

**TABLE 8.** Result of Procedure 2 ( $Y$ =After, Selected Variables When the Number of Variables was Increased to 6 on the Basis of Spearman Rank Correlation Coefficient (Accuracy: 39/71, Spearman Rank Correlation Coefficient: 0.545))

Item	Estimated Value	Standard Error	$\chi^2$ Value	$P$	Odds Ratio	Confidence Interval of Odds Ratio	
						Lower 95%	Upper 95%
ALP	0.0001	0.0002	0.347	0.555	1.000	0.999	1.000
Sex	0.7734	0.2848	7.372	0.006*	2.167	1.267	3.874
Outcome	-0.2769	0.2812	0.969	0.324	0.758	0.429	1.312
Constipation	0.2347	0.2593	0.819	0.365	1.264	0.760	2.110
Appetite loss	-0.0482	0.5401	0.007	0.928	0.952	0.308	2.833
Bone metastasis	0.7390	0.2670	7.660	0.005*	2.093	1.254	3.604
Nausea	0.4772	0.2640	3.266	0.070	1.611	0.971	2.733

\* $P < 0.05$ .

ALP indicates alkaline phosphatase.

still insufficient. Research on optimal palliative therapy for bone pain in which approaches including chemotherapy and radiotherapy are combined is anticipated.<sup>20-22</sup>

There have been a number of reports on sex differences in pain sensitivity.<sup>23-30</sup> Among their reports that there is a sex difference in the sensitivity of  $\kappa$ -opioid receptors, and that, because of their higher sensitivity,  $\kappa$ -opioids produce stronger analgesic effects in females.<sup>27-30</sup> On the other hand, many reports concluded that there is no sex difference, or females more frequently report pain, in many chronic pain types, including cancer pain.<sup>31-50</sup> In the study of the differences between women and men in their experience of cold-pressor pain, Keogh et al reported that women who concentrated on the emotional aspects of their pain may actually experience more pain as a result, possibly because the emotions associated with pain were negative.<sup>41-43</sup> Hau et al found that "testosterone reduced responsiveness to nociceptive stimuli in a wild bird."<sup>44</sup> It was demonstrated that analgesic drugs such as morphine activated GIRK2. Thus, the male has higher threshold of tolerable pain because GIRK2 in male was present more than in female.<sup>45,46</sup> Moreover, there are many studies that proved the involvements of individual variations were larger than the sex differences in threshold of tolerable pain.<sup>47-49</sup> We know that women's pain threshold varies across the menstrual cycle.<sup>50</sup> Pain caused by cancer is multifaceted<sup>12</sup> and more, for example, is very different to that caused by physical injuries. However, as our study showed that cancer pain is exacerbated when the patient is

male significantly for the first time, it may become a preface of the new discussions on sex differences in pain sensitivity in terminal cancer patients.

Unexpectedly, only nausea remained among many symptoms observed in terminal cancer patients. Patients having poorly controlled pain may more often report unpleasant symptoms such as "pain" and "sickness." Reports pain may also be related to the degree of patient satisfaction, that is, they may more often report pain when they are dissatisfied. Among previous studies, Meuser et al<sup>51</sup> discussed the importance of symptomatic relief in the treatment of cancer pain. This study indicated that the alleviation of nausea leads to better pain control. Multivariate analysis using nausea as the dependent variable and adding medication history including antiemetics and anti-cancer agents and opioids as independent variables is considered to be meaningful for further clarification of causative factors of nausea.

When independent variables were reduced one by one from the initial number of 23 in LOOCV, the calculation program stopped when all variables had been entered. As this program was designed to predict the optimal variable by changing the coefficient little by little, the number of variables that can be handled by the program may be surpassed if there are too many variables for the number of data, leading to a suspension of the calculation.

In the selection of independent variables by LOOCV for multivariate analysis using "after" as the dependent variable, sex, bone metastasis, nausea, alkaline phosphatase,

**TABLE 9.** Results of Procedure 3 ( $Y$ =Improvement Factor)

Item	Estimated Value	Standard Error	$\chi^2$ Value	$P$	Odds Ratio	Confidence Interval of Odds Ratio	
						Lower 95%	Upper 95%
Sex	-0.603	0.260	5.369	0.0204*	0.547	0.321	0.898
Nausea	-0.209	0.240	0.757	0.3840	0.811	0.500	1.300
Log (daily dosage of morphine)	-0.161	0.161	1.004	0.3162	0.850	0.614	1.160
Steroids	-0.206	0.237	0.757	0.3842	0.813	0.509	1.291

\* $P < 0.05$ .

(Accuracy: 40/71, Spearman rank correlation coefficient: 0.328).

tase, outcome, constipation, and appetite were included in the combinations that showed satisfactory results when the number of independent variables in the model was increased to 6. When ordered logistic regression analysis was performed using these 7 variables, nausea was not a significant variable. The inclusion of the 7 variables may have reduced the significance of nausea.

In multivariate analysis using the improvement factor as the dependent variable, Spearman rank correlation coefficient was low at 0.328. As the improvement factor was a variable prepared on the basis of a binary expression of subjective pain as "after" or "before," its use in objective evaluation may have been difficult. Selection of the dependent variable is difficult for the objective evaluation of subjective pain. To further improve correlation coefficients, other nonlinear regression analysis methods such as generalized additive models and logistic partial least squares analysis need to be evaluated.

As a result of this study, sex, bone metastasis, and nausea were factors that prevent pain relief. The effects of analgesics, which are reported to be affected by genetic factors, remain largely unclear, and our results do not explain everything. However, statistical identification of sex, bone metastasis, and nausea as factors that prevent pain control is considered to contribute to the establishment of EBM in pain relief and palliative care.

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