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# Mutual relationship between anxiety and pain in the intensive care unit and its effect on medications☆

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ABSTRACT

*Purpose:* Little is known about the relationship between anxiety and pain in intensive care unit (ICU) patients despite its importance. The aims of the present study are to examine the correlation between pain and anxiety during ICU care and to investigate its effects on the dose of opioids and anxiolytics administered.
*Methods:* The study subjects were awake critically ill patients admitted to an ICU over a 2-month period. Trained psychiatrists evaluated the nondelirious, noncomatose patients daily for anxiety and pain using the Numeric Rating Scale for Pain (NRS-Pain), Faces Anxiety Scale (FAS), and Hamilton Anxiety Rating Scale.
*Results:* Daily alterations of anxiety and pain were significantly correlated with one another among 123 patients. Both the FAS and the Hamilton Anxiety Rating Scale were positively correlated with the NRS-Pain ($P < .001$ for both). The NRS-Pain score ($P = .016$) and the FAS score ($P = .007$) both significantly correlated with the dose of anxiolytics. The dose of opioids was unaffected by the severity of pain or anxiety.
*Conclusions:* Pain and anxiety among critically ill patients in the ICU were closely correlated. Pain and anxiety influenced the dose of anxiolytics administered. Therefore, a precise evaluation and comprehensive approach to the management of pain and anxiety are important for treating ICU patients.


## 1. Introduction

Pain and anxiety, as well as delirium, are very important factors in the management of provisions for physical and psychological comfort of patients admitted to the intensive care unit (ICU) [1]. Recently, various aspects of critical care, such as the physical and emotional distress of ICU patients, have become targets of critical care research [2–4]. According to previous studies, distress from pain and anxiety in the ICU is closely linked to delayed physical recovery as well as the patient's psychological quality of life [5,6].

Patients in the ICU are at risk for great pain, primarily because of progressive disease and need for invasive therapies [7]. If acute pain control during ICU care fails, chronic pain can persist, and patients can experience reduced quality of life after leaving the ICU [8]. Furthermore, pain is a major risk factor for postoperative delirium in elderly patients, which is related to mortality [9]. Anxiety or agitation is also commonly experienced and observed in ICU patients [10]. Their anxiety can also be triggered by mechanical ventilation or withdrawal status, potentially delaying wound healing [11]. Furthermore, patients in the ICU who require high, prolonged doses of sedatives and analgesics to reduce anxiety usually experience adverse effects, such as bradycardia, hypotension, gut dysmotility, immobility, weakness, and delirium [12,13].

The new version of clinical practice guidelines for pain, agitation, and delirium (PAD guidelines) emphasizes that pain, agitation, and delirium are not isolated problems [1,14]. Studies of the relationships between pain, agitation, and delirium are needed to verify the hypotheses underlying the new guidelines. Although studies evaluating the consequences and influences of intra-ICU experiences on post-ICU psychiatric symptoms are relatively abundant [15–17], few studies have assessed the emotional and physical distress during the period when patients are actually in the ICU [18]. In fact, it is very difficult to assess those causes of distress that frequently change; evaluating the causes of distress for patients while they are at risk for dying may seem inappropriate because the main concern in the ICU is maintenance of life. Moreover, no study has targeted the correlation between pain and anxiety in the ICU. Several studies have investigated the relationship between pain and anxiety among patients who were not in the ICU but showed mixed results [19–21]. If pain and anxiety are related in ICU patients, a precise and comprehensive approach to their treatment would be beneficial.

In this study, our 2 hypotheses can be summarized as follows: (1) intra-ICU anxiety and pain are closely correlated with each other

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among patients in the ICU, and (2) both anxiety and pain influence the administered doses of opioids and anxiolytics. We expect that intra-ICU anxiety and pain will be correlated in nondelirious, noncomatose, critically ill patients, and that pain and anxiety should be taken into account when determining the dosages of anxiolytics and opioids.

## 2. Materials and methods

### 2.1. Study design and patient selection

This observational study was conducted from March to April 2013 at Gangnam Severance Hospital (South Korea) and included critically ill patients admitted to the ICU. Gangnam Severance Hospital follows the Joint Commission International Standards for hospitals [22] for the admission and management of patients in the ICU. There were 23 beds in the ICU for critically ill patients, including 6 separate care rooms. This study was a part of the ICU Distress and Delirium Management (IDDM) project at Gangnam Severance Hospital. The project was initiated in 2012 to closely evaluate and manage the distress (ie, pain and anxiety) and delirium of ICU patients. As part of the project, using the Confusion Assessment Method for ICU [23], nurses identified whether patients were in a delirious state during every rotation. The nurses also categorized the patients as comatose or noncomatose using the Richmond Agitation-Sedation Scale (RASS) [24]. Each day, around 10 AM, psychiatrists assess the patients and divide them into 3 groups: comatose (RASS score −4 or −5), delirious (Confusion Assessment Method for ICU positive), and nondelirious, noncomatose. In this daily visit, nondelirious and noncomatose patients were evaluated for pain and anxiety using various scales.

All patients admitted to the ICU were initially considered for inclusion in the study. However, some patients could not be interviewed during the daily rotation of psychiatrists around 10 AM, either due to a short ICU stay (<24 hours) or a young age (<6 years). After these patients were excluded, 206 patients were found to have an ICU stay longer than 24 hours and who were older than 6 years. Among these 206 patients, those who were continuously delirious, comatose, or otherwise unable to verbally communicate during their ICU stay were excluded. The final study population consisted of 123 patients (59.7% of the total 206 patients) who were nondelirious and noncomatose at least one time around 10 AM during their time in the ICU (Fig. 1). The psychiatrists conducted routine rounds in the ICU, evaluating and treating patients between 9 AM and noon. If necessary, the psychiatrists also treated patients at other times. However, it should be noted that this study was an observational study, so that daily prescriptions of opioids and anxiolytics were primarily performed by surgeons or anesthesiologists as part of routine patient management under the PAD guidelines. No informed consent was required because all measurements were part of daily routine management, and we obtained ethical approval for conducting our study from the institutional review board at Gangnam Severance Hospital, Yonsei University.

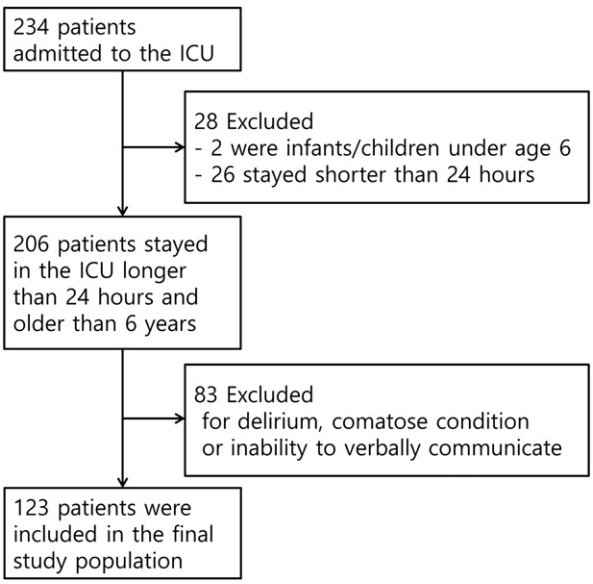


**Fig. 1.** Flowchart of study inclusion criteria.

### 2.2. Assessment of pain and anxiety

The Numeric Rating Scale for Pain (NRS-Pain) was used to evaluate the subjective severity of pain. It is a commonly used, self-reporting pain tool, and scores ranged from 0 to 10 [25,26]. A score of 0 represents no pain and a score of 10 represents the highest pain. Patients were asked to select the severity of their pain on the scale. A score of 4 is commonly the cutoff value for further intervention. The NRS-Pain has shown acceptable responsiveness, validity, and feasibility in detecting and assessing pain among critically ill patients in the ICU [27–29]. The Faces Anxiety Scale (FAS) is a self-reporting scale to evaluate anxiety. This self-reported measure of anxiety is easy to administer and imposes a minimal response burden. The FAS is a single item, 5-point scale, consisting of 5 faces representing increasing levels of anxiety, starting with the first face, which represents "no anxiety." The fifth face represents "extreme anxiety." Patients were asked to check their level of anxiety on this scale. This scale appears easier to administer than other brief anxiety measures [18]. Clinicians also assessed anxiety using the Hamilton Anxiety Rating Scale (HAMA), the most widely used and reliable semistructured assessment scale for treatment-outcome studies of anxiety. This is a 14-item scale, and each item score ranges from 0 to 4. Thus, the total HAMA score varies from 0 to 56. A score of 0 represents no symptoms, whereas a score of 4 means severe symptoms. During the assessment, the rater interviews the patients and can measure both the somatic anxiety and psychic anxiety [30,31].

### 2.3. Data collection and statistical analysis

Data from electronic medical records were collected for each patient, including records of any sedatives and analgesics, such as opioid receptor agonists (morphine, tramadol, remifentanyl, fentanyl, meperidine, and codeine) and benzodiazepines (lorazepam and midazolam), administered during the study period. The equivalent doses of opioids and benzodiazepines were calculated and summed for each patient [32–34], and the total doses were divided by the patients' weights. The equivalent doses were calculated as follows: opioids (1 mg morphine intravenous [IV]/intramuscular [IM] = 25 mg oral tramadol = 5 μg remifentanyl IV = 10 μg fentanyl IV/transdermal = 7.5 mg meperidine IV/IM = 20 mg oral codeine), Benzodiazepine (1 mg lorazepam IV/IM/per os = 2 mg midazolam IV). Data were also obtained on sex; age; length of the ICU stay; mechanical ventilation or restraint status; urgency of admission (elective/emergency); Acute Physiology, Age and Chronic Health Evaluation II (APACHE II) score [35]; mortality at the end of the ICU stay; and surgery prior to ICU admission. Even if this study only focused on opioids and benzodiazepines, information about other important medications was also obtained. All data in this study were routinely recorded electronically during the daily assessment. For analyses, the data were manually coded by 3 psychiatrists, and 10% of the data were manually confirmed by 2 other psychiatrists to reduce the possibility of errors. However, no significant errors were found. Thus, the reliability of the data was confirmed twice.

We analyzed the relationships between the daily alterations in the NRS-Pain and FAS scores, and the NRS-Pain and HAMA scores using a linear-mixed model. In addition, we investigated the influences of pain and anxiety on daily alterations in medication dose during the ICU period using a linear-mixed model. We decided to use linear-mixed model because it can handle many missing data or time-