans (A.A.) ancestry compared to other races, and most patients are affected in earlier decades of their lives. Interestingly, A.A. with the highest SES has 50% more likelihood of being diagnosed with MM.[6] Although A.A. has a higher incidence of MGUS transformation rates to symptomatic myeloma is the same across all ethnic subgroups with lower progression rates for patients from Japan and Mexico.[5]

Disease characteristics like myeloma-related events or high-risk features are different across racial/ethnic subgroups. African American patients are thought to have a lower incidence of specific high-risk cytogenetics abnormalities (deletion of 17p) but higher rates of t(11;14) and 1q amp.[7] A mutational study recently showed that A.A. myeloma patients had a lower prevalence of the high risk p53 mutation, while across all ethnic groups, NRAS and KRAS are the most frequently occurred mutations.[8] Furthermore, the incidence of myeloma-related end-organ damage (e.g., need for kidney dialysis), factors that can delay therapy or put limitations in drug choice, has been reported with varying incidence according to racial/ethnic subgroups, affecting thus disease outcome and prognosis.[9]

A.A. patients with MM, examined on the treatment offered, were less likely to undergo ASCT and be treated with bortezomib, leading to a potential association with the worst prognosis.[10] The age-adjusted odds of receiving ASCT for MM were significantly higher for white than for A.A. patients (odds ratio, 1.75; 95% CI, 1.64–1.86; p=0,01)[11,12] although a recent study from a single center in Minnesota reported that SES was in less than 2% of cases a barrier in order patients to be referred for ASCT.[13] Another single-center study reported that A.A. patients have a time since referral to ASCT longer than Whites.[14] Data from SEER-Medicare data from 2003-2017 shows that ASCT use rates during first-year increases for A.As.[15] Notably, African American patients compared to white Americans after receiving autologous transplant have no difference in disease outcome (PFS or O.S.), meaning that ASCT can overcome biological differences among racial subgroups or that equality of treatment overcomes all racial disparities.[16,17,18] A recent study by Munshi et al. conducted on army veterans showed that O.S. disparities across different races are lost and possibly reversed when all patients have the same insurance and access to health system providers.[19]

Similarly, access to new agents is not equal across ethnic/racial subgroups in health systems where these agents are approved. During the first year after MM diagnosis, White and African American patients had higher bortezomib-only usage, but A.A. had lower lenalidomide usage, whereas Hispanic and Asian patients had higher immunomodulatory drug-only utilization.[10] Furthermore, a substantial increase was seen over the years for both lenalidomide and bortezomib use for all subgroups except Hispanic patients, and a notable increase in bortezomib use was noted for all subgroups except Asian patients.[20] Notably, even today use of novel agents is more distanced from diagnosis for patients with A.A. and Hispanic origin (5,2 and 4,6 months, respectively) compared to Whites (2,7 months).[15]

Novel Anti-Myeloma Agents and Disparities in Myeloma Care According to Race/Ethnicity. Another reason for disparities in myeloma care is participation in clinical trials testing novel anti-myeloma agents. Patients with MM of Asian or Hispanic origin are similarly underrepresented in clinical trials testing new agents in myeloma care. Apart from this, A.A. cancer patients participating in 35 SWOG clinical trials showed that early-stage breast and prostate cancer patients of A.A. origin had a worse outcome; however, an equal survival was noted for myeloma patients.[21] Overall, in myeloma's nine clinical studies till 2011, only 18% of patients were non-Whites and Hispanics.[22,23] Survival data from these studies show equal survival among ethnic groups when receiving treatment on the study protocol. A recent meta-analysis of patients included five clinical trials of myeloma shows increasing participation of minorities over decades, but still, Whites are the racial group most often participated in them.[23] The VISTA study included white race in more than 99% of participants and other trials FIRST, MMY3002, etc. Whites are 75-88% of participants. In this meta-analysis, survival rates, according to race, showed equal probabilities of survival in patients of Asian Pacific ancestry compared to Whites if they received the new anti-myeloma drugs.[24] Dilemmas about different effectiveness of novel anti-myeloma agents, especially monoclonal antibodies, in disease control due to immunological haplotypes were not proved evidence-based since, in a small series of 82 patients treated with either elotuzumab or daratumumab response rates, duration of response and adverse events were similar

Table 1. Data extracted from studies and included in this meta-analysis.

Author	Place	ACST	n=Patients	gender	p value	year	5 year Survical Rate %	HR (95% CI)
Renshaw	South East England)		7733	male	0,09	1985-2004	37 vs 28	
Renshaw	South East England)		7277	female	0,07		36 vs 25	
Rachet	UK (Wales)		1800	male	0,01	1980-2001	25,6 vs 21,2	
Rachet	UK (Wales)		1500	female	0,01		23,8 vs 18	
Krishman	INDIA	<65	142		0,14	1984-1989	29 VS 32	
Hong	USA	<65	346		0,36	2003-2013	57 vs 62	HR: 1,40 (0,96-2,10)
Chan	New Zeland	All	3922		0,026	2004-2016	63 vs 57	HR: 1,10 (1,04-1,16)
Chan	New Zeland	<70	929		0,026	2004-2017	60 vs 52	
Chan	New Zeland	>70	914		0,81	2004-2018	30 vs 27	
Savage	USA (Harlem)		123		0,01	1980-1985	27 vs 18	
Harwood	Australia		6025		0,04	1982-2014	46 vs 39	HR: 1,23 (1,07-1,40)
Sun	USA		33170		0,0001	1981-2010	24,1 vs 16,4	
Sun	USA		736		0,69	1981-1990	26,1 vs 24	
Sun	USA		874		0,09	1991-2000	31 vs 25,9	HR: 1,07
Sun	USA		1874		0,0016	2001-2010	44,2 vs 34,8	HR: 1,24
Costa	USA	<65	10101		0,001	2007-2012	71,1 vs 29,4	HR: 1,45 (1,31-1,61)
Abou Jawde	Nigeria		168		0,69	1997-2003	32 vs 69	
Nandakuma	Australia (West)		249		0,2	1975-1984		HR: 1,37 (0,85-2,21)
Fiala MA	SA (Wasinghto	61%	562		0,015	2000-2009	50 vs 62	HR: 1,54 (1,13-2,09)
Fiala MA	USA (SEER-18)		45505		0,001	2000-2009	27 vs 32	HR: 1,18 (1,15-1,22)
Limei Xu	China	36,30%	773		0,001	2006-2019	79 vs 42	HR: 1,68(1,44-1.81)
Munshi	(VA health System)		15717	14981 male	0,001	2000-2017	46 vs 52	
Munshi	(VA health Sys	> 65			0,63	2000-2017	35 vs 37	HR: 0,86 (0,79-0,94)
Munshi		<65			0,001	2000-2017	52 vs 63	HR: 1,05 (0,98-1,13)
Kristinsson	Sweden		14744		0,005	1973-2005		HR 1.12 (1,03-1,23)
Intzes	Greece		223		0,001	2005-2019	52 vs 29	HR: 2,092 (1,36-3,02)
Intzes	Greece		78		0,1	2005-2020	64 vs 48	
Intzes	Greece		145		0,01	2005-2021	51 vs 27	

across ethnic groups.[25]

Single-center Experience on Myeloma Care in the Muslim Minority of Thrace, Greece. In our single-center cohort of 223 MM patients from East Macedonia and Thrace in Greece, 172 patients were of Greek origin, 39 were of Greek Muslims, and 12 of Balkan origin. The end-organ damage (end-stage renal failure, severe bone disease) were not different across racial subgroups (**Figure 1A**). The presence of Extra Medullary Disease (EMD) prevailed in a higher percentage in Greek Muslims, but other high risk features like ISS stage III and high risk cytogenetics were equally distributed among racial subgroups. Autologous SCT was offered in the same percentage of transplant-eligible patients (48% vs. 46%, p=0,873), and the exposure to both lenalidomide and bortezomib (at least two complete cycles from each agent) was administered at the same percentage of patients (**Figure 1A**). Survival data shows equal median O.S. across racial subgroups, but myeloma patients of Greek Muslim origin had longer PFS after first-line anti-myeloma therapy, but no statistical significance was reached (Log Rank p=0,1, **Figure 1B**).[26]

Access to Medical Centers and Availability of Best Anti-Myeloma Care. Overall, cancer patients in the USA do not have the same probabilities of receiving care and therapy for their disease in NCI institutes, so the different outcomes in all cancers. Access to National Cancer Institute (NCI) and National Comprehensive Cancer Network (NCCN) increased myeloma-related survival after 1996 in places with more than 2 NCI centers or more than 1 NCCN center and only for White patients. Accordingly, for ASCT, the best available anti-myeloma therapy with decreasing mortality rates through decades, disparities exist according to patients' insurance status and hospitals' volume where ASCT took place.[27] Low volume hospitals (<10 ASCT per year) had a crude mortality rate of 3,86% compared to 0,80% for high volume hospitals, and public hospitals had a crude mortality rate of 2,86% vs. 0,78% hospitals caring for patients with other insurance coverage. Facility volume is generally related to myeloma survival. National Cancer database includes 94.777 MM patients and 1333 medical centers, after multivariable analysis, showed that facility volume was independently associated with all-cause mortality for private hospitals. The unadjusted median overall survival by facility volume was 26.9 months for low volume facilities vs. 49.1 months for high volume facilities.[28]

Outside the USA in 15 Latin American countries, the FISH analysis was available in 67% of patients, MRI in 44%, and PET/CT was offered in 66,7% of patients. Treatment availability queries showed that ASCT was available in 11/13 countries, bortezomib, and lenalidomide in more than 90% of reported physicians, and pomalidomide, carfilzomib, and daratumumab is accessible in around 60% of physicians participating in this study. Maintenance therapy was prescribed in almost all indicated patients. However, there were significant differences in access to tests and treatments

A.

	Disease Characteristics					Therapy		
	GFR< 30 ml/min	EMD	ISS III	HR Cytogenetic	Bone Disease	Bort + Len	No New Agents	ASCT
Ethnicity								
Greek n=172	19,30%	23,70%	45,80%	12,20%	54%	44,20%	11%	48%
Greek Muslims n=39	21%	38,50%	38,20%	10,80%	56%	46,2	12,80%	46%
Others n=12	25%	16,70%	33,30%	11%	66,70%	41,7	10%	60%
Chi Square, p=	*0,854*	*0,124*	*0,279*	*0,889*	*0,667*	*0,904*	*0,876*	*0,873*

B.

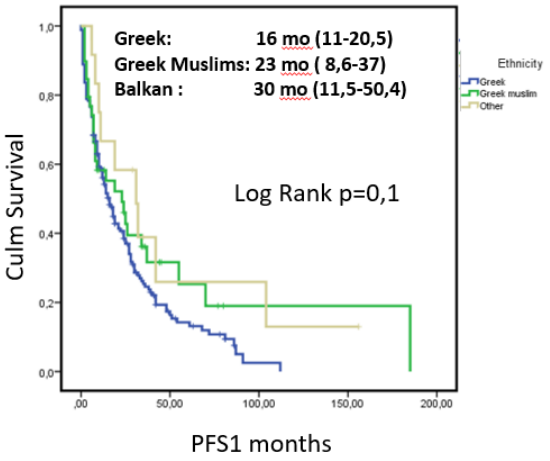

Figure 1. Myeloma care according to ethnicity/race in East Macedonia and Thrace Greece. **A**) Disease characteristics and therapy with new anti-myeloma agents or autologous stem cell transplantation (ASCT) in Greeks and Greek Muslims. **B**) Progression Free Survival after first line treatment according to ethnicity/race (PFS1).

for multiple myeloma between public and private systems. Although patients can be referred to the private or public center for anti-myeloma care, that does not significantly impact patients' survival when the same protocols were utilized. All physicians reported having access to thalidomide and bortezomib. Autologous stem cell transplant (ASCT) is available in most countries (11/13). Lenalidomide is commercially available in 97.9% (96), melphalan in 92.7% (94), daratumumab in 68% (65), pomalidomide in 67% (57), carfilzomib in 60% (57), and ixazomib in 18%. Nevertheless, the commercial availability of these drugs does not mean patients have access to them, as reimbursement issues and local health policies often do not provide them due to their high cost.[29]

Socioeconomic Status and Cancer Survivorship. SES has been linked with survival in a variety of cancers. Afshar et al., in a study from Australia reporting survival data in all cancer patients diagnosed between 2001-2015, found that patients from the most deprived for social sources areas had worst cancer survivorship with patients with lung, colorectal, breast, prostate cancer, and melanoma to have the higher survival gap according to SES.[30] A recent analysis of SEER registry data, including 327078 cancer patients from the USA, showed increased mortality for low SES patients than high SES patients across all races and ethnicities. In high SES patients, Whites had better survival compared to other high SES patients from other races; a difference widened in patients suffering from breast colorectal or prostate cancer.[31]

Socioeconomic Status and Hematological Malignancies. Deprived socioeconomic status has been linked with poor survival and a wide variety of myeloid[32] and lymphoid[33,34] hematological malignancies. Children and young adolescents with acute myeloid (AML) and lymphoid leukemia (ALL) enjoy improvement over decades of survival. Racial disparities are not that sharp now a days, especially for ALL patients, and allogeneic transplants are equally offered across all races, but there is still a gap in donor availability in patients of A.A. origin.[35] In Diffuse Large B-cell lymphoma (DLBCL) patients, conflicting data about SES's effect on survival exists. In the USA, DLBCL patients with no-insurance or Medicaid insurance had inferior survival compared to non-Medicaid insurance.[36] Studies show that patients from urban/rural areas compared to metropolitan areas had the worst survival due to a multifactorial etiology.[37] Delay in diagnosis, low SES, deprivation of financial resources, and, most importantly, fewer probabilities of receiving care in a high volume experienced in the lymphoma medical center are the main reasons for low SES patients' worst outcome. A recent study from the USA shows that low SES patients do not receive chemo-immunotherapy at the same rate, and when therapy is equal, survival rates are not affected by SES, at least for older patients above the age of 65. Hodgkin disease survival in young adults is not different across racial barriers, but Hodgkin disease incidence is strongly related to living in high SES affluent areas.[38] In Follicular lymphoma, a disease with a chronic course with remissions and relapses, similarly to MM, patients below 65 with the USA's worst insurance had a hazard ratio for death 1,96 (H.R 1.96; 95% CI, 1.69-2.28).[39] SES is related to diminish survival rate in mantle cell lymphoma patients as well.[34]

Considering the impact of SES on myeloma survival, many data exist in the literature that supports SES as a prognostic survival factor globally and across all decades. [40,41,42] Some studies are relating to SES and the incidence of myeloma.

Socioeconomic Status and Incidence of Multiple Myeloma. Incidence of myeloma is highly variable among countries but is globally rising through the

decades, reaching 2,1 cases per 100.000 habitants per year.[43] The highest prevalence of myeloma is met in Australia, North America, and Western Europe.[43] Available data about the incidence of MM and SES are conflicting. In population-based studies, MM and its preceded MGUS have been positively related to high SES because of earlier diagnosis.[44] Other studies are reporting a higher incidence of MM in low SES mostly related to occupational hazard[45] with farmers and industrial workers, especially after prolonged exposure to pesticides or other industrial chemicals to be in danger.[46,47] Obesity, a strong risk factor for MGUS development, is often seen in patients with low sociodemographic characteristics.[48] A population case-control study included 206 Black and 367 White MM cases plus 2131 controls found out that low occupation-based SES was significantly associated with an increased risk of MM.[49]

Socioeconomic Status and Myeloma Survival. Plenty of cohort studies reports data on the role of SES on myeloma survival in the literature. In order to extract and analyze all available data, we performed a meta-analysis of published studies.

Search Strategy and Statistical Analysis. We conducted a PubMed search using the following criteria; (myeloma OR plasma cell dyscrasia) AND (socioeconomic status OR social index OR SES), and 288 abstracts were returned. After reading abstracts, we resulted in 29 studies. Three independent reviewers (ES, SI, MS) red full-text articles and 16 studies full-filling our inclusion criteria (reporting five ys survival rate in patients with High or Low SES) were included in this meta-analysis of cohort studies. After selecting studies, data were extracted, and we compared five ys O.S. in High SES and Low SES myeloma patients (Studies Flow Diagram in **Figure 2**).

We separated subgroups according to the geographical area of the study. To synthesize data from different cohort studies, we used the Mosteller and Bush formula, which is the generalization of the z-test. This formula gives weight to each study concerning the number of patients. Under the null hypothesis, the weighted sum still has a normal distribution with mean 0 and variance equals the sum of the weights' square. So we have the formula:

$$U_{wk} = \frac{\sum_{i=1}^{k} g_i \cdot z(p_{1i})}{\sqrt{\sum_{i=1}^{k} g_i^2}} \sim N(0,1)$$

where $g_i = \sqrt{n_i}$, n_i is the number of patients and $z(p_{1i})$ is the standard z value.

In some studies (n=10), Hazzard Ratio (H.R.), and 95% confidence interval for O.S. in High SES and Low SES myeloma patients were reported. By using the RevMan software, a Cochrane tool, we performed a meta-analysis of the reported H.R.

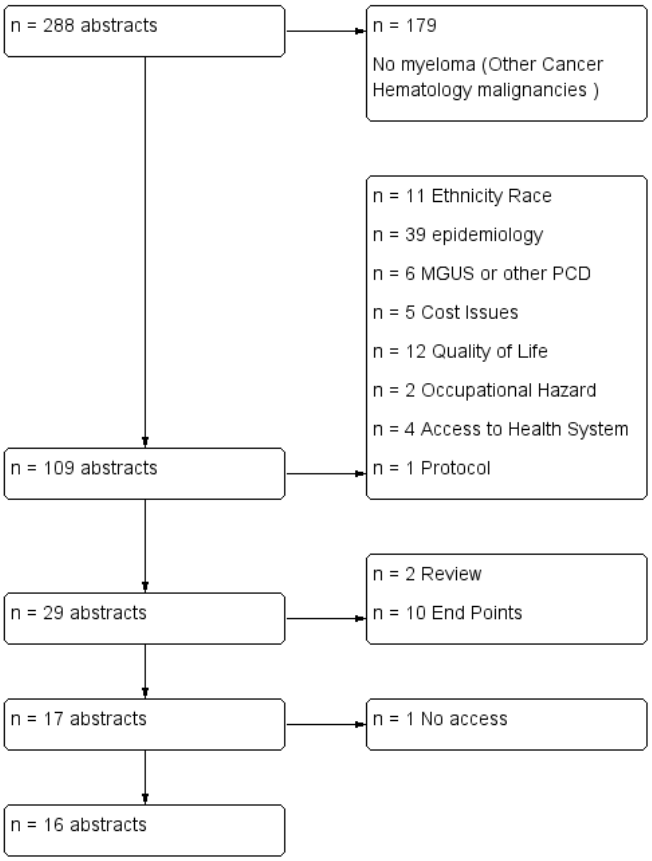

Figure 2. Studies flow diagram and final selection of studies included in this meta-analysis.

Results.

Combined from Eleven Studies Hazzard Ratio for Death in High SES and Low SES Myeloma Patients. A meta-analysis of 10 studies (two of them Sun et al., Fiala et al. gives H.R. in two cohorts) that reported H.R. and 95% CI for survival differences according to SES status of myeloma patients, weighted to sample size of each study and to adopt the hypothesis of random effect returned a combined H.R.: 1,26 (1,13-1,31). In this meta-analysis, 85198 myeloma patients were included demonstrating a better survival probability for high SES patients by 1,26 times compared to low SES patients (**Figure 3A**).

Socioeconomic Status and Disparities in 5 Years Overall Survival of Myeloma Patients According to Geography. In this meta-analysis, we conducted a synthesis of p values by using the Mosteller and Bush formula and included 134363 myeloma patients. We extracted data from studies, and we reported a 5-year O.S. rate in Low and High SES patients. Two studies are reporting separately for women and men (Renshaw and Rachet). We made a synthesis of p values from studies in four geographic areas of the globe; USA included six studies (Sun et al., Costa et al., Savage et al., Hong et al., Fiala cohort, and SEER data), Australia and New Zeeland 3 studies (Chan et al., Harwood et al.,

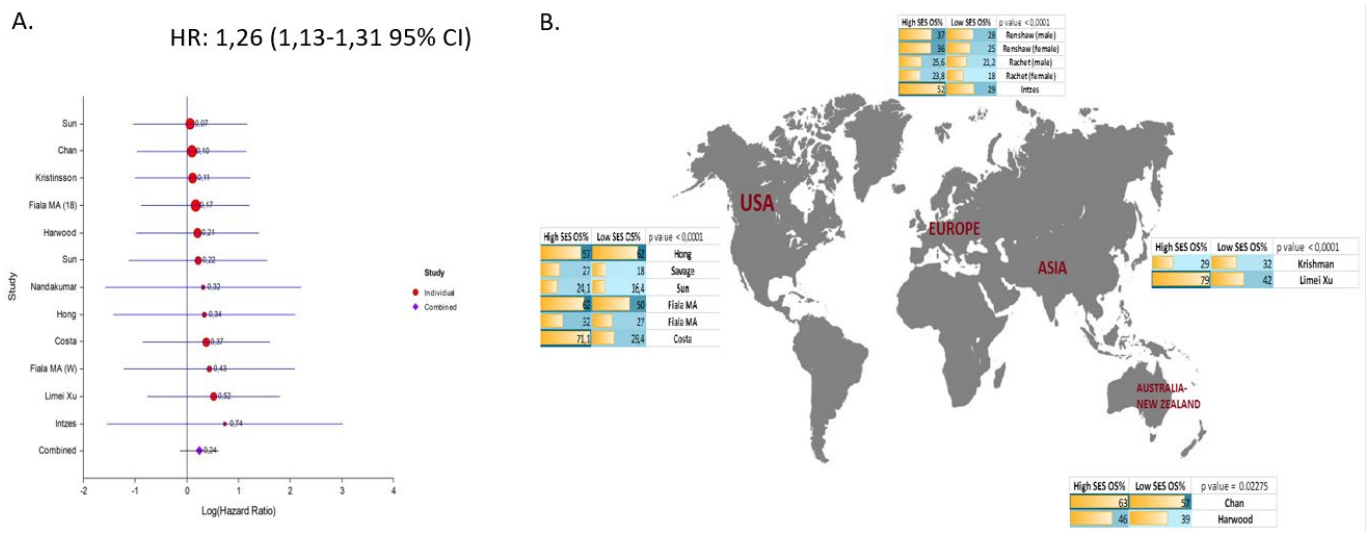

Figure 3. A) Meta-analysis and combination of Hazzard Ratio (H.R.) extracted from 10 studies reporting H.R. (95 % CI) for overall survival (O.S.) according to socioeconomic status (SES). **B**) Synthesis of p values from 16 studies reporting H.R. (95 % CI) for O.S. at 5 years according to SES segregating according to area of the globe that data are coming from. In each table percentage of 5y O.S. from all studies is reported and p values on the top denotes synthesis of p from all studies in this part of the world.

Nandakumar et al.), Europe 3 studies (Renshaw et al., Rachet et al., Intzes eta al), Asia included two studies (Krismann et al., Limei Xu et al.)

USA: Health System Disparities and the Impact of SES on Myeloma Survival. In the United States, there is no single national system of health insurance. Health insurance is purchased in the private marketplace or provided by the government to some groups. Private health insurance can be purchased from commercial insurance companies or non – profit insurers. About 84% of the population is covered by either public (26%) or private (70%) health insurance. Approximately 61% of health insurance coverage is employment-related.

The health care system in the USA is characterized by broad economic inequalities. The life expectancy of the wealthiest Americans now exceeds that of the poorest by 10-15 years. Poor Americans have worse access to health care than do wealthy Americans because many remain uninsured despite coverage expansions since 2010 due to the Affordable Care Act (ACA). Significantly, more than 37 million Americans do not have health insurance, and 41 million more have inadequate access to care.

According to SEER registry reporting data from over than 30.000 myeloma patients diagnosed from 1981 to 2010 in the USA, gap on survival rates according to SES has widened over time (affluent to deprived: 26,1%, 26,8% and 24,8% in the first decade, 31,2%, 28,1%, and 25,9% in the second decade and 44,2%, 40,5%, and 34,8% in the third decade). The Kaplan–Meier survival analyses confirmed the widening survival gaps among SES groups, with p values of 0,0016 during the last decade when more effective anti-myeloma treatments became available.[50]

This decade's focus was made by Costa et al., reporting data from 10,161 cases of MM diagnosed before the age of 65 years from 2007 t0 2012 and included in the SEER-18 registry. In the Cox proportional hazards model, only marital status, insurance status, and county-level income significantly influenced O.S. The cumulative effect of sociodemographic factors associated with shorter survival in the multivariable analysis was statistically significant (p<0,0001). The 4 years OS% reported 71,1%, 63,2% 53,4% and 46,5% for patients with 0, 1, 2, 3 adverse sociodemographic factors.[51]

Fiala et al. reported retrospectively from five-hundred-sixty-two patients eligible for analysis included in medical records from Washington University School of Medicine.

High-SES patients were less likely to have comorbidities at diagnosis than middle-SES and low-SES patients (58% compared to 72% and 76%, p=0.007) and were more likely to have private insurance at diagnosis. High-SES patients were more likely to undergo ASCT than middle-SES and low-SES patients (72% compared to 59% and 52%, respectively, p<0.001). In multivariate analysis of SES, age at diagnosis, year of diagnosis, race, comorbidity score, ASCT utilization, and insurance provider, all other variables except insurance provider, were independently associated with survival.[41]

The same group tested their patients' results in SEER-18 registry reporting from patients recorded until November 2012. 45.505 MM patients were identified for analysis. The median age at diagnosis was 69 years (range 18–85+), and 18 percent were black. In a multivariate model, SES was associated with O.S. [HR 1.18 (95% CI 1.15–1.22) for low-SES relative to high-SES; HR 1.10 (95% CI 1.07–1.13) for middle-SES relative to high-SES].[41]

Hong et al. reported data from 354 transplant eligible patients from the USA, and they did not observe any significant differences in O.S. or Progression-Free Survival (PFS) and relapse rate based on recipient SES at ASCT in univariate analyses or multivariable analysis after adjusting for significant patient-, disease-, and transplantation-related variables.[52]

There is also a small study from Harlem Hospital reporting from 1980 to 1985 and found out that low socioeconomic index resulted in a significantly lower five-year O.S. rate (27 vs. 18%; p=0,01).[42]

We performed the synthesis of p values coming from these six studies (n=89807 pts) by using the Mosteller and Bush formula, and the extracted p-value was <0.0001, meaning that in the USA, there is a statistically significant association between low SES and O.S. across all age groups and decades (**Figure 3B**).

Australia: Health System Disparities and the Impact of SES on Myeloma Survival. The Australian health system involves multiple layers of responsibility and funding provided by governments, individuals, and private health insurers.

Primary care is mostly provided in the community by general practitioners (GPs) who are generally self-employed. G.P.s also operate as 'gatekeepers,' referring patients to specialist medical services where needed. The national public health insurance scheme «Medicare» provides subsidies for most medical and diagnostic and some other health services.

Public hospital treatment is free for people but can be subject to long waiting times for elective surgery. Private hospitals cater to patients who want a choice of doctor and private ward accommodation. For private hospitals, Medicare pays 75 percent of the Medicare schedule fee, with the balance met by private health insurance.

A range of free or low-cost public health services, including immunization and mental health services, are provided by community health facilities. Prescription medicines are dispensed by private community pharmacists paid by the Australian government (under a Pharmacy Agreement) to dispense medicines subsidized under the Pharmaceutical Benefits Scheme (PBS).

An older study from Australia reported data from 249 myeloma patients diagnosed from 1975 through 1984 and found no difference in O.S. according to SES p=0,2 in this decade where chemotherapy was the most effective treatment.[53] Another study from Australia reporting survival data from more than 6000 myeloma patients diagnosed between 1981 to 2014 found that five-year relative survival across all treatment eras for disadvantaged patients was 39% (95% CI 0,36–0,42) vs. affluent patients 46% (95% CI 0,42–0,49) (p<0.001). There was no significant difference in relative survival for the middle class in multivariate analysis than affluent SES patients. Importantly, residence and SES were significant in multivariate testing, demonstrating that each was independently predictive of O.S.[54]

New Zealand: Health System Disparities and the Impact of SES on Myeloma Survival. New Zealand's original indigenous inhabitants are Māori. In 2014, New Zealand had an estimated population of 4,547,000. (2) The population mainly has European ethnicity (74 %), and there are significant Māori (15 %), Pacific Island (7 %), and Asian (12 %) populations (1).

The health care system is has been funded by the government since the early 1940s, and public funding currently accounts for 83 % of total health expenditure Government-owned hospitals provide accident and emergency, inpatient, outpatient, and community care free of charge to all New Zealanders.

Primary health care services such as general practitioner (G.P.), pharmacy, and diagnostic services have traditionally been delivered through privately owned, small independent businesses funded by the government.

A recent study from the New Zealand Cancer Registry performed in the era of modern drugs from 2004 to 2016 has reported in multivariate analysis age [hazard ratio (HR) 1,06, 95% CI 1,05-1,07], socio-economic deprivation (HR 1,10, 95% CI 1,04- 1,16) and 4 regions of the country (HR 1,12, 95% CI 1,05 - 1,19) as negative, and treatment with ASCT (HR 0,66, 95% CI 0,51- 0,87) or bortezomib (HR 0,74, 95% CI 0,64 - 0,86) as positive independent prognostic factors for OS. The most deprived groups had an inferior 3-year OS compared to others (57 vs. 63 %; p= 0,026) and experienced no improvement in survival following the funding of bortezomib despite similar uptake of first line bortezomib.[55]

Synthesis of p values from two cohorts from Australia and a New Zealand cohort(n= 10196 pts) returned a p-value of 0,022 indicated SES as a prognostic factor and in Oceania (**Figure 3B**).

United Kingdom: Health System Disparities and the Impact of SES on Myeloma Survival. The health care system of the United Kingdom has since 1997 been assigned the responsibility for organizing health financing and services to relevant public officials. All U.K. citizens have maintained national health services, which provide universal access to a comprehensive package of services that are mostly free at the point of use. These health services are predominantly financed from general taxation, and 83.5% of total health expenditure in the United Kingdom came from public sources in 2013.

Life expectancy has increased steadily across the United Kingdom, but health inequalities have proved resistant to improvement, and the gap between the most deprived and the most privileged continues to widen

rather than close.

Renshaw et al. reported data from 10,015 myeloma patients diagnosed from 1985 through 2004 and included in the Thames Cancer Registry. When considering patients with myeloma diagnosed in the era of targeted therapies from 2000 to 2004 in both males and females, there was a tendency for higher survival in patients resident in the most affluent areas (males trend p= 0,09, females trend p= 0,07).[56]

Rachet et al., in another U.K. study, reported data from 40.000 myeloma patients according to the year of diagnosis and relative deprivation of social supporting factors (social gap). They found out that the equal myeloma survival for deprived women noted in the late 1980s had wholly reversed by the late 1990s. These vast differences among deprivation groups in survival trends, with no improvement at all in 5-year survival among the most deprived group, but an increase of more than 10% for the most affluent group is expected to be further widened in the future.[57]

Greece: Health System Disparities and the Impact of SES on Myeloma Survival. The Greek national health system provides healthcare benefits/services through a network of public/state providers and contracted private primary, hospital, and ambulatory care providers. Private providers' presence is more obvious in primary care, especially in diagnostic technologies, private physicians' practices, and pharmaceuticals. The system is financed by the state budget, social insurance contributions, and private payments.

The National Organization for the Provision of Health Services (Greek acronym EOPYY) negotiates contracts and remunerates health professionals. At the Pharmacist's, there is usually a co-payment of 25% of medicinal products' cost. Some patients' groups, such as cancer patients, the chronically ill, and pregnant women, receive medicines free of charge or pay a reduced co-payment.

In a recently published study, we retrospectively collected data from 223 myeloma patients treated in our department from January 2005 till December 2019. Based on the intention to treat (ITT), 78 patients were considered transplant eligible (T.E.), and 145 were non-transplant eligible (NTE). In Kaplan Mayer survival analysis, including all MM patients of our cohort, the Low SES groupn=100 had inferior survival compared to High SES patients n=123 [Median O.S. (95% CI) for Low SES: 28 months (18-37,9) High SES: 68 months (55,6-80,4), Long Rank p=0,000) The Low SES effect on O.S. is more evident in the non-transplant eligible (NTE) elderly myeloma patients and those diagnosed at I stage ISS.[26]

The synthesis of p values from the U.K. and Greece studies (n=18533 pts) returned a p-value of <0,0001 suggested that SES remains an important prognostic factor of survival in Europe (**Figure 3B**).

Asia and Africa. A recent study from China by Limei Xu et al. included 773 NDMM patients diagnosed from 2006 to 2019 found out that low SES patients received ASCT at a lower rate and had a worst PFS and O.S. Patients with high education levels had a median overall survival (O.S.) of 122.27 (95% CI: 117.05–127.49) months, which was also better than that of patients with low education levels (58.83 months, 95% CI: 48.87–62.79, p< 0.001). Developing countries contributed two small studies to our analysis. A small cohort from India reporting data from 132 myeloma patients diagnosed during the 80s found similar survival rates for low and middle SES.[58] Similarly, another study from Nigeria reports data from 292 newly diagnosed and relapsed myeloma patients and found no difference in O.S. according to SES p=0,69 in multivariate analysis.[59]

Synthesis of 2 studies from Asia (n=915 pts) returned a p-value of< 0,0001 showing a better survival for high SES myeloma patients compared to low SES and in this part of the world (**Figure 3B**).

Financial Toxicity of Myeloma Treatment. Myeloma is a disease model for drug development that led to 11 new medications' approval since 1998. Although new treatment allows better disease control, they also stress payers' budgets. In 2000, the total all-cause health care cost of myeloma was $3,263 per patient per month (PPPM) ($346 PPPM or 10.6% for myeloma treatment-related drug costs) and increased to $14,656 PPPM in 2014($4,176 PPPM or 28.5% for myeloma treatment-related drug costs).[60] Furthermore, real-world data shows that myeloma patients' treatments are not always given in optimal ways. MacEwan et al. showed that the average duration of treatment by a line of therapy was seven months for the first line, six months for the second line, and five months for the third line.[61] So payments in the real world setting cannot bring the maximum benefit for myeloma patients.

After patients are diagnosed with cancer, the purchase of therapies affects their personal economics (pocket cost) by two ways; first, contributing to calculations of the cost of insurance premiums and second through cost-sharing mechanisms imposed by insurers.[1] Furthermore, employment issues due to myeloma are arising. In a recently published study, five hundred (66%) of the respondents reported that they were employed at the time of diagnosis and treatment onset. However, by the time they completed the study questionnaire, only 33% were employed.[62] In the same study, 29% of participants changed or lost coverage after myeloma diagnosis, including 10% unable to obtain replacement insurance and 35% applied for disability support programs.[62] Considering the ability to work, this is affected by the choice of an anti-myeloma treatment plan. Merola et al. reported that patients who received injectable therapy missed an average of 110 workdays

in the one year after diagnosis, compared with 87 for patients receiving only oral therapy.[63]

Myeloma care's financial toxicity is increasing for both health system payers and for patients' as well. Disparities in myeloma care will widen since the most deprived will fail to meet the need for continuous administration of expensive therapies.

Conclusions. SES is an established poor prognostic factor for survival in many cancers. Differences in SES are a surrogate marker reflecting other factors like ethnicity/race, insurance cover, place of living, accessibility to health services etc. In this meta-analysis, we performed the synthesis of p values from 16 studies that included 134363 MM patients diagnosed from 1975 to 2019 and weighted according to the number of patients included in each study. We demonstrated that SES remains a significant prognostic factor for O.S. in myeloma patients globally (p-value of <0,0001). Synthesis of H.R. from 10 studies shows that high SES myeloma patients have 1,26 (95% CI 1,13-1,31) more probabilities to be alive at five years compared to low SES patients. Financial intoxication of myeloma care on health systems and patients is rising through the decades. Therefore the gap in myeloma care between deprived and affluent patients is expected to widen in the future.

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