

Original Article

Effect of age on dexmedetomidine treatment for ventilated patients with sepsis: a post-hoc analysis of the DESIRE trial

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Aim: There are no definitive data to determine whether age influences the effects of dexmedetomidine (DEX) treatment. Thus, we investigated whether older age was associated with more favorable sedative action by DEX in sepsis patients who required mechanical ventilation.

Methods: This study involved a post-hoc analysis of data from the Dexmedetomidine for Sepsis in the ICU Randomized Evaluation (DESIRE) trial. The patients were categorized based on median age into elderly and younger groups. The two groups were then compared during the first 7 days after ventilation based on proportion of patients with well-controlled sedation (Richmond Agitation–Sedation Scale score between –3 and +1), days free from delirium (based on the Confusion Assessment Method for ICU), and days free from coma (Richmond Agitation–Sedation Scale score between –4 and –5).

Results: One hundred and one patients were assigned to the elderly group and 100 patients were assigned to the younger group. In the elderly group, 50 patients received DEX treatment and 51 patients received non-DEX treatment, with the DEX arm having significantly better-controlled sedation (range, 14–52% versus 16–27%; $P = 0.01$). In the younger group, 50 patients received DEX treatment and 50 patients received non-DEX treatment, with no significant difference in the proportions of well-controlled sedation (range, 20–64% versus 24–60%; $P = 0.73$). There were no significant differences in the numbers of days free from delirium or coma between the groups.

Conclusion: In elderly sepsis patients who require ventilation, dexmedetomidine could be more effective than other sedative agents for achieving proper sedation.

Key words: Delirium, dexmedetomidine, elderly, sedative effect, sepsis

BACKGROUND

DEXMEDETOMIDINE (DEX) IS a potent and selective alpha-2 adrenergic receptor agonist that shows a wide range of pharmacological actions, such as sedative, analgesic, and antisympathetic effects.^{1–3} The sedative and

analgesic effects are expressed through the central alpha-2 receptors in the locus coeruleus of the brain and in the spinal cord, respectively.³ Unlike other sedatives, DEX maintains the patient's alertness and does not suppress breathing.^{4–7} Furthermore, DEX can help keep ventilated patients arousable in the intensive care unit (ICU),⁸ which helps shorten the time to extubation⁸ and increases the number of days free from coma⁹ or delirium.¹⁰ A recent systematic review that included 18 randomized controlled trials (RCTs) revealed that DEX, relative to other sedatives such as propofol and benzodiazepines, was effective in reducing the ICU length of stay.¹¹

In sepsis, acute brain dysfunction is considered a type of organ failure, which can manifest as agitation and delirium.¹² The “ABCDE bundle” has been used to describe a

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treatment concept that focuses on awakening and breathing coordination, delirium monitoring, and exercise/early mobility.¹³ In this context, the management guidelines recommend that DEX is preferable for maintaining a light level of sedation, especially for managing delirium.¹⁴

Although the half-life of DEX is approximately 2 h, the pharmacokinetics of DEX are affected by age, with elderly patients showing decreased drug clearance, which results in prolongation of the elimination and context-sensitive half-lives.^{2,15,16} In clinical practice, DEX treatment alone provides a proper sedation level in elderly patients, but not in younger patients. For example, perioperative DEX treatment of elderly patients has been shown to prevent delirium,^{17,18} support analgesia,¹⁹ improve cognitive function,²⁰ and improve sleep quality.²¹ Subgroup analyses of the SPICE III study (4,000 critically ill patients) also revealed that the 90-day mortality rate was lower for elderly patients who received DEX-based sedation,²² which the authors suggested was related to age-based differences in the pharmacokinetics of DEX.²² However, to the best of our knowledge, no reports have determined whether age influences the effects of DEX treatment in ventilated patients with sepsis. Therefore, the present study evaluated whether older age was associated with a more favorable sedative action for DEX treatment in elderly patients.

METHODS

Study design and patients

THIS STUDY INVOLVED a post-hoc analysis of data from the Dexmedetomidine for Sepsis in the ICU Randomized Evaluation (DESIRE) trial.²³ The DESIRE trial protocol and results have been reported previously, ethical approval was received from all relevant institutional review boards, and all participants provided informed consent prior to enrolment.²³ In brief, the DESIRE trial enrolled 201 patients with sepsis who required ventilation at eight Japanese ICUs, and compared the effects of sedation strategies with DEX (DEX arm) or without DEX (non-DEX arm). The results revealed that the DEX arm showed better-controlled sedation.²³ The present study categorized all patients in the DESIRE trial based on their median age into elderly and younger groups, and evaluated the effects of DEX treatment in each age group.

Data collection

Data were collected regarding age, sex, body weight, initial serum lactate levels, day 1 Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, Sequential Organ

Failure Assessment (SOFA) scores, day 1 SOFA subscores (respiratory, circulatory, renal, hepatic, neurological, and coagulation), any renal replacement therapy, emergency surgery, other sedative agents (propofol, midazolam, and fentanyl), and adverse events (bradycardia and acute coronary syndrome).

The primary outcome was the number of days with well-controlled sedation and days free from delirium or coma during the first 7 days after the start of ventilation. Well-controlled sedation was defined as a Richmond Agitation–Sedation Scale (RASS) score between -3 and $+1$ throughout each day spent in the ICU, and was calculated daily based on the previously reported equation: (proportion of controlled sedation) = (patients with controlled sedation on a given day) / (all patients in the ICU on that same day).²³ Delirium was identified based on a positive result from the Confusion Assessment Method for ICU,² and coma was identified based on a RASS score between -4 and -5 throughout 1 day in the ICU.⁹ The secondary outcome was defined as the total weight-corrected doses of other sedative agents used during the first 7 days after the start of ventilation.

Statistical analysis

Categorical variables were expressed as number (%) and continuous variables were expressed as median (interquartile range [IQR]). Categorical variables were compared using the χ^2 -test or Fisher's exact test, and continuous variables were compared using the Wilcoxon rank sum test. The effects of DEX on sedation control and the occurrence of delirium or coma were evaluated using a generalized linear model (GENMOD procedure with logit function) to account for repeated measurements in the same patient. All statistical tests were two-sided and P -values of <0.05 were considered statistically significant. All analyses were undertaken using JMP Pro software (version 13) and SAS software (version 9.4) (SAS Institute, Cary, NC, USA).

RESULTS

THE MEDIAN PATIENT age was 71 years and 63% of the patients were men. The median APACHE II score was 23 (IQR, 17–29) and the median SOFA score was 9 (IQR, 6–11). The median lactate level was 3.5 mmol/L (IQR, 1.9–5.4 mmol/L). Among the 201 patients, 77 patients received renal replacement therapy (38%) and 73 patients underwent emergency surgery (36%). Based on the median age, 101 patients were assigned to the elderly group (≥ 71 years old) and 100 were assigned to the younger group (< 71 years old) (Fig. 1). The characteristics of the elderly and younger groups are shown in Table 1, although no

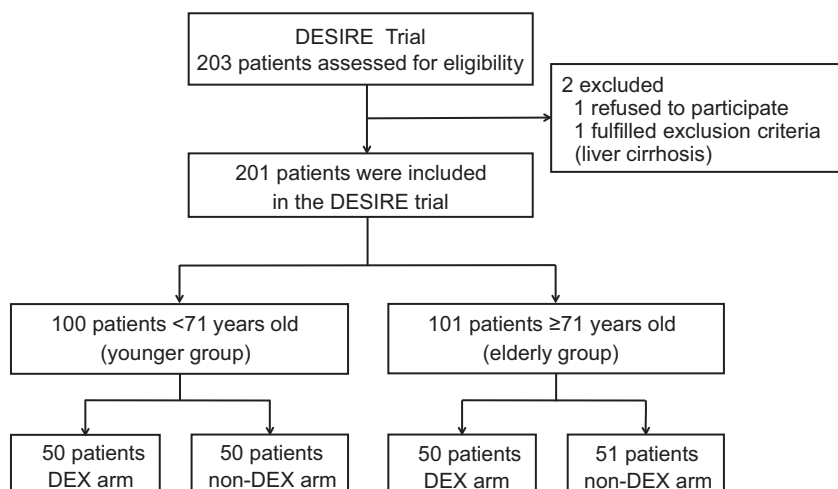


Fig. 1. Study flowchart. DESIRE, Dexmedetomidine for Sepsis in the Intensive care unit (ICU) Randomized Evaluation; DEX, dexmedetomidine.

significant intergroup differences were observed. In the elderly group, 50 patients received DEX treatment and 51 received non-DEX treatment. In the younger group, 50 patients received DEX treatment and 50 patients received non-DEX treatment. The patients' characteristics remained well-balanced after the age-based stratification (Table 2).

In the elderly group, the proportion of patients with well-controlled sedation during the first 7 days was significantly higher in the DEX arm than in the non-DEX arm (range, 14–52% versus 16–27%; $P = 0.01$). However, there was no significant difference between the treatment arms in the younger group (range, 20–64% versus 24–60%; $P = 0.73$) (Fig. 2). In addition, no significant differences were observed in the numbers of delirium-free and coma-free days when we compared the treatment arms in the elderly group (range, 6–32% versus 5.9–17.2%; $P = 0.29$) or in the younger group (range, 6–39.3% versus 14–26.7%; $P = 0.27$) (Fig. 3). Daily sedation levels by the maximum and minimum RASS values for the younger and elderly groups are shown in the Figure S1.

In the elderly group, the total weight-adjusted usages of propofol and midazolam during the first 7 days were significantly lower in the DEX arm than in the non-DEX arm (median propofol use [IQR], 0.2 [0–14.6] mg/kg versus 22.3 [0–64.7] mg/kg, $P = 0.003$; median midazolam use, 0 [0–0] mg/kg versus 0 [0–1.3] mg/kg, $P = 0.001$). In the younger group, only the use of midazolam was significantly lower in the DEX arm (median midazolam use, 0 [0–0.9] mg/kg versus 1.1 [0–3.5] mg/kg, $P = 0.014$) (Table 3). The elderly group had non-significantly higher use of propofol, whereas the younger group had non-significantly higher

use of midazolam. No significant intergroup differences were observed in fentanyl use (Table S1). In the DEX arm, the usages of DEX tended to be lower in the elderly group, but no significant difference was observed between the two groups (Table S1).

The adverse events included nine cases of bradycardia and two cases of acute coronary syndrome (Table 4). In the elderly group, bradycardia was detected in five patients (10%) who received DEX treatment and one patient (2%) who received non-DEX treatment; acute coronary syndrome was detected in one patient (2%) in each treatment arm. There were no significant differences when we compared the adverse events among the treatment arms and between the elderly and younger groups (Tables 4 and S1).

DISCUSSION

THE RESULTS OF this post-hoc analysis of DESIRE trial data suggest that age might influence the clinical effects of DEX. For example, DEX induced better-controlled sedation in elderly patients than in younger patients. The results also suggested that DEX treatment in the elderly group was associated with lower doses for other sedatives. However, no significant age-related differences were observed in the delirium- and coma-free days according to DEX treatment status.

A 2016 systematic review¹¹ summarized the findings from 18 RCTs that compared the effects of alpha-2 agonists (DEX and clonidine) with alternative sedative agents for ventilated patients. Among those studies, 11 trials used the Ramsay Sedation Scale (RSS) score, six trials used the

Table 1. Characteristics of younger (<71 years old) and elderly (≥71 years old) groups of ventilated patients with sepsis

	<71 years old (n = 100)	≥71 years old (n = 101)	P-value
Age, years	63 (49–66)	79 (75–84)	<0.001***
Men	64 (64)	63 (62.4)	0.810
Body weight, kg	56.5 (50–65)	55 (44–65)	0.055
APACHE II score	22 (17–29)	23 (18–30)	0.250
Lactate, mmol/L	3 (1.8–4.8)	3.8 (2.2–6.2)	0.048*
Day 1 SOFA scores			
Overall score	9 (6–11)	8 (6–11)	0.660
Respiratory score	2 (1–3)	2 (1–3)	0.190
Circulatory score	3 (2–4)	3 (2–4)	0.520
Renal score	1 (0–2)	1 (0–3)	0.210
Hepatic score	0 (0–1)	0 (0–1)	0.960
Neurological score	1 (0–3)	1 (0–2)	0.720
Coagulation score	0 (0–2)	0 (0–2)	0.660
Renal replacement therapy	39 (39)	38 (37.6)	0.840
Emergency surgery	30 (30)	43 (42.6)	0.063

Data are shown as n (%) or median (interquartile range).

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

*, ***Statistically significant; * $P < 0.05$; *** $P < 0.001$.

Table 2. Patient characteristics according to dexmedetomidine (DEX) use in younger (<71 years old) and elderly (≥71 years old) groups of ventilated patients with sepsis

	<71 years old (n = 100)			≥71 years old (n = 101)		
	DEX (n = 50)	Non-DEX (n = 50)	P-value	DEX (n = 50)	Non-DEX (n = 51)	P-value
Age, years	63 (49–65)	63 (49–66)	0.72	79 (75–84)	79 (76–83)	0.87
Men	34 (68)	30 (60)	0.40	29 (58)	34 (66.7)	0.37
Body weight, kg	56.5 (50–65)	56.7 (50–65)	0.83	50 (43–60)	60 (47–68)	0.032*
APACHE II score	23 (18–29)	21 (15–28)	0.17	23 (18–29)	24 (16–32)	0.72
Lactate, mmol/L	3.6 (2.1–4.9)	2.7 (1.2–4.7)	0.34	3.9 (2.1–6.3)	3.7 (2.2–6.2)	0.94
Day 1 SOFA score						
Overall score	9 (7–11)	10 (6–11)	0.89	8 (6–11)	9 (5–11)	0.68
Respiratory score	2 (1–3)	2 (1–3)	0.97	2 (1–3)	2 (1–3)	0.82
Circulatory score	3 (2–4)	3 (2–4)	0.93	3 (2–4)	3 (1–4)	0.24
Renal score	1 (0–2)	1 (0–2)	0.35	1 (0.75–2)	1 (0–3)	0.63
Hepatic score	0 (0–1)	0 (0–1)	0.31	0 (0–1)	0 (0–1)	0.91
Neurological score	1 (0–3)	0 (0–3)	0.85	1 (0–2)	1 (0–2)	0.67
Coagulation score	0 (0–2)	1 (0–2)	0.96	0 (0–1)	1 (0–2)	0.11
Renal replacement therapy	19 (38)	20 (40)	0.84	19 (38)	19 (37.3)	0.94
Emergency surgery	14 (28)	16 (32)	0.66	23 (46)	20 (39.2)	0.49

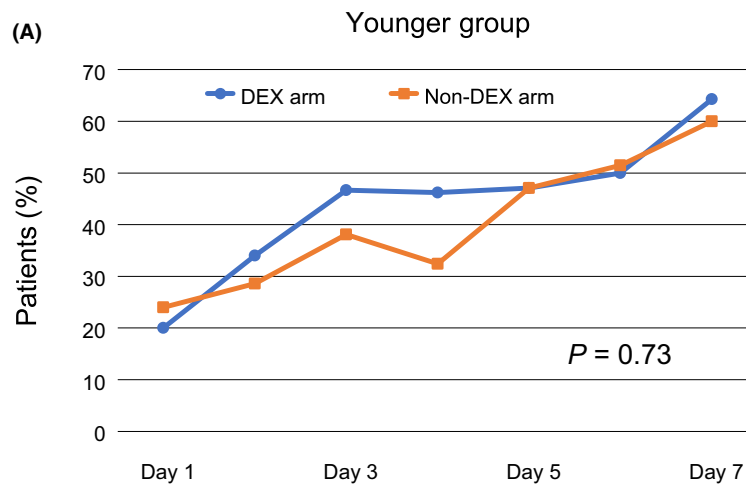
Data are shown as n (%) or median (interquartile range).

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

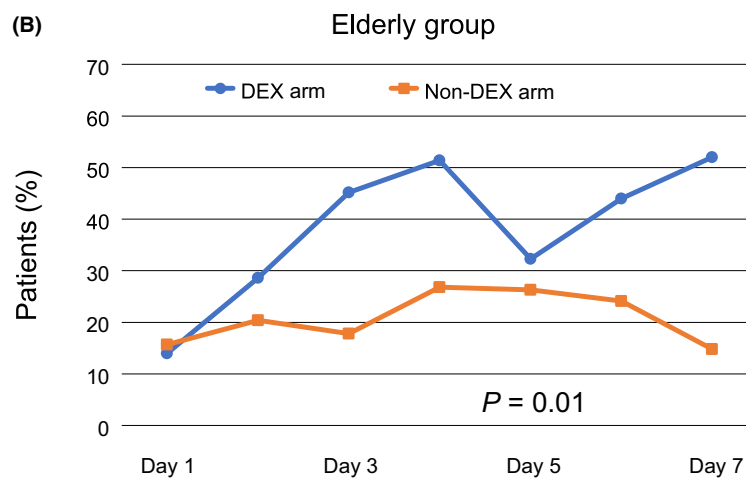
* $P < 0.05$, Statistically significant.

RASS score, and one trial used the Riker Sedation–Agitation Scale (SAS) score for target sedation level measurement. The sedation range of levels were various when using the RASS score, “–2 to 1” or “–3 to 0” when using the RASS

score, and “3 to 4” with the Riker SAS score. This review stated that the optimal level of sedation varies according to patients’ clinical conditions and treatment requirements. So, our RASS score definition as well-controlled sedation was



Number of patients	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
DEX arm	50	50	45	39	34	28	28
Non-DEX arm	50	49	42	37	34	33	30



Number of patients	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
DEX arm	50	49	42	35	31	25	25
Non-DEX arm	51	49	45	41	38	29	27

Fig. 2. Ventilated patients with sepsis with well-controlled sedation for 7 days in the dexmedetomidine (DEX) and non-DEX arms. We used a generalized linear model (GENMOD procedure with logit function) accounting for repeated measurements in the same patient. A, Younger group (<71 years old). B, Elderly group (≥71 years old).

acceptable clinically. Among those studies, four multicenter trials revealed that patients who received DEX were more arousable, more cooperative, and more able to communicate, although those studies did not directly evaluate well-controlled sedation. Seven studies examined differences in

delirium and revealed that there were no significant differences between the sedatives. Nevertheless, the IQR value for age was 40–67 years, which does not encompass the “elderly” age group, whereas the present study had an IQR value for age of 75–84 years. Other studies have examined

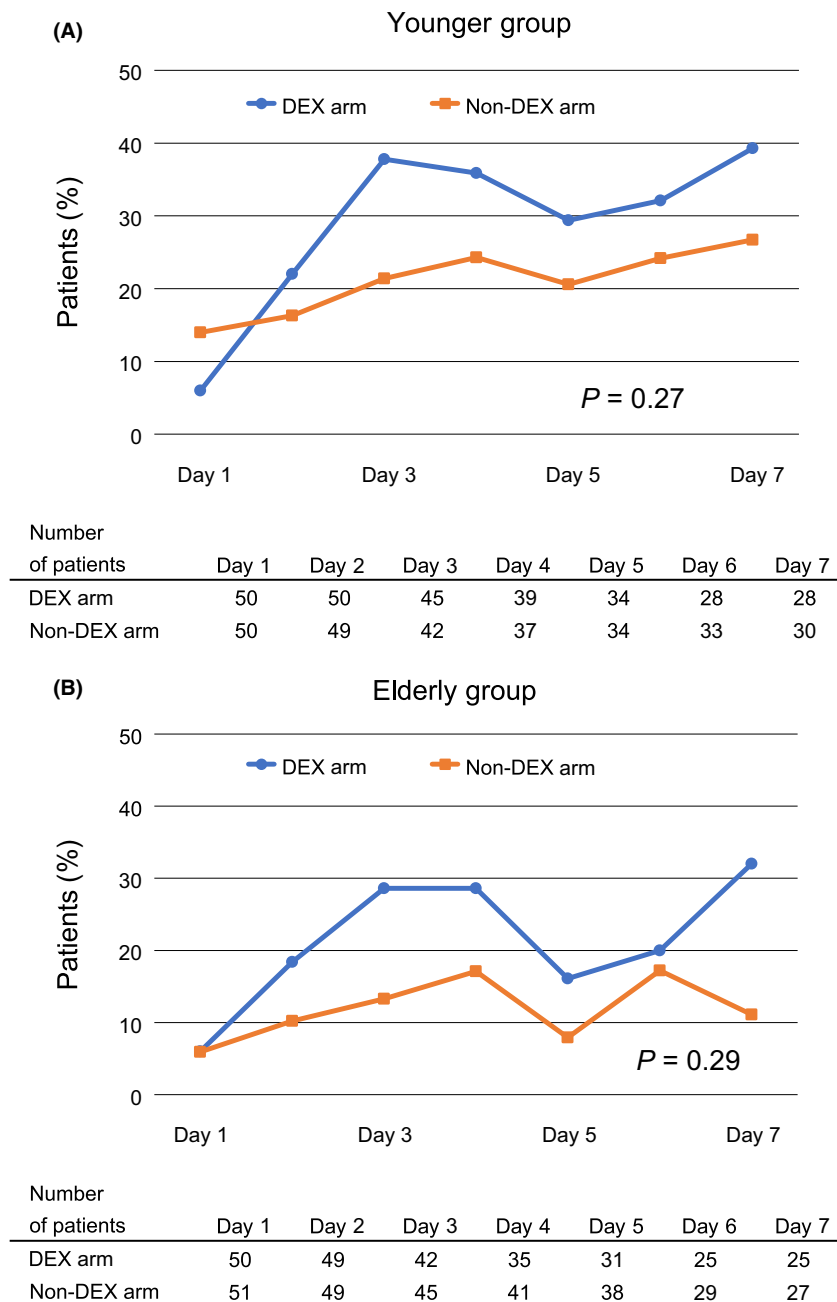


Fig. 3. Ventilated patients with sepsis free from delirium and coma for more than 7 days in the dexmedetomidine (DEX) and non-DEX arms. We used a generalized linear model (GENMOD procedure with logit function) accounting for repeated measurements in the same patient. A, Younger group (<71 years old). B, Elderly group (≥ 71 years old).

the perioperative effects of DEX in elderly patients, such as a recent RCT that revealed DEX-based treatment provided better control over the depth of sedation among surgical patients who were ≥ 70 years old.²⁴ Another RCT by Su *et al.* concluded that prophylactic low-dose DEX treatment

significantly decreased the occurrence of delirium after non-cardiac surgery among patients who were ≥ 65 years old.¹⁷ We are also aware of some studies regarding differences in DEX usage between younger and elderly patients,^{25,26} although they did not report any differences in DEX

Table 3. Use of other sedative agents with or without dexmedetomidine (DEX) in younger (<71 years old) and older (≥71 years old) groups of ventilated patients with sepsis

	<71 years old (n = 100)			≥71 years old (n = 101)		
	DEX (n = 50)	Non-DEX (n = 50)	P-value	DEX (n = 50)	Non-DEX (n = 51)	P-value
Propofol, mg/kg	0 (0–14.4)	4.1 (0–34.3)	0.10	0.2 (0–14.6)	22.3 (0–64.7)	0.003**
Midazolam, mg/kg	0 (0–0.9)	1.1 (0–3.5)	0.014*	0 (0–0)	0 (0–1.3)	0.001**
Fentanyl, µg/kg	55.8 (28.5–90.3)	39.4 (20.8–81.1)	0.26	35 (7–86)	49.7 (13.1–75.2)	0.47

Data are shown as median (interquartile range).

*, **Statistically significant; * $P < 0.05$; ** $P < 0.01$.

Table 4. Adverse events according to dexmedetomidine (DEX) use in younger (<71 years old) and elderly (≥71 years old) groups of ventilated patients with sepsis

	<71 years old (n = 100)			≥71 years old (n = 101)		
	DEX (n = 50)	Non-DEX (n = 50)	P-value	DEX (n = 50)	Non-DEX (n = 51)	P-value
Bradycardia	2 (4)	1 (2)	1.0	5 (10)	1 (2)	0.11
Acute coronary syndrome	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	1.0

Data are shown as n (%).

efficacy. A recent subanalysis of the SPICE III study has also suggested that age might significantly influence the effects of DEX on mortality.²² Therefore, our novel findings suggest that it would be worthwhile considering the differential effects of DEX according to age in future studies.

When we considered patients in the DEX arms (versus the non-DEX arms), the elderly group had lower use of midazolam and propofol, while the younger group had lower use of midazolam. From the pharmacological point of view, the pharmacokinetic and pharmacodynamic profiles of DEX are different in elderly and younger patients, with older patients having longer elimination and context-sensitive half-lives.¹⁶ The use of DEX in elderly patients might also be effective in reducing the need for other sedatives that have a high affinity for gamma-aminobutyric acid A receptors, which are believed to be delirio-genic.⁸

The main adverse effects related to DEX treatment are reportedly hypotension and bradycardia.^{15,27} The present study considered bradycardia and acute coronary syndrome, although we did not observe significant differences in these events according to age or DEX use.

The present study has several limitations. First, the post-hoc nature of the analysis potentially limited the sample size, which might explain the lack of significant differences in the numbers of delirium- and coma-free days. Second, our

definition of well-controlled sedation and the assessment period might not be comparable to those in other studies, although our definition is based on the relevant guidelines and we consider it to be clinically relevant.² Finally, unidentified confounders might exist, although we observed that the patients' characteristics were well-balanced in terms of the variables we considered.

Relative to other sedative agents, DEX could be more beneficial and achieve more suitable sedation of elderly sepsis patients who require ventilation. Chronological age could be a sufficient factor to explain the difference of the effect, knowing there is a huge diversity in older people. However, further prospective studies are needed to validate this finding.

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DISCLOSURE

Approval of the research protocol: This study is a post hoc subgroup analysis of the DESIRE trial, which was a randomized controlled trial that included eight Japanese intensive care units. The original study was approved by the review boards of all relevant institutions.

Informed consent: All participants provided written informed consent prior to enrolment.

Registry and registration no. of the study/trial: Clinicaltrials.gov: NCT01760967; January 1, 2013.

Animal studies: N/A.

Conflict of interest: None.

DATA AVAILABILITY STATEMENT

THE DATASETS GENERATED and analyzed during the current study are not publicly available because of privacy concerns and institutional policy.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Daily sedation levels by the maximum and minimum Richmond Agitation–Sedation Scale (RASS) values in the (A) younger (<71 years old) and (B) elderly (≥ 71 years old) groups of ventilated patients with sepsis. * $P < 0.05$, value of RASS score compared with Wilcoxon rank sums test. DEX, dexmedetomidine.

Table S1. Younger (<71 years old) versus elderly (≥ 71 years old) groups of ventilated patients with sepsis.