Anticholinergic drugs for death rattle in dying patients with cancer: multicentre prospective cohort study

Takashi Yamaguchi ,[1] Naosuke Yokomichi,[2] Takuhiro Yamaguchi,[3] Isseki Maeda,[4] Ryo Matsunuma,[5] Yukako Tanaka-Yagi,[5] Asami Akatani,[1] Kozue Suzuki,[6] Hiroyuki Kohara,[7] Tomohiko Taniyama,[8] Yosuke Matsuda,[9] Nobuhisa Nakajima ,[10] Tatsuya Morita,[2] Satoru Tsuneto,[11] Masanori Mori[2]

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For numbered affiliations see end of article.

Correspondence to
Professor Takashi Yamaguchi, Department of Palliative Medicine, Kobe University Graduate School of Medicine School of Medicine, Kobe 650-0017, Hyogo, Japan; ikagoro@pop06.odn.ne.jp

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ABSTRACT

Background This study aimed to investigate the effectiveness of anticholinergics (AC) for death rattle in dying patients with cancer.

Methods This is a prospective cohort study enrolled Terminally ill adult (20 years or older) patients with cancer who developed substantial death rattle (Back score ≥2) from 23 palliative care units in Japan. AC 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) AC, 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 AC. 56.8% in the AC group and 35.4% in the non-AC group had an improved death rattle at 8 hours after baseline. In the weighted analysis, AC group showed significant improvements in death rattle, with an adjusted OR of 4.47 (95% CI 2.04 to 9.78; p=0.0024). All sensitivity analyses achieved essentially the same results. In the subgroup analysis, ACs were strongly associated with death rattle improvement in men, patients with lung cancer, and type 1 death rattle (adjusted OR 5.81, 8.38 and 9.32, respectively).

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

Trial registration number UMIN-CTR (UMIN00002545).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ 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 insufficient evidence for its efficacy and effectiveness for death rattle.

WHAT THIS STUDY ADDS

⇒ The improvement of death rattle was seen significantly more in patients prescribed anticholinergics than those who did not.
⇒ This improvement was strongly associated with the subgroups of men, lung cancer and type 1 death rattle.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinical research on specific populations should be conducted to confirm the efficacy of anticholinergics for death rattle in terminally ill patients with 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 randomised controlled trials (RCTs) have failed to show efficacy,[9–11] anticholinergics (ACs) are often prescribed for death rattle in daily practice.[12] There are several possible reasons. First, death rattle has been proposed to be

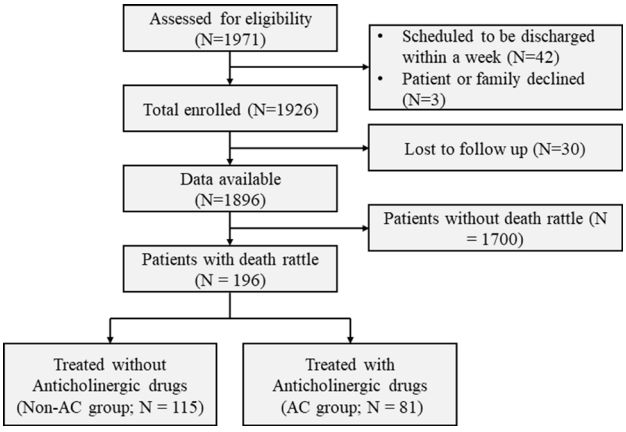

Figure 1 Patient selection flow chart per STROBE. AC, anticholinergic; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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. ACs 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, ACs might decrease the production of saliva and not affect existing salivary accumulation.[16] Therefore, ACs 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 ACs for death rattle. Third, the natural course of death rattle and the effectiveness of ACs in real-world practice have not been sufficiently investigated.

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

METHODS

This study was conducted as a part of the East Asian Collaborative Cross-Cultural Study to Elucidate the Dying Process (EASED), an international, multicentre, 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 patients with cancers admitted to 38 PCUs (23 in Japan, 11 in South Korea and 4 in Taiwan). We used the data from 23 Japanese PCUs in this analysis.

Setting and participants

We consecutively enrolled patients with cancer ≥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 AC according to the clinical guidelines.[19] Although these guidelines do not recommend routine use of AC for death rattle, it allows AC use as an option when death rattle is refractory to other measures. When physicians prescribed AC, the choice of the type and dose of AC 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 hours after substantial death rattle development (T0) until 24 hours 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 this study.[20 21]

Death rattle treatment

We recorded whether ACs were prescribed, as well as the type of AC at each time point. We also recorded whether suctioning was performed at 4 hours ahead of each time point.

Patient characteristics

We collected patients' baseline characteristics at admission, including age, sex, primary tumour site, metastatic lesions (ie, brain, liver and lung), and a history of heart, lung and neuromuscular disease. We also obtained the following data at T0: death

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

Variable	Total	Unweighted cohort			Weighted cohort		
		Non-AC	AC	mean SMD*	Non-AC	AC	mean SMD*
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 tumour 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
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
Oedema, 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

Continued

Table 1 Continued

Variable	Total	Unweighted cohort		mean SMD*	Weighted cohort		mean SMD*
		Non-AC	AC		Non-AC	AC	
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
Cotreatment							
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

Weighted using inverse probability of treatment weighting, based on propensity scores.
*The mean value of SMD across 10 imputed datasets. An absolute SMD greater than 0.1 is interpreted as a meaningful difference.
AC, anticholinergic drugs; SMD, standardised mean difference.

rattle subtype, character of secretion (ie, serous or purulent), presence of crackles on lung auscultation, presence of fluid retention signs (eg, pleural effusion, ascites or peripheral oedema), 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 judgement 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 hours after baseline between patients treated with (AC group) and without (non-AC group) ACs. We defined patients in the AC group as those who started ACs 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 ACs.

First, we constructed two models for PS (ie, the conditional probability of receiving AC) by selecting a set of confounders between treatment assignment (receiving AC) 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 (online 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 10 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 10 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

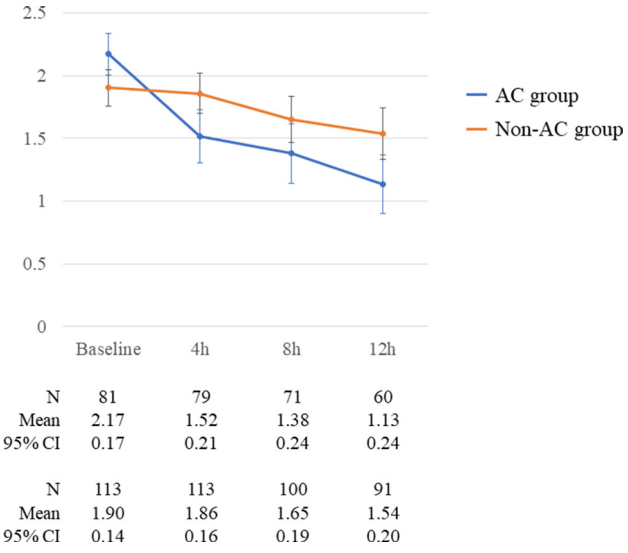

Figure 2 Change of Back's score in AC and non-AC groups. AC, anticholinergic.

IPTW-adjusted OR for death rattle improvement of the AC group vs the non-AC group.

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

In addition, we explored the effect of suctioning on death rattle improvement before starting AC 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) analysing patients with a baseline Back score of only 2 or more, (2) defining the AC group as those who started AC at T0 and T1 only, (3) analysing 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 V.3.5.3 (R Core Team 2019, Vienna, Austria). All p values were two sided. A $p<0.05$ 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 analysed 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 hours after baseline because they had died before then; these were imputed by the last observation values.

Patient characteristics after imputation are summarised in table 1. The mean age was 71.3 years; 38.8% were female. The most common primary tumour 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/day 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, ACs were started at T0 in 31 patients, T1 in 34, T2 in 8, T3 in 5 and T4 in 3.

Table 2 Association of anticholinergics on the severity of death rattle

	N	Adjusted OR	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

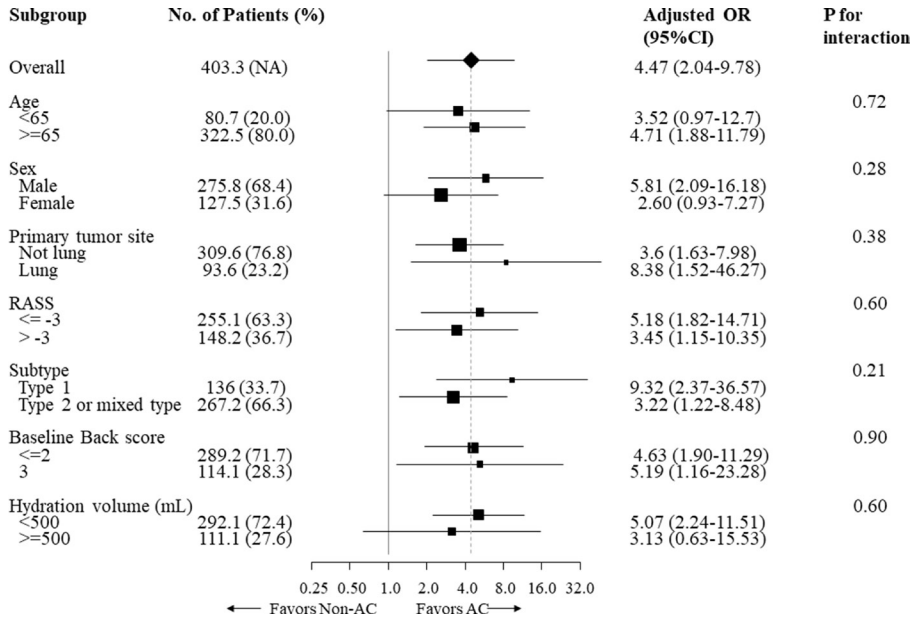

Figure 3 Subgroup analysis. AC, anticholinergic drugs; NA, not available; RASS, modified Richmond Agitation and Sedation Scale.

Scopolamine butylbromide was administered to 59 patients and scopolamine hydrobromide to 22.

Balance of covariates between the non-AC and AC 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, standardised 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 hours 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 to 4.30; p=0.034). In the weighted analyses, the adjusted OR was 4.47 (95% CI 2.04 to 9.78; p=0.00024; 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 AC were strongly associated with death rattle improvement, especially in subgroups of men, lung cancer and type 1 death rattle (ORs 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 AC (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 hours after baseline was 67.6% in the non-suctioning group and 48.9% in the suctioning group (OR 0.48; 95% CI 0.19 to 1.22; p=0.13). In the weighted analysis, the adjusted OR was 0.53 (95% CI 0.19 to 1.51; p=0.24).

Sensitivity analyses

The percentage of improved patients at 8 hours 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 to 10.11; p=0.016), (2) the cohort of those who started AC at T0 and T1 only (OR 3.10; 95% CI 1.64 to 5.87; p=0.00063), (3) the analysis with deletion of missing outcome value (OR 4.62; 95% CI 1.70 to 12.57; p=0.0031), (4) the analysis with PS model 2 (OR 3.39; 95% CI 1.79 to 6.41; p=0.00024) and (5) the multivariate logistic regression (OR 3.48; 95% CI 1.77 to 6.86; p=0.00041). 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 AC for death rattle in real-world terminally ill patients with cancer. This study has several major findings. First, AC reduced death rattle more than the natural course in terminally ill patients with cancer receiving care in PCUs. The previous two

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		
		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 tumour 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
Cotreatment							
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

Weighted using inverse probability of treatment weighting, based on propensity scores.
The mean value of SMD across 10 imputed datasets. An absolute SMD greater than 0.1 is interpreted as a meaningful difference.
Non-SUC, subgroup without suctioning; SMD, standardised mean difference; SUC, subgroup with suctioning.

placebo-controlled RCTs did not find efficacy of AC for death rattle.[10 11] However, one of the studies, including only unconscious terminally ill patients with cancer, showed a tendency for AC 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 patients with non-cancer.[24] Heart and lung disease tend to develop type 2 death rattle which is considered to be less responsive to ACs.[15] Indeed, death rattle improvement after starting AC was observed more frequently in type 1 than type 2 or mixed cases in this study. Moreover, the previous study also included mild death rattle (Back score of 1), whereas this study included the patients only substantial death rattle (Back score of 2 or more), which might have influenced the result. Thus, ACs could have significant role in managing death rattle in terminally ill patients with cancer, selecting cases with type 1 death rattle and substantial intensity, after appropriate non-pharmacological care. Second, suctioning before starting AC and the severity of death rattle did not influence the effectiveness of ACs in this study. Recently, two RCTs showed the efficacy of prophylactic use of AC 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 AC prophylactically for all terminally ill patients with cancer. 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 this study, AC might not be necessarily used prophylactically or started after suctioning in the management of death rattle in terminally ill patients with cancer. Instead, minimal and proper use of AC based on careful evaluation and selection of the patient in need might be more appropriate.

This study has several strengths. First, we included the largest scale of real-world patients to date, and the results were adjusted with IPTW to minimise the influence of potential confounders. Thus, the results of this study are reliable and broadly applicable to terminally patients with cancer in daily clinical practice. Second, although few previous studies had evaluated the subtype of death rattle, this study distinguished the subtypes and showed that ACs were more effective in type 1.

Despite these strengths, this study had limitations. First, due to its observational nature, causality between ACs 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 ACs were not completely standardised despite following AC 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 patients with cancer with type 1 death rattle of substantial intensity to confirm the efficacy of ACs. 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 minimise 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 AC 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 ACs 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 generalised to patients who are not admitted to PCUs.

CONCLUSIONS

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

Author affiliations
[1]Department of Palliative Medicine, Kobe University Graduate School of Medicine School of Medicine, Kobe, Hyogo, Japan
[2]Department of Palliative and Supportive Care, Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan
[3]Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[4]Department of Palliative Care, Senri Chuo Hospital, Toyonaka, Osaka, Japan
[5]Department of Palliative Care, Konan Medical Center, Kobe, Hyogo, Japan
[6]Department of Palliative Care, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Bunkyo-ku, Tokyo, Japan
[7]Department of Palliative Care, Hatsukaichi Memorial Hospital, Hatsukaichi, Hiroshima, Japan
[8]Department of Oncology and Palliative Care, Mitsubishi Kyoto Hospital, Kyoto, Japan
[9]Department of Palliative Care, St Luke's International University, Chuo-ku, Tokyo, Japan
[10]Division of Community Medicine and Internal Medicine, University of the Ryukyus Hospital, Nishihara, Okinawa, Japan
[11]Department of Palliative Medicine, Kyoto University, Kyoto, Japan

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ORCID iDs
Takashi Yamaguchi http://orcid.org/0000-0003-3060-0245
Nobuhisa Nakajima http://orcid.org/0000-0002-5416-1227

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