Effect of anticholinergics for the treatment of death rattle of cancer patients in the last days: a multicenter prospective cohort study

Yamaguchi, Takashi ; Yokomichi, Naosuke ; Yamaguchi, Takuhiro ; Maeda, Isseki ; Matsunuma, Ryo ; Tanaka-Yagi, Yukako ; Akatani, Asami ;…

(Citation)
BMJ Supportive & Palliative Care,13:462-471

(Issue Date)
2023-12

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/0100483312

Effect of anticholinergics for the treatment of death rattle of cancer patients in the last days: a multicenter prospective cohort study

Takashi Yamaguchi, M.D, Ph.D.[1, 2]; Naosuke Yokomichi, M.D.[3]; Takuhiro Yamaguchi, Ph.D.[4]; Isseki Maeda, M.D, Ph.D.[5]; Ryo Matsunuma, M.D.[1, 2]; Yukako Tanaka-Yagi, M.D. [2]; Asami Akatani, M.D. [1]; Kozue Suzuki, M.D.;[6]; Hiroyuki Kohara, M.D, Ph.D. [7]; Tomohiko Taniyama, M.D.;[8]; Yousuke Matsuda, M.D.;[9]; Nobuhisa Nakajima M.D, Ph.D[10] ;Tatsuya Morita, M.D.;[3] Satoru Tsuneto, M.D, Ph.D.;[11] Masanori Mori, M.D.;[3] on Behalf of the EASED Investigators.

[1]Department of Palliative Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

[2] Department of Palliative Care, Konan Medical Center, Kobe, Japan

[3] Department of Palliative and Supportive Care, Seirei Mikatahara General Hospital, Hamamatsu, Japan

[4]Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Japan

[5]Department of Palliative Care, Senri Chuo Hospital, Suita, Japan

[6] Department of Palliative Care, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Tokyo, Japan

[7] Department of Palliative Care, Hatsukaichi Memorial Hospital, Hatsukaichi, Japan

[8] Department of Oncology and Palliative Care, Mitsubishi Kyoto Hospital, Kyoto, Japan

[9] Department of Palliative Care, St Lukes International Hospital, Tokyo, Japan

[10] Division of Community Medicine and Internal Medicine, University of the Ryukyus Hospital, Okinawa, Japan

[11] Department of Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Corresponding Author: Takashi Yamaguchi, M.D, Ph.D.

Department of Palliative Medicine
Kobe University Graduate School of Medicine
7-5-1, Kusunoki-cho, Kobe 650-0017
Japan

Phone: 81-78-382-6531
Fax: 81-78-382-6534
Email: ikagoro@pop06.odn.ne.jp

Word counts: 3039
Tables: 3 + 1supplemental Table
Figures: 3

Abstract

Background: This study aimed to investigate the effectiveness of anticholinergics for death rattle in dying cancer patients.

Methods: This is a prospective cohort study enrolled Terminally ill adult (20years or older) cancer patients who developed substantial death rattle (Back score ≥2) from 23 palliative care units in Japan. Anticholinergic treatment for death rattle was prescribed according to primary physician's decision. The primary outcome was the proportion of patients whose death rattle improved, which was defined as a Back score of ≤1. We compared the proportion of improved cases in patients treated with (AC group) and without (non-AC group) anticholinergics, controlling potential confounders by employing propensity score weighting.

Results: Of the 1896 patients enrolled, we included 196 who developed a substantial death rattle. Of these, 81 received anticholinergics. 56.8% in the AC group and 35.4% in the non-AC group had an improved death rattle at 8 h after baseline. In the weighted analysis, AC group showed significant improvements in death rattle, with an adjusted odds ratio of 4.47 (95% CI, 2.04–9.78; $P = .0024$). All sensitivity analyses achieved essentially the same results. In the subgroup analysis, anticholinergics were strongly associated with death rattle improvement in men, patients with lung cancer, and type 1

death rattle (adjusted odds ratio 5.81, 8.38, and 9.32, respectively).

Conclusions: In this propensity score-weighted analysis, anticholinergics were associated with death rattle improvement in terminally ill patients with cancer who developed substantial death rattle.

Keywords: Death rattle; Anticholinergics; Palliative care; Cancer

Introduction

Death rattle is noisy ventilation due to accumulation of secretions in the pharynx and/or airways. death rattle typically occurs in the last few days of life,[1,2] with a reported prevalence of 13–92% in dying patients.[3] Previous studies have reported that death rattle was often distressing for patients' families[4-7] and for healthcare providers caring for these patients.[8] Thus, management of death rattle is an important issue in end-of-life care.

Although several randomized controlled trials (RCTs) have failed to show efficacy,[9-11] anticholinergics are often prescribed for death rattle in daily practice.[12] There are several possible reasons. First, death rattle has been proposed to be classified into types 1 and 2.[13] Type 1 predominantly occurs due to the accumulation of salivary secretions in the pharynx in the absence of effective swallowing reflexes due to decreased consciousness; this typically develops in the last days of life.[14] Type 2 is predominantly the accumulation of bronchial secretions due to deterioration or weakness of cough, and patients can sometimes still be conscious with this type. Anticholinergics are generally considered to be more effective for type 1.[15] However, previous studies have not clearly distinguished these two subtypes. Second, considering the pharmacological properties, anticholinergics might decrease the production of saliva and not affect existing salivary accumulation.[16] Therefore, anticholinergics were thought

to be ineffective for eliminating the existing accumulation of secretions in the pharynx and proposed to be used preemptively or after suctioning.[17] However, previous studies did not review the influence of death rattle intensity or preceding suctioning on the effectiveness of anticholinergics for death rattle. Third, the natural course of death rattle and the effectiveness of anticholinergics in real-world practice have not been sufficiently investigated.

We aimed to investigate the effectiveness of anticholinergics for death rattle in real-world practice after controlling for potential confounders with propensity score weighting and investigate factors influencing the effectiveness of anticholinergics.

Methods

This study was conducted as a part of the East Asian Collaborative Cross-Cultural Study to Elucidate the Dying Process (EASED), an international, multicenter, prospective cohort study on patients with advanced cancer at palliative care units (PCUs) in Japan, South Korea, and Taiwan.[18] Briefly, the EASED study consecutively enrolled adult cancer patients admitted to 38 PCUs (23 in Japan, 11 in South Korea, and 4 in Taiwan). We used only Japanese data for present study. In accordance with the ethical guidelines for human research of the Ministry of Health, Labor, and Welfare in Japan, informed consent from the patients was waived due to the observational nature of the study. We registered the study at UMIN-CTR (UMIN00002545).

Setting and participants

We consecutively enrolled cancer patients ≥18 years of age who were admitted to participating PCUs for the first time and had locally advanced or metastatic cancer (histological, cytological, or clinical diagnosis). The exclusion criteria were as follows: (1) scheduled discharge within 1 week and (2) refusal of patients or their families to participate. The participants were enrolled from January 2017 to December 2017. For this analysis, we included patients who developed death rattle with a Back score ≥2

during their PCU stay.

Procedures

We defined death rattle as audible sounds at the bedside produced by movement of secretions in the hypopharynx or the bronchial tree in association with respiration. The primary physicians typically visited patients at least twice daily and evaluated whether they had death rattle. Physicians directly ordered anticholinergics according to the clinical guidelines.[19] Although these guidelines do not recommend routine use of anticholinergics for death rattle, it allows anticholinergic use as an option when death rattle is refractory to other measures. When physicians prescribed anticholinergics, the choice of the type and dose of anticholinergic were at the primary physician's discretion. Suctioning for death rattle was performed at the discretion of the physician or nursing staff.

Measurements

All measurements were evaluated by primary physicians within daily practice. The intensity of death rattle and treatments were recorded every 4 h after substantial death rattle development (T0) until 24 h after (T6) or the patient's death, whichever came first.

Death rattle intensity

Death rattle intensity was evaluated with the Back score.[13] The Back score consists of four categories: “inaudible” (0), “audible only very close to the patient” (1), “clearly audible at the end of the bed in a quiet room” (2), and “clearly audible at about 6 m or at the door of the room” (3). We defined substantial death rattle as a Back score of 2 or higher in present study.[20,21]

Death rattle treatment

We recorded whether anticholinergics were prescribed, as well as the type of anticholinergic at each time point. We also recorded whether suctioning was performed at 4 h ahead of each time point.

Patient characteristics

We collected patients’ baseline characteristics at admission, including age, sex, primary tumor site, metastatic lesions (i.e., brain, liver, and lung), and past history of heart, lung, and neuromuscular disease. We also obtained the following data at T0: death rattle subtype, character of secretion (i.e., serous or purulent), presence of crackles on lung

auscultation, presence of fluid retention signs (e.g., pleural effusion, ascites, or peripheral edema), hydration volume, and consciousness level. The subtype of death rattle was classified as one of three categories (type 1, type 2, or mixed) based on clinical judgment by the primary physicians.[14] Consciousness level was assessed using the modified Richmond Agitation and Sedation Scale (RASS), which measured the severity of agitation and sedation on a 10-point scale (+4: combative; +3: very agitated; +2: agitated; +1: restless; 0: alert and calm; −1: drowsy; −2: light sedation; −3: moderate sedation; −4: deep sedation; and −5: unarousable).[22,23] The date of death was recorded at the time of the patient's death.

Statistical analysis

As the primary endpoint, we compared the percentages of improved patients (defined as a Back score ≤1) at 8 h after baseline between patients treated with (AC group) and without (non-AC group) anticholinergics. We defined patients in the AC group as those who started anticholinergics between T0 and T4. The baseline time point of the non-AC group was T0, whereas that of the AC group was the time of starting anticholinergics.

First, we constructed two models for propensity score (PS) (i.e., the conditional probability of receiving anticholinergics) by selecting a set of confounders between

treatment assignment (receiving anticholinergics) and outcome (death rattle improvement) based on previous studies' results[4,14,15,21,24,25] and clinical knowledge. Models 1 and 2 included 18 and 7 variables, respectively (**Supplemental Table 1**). Model 2 was used when the regression model failed to converge with model 1.

Next, under the missing at random assumption, we performed multiple imputation by chained equations to impute missing covariates.[26] The variables included in the imputation models were the same variables as in the PS model. We generated ten complete datasets for subsequent analyses. Missing outcome values were imputed with the last observation.

To account for confounding biases, the observed differences in baseline covariates between the two groups were adjusted by the inverse probability of treatment weighting (IPTW) method.[27,28] With this method, we estimated the PS for each patient using a multivariate logistic regression with the set of confounders after imputation. The PSs from ten imputed datasets were then pooled according to Rubin's rule.[29] Patients in the AC group were weighted by the average treatment effect weight (1/PS), whereas those in the non-AC group were weighted by 1/(1-PS).

Then, a univariate inverse probability weighted logistic regression model was used to estimate the IPTW-adjusted odds ratio (OR) for death rattle improvement of the

AC group versus the non-AC group.

We further performed exploratory subgroup analyses to investigate the IPTW-adjusted OR of the AC versus non-AC group according to the baseline covariates.

In addition, we explored the effect of suctioning on death rattle improvement before starting anticholinergics using an AC group cohort.[30] Following multiple imputations of the missing values, the PS for receiving suctioning was estimated. Then, patients treated with and without suctioning were weighted and IPTW-adjusted OR for death rattle improvement of suctioning group vs. non-suctioning group was calculated.

Lastly, we conducted six sensitivity analyses to assess the robustness of the results: (1) analyzing patients with a baseline Back score of only 2 or more, (2) defining the AC group as those who started anticholinergics at T0 and T1 only, (3) analyzing with listwise deletion of missing values, (4) fitting logistic regression with model 2 in calculating the PS, (5) fitting a traditional multivariate logistic regression model to estimate the OR of AC versus non-AC by adjusting the same covariates as in the primary analysis, and (6) calculating the E-value, which represents the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain the estimated treatment-outcome association.[31]

All statistical analyses were performed with R version 3.5.3 (R Core Team 2019, Vienna, Austria). All *P* values were two-sided. A *P* value of <.05 was considered significant.

Patient and public involvement

Patients and the public were not involved in setting the research question or outcome measures or in the writing of the results.

Results

Patient characteristics

A total of 1896 patients were enrolled in the main study (**Figure 1**). Of these, we analyzed 196 (10.3%) who developed substantial death rattle (115 in the non-AC group and 81 in the AC group).

The missing covariate values imputed by multiple imputations were baseline Back score (1.0%), presence of suctioning (1.0%), secretion character (1.0%), presence of crackles (3.1%), and hydration volume (1.0%). 12.8% (25/196) of the patients did not have a Back score at 8 h after baseline because they had died before then; these were imputed by the last observation values.

Patient characteristics after imputation are summarized in **Table 1**. The mean age was 71.3 years; 38.8% were female. The most common primary tumor site was the gastrointestinal tract (40.8%). The modified RASS was −3 or less in 62.2%, and 29.1% had type 1 death rattle. The baseline Back score was 2 in 57.2% and 3 in 25.2%. 27% received 500 mL/d or more hydration. The median time from T0 to death was 1 day (IQR 1, 3): 1 day (1, 4) in the non-AC group and 1 day (1, 3) in the AC group.

In the AC group, anticholinergics were started at T0 in 31 patients, T1 in 34, T2 in 8, T3 in 5, and T4 in 3. Scopolamine butylbromide was administered to 59 patients

and scopolamine hydrobromide to 22.

Balance of covariates between the non-anticholinergic and anticholinergic groups

Compared with patients in the non-AC group, the AC group had significantly less history of heart or lung disease, asymptomatic ascites, and type 2 death rattle and higher symptomatic pleural effusion, prevalence of baseline Back score of 3, crackles, and receiving ≥500 mL hydration. After PS weighting, standardized differences for all covariates were <0.1, except for liver metastasis (0.11), which indicated that the weighted population in the two groups was comparable **(Table 1)**.

Comparison of death rattle improvement

In both the AC and non-AC group, the mean Back score decreased over time (**Figure 2**). In the unweighted analysis, the proportion of improved patients at 8 h after baseline was 35.4% (40/113) in the non-AC group and 56.8% (46/81) in the AC group (unadjusted OR 2.40; 95% CI, 1.34–4.30; *P* = .034). In the weighted analyses, the adjusted OR was 4.47 (95% CI, 2.04–9.78; *P* = .00024; **Table 2**).

Subgroup analysis

We performed a weighted subgroup analysis comparing the ORs of improved patients in the non-AC group versus the AC group according to the baseline covariates. No significant heterogeneity was found in any subgroup, whereas anticholinergics were strongly associated with death rattle improvement, especially in subgroups of men, lung cancer, and type 1 death rattle (OR 5.81, 8.38, and 9.32, respectively; **Figure 3**).

Effect of suctioning on death rattle intensity

Of 81 patients in the AC group, 34 did not receive suction before starting anticholinergics (non-suctioning group), 46 received suction (suctioning group), and 1 had a missing value. The patient characteristics after imputation and balance between the weighted groups are shown in **Table 3**. The percentage of improved patients at 8 h after baseline was 67.6% in the non-suctioning group and 48.9% in the suctioning group (OR 0.48; 95% CI, 0.19–1.22; $P = .13$). In the weighted analysis, the adjusted OR was 0.53 (95% CI, 0.19–1.51; $P = .24$).

Sensitivity analyses

The percentage of improved patients at 8 h after baseline in the AC group was significantly higher than the non-AC group in the following sensitivity analyses: (1) the

cohort with a baseline Back score of ≥2 only (OR 3.60; 95% CI, 1.28–10.11; *P* = .016), (2) the cohort of those who started anticholinergics at T0 and T1 only (OR 3.10; 95% CI, 1.64–5.87; *P* = .00063), (3) the analysis with deletion of missing outcome value (OR 4.62; 95% CI, 1.70–12.57; *P* = .0031), (4) the analysis with PS model 2 (OR 3.39; 95% CI, 1.79–6.41; *P* = .00024), and (5) the multivariate logistic regression (OR 3.48; 95% CI, 1.77–6.86; *P* = .00041). We applied the E-value method that produced *E* = 3.65 for the estimate **(Table 2)**.

Discussion

To the best of our knowledge, this is the largest study investigating the effectiveness of anticholinergics for death rattle in real-world terminally ill cancer patients. Present study has several major findings. First, anticholinergics reduced death rattle more than the natural course in terminally ill cancer patients receiving care in PCUs. The previous two placebo-controlled RCTs did not find efficacy of anticholinergics for death rattle.[10,11] However, one of the studies, including only unconscious terminally ill cancer patients, showed a tendency for anticholinergic superiority, despite it not reaching statistical significance.[11] The other study was prematurely terminated due to futility in the interim analysis. However, most of the included patients in that study were terminally ill non-cancer patients.[24] Heart and lung disease tend to develop type 2 death rattle which is considered to be less responsive to anticholinergics.[15] Indeed, death rattle improvement after starting anticholinergics was observed more frequently in type 1 than type 2 or mixed cases in present study. Moreover, the previous study also included mild death rattle (Back score of 1), whereas the present study included the patients only substantial death rattle (Back score of 2 or more), which might have influenced the result. Thus, anticholinergics could have significant role in managing death rattle in terminally ill cancer patients, selecting cases

with type 1 death rattle and substantial intensity, after appropriate non-pharmacological care. Second, suctioning before starting anticholinergics and the severity of death rattle did not influence the effectiveness of anticholinergics in the present study. Recently, two RCTs showed the efficacy of prophylactic use of anticholinergics for the prevention of death rattle.[32,33] However, approximately 40–70% of the control group (placebo or observed) did not develop death rattle in these studies. Moreover, in present large-scale real-world study, the incidence of substantial death rattle was only 10.3% in PCUs. Thus, we are not sure whether it is appropriate to use anticholinergics prophylactically for all terminally ill cancer patients. Furthermore, suctioning appears to be invasive or distressing for these patients,[4,34] which could also distress patients' families.[5] According to the results of present study, anticholinergics might not be necessarily used prophylactically or started after suctioning in the management of death rattle in terminally ill cancer patients. Instead, minimal and proper use of anticholinergics based on careful evaluation and selection of the patient in need might be more appropriate.

Present study has several strengths. First, we included the largest scale of real-world patients to date, and the results were adjusted with IPTW to minimize the influence of potential confounders. Thus, the results of present study are reliable and broadly applicable to terminally ill cancer patients in daily clinical practice. Second,

although few previous studies had evaluated the subtype of death rattle, present study distinguished the subtypes and showed that anticholinergics were more effective in type 1.

Despite these strengths, present study had limitations. First, due to its observational nature, causality between anticholinergics and the intensity of death rattle could not be confirmed. Second, although the results of the E-value method produced moderately robust results, we cannot rule out unmeasured confounders affecting these results. Third, given that this was an observational study, the indications and dosages of anticholinergics were not completely standardized despite following anticholinergic treatment according to clinical guidelines.[19] Fourth, the Back score was a physician-reported outcome measure, which might be biased in this unblinded study. Thus, we should conduct a blinded RCT focusing on terminally ill cancer patients with type 1 death rattle of substantial intensity to confirm the efficacy of anticholinergics. Fifth, although we set the inception point as a Back score of ≥2, the baseline Back score was ≤1 in some patients, which might reflect the fact that the intensity of death rattle could quickly change. To minimize influence of this phenomenon, we conducted a sensitivity analysis excluding patients with a baseline Back score of 0–1, which demonstrated essentially the same results. Sixth, we identified missing values in the outcomes and

covariates, mainly due to the patients' death. Given that death rattle develops in the dying phase, missing data due to death are inevitable. We processed missing outcomes with the last observation carried forward in the primary analysis and deleted cases with missing values in a sensitivity analysis, which confirmed the consistency of the results. Seventh, patients in the AC group included those who started anticholinergics between T0 and T4, which could have led to a time bias. However, we do not believe that this seriously affected the results because the results of the sensitivity analysis including patients started anticholinergics at T0 and T1 only were consistent with the main analysis. Eighth, misspecification of the PS model was possible. We attempted to address this by conducting sensitivity analyses with another PS model and multivariate logistic regression, which showed the consistency of the results. Lastly, our results might not be generalized to patients who are not admitted to PCUs.

Conclusions

Anticholinergics were associated with the improvement of death rattle in terminally ill cancer patients in PCUs. We need to conduct RCTs on specific populations to confirm the efficacy of anticholinergics and perform a larger real-world observational study to find the appropriate population for prescribing anticholinergics in

the future.

What is already known on this topic.

- Death rattle is one of the major sign which suggests patient's imminent death.
- Death rattle is often distressing for patients' families and for healthcare providers caring for these patients.
- Anticholinergics are often prescribed for death rattle in daily practice, despite of insufficient evidence for its efficacy and effectiveness for death rattle.

What this study adds:

- After controlling potential confounders by using the propensity score-weighting method, death rattle improvement was significantly greater among patients treated with anticholinergics than among those without.

ACKNOWLEDGEMENT

We are grateful to the cooperation of members of the East-Asian collaborative cross-cultural Study to Elucidate the Dying process (EASED) study Group.

ETHICS STATEMENTS

This study was approved by the institutional review board of Seirei Mikatahara General Hospital (Research No. 16-22) and all participating institutions.

DATA AVAILAVILITY STATEMENT

Relevant anonymized patient level data are available from the corresponding author on reasonable request.

FOOTNOTES

Competing interests: All authors have completed the ICMJE uniform and declare that they have no conflicts of interest.

Funding: This study was supported by JPPS KAKENHI (Grant number 21H02829) and a Grant-in-Aid from the Japan Hospice Palliative Care Foundation. The sponsor did not involve the study design, the collection and management of the data, and manuscript writing.

Contributors: Takashi Yamaguchi, Isseki Maeda, Tatsuya Morita, Satoru Tsuneto and Masanori Mori were responsible for conception and design. Ryo Matsunuma, Asami Akatani, Yukako Tanaka-Yagi, Kozue Suzuki, Hiroyuki Kohara, Tomohiko Taniyama, Yosuke Matsuda and Nobuhisa Nakajima were responsible for collection and assembly of data. Takashi Yamaguchi, Naosuke Yokomichi, Takuhiro Yamaguchi and Masanori Mori were responsible for data analysis and interpretation. All authors were responsible for manuscript writing and final approval of manuscript.

Transparency statement: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported: that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: It is not possible to disseminate results to study participants because we use anonymized data and all participants have already died. We will disseminate the study results to the public through press releases and social media postings.

Provenance and peer review: Not commissioned; externally peer reviewed.

【Reference】

1. Hui D, dos Santos R, Chisholm G, et al. Clinical signs of impending death in cancer patients. Oncologist 2014;19:681-7.

2. Blinderman CD, Billings JA. Comfort Care for Patients Dying in the Hospital. The New England journal of medicine 2015;373:2549-61.

3. Lokker ME, van Zuylen L, van der Rijt CCD, van der Heide A. Prevalence, Impact, and Treatment of Death Rattle: A Systematic Review. Journal of pain and symptom management 2014;47:105-22.

4. Morita T, Hyodo I, Yoshimi T, et al. Incidence and underlying etiologies of bronchial secretion in terminally ill cancer patients: a multicenter, prospective, observational study. Journal of pain and symptom management 2004;27:533-9.

5. Shimizu Y, Miyashita M, Morita T, Sato K, Tsuneto S, Shima Y. Care strategy for death rattle in terminally ill cancer patients and their family members: recommendations from a cross-sectional nationwide survey of bereaved family members' perceptions. Journal of pain and symptom management 2014;48:2-12.

6. Wee BL, Coleman PG, Hillier R, Holgate SH. The sound of death rattle II: how do relatives interpret the sound? Palliat Med 2006;20:177-81.

7. Wee BL, Coleman PG, Hillier R, Holgate SH. The sound of death rattle I: are relatives distressed by hearing this sound? Palliat Med 2006;20:171-5.

8. Wee B, Coleman P, Hillier R, Holgate S. Death rattle: its impact on staff and volunteers in palliative care. Palliat Med 2008;22:173-6.

9. Clark K, Currow DC, Agar M, Fazekas BS, Abernethy AP. A pilot phase II randomized, cross-over, double-blinded, controlled efficacy study of octreotide versus hyoscine hydrobromide for control of noisy breathing at the end-of-life. J Pain Palliat Care Pharmacother 2008;22:131-8.

10. Heisler M, Hamilton G, Abbott A, Chengalaram A, Koceja T, Gerkin R. Randomized double-blind trial of sublingual atropine vs. placebo for the management of death rattle. Journal of pain and symptom management 2013;45:14-22.

11. Likar RM, M.; Rupacher, E.; Pipam, W.; Deutsch, J.; Mörtl, M.; Baumgartner, J.; Grießinger, N.; Sittl, R. A Clinical Study Examining the Efficacy of Scopolamin-Hydrobromide in Patients with Death Rattle (A Randomized, Double-Blind, Placebo-Controlled Study). Zeitschrift für Palliativmedizin 2002;3:15 - 9.

12. Matsunuma R, Suzuki K, Matsuda Y, Mori M, Watanabe H, Yamaguchi T. Palliative care physicians' perspectives of management for terminally ill cancer patients with death rattle: a nationwide survey. Jpn J Clin Oncol 2020;50:830-3.

13. Back IN, Jenkins K, Blower A, Beckhelling J. A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. Palliat Med 2001;15:329-36.

14. Bennett MI. Death rattle: an audit of hyoscine (scopolamine) use and review of management. Journal of pain and symptom management 1996;12:229-33.

15. Wildiers H, Menten J. Death rattle: prevalence, prevention and treatment. Journal of pain and symptom management 2002;23:310-7.

16. Mercadamte S. Death rattle: critical review and research agenda. Support Care Cancer 2014;22:571-5.

17. Mercadante S, Villari P, Ferrera P. Refractory death rattle: deep aspiration facilitates the effects of antisecretory agents. Journal of pain and symptom management 2011;41:637-9.

18. Yamaguchi T, Maeda I, Hatano Y, et al. Communication and Behavior of Palliative Care Physicians of Patients With Cancer Near End of Life in Three East Asian Countries. Journal of pain and symptom management 2021;61:315-22 e1.

19. Yamaguchi T, Goya S, Kohara H, et al. Treatment Recommendations for Respiratory Symptoms in Cancer Patients: Clinical Guidelines from the Japanese Society for Palliative Medicine. J Palliat Med 2016;19:925-35.

20. Morita T, Hyodo I, Yoshimi T, et al. Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2005;16:640-7.

21. Yamaguchi T, Morita T, Shinjo T, et al. Effect of parenteral hydration therapy based on the Japanese national clinical guideline on quality of life, discomfort, and symptom intensity in patients with advanced cancer. J Pain Symptom Manage 2012;43:1001-12.

22. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-44.

23. Imai K, Morita T, Mori M, Yokomichi N, Fukuta K. Development and linguistic validation of the Japanese version of the modified Richmond Agitation-Sedation Scale. Palliative Care Research 2016;11:331-6.

24. Morita T, Tsunoda J, Inoue S, Chihara S. Risk factors for death rattle in terminally ill cancer patients: a prospective exploratory study. Palliat Med 2000;14:19-23.

25. Yokomichi N, Morita T, Yamaguchi T. Hydration Volume Is Associated with Development of Death Rattle in Patients with Abdominal Cancer. Journal of palliative medicine 2022;25:130-4.

26. White IR, Royston P, Wood AM. Multiple imputation using chained equations:

Issues and guidance for practice. Stat Med 2011;30:377-99.

27. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ (Clinical research ed) 2019;367:l5657.

28. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661-79.

29. Rubin DB. Multiple imputation for nonresponse in surveys. Hoboken, N.J.: John Wiley & Sons; 2004.

30. Mercadante S, Marinangeli F, Masedu F, et al. Hyoscine Butylbromide for the Management of Death Rattle: Sooner Rather Than Later. Journal of pain and symptom management 2018;56:902-7.

31. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med 2017;167:268-74.

32. Mercadante S, Marinangeli F, Masedu F, et al. Hyoscine Butylbromide for the Management of Death Rattle: Sooner Rather Than Later. Journal of pain and symptom management 2018.

33. van Esch HJ, van Zuylen L, Geijteman ECT, et al. Effect of Prophylactic Subcutaneous Scopolamine Butylbromide on Death Rattle in Patients at the End of Life: The SILENCE Randomized Clinical Trial. JAMA 2021;326:1268-76.

34. Watanabe H, Taniguchi A, Yamamoto C, Odagiri T, Asai Y. Adverse Events Caused by Aspiration Implemented for Death Rattle in Patients in the Terminal Stage of Cancer: A Retrospective Observational Study. Journal of pain and symptom management 2018;56:e6-e8.

Table 1 Characteristics of patients who developed death rattle and covariate balance between those treated with or without anticholinergics

Variable	Total	Unweighted Cohort			Weighted Cohort [a]		
		Non-AC	AC	mean SMD [b]	Non-AC	AC	mean SMD [b]
N	196	115	81		209	194.3	
Patient characteristics							
Age (mean [SD])	71.3 (13.1)	71.6 (14.2)	70.9 (11.4)	-0.052	72.6 (13.4)	72.6 (10.3)	0.0032
Sex, female (%)	76 (38.8)	45 (39.1)	31 (38.3)	-0.0086	70.0 (33.5)	57.5 (29.6)	-0.039
Past history of heart or lung desease (%)	23 (11.7)	19 (16.5)	4 (4.9)	-0.12	22.6 (10.8)	13.7 (7.1)	-0.038
Past history of neuromuscular disease (%)	20 (10.2)	10 (8.7)	10 (12.3)	0.037	19.9 (9.5)	18.1 (9.3)	-0.0022
Primary tumor site (%)							
Lung	41 (20.9)	21 (18.3)	20 (24.7)	0.064	39.8 (19.0)	53.9 (27.7)	0.087
Gastrointestinal tract	80 (40.8)	46 (40.0)	34 (42.0)	0.02	80.8 (38.7)	76.8 (39.5)	0.0088
Breast	19 (9.7)	15 (13.0)	4 (4.9)	-0.081	18.1 (8.7)	10.5 (5.4)	-0.033
Other	56 (28.6)	33 (28.7)	23 (28.4)	-0.003	70.3 (33.6)	53.1 (27.3)	-0.063
Richmond Agitation and Sedation Scale (%)							
<=-3	122 (62.2)	69 (60.0)	53 (65.4)	0.054	128.4 (61.4)	126.7 (65.2)	0.038
>-3, <=0	62 (31.6)	40 (34.8)	22 (27.2)	-0.076	66.2 (31.7)	56.3 (29.0)	-0.027
>0	12 (6.1)	6 (5.2)	6 (7.4)	0.022	14.4 (6.9)	11.3 (5.8)	-0.011
Metastasis and complications							
Liver metastasis, present (%)	74 (37.8)	43 (37.4)	31 (38.3)	0.0088	90.3 (43.2)	62.3 (32.0)	-0.11
Lung metastasis, present (%)	94 (48.0)	52 (45.2)	42 (51.9)	0.066	90.9 (43.5)	73.6 (37.9)	-0.056
Brain metastasis, present (%)	29 (14.8)	14 (12.2)	15 (18.5)	0.063	23.0 (11.0)	24.0 (12.3)	0.014
Ascites (%)							
Absent	132 (67.3)	72 (62.6)	60 (74.1)	0.11	143.3 (68.6)	139.7 (71.9)	0.033
Asymtomatic	35 (17.9)	26 (22.6)	9 (11.1)	-0.12	33.8 (16.2)	26.0 (13.4)	-0.028
Symptomatic	29 (14.8)	17 (14.8)	12 (14.8)	0.0003	31.9 (15.3)	28.6 (14.7)	-0.0053

Effect of anticholinergics on death rattle

Pleural effusion (%)							
	Absent	108 (55.1)	64 (55.7)	44 (54.3)	-0.013	96.6 (46.2)	90.5 (46.6)	0.0034
	Asymtomatic	34 (17.3)	25 (21.7)	9 (11.1)	-0.11	32.9 (15.8)	24.8 (12.7)	-0.03
	Symptomatic	54 (27.6)	26 (22.6)	28 (34.6)	0.12	79.4 (38.0)	79.0 (40.7)	0.027
Edema, present (%)		123 (62.8)	70 (60.9)	53 (65.4)	0.046	136.9 (65.5)	131.1 (67.5)	0.02
Characteristics of death rattle								
Subtype (%)								
	Type 1	57 (29.1)	33 (28.7)	24 (29.6)	0.0093	75.7 (36.2)	60.4 (31.1)	-0.051
	Type 2	48 (24.5)	36 (31.3)	12 (14.8)	-0.16	45.0 (21.5)	50.7 (26.1)	0.046
	Mixed	91 (46.4)	46 (40.0)	45 (55.6)	0.16	88.3 (42.2)	83.2 (42.8)	0.0058
Back's score (%)								
	0-1	34.4 (17.6)	23.4 (20.3)	11 (13.6)	-0.068	35.1 (16.8)	33.9 (17.5)	0.0068
	2	112.2 (57.2)	70.2 (61.0)	42 (51.9)	-0.092	106.7 (51.0)	113.5 (58.4)	0.074
	3	49.4 (25.2)	21.4 (18.6)	28 (34.6)	0.16	67.3 (32.2)	46.9 (24.1)	-0.081
Secretion character, serous (vs. purulent; %)		109.3 (55.8)	59.3 (51.6)	50 (61.7)	0.098	126.8 (60.7)	108.4 (55.8)	-0.042
Crackles, present (%)		131.8 (67.2)	68.5 (59.6)	63.3 (78.1)	0.19	147.4 (70.5)	118.5 (61.0)	-0.096
Co-treatment								
Suction, present (%)		102.7 (52.4)	56.2 (48.9)	46.5 (57.4)	0.085	111.0 (53.1)	87.9 (45.2)	-0.079
Hydration volume, >=500 mL (vs. <500; %)		52.9 (27.0)	36.6 (31.8)	16.3 (20.1)	-0.12	50.3 (24.1)	60.8 (31.3)	0.073

Abbreviations: AC, anticholinergic drugs; SMD, standardized mean difference; SD, standard deviation.

[a] Weighted using inverse probability of treatment weighting, based on propensity scores. Patients in the non-CDS group were weighted by the average treatment effect weight.

[b] The mean value of SMD across 10 imputed datasets. An absolute SMD greater than 0.1 is interpreted as a meaningful difference.

Table 2 Association of anticholinergics on the severity of death rattle

	N	Adjusted odds ratio	95% CI lower	95% CI upper	P-value
Primary analysis	196	4.47	2.04	9.78	0.00024
Sensitivity analyses					
Patient selection					
Baseline Back's score of 2-3 only	160	3.6	1.28	10.12	0.016
Starting anticholinergics at T0-1 only	180	3.1	1.64	5.87	0.00063
Missing data processing					
Deletion of missing outcome data	171	4.62	1.7	12.57	0.0031
Model fitting					
Propensity score model 2	196	3.39	1.79	6.41	0.00024
Multivariate logistic regression	196	3.48	1.77	6.86	0.00041

Table 3. Characteristics of patients who received anticholinergics and covariate balance between those treated with or without suctioning before starting anticholinergics

Variable		Total	Unweighted Cohort			Weighted Cohort [a]		
			non-SUC	SUC	mean SMD [b]	non-SUC	SUC	mean SMD [b]
	N	81	34.4	46.6		83.4	78.6	
Patient characteristics								
Age (mean [SD])		70.9 (11.4)	70.6 (10.7)	71.2 (11.9)	0.047	71.5 (10.1)	71.6 (11.5)	0.012
Sex, female (%)		31 (38.3)	11 (32.0)	20 (42.9)	0.11	34.1 (40.9)	31.2 (39.7)	-0.013
Primary tumor site (%)								
	Lung	20 (24.7)	9.4 (27.3)	10.6 (22.7)	-0.046	19.0 (22.7)	18.1 (23.0)	0.003
	Gastrointestinal tract	34 (42.0)	17 (49.4)	17 (36.5)	-0.13	36.3 (43.5)	33.7 (42.8)	-0.007
	Breast	4 (4.9)	1 (2.9)	3 (6.4)	0.035	6.3 (7.6)	4.7 (5.9)	-0.016
	Other	23 (28.4)	7 (20.3)	16 (34.3)	0.14	21.8 (26.2)	22.2 (28.2)	0.02
Richmond Agitation and Sedation Scale (%)								
	<=-3	53 (65.4)	21.4 (62.2)	31.6 (67.8)	0.056	53.3 (63.9)	50.3 (64.0)	0.001
	>-2, <=0	22 (27.2)	10 (29.1)	12 (25.8)	-0.033	24.1 (28.9)	22.6 (28.7)	-0.0023
	>0	6 (7.4)	3 (8.7)	3 (6.4)	-0.023	6.0 (7.2)	5.8 (7.3)	0.0014
Characteristics of death rattle								
Subtype (%)								
	Type 1	24 (29.6)	17 (49.4)	7 (15.0)	-0.34	23.3 (28.0)	20.9 (26.6)	-0.013
	Type 2	12 (14.8)	4 (11.6)	8 (17.2)	0.055	13.9 (16.6)	12.5 (15.9)	-0.0072
	Mixed	45 (55.6)	13.4 (39.0)	31.6 (67.8)	0.29	46.2 (55.4)	45.2 (57.4)	0.021
Back's score (%)								
	0-1	11 13.6)	6 (17.4)	5 (10.7)	-0.067	10.0 (12.0)	11.1 (14.1)	0.021
	2	42 (51.9)	18 (52.3)	24 (51.5)	-0.0083	46.9 (56.2)	40.4 (51.4)	-0.048
	3	28 (34.6)	10.4 (30.2)	17.6 (37.8)	0.075	26.5 (31.8)	27.1 (34.5)	0.027

Effect of anticholinergics on death rattle

Co-treatment							
Hydration volume, >=500 mL (vs. <500; %)	16.1 (19.9)	5.0 (14.5)	11.1 (23.8)	0.093	15.5 (18.6)	15.6 (19.8)	0.012

Figure 1. Patient selection flow chart per STROBE.

Figure 2. Change of Back's score in AC and non-AC groups.

Figure 3. Subgroup analysis.

Legends for Figure 3.

Abbreviations: OR, odds ratio; RASS, modified Richmond Agitation and Sedation Scale; AC, anticholinergic drugs.