Palliative and Supportive Care

cambridge.org/pax

Original Article

Cite this article: Kurisu K *et al.* (2022). A decision tree prediction model for a short-term outcome of delirium in patients with advanced cancer receiving pharmacological interventions: A secondary analysis of a multicenter and prospective observational study (Phase-R). *Palliative and Supportive Care* **20**, 153–158. https://doi.org/10.1017/S1478951521001565

Received: 15 March 2021
Revised: 2 August 2021
Accepted: 29 August 2021

Key words:
Cancer; Delirium; Machine learning; Palliative care; Psycho-oncology

Author for correspondence:
Kazuhiro Yoshiuchi, Department of Stress Sciences and Psychosomatic Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail: kyoshiuc-tky@umin.ac.jp

A decision tree prediction model for a short-term outcome of delirium in patients with advanced cancer receiving pharmacological interventions: A secondary analysis of a multicenter and prospective observational study (Phase-R)

Ken Kurisu, M.D.[1], Shuji Inada, M.D., PH.D.[1], Isseki Maeda, M.D., PH.D.[2], Asao Ogawa, M.D., PH.D.[3], Satoru Iwase, M.D., PH.D.[4], Tatsuo Akechi, M.D., PH.D.[5,6], Tatsuya Morita, M.D.[7,8], Shunsuke Oyamada, M.SC.[9], Takuhiro Yamaguchi, PH.D.[10], Kengo Imai, M.D.[8], Rika Nakahara, M.D., PH.D.[11], Keisuke Kaneishi, M.D., PH.D.[12], Nobuhisa Nakajima, M.D., PH.D.[13], Masahiko Sumitani, M.D., PH.D.[14], Kazuhiro Yoshiuchi, M.D., PH.D.[1] and on behalf of the Phase-R Delirium Study Group[1]

[1]Department of Stress Sciences and Psychosomatic Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [2]Department of Palliative Care, Senri-Chuo Hospital, Toyonaka, Osaka, Japan; [3]Department of Psycho-Oncology Service, National Cancer Center Hospital East, Kashiwa, Chiba, Japan; [4]Department of Palliative Medicine, Saitama Medical University, Iruma, Saitama, Japan; [5]Center for Psycho-Oncology and Palliative Care, Nagoya City University Hospital, Nagoya, Aichi, Japan; [6]Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Aichi, Japan; [7]Department of Palliative and Supportive Care, Palliative Care Team, Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan; [8]Seirei Hospice, Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan; [9]Department of Biostatistics, JORTC Data Center, Tokyo, Japan; [10]Division of Biostatistics, Tohoku University School of Medicine, Sendai, Japan; [11]Department of Psycho-Oncology, National Cancer Center Hospital, Tokyo, Japan; [12]Department of Palliative Care Unit, JCHO Tokyo Shinjuku Medical Center, Tokyo, Japan; [13]Division of Community Medicine and Internal Medicine, University of the Ryukyus Hospital, Okinawa, Japan and [14]Department of Pain and Palliative Medicine, The University of Tokyo Hospital, Tokyo, Japan

Abstract

Objective. There is no widely used prognostic model for delirium in patients with advanced cancer. The present study aimed to develop a decision tree prediction model for a short-term outcome.

Method. This is a secondary analysis of a multicenter and prospective observational study conducted at 9 psycho-oncology consultation services and 14 inpatient palliative care units in Japan. We used records of patients with advanced cancer receiving pharmacological interventions with a baseline Delirium Rating Scale Revised-98 (DRS-R98) severity score of ≥10. A DRS-R98 severity score of <10 on day 3 was defined as the study outcome. The dataset was randomly split into the training and test dataset. A decision tree model was developed using the training dataset and potential predictors. The area under the curve (AUC) of the receiver operating characteristic curve was measured both in 5-fold cross-validation and in the independent test dataset. Finally, the model was visualized using the whole dataset.

Results. Altogether, 668 records were included, of which 141 had a DRS-R98 severity score of <10 on day 3. The model achieved an average AUC of 0.698 in 5-fold cross-validation and 0.718 (95% confidence interval, 0.627–0.810) in the test dataset. The baseline DRS-R98 severity score (cutoff of 15), hypoxia, and dehydration were the important predictors, in this order.

Significance of results. We developed an easy-to-use prediction model for the short-term outcome of delirium in patients with advanced cancer receiving pharmacological interventions. The baseline severity of delirium and precipitating factors of delirium were important for prediction.

© The Author(s), 2021. Published by Cambridge University Press

Introduction

Delirium, an acute confusional state characterized by disturbed consciousness and cognitive function, is common among patients with advanced cancer (Centeno et al., 2004; Bush et al., 2018). It causes distress in patients, families, spouses/caregivers, and nurses (Breitbart

et al., 2002; Morita et al., 2004) and is associated with poor clinical outcomes (Witlox et al., 2010). Although the effectiveness of antipsychotics for delirium remains unclear (Neufeld et al., 2016; Burry et al., 2018), short-term use of small-doses of antipsychotics may be considered only for patients with severe distress or risk of harming themselves or others [American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults, 2015; Marcantonio, 2017; Bush et al., 2018; National Institute for Health and Care Excellence (UK), 2019].

However, there is no widely utilized prediction model for the course of delirium in patients with advanced cancer receiving pharmacological interventions. Notably, short-term outcomes of delirium (such as delirium status on day 3) could estimate treatment effectiveness (Tahir et al., 2010) and have been widely used (Elsayem et al., 2010). If clinicians could predict such a short-term outcome of delirium, they could share the information with medical staff or families and allocate nursing care efficiently.

Decision tree, a machine learning algorithm, has been widely utilized for clinical prediction models (Esteban et al., 2015; Brims et al., 2016; Goodman et al., 2016). It has high interpretability because of its complete visualization of prediction rules. Although other machine learning models, such as random forest, can partially visualize influences of predictors (Kurisu et al., 2019; Roger et al., 2020; Tamune et al., 2020), this complete visualization is specific to a decision tree and enables clinicians to utilize the model without software.

The importance of observational studies using real-world data (RWD) has been recognized because they could complement data from randomized controlled studies (Ligthelm et al., 2007; Blonde et al., 2018). The U.S. Food and Drug Administration has also mentioned that real-world clinical data are important for healthcare decisions (U.S. Food and Drug Administration, 2018). However, studies using large-scale RWD are lacking for delirium management in patients with advanced cancer.

Therefore, the present study aimed to develop a decision tree prediction model for a short-term outcome of delirium in patients with advanced cancer receiving pharmacological interventions using large-scale RWD [data from Japan Pharmacological Audit Study of Safety and Effectiveness in Real-World (Phase-R)].

Methods

Phase-R study

The present study is a secondary analysis of Phase-R, a multicenter and prospective observational study (Okuyama et al., 2019; Maeda et al., 2020, 2021; Matsuda et al., 2020; Uchida et al., 2020). Data were collected at 14 palliative care units certified by the Hospice Palliative Care Japan and 9 psycho-oncology settings of tertiary cancer care hospitals or university hospitals across Japan from September 2015 to May 2016. The psycho-oncology setting refers to consultation or liaison with psychiatrists or psychosomatic physicians for patients with cancer admitted to oncology wards. The ethics committee of Osaka University (approval number: 13295) and the institutional review boards at all sites approved the study protocol. According to the guideline by the Ministry of Health, Labor, and Welfare, the requirement for informed consent was waived because the study collected data from records of usual clinical practice (Ministry of Health, Labor, and Welfare, 2008). We used an opt-out method such that patients and families could refuse to participate in the study.

Inclusion criteria were (a) patients with advanced cancer who were diagnosed with delirium according to the Diagnostic Statistical Manual of Mental Disorders, Fifth Edition by trained palliative care physicians or psycho-oncologists (American Psychiatric Association, 2013), and (b) those who received antipsychotics or trazodone for symptom improvement. Trazodone was included because of frequent prescriptions for delirium in Japan (Wada et al., 2018). Exclusion criteria were (a) patients with postoperative delirium and (b) those with alcohol or drug withdrawal delirium.

The definition of study outcome and participants

In the Phase-R project, the Japanese version of the Delirium Rating Scale Revised-98 (DRS-R98) was used to evaluate delirium (Kato et al., 2010). It is a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items. The score for each item ranges between 0 and 3; the maximum total severity score is 39. The severity score of 10 is suggested as the cutoff point for the diagnosis of delirium.

The patients were evaluated by trained palliative care physicians or psycho-oncologists using the DRS-R98 severity items at the beginning of the pharmacological intervention (baseline) and 72 h after the intervention (day 3). We extracted patients' records with a DRS-R98 severity score of $\geq$10 at the baseline from the Phase-R database. As the study outcome, we defined remission as a DRS-R98 severity score of <10 on day 3.

Predictor variables

The following variables measured at the baseline were considered as potential predictors and used in the model development: age, Eastern Cooperative Oncology Group Performance Status (Oken et al., 1982), primary tumor sites, comorbid diseases (diabetes, dementia, brain tumor, and cerebrovascular diseases), oral intake availability, precipitating factors of delirium (Inouye et al., 2014), drugs for delirium management, delirium subtypes, the baseline DRS-R98 severity score, treatment lines of drugs for delirium management (first-, second-, or third-line), and settings (palliative care or psycho-oncology).

The precipitating factors of delirium were estimated by trained palliative care physicians or psycho-oncologists and included opioids, drugs other than opioids, dehydration, non-respiratory infection, respiratory infection, organic damage to the central nervous system, hypoxia, liver failure, renal failure, hypercalcemia, hyponatremia, disseminated intravascular coagulation, and others. The drugs for delirium management were categorized into five groups: typical antipsychotics, serotonin-dopamine antagonists, multi-acting receptor-targeted antipsychotics, aripiprazole, and trazodone. The subtypes of delirium were determined by the Delirium Motor Subtype Scale (Meagher et al., 2008).

Data analysis

We used a *t*-test (Student's or Welch's) or the Mann–Whitney *U* test to compare the means of continuous variables (such as age) between the remitters and non-remitters after examining variance homogeneity using the *F*-test and normality using the Kolmogorov–Smirnov test. In addition, we used Fisher's exact tests or the Chi-squared tests to compare the proportions of categorical variables (such as sex) between the groups.

A decision tree model was developed using the beforementioned outcome and variables. The Gini index was used as the splitting metric. First, we randomly split three-fourths and one-

https://doi.org/10.1017/S1478951521001565 Published online by Cambridge University Press

fourth of the data into the training and test datasets, respectively. Next, using the training dataset, we developed a decision tree model. We optimized the decision tree model's maximum depth by calculating the area under the curve (AUC) of the receiver operating characteristic curve using 5-fold cross-validation. Because a deeper decision tree is more difficult to interpret and tends to overfit (Molnar, 2019), we selected the minimum point among ranges in which the decision tree was constructed, and the AUC was saturated. We then calculated the model performance measured by AUC using the independent test dataset. A set of sensitivity and specificity that maximized the Youden index was also quantified. Finally, we visualized the decision tree model developed using the whole dataset.

All analyses were conducted using an open-source software R (version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria, 2021) with the package "rpart" (version 4.1-15) and "pROC" (version 1.17.0.1). A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 668 records were included, of which 141 (21.1%) had a DRS-R98 severity score of <10 on day 3. Several variables showed significant differences between the remitters and non-remitters (Table 1).

Decision tree model

In the 5-fold cross-validation, the AUC was saturated when the tree's maximum depth was ≥3. The model achieved an average AUC of 0.698 with the parameter set at 3. In the independent test dataset, the model achieved an AUC of 0.718 (95% confidence interval, 0.627–0.810), a sensitivity of 0.605, and a specificity of 0.822.

The model developed using the whole dataset is shown in Figure 1. The overall remission rate was 0.21. The model showed that the baseline DRS-R98 severity score was the most important predictor. Patients with a score of ≥15 and <15 had a remission rate of 0.13 and 0.44, respectively. Hypoxia and dehydration as precipitating factors were the second and third important predictors.

Discussion

In the present study, we developed a decision tree prediction model for the DRS-R98 severity score improvement on day 3 using the RWD of patients with advanced cancer receiving pharmacological interventions. The model achieved moderate prediction accuracy and showed that the baseline DRS-R98 severity score, hypoxia, and dehydration were the important predictive factors, in this order.

Patients with a higher baseline DRS-R98 severity score also had a higher score on day 3. The result is consistent with that of a systematic review of prolonged delirium (Dasgupta and Hillier, 2010). A score of 15 on the DRS-R98 severity scale might be used as the threshold for distinguishing severe and non-severe delirium among patients with advanced cancer who had a DRS-R98 severity score of ≥10. Because both the original and the Japanese versions of DRS-R98 did not investigate the cutoff score for delirium severity determination (Trzepacz et al., 2001; Kato et al., 2010), this result could be a new finding. However, the

Table 1. Descriptive data of the study participants

	Remitters (N = 141)	Non-remitters (N = 527)	p-value
Age (years), mean (SD)	73.20 (11.16)	71.71 (11.39)	0.08[a]
Male sex, n (%)	78 (55.3)	340 (64.5)	0.06[b]
Setting, n (%)			
Psycho-oncology	72 (51.1)	151 (28.7)	<0.01[b]
Palliative care	69 (48.9)	376 (71.3)	
Performance status, mean (SD)	2.96 (0.92)	3.45 (0.71)	<0.01[a]
Primary tumor site, n (%)			
Lung	24 (17.0)	135 (25.6)	0.22[b]
Esophagus/stomach	14 (9.9)	68 (12.9)	
Liver/biliary system/pancreas	33 (23.4)	84 (15.9)	
Colon/rectum	19 (13.5)	52 (9.9)	
Kidney/urinary system/prostate	15 (10.6)	48 (9.1)	
Breast	5 (3.5)	30 (5.7)	
Uterine/ovary	7 (5.0)	29 (5.5)	
Blood	5 (3.5)	19 (3.6)	
Others	19 (13.5)	62 (11.8)	
Brain tumor or metastasis, n (%)	19 (13.5)	92 (17.5)	0.32[b]
Cerebrovascular diseases, n (%)	9 (6.4)	43 (8.2)	0.60[b]
Dementia, n (%)	16 (11.3)	51 (9.7)	0.67[b]
Diabetes, n (%)	29 (20.6)	94 (17.8)	0.53[b]
Oral intake availability, n (%)			
Available	116 (82.3)	276 (52.4)	<0.01[b]
Unavailable	25 (17.7)	251 (47.6)	
Precipitating factors, n (%)			
Opioids	53 (37.6)	221 (41.9)	0.40[b]
Drugs other than opioids	33 (23.4)	103 (19.5)	0.37[b]
Dehydration	9 (6.4)	74 (14.0)	0.02[b]
Non-respiratory infection	39 (27.7)	80 (15.2)	<0.01[b]
Respiratory infection	14 (9.9)	62 (11.8)	0.65[b]
Organic damage to the central nervous system	12 (8.5)	80 (15.2)	0.06[b]
Hypoxia	11 (7.8)	122 (23.1)	<0.01[b]
Liver failure	17 (12.1)	89 (16.9)	0.21[b]
Renal failure	11 (7.8)	57 (10.8)	0.37[b]
Hypercalcemia	4 (2.8)	26 (4.9)	0.36[c]
Hyponatremia	6 (4.3)	43 (8.2)	0.16[b]
Disseminated intravascular coagulation	1 (0.7)	14 (2.7)	0.21[c]
Others	17 (12.1)	36 (6.8)	0.06[b]
Drug for delirium management, n (%)			
Aripiprazole	3 (2.1)	5 (0.9)	<0.01[c]
Typical antipsychotics	54 (38.3)	303 (57.5)	
SDA	31 (22.0)	79 (15.0)	

(*Continued*)

https://doi.org/10.1017/S1478951521001565 Published online by Cambridge University Press

Table 1. (*Continued.*)

	Remitters (*N* = 141)	Non-remitters (*N* = 527)	*p*-value
MARTA	39 (27.7)	131 (24.9)	
Trazodone	14 (9.9)	9 (1.7)	
Treatment line of drugs for delirium, *n* (%)			
First line	121 (85.8)	397 (75.3)	0.02[c]
Second line	16 (11.3)	109 (20.7)	
Third line	4 (2.8)	21 (4.0)	
Delirium subtype, *n* (%)			
Hyperactive	57 (40.4)	175 (33.2)	0.35[b]
Hypoactive	40 (28.4)	156 (29.6)	
Combined	16 (11.3)	83 (15.7)	
Undetermined	28 (19.9)	113 (21.4)	
DRS-R98 severity score			
Baseline, mean (SD)	15.11 (4.75)	20.59 (6.39)	<0.01[a]
Day 3, mean (SD)	5.35 (2.72)	20.97 (6.63)	<0.01[a]

[a]Mann–Whitney *U* test.
[b]Chi-squared test.
[c]Fisher's exact test.
SD, standard deviation; DRS-R98, Delirium Rating Scale Revised-98; SDA, serotonin-dopamine antagonists; MARTA, multi-acting receptor-targeted antipsychotics.

DRS-R98 severity scale has been suggested as unsuitable for evaluating end-stage patients' delirium because of unconsciousness or non-communicativeness (Uchida et al., 2020). This inappropriateness might also affect the association between the baseline severity score and that on day 3.

Hypoxia and dehydration as precipitating factors were the second and third important factors. Because delirium is defined as occurring due to physiological or pharmacological factors (American Psychiatric Association, 2013), the importance of precipitating factors could be biologically plausible. Although hypoxia has been consistently reported to be associated with a poor outcome, the result of dehydration differed among previous studies (Lawlor et al., 2000; Morita et al., 2001; Matsuda et al., 2020). Matsuda et al. (2020) noted that this difference might be explained by the different definitions of dehydration or differences in the baseline condition of study participants. Further studies are required to validate the influence of precipitating factors on the DRS-R98 score improvement.

Notably, drugs for delirium management did not appear in the decision tree model. The result might imply that drug selection is less critical for the course of delirium in real-world clinical settings.

This visually interpretable prediction model could help clinicians easily predict the DRS-R98 scores on day 3, which would help them share the information with medical staff or families and allocate nursing care efficiently. Additionally, the relative importance of predictor variables shown in the model is a new finding and may be useful for clinicians to manage delirium considering these clinical manifestations. Further studies are warranted to compare the prediction ability of this model with that of experienced clinicians to confirm the usefulness of the model.

This study had several limitations. First, because the database included only patients receiving antipsychotics or trazodone, the prediction model could not be applied to those without pharmacological approaches or those receiving other drugs. Second, there were no operational criteria to determine the precipitating factors of delirium (Matsuda et al., 2020). Third, the analysis did not include interventions for the precipitating factors. Fourth, because the outcome measurement was performed on day 3, the model cannot predict a longer-term outcome. This limitation of the

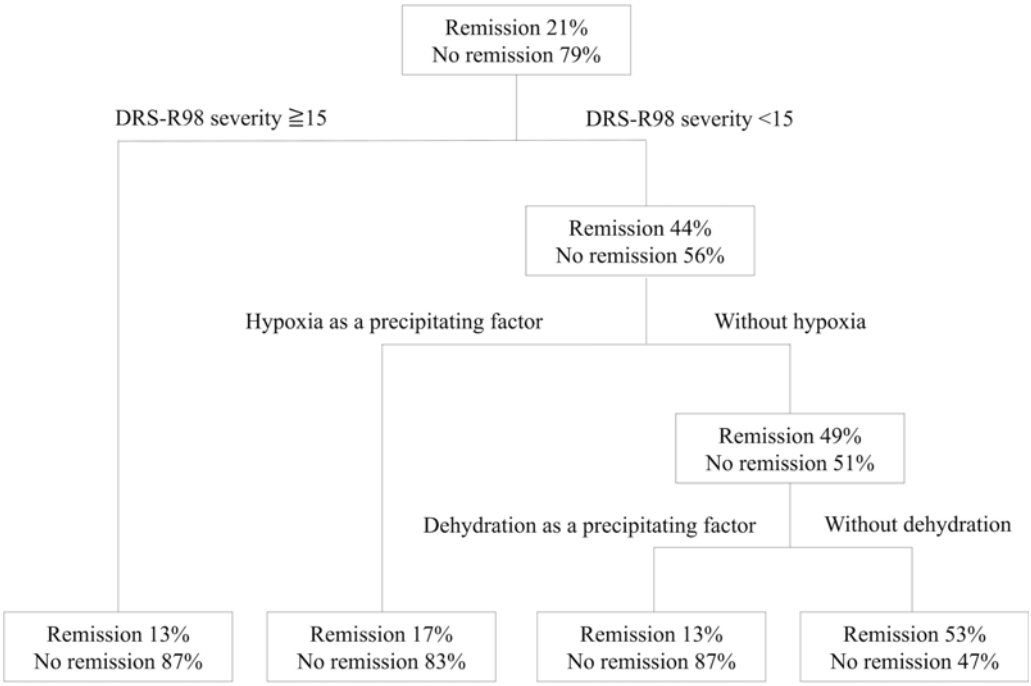

Fig. 1. The decision tree model for delirium of patients with advanced cancer who had a baseline Delirium Rating Scale Revised-98 (DRS-R98) severity score of ≥10. Remission is defined as a DRS-R98 severity score of <10 on day 3.

https://doi.org/10.1017/S1478951521001565 Published online by Cambridge University Press

model may be notable because the DRS-R98 severity score may fluctuate after day 3. Fifth, the AUC of the model was 0.698 for cross-validation and 0.718 for the test dataset, which was a boundary between moderate and low prediction accuracy (Swets, 1988). Finally, the model requires the baseline DRS-R98 severity score, limiting the situations of its utilization. The DRS-R98 is widely utilized for clinical trials (Meagher et al., 2013) and is considered useful for assessing the severity (Oh et al., 2017). However, other evaluation tools, such as the Confusion Assessment Method-Severity Scale, might be desirable for severity evaluation in future studies (Oh et al., 2017).

In conclusion, we developed an easy-to-use prediction model for the short-term outcome of delirium in patients with advanced cancer receiving pharmacological interventions. The model suggested that the baseline severity of delirium and precipitating factors of delirium were important for prediction.

Acknowledgments. We would like to thank the collaborators of the Phase-R study group. The collaborators include the following: Hirofumi Abo, M.D. (Rokkou Hospital); Nobuya Akizuki, M.D., Ph.D. (Chiba Cancer Center); Koji Amano, M.D. (Osaka City General Hospital); Daisuke Fujisawa, M.D., Ph.D. (Keio University Hospital); Shingo Hagiwara, M.D. (Tsukuba Medical Center Hospital); Takeshi Hirohashi, M.D. (Eiju General Hospital); Takayuki Hisanaga, M.D. (Tsukuba Medical Center Hospital); Satoshi Inoue, M.D. (Seirei Mikatahara General Hospital); Shinichiro Inoue, M.D. (Okayama University Hospital); Aio Iwata, M.D. (National Cancer Center Hospital East); Akifumi Kumano, M.D. (Rokkou Hospital); Yoshinobu Matsuda, M.D. (National Hospital Organization Kinki-Chuo Chest Medical Center); Takashi Matsui, M.D. (Tochigi Cancer Center); Yoshihisa Matsumoto, M.D., Ph.D. (National Cancer Center Hospital East); Naoki Matsuo, M.D. (Sotoasahikawa Hospital); Kaya Miyajima, M.D., Ph.D. (Keio University Hospital); Ichiro Mori, M.D., Ph.D. (Garcia Hospital); Sachiyo Morita, M.D., Ph.D. (Shiga University of Medical Science Hospital); Hiroyuki Nobata, M.D. (National Cancer Center Hospital East); Takuya Odagiri, M.D. (Komaki City Hospital); Toru Okuyama, M.D., Ph.D. (Nagoya City University Hospital); Akihiro Sakashita, M.D. (Kobe University Graduate School of Medicine); Ken Shimizu, M.D. (National Cancer Center Hospital); Yuki Sumazaki Watanabe, M.D. (National Cancer Center Hospital East); Keita Tagami, M.D. (Tohoku University School of Medicine); Emi Takeuchi, M.A. (Keio University Hospital); Mari Takeuchi, M.D., Ph.D. (Keio University Hospital); Ryohei Tatara, M.D. (Osaka City General Hospital); Akihiro Tokoro, M.D., Ph.D. (National Hospital Organization Kinki-Chuo Chest Medical Center); Megumi Uchida, M.D., Ph.D. (Nagoya City University Hospital); Keiichi Uemura, M.D. (Hokkaido Medical Center); Hiroaki Watanabe, M.D. (Komaki City Hospital); Ritsuko Yabuki, M.D. (Tsukuba Medical Center Hospital); Toshihiro Yamauchi, M.D. (Seirei Mikatahara General Hospital); and Naosuke Yokomichi, M.D. (Seirei Mikatahara General Hospital).

Funding. This work was supported by a Grant-in-Aid for Scientific Research from the Practical Research for Innovative Cancer Control from the Japan Agency for Medical Research and Development (AMED) [grant number 15ck0106059h0002].

Conflict of interest. The authors declare that they have no conflict of interest.

References

American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults (2015) American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *Journal of the American Geriatrics Society* **63**(1), 142–150.

American Psychiatric Association (2013) *Diagnostic Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association Publishing.

Blonde L, Khunti K, Harris SB, *et al.* (2018) Interpretation and impact of real-world clinical data for the practicing clinician. *Advances in Therapy* **35**(11), 1763–1774.

Breitbart W, Gibson C and Tremblay A (2002) The delirium experience: Delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics* **43**(3), 183–194.

Brims FJ, Meniawy TM, Duffus I, *et al.* (2016) A novel clinical prediction model for prognosis in malignant pleural mesothelioma using decision tree analysis. *Journal of Thoracic Oncology* **11**(4), 573–582.

Burry L, Mehta S, Perreault MM, *et al.* (2018) Antipsychotics for treatment of delirium in hospitalised non-ICU patients. *The Cochrane Database of Systematic Reviews* **6**(6), CD005594.

Bush SH, Lawlor PG, Ryan K, *et al.* (2018) Delirium in adult cancer patients: ESMO clinical practice guidelines. *Annals of Oncology* **29**(Suppl 4), iv143–iv165.

Centeno C, Sanz A and Bruera E (2004) Delirium in advanced cancer patients. *Palliative Medicine* **18**(3), 184–194.

Dasgupta M and Hillier LM (2010) Factors associated with prolonged delirium: A systematic review. *International Psychogeriatrics* **22**(3), 373–394.

Elsayem A, Bush SH, Munsell MF, *et al.* (2010) Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: A preliminary study. *Journal of Pain and Symptom Management* **40**(5), 774–782.

Esteban C, Arostegui I, Garcia-Gutierrez S, *et al.* (2015) A decision tree to assess short-term mortality after an emergency department visit for an exacerbation of COPD: A cohort study. *Respiratory Research* **16**, 151.

Goodman KE, Lessler J, Cosgrove SE, *et al.* (2016) A clinical decision tree to predict whether a bacteremic patient is infected with an extended-spectrum β-lactamase-producing organism. *Clinical Infectious Diseases* **63**(7), 896–903.

Inouye SK, Westendorp RG and Saczynski JS (2014) Delirium in elderly people. *Lancet* **383**(9920), 911–922.

Kato M, Kishi Y, Okuyama T, *et al.* (2010) Japanese version of the delirium rating scale, revised-98 (DRS-R98-J): Reliability and validity. *Psychosomatics* **51**(5), 425–431.

Kurisu K, Yoshiuchi K, Ogino K, *et al.* (2019) Machine learning analysis to identify the association between risk factors and onset of nosocomial diarrhea: A retrospective cohort study. *PeerJ* **7**, e7969.

Lawlor PG, Gagnon B, Mancini IL, *et al.* (2000) Occurrence, causes, and outcome of delirium in patients with advanced cancer: A prospective study. *Archives of Internal Medicine* **160**(6), 786–794.

Ligthelm RJ, Borzì V, Gumprecht J, *et al.* (2007) Importance of observational studies in clinical practice. *Clinical Therapeutics* **29**(6 Pt1), 1284–1292.

Maeda I, Ogawa A, Yoshiuchi K, *et al.* (2020) Safety and effectiveness of antipsychotic medication for delirium in patients with advanced cancer: A large-scale multicenter prospective observational study in real-world palliative care settings. *General Hospital Psychiatry* **67**, 35–41.

Maeda I, Inoue S, Uemura K, *et al.* (2021) Low-dose trazodone for delirium in patients with cancer who received specialist palliative care: A multicenter prospective study. *Journal of Palliative Medicine* **24**(6), 914–918.

Marcantonio ER (2017) Delirium in hospitalized older adults. *The New England Journal of Medicine* **377**(15), 1456–1466.

Matsuda Y, Maeda I, Morita T, *et al.* (2020) Reversibility of delirium in ill-hospitalized cancer patients: Does underlying etiology matter? *Cancer Medicine* **9**(1), 19–26.

Meagher D, Moran M, Raju B, *et al.* (2008) A new data-based motor subtype schema for delirium. *The Journal of Neuropsychiatry and Clinical Neurosciences* **20**(2), 185–193.

Meagher DJ, McLoughlin L, Leonard M, *et al.* (2013) What do we really know about the treatment of delirium with antipsychotics? Ten key issues for delirium pharmacotherapy. *The American Journal of Geriatric Psychiatry* **21**(12), 1223–1238.

Ministry of Health, Labor, and Welfare (2008) The guideline by the Ministry of Health, Labor, and Welfare (in Japanese). Available at: https://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/ekigaku/0504sisin.html (accessed July 29, 2021).

Molnar C (2019) Interpretable machine learning. A guide for making black box models explainable. Available at: https://christophm.github.io/interpretable-ml-book/ (accessed 29 July 2021).

https://doi.org/10.1017/S1478951521001565 Published online by Cambridge University Press

Morita T, Tei Y, Tsunoda J, *et al.* (2001) Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. *Journal of Pain and Symptom Management* **22**(6), 997–1006.

Morita T, Hirai K, Sakaguchi Y, *et al.* (2004) Family-perceived distress from delirium-related symptoms of terminally ill cancer patients. *Psychosomatics* **45**(2), 107–113.

National Institute for Health and Care Excellence (UK) (2019) Delirium: prevention, diagnosis and management. Available at: https://www.nice.org.uk/guidance/cg103. Updated March 14, 2019 (accessed July 29, 2021).

Neufeld KJ, Yue J, Robinson TN, *et al.* (2016) Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: A systematic review and meta-analysis. *Journal of the American Geriatrics Society* **64**(4), 705–714.

Oh ES, Fong TG, Hshieh TT, *et al.* (2017) Delirium in older persons: Advances in diagnosis and treatment. *JAMA* **318**(12), 1161–1174.

Oken MM, Creech RH, Tormey DC, *et al.* (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology* **5**(6), 649–655.

Okuyama T, Yoshiuchi K, Ogawa A, *et al.* (2019) Current pharmacotherapy does not improve severity of hypoactive delirium in patients with advanced cancer: Pharmacological Audit Study of Safety and Efficacy in Real World (Phase-R). *The Oncologist* **24**(7), e574–e582.

Roger E, Torlay L, Gardette J, *et al.* (2020) A machine learning approach to explore cognitive signatures in patients with temporo-mesial epilepsy. *Neuropsychologia* **142**, 107455.

Swets JA (1988) Measuring the accuracy of diagnostic systems. *Science* **240**(4857), 1285–1293.

Tahir TA, Eeles E, Karapareddy V, *et al.* (2010) A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. *Journal of Psychosomatic Research* **69**(5), 485–490.

Tamune H, Ukita J, Hamamoto Y, *et al.* (2020) Efficient prediction of vitamin B deficiencies via machine-learning using routine blood test results in patients with intense psychiatric episode. *Frontiers in Psychiatry* **10**, 1029.

Trzepacz PT, Mittal D, Torres R, *et al.* (2001) Validation of the delirium rating scale-revised-98: Comparison with the delirium rating scale and the cognitive test for delirium. *The Journal of Neuropsychiatry and Clinical Neurosciences* **13**(2), 229–242.

Uchida M, Morita T, Akechi T, *et al.* (2020) Are common delirium assessment tools appropriate for evaluating delirium at the end of life in cancer patients? *Psycho-Oncology* **29**(11), 1842–1849.

U.S. Food and Drug Administration (2018) Framework for FDA's real-world evidence program. Available at: https://www.fda.gov/media/120060/download (accessed July 29, 2021).

Wada K, Morita Y, Iwamoto T, *et al.* (2018) First- and second-line pharmacological treatment for delirium in general hospital setting-retrospective analysis. *Asian Journal of Psychiatry* **32**, 50–53.

Witlox J, Eurelings LS, de Jonghe JF, *et al.* (2010) Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. *JAMA* **304**(4), 443–451.

https://doi.org/10.1017/S1478951521001565 Published online by Cambridge University Press