Original Article

Use of narcotics and sedatives among very preterm infants in neonatal intensive care units in China: an observational cohort study

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Background: Narcotics and sedatives are widely used in neonatal intensive care units for very preterm infants. This study aimed to describe the current use of narcotics and/or sedatives among very preterm infants in Chinese neonatal intensive care units, with an emphasis on infants on invasive mechanical ventilation, and to investigate the association of exposure to narcotics and/or sedatives with neonatal outcomes.

Methods: This was a retrospective observational cohort study that enrolled all infants born at 24^{+0}–31^{+6} weeks and admitted to 57 tertiary neonatal intensive care units in the Chinese Neonatal Network in 2019. A multivariate logistic regression model was used to assess the association between narcotics and/or sedatives exposure and major neonatal outcomes.

Results: Among 9,442 very preterm infants enrolled, 1,566 (16.6%) received at least one dose of narcotics or sedatives, 111 (1.2%) received only narcotics, 1,301 (13.8%) received sedatives solely, and 154 (1.6%) received both narcotics and sedatives during their hospital stay. Of 4,172 very preterm infants who underwent invasive mechanical ventilation, 1,117 (26.8%) received at least one dose of narcotics or sedatives, with 883 (21.2%) only received sedatives. Significant site variation of narcotics/sedatives use existed among hospitals, with the application rate ranging from 0–72.5% in individual hospital. The narcotics and/or sedatives use by very preterm infants was independently associated with increased risks for periventricular leukomalacia, severe retinopathy of prematurity, and bronchopulmonary dysplasia.

Conclusions: Narcotic and/or sedative administration is relatively conservative for very preterm infants in Chinese neonatal intensive care units, with significant variation among hospitals. Since narcotic and sedative use might be related to adverse neonatal outcomes, a pressing and developing need for national quality improvement initiatives is seen with respect to pain/stress management for very preterm infants.

Keywords: Cohort studies; invasive mechanical ventilation; narcotic; premature infant; sedative

*For the list of site investigators of the Chinese Neonatal Network, available at the Appendix 1.

Submitted Dec 17, 2022. Accepted for publication Apr 18, 2023. Published online Jun 02, 2023.
doi: 10.21037/tp-22-672
View this article at: https://dx.doi.org/10.21037/tp-22-672

Introduction

Very preterm infants (VPIs), born at less than 32 weeks of gestation are the most vulnerable population in neonatal intensive care units (NICUs) and would experience numerous painful and stressful procedures during their stay in NICUs (1,2). All neonates—including the most immature babies—respond to pain (3,4), and compelling evidence (5,6) shows that untreated pain in infancy adds extra risks toward adverse short- and long-term neurodevelopmental outcomes. Furthermore, it is alarming that early injury may alter pain processing permanently (7). As the understanding of pain/stress in neonates has advanced considerably, evidence-based guidelines for pain management in infants are being published in many developed countries (8,9).

However, although narcotics and/or sedatives (N/S) are frequently used for VPIs undergoing painful and/or stressful procedures, there is an increasing concern regarding the adverse effects of N/S agents on preterm infants with increases in overall N/S use. Research shows that acute adverse effects occur in infants who receive narcotic agents, including prolonged duration of mechanical ventilation (MV), delayed tolerance of enteral feedings, and subtle tone abnormalities at 36 weeks post-menstrual age (10-13). Long-term follow-up of preterm infants in a multicenter, randomized controlled trial showed that fentanyl infusion during MV was associated with a significant diminution in hand-eye coordination skills (14). Preclinical studies have revealed that neuroapoptosis, as well as long-term functional deficits and atypical behavioral patterns, was associated with benzodiazepines administration (15), and midazolam-induced hypotension is also a concern for clinicians in NICUs (16).

Neonatologists in different countries have reported on their current situations regarding the use of N/S in neonates on national bases, revealing wide variations in the use of N/S among centers and countries (9,16-19). The significant variation that exists in the approaches to pharmacological intervention in pain/stress in different NICUs reflects the controversial nature of this field.

The neonatal intensive care has improved markedly in low- and middle- income countries, including China, over the last few decades. However, until recently, pain management and assessment have not been paid sufficient attention. The status of N/S use in NICUs of low- and middle-income countries remains unreported. The establishment of the Chinese Neonatal Network (CHNN) in 2018 makes it possible to collect data regarding clinical practice as well as outcomes regarding VPIs at different centers throughout China (20). The objectives of this study, then, were to describe the current use of N/S among VPIs in Chinese NICUs, emphasizing VPIs receiving MV, and to investigate the association between exposure to N/S treatments and neonatal outcomes and the duration of MV. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-672/rc).

Methods

CHNN and participating hospitals

CHNN is a national network of Chinese tertiary NICUs that enables the conduct of high-quality collaborative research dedicated to improving perinatal-neonatal health in China (20). Data for the entire year of 2019 was collected from the CHNN databases covering a total of 57 hospitals from 25 provinces throughout China, including three national children's medical centers, four regional children's medical centers, 30 provincial perinatal or children's medical centers and 20 hospitals composed of major referral centers in large cities across China. Fourteen hospitals were free-standing children's hospitals that only admitted outborn infants, and the other 43 were perinatal centers with birthing facilities. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Children's Hospital of Fudan University (No. 2018-296) and individual consent for this retrospective analysis was waived because this study did not directly intervene in the diagnosis and treatment of individual patients.

Study design and population

This retrospective observational study cohort included all VPIs at a gestational age (GA) between 24^{+0} and 31^{+6}

weeks at birth and admitted to the participating centers in 2019. VPIs with major anomalies were excluded. Stillborn babies, delivery-room deaths, and infants transferred to non-participating hospitals within 24 hours after birth were not captured by the database. Re-admissions and transfers between participating hospitals were tracked as data from the same infants; infants were followed-up until NICU discharge/transfer or death.

Data collection

Each participating hospital maintained trained data abstractors responsible for data acquisition, and data were directly entered into a customized database with built-in error checking and a standard manual of operations and definitions. Data were electronically transmitted to the CHNN coordinating center at the Children's Hospital of Fudan University with the patient identity kept confidential. Site investigators were responsible for data-quality control at each site, and the controls intrinsic to the CHNN database were reported in a previous publication (21).

Use of narcotics and/or sedatives

The application of narcotics and sedatives was documented separately in the database for each day of hospitalization, irrespective of indication, type, dosage, and the route of administration. Only N/S used in NICUs were included, excluding N/S during surgery. Narcotic agents included fentanyl and morphine (sufentanil and remifentanil are not used in Chinese NICUs), while sedative agents included midazolam, phenobarbital, chloral hydrate, and diazepam. Both bolus and continuous infusion were included in the analysis of N/S-use rate. Utilization of N/S during invasive MV was defined as N/S use during the period of invasive MV. Information on the availability of site-specific guidelines or assessment tools employed at each participating hospital was not collected.

Definitions

GA was determined using the hierarchy of best obstetric estimate based on prenatal ultrasonography, menstrual history, obstetric examination, or all three elements. If the obstetric estimate was not available or was different from the postnatal estimate of gestation by more than 2 weeks, the GA was estimated using the Ballard Score (22). Small for gestational age (SGA) was defined as a birthweight of <10th percentile for GA according to the Chinese neonatal birthweight values (23); prenatal care was designated as ≥1 pregnancy-related hospital visits during pregnancy; and antenatal steroids (ANSs) referred to steroids administered to mothers antenatally. The Transport Risk Index of Physiologic Stability (TRIPS) score was used as an illness-severity score upon NICU admission (24,25). Intraventricular hemorrhage (IVH) was defined as ≥ grade 3 according to Papile's criteria (26); necrotizing enteral colitis (NEC) was delineated according to Bell's criteria (27,28), and sepsis was characterized as positive blood or cerebrospinal fluid culture and antibiotic therapy or intent for antibiotic therapy use ≥5 days.

Outcomes

We described periventricular leukomalacia (PVL) as the presence of periventricular cysts upon cranial ultrasonographic or magnetic resonance imaging; severe retinopathy of prematurity (ROP) was diagnosed according to the International Classification of ROP (29), and bronchopulmonary dysplasia (BPD) was defined as ventilation or oxygen dependency at 36 weeks of postmenstrual age or at discharge/transfer/death if before 36 weeks (30).

Statistical analysis

Demographic characteristics of mothers and infants were compared between infants with and without the use of any N/S. The Pearson's Chi-squared test was applied to categorical variables and the Student's *t*-test or the Wilcoxon rank-sum test to continuous variables, as appropriate. A Cochran-Armitage trend test was executed to examine the significance of the association between the proportion of N/S use and weeks of GA. Descriptive analyses were performed to correlate the rate and duration of N/S use in the overall study population, with an emphasis on those infants undergoing invasive MV.

To further investigate the association between the use of N/S and neonatal outcomes, a multivariate logistic-regression model was generated adjusted for GA, SGA, sex, TRIPS score, inborn status, intensive resuscitation, respiratory distress syndrome (RDS), NEC, culture-proven sepsis, invasive MV, and any type of surgical intervention. RDS, NEC, sepsis, invasive MV, and surgery were included in the model as these indices may reflect painful or stressful events indicating N/S treatment and relation to mortality and other morbidity. To assess the association between the

duration of N/S use and the duration of invasive MV, a log-linear regression model was created, and an adjusted mean ratio for the duration of invasive MV, with a one- or seven-day increase in N/S use was obtained. Complete-cases analysis for regression model was used. Multiple imputation was not applied since the missing data were <10%.

Data management and all statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA) and set a two-sided P value of 0.05 to determine statistical significance.

Results

Baseline characteristics

From 1st January 2019 to 31st December 2019, 9,520 VPIs were admitted to 57 participating centers included in the CHNN. Seventy-eight VPIs were excluded from the study due to major congenital anomalies, and thus, 9,442 VPIs were ultimately included for analysis.

Overall, 1,566 of the 9,442 (16.6%) VPIs received at least one dose of N/S (N/S group), and 7,876 (83.4%) VPIs never received any N/S during their NICU stays (non-N/S group) (*Table 1*, Figure S1). VPIs in the N/S group exhibited an earlier GA [29.2 (27.9–30.6) weeks versus 30.0 (28.6–31.0) weeks, respectively, P<0.01] and lower birthweight [1,241.8 (321.1) grams versus 1,340.3 (315.8) grams, respectively, P<0.01] than VPIs in the non-N/S group. The proportions of SGA babies and those who received intensive resuscitation in the delivery room were both greater in the N/S group than in the non-N/S group. The incidence rates of culture-proven sepsis, NEC, and RDS were significantly elevated in the N/S group compared to the non-N/S group. The N/S group additionally manifested higher rates of surgical intervention, invasive MV, and non-invasive ventilation, with longer durations of invasive and non-invasive MV (*Table 1*).

Use of N/S among all VPIs

The overall rate of at least one dose of N/S use was 16.6% (1,566/9,442). Of the 1,566 VPIs who received at least one dose of N/S, 111/1,566 (7.1%) received only narcotics, 1,301/1,566 (83.1%) received only sedatives, and 154/1,566 (9.8%) received both narcotics and sedatives during their NICU stays. The use rate for any N/S decreased commensurately with increasing GA (P<0.0001) (*Table 2*).

Use of N/S among VPIs with invasive MV

Of the 4,172 VPIs who underwent invasive MV, 1,117/4,172 (26.8%) received at least one dose of N/S, with N/S courses lasting a median of 50.0% (IQR, 22.2–80.0%) vis-à-vis ventilation duration. The majority of infants using N/S during invasive ventilation received only sedatives (883/4,172, 21.2%), followed by those who received both narcotics and sedatives (131/4,172, 3.1%) and those who received solely narcotics (103/4,172, 2.5%). The rates of N/S use in groups of different GAs were similar (P=0.0975) (*Table 3* and Table S1). Infants who received both narcotics and sedatives underwent the longest duration of N/S treatment (Table S2). For infants who received both narcotics and sedatives, only narcotics, or only sedatives, N/S courses generated a median of 71.9% (IQR, 46.7–89.7%), 60.0% (IQR, 33.3–85.7%), and 45.5% (IQR, 20.0–75.0%) with respect to MV duration, respectively (*Table 3*).

Site variation of N/S use

Figure 1 depicts the frequencies and types of N/S treatment among different hospitals. Children's hospitals (without delivery) and perinatal centers were compared separately because of conceivably disparate disease spectrums. The mean N/S use rates in all VPIs in children's hospitals and perinatal centers were 19.0% and 15.9%, respectively (P<0.001). The highest rate of N/S use was 72.5% in hospital A, while one children's hospital and three perinatal centers never used N/S for admitted VPIs. Sedatives were generally more frequently used in the majority of hospitals. *Figure 2* illustrates the variations in N/S administration to VPIs during invasive MV in Chinese NICUs. The N/S mean use rates by VPIs undergoing invasive MV in children's hospitals and perinatal centers were 30.9% and 29.7%, respectively (P=0.4806). For VPIs on ventilation, the highest rate of N/S use was 90.9% in hospital J. Thirteen hospitals administered N/S to over half of their VPIs during invasive MV, while one specialized children's hospital and six perinatal centers did not provide any N/S to VPIs during ventilation. Sedatives were employed more often for VPIs during ventilation compared with narcotics.

N/S exposure and neonatal outcomes

Mortality rates were 16.2% and 11.2% in the N/S group and non-N/S group, respectively, with the incidence

Table 1 Baseline characteristics of all very preterm infants with and without narcotics and sedatives

Characteristics	Total (N=9,442)	Infants without narcotics and sedative use (n=7,876)	Infants with narcotics and sedative use (n=1,566)	P value
Maternal characteristics				
Maternal age, years, mean (SD)	30.8 (5.0)	30.8 (5.0)	31.1 (5.1)	0.02
Primigravida, n/N (%)	4,755/9,376 (50.7)	3,987/7,822 (51.0)	768/1,554 (49.4)	0.26
Prenatal care, n/N (%)	9,010/9,105 (99.0)	7,522/7,599 (99.0)	1,488/1,506 (98.8)	0.52
Maternal Diabetes, n/N (%)	1,584/9,244 (17.1)	1,306/7,724 (16.9)	278/1,520 (18.3)	0.19
Maternal Hypertension, n/N (%)	1,744/9,262 (18.8)	1,450/7,733 (18.8)	294/1,529 (19.2)	0.66
Antenatal steroid, n/N (%)	6,447/8,511 (75.8)	5,421/7,124 (76.1)	1,026/1,387 (74.0)	0.09
Cesarean section, n/N (%)	5,155/9,394 (54.9)	4,311/7,839 (55.0)	844/1,555 (54.3)	0.60
Infant characteristics				
Gestational age, weeks, median (IQR)	29.9 (28.4–31.0)	30.0 (28.6–31.0)	29.2 (27.9–30.6)	<0.01
Birth weight, grams, mean (SD)	1,323.9 (318.8)	1,340.3 (315.8)	1,241.8 (321.1)	<0.01
SGA, <10th percentile, n/N (%)	641/9,442 (6.8)	511/7,876 (6.5)	130/1,566 (8.3)	<0.01
Sex, female, n/N (%)	4,086/9,431 (43.3)	3,471/7,866 (44.1)	615/1,565 (39.3)	<0.01
Multiple birth, n/N (%)	2,824/9,442 (29.9)	2,351/7,876 (29.9)	473/1,566 (30.2)	0.78
Inborn, n/N (%)	6,022/9,442 (63.8)	5,090/7,876 (64.6)	932/1,566 (59.5)	<0.01
Intensive delivery room resuscitation	2,392/8,824 (27.1)	1,681/7,367 (22.8)	711/1,457 (48.8)	<0.01
TRIPS score on admission, median (IQR)	13 (6–19)	12 (6–19)	19 (8–22)	<0.01
Sepsis, cultural-proven, n/N (%)	859/9,033 (9.5)	614/7,507 (8.2)	245/1,526 (16.1)	<0.01
NEC, n/N (%)	492/9,442 (5.2)	349/7,876 (4.4)	143/1,566 (9.1)	<0.01
RDS, n/N (%)	6,601/9,380 (70.4)	5,301/7,824 (67.8)	1,300/1,556 (83.6)	<0.01
NICU treatment				
Any surgery, n/N (%)	750/9,442 (7.9)	457/7,876 (5.8)	293/1,566 (18.7)	<0.01
Invasive ventilation, n/N (%)	4,172/9,442 (44.2)	2,921/7,876 (37.1)	1,251/1,566 (79.9)	<0.01
Duration of invasive ventilation (days), median (IQR)	5 (2–10)	4 (2–7)	8 (4–16)	<0.01
Non-invasive ventilation, n/N (%)	7,630/9,442 (80.8)	6,318/7,876 (80.2)	1312/1,566 (83.8)	<0.01
Duration of non-invasive ventilation (days), median (IQR)	10 (5–22)	9.00 (5–21)	14.00 (7–25)	<0.01
Length of hospital stay (days), median (IQR)	41 (27–57)	40 (26–54)	50 (33–68)	<0.01

SD, standard deviation; IQR, interquartile range; SGA, small for gestational age; TRIPS score, Transport Risk Index of Physiologic Stability score; NEC, necrotizing enteral colitis; RDS, respiratory distress syndrome; NICU, neonatal intensive care unit.

Table 2 Use of narcotics and sedatives among all very preterm infants in Chinese NICUs by gestational age

Gestational age (week)	No. of infants	Frequency and rate of narcotics and sedative use, n (%)				Duration of narcotics and sedative use (days), median (IQR)†			
		All‡	Only narcotics	Only sedatives	Both	All	Only narcotics	Only sedatives	Both
24	92	24 (26.1)	3 (3.3)	19 (20.7)	2 (2.2)	2.5 (1.0–6.5)	1.0 (1.0–2.0)	2.0 (1.0–6.0)	46.5 (20.0–73.0)
25	228	65 (28.5)	5 (2.2)	47 (20.6)	13 (5.7)	6.0 (2.0–14.0)	21.0 (19.0–45.0)	4.0 (2.0–8.0)	15.0 (6.0–46.0)
26	449	121 (27.0)	12 (2.7)	86 (19.2)	23 (5.1)	5.0 (2.0–10.0)	9.5 (6.5–27.5)	3.0 (1.0–6.0)	15.0 (7.0–38.0)
27	837	186 (22.2)	13 (1.6)	149 (17.8)	24 (2.9)	3.0 (1.0–8.0)	6.0 (2.0–8.0)	3.0 (1.0–6.0)	10.5 (6.0–26.0)
28	1,415	281 (19.9)	20 (1.4)	232 (16.4)	29 (2.1)	3.0 (1.0–7.0)	7.5 (3.5–11.5)	2.0 (1.0–5.0)	16.0 (8.0–27.0)
29	1,763	293 (16.6)	17 (1.0)	256 (14.5)	20 (1.1)	2.0 (1.0–5.0)	3.0 (1.0–7.0)	2.0 (1.0–5.0)	11.5 (7.5–35.0)
30	2,153	313 (14.5)	26 (1.2)	261 (12.1)	26 (1.2)	2.0 (1.0–5.0)	3.0 (2.0–5.0)	2.0 (1.0–4.0)	10.5 (5.0–16.0)
31	2,505	283 (11.3)	15 (0.6)	251 (10.0)	17 (0.7)	2.0 (1.0–5.0)	3.0 (2.0–4.0)	2.0 (1.0–4.0)	7.0 (5.0–12.0)
Total	9,442	1,566 (16.6)	111 (1.2)	1,301 (13.8)	154 (1.6)	3.0 (1.0–6.0)	5.0 (2.0–9.0)	2.0 (1.0–5.0)	12.0 (6.0–27.0)

†, among infants with narcotics and/or sedative use; ‡, P value for trend <0.0001. NICU, neonatal intensive care unit; IQR, interquartile range.

Table 3 Use of narcotics and sedatives among very preterm infants during invasive ventilation in Chinese NICUs by gestational age

Gestational age (week)	No. of infants	Frequency and rate of narcotics and sedative use, n (%)				Proportion of the duration of narcotics and sedatives use in the period of invasive mechanical ventilation (%), median (IQR)†			
		All‡	Only narcotics	Only sedatives	Narcotics & sedatives	All	Only narcotics	Only sedatives	Narcotics & sedatives
24	79	21 (26.6)	3 (3.8)	16 (20.3)	2 (2.5)	33.3 (11.1–46.2)	33.3 (3.7–44.4)	33.3 (9.4–51.7)	60.5 (40.5–80.4)
25	181	52 (28.7)	5 (2.8)	36 (19.9)	11 (6.1)	35.4 (14.5–50.0)	51.2 (46.3–68.3)	31.1 (11.9–50.0)	33.3 (14.7–60.0)
26	331	98 (29.6)	12 (3.6)	65 (19.6)	21 (6.3)	37.0 (17.2–72.7)	83.8 (36.8–96.0)	25.0 (14.3–47.1)	72.7 (47.1–84.0)
27	538	143 (26.6)	15 (2.8)	113 (21.0)	15 (2.8)	47.4 (16.7–75.0)	60.0 (16.7–75.0)	43.8 (14.3–72.2)	70.0 (40.0–100.0)
28	783	210 (26.8)	16 (2.0)	166 (21.2)	28 (3.6)	50.0 (21.4–83.3)	84.0 (46.1–100.0)	40.6 (20.0–77.8)	74.1 (56.3–90.2)
29	763	200 (26.2)	15 (2.0)	167 (21.9)	18 (2.4)	48.1 (24.4–79.5)	63.6 (25.0–100.0)	38.5 (20.0–75.0)	78.2 (50.0–98.7)
30	788	208 (26.4)	21 (2.7)	164 (20.8)	23 (2.9)	50.0 (27.4–85.2)	50.0 (40.0–75.0)	50.0 (25.0–84.0)	71.4 (45.5–88.2)
31	709	185 (26.1)	16 (2.3)	156 (22.0)	13 (1.8)	50.0 (33.3–83.3)	60.0 (36.7–76.2)	50.0 (33.3–81.7)	75.0 (66.7–85.0)
Total	4,172	1,117 (26.8)	103 (2.5)	883 (21.2)	131 (3.1)	50.0 (22.2–80.0)	60.0 (33.3–85.7)	45.5 (20.0–75.0)	71.9 (46.7–89.7)

†, proportion = days of N/S use during invasive mechanical ventilation/days of invasive mechanical ventilation; calculated among infants with narcotics and/or sedative use; ‡, P value for trend =0.0975. IQR, interquartile range; NICU, neonatal intensive care unit.

rates for PVL, BPD, and severe ROP all higher in the N/S group than in the non-N/S group. Logistic regression model controlling for GA, SGA, sex, TRIPS score, inborn status, intensive resuscitation, RDS, NEC, culture-proven sepsis, invasive MV, and any type of surgical intervention demonstrated the independent association between N/S use and increased risks for PVL [adjusted odds ratio: 1.68 (1.31, 2.14)], severe ROP [adjusted odds ratio: 1.59 (1.17, 2.15)], and BPD [adjusted odds ratio: 1.33 (1.16, 1.54)], the N/S use did not contribute to neonatal death [adjusted odds ratio: 0.88 (0.72, 1.08)] (*Table 4*). Of VPIs who underwent invasive MV, with a seven-day increase in N/S use and after adjustment, the duration of invasive MV was 1.1092-fold longer (1.1053, 1.1138).

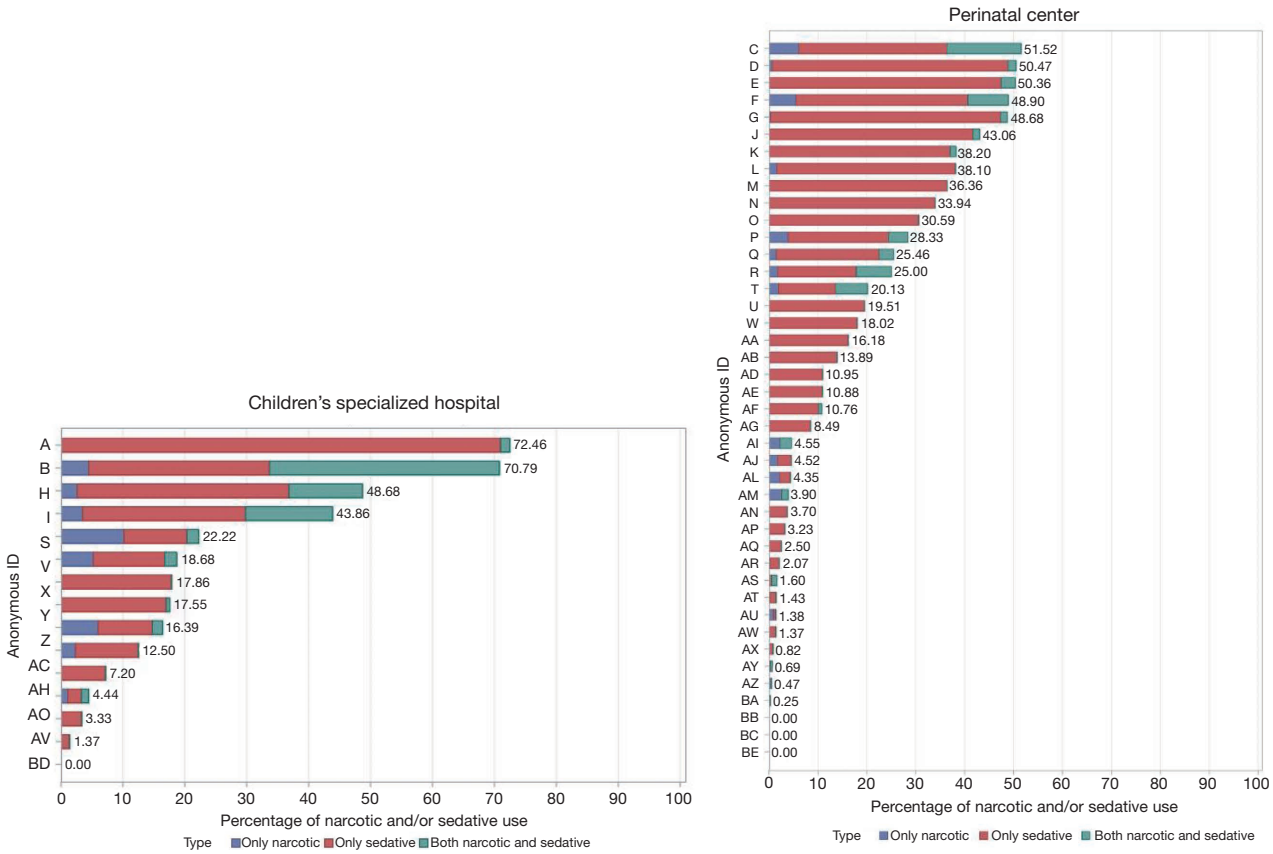

Figure 1 Variations in narcotic and sedative use for VPIs in different Chinese NICUs. The narcotics and/or sedatives use rates of all VPIs in children's hospitals and perinatal hospitals were 18.98% and 15.91% respectively (P<0.0009). NICU, neonatal intensive care unit; VPI, very preterm infant.

Discussion

This is the first multicenter cohort study to report the current use of N/S in Chinese NICUs, comprising a total of 9,442 VPIs. With 57 tertiary NICUs across China enrolled, the data from the present study represent the highest level of neonatal critical care in China. The collective results of this study reveal a low use rate of narcotics for VPIs in Chinese NICUs, with significant variation among sites. The VPIs exposed to N/S were of lower GA as well as birthweight, were more severely ill, and more likely to require surgery treatment or MV. However, after controlling for confounders, the N/S use were significantly associated with adverse neonatal outcomes.

The use of N/S drugs in preterm infants was previously reported in two large multicenter cohort studies (16,18). The EUROpean Pain Audit In Neonates (EUROPAIN) study (18) comprised 6,680 neonate enrollees within 243 NICUs in 18 European countries, with 2,064 preterm infants under 33 weeks, and it showed that sedatives and narcotics were administered to 13% and 15% of infants <33 weeks, respectively. The Canadian Neonatal Network (CNN) (31) reported that sedatives and narcotics were prescribed to 17% and 23%, respectively of 20,744 infants <33 weeks. We herein demonstrated that sedatives and narcotics were respectively given to 15.4% and 2.9% of all VPIs. To our knowledge, the dosage and route of N/S administration are the same in China and other countries. While the rates of sedative use were similar among the three studies, the rate for narcotic use in our study was far lower. The disparities in the narcotic use rate were even more significant when it concerned ventilated VPIs (5.6%, 43.7%, and 70.0% in the CHNN, CNN, and EUROPAIN studies, respectively).

Several reasons may have contributed to the lower narcotics use rate in Chinese NICUs. First, there are

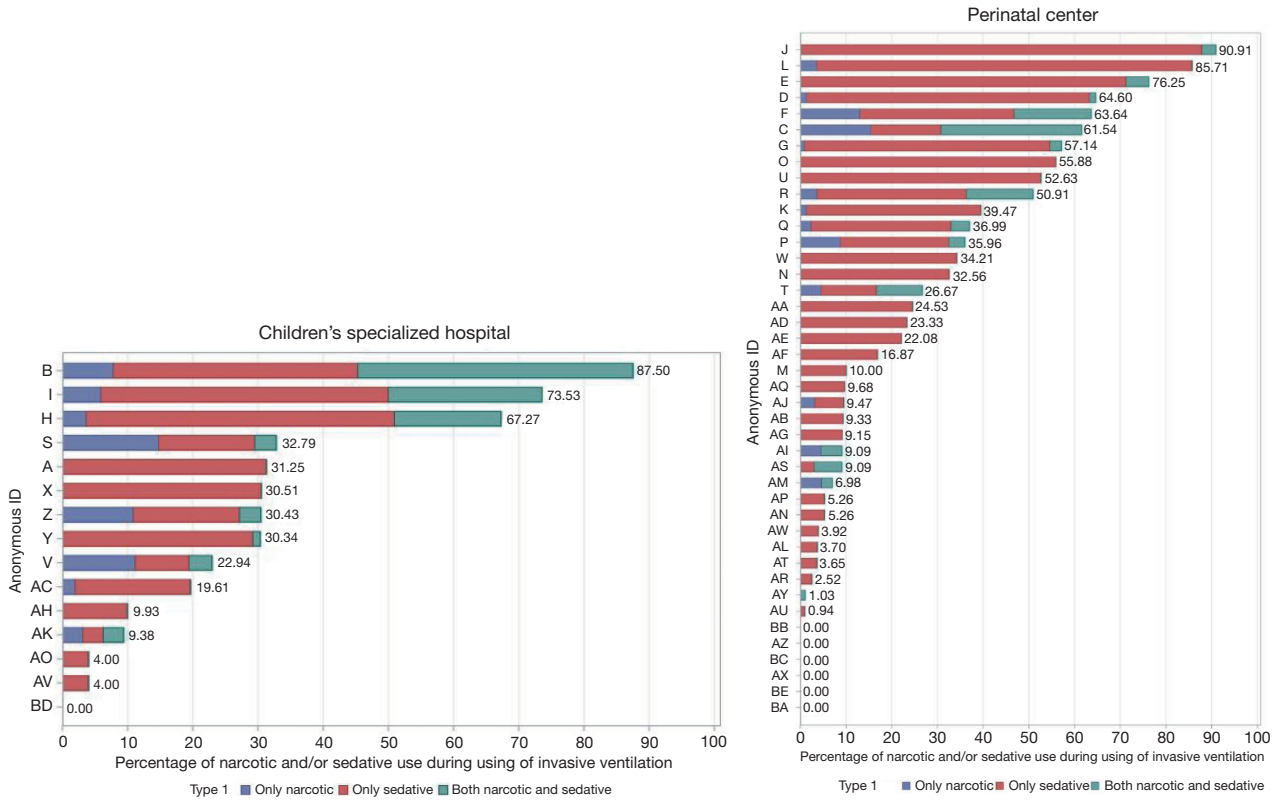

Figure 2 Variation in narcotic and sedative use for VPIs during invasive mechanical ventilation in different Chinese NICUs. The narcotics and/or sedatives use rates of VPIs with invasive mechanical ventilation in children's hospitals and perinatal hospitals were 30.85% and 29.7% respectively (P=0.4806). NICU, neonatal intensive care unit; VPI, very preterm infant.

Table 4 Association between narcotics and sedatives use and neonatal outcomes

Outcomes	Without narcotics and sedative (n=7,876), n/N (%)	With narcotics or sedative (n=1,566), n/N (%)	Crude odds ratio (95% CI)	Adjusted odds ratio[†] (95% CI)
PVL	326/6,883 (4.7)	143/1,414 (10.1)	2.26 (1.84, 2.78)	1.68 (1.31, 2.14)
Severe ROP	213/6,048 (3.5)	101/1,245 (8.1)	2.42 (1.89, 3.09)	1.59 (1.17, 2.15)
BPD	2,471/7,848 (31.5)	859/1,565 (54.9)	2.65 (2.37, 2.96)	1.33 (1.16, 1.54)
Mortality	884/7,876 (11.2)	253/1,566 (16.2)	1.52 (1.31, 1.77)	0.88 (0.72, 1.08)

[†], adjusted for gestational age, sex, Transport Risk Index of Physiologic Stability score, small for gestational age, inborn, intensive resuscitation, respiratory distress syndrome, necrotizing enterocolitis, culture proven sepsis, any surgery, invasive mechanical ventilation. CI, confidence interval; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; BPD, bronchopulmonary dysplasia.

concerns regarding the side effects of narcotics on VPIs and the developing brain. Our study revealed an independent association between N/S use and adverse neonatal outcomes that included PVL, severe ROP, and BPD after adjusting for baseline infant characteristics as well as painful or stressful disease conditions. A CNN study depicted the use of narcotics as associated with a higher risk of death, BPD, severe ROP, and severe neurological injury—as well as a longer duration of invasive MV (32). The Outcome and Prolonged Analgesia in Neonates (NOPAIN) trial revealed a tendency toward more frequent hypotension with adverse neurological effects at higher opioid doses in smaller

babies (33). With the potential adverse impact of narcotics use on neonatal outcomes, the benefits and risks should be cautiously balanced to optimize their use in VPIs. More well-designed prospective studies are therefore needed to confirm the contribution of narcotic use to adverse outcomes and to identify an optimal dose of a narcotic agent. Second, the first Chinese evidence-based Expert Consensus on Neonatal Pain Assessment and Analgesia Management was published in 2020, and since then, the awareness of pain management in neonates has been gradually enhanced in China. Third, narcotics are under strict control in China, with a specific certification required for physicians to prescribe narcotic agents, and this might limit their overall use in China.

For the infants in our study to whom both narcotics and sedatives were administered during MV, N/S treatment conferred a median of 71.9% of the ventilation duration, with the pain and stress caused by invasive MV a typical rationale for N/S use in NICUs. Although sedation with narcotics may be effective in alleviating the agitation caused by invasive ventilation and may thus generate better synchronization, current evidence does not support the routine use of N/S in ventilated newborns. A meta-analysis showed that insufficient data were available to promote the use of intravenous midazolam infusion as a sedative for neonates undergoing intensive care, and it raised concerns about the overall safety of midazolam use in neonates (34). Authors of another meta-analysis were uncertain as to whether opioids exerted any effect on pain or neurodevelopmental outcomes at 18 to 24 months of age and that the use of morphine or fentanyl probably generated little or no effect in reducing the duration of MV and neonatal mortality (35). The newly updated European RDS guidelines also emphasized that routine use of morphine or midazolam infusion in ventilated preterm infants is not recommended, opioids should only be used selectively when indicated by clinical judgement and evaluation of pain indicators (36). As the importance of pain assessment was recognized by clinicians, a series of pain assessment tool was developed in the past decades. Behavioral Observation Scales (BOS) are widely used to assess pain in newborns. Examples of BOS include the Neonatal Infant Pain Scale (NIPS) and the Premature Infant Pain Profile (PIPP). However, there is a wide variation in pain assessment methods among NICUs, with at least six different pain assessment tools in use in China (37). Meanwhile, it was revealed in this study that the variation of the use of N/S was also significant among participating hospitals, with the N/S use rate among all VPIs varying from 0% to 72.5% in different hospitals. Children's hospitals used N/S more frequently overall than their perinatal hospital counterparts, because children's hospitals typically admitted more severe cases that tended to require more N/S treatment. However, the variation remained distinct even among the same type of hospitals. Therefore, a national guideline is urgently needed and then followed by quality-improvement initiatives to standardize country-wide practices.

As the first-ever study to describe the current use of N/S in VPIs on a national basis in China, the strength of our study included its large sample size and valid and reliable data-collection methods. Clinical conditions that might affect the outcomes were also adjusted in our regression model to reduce bias to minimize confounding by indications. There were, however, several limitations to the present study. The types of individual medications used, and their routes of administration were not collected, information on indications for N/S use was not documented, and data on pain assessment by each hospital were not available. Our data only included large tertiary NICUs in China, therefore could not represent situations in lower-level neonatal centers. The study could only reveal the association rather than a causal relation between the exposure to N/S and adverse outcomes. For instance, VPIs with severe ROP are more likely to receive N/S during treatment of their condition without those pharmaceuticals having a specific effect on their disease.

Conclusions

Narcotic and sedative administration is relatively conservative for VPIs in Chinese NICUs, with significant variation among different hospitals. Since narcotic and sedative use might be related to adverse neonatal outcomes, a pressing and developing need for national quality improvement initiatives is seen with respect to pain/stress management for VPIs.

Acknowledgments

Funding: This work was supported by the Canadian Institutes of Health Research (No. CTP87518 to SKL), and Guangxi Clinical Research Center for Pediatric Diseases (No. AD22035121 to YM). The funding organization had no role in the design and conduct of the study; collection,

management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-672/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-672/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-22-672/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-672/coif). SKL reports that he is supported by the Canadian Institutes of Health Research (Grant No. CTP87518). YM reports that she is supported by Guangxi Clinical Research Center for Pediatric Diseases (Grant No. AD22035121). The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics board of Children's Hospital of Fudan University (No. 2018-296) and individual consent for this retrospective analysis was waived because this study did not directly intervene in the diagnosis and treatment of individual patients.

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Cite this article as: Mo Y, Gu X, Li D, Dai W, Xu J, Lee SK, Zhou W, Cao Y, Wei Q, Jiang S; the Chinese Neonatal Network. Use of narcotics and sedatives among very preterm infants in neonatal intensive care units in China: an observational cohort study. Transl Pediatr 2023;12(6):1170-1180. doi: 10.21037/tp-22-672

Appendix 1 The Group Information of Chinese Neonatal Network

Group Information of the Chinese Neonatal Network: Chairmen: Shoo K. Lee, MBBS, Mount Sinai Hospital, University of Toronto; Chao Chen, MD, Children's Hospital of Fudan University. Vice-Chairmen: Lizhong Du, MD, Children's Hospital of Zhejiang University School of Medicine; Wenhao Zhou, Children's Hospital of Fudan University. Site investigators of the Chinese Neonatal Network: Children's Hospital of Fudan University: Yun Cao, MD; The Third Affiliated Hospital of Zhengzhou University: Falin Xu, MD; Tianjin Obstetrics & Gynecology Hospital: Xiuying Tian, MD; Guangzhou Women and Children's Medical Center: Huayan Zhang, MD; Children's Hospital of Shanxi: Yong Ji, MD; Northwest Women's and Children's Hospital: Zhankui Li, MD; Gansu Provincial Maternity and Child Care Hospital: Bin Yi, MD; Shengjing Hospital of China Medical University: Xindong Xue, MD; Shenzhen Maternity and Child Health Care Hospital: Chuanzhong Yang, MD; Quanzhou Women and Children's Hospital: Dongmei Chen, MD; Suzhou Municipal Hospital affiliated to Nanjing Medical University: Sannan Wang, MD; Guizhou Women and Children's Hospital/Guiyang Children's Hospital: Ling Liu, MD; Hunan Children's Hospital: Xirong Gao, MD; The First Bethune Hospital of Jilin University: Hui Wu, MD; Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University: Changyi Yang, MD; Nanjing Maternity and Child Health Care Hospital: Shuping Han, MD; Qingdao Women and Children's Hospital: Ruobing Shan, MD; The Affiliated Hospital of Qingdao University: Hong Jiang, MD; Children's Hospital of Shanghai: Gang Qiu, MD; Maternity and Child Health Care of Guangxi Zhuang Autonomous Region: Qiufen Wei, MD; Children's Hospital of Nanjing Medical University: Youyan Zhao, MD; Henan Children's Hospital: Wenqing Kang, MD; The First Affiliated Hospital of Xinjiang Medical University: Mingxia Li, MD; Foshan Women and Children's Hospital: Xuqiang Ye, MD; The First Affiliated Hospital of Anhui Medical University: Lili Wang, MD; Shanghai First Maternity and Infant Hospital: Jiangqin Liu MD; Yuying Children's Hospital Affiliated to Wenzhou Medical University: Zhenlang Lin, MD; Children's Hospital of Chongqing Medical University: Yuan Shi, MD; The First Affiliated Hospital of Zhengzhou University: Xiuyong Cheng, MD; The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China: Jiahua Pan, MD; Shaanxi Provincial People's Hospital: Qin Zhang, MD; Children's Hospital of Soochow University: Xing Feng, MD; Wuxi Maternity and Child Healthcare Hospital: Qin Zhou, MD; People's Hospital of Xinjiang Uygur Autonomous Region: Long Li, MD; The Second Xiangya Hospital of Central South University: Pingyang Chen, MD; Qilu Children's Hospital of Shandong University: Xiaoying Li, MD; Hainan Women and Children's Hospital: Ling Yang, MD; Xiamen Children's Hospital: Deyi Zhuang, MD; Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine: Yongjun Zhang, MD; Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine: Jianhua Sun, MD; Shenzhen Children's Hospital: Jinxing Feng, MD; Children's Hospital Affiliated to Capital Institute of Pediatrics: Li Li, MD; Women and Children's Hospital, School of Medicine, Xiamen university: Xinzhu Lin, MD; General Hospital of Ningxia Medical University: Yinping Qiu, MD; First Affiliated Hospital of Kunming Medical University: Kun Liang, MD; Hebei Provincial Children's Hospital: Li Ma, MD; Jiangxi Provincial Children's Hospital: Liping Chen, MD; Fuzhou Children's Hospital of Fujian Province: Liyan Zhang, MD; First Affiliated Hospital of Xian Jiao Tong University: Hongxia Song, MD; Dehong people's Hospital of Yunnan Province: Zhaoqing Yin, MD; Beijing Children's Hospital, Capital Medical University: Mingyan Hei, MD; Zhuhai Center for Maternal and Child Health Care: Huiwen Huang, MD; Guangdong Women and Children's Hospital: Jie Yang, MD; Dalian Municipal Women and Children's Medical Center: Dong Li, MD; Peking Union Medical College Hospital: Guofang Ding, MD; Obstetrics & Gynecology Hospital of Fudan University: Jimei Wang, MD; Shenzhen Hospital of Hongkong University: Qianshen Zhang, MD; Children's Hospital of Zhejiang University School of Medicine: Xiaolu Ma, MD; Advisor: Joseph Y. Ting, University of Alberta.

https://dx.doi.org/10.21037/tp-22-672

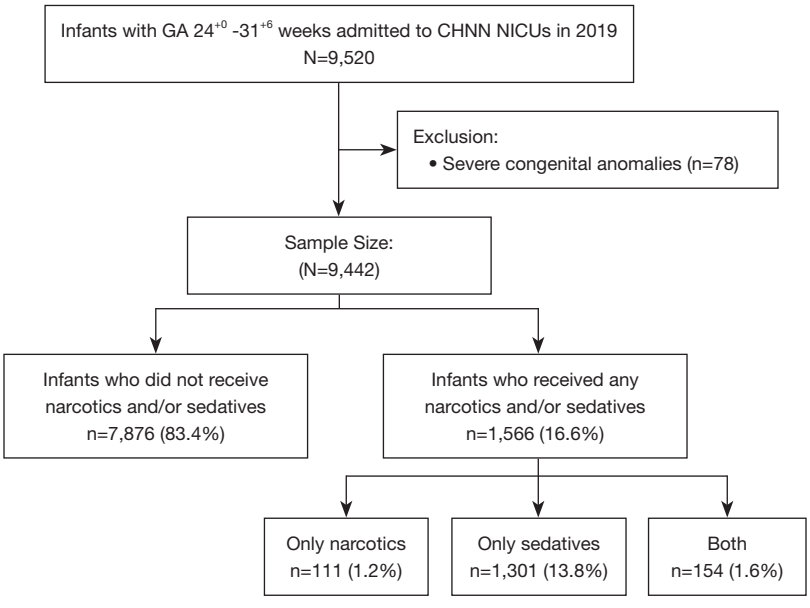

Figure S1 Diagram showing the flow of participants through each stage of the study.

Table S1 Use of narcotics and sedatives by gestational age

Gestational age (weeks)	Total number of VPIs	Unventilated (n=5270)	Ventilated (n=4,172)		
			Number of VPIs	N/S, n (%)	Non-N/S, n (%)
24	92	13	79	21 (26.58)	58 (73.42)
25	228	47	181	52 (28.73)	129 (71.27)
26	449	118	331	98 (29.61)	233 (70.39)
27	837	299	538	143 (26.58)	395 (73.42)
28	1415	632	783	210 (26.82)	573 (73.18)
29	1763	1000	763	200 (26.21)	563 (73.79)
30	2153	1365	788	208 (26.40)	580 (73.60)
31	2505	1796	709	185 (26.09)	524 (73.91)
Total	9442	5270	4172	1117 (26.77)	3055 (73.23)

Table S2 Duration of narcotics and sedatives use concurrent with invasive mechanical ventilation (days)

Gestational age (weeks)	Number of infants	Duration of narcotics and sedatives use in the period of invasive mechanical ventilation (days), median (IQR)			
		All	Only narcotics	Only sedatives	Narcotics and sedatives
24	79	2.0 (1.0-6.0)	1.0 (1.0-8.0)	2.0 (1.0-5.5)	27.0 (17.0-37.0)
25	181	6.0 (2.5-12.0)	19.0 (12.0-21.0)	6.0 (2.0-9.5)	12.0 (3.0-20.0)
26	331	6.0 (3.0-11.0)	9.5 (6.5-22.0)	4.0 (2.0-7.0)	9.0 (6.0-31.0)
27	538	4.0 (2.0-7.0)	5.0 (4.0-6.0)	3.0 (1.0-7.0)	7.0 (2.0-17.0)
28	783	3.0 (1.0-7.0)	5.0 (3.0-10.0)	2.0 (1.0-5.0)	11.0 (4.0-19.0)
29	763	3.0 (1.0-5.0)	2.0 (1.0-6.0)	2.0 (1.0-5.0)	6.0 (4.0-23.0)
30	788	2.0 (1.0-5.0)	3.0 (1.0-4.0)	2.0 (1.0-4.0)	5.0 (4.0-12.0)
31	709	2.0 (1.0-5.0)	2.5 (1.5-4.5)	2.0 (1.0-4.0)	7.0 (4.0-10.0)
Total	4172	3.0 (1.0-6.0)	4.0 (2.0-8.0)	2.0 (1.0-5.0)	8.0 (4.0-17.0)

IQR, interquartile range.

https://dx.doi.org/10.21037/tp-22-672