Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Miller et al. 2012 Meta-analysis	Class I	Three randomized controlled trials including a total of 1477 patients, 974 of whom treated with riluzole, and 503 on placebo.	A pooled hazard ratio (HR) of death was calculated from each study. These were then averaged in a weighted fashion, with weights being inversely proportional to the variance of the natural log-transformation the pooled HRs.	Trachostomy-free survival over all time points.	Pooled hazard ratio was found to be in favor of riluzole (0.84, 95% CI 0.698-0.997) representing a gain of one year survival from 49% to 58%, and median survival increase from 11.8 to 14.8 months.
Rooney et al. 2013 Retrospective cohort	Class III	1,282 cases registered from 1995-2010 to the Irish ALS Registry	Cox proportional hazards and Royston-Parmar flexible parametric modeling methods were used ot examine factors affecting survival.	Proportional hazard ratio of death, as calculated from each of the modeling methods.	Adjusting for covariates, hazard ratio for riluzole favored its use (0.72, 95%CI 0.61-0.85). Unadjusted median survival was found to be 1.46 years for those prescribed Riluzole, versus 0.85 for those who were not (rate ratio 0.65, 95%CI 0.58-0.74).
Stevic et al. 2016 Retrospective cohort	Class III	325 cases of probable or definite ALS diagnosed from 1992-2009 at five sites in Belgrade, Serbia .	Cox proportional hazard regression model to control for covariates	Proportional hazard ratio of death.	Adjusting for covariates, hazard ratio found to be in favor of riluozle (0.57, 95% CI = 0.41-0.79).
Georgoulopoulou et al. 2013 Prospective cohort	Class III	193 patients residing in Modena, Itally, who were diagnosed from 2000-2009 at a single site.	Cox proportional hazard regression model to control for covariates; Kaplan-Meier method for survival calculation.	Survival as defined from onset to death, tracheostomy, or censoring date (December 21, 2011)	Unadjusted, patients on riluzole had a significantly longer median survival 43 vs. 31 months, $p < 0.01$), while outcome to death or tracheostomy did not differ significantly (38 vs 31 months, $p = 0.11$). Covariate-controlled hazard ratios not reported.
Wei et al. 2015 Prospective cohort	Class III	1049 patients with sporadic definite or probable ALS according to El Escorial revised criteria seen at a single centre in south-west	Kaplan-Meier method to determine survival time; Cox proportional	Survival as defined as time from date of onset to date of death, date of tracheostomy, or date of	155 patients were lost to followup; 378 patients died, 516 alive at time of last visit.

		China from May 2006 to March 2014.	hazards method to control for covariates;	last follow-up (censored).	Kaplan-Meier analysis revealed no significant difference in median survival for riluzole use (log-rank p = 0.142). Multivariate modeling through the Cox proportional hazards method found no effect with the use of riluzole (p = 0.919).
Chen et al. 2016 Prospective cohort	Class III	1540 patients diagnosed at a single site in China with sporadic ALS from 2007-2013 according to the Airlie House diagnostic criteria but with inclusion of pure lower motor neuron syndromes classified as a suspected ALS category.	Survival was analyzed with Kaplan-Meier and Cox regression analysis. Riluzole use was also strartified into quartiles based on estimated cumulative defined daily dose.	Survival and tracheostomy, with data censoring at January 31, 2015.	Kaplan-Meier and multivariate Cox regression analysis revealed no significant difference from use of riluzole. Stratified subgroup analysis of patients with a cumulative defined daily dose over the 75th percentile demonstrated a hazard ratio for survival in favour for riluzole (0.488, 95% CI 0.320-0.746).
Mandrioli et al. 2018 Retrospective cohort	Class III	681 patients diagnosed with ALS at a single site in Italy, from 2009-2014.	Survival was analyzed using Kaplan-Meier analysis and Cox proportional hazards models.	Survival to death, tracheostomy, or censoring data	Univariate analysis of riluzole use did not result in increased survival. Calculating riluzole use as a percentage of disease duration, HR of 0.98 in favor of riluzole use was found. Authors uncertain if this represents general acceptance of therapeutic interventions.

Sivori et al. 2007 Retrospective cohort	Class III	97 patients diagnosed with ALS between December 1999-2004 in a single centre in Brazil.	Survival calculated using Kaplan-Meier analysi, stratified based on riluzole and NIV usage	Survival to death	NIV, but not riluzole, on its own improved survival significantly.
Lee et al. 2013 Retrospective cohort	Class III	1149 patients with ALS seen in Taiwan from 1999 to 2008.	Mortality rates estimated using life table analysis. Cox regression models used to estimate covariate hazard rates.	Survival to death, survival to tracheostomy	Adjusting for covariates, hazard rate found to be in favor of riluzole per day (0.32, 95%CI 0.22-0.45(.
Watanabe et al. 2015 Prospective cohort	Class III	451 sporadic ALS patients from 30 centres in Japan, registered from 2006-2012.	Linear mixed-effect modeling and Kaplan-Meier analysis	Tracheostomy-free survival, ALSFRS-R	Adjusting for covariates, hazard ratio in favor for riluzole (0.71, 95%CI 0.83-0.97) but not ALSFRS-R (-1.05, 95%CI -2.58-0.49)
Calvo et al. 2017 Retrospective cohort	Class III	2648 incident ALS cases from 13 Italian centres between 2009-2013.	Kaplan-Meier survival analysis and multivariate Cox regression analysis	Tracheostomy-free survival	Riluzole not found to significantly impact survival
Keren et al. 2014 Prospective/retrospective cohort	Class III	933 ALS patients registered in the South-East England ALS Register between 1990-2012.	Kaplan-Meier survival analysis and multivariate Cox regression analysis	Survival as defined from disease onset to death.	Adjusting for covariates, hazard ratio in favor for riluzole (0.81, 95%CI 0.70-0.95)
Fang et al. 2018 Retrospective cohort	Class III	Reanalysis of 959 patients enrolled in the original dose-ranging clinical trial of riluzole.	Kaplan-Meier product limit distribution to compare time to change between different King's clinical stage; multivariate Cox regression for covariate adjustment	Mean duration spent in each disease clinical stage for each treatment group.	Adjusting for covariates, riluzole at 100mg/d favored longer survival within clinical stage 4 (0.55, 95%CI 0.36-0.83).
Chen et al. 2018 Prospective cohort	Class III	1493 patients with ALS registered from May 2008 to December 2016 at a single centre in China.	Kaplan-Meier analysis; student's t-test.	Mean duration spent in each King's college clinical stage	Long-term riluzole users had significantly longer duration of stage 1 and 2 compared to short-term riluzole use.
Zoccolella et al. 2007 Prospective cohort	Class III	126 incident cases registered 1998-1999 in Puglia, Italy	Kaplan-Meier survival analysis and multivariate Cox regression analysis	Sruvival as defined from diagnosis to death	Overall, adjusted HR for riluzole was in favor of its use but not significantly so (HR 0.51, 95%CI 0.25-1.03, p = 0.06). Subgroup analysis found rliuzole use to be favored for

					bulbar-onset patients (HR 0.26, 95%CI 0.07-0.92, p = 0.04) and elderly (0.36, 95%CI 0.10-0.93, p < 0.04)
Edaravone (MCI-186) ALS19 Study Group, 2017 randomized, double-blind, parallel-group study.	Class I	192 patients with definite/probable ALS, grade 1 or 2 on Japan ALS Severity Classification, ≥2 on all ALSFRS-R items, FVC ≥ 80%, disease duration ≤ 2 years	ANOVA with treatment group and three dynamic allocation factors.	Change in ALSFRS-R score from baseline to end of trial (cycle 6) or discontinuation, for all patients who reached the end of cycle 3	Lease square mean difference between the change of ALSFRS-R score of the groups was statistically significant (2.49, 95%CI 0.99-3.98, p = 0.0013).
Chen L, Zhang B, Chen R, Tang L, Liu R, Yang Y, Yang Y, Liu X, Ye S, Zhan S, et al. Natural history and clinical features of sporadic amyotrophic lateral sclerosis in China. Journal of Neurology, Neurosurgery, and Psychiatry. 2015;86(10):1075–1081. *Prospective cohort*	Class III	1624 patients with ALS referred between 2003-2012 at a single centre in China, followed until May 2013	Kaplan-Meier survival analysis and multivariate Cox regression analysis	Tracheostomy-free survival	Adjusted HR did not significantly favor riluzole
Citation 31, 32 error					

Full Citation	Title	Type of study	Sample Size	Response %	**Summary of Findings**
Chen L, Zhang B, Chen R, Tang L, Liu R, Yang Y, Yang Y, Liu X, Ye S, Zhan S, et al. Natural history and clinical features of sporadic amyotrophic lateral sclerosis in China. Journal of Neurology, Neurosurgery, and Psychiatry. 2015;86(10):1075–1081.	**Natural history and clinical features of sporadic amyotrophic lateral sclerosis in China**	Retrospective cohort (Class III)	1900	**1624 (85%)**	• No data on effect of riluzole use
Wei Q, Chen X, Zheng Z, Guo X, Huang R, Cao B, Zeng Y, Shang H. The predictors of survival in Chinese amyotrophic lateral sclerosis patients. Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration. 2015;16(3–4):237–244.	**The predictors of survival in Chinese amyotrophic lateral sclerosis patients.**	Retrospective cohort (Class III)	1049	**N/A**	• Riluzole had no effect on survival
Calvo A, Moglia C, Lunetta C, Marinou K, Ticozzi N, Ferrante GD, Scialo C, Sorarù G, Trojsi F, Conte A, et al. Factors predicting survival	**Factors predicting survival in ALS: a**	Retrospective cohort (Class III)	2648 incident cases	**100%**	• Hazard ratio of 0.79 of death with Riluzole use

in ALS: a multicenter Italian study. Journal of Neurology. 2017;264(1):54–63.	**multicenter Italian study**				• 44% death in Riluzole vs. 56% no Riluzole = 12% survival benefit
Chen L, Liu X, Tang L, Zhang N, Fan D. Long-Term Use of Riluzole Could Improve the Prognosis of Sporadic Amyotrophic Lateral Sclerosis Patients: A Real-World Cohort Study in China. Frontiers in Aging Neuroscience. 2016;8:246.	**Long-term use of Riluzole Could Improve the Prognosis of Sporadic Amyotrophic Lateral Sclerosis Patients: A Real-World Cohort Study in China**	Retrospective cohort (Class III)	1540	**100%**	• Riluzole did not have any effect as a whole • 3rd quartile of cumuluative daily dose of riluzole saw improved median survival of 88m
Chen X, Wei Q-Q, Chen Y, Cao B, Ou R, Hou Y, Yuan X, Zhang L, Liu H, Shang H. Clinical Staging of Amyotrophic Lateral Sclerosis in Chinese Patients. Frontiers in Neurology. 2018;9:442.	**Clinical Staging of Amyotrophic Lateral Sclerosis in Chinese Patients**	Retrospective cohort (Class III)	1696	**1473 (87%)**	• Riluzole extended duration of stage 1-2
Fang T, Al Khleifat A, Meurgey J-H, Jones A, Leigh PN, Bensimon G, Al-Chalabi A. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. The Lancet. Neurology. 2018;17(5):416–422.	**Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study**	Post-hoc analysis (Class III/IV?)			• Riluzole extends duration of stage 4
Mandrioli J, Malerba SA, Beghi E, Fini N, Fasano A, Zucchi E, De Pasqua S, Guidi C, Terlizzi E, Sette E, et al. Riluzole and other prognostic factors in ALS: a population-based registry study in Italy. Journal of Neurology. 2018;265(4):817–827.	**Riluzole and other prognostic factors in ALS: a population-based registry in Italy**	Retrospective cohort (Class III)	681 incident cases		• Riluzole did not affect survival • Duration of riluzole use associated with better survival
Stevic Z, Kostic-Dedic S, Peric S, Dedic V, Basta I, Rakocevic-Stojanovic V, Lavrnic D. Prognostic factors and survival of ALS patients from Belgrade, Serbia. Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration. 2016;17(7–8):508–514.	**Prognostic factors and survival of ALS patients from Belgrade, Serbia**	Retrospective cohort (Class III)	325 incident cases		• Mean survival improved from 43.2 to 54m uncorrected • Multivariate analysis revealed HR 1.76 survival

					• 0.57 HR of death = 36% death on Riluzole vs. 64% without = 28% survival benefit
Watanabe H, Atsuta N, Nakamura R, Hirakawa A, Watanabe H, Ito M, Senda J, Katsuno M, Izumi Y, Morita M, et al. Factors affecting longitudinal functional decline and survival in amyotrophic lateral sclerosis patients. Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration. 2015;16(3–4):230–236.	**Factors affecting longitudinal functional decline and survival in amyotrophic lateral sclerosis patients**	Retrospective cohort (Class III)	549		• Hazard ratio 1.41 for survival – 41% improvement • HR = 0.71 of death = 42% of death on Riluzole vs 58% without = 16% survival benefit

Full Citation	Title	Type of study	Sample Size	Response %	**Summary of Findings**
Georgoulopoulou E, Fini N, Vinceti M, Monelli M, Vacondio P, Bianconi G, Sola P, Nichelli P, Mandrioli J. The impact of clinical factors, riluzole and therapeutic interventions on ALS survival: a population based study in Modena, Italy. Amyotrophic Lateral Sclerosis &	**The impact of clinical factors, riluzole and therapeutic interventions on ALS survival: a population based study in Modena, Italy.**	Retrospective cohort (Class III)	193	**179 (93%)**	• Riluzole found to be an independent factor for longer median survival by 12m
Lee CT-C, Chiu Y-W, Wang K-C, Hwang C-S, Lin K-H, Lee I-T, Tsai C-P. Riluzole and prognostic factors in amyotrophic lateral sclerosis long-term and short-term survival: a population-based study of 1149 cases in Taiwan. Journal of Epidemiology. 2013;23(1):35–40.	**Riluzole and prognostic factors in amyotrophic lateral sclerosis long-term and short-term survival: a population-based study of 1149 cases in Taiwan.**	Retrospective cohort (Class III)	1149	**1149 (100%)**	• HR of death on Riluzole = 0.34 • 25% chance of death on Riluzole vs. 75% without = 50% survival benefit
Cetin H, Rath J, Füzi J, Reichardt B, Fülöp G, Koppi S, Erdler M, Ransmayr G, Weber J, Neumann K, et al. Epidemiology of amyotrophic lateral sclerosis and effect of riluzole on disease course. Neuroepidemiology. 2015;44(1):6–15.	**Epidemiology of amyotrophic lateral sclerosis and effect of riluzole on disease course.**	Retrospective cohort (Class III)	911	**886 (100%)**	• Survival 15% higher in riluzole group at 6m • Survival 14% lower at 48m

Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). The Cochrane Database of Systematic Reviews. 2012;(3):CD001447.	**Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)**	Meta-analysis (Class I)			• Improves survival from 11.8m to 14.8m
Rooney J, Byrne S, Heverin M, Corr B, Elamin M, Staines A, Goldacre B, Hardiman O. Survival analysis of irish amyotrophic lateral sclerosis patients diagnosed from 1995-2010. PloS	**Survival analysis of irish amyotrophic lateral sclerosis patients diagnosed from 1995-2010.**	Retrospective cohort (Class III)	1282	**1086 (85%)**	• Riluzole increased median survival from 10.2m to 17.5m
Scotton WJ, Scott KM, Moore DH, Almedom L, Wijesekera LC, Janssen A, Nigro C, Sakel M, Leigh PN, Shaw C, et al. Prognostic categories for amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis: Official Publication of the World Federation of Neurology Research Group on Motor Neuron Diseases. 2012;13(6):502–508.	**Prognostic categories for amyotrophic lateral sclerosis.**	Retrospective cohort (Class III)	574	**574**	• Unadjusted median survival improvement from 40m to 65m • Lists relative risk of survival as 1.55
Sívori M, Rodríguez GE, Pascansky D, Sáenz C, Sica REP. Outcome of sporadic amyotrophic lateral sclerosis treated with non-invasive ventilation and riluzole. Medicina. 2007;67(4):326–330.	**Outcome of sporadic amyotrophic lateral sclerosis treated with non-invasive ventilation and riluzole.**	Retrospective cohort (Class III)	97	**97 (100%)**	• Riluzole gave no survival benefit
Zoccolella S, Beghi E, Palagano G, Fraddosio A, Guerra V, Samarelli V, Lepore V, Simone IL, Lamberti P, Serlenga L, et al. Riluzole and amyotrophic lateral sclerosis survival: a population-based study in southern Italy. European Journal of Neurology. 2007;14(3):262–268.	**Riluzole and amyotrophic lateral sclerosis survival: a population-based study in southern Italy.**	Retrospective cohort (Class III)	130	**126 (97%)**	• Use of riluzole associated with 10% reduction in mortality at 12m • Corresponds to increase in survival by 6m • Benefit is transient – no difference at 12m • Improvement most notable in bulbar patients
Keren N, Scott KM, Tsuda M, Barnwell J, Knibb JA, Ellis CM, Leigh PN, Shaw CE, Al-Chalabi A. Evidence of an environmental effect on survival in ALS. Amyotrophic Lateral Sclerosis &	**Evidence of an environmental effect on survival in ALS.**	Retrospective cohort (Class III)	933	**814 (87%)**	• Use of riluzole has HR of 0.81 of death • 45% death on Riluzole = 10% improvement in survival

Frontotemporal Degeneration. 2014;15(7–8):528–533.					
Bensimon G, Lacomblez L, Delumeau JC, Bejuit R, Truffinet P, Meininger V, Riluzole/ALS Study Group II. A study of riluzole in the treatment of advanced stage or elderly patients with amyotrophic lateral sclerosis. Journal of Neurology. 2002;249(5):609–615.	**A study of riluzole in the treatment of advanced stage or elderly patients with amyotrophic lateral sclerosis.**	RCT (Class I)	168	**168**	• Underpowered to detect difference in survival