






# Investigating Factors Associated with the Development of Postnatal Depression After Cesarean Delivery: A Validation Cohort Study

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**Purpose:** This study aimed to validate a proposed association model previously published to determine the clinical relevance of pre-operative determinants in the development of PND after Cesarean delivery (CD).

**Patients and Methods:** Parturients undergoing elective CD under neuraxial anesthesia were recruited for a prospective cohort study between Oct 2021 and Oct 2022 at KK Women's and Children's Hospital, Singapore. Predelivery pain, psychological and mechanical temporal summation, and demographic data were recorded. A follow-up survey was conducted at 6 to 10 weeks after CD. The primary outcome was the incidence of PND, defined as an Edinburgh Postnatal Depression Scale (EPDS) score  $\geq 10$ .

**Results:** A total of 180 patients were recruited for validation. PND 6 to 10 weeks post-delivery occurred in 18.9% of recruited parturients. Multivariate regression analyses showed that higher pre-operative CSI scores ( $p=0.0156$ ), higher anxiety levels about upcoming surgery ( $p=0.0429$ ), increased pre-operative pain scores on movement ( $p=0.0110$ ), and higher pre-operative HADS subscale scores on anxiety ( $p=0.0041$ ) were independently associated with the development of PND weeks post-CD. Lower anticipation of pain medication needs ( $p=0.0038$ ) was independently associated with the development of PND post-CD. The area under curve (AUC) of this multivariable model (training cohort), internal cross validation (training cohort) and external cross validation (validation cohort) were 0.818 (95% CI, 0.746 to 0.889), 0.785 (95% CI, 0.707 to 0.864) and 0.604 (95% CI, 0.497 to 0.710) respectively.

**Conclusion:** The proposed model performed well in a local population. Further refinement is necessary to test the proposed model in populations with social and cultural differences.

**Keywords:** anxiety, obstetrics, pain, postnatal depression

## Introduction

Postnatal depression (PND) remains a significant global health problem with widespread consequences.<sup>1-4</sup> Approximately half of patients may be undiagnosed because of privacy conflicts and the stigma that the diagnosis may lead to abandonment and lack of support.<sup>5</sup> Therefore, it is imperative that PND is identified early so that appropriate interventions can be initiated promptly.<sup>6</sup> Identifying the associated risk factors in the development of PND could be a strategy for early intervention to reduce disease burden, including patient wellbeing and economic costs associated with PND.<sup>7</sup> Among the risk factors identified for PND, Cesarean delivery (CD) has been shown to be significantly associated with the development of PND.<sup>8,9</sup> However, there is limited knowledge regarding the pre-operative factors that is associated with PND.

In our previous study in 2020, we performed a prospective cohort study on Asian women undergoing elective CD under neuraxial anesthesia and found that 21.1% of these parturients developed PND 6 to 10 weeks post-CD.<sup>10</sup> We

developed an association model that demonstrated the risk factors for PND, including increased pre-operative central sensitization, increased anxiety about upcoming surgery, increased pre-operative anxiety, and increased pre-operative pain scores with movement. Interestingly, a greater anticipation of pain medication needs was associated with a decreased risk of PND. The area under the receiver operating characteristic (ROC) for the multivariate model was 0.8177. The study findings suggest the need to manage parturients' pain, expectations, and anxiety during the perioperative period to reduce the likelihood of developing PND. To our knowledge, this is the first study to generate an association model consisting of pre-operative analgesic and psychological factors associated with PND after CD.

The primary aim of this study was to develop and validate a predictive model for CD in women. We aimed to determine the clinical relevance of the pre-operative determinants of PND. Using the previously proposed association model, we aimed to demonstrate the robustness of the model through external validation with another new cohort.

## Materials and Methods

### Ethics

We conducted a prospective cohort study on parturients undergoing elective CD under neuraxial anesthesia at KK Women's and Children's Hospital, Singapore, between May 2018 and Apr 2019 (training cohort), and Oct 2021 and Oct 2022 (validation cohort). This study was approved by the SingHealth Centralized Institutional Review Board (reference number: CIRB 2017/2381) and registered at Clinicaltrials.gov (NCT03645239). The study methodologies were developed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standards and were based on our previous study.<sup>10</sup>

### Patient Recruitment

The study population included healthy (American Society of Anesthesiologists physical status 1 and 2), adult parturients aged 21–50 years, at more than 36 weeks of gestation, and scheduled for elective CD under neuraxial anesthesia. Parturients who were excluded from the study were those who had emergency CD or CD performed under general anesthesia, those who had a history of chronic pain disorders or intravenous drug or opioid abuse, and those who could not communicate in English because standardized validated English questionnaires were administered. Written informed consent was obtained from each patient prior to the study procedure.

### Assessment

Pre-operative information was collected before the CD. This included parturients' demographic data and pain levels (rated on a numerical scale of 0–10 using a Numerical Rating Scale) both at rest and during movement (such as transitioning from a supine to sitting position). Three questions were asked before the surgery to help predict post-Caesarean acute pain:<sup>11</sup> i) How anxious are you about the upcoming surgery, rated on a scale of 0–100 (with 0 indicating not anxious at all and 100 indicating extremely anxious)? ii) How much pain do you expect to experience after surgery, rated on a scale of 0–100 (with 0 indicating no pain at all and 100 indicating the most severe pain imaginable)? iii) How much pain medication do you anticipate needing after surgery, rated on a scale of 0–5 (with 0 indicating none at all and 5 meaning significantly more than the average)?

Mechanical temporal summation (MTS) was performed using a 180-g von Frey filament applied over the parturient's forearm prior to anesthesia. Following the first touch, parturients were asked to rate their pain level on a scale of 0 to 100. Then, ten additional touches were applied within a 1 cm area, each spaced 1 second apart, and the parturient was asked to rate the pain of the final touch. By calculating the difference between the pain scores of the eleventh touch and initial touch, a positive difference indicated the presence of an evoked MTS.

Before the surgery, various questionnaires were administered to the patients. These included: i) the Pain Catastrophizing Scale (PCS), which is a validated tool used to assess negative thoughts and beliefs about pain or painful experiences; ii) the Central Sensitization Inventory (CSI), which measures parturients' responses to an increased pain field and prolonged pain after the removal of the stimulus; iii) the Hospital Anxiety and Depression Scale (HADS), which

evaluates levels of anxiety and depression; and iv) the Edinburgh Postnatal Depression Scale (EPDS), which is a self-report scale specifically designed to assess PND.

We also examined the level of pain experienced by each parturient when they received a local anesthetic injection before spinal anesthesia. We used a numerical rating scale (NRS) ranging from 0 to 10 to measure pain immediately after injecting 2–5 milliliters of 1.0% lignocaine into the skin using a 22 Gauge needle. To minimize the parturient's subjective experience of pain, we used a standardized script to inform the parturient immediately before injecting the local anesthetic. Anesthetic management in the perioperative period was performed by the attending clinician, following standard protocols of care. For CD, we administered single-shot spinal anesthesia consisting of intrathecal hyperbaric bupivacaine (10.5–12 mg), fentanyl (15 µg), and preservative-free morphine (100 µg). Acute post-CD pain, as defined by 24- and 48-hours after CD pain scores at rest and with movement, was recorded accordingly. Pain relief medications, including paracetamol, mefenamic acid, and tramadol, were prescribed according to the hospital protocols until the parturients were discharged. Parturients also completed the HADS to determine their levels of anxiety and depression 48 hours after CD.

An online survey was conducted between 6 and 10 weeks after the CD, similar to our previous study in 2020.<sup>10</sup> This period was selected because a prospective cohort study has showed that acute post-Caesarean pain is associated with PND 6 to 10 weeks after CD.<sup>12</sup> The survey examined the outcomes of PND by using the EPDS questionnaire. Those who did not complete the online survey were contacted by phone to conduct the follow-up surveys. These additional surveys focused on pain experiences, including the duration of pain and its impact on daily life and social activities.

## Statistical Analysis

Sample size calculation was described in our previous study.<sup>10</sup> Post-hoc power calculation is also done. Based on van Smeden et al,<sup>13</sup> number of candidate independent variables, total sample size, and outcome proportion are the three main drivers of a model's mean predictive accuracy and therefore the sample size calculation requires the number of candidate independent variables and the anticipated outcome proportion in the target population to be prespecified. With 5 candidate independent variables and an outcome proportion of 18%, a sample size of at least 200 parturients and 7.3 events per candidate predictor parameter (EPP) is required to target a mean absolute error of 0.07 between observed and true outcome probabilities. Formula used to calculate sample size is as follows:

$$\ln(\text{MAPE}) = -0.508 - 0.544 \ln(n) + 0.259 \ln(\phi) + 0.504 \ln(P)$$

where MAPE = mean absolute prediction error,  $n$  = required sample size,  $\phi$  anticipated incidence of outcome and  $P$  is the number of candidate independent variables.

The outcome of interest of PND at 6 to 10 weeks post-CD was treated as binary data, with “non-PND” group having EPDS < 10, and “PND” group with EPDS ≥ 10. Demographic and clinical characteristics are summarized in terms of PND status. Categorical and continuous variables were summarized as either mean (standard deviation (SD)) or median (interquartile range (IQR)), whichever appropriate, or frequency (percentage), respectively. The difference between “PND” and “non-PND” group was tested using Chi Square test for categorical and two sample independent  $t$ -test for continuous variables. To identify the predictive factors for “PND”, we fitted univariate and multivariable logistic regression models separately. Quantitative association from the logistic regression model was expressed as an odds ratio (OR) with a corresponding 95% confidence interval (95% CI). Variables with  $p < 0.05$ , in the univariate logistic regression model, were chosen for the multivariable model. A stepwise variable selection method was used to determine the predictive model. Two patient cohorts were included in the study.

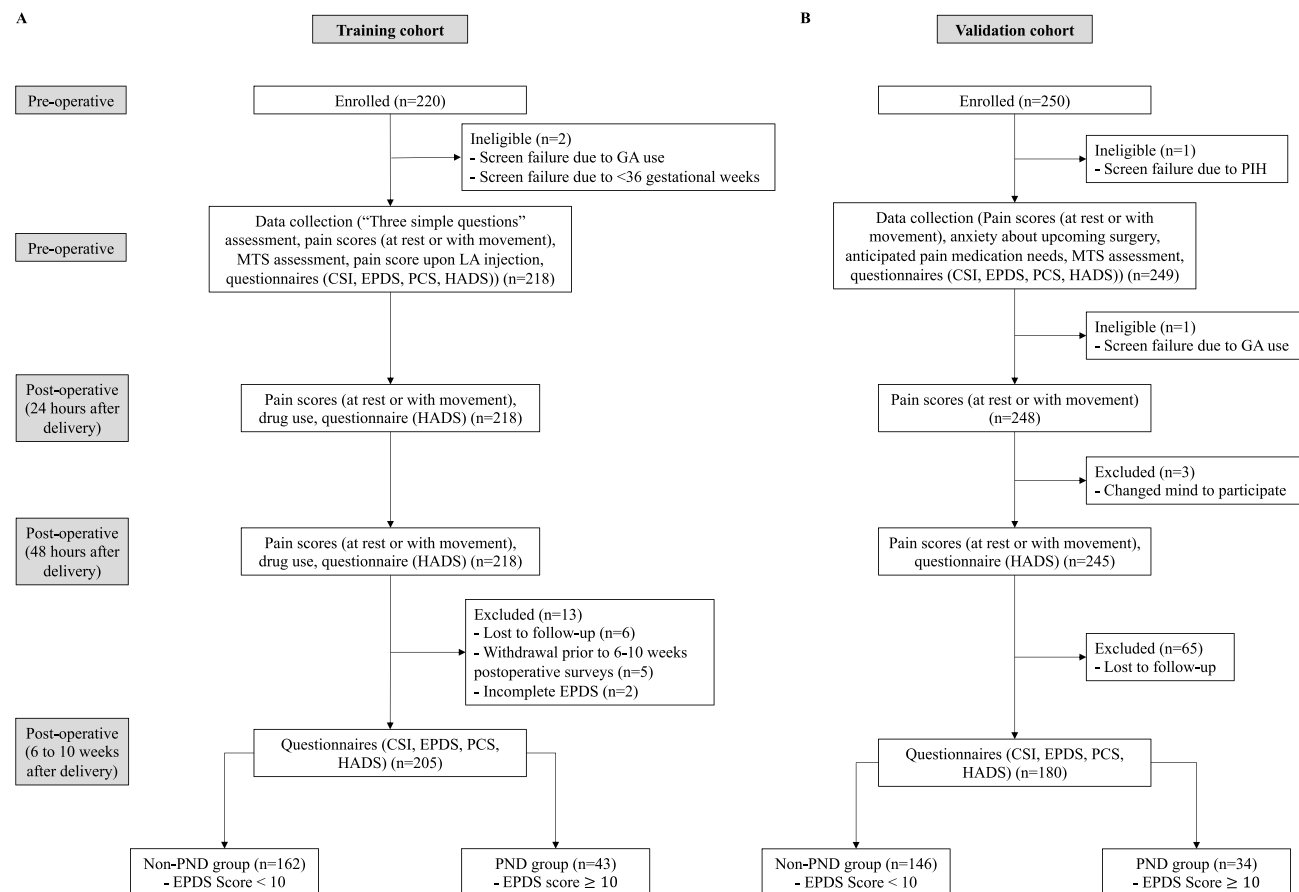
The study cohort between May 2018 and Apr 2019 was used as the training cohort,<sup>8</sup> whereas parturients recruited between Oct 2021 and Oct 2022 was used as the validation cohort. A predictive model for PND was developed using the training cohort and was validated in the validation cohort. The predictive ability of the model was verified using the area under the curve (AUC) from the receiver operating characteristic (ROC) curve based on the final multivariable model. The logistic regression model yielded a score based on a linear combination of the selected variables in the multivariable model. This score could be converted to the predicted probability of PND using the relationship predicted probability =  $e^{\text{score}} / (1 + e^{\text{score}})$ , where  $e$  is the natural exponential function. Youden's scale was used to identify the best cut-off for the

predicted probabilities in the training data, and the cut-off was validated using the validation cohort. Diagnostic measurements, such as sensitivity, specificity, accuracy, and AUC, were reported with the corresponding 95% CI. All tests were two-sided and statistical significance was set at  $p < 0.05$  unless otherwise stated. The analysis was conducted SAS version 9.4 software (SAS Institute; Cary, North Carolina, USA).

## Results

There were 205 parturients in the training cohort, with an overall prevalence of PND 6 to 10 weeks post-CD (21.1%). The validation cohort included 180 patients with an overall prevalence of 18.9% (Figure 1). The demographic and pre-delivery clinical characteristics of both the training and validation groups are summarized in Table 1.

The univariate and final multivariable regression analyses based on the training cohort are shown in Table 2. Covariates independently associated with PND had higher pre-operative pain scores on movement ( $p=0.011$ ), higher pre-operative CSI scores ( $p=0.016$ ), higher pre-operative HADS subscale scores on anxiety ( $p=0.004$ ), higher anxiety levels about upcoming surgery ( $p=0.043$ ), and lower anticipated pain medication needs ( $p=0.004$ ). The AUC of the multivariable model (training cohort), internal cross-validation (training cohort), and external cross-validation (validation cohort) were 0.818 (95% CI, 0.746–0.889), 0.785 (95% CI, 0.707–0.864), and 0.604 (95% CI, 0.497–0.710), respectively. The risk score based on multivariable model using training data was as follows (Table 2):



**Figure 1** Study workflow of the (A) training and (B) validation cohorts. The training cohort was recruited between May 2018 and April 2019, and the validation cohort was recruited between October 2021 and October 2022. Both cohorts were recruited at the same tertiary level care hospital specialized in obstetric and gynaecological population.

**Abbreviations:** CSI, Central Sensitization Inventory; EPDS, Edinburgh Postnatal Depression Scale; GA, general anesthesia; HADS, Hospital Anxiety and Depression Scale; MTS, mechanical temporal summation; PCS, Pain Catastrophizing Scale; PIH, pregnancy-induced hypertension; PND, postnatal depression.

**Table 1** Summary Table Based on the PND Status in Training and Validation Cohorts

Characteristics	Training Cohort			Validation Cohort		
	Non-PND (n = 162)	PND (n = 43)	p – value	Non-PND (n = 146)	PND (n = 34)	p – value
Age (years)	34.9 ± 5.2	34.1 ± 4.4	0.329	33.0 ± 4.5	31.2 ± 5.3	0.069
Race			0.106			0.743
Chinese	96 (59.3)	28 (65.1)		78 (53.4)	17 (50.0)	
Malay	39 (24.1)	4 (9.3)		52 (35.6)	11 (32.4)	
Indian	13 (8.0)	7 (16.3)		9 (6.2)	3 (8.8)	
Others	14 (8.6)	4 (9.3)		7 (4.8)	3 (8.8)	
Past Cesarean delivery	113 (69.8)	22 (51.2)	0.022	96 (65.8)	17 (50.0)	0.087
Pre-operative pain score (with movement; 0–10)	4.4 ± 2.4	4.8 ± 2.8	0.079	2.0 ± 5.4	1.8 ± 2.7	0.757
Anxiety about upcoming surgery (0–100)	49.5 ± 25.2	60.5 ± 20.1	0.004	38.7 ± 27.2	52.6 ± 28.4	0.013
Anticipated pain medication needs (0–5)	3.0 ± 0.7	2.7 ± 1.1	0.079	3.4 ± 1.51	4.0 ± 1.2	0.013
Pre-operative total PCS (0–52)	13.6 ± 10.0	17.3 ± 10.5	0.043	11.0 ± 8.8	19.0 ± 12.6	0.001
Pre-operative CSI (0–100)	52.0 ± 11.0	59.2 ± 12.1	0.001	48.5 ± 10.5	59.3 ± 14.8	< 0.001
Pre-operative HADS-anxiety	6.1 ± 3.0	8.8 ± 3.4	< 0.001	4.9 ± 3.1	7.8 ± 3.9	< 0.001
Pre-operative HADS-depression (0–21)	3.8 ± 2.8	5.6 ± 3.4	0.005	3.1 ± 2.6	4.4 ± 2.7	0.006

**Note:** Continuous and categorical variables were expressed as mean ± SD and frequency (percentages), respectively.

**Abbreviations:** CSI, Central Sensitization Inventory; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PND, Postnatal depression; SD, Standard deviation.

**Table 2** Univariate and Multivariable Logistic Regression Model for PND Based on the Training Cohort

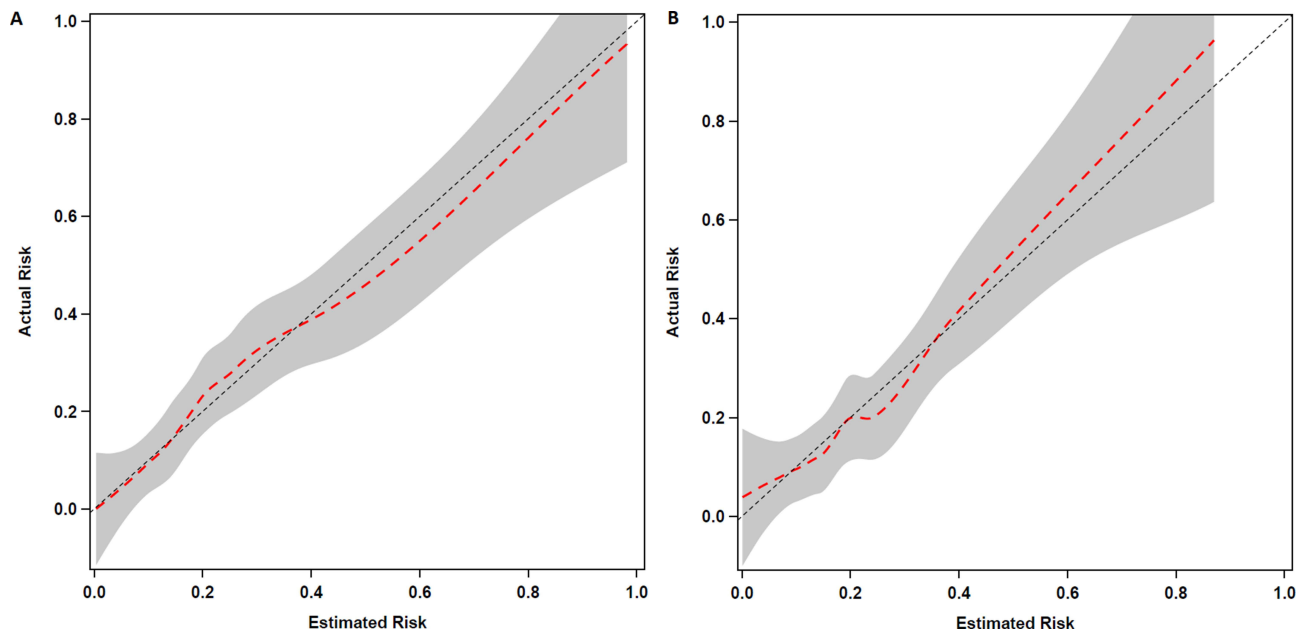
Characteristics	Univariate Logistic Regression		Multivariable Logistic Regression			
	Unadjusted OR (95% CI)	p – value	Estimate	SE	Adjusted OR (95% CI)	p – value
Intercept	–	–	–4.935	1.333	–	–
Age	0.97 (0.90 to 1.04)	0.3692	–	–	–	–
Race (Ref = Chinese)		0.1306 <sup>a</sup>	–	–	–	–
Malay	0.35 (0.12 to 1.07)	0.0333	–	–	–	–
Indian	1.85 (0.67 to 5.07)	0.0728	–	–	–	–
Others	1.00 (0.30 to 3.21)	0.8418	–	–	–	–
Past Cesarean delivery	0.45 (0.23 to 0.90)	0.0241	–	–	–	–
Pre-operative pain score (with movement)	1.49 (1.09 to 2.04)	0.0120	0.503	0.198	1.65 (1.12 to 2.44)	0.0110
Anxiety about upcoming surgery	1.02 (1.01 to 1.04)	0.0112	0.021	0.010	1.02 (1.00 to 1.04)	0.0429
Anticipated pain medication needs	0.65 (0.44 to 0.95)	0.0274	–0.740	0.255	0.48 (0.29 to 0.79)	0.0038
Pre-operative total PCS	1.04 (1.00 to 1.07)	0.0370	–	–	–	–
Pre-operative CSI	1.06 (1.03 to 1.09)	0.0006	0.050	0.021	1.05 (1.01 to 1.09)	0.0156
Pre-operative HADS-anxiety	1.30 (1.16 to 1.46)	<0.0001	0.222	0.077	1.25 (1.07 to 1.45)	0.0041
Pre-operative HADS-depression	1.20 (1.08 to 1.34)	0.0010	–	–	–	–

**Note:** <sup>a</sup>Refers to type 3 or overall p – value.

**Abbreviations:** CI, Confidence interval; CSI, Central Sensitization Inventory; HADS, Hospital Anxiety and Depression Scale; PCS, Pain Catastrophizing Scale; PND, Postnatal depression; SD, Standard deviation; SE, Standard error.

$$\text{Score} = -4.935 + 0.503 * \text{Pre-operative pain score (with movement)} + 0.021 * \text{Anxiety about upcoming surgery} + (-0.740) * \text{Anticipated pain medication needs} + 0.050 * \text{Pre-operative CSI} + 0.222 * \text{Pre-operative HADS-anxiety}.$$

The predicted probability is determined by calculating the exponential of the score. Based on Youden's scale, the best cut-off for this probability was 0.209, with a sensitivity of 76.19% (95% CI, 60.55–87.95%), specificity of 76.25% (95% CI, 68.89–82.61%), accuracy of 76.24% (95% CI, 69.76–81.93%), and AUC of 0.785 (95% CI, 0.707–0.864). Using the same cut-off for this validation cohort, the sensitivity, specificity, accuracy, and AUC were 70.6% (95% CI, 52.52–



**Figure 2** Calibration plots using (A) training and (B) validation cohorts. The x-axis represents the predicted probability of outcome PND calculated using the model. The y-axis represents the actual probability of PND. The blue dotted line is the reference line where an ideal rate would lie, the red dashed line represents the model's performance.

84.90%), 75.34% (95% CI, 67.53–82.09%), 74.44% (95% CI, 67.42–80.64%) and 0.724 (95% CI, 0.644–0.815) respectively. Calibration plots based on the training and validation cohorts are shown in Figure 2.

## Discussion

This study supports that the risk factor model for PND in a previous study is valid and useful for predicting the likelihood of developing PND. Similar to the results of a previous study, our study identified the same five covariates that are independently associated with the development of PND: pre-operative pain scores on movement, pre-operative CSI scores, pre-operative HADS subscale scores on anxiety, anxiety about upcoming surgery, and anticipated pain medication needs.

The main purpose of this study was to validate the proposed determinants of PND found in our previous study.<sup>10</sup> It is important to risk stratify and identify parturients with a high risk of developing PND,<sup>5,14</sup> to the avoidable psychological burden.<sup>15</sup> To our understanding, this is the first study to investigate the pre-operative psychological and analgesic factors associated with the development of PND. With the increasing rate of cesarean sections performed globally,<sup>16</sup> a predictive model is becoming increasingly important.

Although the intended use of CSI in chronic pain populations is to identify patients with central sensitization syndromes, it has also been shown to be associated with postsurgical pain outcomes.<sup>17</sup> It is possible that central sensitization symptoms persist even after surgery.<sup>18</sup> Correspondingly, the experience of pain by parturients after delivery may contribute to their susceptibility to PND. This association is a recognized feature of central sensitization pain disorders, which are associated with mental health problems, increased health care burden, and poor treatment outcomes.<sup>19</sup> Additionally, HADS is also a self-rating tool to assess psychological distress, specifically both anxiety and depression. The HADS has been demonstrated to correlate well with the EPDS in parturients.<sup>20</sup> It is probable that anxiety and depressive mechanisms could lead to alterations in circuits affecting emotion regulation, executive function, and cognitive control.<sup>21</sup>

In addition to the overall anxiety levels measured using the HADS, we also evaluated parturients' specific anxiety related to their upcoming surgery. Our study revealed that anxiety was independently associated with the development of PND. It is known that anxiety is more likely to precede depression through a causal link, suggesting that this is facilitated



by the anxiety response style.<sup>22</sup> It can be argued that parturients with greater pre-operative anxiety possess certain personality traits that result in a defective stress response,<sup>23</sup> predisposing them to PND, among other post-operative complications such as increased post-operative analgesia usage and poor patient satisfaction,<sup>24</sup> and may even arguably influence the parturient's preference for anesthesia modality for CD.<sup>25</sup>

Pain experienced before elective CD was associated with PND development. The common sources of pain pre-delivery experienced in our study include the lower lumbar region, pelvic girdle and lower abdomen, consistent with that found in other studies.<sup>26</sup> The association of pain prior to elective CD and PND has not been widely investigated. Several studies have demonstrated this association and further investigations should be performed.<sup>10,27</sup> It is possible that the intensity and duration of pain may contribute to the psychological and emotional distress experienced by women, thus increasing their vulnerability to PND.<sup>28</sup> The association between higher pain scores before delivery and PND highlights the importance of adequate perioperative pain management.

Higher anticipated pain medication needs are associated with a reduced risk of PND development. One possibility is that individuals who anticipate greater pain medication needs may be more open to acknowledging their conditions and receiving treatment. These parturients would thus be monitored periodically and have access to healthcare support and early interventions if necessary. Alternatively, we can consider measures that prepare the parturients psychologically, including knowledge about pain medication needs, prior to surgery can help to address needs and form an accurate expectation of post-operative outcomes.<sup>29</sup> This may then positively influence the recovery process. Hence, measures should be implemented to improve parturient satisfaction and to reduce the risk of PND. These could include appropriate pre-operative counselling for analgesic control and the management of exaggerated pain expectations.<sup>30</sup>

This study has some limitations. First, it was performed in an Asian population predominantly of Chinese ethnicity. Moreover, we only examined parturients who underwent elective CD under neuraxial anesthesia. Hence, the results of our study may not be generalizable to other populations. The Asian population often downplays their mood symptoms because they fear negative judgments and the social stigma associated with mental health issues.<sup>31</sup> Second, our study conducted follow ups at 6 to 10 weeks postnatal, while studies have shown that occurrence of PND can be anytime within the first year after delivery.<sup>32,33</sup> Third, we used the EPDS questionnaire as a diagnostic tool for PND. However, it is important to acknowledge that the EPDS is not intended for diagnostic purposes but rather serves as a screening tool to identify parturients at risk of PND.<sup>34</sup> The formal diagnosis of PND should still be performed by medically trained healthcare professionals.

## Conclusion

In conclusion, we validated five pre-operative risk factors associated with PND development in parturients undergoing elective CD under neuraxial anesthesia. This study supports that the risk factor model for PND in a previous study is valid and useful for predicting the likelihood of developing PND. Our validated model can help identify at-risk parturients, so that closer monitoring and early intervention can be implemented. Further studies are required to determine whether this model is applicable in different social and cultural contexts.

## Abbreviations

PND, postnatal depression; CD, Cesarean delivery; ROC, receiver operating characteristic; STROBE, STrengthening the Reporting of Observational studies in Epidemiology; MTS, Mechanical temporal summation; PCS, Pain Catastrophizing Scale; CSI, Central Sensitization Inventory; HADS, Hospital Anxiety and Depression Scale; EPDS, Edinburgh Postnatal Depression Scale; NRS, numerical rating scale; SD, standard deviation; IQR, interquartile range; OR, odds ratio; 95% CI, 95% confidence interval; AUC, area under the curve.

## Data Sharing Statement

The datasets generated and analyzed in this study are available to anyone who wishes to access the data by contacting the corresponding author.

## Ethics Approval and Informed Consent

This study was approved by the SingHealth Centralized Institutional Review Board (SingHealth CIRB 2017/2381) and registered on ClinicalTrials.gov (NCT03645239) on 22 Jun 2017. The authors declare that all recruited patients provided informed consent and that this work was conducted in accordance with the Declaration of Helsinki.

## Consent for Publication

All the patients provided informed consent for the use of de-identified data for publication.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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