Received: 23 May 2022 | Accepted: 5 August 2022

DOI: 10.1111/bjh.18410

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Transcriptional signature of *TP53* biallelic inactivation identifies a group of multiple myeloma patients without this genetic condition but with dismal outcome

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Funding information
Consejería de Educación de Castilla y León; Gerencia Regional de Salud, Junta de Castilla y León, Grant/Award Number: GRS 2331/A/21 and GRS 2058/A/19; Asociación Española Contra el Cáncer, Grant/Award Number: CLJUN18010DERA and PROYE20047GUTI; Instituto de Salud Carlos III (ISCIII) co-funded by European Union FEDER funds, Grant/Award Number: PI16/01074, PI19/00674 and FI20/00226

Summary

Biallelic inactivation of *TP53* has been included in the definition of double-hit (DH) multiple myeloma (MM), which entails an ominous prognosis. However, this condition, or even the presence of high-risk cytogenetic abnormalities, cannot accurately capture the 15%–20% of the MM population with a median overall survival below 24 months. This prompted us to look for other MM patients who might have transcriptional characteristics similar to those with DH-*TP53*. In the present study, we analysed RNA-seq, whole-genome and whole-exome sequencing data from 660 newly diagnosed MM (NDMM) patients from the MMRF (Multiple Myeloma Research Foundation) CoMMpass study to characterize the transcriptional signature of *TP53* double-hit (DH-*TP53*) MM. We found 78 genes that were exclusively deregulated in DH-*TP53* patients. A score based on these genes identified a group of 50 patients who shared the same transcriptional profile (DH-*TP53*-like group) whose prognosis was particularly unfavourable [median overall survival (OS) < 2 years], despite not harbouring the biallelic inactivation of *TP53*. The prognostic value of the DH-*TP53* score was externally validated using gene expression data from 850 NDMM patients analysed by microarrays. Furthermore, our DH-*TP53* score refined the traditional prognostic stratification of MM patients according to the cytogenetic abnormalities and International Staging System (ISS).

KEYWORDS
double-hit *TP53* signature, multiple myeloma

INTRODUCTION

Multiple myeloma (MM) is a B-cell neoplasm characterized by great genomic and molecular complexity that largely explains the variability observed during the clinical course and in treatment response.[1] Cytogenetic abnormalities remain the most relevant prognostic factors. Deletion of chromosome 17p [del(17p)], which contains the *TP53* locus, is present in 8%–13% of newly diagnosed MM (NDMM) patients and is probably the cytogenetic alteration associated with the most unfavourable prognosis.[2] *TP53* mutations, which also have a negative impact on survival, are also uncommon, occurring in only 3%–6% of NDMM patients.[3,4] *TP53* mutations are more frequent in patients with del(17p).[5]

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Biallelic inactivation of *TP53*, observed when the two abnormalities are present together, has been included in the definition of double-hit (DH) MM. DH-*TP53*, although rarely seen, entails an ominous prognosis.[6]

Moreover, p53 can be deregulated by other mechanisms different from changes in DNA gene sequence, such as epigenetic regulation or altered expression of its regulators, which eventually lead to p53 dysfunction. The functionality of the different pathways controlled by p53 could be inferred by the expression of their numerous target genes. In this regard, a signature based on three genes (*PUMA, GADD45* and *THBS1*) has been described to be associated with *TP53* status in MM.[7] Furthermore, a transcriptional signature of patients with biallelic inactivation of *TP53* has recently been defined. Interestingly, some relevant pathways deregulated in this signature, such as those related to cell cycle control and MYC regulation, were also altered in the expression signatures specific to biallelic events involving other tumour suppressor genes.[8]

Compared with solid tumours, DH-*TP53* in MM is much more infrequent. However, ultra-high-risk MM, defined as those patients with a median overall survival (OS) less than 24 months, represents 15%–20% of the MM population.[9] Although other high-risk cytogenetic abnormalities may account for this adverse prognosis, cytogenetic alterations of this kind are not present in all patients with such an unfavourable outcome. This prompted us to define the transcriptional signature of DH-*TP53* and to find out if it was present in other patients who did not have biallelic inactivation of *TP53*.

METHODS

Patient cohorts

Genomic and transcriptomic data of 660 NDMM patients from the MMRF CoMMpass study (NTC014554297, https://research.themmrf.org/) were analysed. Survival data were retrieved from the interim analysis 16 release. The characteristics of the population are described in Table S1. Two other gene expression series from the gene expression omnibus (GEO) (GSE4581[10] and GSE136400[11]) comprising a total of 850 patients were selected as the validation cohort.

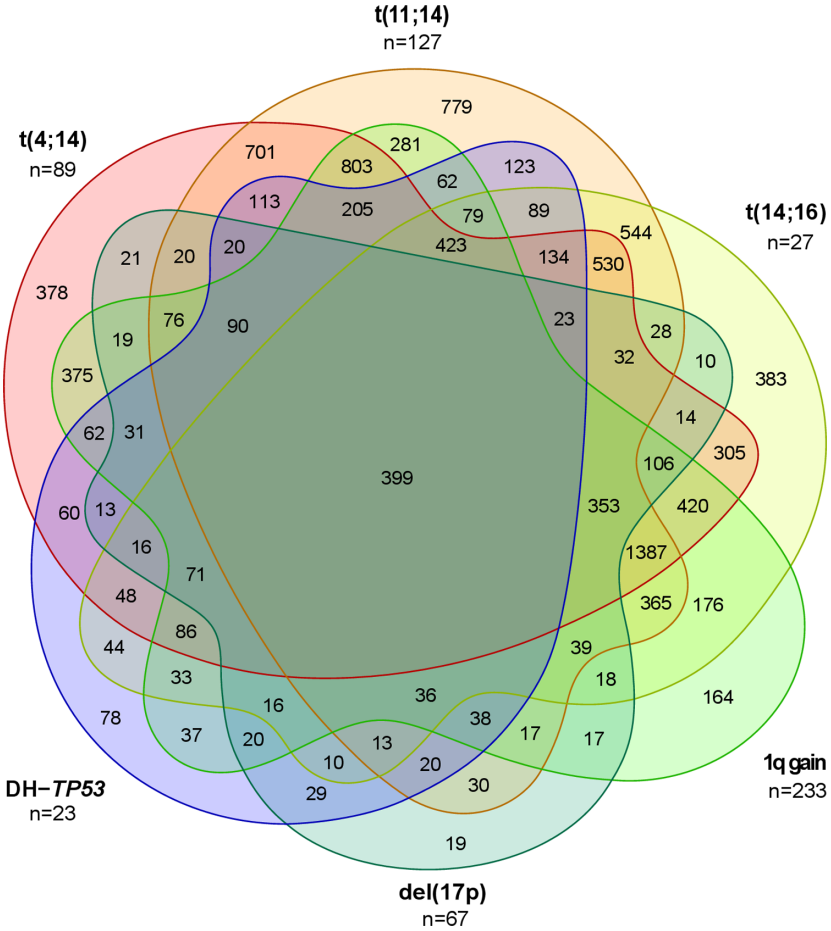


FIGURE 1 Expression signature of *TP53* biallelic inactivation and score generation. Venn diagram indicating the number of differentially expressed genes in the six groups of newly diagnosed multiple myeloma (NDMM) patients defined according to cytogenetic abnormalities and *TP53* mutations. The non-overlapping numbers indicate the differentially expressed genes unique to each group. [Colour figure can be viewed at wileyonlinelibrary.com]

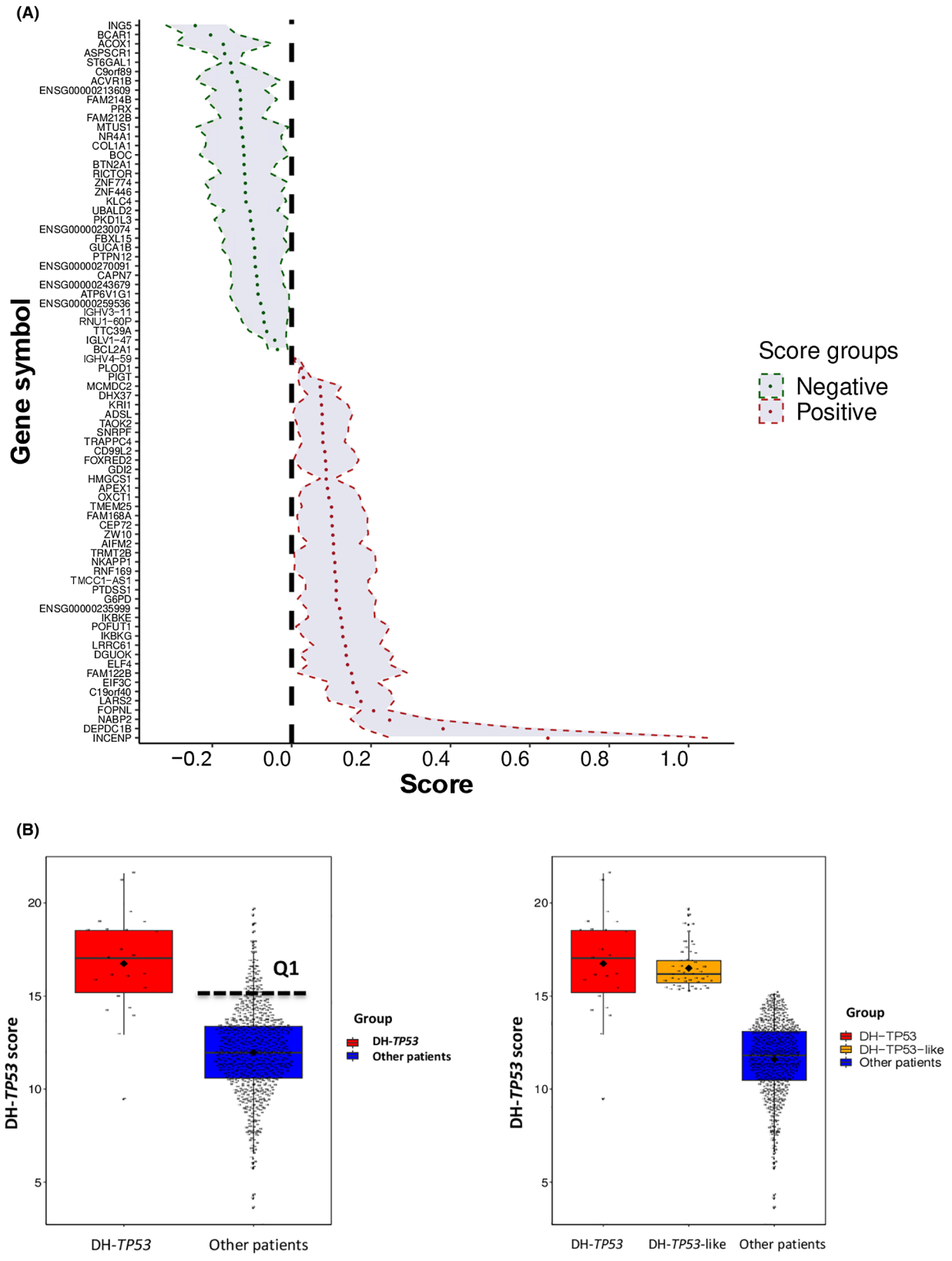


FIGURE 2 Double-hit (DH)-*TP53* score generation. (A) The 78 differentially expressed genes in patients harbouring *TP53* biallelic inactivation are represented according to their scores. (B) Representation of scores for each patient. The first quartile (Q1) of the score in the DH-*TP53* patients is indicated. This is applied to the non-DH-*TP53* group, giving rise to the DH-*TP53*-like group, indicated in yellow. [Colour figure can be viewed at wileyonlinelibrary.com]

Identification of DH-*TP53* signature

Information about *IGH* translocations [t(4;14), t(11;14) and t(14;16)] and copy number abnormalities [1q gain and del(17p)] were obtained from the whole-genome sequencing-based fluorescent *in-situ* hybridization (Seq-FISH) data.[12] Non-synonymous *TP53* mutations assessed by whole-exome sequencing were also included in the analysis. Based on these chromosomal and gene alterations, six groups and a normal FISH group were defined. RNA-seq gene expression in the six groups was compared with the normal FISH group to generate the corresponding lists of differentially expressed genes [false-discovery rate (FDR) < 0.05]. All contrasts were performed using the *DESeq2* R package (version 1.30.1) on HTSeq count data. Genes from the six lists were then gathered to derive a Venn diagram using the *ggplot2* R package (version 3.3.5), which allowed us to determine the exclusive DH-*TP53* signature.

Score generation

The DH-*TP53* signature was used to build a score based on a Spearman correlation coefficient and a scaled Gini index.[13] We used the value of the first quartile of the score in the DH-*TP53* group as the cut-off to determine the DH-*TP53*-like group.

Validation of DH-*TP53* score

To validate the performance of the DH-*TP53* score we processed data from the afore-mentioned two GEO series.[14] Patient scores from these two series were arranged in descending order and split into two groups, based on a moving window of 5% of the patients, to enable the survival analysis to be carried out.

Statistical analysis

Univariable survival analysis was performed in R through the *survival* (version 3.2–7), *survminer* (version 0.4.9) *and ggplot2* packages using the Kaplan–Meier estimator, with progression-free survival (PFS) and OS as end-points. The resulting survival curves were compared using the log-rank test. Multivariable Cox proportional-hazards models were fitted in R through the 'coxph' function of the *survival* package. The multicollinearity among predictor variables was quantified using variance inflation factors with the *car* package (version 3.0–12). The proportional-hazards assumption of these models was evaluated through the evaluation of the Schoenfeld residuals in R. Forest plots for multivariable analyses were drawn using the *forestmodel* package (version 0.6.2). The threshold of significance for unadjusted and adjusted values

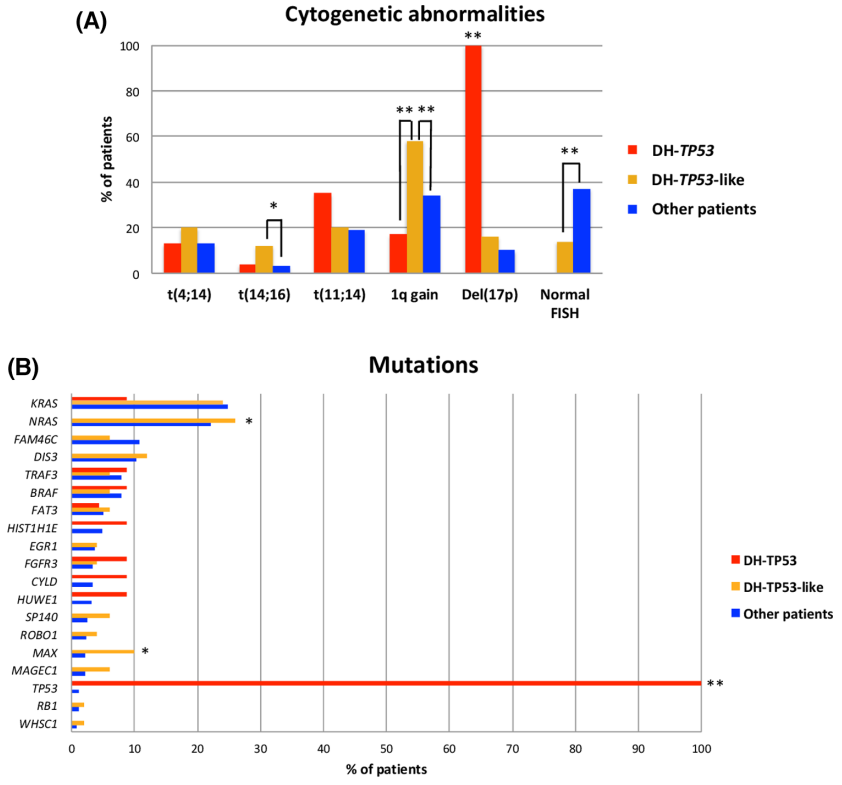


FIGURE 3 Genetic characteristics of the double-hit (DH)-*TP53* and DH-*TP53*-like groups. (A) Association between the most frequent cytogenetic abnormalities in multiple myeloma (MM) and the three groups defined by score and DH-*TP53* condition. (B) Association between the most frequently mutated genes in MM and the three groups defined by score and DH-*TP53* condition. Only non-synonymous mutations are shown. *, $p < 0.05$, **, $p < 0.01$. Note that the proportion of del(17p) and *TP53* mutations is 100% in the DH-*TP53* group by definition. [Colour figure can be viewed at wileyonlinelibrary.com]

of p was set to 0.05. These analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA) and R, version 4.0.4 (R Core Team, Vienna, Austria).

RESULTS

Identification of transcriptional pattern associated with *TP53* biallelic inactivation

The 660-patient cohort was divided into six groups based on their cytogenetic and *TP53* mutation status: t(4;14), t(11;14), t(14;16), 1q gain, del(17p) and DH-*TP53*. Gene expression profiles of these groups were determined by contrasting their RNA-seq data against those of patients with normal FISH (considered as the cases with none of the afore-mentioned abnormalities). Differential expression analyses of the 23 patients harbouring *TP53* biallelic inactivation (DH-*TP53* group) identified 78 genes (FDR <0.05) after subtracting the gene expression signatures of the five other groups (Figure 1). The interactions between the proteins encoded by the genes involved in the DH-*TP53* signature were represented using a weighted functional association network in STRING[15] (Figure S1). We found nine genes (*AIFM, BCL2A1, NR4A1, ING5, APEX1, COL1A1, G6PD, IKBKG, RICTOR*) with direct interactions with *TP53*. *AIFM, BCL2A1, NR4A1* and *ING5* are mainly involved in apoptosis. *APEX1*, a negative regulator of transcription, was upregulated in DH-*TP53* patients, while *NR4A1* and *COL1A1* that positively regulate this process were downregulated.

Development of DH-*TP53* score

All the 78 genes exclusively deregulated in the DH-*TP53* group met the inclusion criteria to be part of the DH-*TP53* score (Figure 2A). Based on this, we assigned the patients with a score above the first quartile of the DH-*TP53* group to a new subgroup named DH-*TP53*-like. This subgroup consisted of 50 out of 660 (7.5%) NDMM patients and did not harbour the combination of the del(17p) and *TP53* mutation. The other 587 MM cases corresponded with those patients who did not present biallelic inactivation of *TP53* or whose scores were less than the selected threshold ('other patients' group) (Figure 2B).

Clinical and biological characteristics of the DH-*TP53*-like group

No statistically significant differences in age, gender and Eastern Cooperative Oncology Group (ECOG) performance status were found between the DH-*TP53* and DH-*TP53*-like groups defined by the score, or between them and the other patients. On the contrary, we detected higher levels of leucocytes, creatinine, beta-2-microglobulin, C-reactive protein and lactate dehydrogenase in the DH-*TP53*-like group than in the 'other patients' group ($p < 0.05$, Table S1).

Considering the most frequent cytogenetic abnormalities observed in MM, we found that t(14;16) was present in 12% (6/50) of the DH-*TP53*-like patients compared with 3% (20/587) of cases included in the 'other patients' group (post-hoc adjusted $p = 0.035$). 1q gain was significantly more frequent in the DH-*TP53*-like group than in the other patients in the population, including those of the DH-*TP53* group ($p = 0.001$). To further analyse 1q gains, we distinguished between 1q gain and 1q amplification (≥4 copies). The *post-hoc* test showed a significantly higher proportion of 1q amplification in the DH-*TP53*-like group compared to the 'other patients' group (16% vs 5%, *post-hoc* adjusted $p = 0.013$), while no statistical differences for 1q gain alone were observed between both groups (Figure S2). Patients with 1p deletion were also enriched in the DH-*TP53*-like group in comparison to the 'other patients' group (50% vs 24%, *post-hoc* adjusted $p < 0.001$). It is noteworthy that no statistically significant differences in the proportion of patients with del(17p) were observed between the DH-*TP53*-like and the 'other patients' groups. The other cytogenetic abnormalities

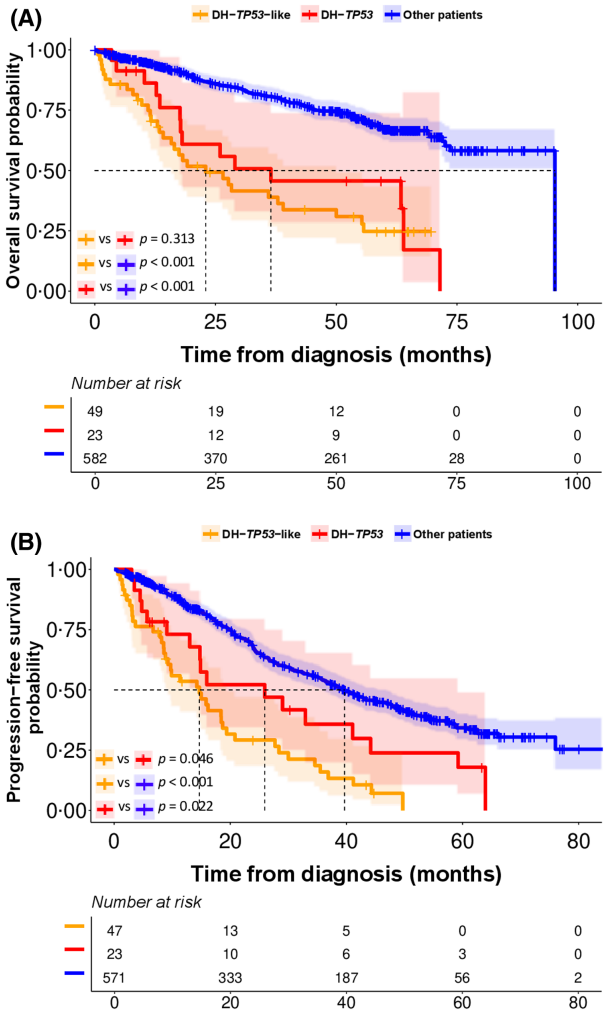


FIGURE 4 Prognosis of the double-hit (DH)-*TP53* and DH-*TP53*-like groups. Probability of overall survival (A) and progression-free survival (B), according to the group defined by the score and DH-*TP53* condition. The log-rank (Mantel–Cox) test p values are shown. [Colour figure can be viewed at wileyonlinelibrary.com]

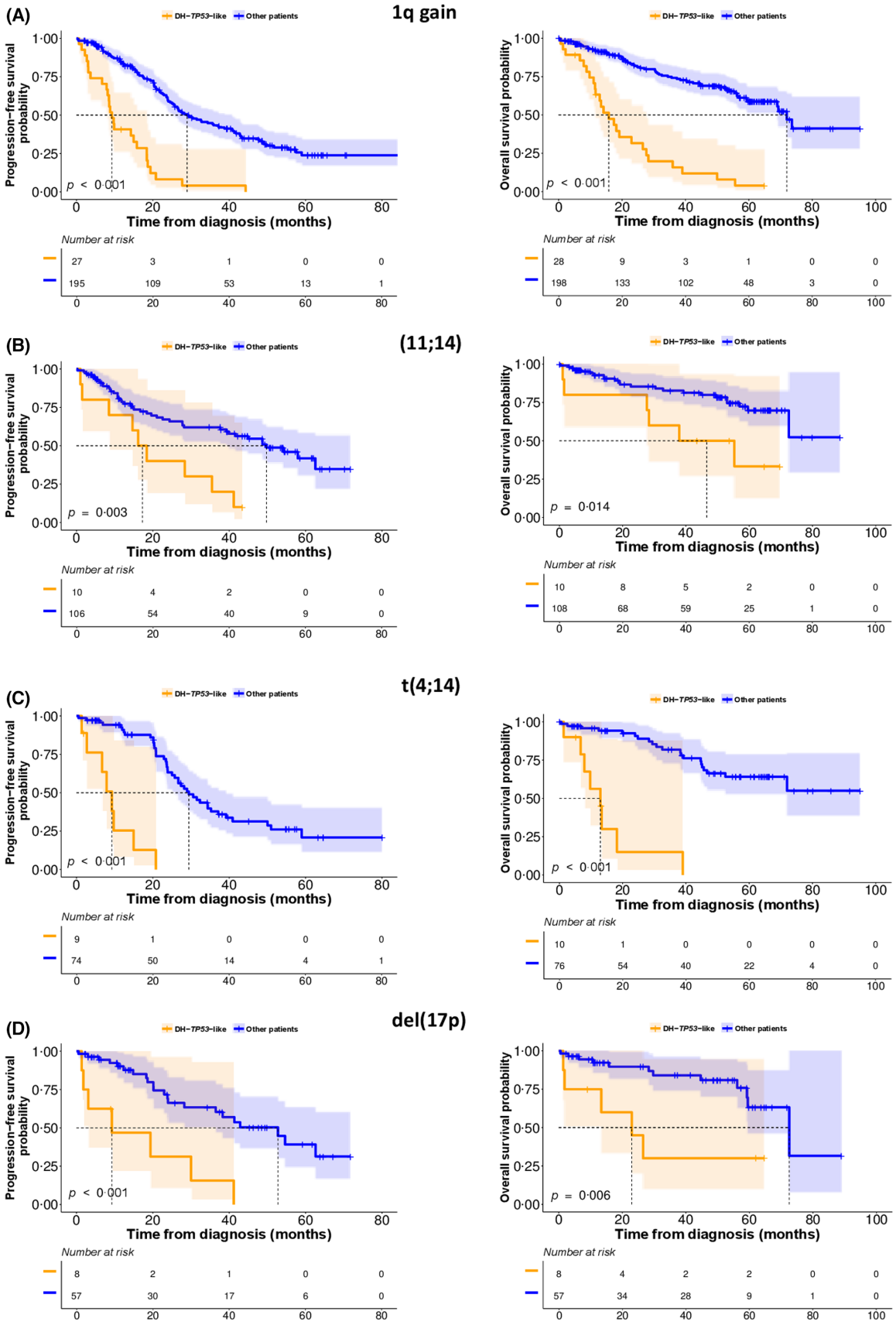


FIGURE 5 Prognosis of cytogenetic abnormalities according to whether patients belong to the double-hit (DH)-*TP53*-like group or not. Probability of progression-free survival and overall survival in the group of patients with 1q gain (A), t(11;14) (B), t(4;14) (C) and del(17p) (D). The log-rank (Mantel–Cox) test *p* values are shown. [Colour figure can be viewed at wileyonlinelibrary.com]

were equally distributed across the DH-*TP53*, the DH-*TP53*-like and the 'other patients' groups (Figure 3A; Table S1).

We next analysed the distribution of the most prevalent mutated genes across the three groups. None of the DH-*TP53*-like patients had any *TP53* non-synonymous mutation, although 4% (2/50) of them harboured other types of *TP53* mutations. Conversely, the DH-*TP53*-like group was enriched for *MAX* mutations relative to the 'other patients' group (*post-hoc* adjusted $p = 0.028$). We also noticed that none of the DH-*TP53* patients had mutations of the *NRAS* gene (Figure 3B).

Prognostic value of DH-*TP53* score

DH-*TP53* caused by combination of the del(17p) and *TP53* mutations had a significantly negative impact on survival (Figure 4). On the other hand, the DH-*TP53*-like group defined by the score had a significantly shorter OS [hazard ratio (HR) 4.07, 95% confidence interval (CI) 2.76–5.98; adjusted $p < 0.001$]and PFS [HR 3.44, 95% CI, 2.46–4.81; adjusted $p < 0.001$] than those without this DH-*TP53* gene expression pattern (Figure 4). The PFS for the DH-*TP53*-like group was even worse than that described for the DH-*TP53* group [HR 1.83, 95% CI, 1.00–3.35; $p = 0.046$] (Figure 4B).

In order to gain more insight into the prognostic value of the *TP53* score, we carried out a survival analysis for the most frequent cytogenetic abnormalities, 1q gain, t(11;14), t(4;14) and del(17p), stratifying samples according to whether they belonged to DH-*TP53*-like group or not. We observed that survival for any of the cytogenetic abnormalities was significantly shortened in the DH-*TP53*-like group ($p < 0.05$) (Figure 5).

We also investigated the impact of the DH-*TP53*-like group on the risk stratification according to International Staging System (ISS). The DH-*TP53*-like group combined with ISS III had a median PFS and OS of 11 and 17 months respectively, whereas for the rest of patients with ISS III median PFS and OS were of 28 and 59 months respectively ($p < 0.001$). Likewise, median PFS and OS of patients with ISS I/II were reduced from 47 and 95 months to 19 and 50 months respectively ($p < 0.001$) when the patients belonged to the DH-*TP53*-like group (Figure 6).

We performed a multivariable Cox model including the DH-*TP53*-like group defined by our score, the age at diagnosis and the well-established high-risk prognostic factors in MM, ISS, high-risk cytogenetic abnormalities and DH-*TP53* group. The DH-*TP53*-like group was selected as an independent factor for PFS with the highest HR [HR 3.84, 95% CI 2.51–5.88; $p < 0.001$] along with the DH-*TP53* group, age, ISS stage III and 1q gain. The negative impact of the DH-*TP53*-like group was also maintained in the Cox model for OS [HR 3.32, 95% CI, 2.31–4.77; $p < 0.001$] (Figure 7).

Validation of the DH-*TP53* score

Finally, we externally validated the DH-*TP53* score in two previously published series: GSE4581 ($n = 414$) and

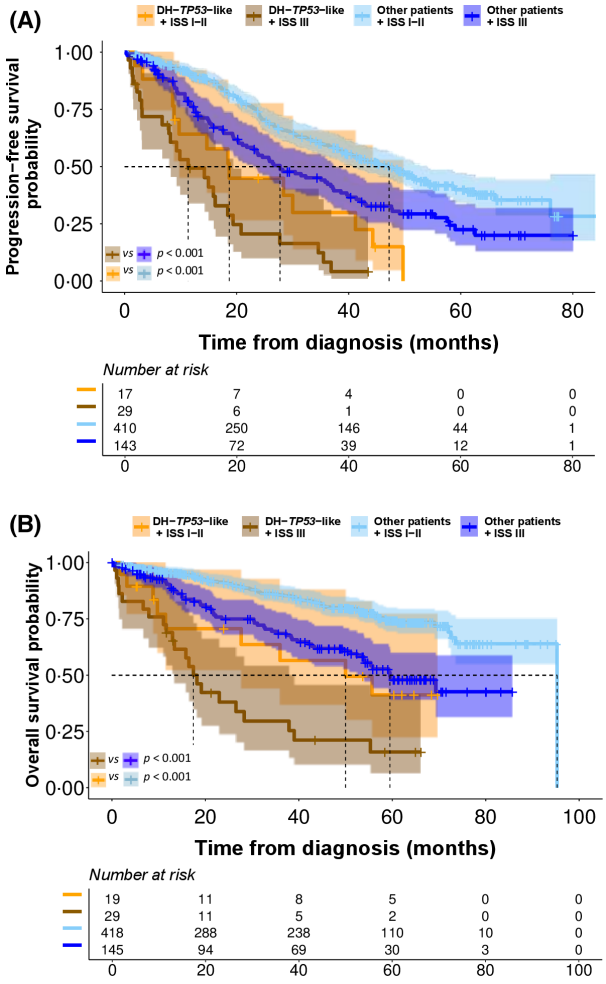


FIGURE 6 Prognosis of the double-hit (DH)-*TP53*-like group according to International Staging System (ISS) index. Probability of progression-free survival (A) and overall survival (B) in the DH-*TP53*-like group and the other patients (excluding DH-*TP53* patients) when combined with ISS stage. The log-rank (Mantel–Cox) test *p* values are shown. [Colour figure can be viewed at wileyonlinelibrary.com]

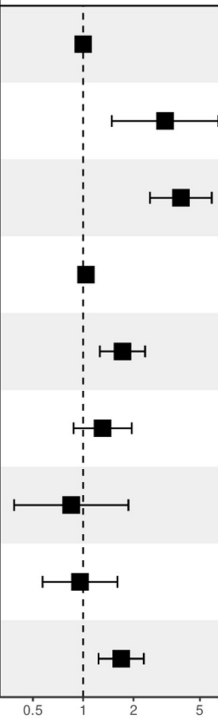
GSE136400 ($n = 436$). Both series included microarray gene expression data from NDMM patients. Using these microarray data, we identified 68 and 63 out of the 78 genes of the DH-*TP53* score, respectively, which were then used to calculate the score. The survival analysis of these two series clearly showed two curves whose separation widened as the cut-off value decreased. Thus, patients with a higher score, between 5% and 25% of the validation cohort, in both datasets showed a particularly adverse prognosis compared with the other patients ($p < 0.001$; Figure S3).

DISCUSSION

TP53 abnormalities, although uncommon at the time of diagnosis, remain one of the most important prognostic factors in MM patients, especially when del(17p) and *TP53* mutation are present together. p53 might be inactivated by other mechanisms, as has been described in other lymphoid

(A) Progression-free survival (PFS)

Variable		N	Hazard ratio	p
Group	Other patients group	565		Reference
	DH-*TP53* group	23	3·09 (1·48, 6·45)	0·003
	DH-*TP53*-like group	48	3·84 (2·51, 5·88)	<0·001
Age		636	1·04 (1·03, 1·06)	<0·001
ISS		636	1·72 (1·26, 2·35)	<0·001
t(4;14)		636	1·31 (0·88, 1·95)	0·188
t(14;16)		636	0·85 (0·39, 1·86)	0·683
del(17p)		636	0·96 (0·57, 1·60)	0·869
1q gain		636	1·69 (1·24, 2·31)	0·001



(B) Overall survival (OS)

Variable		N	Hazard ratio	p
Group	Other patients group	553		Reference
	DH-*TP53* group	23	1·98 (1·07, 3·66)	0·030
	DH-*TP53*-like group	46	3·32 (2·31, 4·77)	<0·001
Age		622	1·03 (1·02, 1·04)	<0·001
ISS		622	1·42 (1·12, 1·81)	0·004
t(4;14)		622	1·39 (1·03, 1·88)	0·033
t(14;16)		622	1·32 (0·79, 2·20)	0·289
del(17p)		622	0·92 (0·62, 1·37)	0·679
1q gain		622	1·36 (1·08, 1·72)	0·010

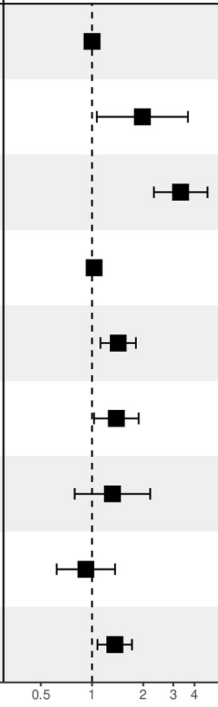


FIGURE 7 Multivariable analysis of PFS and OS. Forest plot of multivariable Cox proportional-hazards models for progression-free survival (A) and overall survival (B) with the hazard ratio for each of the factors included: groups defined by double-hit (DH)-*TP53* score, age [as a continuous variable (years)], ISS III vs I/II, presence of t(4;14), t(14;16), del(17p) and 1q gain. The *p* values for each factor are shown.

malignancies.[16] In order to ascertain this possibility, we searched for the presence of the transcriptional signature associated with DH-*TP53* in NDMM patients who did not present these DNA alterations. Expression signatures of *TP53* status have been defined in solid tumours.[17,18] In MM, previous studies have identified differentially expressed genes related to *TP53* expression[19] and a p53 target gene signature associated with *TP53* gene aberrations.[7] Recently, the impact of the biallelic inactivation of *TP53* on gene expression has been analysed.[8] The novelty of our study is to demonstrate that there are MM patients with very unfavourable prognosis who have a transcriptional signature like that of patients with DH-*TP53*, but without having these *TP53* abnormalities. Strikingly, this DH-*TP53*-like group showed even shorter PFS than DH-*TP53* patients, considered as ultra-high-risk patients.[6]

It should be noted that 60% of patients belonging to DH-*TP53*-like group were classified into ISS stage III, compared to approximately 30% of the DH-*TP53* and 'other patients' groups. This reflects the high tumour mass and renal function impairment observed in DH-*TP53*-like patients and highlights the validity of ISS in discriminating high-risk patients,[20] even after the introduction of novel agents. Nonetheless, in the multivariable Cox model, the DH-*TP53*-like group maintained its independent negative impact on survival.

Cytogenetic alterations do not seem to be the cause of the poor outcomes associated with DH-*TP53*-like group, as the distribution of International Myeloma Working Group (IMWG)-defined high-risk cytogenetic abnormalities[21] was similar to that found in the 'other patients' group. In fact, the adverse prognosis of the patients included in the DH-*TP53*-like group was not properly captured by the revised ISS (R-ISS),[22] since up to 67% of DH-*TP53*-like patients were not classified as high-risk patients. On the other hand, it is noteworthy that patients with 1q gain, at the expense of 1q amplification, and 1p deletion were overrepresented in the DH-*TP53*-like group. In fact, 1q gain was identified as an independent prognostic factor in the multivariable analysis, as has recently been reported in the analysis baseline cohort of the CoMMpass study.[23]

More importantly, the combination of DH-*TP53*-like group and ISS stage significantly improved prediction of outcome in MM. The median OS dropped from 59 months for patients with ISS III to 17 months for patients with ISS III that belonged to DH-*TP53*-like group.

Despite del(17p) being one of the most consistent high-risk cytogenetic abnormalities included in the main risk stratification models, its negative impact is not observed in some MM patients. In this context, different approaches, such as a higher cut-off value for del(17p)[24] and biallelic inactivation of the *TP53* gene,[6] have been published in an attempt to distinguish those patients with del(17p) who have extremely poor outcome. One of the contributions of work in this regard is that among the patients with del(17p) it is possible to identify a subgroup without *TP53* mutations that have a prognosis as poor as that of the patients with *TP53* biallelic inactivation. Furthermore, our DH-*TP53* score refined the prognostic value not only of other cytogenetic abnormalities associated with poor outcome, such as 1q gain and t(4;14), but also of t(11;14), which has usually been linked to favourable outcomes in MM. Thus, patients with 1q gain, t(4;14) or t(11;14) who simultaneously belonged to the DH-*TP53*-like group had a significantly shorter PFS and OS.

An interesting finding emerged when the frequency of the most common point mutations in MM was assessed according to the presence of DH-*TP53* signature. A significantly greater proportion of *MAX* gene mutations was observed in DH-*TP53*-like patients. Loss of function of *MAX* in MM patients has been associated with the proliferative subtype.[23] The enrichment of *MAX* mutations in DH-*TP53*-like patients, who experience a particularly poor outcome, deserves to be investigated extensively. A significantly higher proportion of *NRAS* mutations in the DH-*TP53*-like group was also found.

Taken together, these results emphasize the importance of the transcriptomic deregulation associated with the biallelic inactivation of *TP53* in the identification of high-risk patients. The functional analysis of some of the 78 genes included in the score might provide new insight into the role of *TP53* dysfunction in MM pathogenesis. Additionally, the development of a simplified gene signature, which can be assessed by techniques more standardized in the clinical setting, such as RT-PCR, could help to confirm its prognostic value and to implement a gene expression score in order to identify this set of high-risk patients.

In summary, the DH-*TP53* and DH-*TP53*-like groups share the same transcriptional signature, although the biallelic inactivation of *TP53* is only present in the former group. There are at least two possible explanations for this finding. One is that the activity of p53 is attenuated by mechanisms other than DNA alterations, like overexpression of negative regulators; the other explanation is that the combination of other genetic alterations leads to the deregulation of transcriptional pathways that can be superimposed on those deregulated by the biallelic inactivation of *TP53*.[25,26] The similarities between the transcriptional pathways deregulated by the biallelic inactivation of *TP53* and those deregulated by chromosome 1 abnormalities deserve further studies. Hence, the DH-*TP53* score described in this study could be a useful tool for identifying MM patients with p53 dysfunction, bearing in mind that a portion of these patients are not evidenced through FISH and DNA sequencing analysis.

AUTHOR CONTRIBUTIONS

Cristina De Ramón carried out the statistical analysis, helped design the study and wrote the manuscript; Elizabeta A. Rojas helped with the statistical analysis; Ignacio J. Cardona-Benavides helped prepare the figures; Maria-Victoria Mateos helped with data interpretation; Luis A. Corchete designed the research, performed the bioinformatic analysis, created the figures and wrote the manuscript; Norma C. Gutiérrez conceived the idea and helped design the research, supervised the entire study, wrote the manuscript and provided funding; and all authors reviewed and approved the manuscript.

ACKNOWLEDGEMENTS

This work has been supported by grants from the Instituto de Salud Carlos III (ISCIII) co-funded by European Union FEDER funds (projects PI16/01074 and PI19/00674), the Asociación Española Contra el Cáncer (grant PROYE20047GUTI) and the Gerencia Regional de Salud, Junta de Castilla y León (grants GRS 2058/A/19 and GRS 2331/A/21). Cristina De Ramón, Elizabeta A. Rojas and Ignacio J. Cardona-Benavides have been supported by the Asociación Española Contra el Cáncer (CLJUN18010DERA), the Consejería de Educación de Castilla y León and the Instituto de Salud Carlos III (PFIS-2020: FI20/00226), respectively. The authors thank the MMRF for access to the CoMMpass dataset. The authors would also like to thank Phil Mason for his help in reviewing the English language of the manuscript.

CONFLICT OF INTEREST

Maria-Victoria Mateos receives honoraria and speakers' bureau compensation from Janssen and Celgene, Onyx, Takeda, Novartis, and Bristol-Myers Squibb, unconnected with the submitted work. Norma C. Gutiérrez receives honoraria from Janssen that are unconnected with the work presented here. All the other authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the MMRF CoMMpass study. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available at https://research.themmrf.org/ with the permission of MMRF.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: De Ramón C, Rojas EA, Cardona-Benavides IJ, Mateos M-V, Corchete LA & Gutiérrez NC. Transcriptional signature of *TP53* biallelic inactivation identifies a group of multiple myeloma patients without this genetic condition but with dismal outcome. Br J Haematol. 2022;199(3):344–354. https://doi.org/10.1111/bjh.18410