Computers in Biology and Medicine 42 (2012) 1005–1011

Contents lists available at SciVerse ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Pattern discovery from patient controlled analgesia demand behavior

Yuh-Jyh Hu [a,b,*], Tien-Hsiung Ku [c]

[a] Department of Computer Science, National Chiao Tung University, 1001 Tashuei Rd., Hsinchu, Taiwan
[b] Institute of Biomedical Engineering, National Chiao Tung University, 1001 Tashuei Rd., Hsinchu, Taiwan
[c] Department of Anesthesia, Changhwa Christian Hospital, Changhwa, Taiwan

ARTICLE INFO

Article history:
Received 9 January 2012
Accepted 7 August 2012

Keywords:
Patient controlled analgesia
Pain management
PCA demand
Behavioral pattern
Clustering

ABSTRACT

Unlike previous research on patient controlled analgesia, this study explores patient demand behavior over time. We apply clustering methods to disclose demand patterns among patients over the first 24 h of analgesic medication after surgery. We consider demographic, biomedical, and surgery-related data in statistical analyses to determine predictors for patient demand behavior, and use stepwise regression and Bayes risk analysis to evaluate the influence of demand pattern on analgesic requirements. We identify three demand patterns from 1655 patient controlled analgesia request log files. Statistical tests show correlations of gender ($p=.0022$), diastolic blood pressure ($p=.025$), surgery type ($p=.0028$), and surgical duration ($p<.0095$) with demand patterns. Stepwise regression and Bayes risk analysis show demand pattern plays the most important role in analgesic consumption prediction ($p=0.\mathrm{E}+0$). This study suggests analgesia request patterns over time exist among patients, and clustering can disclose demand behavioral patterns.

1. Introduction

Pain is one of the most commonly reported postoperative symptoms [1]. It is a highly personal experience influenced by multiple factors, including sensitivity to pain, age, genetics, physical status, and psychological factors [2–4]. With the progress of medical science, people gradually became aware of the importance of pain management.

PCA (patient controlled analgesia) is a delivery system for pain medication that makes effective and flexible pain treatments possible by allowing patients to adjust the dosage of analgesics themselves within a preset range of therapy based on therapeutic and toxic effect. According to research [5,6], PCA is one of the most effective techniques for postoperative analgesia and is widely used in hospitals for the management of postoperative pain, especially for major surgeries. Most research on postoperative pain management is limited to evaluating the correlation of patient characteristics, such as demographic attributes, biomedical variables, and psychological states, with postoperative pain intensity or analgesic requirement. Several studies have identified the preoperative predictive factors for postoperative pain and analgesic consumption in various patient groups of different genders, ages, or psychological states [7–11]. However, none of these studies analyzed continual patient demand behavior throughout the PCA therapy. Time-series data analysis is a common practice in various research fields. For example, in the study of sleep in patients with insomnia, time-series data derived from sleep diaries were used to compute conditional probabilities of having insomnia [12]; in biology, a temporal map of fluctuations in mRNA expression of 112 genes during central nervous system development in rats provides a temporal gene expression fingerprint of spinal cord development [13]. Few studies of PCA examined patient demand behavior and its relationship to analgesic drug use [14,15]. We hypothesize that patient demand behavior over time provides different and useful information in PCA administration that is missing in the preoperative factors analyzed earlier.

Our study, unlike previous research, focuses on continual analgesia demand behavior during the postoperative PCA medication. The current study explores and characterizes patient demand behavior. Patient demand behavior is represented by a series of PCA requests over time. We discover distinct and conserved demand patterns from the time-series data and identify the significant patient factors that influence demand behavior. In addition, we compare the predictors for PCA demand behavior and analgesic requirements and evaluate the contribution of demand pattern to analgesic consumption prediction.

2. Materials and methods

2.1. Subjects and statistical tools

The study was conducted from 2005 to 2010 with the approval of Changhwa Christian Hospital (CCH) Institutional Review Board

* Corresponding author at: National Chiao Tung University, Department of Computer Science, 1001 University Rd., Hsinchu 300, Taiwan.
Tel.: +886 35731795.
E-mail address: yhu@cs.nctu.edu.tw (Y.-J. Hu).

0010-4825/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.compbiomed.2012.08.002

Table 1
Summary of patient attributes.

Attribute name	Description	Number	Mean ± sd
Demographic:			
Gender	Patient's gender	986(F)/669(M)	–
Age	Patient's age	–	56.9 ± 15.8
Weight(kg)	Patient's weight	–	63.0 ± 12.6
Biomedical:			
sbp (mmHG)	Systolic blood pressure	–	135.8 ± 22.6
dbp (mmHG)	Diastolic blood pressure	–	69.4 ± 13.8
Pulse(beats/min)	Heart rate	–	81.0 ± 15.4
ASA class*	1: Healthy 2: Mild systemic disease 3: Major systemic disease	184(1)/837(2)/634(3)	–
OP – related:			
op_type**	Surgery type: 1∼8	107(1)/126(2)/411(3) 127(4)/427(5)/109(6)212(7)/136(8)	–
ans_type	SA: spinal anesthesia GA: general anesthesia	1470(GA)/185(SA)	–
op_time(hr)	Surgical duration	–	4.2 ± 2.6
Urgency	E: emergency surgery R: regular surgery	136(E)/1519(R)	–

* ASA class is the commonly used preoperative index of physical status defined by American Society of Anesthesiologists.
** 1: intrathoracic, 2: upper intra-abdominal, 3: lower intra-abdominal, 4: laminectomy, 5: major joints, 6: limbs, 7: head & neck, 8: others.

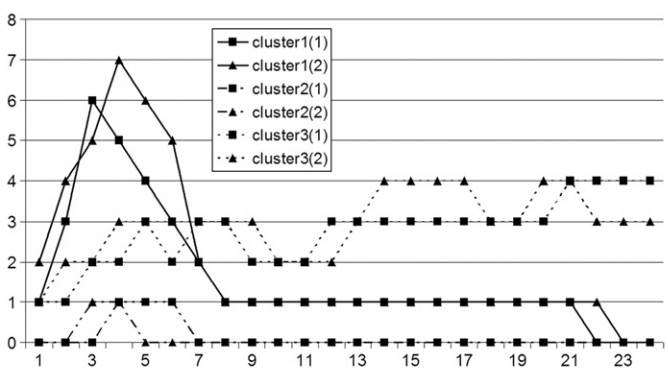

Fig. 1. An illustrative example of PCA demand patterns. Each curve represents the distribution of PCA demand frequency for a patient in 24 h. The X-axis indicates the 24 h time line (1 h to 24 h). The Y-axis represents the number of demand requests in a particular hour.

in Changhwa, Taiwan. Abbott Pain Management Provider (Abbott Lab Chicago, IL, USA) was used for patient controlled analgesia. Instructions were reviewed with patients before initiating PCA therapy. Each patient record contained attributes such as basic health status, age, gender, weight, department code, doctor ID, PCA control parameters, and amount of anesthetic used during different time intervals. Because not all the attributes are relevant to our study or have correct values, after consulting the anesthetists, we discarded irrelevant attributes such as doctor ID and department code before further investigation. We divide the attributes used in analysis into three categories: (a) patient demographic attributes, (b) biomedical attributes, and (c) operation-related attributes. Their values are either categorical or numeric. The attribute descriptions are shown in Table 1. All the statistical analyses were performed using the Statistical Package for the Social Science 10.0 (SPSS Inc. Chicago, IL, USA).

2.2. Analysis of PCA demand behavior

Given the PCA demand frequency within each unit of time, we can represent each patient's PCA demand profile as a time course, as illustrated in Fig. 1. The X-axis represents the 24 h time line, and the Y-axis indicates the number of PCA demand requests in a particular hour. By applying clustering algorithms to the time courses, we identified different patient groups. Patients in the same group are expected to demonstrate similar demand behavior; in contrast, demand behavior of patients in different groups is different. For example, Fig. 1 shows three patient groups, each consisting of two patients with similar demand patterns, and the demand patterns were different among different groups. In practice, we first transform the demand frequency into a sample standard score (i.e., z-score) to normalize the frequency variance in all units of time. This normalization step is to mitigate the influence of large variance on clustering. After normalization, each patient's PCA demand profile is represented by a vector of which each element is a normalized PCA demand frequency in a unit of time.

We use k-medoids algorithms [16,17] to partition the patients into clusters according to their demand behavior. In the current study, we use Euclidean distance to measure the similarity between two PCA demand profile vectors. A medoid is a real data point that has the minimum average distance from all other points in the same cluster. Unlike the k-means algorithm [18], k-medoids mitigates the effect of outliers on the resulting prototypes and ensures that all the resulting clusters are non-empty [19]. To find the appropriate number of clusters, we perform a series of k-medoids clustering algorithm with the value of k varying from 2 to K, a user-specified maximum number of clusters.

We generate bootstrap samples from the dataset by random sampling wit'h replacement [20]. We run k-medoids on the sample to obtain a clustering solution. From B pairs of bootstrap samples from the original data, we produce B pairs of clustering results. Given two clustering solutions C_1 and C_2 from a pair of bootstrap samples, we obtain two partitions of the original data by assigning each observation to the nearest medoid. The number of clusters is determined by reproducibility and stability [21]. If the number of clusters is correct, it is more likely that k-medoids clustering of the bootstrap samples all converges to the real medoids, and reproduce the same partition of the original data. Even if not all clustering results converge to the same medoids, it is well anticipated that the converged medoids will be in the proximity of the real medoids of the clusters, and thus produce stable partitions. We use the adjusted Rand Index [22] to measure the similarity between the two partitions. To determine if the partition of the original data is reproduced, or assess how stable a partition is, we compare the adjusted Rand Index values of the B pairs of bootstrapped partitions.

By iterating the value of k from 2 to K and repeating the same procedure, we obtain different distributions of the adjusted Rand Index values. First, we perform analysis of variance (ANOVA) to determine whether significant statistical evidence existed to show that at least two adjusted Rand Index means differed. Then, we conduct sequential t-tests corrected for multiple comparisons to identify a significant gap between successive differences in bootstrapped adjusted Rand Index values. The most significant jump indicates the most likely number of clusters in the original data.

2.3. Investigation of PCA demand behavioral influence on analgesic consumption

After identifying the PCA demand patterns using the k-medoids algorithm and bootstrapped stability tests, we examine the association between demand patterns and the patient attributes listed in Table 1. We run chi-square tests for the dependence of the demand behavior on those patient attributes, and we conduct ANOVA tests to compare the attribute values among different patient groups according to demand patterns. For all the analyses, a level is set at 0.05 for statistical significance.

Little research explores the relationship between PCA demand patterns and PCA analgesic consumption. We apply stepwise linear regression to compare demographic, biomedical, operation-related, and PCA demand behavioral influences on PCA analgesic consumption. The criterion for inclusion or elimination of patient attributes is that a patient attribute would be included if its partial regression coefficient is significant at the $\alpha=0.05$ level or eliminated if it is not. To further evaluate the individual effect of PCA demand pattern on analgesic consumption, we perform stepwise regression only on patient demographic, biomedical, and surgery-related attributes. We compare the R^2 and adjusted R^2 before and after removing demand patterns. A substantial drop in R^2 and adjusted R^2 indicates that the demand patterns play a significant role in predicting analgesic consumption. In addition, by discretizing PCA dose into ordinal values (e.g., high, medium, and low), we can define a PCA dose classification problem [7]. In classification problems, the action a_i is interpreted as the decision that the class is c_i. Supposing action a_i is taken and the true class is c_j, the decision is correct if $i=j$; otherwise, it is incorrect. We naturally seek a decision rule that minimizes the error rate. Based on the Bayes decision rule, we try to find a decision rule that minimizes the overall risk R [23]. To evaluate the effect of PCA demand behavior on ordinal PCA dose classification, we compute the Bayes risk associated with PCA demand patterns and compare it with other Bayes risks associated with different patient attributes. Because the patient attribute types are mixed, we dichotomize the values of continuous attributes such as weight into categories. Thus, the overall risk associated with attribute x is defined as:

$$R=\sum_{k=1}^{n} R(a_i|x_k)\times p(x_k)$$

where n is the number of categorical values of x. The minimum overall risk is the Bayes risk, defined as (see Appendices):

$$R^*=\sum_{k=1}^{n}(\underset{i}{\operatorname{argmin}}[1-p(c_i|x_k)])\times p(x_k)$$

By comparing the Bayes risks of the patient attributes and PCA demand patterns, we examine their influences on the PCA dose prediction errors; the lower the Bayes risk of a factor, the more this factor contributed to classification accuracy.

3. Results

A total of 5432 PCA log files were collected at Changhwa Christian Hospital from 2005 to 2010. The size of a log file on the PCA device is limited by the Abbott's hardware design. New log data overwrites the old data when the size reaches its limit. To maintain the consistency, the study focused on the demand behavior of the first 24 h PCA medication, and characterized demand patterns based on the first 24 h PCA requests. After discarding those oversized and thus overwritten incomplete log files, we obtained 4632 PCA log files. Of these patients, 2425 were excluded from our study because of missing values in demographic, biomedical, or surgery-related attributes. Moreover, 552 patients whose PCA medication was administered less than 24 h were also removed because the demand behavior analysis was performed over the first 24 h. Our study included 1655 participants after data preprocesses. Their attribute values are summarized in Table 1.

3.1. Identification of PCA demand patterns

We performed bootstrap sampling with replacement on the 1655 patient records and generated 100 pairs of samples. In the current study, we set the maximum number of clusters to be 6. Varying k from 2 to 6, we ran k-medoids on the bootstrap samples and calculated their adjusted Rand Index values. We performed ANOVA and sequential t-tests (with Bonferroni correction) on the adjusted Rand Index groups. The test results are presented in Tables 2 and 3. The ANOVA rejected the null hypothesis that no difference among the adjusted Rand Index means existed. It suggested that one clustering result was more stable and appropriate than the others. From the sequential t-test results, we observed a significant gap between $k=3$ and $k=4$. The mean of the adjusted Rand Index of the four cluster partitions dropped by 0.12, with $p \ll .000001$. It indicated that when $k=3$, the clustering result was the most stable. We thus selected $k=3$ as the number of clusters and identified three PCA patient groups by maximizing the demand behavior similarity among the patients in each group. The group size is 91, 1205, and 359, respectively. Patients in the same group showed a similar demand pattern that was different

Table 2
ANOVA test on different clustering results.

Clusters	Adjusted RI mean (sd)	*F*-value	*p*-value
2	0.81(0.14)	–	–
3	0.74(0.14)	–	–
4	0.62(0.14)	–	–
5	0.56(0.12)	–	–
6	0.50(0.11)	–	–
ANOVA test	–	91.66	$< <.00001$

Based on the low p-value, we rejected the null hypothesis that there was no difference among these clustering solutions.

Table 3
Sequential t-test for successive differences in adjusted Rand Index (ARI) means.

Number of clusters	Adjusted RI (ARI) mean difference	*t*-value	*p*-value
3 vs. 2	−0.07	3.63	.00037
4 vs. 3	−0.12	5.55	$\ll .000001$
5 vs. 4	−0.06	3.32	.0011
6 vs. 5	−0.06	4.00	.00009

A significant drop in ARI from 3-cluster clustering to 4-cluster clustering ($p \ll .000001$) suggested 3-cluster clustering was the most stable clustering solution.

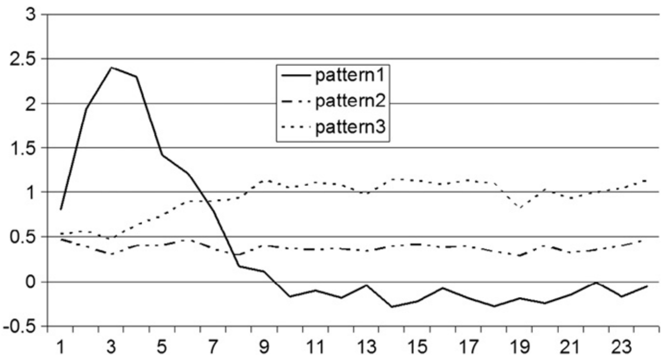

Fig. 2. PCA demand patterns discovered from 1655 subjects. Three patterns are identified from 1655 PCA patient-demand log files. Ninety-one patients' PCA demand behavior matches Pattern 1, 1205 patients' demand behavior matches Pattern 2, and 359 patients' demand behavior matches Pattern 3. The *X*-axis indicates the 24 h time line (1 h to 24 h). The *Y*-axis represents the normalized standard score (*z*-score) of the PCA demand frequency in a particular hour.

Table 4
Chi-square and ANOVA tests on patient attributes and demand patterns.

Attribute name	Chi-square *p*-value (*df**)	ANOVA *p-value*
Demographic		
Gender	0.0022(2)	–
Age	–	0.12
Weight	–	0.47
Biomedical		
sbp	–	0.15
dbp	–	0.025
Pulse	–	0.44
ASA class	0.37(4)	–
OP-related		
op_type	0.0028(14)	–
ans_type	0.36(2)	–
op_time	–	0.0095
Urgency	0.18(2)	–

* *df*: degree of freedom.

among different groups. Fig. 2 presents the average demand pattern of each group. The *X*-axis represents the 24 h time line, and the *Y*-axis is the normalized standard score (*z*-score) of the PCA demand frequency in a particular hour.

3.2. Association between patient attributes and PCA demand patterns

Different PCA demand patterns define different patient groups. We identify three demand patterns from 1655 patients and produce three patient groups. The chi-square test was performed to test the dependence of the patient groups on the categorical patient attributes in Table 1, for example, gender, ASA class, and surgery type. ANOVA was used to compare the differences in weight, age, blood pressure, pulse, and surgical duration among different patient groups. Table 4 shows the results of the chi-square and ANOVA tests. We observed statistically significant differences among PCA demand pattern groups in gender, diastolic blood pressure, surgery type, and surgical duration, respectively. The student *t*-test for differences between means was performed with Bonferroni correction ($\alpha/N=0.016$). The results indicates that Demand Pattern 1 (shown in Fig. 2) is associated with shorter surgical duration than the other two patterns ($p=.0012$; $p=.008$), and Demand Pattern 2 is more associated with lower diastolic blood ($p=.05$) than Pattern 3 ($p=.09$), but shows no significant difference from Pattern 1 ($p=.91$). In contrast, age, systolic blood pressure, and urgency show only a weak association with PCA demand behavior. No significant difference in weight ($p=.47$) or pulse ($p=.43$) is found among demand pattern groups. In addition, no significant statistical evidence is found to reject or accept the hypothesis that the ASA class ($p=.37$) and the type of anesthesia ($p=.36$) are independent of PCA demand pattern.

3.3. Influence of PCA demand behavior on analgesic consumption

Multivariate stepwise linear regression was used to identify major factors influencing PCA analgesic consumption. All demographic, biomedical, and surgery-related attributes and PCA demand patterns were included for regression analysis. We find that PCA demand pattern plays the most significant role in predicting PCA analgesic consumption. The other major factors at the $\alpha=0.05$ level are weight, age, surgical type, urgency, and anesthesia type, as presented in Table 5. To validate further the individual effect of PCA demand pattern on analgesic consumption, we performed stepwise regression only on patient demographic, biomedical, and surgery-related attributes. Three factors are selected at the $\alpha=0.05$ level, as shown in Table 6. They are weight, age, and surgical type, in the order selected. The R^2 and adjusted R^2 are 0.05651 and 0.05479, respectively. Compared

Table 5
Results of stepwise regression analysis of PCA analgesic consumption.

Predicting PCA analgesic consumption.						
Factor attribute	Beta**	B†a	SE‡b	*p*-value	R^2	Adjusted R^2
Step 1						
PCA demand pattern	0.36	3.65	0.23	0.E+0	0.13	0.13
Step 2						
PCA demand pattern	0.36	3.61	0.23	0.E+0	0.15	0.15
Weight	0.15	0.061	0.0089	1.77E−11		
Step 3						
PCA demand pattern	0.36	3.62	0.23	0.E+0	0.17	0.17
Weight	0.16	0.065	0.0089	3.88E−13		
op_type	−0.13	−0.33	0.057	1.64E−8		
Step 4						
PCA demand pattern	0.36	3.60	0.22	0.E+0	0.18	0.18
Weight	0.15	0.059	0.0089	3.16E−11		
op_type	−0.12	−0.31	0.057	4.36E−8		
Age	−0.12	−0.037	0.0071	2.67E−7		
Step 5						
PCA demand pattern	0.36	3.61	0.22	0.E+0	0.19	0.18
Weight	0.15	0.059	0.0089	4.41E−11		
op_type	−0.12	−0.30	0.057	2.17E−7		
Age	−0.12	−0.039	0.0072	7.77E−8		
Urgency	0.047	0.86	0.41	0.037		
Step 6						
PCA demand pattern	0.36	3.60	0.22	0.E+0	0.19	0.18
Weight	0.15	0.059	0.0089	5.39E−11		
op_type	−0.12	−0.31	0.058	7.23E−8		
Age	−0.13	−0.042	0.0074	1.15E−8		
Urgency	0.049	0.89	0.41	0.030		
ans_type	0.046	0.73	0.37	0.049		

** Beta is standardized coefficient.
†a *B* is unstandardized coefficient.
‡b SE is standard error of B.

Table 6
Results of stepwise regression analysis of PCA analgesic consumption without demand patterns.

Predicting PCA analgesic consumption.						
Factor attribute	Beta**	B†a	SE‡b	*p*-value	*R*2	Adjusted R^2
Step 1						
Weight	0.16	0.064	0.0096	3.52E−11	0.026	0.026
0.5						
Step 2:						
Weight	0.15	0.058	0.0096	1.84E−9	0.042	0.041
Age	−0.13	−0.040	0.0077	1.94E−11		
0.5						
Step 3:						
Weight	0.16	0.063	0.0096	8.28E−11	0.057	0.055
Age	−0.12	−0.039	0.0076	4.78E−7		
op_type	−0.12	−0.31	0.061	5.38E−7		

** Beta is standardized coefficient.
†a *B* is unstandardized coefficient.
‡b SE is standard error of B.

Table 7
Summary of PCA dose classes.

Symbolic PCA dose	Low	Medium	High
Dose mean ± sd (mg)	2.06 ± 1.01	5.45 ± 1.10	12.19 ± 4.36
Number of patients	549	565	541

Table 8
The Bayes risks associated with patient attributes.

Attribute name	Bayes risk
Demographic	
Gender	0.656
Age	0.633
Weight	0.629
Biomedical	
sbp	0.743
dbp	0.508
Pulse	0.657
ASA class	0.643
OP-related	
op_type	0.598
ans_type	0.659
op_time	0.657
urgency	0.655
PCA demand pattern	**0.449**

The lowest Bayes risk of demand pattern indicated its greatest contribution to classification.

with the results (R^2=0.18761 and adjusted R^2=0.18465) in Table 5, it is clear that PCA demand pattern makes a significant contribution to analgesic consumption prediction.

We partitioned the 1655 patients into three classes based on the analgesic consumptions within 24 h after PCA was made available. The sizes of the classes are approximately equal, and they correspond to low, medium, and high doses. A summary of the three classes is given in Table 7. We computed the Bayes risk for each patient attribute and PCA demand pattern in analgesic consumption classification. As seen in Table 8, PCA demand pattern incurs the least Bayes risk in classification, which suggests that PCA demand pattern has more influence on analgesic consumption prediction than the other patient attributes.

4. Discussion

Cluster analysis has been widely used in various applications. In biology, it can help biologists categorize genes or proteins with similar functionality into families or derive a hierarchical organization [24]. In business, it helps market analysts identify distinctive groups in their customer databases and characterize customer groups according to purchasing patterns [25]. Many clustering algorithms have been developed. In general, they can be classified into methods such as partitioning methods, hierarchical methods, density-based methods, model-based methods, and constraint-based methods [19,26].

The choice of algorithms depends on the type of data and the goal of applications. Different clustering algorithms have different advantages and limitations. As a means of data exploration and characterization, various clustering methods could be applied to disclose different properties embedded in the data. The objectives of this study are to advocate the importance of demand behavior analysis for PCA administration and to propose using clustering methods to characterize patient demand profiles. By applying a *k*-medoids partitioning method, we discovered different PCA demand patterns in the study participants. Each participant was associated with only one demand pattern. Other clustering algorithms could be applied to identify different types of patterns to address different medical meanings.

The demographic, biomedical, and surgery-related predictors for analgesic consumption are not necessarily a predictor for PCA demand pattern, though a relationship between analgesia requirements and demand behavior exists. Several studies have discovered a significant correlation between age and the dose of opioid required in the postoperative period [4,27–29]. For example, Gagliese et al. and Chang et al. both observed that age was significantly negatively correlated with morphine consumption in their studies [11,30]. However, our study only indicated a weak correlation of age with PCA demand patterns. As mentioned in previous studies, possible causes of the discrepancy in the results could be lack of understanding or misuse of PCA by older and younger patients [8], and a difference in pain sensitivity to morphine between young and elderly patients should be considered in the correlation analysis [31]. More specific studies should be restricted to a narrower age range such as 20 to 60 years, and pain intensity should be included in the correlation modeling to alleviate the limitation of a simple two-variable (age and morphine dose) model.

Chang et al. found that weight was a significant determinant of total PCA requirements in their study of 1308 patients [3]. Likewise, body mass was found to be a significant predictor for pain in the post-anesthesia care unit in Chung et al.'s study among ambulatory surgical patients [1]. Nevertheless, like some other studies that reported no correlation between analgesic consumption and patient weight [8,32,33], our results did not show any significant association between the PCA demand pattern and patient weight. The mean weights of the three demand pattern groups are 61.5 kg, 63.0 kg, and 63.3 kg, respectively. They are all close to the mean weight of the total number of study participants, which is 63.0 kg, showing no significant difference.

The relationship of gender with postoperative pain and analgesic consumption varies among different studies. In Chia et al.'s study of 2298 patients, women consumed significantly less morphine using PCA in the first three postoperative days than men [8]. In contrast, in Cepeda et al.'s study, women experienced more intense pain and had a larger morphine consumption than men [34]; in addition, Chang et al. found no significant correlation between gender and morphine consumption [30]. We found that gender was a significant correlate of PCA demand behavior. This concurred with Chia et al.'s report that gender was an important predictor of postoperative morphine requirement [8]. The chi-square test indicated that significantly more females than expected demonstrated PCA Demand Pattern 1 (see Fig. 2) in our study. Because Demand Pattern 1 indicates an early sharp increase of PCA requests, it suggests that PCA dosage for the first 3 h could be increased for the female patients whose characteristics match those in the Demand Pattern 1 group to increase their satisfaction.

We found a significant association between PCA demand pattern and surgical type as well as surgical duration. These findings agreed with the lessons learned from pain management [35,36] and previous studies of PCA consumption [11,30]. For example, in Gagliese et al.'s study of 123 younger patients [11], gynecological/urological surgery was significantly inversely associated with morphine intake, and the surgical duration was significantly positively associated with morphine intake. Nevertheless, some other studies failed to show any correlation between analgesic consumption and surgical sites or duration [4,8,9]. This inconsistency may be due to the different classifications of surgery; for example, the number of surgical types considered in previous studies was smaller than ours. The chi-square test showed that among those patients revealing Demand Pattern 1, significantly more patients than expected had abdominal surgery, but in contrast, among those patients showing Demand Pattern 2, the number of patients receiving abdominal surgery was significantly smaller than expected. The student *t*-tests revealed that the surgical duration of patients in the Demand Pattern 1 group was significantly shorter than that in the other two pattern groups.

Some researchers have derived predictive models of analgesic requirements or postoperative pain from regression analyses [8,10,11]. Although they identified several positive preoperative correlates, such as age and gender, their coefficients of determination were small, and in some cases, no significant predictors were found. For example, in an analysis of the first 6 h of intravenous patient controlled analgesia required in the ward, no predictors were found to meet $\alpha=0.05$ level [9]. This suggests that predictive factors other than demographic, physiological, and surgical attributes are present that have not been analyzed. We included PCA demand pattern in the multivariate stepwise regression analysis to compare the influence of these factors on PCA consumption prediction. Our results show that PCA demand pattern play the most significant role in predicting analgesic consumption. It increases the value of coefficient of determination from 0.057 to 0.19. In the framework of classification, we discretized the analgesic consumption into a number of symbolic values, such as low, medium, and high. Instead of a numeric value, we aimed to predict a symbolic value of analgesic consumption because this indicator is sufficiently expressive for anesthetists to recognize an abnormality in PCA medications. The Bayes risk analysis indicates that PCA demand pattern causes the least risk in PCA consumption classification. This result is consistent with the findings in the stepwise regression analysis. The stepwise regression analysis and the Bayes risk analysis both demonstrate a significant relationship between PCA demand behavior and analgesic consumption; nevertheless, their predictors are not all the same. Surgery type is a significant predictor for both PCA demand behavior and analgesic consumption. Although age and urgency are found to correlate with analgesic consumption significantly, they only show weak association with PCA demand pattern. Furthermore, our study indicates significant gender-related differences in PCA demand pattern, but gender is ruled out in the multivariate regression analysis for PCA requirement prediction. These conflicting results may be attributed to different medical meanings of demand behavior and analgesic consumption or to other correlated factors that have not been examined in our studies, such as psychosocial factors.

There are a number of limitations in our current study. First, though the patient records have been carefully reviewed, the PCA data used in our analyses were not guaranteed to be free of errors. A small amount of noisy data could occur due to human errors in data entry or misuse of PCA devices by patients. They were not recognized or resolved in the data preprocess. To mitigate the effect of data noise, we used bootstrap replications to ensure the reproducibility and stability of clustering solutions, and statistically significant results were obtained. However, data cleaning is still a crucial step before any form of data exploration, including clustering, and results of this type should be applied with caution within the imitations of clustering algorithms. Second, most previous studies of PCA were conducted on Western patients. Little research focuses on Eastern people such as Taiwanese patients [8,30]. The discrepancy in the analysis results or conclusions might be attributable to the impact of different sociocultural origins. Third, our current study of PCA demand behavior is based on the first 24 h of PCA therapy after surgery. Shorter or longer periods of PCA medication may contain different demand behavioral patterns. Distinct and conserved demand patterns among patients over various lengths of PCA therapy are likely to correlate with different regularities in postoperative pain relief and patient satisfaction. Information of this type may be useful for predicting analgesic requirements and postoperative pain. Last, as a retrospective study, the surveyed variables were not under control, and the medical meanings of the correlation between demand patterns and demographic, biomedical, or surgery-related predictors were still unclear.

In conclusion, we advocate the analysis of PCA demand behavior. To demonstrate its feasibility and significance, in our current study we used clustering algorithms to identify demand patterns. The stability and reproducibility of the clustering solution have been verified by repeated random bootstrap sampling, an idea similar to that of Monti et al. [37]. The results suggest that PCA demand behavioral patterns exist over time among patients. They are correlated with specific demographic, biomedical, or surgery-related attributes, and have influence on analgesic consumption. Other clustering-based methods and alternative approaches are applicable to the study of PCA demand patterns. In particular, various methods have been developed to address the issue of stability in clustering, and to identify consensus clustering. They measure and characterize stability differently. For examples, some assess the stability based on the consensus across multiple subsampling [37], and others focus on the consistency in the partitions produced by different clustering algorithms [38]. These approaches to consensus clustering have been applied to integrating diverse viral gene expression data for further exploration [39], or to evaluating the appropriateness of a previously proposed classification of breast cancer gene expression data [40]. To our best knowledge, this study is the first to introduce an analysis of time-series data derived from PCA demand log files. We have used a clustering method to analyze the 24 h PCA demand profile of 1655 patients. The advantages of a clustering-based approach to data analysis are that it is adaptable to change and helps extract crucial properties that distinguish different data groups. Unlike the application of consensus clustering in earlier works [39,40], our cluster-based study is currently focused on discovering the conserved PCA demand behavioral patterns in different patient groups because the classification of PCA demand behavior is unavailable, and we have only one data source at CCH. A larger-scale and more detailed analysis based on multiple approaches is in progress. We plan to submit these patterns to the department of anesthesia of Changhwa Christian Hospital. After the classification of PCA demand behavior has been determined based on medical knowledge, we can next use the consensus clustering methods to further evaluate the significance of the demand patterns we have identified.

Conflict of interests statement

No competing interests declared.

Acknowledgments

This work was partially supported by National Science Council, Taiwan (NSC 100-2221-E-009-146, NSC99-2218-E-009-002). Thanks go to Shin-Ru Wu and Yu-Ming Tsao for processing the patient records and the manuscript.

Appendices

Based on the Bayes decision rule, we find a decision rule that minimizes the overall risk R.

$$R = \int R(a_i|x) \times p(x)dx$$

where x is a patient's attribute values, $p(x)$ is the probability of x, and $R(a_i|x)$ is risk of taking action a_i with patient attribute value x.

$$R(a_i|x) = \sum_{j=1}^{m} \lambda(a_i|c_j) \times P(c_j|x)$$

where $\lambda(a_i|c_j)$ is the loss incurred by taking action a_i with the true class c_j.

To minimize overall risk, we compute the conditional risk $R(a_i|x)$ for each possible decision, $i=1\cdots m$, and then select the action a_i, of which $R(a_i|x)$ is minimum. The resulting minimum overall risk is called the Bayes risk R^* [26]. Assuming that all errors are equally costly, we define the loss function as the zero-one loss function:

$$\lambda(a_i|c_j) = \begin{cases} 0 & i=j \\ 1 & i \neq j \end{cases} \quad i,j = 1\cdots m$$

with this loss function, the conditional risk function becomes $R(a_i|x)=1-p(c_i|x)$. By discretizing continuous patient attributes into categorical ones, we can redefine the overall risk of the attribute x as

$$R = \sum_{k=1}^{n} R(a_i|x_k) \times p(x_k)$$

where x_k is a legal categorical value of x, and n is the total number of categorical values of x.

The Bayes risk is

$$R^* = \sum_{k=1}^{n} (\underset{i}{\operatorname{argmin}}[1-p(c_i|x_k)]) \times p(x_k).$$

References

[1] F. Chung, V. Un, J. Su, Postoperative symptoms 24 h after ambulatory anaesthesia, Can. J. Anesth. 43 (1996) 1121.
[2] Turk D.C., Okifuji A., Assessment of patients' reporting of pain: an integrated perspective. The Lancet, 353, 1784 (1999).
[3] T. Bisgaard, B. Klarskov, J. Rosenberg, H. Kehlet, Characteristics and prediction of early pain after laparoscopic cholecystectomy, Pain 90 (2001) 261.
[4] P.E. Macintyre, D.A. Jarvis, Age is the best predictor of postoperative morphine requirements, Pain 64 (1996) 357.
[5] S.J. Dolin, J.N. Cashman, J.M. Bland, Effectiveness of acute postoperative pain management: I. Evidence from published data, Br. J. Anaesth. 89 (2002) 409.
[6] B. Walder, M. Schafer, I. Henzi, M.R. Tramer, Efficacy and safety of patient-controlled opioid analgesia for acute postoperative pain. A quantitative systematic review, Acta Anaesthesiol. Scand. 45 (2001) 795.
[7] Y.J. Hu, R.H. Jan, K.C. Wang, Y.C. Tseng, T.H. Ku, S.F. Yang, H.S. Wu, An application of sensor networks with data mining to patient controlled analgesia, Proc. IEEE HealthCom 353 (2010).
[8] Y.Y. Chia, L.H. Chow, C.C. Hung, K. Liu, L.P. Ger, P.N. Wang, Gender and pain upon movement are associated with the requirements for postoperative patient-controlled iv analgesia: a prospective survey of 2298 Chinese patients, Can. J. Anesth. 49 (2002) 249.
[9] P.H. Pan, R. Coghill, T.T. Houle, M.H. Seid, W.M. Lindel, R.L. Parker, S.A. Washburn, L. Harris, J.C. Eisenach, Multifactorial preoperative predictors for postcesarean section pain and analgesic requirement, Anesthesiology 104 (2006) 417.
[10] F. Aubrun, D. Bunge, O. Langeron, G. Saillant, P. Coriat, B. Riou, Postoperative morphine consumption in the elderly patient, Anesthesiology 99 (2003) 160.
[11] L. Gagliese, L.R. Gauthier, A.K. Macpherson, M. Jovellanos, V.W. Chan, Correlates of postoperative pain and intravenous patient-controlled analgesia use in younger and older surgical patients, Pain Med. 9 (2008) 299.
[12] A. Vallieres, H. Ivers, S. Beaulieu-Bonneau, C.M. Morin, Predictability of sleep in patients with insomnia, Sleep 34 (2011) 609.
[13] X. Wen, S. Fuhrman, G.S. Michaels, D.B. Carr, S. Smith, J.L. Barker, R. Somogyi, Large-scale temporal gene expression mapping of central nervous system development, Proc. Nat. Acad. Sci. U.S.A. 95 (1998) 334.
[14] Hu Y.J., Jan R.H., Wang K.C., Tseng Y.C., Ku T.H., and Yang S.F., Analysis of patient controlled analgesia demand patterns, in: Proceedings of Industrial Conference on Data Mining (Short Paper), 17 (2011).
[15] G. De Cosmo, E. Congedo, C. Lai, P. Primieri, A. Dottarelli, P. Aceto, Preoperative psychologic and demographic predictors of pain perception and tramadol consumption using intravenous patient-controlled analgesia, Clin. J. Pain 24 (2008) 399.
[16] Reynolds A.P., Richards G., and Rayward-Smith V.J., The application of K-medoids and PAM to the clustering of rules, in: Proceedings of the Fifth International Conference on Intelligent Data Engineering and Automated Learning, 173 (2004).
[17] H. Park, C. Jun, A simple and fast algorithm for K-medoids clustering, Expert Syst. Appl. 36 (2009) 3336.
[18] E. Forgy, Cluster analysis of multivariate data. Efficiency vs. interpretability of classification, Biometrics 21 (1965) 768.
[19] J. Han, M. Kamber, Data Mining: Concepts and Techniques, second ed., Morgan Kaufmann, San Francisco, 2007.
[20] B. Efron, R.J. Tibshirani, An Introduction to the Bootstrap, Chapman & Hall, New York, 1993.
[21] S. Dolnicar, F. Leisch, Evaluation of structure and reproducibility of cluster solutions using the bootstrap, Market. Lett. 21 (2010) 83.
[22] L. Hubert, P. Arabie, Comparing partitions, J. Classif. 2 (1985) 193.
[23] R.O. Duda, P.E. Hart, D.G. Stork, Pattern Classification, second ed., Wiley New York, 2001.
[24] M.B. Eisen, P.T. Spellman, P.O. Brown, D. Botstein, Cluster analysis and display of genome-wide expression patterns, Proc. Nat. Acad. Sci. U.S.A. 95 (1998) 14863.
[25] S. Dibb, L. Simkin, A program for implementing market segmentation, J. Bus. Ind. Market. 12 (1997) 51.
[26] R. Xu, D.C. Wunsch II, Clustering, Wiley, New Jersey, 2009, IEEE Press.
[27] J.W. Burns, N.B. Hodsman, T.T. McLintock, G.W. Gillies, G.N. Kenny, C.S. McArdle, The influence of patient characteristics on the requirements for postoperative analgesia. A reassessment using patient-controlled analgesia, Anaesthesia 44 (1989) 2.
[28] A.M. Egbert, L.H. Parks, L.M. Short, M.L. Burnett, Randomized trial of postoperative patient-controlled analgesia vs. intramuscular narcotics in frail elderly men, Arch. Int. Med. 150 (1990) 1897.
[29] L. Gagliese, M. Jackson, P. Ritvo, A. Wowk, J. Katz, Age is not an impediment to effective use of patient-controlled analgesia by surgical patients, Anesthesiology 93 (2000) 601.
[30] K.Y. Chang, M.Y. Tsou, K.H. Chan, C.S. Sung, W.K. Chang, Factors affecting patient-controlled analgesia requirements, J. Formos. Med. Assoc. 105 (2006) 918.
[31] F. Aubrun, S. Monsel, O. Langeron, P. Coriat, B. Riou, Postoperative titration of intravenous morphine in the elderly patient, Anesthesiology 96 (2002) 17.
[32] S. Major, Women get greater pain relief than men, Br. Med. J. 313 (1996) 1168.
[33] J.W. Bellville, W.H. Forrest Jr, E. Miller, B.W. Brown Jr, Influence of age on pain relief from analgesics. A study of postoperative patients, J. Am. Med. Assoc. 217 (1971) 1835.
[34] M.S. Cepeda, D.B. Carr, Women experience more pain and require more morphine than men to achieve a similar degree of analgesia, Anesth. Analgesia 97 (2003) 1464.
[35] L.B. Ready, Acute pain lessons learned from 25,000 patients, Region. Anesth. Pain Med. 24 (1999) 499.
[36] L.M. Preble, J.A. Guveyan, R.S. Sinatra, Patient characteristics influencing postoperative pain management, in: R.S. Sinatra, H. Hord, B. Ginsberg, L.M. Preble (Eds.), Acute Pain Mechanisms and Management. St. Louis, Eds.,Mosby Year Book, MO, 1992.
[37] S. Monti, P. Tamayo, J. Mesirov, T. Golub, Consensus clustering: a resampling-based method for class discovery and visualization of gene expression microarray data, Mach. Learn. 52 (2003) 91.
[38] S. Swift, A. Tucker, V. Vinciotti, N. Martin, C. Orengo, X. Liu, P. Kellam, Consensus clustering and functional interpretation of gene-expression data, Genome Biol. 5 (2004) R94.
[39] Kellam P., Liu X., Martin N., Orengo C., Swift S., Tucker A. Comparing, contrasting and combining clusters in viral gene expression data. In: Proceedings of the Sixth Workshop on Intelligent Data Analysis in Medicine (2001).
[40] D. Soria, J.M. Garibaldi, F. Ambrogi, A.R. Green, D. Powe, E. Rakha, R.D. Macmillan, R.W. Blamey, G. Ball, Lisboa PLG, T.A. Etchells, P. Boracchi, E. Biganzoli, Ellis IO. A methodology to identify consensus classes from clustering algorithms applied to immunohistochemical data from breast cancer patients, Comput. Biol. Med. 40 (2010) 318.