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The ability of King's clinical staging and Milano-Torino (MiToS) functional staging in the prediction of amyotrophic lateral sclerosis (ALS) progression: A meta-analysis study

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by functional connectivity alterations in both motor and extra-motor brain regions. Assessing clinical progression in amyotrophic lateral sclerosis (ALS) remains a challenge. Our objective was to assess the effectiveness, utility, precision, and validity of the King's staging system and the Milano-Torino Staging (MiToS) system by comparing them in terms of charting disease progression within a clinical setting.

Methods: A meta-analysis conducted an inclusive literature search in PubMed, Scopus, Web of Science, and Cochrane Library to select appropriate studies that investigated the prognosis of amyotrophic lateral sclerosis (ALS) patients using King's and MiToS staging systems summarizing the progression of each clinical stage via estimating the pooled standardized mean duration of each stage in both staging systems within the total disease course.

Random-effects meta-analysis was performed using R version 4.2.2 "Innocent and Trusting". In addition to investigating the pooled correlation coefficient (r) between the two staging systems, the potential risk of publication bias was checked using the funnel plot asymmetry method.

Results: In our systematic review, we analyzed a collection of eight cohort studies involving a total of 5,277 patients. Our investigation revealed that both the King's and MiToS staging systems proved valuable in monitoring the progression of ALS in our patient population. We observed that the distribution of time spent in individual King's stages was relatively uniform, with the longest duration (35%) occurring at the first stage, and the need for respiratory and/or nutritional support arising after 79% of the disorder progression had transpired.

Conversely, the MiToS system demonstrated its utility in the later phases of the disease, becoming more relevant after 87% of the disease duration had passed, particularly when assessing loss of independence in functional aspects. Furthermore, our analysis unveiled a noteworthy correlation between these two staging systems (correlation coefficient r = 0.75, 95% confidence interval (CI): [0.248; 0.932], p = 0.0078).

Conclusion: While the King's College staging system might be better suited for assessing disease burden stages, evaluating treatment effectiveness, and establishing the duration until functional dependence compared to MiToS, which places a stronger emphasis on fine-tuning levels of dependency, it's worth noting that both systems have their merits in describing disease progression and survival. Additional research is essential to thoroughly assess the distinctions between these staging systems.

Keywords: Amyotrophic lateral sclerosis (ALS), staging systems, King's staging, Milano-Torino (MiToS) staging, meta-analysis.

Introduction

Amyotrophic lateral sclerosis (ALS), or so-called motor neuron disease (MND), is an advanced neurodegenerative condition that impacts the upper motor neurons and lower motor neurons situated in the spinal cord and brain. This leads to a gradual loss of muscle function, culminating in paralysis, and individuals diagnosed with ALS typically face a life expectancy of two to five years (1). Findings from clinical, molecular, and neuroimaging studies have indicated that ALS extends its effects far beyond the motor system (2,3)**.**

Even though the overall lifespan hazard of developing ALS stands at 1 in 300 (4), the current occurrence is notably lower, at approximately 5 cases per 100,000 individuals, primarily due to the grim prognosis associated with the disease. The requirements of ALS patients vary as the condition advances, with early-stage emphasis on diagnosis and therapeutic support, while later stages necessitate interventions such as respiratory assistance, nutritional support, and end-of-life care.

Numerous factors have been linked to prognosis and the advancement of the disease, involving age, genetic variations (e.g., C9orf72), site of onset, biomarkers, plus nutritional and respiratory conditions (5). Several ALS staging approaches have been suggested, serving various

purposes such as aiding in rehabilitation (6), facilitating rapid functional assessment (7), enabling comparisons of distinct treatment models (8,9), supporting biomarker analysis (10), and contributing to health economics (11). It's worth noting that the El Escorial standards furnish a regular of investigative rules rooted in disease progression patterns, although they do not constitute a staging system in themselves (12).

The ALS Functional Rating Scale-Revised (ALSFRS-R), which is the predominant functional assessment tool for ALS and frequently utilized in clinical settings, demonstrates significant predictive value regarding survival upon initial diagnosis (13–15). Nevertheless, it possesses inherent limitations, primarily being multidimensional by combining mean scores from three distinct domains, thus falling short of meeting stringent measurement criteria (16,17). Additionally, it cannot facilitate comparisons between patients in terms of functional and anatomical decline progression.

Additionally, the time to generalization (TTG) is an indicator for the shift from bulbar or spinal envelopment to the general form, has been put forward as a measure of disease progress (18). Nevertheless, TTG has its constraints, as it may not apply to a subset of patients who do not experience a transition to a generalized form as their condition progresses.

ALS patients exhibit varying disease progressions, which pose challenges in predicting prognosis accurately. The management strategies employed vary based on the phase of the illness in which patients are (initial or advanced). To aid in delineating illness phases and establish a consistent framework for tracking disease advancement, two staging systems have been introduced: the King's College London staging system (19) and the Milano-Torino Staging (MiToS) system (20). Research has indicated that both of these systems complement each other effectively. **(Table 1)**

Table 1. Stages of ALS staging systems (King's and MiToS).

Stage	**King's system**	**MiToS system**
0		No functional domains* lost
1	Functional involvement of one CNS region*	One functional domain lost
2	of two CNS regions	Two functional domains lost
3	of three CNS regions	Three functional domains lost
4	4a† = Necessity for a feeding tube	Four functional domains lost
	4b† = Necessity for NIV	
	Mortality	Mortality

*bulbar, arm, or leg, **movement, swallowing, communicating, and breathing, CNS: central nervous system; NIV: non-invasive ventilation, †Stages 4a and 4b are not sequential; stage 4b may overlap 4a if the necessity for a feeding tube and NIV existed.

The King's system employs a five-stage framework for illness burden, which is determined by clinical engagement and the presence of significant respiratory or feeding issues. Frist stage marks the symptoms' onset, while stage 5 denotes the point of death. Notably, this system d approximated from ALSFRS-R scores with a high level of agreement, at 92% concordance (12).

The first three King's stages (1–3) correspond to the engrossment of cranial and spinal domains impacted by the disease, including the bulbar, arm, and leg regions, according to the El Escorial standards (19). Stages 4a and 4b signify advanced disease stages necessitating nutritional and respiratory support, respectively. Furthermore, this system is adept at detecting changes in the early to mid-stages of the disease's progression (21,22).

On the contrary, MiToS encompasses six stages and is grounded in the concept of loss of independence, rated on a scale from 0 to 4, across four functional domains extracted from the ALSFRS-R (20): mobility/self-care, swallowing, communication, and respiration. MiToS exhibits enhanced granularity, particularly in the advanced disease phases (21,22), and is inclined toward capturing more advanced disease states (20,21). In both systems, the ultimate stage is achieved upon the individual's passing. It is expected that the progression through stages follows a unidirectional sequence, with no regression to earlier stages. While it is possible to skip stages, this can only occur in a forward progression.

Breaking down the ALS progression process into stages serves various purposes in the medical field, including facilitating clinical descriptions, communication among healthcare professionals, prognostication, decision-making regarding treatment strategies, resource allocation, and focusing targeted treatment in clinical trials.

While both staging systems measure disease stages effectively and exhibit content validity by aligning with disease progression, it remains unclear to what extent they overlap, potentially making them redundant. Therefore, it is imperative to ascertain that both systems possess general applicability not specific to certain ALS patients.

Consequently, in our study, our goal was to conduct a comparative analysis of the King's and MiToS staging systems methodologies, with a focus on evaluating their performance, utility, precision, and validity in delineating disease progression within a clinical setting.

Methods

The study's research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) and assigned the registration number CRD42023484079.

To ensure a systematic approach to the search process and the subsequent reporting of findings presented in ***Supplementary Appendix S1***, we adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (23).

Our initial step involved conducting thorough searches across several databases, including PubMed, Scopus, Web of Science, and the Cochrane Library. Subsequently, we screened the titles and abstracts of the studies identified. The full texts of identified studies were then evaluated against predetermined inclusion and exclusion criteria.

In cases of any disagreements or discrepancies, we resolved them through discussions, and the final decision was made by the primary author. Following this, the included studies underwent a quality assessment. Ultimately, we synthesized the results and conducted meta-analyses to comprehensively analyze and interpret the collective findings.

Search strategy

We conducted a literature search using a concept-based strategy that centered around keywords associated with the King's staging system (KSS), the Milano-Torino staging system (MiToS), and Amyotrophic lateral sclerosis (ALS). A thorough exploration was carried out across four distinct electronic databases: PubMed, Scopus, Web of Science, and the Cochrane Library.

This search encompassed articles published from the inception of these databases up to July 23, 2023. To ensure comprehensiveness, we devised a search strategy that combined keywords with medical subject heading terms (MeSH). The specific search terms, in addition to the relevant keywords, are detailed in ***Supplementary Appendix S2***.

Study inclusion criteria

We utilized precise criteria in the screening process to assess whether papers were suitable for inclusion in our study. To be considered eligible, we incorporated cohort studies that examined the application of King's clinical and MiToS functional staging systems in individuals with ALS. These studies were then compared, and we recorded the overall prognostic results. Moreover, we limited our inclusion criteria to full-text articles in English, while excluding other types of articles.

Outcome measures

Our main research objective centers on evaluating and contrasting the predictive capabilities of the King's clinical and the Milano-Torino (MiToS) functional staging systems, concerning amyotrophic lateral sclerosis (ALS) progression.

Data extraction

The process of data extraction involved the utilization of a pre-established template. This template encompassed various trial details, such as the name of the primary investigator, year of publication, study design, and sample size. Additionally, we took into account the baseline characteristics of the patients, which included factors such as age, gender, median diagnostic delay (in months with interquartile range (IQR)), the number of deaths, and median survival (in months with IQR).

Furthermore, we scrutinized the outcomes associated with the two staging systems, encompassing both the comparison of outcomes between the two staging systems and the correlation between King's and MiToS stages. The data extraction process was carried out independently by two investigators and was duplicated for accuracy.

Assessment of risk of bias

In our research, we utilized the Newcastle–Ottawa Scale (NOS) (24) as a critical assessment tool to evaluate the included studies. The NOS was employed to gauge the risk of bias in cohort studies.

This tool assessed the quality of observational studies based on three fundamental domains: the selection of subjects, the comparability of individuals concerning demographics and significant potential confounding factors, and the determination of the specified outcome. Each study could

attain a final cumulative score within a range of 0 to 9, with a score of ≥7 indicating classification as a high-quality trial.

Data analysis

We conducted a random-effects meta-analysis with R version 4.2.2-- "Innocent and Trusting" to explore the prognostic outcomes of ALS patients utilizing the King's and MiToS systems. This analysis involved summarizing the duration of each clinical stage by estimating the combined standardized mean duration of these stages within the overall disease course for both staging systems.

Publication Bias

We examined the combined correlation coefficient (r) between the two staging systems and assessed the likelihood of publication bias by employing the funnel plot asymmetry method.

Results

In the initial phase, an extensive search yielded a total of 2,511 results (722 in Pubmed, 227 in Cochrane, 1,488 in Web of Science, and 74 in Scopus). Following the elimination of duplicate records using Endnote software (Version X8.2), the final dataset comprised 233 individual studies.

A thorough examination of titles and abstracts was then conducted to exclude reviews, clinical trials, and case reports, leading to the exclusion of 215 studies. Consequently, 18 papers were subjected to full-text screening and data extraction. Among these 18 papers, 10 did not meet the predefined criteria established before the study's commencement.

Following this rigorous screening process, the remaining eight studies were included in the systematic review, with three of them further incorporated into the subsequent meta-analysis. (**Figure 1**)

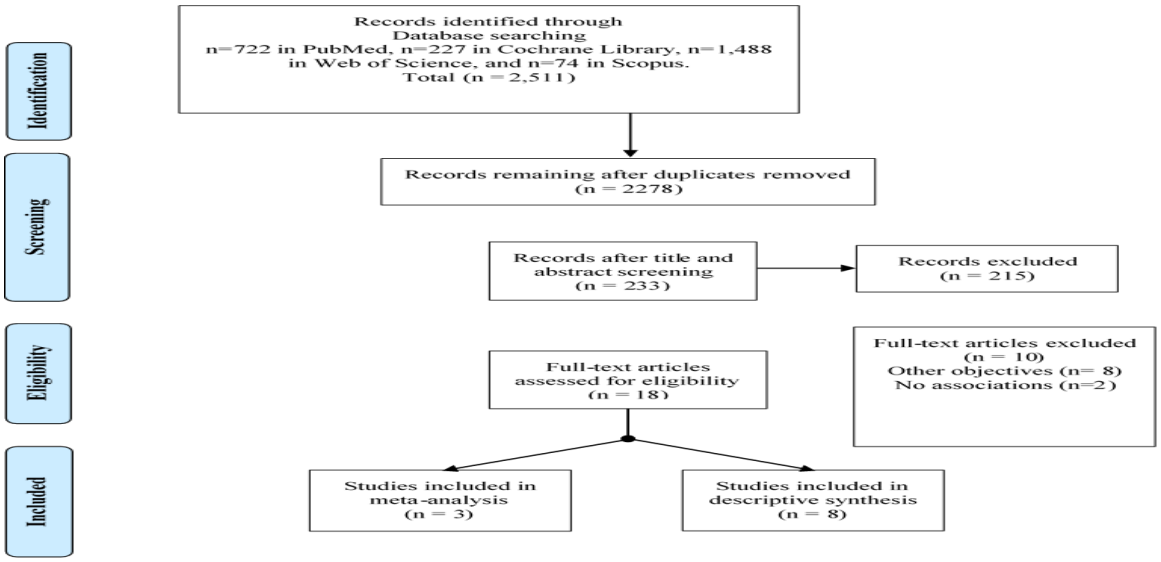

Figure 1. PRISMA 2009 flow diagram.

Study characteristics

Table 2 furnishes an outline of the study details, encompassing participant information. In total, eight cohort studies (comprising a total of 5,277 patients) met the eligibility criteria and were included in the systematic review. Data about participant characteristics and clinical examinations were extracted from files or records. The median survival duration ranged from 20 to 52 months.

Assessment of bias/study quality

Every evaluated cohort study demonstrated high quality, as indicated by Newcastle–Ottawa Scale (NOS) scores exceeding 7. The Newcastle–Ottawa quality assessment criteria can be found in ***Supplementary Appendix S3*** for reference.

Table 2. Characteristics of the included studies

Authors and year	**Study design**	**Sample size**	**Number of Females (%)**	**Age in years mean (SD)**	**Median diagnostic delay (months (IQR))**	**Number of deaths**	**Median survival (months (IQR))**	**Outcomes**	
								Comparison of staging systems outcomes	**The association between King's and MiToS stages**
Abdulaziz et al, 2021 (25)	A multi-ethnic cohort study	117	37 (31.6)	56.7 ±10.8	12.0 (7.0–19.0)	66 (56.4)	31.0 (23.0–44.0)	The correlation coefficient between King's and MiToS = 0.869 ($p<0.0001$)	The robust association with King's Stage 4 and MiToS stage 2 (K4M2) ($p<0.0025$)
Al-Chalabi et al, 2021 (22)	A Retrospective Clinical Trial Cohort Study	137	58 (42%)	60.5 (10)	NR	NR	NR	In the double-blind treatment phase, a lower proportion of individuals progressed in King's stage while receiving edaravone (42.0%, 95% CI 30.4% to 53.6%) compared to those on placebo (55.9%, 95% CI 44.1% to 67.6%). An examination of a ≥2-stage progression in the MiToS stage indicated a more rapid progression in patients within the placebo-edaravone group in comparison to those in the edaravone-edaravone group during the open-label period (log-rank test, $p<0.001$). This suggests that both the King's and MiToS staging systems proved to be valuable tools in assessing clinical progression.	
Balendra et al, 2015 (12)	A clinical trial cohort study	725	246 (34%)	55.6 (54.6 to 56.6)	9.7 (9.1 to 10.3)	260	32.3 (31.4 to 33.2)	In both staging systems, the majority of patients advance sequentially through the stages, with no instances of regression to prior stages. The median duration for transitioning between stages ranged from 3 to 7 months for stages 2 to 4.	

								Both systems exhibit consistency across different populations, substantiating their content validity in evaluating disease progression.	
Fang et al, 2017 (21)	A retrospective clinical trial cohort study	217	66 (30)	NR	NR	56% in (75–84) and 14% in (25–34) years age group	43.6 months	The correlation coefficient between King's and MiToS was 0.54	The strongest association with King's Stage 4 and MiToS stage 2 (K4M2) ($p<0.001$)
Ferraro et al, 2016 (26)	A prospective study	545	245 (45)	NR	NR	272	43 months	In the King's College system, as the stages progressed, there was a noticeable decline in survival rates and an uptick in the number of deaths. Conversely, within the MiToS system, survival curves for intermediate stages exhibited considerable overlap, and the frequency of deaths remained relatively consistent across most stages.	
Luna et al, 2021 (27)	A cohort study	298	137 (46.0)	65.3 (57.4–74.2) Median (IQR)	9.7 (6.2–15.8)	250	29.7 (20.3–48.1)	Subtle modifications in the staging systems seemed to enhance their effectiveness in terms of validity and predictive capabilities. Both the King's and MiToS staging systems incorporate variations that could potentially offer a more appropriate structure for delineating disease progression and survival.	

Romano et al, 2022 (28)	A cohort study	39	10	59.63 ± 12.87	NR	NR	51.82 (±59.61)	The "clinical fingerprint" exhibited predictive capability for both the King's ($p = 0.0001$; $\beta = 7.40$) and MiToS ($p = 0.0025$; $\beta = 4.9$) scores. Consequently, it displayed a negative correlation with the King's (Spearman's rho = -0.6041, $p = 0.0003$) and MiToS scales (Spearman's rho = 0.4953, $p = 0.0040$). The inclusion of the I-clinical significantly enhances the predictive accuracy of both the King's ($F(5.33) = 8.36$; $R2 = 0.56$; $p = 0.0001$; $\beta = -7.40$) and MiToS ($F(5.33) = 7.12$; $R2 = 0.52$; $p = 0.0025$; $\beta = -4.9$) scores. As expected, the disease duration also plays a significant role in predicting both the King's ($p = 0.0015$; $\beta = 0.0069$) and MiToS ($p = 0.0001$; $\beta = 0.0077$) scores.
Thakore et al, 2018 (29)	A cohort study	3199	1,194 (37%)	57 years	NR	719	17 months	While the two systems displayed a moderate correlation, the MiToS stages predominantly leaned to progressive disorder, whereas the King's stages exhibited a more stable distribution. Notably, non-serial progression in the King's system was observed. With advancing age, the hazard ratio (HR) for sequential progression increased by 1.1 per decade for the MiToS system, although this association was not statistically significant for the King's system. The influence of increasing age had a substantial impact on stage-specific mortality for both systems, with HRs ranging from 1.40 to 1.46 per decade. This overall acceleration in progression through stages significantly heightened the risk of transitioning from

								King's stages 1 and 2 to stage 4a, which necessitates the use of a feeding tube. Consequently, it can be concluded that King's staging is more responsive to the observed disease progression in clinical trials compared to MiToS.

IQR: interquartile range; MiToS: Milano-Torino Staging system; HR: hazard risk.

Meta-analysis of two staging systems

King's staging system

The random-effects model incorporated three studies, revealing the combined standardized mean duration for each of the King's clinical stages. Approximately 35% of the disease duration was allocated to King's stage 1 (n = 459) with a 95% confidence interval (CI) of [29.18%; 40.65%]. Notably, there was substantial between-study heterogeneity (I2 = 80.8%) and heterogeneity variance (tau2 = 0.0021), as evidenced by a statistically significant Cochran's Q test for heterogeneity (Q = 10.43, p <0.001).

Furthermore, approximately 51% of the disease duration was attributed to stage 2 (n = 367) with a 95% CI of [37.14%; 64.14%]. Similar to stage 1, there was significant between-study heterogeneity (I2 = 96.9%) and heterogeneity variance (tau2 = 0.0128), supported by a statistically significant Cochran's Q test for heterogeneity (Q = 64.44, p <0.001).

Additionally, about 56% of the disease duration was associated with stage 3 (n = 377) and had a 95% CI of [41.37%; 71.16%]. Again, there was substantial between-study heterogeneity (I2 = 96.9%) and heterogeneity variance (tau2 = 0.0147), as confirmed by a statistically significant Cochran's Q test for heterogeneity (Q = 63.96, p <0.001).

Furthermore, approximately 79% of the disease duration was allocated to stage 4 (n = 393) with a 95% CI of [62.69%; 94.64%]. Similar to the previous stages, there was substantial between-study heterogeneity (I2 = 95.1%) and heterogeneity variance (tau2 = 0.0126), supported by a statistically significant Cochran's Q test for heterogeneity (Q = 20.45, p <0.001).

Approximately 64% of the disease duration was attributed to stage 4A (n = 355) with a 95% CI of [46.40%; 80.64%], and once again, there was substantial between-study heterogeneity (I2 = 96.9%) and heterogeneity variance (tau2 = 0.0148), along with a statistically significant Cochran's Q test for heterogeneity (Q = 32.41, p <0.001).

Additionally, about 69% of the disease duration was associated with stage 4B (n = 352) and had a 95% CI of [57.40%; 80.79%]. This stage also exhibited substantial between-study heterogeneity (I2 = 93.7%) and heterogeneity variance (tau2 = 0.0067), supported by a statistically significant Cochran's Q test for heterogeneity (Q = 15.81, p <0.001). **(Figure 1)**

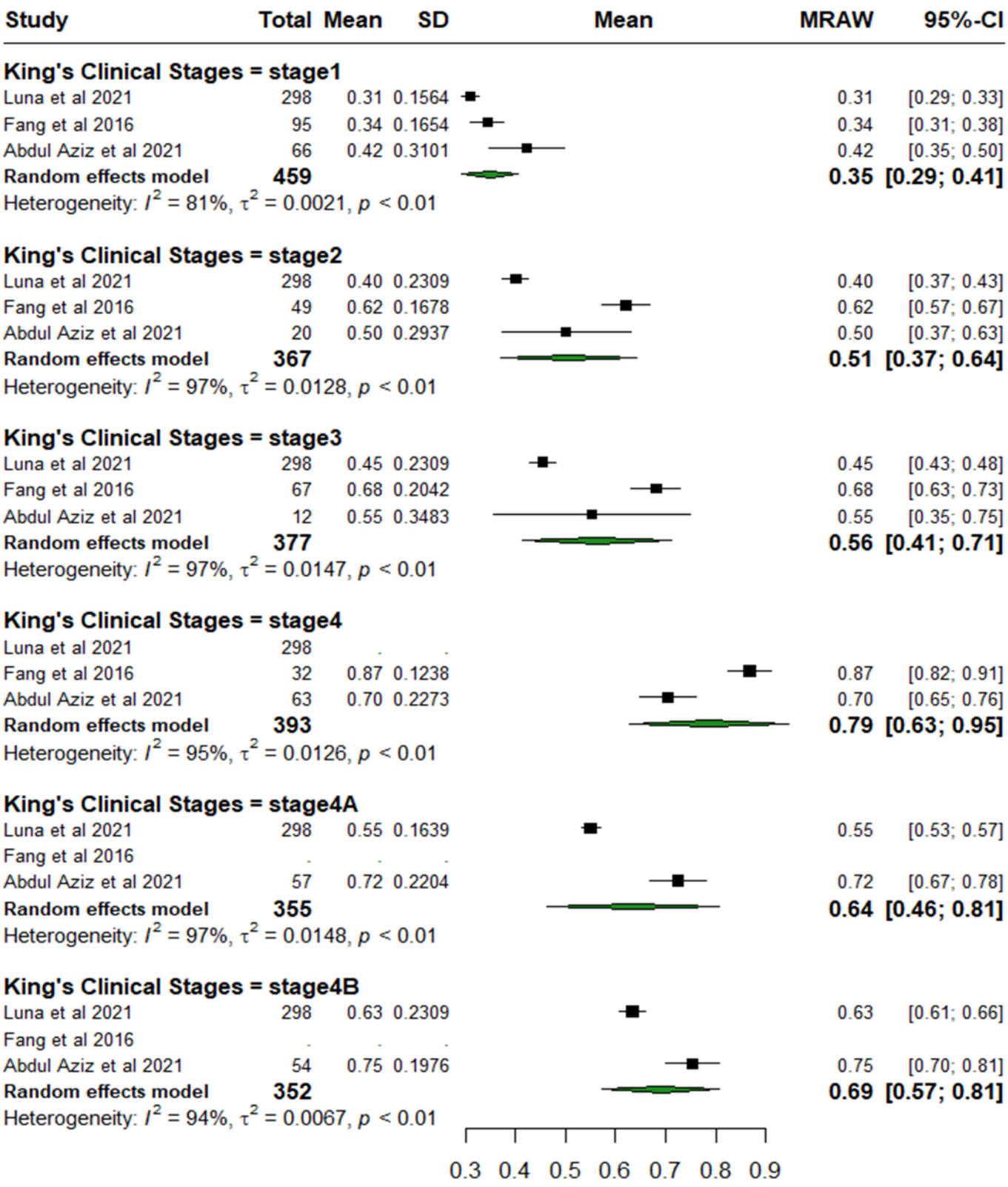

Figure 2. Forest plot for standardized meantime for King's clinical stages among ALS patients

The Milano-Torino (MiToS) staging system

The combined standardized mean duration for each MiToS clinical stage revealed that approximately 36% of the disease duration corresponded to MiToS stage 0 (n = 424) with a 95% confidence interval (CI) of [34.25%; 37.82%]. There was no significant between-study heterogeneity (I2 = 0.0%) or heterogeneity variance (tau2 = 0.0), as indicated by a non-significant Cochran's Q test for heterogeneity (Q = 1.56, p = 0.46).

Additionally, approximately 60% of the disease duration was attributed to stage 1 (n = 429) with a 95% CI of [58.02%; 61.27%]. Similar to stage 0, there was no substantial between-study heterogeneity (I2 = 0.0%) or heterogeneity variance (tau2 <0.0001), as evidenced by a non-significant Cochran's Q test for heterogeneity (Q = 1.42, p = 0.49).

However, around 78% of the disease duration was associated with stage 2 (n = 376) with a 95% CI of [71.03%; 84.09%]. In this case, there was significant between-study heterogeneity (I2 = 79.8%) and heterogeneity variance (tau2 = 0.0027), as confirmed by a statistically significant Cochran's Q test for heterogeneity (Q = 9.91, p <0.001).

Additionally, about 87% of the disease duration was allocated to stage 3 (n = 341) with a 95% CI of [81.83%; 91.72%]. There was noticeable between-study heterogeneity (I2 = 68.6%) and heterogeneity variance (tau2 = 0.0014), supported by a statistically significant Cochran's Q test for heterogeneity (Q = 6.38, p =0.04).

Furthermore, approximately 87% of the disease duration was attributed to stage 4 (n = 310) with a 95% CI of [76.56%; 96.81%]. In this case, there was substantial between-study heterogeneity (I2 = 98.7%) and heterogeneity variance (tau2 = 0.0070), as indicated by a statistically significant Cochran's Q test for heterogeneity (Q = 148.45, p <0.001). **(Figure 2)**

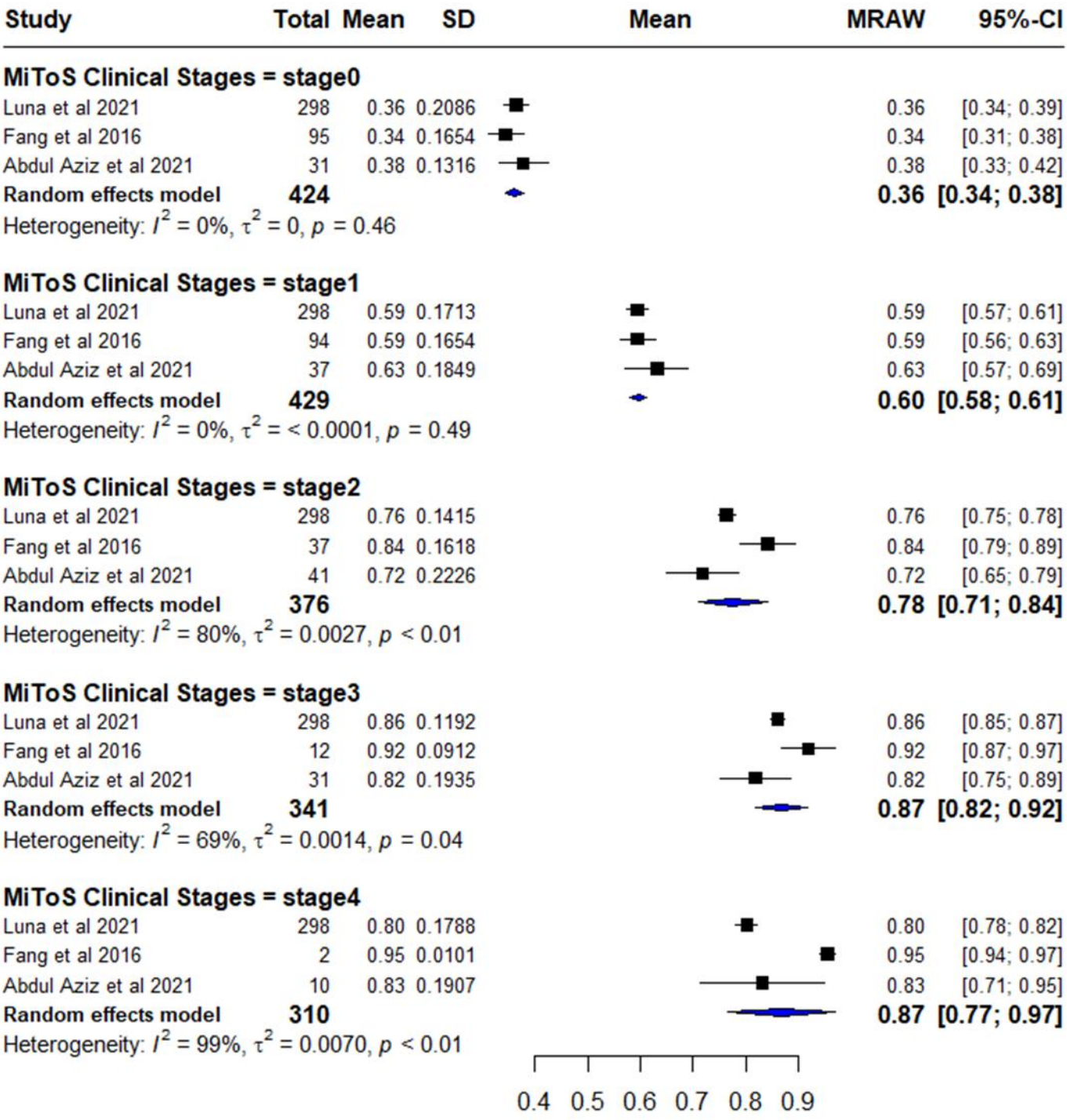

Figure 3. Forest plot for standardized meantime for MiToS clinical stages among ALS patients

Correlation coefficient

The random effects model incorporated 2 studies involving a total of 334 participants, revealing the combined correlation coefficient between the King's and MiToS staging systems (r = 0.75, 95% CI: [0.248; 0.932], p = 0.0078). There was considerable between-study heterogeneity (I2 = 97.4%, 95% confidence interval: [93.6%; 99.0%]) and heterogeneity variance (tau2 = 0.256), as evidenced by a statistically significant Cochran's Q test for heterogeneity (Q = 39.08, p <0.001). **(Figure 3)**

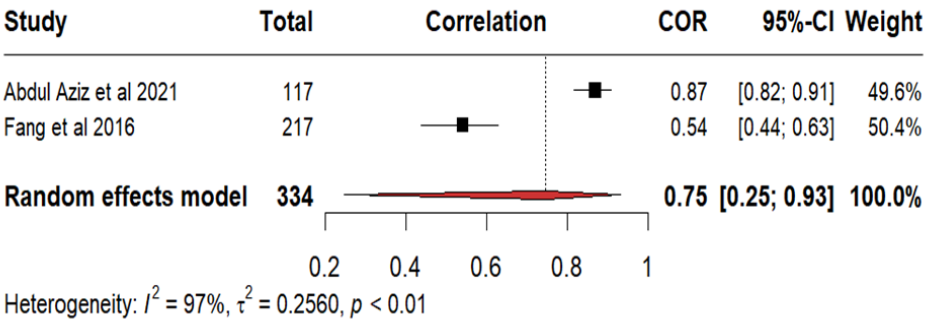

Figure 4. Forest plot for correlation coefficient between King's and MiToS staging systems among ALS patients

The funnel plot showed symmetrical distribution of both studies around the vertical line of the pooled effect size indicating that there was no publication bias evidence. **(Figure 4)**

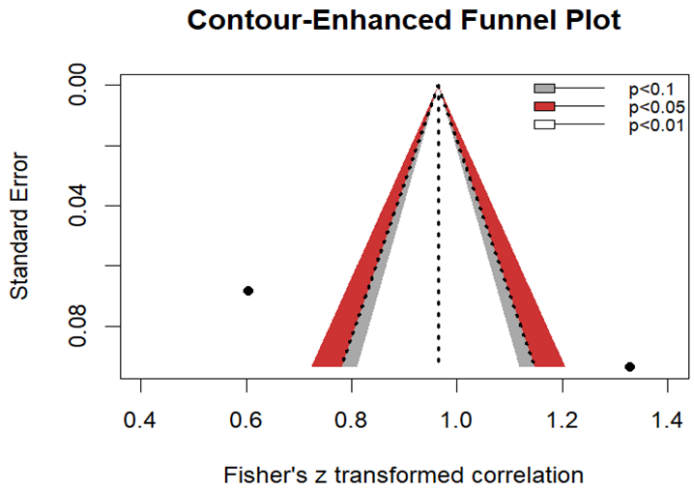

Figure 5. Funnel plot for correlation between King's MiToS staging systems among ALS patients.

Discussion

This review, encompassing eight studies with a total of 5,277 patients, aims to investigate and compare the two King's and MiToS staging systems. It seeks to assess their performance, utility, precision, and validity in mapping the progression of ALS in clinical practice.

Our findings indicate that both the King's and MiToS staging systems prove valuable in delineating the progress of ALS patients. We observed that the progression through the King's stages was relatively equally disseminated, with the lengthiest part (35%) of the disease course occurring at Stage 1. Notably, patients began to require respiratory and/or nutritional support after 79% of the illness progression had transpired.

Conversely, the MiToS staging system demonstrated its utility in disease advanced stages, becoming particularly relevant after 87% of the disease duration had gone, coinciding with a more apparent functional domain loss. Additionally, we identified a significant association between the two both systems ($r = 0.75$, 95%CI: [0.248; 0.932], $p = 0.0078$).

Moreover, we determined that the two disease staging systems discussed complement each other instead of being duplicative, offering distinct information types. The King's system delivers a summary of disease clinical or anatomical dissemination, whereas the MiToS staging system encapsulates disease functional problems.

We identified minor differences within the staging systems that have the potential to enhance their performance, particularly in terms of validity and predictive capabilities. While the patient stages manifested at varied time intervals, notable associations existed between most of stages of two systems. Notably, King's stage 4 most frequently corresponded to MiToS stage 2 (21,25).

The King's system exhibited a progressively escalating hazard with all consecutive stage, and the hazard ratios between neighboring stages exhibited significant disparities. Remarkably, the MiToS system demonstrated the highest performance (C-statistic = 0.792).

An alteration in the MiToS system fused stages 3 and 4 into a unified stage 3, primarily because of the intersection of stages and inconsistencies in the risk rise during transitions between various stages. A simplified system was resulted that exhibited precise predictive capabilities. Across the variations in staging systems, statistically significant differences were observed between every stage for every system. These modifications may prove more advantageous in determining disease course (27).

A particular study undertook a comparison of stages timing, concordance, and association between the two systems (21). There was a modest association between both systems. Their conclusion emphasized that these two systems complement each other, primarily based on the distribution of timeframes. Notably, they identified closely aligned standardized median times (SMT) for stage 3 (0.93) and stage 4 (0.95) within the MiToS system (21)**.** This observation is significant because MiToS depended on independence functional loss, a milestone typically reached after more than 50% of the disease course has transpired (21,25,26).

According to the SMT, we observed an earlier transition from stage 1 to stage 2 and from stage 2 to stage 3 in the cohort from clinical trials (21) and in the prospective clinic cohort (25)**,** respectively. Conversely, in the population-based study (26), the shift from Stage 3 to 4 occurred later, providing further evidence for the possibility of ALS patients with bulbar-onset bypassing the King's system stages.

We also conducted a comprehensive evaluation of the staging systems to assess their predictive capacity for the illness progression. Within the King's College system, there was a reduction in survival rates and an upsurge in mortality rates with advancing stages. In contrast, the MiToS system exhibited survival curves that overlapped for middle stages, with a relatively uniform number of deaths across most stages (26,27). Notably, King's system demonstrated greater sensitivity to the observed disease progression in clinical trials compared to MiToS (29).

Furthermore, both the King's and MiToS staging systems have the potential to identify scenarios in which specific treatments may be optimally utilized. Multiple studies have highlighted the staging systems' role in evaluating therapeutic effectiveness and their utility in the context of clinical trials (22,29–31).

Through retrospective analyses, riluzole has demonstrated its effectiveness in extending the duration of the first four King's stages, as well as the first MiToS stage (22,29–31). In another analysis of the edaravone, researchers observed a deceleration in the progression of the disease from King's Stage 1 to Stage 2. Both the King's ALS clinical staging system and the MiToS system appeared capable of detecting differences in clinical progression between patients randomly assigned to edaravone and those receiving a placebo (22). Another study indicated that the progression of the disease using the MiToS system (for 6 months) could predict outcomes such as death, tracheotomy, or the need for >23-hour non-invasive ventilation at 12 months and 18 months (32).

The King's stage 1 time may hold particular significance for patients, as this phase is characterized by relatively lower disability levels. This aspect may also carry inferences for health finances, as the initial ALS stages had lesser costs compared to the later (11,33,34). According to prognostic factors, the onset of bulbar was linked to an speeded prognosis through the intermediate stages of the MiToS system, particularly involving transitions from King's stages 1 and 2 to 4a (29).

By incorporating the staging systems as primary or secondary endpoints, it becomes feasible to examine the probable impact of any intervention or treatment. This approach can lead to a more effective resources distribution, especially in regions with lower and middle-income levels. Both systems demonstrated a robust correlation with measures of the quality of life (33,34).

To summarize, the King's system exhibits greater consistency (i.e., minor variations in patients' survival in the same stage) and enhanced discriminative capacity (i.e., major variations in patients' survival in different stages) in comparison to the MiToS system. This suggests a stronger predictive capability for King's system, mainly for patient progression and as a consequence detection in clinical trials. While King's clinical staging system effectively distinguishes between early and mid-stage disease, the MiToS staging system excels in distinguishing late-stage disease (21,26).

Specifically, the King's staging system is user-friendly, and supported by standardized process to simplify its application (35). It proves valuable in assessing disease extent, with functional loss (25). On the other hand, the MiToS system, relying on complete function loss in various domains, may be more suitable for estimating healthcare costs and allocating resources (20).

The strength of this study lies in the validation of the staging systems within clinical trial cohorts (12,21,22,25,29) and an incident population-based investigation (26–28). Employing data from clinical and population-based trials offers the findings to be applied to routine clinical practice and are representative of real-world scenarios.

Nonetheless, several limitations are associated with the current study. Firstly, the patient cohorts were relatively small. Also, the retrospective nature of included studies. Additionally, it was observed that an extensive number of patients presented with advanced-stage disease commonly in low- and middle-income countries where limited access to specialized care. This postponement may have led to time underestimation which spent in King's Stage 1 and MiToS Stage 0.

Finally, the absence of prognostic factors data (e.g., cognitive impairment) and aspects of ALS heterogeneity (such as cognitive function, neuropsychiatric symptoms, and upper motor neuron dysfunction) wasn't methodically investigated in all patients. Subsequent investigations are warranted to explore whether the inclusion of additional prognostic factors could enhance the characterization of the disease course.

Conclusion

In conclusion, our comparison of the two ALS staging systems, drawing upon diverse studies, revealed that King's staging is valuable for assessing the stages of disease burden, while both systems prove useful in gauging the time to functional dependence. MiToS, in particular, offers a more refined characterization of levels of dependence. King's staging system exhibits greater sensitivity to the observed disease progression in clinical trials and is more straightforward to apply to retrospective data when compared to MiToS.

There is a compelling imperative for the adoption of both staging systems as a standardized framework for evaluating the disorder course progression and survival in routine clinical practice. This adoption has the potential to enhance healthcare control and randomized clinical trials design. Additional research is warranted to further investigate the nuances within these staging systems.

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