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St. Luke's International University Graduate School of Public Health

Capstone Project

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Impact of Falls in Palliative Care Units in Japan: A Multicenter Prospective Cohort Study

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Abstract

17 **Background**: Falls in patients with advanced cancer present serious problems, but there is no

18 established way to predict them.

19 **Objectives**: This study was a multicenter prospective cohort study performed in palliative care units

20 to develop a falls prediction model.

21 **Method**: Patients who experienced a fall within one month of death will be included in the study,

22 and variables associated with the fall will be analyzed among the background variables. Based on the

23 result of univariate analysis, we performed a multivariate analysis using logistic regression analysis

24 and the classification tree. Finally, through these analyses, we propose a prediction model for falls.

25 **Result**: Among 1896 patients, 1633 patients were eligible for this analysis and 150 of the eligible

26 patients had experienced a fall. Twenty-two variables were found to be associated with falls ($p <$

27 0.05) in the univariate analysis. Using the variables having the p-value that is less than 0.20 as

28 explanatory variables, we performed a multivariate logistic regression analysis. The receiver

29 operating characteristic curve analysis indicated that the value of the area under the curve was 0.80

30 (95%CI: 0.754 - 0.846). In addition, the sensitivity was 71.6% and the specificity was 74.3%. From

31 these results, we found that the performance of the developed prediction model was relatively high.

32 In addition, to confirm the order of the magnitude of importance of explanatory variables on the

33 multivariate logistic regression model, the classification tree analysis was performed using variables

34 that were associated with falls. The most influential variable in predicting falls was the Palliative

35 Performance Scale.

36   **Conclusion**: Factors associated with falls in patients with advanced cancer admitted to a palliative

37   care unit have been identified through this study.

38   *Keywords*: cancer, CART, fall, palliative care units, prediction

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Introduction

It is important to prevent falls in hospitalized patients because a fall is the leading cause of injury for elderly patients and cause serious complications (Bergen et al., 2016). 3.2% of falls occurred and 1.2% of falls caused injury in acute care hospitals. The total number of the injury were as follows: open wounds (rubbing, laceration, skin laceration) 54.9%; closed wounds (damage, hematoma) 34.7%; sprains 2.1%; dislocations 0.7%; vertebral fracture 0.7%; fractures other than vertebral fracture 5.6%; and subdural hematoma 4.0% (Barker et al., 2016). On the other hand, the frequency of falls in patients admitted to the palliative care setting with advanced cancer is high (18 - 50%), and factors such as delirium, age, length of stay, brain tumor, depression, and psychotropic medications have been cited as contributing factors (Stone et al., 2012). Previous studies have evaluated the background factors of falls (Zhang et al., 2018; Goodridge & Marr, 2002), but there are no reports of a multicenter evaluation in a large number of patients with advanced cancer.

The purpose of this study was to identify factors associated with falls as the primary endpoint in palliative care wards in Japan and to propose a method of fall prediction that could be used in clinical practice.

Methods

This was a multicenter post hoc exploratory analysis of, prospective cohort studies of advanced cancer patients who were receiving palliative care in palliative care units in Japan. We compared background variables with the presence of falls within one month of death as the primary endpoint. The study was conducted in accordance with the ethical guidelines for research on human subjects based on the Declaration of Helsinki.

Participants

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63   This study was a part of a multicenter prospective observational study, named East-Asian

64 Collaborative Study to Elucidate the Dying Process (EASED) . This study examined the process of

65 death and end-of-life care in terminally ill cancer patients who admitted to palliative care units in

66 Japan. In this study, we consecutively enrolled patients who were newly admitted to the palliative

67 care units during the research period. All interventions, including all tests and treatment, were

68 performed as usual clinical practice. The inclusion criteria of this study were (a) 18 years old or older,

69 (b) locally advanced or metastatic cancer (including hematological neoplasms), and (c) patients

70 admitted to palliative care units. We excluded patients who were scheduled to be discharged from

71 hospital within a week or who did not wish to participate.

72 **Data Collection**

73   We collected data from the EASED. The data we analyzed were: patient characteristics,

74 symptoms, general condition, and blood test data . We focused on the following factors as possible

75 background factors for falls.

76 *Data on Admission*

77   For the patient background we used: age, gender, metastatic site, systemic complications

78 (Charlson Comorbidity Index (CCI)), and treatment history for cancer. Neurological data included

79 consciousness, delirium, and cognitive function. The presence, cause, and severity of delirium and

80 the history of delirium were recorded. The diagnosis of delirium was based on the American

81 Psychiatric Association DSM-V, the severity of delirium was based on item nine of the Memorial

82 Delirium Assessment Scale (MDAS), and perceptual disturbances and hallucinations were based on

83 the item "perceptual disturbances and hallucinations" of the Delirium Rating Scale R-98.

84 *General Condition and Physician's Prediction of Prognosis*

85   The ECOG PS, the Karnofsky Performance Scale (KPS), the Global Health, and the

86 Palliative Performance Scale (PPS) were used to assess general health. Clinician Prediction of

87 Survival (CPS) based on the physician's experience was recorded.

88 *Medical Treatment*

89   We documented opioid use, opioid dose (converted to oral morphine), antipsychotic use,

90 type of antipsychotic used (haloperidol, risperidone, quetiapine, olanzapine, chlorpromazine, other),

91 and antipsychotic dose (haloperidol 5 mg/day, risperidone 2.5 mg/day, quetiapine 166 mg/day,

92 olanzapine 6.3 mg/day, and chlorpromazine 250 mg/day or higher were considered high doses.). The

93 presence or absence of psychotropic medication use, the type of psychotropic medication used

94 (benzodiazepines, non-benzodiazepines sleeping pills, antidepressants, anticonvulsants,

95 anti-dementia drugs, drugs with Anticholinergic Risk Scale ≥ 2), and the presence or absence of

96 indwelling urinary catheters were all recorded.

97 *Data at Time of Death*

98   Discharge status included discharge from hospital with death and discharge from hospital

99 with survival. Quality of life at the end of life was noted using the Good Death Scale (GDS), which

100 is a   five-item scale developed in Taiwan to assess quality of life at the end of life. The items are as

101 follows based on the original material of GDS (Chang, et al., 2016):

102 1. Has the patient known the fact that he/she is dying?

103   0 = *Complete ignorance*, 1 = *Ignorance*, 2 = *Partial awareness*, 3 = *Complete awareness*

104 2. Could the patient accept his/her illness well?

105   *0 = Complete unacceptance*, 1 = *Unacceptance*, 2 = *Acceptance*, 3 = *Complete acceptance*

106   3. Has the patient arranged everything according to his/her own will?

107   *0 = No reference to the patient's will*, 1 = *Following the family's will alone*, 2 = *Following the*

108   *patient's will alone, 3 = Following both the patient and the family's will*

109   4. Was the timing appropriate for the patient to pass away?

110   *0 = No preparation*, 1 = *The family alone had prepared*, 2 = *The patient alone had prepared*, ,

111   *3 = Both the patient and family had well prepared*

112   5. How about the physical condition of the patient at that time?

113   *0 = A lot of suffering*, 1 = *Suffering*, 2 = *A little suffering*, 3 = *No suffering*

114   Death consideration during hospitalization included expressions of wanting to die quickly

115   and wanting death to be actively hastened and the reasons for these expressions were recorded. The

116   reasons for the desire to die quickly were categorized as follows: 0 = No expression, 1 = Pain, 2 =

117   Dyspnea, 3 = Fatigue, 4 = Other physical symptoms, 5 = Burden on others, 6 = Loss of control over

118   the future, 7 = Inability to take care of oneself, 8 = Nothing to look forward to or play a role in, 9 =

119   Lack of hope, 10 = Fear of death or dying process, 11 = Loneliness, and 12 = Lack of

120   self-worth/meaninglessness of one's existence.

121   Delirium details were recorded as presence or absence of delirium during the hospitalization,

122   the severity of hyperactive delirium (using MDAS), and the final treatment for delirium. The

123   treatment for delirium was categorized as follows: 0: none, 1 = antipsychotics, 2 = antipsychotics

124   plus intermittent sedation (or benzodiazepins for sleep), 3 = shallow continuous sedation with

125   sedatives (*), and 4 = deep continuous sedation with sedatives (*sedatives: midazolam, barbiturates,

126   propofol). Falls during hospitalization within one month before death, complications of falls,

127   purpose of the patient's behavior before the fall, and death within 48 hours of the fall were recorded.

128   The physician recorded all data on a structured data-collecting sheet. Patients were observed

129   from the time of admission until the time of discharge. The observer checked for symptoms while

130   providing usual medical care. Patients whom had difficulty communicating verbally had their

131   symptoms identified based on their proxy's opinion.

132   **Data Analysis and Statistics**

133   For the first step, we calculated descriptive statistics; we calculated the summary statistics

134   for each variable. Next, to investigate the relationship between each continuous variable and the

135   main outcome (fall), we performed the univariate analysis based on the Mann–Whitney U test. Also,

136   based on the Fisher's exact test, we carried out the univariate analysis for the relationship between

137   each categorical variable and fall. Finally, we performed the multivariate analysis for the

138   investigation of the relation between the significant variables on univariate analyses and the outcome

139   (fall) through multivariate logistic regression analysis and classification and regression trees.

140   Significance was accepted at $p < .05$ and statistical analysis was performed with R version 3. 6. 3.

141   **Statement about Institutional Review Board Approval**

142   This capstone project and the EASED study was approved by the Seirei Mikatahara

143   Hospital Institutional Review Board in July 2016.

144   **Results**

145   **Baseline Patients' Characteristics**

146　　　　　　A total of 1,896 patients participated from 22 PCUs in Japan from January 2017 to June

147　　2018. Of the patients enrolled, 263 were excluded because they were discharged alive. Thus, the

148　　total number of patients were evaluated in this study was 1,633. Of the patients included, 150

149　　patients (9.2%) fell within one month of death. Characteristics are summarized in Table 1. Median

150　　age was 74.0 years old. The major comorbidities were cerebrovascular disease were 7.0% (n = 115),

151　　dementia 8.1% (n = 132), and hemiplegia 1.5% (n = 24). The proportions of ECOG PS 0/1 were

152　　0.6% (n = 10), ECOG PS 2 - 6.2% (n = 102), ECOG PS 3 - 40.5% (n = 661) and ECOG PS 4 -

153　　52.7% (n = 860). The median prognosis predicted by the physician at the time of admission was 21

154　　days.

155　　**Univariate and Multivariate Analyses of Factors Associated With Falls**

156　　　　　　In the univariate analysis, to investigate the relationship between the primary outcome that

157　　is "fall or no fall" and the other categorical variable, we performed the Fisher's exact test. In addition,

158　　to assessing the relation between "fall or no fall" and the continuous variable, we carried out the

159　　Mann–Whitney U test. As a result, the following variables were statistically significant in the

160　　univariate analysis: age (continuous variable), gender (categorical variable), cerebrovascular disease

161　　(categorical variable), ECOG PS (categorical variable), KPS (continuous variable), GH (continuous

162　　variable), PPS (continuous variable), palliative care phase (categorical variable), urine catheter

163　　(categorical variable), psychotropic drug (categorical variable), nonbenzodiazepine hypnotics

164　　(categorical variable), antidepressants (categorical variable), Good Death Scale: "Has the patient

165　　known the fact that he/she dying?" (categorical variable), output of suicidal ideation (categorical

166　　variable), statement of reasons for suicidal ideation (categorical variable), suicidal ideation for pain

167　　(categorical variable), suicidal ideation for loss of control for the future (categorical variable),

168　　presence of delirium (categorical variable), severe delirium (categorical variable), therapy for

169   delirium (categorical variable), length of hospital stay (continuous variable), prognosis (continuous

170   variable). These are shown in Table 2.

171   In general, if the number of explanatory variables on the multivariate logistic regression

172   analysis is large, we often face the problem of multicollinearity. In this situation, it can be considered

173   that there is a possibility that the estimated odds ratios were not stable in the logistic regression

174   analysis. In addition, among the important explanatory variables from the point of view of prediction,

175   it was also possible that multiple occurrences of a variable had similar information. For this situation,

176   when we applied the variable selection method to the obtained multivariate logistic regression model,

177   the explanatory variables that were not appropriate from a clinical point of view were selected. From

178   these backgrounds, we next confirmed whether or not there was multicollinearity on the estimated

179   multivariate logistic regression model. With that in mind, we assessed the multicollinearity based on

180   the values of the variance inflation factor and generalized variance inflation factor, As a result, we

181   excluded the three explanatory variables: (a) KPS, (b) statement of reasons for suicidal ideation, and

182   (c) presence of delirium, from the multivariate logistic regression model. We found that the number

183   of candidate explanatory variables was 22 after the univariate analysis, but, by checking the

184   multicollinearity, we finally used the variables that are age, gender, cerebrovascular disease, ECOG

185   PS, GH, PPS, palliative care phase, urine catheter, psychotropic drug, nonbenzodiazepine hypnotics,

186   antidepressants, Good Death Scale ("Has the patient known the fact that he/she dying?"), output of

187   suicidal ideation, suicidal ideation for pain, suicidal ideation for loss of control for the future, severe

188   delirium, therapy for delirium, length of hospital stay, and prognosis as the explanatory variables on

189   the multivariate logistic regression model. With this prediction model, we performed the ROC curve

190   analysis. In this case, the value of AUC was 0.80 (95%CI: 0.754 - 0.846). In addition, the values of

191   sensitivity and specificity were 71.6% and 74.3%, respectively.

Classification Tree Analysis

192

193   Breiman et al. (1984) proposed the classification and Regression Tress (CART) and its

194   method has been used in various fields. In the CART model, there are two advantages relative to the

195   multivariate logistic regression model. The first advantage is that it is possible to visually confirm

196   the relations among explanatory variables and to understand the order of the magnitude of the

197   importance of explanatory variables for the target outcome. The second advantage is that it is

198   possible to obtain the cut-off point in terms of the important explanatory variable to predict the

199   outcome. Therefore, based on the value of the cut-off point, we can develop a guideline to provide

200   appropriate treatment or to give appropriate diagnostic results. In this study, to verify the prediction

201   model obtained from the multivariate logistic regression, we also developed the CART model. The

202   name of "CART" implies the two methods that are the approaches of the classification and

203   regression. In this study, the outcome is "fall or no fall" that is categorical variable. Therefore, by

204   using the classification tree, we were able to verify the developed multivariate logistic regression

205   model. We applied the CART method to the target data in this study with the 19 variables that were

206   statistically significant (p <0.05) in the univariate analysis: age, gender, cerebrovascular disease,

207   ECOG PS, GH, PPS, palliative care phase, urine catheter, psychotropic drug, nonbenzodiazepine

208   hypnotics, antidepressants, Good Death Scale ("Has the patient known the fact that he/she dying?"),

209   output of suicidal ideation, suicidal ideation for pain, suicidal ideation for loss of control for the

210   future, severe delirium, therapy for delirium, length of hospital stay, and prognosis,. In general, we

211   drew a tree figure called a decision tree using the CART method. The node of the top level of

212   decision tree represents the most important variable in terms of classification for the outcome.

213   Likewise, the nodes at the second level of decision tree indicate the second most important variables

214   to classify the outcome. Figure 4 depicts the decision tree and shows that the most important variable

215   in predicting falls was PPS. The second important variables to predict falls were ECOG PS and GH.

216   The third important variable was from the Good Death Scale: "Has the patient known the fact that

217   he/she dying?" and finally the presence of severe delirium.

218   An example of how this might be used in a clinical setting: if a patient spends some time

219   sitting through the day, he or she may have a score of 50 or higher on the PPS (The cut-off point of

220   45 represents the midpoint value between 40 and 50.). If this is the case, falls should be a concern. In

221   addition, if the patient has a PPS score of less than 40, but has comorbid severe delirium, there is still

222   a possibility of a fall. The patient's awareness of his or her own mortality may also be a predictor of

223   falls. In this study, we were able to suggest some clinically noteworthy variables for predicting falls,

224   as described above.

225   **Discussion**

226   What is clinically important about this study is that it shows the prediction of falls with

227   existing assessment measures. In general, whether a patient with advanced disease will fall or not is

228   usually based on the experience of medical personnel. This has led to different judgments depending

229   on the experience of the healthcare provider. This is why it has been so difficult to educate people to

230   anticipate falls. In this study, we showed which items medical professionals should focus on in their

231   clinical evaluation of fall risk. It is hoped that this perspective can be applied to measures and

232   education to prevent falls. "Which patient falls should we pay attention to?" is a question of great

233   clinical importance. It is difficult to pay attention to all patients. It would be unacceptable from the

234   standpoint of cost-effectiveness of medical resources to invest a lot of human resources to prevent all

235   patients from falling. The medical field is faced with the dilemma of patient safety and distribution

236   of medical resources. In addition, there is a concern that prioritizing patient safety over human

237   dignity in the final stages of life may degrade QOL. For example, a patient who wishes to be

238   independent in defecation may be forced to defecate in an unwanted way in order to prioritize safety.

239   The findings from this study may provide a solution to this important dilemma for both

240   patients and providers. It may be possible to prevent falls, with fewer burdens on providers, by

241   identifying patients at higher risk for targeted attention.

242   In addition, the CART analysis revealed a quantitative assessment of items that are effective

243   in predicting falls. Of course, patients who are bedridden with reduced physical function do not fall.

244   In order to predict falls, it is necessary to identify the decline in physical function that is likely to

245   lead to falls. Also, other studies provide suggestions for this clinical concern. As an example, a score

246   of 40 and 50 on the PPS may be a valid cutoff for predicting falls. Therefore, health care providers

247   could consider a specific assessment of whether the patient spends time in a sitting position. By

248   comparing the results of multivariate logistic regression with those of classification tree, both

249   methods revealed that PPS, GH, ECOG PS, and severe delirium were important variables. Moreover,

250   we found that the multivariate logistic regression analysis result was almost similar to the analysis

251   result of the classification tree.

252   The analysis of the Good Death Scale as an explanatory variable is an interesting aspect of

253   this study. The possibility of the influence of the presence of spiritual pain on the prediction of falls

254   is a new finding in the study of falls. It is known that spiritual pain is more likely to manifest in the

255   final stages of life. Especially in situations where bodily functions are declining, the suffering of

256   being unable to take care of oneself tends to be stronger. Patients with high levels of such suffering

257   may have a tendency to behave in ways that are not commensurate with their physical functions. For

258   example, it has been clinically experienced that a patient may attempt to walk to the bathroom alone,

259   even though it is objectively difficult to walk. From this perspective, support for physical functions

260   and consideration of the environment alone may not be sufficient to prevent falls in cancer patients at

261   the end of life. The essential approach of palliative care to alleviate the patient's spiritual anguish

262   may occupy a very important role in preventing falls. The discussion on spirituality is very important

263   in palliative care. Further research is needed on the relationship between spiritual pain and falls. An

264   example would be an intervention study that compared the frequency of falls in groups with and

265   without spiritual care intervention.

266   **Evaluation of Analytical Results Stability**

267   Kashiwagi, Hayashi, Mori, & Otani (2020) proposed an evaluation method for the analysis

268   of results of the CART model. Here, we induced a perturbation at the point of a variable on the

269   classification tree model and quantitatively evaluated the stability of the developed classification tree

270   model. If we use our proposed evaluation approach, we can assess the stability of the magnitude

271   order of importance of the explanatory variables on the target CART model. Also, we can evaluate

272   the ease of coupling between important explanatory variables to predict an outcome. For example,

273   we can use our evaluation approach for classifying the risks to a target outcome. In Kashiwagi, et al.,

274   (2020), used a set of explanatory variables different from the subset of 19 explanatory variables in

275   this study and we performed the CART analysis on the same dataset. After that, we applied our

276   proposed assessment method in terms of stability to the obtained the CART model. As a result, we

277   carried out the classification of risks in the context of predicting "fall or no fall". In addition, we

278   confirmed that the findings acquired by applying our assessment approach were very interesting

279   from the clinical viewpoint. In the future, we are willing to apply its assessment method to the

280   developed CART model based on the subset of explanatory variables used in this study and to get

281   more findings that are important from the point of view of clinical application.

282

283   **Ⅴ. Limitation**

284   This study was conducted as an ancillary study to the EASED study with the primary

285   outcome of prognosis of cancer patients admitted to a palliative care unit. Therefore, the analysis

286   may not have included all factors associated with falls. The same palliative physician completed all

287   observations on the participants. Therefore, while consistency in ratings might be an advantage,

288   observer bias also needs to be considered.   Inter-rater reliability should be developed.

289   **VI. Conclusion**

290   We analyzed the background factors associated with the frequency and prediction of falls in

291   cancer patients admitted to a palliative care ward. The accuracy of predicting falls in the palliative

292   care ward can be improved by focusing on the decline in physical function to the extent that the

293   frequency of falls increases.

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