Effect of sedatives on in-hospital and long-term mortality of critically ill patients requiring extended mechanical ventilation for more than 48 hours

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Abstract

Background

The purpose of this study was to assess the correlation between sedatives and mortality in critically ill patients who required mechanical ventilation (MV) for ≥48 hours from 2007 to 2016.

Methods

We conducted a nationwide retrospective cohort study using population-based healthcare reimbursement claims database. Data from adult patients (aged ≥18) who underwent MV for ≥48 hours between 2008 and 2016 were identified and extracted from the National Health Insurance Service database. The benzodiazepine group consisted of patients who were administered benzodiazepines for sedation during MV. All other patients were assigned to the non-benzodiazepine group.

Results

A total of 158,712 patients requiring MV for ≥48 hours were admitted in 55 centers in Korea from 2007 to 2016. The benzodiazepine group had significantly higher in-hospital and one-year mortality compared to the non-benzodiazepine group (37.0% vs. 34.3%, 55.0% vs. 54.4%, respectively). Benzodiazepine use decreased from 2008 to 2016, after adjusting for age, sex, and mean Elixhauser comorbidity index in the Poisson regression analysis (incidence rate ratio, 0.968; 95% CI 0.954–0.983; p < 0.001) whereas dexmedetomidine sales have continuously increased since the second half of 2010. Benzodiazepine use, older age, lower case volume (≤500 cases/year), chronic kidney disease, and higher Elixhauser comorbidity index were common significant risk factors for in-hospital and one-year mortality.

Conclusion
In critically ill patients undergoing MV for >48 hours, the use of benzodiazepines for sedation was associated with an increased risk of in-hospital mortality and one-year mortality.

**Background**

Sedation is a key practice in intensive care units (ICUs) for minimizing patient discomfort and anxiety, facilitating mechanical ventilation (MV) and enabling essential ICU procedures [1, 2]. In the past, benzodiazepines have been recommended for sedation in patients receiving MV [1]. However, recent evidence suggesting that delirium may be associated with the use of benzodiazepines [3], especially when administered as continuous infusion for deep sedation [4, 5], have led to significant changes in practice guidelines which now suggest the use of non-benzodiazepine agents for sedation [6, 7]. Recent controlled studies have suggested that light sedation using dexmedetomidine-based or propofol-based sedation in ICU patients reduces the ICU length of stay (LOS) and the duration of MV, compared to deeper sedation with benzodiazepines [8]. The transition toward light sedation has been strongly recommended since the 2013 Pain, Agitation, and Delirium guidelines [6]. However, there has been no large scale investigation of the correlation between in-hospital mortality and the type of sedative used in patients who require MV for 48 hours or more.

Our study objective was to assess the correlation between sedatives and mortality in critically ill patients who required MV for 48 hours or more. We hypothesized that non-benzodiazepine-based sedation for patients requiring MV may be associated with lower in-hospital mortality.
Methods

This study was a retrospective cohort study and the study protocol was approved by the institutional review board of Seoul National University Hospital (1801-023-912). The need for informed consent was waived by the institutional review board due to the retrospective design of the study.

Data source and study population

The National Health Insurance Service (NHIS) database contains all claims data for the population covered under the National Health Insurance (NHI) program and the Medical Aid program in Korea. The NHIS provides its database to researchers after de-identifying personal information to help generate real-world evidence [9]. Data from adult patients (aged ≥ 18) who underwent MV for ≥ 48 hours between 2008 and 2016 were identified and extracted from the NHIS database by searching for the NHI codes AJ100, AJ110, AJ120, AJ130, AJ140, or AJ150 during the patients’ hospitalizations. Data on underlying comorbidities such as hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, and cerebrovascular disease were extracted from the database using International Classification of Diseases 10th revision (ICD-10) codes. The Elixhauser comorbidity index, derived from 30 disease entities using ICD-10 codes [10] and shown to correlate with hospital mortality [11], was used as a covariable to adjust for disease severity. The Elixhauser comorbidity system has been shown to be slightly superior to the previously used Charlson comorbidity system at adjusting for comorbidity [12]. Data on in-hospital mortality, ICU LOS, and hospital LOS were also extracted. Because death certificates are automatically reported to the NHI, the patients’ one-year mortality was detected when NHI healthcare coverage was terminated due to...
Definition of groups and case volume

The benzodiazepine group consisted of patients who were administered benzodiazepines for sedation during MV. All other patients were assigned to the non-benzodiazepine group.

The case volumes were categorized as follows: low (< 300 cases/year), medium (300–500 cases/year), and high (> 500 cases/year).

Statistical analysis

We compared the patient characteristics according to the sedative employed; continuous variables were compared using the Mann–Whitney U test, and the categorical variables were compared using the chi-squared test. In-hospital and one-year mortality were assessed using a logistic regression model after adjusting for age, sex, comorbidities, and the mean Elixhauser comorbidity index. We assessed the goodness-of-fit for logistic regression using the Hosmer–Lemeshow test and used a Poisson regression analysis to examine trends across the study period and sedatives after adjusting for age, sex, and mean Elixhauser comorbidity index.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The results were considered statistically significant when the p-value was < 0.05.

RESULTS

Between January 2008 and December 2016, 55 centers in Korea admitted 158,712 patients requiring MV for ≥ 48 hours. Some 39.7% (63,043) of these patients were administered benzodiazepines during their ICU stays, the most commonly employed of which was midazolam (97.6%).
The overall in-hospital mortality rate was 35.4% (56,133/158,712). The benzodiazepine group had significantly higher in-hospital and one-year mortality than the non-benzodiazepine group (37.0% vs. 34.3%, 55.0% vs. 54.4%, respectively, Table 1). The overall median ICU and hospital LOS were 12 days and 26 days, respectively. The median ICU and hospital LOS were longer for the benzodiazepine group than for the non-benzodiazepine group (13 vs. 12 days, 27 vs. 26 days, respectively; Table 1).

Table 1

| Variables                        | Total          | Non-benzodiazepine group | Benzodiazepine group | p value |
|----------------------------------|----------------|--------------------------|----------------------|---------|
| Number of patients               | 158,712        | 95,669                   | 63,043               |         |
| Age (years)                      |                |                          |                      |         |
| median [IQR]                     | 68 [55–76]     | 68 [56–76]               | 67 [55–75]           | < 0.0001|
| 18–49                            | 25,506 (16.1)  | 14,622 (15.3)            | 10,884 (17.3)        | < 0.0001|
| 50–59                            | 25,887 (16.3)  | 15,632 (16.3)            | 10,255 (16.3)        |         |
| 60–69                            | 36,112 (22.8)  | 21,503 (22.5)            | 14,609 (23.2)        |         |
| 70 and older                     | 71,207 (44.9)  | 43,912 (45.9)            | 27,295 (43.3)        |         |
| Sex                              |                |                          |                      |         |
| Male                             | 98,599 (62.1)  | 56,215 (58.8)            | 42,384 (67.2)        | < 0.0001|
| Female                           | 60,113 (37.9)  | 39,454 (41.2)            | 20,659 (32.8)        |         |
| Comorbidities                    |                |                          |                      |         |
| Hypertension                     | 45,729 (28.8)  | 27,779 (29.0)            | 17,950 (28.5)        | 0.0152  |
| Diabetes                         | 17,943 (11.3)  | 10,515 (11.0)            | 7,428 (11.8)         | < 0.0001|
| Coronary artery disease          | 31,075 (19.6)  | 17,435 (18.2)            | 13,640 (21.6)        | < 0.0001|
| Chronic kidney disease           | 16,074 (10.1)  | 9,887 (10.3)             | 6,187 (9.8)          | 0.0008  |
| Cerebrovascular disease          | 28,029 (17.7)  | 19,439 (20.3)            | 8,590 (13.6)         | < 0.0001|
| Elixhauser comorbidity index     | 13.5 (10.3)    | 13.6 (10.5)              | 13.5 (10.0)          | 0.1989  |
| ICU LOS (median[IQR], day)       | 12 [7–22]      | 12 [6–22]                | 13 [7–24]            | < 0.0001|
| Hospital LOS (median[IQR], day)  | 26 [14–50]     | 26 [13–50]               | 27 [15–49]           | < 0.0001|
| In-hospital mortality            | 56,133/158,712 | 32,789/95,669            | 23,344/63,043        | < 0.0001|
| 1-year mortality                 | 86,721/147,534 | 52,068/95,669            | 34,653/63,043        | 0.2598  |

Numbers reported as n (%), median (interquartile range) or mean (standard deviation). Abbreviations: ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SD, standard deviation.

Benzodiazepine use decreased from 2008 to 2016, after adjusting for age, sex, and mean Elixhauser comorbidity index in the Poisson regression analysis (incidence rate ratio, 0.968; 95% CI 0.954–0.983; p < 0.001; Table 2). Since the second half of
2010, dexmedetomidine sales have continuously increased, whereas the use of benzodiazepines has steadily decreased, and the correlation was significant (correlation coefficient, $-0.861; p < 0.001$; Fig. 1).

| Variables                  | Non-benzodiazepine group | Benzodiazepine group |
|----------------------------|--------------------------|----------------------|
| Age (years)                | 0.563 (0.436–0.725)      | 0.973 (0.932–1.016)  |
| Sex                        |                          |                      |
| Male                       | Reference                | Reference            |
| Female                     | 1.287 (0.885–1.872)      | 0.810 (0.748–0.877)  |
| Calendar year              | 1.063 (0.994–1.136)      | 0.968 (0.954–0.983)  |
| Elixhauser comorbidity index| 1.330 (1.068–1.656)      | 0.989 (0.946–1.034)  |

Poisson regression after adjusting for age, sex, and mean of Elixhauser comorbidity index.

Use of sedatives per 100 patients

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.

In the multivariable logistic regression analysis, the benzodiazepine group was associated with higher in-hospital and one-year mortality compared to the non-benzodiazepine group. Older age, lower case volume ($\leq 500$ cases/year), chronic kidney disease, and higher Elixhauser comorbidity index were common significant risk factors for in-hospital and one-year mortality (Tables 3 and 4).
### Table 3
Univariable and multivariable logistic regression analyses for in-hospital mortality

| Variables                      | In-hospital mortality | Unadjusted | Adjusted |               |               |
|-------------------------------|-----------------------|------------|----------|---------------|---------------|
|                               | OR (95% CI)           | p value    | OR (95% CI) | p value       |               |
| Total                         | 56,133/158,712 (35.4)|            |           |               |               |
| Non-benzodiazepine            | Reference             | Reference  |           |               |               |
| Benzodiazepine                | 23,344/63,043 (37.0) | 1.128 (1.104-1.152) | < 0.001 | 1.148 (1.123-1.173) | < 0.001 |
| Age (years)                   |                       |            |          |               |               |
| 18–49                         | 7,919 (31.1)          | Reference  | Reference |               |               |
| 50–59                         | 8,921 (34.5)          | 1.168 (1.125-1.212) | < 0.001 | 1.232 (1.186-1.279) | < 0.001 |
| 60–69                         | 12,957 (35.9)         | 1.243 (1.201-1.286) | < 0.001 | 1.374 (1.326-1.423) | < 0.001 |
| 70 and older                  | 26,336 (37.0)         | 1.303 (1.264-1.344) | < 0.001 | 1.522 (1.474-1.571) | < 0.001 |
| Sex                           |                       |            |          |               |               |
| Male                          | 35,289 (35.8)         | Reference  | Reference |               |               |
| Female                        | 20,844 (34.7)         | 0.952 (0.932-0.973) | < 0.001 | 1.001 (0.979-1.023) | 0.350 |
| Case volume                   |                       |            |          |               |               |
| > 500 /year                   | 19,871 (32.6)         | Reference  | Reference |               |               |
| 300–500 /year                 | 21,110 (35.8)         | 1.154 (1.127-1.182) | < 0.001 | 1.138 (1.110-1.166) | < 0.001 |
| < 300 /year                   | 15,152 (39.2)         | 1.333 (1.298-1.369) | < 0.001 | 1.336 (1.300-1.373) | < 0.001 |
| Comorbidities                 |                       |            |          |               |               |
| Hypertension                  | 9,836 (21.5)          | 0.395 (0.385-0.405) | < 0.001 | 0.364 (0.354-0.374) | < 0.001 |
| Diabetes                      | 4,602 (25.7)          | 0.598 (0.577-0.619) | < 0.001 | 0.758 (0.731-0.787) | < 0.001 |
| Coronary artery disease       | 10,585 (34.1)         | 0.931 (0.907-0.956) | < 0.001 | 0.923 (0.898-0.950) | < 0.001 |
| Chronic kidney disease        | 6,786 (42.2)          | 1.381 (1.336-1.428) | < 0.001 | 1.546 (1.492-1.602) | < 0.001 |
| Cerebrovascular disease       | 9,153 (32.7)          | 0.864 (0.841-0.888) | < 0.001 | 0.904 (0.879-0.931) | < 0.001 |
| Elixhauser comorbidity index  |                       | 1.016 (1.015-1.017) | < 0.001 | 1.018 (1.017-1.019) | < 0.001 |

Numbers reported as n (%) and odds ratio (95% confidence interval)
Abbreviations: CI, confidence interval; OR, odds ratio.
Table 4
Univariable and multivariable logistic analyses for 1-year mortality

| Variables                  | 1-year mortality | Univariable | Adjusted | Adjusted |
|----------------------------|------------------|-------------|----------|----------|
|                            |                  | OR (95% CI) | p value  | OR (95% CI) | p value  |
| Non-benzodiazepine         | 52,068/88,403 (58.9) | Reference   | Reference | Reference   | Reference |
| Benzodiazepine             | 34,653/59,131 (58.6) | 0.988 (0.967–1.009) | 0.260   | 1.017 (0.994–1.040) | 0.143   |
| Age (years)                |                  |             |          |           |
| 18–49                      | 10,359 (43.2)    | 1.382 (1.334–1.433) | < 0.001 | 1.428 (1.376–1.482) | < 0.001 |
| 50–59                      | 12,411 (51.3)    | 1.767 (1.709–1.827) | < 0.001 | 1.933 (1.867–2.002) | < 0.001 |
| 60–69                      | 19,274 (57.4)    | 2.782 (2.699–2.868) | < 0.001 | 3.367 (3.260–3.477) | < 0.001 |
| 70 and older               | 44,677 (67.9)    |             |          |           |
| Sex                        |                  |             |          |           |
| Male                       | 54,836 (59.8)    | 0.895 (0.876–0.914) | < 0.001 | 0.878 (0.859–0.898) | < 0.001 |
| Female                     | 31,885 (57.1)    |             |          |           |
| Case volume                |                  |             |          |           |
| > 500 /year                | 31,755 (55.7)    | 1.194 (1.166–1.222) | < 0.001 | 1.116 (1.088–1.144) | < 0.001 |
| 300–500 /year              | 32,742 (60.0)    |             |          |           |
| < 300 /year                | 22,224 (61.9)    | 1.294 (1.259–1.329) | < 0.001 | 1.241 (1.206–1.276) | < 0.001 |
| Comorbidities              |                  |             |          |           |
| Hypertension               | 20,287 (47.1)    | 0.510 (0.499–0.522) | < 0.001 | 0.395 (0.385–0.405) | < 0.001 |
| Diabetes                   | 8,711 (50.5)     | 0.684 (0.662–0.706) | < 0.001 | 0.783 (0.756–0.810) | < 0.001 |
| Coronary artery disease    | 17,059 (58.6)    | 0.990 (0.964–1.016) | 0.428   | 0.840 (0.817–0.865) | < 0.001 |
| Chronic kidney disease     | 10,244 (69.8)    | 1.699 (1.638–1.763) | < 0.001 | 1.733 (1.665–1.804) | < 0.001 |
| Cerebrovascular disease    | 16,104 (61.8)    | 1.167 (1.136–1.200) | < 0.001 | 1.093 (1.061–1.125) | < 0.001 |
| Elixhauser comorbidity index| 1.027 (1.025–1.028) | < 0.001 | 1.029 (1.028–1.030) | < 0.001 |

Numbers reported as n (%) and odds ratio (95% confidence interval)
Abbreviations: CI, confidence interval

DISCUSSION
In this nationwide study, mechanically ventilated ICU patients who did not receive benzodiazepines had a lower risk of in-hospital mortality and an increased likelihood of earlier ICU discharge compared to patients who were sedated with benzodiazepines.

Critically ill patients have been heavily sedated and immobilized which often resulted in post-intensive care syndrome, leading to severe cognitive dysfunction and neuromuscular disability lasting months to years. [13]. Daily sedation
interruption [14] and the Awakening and Breathing Coordination, Delirium monitoring/management and Early exercise/mobility (ABCDE) bundle [15, 16] reduced the duration of MV, ICU LOS and hospital mortality by reducing pain, oversedation, and delirium. The updated 2018 guidelines recommend using non-benzodiazepine sedatives (either propofol or dexmedetomidine) instead of benzodiazepines for critically ill adults undergoing MV, given the improved short-term outcomes for ICU LOS, MV duration, and delirium [6, 7]. Critically ill patients are susceptible to adverse drug events due to organ dysfunction, unstable hemodynamics, unpredictable absorption, protein binding, and altered pharmacokinetics and pharmacodynamics secondary to drug interactions [17]. When aimed at the same sedation target, benzodiazepines more frequently reach above-target sedative depths than dexmedetomidine [18]. Data from current controlled studies suggest that sedation with dexmedetomidine or propofol instead of benzodiazepines can reduce the ICU LOS and MV duration for critically ill adults [8]. These findings can be explained by a rapid onset of activity, rapid recovery after discontinuation, and easy titration of dexmedetomidine or propofol, whereas benzodiazepines are more likely to accumulate, especially when administered concomitantly with other drugs and administrated as a continuous infusion [19, 20]. Midazolam, the most commonly used benzodiazepine in our data, is not recommended for long-term (≥ 48 hours) sedation [1] because prolonged infusion results in prolonged time-to-awakening due to an accumulation of its active metabolite [21]. However, there are few studies comparing sedatives in terms of clinical outcomes such as mortality in an ICU setting.

The lower in-hospital mortality rate associated with not using benzodiazepines is somewhat contradictory to previous studies, but the similar 1-year mortality rate is
in accord with the existing literature. A recent network meta-analysis that included 52 randomized controlled trials (RCTs) comparing sedatives in MV patients associated dexmedetomidine with a shorter MV duration than benzodiazepines and propofol, and shorter hospital LOS than propofol. The meta-analysis also showed that midazolam was associated with a significantly higher risk of delirium than dexmedetomidine [22]. However, the mortality rate was not significantly different between dexmedetomidine and other sedatives. Another meta-analysis comparing propofol to benzodiazepines that included 16 RCTs showed similar results, with a significant reduction in ICU LOS for patients treated with propofol and no significant difference in mortality between propofol and other sedatives [23]. A recent RCT that examined mortality as a primary outcome of patients with sepsis who required MV demonstrated that using dexmedetomidine for sedation did not show a benefit in terms of mortality [24]. Similarly, an open label clinical trial that compared dexmedetomidine and usual care for early sedation in ICU patients requiring MV also did not show a difference in 90 day mortality [25]. The lack of a difference in the mortality rate could have been due to the study’s lack of power to detect a difference, a limitation the authors acknowledged [23, 26].

Lonardo et al reported that patients sedated with propofol had a lower risk of in-hospital mortality and were more likely to be discharged earlier from the ICU and MV discontinued compared to patients administered benzodiazepines [26]. The authors analyzed only propofol as a non-benzodiazepine sedative, comparing midazolam and lorazepam using a multicenter ICU database (2003–2009) that included 3,300 patients. Similar to their study, our nationwide data (2008–2016) showed that patients administered non-benzodiazepines (including propofol and dexmedetomidine) had a reduced risk of in-hospital mortality and shorter duration
of ICU LOS compared to patients who received benzodiazepines.

RCTs are a standard study design for testing causality and efficacy among treatments. However, they usually include patients with stable vital signs and no organ dysfunction, unlike most critically ill patients. The results of these RCTs are, therefore, increasingly regarded as not accurately reflecting actual clinical practice [27, 28]. Mortality measured in an uncontrolled environment, using all patient data extracted from a nationwide database, is more likely to represent relevant clinical practice outcomes. One of our study’s strengths is that we included all critically ill adult patients requiring MV for ≥ 48 hours to assess the association with sedation and mortality.

In our study, the non-benzodiazepine group consisted of patients treated with propofol or non-sedatives. Non-sedatives are defined in our study as the non-use of sedatives or the use of sedatives not covered by insurance. Korean ICUs have been using dexmedetomidine since the second half of 2010. However, we could not extract data from the NHIS database on dexmedetomidine use because the drug was not yet covered by the NHI in South Korea. Therefore, we assumed the use of dexmedetomidine from its sales volume, which steadily increased from the start, and then sharply increased since the second half of 2012. The trend is significantly related to a decrease in the rate of benzodiazepine use.

Benzodiazepines were significantly associated with in-hospital mortality in the study by Lonardo et al, and in our study, and are a known risk factor for delirium in critically ill patients [3]. Activation of the γ-aminobutyric acid receptor has been proposed as a possible mechanism for this risk [29]. The association between delirium and in-hospital mortality is also well known [30], thereby resulting in increased mortality for patients sedated with benzodiazepines who subsequently
experience delirium. Another plausible explanation for increased mortality in the benzodiazepine group is the longer ICU LOS compared to the non-benzodiazepine group. Prolonged ICU stay is associated with an increase in ICU-related complications, such as delirium and mortality [31].

Our study identified advanced age, low case volume, chronic kidney disease, and a higher Elixhauser index as risk factors for in-hospital and one-year mortality. Previous studies have confirmed that advanced age is a significant risk factor for mortality in critically ill patients [32] and patients requiring MV [33]. A recent study reported that pre-existing chronic kidney disease had a profound effect on the 30-day mortality and 1-year mortality of critically ill patients requiring MV in accordance with our study [34]. Low case volume is associated with higher mortality [35] due to the lower probability of multidisciplinary ICU teams and the implementation of patient care protocols [36, 37].

The NHI program in Korea is a single-payer, universal healthcare system supported by the NHIS, providing health coverage to 97% of the Korean population, while the Medical Assistance Program supports the remaining 3% of the population with the lowest income [38]. Whenever health care is provided, healthcare providers apply for reimbursement to NHIS, which is then recorded in the NHIS database. The breadth and completeness of the NHIS database used in our research is another strength of our study. Only explicit outcomes, such as mortality and LOS, were employed as final results.

Our study had several limitations. First, clinically relevant variables were limited due to the administrative nature of the NHIS database. Risk adjustment is an important issue in studies that use administrative data created without considering research. When analyzing administrative data, it might be best to use indicators
derived from comorbidities to adjust the comorbidities and to assess specific outcomes (such as in-hospital and one-year mortality), as we did in our study. Second, due to the relatively long study period, the outcomes of patients who underwent MV for ≥ 48 hours could have been affected by medical progress during the study period. However, considering the long history of lung protection ventilation, and the universal approach to medical advances, the impact of relatively long research periods is expected to be uniform and minimal. Third, we were unable to distinguish between medical admission and surgical admission, and we were unable to extract diagnoses on ICU admission from the NHIS database. However, patients who underwent MV for < 48 hours were excluded because their disease severity was considered low. According to a comprehensive report on ICUs by the Korean Society of Critical Care Medicine, only 10% of ICU patients were admitted to the ICUs for postoperative care. Therefore, most the study population were severely ill medical patients.

CONCLUSIONS

The use of benzodiazepines for sedating critically ill patients undergoing MV for > 48 hours was associated with an increased risk of in-hospital mortality and one-year mortality. Considering the recent guidelines and the rapid increase in dexmedetomidine use, sedation with dexmedetomidine could have contributed to better short-term and long-term outcomes for patients who required prolonged MV.

List of abbreviations

ABCDE, Awakening and Breathing Coordination, Delirium monitoring/management and Early exercise/mobility; CI, Confidence interval; ICU, intensive care unit; LOS,
length of stay; MV, mechanical ventilation; NHIS, National Health Insurance Service; ICD-10, International Classification of Diseases 10th revision; RCT, randomized controlled trial

Declarations

Ethics approval and consent to participate
The study protocol was approved by the institutional review board of Seoul National University Hospital (1801-023-912). The need for informed consent was waived by the institutional review board due to the retrospective design of the study.

Consent for publication
Not applicable

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest:
Ji-Eun Lee is an employee of Pfizer Upjohn.
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Authors' contributions
HGR is the guarantor of the content of the manuscript.
HL contributed substantially to the study design, data interpretation, and the writing of the first draft and subsequent revisions of the manuscript.
SC, SYO, JL, EJJ, DHK, SY, and JEL contributed substantially to data analysis and interpretation, and the writing of the manuscript.
HGR has contributed substantially to the study design, data analysis and interpretation, and the writing of the first draft and subsequent revisions of the manuscript.

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Figures

Figure 1

The correlation of sales of sedative medications (IQVIA Sales Audit from 2010 3Q)