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ORIGINAL COMMUNICATION

Unveiling the *SOD1*-mediated ALS phenotype: insights from a comprehensive meta-analysis

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Abstract

Background and objectives Amyotrophic lateral sclerosis associated with mutations in *SOD1* (*SOD1*-ALS) might be susceptible to specific treatment. The aim of the study is to outline the clinical features of *SOD1*-ALS patients by comparing them to patients without ALS major gene variants and patients with variants in other major ALS genes. Defining *SOD1*-ALS phenotype may assist clinicians in identifying patients who should be prioritized for genetic testing.

Methods We performed an extensive literature research including original studies which reported the clinical features of *SOD1*-ALS and at least one of the following patient groups: *C9ORF72* hexanucleotide repeat expansion (*C9*-ALS), *TARDBP* (*TARDBP*-ALS), *FUS* (*FUS*-ALS) or patients without a positive test for a major-ALS gene (N-ALS). A random effects meta-analytic model was applied to clinical data extracted encompassing sex, site and age of onset. To reconstruct individual patient survival data, the published Kaplan–Meier curves were digitized. Data were measured as odds ratio (OR) or standardized mean difference (SMD) as appropriate. Median survival was compared between groups.

Results Twenty studies met the inclusion criteria. We identified 721 *SOD1*-ALS, 470 *C9*-ALS, 183 *TARDBP*-ALS, 113 *FUS*-ALS and 2824 N-ALS. *SOD1*-ALS showed a higher rate of spinal onset compared with N-ALS and *C9*-ALS (OR = 4.85, 95% CI = 3.04–7.76; OR = 10.47, 95% CI = 4.32–27.87) and an earlier onset compared with N-ALS (SMD = − 0.45, 95% CI = − 0.72 to − 0.18). *SOD1*-ALS had a similar survival compared with N-ALS ($p = 0.14$), a longer survival compared with *C9*-ALS ($p < 0.01$) and *FUS*-ALS ($p = 0.019$) and a shorter survival compared with *TARDBP*-ALS ($p < 0.01$).

Discussion This study indicates the presence of a specific *SOD1*-ALS phenotype. Insights in *SOD1*-ALS clinical features are important in genetic counseling, disease prognosis and support patients' stratification in clinical trials.

Keywords SOD1 · ALS · Metanalysis · Motor neuron disease · ALS genetics

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Introduction

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by the progressive degeneration of motor neurons, resulting in muscle paralysis, respiratory failure, and ultimately death within a few years of symptom onset [1]. ALS has a multifactorial pathogenesis and a complex genetic background. A subset of cases known as familial ALS (fALS) have a positive family history of ALS or frontotemporal dementia (FTD) [2]. The discovery of the Cu/Zn-binding superoxide dismutase (*SOD1*) mutation in 1993 marked the first genetic association with ALS [3]. Since then, our understanding of ALS-causing genes has expanded [4].

SOD1 mutations account for about 1–2% of ALS cases, making them the leading genetic cause in Asian individuals and the second most common in Europeans [5]. Over 200 mutations in the *SOD1* gene have been associated with ALS, exhibiting variable clinical presentations [6–8]. *SOD1*-mediated ALS is characterized by the predominant involvement of lower motor neurons and a milder degree of cognitive dysfunction [7, 8]. Conversely, age at symptoms onset varies widely, spanning from the second to the eighth decade of life and disease duration also varies across studies [9, 10].

Besides *SOD1*, *C9orf72*, *TARDBP* and *FUS* have been found to be the most common mutated genes in European and Asiatic populations. *C9orf72* hexanucleotide repeat expansion is the most prevalent mutation in populations from European descent and it is associated with both ALS and FTD [5, 11]. *C9orf72* ALS patients have been reported to have peculiar phenotypic features, such as a higher rate of bulbar onset and a shorter survival compared to sporadic ALS patients [12]. *TARDBP* and *FUS* mutations are less common in ALS patients [5]. Notably, *FUS* mutations have been associated with an earlier age at onset and an aggressive phenotype [13].

SOD1-ALS is currently the only ALS subtype potentially susceptible to a target treatment [14]. To facilitate the expedited genetic testing of *SOD1* patients, it is important to develop a thorough comprehension of their phenotypic characteristics. However, several factors have hindered clinicians from accurately distinguishing *SOD1* patients from other ALS subtypes, including the limited number of studies, small sample sizes within *SOD1* cohorts, the high diversity of *SOD1* mutations and the phenotypic heterogeneity of ALS [6, 10]. Therefore, the objective of this study is to elucidate the *SOD1*-mediated ALS phenotype through a meta-analysis of the existing literature.

Materials and methods

This meta-analysis was performed according to the referred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (eTable 1) [15]. Our study did not require a registered research protocol or statement of approval by an ethical committee, because the study is a meta-analysis of already published literature.

Eligibility criteria, information sources and search strategy

We conducted a systematic search of peer-reviewed English language articles in PubMed, Scopus, Embase and Web of Science to investigate the clinical and epidemiological characteristics of *SOD1*-ALS patients. The search included studies published until December 2022, further details are provided in the eMethods in the Supplement.

We included studies that met the following criteria: (1) they were original research conducted in adult humans, and (2) they reported the epidemiological and clinical characteristics of patients with *SOD1* variants (*SOD1*-ALS) and at least one of the following control groups: patients with *C9orf72* hexanucleotide repeat expansion (*C9*-ALS), variants in the *TARDBP* gene (*TARDBP*-ALS), variants in the *FUS* gene (*FUS*-ALS) or those negative for the major-ALS genes (N-ALS). Given the evolving definition of major ALS genes over the past decades, we established the inclusion criteria for the N-ALS group based solely on a clear confirmation of the absence of *SOD1* mutations. The potential implications of this definition, in terms of heterogeneity and its effect on the results, were thoroughly evaluated in subsequent sections. To further minimize the risk of small sample-driven publication bias, confirmation bias, and lower-quality studies—collectively known as the small study effect—we excluded studies that enrolled very small ALS cohorts, arbitrarily defined as fewer than five participants [16]. When multiple studies from the same center fulfilled the inclusion criteria, they were carefully reviewed to avoid potential duplication. Finally, we included in the meta-analysis an unpublished cohort of ALS patients that were followed at ALS clinic of the San Raffaele Scientific Institute (HSR) in Milan. Further details and Committee Ethical approval information are given in the eMethods in the Supplement.

Quality assessment

We assessed the quality and risk of bias in the included articles using the Newcastle–Ottawa Scale [17].

Outcomes of interest

We carefully evaluated the data presented in the included articles and made an unbiased selection of the variables for this meta-analysis. Variables such as sex, site of symptoms onset (bulbar or spinal), age at symptoms onset, survival and the percentage of fALS or sporadic ALS (sALS) cases were consistently reported and included in the analysis. However, variables such as cognitive impairment, disease progression rate, diagnostic delay, and specific motor phenotypes were frequently unreported and, therefore, not included in this meta-analysis. The information of fALS and sALS cases for each group was also collected, but because of its dependence on the study design, it was not included among the studied variables. Instead, it was used as a potential source of heterogeneity in the subgroup analysis. Individual patient survival data were reconstructed by digitizing the published Kaplan–Meier (KM) curves [18]. Further details are given in the eMethods in the Supplement.

Data analysis

Statistical analyses were performed using version 4.0.3 of the R statistical package (R Foundation for Statistical Computing, Vienna, Austria). The Cochran Q test and the I^2 statistic were used to assess the heterogeneity of the studies and to identify a possible variability in the results beyond chance. A random effects meta-analytic model was used to estimate pooled differences in the selected variables and leave-one-out sensitivity analyses were performed to assess the robustness of the results.

To evaluate whether papers that specifically studied fALS cases represented a source of heterogeneity, a subgroup analysis with a mixed-effects model was performed. Moreover, to address the variation in the definition of the N-ALS group among the included studies, which excluded different genes besides *SOD1*, a subgroup analysis was conducted to assess the effect of this definition as source of heterogeneity.

Publication bias was assessed through visual examination of funnel plots and Egger's tests. When significant bias was detected, the trim-and-fill procedure of Duval & Tweedie was employed to estimate the hypothetical effect size, considering the possibility of missing studies. To perform survival analysis, the reconstructed individual patient data were evaluated for the assumption of hazard proportionality using the Grambsch and Therneau test [19]. If the assumption of proportionality was confirmed, a two-sided log-rank test was performed for survival analysis. However, if the proportionality assumption was violated and a significant relationship between residuals and time was observed, differences in restricted median survival time at specific time intervals (60, 120, 180, and 240 months) were utilized for comparison [20].

Data availability

Data extracted from the included studies and used for analysis will be shared in case of interest, email to quattrini.angelo@hsr.it. The analytic code that was used for the analysis is provided in the Supplement 2.

Results

Search results and characteristics of the included studies

Out of 2820 initially identified records, 1615 articles were screened based on titles and abstracts, resulting in 37 articles for full-text review. After a thorough evaluation, 20 articles met the inclusion criteria and were included in the meta-analysis (Fig. 1, eTable 2 and eTable 3) [21–40].

Patient group definition

We identified 721 *SOD1*-ALS, 470 *C9*-ALS, 183 *TARDBP*-ALS, 113 *FUS*-ALS and 2824 N-ALS. Specifically, N-ALS were defined after excluding all the four major genes in 9 studies, encompassing 2130 patients. In 2 studies, N-ALS were defined after excluding these major-ALS genes except for *C9orf72*, including 354 patients and in 3 studies only *SOD1* variants were excluded, including 340 patients.

Study quality assessment

The results of this assessment are given in eTable 4.

Sex

Seventeen studies reported data on the sex prevalence among ALS patients, including 484 *SOD1*-ALS, 330 *C9*-ALS, 69 *FUS*-ALS, 178 *TARDBP*-ALS and 1966 N-ALS. The HSR cohort included 15 *SOD1*-ALS and 355 N-ALS.

The overall heterogeneity among the studies was low, with I^2 values ranging from 0% ($p = 0.46$) for *SOD1*-ALS versus N-ALS and *SOD1*-ALS versus *TARDBP*-ALS ($p = 0.47$) to 25% for *SOD1*-ALS versus *C9*-ALS ($p = 0.23$) (Fig. 2).

In the random-effects meta-analysis, a non-significant trend was observed, indicating a lower male-to-female ratio in *SOD1*-ALS compared with N-ALS (pooled OR = 0.79, 95% CI = 0.56–1.12). No significant differences were found in the comparisons of *SOD1*-ALS with C9-ALS (pooled OR = 0.82, 95% CI = 0.41–1.66),

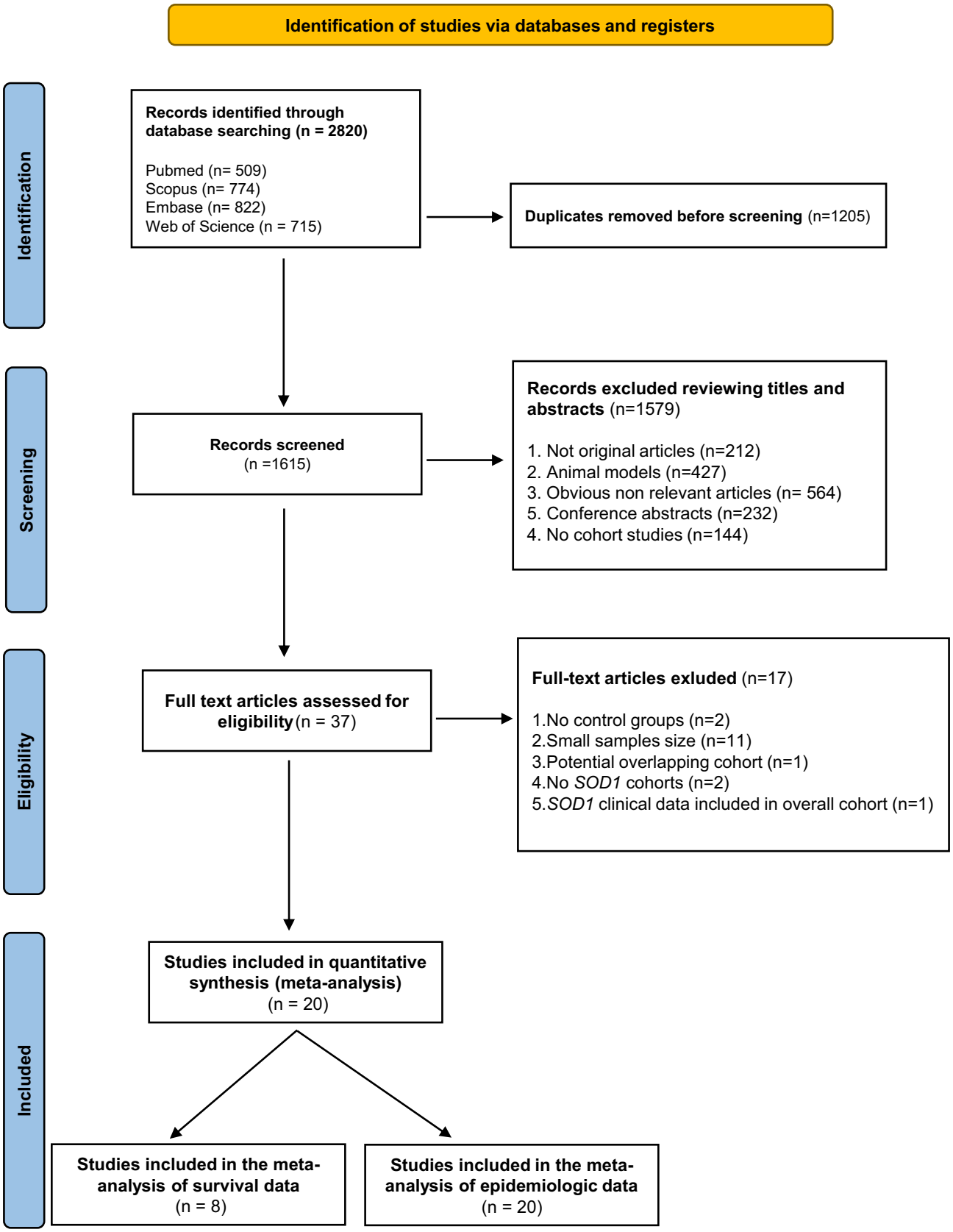

Fig. 1 Flowchart of systematic search and literature selection

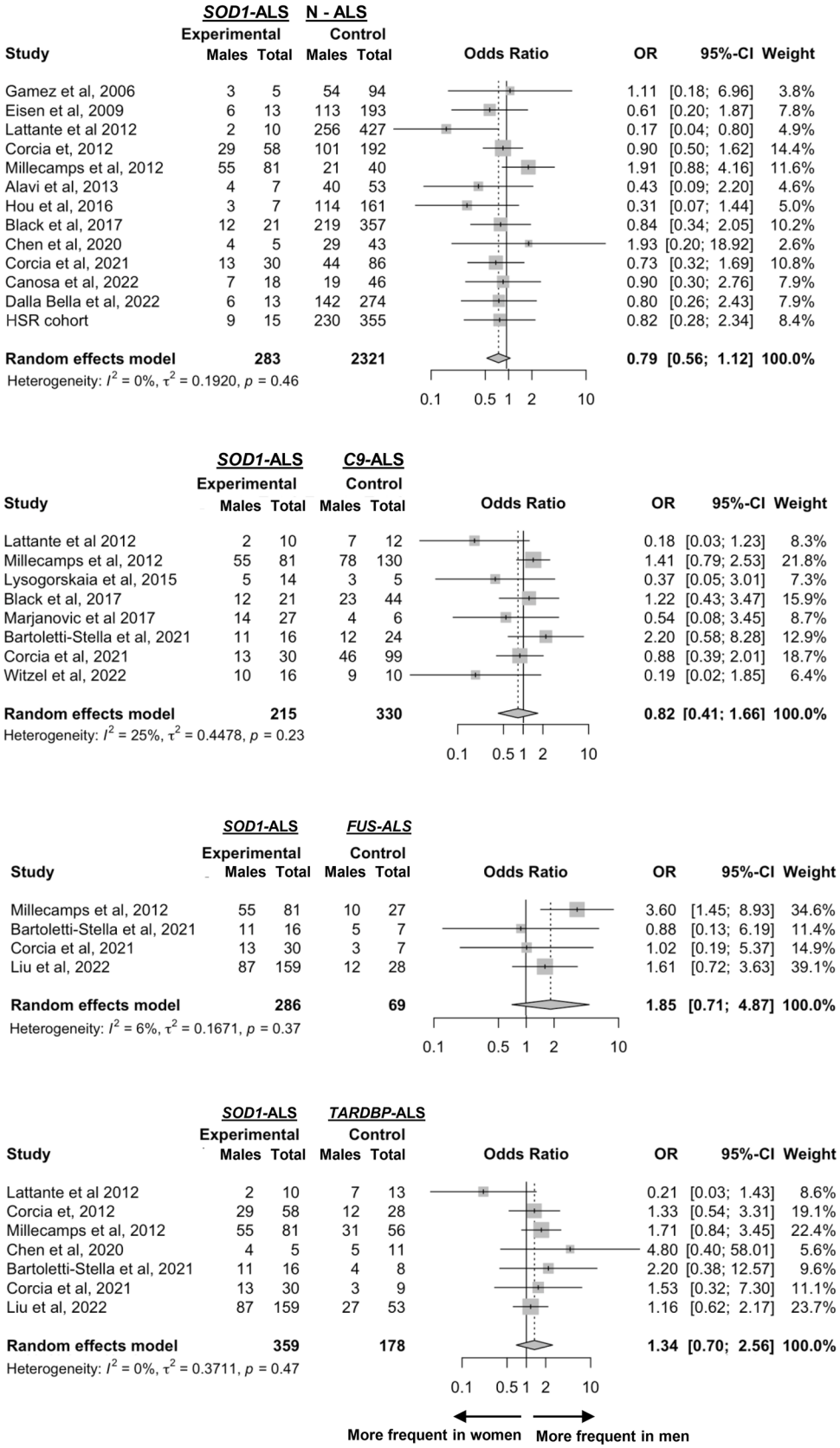

Fig. 2 Forest plots showing men odds ratio between *SOD1*-ALS and other groups (N-ALS, *C9*-ALS, *FUS*-ALS, and *TARDBP*-ALS). *CI* confidence interval, *OR* odds ratio

FUS-ALS (pooled OR = 1.85, 95% CI = 0.71–4.87) and *TARDBP*-ALS (pooled OR = 1.34, 95% CI = 0.70–2.56) (Fig. 2).

Despite the absence of outliers, the leave-one-out analysis showed that excluding the study by Millecamps et al. resulted in a significant difference between *SOD1*-ALS and N-ALS, supporting the observed trend (eTable 5) [35].

Subgroup analyses indicated that the definition of the N-ALS population, whether potentially including major-ALS gene variants or not, did not contribute to the heterogeneity (eFigure 1). Additionally, studies specifically analyzing fALS patients did not represent a source of heterogeneity (eFigure 2).

Funnel plot analysis and Egger's test indicated a low publication bias risk. However, for the comparison of *SOD1*-ALS versus *C9*-ALS, the funnel plot appeared distorted and was confirmed by the Egger's test ($p = 0.04$) (eFigure 3). Nevertheless, the adjusted odds ratio (OR), estimated using the trim-and-fill, did not significantly differ from the OR (*SOD1*-ALS vs *C9*-ALS OR: 1.19, 95% CI 0.52–2.71).

Site of symptom onset

Seventeen studies reported data on the site of symptom onset, including 460 *SOD1*-ALS, 315 *C9*-ALS, 78 *FUS*-ALS, 115 *TARDBP*-ALS and 2633 N-ALS. The HSR cohort included 15 *SOD1*-ALS and 348 N-ALS.

The heterogeneity was low for the comparisons between *SOD1*-ALS and N-ALS ($I^2 = 0\%$, $p = 0.91$) and *C9*-ALS ($I^2 = 0\%$, $p = 0.79$), indicating consistent findings across studies. However, it was moderate for the comparisons between *SOD1*-ALS and *FUS*-ALS ($I^2 = 52\%$, $p = 0.10$) and *TARDBP*-ALS ($I^2 = 69\%$, $p < 0.01$) (Fig. 3).

The random-effects meta-analysis demonstrated that *SOD1*-ALS patients had a significantly higher rate of spinal onset compared with N-ALS and *C9*-ALS patients (pooled OR = 4.85, 95% CI = 3.04–7.76; pooled OR = 10.97, 95% CI = 4.32–27.87). A non-significant trend toward spinal onset was observed when comparing *SOD1*-ALS with *FUS*-ALS (pooled OR = 7.58, 95% CI = 0.75–76.14) and *TARDBP*-ALS (pooled OR = 7.59, 95% CI = 0.85–68.02) (Fig. 3).

The leave-one-out analysis indicated that the study by Liu et al. may have contributed to the high heterogeneity and its exclusion led to a significant difference between *SOD1*-ALS and *TARDBP*-ALS, suggesting it as a potential source of heterogeneity (eTable 6) [32].

Although the comparison between *SOD1*-ALS and N-ALS showed substantial homogeneity, subgroup analysis highlighted a significant difference in the pooled effect sizes among the subgroups defined by the major-ALS genes tested in each study ($p < 0.01$). However, the frequency of spinal onset was significantly higher in *SOD1*-ALS in each of these subgroups (eFigure 4). Studies specifically analyzing fALS patients did not represent a source of heterogeneity (eFigure 5).

Visual examination and Eggers' test did not suggest potential publication bias in the comparison of *SOD1*-ALS and *FUS*-ALS ($p = 0.52$) and *SOD1-ALS* and *TARDBP*-ALS ($p = 0.60$). However, the funnel plot analyses for the comparisons between *SOD1*-ALS and N-ALS ($p = 0.02$) and *SOD1*-ALS and *C9*-ALS showed strong distortion, as confirmed by Eggers' test ($p = 0.04$) (eFigure 6). Nevertheless, the adjusted OR, estimated through the trim-and-fill method, did not significantly differ from the OR (*SOD1* vs N-ALS OR: 4.32, 95% CI [2.66–7.00], *SOD1-C9* OR: 8.82, 95% CI [3.51–22.18]).

Age at symptom onset

Fourteen studies reported data on the age of symptom onset, including 392 *SOD1*-ALS, 317 *C9*-ALS, 137 *TARDBP*-ALS, 71 *FUS*-ALS and 2508 N-ALS. The HSR cohort included 15 *SOD1*-ALS and 242 N-ALS. The heterogeneity was low for the comparison between *SOD1*-ALS and *FUS*-ALS ($I^2 = 20\%$, $p = 0.29$) and *TARDBP*-ALS ($I^2 = 0\%$, $p = 0.45$), indicating consistent findings across studies. However, it was moderate for the comparison between *SOD1*-ALS and *C9*-ALS ($I^2 = 40\%$, $p = 0.40$) and high for the comparison between *SOD1*-ALS and N-ALS ($I^2 = 65\%$, $p < 0.01$), suggesting some variability in the results (Fig. 4).

Our analysis demonstrated an earlier onset for *SOD1*-ALS patients compared with N-ALS (pooled SMD = − 0.45, 95% CI = − 0.72 to − 0.18). A non-significant trend of earlier onset was observed for *SOD1*-ALS compared with *C9*-ALS (pooled SMD = − 0.26, 95% CI = − 0.56 to 0.04) and *TARDBP*-ALS (pooled SMD = − 0.27, 95% CI = − 0.56 to 0.03). Age at symptom onset was similar between *SOD1*-ALS and *FUS*-ALS patients (pooled SMD = − 0.40, 95% CI = − 0.17 to 0.97) (Fig. 4).

The leave-one-out analysis indicated that the study by Black et al. may contributed to the heterogeneity and its exclusion led to a significant difference between *SOD1*-ALS and *C9*-ALS, suggesting a strong statistical trend for earlier onset in *SOD1*-ALS [24]. Similarly, for the comparison between *SOD1*-ALS and *TARDBP*-ALS, the leave-one-out analysis showed that excluding one of the studies by Lattante et al. or Corcia et al. led to a significant difference between the two groups, supporting a strong statistical trend of earlier onset in *SOD1*-ALS (eTable 7) [23, 28].

Subgroup analyses confirmed that the definition of the N-ALS population, potentially including or excluding major-ALS gene variants, did not represent a source of heterogeneity (eFigure 7). Conversely, studies analyzing exclusively fALS patients represented a source of heterogeneity for the comparison between *SOD1*-ALS and *C9*-ALS, suggesting

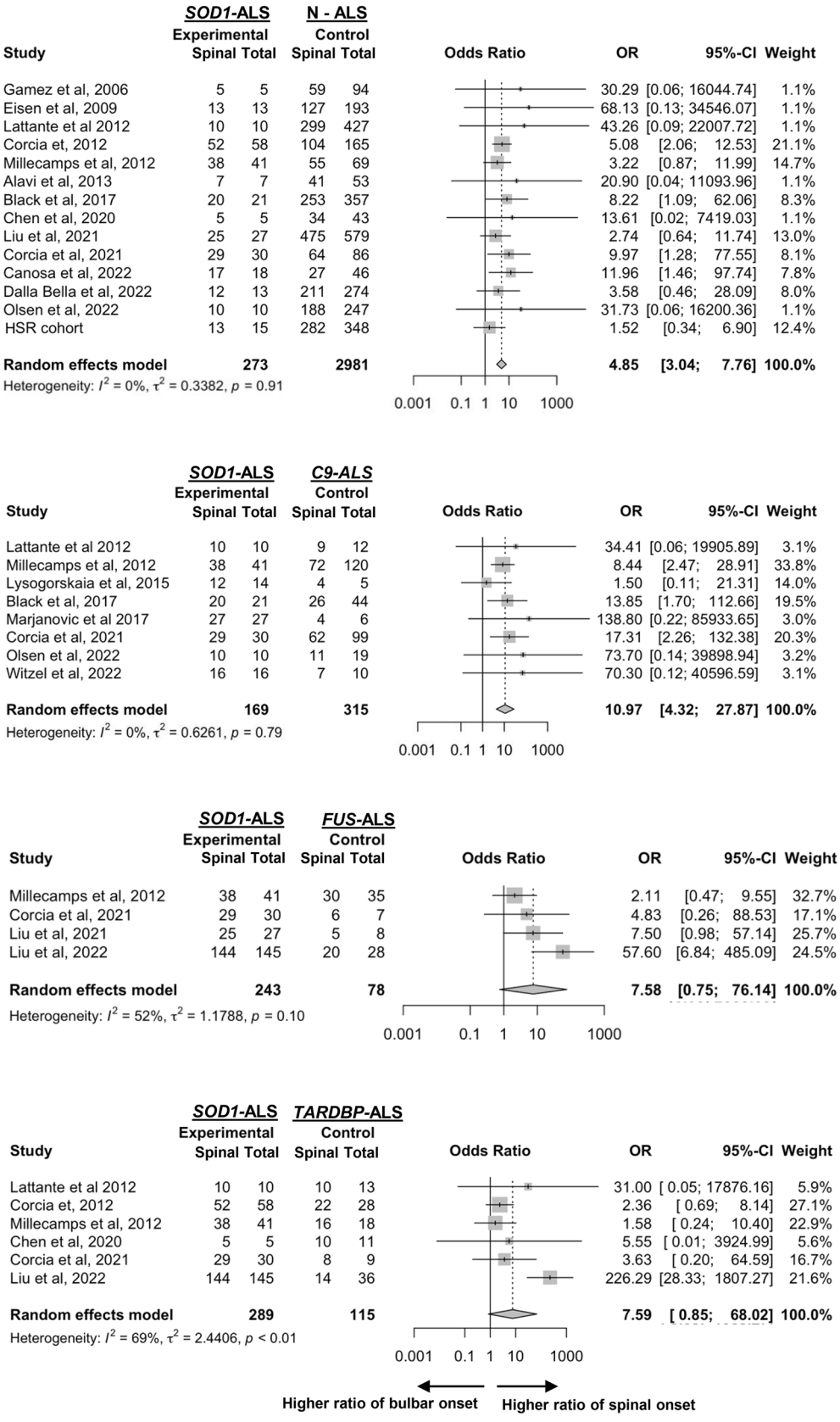

Fig. 3 Forest plots showing spinal-bulbar onset odds ratio between *SOD1*-ALS and other groups (N-ALS, *C9*-ALS, *FUS*-ALS, and *TARDBP*-ALS). *CI* confidence interval, *OR* odds ratio

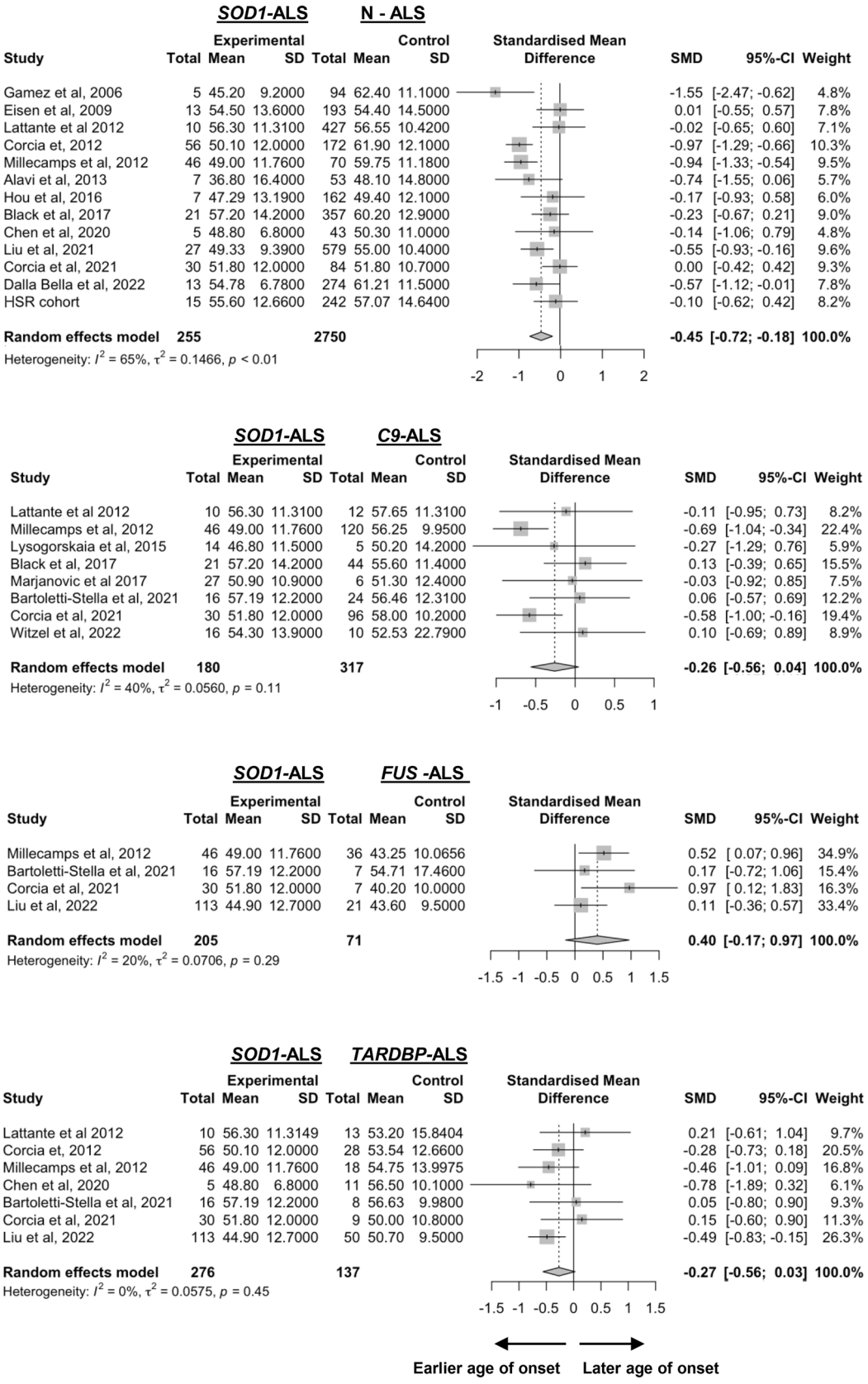

Fig. 4 Forest plots showing the standardized mean difference of the age of onset in *SOD1*-ALS and other groups (N-ALS, *C9*-ALS, *FUS*-ALS, and *TARDBP*-ALS) *SMD* standard mean deviation, *CI* confidence interval

an earlier age at onset in fALS cases carrying *SOD1* variants (eFigure 8).

Visual inspection of the funnel plots suggested a low risk of publication bias which was also confirmed by Eggers' test (*SOD1* vs N-ALS, $p=0.40$; *SOD1*-C9-ALS, $p=0.06$; *SOD1-FUS*, $p=0.68$; *SOD1-TARDBP*, $p=0.24$;) (eFigure 9).

Survival analysis

Individual patient survival data were obtained from 8 studies, including 351 *SOD1*-ALS, 318 *C9*-ALS, 117 *TARDBP*-ALS, 85 *FUS*-ALS and 549 N-ALS. The HSR cohort included 15 *SOD1*-ALS and 337 N-ALS. Survival analysis results are presented in Fig. 5. The log-rank test showed no difference in survival between *SOD1*-ALS and N-ALS patients (median survival of *SOD1*-ALS patients: 47.9 months, 95% CI 45–69.5; median survival of N-ALS patients: 41 months, 95% CI 37.6–45.5, $p=0.14$). *SOD1*-ALS patients had a significantly longer survival compared to *C9*-ALS patients (median survival 30 months, 95% CI 25.3–34.9, $p<0.01$) and *FUS*-ALS patients (median survival 33.6 months, 95% CI 29.8–47.7 $p=0.02$). Conversely, *SOD1*-ALS patients had a significantly shorter survival compared to *TARDBP*-ALS patients (median survival 86.2 months, 95% CI 73.7–121.3, $p<0.01$). The median survival difference between *SOD1*-ALS and *C9*-ALS was confirmed even when considering only fALS cases ($p<0.01$), as well as between familial *SOD1*-ALS (f*SOD1*-ALS) and familial *TARDBP*-ALS ($p<0.01$); while

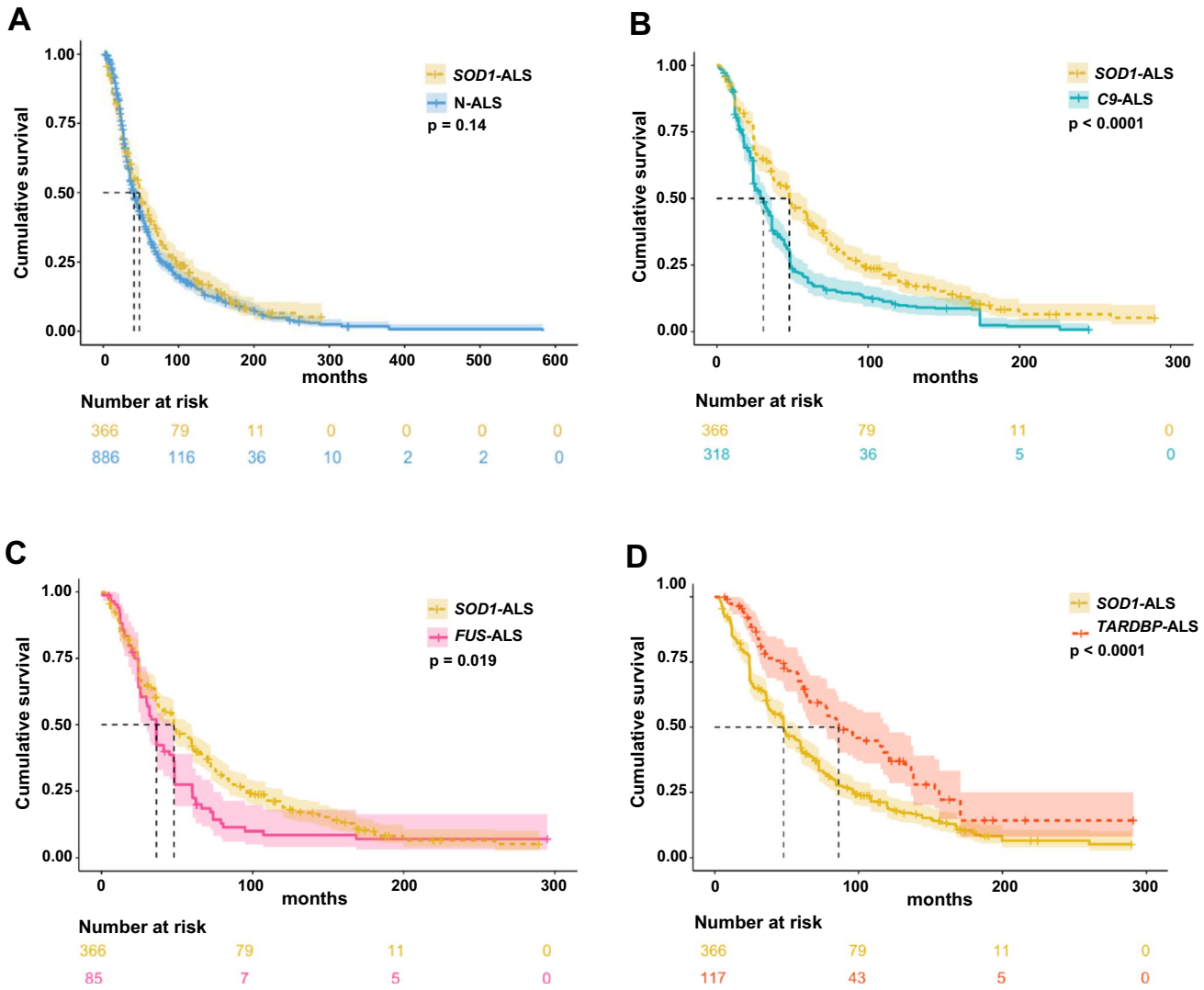

Fig. 5 Kaplan–Meier plots of cumulative survival. **A** *SOD1*-ALS (gold line) and N-ALS (blue line); **B** *SOD1*-ALS (gold line) and *C9*-ALS (green line); **C** *SOD1*-ALS (gold line) and *FUS*-ALS (pink line) (**D**) *SOD1*-ALS (gold line) and *TARDBP*-ALS (orange line). The median survival times are represented by black dotted lines in **A–D**. A 95% confidence interval is presented in the shadowed area

the median survival of f*SOD1*-ALS and familial *FUS*-ALS (f*FUS*-ALS) did not differ ($p = 0.22$) (eFigure 10).

Discussion

The aim of this meta-analysis was to provide a comprehensive description of the main demographic and phenotypic characteristics in a large dataset of *SOD1* patients. Our study revealed that *SOD1*-ALS patients have a predominant spinal onset compared with both N-ALS and *C9*-ALS as well as an earlier age of symptom onset compared with N-ALS, *C9*-ALS, and *TARDBP*-ALS. Additionally, *SOD1*-ALS patients exhibit a distinct survival pattern compared with all other genetic groups.

ALS is slightly more prevalent in males than in females [41]. Our study showed a trend towards a lower male-to-female ratio in *SOD1*-ALS compared with N-ALS, with a tendency toward gender balancing, as reported in a recent study conducted on a large international cohort of *SOD1* patients [42]. Conversely, the male-to-female ratio in *SOD1*-ALS is similar to the other genetic forms of ALS including *C9*-ALS, *FUS*-ALS, and *TARDBP*-ALS. This suggests that differences in sex hormones may have less influence on ALS pathogenesis in the presence of a genetic mutation [43].

Regarding the site of onset, our analysis showed that *SOD1*-ALS patients have a higher frequency of spinal onset compared with N-ALS and *C9*-ALS. The higher frequency of spinal onset in *SOD1*-ALS patients compared with N-ALS patients that we observed confirms results from previous studies on smaller cohorts [24, 28]. This finding is also in line with previous studies indicating that *C9orf72* carriers are more likely to present with bulbar disease compared with sALS and *SOD1*-ALS patients [12, 32, 44]. *SOD1* patients also exhibit a prominent lower motor neuron involvement and are generally spared from cognitive decline, unlike *C9orf72* patients [44]. The biological significance underlying differences in site of onset remains to be elucidated, but proteomic studies comparing bulbar and cervical motor neurons in rats have shown significant differences in the regulation of genes involved in pathways implicated in ALS pathogenesis, suggesting that site of onset may be influenced by metabolic differences among different motor neuron populations [28, 45].

In terms of age at onset, our meta-analysis revealed that *SOD1*-ALS patients have an earlier onset compared with N-ALS. However, when compared with *C9*-ALS and *TARDBP*-ALS cases, the difference in age at onset showed a robust non-significant trend. This finding aligns with the multistep model, which suggests that the number of steps required for neurodegeneration onset is reduced in patients carrying causative gene mutations, with *SOD1* patients requiring the lowest number of steps [13, 35, 46]. We observed a trend for a later age at onset in *SOD1*-ALS patients compared with *FUS*-ALS. Earlier studies on smaller cohorts observed a similar result [35, 47].

Our study did not find a difference in survival between *SOD1* patients and N-ALS cases. Previous studies evidenced that *SOD1* patients may exhibit an heterogeneous natural history of disease duration and to date only the A4V variant is strongly associated with a fast progression [6, 42, 48]. A recent study conducted on a large international dataset of ALS patients with known pathogenic variants in *SOD1* reported lower overall survival in *SOD1* patients compared to sALS cases, but this finding may be influenced by the inclusion of a significant proportion of North American patients where the A4V *SOD1* variant is more prevalent [42]. Conversely, a limited number of studies reported longer survival in *SOD1* patients compared with sALS. However, these results may be attributed to small sample sizes or specific geographic areas [22, 23, 38]. The survival data we obtained need to be contextualized in light of the heterogeneity of the cohorts we included, in which many different mutations were represented. It is essential to conduct further studies to elucidate the heterogeneous survival patterns observed in *SOD1*-ALS patients, which could be influenced by environmental exposure or genetic polymorphism acting as phenotype modifiers [49, 50].

We showed that *SOD1*-ALS patients have a longer survival compared with *C9*-ALS, which is recognized as an unfavorable prognostic factor in ALS [50, 51]. Furthermore, *SOD1*-ALS patients have a longer survival compared with *FUS*-ALS, which confirms the findings of a recent study examining genetic factors for survival [52]. In contrast to *C9*-ALS and *FUS*-ALS, the comparison between *SOD1*-ALS and *TARDBP*-ALS groups showed a shorter disease duration in *SOD1* patients. Consistently, a cohort-based study conducted in China demonstrated that *TARDBP* patients have a longer disease duration compared with *SOD1* and *FUS* patients [34]. KM curves performed on fALS cases confirmed these differences between the genotypes, although the comparison between f*SOD1-ALS* and f*FUS-ALS* patients did not reach statistical significance, likely due to the limited sample size for f*FUS*.

A limited number of studies which did not examine all major-ALS genes considered in our analyses, either due to epidemiological constraints or because the genes had not yet been associated with ALS, were included in the N-ALS group. To address this potential source of heterogeneity, we performed subgroup analyses, which demonstrated that the results obtained comparing *SOD1*-ALS with the different N-ALS subgroups did not significantly differ. An exception was represented by the subgroup analysis concerning site of onset; however, since results from all subgroups pointed in the same direction, this does not affect the interpretation of the main analysis.

Our study has several methodological strengths that make it unique in the context of ALS phenotype characterization. The first point pertains to the unbiased selection of epidemiological and clinical characteristics of *SOD1*-ALS. This approach enables us to provide not only a comprehensive overview of the currently available data but also to highlight the gaps in knowledge regarding relevant phenotype characteristics that still require extensive investigation. Secondly, despite the low heterogeneity observed among the included studies, we made a priori decision to apply a conservative random effects model. This allowed us to incorporate the possibility that the studied groups inherently exhibit heterogeneity due to the specific type of mutations associated with each gene. A further key point of strength is the use of individual survival data reconstructed by digitizing the published KM curves. This method not only overcomes the heterogeneity of data reporting across the included studies but also allows for more flexible analysis management. Additionally, it facilitates the evaluation of the proportionality assumption, which is essential for non-pharmacological time-to-event analyses that require careful assessment of a linear pattern of event distribution over time. Lastly, a notable strength of our work is that the included studies encompassed both Caucasian and Asian populations, providing a comprehensive understanding of the demographic and phenotypic characteristics of ALS patients carrying ninety different *SOD1* mutations (eTable 8). This broad representation of diverse genetic backgrounds strengthens the generalizability and robustness of our findings. Furthermore, the inclusion of the most common *SOD1* mutations, such as D90A and I113T, which are widely prevalent globally, further enhances the significance and relevance of our study [53].

It is important to acknowledge the limitations of our study. Firstly, while our research provides an overall understanding of the *SOD1* phenotype, it cannot predict the phenotype of individual mutations within the *SOD1* gene. Secondly, there is a potential for selection bias as certain *SOD1* mutations described only in clinical reports were excluded from the meta-analysis based on our eligibility criteria. Additionally, it is worth noting that our analysis did not included studies from Latin America, Central America, and African population due to the lack of studies meeting our eligibility criteria. Therefore, the generalizability of our findings to these regions may be limited, highlighting the need for further research in diverse populations.

To our knowledge, this is the first study examining clinical features in a large sample of *SOD1* patients with widespread geographic representation and comparing them to a considerable number of ALS patients genetically negative for the major genes and with *C9orf72*, *FUS* and *TARDBP* variants. Despite the intrinsic phenotypic variability due to different *SOD1* mutations, our study indicates the presence of a specific phenotype in *SOD1*-ALS. Gaining insights into *SOD1* clinical features is important in genetic counseling, disease prognosis and to support patient stratification in clinical trials. The recognition of a typical pattern for *SOD1*-ALS presentation might be useful to prompt swift genetic testing, especially in limited resource settings in which the sequencing of a large panel of genes might not be routinely available. The early recognition of *SOD1*-ALS patients might thus allow the timely administration of potentially effective target treatment and enrollment in future clinical trials.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-12074-6.

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Data availability Data extracted from the included studies and used for analysis will be shared in case of interest, email to quattrini.angelo@hsr.it. The analytic code that was used for the analysis is provided in the Supplement 2.

Declarations

Conflicts of interest The authors do not report any competing interest for this article.

Ethical approval Our study did not require a registered research protocol or statement of approval by an ethical committee, because the study is a meta-analysis of already published literature.

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