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TO THE EDITOR:

Prognostic value and oncogenic landscape of *TP53* alterations in adult and pediatric T-ALL

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Among hematologic malignancies, T-cell acute lymphoblastic leukemia (T-ALL) represents a class of aggressive tumors with dismal clinical outcome in cases of relapsed or refractory disease. Although the intensification of multiagent chemotherapy protocols has dramatically improved prognosis, refractory and relapsed cases are clinically challenging because of limited therapeutic options.[1,2] p53 is a transcription factor and a master tumor suppressor gene frequently altered in cancer.[3] In contrast to carcinomas and other hematologic malignancies, *TP53* alterations (*TP53*^{Alt}), encompassing mutations (*TP53*^{Mut}), and/or pan-exon deletions (*TP53*^{Del}) are remarkably rare at diagnosis in T-ALL, and their clinical implication remains elusive.[4-6] Critically, *TP53*^{Alt} have been reported to be acquired in up to 20% of the relapsed T-ALL cases, where they convey a deleterious prognosis.[7-9] Here, we produce the first comprehensive analysis of *TP53*^{Alt} and the associated oncogenetic landscape in an extensive cohort of 476 patients newly diagnosed with T-ALL.

We investigated the clinical characteristics of *TP53*^{Alt} in 476 patients including 215 adults and 261 children. Adult patients were enrolled in the GRAALL-2003-2005 trial (GRAALL-2003, #NCT00222027; GRAALL-2005, #NCT00327678), and pediatric patients were enrolled in the FRALLE 2000 trial (supplemental Figure 1, available on the *Blood* website). Based on the DNA availability for molecular analysis, 215 adult patients out of 337 and 261 pediatric patients out of 427 were included in this study. No difference in clinical outcomes was observed between the included patients and the entire cohort (supplemental Figures 2 and 3; supplemental Table 1). Diagnostic peripheral blood or bone marrow samples were collected after informed consent was obtained, according to the Declaration of Helsinki. All samples contained ≥80% blasts, immunophenotypic of T-ALL samples, minimal residual disease (MRD) assessment, and multiplex ligation–dependent probe amplification analysis (P383 T-ALL, MRC Holland) were performed as previously described.[10-12]

Genomic analysis was performed using pan-exon targeted next-generation sequencing of DNA extracted from diagnostic samples, and DNA libraries were prepared using the Nextera XT kit (Illumina) and sequenced on a MiSeq (Illumina). The next-generation sequencing panel included 63 genes known to be mutated in T-ALL (supplemental Table 2). Genetic lesion co-occurrences and mutual exclusions were computed using the DISCOVER R package. We performed a computational approach previously described for the detection of copy number variants from next-generation sequencing data,[13,14] including a systematic analysis of the depth of *TP53* gene coverage. This method is based on variations in the depth of coverage of the aligned sequence reads using a locally developed algorithm. The copy number variants detected were confirmed by high-resolution comparative genomic hybridization and/or multiplex ligation–dependent probe amplification analysis (kits P037-CLL-1 and P038-CLL-2, MRC Holland). Diagnostic DNA was hybridized on a Cytogenetics Whole-Genome 2.7M Array (Affymetrix, Santa Clara, CA) (comparative genomic hybridization array), according to the manufacturer's recommendations. Data analysis was performed using Chromosome Analysis Suite software (Affymetrix). Gene copy number aberrations were compared with the Database of Genomic Variants[15] to study only somatic aberrations.

Comparisons of categorical and continuous variables between subgroups were performed using Fisher exact test and the Mann-Whitney test, respectively. Overall survival (OS) was calculated from the date of diagnosis to the last follow-up date,

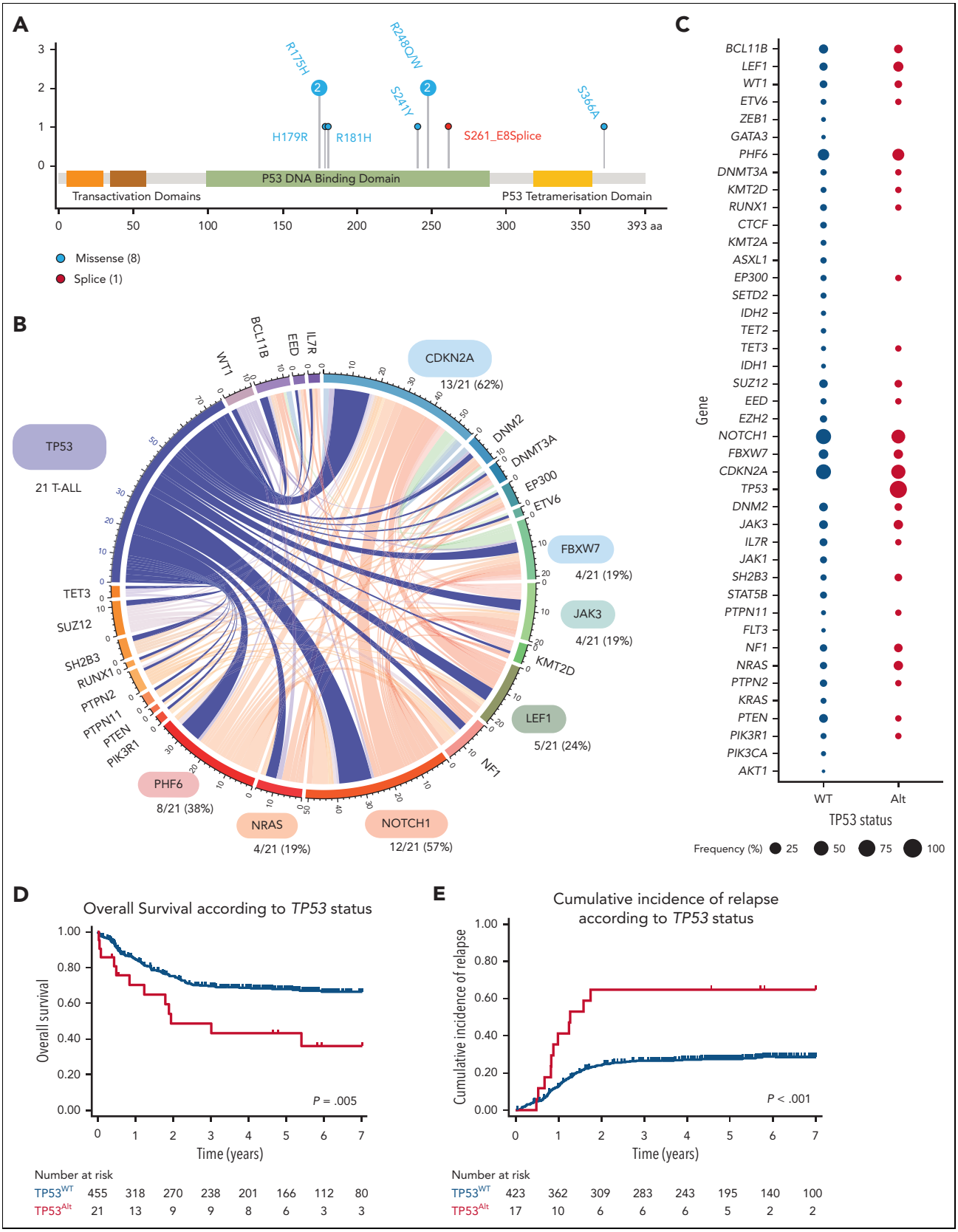

Figure 1. *TP53* alterations in the GRAALL03/05 and FRALLE2000 studies. (A) Lollipop plots indicating *TP53* mutations in 476 patients with T-ALL. More details on the pathogenicity of the *TP53* mutations are provided in supplemental Table 4. (B) Circos plots illustrating pairwise relationships across relatively common mutated genes in $TP53^{Alt}$ T-ALL. The width of the ribbon corresponds to the number of cases with the simultaneous presence of a first and second gene mutation. (C) Frequency of alterations per gene in $TP53^{Alt}$ vs $TP53^{WT}$ T-ALL. The width of the circles is proportional to the frequency of alterations observed in the 2 T-ALL subgroups ($TP53^{Alt}$ in red vs $TP53^{WT}$ T-ALL in blue). (D-E) Clinical impact of $TP53^{Alt}$ in the GRAALL0305 and FRALLE2000 studies. OS (D) and CIR (E) are shown. The red curve represents patients with $TP53^{Alt}$ T-ALL and the blue curve represents patients with $TP53^{WT}$.

Table 1. Clinicobiological and outcome characteristics of adult and pediatric T-ALL (GRAALL and FRALLE protocols) according to *TP53* status

Variable	*TP53*^{Alt} n = 21 (4%)	*TP53*^{WT} n = 455 (96%)	Total N = 476	*P* value*
Male (%)	14/21 (67)	343/455 (75)	357/476 (75)	.4
Age, y†	23.4 (4.0-51.8)	15.3 (1.1-59.1)	15.3 (1.1-59.1)	.5
WBC, g/L†	25 (5-674)	66 (0-980)	64 (0-980)	**.01**
CNS involvement (%)‡	3/21 (14)	48/453 (11)	51/474 (11)	.5
Immunophenotype (%)				
Early thymic precursor phenotype	6/16 (38)	50/291 (17)	56/307 (18)	.09
Immature (IM0/δ/γ)§	8/20 (40)	81/399 (20)	89/419 (21)	**.048**
αβ lineage	6/20 (30)	205/399 (51)	211/419 (50)	.07
Mature TCRγδ	3/20 (15)	63/399 (16)	66/419 (16)	>.9
Oncogenetic classification (%)				
TLX1	1/18 (6)	53/397 (13)	54/415 (13)	.5
TLX3	2/18 (11)	70/397 (18)	72/415 (17)	.8
SIL-TAL1	1/18 (6)	56/397 (14)	57/415 (14)	.5
CALM-AF10	0/18 (0)	13/397 (3)	13/415 (3)	>.9
High-risk classifier‖	13/21 (62)	196/455 (43)	209/476 (44)	.12
Treatment response (%)				
Prednisone response	13/21 (62)	246/446 (55)	259/467 (55)	.7
Chemosensitivity	12/21 (57)	325/446 (73)	337/467 (72)	.1
MRD1 >10^{-4}	9/12 (75)	114/328 (35)	123/340 (36)	**.01**
Complete remission	17/21 (81)	423/455 (93)	440/476 (92)	.07
Allo-HSCT	4/20 (20)	97/436 (22)	101/456 (22)	.7
Outcome, %				
5-y CIR (95% CI)	65 (11-43)	27 (23-32)	29 (25-33)	**<.001**
5-y OS (95% CI)	48 (26-67)	72 (68-76)	71 (67-75)	**.005**

	Univariate and multivariate analysis¶					
	Univariate			Multivariate		
	Specific HR	95% CI	*P* value	Specific HR	95% CI	*P* value
CIR						
Age, y	1.01	0.98-1.03	.57	—	—	—
CNS	1.57	0.85-2.59	.08	1.28	0.77-2.13	.34
Log (WBC)	1.62	1.2-2.18	**.002**	1.62	1.19-2.19	**.002**
Prednisone response	0.67	0.47-0.95	**.03**	0.93	0.64-1.35	.70
High-risk classifier§	2.78	1.94-3.99	**<.001**	2.58	1.78-3.74	**<.001**
TP53^{Alt}	3.11	1.67-5.78	**<.001**	2.90	1.55-5.44	**.001**

MRD1 correspond to MRD evaluation after induction and was performed by allele-specific oligonucleotides polymerase chain reaction. TCR status and oncogenic were performed as described in supplemental Methods.

P < .05 are indicated in bold.

allo-HSCT, allogeneic hematopoietic stem cell transplantation; CNS, central nervous system; WBC, white blood count.

*Statistical tests performed: Fisher exact test and Wilcoxon rank-sum test.

†Statistics presented: median (minimum-maximum).

‡CNS involvement: CNS3 in FRALLE2000 trial, CNS2 and/or CNS3 in GRAALL2003 and GRAALL2005 trial.

§T-ALL are divided into 3 subclasses as following: (1) immature (no detectable TCRβ variable diversity joining): IM0 (TCRδ and TCRγ germ line), IMδ (TCRδ rearranged but not TCRγ), and IMg (both TCRδ and TCRγ rearranged); (2) T-ALL with TCRαβ lineage (including both early-cortical IMb/pre-αβ and mature sTCRαβ$^+$); and (3) mature sTCRγδ.[12]

‖Low-risk classifier: *NOTCH1* and/or *FBXW7* (*N/F*) mutation without *N/K-RAS* and *PTEN* (*R/P*) alteration. High-risk classifier: *N/F* mutation with *R/P* alteration, *N/F* WT with or without *R/P* alteration.[10,16]

¶Univariate and multivariate Cox analyses stratified on protocol.

Table 1 (continued)

	Univariate and multivariate analysis¶					
	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
OS						
Age	1.03	1.01-1.05	**.001**	1.05	1.03-1.07	**<.001**
CNS	2.00	1.28-3.14	**.002**	1.64	1.02-2.64	**.04**
Log (WBC)	1.99	1.48-2.67	**<.001**	2.01	1.51-2.86	**<.001**
Prednisone response	0.54	0.38-0.76	**<.001**	0.83	0.57-1.20	.31
High-risk classifier	2.93	2.06-4.17	**<.001**	2.90	2.01-4.18	**<.001**
$TP53^{Alt}$	2.34	1.30-4.24	**.005**	2.87	1.56-5.26	**.001**

MRD1 correspond to MRD evaluation after induction and was performed by allele-specific oligonucleotides polymerase chain reaction. TCR status and oncogenic were performed as described in supplemental Methods.

P < .05 are indicated in bold.

allo-HSCT, allogeneic hematopoietic stem cell transplantation; CNS, central nervous system; WBC, white blood count.

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‖ Low-risk classifier: *NOTCH1* and/or *FBXW7* (*N/F*) mutation without *N/K-RAS* and *PTEN* (*R/P*) alteration. High-risk classifier: *N/F* mutation with *R/P* alteration, *N/F* WT with or without *R/P* alteration.[10,16]

¶Univariate and multivariate Cox analyses stratified on protocol.

censoring patients alive. The cumulative incidence of relapse (CIR) was calculated from the complete remission date to the date of relapse, and censoring patients alive without relapse at the last follow-up date. Relapse and death in complete remission were considered to be competitive events. Univariate and multivariate analyses to assess the impact of categorical and continuous variables were performed using the Cox model. The proportional-hazards assumption was checked before conducting the multivariate analyses. In the univariate and multivariate analyses, age and log10 (white blood count) were considered continuous variables. All the analyses were stratified during the trial. Variables with $P < .1$ in univariate analysis were included in the multivariable models. Statistical analyses were performed using the STATA software (STATA 12.0 Corporation, College Station, TX). All *P* values were 2-sided, with $P < .05$ denoting statistical significance. Additional details are included in the supplemental Methods.

The incidence of $TP53^{Alt}$ at the time of diagnosis in this cohort was 4% (21/476). $TP53^{Mut}$ was detected in 9 patients (6 adults and 3 pediatric cases) (Figure 1A; supplemental Tables 3 and 4), $TP53^{Del}$ was identified in 15 patients (7 adult and 8 pediatric cases), and 3 patients harbored both $TP53^{Mut}$ and $TP53^{Del}$. Patients with $TP53^{Alt}$ did not significantly differ from patients with *TP53* wild-type ($TP53^{WT}$) regarding sex, age, and central nervous system involvement (Table 1), but were associated with an immature phenotype (combining IM0 T-ALL; T-cell receptor δ [TCRδ] and TCRγ germ line, IMδ T-ALL; TCRδ rearranged but not TCRγ and IMg T-ALL; both TCRδ and TCRγ rearranged)[12] (8/20 [40%] vs 81/399 [20%], $P = .048$). The oncogenetic landscape of $TP53^{Alt}$ was comparable to that of $TP53^{WT}$ T-ALLs (Figure 1B-C; supplemental Figures 4-6; supplemental Table 5). To investigate the prognostic value of $TP53^{Alt}$, survival analyses were performed on the series of 476 patients. $TP53^{Alt}$ did not confer an increased poor prednisone response, defined by a peripheral blood blast count >1.0 × 10^9/L at the end of the induction phase (38% vs 45%, $P = .7$) (Table 1). Although $TP53^{Alt}$ did not significantly influence the morphological complete response rate at the end of the induction course (81% vs 93%, $P = .07$), patients harboring $TP53^{Alt}$ were associated with delayed early medullary blast clearance, as confirmed by the end of induction MRD1 assessment, with more positivity (≥10^{-4}) in $TP53^{Alt}$ than in $TP53^{WT}$ cases (75% vs 35%, $P = .01$). Patients (both adult and pediatric) with $TP53^{Alt}$ had an inferior outcome compared with $TP53^{WT}$ (Table 1; Figures 1D-E; supplemental Figure 7), with an increased CIR (5-year CIR: 65% vs 27%; specific hazard ratio [HR], 3.1; 95% confidence interval [CI], 1.67-5.78; $P < .001$) and a shorter OS (5-year OS: 48% vs 72%; HR, 2.34; 95% CI, 1.30-4.24; $P = .005$). In multivariate analysis, $TP53^{Alt}$ predicted a statistically lower OS (HR, 2.87; 95% CI, 1.56-5.26; $P = .001$) and higher CIR (specific HR, 2.90; 95% CI, 1.55-5.44; $P = .001$) even after adjustment on the 4 genes *NOTCH1/FBXW7/RAS/PTEN* (*NFRP*) classifier, which identified patients with a poor prognosis in both GRAALL and FRALLE trials.[10,16]

The limited number of MRD1 assessments available for patients with $TP53^{Alt}$ T-ALL (12/21, 57%) did not allow us to include this end point in the multivariate analysis, justifying further studies to establish whether this alteration remains an independent prognostic factor when combined with MRD1 status in T-ALL.

This study provides the largest comprehensive analysis of $TP53^{Alt}$ in T-ALL, describing, for the first time, their clinical profile and, most importantly, the extremely poor prognostic impact associated with $TP53^{Alt}$ at diagnosis in T-ALL, urging the

need to develop innovative targeted therapies for patients harboring *TP53*^{Alt}.

Approximately 25% of pediatric patients and 50% of adult patients with T-ALL relapse, with a 5-year survival rate of less than 20% in both age groups.[1,2] The sole therapeutic approaches with curative potential for T-ALL relapsed cases are limited to conventional chemotherapy or hematopoietic stem cell transplantation. Molecular genetic analyses and sequencing studies have recently led to the identification of recurrent T-ALL alterations associated with prognosis, allowing for the refinement of the stratification of relapse risk.[10,14,17,18] However, a significant proportion of T-ALL relapses remain unpredicted, underlining the need for new predictive markers.

Negative outcomes observed in *TP53*^{Alt} T-ALL are likely to be related to p53-induced therapeutic resistance previously described for other malignancies, combined with loss of p53 tumor suppressor activity and acquisition of novel functions that disrupt the DNA damage response pathway.[19,20] APR-246 (eprenetapopt), a small molecule interacting with mutated p53 protein to restore its WT conformation,[21,22] has recently shown promising results in myeloid malignancies and B-cell ALL,[23-26] justifying further studies to explore the potential efficacy of this new drug in T-ALL *TP53*^{Mut}.

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Authorship

Contribution: V.A., O.H., M.S., and G.P.A. conceived and designed the research and oversaw the project; M.B., C.G., N.G., J.-M.C., F.H., Y.C., Y.L.B., E.M., V.G., A.P., P.R., A.B., D.B., O.H., N.B., and V.A. provided study materials or patients; M.S., G.P.A., G.H., L.C., and V.A. performed molecular analyses; M.S. and G.P.A. collected and assembled data; N.B. and M.S. performed statistical analysis; M.S., G.P.A., R.B., O.H., V.A., and N.B. analyzed and interpreted data; and M.S., G.P.A., N.B., and V.A. wrote the manuscript.

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Footnotes

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Data are available on request from the corresponding author, Vahid Asnafi (vahid.asnafi@aphp.fr).

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TO THE EDITOR:

Diffuse myocardial fibrosis occurs in young patients with sickle cell anemia despite early disease-modifying therapy

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We read with great interest the recent report from Niss et al.[1] Our group has recently reviewed data from a similar population at our institution, which does not support the conclusion of Niss et al that diffuse myocardial fibrosis is prevented by early initiation of disease-modifying therapy (DMT).

Cardiovascular complications are the leading cause of early mortality in patients with sickle cell anemia (SCA).[2] Yet, the pathobiology of sickle cell cardiomyopathy is incompletely understood and likely multifactorial.[3] Chronic anemia leads to global cardiac enlargement and myocardial hypertrophy. Global cardiac chamber dilation is a common feature in patients with SCA, and enlarged left atrial (LA) volume is a marker of diastolic dysfunction in SCA.[4] Repetitive microvascular ischemic insults and associated reperfusion injury may contribute to diffuse myocardial fibrosis and myocardial remodeling in individuals with SCA.[5-7]

Cardiovascular magnetic resonance (CMR) imaging is the only noninvasive method capable of accurately and reproducibly assessing heart size and function as well as characterizing the myocardium. Emerging data suggest that patients with SCA develop diffuse myocardial fibrosis,[1,5-7] detected by quantifying the myocardial extracellular volume (ECV). Increased ECV fraction correlates strongly with histologically quantified myocardial fibrosis.[8] Our goal was to estimate the prevalence of diffuse myocardial fibrosis in a cohort of young individuals with SCA.

At our institution, all patients with SCA undergo cardiac surveillance starting at 16 years of age, which comprises a clinical assessment by a cardiologist and an echocardiogram. The presence of LA dilation (LA volume > 34 mL/m^2), left ventricular dilation, or prominent trabeculations seen by echocardiogram led to patients being referred for CMR (detailed echocardiographic data in supplemental Table 1, on the *Blood* website). We performed a retrospective chart review of pediatric and young adult patients with SCA who underwent CMR at our institution between 2020 and 2021. Demographic and clinical information was obtained from reviewing the electronic medical record. A waiver of the requirement for informed consent was granted by the institutional review board for use of deidentified data.

CMR was performed on a 1.5T scanner (Avanto Fit; Siemens Medical Solutions, Inc, Erlangen, Germany). The protocol