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The value of serum uric acid as a prognostic biomarker in amyotrophic lateral sclerosis: Evidence from a meta-analysis

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ABSTRACT

Objective: To determine the value of uric acid (UA) as a prognostic biomarker for amyotrophic lateral sclerosis (ALS) using a meta-analysis of hazard ratio-based studies.
Methods: We included data from Tokushima University (47 patients with ALS) and three previous studies (1835 patients with ALS) with a hazard ratio (HR) identified by a systematic computational search. A total of four studies and 1882 patients were enrolled in the pooled analysis. We pooled HRs of death or tracheostomy, which were estimated by a Cox proportional hazard model, using a random-effects model. Heterogeneity was assessed by Q statistic, and a p value < 0.1 was considered significant heterogeneity. Furthermore, sensitivity analysis was performed to assess the effect of each single study and the robustness of the summary effect. We evaluated publication bias by visual assessment of the funnel plot and Egger's test, and adjusted the bias using a trim-and-fill method.
Results: This meta-analysis revealed that UA could be a prognostic factor for ALS (all, HR = 0.87, $p < 0.001$; men, HR = 0.83, $p < 0.001$; women, HR = 0.76, $p < 0.001$). The included studies were homogeneous (all, $p = 0.43$; men, $p = 0.9$; women, $p = 0.49$). Sensitivity analysis confirmed the robustness of these summary effects. Publication bias was detected, which was adjusted for by a trim-and-fill method. The adjusted results showed significant summary effects (all, HR = 0.88, $p = 0.002$; men, HR = 0.83, $p < 0.001$; women, HR = 0.77, $p < 0.001$).
Conclusion: The present meta-analysis suggests that the serum UA level could be a prognostic biomarker in patients with ALS. Sensitivity analyses and the trim-and-fill method supported the robustness of these results.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration of motor neurons, causing weakness of the limbs, bulbar, and respiratory muscles [1]. The mean survival time of patients with ALS is considered to be three to five years from the onset of symptoms, although it has a wide range [2]. It is important to categorize patients with ALS by prognosis for clinical trials, but only a few prognostic factors have been reported, including blood uric acid (UA), albumin, creatinine, lipids, apolipoproteins, neurofilament light chain, and body mass index (BMI) [3–11], using hazard ratios (HR). It was demonstrated in animal ALS models that UA serves as an antioxidant to protect neurons [12,13]. Considering these findings, UA could be a candidate prognostic biomarker, based on its neuroprotective effect. However, the prognostic value of UA remains controversial [4–6,14–18]. A meta-analysis could yield robust evidence for UA as a prognostic biomarker. One previous meta-analysis reported an association between serum UA and risk of death in ALS patients [19], but it combined the HR and the odds ratio (OR) to estimate the main effects of serum UA on prognosis. The HR is derived from a time-to-event analysis, while the OR ignores time. Therefore, the HR is preferable for survival analysis [20], and an HR-based meta-analysis would be expected to provide more robust evidence. Furthermore, we applied a trim-and-fill method to address the important issue of potential publication bias in our meta-analysis. The aim of this study was to establish HR-based evidence that serum UA could be a prognostic biomarker for ALS using

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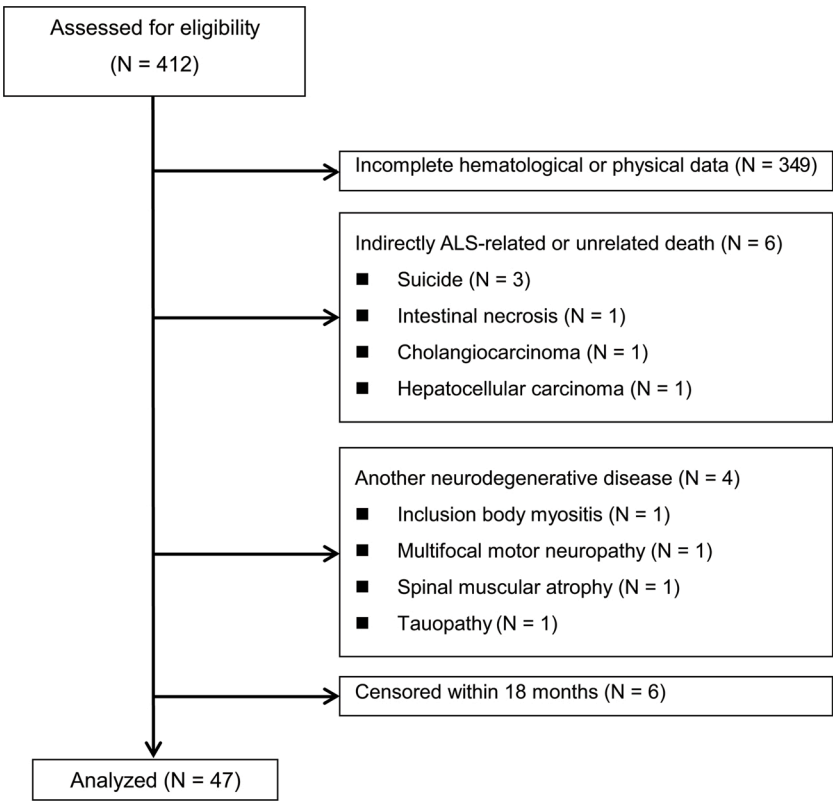

Fig. 1. Flowchart of the retrospective study.

time-to-event information and adjustment for publication bias.

2. Materials and methods

2.1. Subjects and statistics

All patients were recruited from 1st January 2006 to 30th November 2017. A total of 412 consecutive patients with ALS were potentially eligible for this longitudinal study. The baseline was defined as the first medical examination. The inclusion criteria were: (1) patients were diagnosed with possible, probable, or definite ALS according to the El Escorial criteria; (2) the serum UA level at baseline was described; (3) the follow-up duration was > 18 months without any events, or patients were followed until the time of death or tracheostomy. The exclusion criteria included: (1) a diagnosis of other types of neurodegenerative disorders; (2) the cause of death was suicide or cancer. Of the 412 patients identified in this study, 47 patients who met the inclusion and exclusion criteria were included for further analysis (Fig. 1). This study was approved by the institutional ethical committee of Tokushima University Hospital.

For statistics, a Cox proportional hazard model was used to evaluate prognostic factors. A p value < 0.05 was considered significant. These statistical analyses were performed using the survival and survminer packages of R software version 3.5.1 (http://www.r-project.org).

2.2. Search strategy, study selection and data extraction

The present meta-analysis was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement [21]. Two researchers (S.H. and N.M.) independently performed computational searches through PubMed and Scopus in September 2018, using the following syntax: ("amyotrophic lateral sclerosis" OR "ALS") AND ("uric acid" OR "urate"). Studies were included if they fulfilled the following criteria: (1) patients were diagnosed with possible, probable, or definite ALS according to the El Escorial criteria; (2) the serum level of UA was measured at baseline; (3) the values of the HR and the 95% confidence interval (CI), or data allowing the estimation of the HR and the 95% CI according to the formulae, were available [20]; (4) the endpoint was defined as death or tracheostomy; (5) they were written in English. Further studies were sought by manual searching of references in relevant reviews and papers. We extracted UA level, event-free survival time, age, sex, BMI, and creatinine level from each study. The corresponding authors were contacted if missing data was observed. At the end of the review process, any discrepancies were resolved by mutual agreement between the two researchers (S.H. and N.M.).

2.3. Data synthesis and statistics

We applied HR, calculated according to the Cox proportional hazard model, to data synthesis. A random-effects model was used for estimating the pooled effect size, because underlying effects could differ across the studies included in this analysis. The inverse-variance method was used to assign weights for this meta-analysis [20]. We identified and qualified the heterogeneity using the Q statistic (p), and the statistics provided the between-studies standard deviation (τ) and the ratio of true heterogeneity to the total observed variation (I^2) [22]. DerSimonian and Laird's method of moments estimator was applied to calculate the variance of the effect of UA [23].

Sensitivity analysis was performed to assess the effect of each single study and the robustness of the summary effect. Publication bias was evaluated by visual inspection of funnel plot asymmetry and Egger's linear regression test [24]. The trim-and-fill method allows for adjustment of unpublished studies to overcome publication bias [25]. In detail, this method generates a symmetric funnel plot by addition and/or removal of studies, which helps to estimate the true center of the funnel [25,26]. A p value < 0.1 for the Q statistic was considered significant heterogeneity. All analyses were carried out using Review Manager

Table 1
Characteristics of studies included in the present meta-analysis.

Baseline characteristics	The present study	Paganoni 2017	Oh 2015	Kataoka 2013
Number of patients	47	1736	65 [a]	34 [a]
Age at evaluation, y	67.5 ± 10.3	55.0 ± 12.1	55.4 ± 11.3 [a]	75.2 ± 3.9 [a]
Women, %	40.0	36.7	46.2 [a]	50.0 [a]
UA, mg/dl	5.0 ± 1.4	5.0 ± 1.3	4.4 ± 1.2 [a]	4.9 ± 1.3 [a]
Riluzole use at baseline, %	20.7	N/A	27.2	35.3
Adjusted or raw data	Raw	Adjusted	Raw	Raw
Adjusted factor	Sex	Age, BMI, Cre, Duration, Sex	Sex	Sex
Disease duration, m [a]	13.3 ± 6.0	10.5 ± 8.7	12.8 ± 6.2 [a]	15.9 ± 3.2 [a]
ALSFRS-R score [a]	37.9 ± 5.6	N/A	40.0 ± 4.9	N/A
BMI, kg/m^{2a}	21.2 ± 3.5	25.3 ± 4.5	22.6 ± 3.4	N/A
Longest follow-up period, m	18	< 20	18 [a]	18 [a]
Bulbar onset, %	30	N/A	27.2	35.3
At the start of survival duration	Enrollment	Enrollment	Enrollment	Symptom onset
Imputation for missing data	Nothing	Heights (average)	Nothing	Nothing
Univariate or multivariate	Univariate	Multivariate	Univariate	Univariate
Single or Multicenter study	Single center	Multicenter	Single center	Single center

Data represent the average ± standard deviation.
Abbreviations: ALSFRS-R; amyotrophic lateral sclerosis functional rating scale-revised; BMI, body mass index; Cre, creatinine; N/A, not available; UA uric acid.
[a] Calculated from the raw data.

(RevMan) version 5.3.5 for Windows (http://ims.cochrane.org/revman) and the meta package within the R statistical computing environment version 3.5.1 (http://www.r-project.org).

3. Results

3.1. Retrospective study

The study characteristics are shown in Table 1. The Cox proportional hazard model showed that the UA level significantly contributed to prognosis only in women (HR = 0.45, 95% CI: 0.22–0.93, $p = 0.03$) but not in all (HR = 0.76, 95% CI: 0.54–1.07, $p = 0.12$) or men (HR = 0.89, 95% CI: 0.61–1.30, $p = 0.55$).

3.2. Meta-analysis

A flowchart of the inclusion process is shown in Fig. 2. Of the four potential studies, only three were finally included in this meta-analysis because one study did not show the required dataset. One study [6] provided the HR, 95% CI and number of subjects separately by sex, and the other studies [14,17] provided raw data. We enrolled patients with more than 18 months follow-up or events.

A total of 1882 patients (1179 men and 703 women) were involved in the pooled analysis. The characteristics of these studies are summarized in Table 1. The pooled mean baseline characteristics were as follows: age (range 55.0–75.2 years), women (range 36.7–50.0%), UA (range 4.4–5.0 mg/dl), disease duration (range 10.5–15.9 months), ALSFRS-R (range 37.9–40.0), BMI (range 21.2–25.3 kg/m^2), riluzole use (20.7–35.3%), the longest follow-up period (range 18–20 months), and bulbar onset (range 27.2–35.3%).

The pooled HRs were 0.87 in all (95% CI: 0.80–0.94, $p < 0.001$, n = 1882, Fig. 3a), 0.83 in men (95% CI: 0.75–0.91, $p < 0.001$, n = 1179, Fig. 3b), and 0.76 in women (95% CI: 0.66–0.86, $p < 0.001$, n = 703, Fig. 3c). These studies were homogenous in all ($p = 0.43$, $I^2 = 0\%$, τ^2

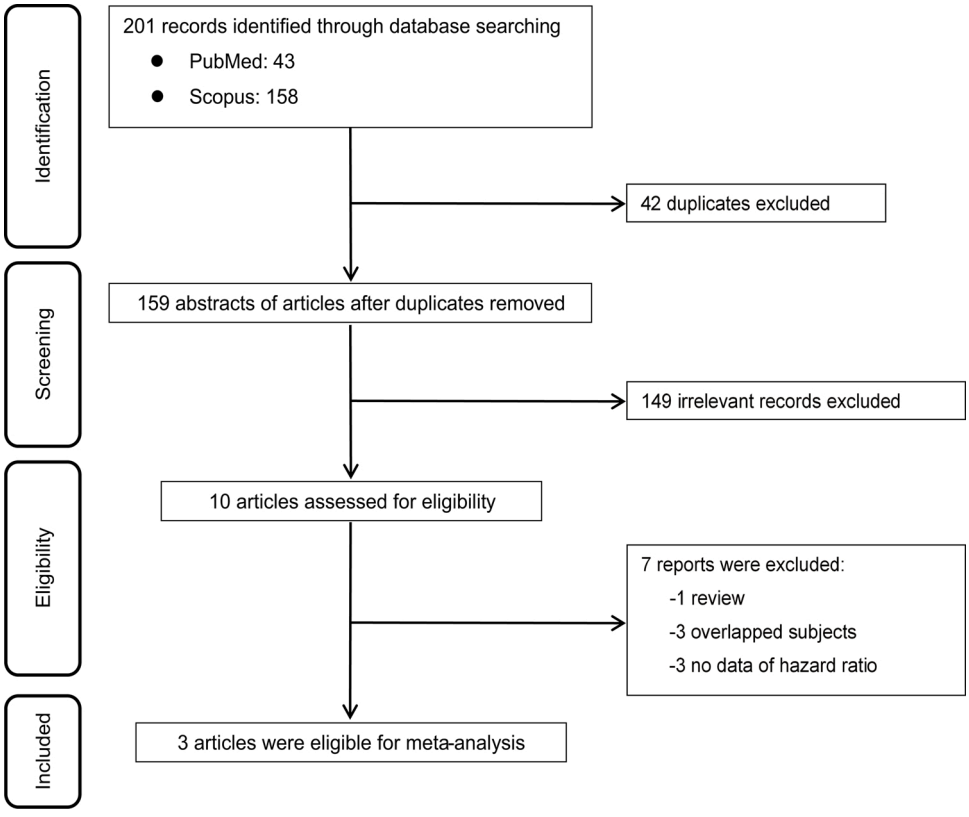

Fig. 2. Flowchart of the computational search and assessment of eligibility.

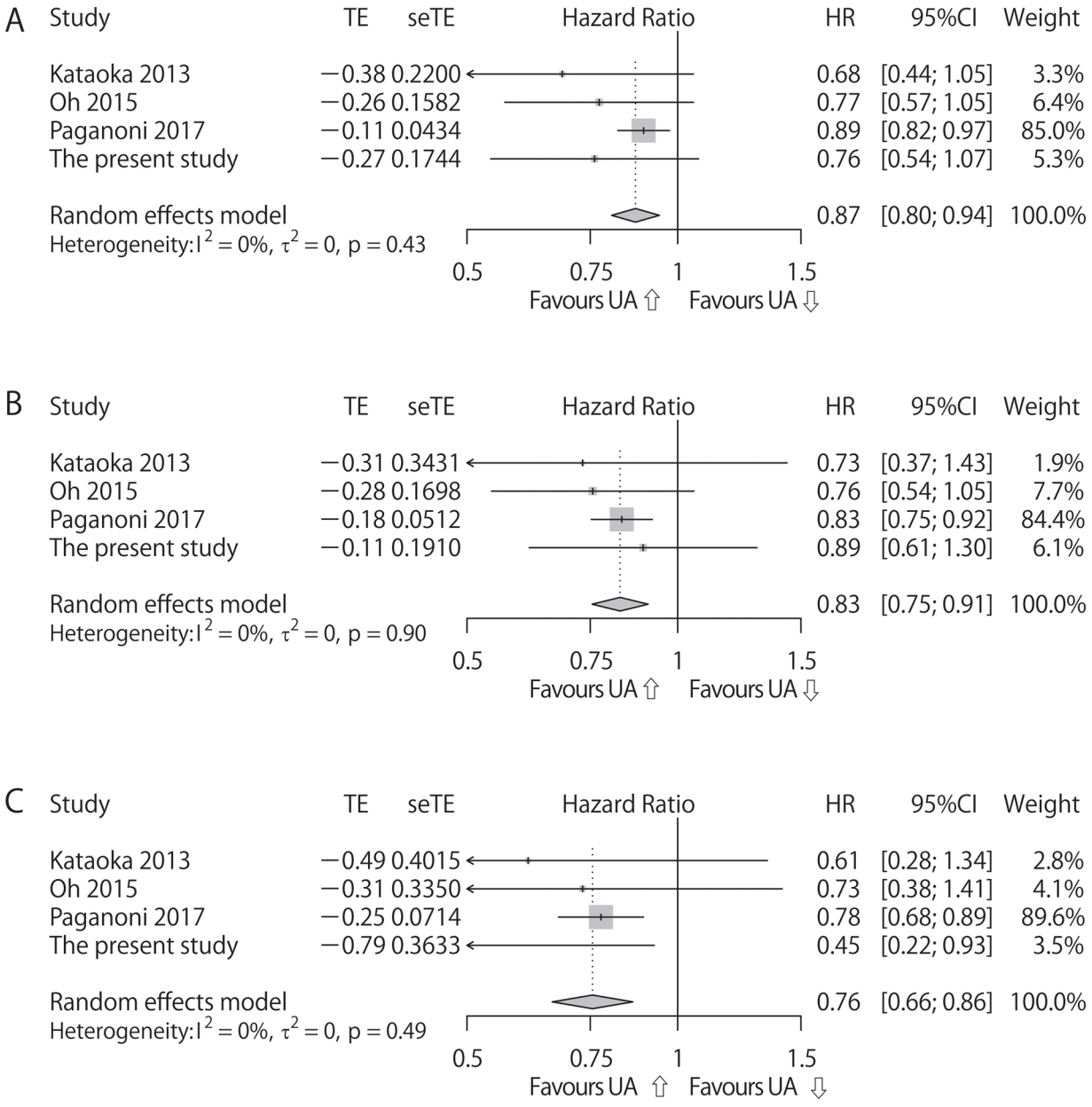

Fig. 3. Forest plots of hazard ratios with 95% confidence intervals in the present meta-analysis Forest plot of included studies in all (a), men (b), and women (c). All these results show that UA could be a good prognostic factor for ALS survival. The studies included are homogenous. The funnel plot demonstrates the possibility of publication bias.

= 0.00, Fig. 3a), men ($p = 0.90$, $I^2 = 0\%$, $\tau^2 = 0.00$, Fig. 3b), and women ($p = 0.49$, $I^2 = 0\%$, $\tau^2 = 0.00$, Fig. 3c). Sensitivity analysis demonstrated the robustness of the present results in all (Fig. 4a), men (Fig. 4b), and women (Fig. 4c). All the funnel plots appeared asymmetrical (Fig. 5a–c). Moreover, Egger's linear regression test revealed a potential publication bias in all ($p = 0.005$), but not in men ($p = 0.6$) or women ($p = 0.2$). To address publication bias affecting the results, the trim-and-fill method was employed, which confirmed the existence of significant differences in all comparisons (all, HR = 0.88, 95% CI: 0.82–0.96, $p = 0.002$, Fig. 5d; men, HR = 0.83, 95% CI: 0.76–0.91, $p < 0.001$, Fig. 5e; women, HR = 0.77, 95% CI: 0.68–0.89, $p < 0.001$, Fig. 5f).

4. Discussion

Our meta-analysis including data from our institute revealed an association between serum UA and the prognosis of patients with ALS, whereby increased serum UA levels indicated a good prognosis. This was supported by a sensitivity analysis and the trim-and-fill method. Furthermore, several lines of evidence have implicated serum UA as a reliable prognostic biomarker for other neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease [27–29]. Therefore, the prognostic power of UA is common among neurodegenerative disorders, and is possibly derived from a neuroprotective effect provided by UA, a purine metabolite that exhibits antioxidant activity [30–34]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) induce oxidative stress, which impairs membrane lipids and deoxyribonucleic acid (DNA) [35]. Indeed, patients with sporadic ALS show increased oxidative DNA damage [36,37]. Magnetic resonance imaging (MRI) has revealed iron-related alterations in the brain [38], which could accelerate the production of ROS and RNS [39]. Diacetyl-bis (N^4-methylthiosemicarbazone) positron emission tomography reported an increased level of oxidative stress in the motor cortex of patients with ALS [40]. As described above, previous studies have indicated that oxidative stress contributes to the pathology associated with ALS. A

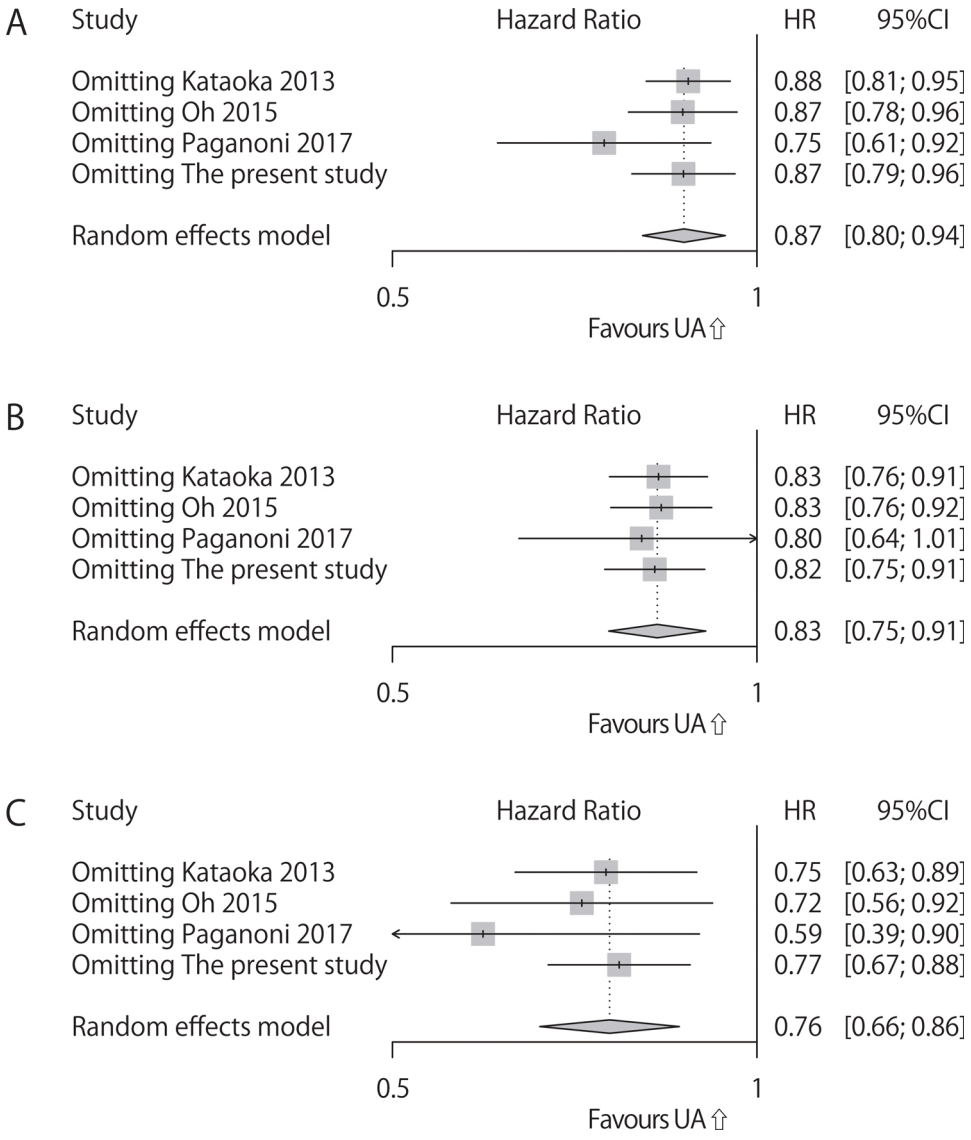

Fig. 4. Sensitivity analysis in the present meta-analysis.
Sensitivity analysis demonstrated the robustness of our results in all (a), men (b), and women (c).

clinical trial is underway examining the effect of inosine, a precursor of UA, on ALS (NCT03168711) and PD [41] (NCT02642393) via the reduction of oxidative stress.

The effect of UA on the prognosis of ALS has been reported to depend on sex [3,6], and so we conducted meta-analyses separately by sex. We observed no significant difference between the sexes, suggesting that UA is a common prognostic factor.

However, several limitations should be taken into consideration. First, the language-limiting search and inclusion of a moderate number of studies could cause publication bias, even though this bias was adjusted for using the trim-and-fill method. Second, our meta-analysis included cases with possible ALS, which leaded to a risk of misdiagnosis. Third, dietary preferences and habits were not investigated, although they have been suggested to be possible confounding factors associated with UA and survival. These data could improve results by allowing adjustment for the effect of diet. Fourth, other factors related to survival were ignored in this meta-analysis. Albumin, creatinine, lipids, apolipoproteins, neurofilament light chain and BMI have also been found to be prognostic factors [4,7–11]. Meta-analyses of these factors would to help to identify reliable prognostic biomarkers, as shown in this study. Ultimately, a combination of reliable biomarkers would produce a robust tool to predict prognosis using multivariate methods.

5. Conclusion

In summary, our meta-analysis has provided robust evidence that an elevated level of serum UA could increase the survival of patients with ALS, supported by sensitivity analysis and the trim-and-fill method.

Ethical approval

The present study performed in Tokushima was approved by the institutional ethical committee of Tokushima University Hospital.

Statistical analysis

Conducted by Shotaro Haji (academic) and supervised by Wataru Sako (academic).

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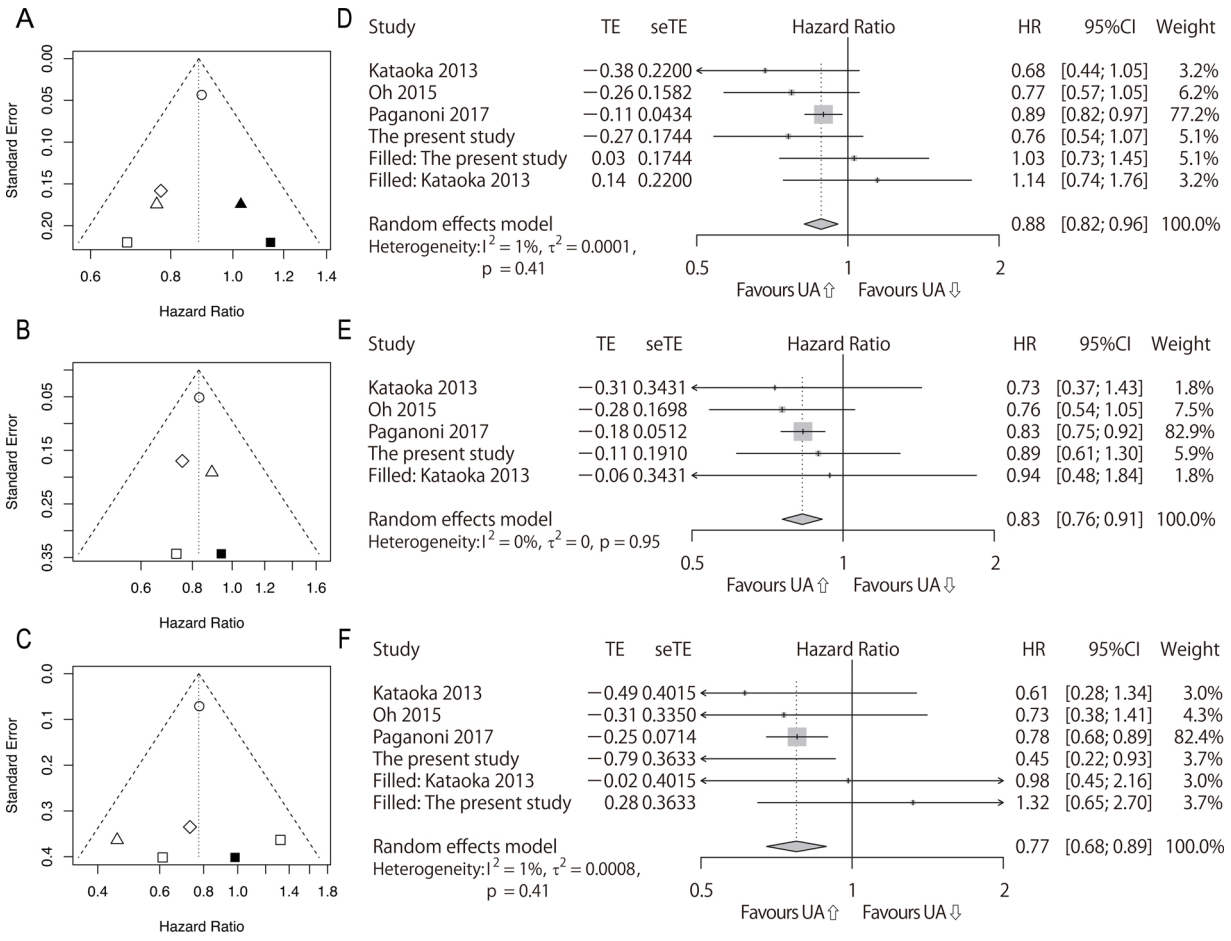

Fig. 5. Forest plot and funnel plot adjusted by the trim-and-fill method To adjust the publication bias, a trim-and-fill method was applied to adjust for publication bias. Funnel plots adjusted by the trim-and-fill method are shown for all (a), men (b), and women (c). The trim-and-fill method demonstrated that UA was a significant prognostic factor in all (d), men (e), and women (f). Published studies are depicted as closed markers, while studies imputed by the trim-and-fill method are represented with open markers.
□, Kataoka 2013; ⋄, Oh 2015; ○, Paganoni 2017; △, the present study 2018; ■, imputed study corresponding to Kataoka 2013; ▲, imputed study corresponding to the present study 2018.

agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Shotaro Haji: Methodology, Formal analysis, Investigation, Data curation, Visualization. **Wataru Sako:** Conceptualization, Methodology, Validation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Nagahisa Murakami:** Investigation, Writing - review & editing. **Yusuke Osaki:** Writing - review & editing. **Takahiro Furukawa:** Writing - review & editing. **Yuishin Izumi:** Writing - review & editing, Supervision. **Ryuji Kaji:** Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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