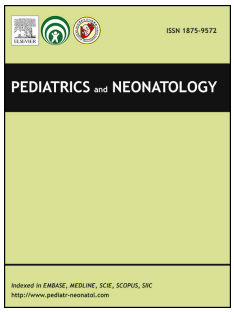

Changing risk factors for postpartum depression in mothers admitted to a perinatal center

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INTRODUCTION

Mothers often experience depressive mood, or so-called “baby blues”, within the first week after delivery; most improve over the two subsequent weeks.[1] However, some mothers progress from depressive mood to major postpartum depression (PPD) toward four weeks after delivery.[2] Some regional studies in an Asian developed country reported that PPD occurs in 8.7–18.8% of postpartum women.[3–5] PPD is a leading cause of infantile death from child abuse, and 20–40 cases are reported annually in Japan.[6,7] Nevertheless, the precise mechanisms underlying the development of progressive mood disorder have not been fully understood.

The Edinburgh Postnatal Depression Scale (EPDS) is commonly used in screening for PPD. It has been adapted and validated in many languages and is used globally for postpartum depression-screening, which is conducted within eight weeks after childbirth. The internal consistency and test-retest reliability of the Japanese version of the EPDS (EPDS-J) was validated for Japanese individuals.[8] The EPDS is a 10-item questionnaire consisting of 4 questions for each item, which are scored from 0 to 3 according to the severity of clinical depression symptoms (total score of 30). A score of ≥12 is the global standard for indicating a risk of developing PPD. On the other hand, a score of ≥9 has been accepted as a useful cut-off to assess the risk of developing PPD in the Japanese population.[8,9]

Perinatal centers provide intensive care for high-risk pregnant women. Infants born to these mothers receive medical support in a neonatal intensive care unit (NICU). Thus, the postnatal mother requires active mental care to manage her physical and psychological stress due to the neonatal-maternal outcomes. Recent advances in NICU medicine have

dramatically improved the survival rate of periviable infants and extremely preterm infants near the limit of viability. In contrast, several studies have reported increasing rates of neurodevelopmental disability among periviable survivors in comparison to previous decades.[10,11] In this setting, the neonatal outcomes are critical for parents to control their psychological burden.

For the early screening and optimal care of PPD in mothers entering a perinatal center, the present study aimed to ascertain clinical factors which were associated with the deterioration of the EPDS-J score during the first month after delivery. We then analyzed the risk factors for PPD at birth and at four weeks after birth based on the cut-off values and postnatal alterations in mothers who were managed in a tertiary perinatal center in Japan.

MATERIALS AND METHODS

Study population

Our prospective study recruited all pregnant women (n = 1,335) who delivered in National Hospital Organization Kokura Medical Center from January 1, 2018, to December 31, 2019. This facility is one of three tertiary perinatal centers covering 16.7–18.5% of childbirths in the region. In our hospital, all newborns are hospitalized with their mothers within the first week after delivery. Fifty-seven mothers were excluded from the 1,335 mothers because they had a stillborn fetus or fetal death (n = 12) or multiple pregnancy (n = 35); one foster mother was excluded (n = 1). The EPDS-J was conducted in the first and fourth weeks after childbirth. As a result, the study population included 1,287 mothers who delivered a single

live-born infant and received a follow-up examination at four weeks after childbirth (**Figure 1**).

Clinical information and management

The maternal characteristics included maternal age, fertility treatment, pregnancy history, mode of delivery, and hypertensive disorders of pregnancy (HDP). HDP was defined by the criteria of the International Society for the Study of Hypertension in Pregnancy.[12] Several studies reported that mothers feel depressed when their baby is delivered without a good status.[13,14] The neonatal characteristics included sex, gestational age (GA), Apgar score at 1-minute after birth, and admission to the NICU in our center. GA was determined based on the last menstrual period according to the best obstetric estimate, standard parameters, and ultrasonography. Clinical information was also collected for mothers whose infants were admitted to the NICU, including congenital anomalies, complications, airway support (continuous positive airway pressure or assisted ventilation), duration of hospitalization, and outcomes. All admitted mothers completed the EPDS-J at the first and fourth weeks after delivery. A score of ≥9 indicated that the mother was at risk for PPD. Mental counseling was recommended for mothers with a score of >9 at four weeks, and the mothers were then introduced to psychiatrists employed by our center as necessary.

Ethics

Our study design complied with the standards of the Declaration of Helsinki and the current ethical guidelines and it was approved by the institutional ethics board (Kokura Medical Center REC2019-023). Written informed consent for participation in this study was not

obtained from the subjects because this observational retrospective study collected and analyzed data anonymously after an opt-out notification on admission. Information about the study was provided on the hospital website (https://kokura.hosp.go.jp/senmon/rinshokensabu/sinsa.html) and the subjects would be excluded from the study upon request.

Statistical analyses

The clinical data analysis was performed using EZR version 1.41 (Jichi Medical University Saitama Medical Center, Saitama, Japan). Categorical data were expressed as the frequency and percentage, and chi-squared tests were used to evaluate differences. P values of <0.05 were considered to indicate statistical significance. A multiple logistic regression analysis was performed to determine adjusted odds ratios (aORs) and 95% confidence intervals (95% CI).

RESULTS

Clinical features

The characteristics of the study subjects are presented in **Table 1**. A total of 433 (33.6%) mothers delivered at ≥35 years of age, and 687 (53.4%) mothers were primiparous. Cesarean section (CS) was performed for 654 (50.8%) mothers. Apgar scores at 1-minute of <7 were recorded in 158 newborn infants (12.3%). Four hundred ninety-eight (38.7%) neonates were admitted to the NICU. EPDS-J scores of ≥9 were recorded in 253 mothers (19.7%) within the first week after delivery and 142 mothers (11.4%) at the fourth week after delivery. The mean

and standard deviation (SD) EPDS-J scores were 5.03 ± 0.12 within the first week and 3.79 ± 0.10 at the fourth week. These scores decreased in the four weeks after birth (p <0.01) (**Figure 2A**). Seventy-five (5.8%) mothers' scores worsened from <9 within the first week after birth to ≥9 at the fourth week, while 189 (14.5%) had scores that improved in this time-period (**Figure 2B**).

Factors associated with EPDS-J scores of ≥9

Table S1 shows the variables associated with EPDS-J scores of ≥9 in the study subjects (n = 1,287). Within the first week after birth, a multivariable logistic analysis identified primiparity (aOR 2.15, 95% CI 1.59–2.93, p <0.01), CS (aOR 1.52, 95% CI 1.14–2.03, p <0.01), and Apgar score at 1-minute of <7 (aOR 1.67, 95% CI 1.12–2.51, p = 0.01) as factors associated with a high EPDS-J. At the fourth week after delivery, primiparity (aOR 2.02, 95% CI 1.37–2.97, p <0.01) was the only significant variable. **Table S2** presents the factors significantly associated with worsened EPDS-J scores at four weeks after birth. The deterioration of EPDS-J was positively correlated with maternal aging (aOR 1.88, 95% CI 1.01–3.51, p <0.05) but negatively correlated with CS (aOR 0.38, 95% CI 0.21–0.70, p <0.01). NICU admission was not associated with a worsened EPDS-J score at either point after birth.

Characteristics of the NICU and the non-admission groups

Table 2 illustrates the characteristics of mothers whose infants were admitted to the NICU (NICU group) and those who were not (non-admission group). Significant differences between the two groups were observed in HDP (NICU *vs.* non-admission: 12.0% *vs.* 3.9%, p

<0.01), preterm birth (39.5% *vs.* 4.0%, p <0.01), and low Apgar score (24.9% *vs.* 4.3%, p <0.01). In the NICU group, 30 (6.0%) neonates had major anomalies. After admission, 101 (20.3%) patients received respiratory support. At the second surveillance, 119 (23.9%) infants remained in the NICU (**Figure 1**). The NICU group had a higher proportion of mothers at risk for PPD than the non-admission group within the first week (24.5% *vs.* 16.6%, p <0.01), but this was not so at the fourth week (10.8% *vs.* 11.1%, p = 0.86).

Factors associated with EPDS-J scores of ≥9 in the non-admission group

Table S3 presents variables associated with EPDS-J scores of ≥9 in the non-admission group. Primiparity (aOR 2.16, 95% CI 1.43–3.26, p <0.01) and low Apgar (aOR 2.31, 95% CI 1.07–4.98, p = 0 .03) were associated within the first week, and primiparity remained significant at the fourth week (aOR 2.50, 95% CI 1.52–4.11, p <0.01). The factors associated with the proportion of mothers with worsened scores are listed in **Table S4**. CS was negatively correlated with the deterioration of the EPDS-J score (aOR 0.42, 95% CI 0.20–0.89, p <0.05) (**Figure 3B**).

Factors associated with EPDS-J scores of ≥9 in the NICU group

Table S5 shows the factors associated with high EPDS-J scores in the NICU group. Within the first week after childbirth, primiparity (aOR 2.40, 95% CI 1.49–3.89, p <0.01), CS (aOR 1.66, 95% CI 1.06–2.59, p <0.05), and respiratory support (aOR 2.20, 95% CI 1.22–3.95, p <0.01) were significant factors. At the fourth week after delivery, infant anomaly (aOR 3.35, 95% CI 1.31–8.56, p = 0.01) was the only significant factor. Worsened scores were positively associated with infant anomaly (aOR 6.61, 95% CI 1.11–39.3, p <0.05) but

negatively associated with respiratory support (aOR 0.09, 95% CI 0.01–0.65, $p = 0.01$) (**Table S6**).

The mental outcomes of mothers with an increased risk of PPD

Among 142 mothers who had scores of ≥9 at the fourth week, 38 (26.8%) received a recommendation to visit a mental health clinic, and 26 (18.3%) received counseling from clinical psychiatrists (**Table S7**). Of the four mothers who did not have a prenatal psychiatric diagnosis, three (UPD01, 03, and 08) were ≥35 years of age and primiparous. Furthermore, a primiparous 43-year-old woman who delivered by CS was diagnosed with major PDD (UPN03). Risk factors for PPD in individual mothers who had an infant with an anomaly did not differ according to the type of anomaly (**Table S8**). Among 30 mothers whose infants had any anomalies, 5 (UPD34–38) had a low score of <9 in the first week but a high score of ≥9 at four weeks. However, they did not require psychiatric consultation and did not develop psychiatric disorders (**Table S7**).

DISCUSSION

This is the first study to assess the impact of EPDS changes within four weeks after delivery on the development of major PPD in mothers whose newborns were admitted to the NICU. The mean EPDS-J scores declined after delivery; however, the scores increased, representing an increased risk of PPD, in 75 of 1287 (5.8%) mothers in our perinatal center. CS and neonatal respiratory support at delivery were associated with improved EPDS-J scores. On the other hand, maternal aging and infant anomaly were associated with worse scores.

Appropriate assessment and support could protect puerperants with infant anomalies from developing psychiatric disorders, while advanced-aged women developed major PPD. These results suggest that older high-risk pregnant women require active mental care due to increased risk factors for PPD.

Depressive mood after childbirth progresses to major PPD, the leading cause of fatal child abuse. In this single institutional cohort, we determined the EPDS-J scores sequentially in all mothers to determine the factors associated with worsened scores. The EPDS-J scores decreased at four weeks after birth (**Figure 2A**). Previous Japanese studies reported that puerperant women showed deteriorated EPDS-J scores within the first week and that the scores improved over the two following weeks.[2] However, 142 (11.4%) mothers still showed high EPDS-J scores at four weeks after delivery (**Table 1**). In 75 (5.8%) of these mothers, the score worsened from <9 within the first week to ≥9 at the fourth week (**Figure 2B**). A longitudinal population-based study showed that 8.4–20.8% of mothers had EPDS-J scores of ≥9 during the first month after delivery.[15–17] The incidence of PPD in Japan is reported to be 8.7–14.3%,[3] and it was estimated to be 7.2–9.6% in one meta-analysis.[16] The prevalence of anxiety or depression in the general population is reported to be 4.2%.[18] The low incidence of PPD in our center—0.23% in the overall population and 5.8% in mothers with worsened scores—may account for the targeted support for high-risk mothers. DSM-5 defines "Peripartum/Perinatal Depression" as depression occurring in the antenatal and postpartum periods.[19] However, the psychiatrists recommended the term "Postnatal Depression" to evaluate the postnatal depressive symptoms during the first month postpartum.

Many regional cohorts reported that primiparity was a risk factor for depressive

symptoms during the first month postpartum.[20–22] After delivery, primiparous mothers face the responsibility of childcare, which they have not previously experienced. They may be concerned about crying and feeding their baby all day and night, resulting in sleep disturbance.[23] Childcare without help further burdens them with responsibility. A study of a Japanese regional cohort[24] and a prospective study of mothers whose infants were hospitalized in the NICU in other developed countries[25] reported that maternal aging was associated with an increased risk of PPD. However, path model analysis in mainland China[26] and Israel[27,28] showed that younger maternal age was a risk factor for PPD. Other community-based or regional cohort studies did not report maternal age as a risk factor for PPD.[29] These discrepant results may be explained by the different timing of data collection or the background characteristics of the study population.

The mode of delivery is reported to be a risk factor for PPD.[30–32] A meta-analysis concluded that CS was associated with PPD.[33] Above all, emergency CS is a traumatic experience for mothers.[34] Bed rest, difficult self-care, and post-surgical or anesthesia-related complications burden mothers after CS. On the other hand, cross-sectional studies in Turkish[31] and Chinese[26] cohorts showed that the mode of delivery did not affect the PPD score at 4–6 weeks postpartum.

NICU admission was not a risk factor for PPD in the present study, while previous studies reported that mothers whose infants were admitted to NICU had high rates of PPD.[25] We identified infant anomaly and respiratory support for the infant as risk factors for PPD in the mothers of infants who were admitted to the NICU. However, any mothers diagnosed with psychiatric disorders did not have those neonatal comorbidities. These results implied

that adequate mental care to prevent PPD was provided to mothers whose neonates were admitted to the NICU. Mothers whose infants are admitted to the NICU are more likely to be anxious, but their mental state may protect them from PPD by promoting engagement with medical staff.

The present study was associated with some limitations. First, the study subjects included at-risk mothers treated in 1 of 4 tertiary perinatal centers in the Kitakyushu area. This may be a source of bias and should be considered when generalizing our results to other areas. Second, multiple pregnancies are a stressful event for pregnancy and child-rearing that affects the onset of PPD. This study was designed to explore the interaction between the maternal and neonatal clinical courses. Thus, due to the complexity of analyzing each piece of neonatal information, mothers with multiple pregnancies were excluded from the study population. Third, this study lacked data on the economic and educational background of the subjects, along with the key persons during maternity, which would have affected the risk of developing PPD. Fourth, in a previous report on women with postpartum depression, the onset was most frequently within the first few months of parturition [20]; thus, the surveillance schedule is another limitation. Nevertheless, we conducted the EPDS-J in the first week and at four weeks after delivery. Further studies are needed to clarify the optimal frequency and timing of postnatal visits to improve maternal mental health.[35]

The present study revealed the clinical factors associated with the worsening of EPDS-J scores. PPD may lead to child abuse. Accidental death, including filicide, is Japan's second-highest cause of infant death. Accordingly, medical staff who provide perinatal care need to assess the mental status of older mothers.

COI statement: The authors declare no conflicts of interest in association with the present study.

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FIGURE LEGENDS

Figure 1 Outline of the prospective cohort.

The study subjects included 1,287 mothers who delivered a single live-born infant in our institute between 2018 and 2019 and who completed the Edinburgh postnatal depression scale-Japanese version (EPDS-J) at one and four weeks after delivery. NICU, neonatal intensive care unit.

Figure 2 The Edinburgh postnatal depression scale-Japanese version (EPDS-J) score in each subject within the first week and at the fourth week after delivery.

A: Open circles show the scores of each subject. The mean (and standard deviation) EPDS-J scores decreased throughout the four weeks; the change was statistically significant (p <0.01). **B:** Solid lines indicate 75 (5.8%) mothers whose scores worsened from <9 within the first week to ≥9 at the fourth week. Dotted lines 189 (14.5%) indicate mothers whose scores improved.

Figure 3 Graphical summary of the present study.

A: In the overall study subjects, primiparity was a risk factor for postpartum depression (PPD) within the first week and at the fourth week after delivery. Maternal age ≥35 years was associated with a worsened the Edinburgh postnatal depression scale-Japanese version (EPDS-J) score at four weeks. Cesarean section (CS) ameliorated the EPDS-J scores during the four weeks. **B:** In mothers whose neonates were not admitted to the neonatal intensive care unit

(NICU), primiparity and CS—but not older maternal age—were identified as risk factors. **C:** In mothers whose neonates were admitted to the NICU, infant anomaly was associated with worse EPDS-J scores at both the 1st week after delivery and at the 4th week after delivery. Neonatal respiratory support was a risk factor for PPD within the 1st week but not at the 4th week.

Table 1 Characteristics of the study subjects (n = 1,287)

	n	**%**
Mothers		
Age ≥35 years	433	33.6
Fertility treatment	178	13.8
Primiparity	687	53.4
CS	654	50.8
HDP	91	7.1
Neonates		
Male	664	51.6
GA <37 weeks	229	17.8
Apgar score at 1-minute <7	158	12.3
NICU admission ≥4 weeks after birth	498	38.7
EPDS-J		
≥9 within the first week	253	19.7
≥9 at the fourth week	142	11.4

CS, Cerean section; HDP, hypertensive disorders of pregnancy;
GA, gestational age; NICU, neonatal intensive care unit;
EPDS-J, Edinburgh postnatal depression scale-Japanese version

Table 2 Characteristics in the NICU and the non-admission groups

	NICU ***n* = 498**		**Non-admission** ***n* = 789**		
	n	**%**	***n***	**%**	***p***
Mothers					
Age ≥35 years	155	31.1	278	35.2	0.10
Fertility treatment	65	13.0	113	14.3	0.52
Primiparity	275	55.2	412	52.2	0.29
CS	262	52.6	392	49.6	0.31
HDP	60	12.0	31	3.9	<0.01
Neonates					
Male	271	54.4	393	49.8	0.11
GA <37 weeks	197	39.5	32	4.0	<0.01
Apgar at 1-minute <7	124	24.9	34	4.3	<0.01
Small-for-gestational-age	39	7.8			
Major anomaly	30	6.0			
Respiratory support	101	20.3			
NICU admission ≥4 weeks	119	23.9			
EPDS-J					
≥9 within the first week	122	24.5	131	16.6	<0.01
≥9 at the fourth week	54	10.8	88	11.1	0.86

CS, Cerean section; HDP, hypertensive disorders of pregnancy; GA, gestational age; NICU, neonatal intensive care unit; EPDS-J, Edinburgh postnatal depression scale-

Figure 1

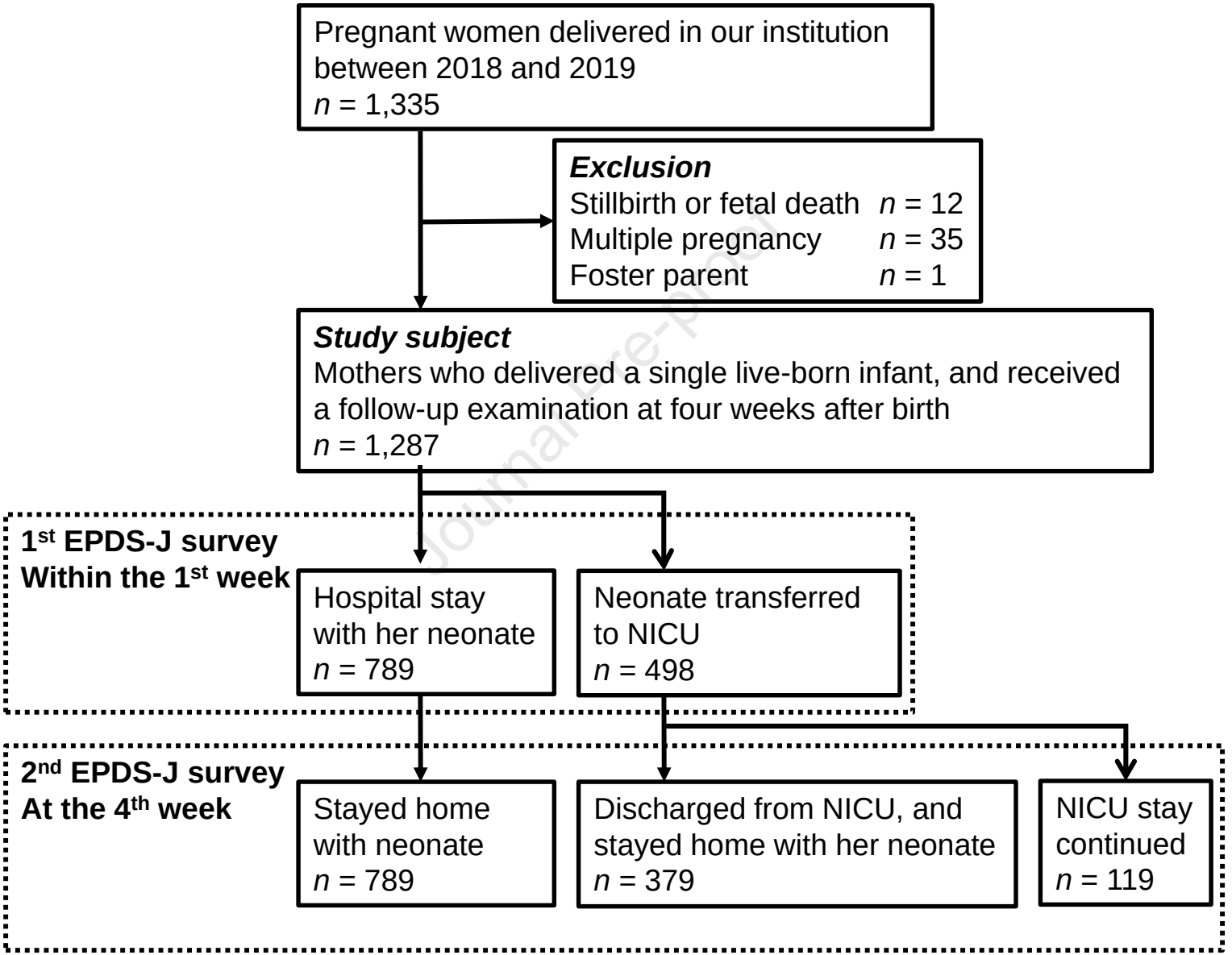

Figure 2

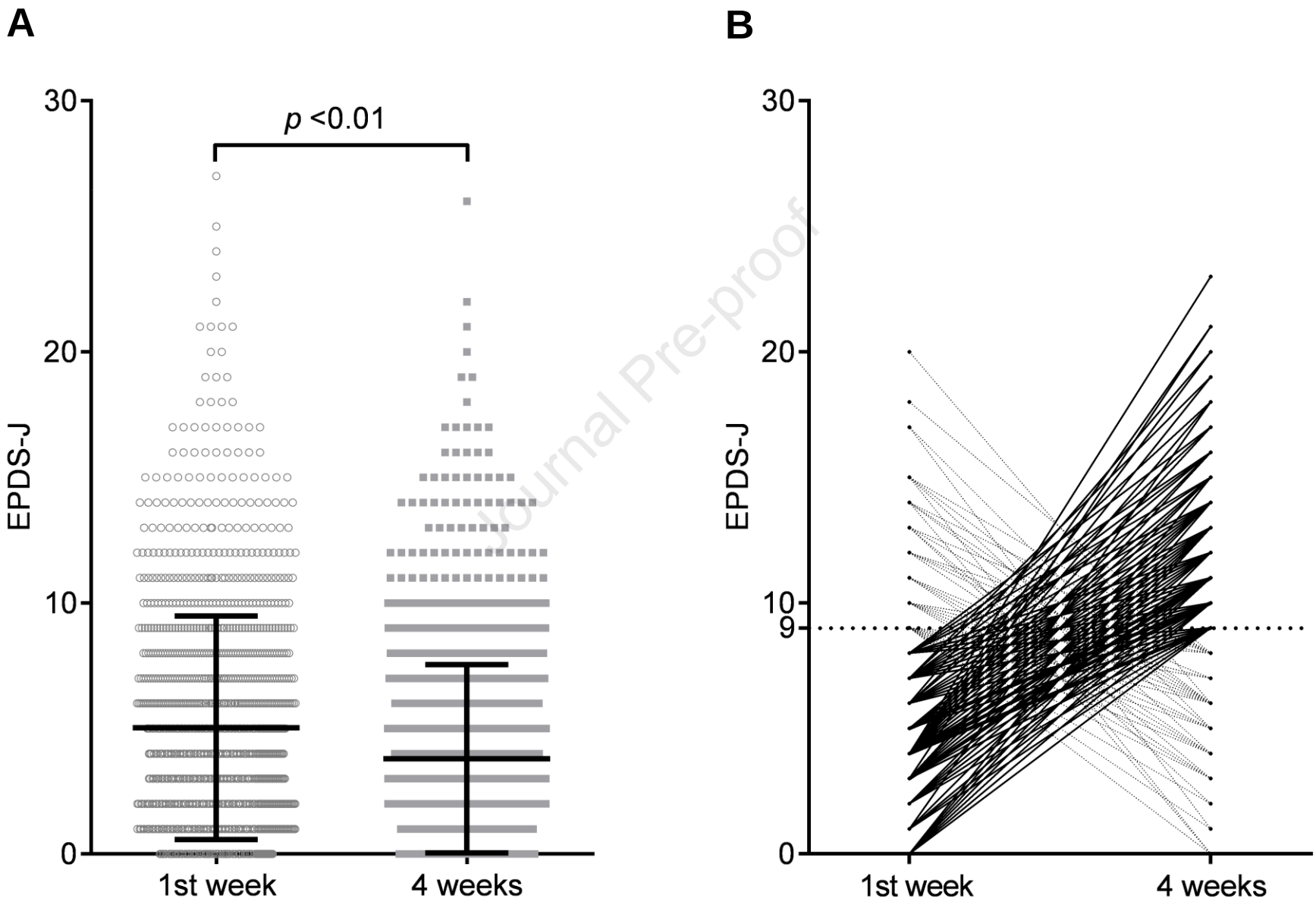

Figure 3