An Analysis of Patient Variables That Influence Intravenous Patient-controlled Analgesic Use of Morphine with Quantile Regression

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ABSTRACT

Background: Previous studies using linear regression analysis have shown that age, weight, gender, and the site of operation affect intravenous patient-controlled analgesia (IVPCA) narcotic use. However, there are inconsistent observations in the literature. The authors postulate that patient variables could have different effects at various doses of narcotics. To test this hypothesis, the authors analyzed the effect of patient variables on increasing doses of IVPCA narcotic with quantile regression.

Methods: The authors collected retrospective data from 1,782 patients who received IVPCA for a minimum of 3 days after surgery. The authors used stepwise linear regression model to identify variables that significantly affected the total IVPCA requirements. Quantile regression model was further applied to assess the effects of selected variables on the ascending percentiles of IVPCA narcotic use.

Results: Gender, age, body weight, cancer, and surgical site were identified as significant predictors for IVPCA demand. Body weight had the most and cancer had the least significant effects on total IVPCA demands. The results of quantile regression model revealed that the determinants under consideration varied with different percentiles of IVPCA demand. The patient variables correlated with IVPCA narcotic use differently when the dose exceeded the seventieth to eightieth percentiles compared with other percentiles of narcotic use.

Conclusions: The authors' findings highlight the heterogeneous postoperative pain requirements among patients and the consequent complex process of efficiently managing postoperative pain.

INTRAVENTOUS patient-controlled analgesia (IVPCA) is commonly used to manage acute postoperative pain and is well accepted by both patients and medical personnel. Although evidence suggests that patient-controlled epidural analgesia can provide better pain control than IVPCA in selected clinical circumstances,1–3 physicians often choose IVPCA because it has a simple route of administration and is safe.4,5 To improve patient satisfaction and pain control, physicians must adjust the IVPCA dosage to meet individual analgesic demand. Currently, there are very few evidence-based protocols to help physicians select an IVPCA drug protocol for a heterogeneous group of patients.

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Previous studies have shown that age, gender, body weight, and the site of operation significantly affect postoperative analgesic use. These studies used linear regression to examine the relationships between variables and IVPCA demands. However, there are a number of limitations when applying linear regression to IVPCA datasets. Linear regression as a single analytic step gives an incomplete picture of the relationships between variables, because it summarizes only mean responses of the dependent variable corresponding to a set of explanatory variables. An analysis that uses the conditional mean may place too much emphasis on central tendency in the data and accidentally ignores important detail about the outliers of a response curve. This can create a significant clinical problem, because the method does not provide any information about how to manage postoperative pain in patients who use more or less than the mean of the response distribution.

More information can be obtained by using an analytic technique that is specifically designed to examine how variables behave in the entire distribution of narcotic use. Quantile regression meets this analytic challenge. Quantiles are defined as points or sets of data taken at regular intervals from the complete distribution of a variable. Quantile regression is a more robust statistical methodology when it is necessary to estimate the response of median or specific quantiles. The median helps in the identification of statistical patterns based on the complete range of responses. This is particularly useful for the data with significant outliers. Thus, we chose this statistical method for IVPCA analysis because of the wide range of clinical responses to postoperative pain management. The semiparametric nature of quantile regression also relaxes essential distributional assumptions in the linear regression model. In other words, it provides a detailed way to explore sources of heterogeneity in the dependent variables under study. These advantages make quantile regression a useful tool to investigate the complex relationships between IVPCA requirement and patient demographic variables.

We hypothesize that multiple factors affect IVPCA requirements, which are not evident in linear regression analyses but may be uncovered by quantile regression analysis. To test our hypothesis, we conducted a two-step regression analysis. We first used a stepwise linear regression model to find correlates between IVPCA requirement and patient characteristics. We then used quantile regression analysis to measure the relationships between total morphine use and the patient characteristics identified by the linear regression analysis.

Materials and Methods

Patients

After approval for this study from the Institutional Review Board of the Taipei Veterans General Hospital (Taipei, Taiwan, R.O.C.), we retrieved data from the charts of patients who were admitted to the Taipei Veterans General Hospital between January 2006 and December 2007. We included data from all patients who met the following criteria: 15–90 yr of age, able to provide informed consent, received general anesthesia for surgery without concurrent neuraxial techniques, and used postoperative IVPCA for at least 3 days. We excluded from the study those patients who required postoperative ventilator support or intensive care beyond 24 h and patients who had surgical or anesthetic complications that required an escalation in the acuity of their care. After surgery, all patients were transferred to the postanesthesia care unit where IVPCA was initiated.

IVPCA Management and Pain Assessment

All study patients used the same model of infusion pump (Aim® plus system; Abbott Laboratories, North Chicago, IL). Analgesic administration was performed in the following way: all patients received a 0.05 mg/kg bolus intravenous injection of morphine sulfate as a loading dose for immediate pain control when they entered the postanesthesia care unit. IVPCA morphine was then administered in a standard solution of 1 mg/ml morphine in normal saline. The pump was set to deliver 0.5–1.5 mg of morphine on demand with a lockout interval between 5 and 10 min. All pumps were set to deliver a continual basal infusion of morphine between 0 and 1.5 mg/h. Ninety-eight percent of the study population received an initial basal infusion rate of 1 mg/h or less, and 53% of them received a rate of less than 0.5 mg/h. The IVPCA hospital team visited all patients at least once each day during the study period. The team used a verbal rating score to record a pain score, where 0 = no pain and 10 = the worst pain. The IVPCA team staff recorded the total IVPCA dose administered at the end of the third day. We collected patient information that included age, gender, weight, height, body mass index, and type of surgery including the site of surgery and the underlying disease.

Statistical Analysis

Continuous variables were expressed as the mean and SD, and discrete factors were presented as the absolute number and percentage. Because the site of surgery influences IVPCA requirements, the operations were classified into nine categories based on the anatomic site of surgery. These included extremity, spine, thorax, upper abdomen, head and neck, cardiovascular, gynecologic, genitourinary, and colorectal surgeries. We defined orthopedic surgeries involving extremities as the reference group for the factor “surgical site” in the following analyses.

One-way ANOVA was used to compare age, weight, height, body mass index, intraoperative fentanyl dosage, and total IVPCA morphine use among the nine distinct surgical sites. When there were significant differences among groups, post hoc analysis was conducted with Scheffé multiple comparison procedure. Distribution of gender and procedures involving cancer among surgical sites were compared with chi-square test. A P value less than 0.05 was considered statistically significant.
Stepwise linear regression was used to select variables, which could predict total IVPCA morphine use. The entry and exit criteria were set at a significance level of 0.05 and 0.10, respectively. The variables included weight, height, age beyond 60 yr, gender (coded as 1 for male and 0 for female), cancer (0 for noncancer and 1 for cancer), intraoperative fentanyl dosage, and surgical sites (eight dummy variables). The variable “age beyond 60 yr” was defined as age minus 60 for those who were older than 60 yr. For patients younger than 60 yr, the value of this variable would be set at 0.

We replaced the original age with the new variable age beyond 60 yr due to a negative linear trend observed between IVPCA requirements and age (data not shown). We did not include initial infusion rate as a variable for analysis because it was related to both the patients’ attributes and IVPCA demand. We did not measure in this study. Therefore, we evaluated the effect of weight on IVPCA use in distinct types of surgery. The goodness of fit for a quantile regression model at a specific quantile could be assessed with pseudo $R^2$, which is an analog of the $R^2$ statistic in linear regression. However, the pseudo $R^2$ is not comparable with its least square analog, because it is a local measure instead of a global index of goodness of fit. The estimated coefficients of independent variables with their 95% CI were plotted against their conditional quantiles of response variables. All statistical analyses were performed with the Stata software version 8.0 (Stata Corp, College Station, TX).

### Results

#### Patient Demographics

There were 1,782 patients enrolled in the analysis. The mean pain score with SD on the first, second, and third postoperative days were $3.0 \pm 0.3$, $2.3 \pm 0.5$, and $2.1 \pm 0.4$, respectively. Patients’ characteristics and total morphine requirements are summarized in Table 1. The variables we compared between distinct surgical sites were statistically significant (all $P < 0.001$). Patients who received gynecologic and head and neck surgeries had the lowest mean age. Orthopedic patients receiving spine or extremity surgeries had the highest body mass index. Patients undergoing cardiovascular operations used the most intraoperative fentanyl, and those who received thoracic surgeries used more morphine during the 3-day IVPCA course than any other group.

#### Table 1. Demographic Data and Total IVPCA Requirements of Patients with Different Surgical Groups

<table>
<thead>
<tr>
<th>Surgical Site</th>
<th>Spine</th>
<th>Colorectal</th>
<th>Thorax</th>
<th>Cardiovascular</th>
<th>Head and Neck</th>
<th>Upper Abdomen</th>
<th>Genitourinary</th>
<th>Gynecologic</th>
<th>Extremity</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>475</td>
<td>204</td>
<td>39</td>
<td>108</td>
<td>65</td>
<td>245</td>
<td>42</td>
<td>218</td>
<td>386</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62.6 (16.7)</td>
<td>67.6 (13.6)</td>
<td>56.1 (22.6)</td>
<td>67.6 (13.9)</td>
<td>46.9 (14.5)</td>
<td>61.1 (16.4)</td>
<td>62.5 (14.1)</td>
<td>46.8 (13.4)</td>
<td>60.6 (18.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;60 yr</td>
<td>312 (65.7%)</td>
<td>147 (72.1%)</td>
<td>21 (53.8%)</td>
<td>83 (76.3%)</td>
<td>12 (18.5%)</td>
<td>142 (58.0%)</td>
<td>24 (57.1%)</td>
<td>36 (16.5%)</td>
<td>225 (58.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>211 (44.4%)</td>
<td>80 (39.2%)</td>
<td>12 (30.8%)</td>
<td>33 (30.6%)</td>
<td>17 (25.2%)</td>
<td>90 (36.7%)</td>
<td>17 (40.5%)</td>
<td>218 (100.0%)</td>
<td>159 (41.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>13 (2.7%)</td>
<td>178 (87.3%)</td>
<td>25 (64.1%)</td>
<td>0 (0.0%)</td>
<td>49 (75.4%)</td>
<td>102 (41.6%)</td>
<td>29 (69.0%)</td>
<td>85 (39.0%)</td>
<td>20 (5.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.1 (11.7)</td>
<td>60.1 (11.1)</td>
<td>60.9 (12.3)</td>
<td>64.4 (11.9)</td>
<td>66.7 (14.3)</td>
<td>61.6 (11.3)</td>
<td>63.6 (11.9)</td>
<td>57.1 (10.5)</td>
<td>66.1 (13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.3 (8.9)</td>
<td>159.7 (8.8)</td>
<td>163.2 (8.4)</td>
<td>162.2 (8.7)</td>
<td>166.0 (7.1)</td>
<td>162.4 (8.3)</td>
<td>161.3 (8.2)</td>
<td>156.9 (5.7)</td>
<td>161.2 (8.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>25.3 (3.8)</td>
<td>23.5 (3.8)</td>
<td>22.9 (4.4)</td>
<td>24.4 (3.8)</td>
<td>24.2 (5.1)</td>
<td>23.3 (3.6)</td>
<td>24.3 (3.5)</td>
<td>23.2 (4.1)</td>
<td>25.4 (4.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraoperative fentanyl (mg)</td>
<td>178 (62)</td>
<td>165 (38)</td>
<td>176 (41)</td>
<td>447 (217)</td>
<td>212 (85)</td>
<td>170 (61)</td>
<td>180 (41)</td>
<td>155 (29)</td>
<td>157 (21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total morphine (mg)</td>
<td>64.7 (31.1)</td>
<td>74.7 (31.0)</td>
<td>94.7 (41.1)</td>
<td>49.8 (25.4)</td>
<td>81.0 (34.9)</td>
<td>79.9 (38.6)</td>
<td>77.1 (43.7)</td>
<td>47.2 (21.3)</td>
<td>63.0 (30.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Selected Factors in the Stepwise Linear Regression Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unstandardized β</th>
<th>SE</th>
<th>Standardized β</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>9.29</td>
<td>4.09</td>
<td></td>
<td>0.023</td>
</tr>
<tr>
<td>Weight</td>
<td>0.86</td>
<td>0.06</td>
<td>0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age beyond 60 yr*</td>
<td>-1.07</td>
<td>0.09</td>
<td>-0.26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>8.88</td>
<td>1.57</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer†</td>
<td>7.04</td>
<td>1.99</td>
<td>0.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Surgical site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>3.44</td>
<td>1.91</td>
<td>0.05</td>
<td>0.072</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>-9.41</td>
<td>3.05</td>
<td>-0.07</td>
<td>0.002</td>
</tr>
<tr>
<td>Thorax</td>
<td>30.29</td>
<td>4.84</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>10.97</td>
<td>4.70</td>
<td>0.05</td>
<td>0.020</td>
</tr>
<tr>
<td>Colorectal</td>
<td>13.76</td>
<td>2.93</td>
<td>0.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Upper abdomen</td>
<td>17.51</td>
<td>2.40</td>
<td>0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>4.43</td>
<td>4.03</td>
<td>0.02</td>
<td>0.272</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>-12.12</td>
<td>2.65</td>
<td>-0.12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Reference surgical site: extremity. Model fit: \( R = 0.558; R^2 = 0.312; \) adjusted \( R^2 = 0.307. \)

* The variable "age beyond 60 yr" equals original age minus 60 for those who were older than 60 yr. For patients younger than 60 yr, this variable would be fixed at the value of 0. † Cancer means surgical procedures for malignant diseases.

SE = Standard error of regression coefficient.

Results of Stepwise Linear Regression

The stepwise model selection in linear regression analysis is presented in table 2. The selected variables include gender, cancer, weight, age beyond 60 yr, and surgical site. On average, men used 8.88 mg more morphine than did women during their 3-day IVPCA courses. Patients with cancer also used more morphine. Body weight was positively correlated with IVPCA morphine use. An increase of 1 kg in body weight increased the total morphine requirement by 0.86 mg. Age was negatively associated with morphine requirement. For patients older than 60 yr, each year beyond 60 yr would decrease the total morphine use by 1.07 mg. For example, an 80-yr-old patient would use 21.4 mg less morphine than a 60-yr-old patients with similar conditions.

The surgical sites also had significant effects on IVPCA morphine total dose used. After adjustment for the effects of weight, age, gender, and cancer, patients receiving thoracic surgeries used the most morphine, followed by upper abdominal and then colorectal surgeries. Patients who had thoracic surgeries used 30.29 mg more morphine than those who underwent extremity surgeries. There was no significant difference in IVPCA morphine requirements for patients undergoing spine, extremity, and head and neck surgeries. Patients receiving cardiovascular and gynecologic operations used less morphine than those who received extremity surgeries. No correlation between intraoperative fentanyl dose and postoperative IVPCA narcotic use was found using univariate or multivariate analyses. The \( R \) and adjusted \( R^2 \) of the selected model are 0.558 and 0.307, respectively.

We performed a subanalysis to test the correlation between weight and IVPCA use in all types of surgery. In our dataset, we found that weight was associated with IVPCA use in every type of surgery (see table 1, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates the weight effect on IVPCA use in each type of surgery). Therefore, the correlation extended beyond extremity and spine surgery. The variable behaved as an independent predictor of IVPCA use.

Results of Quantile Regression

Table 3 shows the estimated coefficients of selected variables from quantile regression analysis at percentiles of 0.1, 0.25, 0.5, 0.75, and 0.9. Effects of body weight, age beyond 60 yr, and gender were significant in all these quantiles. The effect of weight on IVPCA morphine requirements increased gradually from 0.53 at the tenth percentile, 0.69 at the twenty-fifth percentile, 0.9 at the fiftieth percentile and culminated at 1.06 in the eightieth percentile. The effect of weight decreased at the ninetieth percentile (see fig. 1, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates weight effect on IVPCA requirement at different quantiles).

Age beyond 60 yr had a negative effect on IVPCA requirements. The magnitude of change increased steadily from \(-0.35\) at the tenth percentile, \(-0.63\) at the twenty-fifth percentile, \(-1.04\) at the fiftieth percentile, to \(-1.24\) at the seventy-fifth percentile. From the eightieth percentile on, a steep fall in the slope was noted (see fig. 1, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates age effect on IVPCA requirement at different quantiles). The effect of gender (male vs. female) fluctuated from 7.32 at the tenth percentile, 7.09 at the twenty-fifth percentile, 7.62 at the fiftieth percentile to 7.49 at the seventy-fifth percentile. There was a steep rise in the effect of gender noted from the eightieth percentile on. This effect culminated in the ninetieth percentile (13.97). Afterward, the effect of gender decreased (see fig. 1, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates gender effect on IVPCA requirement at different quantiles).

A diagnosis of cancer did not exert a significant effect in the tenth and ninetieth percentiles (table 3). However, can-
Table 3. Quantile Regression Analysis for Selected Variables at the 10, 25, 50, 75, and 90th Quantiles of Total IVPCA Requirements

<table>
<thead>
<tr>
<th>Quantile</th>
<th>Constant</th>
<th>Weight</th>
<th>Age Beyond 60 yr</th>
<th>Gender (F vs. M)</th>
<th>Cancer</th>
<th>Spine</th>
<th>Head &amp; Neck</th>
<th>Gynecologic</th>
<th>Cardiovascular</th>
<th>Genitourinary</th>
<th>Colorectal</th>
<th>Upper Abdomen</th>
<th>Thorax</th>
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</thead>
<tbody>
<tr>
<td>0.1</td>
<td>β</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>-4.75</td>
<td>0.53</td>
<td>-0.35</td>
<td>7.32</td>
<td>5.98</td>
<td>2.68</td>
<td>5.61</td>
<td>-2.30</td>
<td>-10.41</td>
<td>-3.69</td>
<td>7.19</td>
<td>2.92</td>
<td>16.72</td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>0.09</td>
<td>0.13</td>
<td>2.32</td>
<td>3.14</td>
<td>2.69</td>
<td>7.71</td>
<td>3.17</td>
<td>5.44</td>
<td>7.92</td>
<td>4.53</td>
<td>4.21</td>
<td>7.18</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.007</td>
<td>0.002</td>
<td>0.057</td>
<td>0.318</td>
<td>0.467</td>
<td>0.469</td>
<td>0.056</td>
<td>0.642</td>
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<tr>
<td>0.25</td>
<td>β</td>
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<td></td>
<td>1.37</td>
<td>0.69</td>
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<td>7.09</td>
<td>8.73</td>
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<td>-5.80</td>
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<tr>
<td></td>
<td>SE</td>
<td>0.07</td>
<td>0.10</td>
<td>1.71</td>
<td>2.05</td>
<td>1.88</td>
<td>4.51</td>
<td>2.47</td>
<td>2.71</td>
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<td>3.16</td>
<td>3.19</td>
<td>7.93</td>
</tr>
<tr>
<td></td>
<td>P</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.779</td>
<td>0.224</td>
<td>0.001</td>
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<td>β</td>
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<tr>
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<td>5.07</td>
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<td>5.59</td>
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<tr>
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<td>2.17</td>
<td>4.04</td>
<td>2.48</td>
<td>3.47</td>
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<td>3.18</td>
<td>2.98</td>
<td>6.58</td>
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<tr>
<td></td>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.759</td>
<td>0.359</td>
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<tr>
<td>0.75</td>
<td>β</td>
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Reference surgical site: extremity. The regression coefficients of various quantile functions could be used to predict total morphine requirements at distinct demand levels of intravenous patient-controlled analgesia (IVPCA). For example, a 50-yr female with body weight of 60 kg, receiving leg surgery due to a benign cause, would be expected to consume 28 mg morphine at the 10th quantile (0.53 \times 60 - 0.35 \times 0 + 7.32 \times 0 + 5.98 \times 0 - 4.75), 43 mg at 25th quantile, 59 mg at 50th quantile, 76 mg at 75th quantile and 92 mg at 90th quantile. In contrast, only one predictive value of 61 mg could be obtained from prediction of linear regression under the same condition.

SE = bootstrapping standard error of regression coefficient in quatile regression analysis.

cer exerted a significant effect on IVPCA requirements from the twentieth to the eighty-fifth percentile. The values were 8.73 at the twenty-fifth percentile, 8.37 at the fiftieth percentile, and 6.58 at the seventy-fifth percentile (see fig. 1, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates cancer effect on IVPCA requirement at different quartiles). The effects of distinct surgical sites were not significant at the tenth percentile, except thoracic surgeries (P = 0.02). When age, gender, weight, and procedures involving cancer (yes or no) were controlled, patients who had thoracic surgeries still used 16.72 mg more morphine than those who underwent extremity surgeries at the tenth percentile of IVPCA requirements (table 3).

The differences in IVPCA morphine use between thoracic and extremity surgeries increased from 17.57 at the twenty-fifth percentile, 25.92 at the fiftieth percentile, 31.93 at the seventy-fifth percentile to 34.12 at the ninetieth percentile (see fig. 2, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates the difference in morphine use between thoracic and extremity surgeries). Patients undergoing genitourinary surgery used more IVPCA morphine than the reference group from the fiftieth percentile to the eighty-fifth percentile (see fig. 2, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates the difference in morphine use between genitourinary and extremity surgeries). The difference in IVPCA requirements between patients having colorectal surgeries and the reference group was significant from the quantile of 0.15 (see fig. 2, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates the difference in morphine use between colorectal and extremity surgeries). The discrepancy increased gradually until the seventieth percentile. For patients receiving upper abdominal surgery, significant difference in IVPCA demand was found from the twentieth percentile, and the gap increased until the fiftieth percentile (22.91 mg). Afterward, it remained steady up to the eighty-fifth percentile, and then the curve went upward finally (see fig. 2, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates the difference in morphine use between upper abdominal and extremity surgeries).

There was no significant difference in IVPCA requirements between patients having extremity surgeries and those who underwent head and neck surgeries throughout the selected quantiles (table 3). For patients receiving spine surgeries, the difference in IVPCA requirements was not significant until the seventy-fifth percentile (see fig. 3, Supplemental Digital Content 1, http://links.lww.com/ALN/A563, which illustrates the difference in morphine use between spine and extremity surgeries). Patients who had cardiovascular surgery used less morphine.
than the reference group at the quantiles of 0.25, 0.5, and 0.9
(−8.65, −8.49, and −11.34, respectively; table 3). Patients
undergoing gynecologic surgeries used significantly less mor-
phine from the twentieth percentile, and the difference in-
creased in the higher percentiles (see fig. 3, Supplemental Digital
Content 1, http://links.lww.com/ALN/A563, which illustrates
the difference in morphine use between gynecologic and ex-
tremity surgeries).

Table 3 also provides the information about model fit
at the selected quantiles. The fit statistics pseudo $R^2$
in-
creased gradually from 0.09 at the tenth percentile, 0.14 at
the twenty-fifth percentile, 0.2 at the fiftieth percentile,
0.23 at the seventy-fifth percentile to 0.23 at the ninetieth
percentile. The model fit statistics at distinct quantiles are
illustrated (see fig. 4, Supplemental Digital Content 1,
http://links.lww.com/ALN/A563, which illustrates
the model fit statistics at distinct quantiles). Adding the vari-
ables of surgical site obviously improved the model fitting,
especially for higher quantiles. Model comparison could
be performed through evaluation of pseudo $R^2$ at specific
or whole quantiles.

**Discussion**

This is the first study to analyze how patient and surgical
variables affect total IVPCA analgesic use using quantile re-
gression. We showed that gender, body weight, age, and
operation sites and a diagnosis of cancer affect IVPCA use.
Quantile regression disclosed a more complex relationship
between morphine use and patient variables compared with
linear regression analysis. The magnitude and direction that
the study variables exerted varied in different narcotic quan-
tiles. We were unable to uncover a similar amount of detail
using a linear regression analysis.

**Heterogeneity**

Linear regression analysis only asks if there is a relationship
between several dependent and independent variables. We
used linear regression to identify correlations between pa-
tient variables and narcotic use. The analysis identified all
variables as having a greater or lesser effect on IVPCA narc-
ocic use. This type of analysis does not consider that vari-
able such as age could have different effects at various doses
of narcotics. We used quantile regression in our analysis to
identify dose-dependent effects that the patient demographic
variables may exert. In this statistical technique, we divided
the complete range of IVPCA narcotic used into equal sized
packages. These quantiles of narcotic data are numbered as
percentiles from the lowest doses and ascend in numerical
order to the highest doses. This technique allowed us to view
what effect each demographic variable had in individual
quantile.

The effects of selected variables on total IVPCA require-
ments continuously changed in magnitude and direction in
distinct quantiles. This finding was not displayed in our lin-
ear regression analyses. For example, linear regression analy-
sis showed that every 1 kg of body weight increased total
morphine requirements by 0.86 mg. In contrast, quantile
regression analysis shows that the relationship between body
weight and narcotic use is not that simple. Rather, there was
a gradual increase in narcotic use from lower to higher quan-
tiles. However, at the highest quantiles (highest doses of nar-
cotic used), there was an abrupt decrease in the effect of
weight.

In general, we found that patients who used more mor-
phine (above the seventieth to eightieth percentiles) had dif-
ferent characteristics than patients whose narcotic use placed
them in lower percentiles. In these higher quantiles, the ef-
ects of gender and age increased but the effect of body
weight decreased. We were surprised that the variable of
cancer was eliminated when morphine use exceeded the last
twenty-fifth percentile as our previous study presented a
nonspecific positive correlation between surgery for cancer
and narcotic use.9 These observations are novel and may help
explain the complex pattern of narcotic use in postoperative
surgical populations.

**Gender, Body Weight, and Age**

Similar to most investigators, we identified a male gender
bias in postoperative morphine use.6,8–10,20–22 However,
there is still disagreement in the literature about this find-
ing,5,23,24 Although most of the 18 studies found that men
used more analgesics, only 8 studies showed no gender bias.
Male gender showed a dominant effect over female in all
quantiles, but it did not exert the same degree of influence on
IVPCA use in all percentiles. This finding suggests that there
are a number of factors expressed in male gender. The iden-
tification of these contributing factors requires further analy-
sis. However, the finding suggests that analysis of pharma-
ologic data using male gender as a single characteristic may be
inadequate.

Body weight had the greatest effect on IVPCA use when
compared with all other factors in our study. Weight had the
largest effect in the first step linear regression, and this find-
ing is similar to other studies.7–9,25 A simple correlation,
however, was not evident in all studies.6,20

We found that age negatively correlated with IVPCA use.
Although age effect was not concordant in different studies,
most other investigations have reported similar findings.5–8
Although Macintyre et al.9 identified age as the most signif-
icant determinant of postoperative IVPCA morphine use,
Tsui et al.10 found that age was influential only in the first to
sixteenth hour of patient-controlled analgesia course. This
may be due to age-related differences in pharmacokinetics
and drug sensitivity.9 Our findings from quantile regression
analysis support those by Tsui et al.,10 which show that the
relationship between age and narcotic use is not simple.
We found that age was significant in distinct quantiles and other
factors (e.g., cancer or gender) interacted with age to create
patterns of narcotic use that were distinct in the lowest and
highest percentiles.

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The site or type of surgery is a significant factor that determines IVPCA use in our study. This finding was similar to other studies.\(^7\) We classified all patients into nine groups based on their surgical sites and found that patients who had thoracic and abdominal surgeries used more morphine. Cheung et al.\(^26\) reported similar findings. Our studies showed that cancer influenced total IVPCA use. The total IVPCA dose of morphine was greater in patients with cancer than in those with benign diseases. However, quantile regression analysis showed that this correlation fails in patients whose demand level was below the fifteenth percentile or exceeded the eighty-fifth percentile. Other investigators concurred with this finding.\(^7,27\) Thus, a diagnosis of cancer was not significant in the largest and the smallest doses of narcotic.

Limitation
We could not construct a simple protocol to predict postoperative morphine demands using our findings. However, we demonstrated that patient variables influence IVPCA use in a dose-dependent fashion and an interaction between variables that could not be isolated by linear regression analysis. Stepwise linear regression accounted only for 31% of variation in IVPCA requirements. By using quantile regression analysis, we uncovered additional detail about how patient variables exert different effects at various drug dosages. This was evident in the highest and lowest doses of narcotic used. Further investigation is needed to unravel the role that each factor plays on IVPCA narcotic use in various percentiles of the distribution curve. Our study was also not designed to explain why the variables behave differently in the outlying percentiles. We suggest that unique combinations of attributes that occur in different percentiles may be partially responsible, or there could be other factors that we have not identified in this study.

The relationship between weight and IVPCA use did not consider the important variables of preoperative pain score and narcotic use. These two are likely to be influential in orthopedic and spine surgery where the variable of body weight had a strong correlation with IVPCA narcotic use. Therefore, we performed a sub-analysis that strongly suggested that body weight was an independent predictor of IVPCA narcotic use. We understand that the analysis does not provide the same strength of evidence that a direct analysis of the variables of pain score and narcotic use would. However, we suggest that this analysis does improve the validity of our original observation. We believe that this issue deserves an independent study to identify how these two factors modify IVPCA use in linear and quantile regression. There was little information in the literature about the effects of preoperative pain and narcotic use on postoperative narcotic use. This is probably because each covariate (preoperative pain or narcotic use) needs to be quantified over time in a longitudinal dataset. Thus, investigators would have to develop models that incorporate a weighted measure of pain scores and narcotic use over time. The models would have to be tested against a number of study populations. Even though the complexity of this issue does not minimize its importance, it probably explains why investigators have not addressed this issue in previous studies.

Clinical Implication
We have shown that linear regression does not accurately predict IVPCA morphine use, especially in the lower or upper tail of distribution. Therefore, clinical protocols for IVPCA narcotic use derived from linear regression can be inaccurate. This is especially true for patients who use the least and the most amount of IVPCA narcotic. Our findings suggest, however, that factors identified by linear regression analysis do have predictive value in patients who use doses of narcotics in the middle of the distribution curve.

Quantile regression was able to explain some of the inconsistent findings reported in previous studies about how specific patient variables affect narcotic use. We confirm the findings of other investigators who found complex correlations between IVPCA use and patient variables. Our data add a new concept to the predictive value of patient demographics. This is the actual dose of drug used by a patient. This finding shows that physicians cannot use single-patient demographics to predict or explain IVPCA use in patients at the lower and higher ends of the distribution curve. In view of our findings, we suggest that clinical studies on IVPCA demand use should be reported based on the quantiles of response.

Conclusion
Our study shows that gender, diagnosis of cancer, body weight, age beyond 60 yr, and site of surgery are significant predictors of total IVPCA consumptions. When all factors are considered, body weight is the strongest, and cancer the weakest determinant. By using quantile regression, we demonstrated the dynamic influences of all predictors. These results offer practical information for clinicians to manage postoperative pain and improve the quality of pain control.

References
6. Burns JW, Hodsman NB, McIntott TT, Gillies GW, Kenny