Title

Does a Multiple Myeloma Polygenic Risk Score Predict Overall Survival of Patients with Myeloma?

Journal

Cancer Epidemiology, Biomarkers & Prevention, 31(9)

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Publication Date

2022-09-02

DOI

10.1158/1055-9965.EPI-22-0043

Peer reviewed

HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2024 September 05.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2022 September 02; 31(9): 1863–1866.

doi:10.1158/1055-9965.EPI-22-0043.

Does a Multiple Myeloma Polygenic Risk Score Predict Overall Survival of Myeloma Patients?

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Abstract

Background: Genome-wide association studies (GWAS) of multiple myeloma (MM) in populations of European ancestry (EA) identified and confirmed 24 susceptibility loci. For other cancers (e.g. colorectum and melanoma), risk loci have also been associated with patient survival.

Methods: We explored the possible association of all the known risk variants and their polygenic risk score (PRS) with MM overall survival (OS) in multiple populations of EA (IMMEnSE consortium, InterLymph consortium, CoMMpass and the German GWAS) for a total of 3748 MM cases. Cox proportional hazards regression was used to assess the association between each risk SNP with OS under the allelic and codominant models of inheritance. All analyses were adjusted for age, sex, country of origin (for IMMEnSE) or principal components (for the others) and disease stage (ISS). SNP associations were meta-analyzed.

Results: SNP associations were meta-analyzed. From the meta-analysis, two MM risk SNPs were associated with OS ($p<0.05$), specifically *POT1-AS1*-rs2170352 (HR=1.37, 95% C.I.=1.09–1.73, p=0.007) and *TNFRSF13B*-rs4273077 (HR=1.19, 95% C.I.=1.01–1.41, p=0.04). The association between the combined 24 SNP MM-PRS and OS, however, was not significant.

Conclusions: Overall, our results did not support an association between the majority of MM risk SNPs and OS.

Impact: This is the first study to investigate the association between MM PRS and OS in MM.

Keywords

Multiple myeloma; susceptibility; overall survival; polygenic risk score

Introduction

Multiple myeloma (MM) is a hematologic malignancy where malignant plasma cells accumulate in the bone marrow. Genome-wide association studies (GWASs) conducted in subjects of European ancestry (EA) have identified 24 germline MM susceptibility loci, with an additional one specific to the t(11;14) translocation[1]. Since the effect sizes of single-nucleotide polymorphisms (SNPs) at these loci are small (odds ratios (ORs) ranging from

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Conflict of interest: The authors declare no potential conflicts of interest.

1.10 to 1.40), individual SNPs are not strong predictors of MM risk, but their combination into a polygenic risk score (PRS) may improve risk stratification[2]. To date, MM-PRS has not been evaluated in association with overall survival (OS) of MM patients. The 5-year survival of MM patients is 55.6%, according to the National Cancer Institute Surveillance, Epidemiology and End Results Program (https://seer.cancer.gov/statfacts/html/mulmy.html). For other cancers (e.g., colorectal and melanoma) risk loci have also been associated with patient survival[3,4]. Thus, we tested if MM risk SNPs and a PRS of these SNPs were associated with OS of MM patients.

Materials & Methods

The association between MM OS and known risk loci was studied in four consortia of EA participants: The International Multiple Myeloma rESEarch consortium (IMMEnSE), the International Lymphoma Epidemiology Consortium (InterLymph), the Multiple Myeloma Research Foundation (MMRF) CoMMpass Study (https://themmrf.org/finding-a-cure/our-work/the-mmrf-commpass-study), and a German GWAS, described elsewhere[1,2,5]. Characteristics of MM cases from the four consortia are reported in Table 1. We included MM cases diagnosed from 2001 to 2015 according to the International Myeloma Working Group (IMWG) criteria. Median age for the four studies was 60.6. Studies were approved by local ethics review committees, and all participants provided written informed consent. SNP genotypes of interest were obtained from GWAS data performed with SNP arrays for InterLymph and the German GWAS, low-pass whole genome sequencing or whole exome sequencing for CoMMpass. All 24 SNPs had an imputation score >0.9 across platforms. TaqMan genotyping was used for IMMEnSE.

Polygenic Risk Score (PRS)

The PRS was constructed using the published per-allele odds ratios (ORs) (https://www.ebi.ac.uk/gwas/) associated with MM risk. The log ORs for each SNP were multiplied by the number of risk alleles (0, 1, or 2) for that SNP and summed, resulting in a unique score for each person:

$$PRS_j = \sum_{i=1}^{24} n_{ij}\ ln(OR_i)$$

In the above equation, $n_{ij} = \{0, 1, 2)$ is the number of risk alleles carried at the i^{th} SNP by the j^{th} individual, and OR_i is the per-allele OR for MM risk. The previously identified variant specific to MM cases with $t(11; 14)$ translocation[1] was not included in the PRS.

Statistical Analysis

Overall survival (OS) was defined as time from date of MM diagnosis to date of death or last known follow-up. Cox proportional hazards regression was used to assess the independent associations between each SNP and MM OS, considering the allelic and codominant model of inheritance, adjusted for age, sex, principal components (PC, for InterLymph, CoMMpass and German GWAS) or country of origin (for IMMEnSE) and disease stage (ISS). Hazard

ratios (HRs) and 95% confidence intervals (CIs) were estimated. Cox proportional hazards regression was also used to assess the association of MM-PRS with MM OS, adjusted for age, sex, disease stage (ISS) and PCs or country of origin. The 24-SNP MM-PRS was evaluated as a continuous variable, per standard deviation (SD). Meta-analysis using a fixed effects model was then used to estimate overall associations, across the four datasets of individual SNPs and PRS with MM OS. Heterogeneity was assessed using Cochrane Q and I^2 statistic. Power calculations were performed using survSNP R-Package 0.25, RetroDesign, survivalEpi R Packages. All other analyses were performed with R version 4.1.0 (2021–05-18).

Results

There was no association between MM-PRS and OS ($p>0.05$) (Figure 1). When looking at individual SNPs, two of them were associated with OS with the allelic model ($p<0.05$): *POT1-AS1*-rs2170352 (HR=1.37, 95% C.I.=1.09–1.73, p=0.007) and *TNFRSF13B*-rs4273077 (HR=1.19, 95% C.I.=1.01–1.41, p=0.04).

Discussion

This is the first study to investigate the association between MM risk loci, PRS and OS in MM. Given prior evidence in other cancers, we hypothesized that known risk loci might also be associated with OS. Given the total sample size (N=3748) and number of events (N=1301) included in the meta-analysis, we had at least 80% power (alpha=0.002) to detect HRs above 1.2 for common SNPs (e.g., MAF=0.2) and 1.6 for rarer SNPs (e.g., MAF=0.02), and for the MM-PRS model we had 80% power to detect minimum hazard ratios of 1.17. Overall, our results did not support an association between the majority of MM risk SNPs and OS. We also observed no statistically significant association between MM-PRS score and OS. However, the meta-analysis of the single SNPs showed that *POT1-AS1*-rs2170352 and *TNFRSF13B*-rs4273077 were associated with OS ($p<0.05$). *POT1-AS1* is part of the shelterin complex and plays an important role in telomere regulation[6]. Studies in gastric, breast, and colon cancer have shown that telomere dysregulation affects survival outcomes[6]. *TNFRSF13B* encodes for a B-cell activating factor receptor of the TNF receptor family called TACI, which is associated with common variable immunodeficiency and inflammation activation[7], both of which impact MM survival.

Our study has some limitations, although they are unlikely to change our null result: 1) the IMMEnSE cohort used the ‘country of origin’ variable to adjust for possible population stratification, as genome-wide data are unavailable, 2) in some of the cohorts there is a slightly longer follow-up and lower staged MM cases, 3) survival outcome is limited to only OS available across cohorts. In conclusion, our data support a lack of association between a PRS based on MM risk alleles identified to date and overall survival of MM patients.

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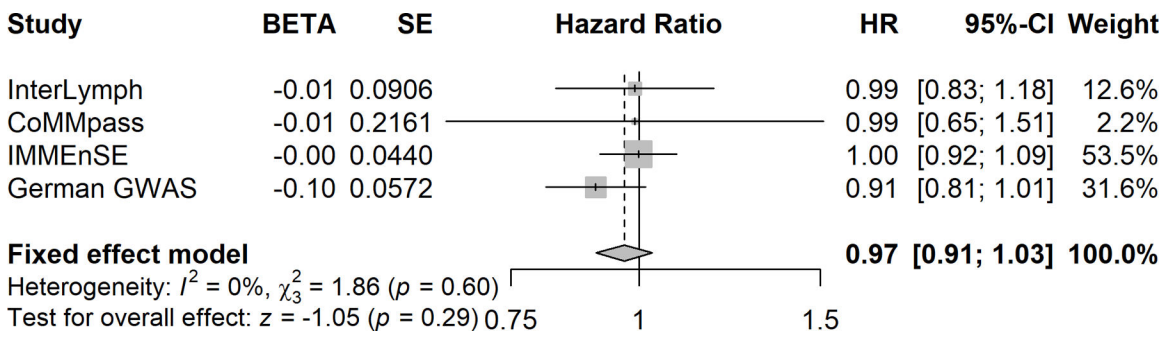

Figure 1. Forest plot of 24-MM PRS and OS association.

24-SNP MM-PRS was evaluated as a continuous variable, per standard deviation (SD). Meta-analysis using a fixed effects model was then used across all four datasets. HR=hazard ratio, 95% CI= 95% confidence interval.

Table 1.

Characteristics of MM cases with complete data on overall survival and stage.

Study	InterLymph[a]	CoMMpass[b]	IMMEnSE[c]	German GWAS[d]	Totals
Overall number of cases	1277	439	1002	1030	3748
Sex (n, %)					
Male	777 (60.8)	266 (60.6)	531 (53.0)	609 (59.1)	2183
Female	500 (39.2)	173 (39.4)	471 (47.0)	421 (40.9)	1565
Median age (range)	61 (26–90)	65 (27–93)	61 (22–93)	58 (27–72)	61 (22–93)
ISS Stage (n, %)					
1	334 (26.2)	159 (36.2)	330 (33.0)	421 (40.9)	1244 (33.2)
2	593 (46.4)	146 (33.3)	323 (32.2)	341 (33.1)	1403 (37.4)
3	350 (27.4)	134 (30.5)	349 (34.8)	268 (26.0)	1101 (29.4)
Median follow-up time in months (percentiles 25th-75thpercentiles)	58 (29.9–87.3)	39.9 (27.0–47.6)	39 (20.5–69.47)	65 (55–82)	50.5 (20.5–87.3)
Status at follow-up (n,%)					
Alive	746 (58.4)	327 (74.5)	739 (73.7)	635 (61.6)	2447 (65.3)
Deceased	531 (41.6)	112 (25.5)	263 (26.3)	395 (38.4)	1301 (34.7)

[a] InterLymph genotyping was performed with multiple platforms (Affymetrix, Human660W-quad Beadchip, and Illumina arrays 610 Quad, Omni5, OmniExpress Beadchip, and OncoArray) and imputed to the Haplotype Reference Consortium.

[b] CoMMpass: Germline calls via GenomeGPS using low-pass whole genome sequencing and imputed to the Haplotype Reference Consortium.

[c] IMMENSE: genotyping was performed with TaqMan technology.

[d] German GWAS: Genotyping was performed using Illumina Human OmniExpress 12 v1.0 arrays